REVIEW OF LYMPHOMA CLASSIFICATION

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Key words: Historical review; Lymphoma Classification;

ABSTRACT

Lymphomas are malignant neoplasms characterized by the proliferation of cells native to the lympoid tissue i.e lymphocytes, histiocytes and their precursors and derivatives. These heterogenous neoplasms are of the monoclonal origin. Lymphoma have been broadly classified into two main categories; Hodkin disease (HD) and non-Hodgkin lymphoma (NHL). Where as HD has had a fairly stable classification scheme over the years since Rye classification into being, NHL has had the most unstable classification schemes. First to come into being were Gall and Mallory, Rappaport and Doffman classifications. Others that followed later were Benneth, farrer- Brown Henry, Lukes Collins and Kiel classifications which were later harmonized by a working formulation for clinical usage. The last to come into being was the REAL classification which has been modified and adopted by the W.H.O. The working forrmulation for clinical usage is still the most workable classification for our own environment.

INTRODUCTION

Lymphomas are heterogenous group of lymphoid disorders that are common in our environment. They are a very important group of diseases because they affect all age groups and while some are indolent, some are very aggressive. While most of them are localized to the lymphoid organs, some are seen in non lymphoid organs like the brain and serious cavities. A very accurate classification scheme of prognostic and therapeutic significance is therefore necessary. The aim of this review, therefore, is to highlight the previous classification schemes, their pitfalls and to up date our selves with the current classification scheme

Definition: lymphomas are malignant neoplasms characterized by the proliferation of cells native to the lymphoid tissues i.e lymphocytes and histiocytes and their precursors and derivatives. Like other neoplasms, lymplomas are of monoclonal origin. Primarily they include malignant lymphoreticular neoplasms that are localized at the time of diagnosis and arise preferentially in the lymp node. The systemic and leukaemic proliferations are not included under the lymphomas.

CLASSIFICATION SCHEME

The lymphomas have been broadly classified in to two; Hodgkin disease (HD) and non Hodgkin lymphomas (NHL). Where as HD has had a more stable classification scheme with very few evolutional changes, NHL has had the most unstable classification schemes. This had led to considerable confusion in various countries as to which classification scheme to follow.

HODGKIN DISEASE

Unlike the NHL, the evolution of HD has been relatively more stable. Its classification scheme has undergone only a few changes over the years.

Jackson and parker classification

This was first proposed in 1947 and classified HD into 3 groups:

i. Hodgkins paragranuloma
ii Hodgkin granula
iii Hodgkin sarcoma

This suffered a lot of criticisms as it lacked sufficient detail for clinical use

Rye classification:

Lukes and associates brought up the proposal for this classification which was

recommended at the conference on HD in Rye, York in September 1965.

HD was classified into four subtypes:

i Lymphocyte predominant
ii mixed cellularity
iii Lymphocyte depleted
iv nodular scleroses

Since then the 4 subtypes have been universally accepted until a few years ago when on an entity was added; the lymphocyte rich sub type.

Current HD classification:

i Lymphocyte predominant
ii Mixe cellularity
iii Lymphocyte depleted
iv Nodular scleroses
v Lymphocyte rich

The most distinctive feature of H D is the presence of neoplastic giant cells called the Reed-Sternberg (RS) cells and its variants mixed with a variable inflammatory infiltrate.

NON HODGKIN'S LYMPHOMA (NHL)

NHL'S are a diverse group of neoplasms for which a classification has evolved through the 20th century based on new clinical entities and new diagnostic and pathologic techniques.[4] Few areas of pathology have as much controversy as confusion and the classification of NHL. Regrettably, even among expert "Lymphomaniacs" there has been no unanimity regarding the best approach, and until the recent past there were more classifications than experts[1]

Gall and Mallory classification.

