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Centrocytic Lymphoma: A Morphometric Study with Comparison to Other Small Cleaved Follicular Center Cell Lymphomas and Genotypic Correlates

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Centrocytic lymphoma (ML,CC) is distinguished from other cleaved follicular center cell (FCC) lymphomas in the Kiel classification by the lack of noncleaved FCC and not by morphological differences between the centrocytes (cleaved cells). Immunophenotypic and genotypic studies, however, have shown that the centrocytes in ML,CC are distinct from those of other small cleaved FCC lymphomas (ML,FCC,SC). To morphologically compare the cells of ML,CC with nine previously studied ML,FCC,SC and to relate the findings in ML,CC to the varied descriptions of lymphomas of intermediate differentiation, a morphometric analysis of 22 ML,CC was performed. Nuclei in ML,CC were, on average, significantly larger, rounder, and had less frequent nucleoli than those in ML,FCC,SC; however, the proportion of small round lymphocytes did not differ. Among the ML,CC, the only apparent immunophenotypic/genotypic correlate that was identified was greater nuclear ellipticity for the biopsies lacking chromosome 11q13 bcl-1 or PRAD1 rearrangement. Repeat biopsies in four patients with ML,CC showed an increase in nuclear size. These data demonstrate that a lack of transformed cells is not the only morphological difference between ML,CC and ML,FCC,SC. The morphological distinction, however, is not based on the proportion of small round lymphocytes present. In addition, the morphometric parameters illustrate the nuclear variability among ML,CC and demonstrate how the disease may evolve over time. (Am J Pathol 1993, 142:329–337)

Centrocytic lymphoma (ML,CC, originally called germinocytoma) was first reported by Lennert et al and included in the 1974 Kiel classification of the non-Hodgkin's lymphomas.[1–3] ML,CC was defined as a lymphoma composed exclusively of centrocytes (cleaved cells). Unlike other lymphomas composed of cleaved follicular center cells (centroblastic/centrocytic), ML,CC lacked transformed or noncleaved follicular center cells (germinoblasts/centroblasts). ML,CC may also have admixed small round lymphocytes even though they were originally reported to be absent.[4]

Among those not using the Kiel or Lukes/Collins classifications, ML,CC is often considered equivalent to lymphocytic lymphomas of intermediate differentiation, although the terminology and definition for the latter has been quite variable. Malignant lymphoma of lymphocytic type, intermediate differentiation, was originally described as having an apparent mixture of small lymphocytes, similar to those of well differentiated lymphocytic lymphomas, and larger atypical cells with nuclear clefts, nucleoli, and mitoses.[5] Malignant lymphoma, intermediate lymphocytic type, was described as consisting predominantly of small lymphoid cells with slightly irregular or indented nuclei admixed with no more than 30% lymphoid cells with entirely round nuclei and no more than 30% lymphoid cells with angulated and cleaved nuclei.[6] Lymphocytic lymphoma of intermediate differentiation is now described in most instances as being composed of small lymphocytes with scanty cytoplasm and irregular or cleaved nuclei, intermingled in some instances with a lesser number of cells with more rounded nuclei.[7] Some cases can have a more blastic morphology.

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These morphological descriptions raise several questions. Is the cytological difference between a centrocytic and noncentrocytic cleaved follicular center cell (centroblastic/centrocytic) lymphoma principally an absence of centroblasts (noncleaved/transformed) cells in the former or do the centrocytic cells in the two cleaved cell lymphomas differ morphologically? Immunophenotypic and genotypic studies have demonstrated marked differences between the predominant cells in centrocytic and other cleaved follicular center cell lymphomas.[4,8–13] Which of the descriptions of lymphocytic lymphoma of intermediate differentiation best fits the actual findings in centrocytic lymphoma? Are centrocytic lymphomas distinct from other cleaved cell lymphomas because there is an admixture of small round (well differentiated) lymphocytes or because the cells are not as cleft?

