

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

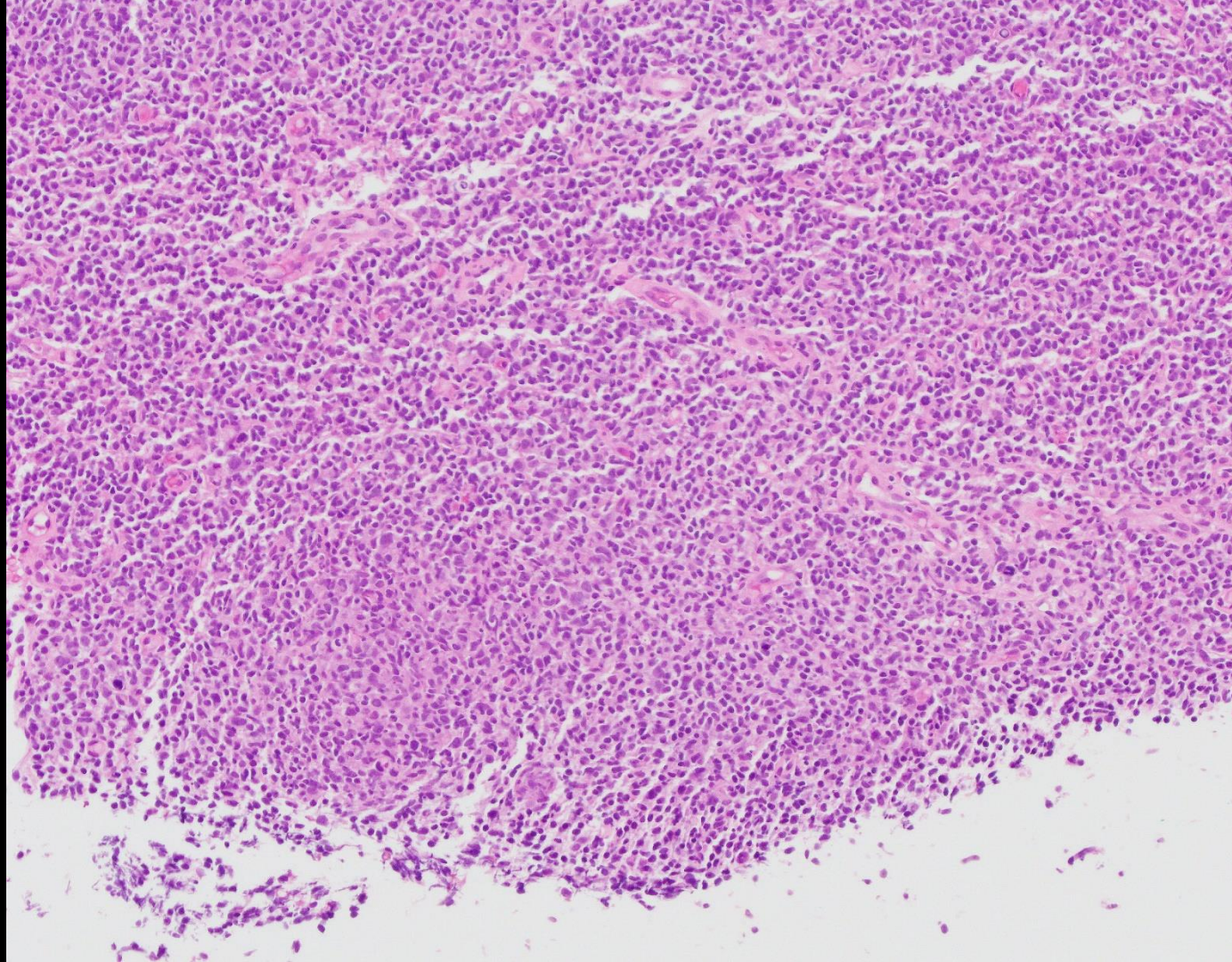
1. Describe features characteristic of FL, and outline an approach to diagnosis that includes consideration of small biopsy specimens.
2. Discuss morphologic and immunophenotypic variants of FL that may confound the diagnosis.
3. List clinically significant subtypes of FL, and describe how they are recognized.

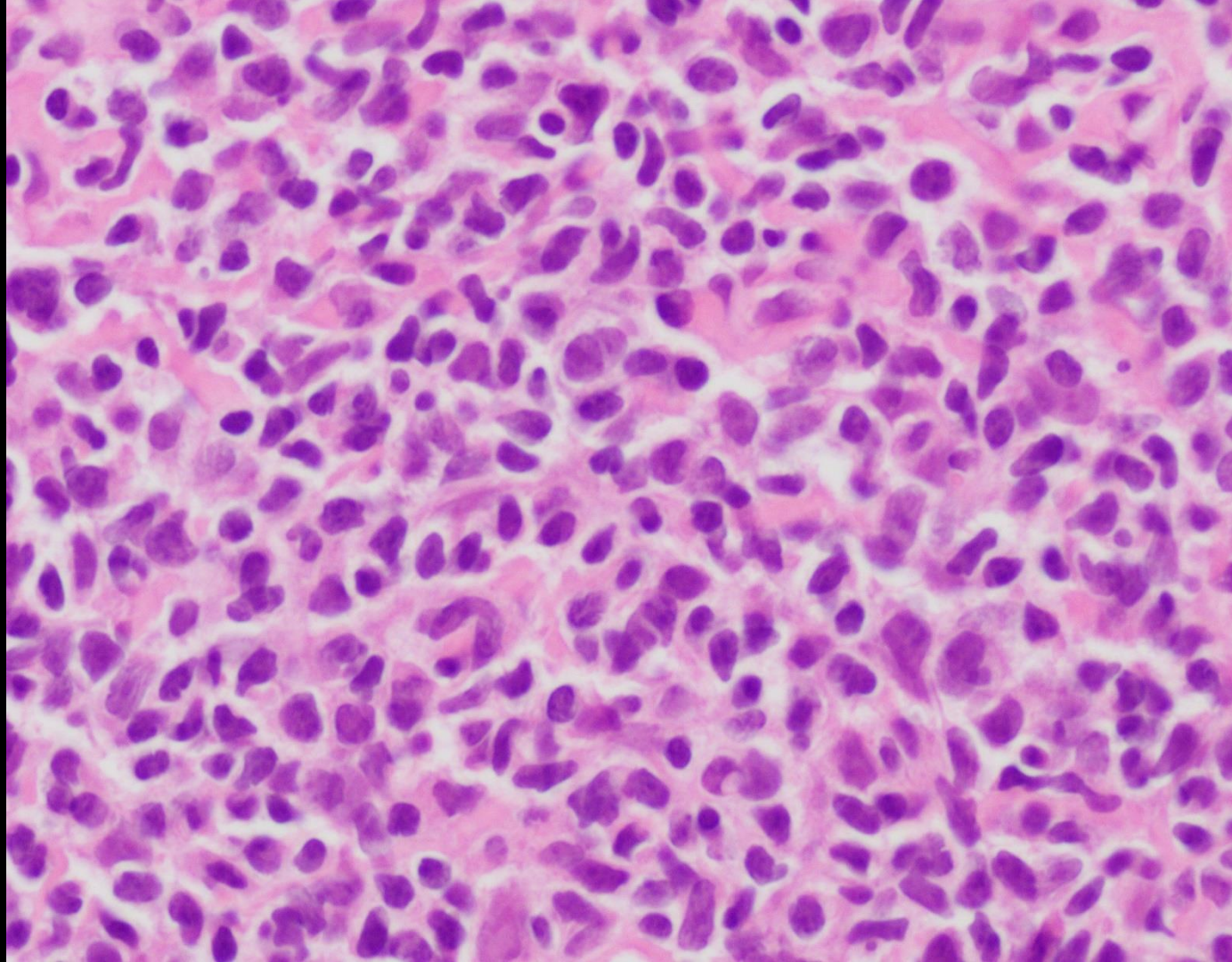
86 year old female

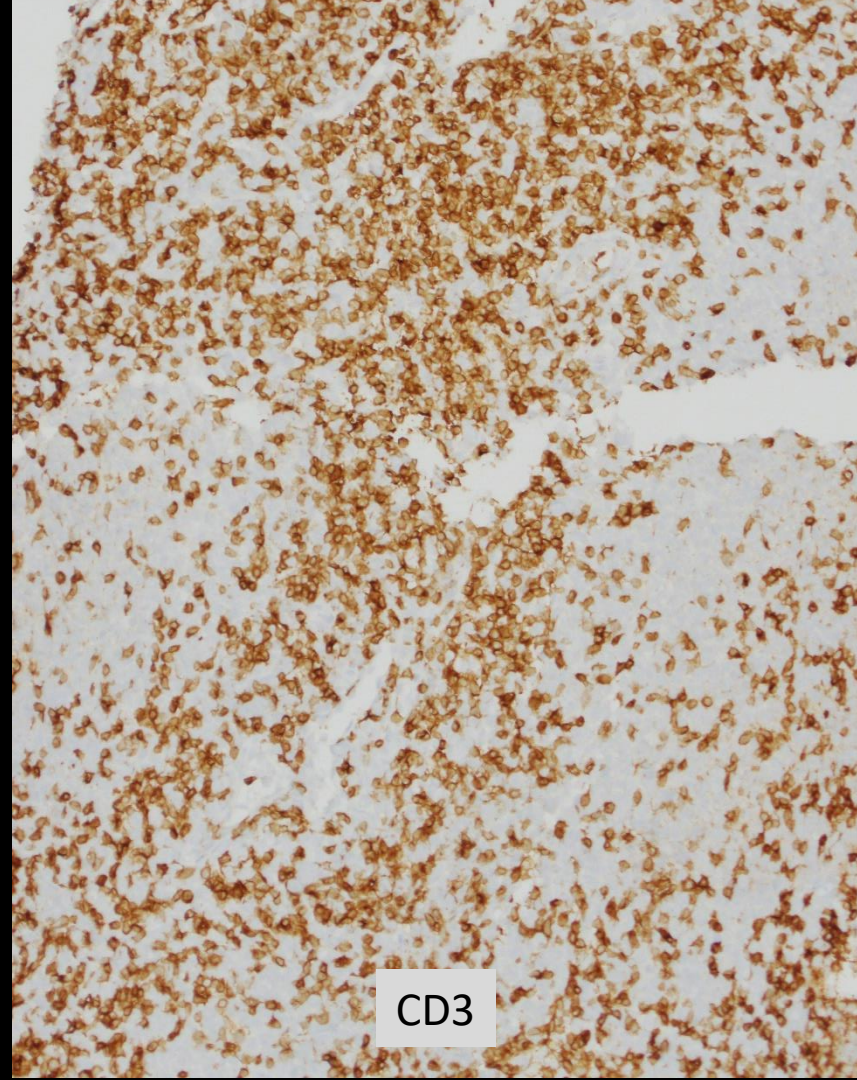
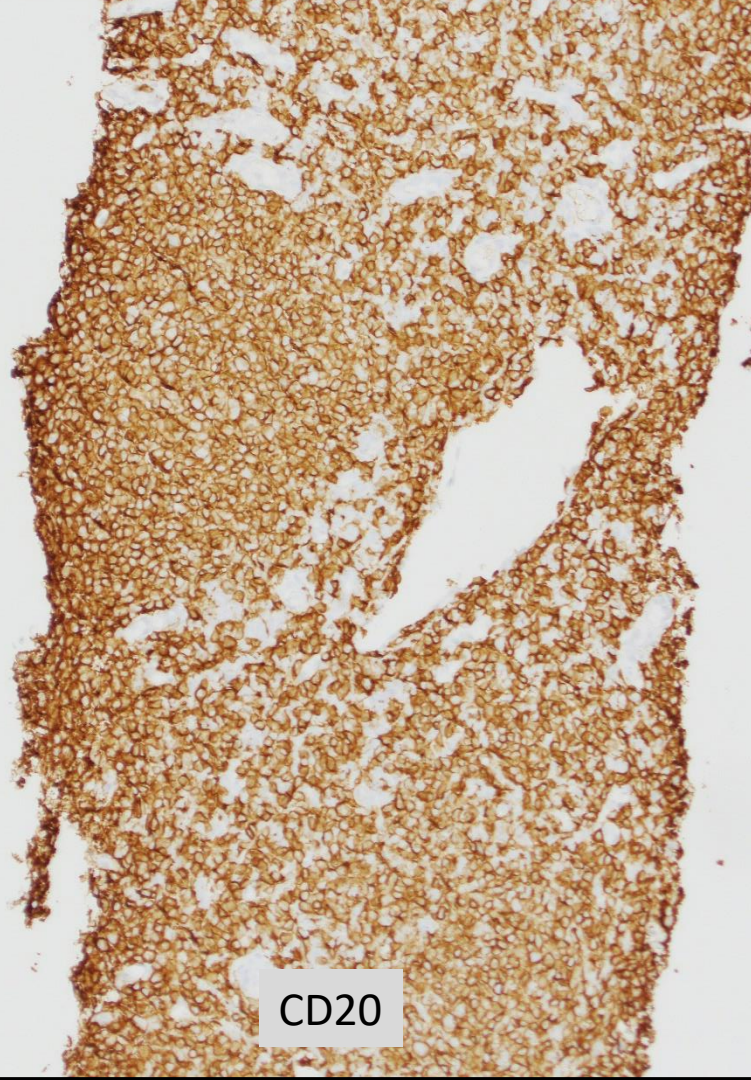
Widespread lymphadenopathy (up to 3cm)

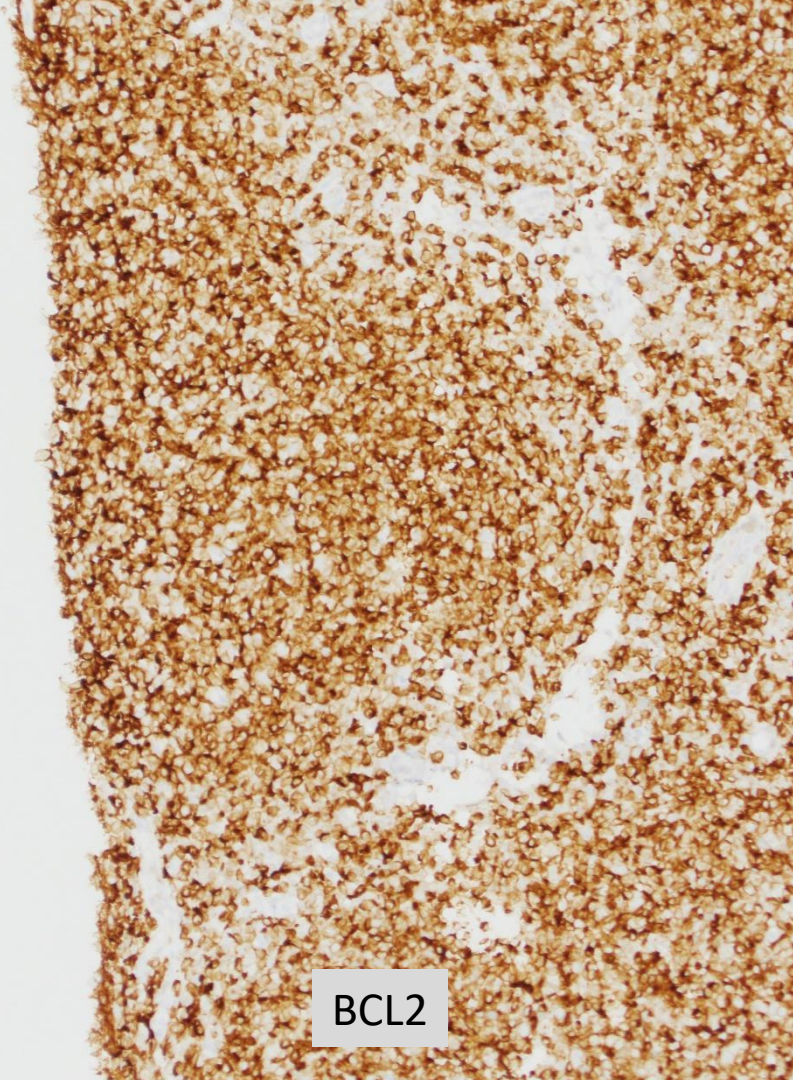
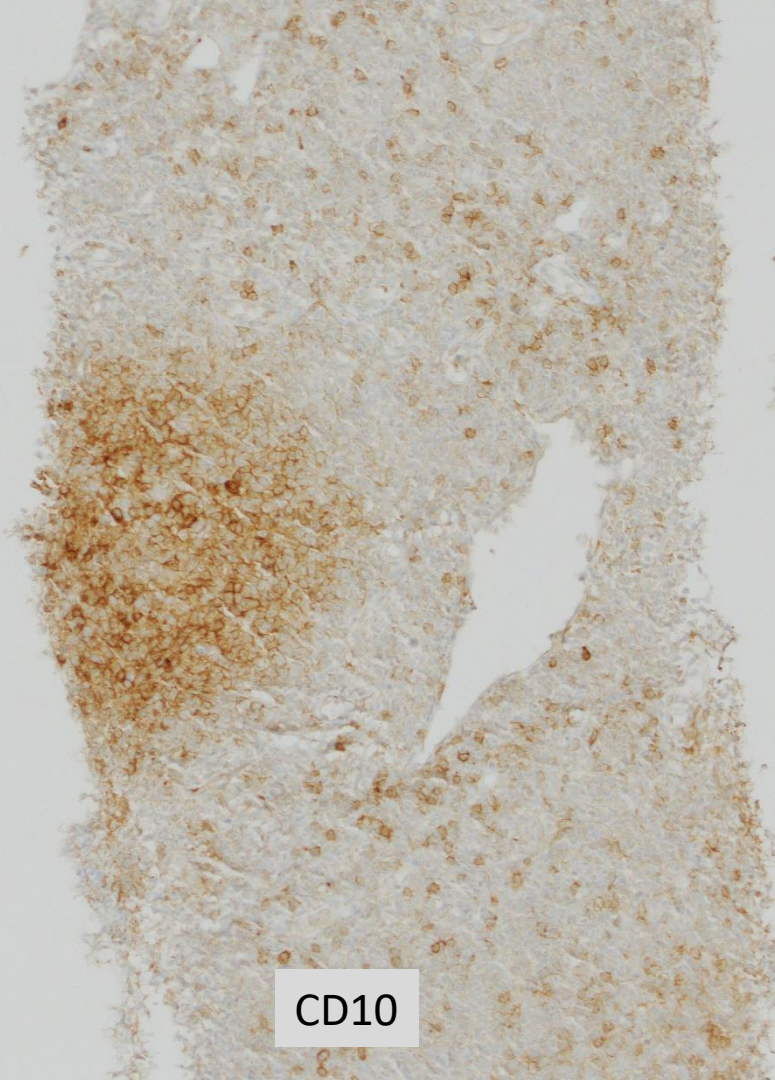
Core biopsy of inguinal lymph node

