Updated WHO classification of hematolymphoid neoplasms
It’s now time for the next part of our journey

• Introduction (SHS) -- brief
• Small B-cell lymphomas (SHS)
• Aggressive B-cell lymphomas (EC)
• COFFEE BREAK
• Peripheral T-cell lymphomas (Elaine S. Jaffe)
• Acute leukemias and myelodysplastic syndromes (Dan Arber)
• Myeloproliferative neoplasms (Attilio Orazi)
THE INTRODUCTION
Current WHO monograph was published in September, 2008
After lobbying by the 2008 editors who felt it was time for an update

- it was agreed to proceed with an update of the 2008 WHO.
  - Not to be a truly new 5th edition since other volumes still pending in the 4th edition of the WHO tumour monograph series
  - Not supposed to have any truly new entities

- Editors started meeting at sites around the world in 2012.
This effort takes a village......

- WHO classification was not delivered from on high by Charlton Heston (nor did it come from Hillary Clinton)
March 31-April 1, 2014
Clinical Advisory Committee meetings
(lymphoid & myeloid)
Additional small meetings, polls & telephone calls among the editors & with those responsible at IARC or working with IARC for the update.
Major changes of plan along the way

2012

Web-based only

2014

• Web-based
• E-book
• Print versions

2016

• Print version for now
• E-book & web-based to follow?
September, 2016

- Chapters are all written
- Copy-editing in process (to be completed by late September)
- After layout complete, PDF’s of chapters sent to authors/editors for review (process takes “several” months)
- Latest expectation is for publication in early, 2017.

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The 2016 revision of the World Health Organization classification of lymphoid neoplasms

(Blood. 2016;127(20):2375-2390)

Steven H. Swerdlow,¹ Elias Campo,² Stefano A. Pileri,³ Nancy Lee Harris,⁴ Harald Stein,⁵ Reiner Siebert,⁶ Ranjana Advani,⁷ Michele Ghielesini,⁸ Gilles A. Salles,⁹ Andrew D. Zelenetz,¹⁰ and Elaine S. Jaffe¹¹
The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia

(Blood. 2016;127(20):2391-2405)

Daniel A. Arber,¹ Attilio Orazi,² Robert Hasserjian,³ Jürgen Thiele,⁴ Michael J. Borowitz,⁵ Michelle M. Le Beau,⁶ Clara D. Bloomfield,⁷ Mario Cazzola,⁸ and James W. Vardiman⁹
General comments about the revised lymphoma classification

• Some alterations in the actual classification (highlighted in yellow)

• Some changes in criteria for existing entities

• Incorporation of new information published over the last ~8 years relating to existing entities with some important diagnostic/prognostic/therapeutic implications.
Shouldn’t be any shockers for those who keep up on the lymphoma literature

- The entities in the WHO classification and the criteria for their recognition are based on published data & often simply serve to codify evolving pre-existing practices.
The ongoing evolution of the WHO classification & Bluebook – what to look out for

Since the monograph is not published yet, changes are possible; however, it is in the hands of IARC & the summary of the major changes is published in the Blood manuscript.
The small B-cell lymphoid neoplasms
Even greater concern & certainty about cases we used to diagnose as overt lymphoid neoplasms but aren’t considered as such in 2016
Monoclonal B-cell lymphocytosis

- Monoclonal PB lymphocyte populations up to $5 \times 10^9$/L either with the phenotype of CLL, atypical CLL (CD5+, bright CD20, some include if CD23-) or non-CLL (CD5-) B-cells in the absence of other lymphomatous features.
Monoclonal B-cell lymphocytosis – was included in 2008 monograph but with more uncertainties than in 2016

- Unknown if it was a precursor of CLL.
- Some might prefer to consider these as low count CLL.
Virtually all overt cases of CLL are preceded by MBL

- “B-cell clones as early markers for chronic lymphocytic leukemia” NEJM 360:659, 2009
  - Prospective study of 77,469 healthy adults – 45 developed CLL
  - “In peripheral blood obtained up to 77 months before a CLL diagnosis, prediagnostic B-cell clones were present in 44/45 patients with CLL.”
  - ~23% of the cases were unmutated
No longer much of a question as to what to call cases that formerly would be considered “CLL with a low count”
“Low count” MBL is very different from “high count” MBL, because it has significant differences from CLL and there is “limited, if any, risk of progression” even if they do share some of the same cytogenetic abnormalities. – cutoff for WHO is 500 neoplastic B-cells (0.5 x 10^9/L)
High count (clinical) MBL & Rai 0 CLL
(Clin Cancer Res;19:5890, 2013)

