THE FAB/MIC/WHO PROPOSALS FOR THE CLASSIFICATION OF THE CHRONIC LYMPHOID LEUKEMIAS

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The chronic lymphoid leukemias (CLL) comprise a very heterogeneous group of neoplastic disorders. Until the publication of the French-American-British (FAB) proposals, there did not exist a uniform approach to classification that considered morphologic as well as immunologic issues. Thirteen different subtypes of CLL were described with detailed morphologic/immunologic profiles for each disorder. The Morphologic, Immunologic, Cytologic (MIC) proposals emphasized the importance of cytogenetics. The WHO proposals incorporated all of the above and added molecular genetics. The final result is a comprehensive diagnostic approach that should permit recognition of the vast majority of cases and permit appropriate therapeutic choices.

For the classification of chronic lymphoid leukemias (CLL) the first decision made by the French-American-British (FAB) Cooperative Leukemia Study group (Fig 1) was to employ flow cytometry to separate CLL into two broad categories: B-CLL and T-CLL (1).

It was recognized that certain cytomorphologic features were so strongly associated with a specific diagnosis that markers were of minor interest [e.g. Sézary cells (T cell) or hairy cell leukemia (B cell type)]. In some cases, however, a precise assignment could not be made (leukemic form of mantle cell lymphoma from CLL, mixed cell type). In addition, the significance of cytogenetic studies was beginning to impact on the recognition of basic molecular defects. At the time of publication, relatively little information was available, except for the association of t(14;18) with follicular lymphoma, trisomy 12 in "B" CLL, t(11;14) in B-prolymphocytic leukemia (PLL) and inv(2) in T-cell PLL.

Some of the markers recommended are no longer in vogue (mouse resetting, for example) and others had not yet been described (cytoplasmic CD23). Nonetheless, we were able to provide guidelines for the utilization of 10 markers in B-CLL and 10 in T-CLL.

As in Workshops that preceded the writing of the paper, a large number of cases were provided (110 in total). Actually, three Workshops were held between May 1985 and October 1987. In instances where there was disagreement (20/110), cases were reviewed via television projection microscope, additional information made available, including lymph node and bone marrow biopsy (hematoxylin and eosin, H&E) material and, on occasion, electron microscopy.

For B-CLL, four morphologic cell types were described and representative illustrations provided (small lymphocytes, large

Figure 1: *FAB Cooperative Group members. Left to right: Drs Catovsky, Flandrin, Gralnick, Daniel, Galton, Bennett and Sultan.*

lymphocytes ("mixed cell"), prolymphocytes, pleomorphic prolymphocytes (seen in CLL/PLL) and cleaved cells (follicular lymphoma)). A separation of CLL from CLL mixed cell type was made on the basis of finding more than 10% of large cells and/or prolymphocytes. If more than 55% prolymphocytes were found, a diagnosis of B-PLL was made.

For the B-CLL, nine different disease groupings were described (CLL; mixed type; PLL, Hairy Cell Leukemia (HCL), follicular lymphoma, leukemic; intermediate (mantle cell); splenic lymphoma with villous lymphocytes (SLVL) [now referred to as splenic marginal zone lymphoma], plasma cell leukemia and Waldenstrom's macroglobulinemia).

For each of these subtypes, representative photomicrographs were produced in several color plates. Selective examples are presented in Fig 2 and immunologic markers were described as characteristically positive or negative, as well as the degree of positivity (10–100%). In CLL, cytoplasmic CD23 had not been described the time of publication nor had CD38 been examined critically.

92% of the "B" chronic lymphoid leukemias are represented by typical "B" chronic lymphocytic leukemia. However, it is important to recognize the other eight types because of prognostic and therapeutic differences.

T LYMPHOID LEUKEMIAS

We described only four types of the T-cell chronic leukemias. Again, there was emphasis on a limited number of markers (CD2, CD3, CD4, CD5, CD7, CD8, CD25). In contrast to B lymphoid leukemias, no specific pattern was recognized. In T-CLL, CD2, CD3, CD4 and CD8 were strongly expressed, but this pattern was seen also in T-PLL and adult T-cell leukemia lymphoma (ATLL) (except for $CD25^+$) and Sézary syndrome. Fortunately, morphologic differences allowed for clear separation in most cases (prolymphocytes with a large single prominent nucleolus and irregular nuclear outline; granular lymphocytes; cerebriform cells in Sézary syndrome; and polylobated, clover leaf nuclei in ATLL).

Perhaps, we chose an incorrect term, namely T-CLL, rather than utilizing the more currently accepted term: large granular lymphocyte leukemia (LGLL), since we indicated that "most cases are large granular lymphocytes". We recognized that the phenotype is that of so called Tγ lymphocytes and that "T-cell receptor studies show the genes to be rearranged".