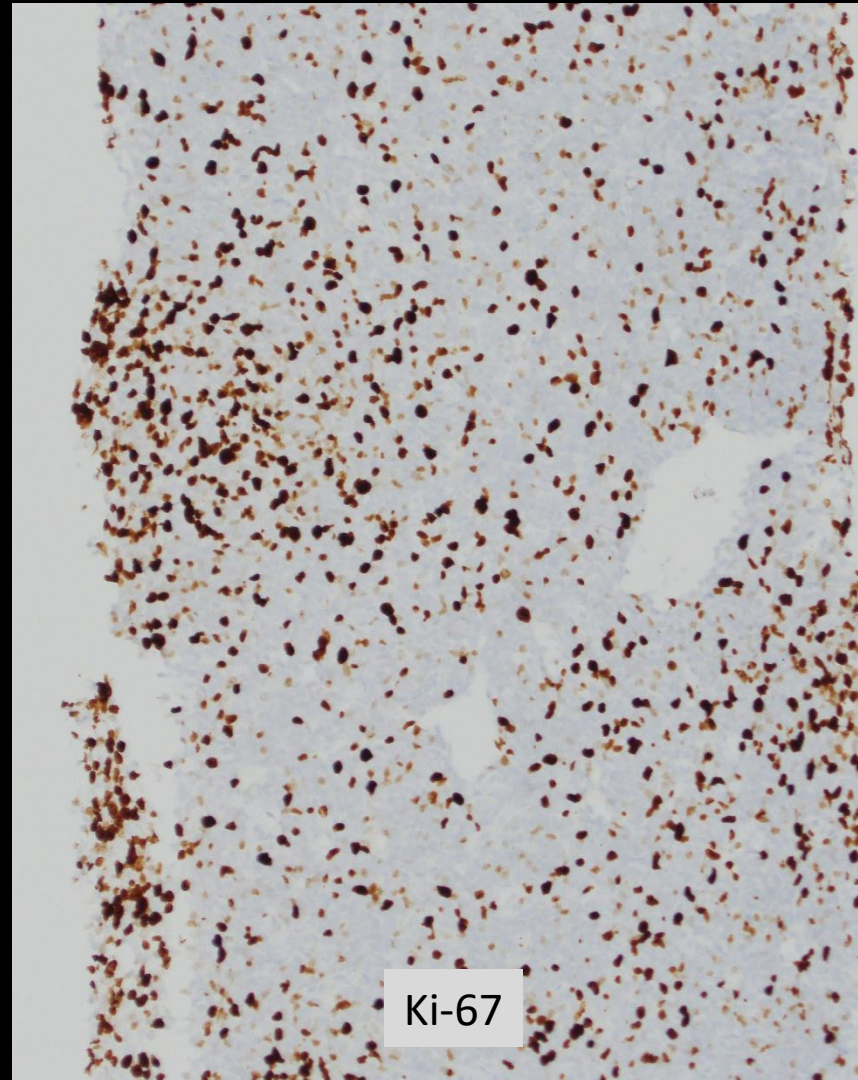
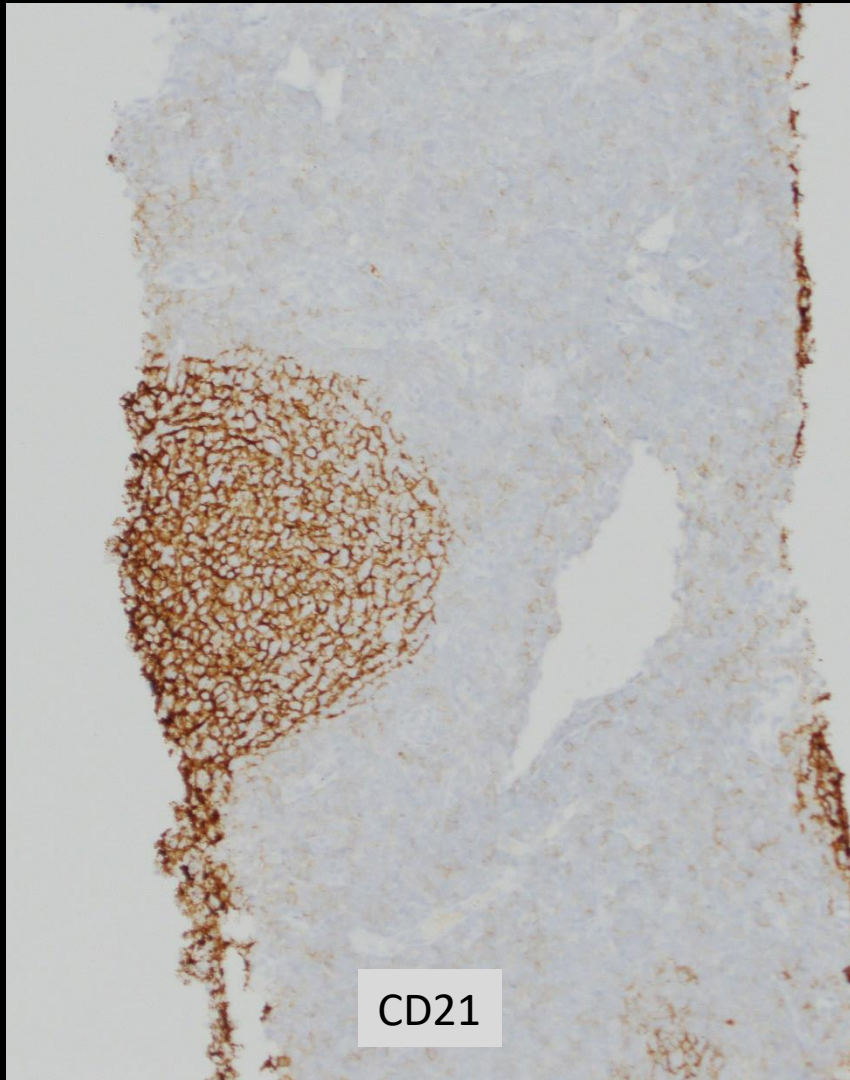












Follicular lymphoma

- 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

Hu Q et al., *Am J Clin Pathol* 2013;140:238-247

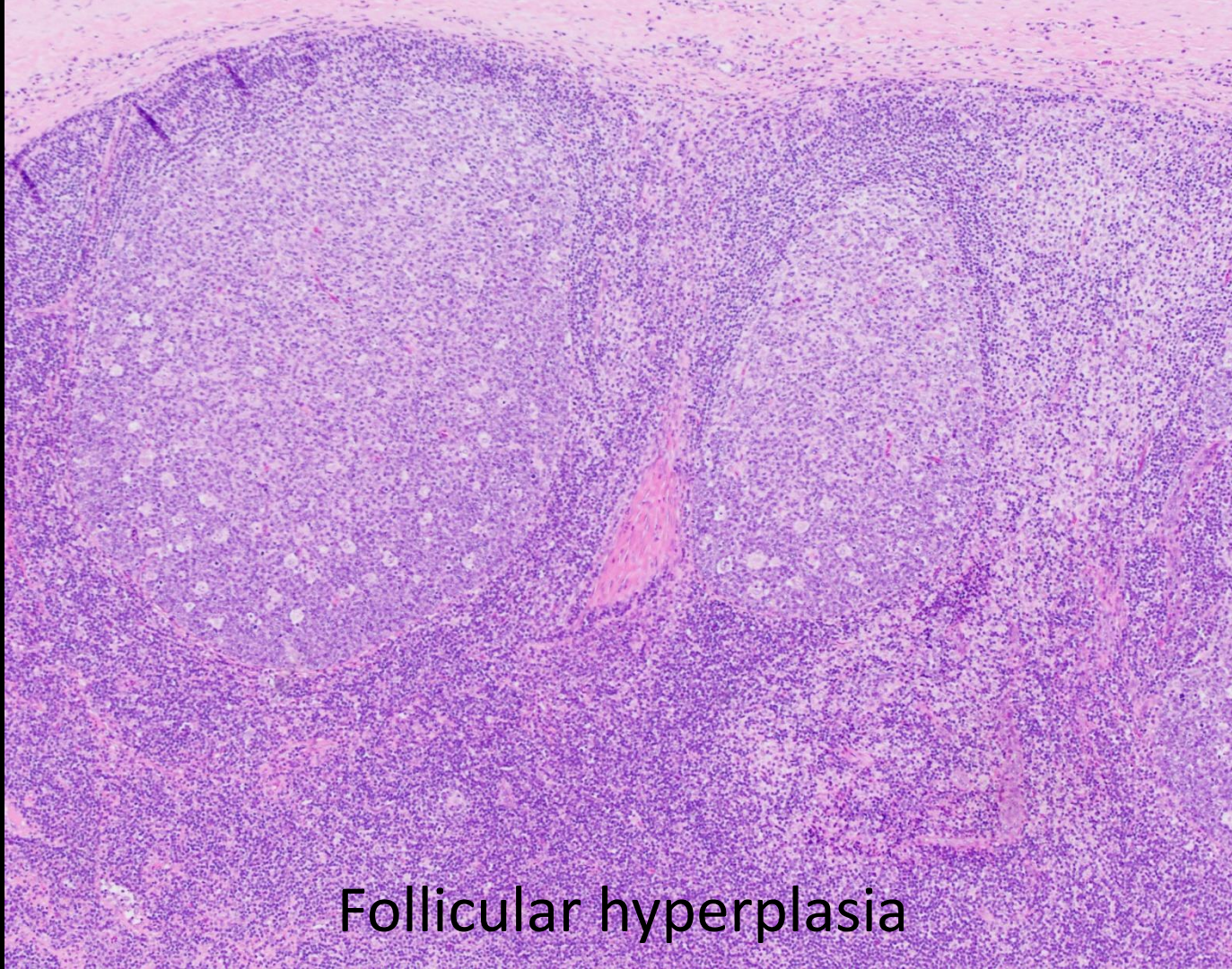
Merzianu M et al., *Am J Clin Pathol* 2018;150:393-405

Small specimens

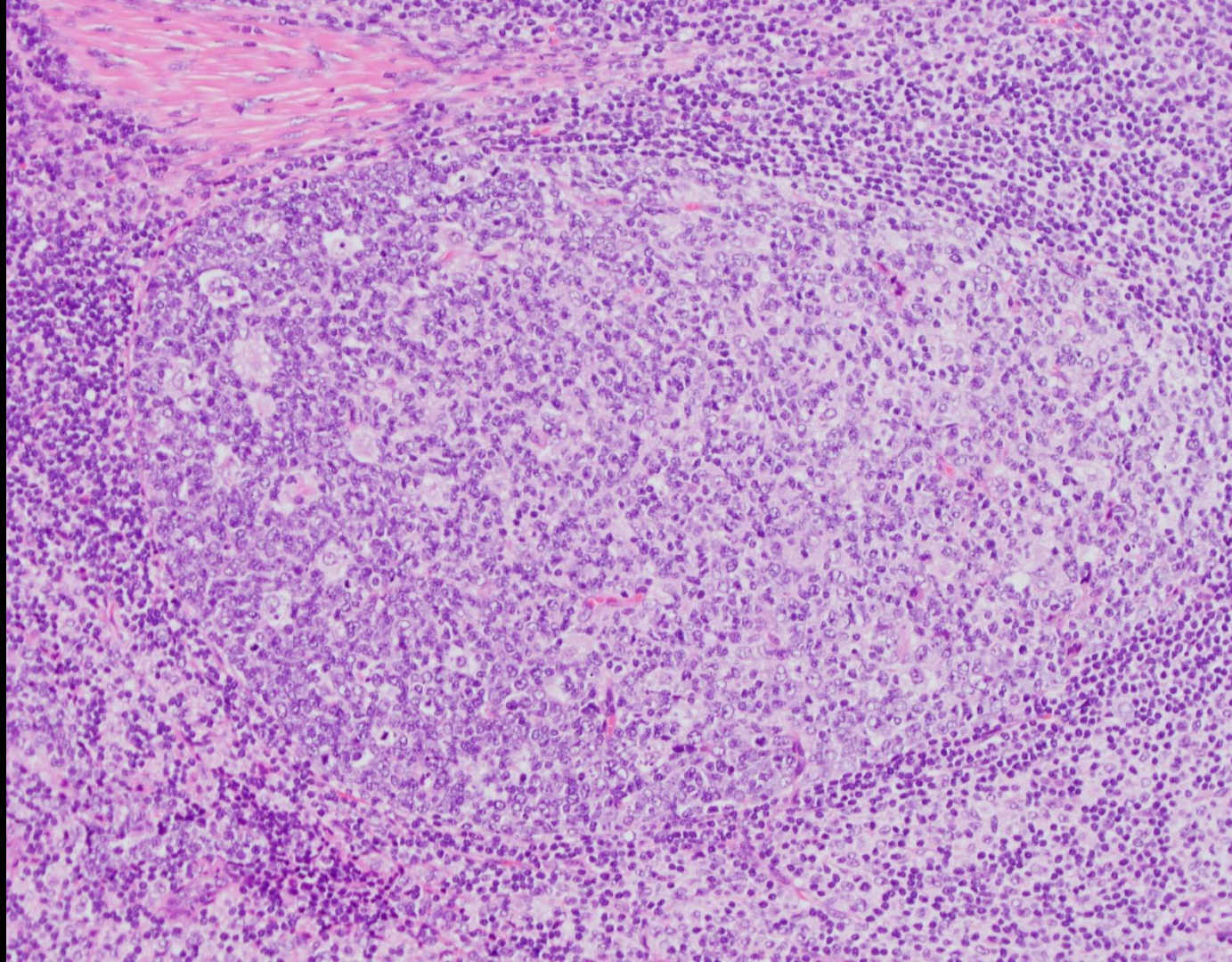
- Interpretation:
 - CD21 and/or CD23 to highlight follicular growth
 - Ki-67 to avoid missing something higher grade, and distinguish from highly proliferative FH
 - Gather enough information to be confident of excluding other diagnostic considerations
 - Consider if the specimen is representative

