Centrocytic Lymphoma: A Distinct Clinicopathologic and Immunologic Entity

A Multiparameter Study of 18 Cases at Diagnosis and Relapse

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The clinical, pathologic, and immunologic aspects of malignant lymphoma of centrocytic type (ML,cc) were studied at diagnosis and often at relapse in 18 patients. The typical patient was a middle-aged or older man with adenopathy, often massive splenomegaly, hepatomegaly, marrow involvement, and, not infrequently, peripheral blood involvement. Histopathologically, ML,cc had a diffuse or vaguely nodular growth pattern with, predominantly, cells resembling centrocytes (cleaved follicular center cells) sometimes with admixed small round lymphocytes but with virtually no transformed cells. In 2 cases the neoplastic cells formed a mantle zone around reactive-appearing follicles. Cell suspensions and frozen sections revealed the monoclonal B-cell nature of all but 1 nonmarking case, and the polyclonality of the follicles in the 1 mantle zone case tested. The B cells had some, but not all, characteristics of both normal mantle and follicular center cells when eight nodes were studied with the use of a panel of monoclonal antibodies, peanut lectin, and endogenous alkaline phosphatase activity. Of 13 patients who underwent repeat biopsies, 1 developed a high grade unclassifiable B-cell lymphoma, and 6 had less marked changes. None of 7 patients tested had a change in light chain class. In conclusion, ML,cc is a distinct entity separable from other B-cell lymphomas in which either centrocytes or small round lymphocytes predominate. (Am J Pathol 1983, 113:181–197)

MALIGNANT LYMPHOMA of "centrocytic" type (ML,cc) has been defined as a B-cell lymphoma composed exclusively of centrocytes (cleaved follicular center cells) without any centroblasts (transformed or noncleaved follicular center cells). The latter criterion has been used to distinguish ML,cc from the other follicular center cell lymphoma in which centrocytes predominate (centroblastic/centrocytic/follicular or diffuse). Recognized initially by Lennert and colleagues, ML,cc was included as a distinct entity in the Kiel classification published by the European Lymphoma Study Group in 1974.[1] Because it is not recognized as a distinct entity in any other classification, ML,cc has not been as extensively studied as other B-cell lymphomas. Analysis of well-studied cases of ML,cc has strongly suggested that this is a distinct clinicopathologic entity, and this conclusion is supported by those series of lymphomas that include a predominance of centrocytic cases.[2–6] We studied 18 cases at diagnosis and often at relapse using a clinical, pathologic and immunologic approach to further describe ML,cc, to study how it changes over time, and to discover which normal lymphoid cell the cells of a centrocytic lymphoma most closely resemble.

Patient Population

Eighteen patients were selected because they had definite ML,cc as seen with light microscopy, by the criteria of the European Lymphoma Study Group,[1] and also underwent immunologic phenotype studies of involved solid tissue at least once during the course of their disease. These patients were selected over a

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Table 1—Clinical Features at Presentation

Feature	Number of patients (N = 15)
B symptoms	
Present	7
Absent	8
Adenopathy	
Supra- and infradiaphragmatic	13
Supradiaphragmatic only	2
With 1 or more nodes ≥3 cm	8
Splenomegaly	
Massive* (>10 cm)	7
Minor-moderate (1-4 cm)	4
Absent	4
Hepatomegaly	
Massive (>10 cm)	1
Minor-moderate (1-8 cm)	10
Absent	4
Biopsy-proven extranodal involvement†	2/18
Marrow involvement	
Present	14
Absent	1
Stage	
III	1
IV	14

* Measurement is centimeters below costal margin.
† Colon and eyelid (refers to diagnostic biopsies at initial presentation only and includes all 18 patients).

time period when a total of 706 non-Hodgkin's lymphomas were seen at St. Bartholomew's Hospital, including 66 centrocytic lymphomas, 188 centroblastic/centrocytic lymphomas, and 151 lymphocytic lymphomas.

The 17 patients on whom clinical data were available ranged in age from 41 to 70 years, with a median of 56. All but 1 were male. Presentation features from the 15 patients in whom pretreatment data were available (except as noted) are summarized in Tables 1 and 2.

All median survival times were measured from the date of the initial biopsy and were calculated with the use of life table analyses with comparison of survival times evaluated by use of the log rank test.[7] Unlike all the other survival data shown, evaluations of the prognostic significance of clinical findings at presentation included only the 15 patients with pretreatment data. Other statistical comparisons were done using the chi-square test, with Yates' correction, or the Fisher exact test.

Materials and Methods

Pathologic Review

Histologic sections from tissue biopsy specimens, including all patients' pretreatment specimens, stained with hematoxylin and eosin (H&E) and usually Giemsa, periodic acid-Schiff, methyl green pyronin-alcian blue, and for reticulin were reviewed. All tissue had been fixed in formalin and/or formol sublimate. Resin-embedded sections were available in 1 case. The following involved tissues were reviewed: 40 lymph nodes, 5 spleens, 4 liver biopsy specimens, 3 biopsy specimens from the region of Waldeyer's ring, and 10 specimens from other extranodal sites.

Immunologic Studies

Cell suspensions from tissue (28), peripheral blood (7), or pleural fluid (1) were prepared and phenotyped as detailed previously.[8,9] Twelve of these cases were included in those publications. In many cases, acetate washing was done to remove cytophilic antibodies. Some suspensions were evaluated with the use of the following monoclonal antibodies: OKT or T1, T3, T4, T6, T8, and T9 (Dr. G. Goldstein, Ortho Pharmaceuticals, Raritan, NJ, Coulter Electronics, Hialeah, Fla), Leu-1, -2a, and -3a (Becton-Dickinson, Sunnyvale, Calif), CA-2, DA-2 (Dr. W. Bodmer), J5 (Dr. J. Ritz, Dr. S. Schlossman, Coulter Electronics), and UCHTl (Dr. P. Beverley). The second antibody was FITC-conjugated goat anti-mouse immunoglobulin (Ig) absorbed against pooled human IgG-M on CNBR sepharose columns (Pharmacia, Inc., Piscataway, NJ). Some cases were evaluated with the use of FITC-peanut lectin.

Fresh tissue from 8 node biopsies (6 patients) was frozen in OCT compound, Tissue Tek II (Lab-Tek Products, Naperville, Ill), stored at −156 C, and later sectioned. Sections were fixed in acetone and immunostained by the "ABC" avidin-biotin technique.[10] (ABC conjugate, Vector Laboratories, Burlingame, Calif; biotinylated secondary antibodies, Tago Laboratories, Burlingame, Calif). Sections were stained with $F(ab)_2$ rabbit anti-human Ig heavy and light chains, with some of the monoclonal anti-

Table 2—Hematologic Data at Presentation

Finding		Number of patients (n = 15)
White blood cells (×10⁹/l)	<5	2
	5-10	4
	>10	9
Lymphocytes (×10⁹/l)	<2	4
	2-4	3
	4.1-15	4
	>15	4
Hemoglobin (g/dl)	≤10	4
	10.1-12	4
	12.1-14	3
	>14	4
Platelets (×10⁹/l)	<100	2
	101-150	4
	>150	9

bodies described above and with some or all of the following: monoclonal anti-κ, -λ, -IgG, -IgA, -IgM, and -IgD (Seward Laboratory, London, England), T11 (Coulter Electronics), OKT10 (Dr. G. Goldstein), Leu-7 (Becton-Dickinson), BA-1 and BA-2 (Dr. J. Kersey, Dr. T. LeBien), 33.1 (Dr. G. E. Marti, Dr. T. J. Kindt), RFA-2 (Dr. G. Janossy), B1 (Coulter Electronics), and biotinylated peanut lectin (Vector Laboratories).

Endogenous alkaline phosphatase activity was assayed by rehydrating the acetone-fixed sections in phosphate-buffered saline, pH 7.6, for 5 minutes and then incubating the slides in the freshly made and filtered substrate for 30 minutes (12 mg fast blue BB salt [Raymond A. Lamb, London] in 10 ml naphthol AS-MX phosphate, 0.025%, pH 8.6 [Sigma Chemical Co., St. Louis, Mo]). The slides were then washed in distilled water for 5 minutes and mounted.

Frozen sections of 4 tonsils, 7 reactive lymph nodes, and 4 spleens were analyzed as controls. A brief summary of the specificities of some of the reagents used to phenotype the cases is in Table 3.

Results

Pathologic Features

Lymph Nodes at Presentation

The lymph nodes showed marked architectural effacement by a relatively monomorphic lymphoma growing diffusely (10 cases) or with vague nodules in at least some areas (6 cases) (Figure 1). One of the latter cases had a rare, more discrete nodule. Residual normal-appearing or atrophic follicular centers were present in 4 cases. In 2 of the latter cases, some of the follicular centers were within the vague nodules, creating the appearance of a wide lymphomatous mantle zone (Figure 1). Residual sinuses were present in 9 cases. Capsular invasion was virtually absent (3 cases), focal (6), or very extensive (4). Hyalinized vessels were present in 11 of the cases, and the vasculature was prominent in half of all nodes (Figure 2).

