Linfoma folicular. Linfoma linfoplasmocítico y linfoma nodal de la zona marginal
Relative incidence of ML

Seer data (HL vs NHL) & NHL Classification project, Blood 89:3909
Introducing type D

• Follicular lymphoma
  • What is it?
  • Making the diagnosis using a multiparameter approach – emphasizing histopathology & immunophenotypic studies
• Important variants
• Lymphoplasmacytic lymphoma
• Nodal marginal zone lymphoma
An “oldie but goodie”
Follicular lymphoma

Blast
Naïve B-cells
FCC - ag selection/Ig somatic hypermutation
Memory B-cells/marg zone
Follicular lymphoma – according to the 2008 WHO classification

• Neoplasm composed of follicle center B-cells (usually centrocytes & centroblasts) that usually but not always has at least in part a follicular growth pattern.

• Diffuse areas with predominantly centroblasts must be given a separate diagnosis of diffuse large B-cell lymphoma.

• 1° cutaneous “follicular lymphomas” are considered a part of a totally separate entity – 1° cutaneous follicle center lymphoma.
Making the diagnosis
Evaluating follicular lymphoid proliferations – 2 major decisions

• Hyperplastic versus neoplastic follicles
  – Follicular hyperplasia versus follicular lymphoma – a classic dilemma

• Are the neoplastic follicles really a “follicular lymphoma” or could they represent some other type of lymphoma involving follicles?
  – Mantle cell lymphoma
  – Marginal zone lymphoma
  – Other
Follicular lymphoma vs follicular hyperplasia -- histopathology

- Architectural effacement with loss of sinuses and numerous closely packed follicular structures in at least focal portions of the lymph node
  - although even some overt FL can have some intact sinuses & reactive follicles!
- Homogeneous follicles often with numerous centrocytes (cleaved cells) & without tingible body macrophages or mitoses
  - although some cases have more heterogeneous follicles with more centroblasts/transformed cells, mitotic figures and sometimes tingible body macrophages.
Follicular lymphoma vs follicular hyperplasia

- Interfollicular and capsular infiltration by centrocytes
  - although some FL are predominantly intrafollicular and oftentimes the interfollicular neoplastic cells are smaller and less “cleaved” or angulated than those in the follicles (maturing towards memory cells).

- Occasionally significant dysplasia

- Don’t rely on mantles vs. none, irregular follicles vs. uniform size and shape, presence vs. absence of plasma cells.
Hyperplastic follicle -- polar
Some follicular lymphomas resemble progressive transformation of germinal centers (floral pattern)
Follicular lymphomas may show marginal zone differentiation
Follicular lymphomas with plasmacytic differentiation include two subtypes

Joel F Gradowski¹, Elaine S Jaffe², Roger A Warnke³, Stefania Pittaluga², Urvashi Surti⁴, Leena A Gole⁵ and Steven H Swerdlow¹,*

Very plasmacytic

6/6 with isolated BCL2-R had interfoll pc

6/7 without BCL2-R had mostly intra/perifoll pc.

More plasmacytoid

CD138

CD138
Phenotypic studies – another critical tool in the diagnosis of FL

- Two major techniques
  - Paraffin section immunohistochemistry
  - Flow cytometric studies
- Both have advantages & disadvantages and sometimes need to use both.
Looking for evidence to support the presence of a neoplasm & to help classify it as a follicular lymphoma

- Plenty of exceptions to our rules but don’t let them paralyze you.
- Flow cytometric evidence to support a B-cell neoplasm
  - Light chain class restriction (SIg best analyzed by flow cytometry)
  - Combinations of antigens not seen normally (CD10 & BCL2)
  - Phenotypic “aberrancies” (eg, dimmer than usual CD19 on CD10+ B-cells)

[Diagram: Dimmer CD19 on CD10+ versus CD10- smaller B-cells: 100% specific & 44% sensitive for FL vs FH.]

