MINI REVIEW

Update on classification of lymphomas

Robin Sabharwal, Keya Sircar[1], Shamindra Sengupta, Bhudev Sharma

Department of Oral Pathology and Microbiology, D. J. College of Dental Sciences and Research, Ghaziabad, Uttar Pradesh, [1]Department of Oral Pathology and Microbiology, Faculty of Dentistry, Jamia Millia Islamia, New Delhi, India

ABSTRACT

Lymphomas constitute approximately 5% of all malignant neoplasms of the head and neck. They are divided into two major subtypes, Hodgkin's lymphomas and non-Hodgkin's lymphomas, depending on the presence or absence of Reed–Sternberg cells. Controversy in the classification of lymphomas dates back to the first attempts to formulate such classifications. Much of this controversy arose from the assumption that there must be a single guiding principle, a "gold standard" for classification. Earlier classifications of lymphomas were based on the morphology, treatment response, and survival and some were based on cell lineage and differentiation. The International Lymphoma Study Group (I.L.S.G.) developed a consensus list of lymphoid neoplasms, which was published in 1994 as the "Revised European-American Classification of Lymphoid Neoplasms" (REAL). The classification was based on the principle that a classification is a list of "real" disease entities, which are defined by a combination of morphology, immunophenotype, genetic features, and clinical features and there cannot be a single "gold standard."

Key words: Classification, lymphoma, Reed-Sternberg cells, reticuloendothelial system

Introduction

The malignant lymphomas constitute a group of neoplasms of varying degrees of malignancy, derived from the basic cells of lymphoid tissue, the lymphocyte, and histiocytes in any of their developmental stages.

Lukes defined malignant lymphoma as "a neoplastic proliferative process of the lymphopoietic portion of the reticuloendothelial system, that involves cells of either the lymphocytic or histiocytic series in varying degrees of differentiation, that occurs in an essentially homogeneous population of a single cell type." The character of histological involvement is either diffuse (uniform) or nodular form and the distribution of involvement may be regional or systemic (generalized); however, the process is basically multicentric in character.[1]

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The main cells of the immune system are the T and B lymphocytes that arise from the thymus and the bone marrow, respectively. On maturation, these cells pass into reticulo-endothelial system.[2]

The reticulo-endothelial system includes the following:
Primary lymphoid organs: The primary lymphoid organs are involved in lymphocyte development. They include the bone marrow and the thymus.
Secondary lymphoid organs: After maturation, lymphocytes migrate to the secondary lymphoid organs, which include the spleen, lymph nodes, and mucosa associated lymphoid tissue (MALT).

The Thymus

The thymus is a bilobed structure organized into cortical and medullary areas. The cortex is densely populated with immature T cells, which migrate to the medulla to undergo selection and maturation.[3]

Lymph Nodes

The major compartments of the lymph node include the cortex, par cortex, medullary cords, sinuses, and the connective tissue framework.[4,5]

Corresponding Author: Dr. Robin Sabharwal, D.J College of Dental Sciences and Research, Ghaziabad, Uttar Pradesh, India.
E-mail: robin.sabharwal@yahoo.co.in

The Cortex

The cortex is predominantly B cell region of lymph node. Scattered in the cortex are primary follicles (rounded aggregates of small lymphocytes with round or irregular nuclei) and secondary follicles (with germinal center). Within days of antigenic stimulation, the primary follicles enlarge and are transformed into pale staining germinal centers.[6] In some reactive conditions, a rim of B cells with slightly more cytoplasm accumulates outside of the mantle zone; cells occupying this region are called marginal zone B cells.[7,8]

Both the primary and secondary follicles are rich in follicular dendritic cells.[9] In the germinal centers, besides the predominant component of B cells in the center, large non-cleaved cells (centroblasts) and small cleaved cells (centrocytes) as well as small T lymphocytes and tingible body macrophages are present. Occasionally, plasma cells can be found within the germinal centers.[10]

Medullary Cords

The medullary cords are packed with mature plasma cells and contain both B and T lymphocytes.

The Paracortex

It is the zone between the peripheral cortex and inner medulla. Paracortex is the T zone of lymph node. It is rich in endothelial venules and is populated predominantly by T cells (CD4+ more than CD8+) admixed with occasional immunoblasts. Isolated B lymphocytes and plasma cells are also present.[11,12]

Paracortex hyperplasia typically occurs in response to viral infection, hypersensitivity state, or regional tumor. Nodules (T nodules) are sometimes formed and closely about the B cell follicles, together forming the so called composite nodules.[13]

Sinuses

Multiple afferent lymphatics drain into the lymph node from the convex side. They drain into sub-capsular sinuses, which are connected with cortical and medullary sinuses and then drain out of the node via an efferent lymphatic at the nodal hilum. The sinuses often contain histiocytes and some lymphoid cells.[14,15]

Connective Tissue Framework

The lymph node is contained in a thin fibrous capsule, which is in continuity with fibrous trabeculae that penetrate the node.