Most cells in all nodes closely resembled centrocytes (CCs), with, however, variations in cell size, the degree of nuclear irregularity, and the amount of chromatin dispersal (Figure 3). Small centrocytes (SCCs) predominated in all nodes. Three also had a small (5–25%) or moderate (26–50%) number of large centrocytes (LCCs). In some cases the larger cells tended to be within the vague nodules, giving more of an impression of neoplastic follicles. Five nodes had a definite population of small round lymphocytes (SRLs) either in small (3 cases) or moderate (2 cases) numbers (Figure 4). Transformed lymphocytes were rare to absent. The mitotic count was extremely variable, with 0–10 mitoses per 30 high-power fields (HPFs) in 7 nodes, 11–20/30 HPFs in 4, and more than 20/30 HPFs in 5. Macrophages were present in moderate numbers in 5 cases, rarely creating a starry sky appearance. Analysis, which included follow-up biopsies, showed that the prominence of macrophages tended to be associated with a higher mean mitotic count ($P = 0.07$). Two cases had a moderate number of plasma cells judged not to be a part of the lymphoma, and 2 had a moderate number of mast cells. No case had a significant number of epithelioid histiocytes or eosinophils.

Other Tissue at Presentation

In 2 cases only extranodal tissue was available at the time of presentation. The lymphoma in both was similar to that described above, with a colonic lesion showing vague nodularity, an eyelid lesion growing diffusely, and both having hyalinized vessels. The colonic tumor had predominantly SCCs and a moderate number of SRLs and 0 mitoses/30 HPFs. The lid lesion had predominantly LCCs and 10 mitoses/30 HPFs.

Splenic and Hepatic Pathology

Five patients underwent splenectomy. Macroscopic data, where available, revealed splenic weights of 820, 1500, 3425, and 3700 g and a grossly prominent white pulp. Microscopically, all had lymphomatous involvement, with an expanded white pulp and variable degrees of red pulp infiltration. One case had some vague nodularity, and 1, hyalinized vessels. No normal marginal zones were present and generally no residual follicles.

Four liver biopsies from 3 patients all demonstrated lymphomatous involvement in the portal tracts, with variable numbers of CCs in the sinuses. There was focal loss of the portal tract limiting plate.

Other Extranodal Tissues

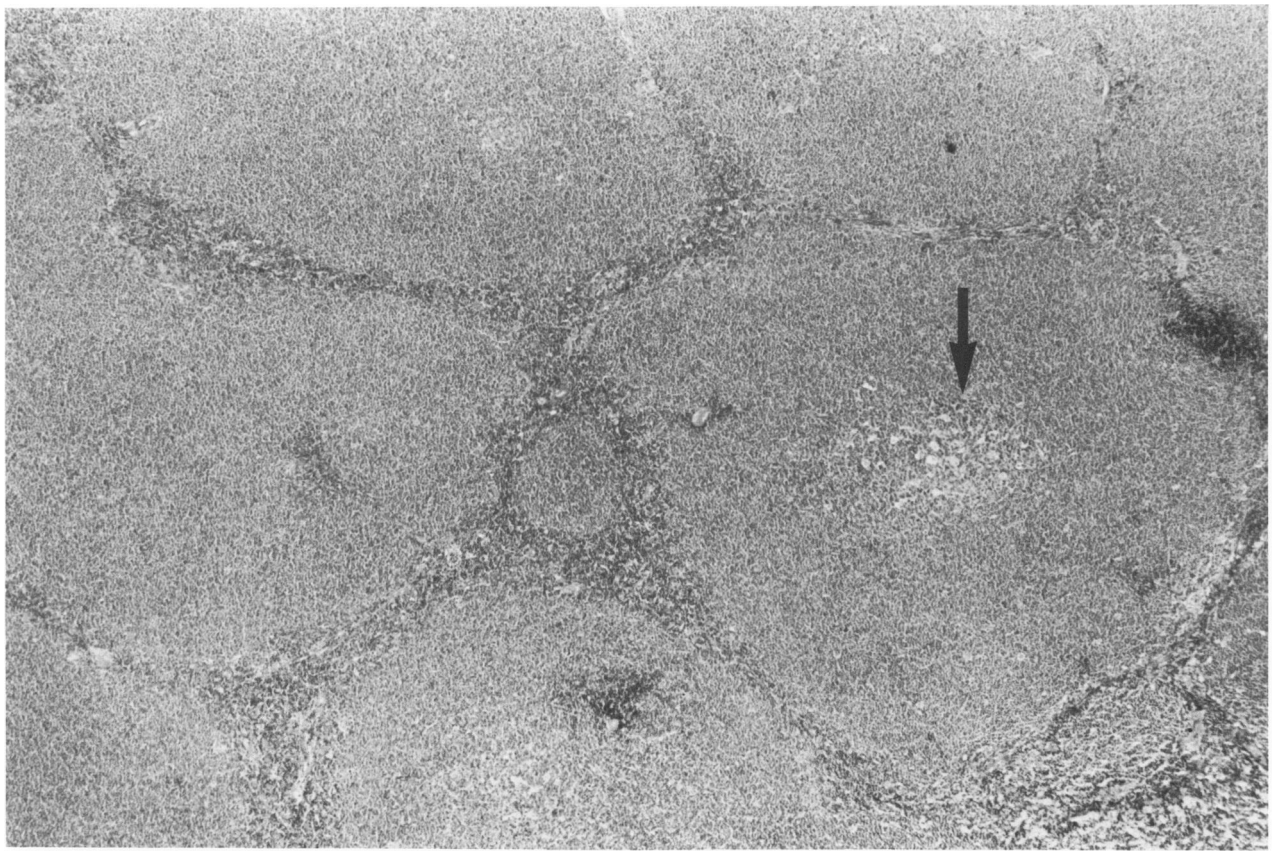
Seven patients had pathologically confirmed lymphoma at sites other than lymph node, spleen, or liver. Two had soft tissue infiltration in the region of the parotid (infiltration of salivary gland seen in 1) for which a nodal origin cannot be ruled out. One presented with lid involvement (see above). The patient who had a partial colectomy at diagnosis also had lymphoma in subsequent rectal, Waldeyer's ring, and conjunctival biopsies. Two other patients also had involvement of Waldeyer's ring. One with tongue

Table 3—Reactivity of Lymphoid Cells With Selected Monoclonal Antibodies and Other Reagents

Marker	Reported reactivity with lymphoid cells	Non-T-lymphoid neoplasms reported positive for marker	St. Bartholomew's Hospital results on frozen sections of reactive lymph nodes and tonsils	Reference
B1	All B cells except plasma cells; B-cell-specific	Common ALL (75%), CLL, PDL (N or D), HL (N or D), WM	MZ cells and GC cells	11, 12
BA-1	All B cells except plasma cells	Most non-T, non-B-ALL, pre-B ALL, CLL, WDL, PDL, HL, BL (60%)	Predominantly stains MZ cells with variable staining of GC in a reticular pattern	13
BA-2	Early lymphoid cells (50% bone marrow TdT* cells); peripheral lymphocytes negative	Non-T, non-B-ALL (77%), CLL (50%)	Variable staining of GC in a reticular pattern; MZ cells negative	14
RFA-2	Peripheral T cells and some B cells strongly positive; bone marrow lymphocytes negative	CLL	MZ cells strongly positive; GC cells negative, except for few scattered cells (probably T cells); interfollicular cells strongly positive	15
33.1	DR-related antigen expressed 1000× more strongly on EBV-transformed B-cell lines than PBLs	CLL	MZ and GC cells	16
CA2-11 (αHLA/DR)	Early lymphoid cells; all B cells except some plasma cells; small subset of T cells (activated plus other)	Non-T ALL, most B-cell neoplasms (usually not myeloma)	Mantle and GC cells; scattered interfollicular cells	17–19
J5	~1% bone marrow cells; ~5% cells in fetal liver	Non-T ALL (80%), BL (83%), PDL,N (100%), PDL,D (13%)	± Weak GC staining	20
T11	Cells expressing sheep erythrocyte receptor (pan-T)	None*	Most interfollicular cells positive. MZ, rare positive cells; GC, some positive cells, sometimes along inner edge of mantle	21, 22
UCHT1	Pan-T	None	Similar to T11	23
Leu-1	Pan-T; probably on small proportion of normal B cells	B-CLL, some B-cell lymphomas	Similar to T11	5, 15, 24–28
Leu-3a	T helper/inducer subset	None*	Majority of T cells positive, in similar distribution to T11	28
Leu-2a	T cytotoxic/suppressor subset	None*	Minority of T cells positive, mainly in interfollicular areas with, usually, only rare positive cells in follicle	28
Leu-7 (HNK-1)	NK, K, and other medium to large granular lymphocytes	None	Scattered cells in GC; rare cells positive in mantle and interfollicular areas	29
Peanut agglutinin	Some early lymphoid cells in bone marrow; cortical thymocytes; GC B cells and plasma cells	Some follicular lymphomas; some lymphoblastic lymphomas; plasmacytoma and myeloma	Some GC cells positive; MZ cells negative	30
Endogenous alkaline phosphatase	Mantle zone B cells; occasional GC blast cell	ML,cc; ML,CB; ML,CB/cc; ML,I (50%); PDL,N (57%); 1 case of ML,L	Mantle cells weakly positive in some cases; occasional GC cell positive	31, 32