• Similar with regard to numerous parameters
  – CD38 & ZAP-70
  – \textit{NOTCH1} & \textit{SF3B1} mutations
  – Major CLL cytogenetic abnormalities
  – IGHV/IGHD/IGHJ gene usage
  – Overall prevalence of stereotyped \textit{IGHV} gene sequences
  – Gene & miRNA signatures

• \textit{IGHV}-mutated cases more frequent in cMBLs
• Tendency for more adverse prognostic indicators in CLL vs MBL.

Older studies looked at some of the above with similar conclusions
The updated WHO

• Updated WHO will retain current criteria for MBL even if they are imperfect & remain somewhat controversial

• NEW: Enhanced section on MBL

• NEW: Will require the distinction of “low” from “high” count MBL – the latter but not the former requires routine/yearly follow-up.

• NEW: Will require that the MBL population be present for at least 3 months (not really new but new for WHO monograph)
Lymph node infiltration by CLL-type cells without PC & in the absence of lymphadenopathy >1.5cm on CT scan who otherwise have MBL “may represent a nodal equivalent of MBL rather than SLL”.

- From monograph section on MBL

Based on single retrospective study, relatively short follow-up.
Revision will also deal (briefly) more with non-CLL type monoclonal B-cell lymphocytosis.

**LYMPHOID NEOPLASIA**

Clonal B-cell lymphocytosis exhibiting immunophenotypic features consistent with a marginal-zone origin: is this a distinct entity?

Ailiki Xochelli,¹ Christina Kalpadakis,² Anne Gardiner,⁹ Panagiotis Baliakas,¹,⁴ Theodoros P. Vassilakopoulos,⁵ Sarah Mould,³ Zadie Davis,³ Evangelia Stalika,¹ George Kanellis,⁶ Maria K. Angelopoulou,⁵ Neil McIver-Brown,³ Rachel Ibbotson,³ Sotirios Sachanas,⁷ Penelope Korkolopoulou,⁶ Anastasia Athanasiadou,¹ Achilles Anagnostopoulos,¹ Helen A. Papadaki,² Theodora Papadaki,⁶ Kostas Stamatopoulos,¹,⁴,⁹ Gerassimos A. Pangalis,⁵,⁷ and David Oscier³

*(Blood. 2014;123(8):1199-1206)*

Molecular lesions of signalling pathway genes in clonal B-cell lymphocytosis with marginal zone features

*British Journal of Haematology, 2014, 167, 697–726*
The revision will:

• eliminate the option to diagnose CLL with $<5 \times 10^9/L$ PB CLL cells in the absence of extramedullary disease even if there are cytopenias or disease-related symptoms.
  – Can have MBL with other cytopenias, symptoms.

• As before, requirement for CLL to persist at least for 3 months but still subject to change (as of early February)
New information about proliferation centers in CLL/SLL that will impact the chapter

- Cyclin D1+ in 20-30% of CLL/ SLL but no CCND1 rearrangements or extra copies (AJCP 138:132, 2012)
- MYC+ in all CLL/SLL without MYC rearrangements or extra copies (Br J Haematol. 2015 Nov 16)
- PI3K P85+ in 32/34 CLL/SLL (too new for monograph)
Proliferation centers are the site of BCR signaling that is of critical importance in driving CLL cells & is an important therapeutic target.

*Blood.* 2013;122(23):3723
The revision will discuss how the extent and proliferative fraction in proliferation centers has clinical implications

- 3 of 4 relatively recent studies highlight the clinical importance of PC when large and/or have “high” proliferative fraction, even with selected multivariate analyses (among those who ended up with LN biopsy, not random or all at initial dx).
  - One 2014 study found expanded PC and higher Ki-67 didn’t affect prognosis (all pre-rx) (Sachanas, 2014)
2010 (Giné, et al) -- “expanded PCs” (>20x field) & high proliferative rate (>2.4 mitoses/PC or Ki-67>40%/PC) associated with adverse prognosis (remained important with multivariate analysis).

2012 (Ciccone, et al) Histopath + FISH – “the PCs-rich pattern [confluent PCs] was the only predictive factor of an inferior survival at multivariate analysis.”
Is histologically aggressive CLL/SLL equivalent to classic Richter’s transformation (DLBCL)?