One of the earliest classification schemes was that proposed by Gall and Mallory in 1942 which was based on cytology and used the following terminology for malignant lymphomas of the non Hodgkin's types.[4]

i Reticulum cell sarcoma
Ii Lymphosarcoma
iii giant follicular lymphoma

This classification system however lacked sufficient detail for clinical use. It did not give the clinician any clue to whether it was an aggressive tumor or an indolent type and it also had no prognostic value.

Rappaport classification

This was proposed in 1966 and it was based upon two marpolic features; the cytologic appearance of the cells as seen in routine histology and growth pattern of the cells as nodular or diffuse infiltration through out the node. When this classification was presented by Rappaport, knowledge about lymphocyte subsets, their activation and their specific anatomic location was in its rudimentary stage. Thus the classification system identified lymphocyte and histiocyte tumours. The lymphocyte tumours were graded as well differentiated tumours.

The Rappaport classification was widely employed in the United States because it was readily learned and highly reproducible and more importantly because it was clinically useful. For example, a multitude of clinic pathologic studies has redemonstrated that nodular architecture is associated with a prognosis that is significantly superior to that of the diffuse pattern.

However in the early 1970's a better understanding of the immune system raised questions regarding the scientific validity of Rappaport's classification. Therefore 3 important points were raised.

1. It was now clear that lymphocytes found to be morphologically identical were functionally heterogenous. Two classes of lymphocytes (T&B) and several subpopulations were identified and this classification related the NHLs to these normal populations.
2. Transformed lymphocytes look deceptively similar to histiocytes and thus the vast majority of the histioaticocytic lymphomas were later found to be related to transformed lymphocytes rather than macrophages.

3. The criteria for characterizing lymphocytes as well differentiated, moderately differentiated or poorly differentiated was not satisfactory. With the above short comings in Rappaport's classification, many classification systems emerged between 1973 and 1974 but most prominent were Lukes Collins and Kiel classifications. Others were Dorfmans and Bennette, farrer-brown and Henry classifications.

Table 1: Rappaport Classification

Nodular	Diffuse
Lymphocytic lymphoma	Lymphocytic lymphoma
Poorly differentiated	Poorly differentiated
Moderately differentiated	Moderately differentiated
Well differentiated	Well kdifferentiated
Lymphoma, mixed cell type Reticulum	Lymphoma, mixed type Reticulum
Cell sarcoma	Cell sarcoma undifferentiated, Burkitts and non Burkitts.

Dorfman Classification

Dorfman in his proposal recognized the work of Jaffe et al which illustrated the role of new immunology techniques in the identification of cellular elements comprising the nodular lymphomas and provided evidence supporting their origin from follicular B lymphocytes. Dorfman criticized the validity of differentiation of lymphocytes and the origin of the histiocytic tumours as stated in Rappaport classification. He then proposed a classification system that grouped NHLs into follicular and diffuse types. See table 2. This classification does not give sufficient clinicopathological correlation since not all diffuse NHLs had the same prognosis.

Table 2: Dorfman's classification

Follicular	Diffuse
Small lymphoid	Small lymphocytic (SL) (CLL)
Mixed small and large lymphoid	Atypical small lymphocytic
Large lymphoid	Convuloted lymphocytic (thymic)
	Large lymphoid
	Mixed small and large lymphoid
	Histiocytic
	Burkitts lymphoma
	Mycosis fungoides,
	Undefined

Bennett, farrer - Brown and Henry Classification

This classification was first presented in 1973 before the Dorfman classification at a workshop on classification of NHLS in, however this was represented after the emergence of Dorfman classification.[7] In this classification, apart from dividing the NHLs into follicular and diffuse types , it also graded them into 2 grade. This had a slight advantage over Dorfman classification because of the attempt at prognosticating which led to the grading.

