UPDATE ON WHO CLASSIFICATION OF LYMPHOMA

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Lymphoma Classification

- A language for communication between individuals practising the same discipline
- Histopathologically based
- Reproducible
- Clinically relevant
- **Sufficiently flexible to allow updating**

Getting to where we are today

Rappaport

Lukes-Collins

Kiel

NCI - WF

French-American-British

REAL (ILSG)

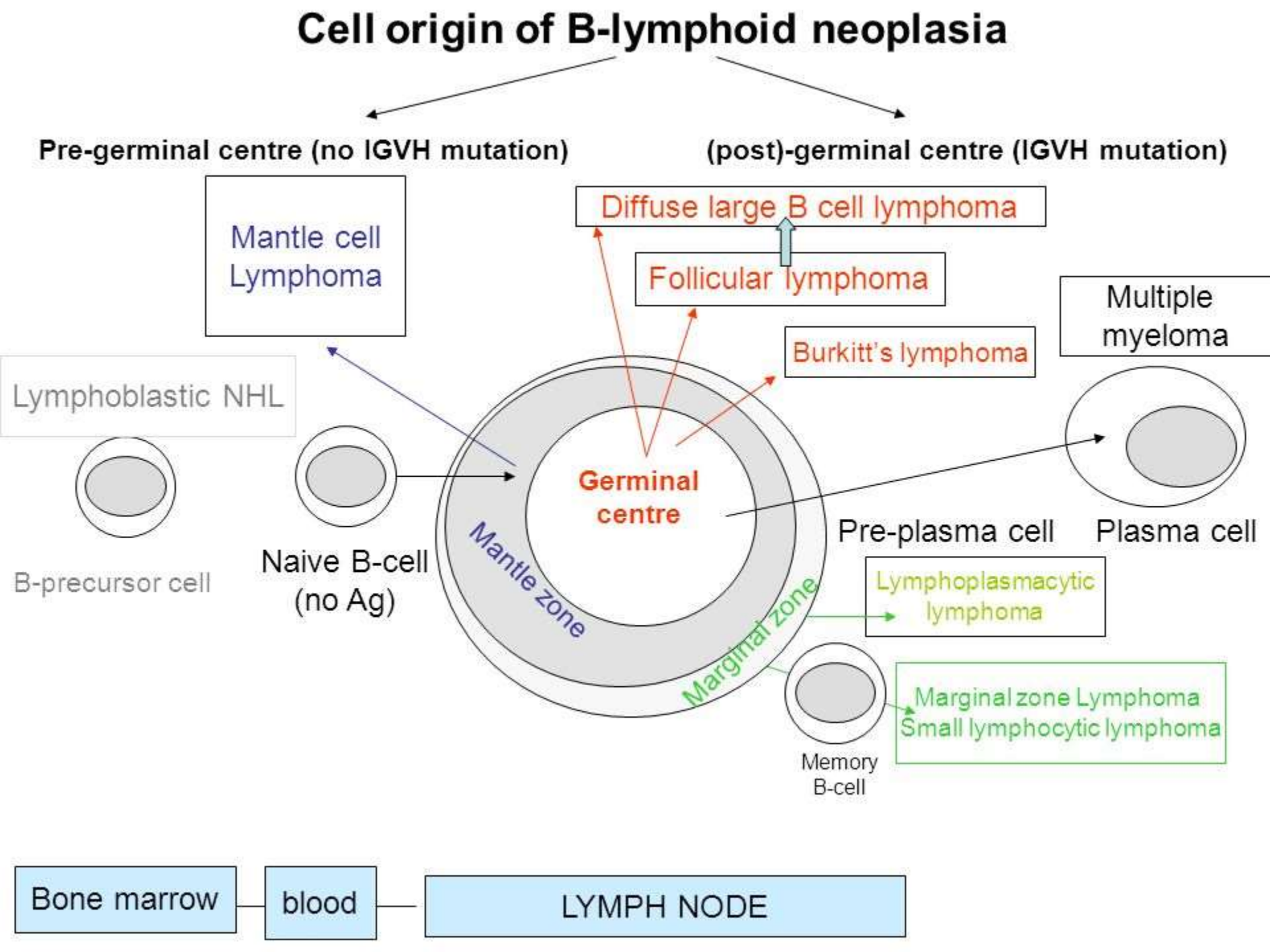
WHO - 2008

WHO -- 2001

World Health Organization

Courtesy of Steve Swerdlow

SHS


Cell origin of B-lymphoid neoplasia
Pre-germinal centre (no IGVH mutation)
(post)-germinal centre (IGVH mutation)
Mantle cell Lymphoma
Diffuse large B cell lymphoma
Follicular lymphoma
Multiple myeloma
Burkitt's lymphoma
Lymphoblastic NHL
Germinal centre
Mantle zone
Marginal zone
Pre-plasma cell
Plasma cell
B-precursor cell
Naive B-cell (no Ag)
Lymphoplasmacytic lymphoma
Marginal zone Lymphoma
Small lymphocytic lymphoma
Memory B-cell
Bone marrow
blood
LYMPH NODE

Principles of the REAL/WHO Classification

- Morphology
  - May be sufficient for diagnosis in many cases
- Immunophenotype and Genetics
  - Often helpful in differential diagnosis
  - Have played a major role in defining disease entities
- Clinical features
  - Play an important part in disease definition
  - Nodal and extranodal neoplasms are not equivalent
- Postulated normal cell counterpart
  - Helpful but not always possible
  - Cannot be the sole basis for classification
- The relative importance of each feature varies among diseases - no “gold standard.”

Principles of the WHO Classification

- 2008 classification emphasises in addition the importance of:
- Anatomic site
  - MALT lymphoma vs lymphoplasmacytic lymphoma
  - Diffuse large B-cell Lymphoma
    - Primary mediastinal lymphoma
    - Primary CNS lymphoma
  - Follicular lymphoma
    - Nodal, skin, GI, thyroid
- Age
  - Paediatric follicular lymphoma
  - Paediatric marginal zone lymphoma
  - EBV+ lymphoma of the elderly