Some report it is and some report it isn’t.
In situ follicular lymphoma

CD10

BCL2
In situ follicular lymphoma

- Now to be known as “in situ follicular neoplasia”
  - FL-like B-cells of uncertain/undetermined significance had been suggested but had a very short half-life
- Need to distinguish these cases from partial involvement by FL which has a much greater chance of developing an overt FL/DLBCL (look like overt FL but are more focal).
What else have we learned since the 2008 monograph?

- Cannot predict which cases will be associated or will develop an overt FL/DLBCL based on the extent of the “in situ” lesions (# or % abnormal follicles or degree of involvement within the abnormal follicles).
- May have “+” flow cytometric studies with in situ FN.
- In situ FN have fewer cytogenetic abnormalities than partial & especially overt FL, but not very useful clinically yet.
- Learning more about the relationship to the circulating cells with t(14;18) which are thought to reside in GC even in the absence of recognizable in situ FN.
Additional clinical support for not considering ISFN as an overt lymphoma from several studies – be careful to fully assess the clinical situation!

None of their incidental cases showed progression but in 12 cases clinically suspicious for a LPD, they found other lymphomas (including, eg FL) in the same or other lymph nodes.
Pediatric follicular lymphoma will be promoted to a definite entity with refined criteria & slight name change.

- Recognized as a provisional entity/FL variant in 2008 monograph.
Can occur in adults – so now pediatric-type FL in new WHO

• Need to be more cautious in adults to be sure not misdiagnosing a more aggressive grade 3 FL of ordinary type.

• Refined criteria for 2016: Requires presence of large expansile highly proliferative follicles that are often composed of more blastoid rather than classic centroblastic cells, no diffuse areas, no $BCL2$ rearrangements, typically high Ki-67
  – Others have reported grade 1-2 cases, BCL2 protein can be positive

• Expect to find localized disease

# Diagnostic features of pediatric type follicular lymphoma

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<td><strong>Morphology</strong></td>
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| Morphology | At least partial effacement of nodal architecture (required)  
| | Pure follicular proliferation (required) ¶  
| | Expansile follicles*  
| | Intermediate-sized ‘blastoid’ cells (not centrocytes)*  |
| **Immunohistochemistry (required)** |  |
| BCL6+ |  
| BCL2 negative / weak |  
| High proliferation fraction (>30%) |  |
| **Genomics (required)** |  |
| No BCL2, BCL6, IRF4, or IG rearrangement |  
| No amplification of BCL2 |  |
| **Clinical** |  |
| Nodal disease (required) |  
| Stage I-II (required) |  
| Age <40* |  
| Male >> Female |  |

*Common features of PTFL, but not required
¶ Any component of DLBCL or presence of advanced stage disease excludes PTFL
Some cases have been reported with deletion in 1p36, and deletions or mutations affecting *TNFRSF14*, but data were limited.

Recurrent loss of heterozygosity in 1p36 associated with *TNFRSF14* mutations in *IRF4* translocation negative pediatric follicular lymphomas

Idoia Martin-Guerrero,1* Itziar Salaverria,1* Birgit Burkhardt,3,4 Monika Szczepanowski,5 Michael Baudis,6 Susanne Bens,2 Laurence de Leval,7 Africa Garcia-Orad,2 Heike Horn,8 Jasmin Lisfeld,9 Shoji Pellissery,1 Wolfram Klapper,5 Iiske Oschlies,5 and Reiner Siebert1
Genome-wide analysis of pediatric-type follicular lymphoma reveals low genetic complexity and recurrent alterations of *TNFRSF14* gene

Janine Schmidt,¹ Shunyou Gong,² Teresa Marafioti,³ Barbara Mankel,¹ Blanca Gonzalez-Farre,⁴ Olga Balagué,⁴ Ana Mozos,⁵ José Cabeçadas,⁶ Jon van der Walt,⁷ Daniela Hoehn,⁸ Andreas Rosenwald,⁹ German Ott,¹⁰ Stefan Dojcinov,¹¹ Caoimhe Egan,² Ferran Nadeu,⁴ Joan Enric Ramis-Zaldívar,⁴ Guillem Clot,⁴ Carmen Bárcena,¹² Vanesa Pérez-Antonio,¹² Volker Endris,¹³ Roland Penzel,¹³ Carmen Lome-Maldonado,¹⁴ Irina Bonzheim,¹ Falko Fend,¹ Elias Campo,⁴ Elaine S Jaffe,² Itziar Salaverria,⁴ Leticia Quintanilla-Martinez¹
Pediatric-Type Nodal Follicular Lymphoma: A Biologically Distinct Lymphoma With Frequent MAP Kinase Pathway Mutations

