Follicular lymphoma update

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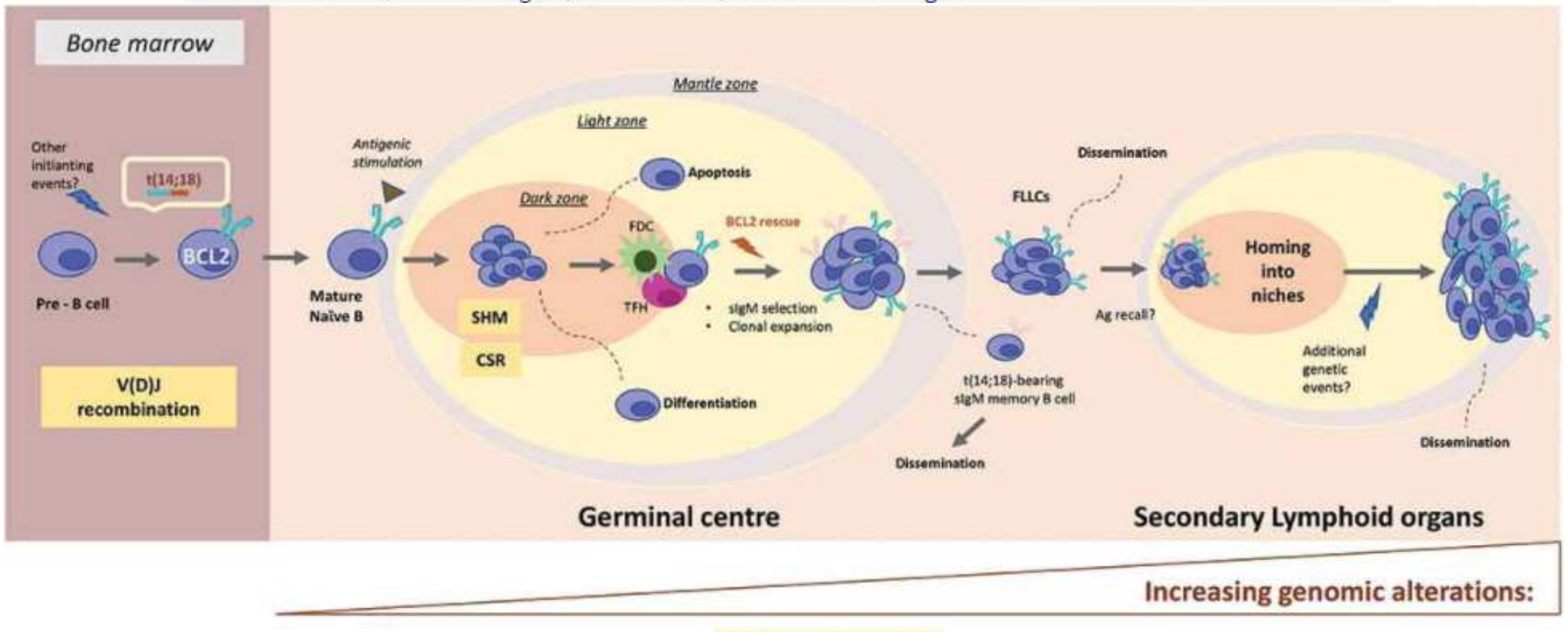
An analysis of genetic targets for guiding clinical management of follicular lymphoma

Ruth Alonso-Alonso, Marta Rodriguez, Daniel Morillo, Raul Cordoba & Miguel A Piris