Evidence to support diagnosis of FL
Realize it is not a specific phenotype

CD20+

CD5+
- Cyclin D1-
  - Variable
    - DLBCL
  - CD23+ FMC7-
    - CLL/SLL
CD5-
- Cyclin D1+
  - CD23- FMC7+
    - MCL
  - CD10+
    - Bcl-6+
      - FL
      - DLBCL Burkitt
  - CD10-
    - Bcl-6-
    - Bcl-6+
      - MZL/MALT LPL
      - DLBCL
Paraffin section IHC

- Looking for CD20+ CD10+ (or at least BCL6+) germinal centers with BCL2 expression.
  - Vast majority of low grade FL and still majority of higher grade FL are BCL2+

- BE CAREFUL: Not all “nodules” of BCL2+ cells are follicular lymphomas.
  - Primary follicles or mantle zones cut tangentially
  - Follicles with numerous T-cells may appear BCL2+
  - Other lymphomas that have follicular colonization

- BE CAREFUL: Some FL are truly BCL2- or appear to be BCL2- by immunohistochemistry (other BCL2 stains such as the E17 clone may be useful)
BCL-2 IMMUNOSTAIN

FOLLICULAR HYPERPLASIA

FOLLICULAR LYMPHOMA
The CD10 highlights the germinal centers
Reviewing CD10 immunostains

- Significant numbers of CD10+ cells outside of follicles also helpful in ddx FL vs FH – sign of invasion (but may be “down regulated”).
  - Sometimes see extrafollicular scattered lymphoblasts/hematogones that are strongly CD10+ in peripheral lymphoid tissue

- Remember
  - Not all FL are CD10+.
  - CD10 is not specific for FCC or even B-cells (neutrophils, subset of normal and neoplastic lymphoblasts, small subset of mature T-cells & some T-cell lymphomas, some myelomas, some epithelial cells, some reticular cells)
This is not simply follicular hyperplasia!
Other paraffin-reactive stains

• **BCL6**
  – More limited utility but can be helpful – GC may stand out better, expected to be positive in CD10- cases.
  – Not lineage or GC specific.

• **Ki-67 (nuclear proliferation marker)**
  – In contrast to most normal follicles that have many positive cells, most FL have relatively few.
  – May complement grading of FL (stay tuned)
K & \lambda\ stains not usually needed or that helpful but sometimes useful in a pinch
Kappa (left, neg.) & Lambda (right, pos.) stains are tough!
Should be FL but follicles show variable sizes & shapes, Bcl-2 negative & reported FCIPS “polyclonal”
FCIPS called polyclonal but actual results: kappa – 21%  lambda – 39%
Ought to be but......

But be sure it’s not just non-specific staining 😞

IgD saves the day!

CD3

Bcl-2 hard to interpret
Can use cytogenetic FISH studies to demonstrate t(14;18)(q32;q21), translocation between \( IGH \) & \( BCL2 \)
Most FL have *BCL2* translocations (even in some BCL2- cases) -- although some FL do not & some non-FL do!

Many FL without *BCL2* translocation have *BCL6* translocation.

*IGH/BCL2* translocation proven by FISH (can also infer from classical cytogenetic studies but can’t distinguish from *IGH/MALT1* translocation)
FL also usually have additional cytogenetic abnormalities, some of which may be of prognostic utility.
Don’t forget about molecular studies to help establish clonality

• But also remember about issues of false negative results especially if using more limited primers and about false positive results especially if using very sensitive techniques or if there are few B-cells present.
Once you are ready to diagnose a FL, you must decide on a growth pattern (Follicular, follicular & diffuse, focally follicular/predominantly diffuse) & a grade (1-2, 3a or 3b)
WHO counting method

- Count (or “estimate”) the number of large transformed cells/centroblasts within neoplastic follicles in 10 random but representative high power fields.
- Large centrocytes are NOT counted.
- FL, grade 1-2: 0-15 centroblasts/hpf
- FL, grade 3: > 15 centroblasts/hpf
  - 3a: admixed centrocytes (cleaved cells).
  - 3b: no residual centrocytes.
Grading of FL

• Size of your HPF will make a big difference – check the WHO monograph
• Many actually count very few, if any, cases (use it as a guide).
• Grade 3 FL are important to recognize as considered more aggressive but, at least to some, potentially curable.