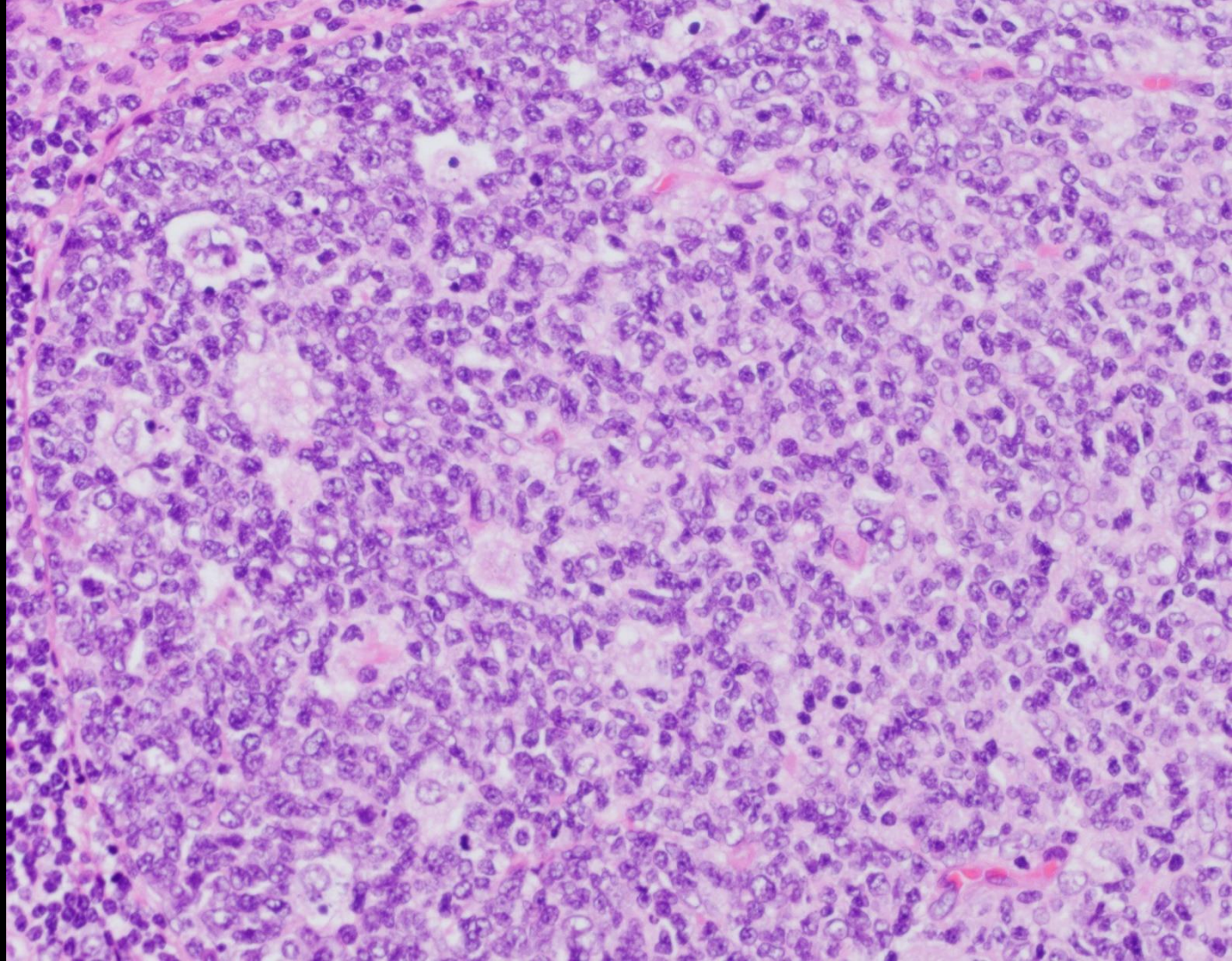
FL differential diagnosis

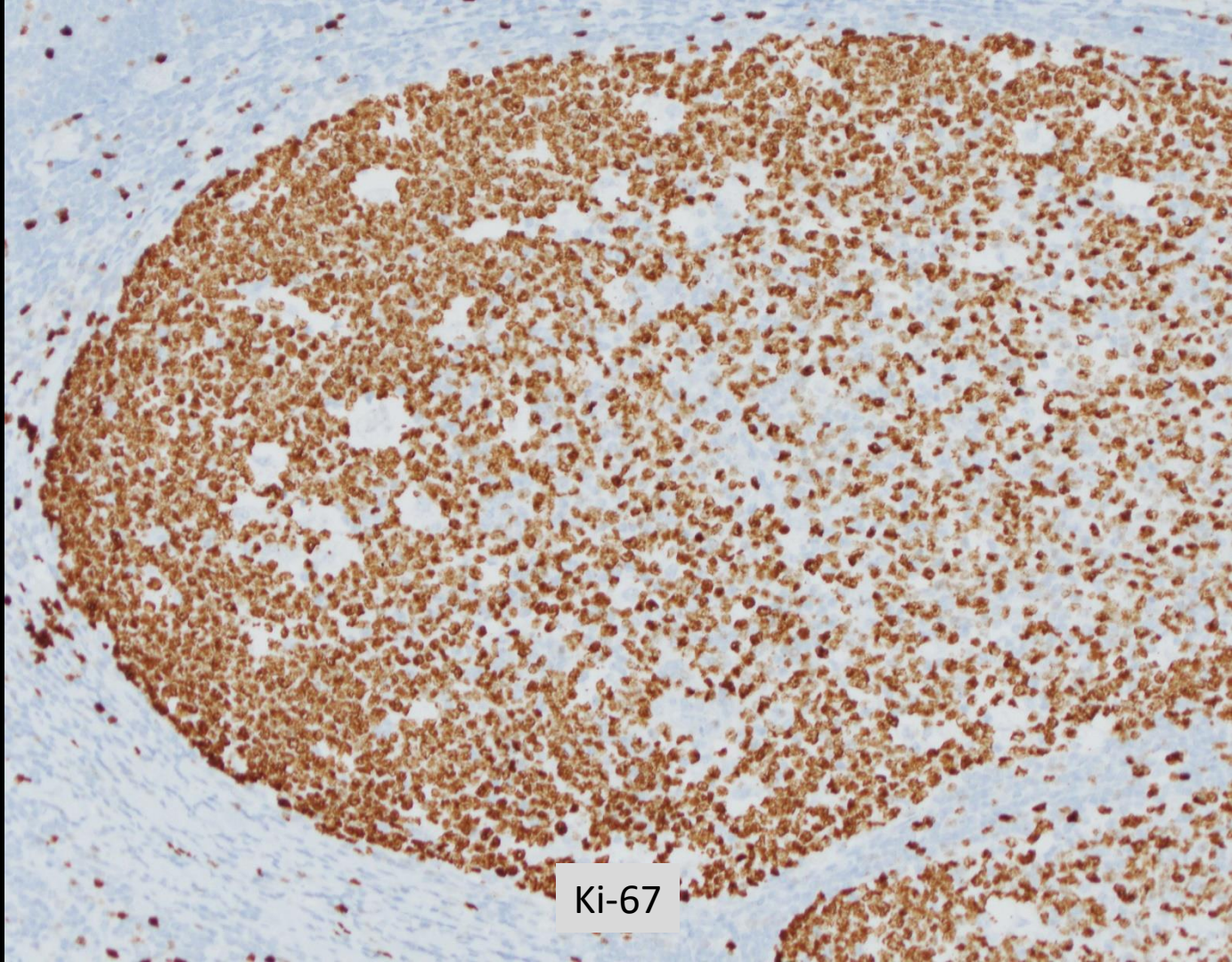
- Follicular hyperplasia
- Low-grade lymphoma e.g. marginal zone lymphoma, lymphoplasmacytic lymphoma
- Higher grade lymphoma e.g. diffuse large B-cell lymphoma



Follicular hyperplasia







Ki-67

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

A histological slide showing a dense population of small, dark-staining lymphocytes. The cells are arranged in a somewhat disorganized pattern, with some larger, pale-staining cells interspersed. The overall appearance is that of a lymphoid infiltrate, consistent with the caption's description of follicular lymphoma resembling PTGC. The background is a light pinkish-purple hue, typical of a hematoxylin and eosin (H&E) stain.

Follicular lymphoma, resembling PTGC

Bcl-2 negative follicular lymphoma

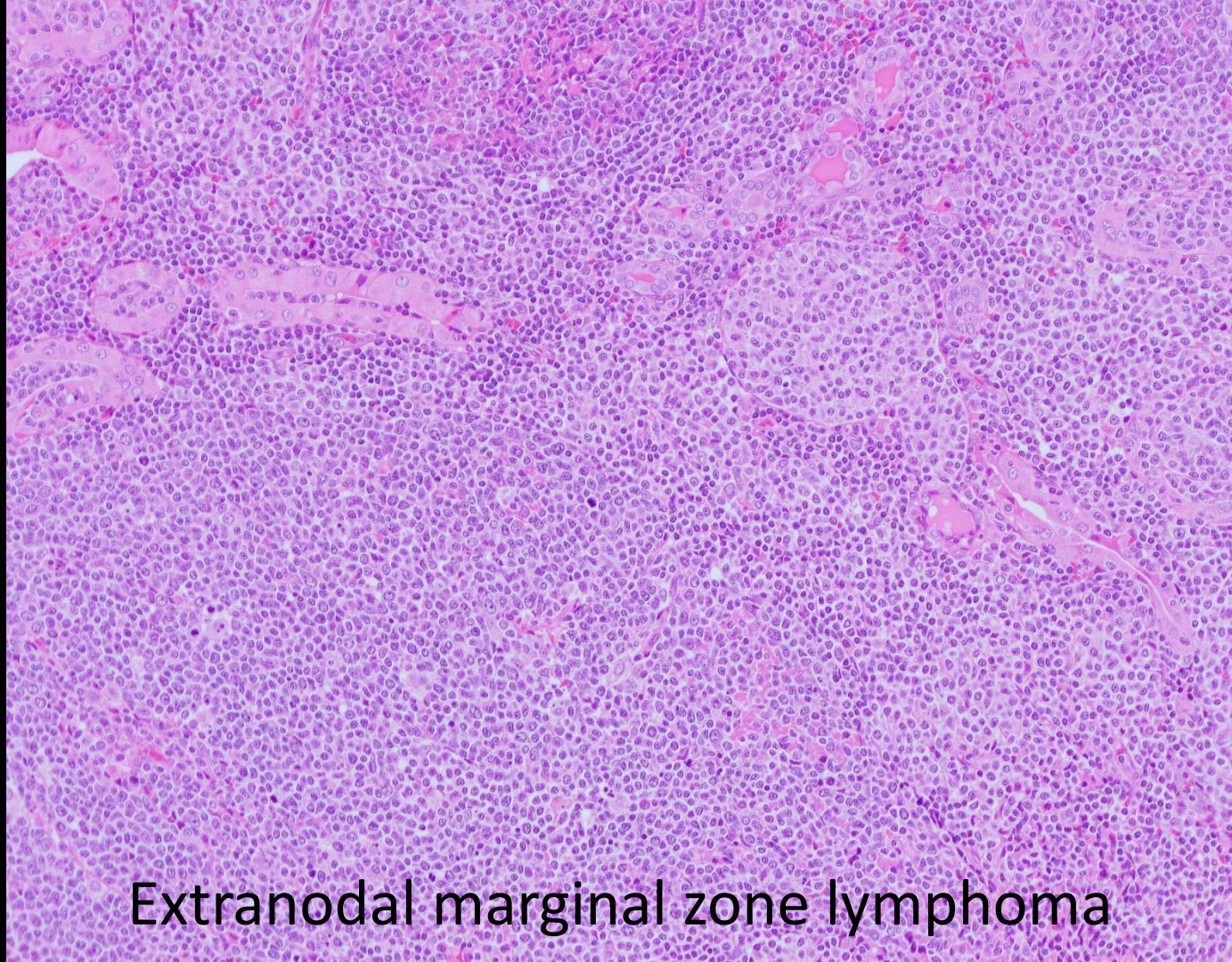
- 10-15% follicular lymphoma grade 1-2
- More frequent in grade 3 and some subtypes, especially if lack BCL2 gene rearrangement
- BCL2 mutation may alter epitope, with decreased detection by IHC. May detect with E17 antibody clone cf. routinely used SP66

EBV+ follicular lymphoma

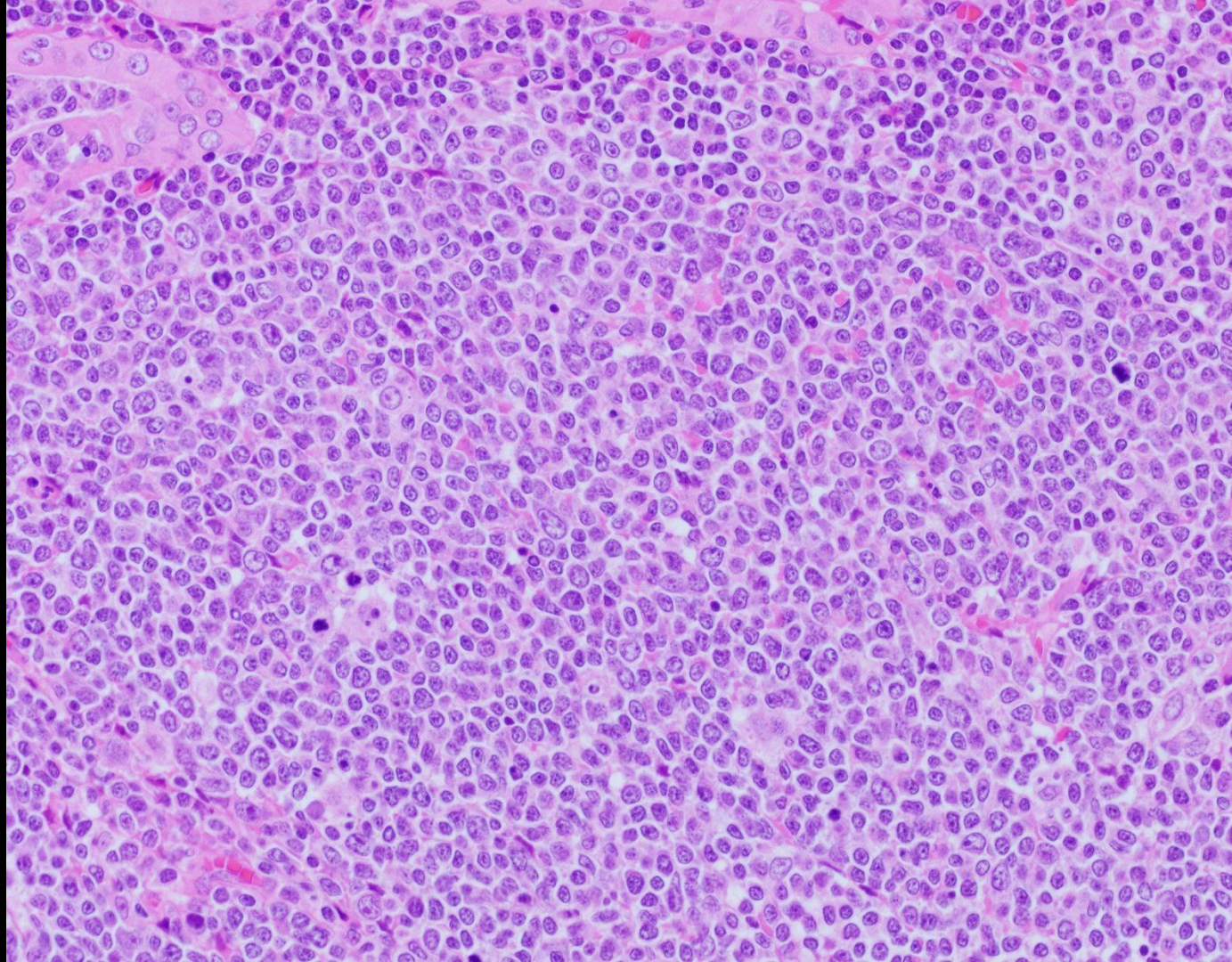
- Rare (2.6% unselected follicular lymphoma)
- No distinct morphologic or immunophenotypic characteristics
- Uncertain clinical significance :
 - Majority progress to higher-grade FL or DLBCL?
 - Worse overall survival, but not event free survival?