Molecular/genetic evaluation I do on follicular lymphomas

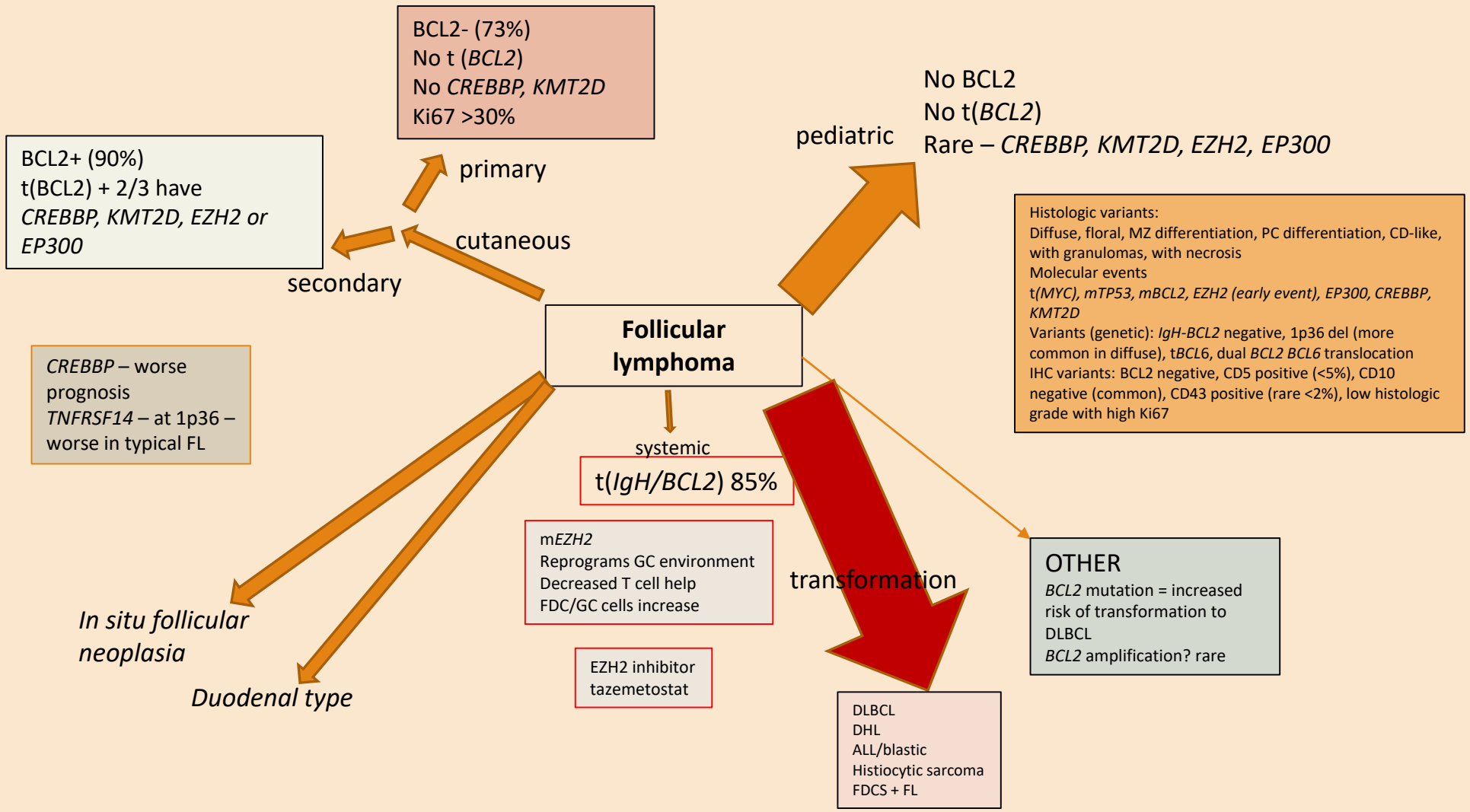
Mutations tested

Cytogenetic abnormalities tested

DUSP22-IRF4 by FISH

TNFRSF14 (1p36) by FISH

MUTATIONS	Effect on prognosis	Other	Frequency
ARID1A	favorable		
BCL2		Increased risk of transformation	85-90*
BCL6			45*
CDKN2A	unfavorable	Increased risk of transformation; *TSG*	
CREBBP	unfavorable	Escape from immune surveillance	33
EP300	unfavorable		10
EZH2	favorable	Targeted therapy	60
FAS			5
KMT2D			85
MAP2K1		Pediatric type	
MEF2B	favorable		15
PIK3CA			
SOCS1		Increased risk of transformation	
TNFAIP3			20
TNFRSF14	unfavorable	Diffuse pattern (?); pediatric	45-65


BCL2- (73%)
No t (*BCL2*)
No *CREBBP, KMT2D*
Ki67 >30%
primary
BCL2+ (90%)
t(BCL2) + 2/3 have
CREBBP, KMT2D, EZH2 or EP300
cutaneous
secondary
pediatric
No BCL2
No t(*BCL2*)
Rare – *CREBBP, KMT2D, EZH2, EP300*
Histologic variants:
Diffuse, floral, MZ differentiation, PC differentiation, CD-like, with granulomas, with necrosis
Molecular events
t*(MYC), mTP53, mBCL2, EZH2 (early event), EP300, CREBBP, KMT2D*
Variants (genetic): *IgH-BCL2* negative, 1p36 del (more common in diffuse), t*BCL6*, dual *BCL2 BCL6* translocation
IHC variants: BCL2 negative, CD5 positive (<5%), CD10 negative (common), CD43 positive (rare <2%), low histologic grade with high Ki67
Follicular lymphoma
CREBBP – worse prognosis
TNFRSF14 – at 1p36 – worse in typical FL
systemic
t(*IgH/BCL2*) 85%
m*EZH2*
Reprograms GC environment
Decreased T cell help
FDC/GC cells increase
EZH2 inhibitor tazemetostat
transformation
OTHER
BCL2 mutation = increased risk of transformation to DLBCL
BCL2 amplification? rare
In situ follicular neoplasia
Duodenal type
DLBCL
DHL
ALL/blastic
Histiocytic sarcoma
FDCS + FL

Duodenal type follicular lymphoma

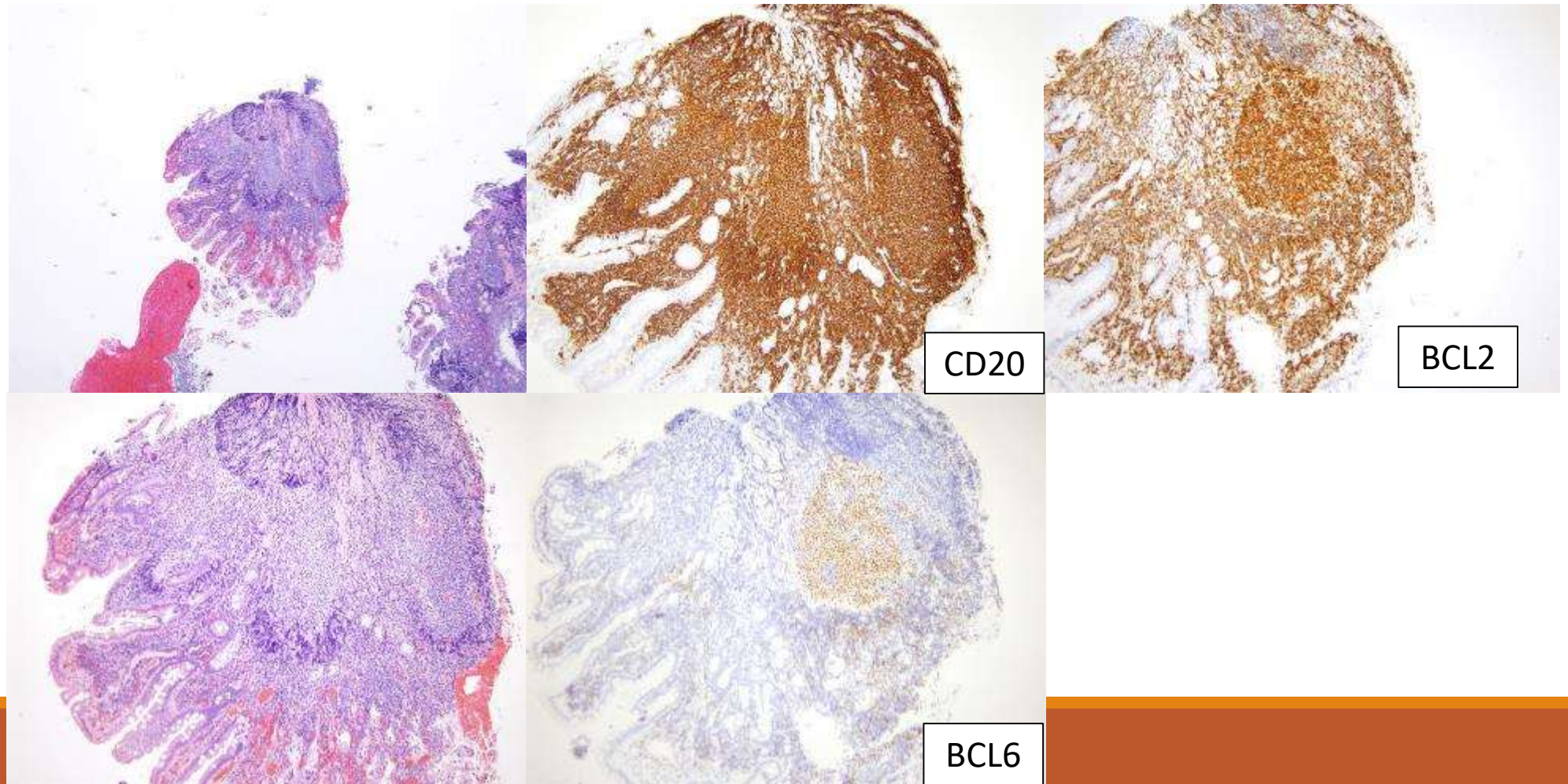
Limited stage (IE or IIE)