To address these questions concerning the nuclear features of ML,CC, plastic-embedded sections from 22 ML,CC were analyzed using a morphometric method that had previously been applied to reactive follicular proliferations and to typical follicular center cell lymphomas.[14–16] Immunophenotypic data were available for 21 of the specimens and genotypic data for 16.[9–11] The nuclear features of the ML,CC were compared with those of nine previously reported typical noncentrocytic small cleaved follicular center cell lymphomas.[14]

Materials and Methods

Case Selection and Description

Twenty-two specimens from 16 patients were selected if they fulfilled the criteria for ML,CC as defined in the Kiel classification and if a B5 fixed paraffin block was available.[1–4] One specimen showed definite histological progression of the ML,CC. The specimens included 12 lymph nodes, 2 spleens, 5 orbit/conjunctiva, 1 colon, and 2 marrow biopsies. Immunophenotypic studies demonstrated monoclonal B cell populations in all 21 tested cases (κ, 13; λ, 8) and the remaining case was marrow from a patient with a monoclonal κ ML,CC. CD5 (Leu 1) was expressed by more than than 80% of the B cells in nine tested cases (estimated from single color flow cytometric immunofluorescent studies using previously described methods) and by a smaller proportion of the B cells in eight.[17] As reported elsewhere, Southern blot genotypic studies were performed using DNA from 16 of the cases that had snap-frozen tissue available.[9–11] All cases showed immunoglobulin gene rearrangements using J_H and J_K probes and 11 (10 of 13 patients) revealed rearrangements of the chromosome 11q13 *bcl*-1 and PRAD1 breakpoint loci using the *bcl*-1 probes MTC, p94PS, p11EH, p210, and PRAD1 probes B and D.[9–11] The morphometric results for the ML,CC were compared with those for nine previously reported noncentrocytic small cleaved follicular center cell lymphomas.[14]

Tissue Preparation

As previously described, representative portions from each tissue block were removed, deparaffinized, and then embedded in glycol methacrylate monomer.[14,15] A small portion of a similarly processed reactive tonsil was also included in each block as an internal control for the microdensitometry. The blocks were then cut at 1 μ and stained with periodic acid-Schiff (PAS)–hematoxylin.

Morphometric Analysis

In each case, morphometric analysis was performed on 300 to 304 nuclei using a Bioquant Image Analyzer (R&M Biometrics, Nashville, TN) and a method identical to that previously described except that a magnification of ×6970 was used because of updated equipment.[14–16] All lymphoid cells in each field studied were included in the analysis. Briefly, the perimeter of each nucleus, the nuclear area, the longest axis, and the two longest perpendicular axes were directly measured. From these measurements, two nuclear shape indices were calculated that reflect the nuclear ellipticity (nuclear contour index of ellipticity, NCIe) and the nuclear irregularity (nuclear contour index of nuclear irregularity, NCIni).[15] Increasing values from 3.54 reflect increasing ellipticity and irregularity. In addition the presence of nucleoli was recorded. The proportion of small round lymphocytes was also calculated for each case by determining the number of nuclei with a nuclear area and nuclear irregularity index smaller than that of an average mantle zone lymphocyte as determined from a previous study (NA $<$ 23.0 μ^2, NCIni $<$ 3.79).[16]

Finally, a chromatin dispersal index was calculated by comparing the proportion of picture elements (pixels) falling below a given threshold of darkness in a test cell to similar data for the control tonsil mantle zone cell nuclei present in the same section.[16] By definition, the mean chromatin dispersal index for the tonsil cells is 1.0, with values below that indicating more dispersed chromatin.

The data were analyzed with the StatView II program (Abacus Concepts, Inc., Berkeley, CA) on a

Macintosh IICX computer using the Mann-Whitney *U* test for nonparametric comparisons.

Results

Centrocytic lymphomas demonstrated variation in nuclear area, nuclear ellipticity, nuclear irregularity, degree of chromatin dispersal, proportion of cells with nucleoli, and proportion of morphometrically defined small round lymphocytes (Figures 1 to 3, Table 1). In comparison with the noncentrocytic small cleaved follicular center cell lymphomas, those of centrocytic type had significantly larger but less elliptical and less irregular nuclei and less frequent nucleoli. As illustrated, however, all of these features demonstrated a variable degree of overlap between the two types of lymphoma. Dividing the nuclear areas into five subsets revealed a significantly greater proportion of the smallest nuclei in the small cleaved cell group, greater numbers of intermediate sized nuclei in the centrocytic group, and statistically similar proportions of the largest cells (Table 2). There was no difference in the chromatin dispersal index and no difference in the proportion of morphometrically defined small round lymphocytes between the centrocytic and noncentrocytic small cleaved follicular center cell (FCC) lymphomas. Comparison of the standard deviations for the nuclear area and ellipticity and irregularity indices showed significantly smaller mean values for the ML,CC (Figure 4, Table 3).