Abbreviations: ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; PDL, poorly differentiated lymphocytic lymphoma; N, nodular; D, diffuse; HL, histiocytic lymphoma; WM, Waldenstrom's macroglobulinemia; MZ, mantle zone; GC, germinal center; WDL, well-differentiated lymphocytic lymphoma; BL, Burkitt's lymphoma; TdT, terminal deoxynucleotidyl transferase; DR, D region; EBV, Epstein-Barr virus; PBL, peripheral blood lymphocytes; NK, natural killer cells; K, killer cells; ML,cc, centrocytic lymphoma; ML,CB, centroblastic lymphoma; ML,CB/cc, centroblastic/centrocytic lymphoma; ML,I, malignant lymphocytic lymphoma of intermediate differentiation; ML,L, malignant lymphoma, lymphocytic type.

* Exceptions: see Aisenberg et al.[22]



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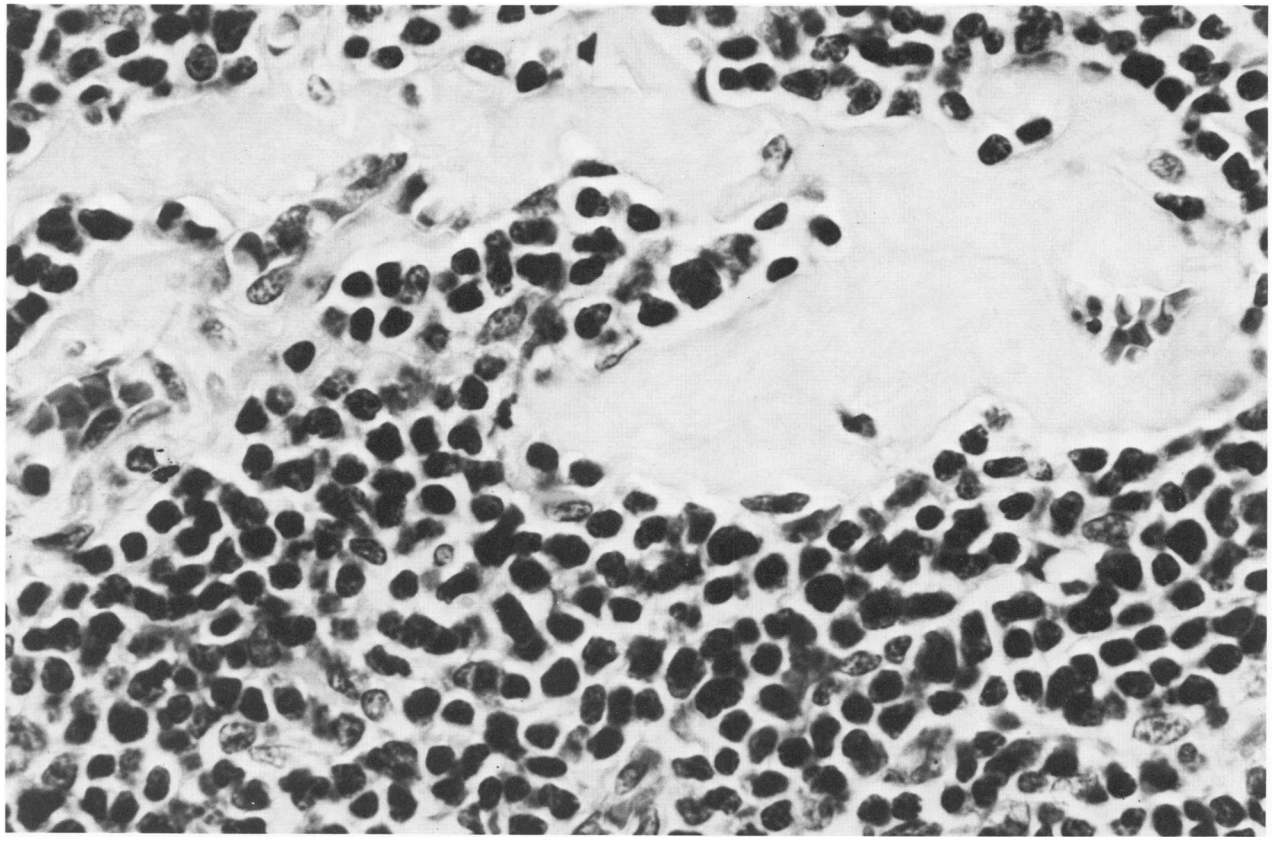

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Figure 1 — The vague nodules are better demarcated here by smaller lymphocytes than in most other cases. Notice how in some places the monomorphic lymphoma cells grow as a wide mantle zone around reactive-appearing germinal centers (*arrow*). (H&E, ×31) **Figure 2** — Notice among the centrocytes the very prominent hyalinized vessel. (H&E, ×500)

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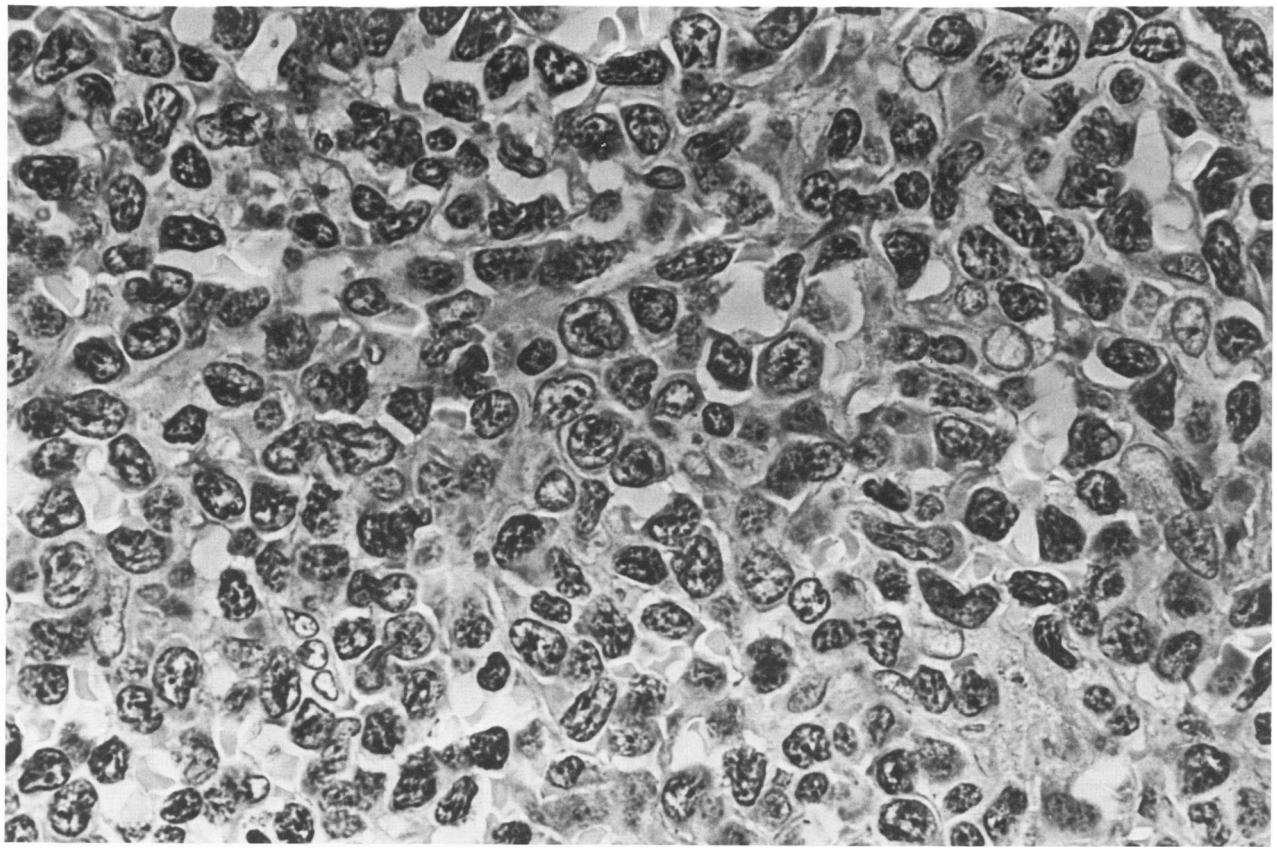