Localized; small intestine

Typical morphologic and IHC features

Key point: "*at least minimal clinical staging is recommended to exclude systemic follicular lymphoma which is associated with a significantly worse prognosis*"

Duodenal type follicular lymphoma



CD10 negative FL

Often positive for

MUM1*

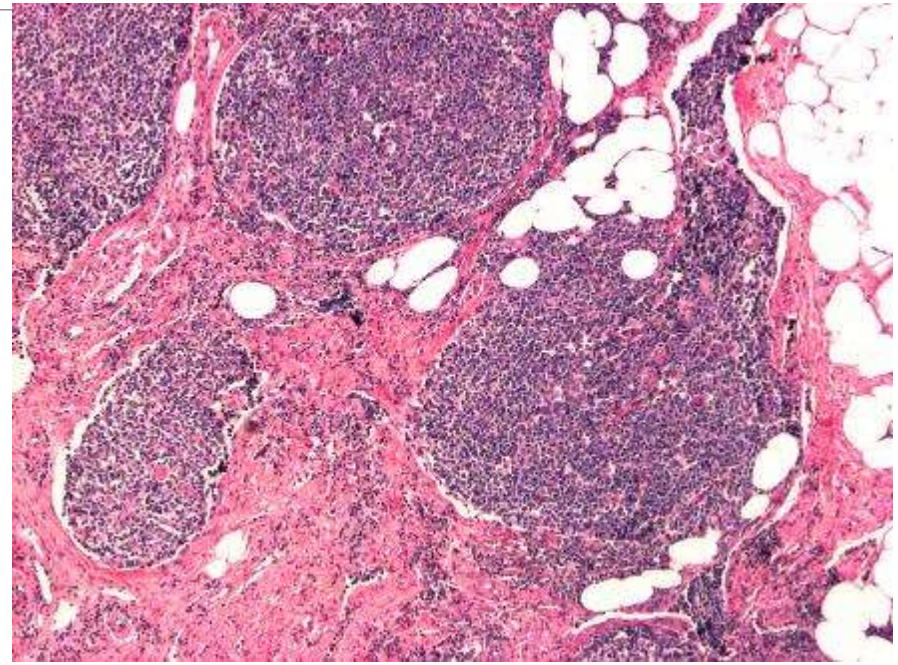
Lack *IGH/BCL2*

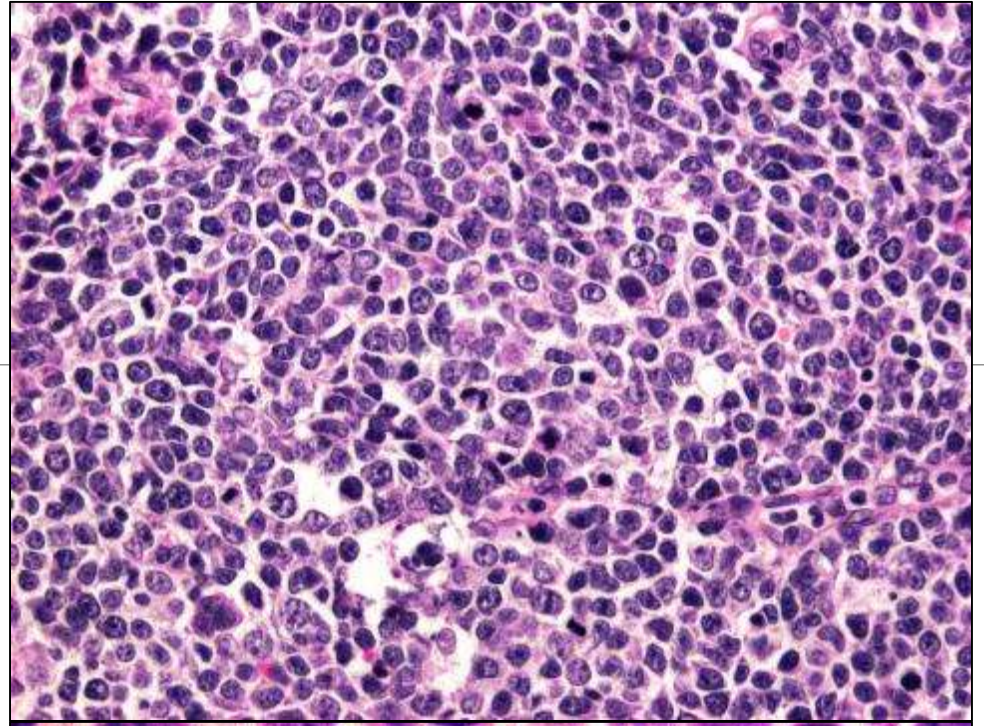
Often amplification of *BCL6*

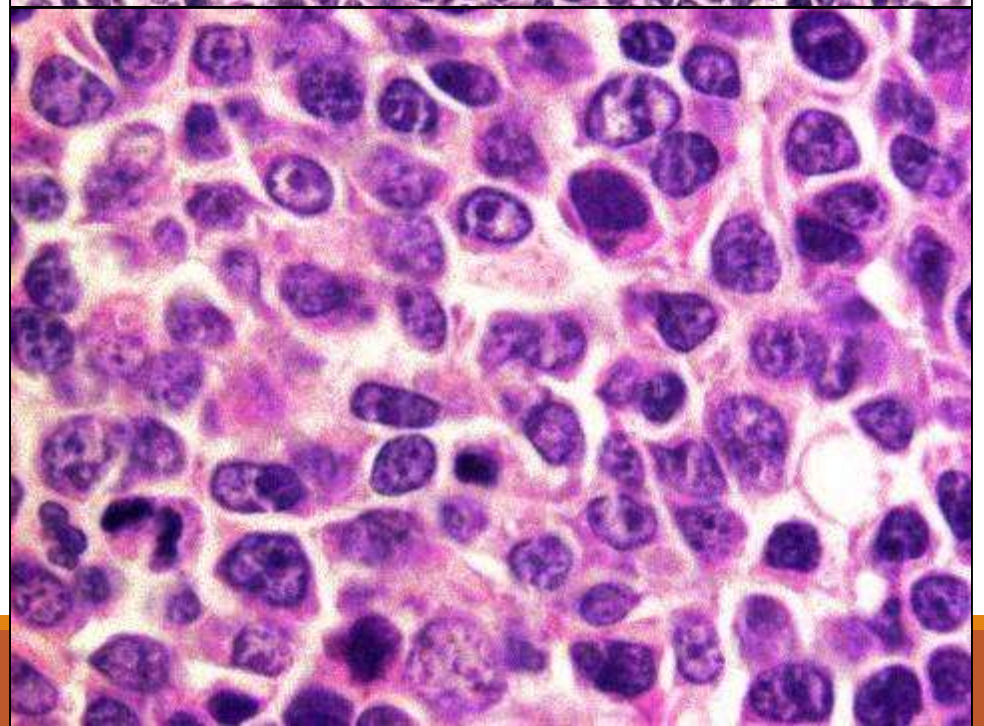
Elderly

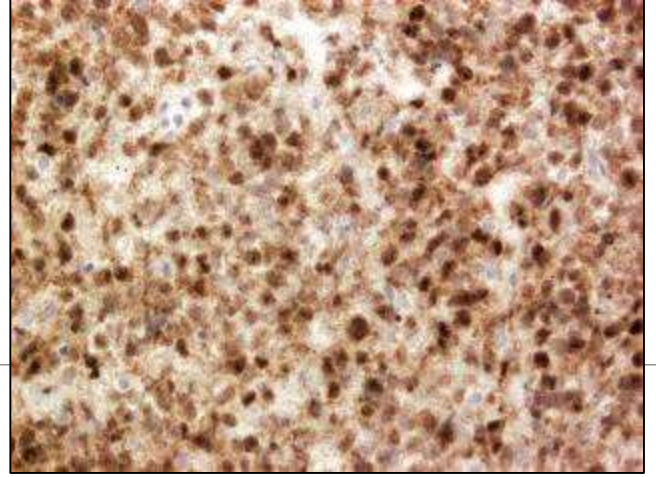
High grade – 3A/3 or 3B/3

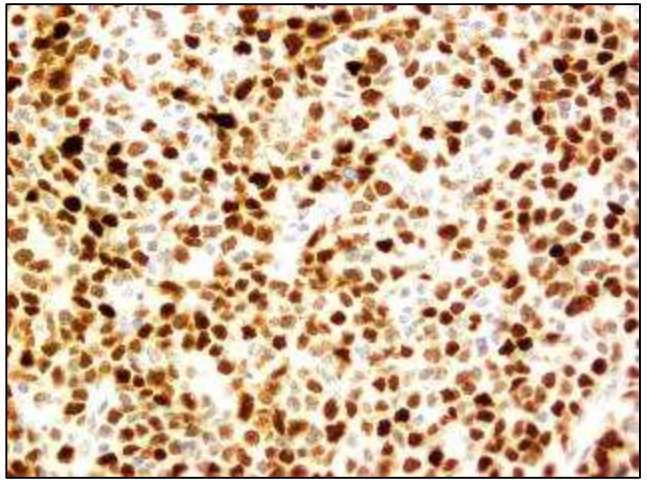