  • Ongoing discussions and publications as to where grade 3A cases best belong (possibly with grade 1-2) and where grade 3B cases belong (possibly with DLBCL at least if no BCL2 rearrangement).
Additional caveats

• Beware of cases that might look like they have mostly cleaved cells/centrocytes but which are blastoid or look “different” in other ways – don’t be fooled!

• Don’t only count areas with greatest number of large cells unless clearly a distinct area

• Areas of diffuse large B-cell lymphoma seen together with a FL must be separately designated (and the proportion of area involved given).

• Ki-67 stains may be of help but no agreed upon rules as to how to use it.
Low Histologic Grade Follicular Lymphoma With High Proliferation Index

Morphologic and Clinical Features

Sa A. Wang, MD,* Lan Wang, MD,* Ephraim P. Hochberg, MD,† Alona Muzikansky, MS,‡ Nancy Lee Harris, MD,* and Robert P. Hasserjian, MD*


Overall survival

Disease specific survival

LG- low grade, LPI-low prolif index, Ki-67<30%, HPI – high prolif index
Other pathologic prognostic markers

Impact of the tumor microenvironment on prognosis in follicular lymphoma is dependent on specific treatment protocols

Daphne de Jong,1 Ad Koster,2 Anton Hagenbeek,3 John Raemaekers,4 Dennis Veldhuizen,1 Sabien Heisterkamp,1 Jan Paul de Boer,5 and Martine van Glabbeke6

haematologica | 2009; 94(1) | 70 |
FL with architectural preservation

“in situ” follicular lymphoma

F. L. Wright’s “Fallingwater” house outside of Pittsburgh
How I treat: diagnosing and managing "in situ" lymphoma

Antonino Carbone and Armando Santoro

The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications

Elias Campo,¹ Steven H. Swerdlow,² Nancy L. Harris,³ Stefano Pileri,⁴ Harald Stein,⁵ and Elaine S. Jaffe⁶

(Blood. 2011;117(19):5019-5032)

In view of the uncertain clinical behavior of FL in situ and MCL in situ, the terminology of FL- or MCL-like B cells of significance, in parallel with MGUS, was suggested for these tissue-based lesions at the recent EAHp/SH meeting in Uppsala, Sweden.

J Hematopathol 2012, 5:169 – the workshop report
LN with an intact architecture but scattered germinal centers with variably dense populations of BCL2+ CD10+ (monoclonal) centrocytes.
Flow cytometric studies can detect CD10+ light chain restricted B-cells in FLBUS – don’t use them to overdiagnose an overt follicular lymphoma (eg, if you have fine needle aspirate)

- 6/15 cases CD10+ LCR+ B-cells plus 2/8 additional cases had CD10+ BCL2+ population (latter 2 were among 4 with significant Slg- CD10+ cells).
- Positive flow study (53%) was more likely if higher % of BCL2+ follicles.

Pillai & Swerdlow, submitted
In situ follicular lymphoma

- Considered important to recognize as distinct because many cases seem to not progress & develop more overt FL
- Problem is that other cases have overt FL either at the same time or subsequently
Thyroid with H.T. & “in situ” FL?
A work in progress...

In situ localization of follicular lymphoma: description and analysis by laser capture microdissection

Peijie Cong, Mark Raffeld, Julie Teruya-Feldstein, Lynn Sorbara, Stefania Pittaluga, and Elaine S. Jaffe

- 5 patients with synchronous FL elsewhere
- 3/13 developed FL (<1-6 years)
  - f/u in 10 patients without FL 2-96 mo. (median 15.5 mo.)

