World Health Organization Classification of lymphomas: A work in progress

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Summary

The World Health Organization (WHO) publishes classification handbooks for all neoplastic diseases. The last WHO Classification of leukemias and lymphomas was published in 1976. Since that time, through cytogenetics and molecular biology, it has been shown that many hematopoietic neoplasms are associated with a unique genetic profile. Similarly, the development of widely available and routinely applied monoclonal antibodies has allowed the identification of a unique immunophenotypic profile for most leukemias and lymphomas. These techniques have permitted the recognition of a number of distinct disease entities, and also enhance both diagnostic accuracy and reproducibility.

The WHO Classification has been developed under the joint auspices of the European Association for Hematopathology (EAHP) and the Society for Hematopathology (SH). First organized in 1995, the Steering Committee appointed 10 committees covering T-cell and B-cell lymphomas and leukemias, myeloid and histiocytic tumors. The committees were asked to develop a list of diseases within their topic area, and to establish definitions of each disease according to established criteria. The WHO Classification uses the principles of the R.E.A.L. Classification, which defines each disease according to its morphology, immunophenotype, genetic features, postulated normal counterpart, and clinical features. Morphologic and clinical variants of individual diseases are discussed in the text, and their use is optional. The proposed classification was presented at the USCAP meeting in 1997, the site of the first joint meeting of the EAHP and SH. The presentation was followed by an open forum attended by EAHP and SH members.

The Steering Committee also appointed a Clinical Advisory Committee to ensure that the classification meets clinical needs, and to resolve questions of clinical significance. The proposed WHO Classification for lymphomas is similar to the R.E.A.L. Classification for lymphomas, with minor modifications and reassessment of provisional categories based on new data since 1994.

Key words: B cell, Hodgkin’s disease, leukemia, lymphoma, non-Hodgkin’s lymphoma, T cell

Introduction: The approach to hematopathology in the modern era

The classification of hematological malignancies has undergone significant reappraisal in recent years. These changes have resulted from insights gained through the application of immunological and molecular techniques, as well a better understanding of the clinical aspects of lymphoma and leukemia through advances in diagnosis, staging and treatment. A multifaceted approach to both disease definition and diagnosis is now the state of the art.

While morphology is still the starting point for pathologic diagnosis, immunologic and molecular techniques have been crucial in defining disease entities, and are often useful in differential diagnosis. The pathologist must also be cognizant of the clinical history, as the site of presentation and other clinical parameters are an important aspect of the diagnosis.

The World Health Organization (WHO) publishes classification handbooks for pathologists for all neoplastic diseases, known as ‘bluebooks’. The last WHO Classification of leukemias and lymphomas was published in 1976 [1]. Since that time we have experienced a revolution in our ability to accurately diagnose and classify hematopoietic malignancies. Through cytogenetics and molecular biology, it has been shown that many hematopoietic neoplasms are associated with a unique genetic profile, and that these genetic changes often have a direct bearing on the pathogenesis of the disease and its clinical behavior. Similarly, the development of widely available monoclonal antibodies, in particular those applicable to routinely processed material, has allowed the identification of a unique immunophenotypic profile for most leukemias and lymphomas. With these techniques a large number of newly-defined disease entities has been recognized. Moreover, the use of these techniques enhances both diagnostic accuracy and reproducibility [2].

A new WHO Classification for hematologic malignancies is being developed through the joint auspices of the Society for Hematopathology (SH) and the European Association of Hematopathology (EAHP). A Steering Committee, appointed by the two societies, includes
The classification of lymphomas in the past has been controversial, and it has been difficult to establish an internationally accepted scheme. Indeed, the classification of hematopoietic and lymphoid malignancies. The committees are composed of international experts in their respective fields, a total of 52 participants. In addition, to assure that the classification is clinically relevant, more than 35 expert clinicians in the field of leukemia and lymphoma were appointed to a Clinical Advisory Committee, chaired by Drs C. Bloomfield and T. A. Lister.

The WHO Classification is a product of this consensus-building process, and utilizes the expertise of multiple individuals. The WHO Classification is based on the principles of the Revised European–American Classification of Lymphoid neoplasms (R.E.A.L.), which noted that lymphoma was not a single disease, but in fact multiple diseases, each with distinctive features [3]. It proposed that individual disease entities could best be defined by a combination of morphology, immunophenotype, genetic features, clinical features, and should be classified according to possible according to the postulated normal counterpart of the neoplastic cells. This review will focus on the classification of neoplasms derived from mature T cells, B cells, and NK cells, with emphasis on the malignant lymphomas. However, the WHO scheme will use the same concepts of disease definition for the lymphoblastic, myeloid, and histiocytic neoplasms.