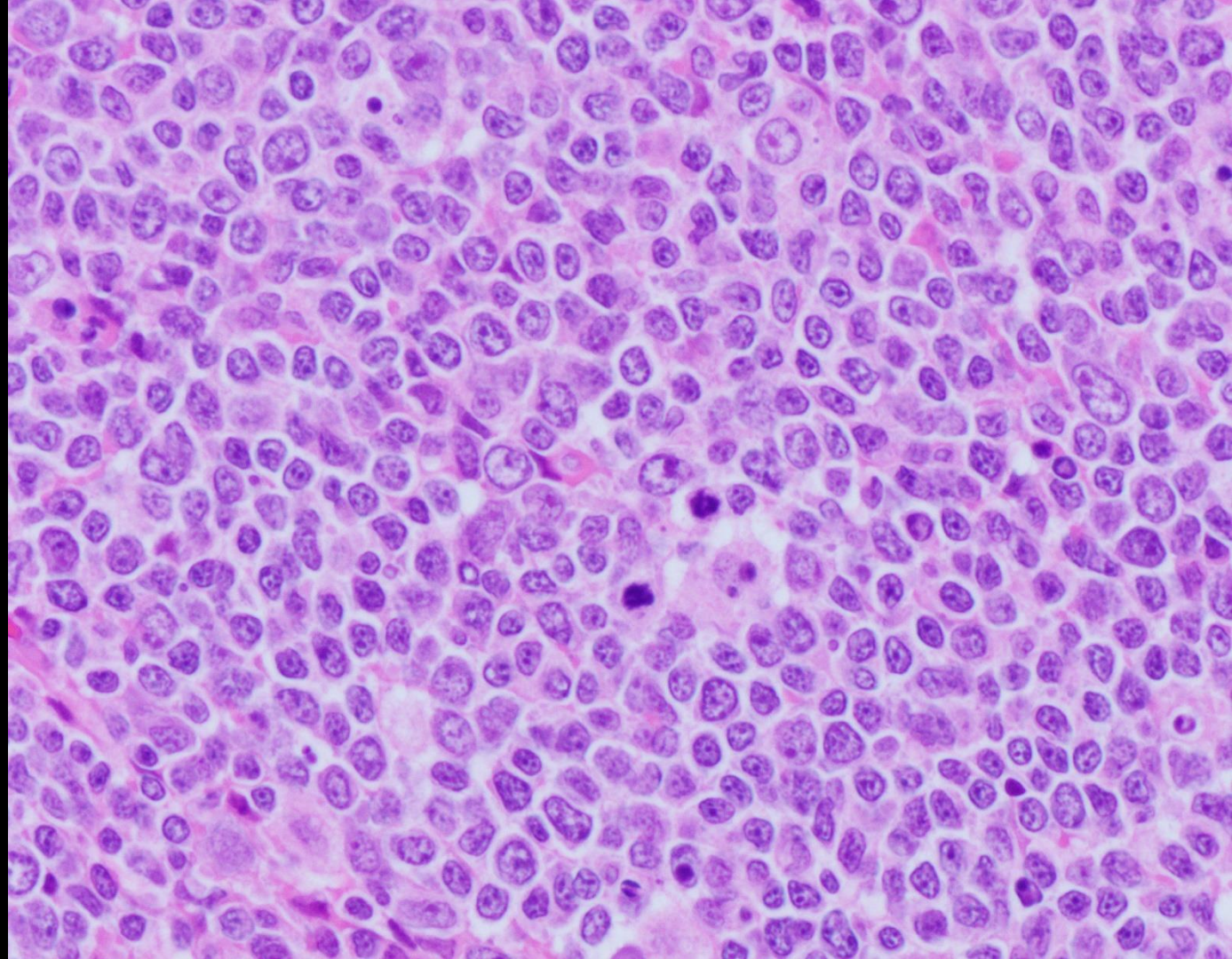
FL differential diagnosis

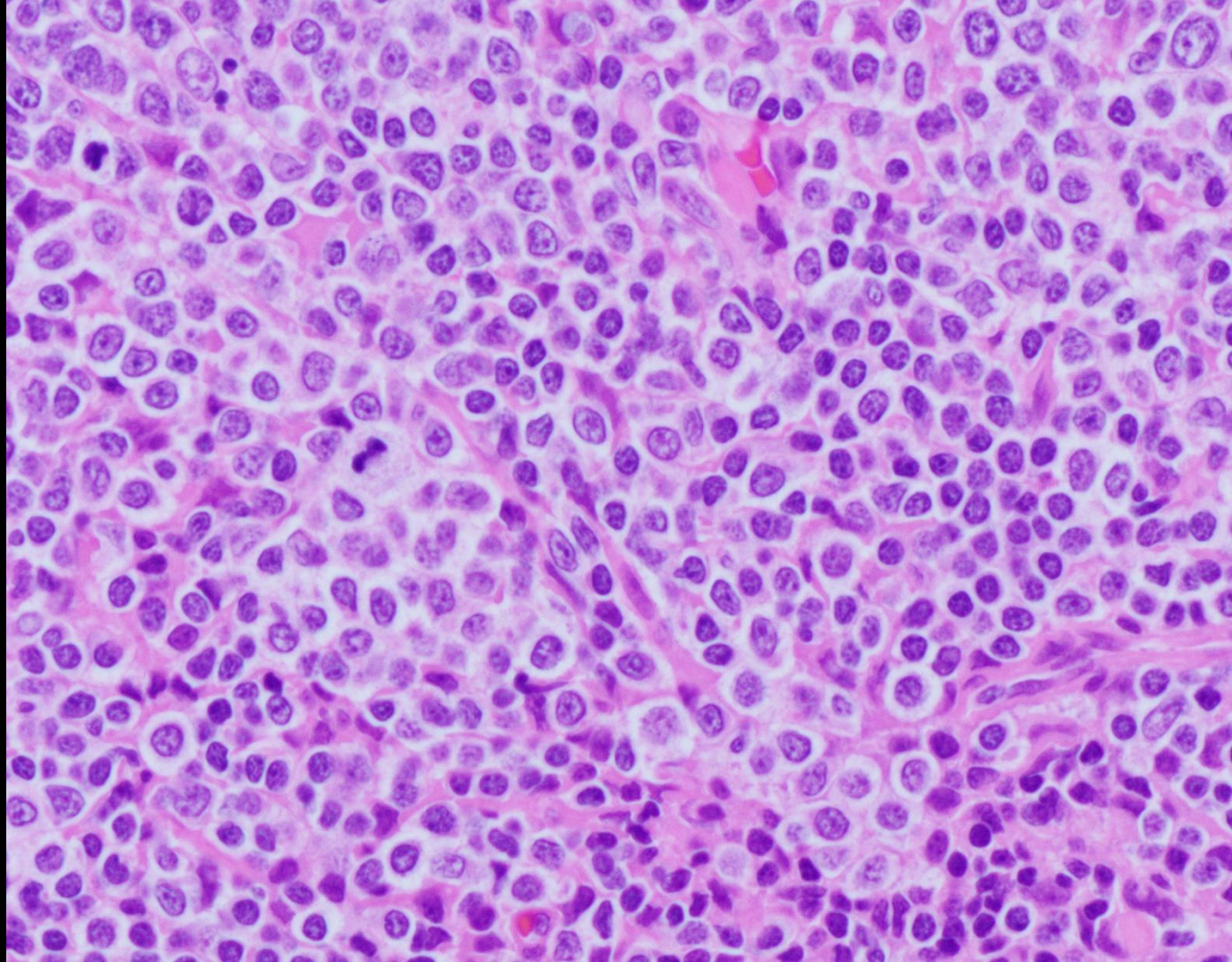
- Follicular hyperplasia
- Low-grade lymphoma e.g. marginal zone lymphoma, lymphoplasmacytic lymphoma
- Higher grade lymphoma e.g. diffuse large B-cell lymphoma

