Classification of Non-Hodgkin’s Lymphoma: A Proposal

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Key Words. Non-Hodgkin’s lymphoma · Small lymphocytic lymphoma · Follicular cleaved lymphoma · Large cell lymphoma · Burkitt’s lymphoma · Lymphoblastic lymphoma · Linear dynamic theory · Non-linear dynamics

ABSTRACT

The pathology community has traditionally classified the non-Hodgkin’s lymphomas (NHL) according to their histogenetic characteristics, an approach that has fostered the proliferation of multiple, often conflicting, lymphoma classification schemes with limited clinical relevance. The scientific acceptance of these histogenetically pure schemes is based on an implicit belief that all that is scientifically sound must adhere to linear dynamic theory; that is, that the elemental components of a system in a linear and direct fashion control the behavior of the whole. Non-linear dynamic theory, however, which has recently acquired acceptance within the scientific community, offers another equally valid approach to the classification of the NHL by acknowledging the inherent indeterminacy of nature. In other words, rather than classifying the NHL according to their cell of origin in the hopes that the elemental unit will predict the clinical outcome, we propose that pathologists accept the premise that nature is inherently unpredictable and define the NHL according to their clinical characteristics, such as natural history and response to therapy. Using these criteria, a proposed classification is discussed containing two major subtypes of lymphomas (indolent and aggressive) which can be further subdivided into five groups: the low-grade, or indolent, group includes the small lymphocytic and the follicular cleaved cell (small, and small, mixed) categories, while the high-grade, or aggressive, group includes the large-cell, the Burkitt’s lymphoma, and the lymphoblastic lymphomas. Each of these groups is discussed in detail, with comparisons to the Revised European American Lymphoma classification to demonstrate clinical relevance. Although it is clear to us that the proposed scheme presented in this manuscript is not the only clinically valid one that can be constructed, it is equally clear that any scheme that is developed—in order to be considered valid—must be guided principally by its clinical relevance. The Oncologist 1997;2:235-244

BASIS OF CONTROVERSY

Introductory Comments

“The Non-Hodgkin’s Lymphomas are a diverse group of neoplasms, the pathological classification of which has long been a controversial subject [1].” This statement was issued by the Non-Hodgkin’s Lymphoma Pathologic Classification Project in 1982, acknowledging the difficulty in creating a universally accepted, “scientifically based” classification scheme of the non-Hodgkin’s lymphomas (NHL). Several factors have contributed to the ambiguous and controversial aspects of the NHL classifications, beginning with the definition of a “scientifically based” schema.

The pathology community, which usually establishes the classifications of neoplasias, appears to consider the words “scientifically based” to be synonymous with “histogenetically based.” That is, the classification of a given neoplasm should be based upon its histogenetic qualities. Implicitly, then, there is a belief (at least among most pathologists) that the fundamental type of cell which comprises a tumor determines the biologic behavior—and therefore clinical expression—of the various neoplasms within a given organ.

Although this “histogenetic” approach to the classification of neoplasias may work well in many situations, there are some obvious drawbacks to this theory which become apparent when it is applied to the NHL. In addition to its limited clinical relevance, a histogenetically based classification of a given neoplasm requires scientific agreement as to what exactly comprises the cell of origin. In the case of NHL, such a consensus has yet to be reached, in part due to the continual discovery of new types of lymphoid cells and in part due to the expression of aberrant markers on neoplastic lymphoma cells.
Because these factors preclude the definitive establishment of a histogenetically based—and therefore “scientifically based”—classification scheme, they end up fostering the proliferation of multiple, often conflicting lymphoma classification schemes. The Revised European American Lymphoma (REAL) classification is but the latest attempt. In spite of these limitations, the pathology community continues to pursue the elusive histogenetic perspective, believing it to be the “gold standard” for classification of the NHL.

Historical Perspective

During the 1970s, an entirely new approach to hematologic malignancies was created by the then-novel field of immunology. Given this new investigative tool, it appeared as though the academic hematopathologists were within reach of the histogenetic classification they so desired. However, the classification scheme proved faulty. Neoplastic cells were found to have aberrant expression of immunological markers, thus clouding definitive identification. In addition, pathologists continued to be divided on the topic of what constituted the “cells of origin” of the immune system. As a result, this promising “immunologic” perspective became yet another disappointing stumbling block in a long path of ambiguity and controversy about the classification of the NHL.

