



MASSACHUSETTS
GENERAL HOSPITAL

PATHOLOGY

HARVARD
MEDICAL SCHOOL



Current Concepts in Hematopathology 2022

WHO Update: Follicular Lymphoma Related Entities

Abner Louissaint, Jr. MD, PhD

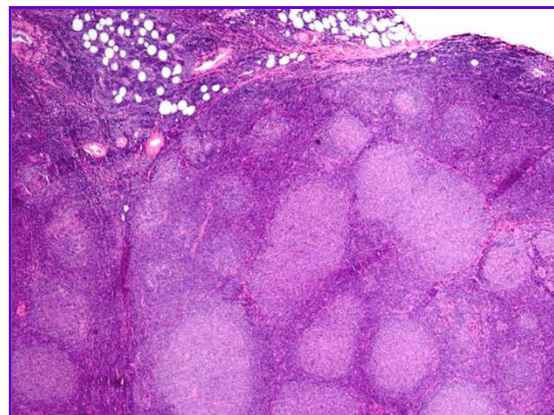
*Medical Director, Hematology Core Lab, Massachusetts General Hospital
Associate Professor of Pathology, Harvard Medical School*

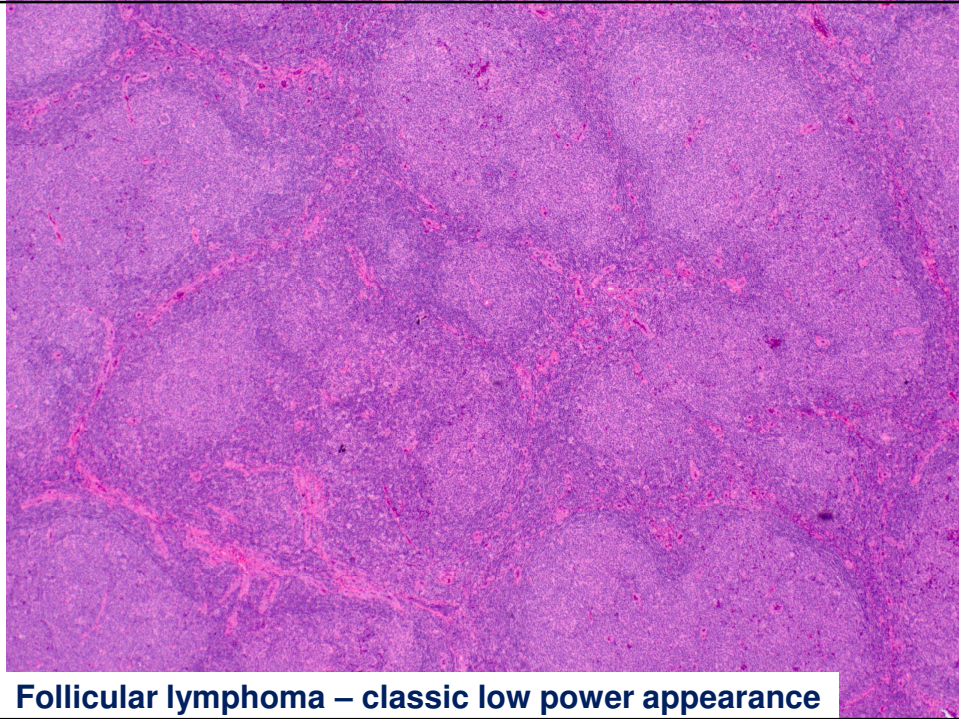
Follicular Lymphoma

- Neoplasm of germinal center B cells - (centrocytes / centroblasts)
- Follicular growth pattern
- 20% of All lymphomas
- Mean Age: **6th decade**
- **M:F = 1:1.7**

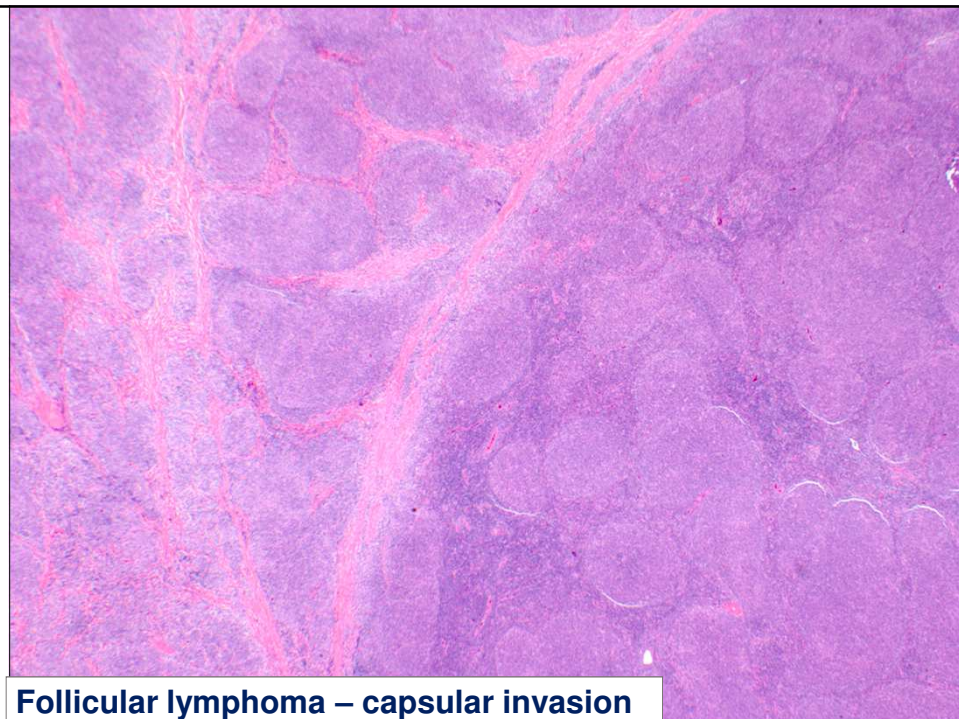
Variable clinical course

- 70% advanced stage
- Multiple relapses
- Sites: lymph nodes, marrow, spleen;
- Usually stage III/IV
- High grade transformation may occur
- Diffuse large B-cell lymphoma
- B-lymphoblastic lymphoma/leukemia (rare, very poor prognosis)

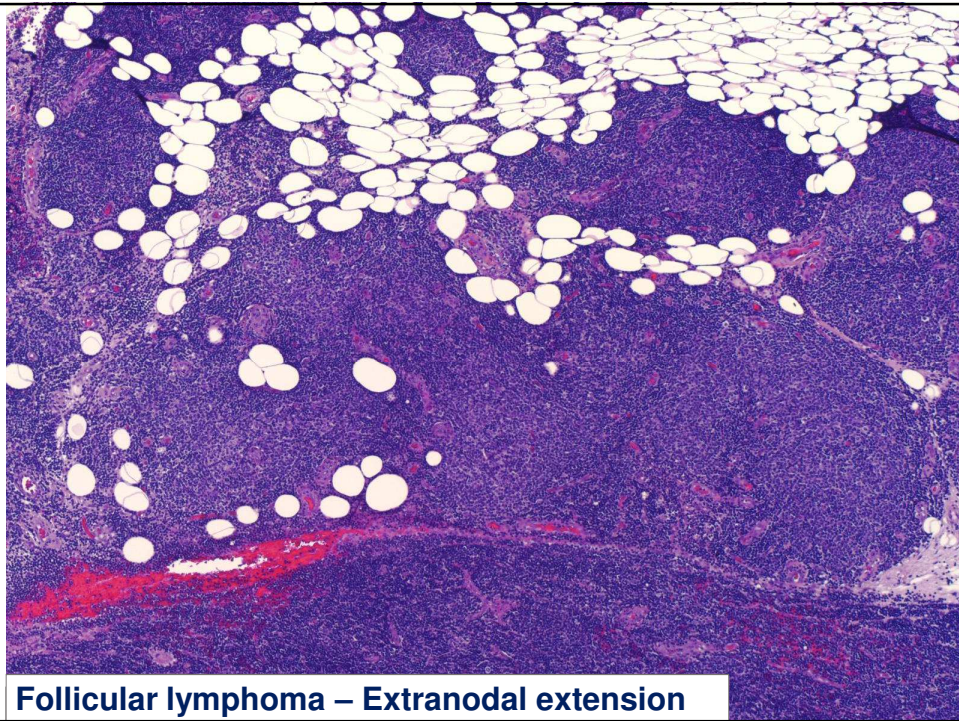




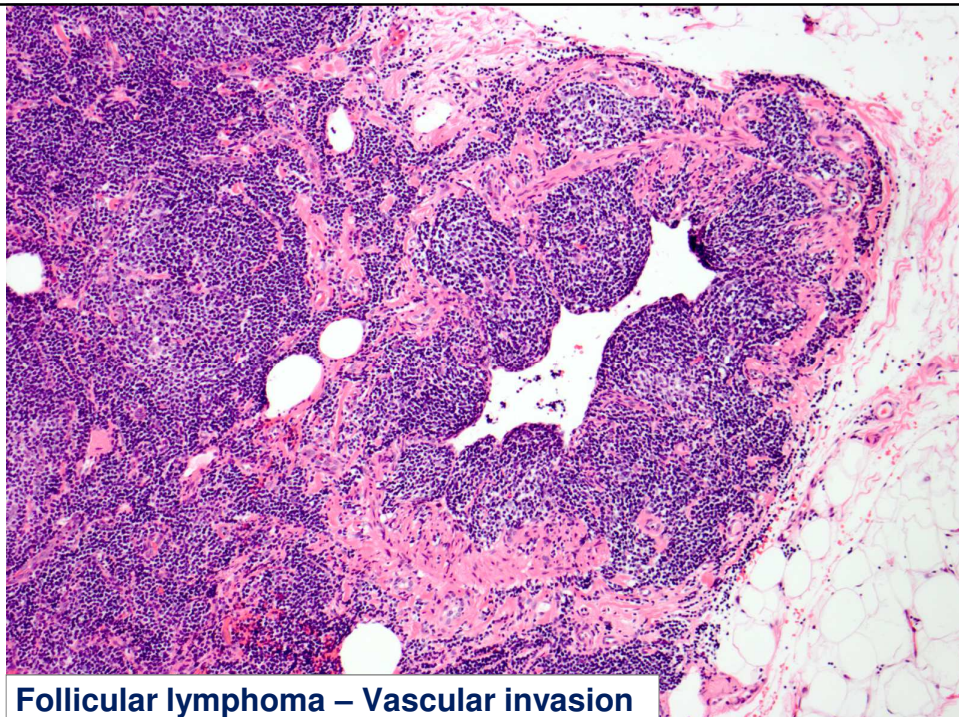
Follicular lymphoma – classic low power appearance



Follicular lymphoma – capsular invasion



Follicular lymphoma – Extranodal extension



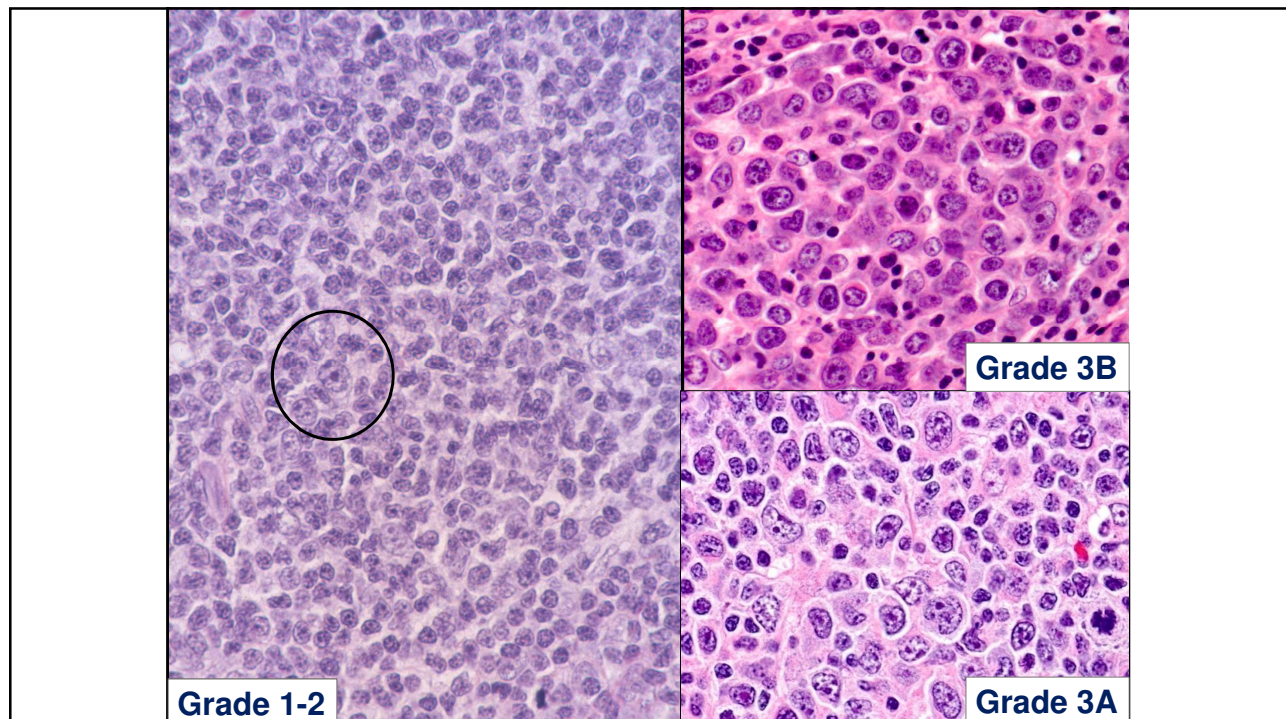
Follicular lymphoma – Vascular invasion

Follicular lymphoma: Grading

Grading	Definition
Grade 1-2 (low grade)	0-15 centroblasts per hpf*
1	0-5 centroblasts per hpf*
2	6-15 centroblasts per hpf*
Grade 3	>15 centroblasts per hpf*
3A	Centrocytes present
3B	Solid sheets of centroblasts

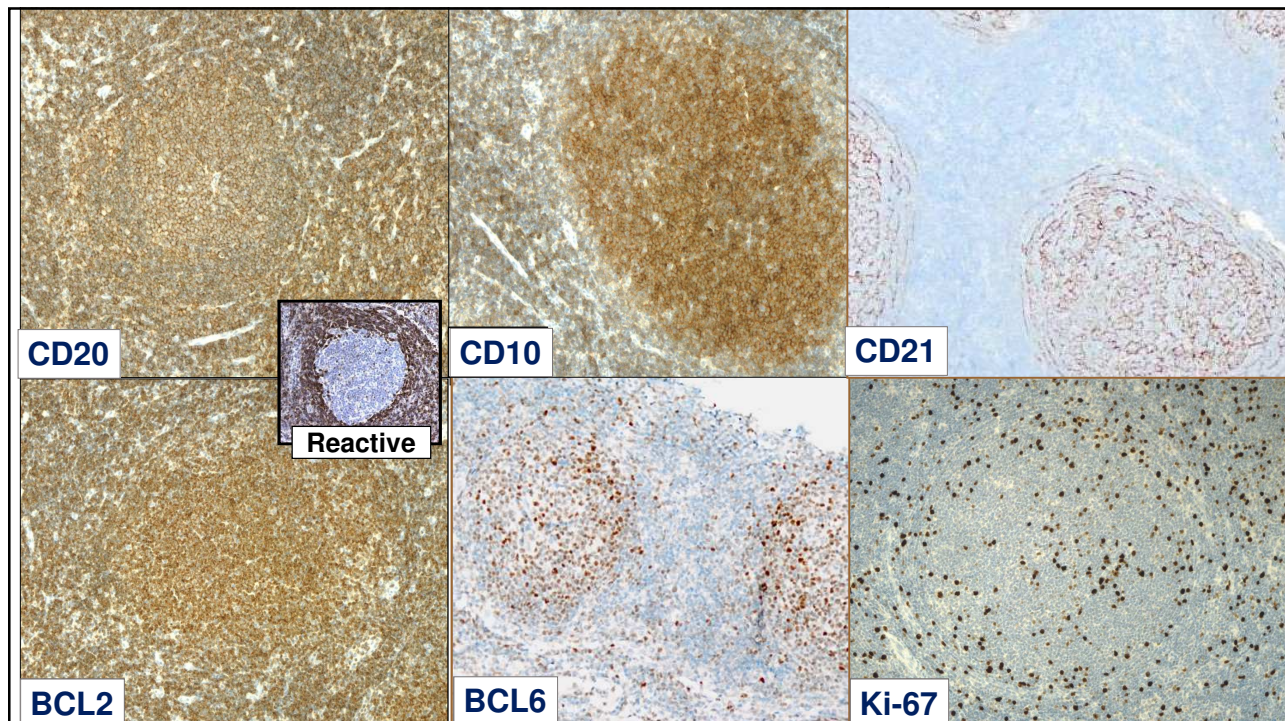
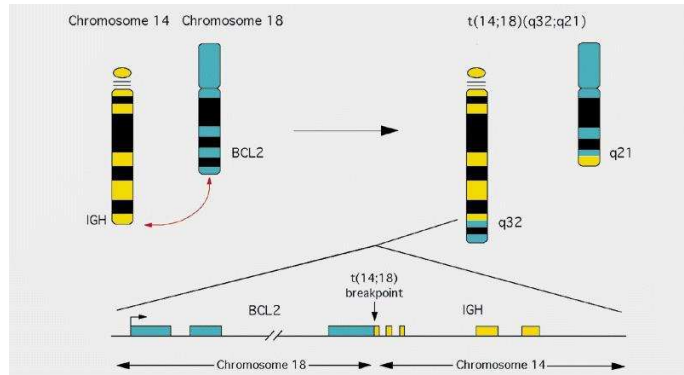
Diffuse areas of grade 3 =
Diffuse large B-cell lymphoma