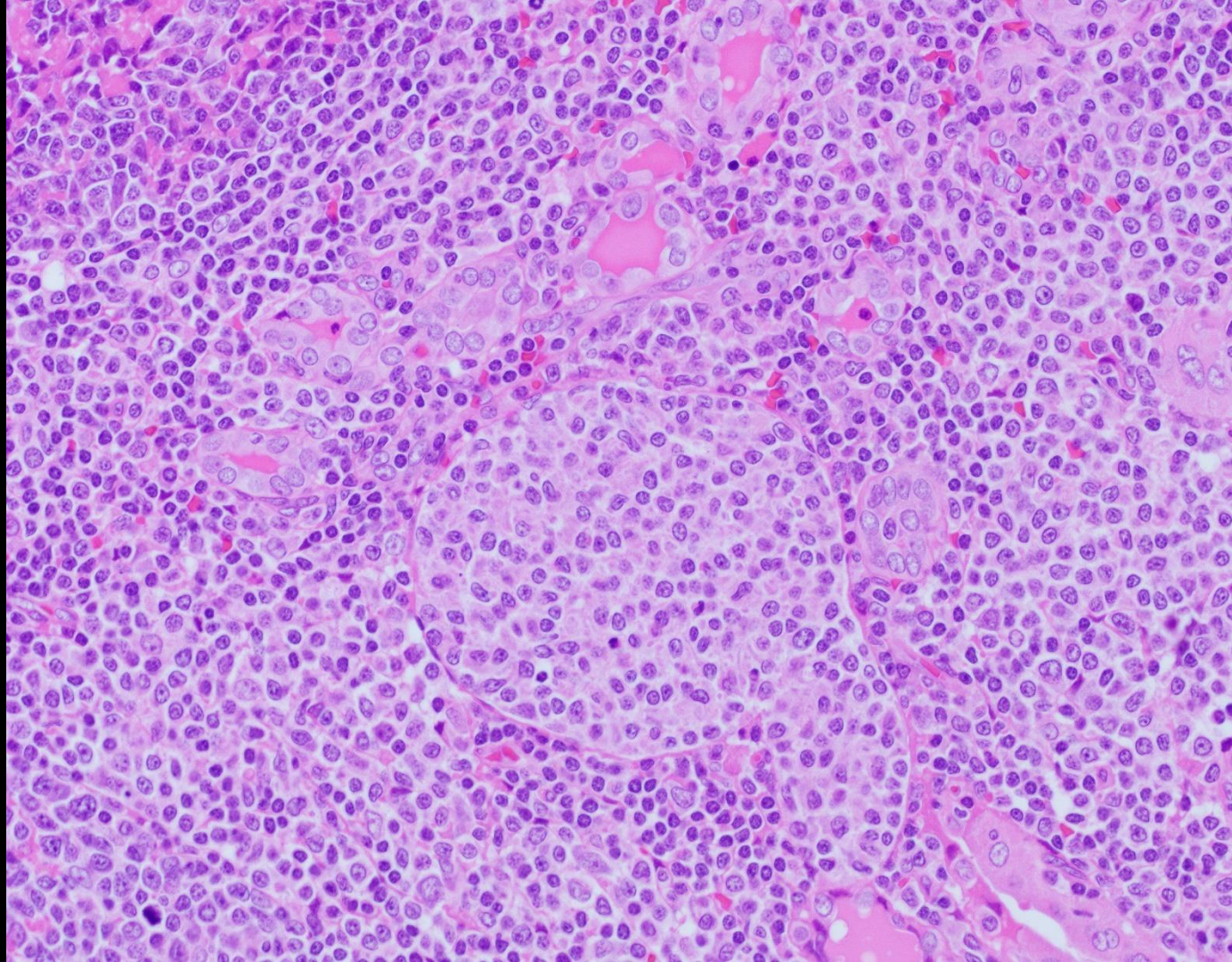


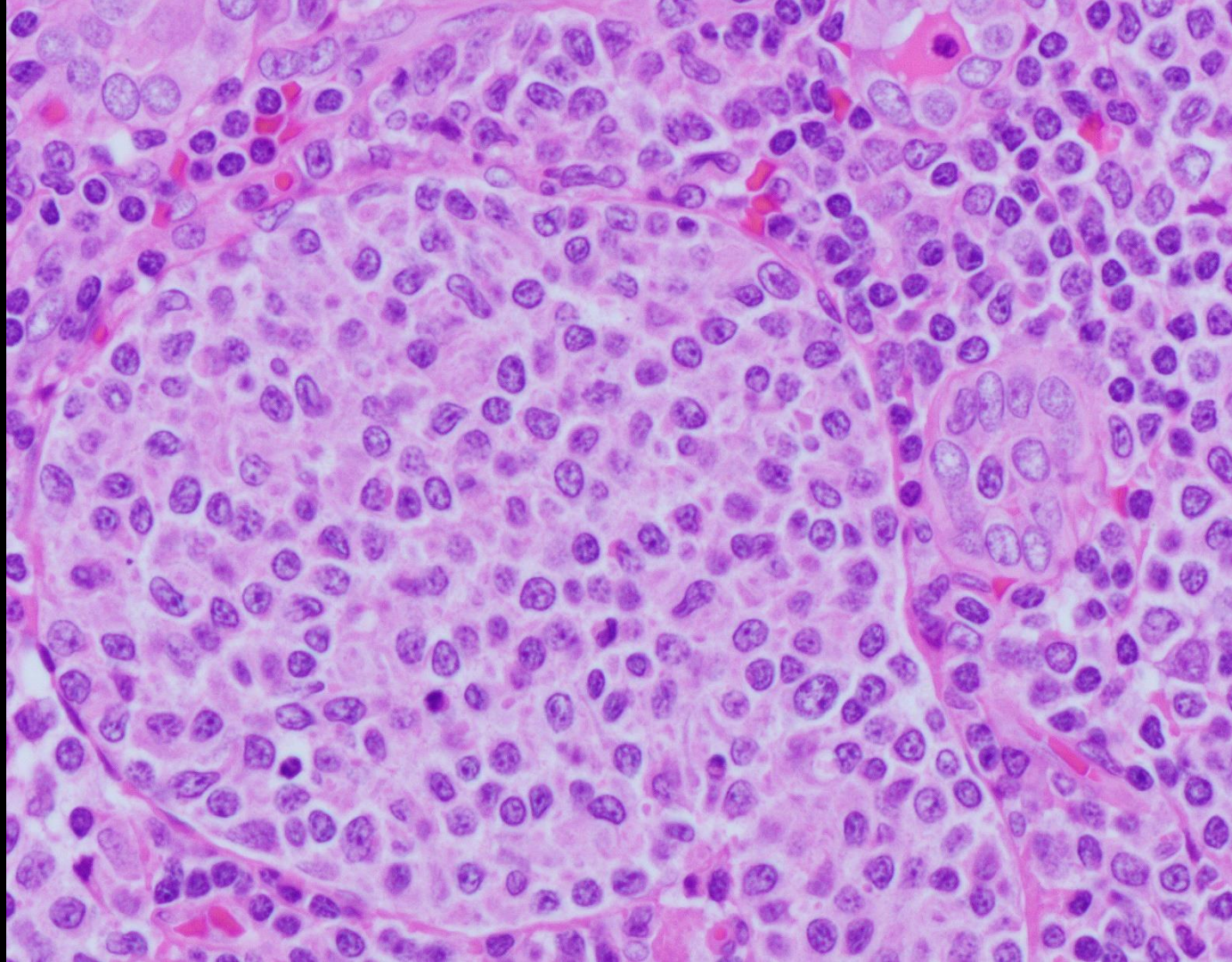
Extranodal marginal zone lymphoma

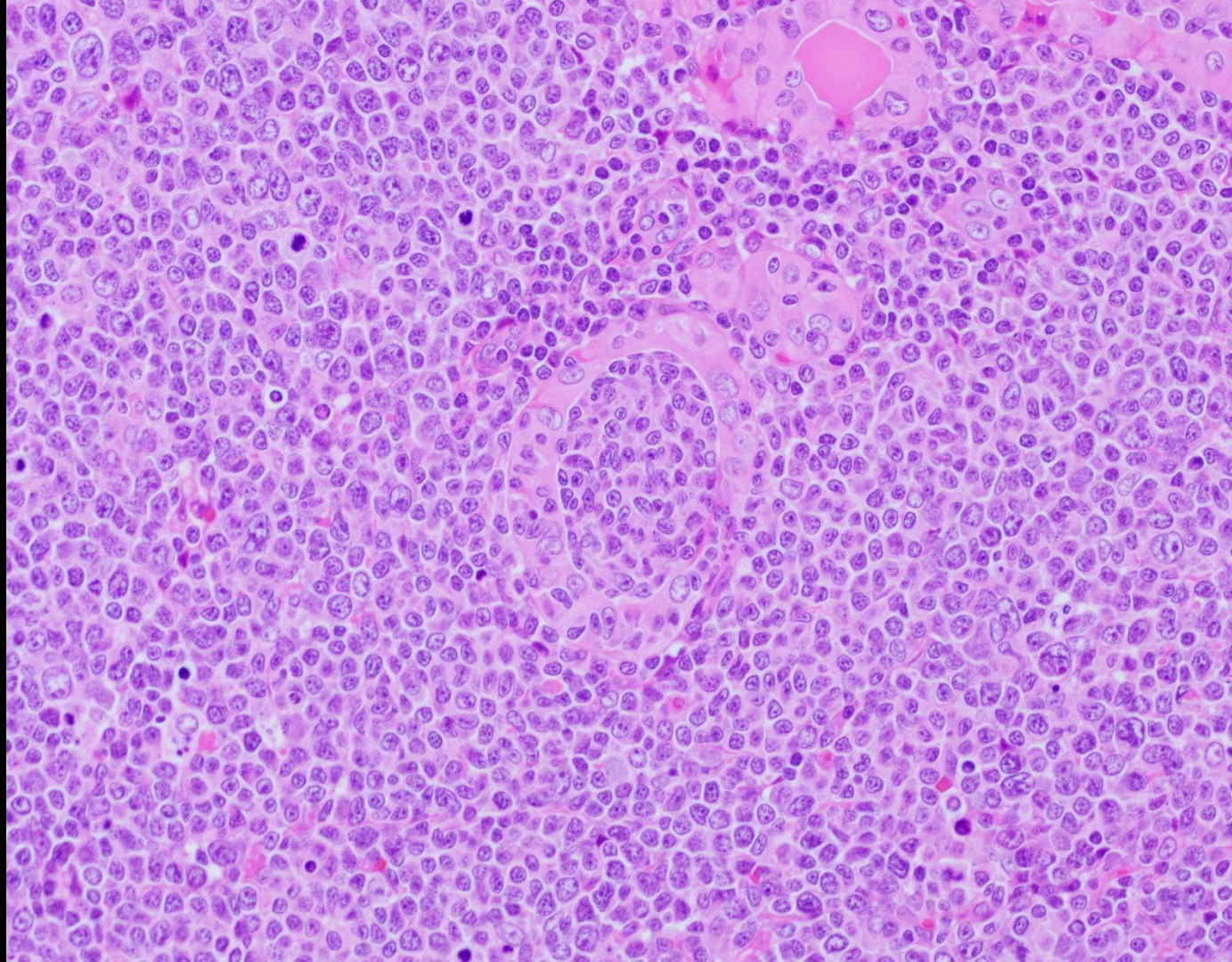


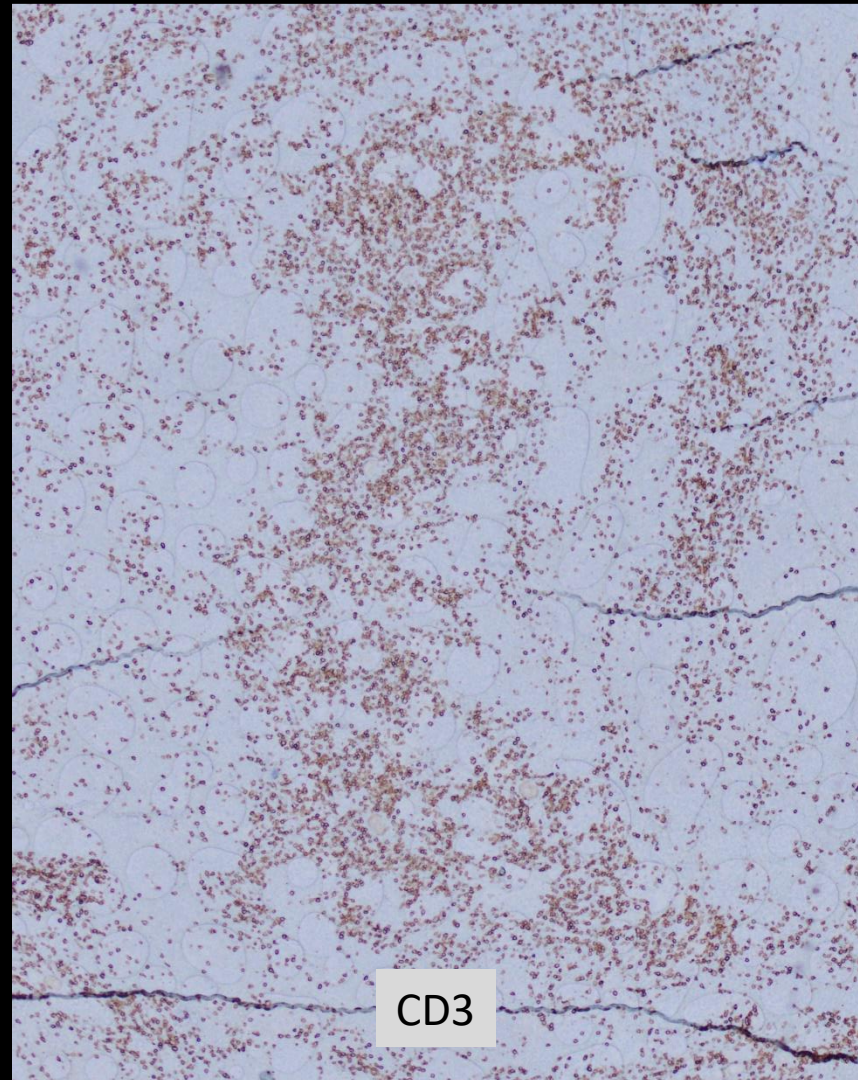
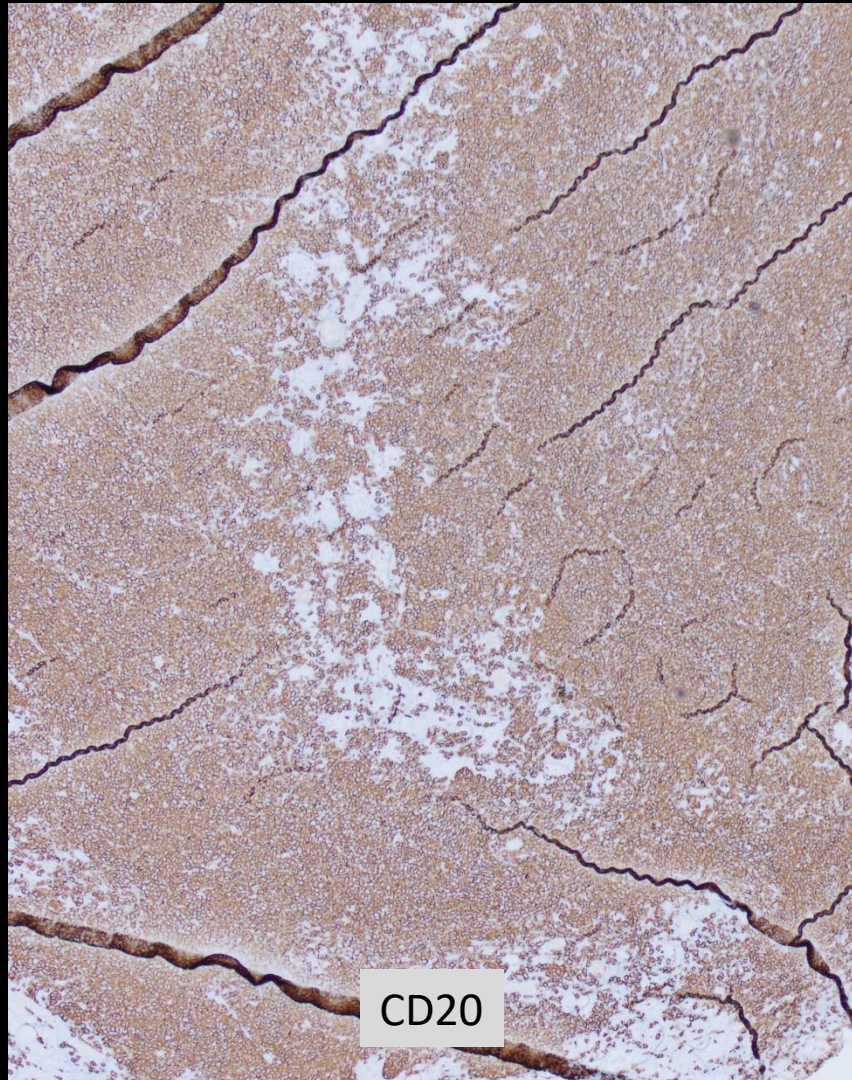


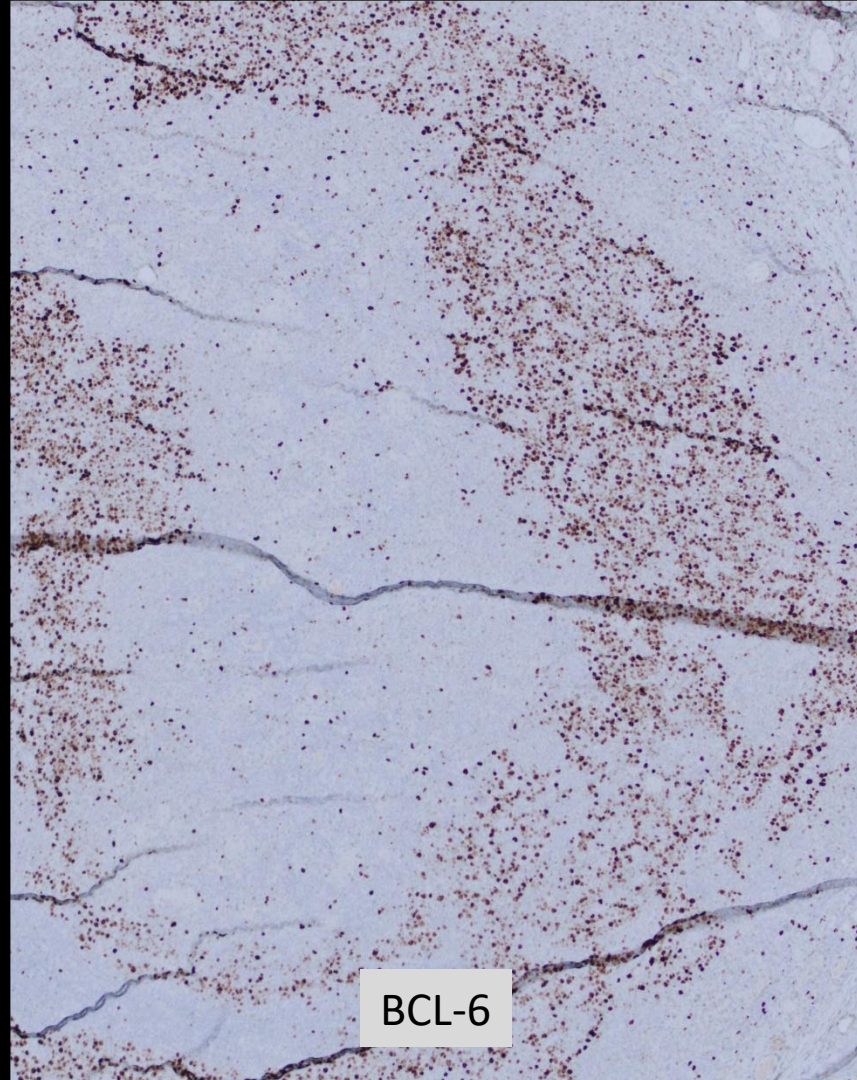
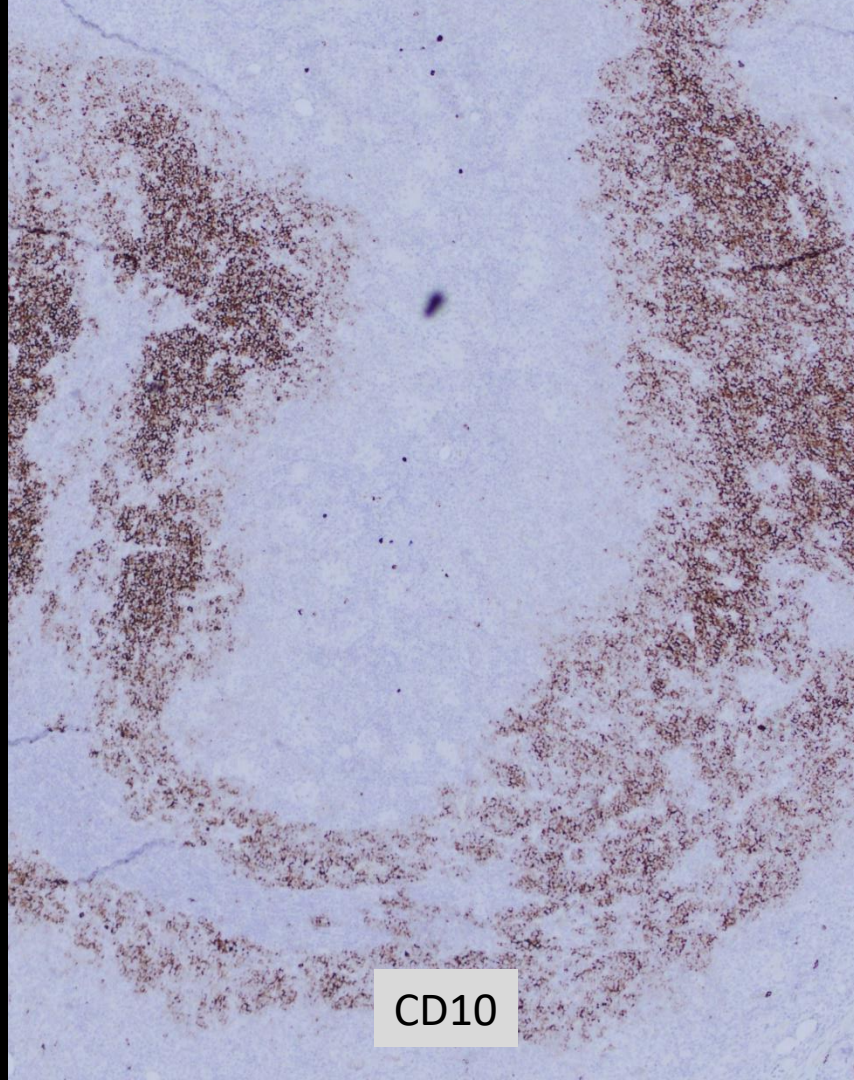