In an attempt to find a common approach to the NHL, the National Cancer Institute sponsored a multinational study which culminated with the 1982 publication of a consensus classification, better known as the “Working Formulation” (WF) [1]. The WF is essentially a clinically based classification that borrowed terms from histogenetically based classifications of that time. Although many acknowledged the advantages of a clinically relevant scheme, the WF was a subject of ongoing controversy from its inception. Many pathologists—including recognized experts in the field who had actually helped formulate the new classification—criticized the WF for the heterogeneity of cell types which could be found within any given category. Thus, the dominant thought pattern among many pathologists continues in spite of the clinical success of the WF: that is, a classification is perceived as insufficient—in spite of establishing clinically relevant groups—if it is not rooted in histogenic precepts.

Scientific Foundations of a Clinically Valid Classification Scheme

It is the contention of this paper that demonstrable clinical relevance of NHL groups should be the most important factor determining their validity, even though histogenetic heterogeneity may exist within the categories. Although reasonable, this perspective is not universally accepted. As discussed in the previous sections, the predominant mode of thought to date has been one in which histogenetically pure, yet possibly clinically heterogeneous, classifications supersede a classification system which is clinically based (and therefore relevant) but histogenetically heterogeneous. One question is raised by this seemingly paradoxical situation: why are pathologists willing to accept histogenetically pure categories as the basis of classification schemes, even though those same categories may be clinically heterogeneous? (Or, stated as its corollary, why are clinically relevant groupings, albeit histogenetically impure, considered inadequate?). The remainder of this section will attempt to answer this question and, in so doing, argue that classification schemes based on clinically relevant criteria should be considered as scientifically sound as those schemes based on histogenetic qualities.

To better compare and contrast the arguments for histogenetic classifications and clinical classifications, it would be helpful to digress and discuss briefly the concepts of linear and non-linear dynamics [2,3] and how they relate to these two types of classifications of neoplasias. Linear dynamics can be simplistically described as the linear and mechanistic conceptualization of causality and may be expressed diagrammatically by the following: A → B → C → D (i.e., A causes B which causes C which causes D). In essence, linear dynamics proposes that the elemental components of a system in a linear and direct fashion control the behavior of the whole. Substituting “cell types” for “elemental components of a system” and “neoplasia” for “whole,” one can demonstrate the parallel logic of linear dynamics and histogenetic perspectives: it is the cell type which, in a linear and direct fashion, controls the behavior of the neoplasia. This ability to construct histogenetically based classification systems within the framework of linear dynamics is what has heretofore identified them as being scientifically sound.

Non-linear dynamics is a different scientific paradigm which accepts, as an integral and ubiquitous property of nature, a greater degree of uncertainty and indeterminacy than has traditionally been the case with linear dynamics. Whereas linear dynamics provides a rigid framework in which A absolutely results in B which determines C which causes D), in essence, non-linear dynamics acknowledges that A might result in B, but it could also result in B1, B2, B3, etc. B, B1, B2, and
B3 may then result in a variety of Cs, and so forth. In other words, the final outcome (e.g., clinical behavior, which can be identified as D) of the chain of events cannot be precisely predicted along a narrow pathway, given the knowledge of the elemental parts. Nature is inherently uncertain, and therefore the behavior of the whole may not necessarily be foretold by the nature of the basic elements. Thus, this particular paradigm accepts that indeterminacy occurs within certain boundaries of possibilities. This theory, also known as the mathematics of chaos, has recently been accepted as a scientifically sound perspective within the scientific community [2, 3].

What the debate between histogenetically and clinically based classifications of the NHL boils down to, then, is essentially a debate between linear and non-linear dynamics. The histogenetic perspective of the NHL is, as previously discussed, a paradigm of linear dynamics: A, within a definable pathway, determines D, or, from a pathologic standpoint, cell type determines clinical behavior. The variables in this equation are the elemental units (the “As”). All other events along the pathway (the Bs, Cs, etc.) can be precisely predicted, given a full understanding of the starting points. In this paradigm, then, histogenetically pure categories are of paramount importance; clinical heterogeneity is an unfortunate sequela which, for now, until all the Bs, Cs, etc., are known, must be tolerated for the sake of “scientific soundness.” On the other hand, there is the non-linear approach to nature, an equally valid paradigm which acknowledges the indeterminacy and uncertainty of biology, and grants histogenetic leniency in categories which are nonetheless clinically relevant. Within the framework of linear dynamics, the clinical expression of a neoplasm, which clearly reflects this limited uncertainty, is a valid and scientifically sound parameter by which to gauge the validity of a classification scheme.

**A Simple Classification Scheme**

**General Views about NHL Classifications**

As noted above, a classification system should be considered scientifically sound whether it is histogenetically based or clinically based. Acknowledging the validity of this statement forces the pathologist to judge a classification system more carefully, based on its other merits (i.e., utility, reproducibility, simplicity, etc.), rather than instinctively dismissing it as unscientific merely because it is clinically based. It is just such a clinically based classification scheme that will now be presented.