Analysis of nuclear area, ellipticity, irregularity, chromatin dispersal, proportion of cells with nucleoli, and proportion of small round lymphocytes did not demonstrate significant differences when κ positive (13) versus λ positive (7) specimens were compared

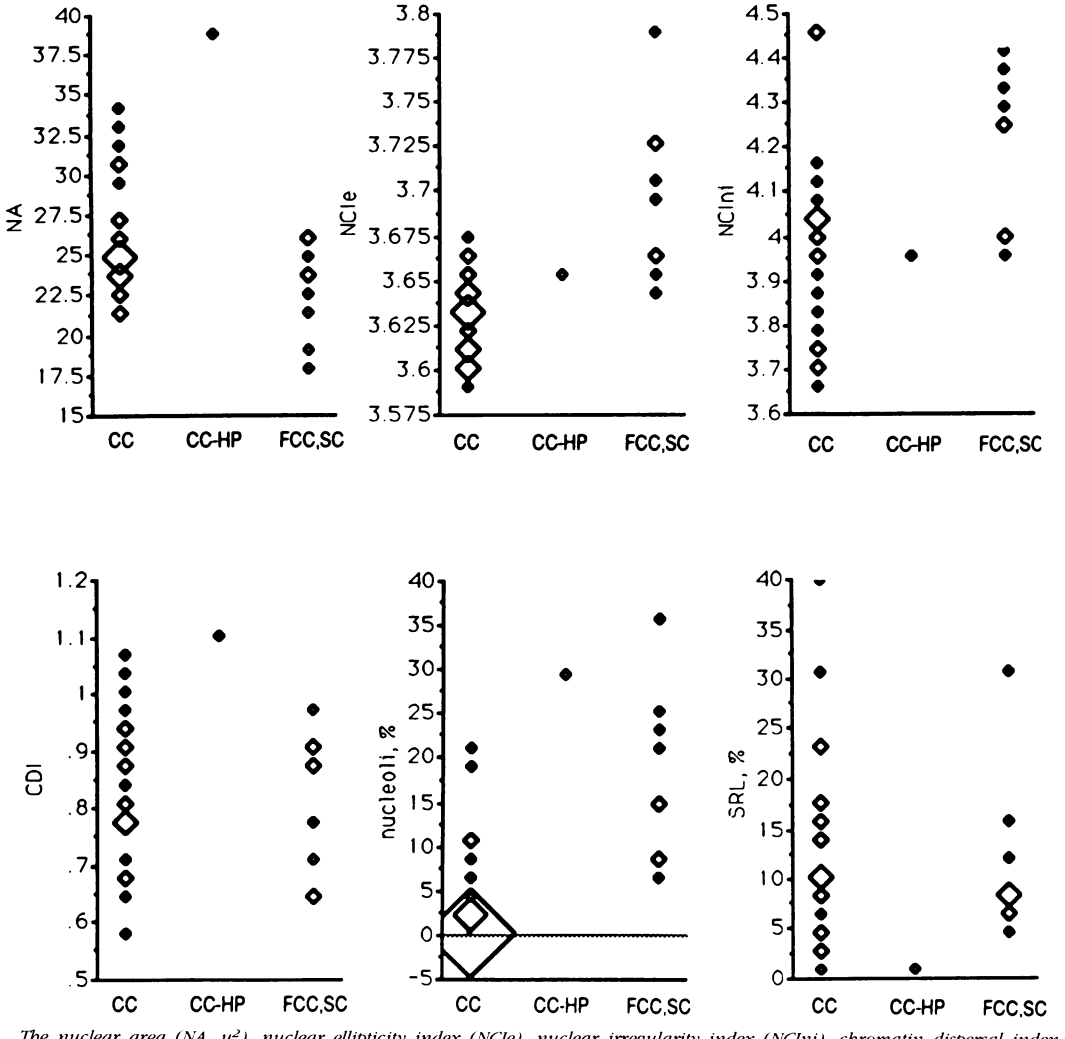

Figure 1. *The nuclear area (NA, μ²), nuclear ellipticity index (NCIe), nuclear irregularity index (NCIni), chromatin dispersal index (CDI), proportion of nuclei with nucleoli, and the proportion of morphometrically defined small round lymphocytes (SRL) for the individual cases of centrocytic lymphoma (CC), centrocytic lymphoma with histological progression (CC-HP), and follicular center cell lymphoma of noncentrocytic small cleaved cell type (FCC-SC) are shown. Overlapping points are represented by proportionally larger diamonds. Mean values for normal mantle zone cells are: NA, 23.0 ± 4.4 μ²; NCIe, 3.61 ± 0.08; NCIni, 3.79 ± 0.22; CDI, 1.0 ± 0.20.*[16]

