Follicular Lymphoma

Biology and Pathology Update Partially

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Lymphoma Classification

- SLL/CLL
- MZL
- BURKITT
- PEL
- MM
- SHM
- Virgin B-cells
- CD5+ B cells
- CD5- B cells
- Follicular Center
- Follicular Mantle
- Marginal Zone
- FLC G3
- DLBCL
- Hodgkin's Disease
- plasmacells
- memory B-cells
Follicular Lymphoma Diagnosis

Pathology Diagnostic tasks:

- Classification of disease
- Stratification of prognosis
- Identification of therapeutic targets
- Evaluation of treatment outcome
Follicular Lymphoma  Prototype of Low Grade B-cell Lymphoma
Definition of Follicular Lymphoma

- Lymphoma of follicular centrocytes and centroblasts
- Immunoprofile: CD20+, CD10+, CD5-, CD23-, Bcl2+, Bcl6+
- Molecular and Genetic: t(14;18) and bcl-2 over-expression
- Variable histologic patterns with most of them showing more or less a follicular pattern.
The second most common B-cell lymphoma

- FL accounts about 20% of all lymphomas with the highest incidence in US and Western Europe.
- FL affects predominantly adults with a mean age of 60.
- FL slightly affects more females (M:F ratio of 1:1.7).
- FL involves mostly lymph nodes. BM involvement 40-70%.
- Most of the patient in advanced stages at diagnosis and only a third in stage I & II.
- Most patients progress to DLBCL, about 3% per year.
- Most of the FL patients are asymptomatic and 20% have spontaneous regression.
- Easy diagnosis with the highest agreement rate.
Follicular Lymphoma Diagnosis

- FL typically express CD19, CD20, CD22, CD10, BCL-2, BCL-6, and CD79,
- FL less frequently express CD43 and even CD5.
- Over-expression of BCL-6 is often associated with a weak or absent expression of BCL-2.
- FL with marginal zone differentiation has down-regulated CD10 and BCL-6 expression in the marginal zone compartment.
- Grade 3b FL express CD10 only in 50% of cases.
- CD10 and BCL-2 are brighter in FL than those in RFH, but not always.
- Ki-67+ fraction is much less in FL than that in RFH.
Follicular Lymphoma Pathology

**Fig 1.** Overall survival (OS) and failure-free survival (FFS) in 580 assessable stage IV follicular lymphoma patients in five consecutive studies spanning 25 years.

Follicular Lymphoma Treatment

Cigudosa, JC. Haematologica | 2008; 93(5)

Peripheral Blood Involvement by Follicular Lymphoma

Circulating neoplastic lymphocytes can be found in many patients with follicular lymphoma

- 18% by standard light microscopy and 60% by PCR

- Cleaved cells appear to have notched nuclei, termed "buttock cells"

- No known specific correlation between circulating cells and remission/relapse or prognosis

- More common with Stages III and IV
# Grading Follicular Lymphoma

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<tr>
<th>Grading</th>
<th>Definition</th>
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<tr>
<td>Grade 1</td>
<td>0-5 centroblasts / HPF</td>
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<td>Grade 2</td>
<td>6-15 centroblasts / HPF</td>
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<tr>
<td>Grade 3a</td>
<td>&gt;15 centroblasts / HPF with centrocytes</td>
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<tr>
<td>Grade 3b</td>
<td>&gt;15 centroblasts / HPF without centrocytes</td>
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<tr>
<td>Follicular</td>
<td>&gt; 75% follicular nodules</td>
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<tr>
<td>Follicular / Diffuse</td>
<td>25 - 75% follicular nodules</td>
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<tr>
<td>Focally follicular</td>
<td>&lt; 25% follicular nodules</td>
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</table>

Follicular / Diffuse:
- >75% follicular nodules
- 25-75% follicular nodules
- <25% follicular nodules
Morphologic Criteria of FL (Stanford Criteria)