Reporting of pattern	Proportion follicular
Follicular	>75%
Follicular and diffuse	25-75% **
Focally follicular	<25% **



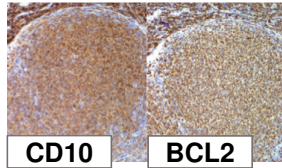
BCL2 Translocations in Follicular Lymphoma

- Present in up to 85-90% of low grade advanced stage cases; 50% of grade 3 FL
- Translocation t(14;18)(q32;q21) juxtaposes *BCL2* on 18q21 to regulatory sequences and enhancer elements of the Ig heavy chain

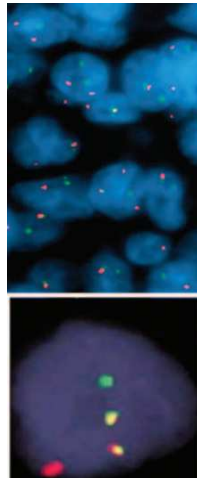


Evidence of Clonality in follicular lymphoma

IHC

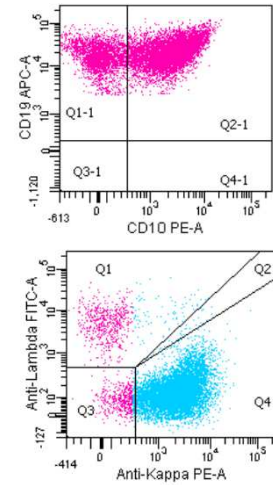


FISH

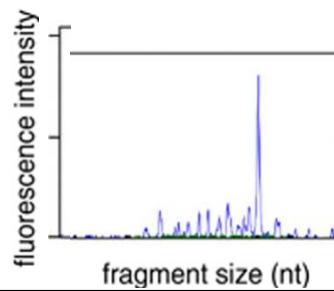


IGH and BCL2 dual color
dual fusion FISH probes

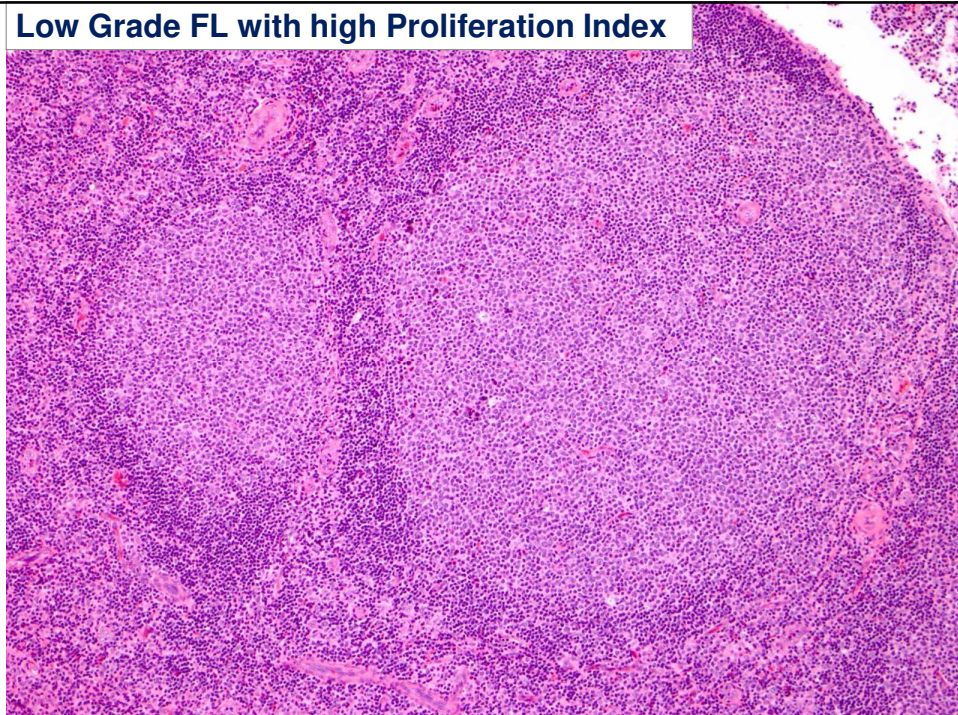
Flow Cytometry



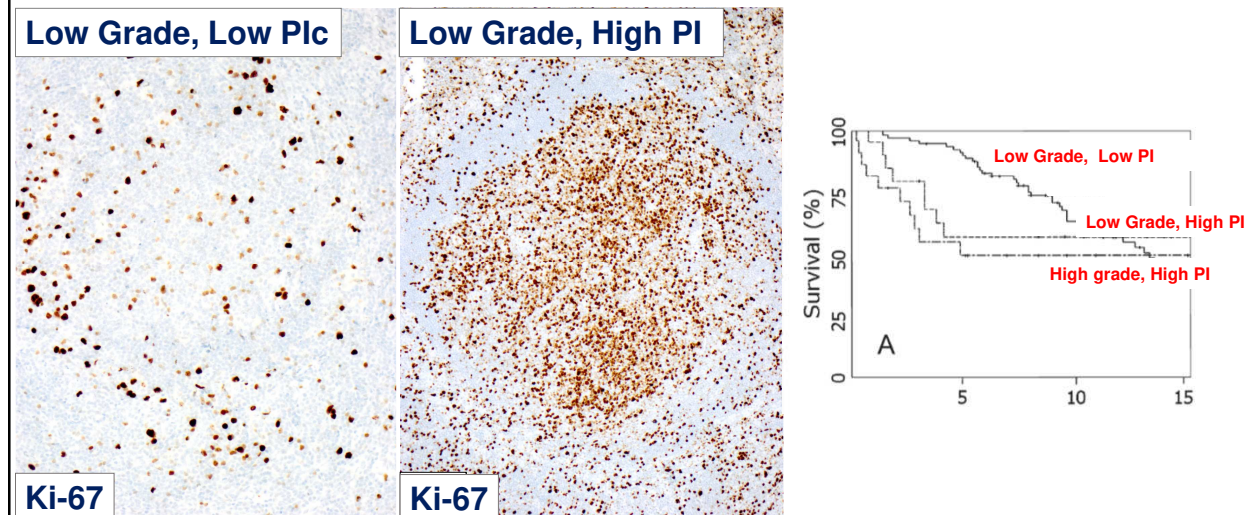
PCR: Monoclonal IGH



Low Grade FL with high Proliferation Index



Low Grade Follicular Lymphoma with High Proliferation Index



Important and Evolving Issues in FL diagnosis

- Recognition of new FL-related entities with distinct pathologic and molecular genetic features, and distinct clinical behavior
 - **BCL2 negative FL-related entities**
 - **Extranodal FL-related entities**

Follicular Lymphoma Variants and Related Entities

Variants

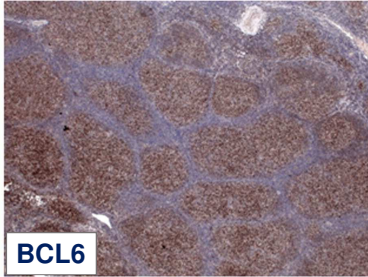
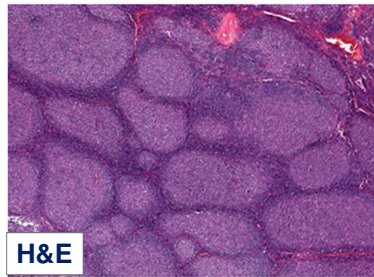
- In situ follicular neoplasia
- Duodenal-type follicular lymphoma
- Extranodal follicular lymphoma
- FL with predominantly diffuse growth pattern and 1p36 deletion

Distinct Entities

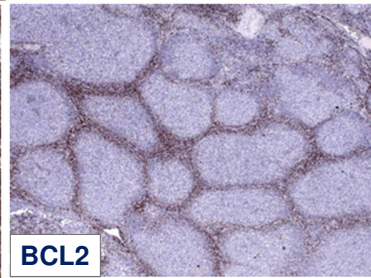
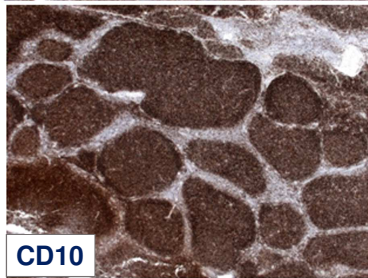
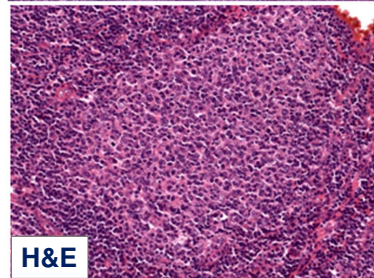
- **Primary cutaneous follicle center lymphoma**
- **Pediatric-type follicular lymphoma** **New*
- **Large B-cell lymphoma with IRF4 translocation** **New*

Scenario #1: BCL2 Negative Follicular Lymphoma

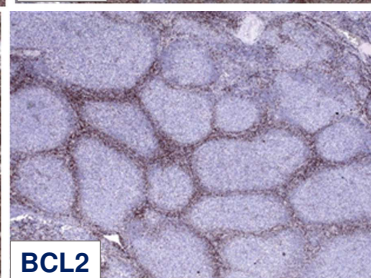
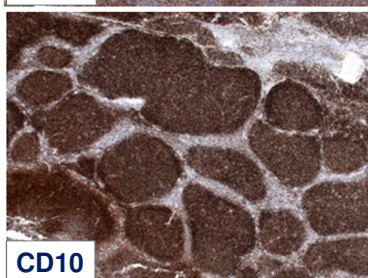
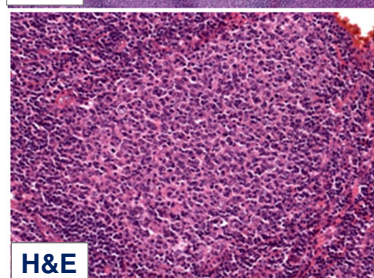
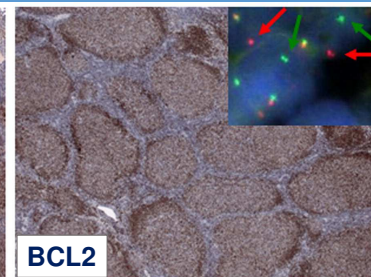
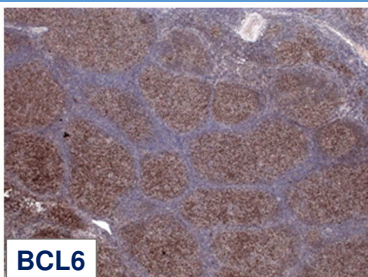
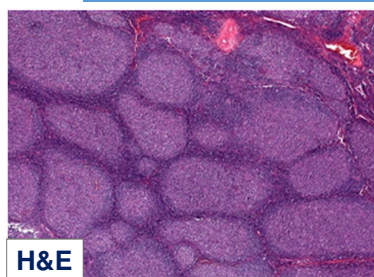
Scenario #1: BCL2 negative Follicular Lymphoma



- 68 year old F with Stage III FL (cervical node)
- Clonal CD10+ population by flow cytometry
- **FISH BCL2 Gene rearrangement positive**

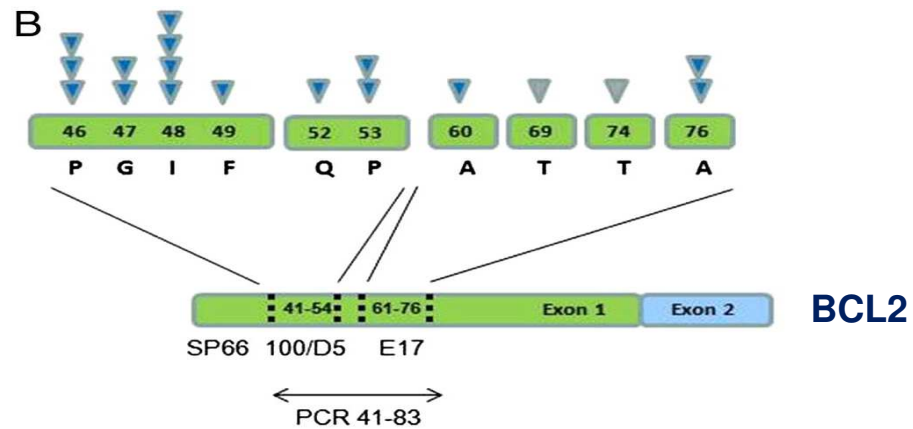


Missense mutations in BCL2 impact BCL2 staining with standard antibodies



Quintanilla-Martinez et. al/ Human Pathology 2013

Missense mutations in *BCL2* impact BCL2 staining with standard antibodies

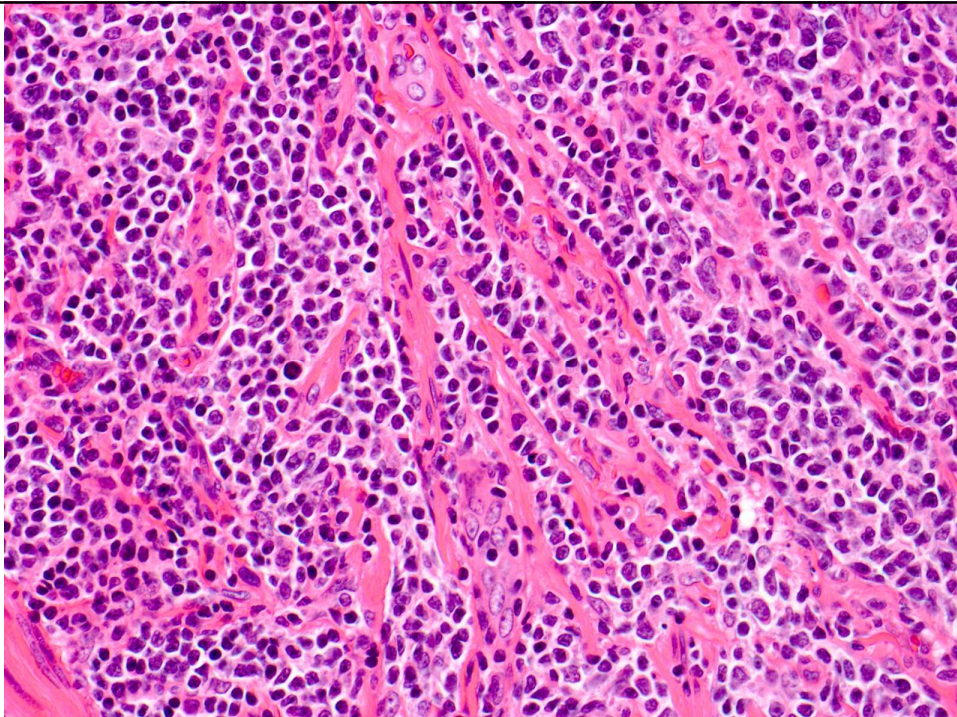
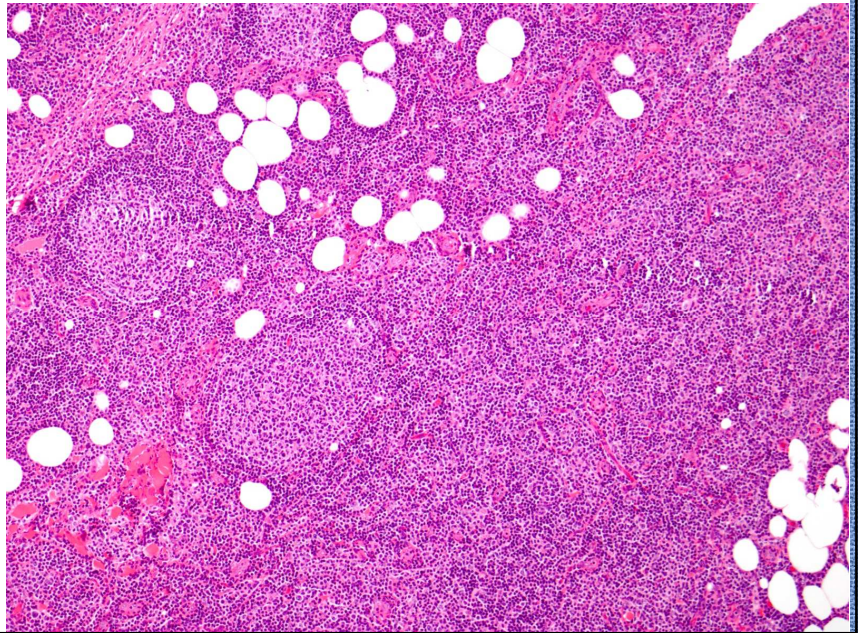