In contrast to relying exclusively on cytomorphologic and cytochemical features used in our previous proposals (except M0 and M7), we indicated that "determination of the membrane phenotype" was critical as well as requiring a bone marrow biopsy and "histologic assent of lymph nodes and spleen" whenever possible. Selected examples of the morphologic subtypes are illustrated in Fig 2. We concluded by hoping that "in the field of the chronic B- and T-cell leukemias, our proposals will serve as a basis for further work, discussion and improved clinical practice".

Within a year of publication of these proposals, the Morphologic, Immunologic and Cytogenetic (MIC) Cooperative Study Group met for the fourth and final time in Leuven, Belgium, November 8–10, 1989 (2). Three previous meetings had focused on the

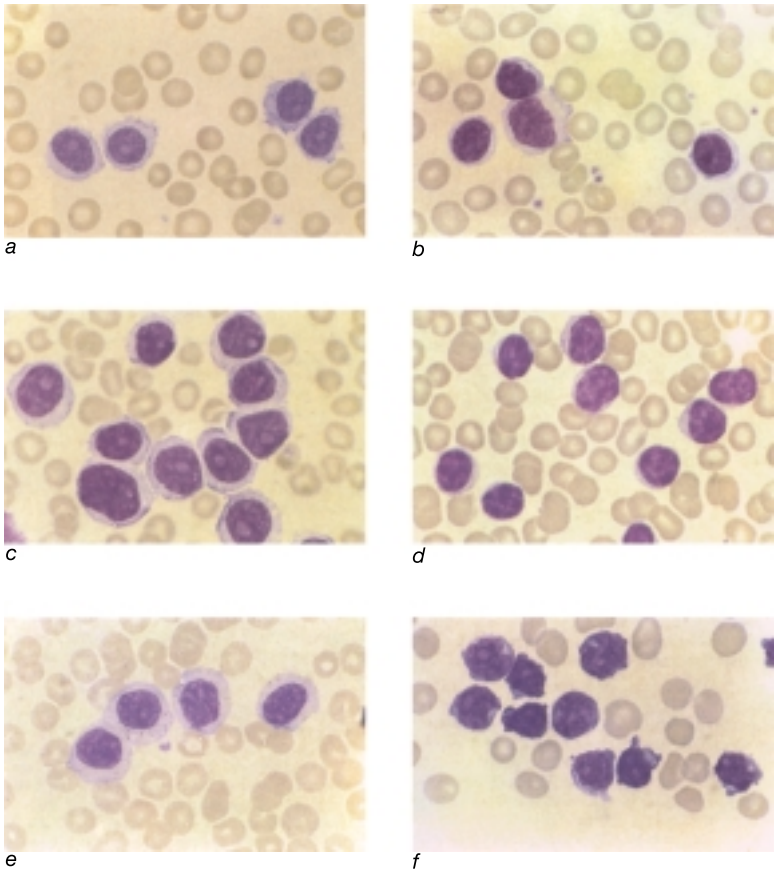

Figure 2: *Representation examples of selected types of "B & T" CLL*. a. Hairy cell variant. b. Intermediate NHL (mantle cell). c. B-PLL. d. CLL typical morphology. e. LGLL ("T-cell CLL"). f. T-PLL. *Composite from Bennett et al. (1).*

importance of examining the immunologic and cytogenetic profiles of the acute myeloid leukemias, acute lymphoid leukemias and myelodysplastic syndromes, along with standard morphology and cytochemistry (3–5). Each of the "Workshops" was adjusted in regard to participation, to reflect the expertise of the subject matter.

Conclusions from this meeting included: replacing the term "T-CLL" with "large granular lymphocyte leukemia: LGLL". A variety of clonal and nonclonal karyotypic changes were discussed, including trisomy 12, 13q aberrations, 14q+ and t(11;14); in B-PLL and inv(2) in T-PLL. The MIC group established a registry for referral of information on many of these rare disorders. Unfortunately, little interest was shown and no follow-up workshop took place.

Over the next decade the "Marsden" program would continue to publish, describe and fine tune many of the CLL. For example, in 1997 (6) nine cases of Sézary cell leukemia, with similarities to T-PLL and chemosensitivity to Campath-1H, were described. In fact, by the mid 1990s over 175 cases of "mature T-cell leukemia and related disorders" were studied, making this one of the largest groups of cases in any academic center worldwide.

In 1994, there appeared proposals from the International Lymphoma Study Group (7). Referred to as the "REAL" classification, this system rapidly became acceptable universally. However, it incorporated virtually all of the chronic B- and T-CLL. One suspects that the rationale for this was the identical lymph node histology in CLL whenever this material was available and the common evolution of many of the non-Hodgkin lymphomas (NHL) to a leukemic terminal phase.

In 2001, the WHO Classification of Tumors of Hematopoietic and Lymphoid Tissue was developed in collaboration with the Society of Hematopathology and the European Association for Hematopathology (8). Professor Catovsky was appointed as committee chair for the chronic B- and T-cell leukemias. This resulted in a clear separation of the leukemias from extranodal and nodal lymphoma.

In contrast to the FAB proposals, there is discussion of the genetics and molecular oncogenic events for each subtype. The recent data of the presence of somatic mutations of the V gene in 50–60% of patients is mentioned, as well as information on CD38 (9) in CLL.

