Doença linfoproliferativa B: nova classificação da OMS (WHO 2008)

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HIAE, April 2009
Overview

- Brief history of lymphoma classification
- Changes for WHO 2008
  - Precursor neoplasms
  - Small clonal populations
  - Follicular lymphoma issues
  - DLBCL categories
  - Mature T cell neoplasms
Need for classification

- Diseases must be clearly defined
  - Diagnosis and treatment

- Need for consensus on terminology and definitions
  - Essential for both clinical practice and research

- Diseases should be clinically distinctive
  - Mutually exclusive (non-overlapping categories)
  - Collectively exhaustive (all diseases should be identified)
Need for classification

- Lumping diverse entities into broad prognostic groups, (i.e. Working Formulation)
  - Obscures distinctive features of rare diseases
  - Distorts data on more common diseases

- Defining distinct entities facilitates advances in:
  - Pathogenesis, epidemiology
  - Diagnostic, prognostic, predictive factors
  - Novel approaches to treatment
Classification Principles

- Define distinct disease entities
  - Can be recognized by pathologists
  - Have clinical relevance

- Each entity defined by numerous features
  - Morphology, immunophenotype, genetics and clinical features

- Diseases sorted according to
  - Postulated normal counterpart
  - Stage of differentiation to the extent possible
  - Clinical and morphologic similarities
Classification according to WHO

- Morphology
  - Principal basis for classification
  - Often sufficient for diagnosis

- Immunophenotype and Genetics
  - Important part of the definition of a disease entity
  - Objective data permit consensus
  - Immunophenotyping typically used for diagnosis in most cases
  - Useful in differential diagnosis and prognosis
  - Improve reproducibility

- Clinical findings
  - Part of the definition of a disease entity
  - Nodal vs extranodal
  - Primary site (skin, CNS, GI, mediastinum)
Brief History of Lymphoma Classification

- **1940s - Gall and Mallory**
  - Not clinically useful

- **1950s - Rappaport**
  - Recognized importance of growth pattern

- **1970s - Lukes and Collins, Kiel**
  - Added knowledge that lymphomas are part of immune system, derived from T and B cells
Sir: The announcement in *The Lancet* of two more classifications of non-Hodgkin's lymphomas encourages me to put forward my classification of these classifications:

Well defined, high-grade oligosyllabic

Poorly differentiated, polysyllabic

Unicentric

Multicentric, cycnophilic (Gk. κυκνός = swan)

Cleaved and convoluted types

This system makes no claim to be comprehensive or even comprehensible, so there may well be scope for other classifications of classifications and ultimately, one hopes, a classification of classifications. At that point we shall need a conference in the Caribbean.

H. E. M. Kay
History of Lymphoma Classification

- 1982 – Working formulation
  - Attempted to unify the complex and confusing lymphoma terminology
  - Improve communication between pathologists and clinicians in different parts of the world
  - WF – North America, Kiel – Europe
History of Lymphoma Classification

- 1980s and 1990s
  - Rapid increase in knowledge of immune system biology
  - Immunology and genetics allowed recognition of previously unrecognized types of NHL
History of Lymphoma Classification

- 1994 - Revised European-American Lymphoma (REAL) classification
  - ILSG recognized the existence of the new entities and proposed a new classification
  - Validated by a multi-institutional study involving 1378 cases (The Non-Hodgkin’s Lymphoma Classification Project)
  - Both reproducible and clinically relevant
History of Lymphoma Classification

- 2001 – WHO classification
  - Joint project of the Society for Hematopathology and European Association of Hematopathologists
  - More comprehensive including myeloid, histiocytic and mast cell neoplasms
  - Lymphoma component merely an update of REAL classification with minor changes
WHO 2008 4th Edition
Mature B-cell Neoplasms

Chronic lymphocytic leukaemia / small lymphocytic lymphoma
B-cell prolymphocytic leukaemia
Splenic marginal zone lymphoma
Hairy cell leukaemia
Splenic lymphoma / leukaemia, unclassifiable
Lymphoplasmacytic lymphoma
Heavy chain diseases
Plasma cell neoplasms
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone lymphoma
Follicular lymphoma
Primary cutaneous follicle centre lymphoma
Mantle cell lymphoma
Mature B-cell Neoplasms ... (cont.)

- Diffuse large B-cell lymphoma (DLBCL), NOS
- T-cell/histiocyte-rich large B-cell lymphoma
- Primary DLBCL of the CNS
- Primary cutaneous DLBCL, leg type
- EBV positive DLBCL of the elderly
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK positive large B-cell lymphoma
- Plasmablastic lymphoma
- Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
- Primary effusion lymphoma
- Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma
WHO 2008: Updates

- **Myeloid neoplasms**
  - New genetic information – new categories
- **Lymphoid neoplasms**
  - Genetic categories of ALL/LBL
  - Small clonal lymphoid populations
  - Consensus guidelines for some diseases
  - New diseases/subtypes/variants/grading
  - Borderline (grey zone) categories
Precursor Neoplasms