Principles of the WHO Classification

- **Lymphomas may be genetically heterogeneous**
  - **Follicular lymphoma**
    - **t(14;18)-, t(3;14)+, translocation silent**
  - **MALT lymphoma**
    - **t(1;14)/*BCL10-IGH,* t(11;18)/*API2-MALT1,* t(14;18)/*IGH-MALT1***
    - **t(3;14)/*FOXP1-IGH,* t(3;14)/*BCL6-IGH,* t(5;14)(q34;q32)**
    - **t(9;14)(p11~12;q32), t(1;14)(q32;q32), t(6;7)(q25;q11), t(2;14)(p21;q32**
- **Lymphomas may show capacity for lineage plasticity**

Review Series

THE UPDATED WHO CLASSIFICATION OF HEMATOLOGICAL MALIGNANCIES

The 2016 revision of the World Health Organization classification of lymphoid neoplasms

Steven H. Swerdlow,[1] Elias Campo,[2] Stefano A. Pileri,[3] Nancy Lee Harris,[4] Harald Stein,[5] Reiner Siebert,[6] Ranjana Advani,[7] Michele Ghielmini,[8] Gilles A. Salles,[9] Andrew D. Zelenetz,[10] and Elaine S. Jaffe[11]

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A revision of the nearly 8-year-old World Health Organization classification of the lymphoid neoplasms and the accompanying monograph is being published. It reflects a consensus among hematopathologists, geneticists, and clinicians regarding both updates to current entities as well as the addition of a limited number of new provisional entities. The revision clarifies the diagnosis and management of lesions at the very early stages of lymphomagenesis, refines the diagnostic criteria for some entities, details the expanding genetic/molecular landscape of numerous lymphoid neoplasms and their clinical correlates, and refers to investigations leading to more targeted therapeutic strategies. The major changes are reviewed with an emphasis on the most important advances in our understanding that impact our diagnostic approach, clinical expectations, and therapeutic strategies for the lymphoid neoplasms. (*Blood*. 2016;127(20):2375-2390)

The 2016 revision of the World Health Organization classification of lymphoid neoplasms

(*Blood*. 2016;127(20):2375-2390)