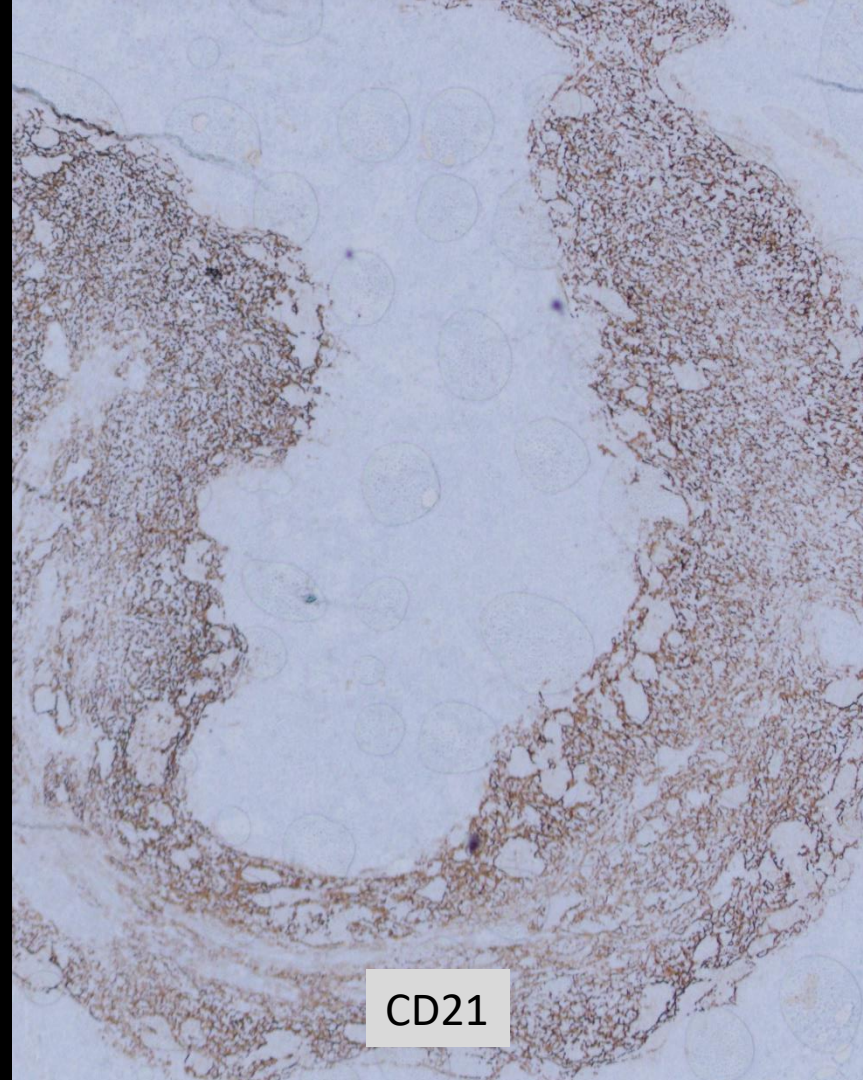
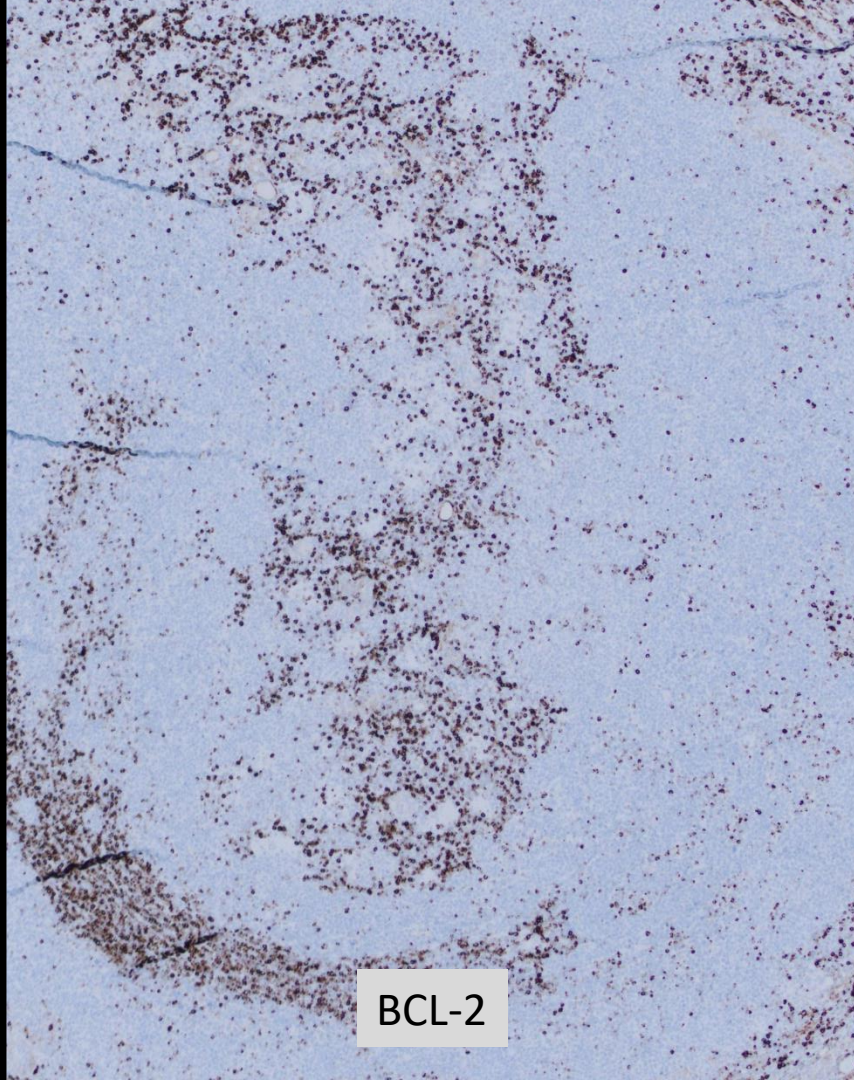








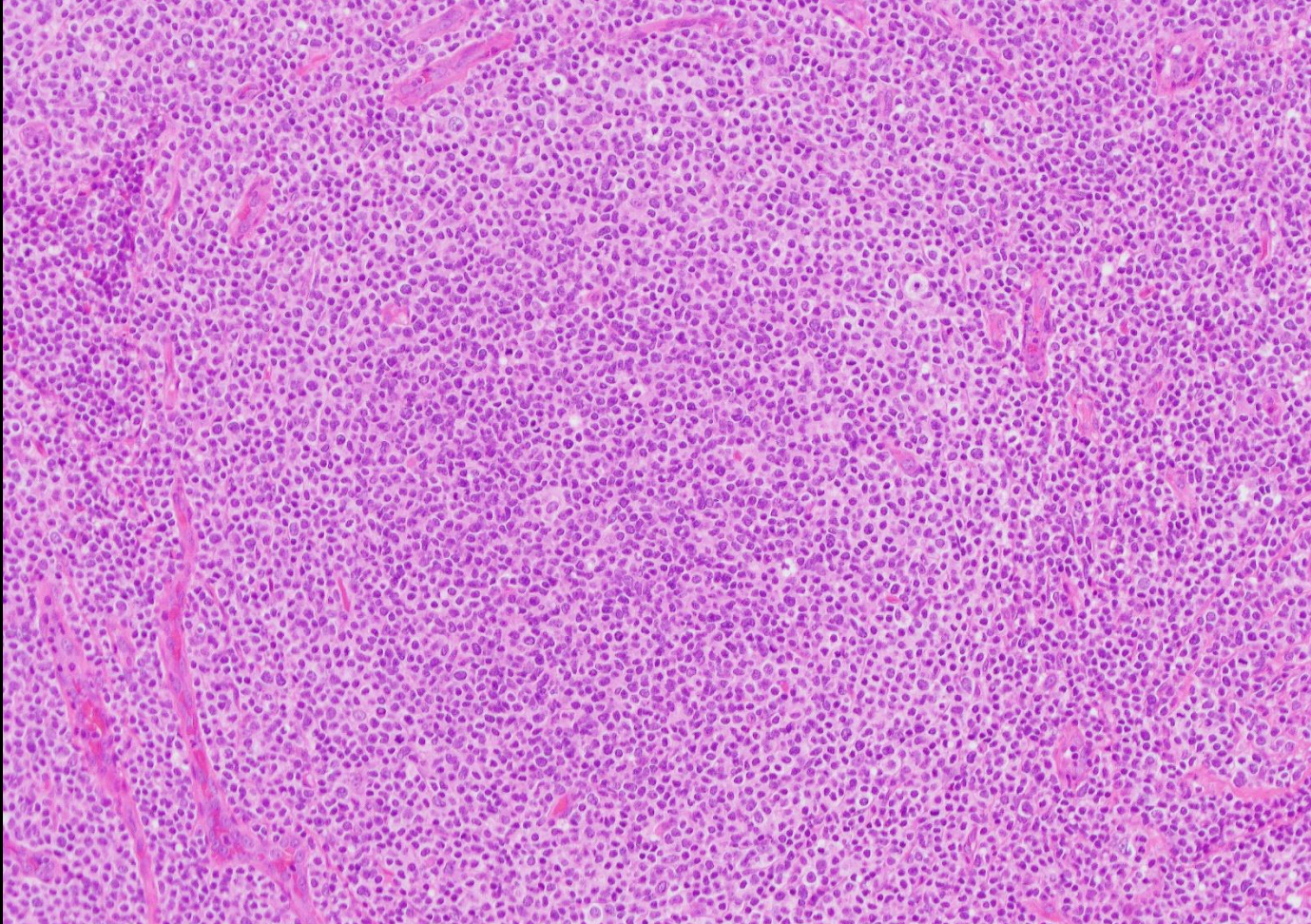




Follicular vs. marginal zone lymphoma

- 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

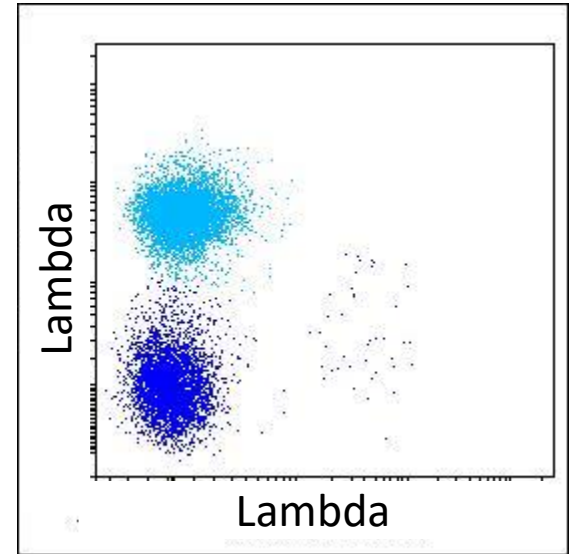
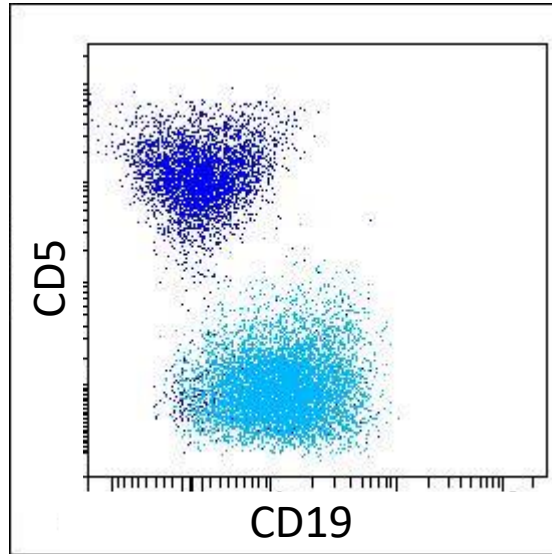
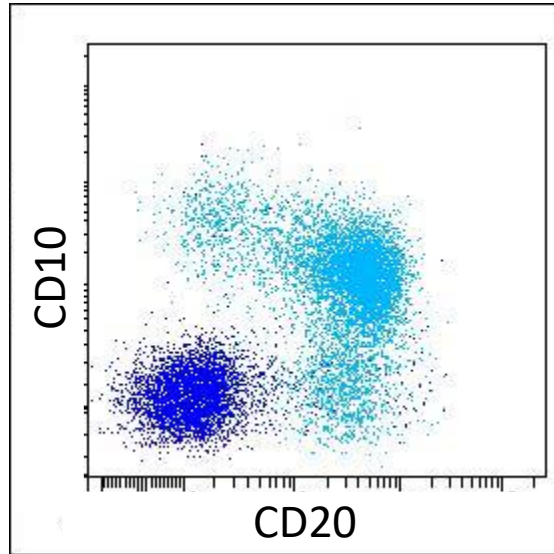
CD10-, MUM1+ follicular lymphoma

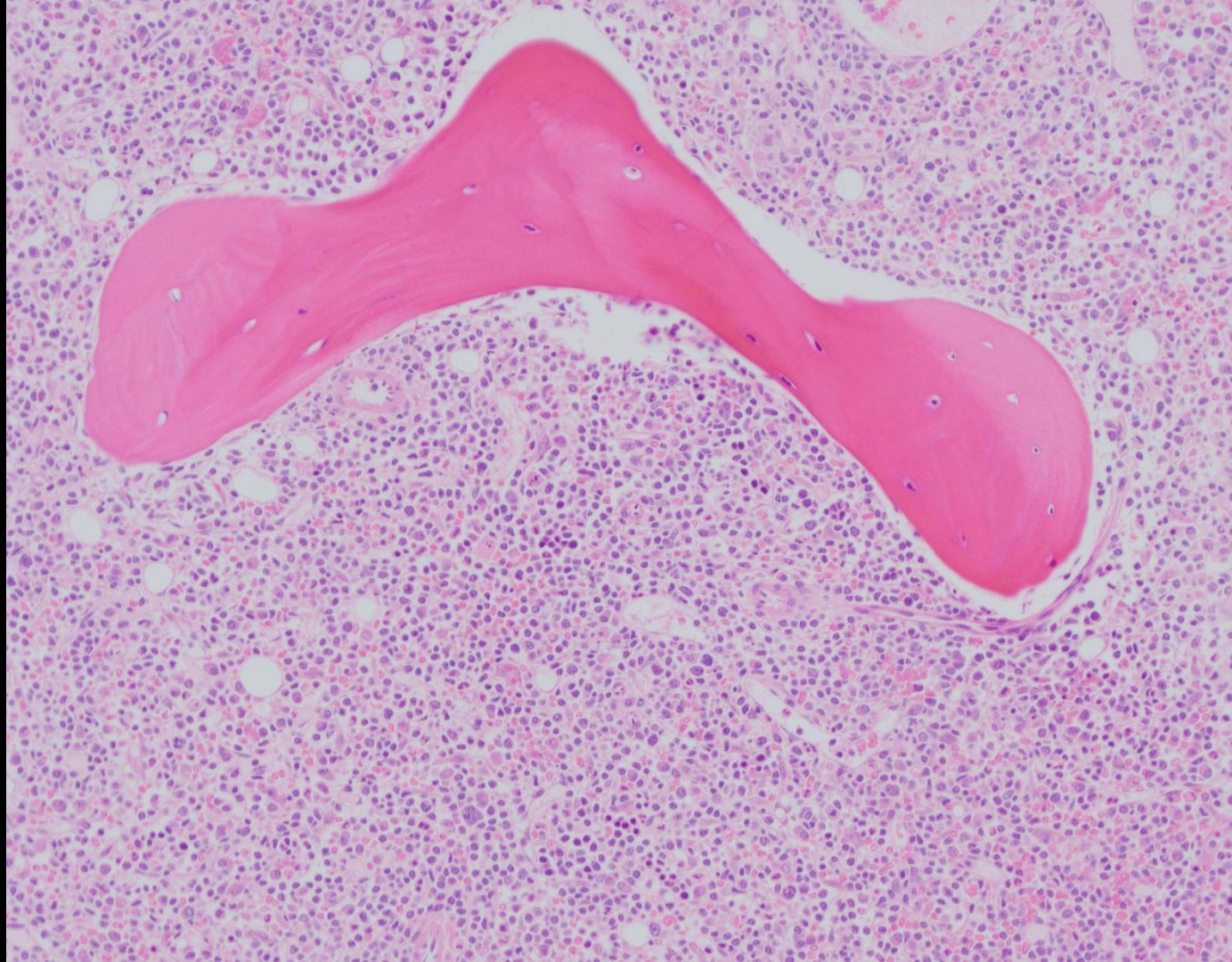
- Frequently elderly patients
- Often high grade follicular lymphoma (3A or 3B)
- Lack IGH-BCL2 rearrangement, but often BCL6 amplification and BCL2 amplification/gain
- Must also distinguish from large B-cell lymphoma with IRF4 rearrangement, which may have a partial follicular growth pattern (usually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