* need to distinguish from large B cell with *IRF4* translocation

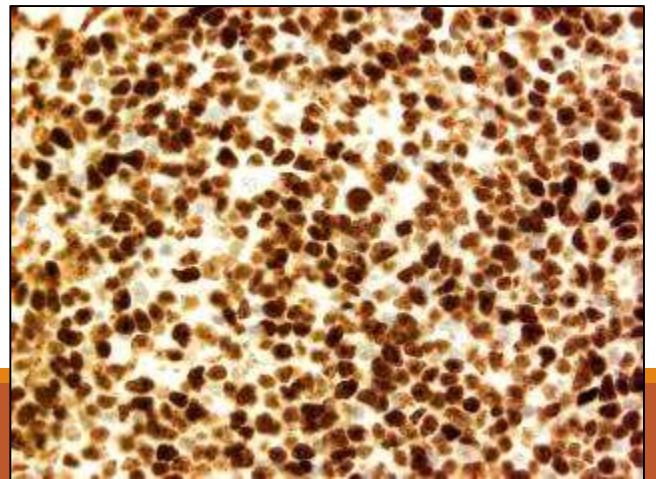












Testicular follicular lymphoma

Higher frequency in children

Lack *IGH/BCL2* translocation

Typically grade 3A/3

Good prognosis even without systemic therapy

3q27 and/or *BCL6* rearrangements are seen more frequently

Diffuse follicular lymphoma variant

Absence of *IGH/BCL2*

Microfollicles

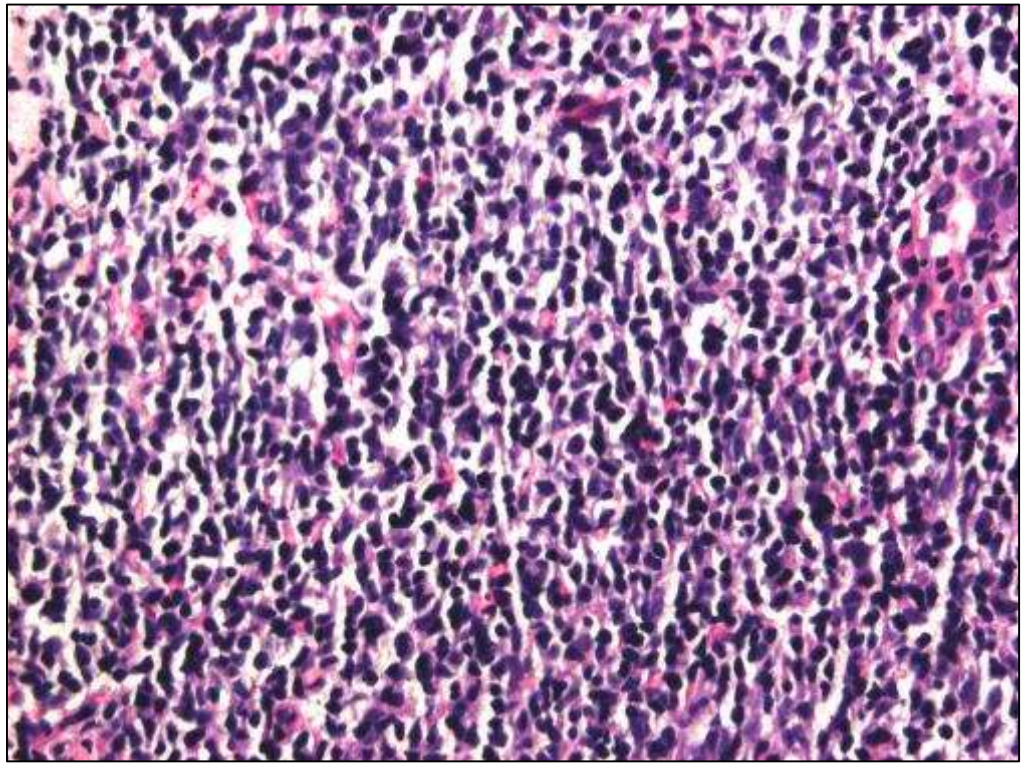
Inguinal region

Large masses, but tend not to disseminate

CD10+, CD23+*

Deletion of 1p36 common

STAT6 mutation common (*this causes the CD23 overexpression)