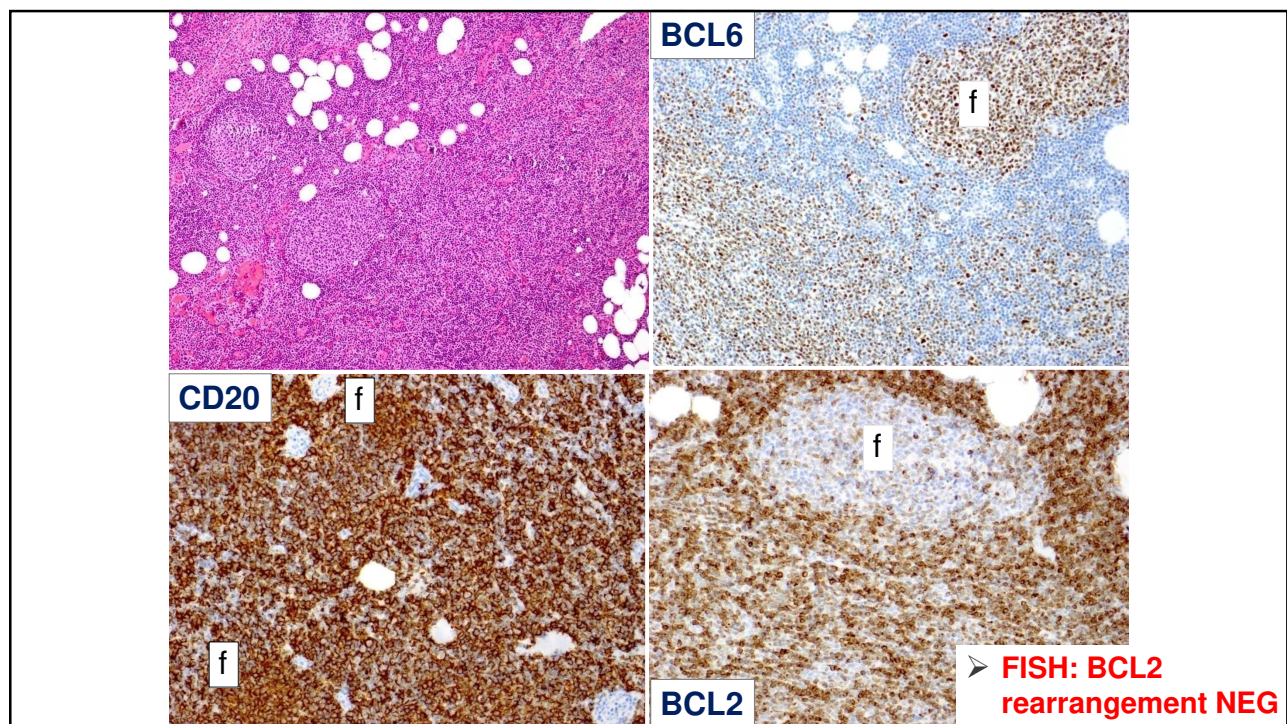
Quintanilla-Martinez et. al Human Pathology 2013

Scenario #2: *BCL2* Negative Follicular Lymphomas Lacking *BCL2* breaks

Scenario #2: Case 1

- 42 year old man
- Inguinal lymphadenopathy
- Limited stage
- Clonal CD10+ population by flow cytometry





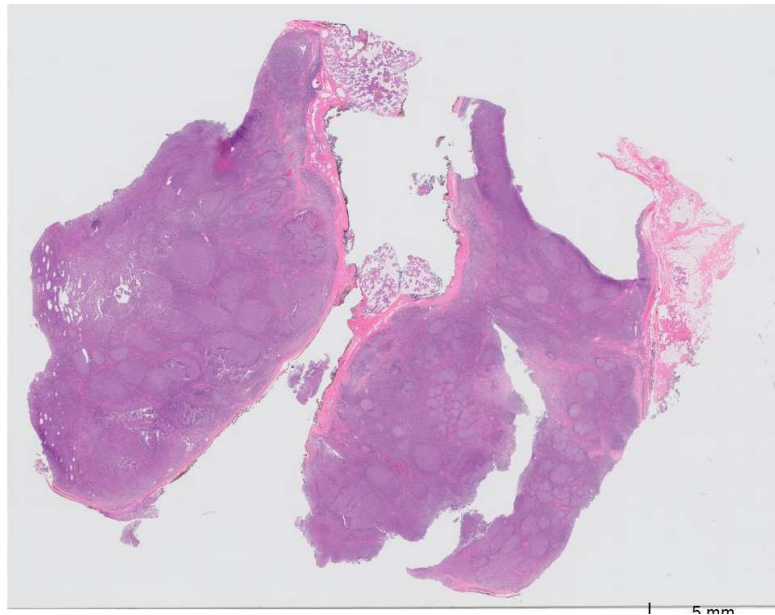
Follicular Lymphoma with Predominantly Diffuse Growth Pattern and 1p36 Deletion

- Characterized by a predominantly diffuse architectural pattern
- Often large and inguinal lymphadenopathy (80% of cases)
- Low grade (grade 1-2)
- **Lack *BCL2* rearrangement** but harbor **1p36 deletion** by FISH or karyotype
- ***STAT6* mutations** frequent
- BCL2 expression variable
- Favorable Prognosis

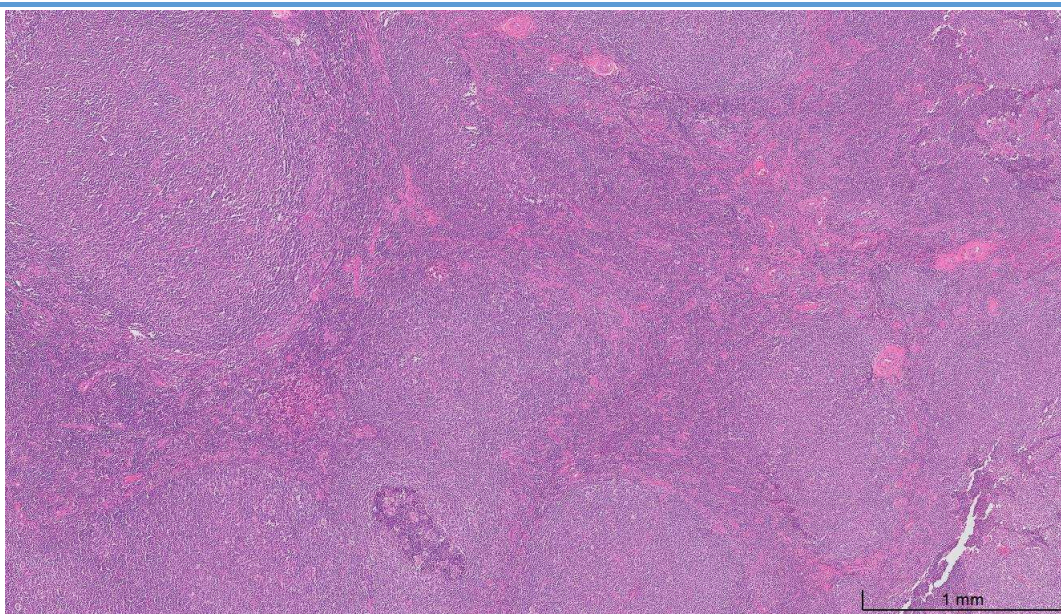
Scenario #2: Case 2

- 28 year old man with childhood asthma status post tonsillectomy (pathology showed benign lymphoid hyperplasia).
- Six months later he felt a painless lump on the left side of his face.
- Imaging found a 2.1 x 2.1 x 1.5 cm preauricular mobile mass within the parotid gland.
- FNA showed viably sized atypical lymphocytes, including large cells with irregular nuclei and prominent nucleoli. Flow showed a CD10+ B cell population with monoclonal kappa light chain expression cell population.
- Clinical Differential: Follicular lymphoma, DLBCL, Large B-cell lymphoma with IRF4 rearrangement, Burkitt lymphoma

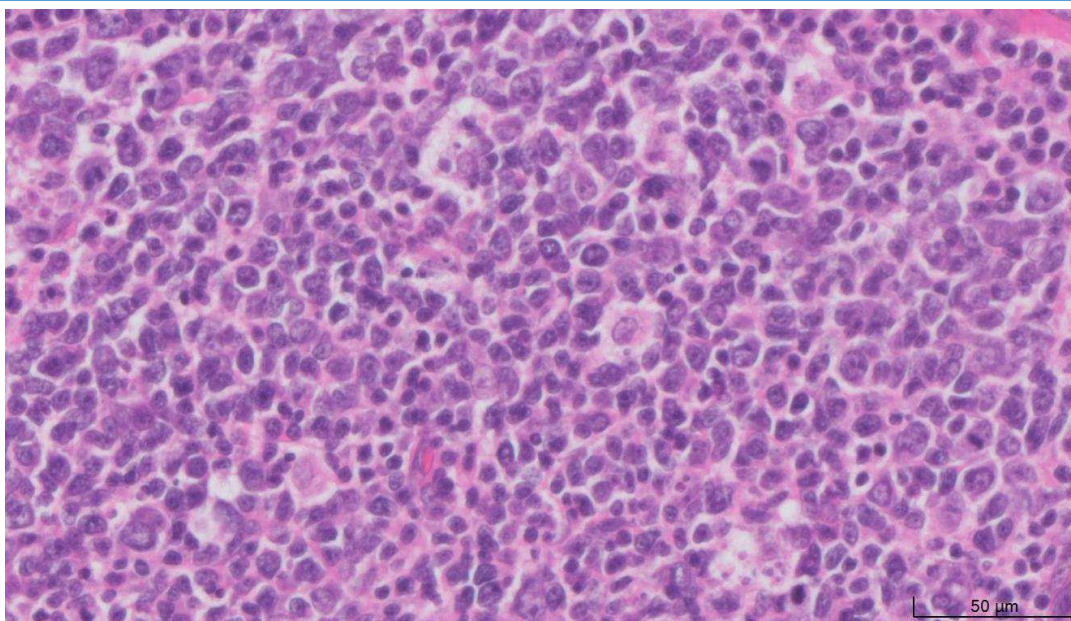
Case 2

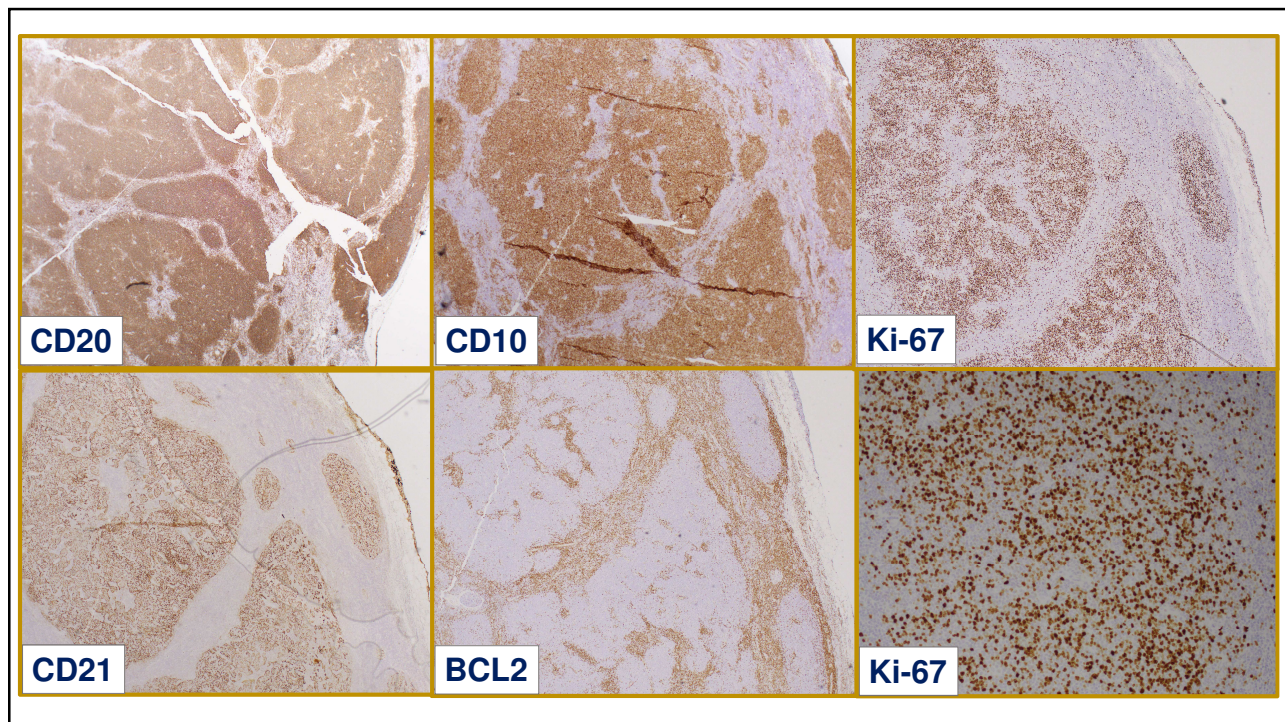


Case 2



Case 2





Additional Information

- MUM1 IHC is negative
- FISH for BCL2 and BCL6 gene rearrangements are negative
- Imaging shows that disease is localized

Diagnosis : Pediatric-Type Follicular Lymphoma

Early Series of FL in Children Identify Common Features

Series	Cases	Ages	M/F	Site(s)	Stage I	Tx(s)	Outcome	
Frizzera 1979	8	3-13	6/2	Mostly LN, 1 ileal mass	75%	All XRT +/-chemo, excision	<u>All</u> alive w/o disease	M>>F
Winberg 1981	12	3-19	11/1	All LN, with 8 head/neck	42%	5 XRT, 6 chemo, 1 excision only	<u>All</u> stage I disease-free	Limited stage
Pinto 1990	20	3-20	15/5	7 tonsil, 13 LN (5 head/neck)	75%	Chemo, excision; 3 tx deferred	<u>All</u> durable remission	Head & Neck
Ribiero 1992	17	11.7 med.	Most M	Most tonsil, head/neck LN	Most	<i>not reported</i>	<u>94%</u> stage I disease-free	High histologic grade
Atra 1998	7	4-13	4/3	All LN, with 5 neck/tonsil	100%	3 excision only , 4 exc+chemo	<u>86%</u> durable remission	Commonly lack aberrant bcl2
Lorsbach 2002	23	3-20	16/7	LN/tonsil/extranodal	79%	All chemo, 3 also rcv'd XRT	<u>All</u> stage I disease-free	Durable remission

Format adapted from Agrawal R, Wang J. Ach Pathol Lab Med 2009;133(1):142-146

"Pediatric Follicular Lymphoma" - Provisional Status in 2008

- Pediatric age
- Increased proportion lack BCL2 protein expression and t(14;18)
- Often localized
- Grade 3 morphology
- Tend to have large expansile follicles with architectural effacement
- Excellent Prognosis (the majority disease free at time of last follow-up)

"Pediatric follicular lymphomas have many features indistinguishable from those seen in adults..."

Critical Issues in the Diagnosis of Pediatric FL

1. Evolving management of pediatric FL case

- *Additional experiences demonstrate no progression/ recurrence with excision alone*

1. Young adults (20's and 30's) present with pediatric FL – like lesions

- *Do adult patients have the same highly indolent disease?*
- *How should patients be diagnosed and treated?*
- *FL, grade 3 - or Pediatric FL ?*

Pediatric-type nodal follicular lymphoma: an indolent clonal proliferation in children and adults with high proliferation index and no *BCL2* rearrangement

Abner Louissaint Jr,¹ Adam M. Ackerman,¹ Dora Dias-Santagata,¹ Judith A. Ferry,¹ Ephraim P. Hochberg,² Mary S. Huang,² A. John Iafrate,¹ Daniel O. Lara,¹ Geraldine S. Pinkus,³ Itziar Salaverria,⁴ Zakir Siddiquee,¹ Reiner Siebert,⁴ Howard J. Weinstein,² Lawrence R. Zukerberg,¹ Nancy Lee Harris,¹ and Robert P. Hasserjian¹

¹The James Homer Wright Pathology Laboratories, MA General Hospital, Boston, MA; ²Massachusetts General Hospital Cancer Center, Boston, MA; ³Department of Pathology, Brigham & Women's Hospital, Boston, MA; and ⁴Institute of Human Genetics, University Hospital Schleswig-Holstein Campus Kiel/Christian-Albrechts University Kiel, Kiel, Germany

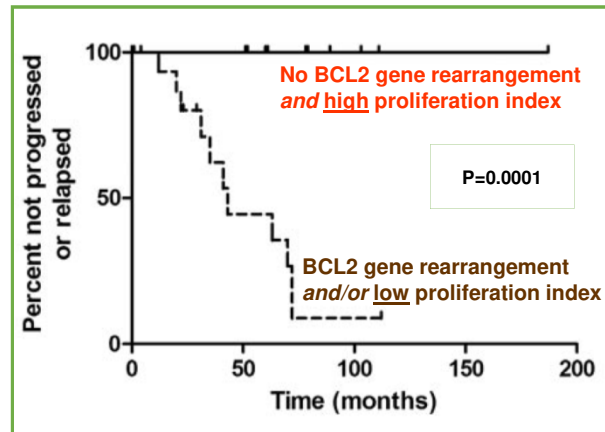
BLOOD, 20 SEPTEMBER 2012 • VOLUME 120, NUMBER 12

Follicular Lymphomas in Children and Young Adults A Comparison of the Pediatric Variant With Usual Follicular Lymphoma

Qingyan Liu, MD,* Itziar Salaverria, PhD,† Stefania Pittaluga, MD, PhD,*
Armin G. Jegalian, MD, PhD,* Liqiang Xi, MD,* Reiner Siebert, MD,† Mark Raffeld, MD,*
Stephen M. Hewitt, MD, PhD,* and Elaine S. Jaffe, MD*

