Lymphoma classification: a still ongoing journey

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Dedicated to the memory of Prof. Dr. Med. Dr. m.h.c. Karl Lennert (1921-2012), my Mentor and Friend
Rappaport’s Classification 1956 and 1966

Very simple with some clinical impact
One-man vision
Histogenetically incorrect:
Well and poorly differentiated
Histiocytic
In 1974, after the London Conference in 1973, several new classification proposals were published in The Lancet. In fact, it was felt that the Rappaports’ one was inadequate in the light of new immunology data.
Lukes and Collins Classification, 1974

Histogenetically sound

No immediate clinical-prognostic impact
THE LANCET, AUGUST 17, 1974

PROPOSED CLASSIFICATION OF NON-HODGKIN’S LYMPHOMA

Kiel classification

Low-grade malignancy
Malignant lymphoma (M.L.)—lymphocytic (C.L.L. and others)
M.L.—lymphoplasmacytoid (immunocytic)
M.L.—centrocytic
M.L.—centroblastic—centrocytic

High-grade malignancy
M.L.—centroblastic
M.L.—lymphoblastic
Burkitt type
Convoluted-cell type
Others
M.L.—immunoblastic

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R. GERARD-MARCHANT.
IRIS HAMLIN.
K. LENNERT.
F. RILKE.
A. G. STANSFELD.
J. A. M. VAN UNNIK.

Signing off on the Kiel classification.
Novelty I: based on physio-pathologic concepts and provided with prognostic value
Novelty II: strict correlation with clinics

Prof. Dr. Med. Günter Brittinger
Novelty III: based on consensus
European Lymphoma Club

R. Gerard-Marchant.
Iris Hamlín.
K. Lennert.
F. Rilke.
A. G. Stansfeld.
J. A. M. van Unnik.
1978: Malignant Lymphomas Other Than Hodgkin’s Disease.
Letter: Classification of non-Hodgkin's lymphomas.
Kay HE.

A practical classification of lymphomas.
Higby DJ.
National Cancer Institute Sponsored Study of Classifications of Non-Hodgkin’s Lymphomas

Summary and Description of a Working Formulation for Clinical Usage

THE NON-HODGKIN’S LYMPHOMA PATHOLOGIC CLASSIFICATION PROJECT*

An international multi-institutional clinicopathologic study of 1175 cases of non-Hodgkin’s lymphoma sponsored by the National Cancer Institute has been completed. Histologic slides and clinical records were examined from previously untreated patients seen during the period between July 1971 and December 1975 at four institutions, three in the United States and one in Italy. The reproducibility and clinical relevance of the six major classifications of the non-Hodgkin’s lymphomas was tested by six “expert” pathologists, each a proponent of a major classification, and six very experienced pathologists not identified with one of the major classifications. Immunologic methods were not employed in the study design. A summary of the methods employed and the conclusions of the study is described. The major conclusion was that all six classifications were valuable and comparable in reproducibility and clinical correlations. The clinical significance of a follicular architecture, independent of cell type was confirmed. A working formulation of non-Hodgkin’s lymphomas is described which separates the disease into ten major types utilizing morphologic criteria only. Subtypes are also described which allow translation of all of the major classifications into comparable groups. Histologic criteria are presented for each major type and equivalent terms are given for each type in the six major classifications. The formulation is not proposed as a new classification but a means of translation among the various systems and to facilitate clinical comparisons of case reports and therapeutic trials. The report contains commentaries by five of the “expert” pathologists on the value and conclusions of this unique study.

Working Formulation for clinical usage

Low-grade

A. Small lymphocytic (consisted with CLL, plasmacytoid)
B. Follicular (predominantly small cleaved, diffuse areas, sclerosis)
C. Follicular (small cleaved and large cell, diffuse areas, sclerosis)

Intermediate-grade

D. Follicular (predominantly large cell)
E. Diffuse (small cleaved cell, sclerosis)
F. Diffuse (mixed, small and large cell, sclerosis, epithelioid component)
G. Diffuse (large cell, cleaved and non-cleaved)

High grade

H. Large cell (immunoblastic: plasmacytoid, clear cell, polymorphous, epithelioid component)
I. Lymphoblastic (convoluted, non-convoluted)
J. Small non-cleaved cell (Burkitt’s, follicular areas)
Commentary