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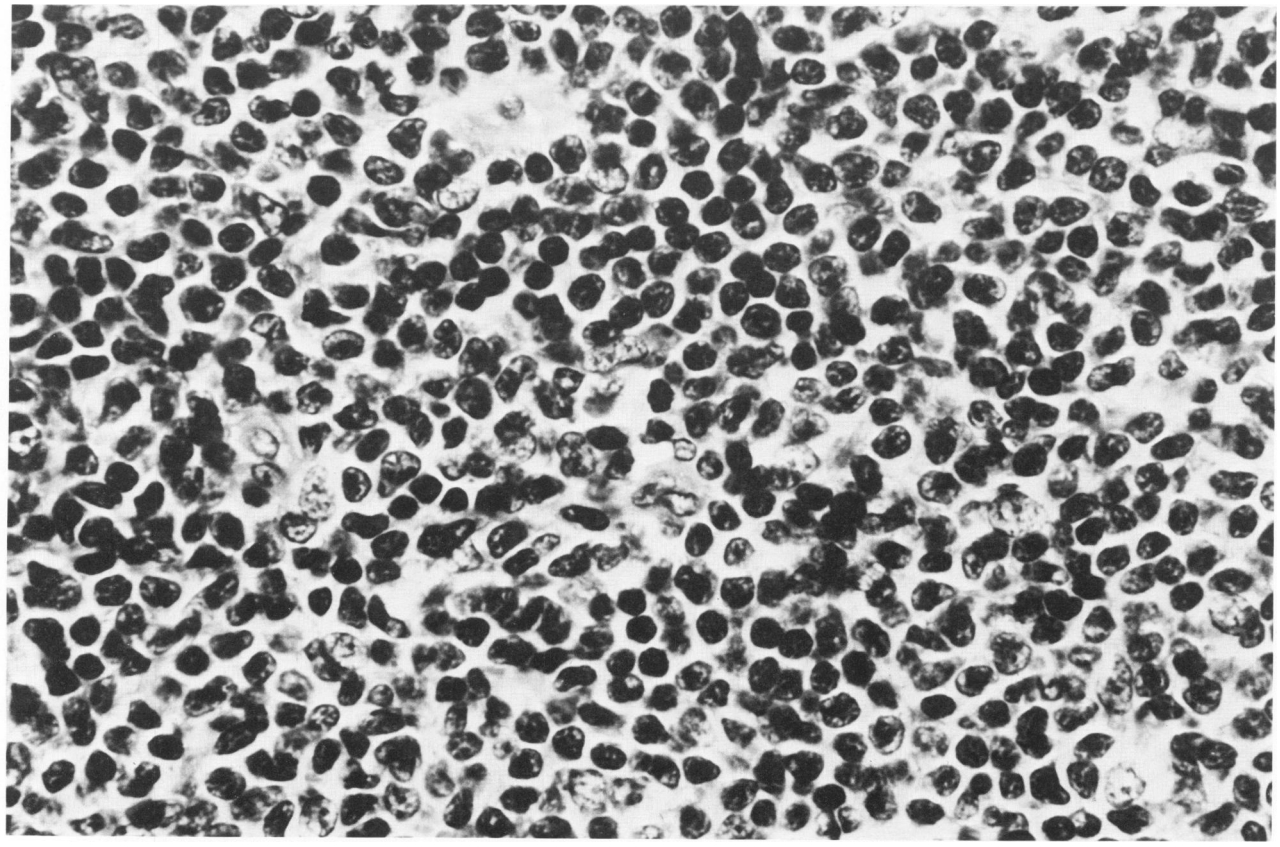

Figure 3 — The marked nuclear irregularity of these cells and the amount of chromatin dispersal show them to be more like the centrocytes of normal or neoplastic germinal centers than normal mantle zone cells. There is an admixture here of both small and large centrocytes. (Giemsa, resin-embedded, ×500) **Figure 4** — In this case there were predominantly small centrocytes but also some admixed small round lymphocytes. (H&E, ×500)

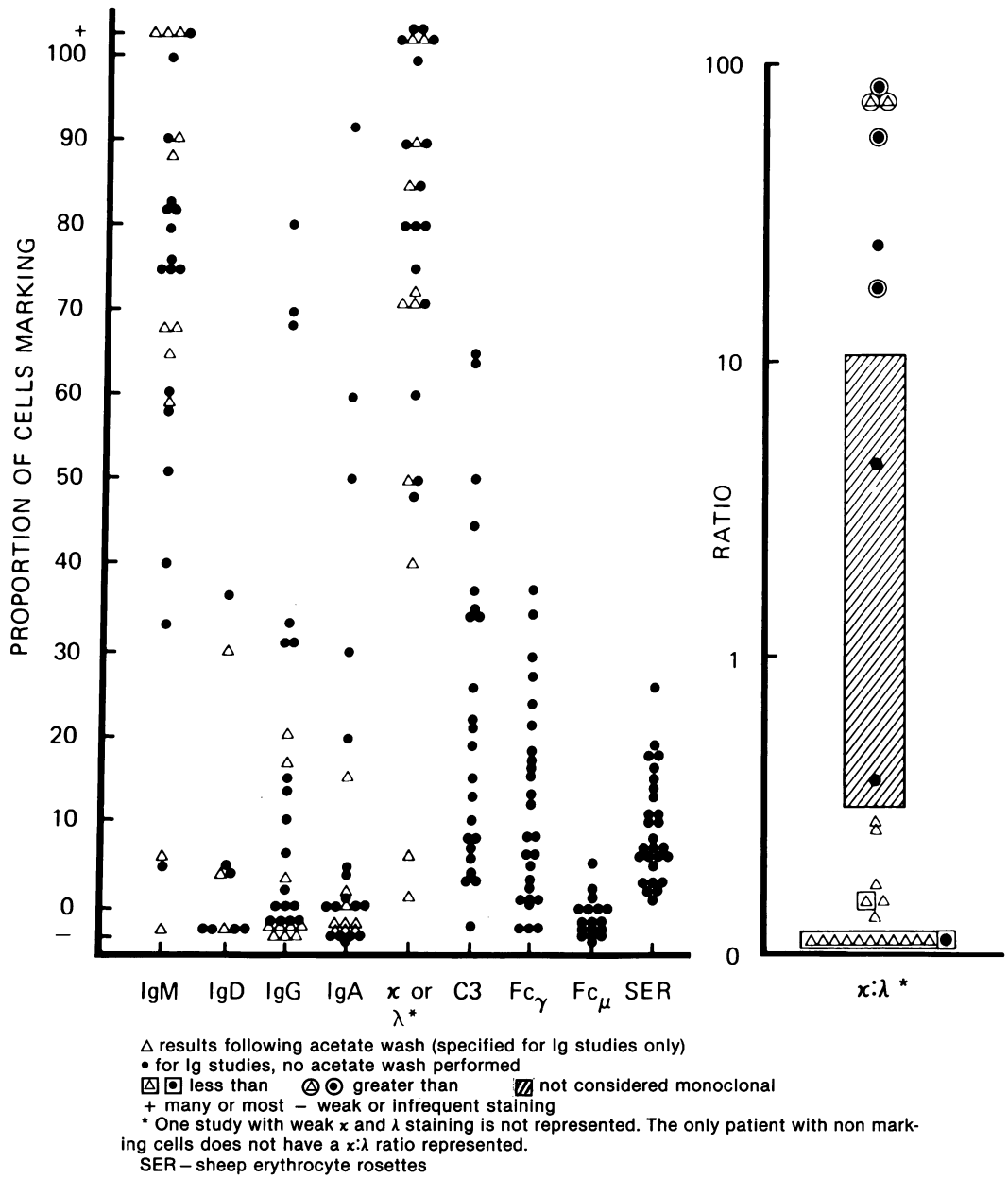

Figure 5—Suspension phenotypes of all solid tissue specimens. This includes 22 nodes, 2 Waldeyer's ring biopsies, 3 spleens, and 1 soft tissue and salivary gland specimen (? node). Only the proportion of cells bearing the predominant light chain is represented. Three to five specimens were also studied with each of the following reagents: OKT6 (<1-2% positive cells), OKT9 (<1%, <1%, 23%), DA2 (α-HLA/DR, 14-68%), J5 (anti-common ALL, <1% in 3, weak + in 1), and peanut lectin (<1% in 4, 6%). Not all cases were tested with each reagent.

involvement also had biopsy-proven colonic involvement. The other with tonsillar involvement also had lymphoma in a skin biopsy. The tongue biopsy demonstrated epithelial invasion, but the skin biopsy had a Grenz zone with dense reticular dermal and subcutaneous infiltration. The seventh patient had gastric biopsies showing lymphomatous infiltrations.