In situ follicular neoplasia

Up to 70% of individuals may have *IGH/BCL2* translocations in cells in blood

Increased incidence with

- Exposure to pesticides
- Hepatitis C patients
- Increased age

These are not naïve B cells

In situ follicular neoplasia

~2% of randomly selected LN biopsy have ISFN

Increased in older patients

Have t(*IGH-BCL2*) but lack other genetic abnormalities

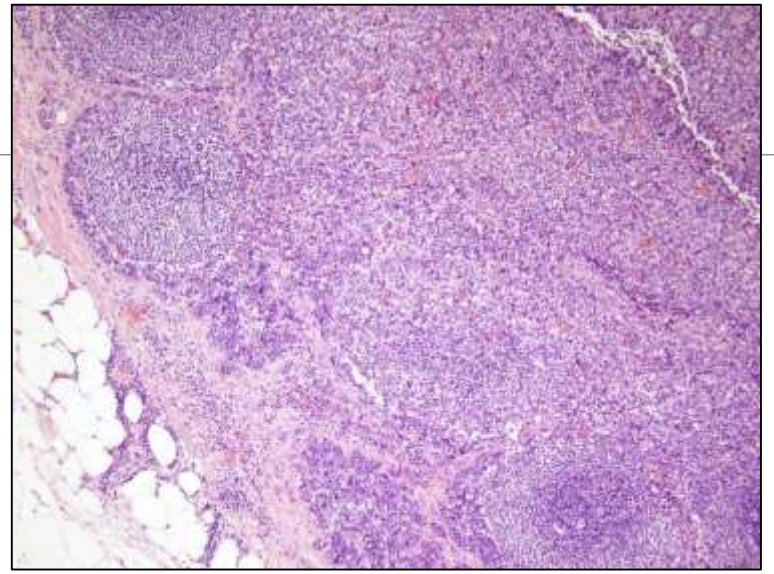
Follow-up

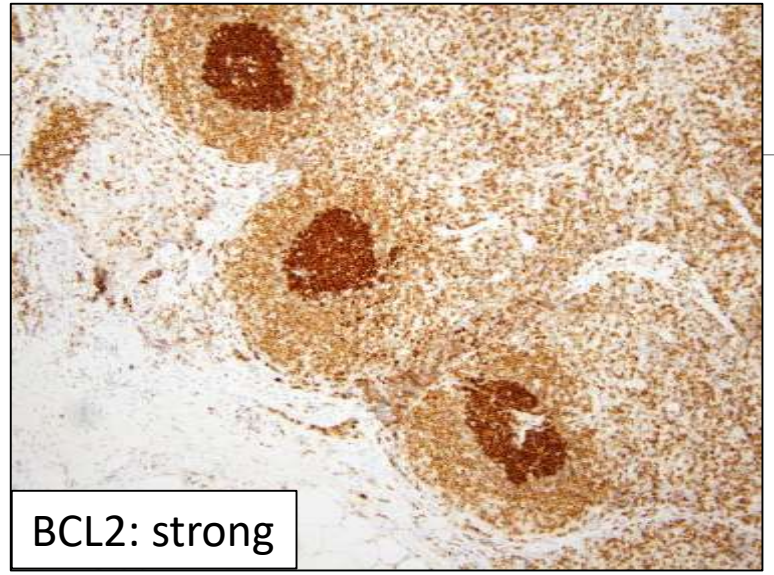
- 78% - No evidence of follicular lymphoma
- **3**% subsequent follicular lymphoma

Partial involvement by FL

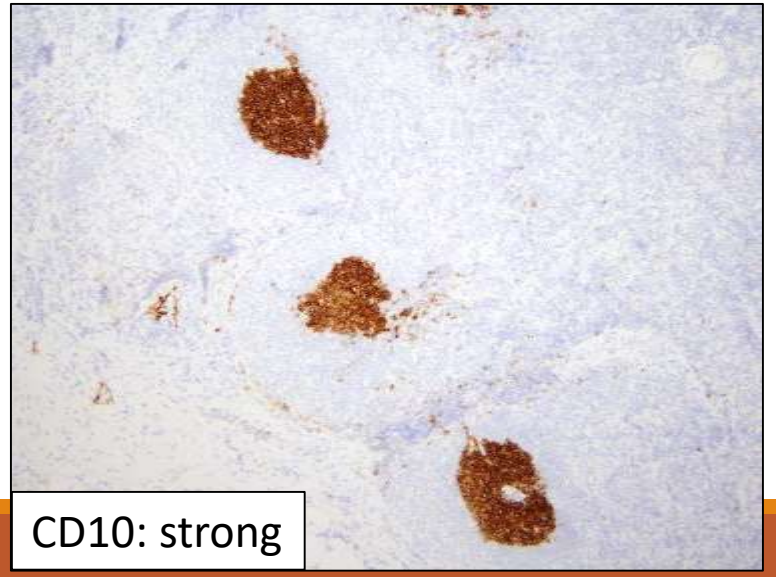
- 66% - no evidence of follicular lymphoma (28 months average f/u)
- **33**% - developed B cell lymphoma

In situ follicular neoplasia

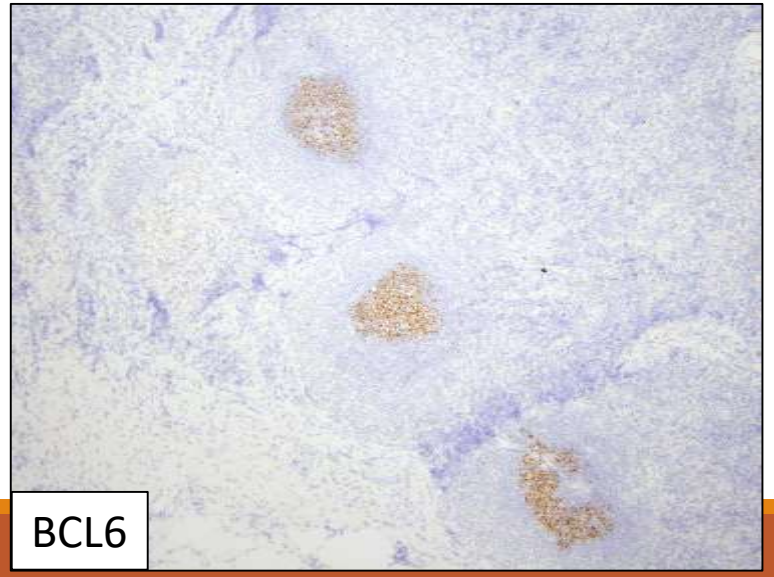




BCL2: strong



CD10: strong



BCL6

In situ FN	Partial involvement by FL
Normal architecture (low magnification)	At least focally altered architecture
Normal follicles size	Increased size in follicles
Sharp border of follicles	Irregular borders of follicles
Intact mantle zones	Abnormal or attenuated mantles
Scattered	Abnormal follicles are clustered together
Strong BCL2 expression Strong CD10 expression	Weak BCL2 expression Weak CD10 expression
Almost pure centrocytes	Mixed cytologic composition