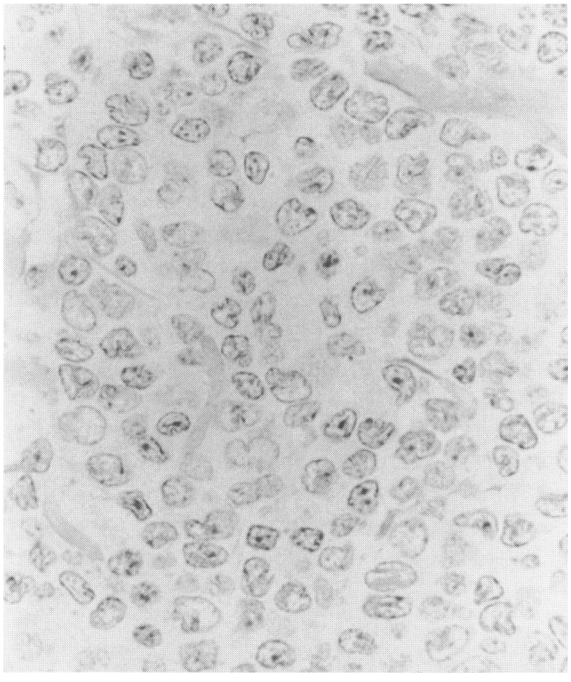

Figure 2. *Note the marked nuclear irregularity in the majority of the cells present in this centrocytic lymphoma, which demonstrated bcl-1 gene rearrangement (nuclear area, 24.6 μ²; NCle, 3.65; NCIni, 4.44; small round lymphocytes, 3%). PAS–hematoxylin-stained plastic-embedded section; original magnification, ×750.*

or when those with marked (8) versus less marked (8) CD5 positivity were compared (data not shown). Similar comparisons for the 11 specimens with *bcl*-1 or PRAD1 rearrangements versus the 4 without only revealed a significant difference for the nuclear ellipticity index (3.62 ± 0.02 versus 3.64 ± 0.01, $P < 0.04$). The single case with overt histological progression is not included in these comparisons.

Four patients had two biopsies from 10 to 42 months apart including the one patient with overt histological progression. The only significant difference between the earlier and later biopsies that could be demonstrated was an increase in nuclear area that was present in all four cases (Figures 5 and 6, Table 4). Marrow biopsies from two of these patients were not included in this comparison, but, in both cases, the lymphoid cells in the marrows had a smaller mean nuclear area (including the patient with overt histological progression in a lymph node).

Discussion

ML,CC is defined in the Kiel classification as a malignant lymphoma composed exclusively of centrocytes (cleaved cells) and lacking centroblasts (large noncleaved or transformed follicular center cells).[1–4] Thus, by definition, ML,CC are distinguished from the much more common conventional cleaved FCC lymphomas not because of a morphological difference in the predominant centrocytes, but because of the lack of transformed cells. In spite of this basic definition, morphological, immunophenotypic, and genotypic studies have shown very definite differences between centrocytic and noncentrocytic cleaved cell lymphomas, which could not be accounted for by a simple absence of a small percentage of centroblasts in the former type of lymphoma. In contrast to ML,CC, cleaved FCC lymphomas usually have a nodular (± diffuse) growth pattern, are CD5 negative but often CD10 positive, and lack *bcl*-1/PRAD1 gene rearrangements but often have *bcl*-2 gene rearrangements.[1–4,8–13,18,19]

These differences lead one to question whether, even if morphologically similar, there are cytological differences between the centrocytic and noncentrocytic cleaved cell lymphomas. Some possible differences have been suggested from the morphological descriptions of lymphocytic lymphomas of intermediate differentiation/intermediate lymphocytic lymphomas, which are often considered to be similar to ML,CC. Some suggest that the distinguishing feature is the presence of small, round, well differentiated lymphocytes admixed with the cleaved cells or a predominance of small lymphocytes with slightly