Given the numerous classification proposals already in existence, one might ask: why create another system? There is only one answer; the authors would like to illustrate that it is possible to create a classification scheme that is both simple and clinically relevant. To emphasize the relevance of this new proposal, this article will contrast the new categories with those of the REAL classification [4].

When creating a new classification system, then, the first question which must be answered is: what is a clinically relevant scheme? Obviously, a number of answers could be given to this query; however, for the purpose of this paper, the authors have defined “clinical relevance” by two characteristics: the natural history of the lymphomas and their response to therapy. (The term “response to therapy” refers to a significant alteration, e.g., often complete remission in the natural course of the lymphoma induced by current treatment modalities.) Based on these two parameters, the natural history of the disease and the response to therapy, two basic groups of NHL can be identified: the indolent lymphomas and the aggressive lymphomas. The indolent lymphomas, as their name implies, tend to have a prolonged clinical course with or without treatment, whereas the aggressive lymphomas (at least without treatment) do not. Paradoxically, the aggressive lymphomas have a better response to therapy, frequently achieving a true “cure,” while the indolent lymphomas are typically treatable but not curable.

**Basis of the Classification of NHL**

The two characteristics used here to define the fundamental groups of lymphomas are the natural history of the disease and the relative response to therapy. Therefore, clinicopathologic correlations are of paramount importance. Borrowing terms from the WF, we will refer to these two groups as the low-grade (indolent) lymphomas and the high-grade (aggressive) lymphomas. Each of the two main groups can be subdivided into a number of categories, but since the purpose of this paper is to create a classification scheme that is both simple and clinically relevant, only five distinct categories need be discussed (Table 1); two categories lie within the low-grade group, and will be referred to as the small lymphocytic and the follicular; one category exists within the high-grade group, and will be referred to as the large cell, the Burkitt’s lymphoma, and the lymphoblastic lymphomas. It is assumed that the reader of this article is well-versed in the field of NHL, making it unnecessary to define in detail each of these five categories. Therefore, the discussion of the
categories will focus on describing their general characteristics and contrasting them with their REAL counterparts.

The subdivisions delineated above have been drawn based upon convention, clinical expression, and response to therapy of the various cases. (Notice that immunophenotype is not a defining characteristic, although it does correlate with some of these categories). It is the contention of this article that these five categories identify the most significant clinical groups of NHL, although there is unquestionably significant histogenetic heterogeneity within each category. Some readers may argue that there is also a certain amount of clinical heterogeneity in these groupings. It should be noted, however, that such clinical variance is inconsequential and does not significantly affect the characteristics of the category in regard to therapy response.

One final comment before we turn to a discussion of the individual categories: the classification scheme proposed in this paper is one that is intended to be clinically relevant, not necessarily histogenetically pure. To emphasize the simplicity of this classification scheme, the categories are summarized in Table 1.

### Table 1. Proposed classification for non-Hodgkin's lymphoma

<table>
<thead>
<tr>
<th>Category</th>
<th>Encompasses most of the REAL groups of:</th>
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| A. Small lymphocytic lymphoma | ▶ B-CLL/B-PLL/B-SLL  
▶ Lymphoplasmacytoid lymphoma/immunocytoma  
▶ Mantle zone lymphoma  
▶ Marginal zone lymphoma |
| B. Follicular cleaved cell (small and small, mixed) | ▶ Follicular center lymphoma, follicular  
(see text for further elaboration and exceptions to this category) |
| B-CLL = B-cell chronic lymphocyte leukemia; B-PLL = B-cell prolymphocytic leukemia; B-SLL = B-cell small lymphocytic lymphoma. |
and utility of a clinical scheme, we will contrast these categories with those of the REAL system, which is essentially histogenetically based. The difference between these two approaches is already manifest in the nature of the fundamental groups of NHL. It is the belief of these authors that the subdivision of NHL into two major categories—the low-grade and the high-grade groups—should be the cornerstone of any clinically relevant classification scheme. Such is not the case with the REAL classification, which defines three major clinically variable categories: B-cell, T-cell, and Hodgkin’s disease. The authors of the REAL system acknowledge the clinical heterogeneity of their groups when they comment on the fact that “many of these distinct lymphoma entities have a range of morphologic grade and clinical aggressiveness, making it difficult to arrange them according to a spectrum from low to high grade, indolent to aggressive behavior [4].”

Tolerance of such clinical variance in the REAL classification is indicative of the willingness to combine low-grade and high-grade lymphomas in order to maintain histogenetic purity. This provides a stark contrast to our proposed classification system in which clinical relevance supersedes histogenetic homogeneity.