Immunologic Features

The suspension phenotypes from solid tissues are summarized in Figure 5 and Table 4. Seventeen of the 18 patients had an unequivocal (16) or probable (1 with weak frozen section staining) monoclonal B-cell neoplasm. One had nonmarking cells. There were 11 λ-bearing cases and only 6 with κ. IgM was definitely (16) or probably (1) present on the neoplastic cells in all but the 1 nonmarking case. Other heavy chain isotypes were present in some cases on a minor proportion of the cells. In individual studies heavy chain or light chain classes were less definite because of the presence of cytophilic antibody.

Suspension phenotyping was performed on the peripheral blood of 7 patients. Two demonstrated a

Table 4—Immunohistologic Results with Comparison to Suspension Studies*

Patient	Predominant B-cell Ig		Leu-1+ non-T cells in FZ (SP, Leu-1/T ratio‡	T_h:T_s ratio FZ(SP)	Monoclonal antibodies§								PNL	AlkP
	FZ	SP†			BA-1	BA-2	B1	RFA-2	CA-2	33.1	J5	Leu-7‖		
1														
a	Mλmcl	Mλmcl	+	<1	+	±	+	+	+	±	–	f	–	–
b	Mλmcl	M(GA)λmcl	+ (15.3)	<1 (.27)	+	±	+	+	+	+	–	m	–	–
c	Mλmcl		+	<1							–	–	–	–
2	Prob. Mλmcl		–	<1	+	±	+	+			–	f	–	
3	Mλmcl	MGλmcl¶	–	<1	+	±	+	+	+	±	–	f/m	–	+**
4	Mλmcl	M(G)λmcl	+ (2)	>1 (2.5)	+	±		+	±	±	–	m	–	±
5	Mκ mcl	MAG(D)κ¶ not mcl	+ (2.4)	<1 (.30)	+		+	+	±	±	–	m	–	+
6	κ mcl prob. MD	κ mcl	–††	~1 (1.1)	+	+	+	+		+	–	f	–	±

Abbreviations: Ig, immunoglobulin; FZ, frozen section; SP, suspension; T_h, T helper; T_s, T suppressor; Ca-2, αHLA-DR; PNL, peanut lectin; AlkP, alkaline phosphatase; mcl, monoclonal; +, positive or present; –, negative or absent.

* The first three studies are from 1 patient (third, fourth, and fifth repeat biopsies). All other patients were studied once. Some monoclonal antibodies were used only on sections. All blanks represent studies not done. The last patient's immunohistologic results are described in detail in the text. Unless stated, all results refer to frozen section studies.

† Heavy chains in parentheses were on less than half the number of cells bearing the major heavy chain but on ≥10% of total cells.

‡ T cells = (%OKT3 + UCHT1)/2.

§ See Table 3 for explanation of reactivity with normal and other neoplastic lymphoid cells.

‖ Few (f) or moderate (m) number of scattered presumably nonneoplastic positive cells. Even m represents a very low percentage of total cells.

¶ No acetate wash.

** This was the only case with a majority of cells strongly positive.

†† On repeat biopsy done after the completion of our study there were Leu-1+ T^- cells both in frozen section and suspension studies.

monoclonal population of B cells with 3% and 41% sheep erythrocyte rosettes (SER) (lymphocyte count, 376 and 6.2 × 10^9/l). Four cases had more B than T cells (SER 15–35%), and all 3 tested showed a predominance of the light chain class expressed in their definitive phenotype (lymphocyte count, 1.5 and 13.4 × 10^9/l, and unknown where κ:λ ratio tested). The seventh patient had 38% SER, 4% κ, and 9% λ with a lymphocyte count of only 1.3 × 10^9/l (node—probable monoclonal λ). One suspension phenotype done on pleural fluid (cytologic findings: degenerative changes with some cells consistent with CCs and some plasma cells) showed 29% κ, 18% λ, and 41% SER (node—monoclonal λ).

Frozen section immunostaining was done on 8 lymph nodes from 6 patients. The results, except for those discussed below, are summarized in Table 4. All cases had a moderate number of T cells ($T11^+$, $UCHT1^+$) scattered throughout the much more frequent B cells.

The case that histologically exhibited a focal mantle zone phenomenon and had even more frequent residual follicular remnants (Patient 6, Table 4) had nodules and more diffuse areas that stained diffusely and often weakly with αIgM, αIgD, ακ, and B1. The nodules contained a moderate number of admixed T cells ($T11^+$, $UCHT1^+$, $Leu\text{-}1^+$) and were surrounded by bands which contained many T cells, some plasma cells ($T10^+$, κ and λ^+) and other B cells. Whereas the overall T helper/T suppressor (T_h/T_s, Leu-3a/Leu-2a) ratio was approximately 1, there appeared to be a predominance of T_s cells in the nodular areas and of T_h cells in the surrounding bands. Scattered alkaline-phosphatase–positive lymphocytes were present within the nodules, but not in the follicular remnants. The positivity in the bands was predominantly associated with reticular cells and small blood vessels. Within some of the nodular areas and in the more diffuse areas were residual follicular centers that stained with αIgM, αIgG, αIgA, ακ, αλ, and peanut lectin (Figure 6). The αIgM, αIgG, ακ, and αλ staining was focally very intense, resembling the pattern seen in normal follicles. Pericellular polyclonal staining of B cells within the follicles was also seen. Surrounding the polyclonal follicles were scattered lymphocytes distinct from the lymphoma cells because of intense pericellular staining with αIgM, αIgD, ακ, and αλ. This is the phenotype of most normal mantle cells (data not shown).

Disease Evolution

Morphologic Changes

Thirteen patients had at least 2 tissue biopsies more than 6 months apart. One demonstrated a major change to an unclassifiable high-grade lymphoma (Figure 7). Although of proven B-cell origin, the cells were not cytologically identifiable as centrocytes, centroblasts, or B-immunoblasts. Two patients had moderate and 4, minor changes, usually with an increase in cell size and chromatin dispersal (Figure 8). One of these patients developed foci of round to oval partially and completely transformed cells, some of which had prominent nucleoli (Figure 9). These were rare to absent in other cases. The cytologic pattern was unchanged in 7 cases. The mitotic rate frequently more than doubled over time but also occasionally fell. Changes in growth pattern sometimes occurred, but not in a consistent way. Subsequent biopsies in the 2 mantle zone cases demonstrated complete loss of this pattern (no cytologic change was present, including one biopsy taken after the completion of our study). The time from diagnosis to cytologic change ranged from 7 to 112 months (all but 1 less than 3 years), and from cytologic change to death, from 3 to 18 months. The biopsies in which no change was demonstrable were performed between 7 months and 7 years after the initial diagnosis.

Immunologic Changes

Seven patients were studied at least twice. The predominant light chain class remained the same in all. In 1 patient (see Table 4), three separate studies demonstrated a constant population of Leu-1–positive B cells, a constant low T_h/T_s ratio, and a constant alkaline phosphatase negativity of B cells (another patient at rebiopsy following the completion of our study showed no change in light chain class but did acquire Leu-1 positivity on B cells). It was impossible to evaluate changes in heavy chain isotype accurately because of the presumed presence of cytophilic IgG and/or IgA in some cases with IgM. Changes in phenotype were also evaluated by comparing those from first or second biopsies with those from later biopsies. The results are summarized in Table 5.

Prognosis

Of 15 evaluable patients, 1 went into complete remission, 11 went into partial remission, and 3 showed no response after their initial therapy. Eleven of the patients had received chlorambucil or chlorambucil plus prednisone. Four received more intensive chemotherapy. Median survival was 45 months, and only 2 patients survived more than 5 years (4 are alive at 9–45 months). This was not significantly different from the entire group of patients with ML,cc managed at St. Bartholomew's Hospital ($P = 0.42$).