The committees have been working since 1995 to establish a consensus on the diseases to be identified. The Steering Committee and the Committee chairs met on several occasions between 1995 and 1997 for ongoing discussions, to reach agreement on terminology and diagnostic criteria. The draft classification was presented to the memberships of the United States–Canadian Academy of Pathology (USCAP), SH and EAHP at a symposium held in March, 1997, the site of the first joint meeting of the SH and EAHP [4]. This presentation was followed by an open forum for members of the SH and EAHP at which detailed vetting of the proposal took place. In November, 1997 a three-day Clinical Advisory Committee meeting was held in Airlie, Virginia. Participating in this meeting were 36 expert clinicians, WHO committee members, and the Executive Committees of both the EAHP and SH. The agenda of the meeting focused on questions of clinical importance related to the classification of hematopoietic and lymphoid malignancies.

**Historical background of the classification of lymphomas**

The classification of lymphomas in the past has been controversial, and it has been difficult to establish an internationally accepted scheme. Indeed, the controversies of the 1970s led to the development of the Working Formulation (WF) for the non-Hodgkin's lymphomas (NHL), following a National Cancer Institute-directed study to evaluate 'competing' classification schemes [5]. This initiative was spearheaded by clinicians. Since the pathologists could not agree on disease definition or terminology, the clinicians based the classification on clinical outcome using standard treatment protocols from the 1970s. The resultant clinical groupings identified in the WF were admittedly heterogeneous. For example, 'diffuse mixed small- and large-cell lymphoma' included a wide variety of both B-cell and T-cell lymphomas. It is therefore not surprising that pathologists could not use these categories reproducibly [6].

The original intent of the WF proposal was to have it serve as a common language to translate among classifications, and not to serve as a free-standing classification scheme. However, because it was a convenient guide to therapy, it quickly became popular among clinicians, and was adopted for use in many centers in the US for clinical trials. In reality the WF was in essence the Rappaport classification with updated terminology from Lukes and Collins [7]. It substituted the term 'large cell' for 'histiocytic' and divided the 'histiocytic' lymphomas of the Rappaport scheme into two subgroups: large cell (cleaved or noncleaved) and large-cell immunoblastic. This separation split the large-cell lymphomas between the intermediate- and high-grade categories, a division that has been controversial and not supported by subsequent analyses [8].

Another more basic flaw in the WF is that it was based on treatment outcome, not on the recognition of individual disease entities or the cell of origin for a malignant neoplasm. This conceptual approach was a significant deviation from the way in which classification systems have been developed for neoplasms in other tissues. It lumped diseases that shared a similar cell size and median survival into single categories, despite the fact that they might be of different cellular (B- and T-cell) origins, and might have completely different clinical presentations and even treatments. At the time the WF was proposed immunophenotyping was felt to be beyond the reach of the routine pathology laboratory, and the classification therefore was based on morphology alone.

Today we have a wide battery of monoclonal antibodies reactive in routinely-processed paraffin sections, and the polymerase chain reaction (PCR) technique permits molecular analysis of most specimens. The use of these new biological approaches has transformed our understanding of lymphoid neoplasia. Immunophenotypic and genotypic studies have permitted an impartial analysis of questions that were unresolved when addressed with only routine hematoxylin and eosin stained sections. Indeed, a broad international consensus has emerged on many topics. This consensus was embodied in the Revised European–American Classification of Lymphoid Neoplasms (R.E.A.L. Classification) published by the International Lymphoma Study Group in 1994 [3].
Prior classification schemes for lymphoma were based exclusively on one or two major principles. For example, the Working Formulation segregated lymphomas into clinical groups, based on the clinical outcome (survival), using data from a large retrospective study performed in the 1970s [5]. The Kiel Classification, popular in Europe, was based on the principle that lymphomas should be related to their normal counterparts, and that a normal cell of origin could be identified for virtually all lymphoma subtypes [9, 10]. The R.E.A.L. Classification recognized that cell of origin (B, T, or NK cell) was an important, and perhaps overriding premise for lymphoma classification. However, it also felt that cell of origin could not be the only basis for classification. Firstly, the normal counterpart cannot be readily identified for all lymphoma subtypes; and secondly, it ignores many other important factors, such as molecular and cytogenetic abnormalities.