Abner Louissaint Jr., MD, PhD1,2*, Kristian T. Schafernak, MD, MPH3, Julia Geyer, MD4, Alexandra E. Kovach, MD5*, Mahmoud Ghandi, PhD13, Dita Gratzinger, MD, PhD6, Christine G. Roth, MD7, Christian N Paxton, PhD8, Sunhee Kim2, Chungdak Namgyal9, Elizabeth A. Morgan9, Donna S. Neuberg10, Sarah T. South, PhD11, Marian H. Harris, MD, PhD5*, Robert P. Hasserjian, MD1, Ephraim P. Hochberg, MD12, Levi A. Garraway, MD, PhD2,13, Nancy Lee Harris, MD1 and David M. Weinstock, MD2,13
Although the recent studies raised the possibility that these cases are not “truly malignant” or represent a “benign clonal proliferation with low malignant potential”, they will continue to be diagnosed as a lymphoma – although in many circumstances surgical excision may be sufficient therapy.
Distinctive cases with *IRF4* translocations (some included in ped FL in the past) will be segregated & made a new provisional entity – “Large B-cell lymphoma with IRF4 rearrangement”

Requires FISH studies as rearrangement cryptic.

*(Blood. 2016;127(20):2375-2390)*
“Large B-cell lymphoma with IRF4 rearrangement”

- Most commonly in children/young adults
- Follicular, follicular & diffuse or entirely diffuse
  - May have $BCL6\,R$ but not $BCL2$.
- Some otherwise similar cases lack a demonstrable $IRF4\,translocation$ (but may have IGH rearrangements)
- Involve Waldeyer ring &/or cervical lymph nodes, low stage
- Considered to be more aggressive than other pediatric FL but do well when treated
Other FL-related issues

- The special nature of duodenal (vs generic GI tract) FL will be addressed & “duodenal-type” FL recognized as a variant – another very indolent & localized lymphoma with features overlapping in situ FN & MALT lymphomas
  - May have involvement elsewhere in GI tract
  - Some cases rx with “watch & wait” strategy
Recognize a largely diffuse FL variant with 1p36 deletion (often large, localized & inguinal, often with some small follicular structures) – 1p36 deletion is not a specific abnormality.

Diffuse not just a sampling issue
FL chapter will also recognize the distinctive nature of testicular FL

• More frequent in children, but may be seen rarely in generally young adults

• Like pediatric-type FL, lack BCL2 translocation & usually Grade 3A, but have a good prognosis, sometimes even without additional therapy beyond surgical excision.

Primary Follicular Lymphoma of the Testis and Epididymis in Adults
Chris M. Bacon, MBChB, PhD, MRCPath,* Hongtan Ye, MD, PhD,* Timothy C. Diss, PhD,† Christopher McNamara, MBBS, FRCP,A, FRACP,‡ Brian Kueck, MD,§ Robert P. Hasserjian, MD,¶ Ana Z.S. Rohatiner, MD, FRCP,* Judith Ferry, MD,¶ Ming-Qing Du, MD, PhD,* and Ahmet Dogan, MD, PhD, MRCPath§

Mantle cell lymphoma: used to think about it as a hopeless situation for the patients.
Great interest in the indolent end of mantle cell lymphomas & the growing belief that MCL develops along 2 distinct pathways

• There are two more indolent types of mantle cell lymphoma recognized.

• In situ mantle cell neoplasia – an “early” lesion not specifically related to one or the other pathway.

• Leukemic non-nodal MCL which is most commonly composed of SOX11- B-cells with mutated IGH.

• See the Blood publication summarizing the new classification (or wait for the new monograph).
MCL, leukemic non-nodal type

- Better established at time of 2008 monograph (PB, BM with or without splenic involvement)
- “Monoclonal asymptomatic lymphocytosis, cyclin D1-positive (MALD1)”
  - Clin Cancer Res; 20(4); 1007–19.
“in situ” MCL

- Will be discussed in greater detail and given a new name – in situ mantle cell neoplasia.
- Indolent but may be disseminated.
- Often do not progress, but some cases do.