Am J Surg Pathol • Volume 37, Number 3, March 2013

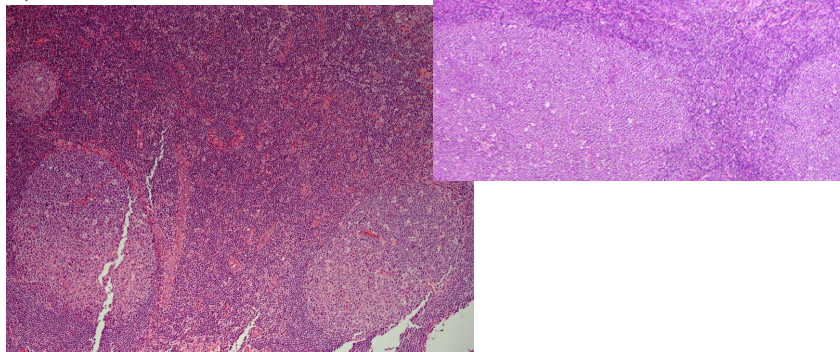
‘Pediatric-type FL’ characterized by high PI and Absence of *BCL2/BCL6/IRF4* rearrangements



Louissaint *et. al* Blood 2012

Pediatric Follicular Lymphoma

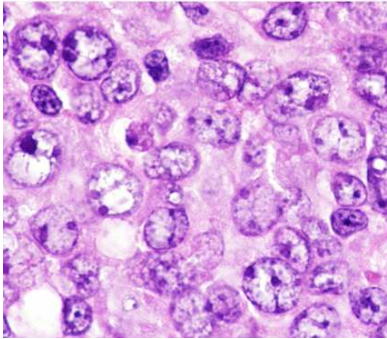
- No BCL2, BCL6, IRF4 or CBFA2T3 Breaks
- Effaced nodal architecture
- Often irregular shaped follicles
- Prominent starry sky pattern, but without polarization



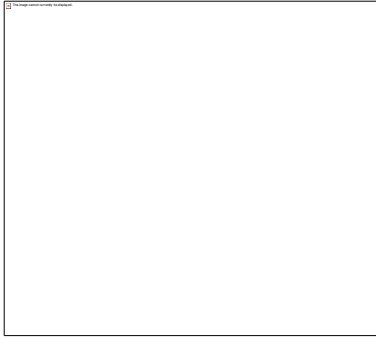
Liu *et. al* AJSP 2013

Unique Cytological Features of PTFL

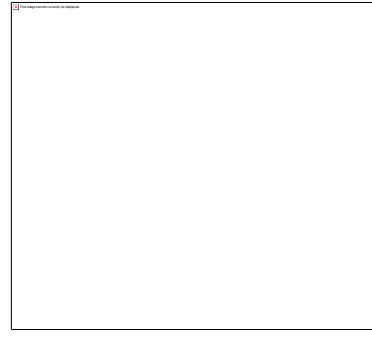
Typical Centroblasts



Blastoid Cells of Pediatric-Type FL



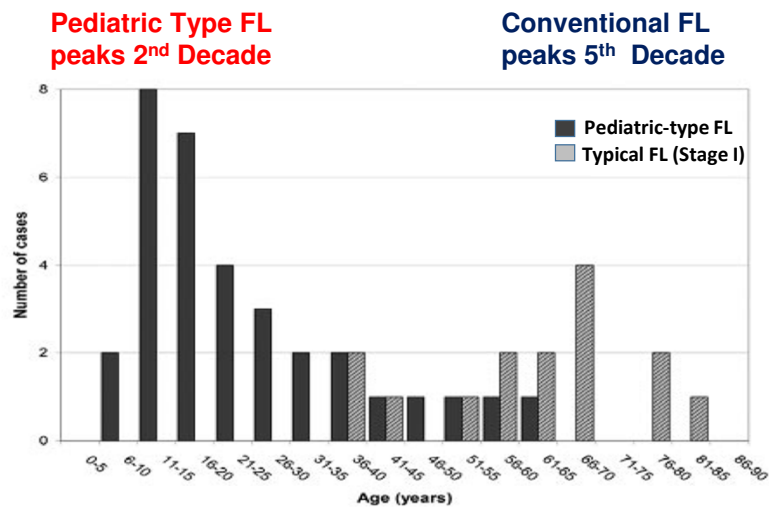
*Small to medium sized
blastoid cells
resembling centrocytes*



*Medium-sized to large
blastoid cells with finely
clumped chromatin*

Liu et. al AJSP 2013

Frequency of “Pediatric-type FL” by Age



Louissaint et. al Blood 2012

Genome-wide analysis of pediatric-type follicular lymphoma reveals low genetic complexity and recurrent alterations of *TNFRSF14* gene

Janine Schmidt,¹ Shunyou Gong,² Teresa Marafioti,³ Barbara Mankel,¹ Blanca Gonzalez-Farre,⁴ Olga Balagué,⁴ Ana Mozos,⁵ José Cabeçadas,⁶ Jon van der Walt,⁷ Daniela Hoehn,⁸ Andreas Rosenwald,⁹ German Ott,¹⁰ Stefan Dojcinov,¹¹ Caoimhe Egan,² Ferran Nadeu,⁴ Joan Enric Ramis-Zaldivar,⁴ Guillem Clot,⁴ Carmen Bárcena,¹² Vanesa Pérez-Alonso,¹² Volker Endris,¹³ Roland Penzel,¹³ Carmen Lome-Maldonado,¹⁴ Irina Bonzheim,¹ Falko Fend,¹ Elias Campo,⁴ Elaine S. Jaffe,^{2,*} Itziar Salaverria,^{4,*} and Leticia Quintanilla-Martinez^{1,*}

¹Institute of Pathology and Neuropathology, Eberhard Karls University of Tübingen and Comprehensive Cancer Center, University Hospital Tübingen, Tübingen, Germany; ²Hematopathology Section, Laboratory of Pathology, National Cancer Institute, Bethesda, MD; ³Department of Cellular Pathology, Barts and The London NHS Trust, London, United Kingdom; ⁴Hematopathology Unit, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain; ⁵Pathology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; ⁶Pathology Department, Instituto Português de Oncologia, Lisboa, Portugal; ⁷Department of Histopathology, Guy's and St. Thomas Hospitals, London, United Kingdom; ⁸Department of Pathology and Cell Biology, Columbia University Medical Center, New York, NY; ⁹Institute of Pathology, University of Würzburg, and Comprehensive Cancer Center Mainfranken, Würzburg, Germany; ¹⁰Department of Clinical Pathology, Robert-Bosch-Hospital and Dr. Margarete Fischer-Bosch Institute of Clinical Pharmacology, Stuttgart, Germany; ¹¹Department of Pathology, All Wales Lymphoma Panel, University Hospital of Wales, Cardiff, United Kingdom; ¹²Hospital Universitario 12 de Octubre, Madrid, Spain; ¹³Institute of Pathology, University Hospital Heidelberg, Heidelberg, Germany; and ¹⁴Department of Pathology, Instituto Nacional de Cancerología, Mexico City, Mexico

BLOOD, 25 AUGUST 2016 • VOLUME 128, NUMBER 8

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

Abner Louissaint Jr.,^{1,2} Kristian T. Schafernak,³ Julia T. Geyer,⁴ Alexandra E. Kovach,⁵ Mahmoud Ghandi,⁶ Dita Gratzinger,⁷ Christine G. Roth,⁸ Christian N. Paxton,⁹ Sunhee Kim,⁹ Chungdak Namgyal,¹⁰ Ryan Morin,¹¹ Elizabeth A. Morgan,¹⁰ Donna S. Neuberg,¹² Sarah T. South,¹³ Marian H. Harris,⁹ Robert P. Hasserjian,¹ Ephraim P. Hochberg,¹⁴ Levi A. Garraway,^{2,6} Nancy Lee Harris,¹ and David M. Weinstock^{2,6}

¹Department of Pathology, Massachusetts General Hospital, Boston, MA; ²Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; ³Department of Pathology and Laboratory Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL; ⁴Department of Pathology and Laboratory Medicine, Weill Cornell Medical College/New York-Presbyterian Hospital, New York, NY; ⁵Department of Pathology, Boston Children's Hospital, Boston, MA; ⁶Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, MA; ⁷Department of Pathology, Stanford University School of Medicine, Stanford, CA; ⁸Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, PA; ⁹ARUP Institute for Clinical and Experimental Pathology, Department of Pathology, University of Utah, Salt Lake City, UT; ¹⁰Department of Pathology, Brigham & Women's Hospital, Boston, MA; ¹¹Department of Molecular Biology and Biochemistry, Simon Fraser University, Burnaby, BC, Canada; ¹²Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA; ¹³ARUP Laboratories, Department of Pathology, University of Utah, Salt Lake City, UT; and ¹⁴Department of Medicine, Massachusetts General Hospital, Boston, MA

BLOOD, 25 AUGUST 2016 • VOLUME 128, NUMBER 8

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

Michael G. Ozawa^{1,6}, Aparna Bhaduri^{2,6}, Karen M. Chisholm³, Steven A. Baker¹, Lisa Ma¹, James L. Zehnder^{1,4}, Sandra Luna-Fineman⁵, Michael P. Link⁵, Jason D. Merker⁴, Daniel A. Arber¹ and Robert S. Ohgami¹

¹Department of Pathology, Stanford University, Stanford, CA, USA; ²Program in Epithelial Biology, Stanford University, Stanford, CA, USA; ³Department of Laboratories, Seattle Children's Hospital, Seattle, WA, USA; ⁴Division of Hematology, Department of Medicine, Stanford University, Stanford, CA, USA and ⁵Department of Pediatrics, Stanford University, Stanford, CA, USA

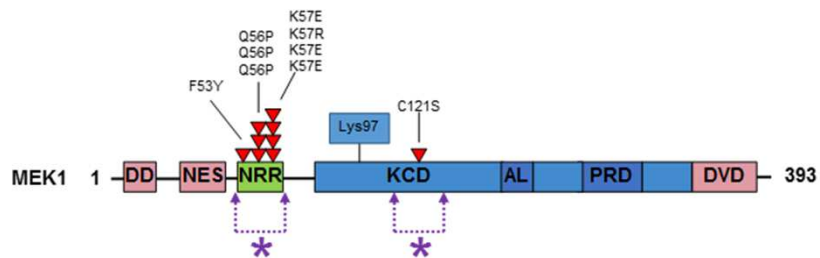
MODERN PATHOLOGY (2016) 29, 1212–1220

MAPK Pathway Mutations Occur in Both Pediatric and Adult PTFL

	PTNFL <18															PTNFL >18									
Age	4	14	18	5	15	16	17	16	7	11	14	14	15	15	27	28	38	41	30	60	20	29	30	53	
MAP2K1	Q56P	K57E	K57R	K57E	K57E	F53Y									Q56P	C121S	Q56P								
MAPK1							N297D											D321G							
RRAS																			G39S						

Louissaint et. al Blood 2016

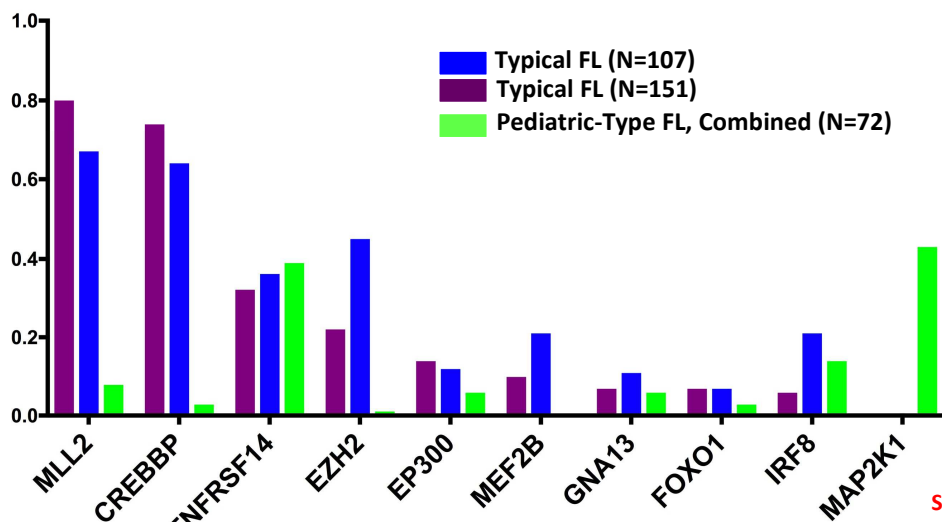
Activating MAP2K1 Mutations in PTFL



(Seen also in Melanoma, Langerhans Cell Histiocytosis,
BRAF negative hairy cell leukemia)