Classification of Lymphomas

Lymphoma classification has been the subject of numerous debates. Some classifications have stressed the practical and clinical aspects of lymphomas, emphasizing morphological approaches and clinical behavior. Others have stressed more biological issues, often including schemes based on putative cell of origin and cellular differentation pathways, emphasizing on immunological and molecular biological studies.[16,17]

Rappaport Classification

Henry Rappaport and colleagues proposed the first modern classification of non-Hodgkin lymphoma in 1956. They emphasized that the classification should be clinically useful, scientifically accurate, reproducible, and easily taught and learned. Rappaport divided non-Hodgkin's lymphoma (NHL) into two major subtypes:[18,19]

Nodular, which retain some of the features of a normal lymph node. The neoplastic cells form lymphoid nodules rather than lymphoid follicles with germinal centres.

Diffuse, which is characterized by effacement of the normal lymph node architecture and possible infiltration of neoplastic cells outside the capsule of the involved lymph node.

NHL was further classified according to the degree of differentiation of neoplastic cells into well-differentiated, poorly differentiated, and histiocytic types.

Nodular NHL
- Lymphocytic, well-differentiated
- Lymphocytic, poorly differentiated
- Lymphocytic and histiocytic, mixed

Diffuse NHL
- Lymphocytic, well-differentiated
- Lymphocytic, poorly differentiated
- Lymphocytic and histiocytic, mixed

Histiocytic
- Lymphoblastic
- Diffuse undifferentiated, Burkitt's, and non-Burkitt's

The objections to this classification included the following:[20,21]

The term histiocytic lymphoma was found incorrect

since almost all lymphomas were of lymphoid origin. With the identification of T and B cells and their subpopulations made possible, the Rappaport classification was found to be incomplete as regards to the cell of origin of different subtypes of NHL.

Lukes and Collins Classification (1974)

In 1974, Lukes and Collins[22] introduced the first lymphoma classification based on the cell of origin and alterations in lymphocyte transformation. They identified that the majority of the malignant lymphomas were B-lineage neoplasms. New cytological terms like small and large cleaved cells and small and large noncleaved cells, related to the normal germinal center cells were introduced. In addition, the term immunoblastic sarcoma was first used. This classification system does not consider the tissue architecture.

U Cell (Undefined) Cell Type

T cell types
- Mycosis fungoides and Sezary syndrome
- Convoluted lymphocyte
- Immunoblastic sarcoma (of T cells)
- Hodgkin's disease

B cell type
- Small lymphocyte (CLL)
- Plasmacytoid lymphocyte
- Follicular center cell (FCC) types (follicular, diffuse, follicular, diffuse, and sclerotic)
- Small cleaved
- Large cleaved
- Small non-cleaved
- Large non-cleaved
- Immunoblastic sarcoma (of B cells)
- Histiocytic type
- Unclassifiable

Kiel Classification (1974)

This classification was a modification of concept proposed by Lennert and Luke. Lymphomas were divided into low grade and high grade variants. In general, low grade neoplasms were composed of cells with more mature cytological characterstics as indicated by frequency of suffixes "cystic" or "cytoid," while the high grade lymphomas were composed of cells with immature cytologic characterstics as indicated by the frequency of the suffix "blast." The Kiel classification introduced the term "centrocytes" equivalent to Lukes and Collins "cleaved cells" and "centroblasts" equivalent to "non-cleaved cells."[23] In 1988, the Kiel classification was extensively updated [Table 1].[24] This revision contained several major changes from its original 1974 version. In this the primary seperation was now done according to cell lineage, clearly distinguishing between B and T cell neoplasms.

Low-grade malignancy
- Malignant lymphoma—Lymphocytic (CLL and others)
- Malignant lymphoma—Lymphoplasmacytoid (immunocytic)
- Malignant lymphoma—Centrocytic
- Malignant lymphoma—Centroblastic-Centrocytic-follicular, follicular and diffuse, with and without sclerosis

High-grade malignancy
- Malignant lymphoma—Centroblastic
- Malignant lymphoma—Lymphoblastic
- Burkitt type
- Convoluted cell type
- Malignant lymphoma—Immunoblastic

Working Formulation of NHL for Clinical Usage

The working formulation of NHL is essentialy a modified Rappaport classification utilizing updated, expanded categories with altered terminology. Critique of working formulation was offered by Lennert and Lukes. Both pointed out that entitites that were biologically unrelated were grouped together (diffuse mixed and diffuse large). One more criticism of this classification was the lack of

Table 1: Updated Kiel Classification Of Non-Hodgkin's Lymphoma (1988)[24]

B cell	T cell
Low grade	**Low grade**
Lymphocytic-chronic lymphocytic and prolymphocytic leukemia; hairy cell leukemia	Lymphocytic-chronic lymphocytic and prolymphocytic leukemia
Lymphoplasmacytic/cytoid	Lymphoepithelioid
Plasmacytic	Angioimmunoblastic
Centroblastic/centrocytic	T zone
Centrocytic	Pleomorphic, small cell
High grade	**High grade**
Centroblastic	Pleomorphic, medium and large cell
Immunoblastic	Immunoblastic
Large cell anaplastic	Large cell anaplastic
Burkitt lymphoma	
Lymphoblastic	Lymphoblastic
Rare types	Rare Types

capability to be updated. The term "Working" implied that the classification was temporary and could be modified as necessary. However, this has not occurred until date, perhaps because the working formulation was established by a study group no longer in existence.[25]