These results suggest that at least close to half of these cases (8/18; 44%) represent homing to and early colonization of reactive GCs by FL. Other cases might represent FL at the earliest stage of development, or a preneoplastic event, requiring a second hit for neoplastic transformation.

(Blood. 2002;99:3376)
Partial involvement by FL in situ: clinical implications and comparisons with partial involvement by follicular lymphoma

Armin G. Jegalian, Franziska C. Eberle, Svetlana D. Pack, Mariya Mirvis, Mark Raffeld, Stefania Pittaluga and Elaine S. Jaffe
Table 1. Diagnostic features of FLIS and PFL

<table>
<thead>
<tr>
<th>FLIS</th>
<th>PFL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Architecture intact</td>
<td>Altered architecture</td>
</tr>
<tr>
<td>Follicle size normal</td>
<td>Follicle size often expanded</td>
</tr>
<tr>
<td>Involved follicles widely scattered</td>
<td>Involved follicles grouped together in LN</td>
</tr>
<tr>
<td>Intact cuff with sharp edge to GC</td>
<td>Blurred edge to GC and attenuated cuff</td>
</tr>
<tr>
<td>Very strong expression of BCL2 and CD10</td>
<td>BCL2 and CD10 more variable in intensity</td>
</tr>
<tr>
<td>Almost pure centrocytes</td>
<td>Centrocytes with few centroblasts</td>
</tr>
<tr>
<td>Atypical cells confined to GC</td>
<td>Atypical cells (CD10+/BCL2+ B cells) may be found outside the GC</td>
</tr>
</tbody>
</table>

GC indicates germinal center.
Montes-Moreno, et al, 2010
Intrafollicular neoplasia/FLIS (13)

- Splenic marginal zone lymphoma – 2
- Hodgkin lymphoma – 2 (one also with subsequent FL, grouped with FL)

- No ML
- Subsequent FL/DLBCL
- Concurrent FL
- Other ML
Other lymphomas (6 without any FL/DLBCL): CLL/SLL – 2, MALT lymphoma – 1, In situ MCL – 1, PTCL, NOS – 2 (one also with overt FL), classical Hodgkin lymphoma – 2 (both with synchronous or metachronous overt FL)
Extent of FLBUS does not predict association with FL/DLBCL
Proportion of BCL2+ cells in involved follicles also does not predict FL/DLBCL

<25% BCL2 positive cells (solid gray), GC with 25-95% BCL2 positive cells (dotted) and GC with >95% BCL2 positive cells (solid black)
“in situ” is a bit of a misnomer as dissemination is still c/w “in situ” FL

Follicular Lymphoma of the Spleen
Multiparameter Analysis of 16 Cases

Matthew T. Howard, MD,1 Scott Dufresne, MD,2 Steven H. Swerdlow, MD,2 and James R. Cook, MD, PhD1

• 3 cases with in situ growth pattern in spleen but with splenic hilar or cystic duct lymph node in situ-type involvement.

• “…FL with an in situ growth pattern is not necessarily restricted to one anatomic site but may be disseminated.”

Am J Clin Pathol 2009;131:656
Dissemination of in situ FL can extend to the PB

• “In situ localization of follicular lymphoma: evidence for subclinical systemic disease with detection of an identical $BCL-2/IGH$ fusion gene in blood and lymph node.”
  – Complicated by light chain restricted CD10+ interfollicular plasma cells, Leukemia 23:1176, 2009

• Consistent with current belief that circulating cells with $BCL-2/IGH$ present in up to 66% of healthy individuals >10 yrs. old mostly show evidence of GC transit and may live in the germinal center niche.
Roulland, et al: “… in healthy individuals, t(14;18) is actually carried by an expanding population of atypical B cells issued from [GC], displaying genotypic & phenotypic features of FL, & prone to constitute potent premalignant FL niches.” JEM 203:2425, 2006
Is overt FL preceded by in situ FL?