Louissaint *et. al* Blood 2016

Recurrent Mutations in PTFL



Schmidt *et. al* Blood 2017

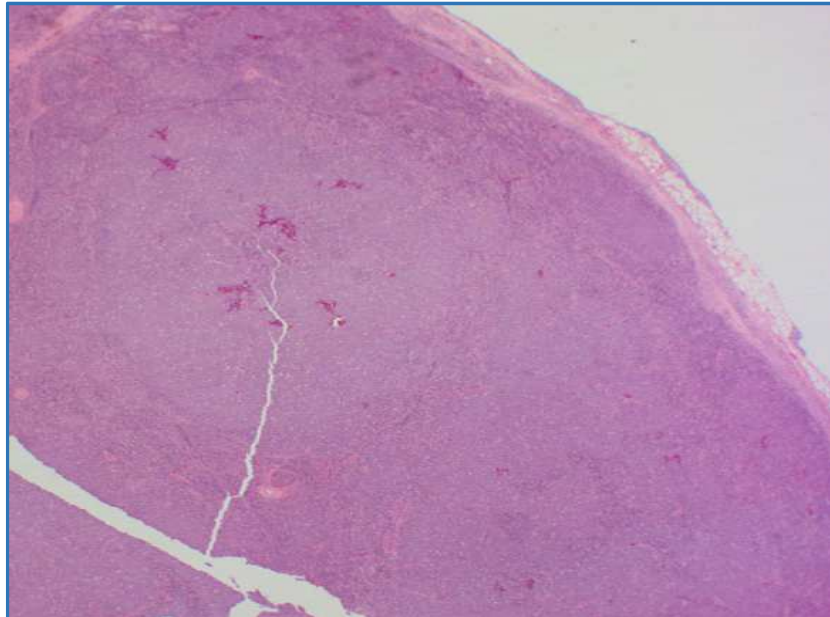
Louissaint *et. al* Blood 2016

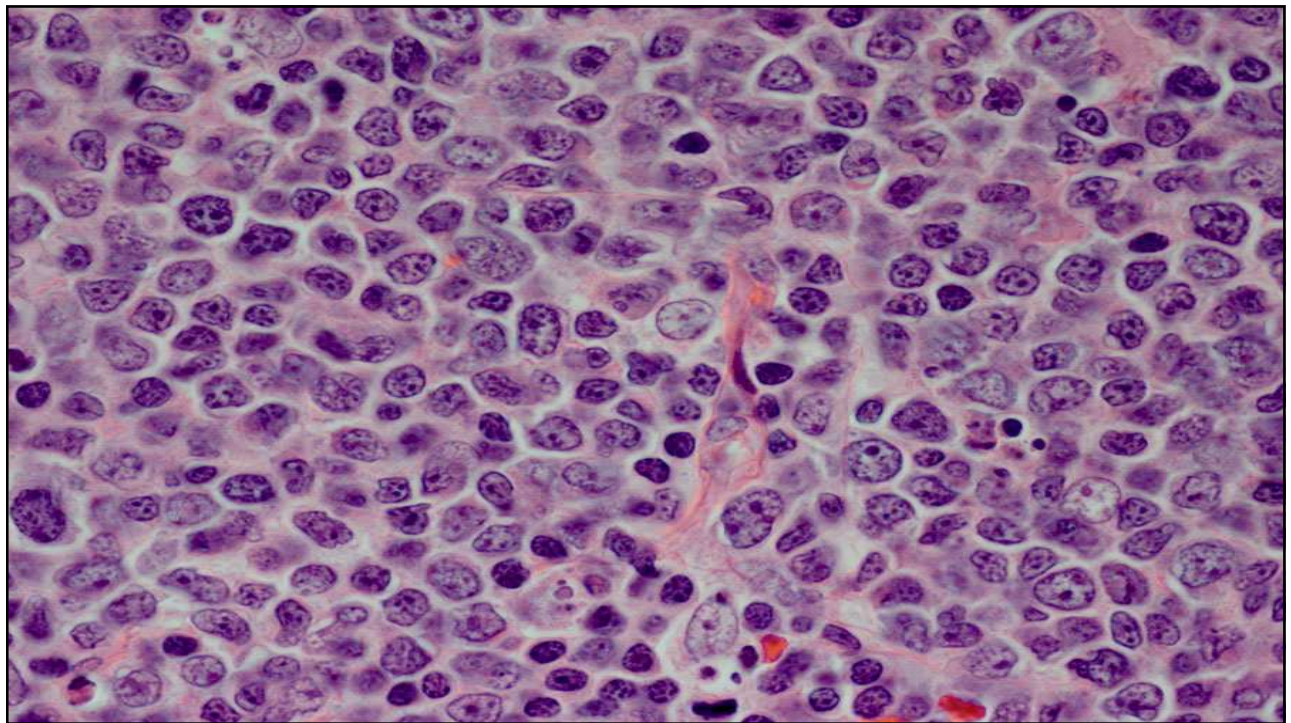
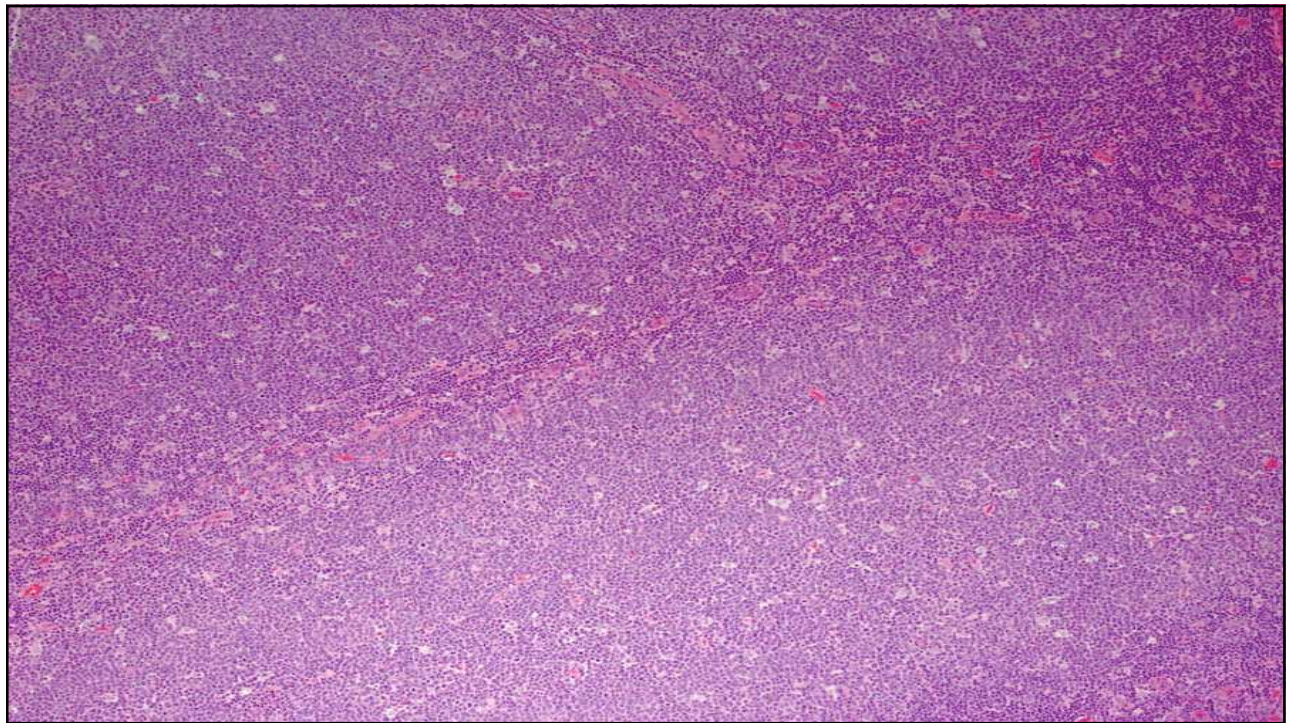
Ozawa *et. al* Modern Pathology 2016

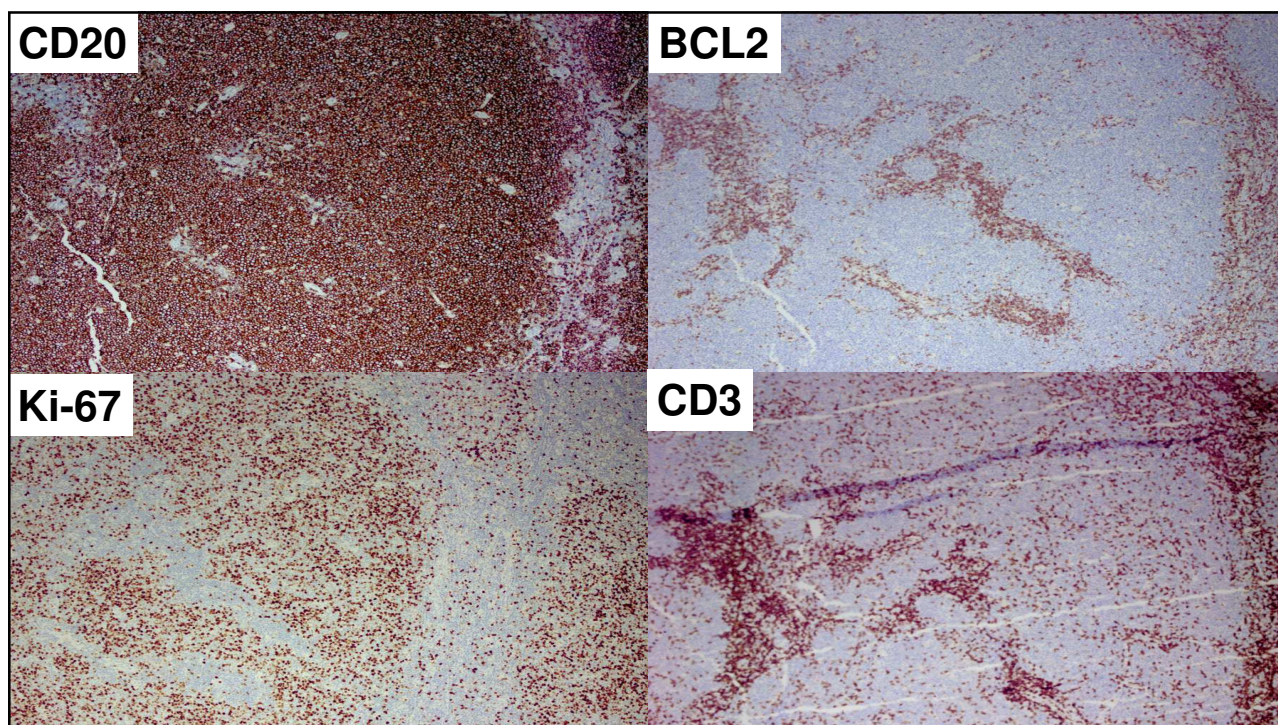
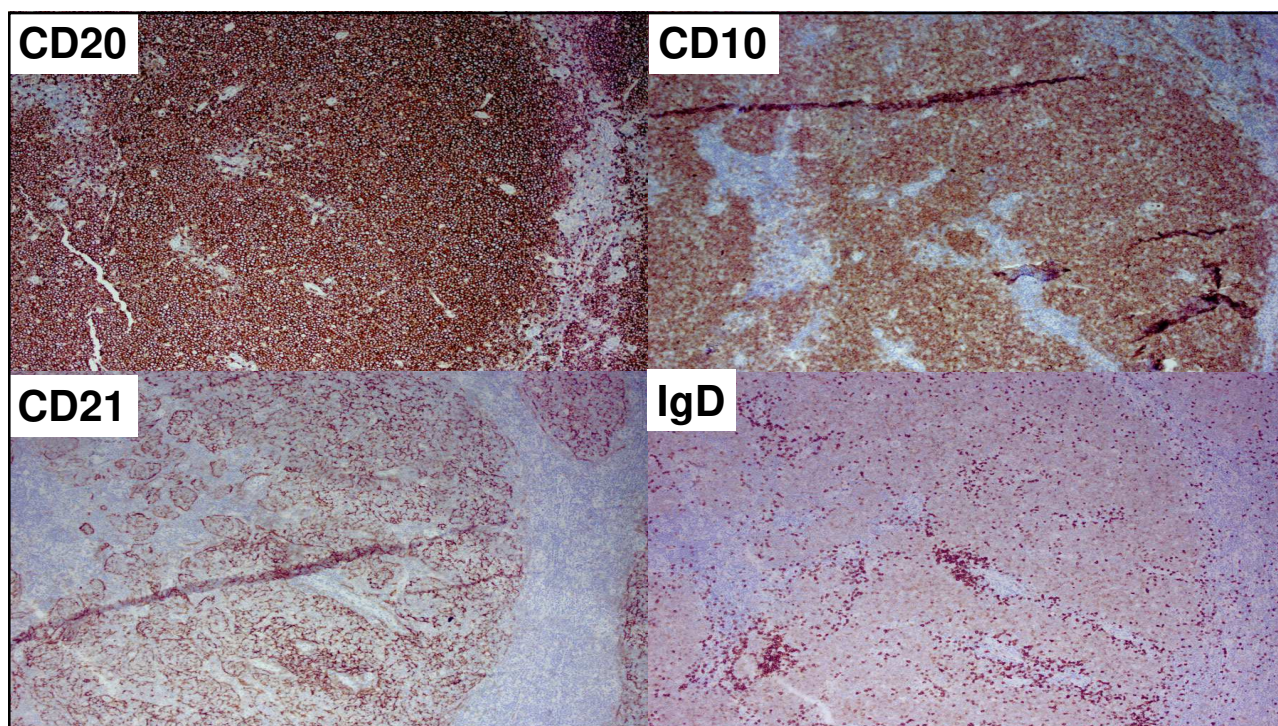
Pediatric-Type Follicular Lymphoma WHO 2016 Primary Diagnostic Criteria:

Morphology	At least partial effacement of nodal architecture (required) Pure follicular proliferation (required) ^a Expansile follicles ^b Intermediate-sized so-called blastoid cells (not centrocytes) ^b	Grading is not used
Immunohistochemistry (required)	BCL6 positivity BCL2 negativity or weak positivity High proliferative fraction (> 30%)	
Genomics (required)	No <i>BCL2</i> , <i>BCL6</i> , <i>IRF4</i> , or aberrant IG rearrangement No <i>BCL2</i> amplification	NO advanced stage disease
Clinical features	Nodal disease (required) Stage I–II disease (required) Patient age < 40 years ^b Marked male predominance	
^a The presence of any component of diffuse large B-cell lymphoma or advanced-stage disease excludes PTFL		NO DLBCL component!
^b These are common features of PTFL, but not required for diagnosis.		

25 year old man with cervical lymphadenopathy







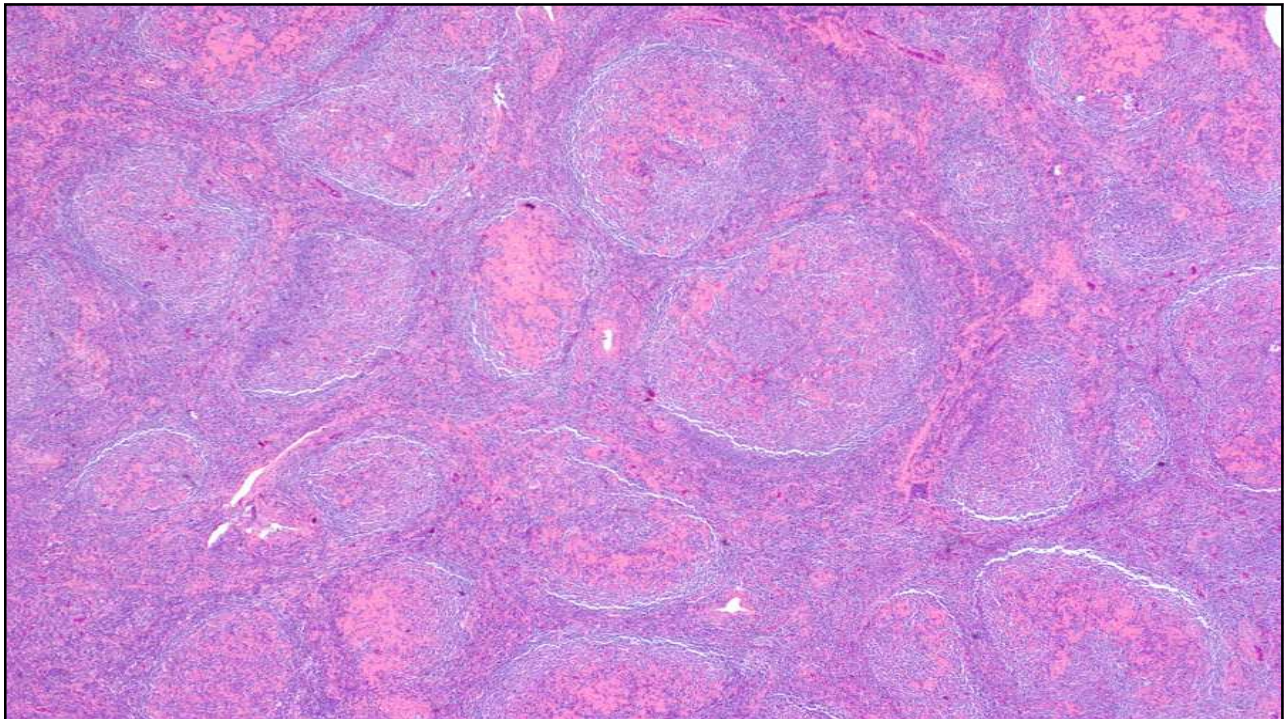
Is this a nice classic case of PTFL?

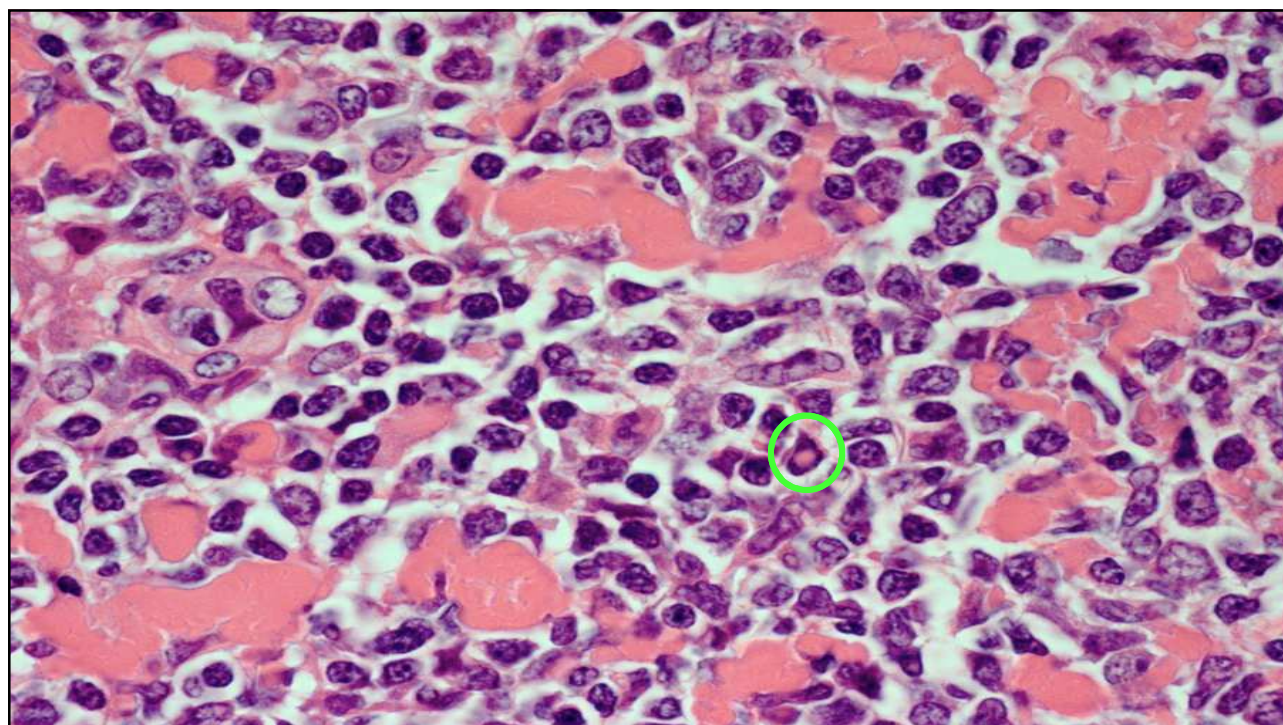
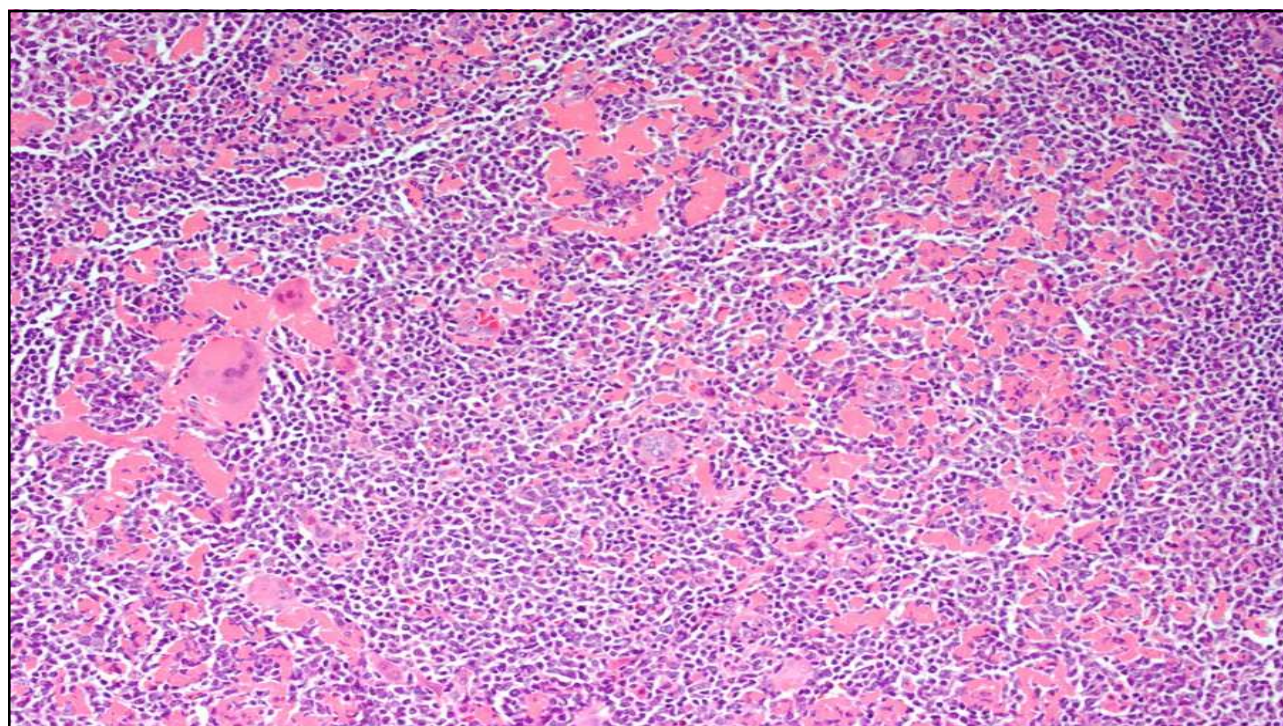
Answer: Do the FISH for *BCL6* and *BCL2* rearrangement