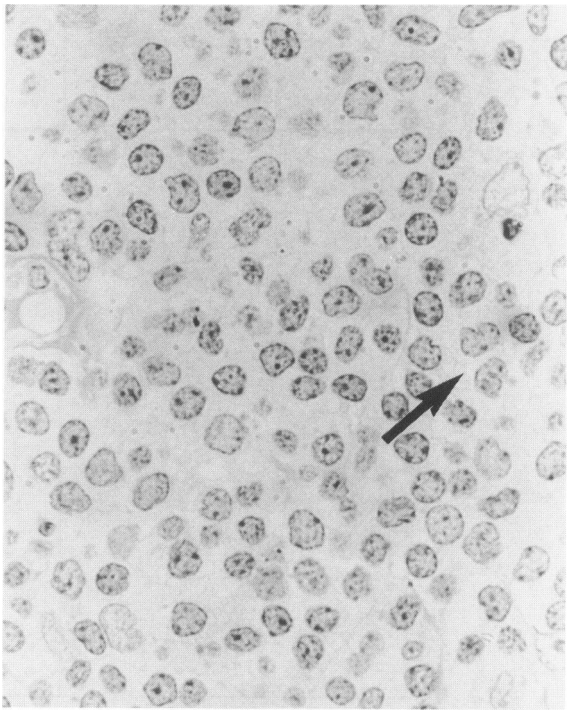

Figure 3. *Although some cleft nuclei (arrow) are present in this centrocytic lymphoma which also demonstrated bcl-1 gene rearrangement, many of the lymphocytes present are very round (nuclear area, 25.6 μ²; NCle, 3.59; NCIni, 3.68; small round lymphocytes, 30%). PAS–hematoxylin-stained plastic-embedded section; original magnification, ×750.*

Table 1. *Morphometric Comparison of Nuclei in Centrocytic and Noncentrocytic Small Cleaved FCC (Centroblastic/Centrocytic) Lymphomas*

Parameter	ML,CC (21)*	ML,CC-hp (1)	ML,FCC,SC (9)	P (CC vs SC)†
NA (μ^2)	26.3 ± 3.8	39.3	22.7 ± 2.8	<.03
NCIe	3.63 ± 0.02	3.65	3.70 ± 0.05	<.001
NCIni	3.96 ± 0.22	3.97	4.2 ± 0.17	<.02
CDI	0.83 ± 0.13	1.09	0.82 ± 0.13	NS
Nucleoli (%)	4.3 ± 6.2	30	17.4 ± 9.6	<.001
SRL (%)	13.4 ± 9.6	1	11.4 ± 7.7	NS

NA, nuclear area; NCIe, nuclear contour index of ellipticity; NCIni, nuclear contour index of nuclear irregularity; CDI, chromatin dispersal index; SRL, morphometrically defined small round lymphocytes; ML,CC, centrocytic lymphoma; ML,CC-hp, centrocytic lymphoma with overt histological progression; ML,FCC,SC, noncentrocytic small cleaved follicular center cell (centroblastic/centrocytic) lymphoma; NS, not significant.

* The number of biopsies studied is in parentheses. All results are given as means ± standard deviation.

† Mann-Whitney *U* nonparametric test.

irregularly shaped nuclei and an exclusion of cases with more than 30% cleaved cells.[5,6,20]

The morphometric data substantiate the belief that the nuclei of the predominant cells in ML,CC, on average, do differ from those in noncentrocytic cleaved FCC lymphomas, even though they are not always distinguishable. The cells in ML,CC tend to have larger nuclear areas than small cleaved cells, less irregularly shaped and less elliptical nuclei, and less frequent nucleoli. These findings explain, in part, why the predominance of small lymphoid cells with slightly irregular or indented nuclei has been stressed as a feature of intermediate lymphocytic lymphoma.[6,20] The lower standard deviations of the nuclear size and shape parameters in ML,CC supports the subjective impression that these lymphomas often appear relatively monomorphic and again emphasize the statistically significant morphological differences between centrocytic and noncentrocytic cleaved cell lymphomas.

The chromatin dispersal index data support the non-transformed nature of ML,CC as the mean value was very similar to that for the other small cleaved FCC lymphomas. As with the other nuclear features, there was a wide variation in the chromatin dispersal index for the ML,CC, which sometimes can even resemble lymphoblastic lymphomas with very dispersed chromatin and a high mitotic rate.[4,7]

In spite of the significant differences documented between centrocytic and noncentrocytic small cleaved FCC lymphomas, there is a marked overlap between the two entities in terms of their nuclear morphology lending support to the original definition of Lennert et al.[1,2] The data illustrate the great range in the morphological appearance of ML,CC and support our previously published subjective opinion that the morphology of the cells of ML,CC showed considerable variation in the degree of their nuclear irregularity and chromatin dispersal.[4] In particular, although many ML,CC have nuclei rounder than those in other cleaved FCC lymphomas, in some cases with a characteristic phenotype and genotype, the nuclei are very irregularly shaped. These latter cases should not be excluded from ML,CC, nor should the cases without marked nuclear clefts.