- Prior “benign” lymphoid tissue biopsies from patients who were diagnosed with an overt FL, were retrieved (N=6)
- Stained for BCL2, CD10, CD20 and CD3
- 5/6 showed in situ FL! Only negative case was $1^\circ$ cutaneous FCL.
• Of 8 cases with prior lymph node biopsies from patients with subsequent follicular lymphoma (diagnosed 9-186 months later)
  – 6 showed in situ FL, 2 usual FL
• Both these studies support that at least most FL are preceded by in situ FL/FLBUS even if in situ FL/FLBUS has a low rate of progression
  – Analogous to the CLL/monoclonal B-cell lymphocytosis story.
Learning more & more about the molecular landscape of follicular lymphomas & their precursor lesions

Grandma Moses
Blood
Green, et al, 2013

- Hierarchy in somatic mutations arising during genomic evolution and progression of follicular lymphoma.
Other FL variants worth knowing about
Duodenal follicular lymphomas

- Frequently found incidentally as multiple small polyps
- Usually CD10+, BCL2+, BCL2/IGH+, grade 1-2
- Often (NOT always) localized
- Patients do very well, sometimes without therapy or with just excision
  - No recurrences even if just surgical rx, no deaths

Is this almost like another type of “in situ” FL occurring in the duodenum, or as has been suggested a lymphoma with features intermediate between a FL & a MALT ML?

• Some other distinctive features (no time to discuss)
  – $\alpha 4\beta 7$ integrin expression (like other GI ML)
  – Frequent IgA+ unlike many FL
    • AJP 162:105, 2003 (small study)
  – Report that $IGVH$ usage is more like in certain MALT lymphomas & unlike FL, lack activation-induced cytidine deaminase (AID) & FDC only at edge of follicles.
Pediatric follicular lymphoma

- Compared to adult type, more often localized, BCL2-/+; **no t(14;18)**, more often grade 3 with large expansile or irregular follicles but do well.
Some more recently emphasized concepts regarding pediatric FL

- Male predominance, also occur in adults
- Frequent head & neck location
- In spite of high Ki-67, cytology of the neoplastic cells may not resemble classic centroblasts – some consider the cells “blastoid” and others categorize half their cases as grade 1-2 (the pleasures of hematopathology!)
- Small subset with IRF4 (MUM1) translocations (Blood 2011, 118:139)
• Pediatric type FL defined essentially as nodal FL without $BCL2$ rearranged & with Ki-67% $>30\%$: all found to be stage I (in discussion also use this as a criterion).
  – Need to exclude cases associated with DLBCL
  – Be careful as other cases that might fit these criteria need to be excluded, eg because there is focal DLBCL.
• 6 cases with prominent, clonal, CD10+ B-cell populations identified by flow cytometry & confirmed by molecular methods with histologic features of reactive follicular hyperplasia & without evidence of bcl-2 overexpression or the t(14;18) – ~0.8-1.1% of reactive LN
• Clonal CD10+ B cells represented ≥20% of the total B cells
• 5 in young males (8-28 years) with no known immunologic abnormality; 1 in HIV+ female
• No evidence of lymphoma (13-56 mo f/u)
“The relationship, if any, of the biopsy specimens in the 4 youngest patients to previously reported cases of “pediatric follicular lymphoma” is uncertain. A review of the photomicrographs in previous publications on this entity shows apparent nodal effacement with cytologic features ranging from grades 1 to 3, while none of the tissue samples in our series were effaced. However, in all of the previous reports of pediatric follicular lymphoma, at least a subset of the lymphomas were negative for bcl-2 expression and the t(14;18), and many of the patients entered a subsequent clinical remission, even without systemic chemotherapy. Hence, our findings raise the possibility that some clonal B-cell proliferations diagnosed as pediatric follicular lymphoma might have represented an aberrant immune response as opposed to a neoplastic process.”
And be careful even in adults!