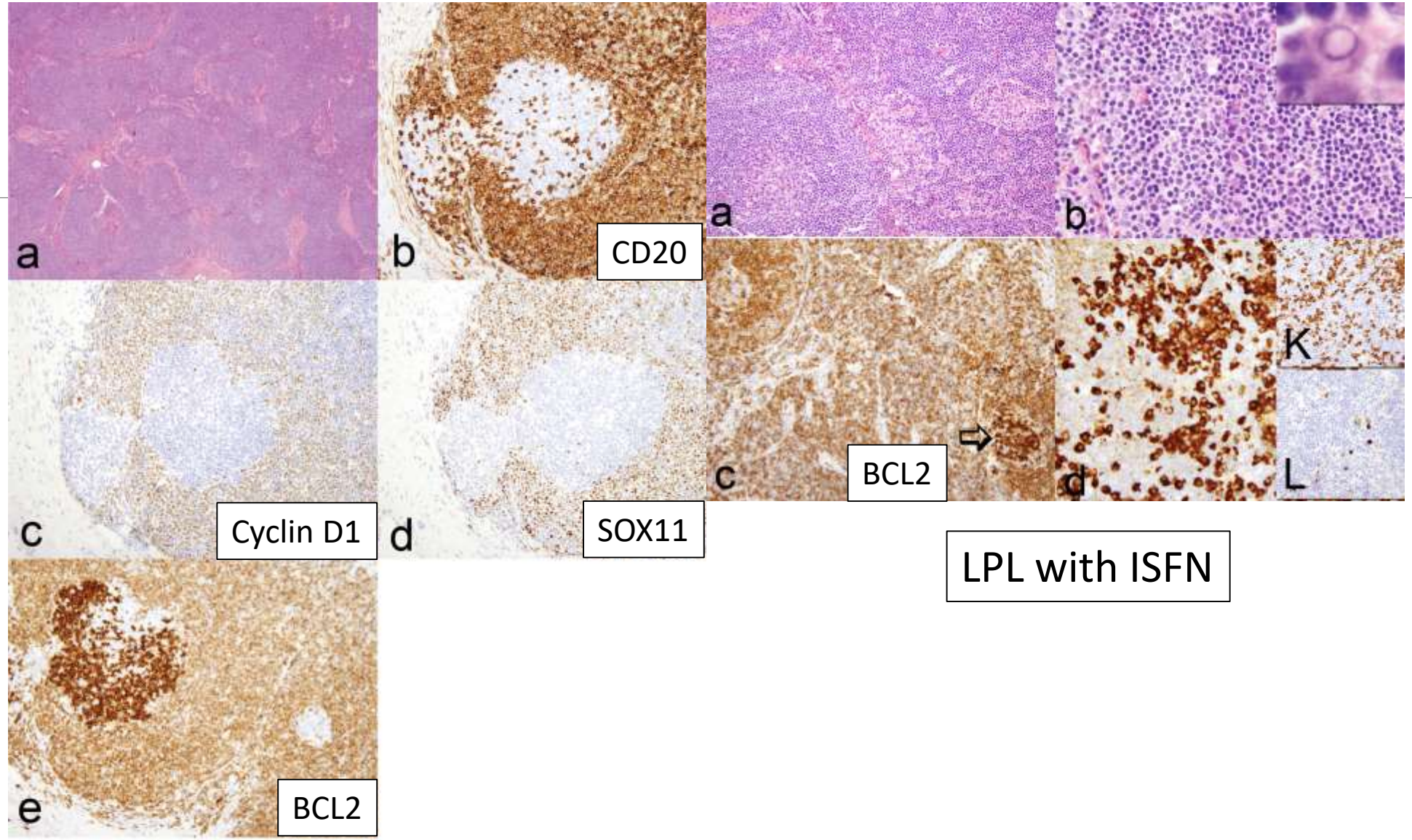
In situ FN	Partial involvement by FL
Ki67 low	Ki67 low
By definition “low grade”	Can be higher grade
IGH-BCL2 present	*IGH-BCL2* present

- In situ FN can recur!
- Reporting should include number of follicles and percent of node involvement
  - (# + %)

	FL	ISFN	FH
BCL2	+	**Focally +**	-
Ki67	Low	**Focally low**	High
CD20	Diffuse positive	Diffuse positive	Diffuse positive
BCL6/CD10	Diffuse positive	Diffuse positive	Diffuse positive
CD21	Dendritic cell networks	Dendritic cell networks*	Dendritic cell networks*