**THE LOW-GRADE LYMPHOMAS**

Low-grade lymphomas generally tend to present in asymptomatic, older individuals (>50 years of age) who experience painless generalized adenopathy and frequently have bone marrow involvement at the time of presentation. In spite of the diffuse anatomic involvement (advanced anatomic stage), these patients typically have a very indolent clinical course; paradoxically, though, these lymphomas prove to be incurable by present medical modalities and usually recur after apparently complete remissions. The two subcategories to be discussed in this group are the small lymphocytic and the follicular cleaved cell (small, and small, mixed).

**Small Lymphocytic Lymphomas**

**Introduction**

Small lymphocytic lymphomas (SLL) are the only examples of diffuse lymphomas in the low-grade category. SLL is composed of small, round lymphocytes which, on the whole, have regular nuclei. (These lymphomas may, however, show some nuclear irregularity, which has created significant debate among pathologists as to the clinical grade. This controversy can be traced back to the Rappaport classification, which proposed the concept of an “intermediate lymphoma” based on the degree of nuclear irregularity in the small lymphocytes; however, innumerable attempts to correlate prognosis with the degree of cytologic irregularity have not shown a consistent relationship.)

Patients with SLL, as mentioned above, experience a long clinical course marked by extended disease-free periods, but invariably succumb to the lymphomas in the end. The SLL are responsive to treatment but are not curable. They generally have a median time course of approximately 8-10 years.

**SLL versus the REAL Classification**

The REAL classification describes four groups of lymphomas that appear to be closely related to the SLL. These groups are: A) B-cell chronic lymphocytic leukemia (B-CLL)/prolymphocytic leukemia (B-PLL)/small lymphocytic leukemia (B-SLL); B) lymphoplasmacytoid lymphoma/immunocytoma; C) mantle zone lymphoma, and D) marginal zone lymphoma. Although each of the REAL categories might initially appear to have distinct characteristics that warrant separation, upon closer examination it will become evident that the parameters which divide them are actually quite nebulous. In other words, these four categories can quite easily be combined into one simple category (our small lymphocytic lymphoma category) which may be histogenetically heterogeneous but nonetheless clinically relevant. With this goal in mind, each of these categories will be addressed individually and compared and contrasted to the proposed category of the small lymphocytic lymphomas.

**B-CLL/B-PLL/B-SLL**

Of the four REAL classification groups to be discussed in this setting, the B-CLL/B-PLL/B-SLL category is most similar to the proposed SLL. These lymphomas are composed of small, round lymphocytes with regular nuclei and have been described as having a “clinically indolent” course. (Although no specific survival data for this group are supplied, it is presumed that the authors of the REAL classification meant a median survival of approximately eight years.) Since they are so similar in nature to the proposed SLL, no further discussion is warranted. It is worth noting, however, that the B-PLL, depending on how it is defined, may not be considered an example of SLL.

**Lymphoplasmacytoid Lymphoma/Immunocytoma**

The REAL classification describes this group as those tumors consisting of “small lymphoid cells that show maturation to plasma cells.” The authors qualify this description, however, by stating that such a definition encompasses a large group of tumors that “may occasionally show maturation to plasmacytoid or plasma cells containing Clg, including B-CLL, mantle cell, follicle center, and marginal zone lymphomas.” Given the diverse group of tumors encompassed by the title “lymphoplasmacytoid lymphoma/immunocytoma,” the REAL authors feel—and we tend to agree—that these tumors may be
classified more appropriately according to their major features. It is our opinion that most of the so-called lymphoplasmacytoid lymphomas/immunocytomas can therefore be more generally categorized under our broad general heading of SLL.

One exception to this rule—acknowledged by the REAL classification—are those cases which appear to be a “distinct disorder of small lymphoid cells that show maturation to plasma cells without features of other lymphoma types” that also “have monoclonal serum paraprotein of IgM type;” in addition, “hyperviscosity may occur.” This particular subset of lymphoplasmacytoid lymphomas basically describes Waldenström’s macroglobulinemia.

Mantle Zone Lymphoma

The REAL classification defines the mantle zone lymphomas (ManZL) as being composed of “small or medium-sized lymphocytes” which, in most cases, have “irregular or cleaved” nuclei. In some cases, the cells are nearly round, and in others they may be very small and resemble small lymphocytes. In essence, then, these are lymphomas of small lymphocytes, and, as such, resemble the proposed SLL quite closely. In fact, the primary histogenetic distinction of the ManZL from the SLL is based on immunophenotypic characteristics; specifically, the ManZL express CD5 but not CD23, whereas the SLL express both CD5 and CD23.