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Table 1. 2016 WHO classification of mature lymphoid, histiocytic and dendritic neoplasms[1]

Table 2. Highlights of changes in 2016 WHO classification of lymphoid, histiocytic and dendritic neoplasms

(not all shown on this slide)

WHO Classification
2016 Revision

ADDITIONAL GENETIC DATA

Hairy cell leukaemia

- BRAF V600E
- MAP2K1 in most cases that use IGHV4-34 (lack BRAF mut)

Lymphoplasmcaytic lymphoma

- MYD88 L265P

Burkitt lymphoma

- TCF3 or ID3 mutation in ≈70%

T-cell large granulacytic leukaemia

- STAT3 and STAT5B in subset (more aggressive behaviour)

Anaplastic lymphoma, ALK- (definite entity)

- Derrangement of region including DUSP22 and IRF4 on 6p25 associated with monomorphic appearance , lack of cytotoxic granules and superior prognosis

Principles of the WHO Classification
2016 Revision

- **Nomenclature influenced by clinical behaviour**

  Lymphoma

  Lymphoproliferative disorder

  Neoplasia

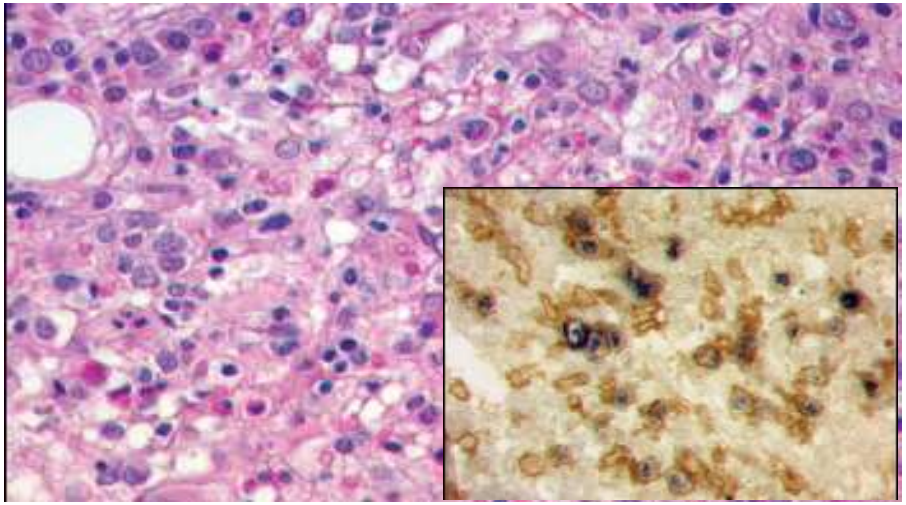
WHO Classification
2016 Revision

Name Changes

- **EBV+ diffuse large B cell lymphoma NOS**
  - Replaces EBV+ diffuse large B cell lymphoma of elderly
  - Recognition that can be seen in younger individuals
  - Does not include EBV+ lymphomas that can be given more specific classification

WHO Classification
2016 Revision

Promotions

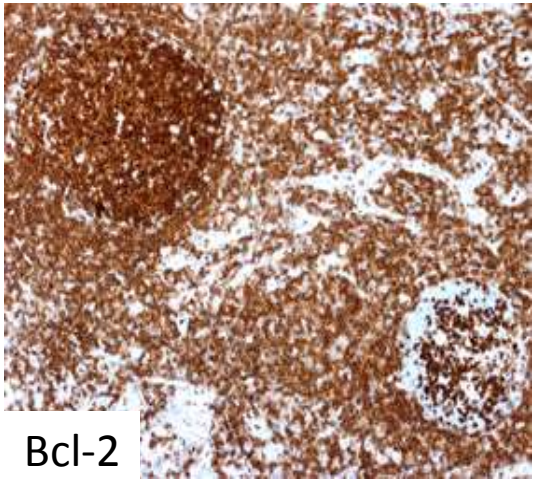


Systemic EBV+ T cell LYMPHOMA of childhood

- Promoted from lymphoproliferative disorder
- Fulminant behaviour
- Distinguish from chronic active EBV infection