Clinical and pathologic features of prognostic significance are listed in Table 6. Five of the 6 patients

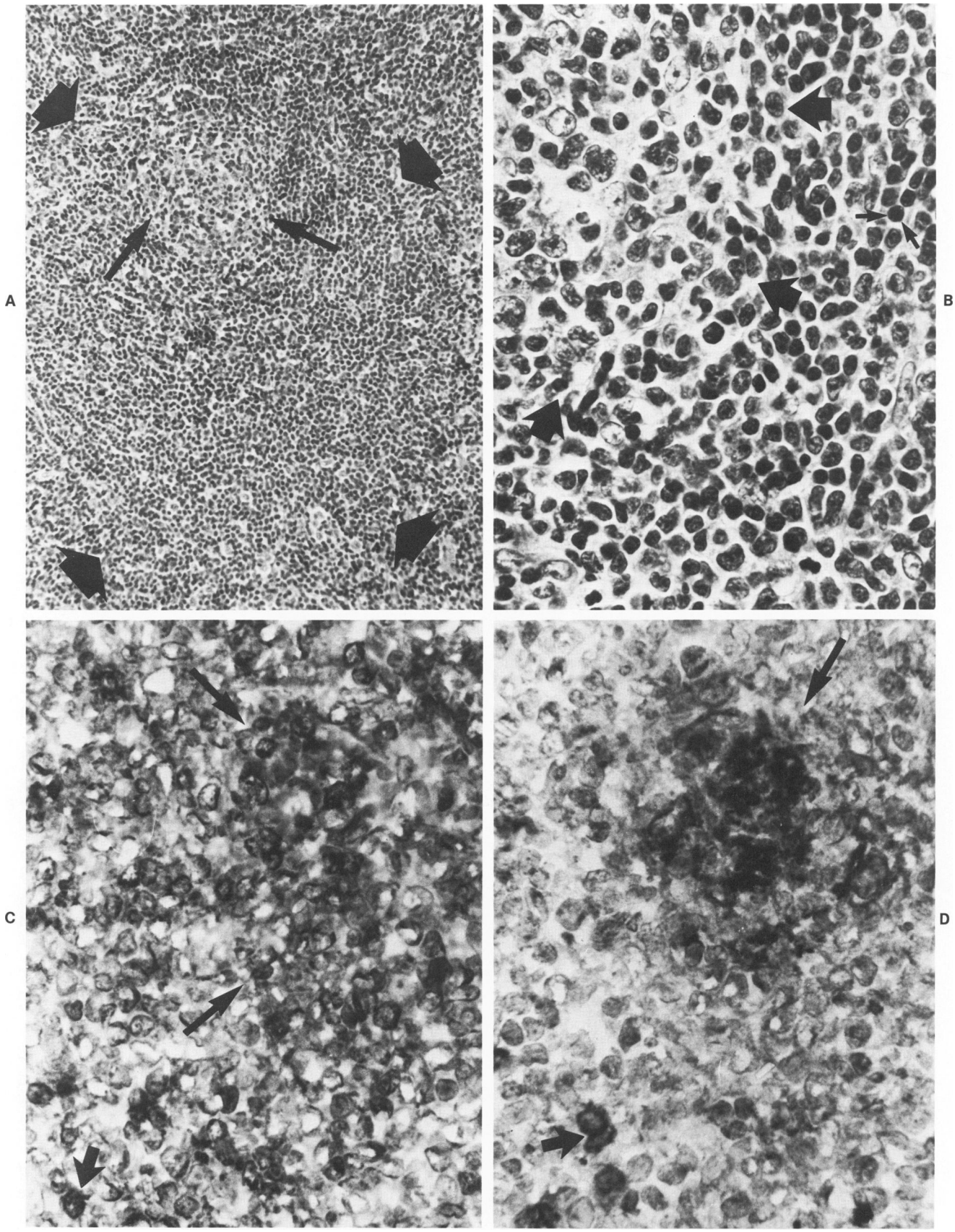

Figure 6A – Notice the residual germinal center (*thin arrow*) within the vague nodule (*thick arrow*). **B** – Notice the greater admixture of cell types in the reactive appearing germinal center (*thick arrow*), compared with the more monomorphic lymphoma. Some probably residual round mantle zone cells are also present (*thin arrow*). **C** – Immunohistochemical staining with $\alpha\kappa$ antibody marks a residual follicle strongly (difficult to see here, *thin arrow*). Notice the occasional strongly stained cells outside the germinal center (*thick arrow*). Similar cells stained strongly with αIgM and αIgD. **D** – Immunohistochemical staining with $\alpha\lambda$ antibody identifies a residual follicle that has a darker and paler staining area (*thin arrow*). Although occasional cells outside the follicle marked strongly as with $\alpha\kappa$ (*thick arrow*), the majority of cells were negative (very few illustrated here). Suspension studies showed a κ/λ ratio of 23.7. (**A**, H&E, × 125; **B**, H&E, × 500; **C** and **D**, immunoperoxidase with hemalum counterstain, × 500)

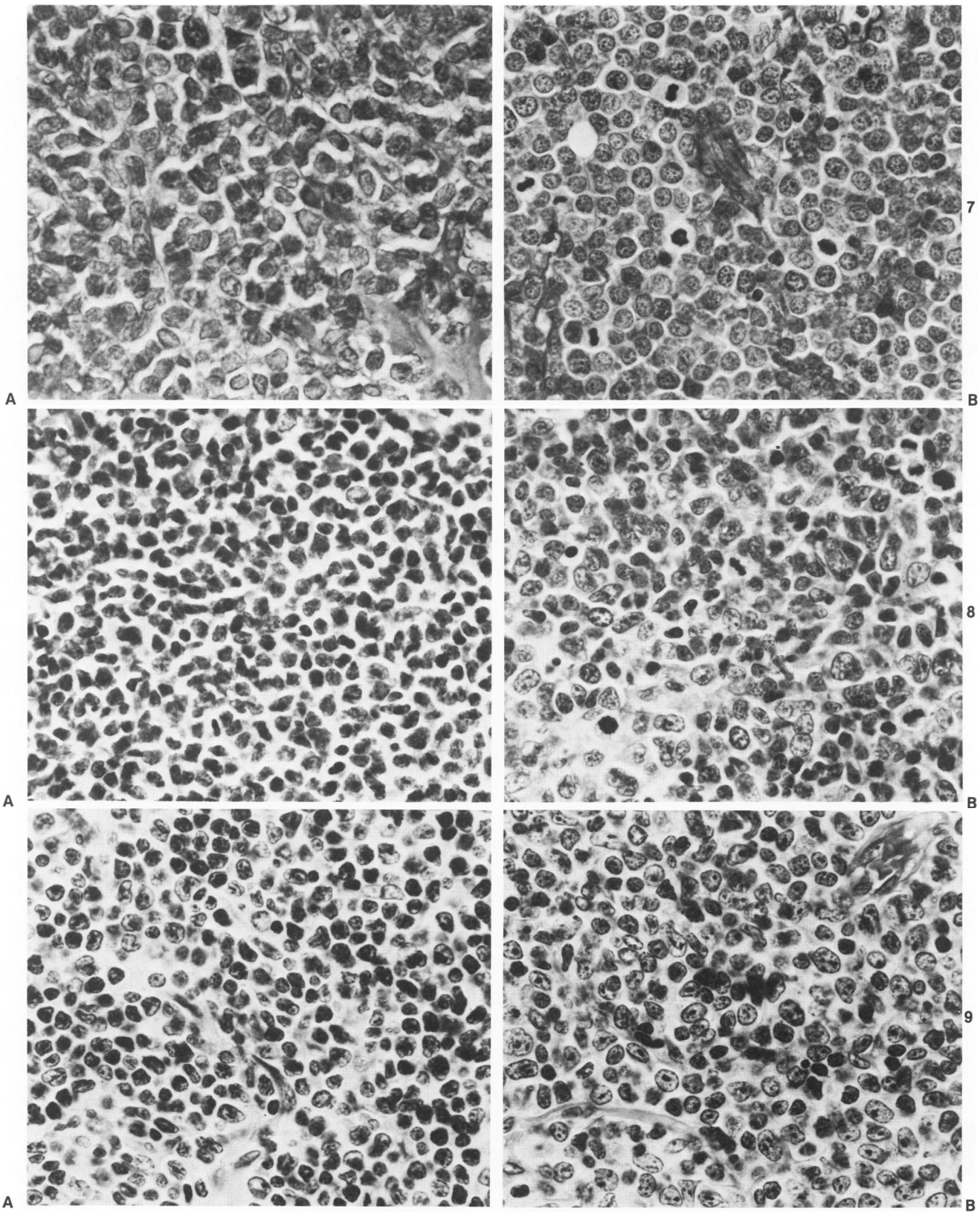

Figure 7A — This patient presented with eyelid and nodal involvement. Notice the irregularly shaped large centrocytes in the node. **B** — Biopsy almost 3 years later demonstrated this high-grade unclassifiable lymphoma of cells with round nuclei, dispersed chromatin, and a high mitotic count. The patient died 9.5 months later. (PAS, ×500) **Figure 8** — Notice the increase in cell size between the earlier biopsy (**A**) and the one from almost 2.5 years later (**B**). Even in the later biopsy some small cells remain. (H&E, ×500) **Figure 9** — The initial biopsy (**A**) shows typical centrocytic lymphoma. The later biopsies, beginning just over a year after diagnosis, contained some larger, rounder cells with more prominent nucleoli. (H&E, ×500)

Table 5—Immunologic Phenotypes: Early Versus Later Biopsies

Feature	Mean proportion of cells marking ± SD: First or second biopsies	Later biopsies	P
IgM*	74.8 ± 13.4	74.0 ± 18.8	NS
κ or λ *	79.5 ± 13.8	67.3 ± 15.7	$0.05 < P < 0.1$
C3	30.3 ± 20.2	7.6 ± 6.6	$P < .001$
Fcγ	11.9 ± 11.3	13.7 ± 12.7	NS
SER	11.2 ± 6.8	7.0 ± 4.0	$0.05 < P < 0.1$

NS, not significant; SER, sheep erythrocyte rosettes.
* Only cases showing IgM or light chain were included in these comparisons.

with small round lymphocytes had a very low mitotic rate (0–2/30 HPFs), and half of those with pretreatment clinical data had an initial lymphocyte count of less than 4×10^9/l.