Table 3: Benett, Farerr- Brown and Henry Classification

Follicular lymphomas	
Follicle cell predominantly small	
Follicle cell mixed small and large	
Follicle cell predominantly large	
Diffuse lymphomas	GRADE ONE
Lymphocytic well differentiated	
Lymphocytic intermediate differentiation	
Lymphocytic poorly differentiated	
Mixed small lymphoid and undifferentiated L.C	
Undifferentiated large cell	
Plasma cell	GRADE TWO
True histiocytic	
Unclassified	

Lukes Collins classification (1973)

The recognition that NHL tumours were neoplasms of the immune system led to the development of immunologically based classification system.[8] (to correlatel lymphoid neoplasms to normal B- cell and T- cell encounter parts the Lukes- Collins and kiel classification were develop.[8] these classification systems were similar).

Lukes Collins classified NHLs into 3 categories: Tumours of T-cells, B- cells or histiocytes. These authors also sought correlation between cytological patterns in lymphomatous nodes and those evoked by antigenic challenge of lymphocytes. In the germinal centres of lymph nodes, 4 distinctive morphologic stages can be identified in the process of transformation of small resting B cells into immunoblasts. These stages include (1) small-cleaved cells, (2) large cleaved cells. (3) small non cleaved cells and (4) large non cleaved cells (see fig 1). These cells differ with respect to cell size, nuclear configuration (clefts or folds), nuclear chromatin pattern, number of nucleoli and decree of mitotic activity. The large non-cleaved FCC cleave and leave the follicle to further enlarge and become immunoblasts from where we get either plasma or cells or small memory B cells.

It has been proposed that B cell tumours may be composed of cells arrested along this differentiation pathway.

Lukes also proposed that the nodular Architecture in certain lymphomas is related to their origin from germinal centres (FCC) and also as an attempt to reproduce (differentiate) a normal structure. Now immunophenotyping and molecular studies have confirmed the B-cell origin of nodular lymphomas unlike before when it was only based primarily on morphological studies.

However in this classification system there was no emphasis about the clinical and prognostic significance of relating these tumours to their normal counterparts in immune system. It was also observed that immunologically homogenous categories were not of uniform clinical behaviour. The majority (65 to70%) of NHLs are of B-cell origin but there is a great variation in their prognosis.[1] Follicle lymphomas at one extreme were highly aggressive. It was therefore clear that histogenic similarity does not translate into uniform prognosis.

Table 4: Lukes Collins classification

I undefined cells

II T.cell types
1. convoluted lymphocyte
2. immunoblastic

III B. cells types
1. small lymphocytic (CLL)
2. plasymacytoide lymphocyte
3. FCC (follicular,diffuse,and follicular and diffuse and sclerotic)
   (a) small cleaved
   (b) large cleaved
   (c) small non- cleaved
   (d) large non- cleaved
   (e) large non- cleaved
4. Immunoblastic sarcoma (B. cell)

Kiel classification (1974)

The kiel classification was similar to Lukes collin classification. It was proposed in 1974 based on the concept of K. lennert and of R. Lukes by Gerard merchant and co- workers including Lennert himself. These workers criticized Dorfmans classification based on the facts that the terms like "mixed small and large lymphoid" are purely descriptive they convey nothing about malignancy of the tumour to the clinician.[9] The kiel classification suffered similar criticism like the Lukes Collins classification. In addition, it was also observed that some NHLs grouped as low grade and high grade could actually be of intermediate grade if properly studied.

Table 5: kiel classification

Low- grade malignancy	cell type
Lymphocytic (CLL)	B or T
Lymphoplasmacytic	B
Plasmacytic	
FCC Tumours (predominantly centrocytic)	B
Follicular	
Diffuse	
High grade malignancy	
Lymphoblastic	B or T
Burkitts type	
Convoluted	
Large cells	
Immunoblastic	B or T
Centroblastic	B
Others	

The working formulation by WHO

Following the lack of consensus that existed as to which system was satisfactory that led to confusion and controversy, there was need to unify terminology and development of consensus. In that attempt the working formulation for clinical use was proposed in1982. This identified specific lymphoma subtypes with alphabetical letters (A to J) and grouped them into three clinical prognostic groups (low intermediate and high).