WHO recommendation (Mann-Berard) entails counting 20 hpf using 40x objective
Record mean number of large noncleaved cells. Using the table below
Grade 1 is at the low cutoff or below
Grade 2 is above the low cutoff to the high cutoff
Grade 3 is above the high cutoff

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<th>Microscope Type</th>
<th>Eyepiece</th>
<th>Low Cutoff</th>
<th>High Cutoff</th>
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<td>15</td>
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<tr>
<td>American Optical</td>
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<td>Nikon</td>
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<tr>
<td>Nikon</td>
<td>15x</td>
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*Modifications for other microscopes from Warnke et al. AFIP Fascicle.*
Figure 2. Structural features of FL 3. (A) FL 3a. Note that the neoplastic follicular infiltrates are poorly demarcated to the surrounding interfollicular zone and seem to merge with the T-cell area. (B) In contrast, in FL 3b, follicles are sharply demarcated, and there is no merging with the interfollicular infiltrate. Original magnification, 150. Stained with Giemsa.

### Table 2. Features distinguishing grade 3a versus 3b follicular lymphoma.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Grade 3a</th>
<th>Grade 3b</th>
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</thead>
<tbody>
<tr>
<td>Morphology</td>
<td></td>
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<tr>
<td>Centroblasts</td>
<td>Present, more than 15 per HPF, but admixed centrocytes</td>
<td>Almost exclusively large centroblasts</td>
</tr>
<tr>
<td>Diffuse areas</td>
<td>Uncommon</td>
<td>Frequent</td>
</tr>
<tr>
<td>Demarcation of follicles</td>
<td>Usually sharp</td>
<td>Poorly defined, may merge with areas of DLBCL</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>Commonly involved, typically paratrabecular small centrocytes</td>
<td>Infrequent involvement. If positive, typically concordant large centroblasts</td>
</tr>
<tr>
<td>Immunophenotype</td>
<td>Typically CD10*, Bcl-6*, Bcl-2*, MUM1*, p53 usually negative and lack cytoplasmic immunoglobulin</td>
<td>Often CD10*, Bcl-6*, Bcl-2*, MUM1*, p53 expressed in 1/3 cases and cytoplasmic immunoglobulin often present</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>t(14;18) common, clonal evolution with numerous secondary changes</td>
<td>t(14;18) uncommon; BCL6 translocations present, mutually exclusive of t(14;18)</td>
</tr>
<tr>
<td>Mean number of karyotypic alterations</td>
<td>6.5</td>
<td>8.9</td>
</tr>
</tbody>
</table>

*Johnson NA and Gascoyne RD. Haematologica, 2008; 93(7)*
Follicular Lymphoma Diagnosis

Follicular lymphoma is not a single disease

-Heterogeneous response to treatment

-Different length of chronic phase before transformation

-Morphologic variants

-Immunophenotypic and molecular variants

-Influence of anatomic sites and microenvironment

-Host and tumor interaction
Follicular Lymphoma Diagnosis

Morphologic Criteria of FL (Stanford Criteria)

1. Uniform, densely packed follicles
   Frequently back to back. May coalesce, simulating diffuse areas. Median 47 follicles per 40x field (4x objective, 10x eyepiece), Compare to 30 per 40x field for reactive ones.

2. Obliterates nodal architecture
   Compression of interfollicular stroma and vessels. Highlighted by reticulin stain. Extracapsular follicles may be seen

3. Follicular population uniformly atypical
   Small cells have cleaved, twisted, indented, elongated, angulated nuclei. Large cells may be cleaved or non-cleaved. Interfollicular zone typically composed of small reactive cells. Occasionally made up of neoplastic cells. Epithelioid histiocytes may rarely be seen.

4. Ill defined mantle zones in most cases
   Usually indistinct borders

5. Tingible body macrophages infrequent
   More frequent following steroid treatment

6. No polarization of follicles
   Occasionally seen in grade 2 follicular lymphoma

7. Mitotic figures less frequent in follicular lymphoma than reactive hyperplasia
Morphologic Criteria of FL

Special histologic features

**Plasma cells** may be prominent in 10% of cases, which may be monotypic or polytypic. Usually interfollicular. If intra-follicular, the name follicular plasmacytoma has been used.