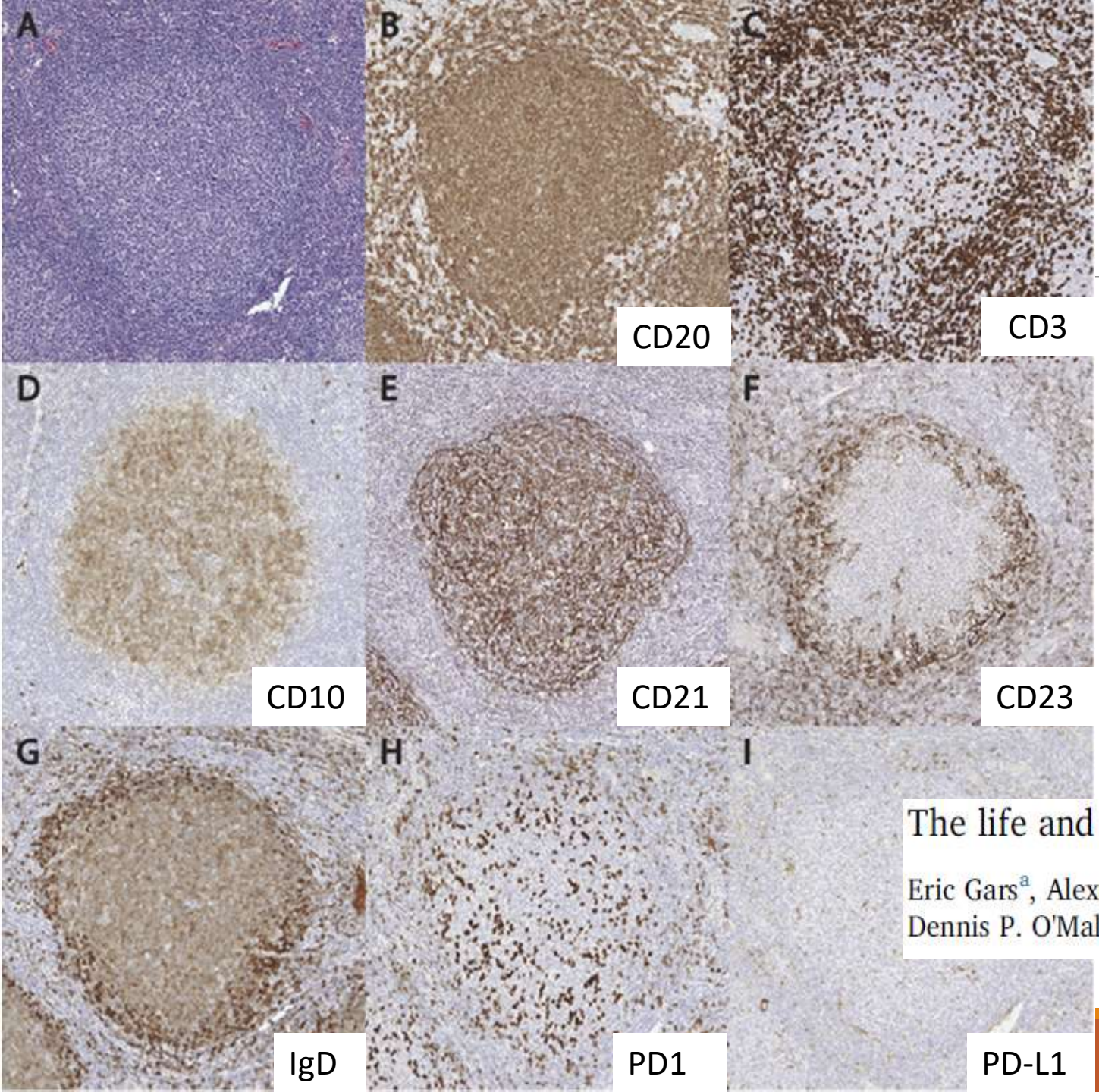
*May be disrupted

In situ follicular neoplasia with other lymphomas



MCL with ISFN

LPL with ISFN



Interesting things:
Compare CD21 and CD23

The life and death of the germinal center

Eric Gars[a], Alexandra Butzmann[b], Robert Ohgami[b], Jayalakshmi P. Balakrishna[c], Dennis P. O'Malley[d,e,*]

Pediatric type follicular lymphoma

FOXP1 expression

IRF8 mutation

MAPK1 mutation (43%)

M:F 10:1

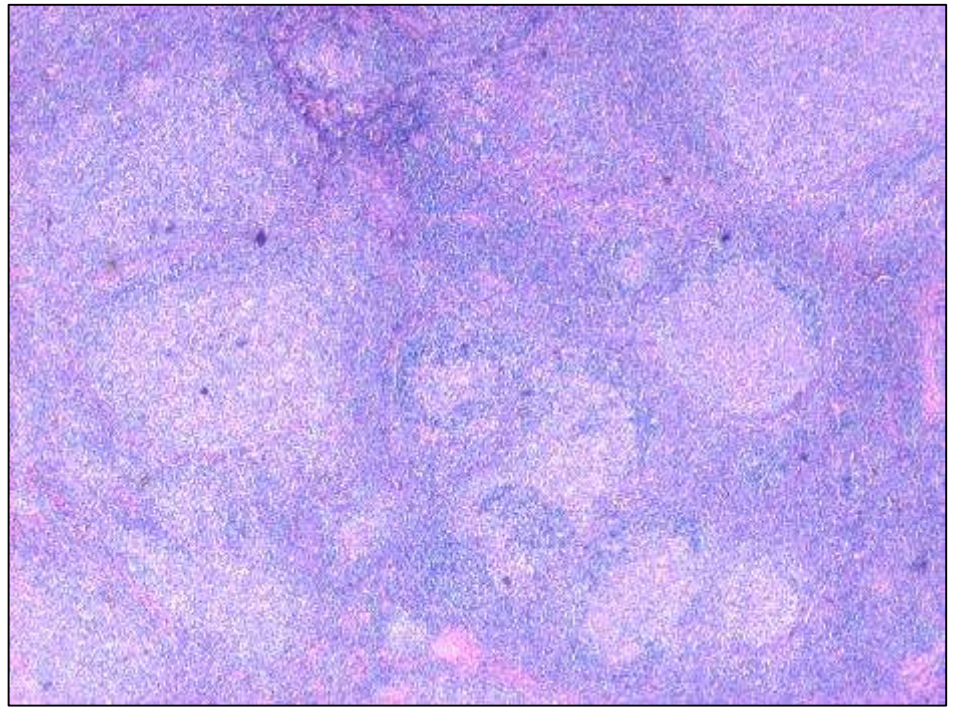
Median age 14-17 years

Most 3A/3 or 3B/3

Lack *BCL2, BCL6* or *IRF4* rearrangements

Head and neck 80-90%

TNFRSF14 30-50%, *IRF8* 10-50%, *MAP2K1* 10-40%




Pediatric-type nodal follicular lymphoma: a biologically distinct lymphoma with frequent MAPK pathway mutations


Novel markers in pediatric-type follicular lymphoma


A study of the mutational landscape of pediatric-type follicular lymphoma and pediatric nodal marginal zone lymphoma

Large B cell lymphoma with *IRF4 (MUM1)* rearrangement*

Uncommon (0.05% of LBCL)