WHO Classification
2016 Revision

Relegations


Bcl-2

- **In-situ Follicular NEOPLASIA**
  - From in-situ lymphoma
  - Recognition of low risk of progression to overt lymphoma

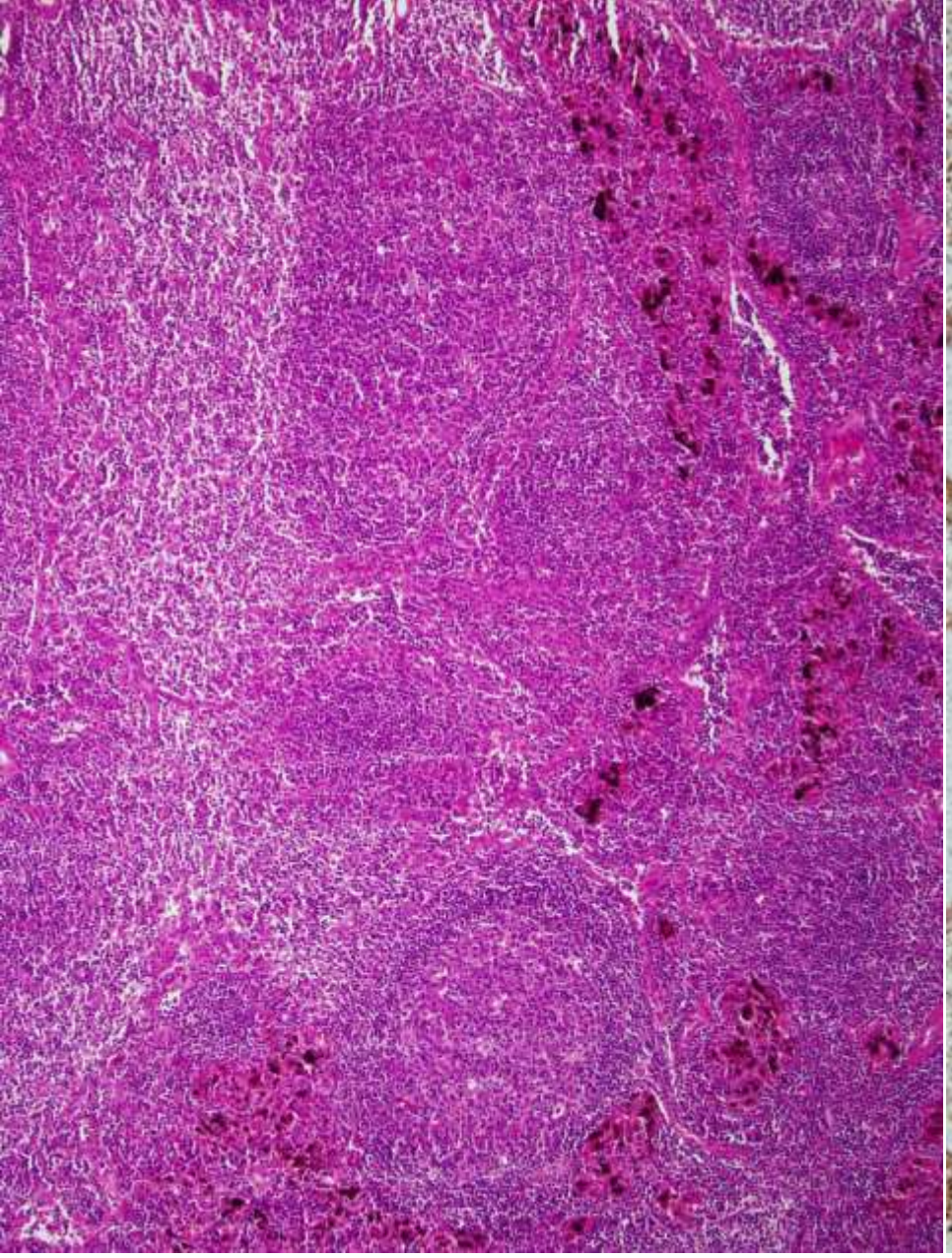
In-situ Follicular Neoplasia

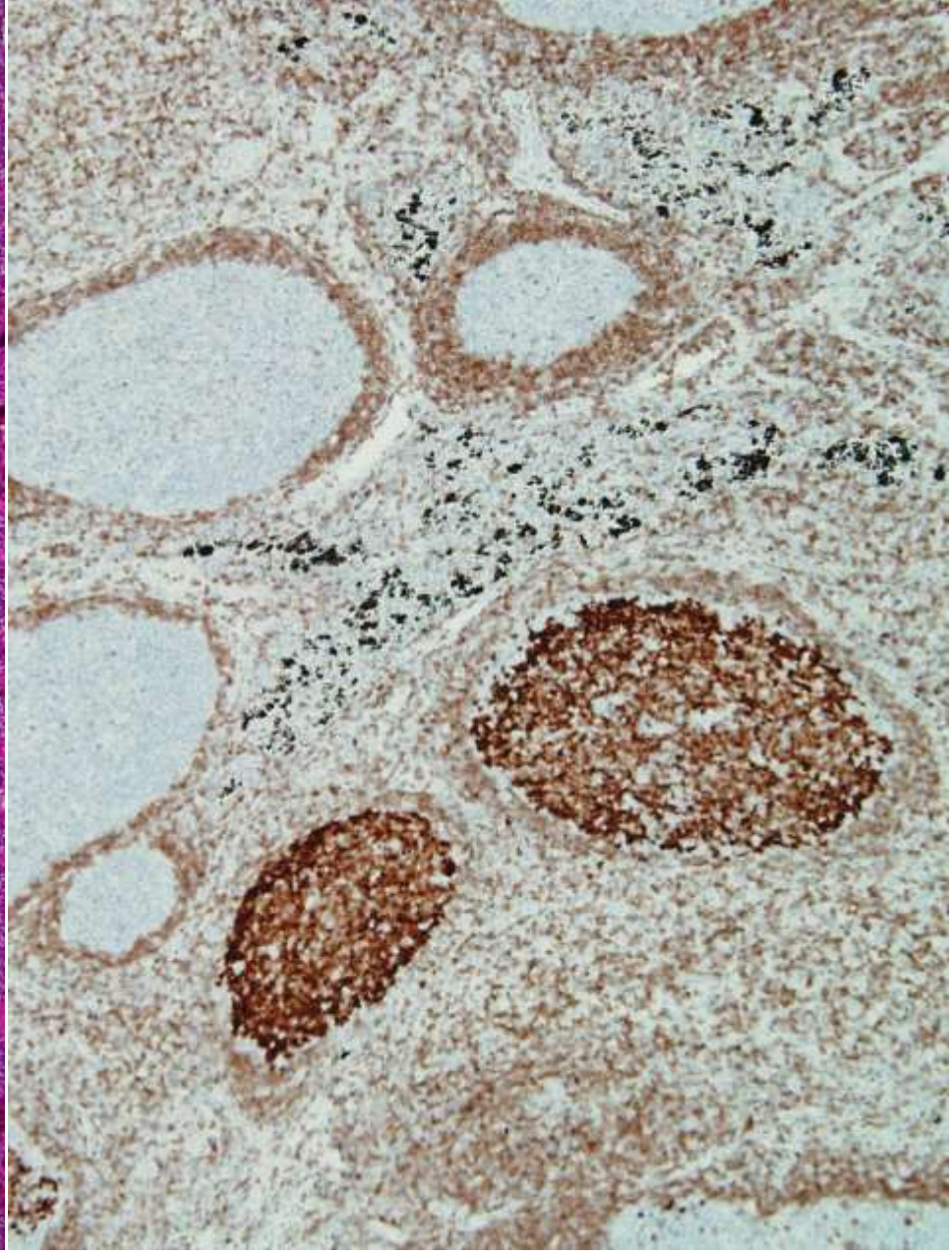
- Must be distinguished from partial involvement by overt follicular lymphoma
- No follicular lymphoma in other nodes
- No previous history of follicular lymphoma

In-Situ Follicular Neoplasia

- Present in 2% of unselected LNs

- Follicular lymphoma-like B cells
  - Uncommon <18yrs
  - 70% adults >50yrs
  - Risk of progression to FL about 5%
  - Risk of progression higher if high levels of cells