This classification was based solely on morphologic criteria, particularly the pattern of tumour growth within lymph nodes (nodular or diffuse) and cell size (small, large or mixed). This approach had the advantage of being simple and has been widely used. However, further immunophenotypic and genotypic characterisation of lymphoid neoplasms made it clear that a number of distinct entities had been lumped together or completely ignored in the working formulation (e,g mantle cell lymphoma and marginal zone lymphoma), which have proven to be fairly unique in their clinical behaviour and response to therapy.[10] A division then occurred in the acceptance of the new classification and the working formulation was only adopted by North America and some Afro-Asian countries.

TABLE 6: The working formulation (WHO)

Low grade

(a) Small lymphocyte

(b) Follicular predominantly small cleaved cells

(c) Follicular mixed small cleaved and large cells

Intermediate Grade

(d) Follicular predominantly large cells

(e) Diffuse small cleaved cells

(f) Diffuse mixed small and large cells

(g) Diffuse large cells

High Grade

(h) Large cell immunoblast

(i) Lymphoblastic

(j) Small non cleaved cells

REAL classification

In 1993, the international lymphoma study group (ILSG) met in Berlin, Germany and attempted to arrive at a consensus regarding the categories of lymphoid neoplasms that could be reliably recognised at that time. The group found that initially, identical diseases were given different names and had variable criteria for diagnosis among the currently used classification systems.[12] Ideally lymphomas should be classified according to their presumed normal counterparts to provide the best information about disease biology, natural history and response to treatment. However, defining lymphoid compartments in humans and identifying movement of cells between these compartments is fraught with uncertainties. Additionally some well-defined lymphoma types lack obvious normal counterparts. Therefore our current understanding of both the immune system and lymphomas appears to be inadequate to support a biologically current lymphoma classification. The ILSG concluded that the most rational approach to lymphoma categorisation was to define the disease based on currently available morphologic and genetic techniques as well as clinical

presentation that define a distinct entity. This compilation was called the **RevisedEuropean American classification of lymphoid neoplasm or REAL classification.**

This classification is simply a list of well-defined" Real" disease entities. Many of these entities have distinctive clinical presentation and natural histories. See tables 7 and 8.

Table 7: REAL classification

*	Precursor	B or T cells Neoplasms
		B lymphoblastic leukaemia (lymphoma)
		T lymphoblastic (Leukaemia)
*	Peripheral	B- cell Neoplasm
		CLL/SLL
		Lymphoplasmacytic lymphoma
		Manttle cell lymphoma
		Follicular lymphoma (Grade I-III)
		Marginal zone lymphoma
		Hairy cell leukaemia
		Plasmacytoma/ myeloma
		Burkitts lymphoma
+	Peripheral	T. cell and natural killer cell neoplasms
		T. cells CLL
		Large granular lymphocytic leukaemia
		Mycosis fungoides and sezary syndrome
		Pheripheral T. cell lymphoma unspecified
		Angio immunoblastic T-cell lymphoma
		Angioncentric lymphoma (NK/T-cell)
		Intestinal T- cell
		Adult T- cell leukaemia /lymphoma
		Anaplastic large cell lymphoma

WHO/REAL classification

A project to update and revise the REAL system was initiated by the world Health Organisation (WHO) in 1995. Its consensus was published in 1999. The WHO classification, like REAL, incorporates a number of tumour characteristics and is designed to enable disease identification by pathological examination while maintaining clinical relevance. With the use of the WHO classification, treatment is determined by the identifying the specific lymphoma type and, if relevant, by considering tumour grade and other prognostic factors.[13, 14]

CONCLUSION

This review has identified some common factors in the evolution of NHL classification. There is general consensus on the following:

1. Lymphomas can be nodular (follicular) or diffuse
2. The cells could be either large or small.
3. Most lymphomas are derived either from T-cells, B-cells or macrophages.
4. Some of these lymphomas are indolent while others are aggressive.
5. It is also clear from this review that the most workable classification system for our environment is the working formulation for clinical usage. This is because it is based solely on morphology and clinical features which is what is available to us and also because it is simple and easily comprehensible to our clinicians.

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