The R.E.A.L. Classification was based to a significant degree on the original and Updated Kiel Classifications, which proposed that lymphoid malignancies could be related to their normal counterparts in the T- and B-cell systems [10]. (The Lukes-Collins classification took a similar conceptual approach [7].) However, while most prior classification schemes had relied strictly on morphology or immunophenotype for the definition of entities, the R.E.A.L. Classification departed from these traditional schemes and represented a new paradigm for the classification of lymphomas. It emphasized that each disease was a distinct entity, defined by a constellation of laboratory and clinical features; i.e., morphology, immunophenotype, genetic features, clinical presentation, and course. It further noted that the site of involvement (e.g., nodal vs. extranodal) was often a signpost for important underlying biological distinctions. It was the inclusion of clinical criteria that was one of the most novel aspects of the ILSG approach. For example, extranodal lymphomas were not simply extranodal involvement by nodal diseases, but in many instances distinctive entities. Lymphomas of the mucosal associated lymphoid tissues (MALT) are a prime example of this principle [11], but the principle is equally applicable to the T-cell lymphomas [12].

The R.E.A.L. Classification also stressed the distinction between histological grade and clinical aggressiveness, and emphasized that histologic grade should be applied within individual diseases, not across the entire spectrum of lymphoid neoplasms. Finally, in an attempt to reduce unnecessary complexity and improve reproducibility, the categories of peripheral T-cell lymphoma, unspecified, and diffuse large B-cell lymphoma were created. This decision was based on the fact that cytologic subclassification of these categories had not yet been proven to be biologically or clinically important [13, 14].

Interrelationship of the WHO and R.E.A.L. Classifications

The R.E.A.L. Classification was based on the building of consensus through the input of 19 expert hematopathologists with a primary interest in lymphoma. Moreover, it relied on previously published biological, pathological and clinical studies, rather than on theoretical and untested proposals. Following its publication, an international study directed by Dr J. Armitage sought to determine if the R.E.A.L. Classification could be readily applied by a group of independent expert pathologists [2]. Other goals of the international lymphoma classification project were: 1) to determine the role of immunophenotyping and clinical data in the diagnosis of disease entities; 2) to determine both intraobserver and interobserver reproducibility in the diagnosis of the various entities; 3) to further investigate the clinical features and/or epidemiology of the various entities; and 4) to determine if clinical groupings would be practical or useful for clinical trials or practice.

The conclusions of that study affirmed the principles of the R.E.A.L. Classification. Virtually all cases could be classified in this classification. Intraobserver and interobserver rates of reproducibility were excellent, in the range of 85%–95% for most diagnostic categories [2]. It was felt that the use of precise disease definitions, as provided by the REAL scheme, enhanced diagnostic accuracy, and reduced subjectivity on the part of pathologists. The use of immunophenotyping also enhanced reproducibility; nevertheless, there were some diagnoses for which immunophenotyping was not required, such as follicle center lymphoma and B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma. However, immunophenotyping was found to be essential for some diagnostic categories, such as most peripheral T-cell lymphomas. Furthermore, this distinction was found to be clinically important; peripheral T-cell lymphomas had a much poorer survival rate than B-cell lymphomas of similar morphology.

Interestingly, this study also highlighted the importance of clinical factors, such as the international prognostic index (IPI) for predicting prognosis and providing a guide to clinical management [15]. There was a wide range in survival within most disease entities based on the risk factors identified in the IPI [2]. This result suggests that it can be misleading to stratify different diseases into risk groups based only on histologic criteria. Treatment planning must take into consideration clinical factors, as well as the histologic diagnosis. Moreover, when the diseases were grouped according to post-treatment survival, it was noted that the entities included within each group were heterogeneous, requiring markedly different treatment approaches. For example, the lymphomas in the best risk group were T/null anaplastic large-cell lymphomas, marginal zone lymphomas of MALT-type, and follicle center lymphomas. Clearly the treatment approaches for these diseases are completely different, indicating that clinical groupings...
by survival are not useful. One must approach each disease entity individually, considering both the diagnosis, the patient’s risk factors, and the known idiosyncrasies of each disease with regard to treatment.

The study also confirmed previous epidemiological observations, such as the increased frequency of nasal T/NK angiocentric lymphoma among Hong Kong Chinese, as compared with patients from North America and Western Europe [16]. The distinctive clinical features of mediastinal large B-cell lymphoma and T/null anaplastic large-cell lymphoma were also confirmed [17, 18].

Since the WHO Classification is based upon the same principles of disease definition as the R.E.A.L. scheme, it is therefore – not surprisingly – very similar to it (Table 1). However, since the publication of the R.E.A.L. Classification in 1994, significant new data have been generated for some categories of lymphoma and leukemia. These new studies permit resolution of entities that were listed as provisional in the original classification. Some of the provisional entities have been retained, including hepatosplenic gamma/delta T-cell lymphoma and subcutaneous panniculitis-like T-cell lymphoma [19-22]. However, ‘Hodgkin’s-like anaplastic large-cell lymphoma’ was felt upon further analysis to be resolvable into either an aggressive form of Hodgkin’s disease, or a nodular variant of T/null anaplastic large-cell lymphoma in most cases [23-25]. It is therefore eliminated as a category in the WHO scheme. The category of high-grade B-cell lymphoma, Burkitt-like was likewise felt to be heterogeneous, resolvable in most cases into either Burkitt lymphoma or a large B-cell lymphoma (see below).