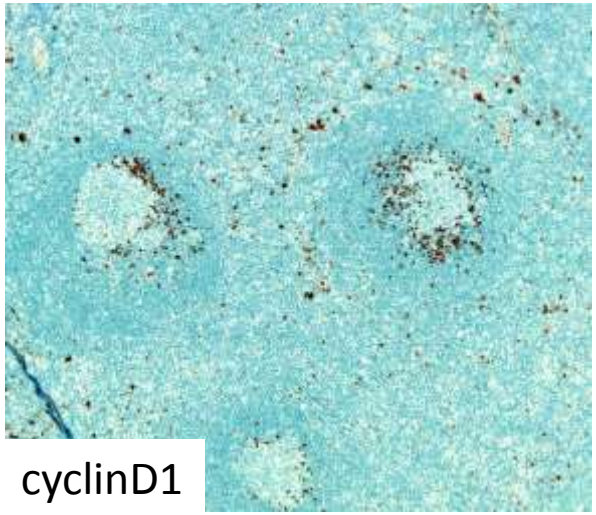
Cannot be diagnosed without staining for bcl-2 protein

Is Follicular Lymphoma Preceded by ISFN?

- Pillai et al, Haematologica 2013
  - 4/4 pts with FL and previous “reactive” lymph nodes had ISFN
- Mendes et al Histopathology 2015
  - 1380 cases of FL
  - 12 previous resections with lymph nodes or extranodal lymphoid tissue
    - F:M 8:4
    - Median age at diagnosis of FL 67yrs (range 46-95)
  - 10/12 showed ISFN
    - Mean interval to FL 97.5m (range 6-264m)