Splenic lymphoma with circulating villous lymphocytes (SLVL) was renamed "splenic marginal zone lymphoma" in a chapter written by Professor P.C. Isaacson. No mention is made of the range of white blood counts, but circulating villous lymphocytes with "short polar villi" are mentioned. This is a very rare disorder (less than 1% of lymphoid disorders) and it is unclear how many patients are diagnosed from the peripheral blood findings or as a result of having had a splenectomy. The immunophenotype is usually $CD20^+$, $CD5^-$, $CD10^-$, $CD23^-$ and $CD103^-$. Which term is preferred will depend on the clinical presentation and whether extranodal tissue is obtained in addition to a careful examination of the blood film and marker studies. Of interest is the difficulty in separating B-PLL from the blastic phase of mantle cell lymphoma. Professor Catovsky points this out with great clarity in the B-PLL chapter. In B-PLL, the immunophenotype is most often IgM-strongly positive, $CD19^+$, $CD20^+$, $FMC7^+$ and $CD5^-$ in 60–70% of cases. In mantle cell lymphoma, the expression of CD5 is seen much more often, along with overexpression of Cyclin D1 mRNA (not studied well in B-PLL). In both situations, abnormalities involving 14q32 [in particular, t(11;14)] have been described.

For some of the "B" chronic lymphoid leukemias it may be necessary to have additional tissue available, including lymph nodes and (or) spleen. Histopathology can be useful in identifying patterns of involvement such as pseudo follicles or mantle zones.

The WHO proposals follow the FAB chronic T-cell leukemia proposals with two notable exceptions. First, Sézary syndrome is considered under the cutaneous lymphomas, rather than as a leukemia; even though circulating cerebriform T cells are always present. Secondly, a relatively new disorder described by Chan (10) in the early 1990s is included, namely "aggressive NK-cell lymphoma". The circulating cells resemble LGL, but are more atypical. The immunophenotype is $CD2^+$, surface $CD3^-$ and $CD56^+$, in contrast to LGL ($CD3^+$, $CD4^+$, rarely $CD56^+$ or $CD57^+$).

Finally, where are we headed? Surely, another classification is not necessary at this point. However, as molecular genetics and the emerging field of genomics (via microchips) continue to expand our knowledge of the genetic makeup of hematopoietic malignancies, it is likely that we will revisit, selectively, classification issues in the near future. Hopefully, our therapeutic strategies will be more rationally based as well.

Acknowledgment

The efforts of Vickie Saporito are appreciated for the manuscript processing and preparation of the figures.

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REFERENCES

1 Bennett JM, Catovsky D, Daniel MT, *et al.* Proposals for the classification of chronic (mature) B and T lymphoid leukaemias. *J Clin Pathol*, **42**: 567–584, 1989.

2 Bennett JM, Juliusson G, Mecucci C. Meeting Report. Morphologic, immunologic, and cytogenetic classification of the chronic (mature) B and T lymphoid leukemias: Fourth Meeting of the MIC Cooperative Study Group. *Cancer Res*, **50**: 2212, 1990.

3 Bennett JM, Berger R, Catovsky D, *et al.* Morphologic, immunologic and cytogenetic (MIC) working classification of acute lymphoblastic leukemias. *Cancer Genet Cytogenet*, **23**: 189–197, 1986.

4 Bennett JM, Berger R, Catovsky D, *et al.* Morphologic, immunologic and cytogenetic (MIC) working classification of the acute myeloid leukemias. Second MIC Cooperative Study Group. *Br J Haematol*, **68**: 487–494, 1988.

5 Bennett JM, Berger R, Brunning RD, *et al.* Recommendations for morphologic, immunologic, and cytogenetic (MIC) working classification of the primary and therapy-related myelodysplastic disorders. *Cancer Genet Cytogenet*, **32**: 1–10, 1988.

6 Pawson R, Matutes E, Brito-Babapulle V, *et al.* Sezary cell leukaemia. a distinct T cell disorder or a variant form of T prolymphocytic leukaemia? *Leukemia*, **11**: 1009–1013, 1997.

7 Harris NL, Jaffe ES, Stein H, *et al.* A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood*, **84**: 1361–1392, 1994.

8 Jaffe ES, Harris NL, Stein H, *et al.* World Health Organization Classification of Tumours. *Pathology and Genetics of Tomours of Haematopoietic and Lymphoid Tissues*. IARC Press, Lyon, 2001.

9 Damle RN, Wasil T, Fais F, *et al.* Ig V gene mutation status and CD38 expression as novel prognostic indicators in chronic lymphocytic leukemia. *Blood*, **94**: 1840–1847, 1999.

10 Chan JK, Sin VC, Wong KF, *et al.* Nonnasal lymphoma expressing the natural killer cell marker CD56: a clinicopathologic study of 49 cases of an uncommon aggressive neoplasm. *Blood*, **89**: 4501–4513, 1997.