- Blastic plasmacytoid dendritic cell neoplasm
  - Formerly “blastic NK-cell lymphoma/leukemia”
- Acute leukemias of ambiguous lineage
  - Acute undifferentiated leukaemia (AUL)
  - Mixed phenotype acute leukaemia (MPAL) (+/- recurrent genetic abnormalities)
- T-lymphoblastic lymphoma/leukemia (T-ALL)
- B-lymphoblastic leukemia/lymphoma (B-ALL)
  - Genetic subtypes
Blastic plasmacytoid dendritic cell neoplasm
Blastic plasmacytoid dendritic cell neoplasm
B-lymphoblastic leukemia/lymphoma (B-ALL)

- B Lymphoblastic Leukemia/Lymphoma, not otherwise specified
- B lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
  - B lymphoblastic leukemia/lymphoma with t(9;22) (q34;q11.2); BCR/ABL
  - B lymphoblastic leukemia/lymphoma with t(v;11q23); MLL rearranged
  - B lymphoblastic leukemia/lymphoma with t(12;21) (p13;q22); TEL/AML1 (ETV6-RUNX1)
  - B lymphoblastic leukemia/lymphoma with hyperdiploidy
  - B lymphoblastic leukemia/lymphoma with hypodiploidy (Hypodiploid ALL)
  - B lymphoblastic leukemia/lymphoma with t(5;14)(q31;q32)(IL3-IGH)
  - B lymphoblastic leukemia/lymphoma with t(1;19)(Q23;P13.3); (E2A-PBX1; TCF3/PBX1)
Small clonal lymphoid populations
Small clonal lymphoid populations

- Impact of flow cytometry
  - Detection of small clones of lymphoid cells in blood, bone marrow, lymph nodes of healthy persons
- Have been found in 3.5-5.5% of healthy adults

Rawstron AC. Blood 2002;100:635-639
Ghia P. Blood 2004;103:2337-2342
Monoclonal B-cell lymphocytosis

- Most have immunophenotype of CLL
- Smaller percentage CD5-/CD10-
- Absolute lymphocyte count <5.0 x 10^9/L
- No lymphadenopathy, organomegaly and no associated autoimmune or infectious disease
Monoclonal B-cell lymphocytosis

- Very small proportion progresses to clinical disease
  - rate of progression approximately 5% over 5 years
  - majority occurring >3 years of follow-up
- ? Analogous to MGUS (MLUS)
- ? Early SLL
Follicular lymphoma grading issues
FL grading issues

- Grading poorly reproducible among pathologists
  - 61-73% agreement

  Blood 1997;89:3909-18

- Variability of field width among different high power objectives
- Identifying centroblasts - large centrocytes and small centroblasts
**Do we need to grade?**

- FL1 and FL2 are generally considered to have an indolent behavior
- Clinical course of FL3 is a subject of intense debate
- Different therapeutic approaches are sometimes applied to the indolent (FL1-FL2) and aggressive (FL3) forms

Ganti AK et al. Ann Oncol 2006;17:920-7
Gene expression profiling for FL

  - Clinical aggressiveness can be associated with specific molecular signatures partially independent from histological grade
  - Used a profile of 81 genes to distinguish low-grade from high-grade disease

  - Genes that best defined the prognostic signatures in FL were expressed primarily by T cells, macrophages, or dendritic cells, but not by the tumor cells themselves
Gene expression profiling for FL

- Piccaluga et al. Haematologica 2008; 93(7):1033-38
  - Gene expression profile of FL is relatively homogeneous, independent of the histological grade
  - FL3b cases constitute a clearly distinct subgroup among FL
    - profile closer to FL than to DLBCL
FL grading: WHO 2008

- Suggestion to simplify or eliminate grading
  - FL 1-3A: “follicular lymphoma” - one disease with no grades
  - FL 3B: “follicular” variant of diffuse large B-cell lymphoma
Insufficient data at this time to warrant:
- Lumping FL3B with DLBCL, or
- Eliminating grading altogether

FL1 and FL2 do not differ from one another
- Could call them both FL1
  - FL3A becomes FL2, FL3B becomes FL3
- What about patients whose tumors have been classified in WHO 3rd ed and who are still alive and on treatment?
Could change the nomenclature

- FL low grade (FL 1&2)
- FL intermediate grade (FL 3A)
- FL high grade (FL 3B)

Not clear that FL3B is more aggressive than FL3A
FL grading: WHO 2008

Conclusion

- Grading still based on proportion of centroblasts
  - FL1-2 = CB rare ("low grade")
  - FL3A = CB numerous (>15/hpf); centrocytes still present
  - FL3B = sheets of centroblasts

- Issue will be revisited when more data available from GEP and prognosis
Intrafollicular neoplasia ("In-situ" follicular lymphoma)

- Majority are normal or reactive-appearing lymph nodes/lymphoid tissue
  - One or more follicles with Bcl2+ CD10+ clonal B cells
- Often an incidental finding
- Minority with overt FL elsewhere (earlier, concurrent, later)
- Most no FL
- Nodal equivalent of small clones of BCL2+ cells in blood of normal subjects?
  - 2nd “hit” required for FL
- Evaluate for FL, no need for treatment
Primary Cutaneous Follicle Center Lymphoma