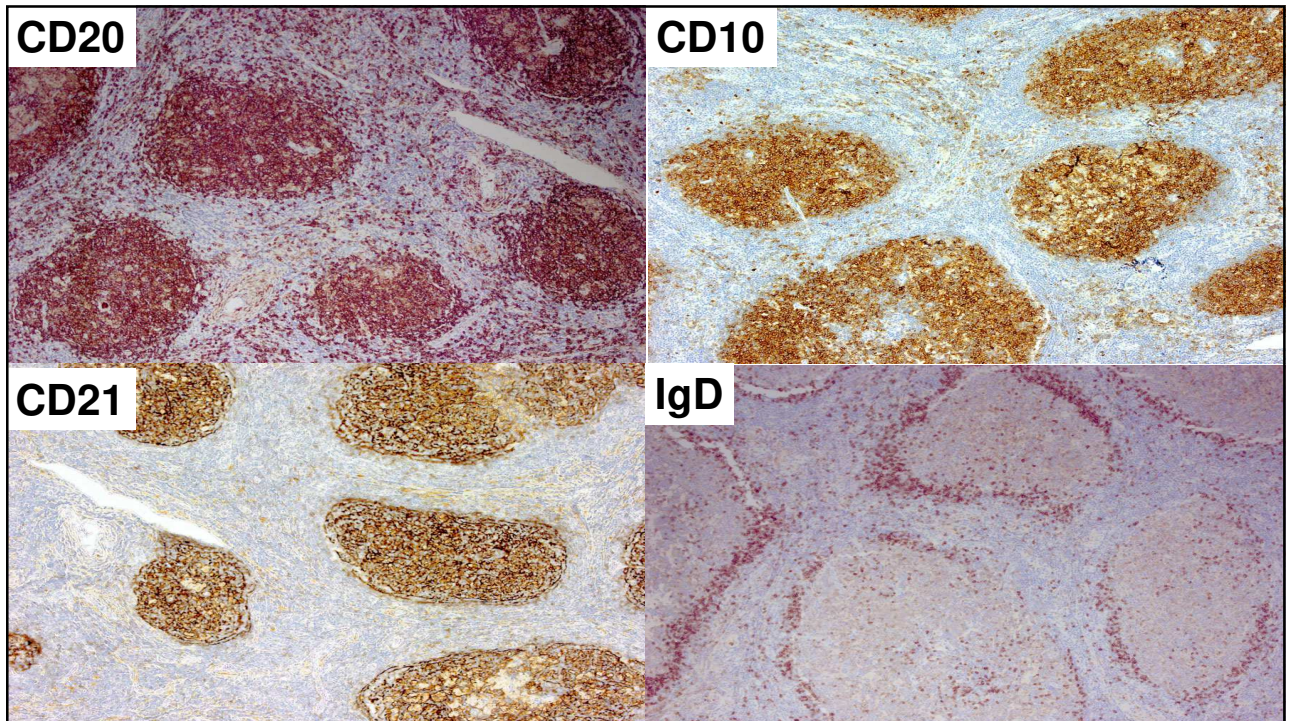
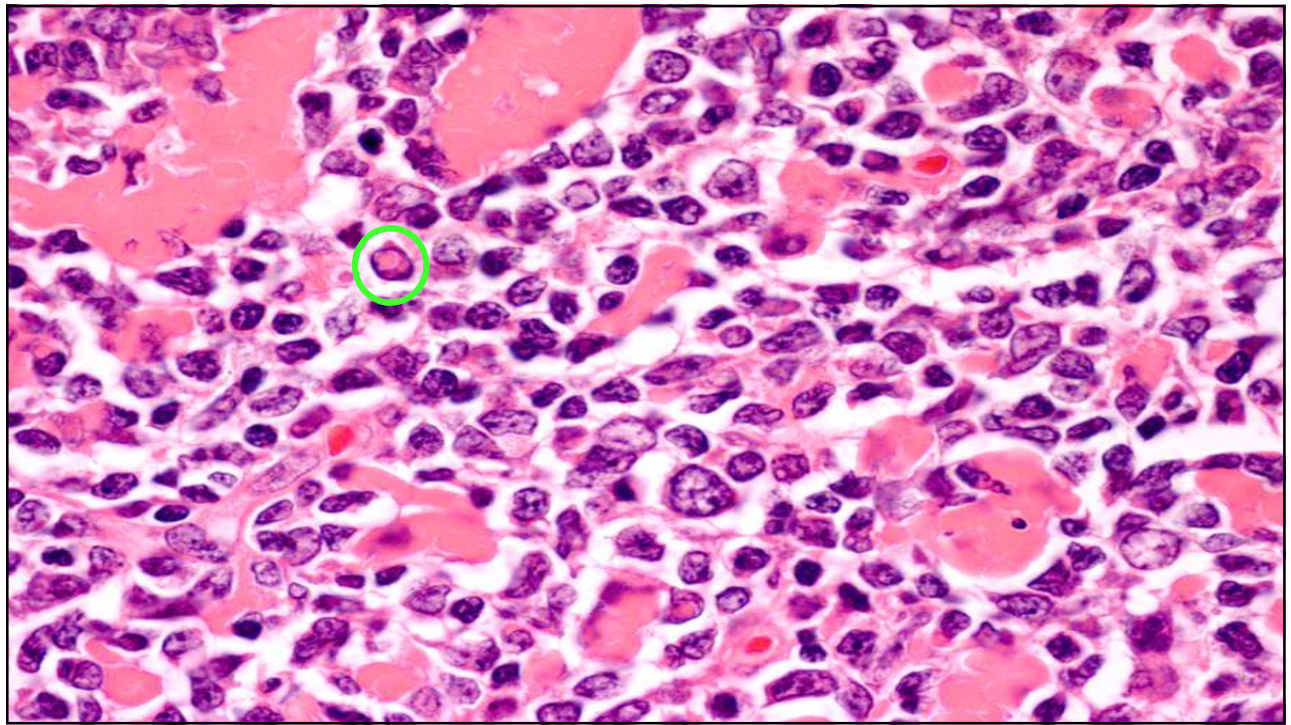
**No *BCL2* gene rearrangement;
BCL6 Rearrangement is present!**

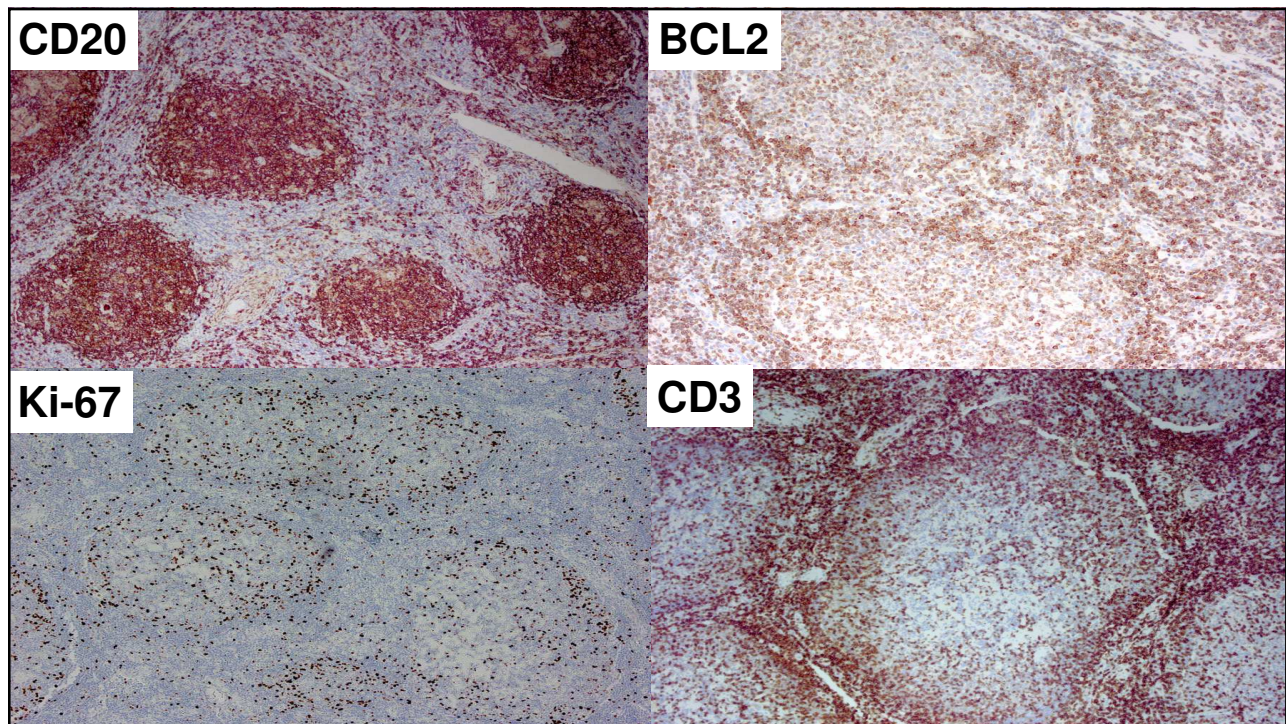
This is a conventional *BCL2* negative Follicular lymphoma

Later: CT shows axillary lymphadenopathy





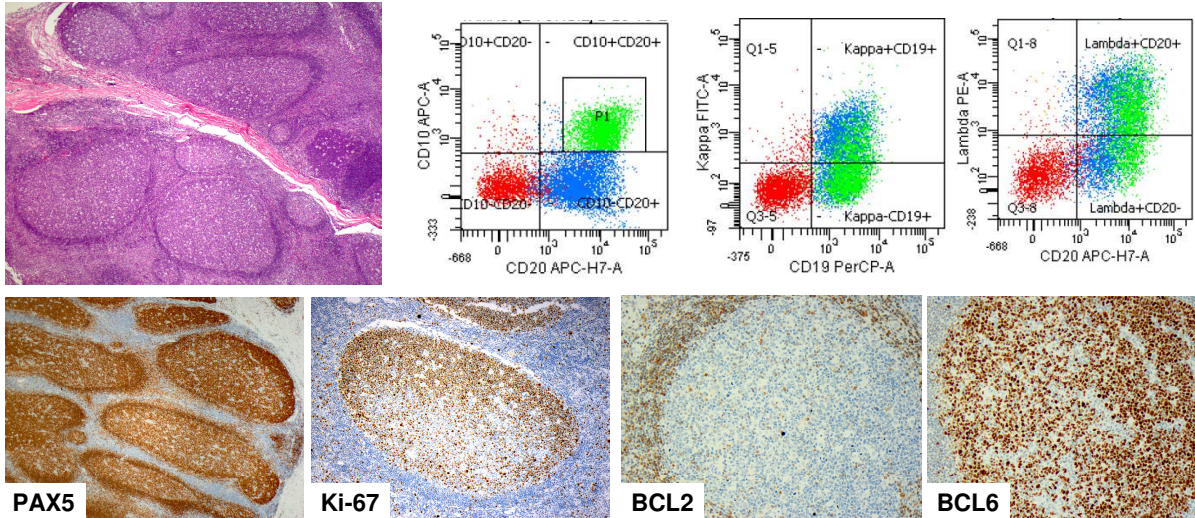




**Morphology and Immunohistochemistry are not
sufficient to diagnose PTFL!**

Consider all clinical features in the WHO “blue box” and
do the appropriate molecular genetic studies
to rule out both *BCL2*, *BCL6* and *IRF4* gene rearrangements

Architectural Effacement Distinguishes PTFL from Follicular Hyperplasia with clonal B cells



Pediatric-Type Follicular Lymphoma

- PTFL is a clinically and biologically distinct, indolent lymphoma of children and adults, most commonly <40 years of age .
- Benign proliferation with rare progression even after surgical excision alone

Criteria:

- Expansile follicles composed of medium-sized blastoid cells (**Grading is not used**)
- BCL2 negative/dim ; High proliferation fraction (>30%);
- No *BCL2*, *BCL6* and *IRF4* rearrangements.
- NO areas of DLBCL
- Not advanced stage

Red flags: Non-peripheral lymphadenopathy; CD10 loss; strong MUM1 expression, Classic grade 1-2 histology