The spectrum of nuclear morphology in ML,CC and the similarities to noncentrocytic small cleaved FCC lymphomas both emphasize that the diagnosis of ML,CC must be based on more than just the morphological appearance of the predominant cells present. Recognition also comes, in part, from the low power appearance of the lymphoma, including the invariable absence of proliferation centers, the critical absence of neoplastic transformed cells, and the immunophenotype.[1–4,7] Although not specifically addressed in this study, many features also have to

Table 2. *Comparison of Proportion of Cells with Different Nuclear Areas in Centrocytic and Noncentrocytic Small Cleaved FCC (Centroblastic/Centrocytic) lymphomas*

NA (υ^2)*	ML,CC (21)†	ML,CC-hp (1)	ML,FCC,SC (9)	P (CC vs SC)‡
<22.70	33.5 ± 17.8	2	57.5 ± 15.4	<.007
22.7–26.47	24.6 ± 7.0	7	16.2 ± 4.8	<.004
>26.47–30.24	17.4 ± 5.5	11	11.1 ± 5.1	<.009
>30.24–60.40	23.7 ± 17.2	75	15.1 ± 8.6	NS
>60.40	0.4 ± 1.2	5	0.4 ± 0.5	NS

See Table 1 for abbreviations.

* As determined in our previous study, the mean nuclear area for cells in ML,FCC,SC was 22.7 υ^2 and for ML,FCC, large noncleaved was 60.4 υ^2.

† The number of biopsies studied is in parentheses. All results are given as the mean percentage of nuclei in each category ± standard deviation.

‡ Mann-Whitney *U* nonparametric test.

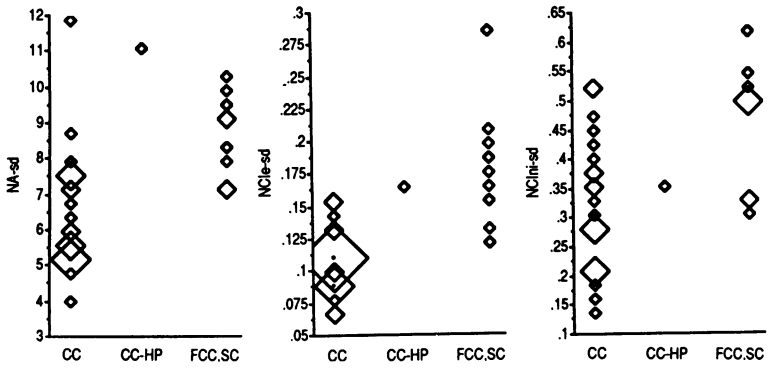

Figure 4. *The standard deviation (sd) of the nuclear area (NA), nuclear ellipticity index (NCIe), and nuclear irregularity index (NCIni) for the individual cases of centrocytic lymphoma (CC), centrocytic lymphoma with histological progression (CC-HP), and follicular center cell lymphoma of noncentrocytic small cleaved cell type (FCC,SC) are shown. Overlapping points are represented by proportionally larger diamonds.*

be considered when distinguishing ML,CC from small lymphocytic lymphoma/B-CLL, in which neoplastic cells can also demonstrate some nuclear irregularity.[21]

The morphometric data also demonstrate that the presence of admixed small round lymphocytes is not what distinguishes ML,CC from other cleaved FCC lymphomas. On the other hand, the data strongly suggests that, as we previously have stated, the presence of admixed small round mantle zone-like lymphocytes should not rule out the diagnosis of a ML,CC.[4] It is possible, however, that the presence of a certain proportion of small round lymphocytes could be used to help subdivide centrocytic lymphomas into more than one prognostic category. Our previous study did demonstrate the presence of small round lymphocytes to be associated with a better prognosis.[4] The proportion of the small round lymphocytes that are T cells, versus the proportion that are neoplastic B cells similar to those of a small lymphocytic lymphoma, could only be determined with immunohistological studies. This information would be of biological and potential clinical interest although morphological categorization of non-Hodgkin's lymphomas is generally based on an evaluation of all lymphoid cells present, not just an evaluation of cells proven to be a part of the neoplastic clone.

