Follicular lymphoma: review and refresh

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Disclosures

I do not have financial/other relationships with the manufacturer(s) of commercial product(s) or provider(s) of commercial service(s) that would affect my views discussed in this educational activity.
Follicular lymphoma (FL): review and refresh

1. Describe features characteristic of FL, and outline an approach to diagnosis that includes consideration of small biopsy specimens.

2. Discuss morphologic and immunophenotypic variants of FL that may confound the diagnosis.

3. List clinically significant subtypes of FL, and describe how they are recognized.
86 year old female
Widespread lymphadenopathy (up to 3cm)
Core biopsy of inguinal lymph node
Follicular lymphoma

- Abnormal infiltrate mature lymphoid cells
- Effacing normal lymph node architecture
- Usually at least partial follicular growth pattern
- Mixture of centrocytes and centroblasts, with lack of polarization and lower than expected proliferation rate
- Germinal center B-cell immunophenotype:
  - CD20+, CD10+, Bcl-6+ (and usually abnormal Bcl-2+)
- $IGH/BCL2$ gene rearrangement
Small specimens

• Optimize collection / processing:
  – Core & FNA, with allocation for flow cytometry
  – 14-18 gauge needle, 4+ cores, >1cm in length
  – Gross into multiple blocks
  – Cut unstained slides for possible further studies

Frederikson JK et al., *Arch Pathol Lab Med* 2015;139:245–251
Merzianu M et al., *Am J Clin Pathol* 2018;150:393-405
Small specimens

• Interpretation:
  – CD21 and/or CD23 to highlight follicular growth
  – Ki-67 to avoid missing something higher grade, and distinguish from highly proliferative FH
  – Gather enough information to be confident of excluding other diagnostic considerations
  – Consider if the specimen is representative

Choi SM etal., Arch Pathol Lab Med 142;1330-1340: 2018
FL differential diagnosis

- Follicular hyperplasia
- Low-grade lymphoma e.g. marginal zone lymphoma, lymphoplasmacytic lymphoma
- Higher grade lymphoma e.g. diffuse large B-cell lymphoma
Follicular hyperplasia
Follicular lymphoma vs. hyperplasia

• Follicular hyperplasia may demonstrate clonality

• Follicular lymphoma has challenging variants:
  – Morphologic variants:
    • Floral (progressive transformation)
    • Castleman-like (regressive transformation)
  – In situ follicular neoplasia
  – Bcl-2 negative follicular lymphoma
  – EBV positive follicular lymphoma
Follicular lymphoma, resembling PTGC
Bcl-2 negative follicular lymphoma

• 10-15% follicular lymphoma grade 1-2
• More frequent in grade 3 and some subtypes, especially if lack BCL2 gene rearrangement
• BCL2 mutation may alter epitope, with decreased detection by IHC. May detect with E17 antibody clone cf. routinely used SP66

Adam P et al., *Hum Pathol* 44(9);1817-1826: 2013
EBV+ follicular lymphoma

• Rare (2.6% unselected follicular lymphoma)
• No distinct morphologic or immuno-phenotypic characteristics
• Uncertain clinical significance:
  – Majority progress to higher-grade FL or DLBCL?
  – Worse overall survival, but not event free survival?

Gollub et al., *Modern Pathology* 2017;30:519-529
Mackrides et al., *Am J Hematol* 2019;94:E62-64
FL differential diagnosis

• Follicular hyperplasia

• Low-grade lymphoma e.g. marginal zone lymphoma, lymphoplasmacytic lymphoma

• Higher grade lymphoma e.g. diffuse large B-cell lymphoma
Extranodal marginal zone lymphoma
Follicular vs. marginal zone lymphoma

- MZL with follicular colonization
- MZL positive for CD10 (rare)
- FL with lack of demonstrable CD10
- FL with marginal zone differentiation
- FL with plasmacytic differentiation
Follicular lymphoma with MZ differentiation
CD10 negative follicular lymphoma

- Absence CD10 more frequent in grade 3 FL
- CD10 expression stronger in follicles than interfollicular areas, bone marrow and PB
- Reported discordance IHC vs. flow cytometry:
  - interfollicular cells, Fluorochrome selection (FITC)
- Consider CD10-, MUM1+ FL
CD10-, MUM1+ follicular lymphoma

- Frequently elderly patients
- Often high grade follicular lymphoma (3A or 3B)
- Lack IGH-BCL2 rearrangement, but often BCL6 amplification and BCL2 amplification/gain
- Must also distinguish from large B-cell lymphoma with IRF4 rearrangement, which may have a partial follicular growth pattern (usually MUM1+, but CD10+, variably Bcl-2+)

Karube et al., Blood 2007;109:3076-307
Salaverria et al., Blood 2011;118:139-147
FL with plasmacytic differentiation

- Inter-follicular plasma cells:
  - Positive *BCL2* rearrangement

- Intra-follicular plasma cells:
  - Negative *BCL2* rearrangement (MZL?)