Ages 0 to 18: conventional FL is extremely rare, likely PTFL

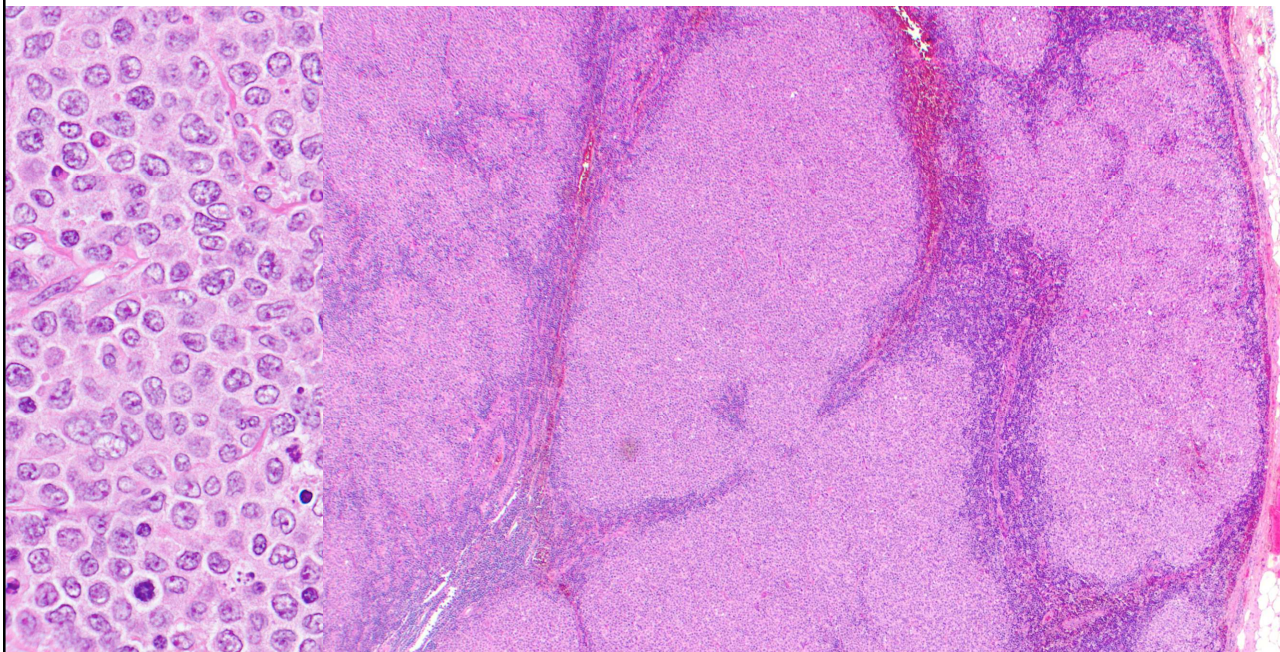
Ages 18-40: Rely on criteria

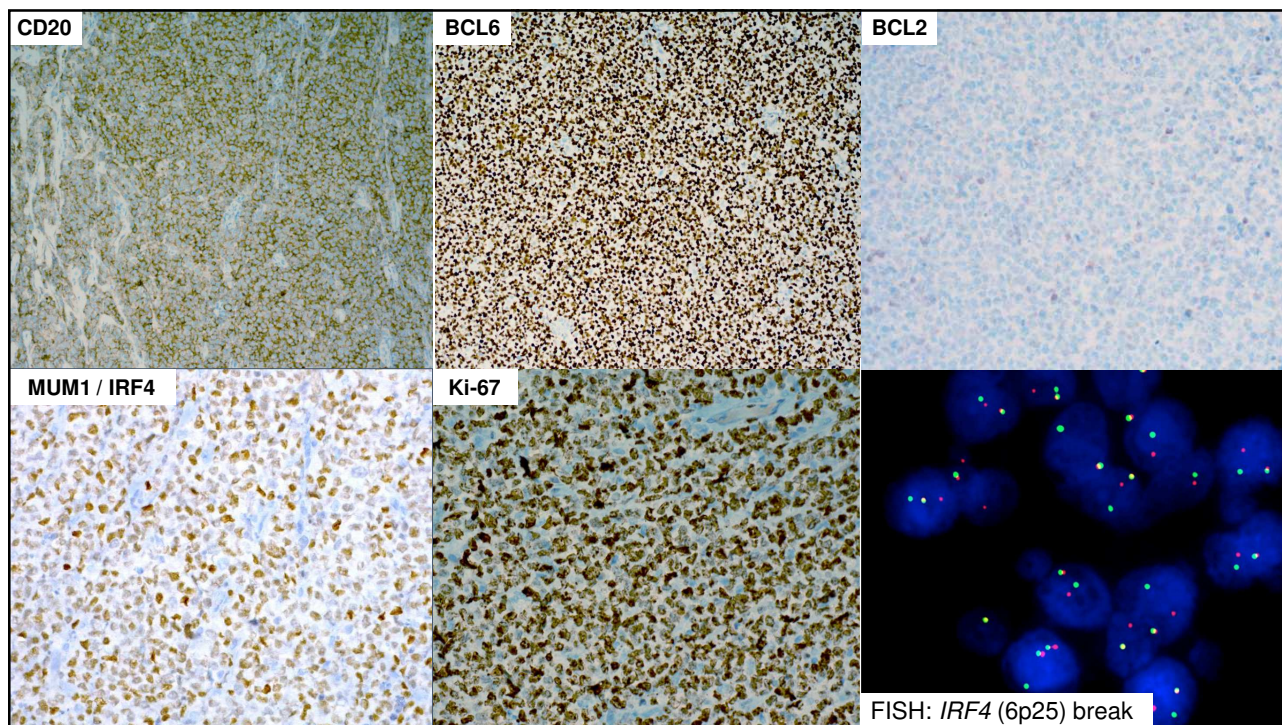
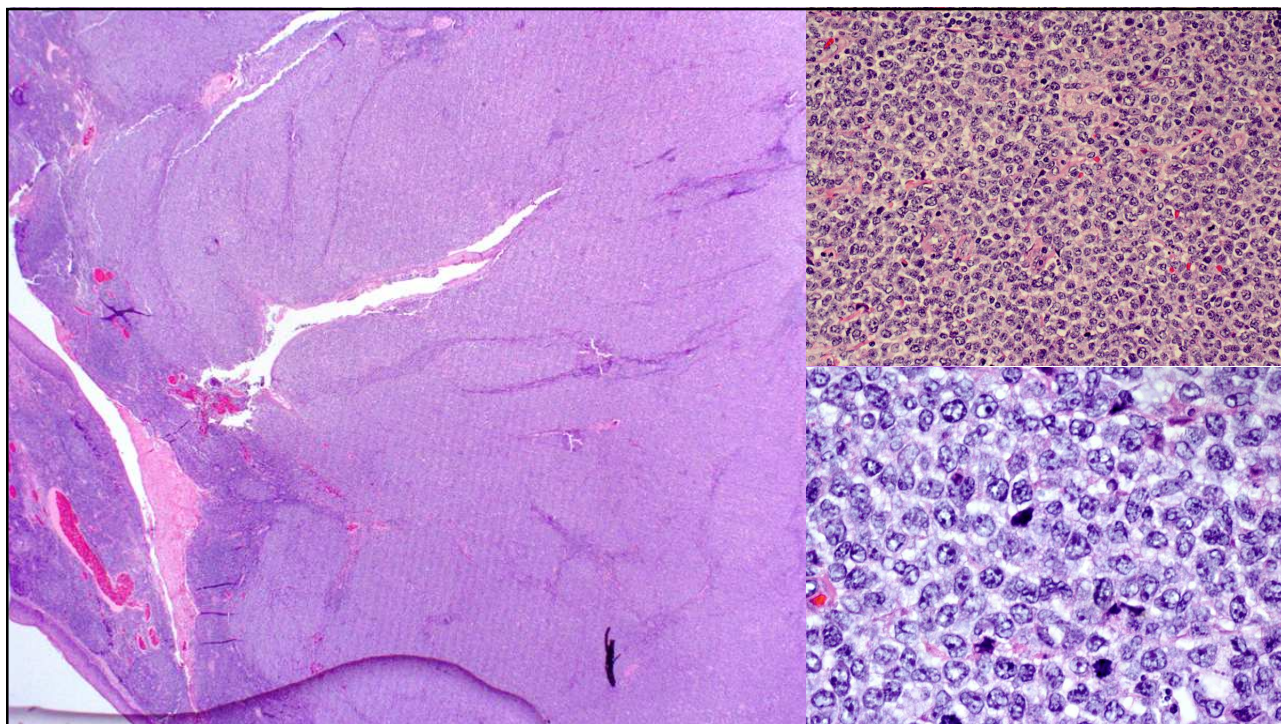
Age >40: Be cautious with diagnosis

Extranodal, BCL2 negative Follicular Lymphoma

- Some extranodal FL lack BCL2 expression and ***BCL2*** rearrangement
- Tend to be localized with good prognosis
 - Conjunctival follicular lymphoma (looks like PTFL)
 - Testicular follicular lymphoma
 - Ovarian Follicular lymphoma
 - Thyroid Follicular lymphoma

Scenario #2: Case 3





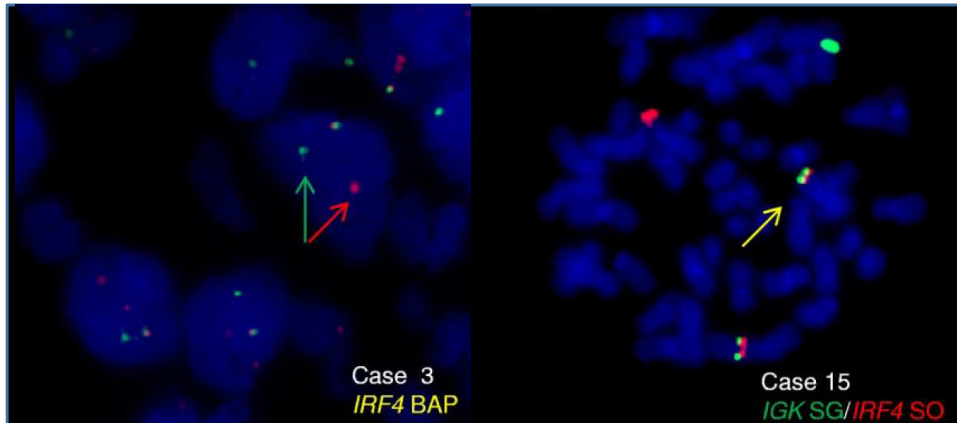


blood

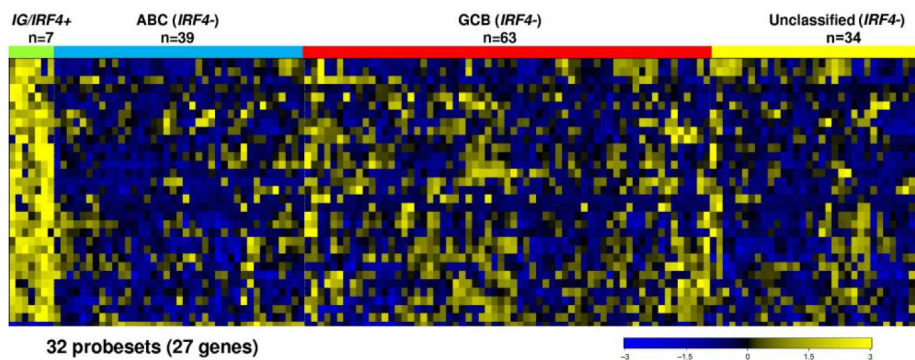
Translocations activating *IRF4* identify a subtype of germinal center-derived B-cell lymphoma affecting predominantly children and young adults

Itziar Salaverria, Claudia Philipp, Ilse Oeschles, Christian W. Kohler, Markus Kreuz, Monika Szczepanowski, Birgit Burkhardt, Heiko Trautmann, Stefan Gesk, Mirosław Andrusiewicz, Hilmar Berger, Miriam Fey, Lana Harder, Dirk Hasenclever, Michael Hummel, Markus Loeffler, Friederike Mahn, Idola Martin-Guerrero, Shoji Pellissery, Christiane Pott, Michael Pfreundschuh, Alfred Reiter, Julia Richter, Maciej Rosolowski, Carsten Schwaenen, Harald Stein, Lorenz Trümper, Sven Wessendorf, Rainer Spang, Ralf Küppers, Wolfram Klapper, Reiner Siebert, for the Molecular Mechanisms in Malignant Lymphomas Network Project of the Deutsche Krebshilfe, the German High-Grade Lymphoma Study Group and the Berlin-Frankfurt-Münster-NHL trial group

Blood, 2011



IG/*IRF4* rearranged Lymphoma is Different from GCB and ABC DLBCL



Salaverria et. al, *Blood*, 2011

	Pediatric-Type FL	IRF4 rearranged Large B-cell Lymphoma
Age Peak	15-17	9-12
M:F	M>>>F	M=F
Stage	<u>Always</u> Limited Stage	Often Limited Stage (not always)
Location	Head & Neck LN	Waldeyer Ring (Frequent) Head & Neck LN

	Pediatric-Type FL	IRF4 rearranged Large B-cell Lymphoma
Architecture	Expansile follicles NO DLBCL	DLBCL (often with FL component)
Cytology	Small to medium-sized 'blastoid' cells (often)	Often Classic centroblasts (but sometimes blastoid)
Genetics	No IRF4, BCL6 or BCL2 rearrangements	IRF4 rearranged BCL6 rearranged (some) <u>No</u> BCL2 rearrangements
Proliferation fraction	High	High
Immunophenotype	MUM1/IRF4 Negative BCL2 Negative	MUM1/IRF4+++ BCL2++ (variable)

What we know about prognosis

	Pediatric-Type FL	IRF4 rearranged Large B-cell Lymphoma
Prognosis	Benign Neoplasm with Excellent Prognosis after resection only	Relatively good prognosis after chemotherapy
	Resection & Observation Sufficient	Chemotherapy Required

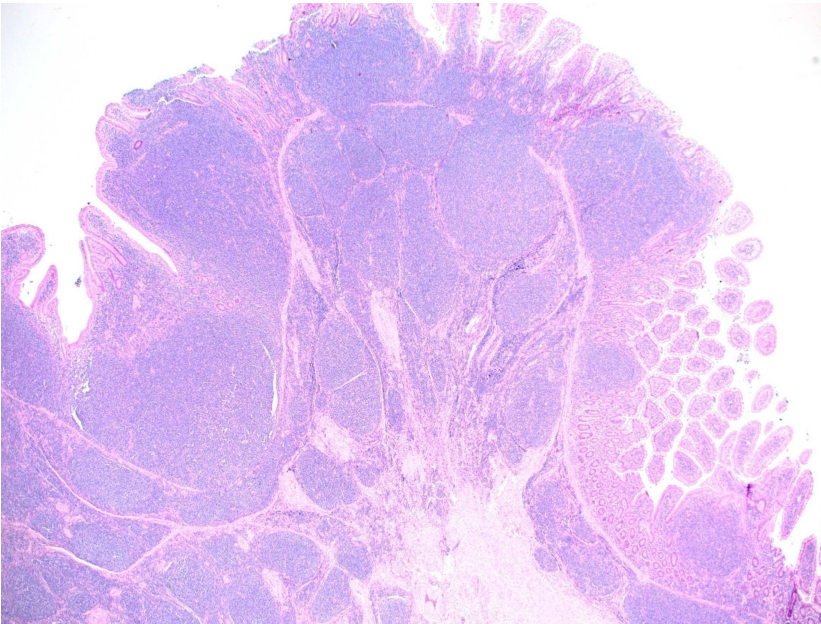
Salverria et. al, Blood 2011;
Louissaint et al, Blood, 2012;
Liu et. al, AJSP 2013

Large B-cell Lymphoma with IRF4 rearrangement

- New provisional entity; occurs commonly in children and young adults, and commonly involves tonsils and Waldeyer ring tissues
- Characterized by *IRF4* rearrangement, and absence of *BCL2* rearrangements; Usually has DLBCL component with some FL component
- It IS NOT equivalent to Pediatric-type follicular lymphoma
- Think of it when you see (1) localized FL3 / DLBCL localized to Waldeyer ring or (2) Localized high-grade FL with strong MUM1 expression in young patient
- MUM1/IRF4 stain can be used as a screen and followed with *IRF4* FISH.

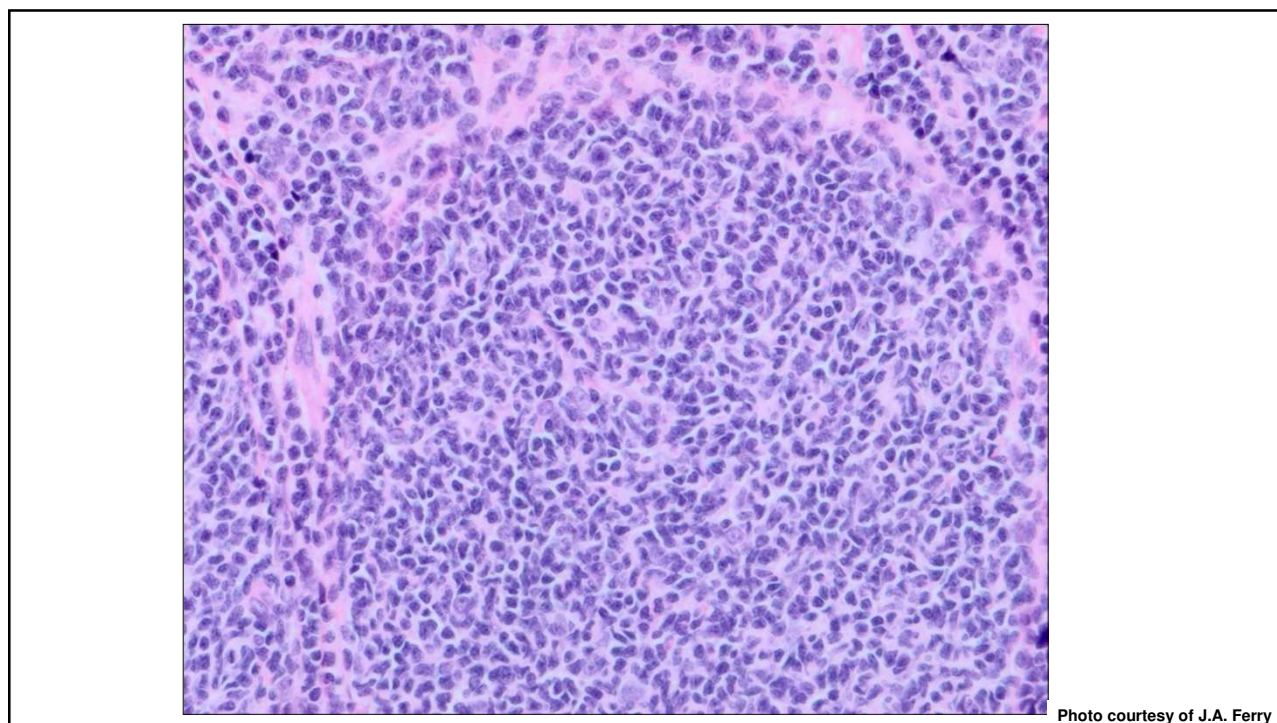
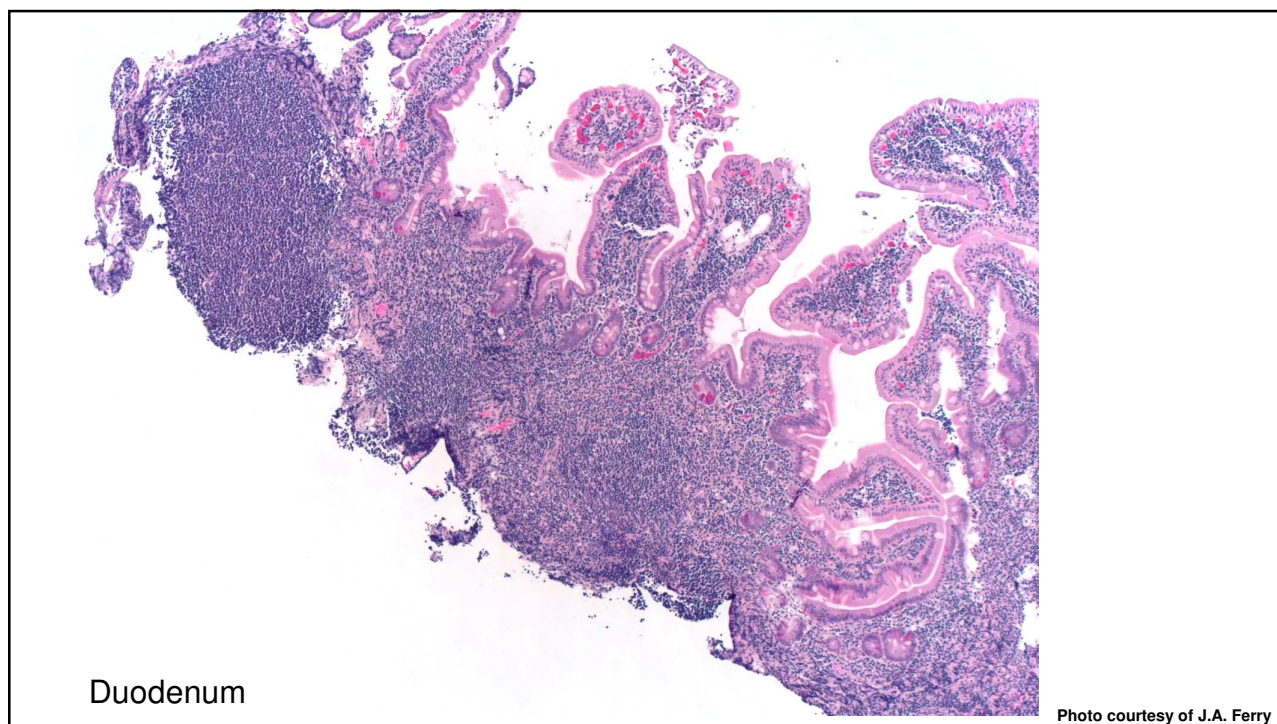
Scenario #3:
***BCL2 Positive Follicular Lymphoma-related entities
with Limited Stage Disease***