Low Grade

- Small lymphocytic, consistent with CLL, plasmacytoid
- Follicular, predominantly small cleaved cell, diffuse areas, sclerosis
- Follicular, mixed small cleaved and large cell, diffuse areas, sclerosis

Intermediate Grade

- Follicular, predominantly large cell, diffuse areas, sclerosis
- Diffuse, small cleaved cell, sclerosis
- Diffuse, mixed small and large cell, sclerosis, epithelioid cell component
- Diffuse, large cleaved cell, non-cleaved cell, sclerosis

High Grade

- Large cell, immunoblastic, plasmacytoid, clear cell, polymorphous, epithelioid cell component
- Lymphoblastic, convoluted, non-convoluted
- Small non-cleaved cell, Burkitt's, follicular areas

Miscellaneous

Composite, mycosis fungoides, histiocytic, extramedullary plasmacytoma, unclassifiable, and others

Proposed WHO Classification of Lymphoid Neoplasms

Difficulties in lymphoma classification arose from the assumption that there had to be a single guiding principle, a "gold standard," for classification. The International Lymphoma Study Group (I.L.S.G.) developed a consensus list of lymphoid neoplasms, which was published in 1994 as the "Revised European-American Classification of Lymphoid Neoplasms" (R.E.A.L.). The classification was based on the principle that a classification is a list of "real" disease entities, which are defined by a combination of morphology, immunophenotype, genetic features, and clinical features. The relative importance of each of these features varies among diseases, and there cannot be any one "gold standard."[26]

In some tumors, morphology is paramount, in others, it is immunophenotype, a specific genetic abnormality or clinical features. An international study of 1300 patients, supported by the San Salvatore Foundation, was conducted to determine whether the R.E.A.L. classification could be used by expert pathologists and whether it had clinical relevance. Since 1995, the European Association of Pathologists (EAHP) and the Society for Hematopathology (SH) have been developing a new World Health Organization (WHO) classification of hematologic malignancies using an updated R.E.A.L. classification for lymphomas and applying the principles of the R.E.A.L. The International Lymphoma Study showed that the R.E.A.L classification could be used by pathologists, with inter-observer reproducibility better than for other classifications (>85%). Immunophenotyping was helpful in some diagnoses, but not required for many others.[27]

Based on experience with the R.E.A.L classification for several years and on input from the committees, several changes were proposed for the WHO version. These included some changes in nomenclature, splitting some categories that were believed to be heterogeneous and adopting some "provisional" entities as "real."[28]

B Cell Neoplasms

1. Precursor B cell neoplasm
   Precursor B lymphoblastic leukemia/lymphoma (precursor B cellacute lymphoblastic leukemia)
2. Mature (peripheral) B cell neoplasms:
   B cell chronic lymphocytic leukemia/small lymphocytic lymphoma
   B cell prolymphocytic leukemia
   Lymphoplasmacytic lymphoma
   Splenic marginal zone B cell lymphoma (6 villous lymphocytes)
   Hairy cell leukemia
   Plasma cell myeloma/plasmacytoma
   Extranodal marginal zone B cell lymphoma of MALT type
   Nodal marginal zone B cell lymphoma (6 monocytoid B cells)
   Follicular lymphoma
   Mantle cell lymphoma
   Diffuse large B cell lymphoma
   Mediastinal large B cell lymphoma
   Primary effusion lymphoma
   Burkitt lymphoma/Burkitt cell leukemia

3. T and NK Cell Neoplasms
   Precursor T cell neoplasm
   Precursor T lymphoblastic lymphoma/leukemia (precursor T cellacute lymphoblastic leukemia)
   Mature (peripheral) T cell neoplasms**
   T cell prolymphocytic leukemia
   T cell granular lymphocytic leukemia
   Aggressive NK cell leukemia
   Adult T cell lymphoma/leukemia (HTLV11)
   Extranodal NK/T cell lymphoma, nasal type
   Enteropathy-type T cell lymphoma
   Hepatosplenic T cell lymphoma
   Subcutaneous panniculitis-like T cell lymphoma
   Mycosis fungoides/Sezary syndrome
   Anaplastic large cell lymphoma, T/null cell, primary cutaneous type
   Peripheral T cell lymphoma, not otherwise characterized
   Angioimmunoblastic T cell lymphoma
   Anaplastic large cell lymphoma, T/null cell, primary systemic type
4. Hodgkin lymphoma (Hodgkin's disease)
   Nodular lymphocyte predominance Hodgkin's lymphoma
   Classical Hodgkin's lymphoma
   Nodular sclerosis Hodgkin's lymphoma (Grades 1 and 2)
   Lymphocyte-rich classical Hodgkin's lymphoma
   Mixed cellularity Hodgkin's lymphoma
   Lymphocyte depletion Hodgkin's lymphoma

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