With this histogenetic distinction dividing the ManZL from the proposed SLL, let us examine the clinical differences, if any, that separate these two groups. The ManZL are described as being “moderately aggressive,” with a median survival of three to five years. The SLL, on the other hand, are usually more indolent, with an average survival of approximately eight years. Initially, then, the ManZL appear to be more aggressive than their relatively indolent counterparts, the SLL. However, upon further examination, it becomes evident that under the REAL classification, the ManZL category includes lymphomas composed of cells other than those seen in small lymphocytic proliferations. For example, under the general heading of “Mantle Zone Lymphomas,” the authors of the REAL classification have included cases that have “larger nuclei with more dispersed chromatin and a high proliferation fraction.” The authors accurately state that “these resemble lymphoblastic lymphomas” so much so, in fact, that they go on to include ManZL in the differential diagnosis of acute lymphoblastic leukemias (ALL) [4]. The question then arises whether the distinction between the SLL and the ManZL—that is, the marked difference in clinical survival time—is truly a valid distinction between two types of small lymphocytic proliferations, or whether it is a reflection of the “other” more aggressive types of lymphomas included under the ManZL heading? A definitive answer to this question cannot be ascertained from the manuscript; if, however, the relatively more rapid natural course of the ManZL is secondary to more aggressive subtypes of lymphomas included within that category, then we must be skeptical about accepting this criterion as a valid point of distinction between the ManZL and the SLL. What we may be left with, then, is a purely histogenetic distinction—the immunophenotypic variances previously discussed—as the sole boundary between two categories which are otherwise behaviorally similar, with considerable clinical overlap.

Marginal Zone Lymphomas

Marginal zone lymphomas (MarZL) in the REAL classification are composed mostly of small lymphocytes which, like the ManZL, display a certain degree of nuclear anisocytosis. Because these MarZL frequently present in organs of the mucosal associated lymphoid tissues (MALT), they have sometimes been referred to as MALTomas. In order to analyze the clinical limitations of this category, two questions must be addressed: A) are the lymphomas in this category significantly different from SLL? and B) are most of the cases in this category truly lymphomas?

Keeping in mind the situation encountered with the ManZL, that is, the inclusion of atypical and more aggressive lymphomas in an otherwise small lymphocytic category, let us first address our comparison to those cases of MarZL which are unequivocally lymphomas. By “unequivocally lymphoma,” we mean those cases in which there is evidence of spread beyond the confines of a very limited site. (This definition of lymphoma is submitted at this time only to address the problems associated with the small lymphocytic proliferations in mucosal organs. Clearly, “unequivocal lymphomas” of large-cell morphology which are confined to a very limited anatomic site are frequently encountered).

Within these parameters, the MarZL are actually quite similar to the SLL: A) they are tumors of adults, many of whom have autoimmune disease; B) they tend to have a very indolent course with long disease-free intervals, but generally are thought to be incurable with current treatment modalities (although definitive data on this point are still forthcoming), and, C) on occasion, they may undergo transformation into large-cell lymphomas. In light of the natural history and clinical expression, then, the MarZL and the proposed SLL appear to be very clinically similar disease entities.

The second question to be addressed, though, is whether all of the cases included in the MarZL category are truly lymphomas. In other words, what about those cases which are not “unequivocally” lymphomas? To answer this question fully, one must understand how these cases originally came to be accepted as lymphomas. Judging from the literature, these tumors were initially defined as lymphomas based to a significant degree on evidence of clonality. Biologically, however, most of these cases behave rather peculiarly in
comparison with most other “unequivocal” lymphomas; specifically, many of these MALTomas have not spread to other anatomic sites at presentation. In addition, recent evidence has suggested that many of those lymphomas associated with the stomach are also associated with bacteria and have been found to be curable with antibiotics.

Perhaps in any other case of lymphoid processes associated with bacteria and responsive to antibiotics, and which show no evidence of spread, the diagnosis of inflammation would be acceptable. However, the presence of clonality (noted in most of these cases) presents a significant argument for classifying these processes as lymphomas. Recent publications have shown, though, that even tonsillar follicular hyperplasia may demonstrate some element of clonality, thus proving that clonality per se is not the sine qua non of neoplasia [5]. It is possible then, that the clonal proliferations of MALT lymphocytes represent clonal reactions, while others may be incipient or real neoplasias from their inception. Be that as it may, it is obvious that clonality alone does not predict which of these processes will disseminate and behave as clinical lymphomas.