- Only 1/8 developed FL.

Light-chain-restricted germinal centres in reactive lymphadenitis: report of eight cases

S H Nam-Cha,^1^ B San-Millán,^1^ M Mollejo,^1^ M García-Cosio,^2^ G Garijo,^3^ M Gomez,^4^ R A Warnke,^5^ E S Jaffe^6^ & M A Piris^1^

*Histopathology* 2008, 52, 436
67 F with mass in axilla
Double κ & λ
Other follicular & other florid lymphoid proliferations that may mimic lymphomas & be clonal

Florid Reactive Lymphoid Hyperplasia of the Lower Female Genital Tract (Lymphoma-like Lesion): A Benign Condition That Frequently Harbors Clonal Immunoglobulin Heavy Chain Gene Rearrangements

Julia Turbiner Geyer, MD,* Judith A. Ferry, MD,* Nancy L. Harris, MD,* Robert H. Young, MD,* Janina A. Longtine, MD,† and Lawrence R. Zukerberg, MD*

Am J Surg Pathol 2010;34:161
Lymphoplasmacytic lymphoma

Blast

Naïve B-cells

FCC - ag selection/Ig somatic hypermutation

Memory B-cells/marg zone
Lymphoplasmacytic Lymphoma and Other Non–Marginal Zone Lymphomas With Plasmacytic Differentiation

Pei Lin, MD,¹ Thierry J. Molina, MD, PhD,² James R. Cook, MD, PhD,³ and Steven H. Swerdlow, MD⁴

LPL - not a new entity

Lukes/Collins classification

• Small lymphocyte (CLL)
• Plasmacytoid lymphocyte
• Follicular center cell types
  – Small cleaved
  – Large cleaved
  – Small noncleaved
  – Large noncleaved
• Immunoblastic lymphoma
Basic description of LPL as originally defined

• Lennert in collaboration with Stein, Mohri, Kaiserling & Müller-Hermelink (1978):
  – ML “composed predominantly of lymphocytes, but containing also plasmacytoid or typical plasma cells as essential components. It shows a diffuse growth pattern.”
  – paraprotein (IgM>IgG>IgA)
  – leukemic
But making this diagnosis has gotten more complicated

- Many small B-cell lymphomas can have plasmacytic differentiation – LPL is a diagnosis made after excluding other lymphomas with plasmacytic differentiation.
  - Marginal zone lymphomas (nodal, extranodal/MALT, splenic)
  - CLL/SLL
  - Follicular lymphomas
  - Mantle cell lymphomas (very rare)
Additional problems

• Some cases have a moderate number of large transformed cells (ddx DLBCL) and DLBCL can have plasmacytic differentiation – no clearcut criteria
• Plasmacytic neoplasms can co-exist with lymphoid neoplasms – not “lymphoplasmacytic” & some PCM can appear quite lymphoid
• HCV-associated clonal lymphoplasmacytic proliferations can be associated with HCV infection that may not behave like a neoplasm (but cases of LPL can be associated with HCV).
The 2008 WHO approach

- LPL is a neoplasm of small B lymphocytes, plasmacytoid lymphocytes, and plasma cells, usually involving bone marrow and sometimes lymph nodes and spleen, which does not fulfill the criteria for any of the other small B-cell lymphoid neoplasms that may also have plasmacytic differentiation.

- Although often associated with a paraprotein usually of IgM type, it is not required for the diagnosis.
2008 WHO more explicitly recognizes inability to make an absolutely definitive diagnosis in some cases

- “Because the distinction between LPL and one of these other lymphomas [with plasmacytic differentiation], especially some marginal zone lymphomas (MZL), is not always clear-cut, some cases may need to be diagnosed as a small B-cell lymphoma with plasmacytic differentiation and a differential diagnosis provided.”
WM is defined as LPL with bone marrow involvement and an IgM monoclonal gammopathy of any concentration.