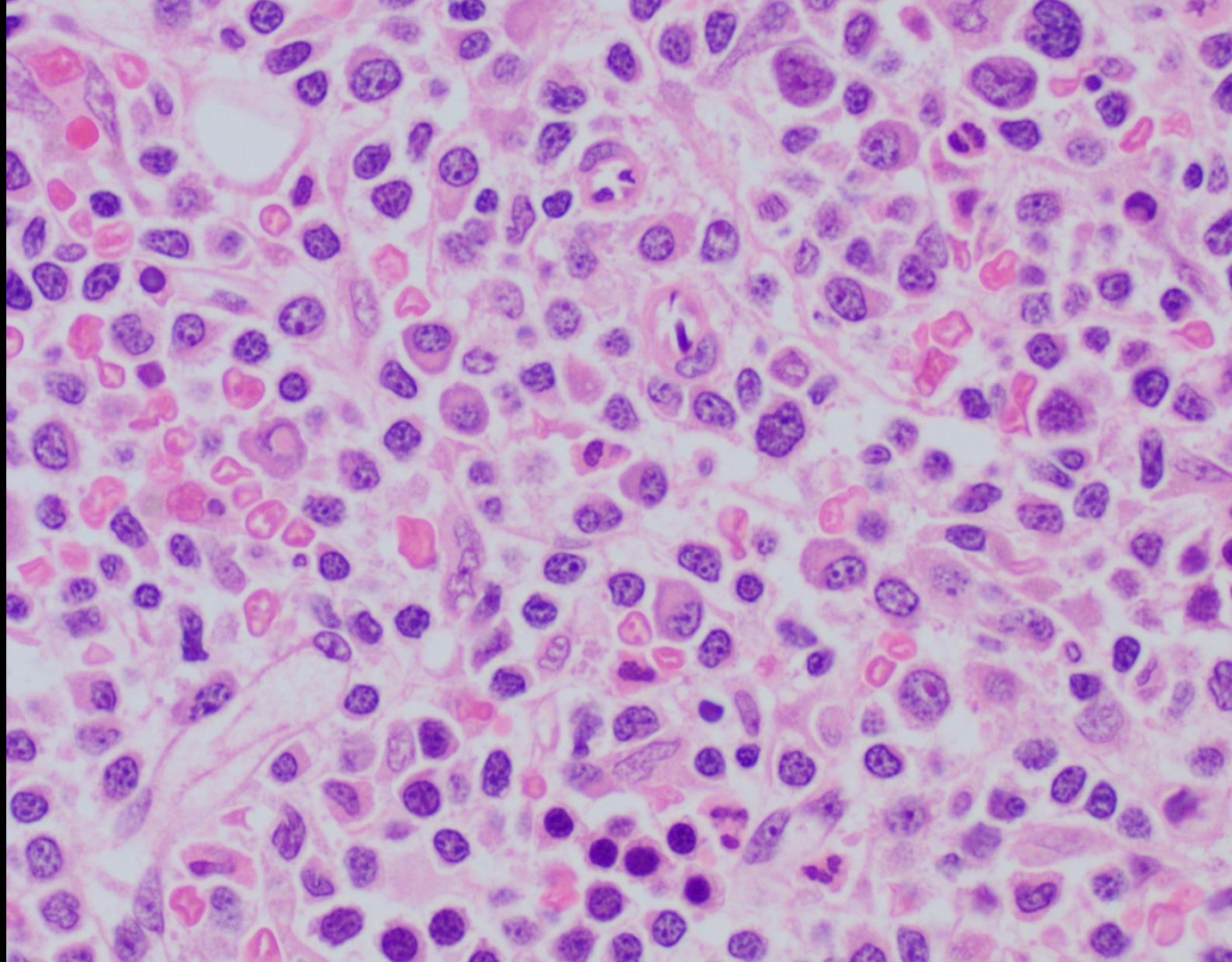
FL with plasmacytic differentiation

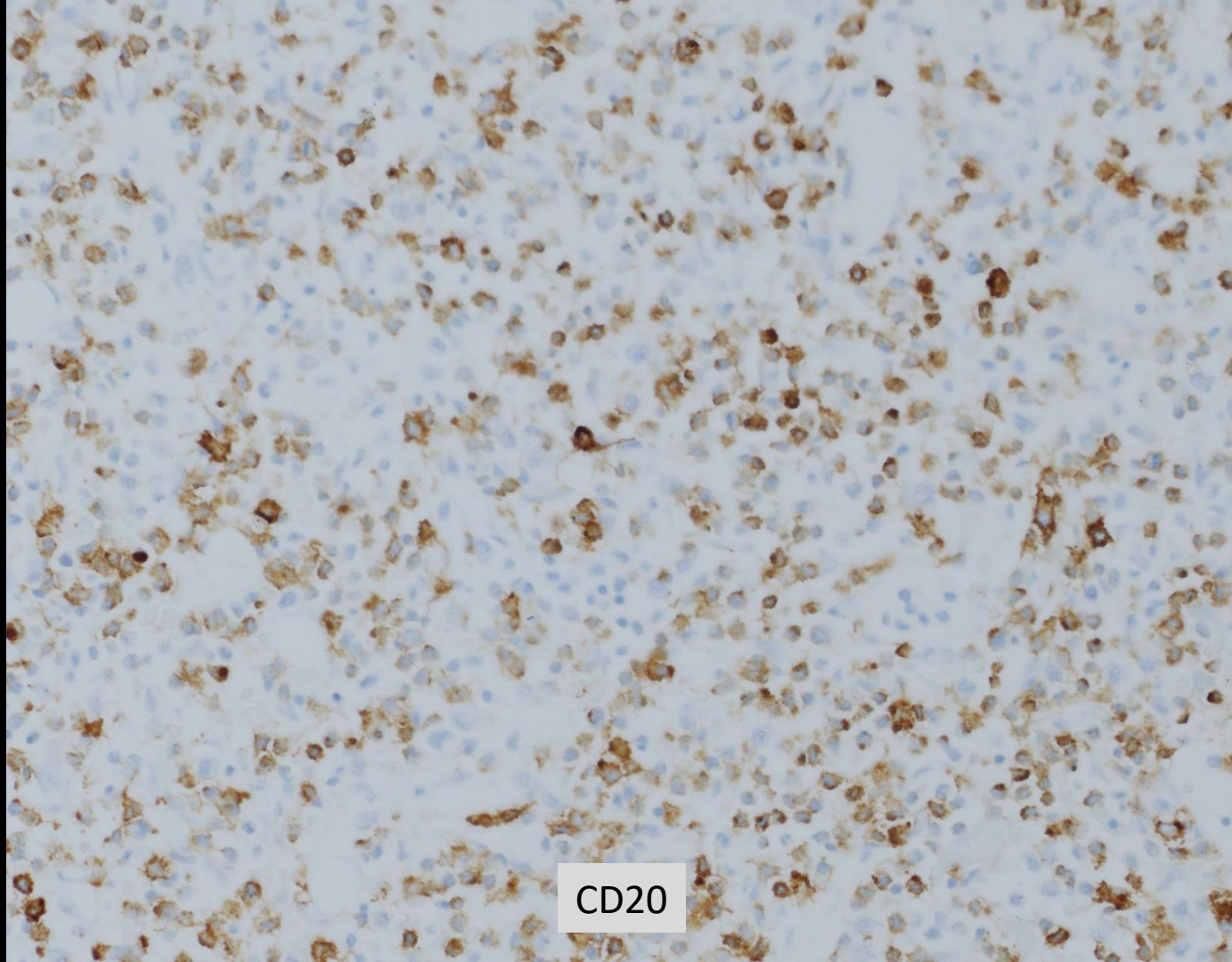
- Inter-follicular plasma cells:
 - Positive *BCL2* rearrangement
- Intra-follicular plasma cells:
 - Negative *BCL2* rearrangement (MZL?)
- Must also distinguish from lymphoplasmacytic lymphoma

History of low-grade B-cell lymphoma, possible follicular lymphoma, status-post therapy. Also, IgM monoclonal gammopathy

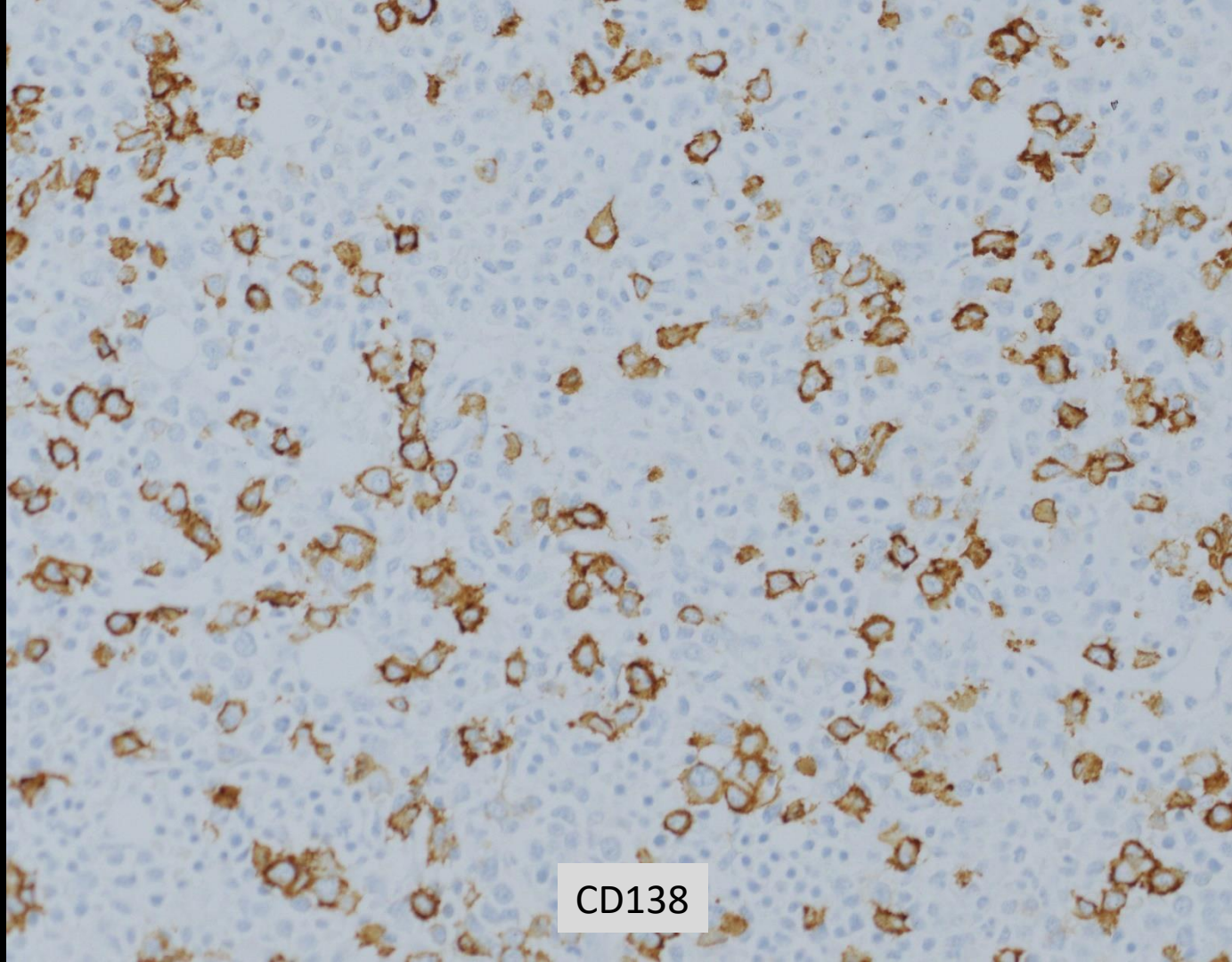








CD20



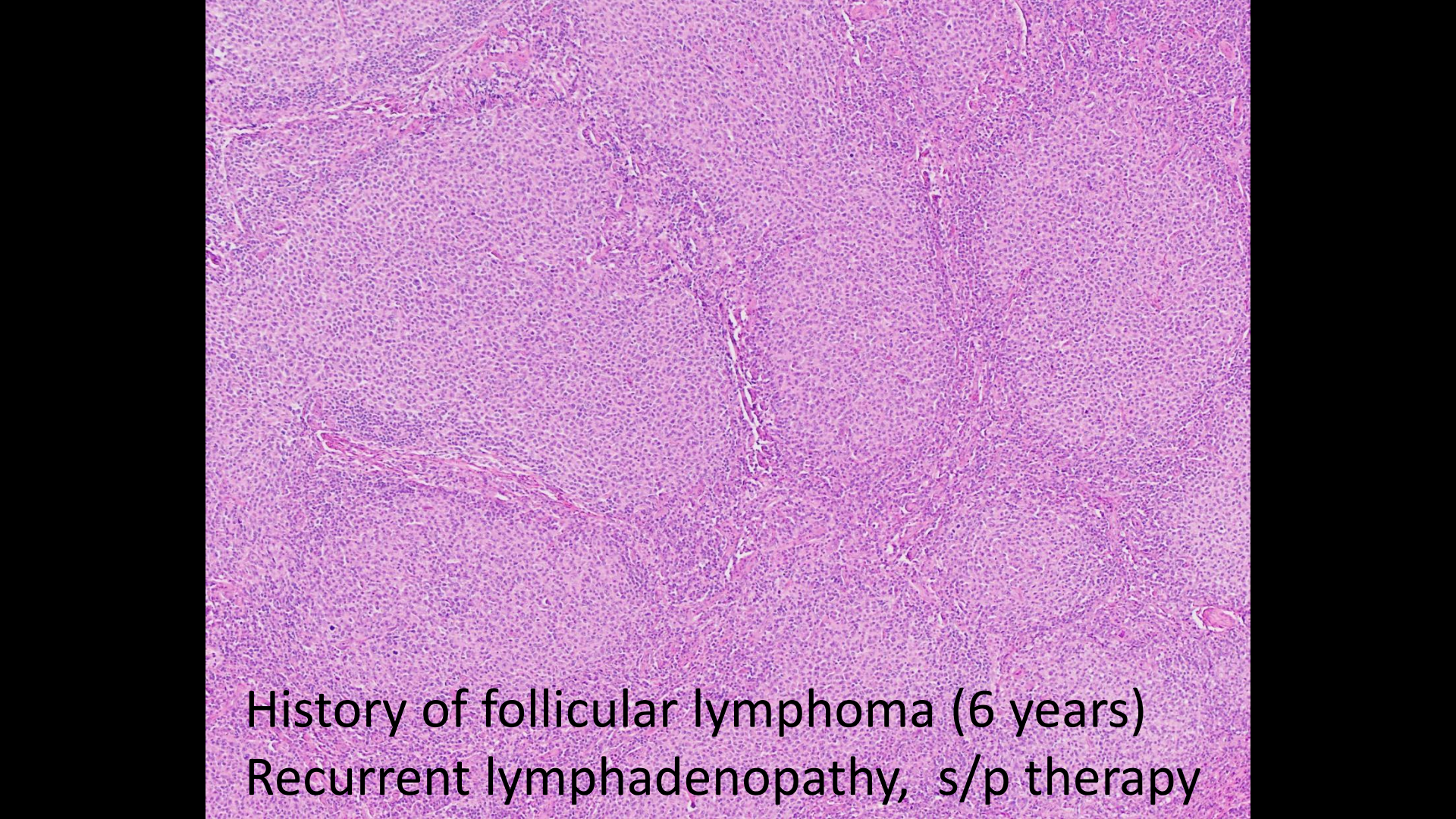
CD138

Lymphoplasmacytic lymphoma (LPL)

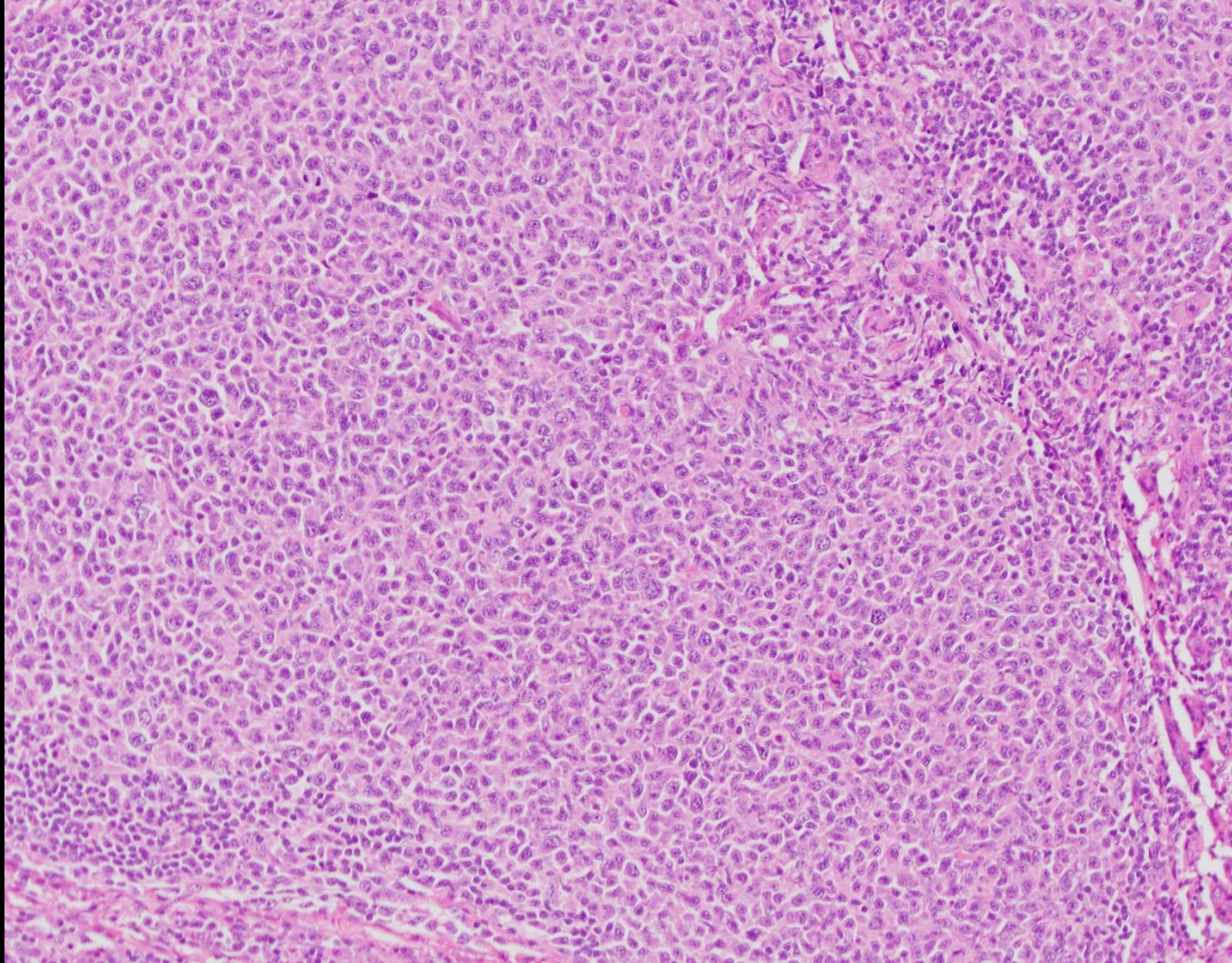
- Must distinguish from other lymphoma with plasmacytic differentiation e.g. MZL, FL
- LPL can be CD10 positive:
 - May vary within and between specimens
 - Negative for other GC markers e.g. Bcl-6
- Useful to evaluate for MYD88 L265P mutation