Previous morphometric studies of ML,CC have produced conflicting data based on relatively small numbers of cases. Van der Valk et al[22] found that ML,CC and intermediate lymphocytic lymphomas had smaller nuclear areas and greater overall nuclear irregularity than centroblastic/centrocytic lymphomas, but, more similar to our study, a lower standard error of the mean for the nuclear area of the former two types of lymphoma. In contrast, Oudemans et al[23] report a larger mean nuclear area for ML,CC compared with follicular centroblastic/centrocytic lymphomas but similar nuclear contour indices. Differences in morphometric techniques may account for some of the contradictory findings but differences in the initial categorization of the lymphomas probably plays a much greater role.

Another classic feature which distinguishes ML,CC from noncentrocytic cleaved FCC lymphomas is their lack of transformation to noncleaved FCC lymphomas.[3,4] The morphometric data demonstrates however, that, even in the absence of overt histological transformation, centrocytic lymphomas show morphological evolution over time, with the most consistent finding being an increase in nuclear area. Three of four cases did demonstrate an increase in the proportion of cells with nucleoli and our previous study showed a frequent increase in the mitotic rate.

In addition to facilitating comparison of different types of lymphoma, morphometric studies permit morphological comparisons between different subgroups within a single histopathological category.

Table 3. *Comparison of Standard Deviations for Nuclear Size and Shape Indices for Centrocytic and Noncentrocytic Small Cleaved FCC (Centroblastic/Centrocytic) Lymphomas*

Parameter	ML,CC (21)*	ML,FCC,SC (9)	P (CC vs SC)†
NA-std deviation	6.5 ± 1.7	8.6 ± 1.2	<.002
NCIe-std deviation	0.11 ± 0.02	0.18 ± 0.05	<.001
NCIni-std deviation	0.33 ± 0.12	0.46 ± 0.11	<0.2
CDI-std deviation	0.29 ± 0.07	0.31 ± 0.04	NS

std, standard; see Table 1 for other abbreviations.
* The number of biopsies studied is in parentheses. All results are given as means ± standard deviation.
† Mann-Whitney *U* nonparametric test.

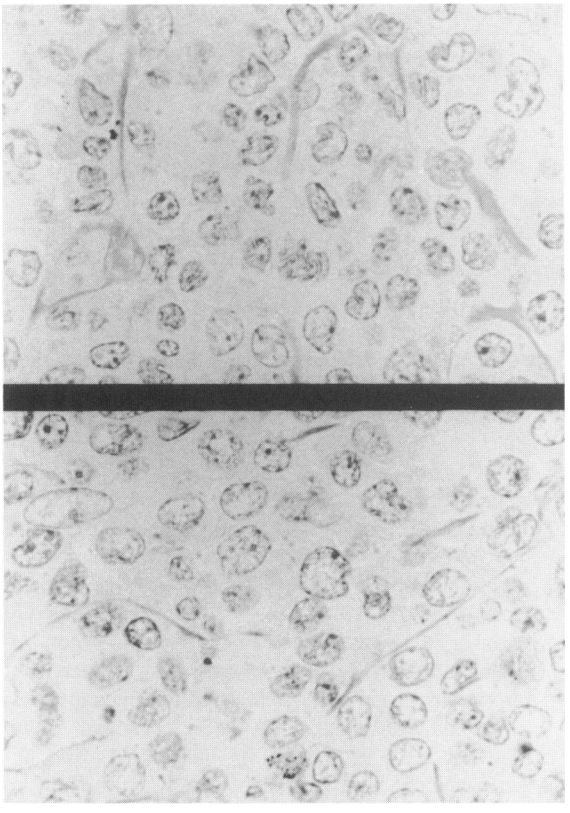

Figure 5. *This patient with a centrocytic lymphoma had a lymph node biopsy (top) followed by a splenectomy approximately 10 months later (bottom). Note the increase in nuclear area and a decrease in nuclear irregularity in the later specimen (nuclear area, 26.4 versus 31.0 μ^2; NCle, 3.61 versus 3.60; NCIni, 3.97 versus 3.72). Both specimens demonstrated the same p94PS bcl-1 breakpoint rearrangement. PAS–hematoxylin-stained plastic-embedded sections; original magnification, ×750.*

One distinctive feature of ML,CC is their unusual λ predominance in some series, which raises the question as to whether the λ positive cases represents the most typical cases.[4,7] CD5 positivity is another characteristic feature of ML,CC, and yet, some cases have little or no CD5 expression.[4,7,11] Although limited by a lack of many cases with very little CD5 positivity, no morphological correlates of κ versus λ expression or of more or less marked CD5 expression could be identified, suggesting that these features do not distinguish different morphological subsets of ML,CC. Analysis of the genotypic data is more confusing in that a single very subtle difference was documented between the cases showing *bcl*-1/PRAD1 rearrangement and the very few that did not. Because messenger RNA overexpression of the putative *bcl*-1 oncogene designated PRAD1 or cyclin D1 has been documented in seven of seven ML,CC (including four cases without demonstrable *bcl*-1 MTC rearrangements), the significance of this finding is questionable.[24,25] It may be that in the future, CD5 negative cases or those without *bcl*-1/PRAD1 mRNA will be excluded from ML,CC, whatever their morphology.