- Must also distinguish from lymphoplasmacytic lymphoma

Gradowski JF et al., *Mod Pathol* 2010;23:71-79
History of low-grade B-cell lymphoma, possible follicular lymphoma, status-post therapy. Also, IgM monoclonal gammopathy
Lymphoplasmacytic lymphoma (LPL)

• Must distinguish from other lymphoma with plasmacytic differentiation e.g. MZL, FL

• LPL can be CD10 positive:
  – May vary within and between specimens
  – Negative for other GC markers e.g. Bcl-6

• Useful to evaluate for MYD88 L265P mutation
FL differential diagnosis

• Follicular hyperplasia
• Low-grade lymphoma e.g. marginal zone lymphoma, lymphoplasmacytic lymphoma
• Higher grade lymphoma e.g. diffuse large B-cell lymphoma, *MYC & BCL2 &/or BCL6* rearrangements, large B-cell lymphoma with IRF4 rearrangement
History of follicular lymphoma (6 years)
Recurrent lymphadenopathy, s/p therapy
Cytogenetic studies:

67-70,XX,+X,+1,psu

der(12;1)(p13;p13)add(1)(q32),der(1;17)(q10;q10),+2,
del(2)(p11.2)x2,+add(3)(q27),+del(3)(q21),+4,+5,+add(6)(q11),
+add(6)(q13),add(8)(q24.1),+9,+del(10)(q22q24),+11,+12,+12,
+12,+14,t(14;18)(q32;q21)x2,+17,+18,+19,+20,+20,+21,+22,
+mar[cp20]

Fluorescence in situ hybridization studies:

• 75% of nuclei have a MYC rearrangement, a BCL6 rearrangement, and IGH/BCL2 fusion (“triple-hit”)
FL with MYC & BCL2 &/or BCL6 rearrangements

- Different disease than high-grade B-cell lymphoma with MYC & BCL2 &/or BCL6
- Gain of MYC often associated with transformation
- Double-hit FL often has at least some areas grade 3
- Usually associated with high MYC protein expression
- Standard FL therapy seems sufficient

Miyaoka M et al., Mod Pathol 31;313-326: 2018
Ziembas JB et al., Am J Clin Pathol 153;672-685: 2020
Large B-cell lymphoma with IRF4 rearrangement

- Diffuse, follicular & diffuse, or follicular
- Medium-size cells, chromatin more open than centrocytes, small basophilic nucleoli
- Most CD10+ (2/3), Bcl-6+, Bcl-2+, MUM1+
- Proliferation rate high, but no starry-sky
- Cryptic rearrangement IRF4 gene (FISH IRF4/IGH)
- Primarily children and young adults
- Favorable outcome

Lim MS et al., Am J Clin Pathol 152;277-301: 2019
Clinically significant subtypes FL

- Grade 1-2, & 3A vs. 3B follicular lymphoma?
- In situ follicular neoplasia
- Duodenal-type follicular lymphoma:  
  - Localized 2nd portion, grade 1-2, good prognosis
- Testicular follicular lymphoma:  
  - Often children, lack BCL-2 gene rearrangement, grade 3A, good prognosis
- Pediatric-type follicular lymphoma...
Pediatric-type follicular lymphoma

- Children, young adults & older
- Localized disease, primarily head & neck
- Pure follicular proliferation
- Expansible follicles with intermediate-size cells
- High proliferation index
- Lack \textit{BCL2}, \textit{BCL6} and \textit{IRF4} gene rearrangements
- Good prognosis, sometimes just with excision

Ozawa MG et al., \textit{Mod Pathol} 2016;29:1212-1220
Follicular lymphoma (FL): review and refresh

• FL diagnosis possible from small specimens
• Usually requires morphology and phenotyping
• Must distinguish from follicular hyperplasia
• Also, distinguish from MZL, LPL, HGBCL and large B-cell lymphoma with IRF4 rearrangement
• Recognize FL subtypes of clinical significance e.g. duodenal, testicular, pediatric-type