Discussion

Centrocytic lymphoma (ML,cc) was first proposed as a distinct entity by Lennert.[1-3] ML,cc was separated from those tumors which usually exhibit a definite follicular pattern and for which there was good evidence of an origin from follicular center cells.[3,5,33] The neoplastic follicles of the latter lymphoma, although usually consisting predominantly of centrocytes (cleaved follicular center cells, cFCCs), also contained a variable population of centroblasts (noncleaved/transformed FCCs). These lymphomas are designated as centroblastic/centrocytic (CB/cc) in the Kiel classification.

The present study supports the proposition that centrocytic lymphoma is a distinct clinical, morphologic, and immunologic class of lymphoma. Preliminary analysis of all non-Hodgkin's lymphoma patients treated at St. Bartholomew's Hospital between 1972 and 1982 showed fundamental differences in the clinical and laboratory findings at presentation between patients whose initial biopsies showed ML,cc and those with follicular (ML,CB/cc/F) lymphoma. The patients with ML,cc are more likely to be males ($P = 0.03$), to have massive splenomegaly ($P = 0.01$), moderate hepatomegaly ($P = 0.02$), marrow involvement ($P = 0.03$), and a peripheral blood lymphocytosis ($P = 0.01$). In the cases reported here, Waldeyer's ring and the gastrointestinal tract were the most common sites of biopsy-proven extranodal lymphoma.

In common with the findings in other series,[3,34,35] the prognosis of all patients with ML,cc treated at St. Bartholomew's Hospital is worse than that of patients with ML,CB/cc/F or ML,CB/cc of unspecified growth pattern but no different from that of those with ML,CB/cc/D. The NCI-sponsored study of classifications of non-Hodgkin's lymphomas also supports subdividing the cleaved cell lymphomas for prognostic purposes, with those categories said to include ML,cc having an intermediate prognosis.[6] Although the survival curve of ML,cc, large cell predominant type, currently appears to plateau at 4 years from diagnosis, while that of the ML,cc small cell type does not, there is no significant difference in patient survival ($P = 0.13$). More clinicopathologic studies are necessary to know how the survival of ML,cc compares with other lymphomas of an equivalent stage and with similar therapy.

Three presentation features of adverse prognostic importance were identified: a peripheral blood lymphocyte count greater than 4×10^9/l, a high mitotic rate and the absence of admixed small round lymphocytes in the tumor. The prognostic importance of a morphologic change cannot be assessed.

Morphologically, the diagnostic criteria for ML,cc in a lymph node are architectural effacement by a relatively monomorphic lymphoid infiltrate composed predominantly of cells with at least somewhat cleaved nuclei and with relatively clumped chromatin which resemble the centrocytes of normal follicular centers. All but one of our cases had predominantly small centrocytes, but large centrocytes were sometimes admixed. Because our cases included only one of large cell type, we were unable to compare the possible clinicopathologic differences between large and small cell ML,cc.

The morphology of the cells of ML,cc showed considerable variation in the degree of their nuclear irregularity, chromatin dispersal (generally without prominent nucleoli), and proliferative rate. In contrast to any of the lymphomas of definite FCC origin, transformed cells either of centroblastic or immunoblastic type are generally absent. This is the basic criterion in the Kiel classification, which distinguishes ML,cc from other cleaved cell lymphomas (CB/cc). High mitotic rates in normal follicles or FCC lym-

Table 6—Clinical and Pathologic Features at Presentation with Prognostic Significance

Features	Survival*	P
Lymphocyte count, peripheral blood		
≤4 × 10⁹/l	52	$P = 0.03$
>4 × 10⁹/l	17	
Mitotic rate		
≤20/30 HPFs	45	$P = 0.01$
>20/30 HPFs	16	
Small round lymphocytes		
Present	85	$P = 0.02$
Absent	34	

* Median, in months.

phomas are usually associated with transformed FCC-type cells, whereas high mitotic rates in ML,cc are not. Rapidly dividing cells in ML,cc may resemble the cells in lymphoblastic lymphomas or leukemias (especially of the non-B, non-T cell type) which are clinically even more aggressive than ML,cc. Some times this creates diagnostic difficulties.

Some cases have admixed small round lymphocytes, but the morphologic distinction from (small) lymphocytic lymphoma (ML,L) is usually apparent, because ML,cc never has the proliferation centers that are characteristic of most cases of ML,L.[3,33] ML,L is also distinguished in well-processed sections by having cells with only round nuclei and by the invariable presence of at least occasional transformed lymphocytes.[3,33,36] In our experience, borderline cases between ML,L and ML,cc occasionally occur.

Some retention of normal architecture is not uncommon (sinusoidal preservation or less commonly residual follicular centers). Although most often diffuse, vaguely nodular areas were present in about 40% of the cases. Unlike the definite follicles seen in most cases of ML,CB/cc,[3] the absence of definite follicle formation here suggests that the proliferating cells of ML,cc even if morphologically similar to FCCs, appear to lack the capacity for follicle formation usually present in the cells of ML,CB/cc. This incapacity may reside in the nature of the associated T cells, which are critical in germinal center formation. This could represent a primary or secondary alteration in T-cell subpopulations. Centrocytic lymphomas are usually easily distinguished from diffuse FCC lymphomas (CB/cc or CB) by their lack of transformed cells and, in our experience, the lack of a preceding follicular lymphoma.

Even in the absence of a follicular pattern, the presence of dendritic reticulum cells (DRCs) in some cases of centrocytic lymphoma has been used to argue for their germinal center origin, but DRCs occur in primary follicles as well.[2] Their presence supports a follicular origin for ML,cc, although not necessarily an origin from germinal centers.

When residual follicular centers were present within the vague nodules of ML,cc, the centrocytes appeared to be growing as a wide follicular mantle. Lennert has also described this pattern in newly infiltrated nodes.[3] Both our cases showing this pattern had more typical areas without follicles in the same node, and both showed disappearance of follicles in later biopsies. Even in these 2 cases the proliferating cells were distinct from small round mantle lymphocytes, some of which were present around the residual follicles. Immunohistologic studies in the one case tested confirmed the presence of polyclonal follicular remnants and a small population of polyclonal mantle lymphocytes. These findings suggest that ML,cc cells are distinct from normal or neoplastic FCCs, which do not grow as mantles around *reactive* germinal centers. They also suggest that ML,cc cells are distinct from mantle cells.

The presence of hyalinized vessels is characteristic of ML,cc but is neither specific nor necessary for the diagnosis. Plasma cells, when present, never appeared to be a part of the lymphoma and, when identified in immunohistologic studies, were polyclonal. The polyclonality of the plasma cells, the lack of transitional forms, and the irregularity of the nuclei all distinguish ML,cc from lymphoplasmacytic/-cytoid lymphoma. Cytoplasmic immunoglobulin, *per se*, does not.[2,37] Macrophages were sometimes abundant.

The morphologic findings and criteria that we have described are similar but not identical to those defined by Lennert and colleagues.[2,3] We felt that a rare probable transformed lymphocyte does not rule out this diagnosis. Tolksdorf et al stated that "nearly all tumour cells had more or less cleaved nuclei" and that follicle mantle lymphocyte-like cells were completely absent, whereas we felt that small round lymphocytes in the presence of a predominant population of centrocytelike cells did not rule out a diagnosis of ML,cc.[2]

Centrocytic lymphoma is of B-cell origin. The cells in ML,cc are generally positive with B1, BA-1, BA-2, RFA-2, 33.1, and αHLA/DR. In normal node and tonsil this set of monoclonal antibodies includes some which identify essentially all B cells but also one (BA-2) that marks germinal centers but not mantles, and one that marks predominantly mantles (RFA-2) (see Table 1). Although ML,cc has a characteristic staining pattern with these antibodies, they cannot be used independently to distinguish ML,cc from all other small B-cell neoplasms. Along with Ig staining, some can be useful in ruling out the occasional T-cell lymphomas that resemble ML,cc morphologically.