Cyclin D1
Major impact of newer molecular studies, including on the small B-cell neoplasms
Hairy cell leukemia

- 2008 WHO monograph: “No cytogenetic abnormality is specific for HCL”
- 2011: *BRAF* V600E mutations in almost all HCL but not in HCL-variant or other small B-cell neoplasms
  - Identical to mutation seen in 40-45% papillary thyroid carcinomas, ~50% melanoma, >50% Langerhans cell histiocytosis, rare other B-cell lymphomas & myeloma

Arch Pathol Lab Med. 2011;135:569
2014: MAP2K1 mutations in HCL-v (42%) & IGHV4-34 HCL (71%), lack BRAF V600E mutations

Nature Genetics 46:8, 2014

• NEW from the monograph: “Whether cases that lack BRAF V600E mutation, use the IGHV4-34 family and have MAP2K1 mutations are most closely related to classic HCL or HCL-variant remains to be established.”
Lymphoplasmacytic lymphoma

- 2008 WHO: “No specific chromosomal or oncogene abnormalities are recognized.”
  - Previously reported $PAX5$ translocations $[t(9;14)]$ rarely if ever found
  - Del 6q in >50% BM-based cases but not at all specific
MYD88 L265P Somatic Mutation in Waldenström’s Macroglobulinemia

Steven P. Treon, M.D., Ph.D., Lian Xu, M.S., Guang Yang, Ph.D., Yangsheng Zhou, M.D., Ph.D., Xia Liu, M.D., Yang Cao, M.D., Patricia Sheehy, N.P., Robert J. Manning, B.S., Christopher J. Patterson, M.A., Christina Tripsas, M.A., Luca Arcaini, M.D., Geraldine S. Pinkus, M.D., Scott J. Rodig, M.D., Ph.D., Aliyah R. Sohani, M.D., Nancy Lee Harris, M.D., Jason M. Laramie, Ph.D., Donald A. Skifte, Ph.D., Stephen E. Lincoln, Ph.D., and Zachary R. Hunter, M.A.

MYD88 L265P mutations in ~90% LPL (including 3/3 non-IgM secreting – IgG-2 & IgA-1)

MYD88-Directed NF-κB Signaling
Brief review of the literature

Rare FL, HCL & no MCL *MYD88*+; 6.5-29% non-GC/ABC DLBCL; ~60% DLBCL, leg type – adverse prognostic factor; up to 94% CNS DLBCL, ↑ testis DLBCL
Observations based on MYD88 mutated neoplasms will impact the diagnostic criteria for LPL (importance of monotonous lymphoplasmacytic proliferation & acceptance of follicular colonization)

**MYD88 L265P mutation analysis helps define nodal lymphoplasmacytic lymphoma**

Fatima Hamadeh¹, Stephen P MacNamara¹, Nadine S Aguilera², Steven H Swerdlow³ and James R Cook¹
**MYD88** studies also will impact WHO approach to MGUS

- Will distinguish IgM MGUS that may be **MYD88** mutated from non-IgM MGUS which does not have **MYD88** mutations.
  - IgM MGUS is more closely related to LPL & other lymphomas & will be discussed in LPL chapter, non-IgM MGUS is more closely related to plasma cell neoplasms & will be discussed in plasma cell neoplasm chapter

- Further supported by the observation of **CXCR4** mutations in ~30% LPL, 20% IgM MGUS but not in IGG/A MGUS!
Literature somewhat inconsistent regarding clinical implications, integrated risk profile not fully established, not a part of routine practice at this time & will not be recommended in new WHO.
55% of cyclin D1- MCL had **CCND2** translocations with IG partner in most and light chain partner in many (15/22).

- Unlike 1 prior report, found none with **CCND3** translocations.
Much has been learned about mutational abnormalities in FL even with a proposed prognostic model incorporating some of the findings, but while they will be discussed, “Whether mutational analysis should be performed routinely for diagnostic, prognostic or therapeutic purposes and if it should be integrated with other pathologic and clinical prognostic factors remains to be determined.” (from WHO Blood publication)
• Described the process by which the 2008 WHO classification of lymphomas & monograph are being revised.

• Provide a glimpse at the major updates regarding the small B-cell lymphoid neoplasms in the upcoming 2016/2017 WHO classification and monograph.