**Sclerosis** may be present and may be broad of fine bands. Old term is nodular sclerotic lymphosarcoma.

**Amorphous extracellular material deposition** may be present, which are PAS positive, diastase resistant. EM shows membrane bound vesicles. Similar finding sometimes seen in reactive follicles.

**Rosettes of lymphoma** cells surrounding eosinophilic material is seen in some cases. Center of rosette stains as cell membranes and EM shows cytoplasmic processes.

**Infarction, granulomas**, etc. may sometime coexist.

**Pleomorphic cells** with cerebriform and multilobated nuclei occasionally prominent can be seen. Immunoblastic or plasmablastic features. Cytological similar to usual immunoblastic diffuse large B cell lymphoma. Prominent nucleolus, abundant basophilic cytoplasm. Rare, significance unknown.
Follicular Lymphoma Diagnosis: Morphologic Criteria

- Following variants have distinct clinicopathologic features
  - Primary cutaneous follicular lymphoma
  - Diffuse follicle center lymphoma
  - Follicular lymphoma in situ and partial involvement
  - Pediatric follicular lymphoma
  - Primary gastrointestinal follicular lymphoma
  - Extranodal follicular lymphoma NOS
Follicular Lymphoma Diagnosis: Morphologic Criteria

- Signet ring cell variant follicular lymphoma
- Reverse or inverse variant follicular lymphoma
- Floral variant follicular lymphoma
- Follicular lymphoma with marginal zone differentiation
- Hyaline vascular follicular lymphoma
Follicular Lymphoma with plasmacytic differentiation

FROM: Modern Pathology 2010. Follicular lymphomas with plasmacytic differentiation include two subtypes
Joel F Gradowski, Elaine S Jaffe, Roger A Warnke, Stefania Pittaluga, Urvashi Surti, Leena A Gole and Steven H Swerdlow
Many B-cell lymphomas with plasmacytoid morphology are positive for IL-6/IL-6R.
- Plasmacytoid immunoblastic lymphoma
- Plasmacytoid marginal zone cell lymphoma
- Plasmacytoid follicular lymphoma
- Polymorphic immunocytoma

Some B-cell lymphomas with plasmacytoid morphology are negative for IL-6 and require exogenous IL-6 for growth:
- Small lymphocytic lymphoma
- Hairy cell leukemia
Follicular Lymphoma with plasmacytic differentiation

FROM: Modern Pathology 2010. Follicular lymphomas with plasmacytic differentiation include two subtypes
Joel F Gradowski, Elaine S Jaffe, Roger A Warnke, Stefania Pittaluga, Urvashi Surti, Leena A Gole and Steven H Swerdlow
Follicular Lymphoma with Marginal Zone Differentiation

- Follicles surrounded by rim of pale monocytoid cells
- Centers of follicles have usual population of follicular lymphoma
- Both cell populations composed of the same clone
- May be confused with marginal zone lymphoma or reverse (inverse) variant of follicular lymphoma
- Shorter survival has been reported in some cases
Follicular lymphoma (FL) of Spleen

- Frequently lack BCL2 expression.
- Two morphologic patterns were identified: one with architectural abnormalities (AA) and one with an extensive architectural preservation (AP) pattern.
- Often grade 1 histologic features.
- All cases displayed a CD10+/BCL2+ phenotype.
- Cytogenetics and FISH identified IGH/BCL2 or BCL6 translocations in all tested cases.
- Frequently display an exclusively intrafollicular growth pattern resembling so-called in situ FL.
Howard, HT et al. Am J Clin Pathol May 2009 vol. 131 no. 5 656-662
Blastoid or Blastic Transformation of Follicular Lymphoma

- Diffuse as well as follicular histologic patterns

- Medium sized lymphoid cells with round nuclei, fine chromatin, inconspicuous nucleoli, and high mitotic rate.