Diffuse or follicular

Children and young adults

M:F 1:1

Waldeyer ring or head & neck

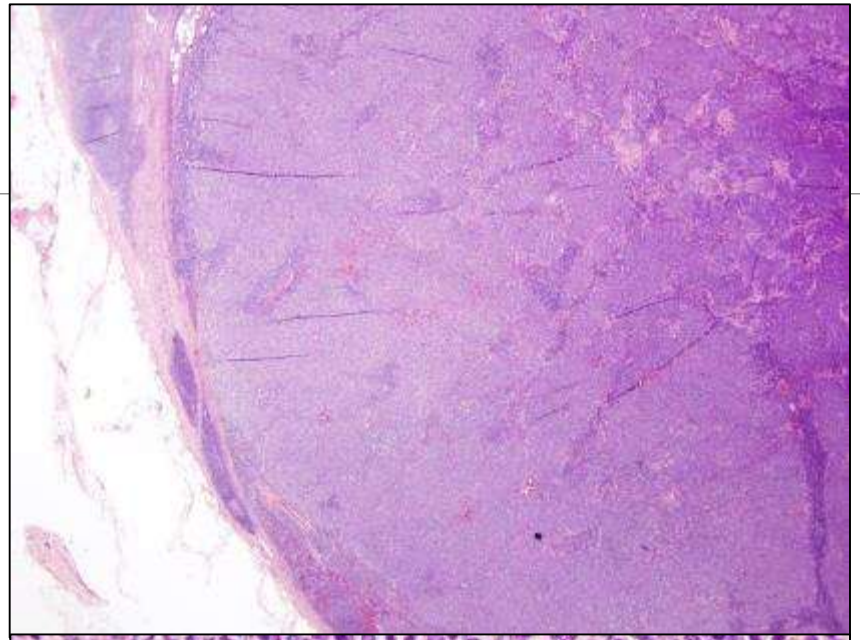
Localized/isolated adenopathy (Stage I or II)

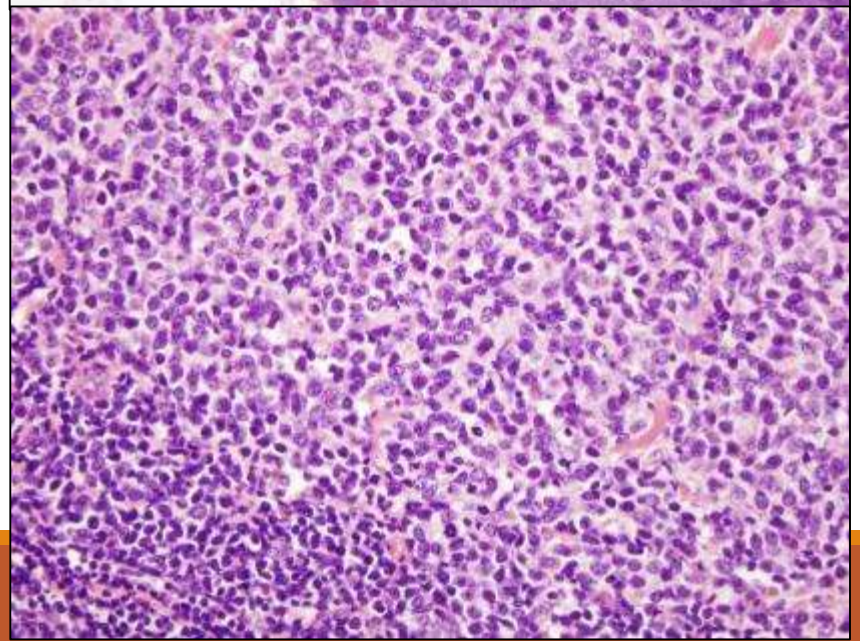
Positive IHC:

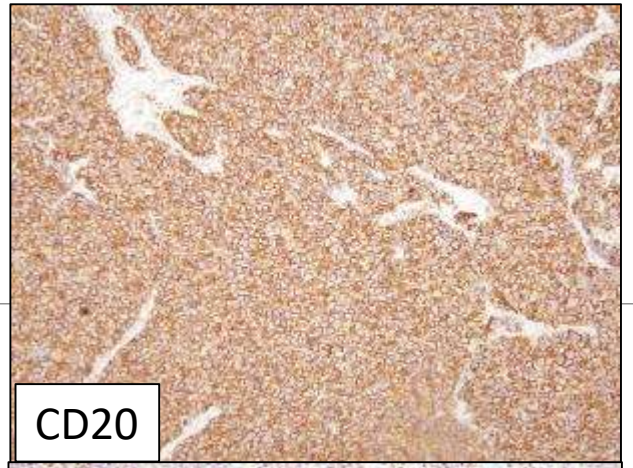
CD10 (66%), BCL2 (66%), BCL6, CD20, **MUM1***, high proliferation rate

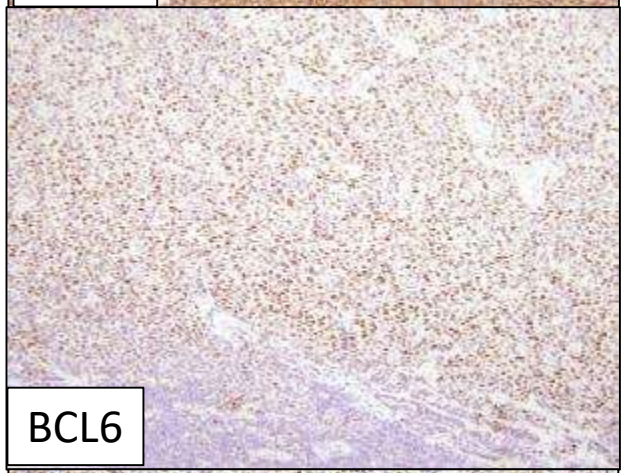
Good prognosis with therapy

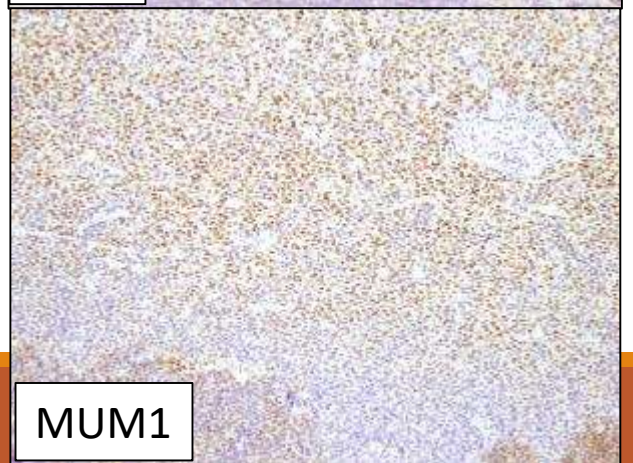
LBCL with t(*IRF4*)*











Some thoughts about FL

In young patient, probably add FOXP1 (pediatric type) and MUM1 (LBCL with IRF4)

I recommend doing regular sequencing on FL cases (EZH2 therapy; prognosis, subtypes) *if your clinicians would act on results*

I recommend 1p36 FISH

There are lots of variants by histology; I suspect there will be new types identified by molecular features

Questions?

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