WHO Classification
2016 Revision

Relegations

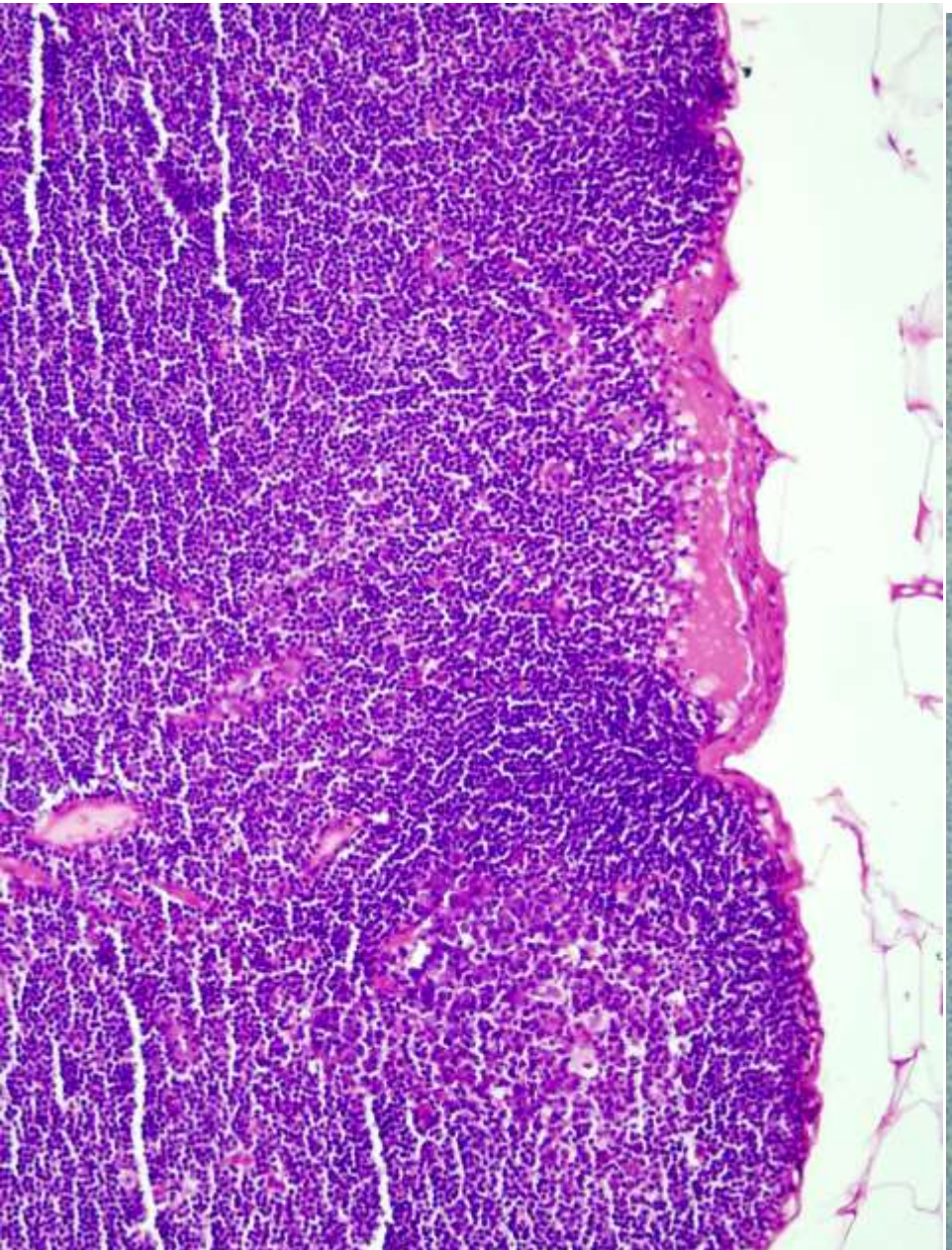

cyclinD1

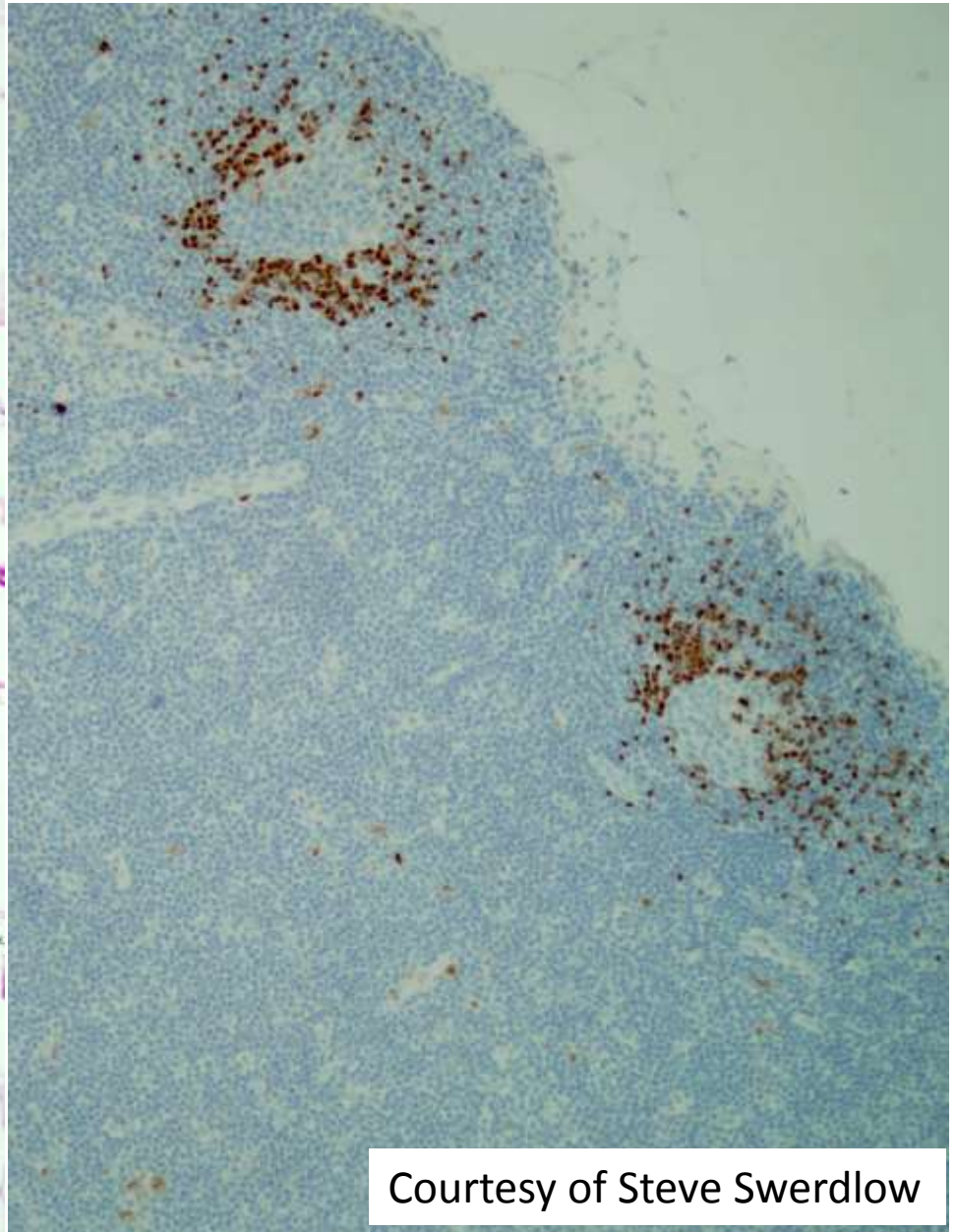
- **In-situ Follicular NEOPLASIA**
- **In-situ mantle cell NEOPLASIA**
  - From in-situ lymphoma
  - Recognition of low risk of progression to overt lymphoma