In summary, the morphometric data serve to quantify our previous subjective description of ML,CC, illustrate the spectrum in nuclear morphology which is acceptable for this clinicopathological/immunophenotypic/genotypic entity, and suggest that a lack of centroblasts or transformed FCC is not the only cytomorphological difference between centrocytic and noncentrocytic small cleaved FCC lymphomas. Nevertheless, the great overlap in nuclear features between these two types of lymphoma demonstrates why the predominant cells in ML,CC are considered to be similar to centrocytes (cleaved cells) and illustrates that features other than the morphological appearance of the predominant cell types must be utilized to distinguish centrocytic and noncentrocytic small cleaved FCC lymphomas. The findings are consistent with the great similarity between ML,CC and lymphocytic lymphoma of intermediate differentiation (mantle cell lymphoma) in which the proportion of admixed small round lymphocytes is not critical to the diagnosis and in which

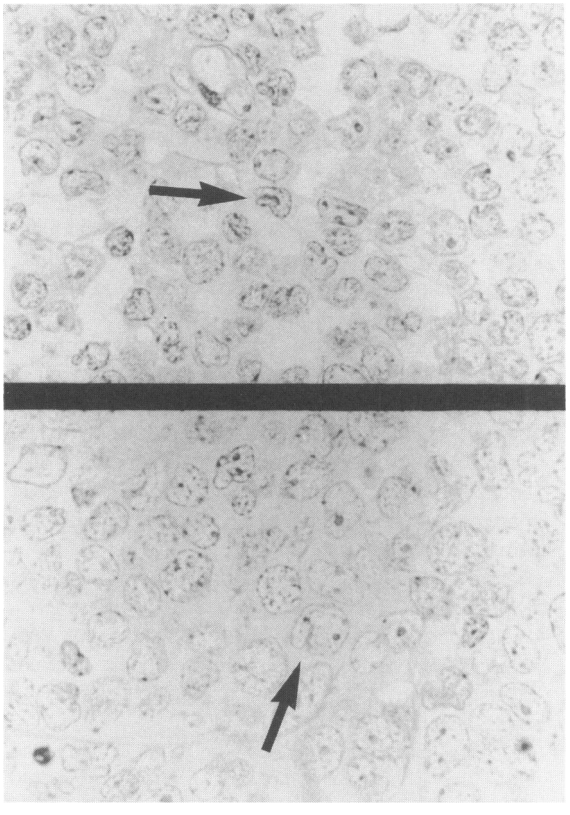

Figure 6. *The orbital biopsy (top) demonstrated a CD5 positive centrocytic lymphoma with both cleft (arrow) and rounder cells. The subsequent lymph node biopsy performed almost one year later showed overt histological progression with much larger nuclei many of which had very dispersed chromatin (nuclear area, 31.5 versus 39.3 μ^2). Nuclear clefts could still be identified (arrow). A bcl-1 gene rearrangement could not be documented.*

Table 4. *Comparison of Early Versus Later Biopsies of Centrocytic Lymphoma (Excluding Marrow Biopsies)*

Parameter	Earlier biopsies (4)*	Later biopsies (4)	*P* value†
NA (υ^2)	25.9 ± 4.2	34.3 ± 3.6	<.05
NCle	3.62 ± 0.02	3.62 ± 0.02	NS
NCIni	3.93 ± 0.16	3.83 ± 0.13	NS
CDI	0.84 ± 0.13	0.82 ± 0.21	NS
Nucleoli (%)	5.8 ± 5.1	14.3 ± 12.9	NS
SRL (%)	15.8 ± 16.1	6.3 ± 5.1	NS

See Table 1 for abbreviations.
* The number of biopsies studied is in parentheses. All results are given as means ± standard deviation.
† Mann-Whitney *U* nonparametric test.

a high proportion of cells with very irregular nuclear contours can be present.[7]

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