Additionally, minor changes in terminology were suggested for some entities, such as the use of the term ‘follicular lymphoma’ rather than ‘follicle center lymphoma’, and ‘nasal T/NK cell lymphoma’ for ‘angiocentric lymphoma’ [16], ‘Lymphoplasmacytoid lymphoma’ of the R.E.A.L. scheme reverts to the original Kiel Classification term of ‘lymphoplasmacytic lymphoma’. Subclassification of anaplastic large-cell lymphomas into systemic and primary cutaneous types also is more precisely defined [26, 27].

Finally, the International Lymphoma Classification Project identified a few entities for which reproducibility was suboptimal, suggesting that clarification of diagnostic criteria for these entities would be helpful [2]. These include nodal marginal zone B-cell lymphoma, lymphoplasmacytoid (lymphoplasmacytic) lymphoma, and Burkitt-like lymphoma. The definition of nodal marginal zone lymphoma and lymphoplasmacytic lymphoma is still controversial, as specific genetic and immunophenotypic markers for these categories have not been identified. The category of ‘Burkitt-like lymphoma’ was provisional in the R.E.A.L. Classification, and was expected (by definition) not to be reproducible. It is not included in the WHO Classification; however, it is noted that some Burkitt lymphomas may display atypical cytologic features [28]. Such cases are considered atypical variants of Burkitt lymphoma, rather than ‘Burkitt-like lymphoma’. Endemic, sporadic, and AIDS-associated Burkitt lymphoma variants also are delineated in the WHO scheme. These Burkitt-lymphoma variants must be distinguished from large B-cell lymphomas of
centroblastic or immunoblastic type that display a prominent starry sky and intermediate cell size [29]. Such cases are retained within the category of large B-cell lymphoma.

The proposed classification incorporates minor changes in the recognized subtypes of Hodgkin’s disease and anaplastic large-cell lymphoma, reflecting recent developments in this field. Importantly, the WHO classification retains the basic division of this lymphoma into classical Hodgkin’s disease and nodular lymphocyte predominant Hodgkin’s disease that was proposed by the R.E.A.L. Classification. The classification also proposes a nosological change, suggesting the term Hodgkin lymphoma, rather than Hodgkin’s disease. More than 150 years since the original description of Hodgkin’s disease, it seems time to acknowledge that this disease is indeed a lymphoma, and not an atypical reactive or inflammatory process, an uncertainty reflected in the original designation of ‘Hodgkin disease’. The omission of the possessive form of ‘Hodgkin’s’ is a stylistic change imposed by the WHO, and one that may not be adopted in common use. The classification also retains the provisional subtype of lymphocyte-rich classical Hodgkin's lymphoma (disease), proposed in the original R.E.A.L. Classification.

As noted above, the category of Hodgkin’s-like anaplastic large-cell lymphoma is omitted in the proposed WHO scheme. It is now felt that these cases can be resolved as either Hodgkin’s lymphoma or anaplastic large-cell lymphoma with the use of a battery of immunocytochemical and, if needed, molecular techniques. Most cases to which this term was previously applied are felt to be examples of histologically aggressive Hodgkin’s disease, either nodular sclerosis grade II, or lymphocytic depletion. Additionally, it is noted that systemic anaplastic large-cell lymphoma and primary cutaneous anaplastic cell lymphoma are biologically and clinically distinct, and that the primary cutaneous form is part of the spectrum of CD30-positive T-cell lymphoproliferative disease of the skin [26, 27, 30]. Expression of the anaplastic large-cell lymphoma kinase (ALK-1), as a consequence of the t(2;5), is seen only in systemic anaplastic large-cell lymphoma, and not in primary cutaneous anaplastic large-cell lymphoma [26, 27]. ALK-1 expression also was not seen in cases classified as ‘Hodgkin’s-like anaplastic large-cell lymphoma’, confirming again that most cases with this histology are biologically related to Hodgkin’s disease, and not anaplastic large-cell lymphoma [30, 31].

Conclusion

The WHO Classification, when complete, will represent the first true worldwide consensus on the classification of hematologic malignancies. Proponents of other classifications [Working Formulation, Kiel, R.E.A.L., and French–American–British (FAB)] have agreed to adopt this classification as the new international standard.

We hope that the process of disease definition, consensus building, and clinical input will be a useful model for future efforts in the pathologic classification of diseases.

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