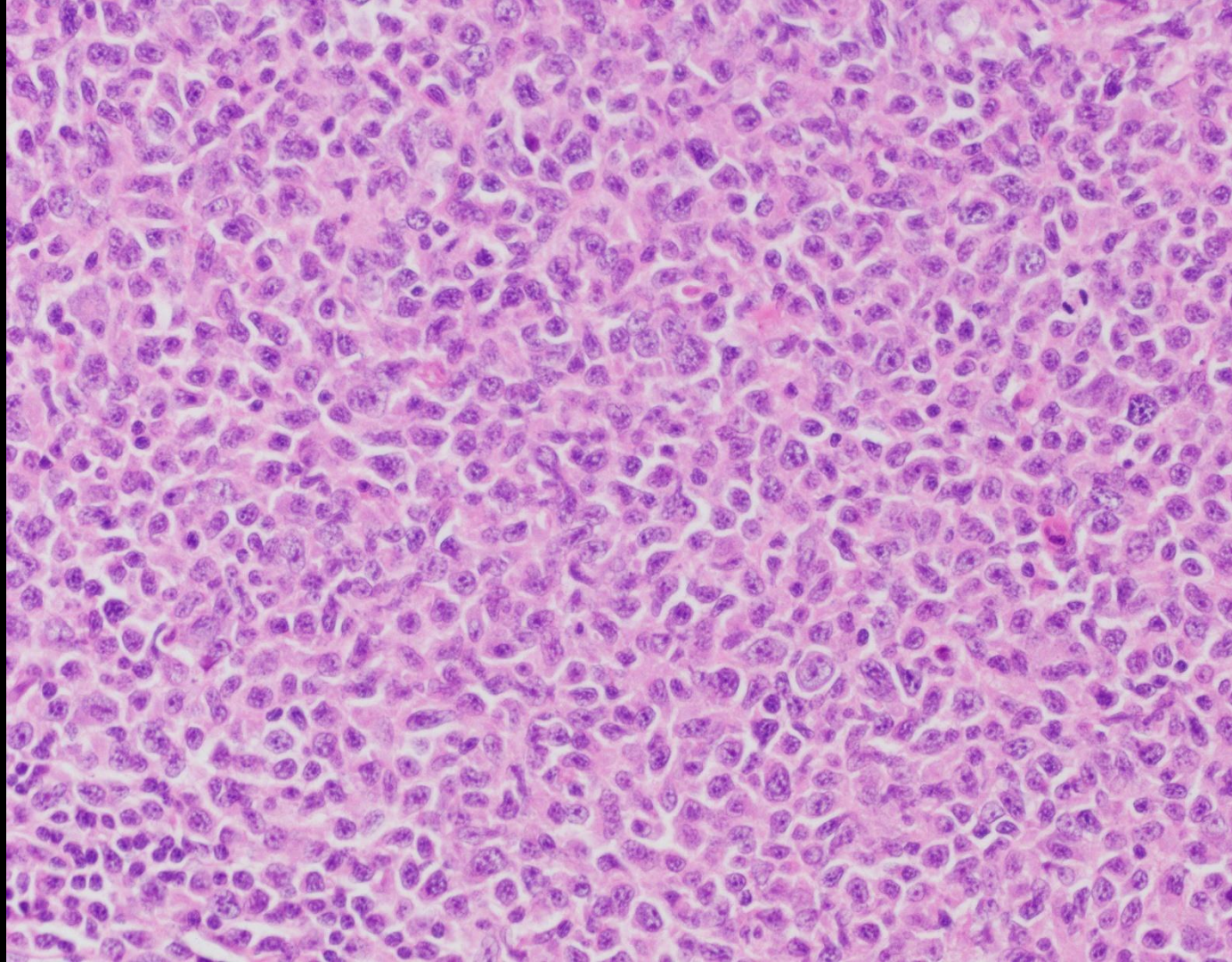
FL differential diagnosis

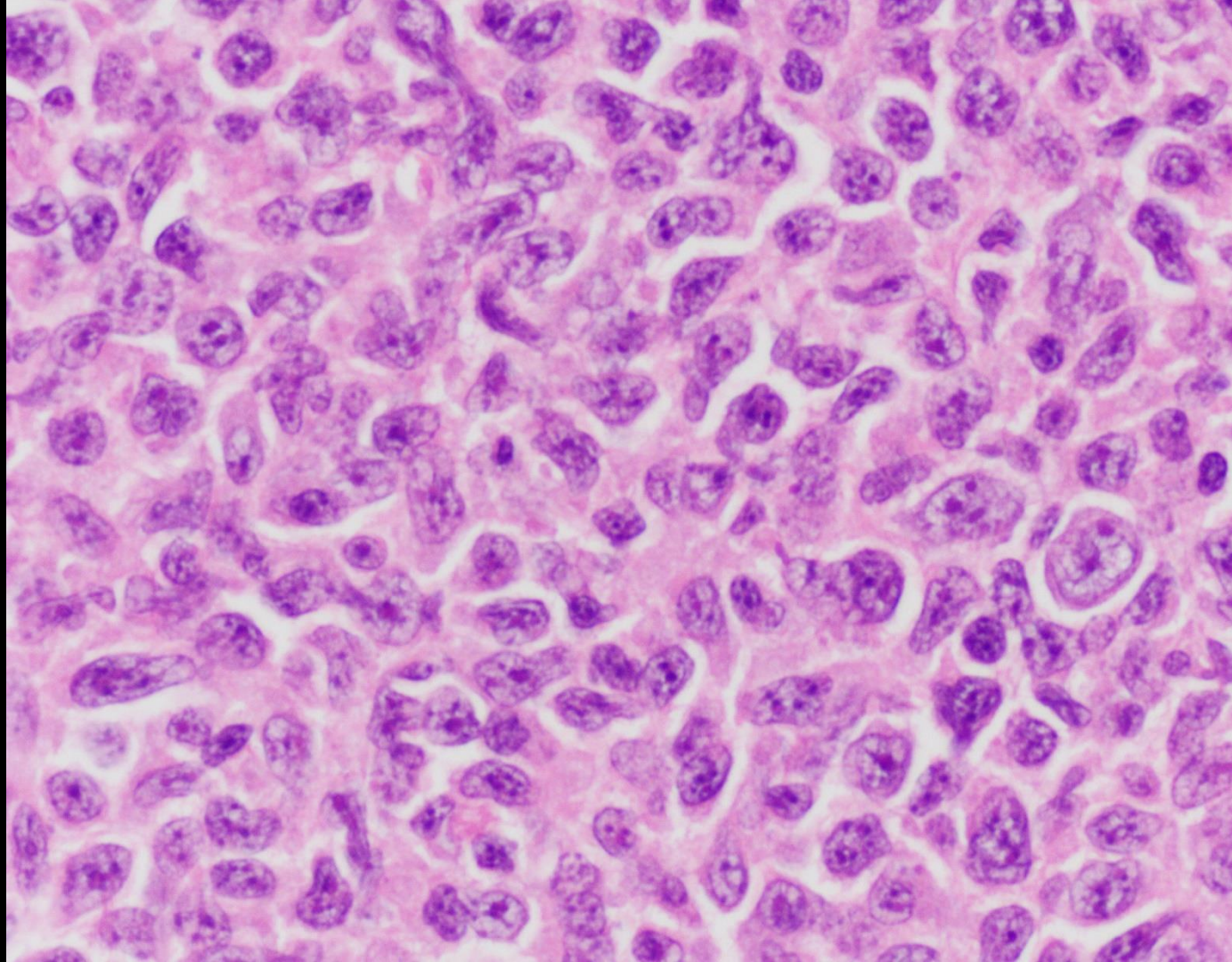
- Follicular hyperplasia
- Low-grade lymphoma e.g. marginal zone lymphoma, lymphoplasmacytic lymphoma
- Higher grade lymphoma e.g. diffuse large B-cell lymphoma, *MYC* & *BCL2* &/or *BCL6* rearrangements, large B-cell lymphoma with *IRF4* rearrangement

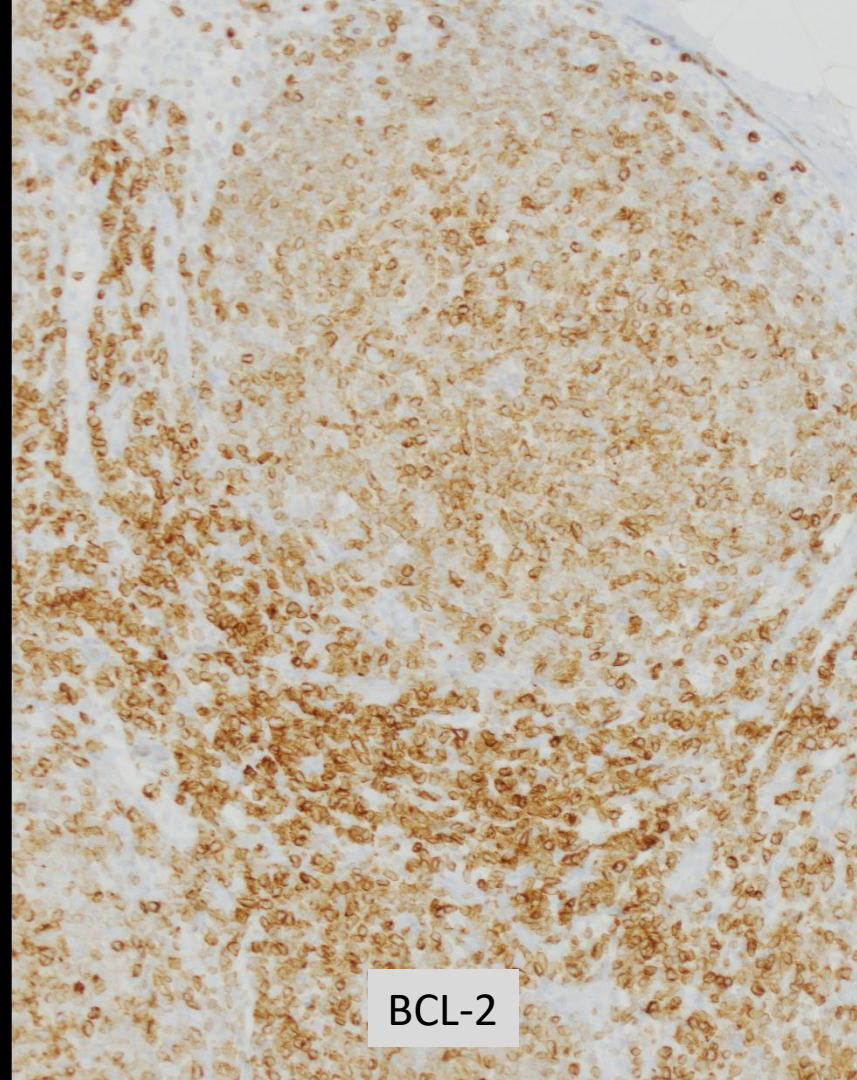
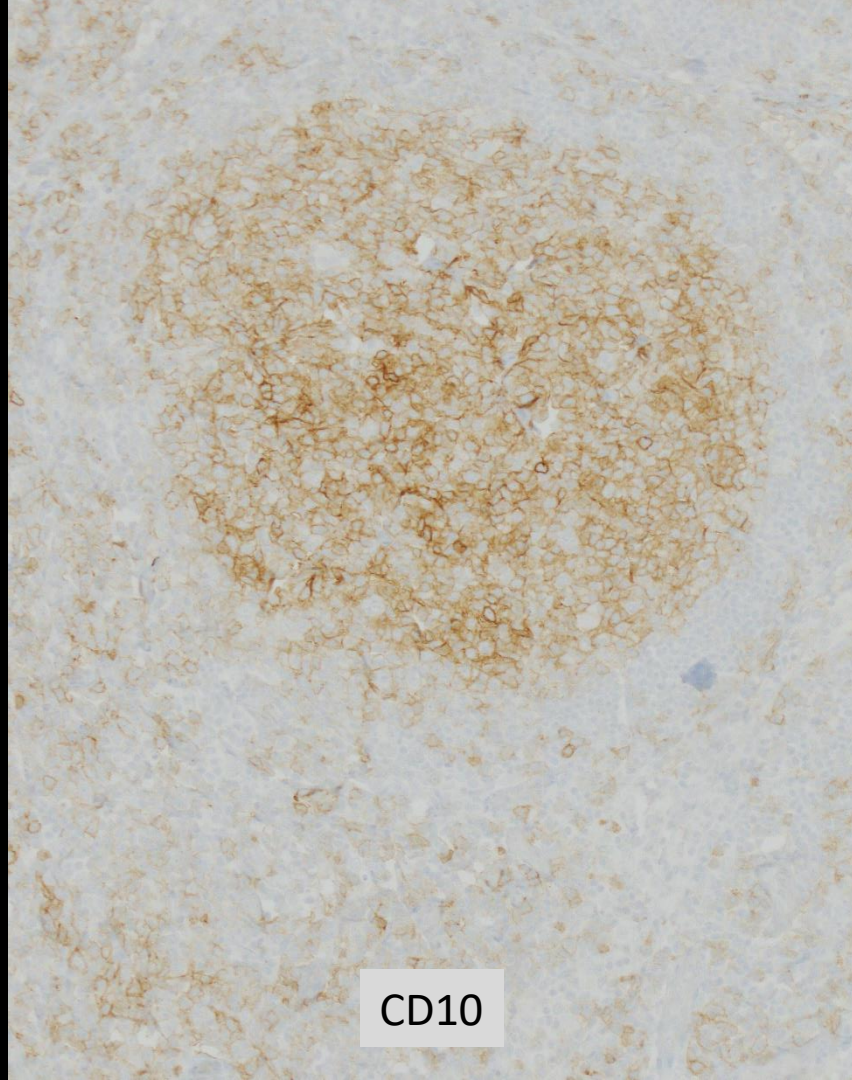
A histological slide of a lymph node stained with hematoxylin and eosin (H&E). The image shows a dense population of small, dark-staining lymphocytes. There are several distinct follicles of varying sizes, some with a more organized structure and others appearing more diffuse. The overall architecture is consistent with a lymphoproliferative disorder, specifically follicular lymphoma. The text at the bottom provides clinical context: 'History of follicular lymphoma (6 years) Recurrent lymphadenopathy, s/p therapy'.

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

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

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
- Expansile follicles with intermediate-size cells
- High proliferation index
- Lack *BCL2*, *BCL6* and *IRF4* gene rearrangements
- Good prognosis, sometimes just with excision

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