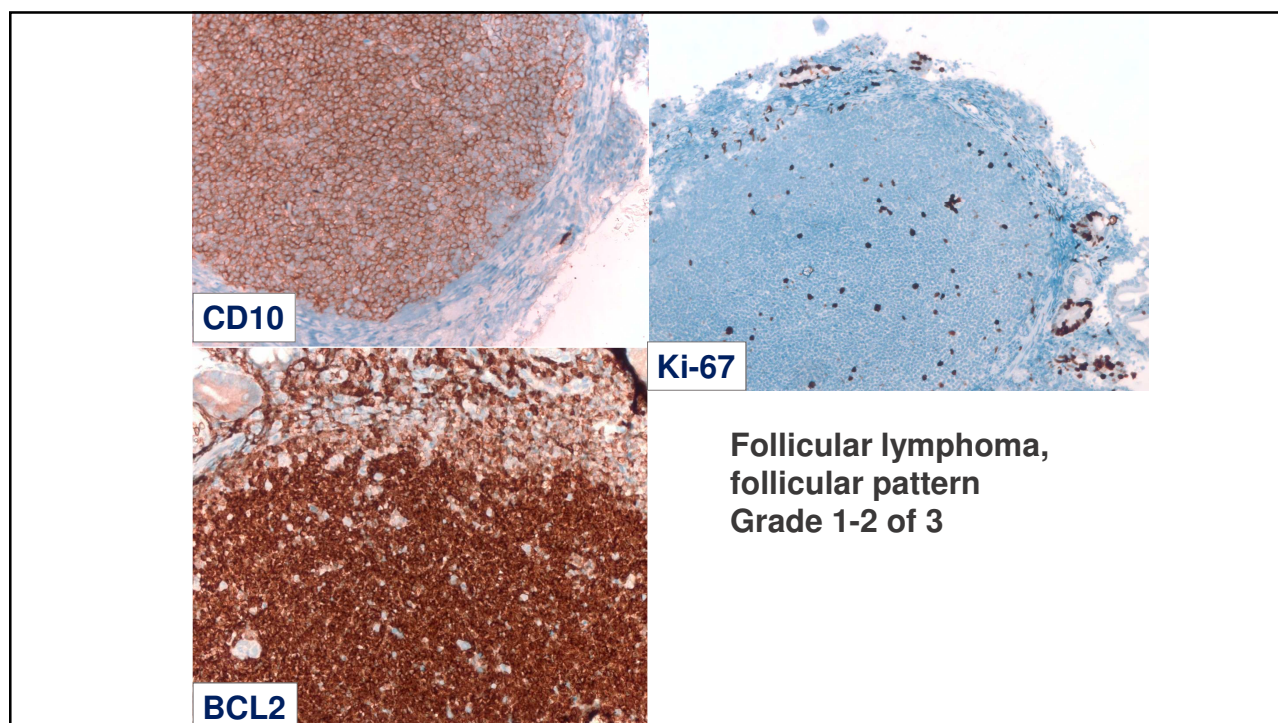
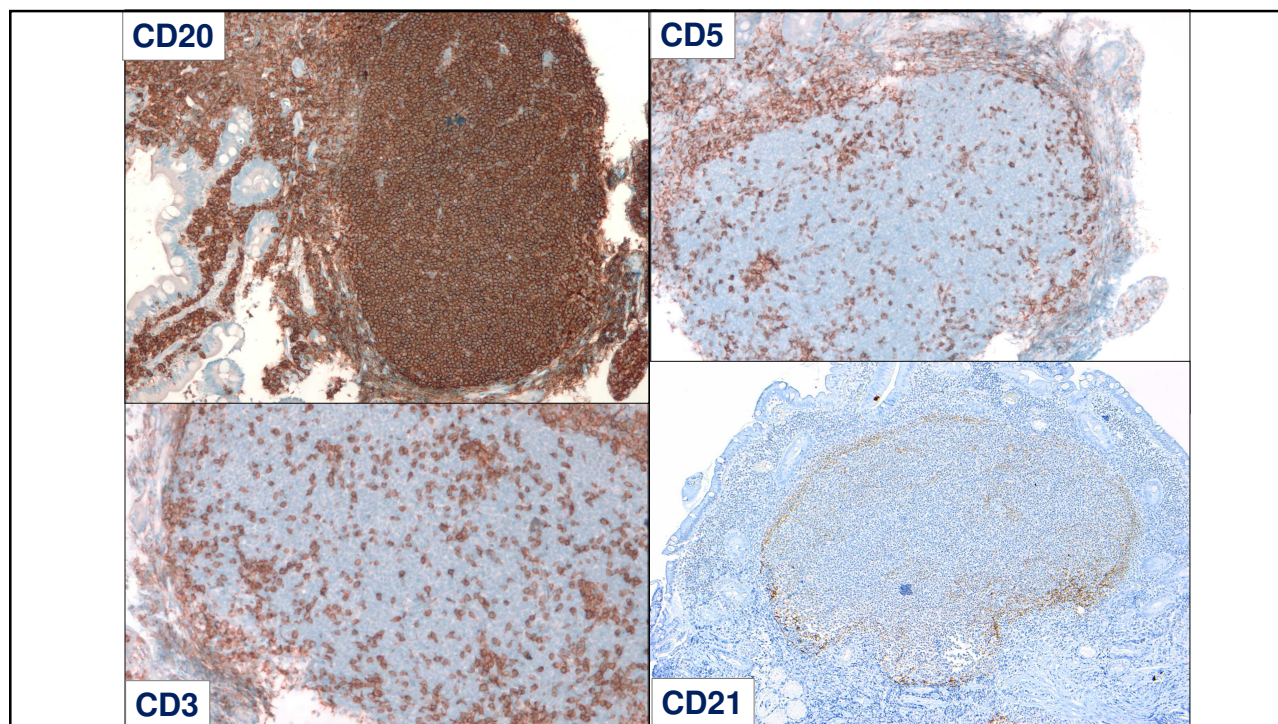
Scenario #3: Case 1



Duodenal biopsy from middle-aged woman

Photo courtesy of J.A. Ferry

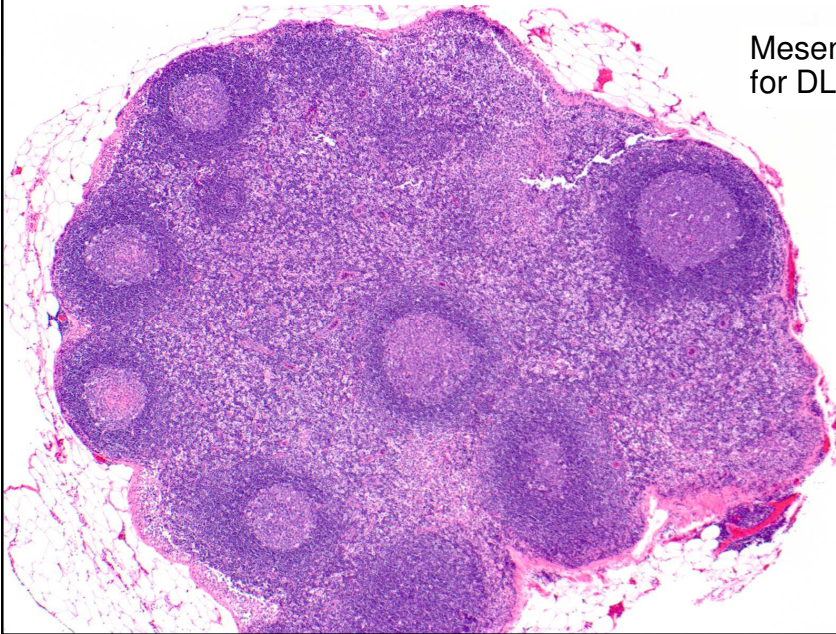




Duodenal-type Follicular lymphoma

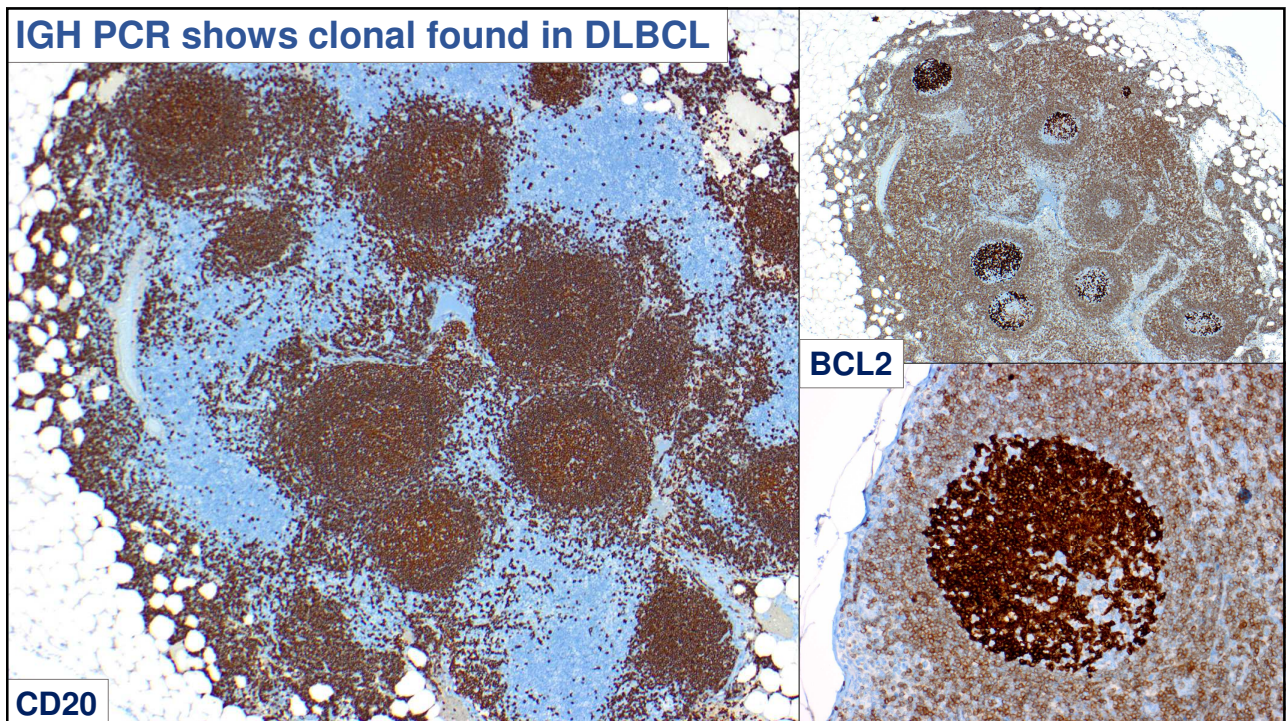
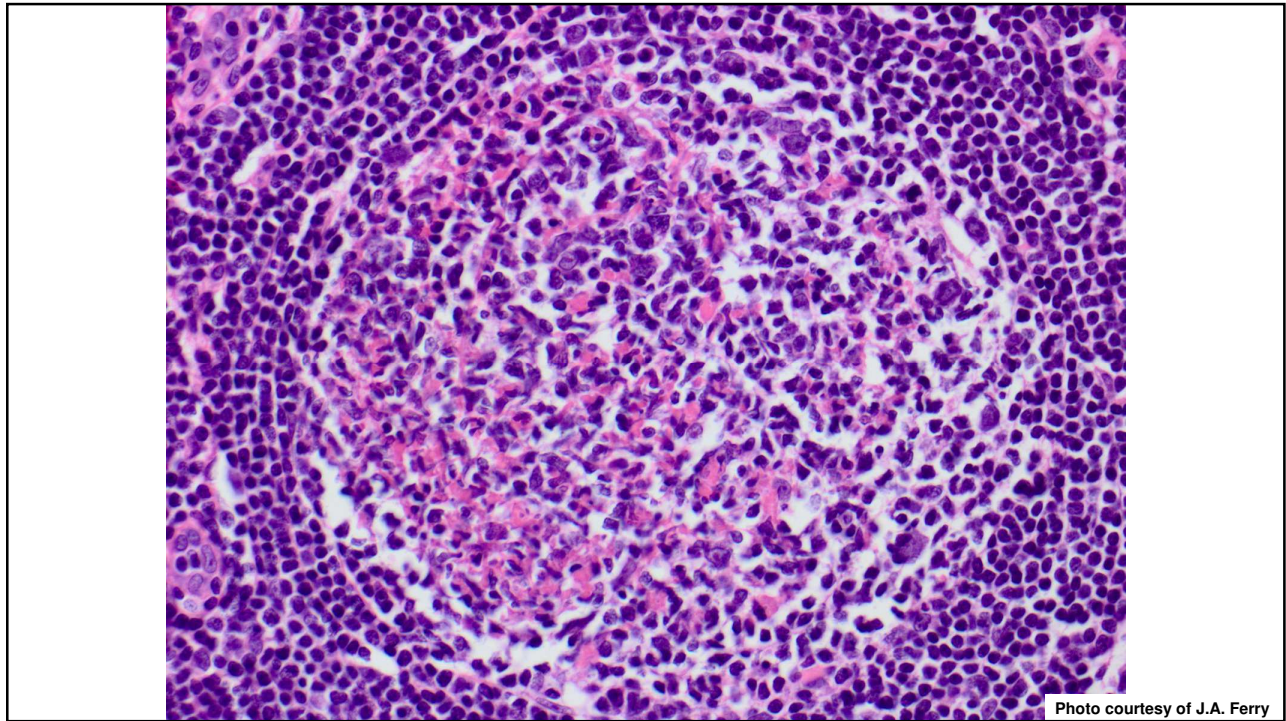
- GI follicular lymphoma represents <4% of all primary GI lymphomas
- Often polyps incidentally identified in middle age (M=F)
- Most often involve 2nd portion of duodenum
- Most patients have localized disease with excellent course even without therapy.
- Low grade
- BCL2 expressed with t(14;18) present
- CD21 shows less staining and periphery of follicles
- Mutational burden lower than classic nodal FL
- Classic FL can involve FL, can involve muscularis propria and show more variation in histologic grade

Scenario #3: Case 2



Mesenteric node from GI resection
for DLBCL

Photo courtesy of J.A. Ferry



In-situ follicular neoplasia (formerly FL in-situ)

- Defined as partial or total colonization of germinal centers by clonal B cells carrying BCL2 translocation (nodal or extranodal sites)
- Distinct from partial involvement by FL, which is treated like FL clinically
- Usually not histologically apparent
- Strong BCL2 expression identified in centrocytes in otherwise reactive germinal centers

In-situ follicular neoplasia occurs in various contexts

- **Patients with no other evidence of lymphoma on staging:**
 - Prognosis is excellent
 - 5% or fewer develop overt lymphoma
- **Patients with follicular lymphoma in other sites:**
 - May represent precursor lesion (occur first)
 - May represent involvement of reactive follicles by overt lymphoma
- **Patients with concurrent lymphoma of other types:**
(e.g. CLL, MCL MZL, DLBCL)
 - May or may not be clonally related

Summary

BCL2 negative follicular lymphoma with present *BCL2* rearrangement :

- Mutational interference with antibody staining

BCL2 negative follicular lymphoma with no *BCL2* rearrangement :

- Follicular lymphoma with predominantly diffuse growth pattern and 1p36 deletion
- Pediatric-Type Follicular lymphoma (*BCL2* and *BCL6* FISH, MUM1 negative; high PI)
- Follicular hyperplasia with clonal B cells (no architectural effacement)
- Large B-cell lymphoma with IRF4 rearrangement (type of diffuse large B-cell lymphoma!)
- Localized extranodal follicular lymphoma (Conjunctival, testicular, thyroid, ovary - Some with absent *BCL2* / *BCL6* rearrangements have excellent prognosis)
- If not one of these, likely BCL2 negative classical FL (often harbor *BCL6* rearrangements)
 - often high-grade, often aggressive

Summary

BCL2 positive follicular lymphoma with *BCL2* rearrangement with limited stage disease

- Duodenal type follicular lymphoma (excellent prognosis)
- In situ follicular neoplasia (often found when you shouldn't have done the *BCL2* stain; occurs in many contexts)

Thank you