**Summary of the SLL**

The authors have proposed that one of the subgroups of the low-grade lymphomas be that of small lymphocytic lymphomas. This category, as mentioned earlier, would essentially encompass four of the REAL classification categories: B-CLL/B-PLL/B-SLL; the lymphoplasmacytoid lymphomas/immunocytomas; the ManZL, and the MarZL. As examination of these four categories reveals, each, when looking solely at the cases which fit the clinical and histological criteria respectively for “unequivocal” lymphoma and for small lymphocytic proliferations, is virtually identical to the proposed SLL. The parameters which divide these categories consist primarily of histogenetic criteria. Thus, it is possible to combine the four into one (the proposed SLL category), thereby simplifying the classification of these lymphomas without compromising clinical relevancy.

**Follicular Cleaved Cell (Small and Small, Mixed)**

**Introduction**

In this manuscript, the term “follicular lymphoma” is used to describe a histologic pattern, not a histogenetic concept. In other words, “follicular lymphoma” refers to a lymphoma demonstrating a nodular growth pattern histologically. This definition is in distinction to the *Lukes and Collins* concept of “follicular center cell lymphoma,” a histogenetic term implying that the origin of the lymphoma cells is from the germinal center of the lymph nodes. Although most follicular lymphomas (i.e., nodular lymphomas) are follicular center-cell lymphomas (i.e., derived from cells of the germinal centers), the opposite is not always true; many follicular center-cell lymphomas are not follicular lymphomas, as they do not necessarily demonstrate a follicular pattern of growth.

The cellular composition of follicular lymphomas (as defined above) can be somewhat problematic when one is attempting to create a clinically relevant classification scheme. The follicular lymphomas may consist of predominantly small cleaved cells, a mixture of small and large cleaved cells, or predominantly large cells. Most of the follicular lymphomas clinically behave as low-grade lymphomas, with the probable exception of the follicular lymphomas composed primarily of large cells. Since the latter group tends to behave clinically more like the high-grade lymphomas, it will be classified as such, under the “Large-Cell” heading.

Cellular composition is not the only confounding morphologic variable of these follicular lymphomas; there is also the issue of the diffuse growth pattern that is noted with some frequency in these cases, especially the large-cell type. The data support the view that within the predominantly small cleaved lymphomas and the lymphomas composed of a mixture of the small cleaved and large cells, if the nodular growth pattern is greater than 50% of the specimen, the lymphomas behave like follicular lymphomas. If the nodular growth pattern is less than 50% of the specimen, the tumors may behave more aggressively. Therefore, only those cases that demonstrate >50% nodular growth pattern (keeping in mind the problems of sampling artifact and representativeness) should be included under the category of Follicular, Cleaved Cells.

**Follicular Cleaved Cell (Small and Small, Mixed) versus the REAL Classification**

The REAL classification equivalent of the follicular cleaved cell (small and small, mixed) is the group referred to as “Follicular Center Lymphoma, Follicular.” Before proceeding further, let us clarify that the term “follicular lymphoma,” as it is used here, describes a histologic pattern, not a histogenetic concept.

Again, the REAL classification preserves histogenetic purity at the expense of clinical relevance, as the follicular small cleaved (a low-grade tumor) has been grouped with the follicular large cell (a high-grade tumor) under the same heading apparently because they share similar histogenesis. (For the same reasons, clinically similar groups such as follicular small cleaved and nodular lymphomas of the mantle zone, both of which are low-grade lymphomas, are separated because they are histogenetically different).

In order to deal with the problem of the histologic growth pattern of these tumors, the REAL classification has proposed a provisional category known as “Follicle Center Cell Lymphoma,
Diffuse,” in which the histologic pattern of the node is entirely diffuse—i.e., no nodular growth pattern can be identified. The only apparent reason for creating this category is the fact that the lymphomas in this subgroup, which are otherwise identical to those in the “Follicle Center Cell Lymphoma, Follicular” category, have a worse prognosis than their nodular counterparts.

Interestingly enough, although the REAL classification is sufficiently concerned with prognostic capabilities to create the “diffuse” subclassification for those more aggressive follicular center-cell tumors, it apparently does not seem to feel the same need to subdivide the aggressive follicular center-cell tumors, it apparently does not seem to feel the same need to subdivide the “Follicle Center Cell Lymphoma, Follicular” classification based on the proportion of nodular and diffuse growth patterns, even though this ratio, as expressed in the REAL classification manuscript, “is also related to prognosis.” Why the distinction, then? If the diffuse growth pattern, which indicates a poorer prognosis for the follicular tumors, is enough to warrant its own category, why not also subclassify those tumors which have a poorer prognosis based on the ratio of nodular to diffuse growth patterns? Also, as alluded to earlier, why not separate those follicular tumors which are composed primarily of large cells and which therefore have a poorer prognosis as well?