- Expression of CD10, BCL6, and BCL2 and often TdT negative / cyclin D1 negative.

- Aberrant expression of CD43, MUM-1, CD57 and CD5 occasionally.

- Poor prognosis.
LYMPHOCYTE CYTOMORPHOLOGY

GERMINAL CENTER

SNC → LNC → LC → SC
Chromosome topology in a nucleus

Nature Reviews | Cancer
DNA Breaks Normally in Germinal Center

Figure 2: The positioning of the 23 pairs of chromosomes within the nucleus (here labeled with red, green, and blue dyes) as a cell goes through the cell cycle may significantly influence gene expression.

Figure 3: If the protein ATM (blue and yellow) is mutated, double-strand DNA breaks can go unrepaird and result in genomic damage that can be passed on to daughter cells. If unchecked, this damage can promote the development of lymphomas and the rare disorder ataxia telangiectasia.
The Role of GC in the Pathogenesis of B-cell Lymphoma

- Malignant transformation appears to occur in the germinal center.
- The increased genetic alterations are likely associated with receptor editing, somatic hyper-mutation and class switch.
- Most of the B cell lymphomas, including FL, express antigen receptor (BCR).
- Early lymphomas could be antigen dependent and advanced / aggressive lymphomas are antigen independent.
- Early follicular lymphoma is follicular dendritic network dependent.
- A B-cell lymphoma is defined by the combination of the transformation event and the stage of differentiation at transformation.

Cancer Stem Cell Theory

The cancer stem cell (CSC) hypothesis states that tumors are composed of a heterogeneous population of cells, within which resides a small population of cancer stem cells or CSCs that are responsible for the maintenance and propagation of the tumors and are the likely cause of disease relapse and metastasis. These cells possess many of the same stem cell properties found in normal stem cells including: (i) the ability for self-renewal; (ii) the ability to differentiate; (iii) increased drug transport pumps (i.e. ABCG2, MDR-1); (iv) activation of anti-apoptotic pathways; (v) increased telomerase activity; (vi) activation of transcription factors required for self-renewal (i.e. BMI-1, Nannog); and (vii) the ability to migrate.
Cancer Stem Cells
Pathogenesis of Follicular Lymphoma

A: Loci IGH | IG somatic mutations | Oncogene: BCL2 | CCND1

Progenitor B cell → Immature B cell → Immature B cell (pre-malignant) → BCL2-IGH translocation → SHM, CSR → Germinai-center B cell → Hodgkin's lymphoma: Reed-Sternberg cell → Follicular lymphoma cell
Bone Marrow Niche
Follicular dendritic cell (FDC) signalling molecules.

Park CS. Immunology, 2004:114, 2–10
Figure 2. Representation of the two immune patterns observed in FL patients significantly associated with their clinicobiological features. The immunosurveillance pattern (predominantly T lymphocytes and macrophages) is associated with grade 3 FL and an indolent clinical behavior. The immune-escape pattern (predominantly CD57+ T cells) is associated with low-grade FL and an aggressive clinical behavior (reprinted with the permission of the Journal of Clinical Oncology).
Microarray profile predict survival:
Tumor infiltrating immune cells.

Table 2. Predictive Power of Gene-Expression Signatures in Follicular Lymphoma.*

<table>
<thead>
<tr>
<th>Gene-Expression Signature</th>
<th>P Value for Contribution to Model in Test Set</th>
<th>Relative Risk of Death (95% CI)*</th>
<th>Effect of Increased Gene Expression on Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune-response 1</td>
<td>&lt;0.001</td>
<td>0.15 (0.05–0.46)</td>
<td>Favorable</td>
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<tr>
<td>Immune-response 2</td>
<td>&lt;0.001</td>
<td>9.35 (3.02–28.90)</td>
<td>Unfavorable</td>
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Tumor Microenvironment:

- Stromal cells including macrophages, dendritic cells, and fibroblasts, and the tumor supportive mesenchyme
- Lymphocytes and immunomodulation
- Blood vessels and angiogenesis
- Soluble factors: chemokines, hormones, cytokines, etc.
Environmental Factors of Follicular Lymphoma