- IgM paraprotein without LPL is NOT WM
- Level of IgM paraprotein is irrelevant
Classical morphologic findings in LPL

- Bone marrows with intertrabecular interstitial infiltrate of small lymphocytes (paratrab/diffuse infiltrates), plasmacytoid lymphocytes & plasma cells, often with Dutcher bodies (not specific).

- Lymph nodes with intact sinuses and a lymphoplasmacytic proliferation, sometimes with small follicles but usually without large germinal centers or prominent follicular colonization.
Bone marrow with typical interstitial infiltrate

Mast cells

PAS
Cytology not uniform with varying % of lymphocytes and plasma cells (pc) – post-therapy may have high % pc
2.3 gm IgM kappa paraprotein with hyperviscosity, BM involved
Cases with variant histopathologic appearances where there will be more questions about the real diagnosis.

- Vaguely nodular & somewhat more polymorphous, epithelioid histiocytes
- Others (more plasmacytic, diffuse but polymorphous, small foci of possible marginal zone cells)
Immunophenotype

• Light chain restricted lymphocytes (flow cytometry, PSIP only in some laboratories) & light chain restricted plasma cells (PSIP)
  – Usually IgM+ but sometimes IgG+ & rarely IgA+. IgD is not found in most cases.

• CD5- (as high as 43% +), CD10- (rarely positive, BCL6 expected to be -), usually CD23- (as high as 52%+, 58% in workshop)
  – CD5 & CD23 positivity usually only partial

• Often CD25+, CD38+
Plasma cells in LPL

- Plasma cells are CD138+.
- Unlike in plasma cell myeloma, the plasma cells are usually (not always) CD19+ (like non-neoplastic plasma cells).
  - Morice, et al, 2009

Nuclear Protein Dysregulation in Lymphoplasmacytic Lymphoma/Waldenström Macroglobulinemia

Mark J. Roberts, MD,1 Amy Chadburn, MD,1 Shuo Ma, MD, PhD,2 Elizabeth Hyjek, MD, PhD,3 and LoAnn C. Peterson, MD1

Am J Clin Pathol 2013;139:210-219
Although most CD138+ plasma cells in LPL are PAX5- & IRF4/MUM1+ (as expected), presence of PAX5 & absence of IRF4/MUM1 in the CD138+ plasma cells in LPL is more common than in normals, myeloma and marginal zone lymphomas.
Cytogenetic findings

- Unlike what has been taught in the past, **PAX5** translocations are rarely if ever found in LPL.
- Other B-cell lymphoma-associated translocations **NOT** found (eg, **CCND1, MALT1, BCL10, BCL2**). *possible rare exceptions*
- Infrequent trisomies 3, 12, 18 but trisomy 4 reported in 20%
- 6q21 deletions occur in up to 63% bone marrow based LPL/WM -- not at all specific and does not identify distinctive subgroup.
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. Skifter, 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
Non-LPL with *MYD88* L265P mutations (occasional other *MYD88* mutations also reported)

- **MZL (7%)**
  - 1 MALT, 1 splenic, 1 nMZL – latter 2 had IgM paraprotein, extensive BM+, features overlapped WM

- **Splenic MZL (4%)**
  - 2/2 with plasmacytic differentiation, IgM paraprotein, both BM+

- **Nodal marginal zone lymphoma (0%)**

- **MALT lymphoma (4-9 %)**
  - 2/2 ocular MALT with plasmacytic differentiation, IgM paraprotein, 1/2 BM+; 2 orbital MALT, 1/2 BM+; 5 gastric MALTs, no other information

- **CLL (3%)**

- **DLBCL, ABC type (14-29%)**

- **Very rare DLBCL, GCB & Burkitt lymphoma**

Almost time for lunch!
It’s time for..
Marginal zone lymphomas

- Nodal *marginal zone lymphoma*
- Splenic *marginal zone lymphoma*
- Extranodal *marginal zone lymphoma* of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone lymphoma