One possible reason the REAL classification does not make these distinctions may have to do with the perceived difficulty of the recognition by the pathologist of these morphologic parameters. This may be a valid point, but in most follicular lymphomas (nodular growth pattern) in which either the cell size or the proportion of different histologic growth patterns is an issue, a decision on these histologic variables can be reached. Therefore, a clinically relevant classification scheme should take these prognostically significant subgroups and set them apart, rather than incorporating them with other less aggressive low-grade lymphomas merely to preserve histogenetic homogeneity.

Summary of the Follicular Cleaved Cell (Small and Small, Mixed)

Follicular cleaved cell (small and small, mixed) lymphoma is the second proposed subgroup of the low-grade lymphomas. As a rule, it demonstrates a growth pattern with significant nodularity and is composed of variable mixtures of small and large cells. As discussed, it is important that the percentage of nodular versus diffuse growth patterns and the composition of large cells that make up these cases be taken into account in order to identify follicular lymphomas that are prognostically similar. Such differentiation may create distinct categories among histogenetically similar tumors, but the end result is a classification scheme with clinically homogeneous groups.

The High-Grade Lymphomas

The key defining characteristic of these lymphomas, as mentioned earlier, is their aggressive natural history and their paradoxically good response to therapy, which quite often effects complete cures in these patients. The three categories in this group are the large-cell lymphomas, the Burkitt’s lymphomas, and the lymphoblastic lymphomas.

Large-Cell Lymphomas

Introduction

The large-cell lymphomas (LCL) are composed predominantly of large-sized lymphocytes and demonstrate a more aggressive clinical behavior. Their natural history demonstrates a shorter median survival time than that of the low-grade lymphomas, but these tumors tend to respond well to chemotherapy, frequently achieving remissions and even cures. Although most of these cases demonstrate a diffuse growth pattern, large-cell follicular variants should probably also be included in this category.

Large-Cell Lymphomas versus the REAL Classification

The REAL classification system has several categories which would fall under the proposed LCL heading, including Large B-Cell Lymphomas, Peripheral T-Cell Lymphomas, Primary Mediastinal (Thymic) Large B-Cell Lymphomas, Anaplastic Lymphomas, and Angiocentric Lymphomas.

In their manuscript, the authors of the REAL classification make the following observation: “Based on … the difficulty of subclassifying large cell lymphomas on routine histologic sections, and the fact that treatment is currently similar for all types, we believe that with the current knowledge and methods it is impractical to subclassify these tumors, and they should all be designated large B-cell lymphoma” [4].

Such a statement is obviously one to be embraced from a clinical standpoint. However, it is the opinion of these authors that the REAL classification stopped short of an effective goal; that is, instead of merely grouping all of the large B-cell lymphomas, they should have also included, based on “the fact that treatment is currently similar for all types,” the various other categories to be discussed.
For instance, why not also include primary mediastinal (thymic) large B-cell lymphoma if, as described by the authors of the REAL classification, “cure rates similar to that for other large cell lymphomas” are reported? In fact, why limit this approach to the B-cell line? Why not enlarge the category to include entities such as the peripheral T-cell lymphomas which are, according to the REAL classification, “rather aggressive, although potentially curable?” Why not include the angiocentric lymphomas, whose “clinical course appears to depend on the proportion of large cells?” In fact, why not even include the anaplastic large-cell (CD30+) lymphomas in which “the systemic form appears to behave similarly to other large-cell lymphomas?” Each of the aforementioned T-cell lymphomas is an aggressive disease that is potentially curable, just as the B-cell large-cell lymphomas are. The exceptions to this rule are the T-cell lymphomas in patients with a previous history of mycosis fungoides and in patients infected with HTLV-1, both of which should be identified as such.

Burkitt’s Lymphoma

Introduction

These lymphomas tend to be diffuse tumors composed of medium-sized cells with a high mitotic index, a feature associated with a high cell death rate. It is this latter peculiarity that triggers a tissue macrophage response that creates the typical, although not diagnostic, “starry sky” histological pattern. Lymphomas with these features were first described by Dr. Burkitt in Africa, earning them the eponym “Burkitt’s lymphoma.” In some areas of Africa, these lymphomas are endemic, frequently presenting as jaw tumors in very young children. In the U.S., these lymphomas are also seen in children and young adults, and account for approximately 30% of childhood NHL. However, in the U.S., these lymphomas occur sporadically, frequently presenting, especially in children, as ileal masses. This lymphoma, along with the large-cell lymphomas, is also quite prevalent among AIDS patients.