Other phenotypic markers also reveal the cells of ML,cc to have some features in common with mantle zone cells and some features in common with cleaved FCCs, although they are not identical with either. The cells also show both similarities to and differences from ML,L/B-CLL cells. Like many normal or neoplastic follicular center cells, the B cells in ML,cc express predominantly surface IgM, possibly with other heavy chain isotypes.[37] Although the lack of frequent IgD positivity in ML,cc is more typical of follicular center than mantle cells, a small population of IgM^+ IgD^- cells might occur in normal mantle zones. Others report a higher frequency of IgD posi-

tivity on an unstated proportion of cells in ML,cc.[5] Unlike many normal or neoplastic FCCs, but similar to mantle cells,[20,30,38] none of the cells in our cases had definite J5 (anti-common-ALL antigen) or peanut lectin positivity. All but one "null" cell case showed a predominant monoclonal population most often with λ light chain. Lambda predominance was not found in ML,cc by Tolksdorf et al, but was found in ML,cc by Stein et al and by Leech et al in cases of *diffuse* lymphoma of cleaved follicular center cell type (many of which may have been ML,cc).[2,5,39] This is another distinguishing feature of ML,cc, because predominance of λ^+ cases is not reported in lymphomas of CB/cc, cleaved follicular center cell, or (small) lymphocytic type.[8,40]

Unlike ML,L/B-CLL, SIg staining is usually intense in ML,cc, and few cells form mouse erythrocyte rosettes.[2,4] Differences in the ratio of C3b:C3d are also described.[4] The common presence of some endogenous alkaline phosphatase activity also distinguishes ML,cc from almost all cases of ML,L/B-CLL but does not distinguish it from some other B-cell lymphomas (unpublished data).[31,32] In normal nodes, endogenous alkaline phosphatase activity is found mainly in mantle cells, but positivity in a lymphoma clearly does not imply a mantle cell origin.[31] In contrast, both ML,cc and ML,L/B-CLL frequently have B cells positive for Leu-1 (or Leu-1 equivalent), but these also occur in certain follicular lymphomas (unpublished data).[5,24-27]

Phenotypic studies never demonstrated a change in light chain predominance in repeat biopsies. In later biopsies there did appear to be a decrease in the number of cells expressing complement receptors. One could speculate that the cells present later in the disease are even less like follicular center cells than were the cells originally.[41-44]

Another feature that distinguishes centrocytic from follicular lymphoma is the relatively low proportion of T cells present in ML,cc. Follicular lymphomas usually have more numerous T cells.[2,4,8,41,45] Diffuse lymphomas of follicular origin (CB/cc/D) also appear to have a moderate number of T cells.[8] An increased proportion of T suppressor (T_s) cells was associated with the centrocytic lymphomas in most cases tested. T_s cells are usually infrequent in normal follicular centers (unpublished data).[11] T helper cells clearly predominated in only 1 case, which had the highest mitotic count at diagnosis and many large centrocytes. Unlike ML,CB/cc,[46] Leu-7-positive (NK/K) cells were present but generally infrequent in ML,cc.

Repeat biopsies never showed transformation of the type seen in follicular or diffuse CB/cc (definite FCC) lymphomas.[3,47,48] This provides more evidence that centrocytic lymphomas are separable from those of definite FCC origin. In his extensive experience, Lennert reports seeing only one case of ML,cc transform to a B-immunoblastic lymphoma (ML,IB) and never transformation to a ML,CB.[3] In our series there was one major change to a morphologically different but unclassifiable high-grade B-cell lymphoma which did not fulfill the criteria for either ML,CB or ML,IB (transformed or noncleaved FCC lymphoma). Similar to the changes described by Lennert,[3] morphologic changes of increasing cell size and chromatin dispersal, sometimes with greater nuclear irregularity, occurred to a varying degree in about half our evaluable cases. In addition to these changes, one case of ML,cc showed foci of transformation to lymphoid cells similar to the transformed cells of ML,L/CLL, or "prolymphocytes."

Several other proposed entities have been described which clearly contain a large proportion of ML,cc cases. None of these categories is equivalent to ML,cc, and all are defined by morphologic characteristics alone.

Malignant lymphocytic lymphoma of intermediate differentiation (ML,I), was initially described by Berard and colleagues as a diffuse or sometimes vaguely nodular lymphoma composed of cells with sparse cytoplasm and round to slightly clefted and irregular nuclei with clumped chromatin.[31,49] The same group has also described ML,I as a mixture of cells similar to those in diffuse well-differentiated lymphocytic lymphoma and of cells similar to cleaved cells of nodular lymphomas.[50] Normal-appearing follicular centers are sometimes found.[31] Immunologic studies revealed monoclonal B-cell populations with SIg of intermediate density, usually of the IgM or IgM+D type, and relatively few T cells.[49] Complement receptors are present and closer in type to those found in ML,L/CLL than those in follicular lymphoma.[51] Alkaline phosphatase positivity was reported in 3/6 cases.[49] The description of these cases is very similar to the subset of ML,cc with admixed small round lymphocytes, but most of our cases which lacked these cells would not be included in this category, according to the published criteria. Neither alkaline phosphatase positivity nor Leu-1 positivity distinguished these two groups of ML,cc.

Rappaport and colleagues have proposed a similar entity of malignant lymphoma, intermediate lymphocytic type, of unknown immunologic phenotype.[52] Although similar in its cell composition to the ML,I described above, it differs in the presence of proliferation centers similar to those seen in ML,L/B-CLL (in 21% of cases) and in its nonindolent course.[52]

Thus, as well as excluding most of our cases, this definition of ML,I includes many cases which are clearly not of centrocytic type.

The same authors also described "mantle-zone lymphoma: a follicular variant of intermediate lymphocytic lymphoma" (MZL), composed of cells similar to those in ML,I but with wide lymphomatous mantle zones around nonneoplastic-appearing germinal centers.[53] Here no proliferation centers are described even in the diffuse areas, suggesting that, unlike the author's conclusions, MZL is a variant of only a subset of ML,I. In apparent contrast to our cases, scattered large cells in various stages of transformation (not illustrated, of uncertain type) were reported in many cases and were prominent in 2 cases. Immunologic studies were reported in only 2 cases (both of which were λ monoclonal); and, unlike our study, no immunohistologic studies were performed. Although of unknown significance, they distinguish these cases from rare ones (including one reported by others as related to ML,I) where the cells in the mantle zones look more like cleaved cells.[53,54] Thus, at least many of the cases of MZL probably represent a small subset of ML,cc. Further studies are necessary to determine whether this is a meaningful subset. It must be stressed that MZL is not necessarily a lymphoma of the *predominant* mantle zone cells and also that residual germinal centers can be present in a wide variety of other lymphomas.

Intermediate lymphocytic lymphoma, as defined by Evans et al, includes cases of small lymphocytic lymphoma with ≥30 mitoses/20 HPFs and is therefore not comparable to ML,cc.[36]

Thus, the published descriptions of ML,I by three groups of hematopathologists differ significantly from each other, and none is equivalent to ML,cc. Although described as a B-cell neoplasm by one group,[31,49,50] no immunologic criteria are included. There is thus a possibility that T-cell lymphomas, which may mimic B-cell ML,I closely, may appear in this category.

Prolymphocytic leukemia (PLL) is another lymphoid neoplasm that may resemble ML,cc morphologically, phenotypically, and sometimes clinically.[55] The reported descriptions suggest that while many cases of PLL are easily distinguished from ML,cc (eg, those with round nuclei and prominent nucleoli or those with T-cell markers), others are probably identical.[56-59] Other morphologic categories felt to be most closely related to ML,cc are listed in the NCI Working Formulation report.[6]

In conclusion, centrocytic lymphoma is a distinct clinicopathologic entity recognized morphologically and immunologically. Although homogeneous in many ways, there is a morphologic spectrum ranging from cases with admixed small round lymphocytes and low mitotic counts (probably of better prognosis) to cases composed entirely of cleaved cells often with more dispersed chromatin and high mitotic counts. The predominant cell in ML,cc morphologically closely resembles the centrocyte of a follicular center; however, in spite of similarities, the centrocytes of a centrocytic lymphoma are phenotypically distinct from most of those found in normal or neoplastic follicles. Further distinctions from other FCC lymphomas include a morphologically different dividing cell, a different growth pattern including the lack of follicular nodules and occasional mantle zone growth around reactive polyclonal follicles, a different type of "transformation," and different clinical features. For all these reasons, ML,cc must be considered distinct from other cleaved cell lymphomas. The cells of ML,cc also have some features of mantle cells but once again show striking differences both morphologically and phenotypically. Distinction from lymphocytic lymphoma/B-CLL or lymphoplasmacytic/-cytoid lymphoma is usually very apparent.

Thus, the cells of a centrocytic lymphoma do appear to be related to the lymphoid follicle but are not easily placed into either the mantle or germinal center compartment. They may represent either cells in transition from one compartment to the other but blocked in their development or the expansion of a minor cell population. Because not all cells that enter follicular centers and proliferate are necessarily of similar derivation (some may be virgin B cells and others memory cells),[60-62] neoplastic transformation and proliferation could lead to a variety of lymphomas with similar appearance but distinct phenotypes.

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