- Clinical
  - Solitary or grouped plaques and tumors, mainly on scalp, forehead or trunk, rarely legs
  - Dissemination to extracutaneous sites is uncommon
  - Excellent prognosis regardless of growth pattern (follicular or diffuse), number of centroblasts, or whether localized or multifocal
Primary Cutaneous Follicle Center Lymphoma

- **Histology**
  - Nodular to diffuse infiltrates
  - Sparing of the epidermis
  - Follicular growth pattern more common in scalp lesions
  - Centrocytes (often large and multilobated), relatively few centroblasts, many reactive T cells

- **Immunophenotype**
  - CD20+, Bcl6+ CD10-/+ Bcl2-/+ 

- **Genetics**
  - BCL2 usually germline
Primary cutaneous follicle center lymphoma
Pediatric FL and NMZL

- Similar clinical features
  - Localized in head and neck region
  - Median age – FL 11, NMZL 16
  - Male predominance – FL 2:1, NMZL 5:1
  - Good prognosis, some with minimal to no therapy
Pediatric FL and NMZL

- **Similar morphology**
  - Follicular hyperplasia, PTGC, follicle lysis
  - NMZL – extrafollicular monocytoid B cells
  - FL – often grade 3

- **Immunophenotype**
  - NMZL – CD20+, Bcl6-, Bcl2-
  - FL – CD10+, Bcl6+, Bcl2-, CD43+/−
Pediatric FL and NMZL

- Genetics
  - IgH – clonally rearranged
  - BCL2 – germline, no t(14;18)

- Are these truly malignant?
- Are we doing a favour by making this diagnosis?
Pediatric NMZL

CD20

CD21

CD10

Bcl2

IgD

2x

10x
DLBCL classification
Aggressive B cell neoplasms

- New categories for DLBCL
  - primary extranodal sites
  - viral associated
- Borderline categories
  - DLBCL – BL
  - PMBC – NSHL
DLBCL categories

- Diffuse large B-cell lymphoma, not otherwise specified
  - GCB/ABC, morphologic variants
  - T cell/histiocyte rich large B-cell lymphoma
  - Primary CNS DLBCL
  - Primary cutaneous DLBCL ("leg type")
  - EBV+ DLBCL of the elderly
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK positive DLBCL
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- Primary effusion lymphoma
- Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
Grey zone between BL and DLBCL

- Occasional cases have morphologic features in between
  - Intermediate to large cells, mitoses, starry-sky pattern
- 2001 WHO - atypical Burkitt lymphoma
  - Morphologically intermediate between BL and DLBCL
    - >95% Ki-67 fraction
    - Immunophenotype of BL (CD10+ Bcl6+ Bcl2-)
    - MYC rearranged, BCL2 germline
      - Dx made when more likely Burkitt than DLBCL
      - Others: classify as DLBCL
Grey zone between BL and DLBCL


Both looked at GEP to distinguish between BL and DLBCL

- Cases called classical BL – all had GEP of BL
- Cases called atypical BL – 5% not GEP of BL
- Cases called DLBCL – 15-30% GEP of BL
- 20% of cases had GEP between BL and DLBCL
- Cases with MYC rearrangement and not GEP of BL had worse prognosis than BL or DLBCL
Conclusions

- There are cases that cannot be definitively classified as aBL vs DLBCL
- May be biologically and clinically different
- Provisional category: B-cell lymphoma, unclassifiable, intermediate between BL and DLBCL
  - A heterogeneous category that needs to be further refined; not a distinct entity
  - Allows classification of cases not meeting criteria for classical BL or DLBCL
  - Individualized decisions about treatment
Conclusions

- **Immunophenotype**
  - CD10+ Bcl6+ Bcl2+/-
  - Ki67 high or intermediate

- **Genetics**
  - *MYC, BCL2*, both (double hit), complex karyotypes

- **Clinical**
  - May occur in pts with previous FL
  - Aggressive, short survival (especially double hit cases)
B-cell lymphoma intermediate between DLBCL (PMBL) and CHL (NSHL)

- a.k.a. BCLWFIBDLBCLCHL
- Another grey zone with mediastinal masses, often in young adults (M>F)
- Overlapping histology, immunophenotype and GEP
  - Large cells, lacunar, RS like, variable sclerosis, fibrous bands, inflammatory background
  - CD45+ CD30+ Pax5+ CD20+/- CD79a+/- CD15+/- CD10- Bcl6-/+ 
- Often aggressive - ? Treat as DLBC or CHL
Lymphoma Classification: Where now?

- Further assessment of small B-cell neoplasms
  - Significance of early clonal lesions
  - Pediatric FL and NMZL: are they really malignant?
  - Practical method to risk stratify FL by pathologic features

- Subclassification/risk stratification of DLBCL

- Gray-zones: clarify

- Further characterization/defining of mature T-cell neoplasms

- Incorporate new information from gene expression profiling
  - Panels of antigens for immunophenotyping in classification, prognosis