As with other high-grade lymphomas, the Burkitt’s lymphomas have a very aggressive natural history; however, modern therapy can induce lasting remission in over 60% of cases [6]. Unlike large-cell lymphoma, the therapeutic decision in Burkitt’s lymphomas often calls for a more intense chemotherapeutic regimen, often including central nervous system (CNS) prophylaxis. In addition, there is a higher risk of tumor lysis syndrome in these cases.

Burkitt’s Lymphoma versus the REAL Classification

The histologic distinction between Burkitt’s lymphoma and large-cell lymphoma is not always clear. The REAL classification has created a provisional category, “High Grade B-Cell Lymphoma, Burkitt-like,” which may be the perfect solution to ambiguous cases in this area. At times, clinical information may help the diagnosis of one entity or the other; for example, if the lymphoma in question is seen in a young child presenting with an ileal mass, the likely diagnosis given the histologic pattern will be Burkitt’s lymphoma. Since such clear-cut clinical scenarios are not always available, the pathologist should be encouraged to obtain as much clinical information about the patient and the presenting complaints as possible in order to aid his or her decision.

Lymphoblastic Lymphomas

Introduction

Lymphoblastic lymphomas typically present in young patients, usually in the second or third decade of life. At presentation, the patient is often noted to have a large mediastinal mass, rather like T-cell ALL. If left untreated, a hematologic picture of ALL frequently develops, with involvement of the bone marrow and peripheral blood.

Histologically, these lymphomas consist of medium-sized cells with finely stippled nuclear chromatin similar to the blasts of ALL. The tumor shows a high mitotic rate which may impart a “starry sky” pattern similar to Burkitt’s lymphoma.

When first described in the mid-70s, the median survival of these lymphomas was approximately 8-17 months, with a few long-term survivors. Recognition of the close association with ALL has led to therapy adjustment. Today these lymphomas are treated with protocols similar to those for ALL, which has significantly increased the average survival period; now patients with lymphoblastic lymphoma have a 40% five-year survival rate [7].

Lymphoblastic Lymphomas versus the REAL Classification

The REAL classification has three groups which are equivalent to the proposed lymphoblastic lymphoma group: immature B-cell lymphoblastic lymphoma, “blastic” variant of mantle zone, and T-cell lymphoblastic lymphoma. The prognostic significance of segregating these cases into these groups is unclear clinically, as are any therapeutic distinctions based on lymphoblastic cell subtype.

SUMMARY

The most important message the authors are trying to convey in this paper is that clinically based classification schemes which are both simple and relevant can be achieved. We have tried to demonstrate the biases of the
scientific community toward histogenetically based schemes, biases historically founded within the framework of linear dynamics theory. At the same time, however, pathologists should familiarize themselves with non-linear dynamics, a theory that acknowledges and accepts a degree of inherent unpredictability within nature. It is within this more lenient framework of the “mathematics of chaos” that clinically based classification schemes find their legitimacy—a legitimacy, it should be noted, every bit as valid as its histogenetic counterparts.

Although the medical profession has heretofore maintained a somewhat skeptical attitude toward clinically based schemes, we have tried within the confines of these pages to not only establish the legitimacy of just such schema, but also to point out their efficacy. A simpler classification scheme that is clinically relevant is most helpful in the interaction between pathologist and clinician, and thus ultimately greatly benefits the patient. The pathologist may still call upon other classification schemes, such as the REAL classification system, to expound upon the nuances of the histogenetic and immunologic, and other characteristics of the lymphoma in question. However, as far as conveying the important information to the clinician, i.e., the natural history of the lymphoma and its response to therapy, a simple, clinically relevant scheme is essential.

What the REAL classification system effectively does is preserve the homogeneity of groups based largely on immunophenotyping; clinical heterogeneity is effectively ignored. Issues of immunophenotypic false positivity, false negativity, variance in testing from lab to lab, and complexity of interpretations are also neglected.

What we propose is to maintain clinical homogeneity of grouping while being less rigorous about the immunophenotyping process. We do recognize that we are presently in a transition period during which the shift is moving away from classic morphology. We question the wisdom of compromising the clinical homogeneity of these newer immunophenotyping studies the value of which on a routine basis (as opposed to a selected process) is uncertain.

We wish to emphasize that monoclonality does not necessarily mean clonogenicity and also to remind the reader that the fundamental problem both clinically and microscopically in lymphoma is to distinguish reliably malignant lymphoproliferative processes from inflammation.

It is clear to us that the proposed scheme presented in this manuscript is not the only clinically valid one that can be constructed; however, it is equally clear that any scheme that is developed, in order to be considered valid, must be guided principally by its clinical relevance.

**A simpler classification scheme that is clinically relevant is most helpful in the interaction between pathologist and clinician, and thus ultimately greatly benefits the patient.**

REFERENCES