Karl Lennert

This NCI-sponsored study has proved successful in attaining one of its main goals, namely, determination of the clinical relevance of the proposed classifications. The “Working Formulation” presented herein represents only a simplified, skeletized method for histologically subdividing non-Hodgkin’s lymphomas into categories which carry prognostic implication in relation to recent therapeutic modalities. While recognizing the practical value of such a compromise measure, I must express certain reservations. Firstly, within this Formulation lymphoma entities which are biologically closely related are separated and entities biologically unrelated are grouped together. Secondly, all considerations regarding immunologic identities of lymphomas have been excluded. It would mean a great setback for lymphoma research if the purpose of this Formulation is generally misunderstood, and if there results an attitude of resignation towards further and more profound characterization of these tumors.
A major international study was subsequently undertaken under the auspices of the National Cancer Institute to compare the major existing classifications and provide a way to translate between them, which led to the publication of the NCI Working Formulation in 1982 (Figure 3). While some involved in the project believed that the Working Formulation was dead on arrival, others rallied behind it and it became a widely used classification with 10 categories divided into three clinical grades. It was once again a strictly morphologically based classification and included some very heterogeneous categories that included multiple types of lymphomas while dividing up other lymphoma entities into more than one category. The concept seemed to evolve that what was important was just to say if a lymphoma was one of the ‘good’ ones (low grade) or ‘bad’ ones (intermediate or high grade). If only life were that simple!
1988: The Updated Kiel Classification
Certificate of Competence in Lymphoma

**B**

**Low-grade malignant lymphomas**
Lymphocytic (CLL, PLL, HCL)

Lymphoplasmacytic/-cytoid (immunocytoma)
Plasmacytic
Centroblastic-centrocytic
  follicular ± diffuse
  diffuse
Centrocytic (mantle cell)
Monocytoid, including MZL

**High-grade malignant lymphomas**
Centroblastic

Immunoblastic
Burkitt’s lymphoma
Large Anaplastic (Ki-1+)
Lymphoblastic

**Rare types**

**T**

Lymphocytic (CLL, PLL)
Small cerebriform (MF, SS)
Lympho-epithelioid (Lennert’s)
Angioimmunoblastic
T-zone lymphoma

Pleomorphic, small cell (HTLV-1±)

Pleomorphic, medium-sized and large cell (HTLV-1±)
Immunoblastic (HTLV-1±)
Large Anaplastic (Ki-1+)
Lymphoblastic

**Rare types**
No communication between Europe and USA with detriment for patients and science
Produced by consensus at two meetings held in Berlin, April 1993 and Boston, May 1994, by haematopathologists not authors of previous classifications.

Based on entities

No histological grade of malignancy

Immunologically oriented

Many entities already present in the Kiel Classification

Hodgkin lymphoma added to the list
World Health Organization Classification of Tumours

Pathology & Genetics

Tumours of Haematopoietic and Lymphoid Tissues

Edited by Elaine S. Jaffe, Nancy Lee Harris, Harald Stein, James W. Vardiman
10000 copies in October 2008
10000 copies in January 2009
10000 copies in September 2009
10000 copies in October 2010
The WHO classification of tumours of the haematopoietic and lymphoid system is based on the principles initially defined in the “Revised European-American Classification of Lymphoid Neoplasms” (REAL), from the International Lymphoma Study Group (ILSG) (898). In the WHO classification, these principles have been applied as well to the classification of myeloid and histiocytic neoplasms. The guiding principle of the REAL and WHO classifications is the attempt to define “real” diseases that can be recognized by pathologists with available techniques, and that appear be distinct clinical entities. There are 3 important components to this process. First, recognizing that the underlying causes of these neoplasms are often unknown and may vary, this approach to classification uses all available information – morphology, immunophenotype, genetic features, and clinical features – to define diseases. The relative
The Diagnosis of Lymphoid Neoplasms is an Integrated Process

Clinical Information

Cell of origin

Morphological Patterns
  • Architecture
  • Cytology

Phenotype

Cytogenetics

Molecular Biology

Sample
  Tissue
  Cytology

DIAGNOSIS
  Specific Entity
  Prognosis
  Therapeutic Targets

CD43 PE
CD19 TC

Cell of origin

Sample
  Tissue
  Cytology
Imprints

Wright, cytochemistry, immunocytochemistry

Cryo-preservation

Immunohistochemistry, molecular biology

Fresh

No FNA

Routine techniques

Morphologic analysis, immunohistochemistry, molecular biology

Electron microscopy

Cell cultures

Vaccine

Cell suspensions

FACS analysis, cytogentics, molecular biology
From rigid protocols applied to all patients....
tailored therapy
(from bench to the bedside)
Dear Steve:

We are pleased to inform you that Dr Wild agreed to your proposals. We are now preparing documents for the Agreement for Performance of Work (APW) with Dr Vardiman, which will be sent to him shortly. Materials including text, figures, tables and references will be also ready by September 15.

With best regards,

Hiroko
CAC Meeting Summary
Update of the WHO Classification

Chicago University, March 31 – April 1, 2014
To be continued.
Lymphoma studying: which approach?

- Knowledge in depth of each entity.
- Multi-disciplinary approach.
- Integration of all pieces of information by the pathologist.
- Keep an Open Mind.
Truth is rarely pure
and never simple

Oscar Wilde
The importance of being Ernest
Salvador Dalí, 1975
SANDRO BARTOCCIONI
GIANNI BONADONNA
FRANCESCO SARTORI
DALL’ALTRA PARTE
Tre grandi medici si ammalano gravemente e raccontano la loro storia. La paura, la sofferenza, la lotta per sopravvivere. E la proposta per rifare una Sanità che curi davvero. A cura di Paolo Barnard.