Blast → Naïve B-cells → FCC - ag selection/Ig somatic hypermutation → Memory B-cells/marg zone
Nodal marginal zone lymphoma – a rare & heterogeneous entity

- Expert pathologist agreement with consensus diagnosis in NHL classification project study was 63%.
- Considered indolent, 5 year OS 55 - 85%, 5 year FFS 22-29%.
  - Some series have many rx’d with CHOP!
- Stage III/IV: 41-88%
- Pediatric cases separately designated in 2008 WHO classification – more often localized & have an excellent prognosis.
Histopathology
Histopathologic appearance is not uniform
Histopathologic issues

• Prominent monocytoid cells not always (or often not) present, complicating definitive diagnosis.
  – In some series, the diagnosis becomes one of exclusion – if not characteristic consider a less specific dx
• Don’t confuse large cells in follicles with evidence of transformation.
Plasmacytic differentiation may be present (21-44%) • Distinction from lymphoplasmacytic lymphoma sometimes problematic. • *MYD88* L265P mutations rare • Less frequent BM involvement (versus LPL 100%) • nMZL might be more frequently unmutated vs 0% LPL (Garchard, et al, 2012) & less frequently have evidence of selection pressure (literature varies) • Different biased IGH chain usage and CDR lengths (literature varies)
How many large cells is OK?

- Variable numbers of large transformed cells described without clearcut criteria for transformation – WHO doesn’t accept sheets of transformed cells
  - Focal ↑ in large cells in 25%; Large cells >20% of tumor cells in 57% of cases; >50% large cells in half of cases; >20% in 16% & 41-50% in 6%; “MALT+DLBCL” type
- Be careful – at least comment if there are prominent large/transformed cells.
Ancillary studies

- Phenotypically, like other marginal zone lymphomas (CD5-, CD10-, cyclin D1-)
  - Exceptions will occur
- No consistent cytogenetic abnormalities
  - Do not have t(11;18).
  - Some have trisomies similar to MALT lymphomas (+3, +18) or 3q27 translocation.
- Heterogeneous regarding IgD, CD43, IRF4/MUM-1, CD38.
A minority of nMZL resemble LN involved by a SMZL
Campo, et al, AJSP 1999

• Polymorphic proliferation around and infiltrating germinal centers without a well-defined mantle zone creating a nodular/vaguely nodular appearance – like nodes involved by SMZL
  – Some cases – proliferation within an attenuated mantle zone
  – IgD+
    • vs IgD- “MALT-type”
Pediatric nMZL often demonstrate PTGC-like lesions (less commonly in adults)
Differential diagnosis

- Benign
  - Toxo (epithelioid histiocytes inside & outside of hyperplastic follicles)
  - CMV (inclusions)
  - Other (can be very difficult if marked monocytoid B-cell hyperplasia, not common) – ancillary studies
Differential diagnosis - neoplasms

- MALT lymphoma presenting in LN
- FL with marginal zone differentiation
  - Possibly adverse prognostic indicator in FL but not clear
- Marginal zone lymphoma mimics
  - “monocytoid-appearing” MCL
  - CLL/SLL with large pale-appearing proliferation centers without many paraimmunoblasts
- Lymphoplasmacytic lymphoma
- T-cell neoplasms
Time to conclude

• Follicular lymphoma
  – Making the diagnosis
  – Specific types of follicular lymphoma to recognize

• Lymphoplasmacytic lymphoma
  – An entity where a specific diagnosis is not always possible but where sequencing studies have led the way to the first real positive molecular cytogenetic finding to help make the diagnosis (even if not 100% specific)

• Nodal marginal zone lymphoma
  – Another sometimes difficult to diagnose small B-cell lymphoma that shouldn’t be used as a wastebasket!
¡Muchas gracias!