<table>
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<tr>
<th>Normal Germinal Center</th>
<th>Follicle of Follicular Lymphoma</th>
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<tr>
<td>Survival and proliferation signals for B cells from dendritic cells and T cells</td>
<td>Survival and proliferation signals for follicular-lymphoma B cells from dendritic cells and T cells?</td>
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<tr>
<td>Follicular dendritic cell</td>
<td>Follicular lymphoma B cells</td>
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<tr>
<td>T cell</td>
<td>Removal of (apoptotic) follicular lymphoma cells by macrophages</td>
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<tr>
<td>B cells</td>
<td>Macrophage</td>
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<td>Removal of apoptotic B cells by macrophages</td>
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</table>

Follicular Lymphoma Pathology

Follicular Lymphoma: Treatment: Minimal Residual Disease

de Jong D et al, Haematologica | 2009; 94(1)

Table 1. Comparison of published data and results from this study on clinicopathological correlations for T-cell populations, macrophages and follicular dendritic cells.

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<th>Lea²</th>
<th>Giae²</th>
<th>Carroli¹</th>
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**Table Legend:**
- **Legend:**
  - Good: statistically significant association with good, respectively poor prognosis.
  - Poor: borderline significant or trend to good, respectively poor prognosis, in bold.
  - nd: no association with prognosis.
  - e.g.: end-of-spectrum analysis, PFS: progression-free survival, OS: overall survival, DSS: disease-specific survival, CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone, R: rituximab, MCP: mitoxantrone, chlorambucil, prednisone, BP: VACOP: bleomycin, cyclophosphamide, vincristine, prednisone, RT: radiotherapy, *personal communication, performed on the same series (R. Gascoyne), *specifically stated as perifollicular, †PFS only, not OS, *based on flow data.

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Factors that may affect treatment response

- Tumor characteristics
- Tumor microenvironment.
- Treatment history.
Bone Marrow Involvement by Follicular Lymphoma

• Paratrabecular nodules are characteristic and virtually diagnostic of involvement

• Architecture frequently more useful than cytology for grade 1 cases

• Typically increased reticulin fibers present

• Non-paratrabecular nodules are probably benign, most of the time.

• Grade 1 follicular lymphoma in marrow in a patient with diffuse large B cell lymphoma suggests that the large cell lymphoma is derived by transformation of the follicular lymphoma
Bone Marrow Biopsy: Staging and Re-staging

- Unilateral versus bilateral BM biopsy
- Aspiration versus core biopsy
- Morphology versus flow versus molecular testing
- What is the true rate of BM involvement?
Quality of BM Staging Biopsy

Normally a 2cm long BM is ideal for adequate assessment of lymphoma involvement.

<table>
<thead>
<tr>
<th>Length of core (mm)</th>
<th>No. of cases</th>
<th>Number (%) of positive cases</th>
<th>Increase</th>
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<tbody>
<tr>
<td></td>
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<td>Before review</td>
<td>After review</td>
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<tr>
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<td>33</td>
<td>5 (15)</td>
<td>6 (18)</td>
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<tr>
<td>&gt;30</td>
<td>36</td>
<td>8 (22)</td>
<td>12 (33)</td>
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<td>Total</td>
<td>172</td>
<td>29 (17)</td>
<td>47 (27)*</td>
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</table>

*P = 0.042 for trend.
BM FL Tumor Burden by PCR After R-CHOP

- 100% BM involvement by FL using PCR
- After 1 cycle of R-CHOP, 80% patients negative.
- After 3 cycles, 80% patient negative.
- After 8 cycles, 100% patients negative.
Follicular Lymphoma: Summary

• Follicular lymphoma is not a single, uniform disease.
• It can have many morphologic variants
• Primary anatomic location is important
• Lymphoma stem cell may be the explanation
• Prognosis should be treatment defined
• Adequate sampling and test selection are still important