In-situ Mantle Cell Neoplasia

- Low rate of progression
- Rarer than ISFN
- Often found incidentally, sometimes in association with other NHL
- Distinguish from mantle cell lymphoma with pure mantle zone pattern

In-situ Mantle Cell Lymphoma





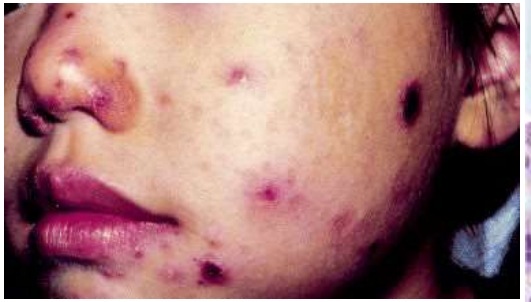
Courtesy of Steve Swerdlow

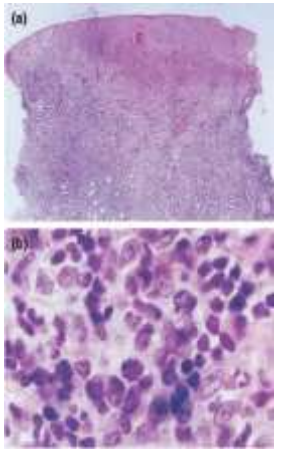
Is Mantle cell Lymphoma Preceded by ISMCN?

- Mendes et al Histopathology 2015
  - 126 cases of MCL
  - 2 previous resections with lymph nodes
    - F:M 1:1
    - Age at diagnosis of MCL 71 & 79yrs
  - 2/2 showed ISMCLN
    - Intervals 120m and 240m

WHO Classification
2016 Revision

Relegations





- **In-situ Follicular NEOPLASIA**
- **In-situ mantle cell NEOPLASIA**
- **Hydroa vacciniforme-like LYMPHOPROLIFERATIVE DISORDER**
  - From lymphoma
  - Relationship with chronic active EBV infection with a variable clinical course

WHO Classification
2016 Revision

Relegations

- **In-situ Follicular NEOPLASIA**
- **In-situ mantle cell NEOPLASIA**
- **Hydroa vacciniforme-like LYMPHOPROLIFERATIVE DISORDER**
- **Primary cutaneous CD4+ small/mediumT-cell LYMPHOPROLIFERATIVE DISORDER**
  - Limited clinical risk
  - Localised disease
  - Similar to clonal drug reaction

2016 Revision of WHO Classification of Lymphoma

- Hodgkin lymphoma
- Indolent B cell lymphoma
- Aggressive B cell lymphoma
- T cell lymphoma

2016 Revision of WHO Classification of Lymphoma

- Hodgkin lymphoma
- Indolent B cell lymphoma
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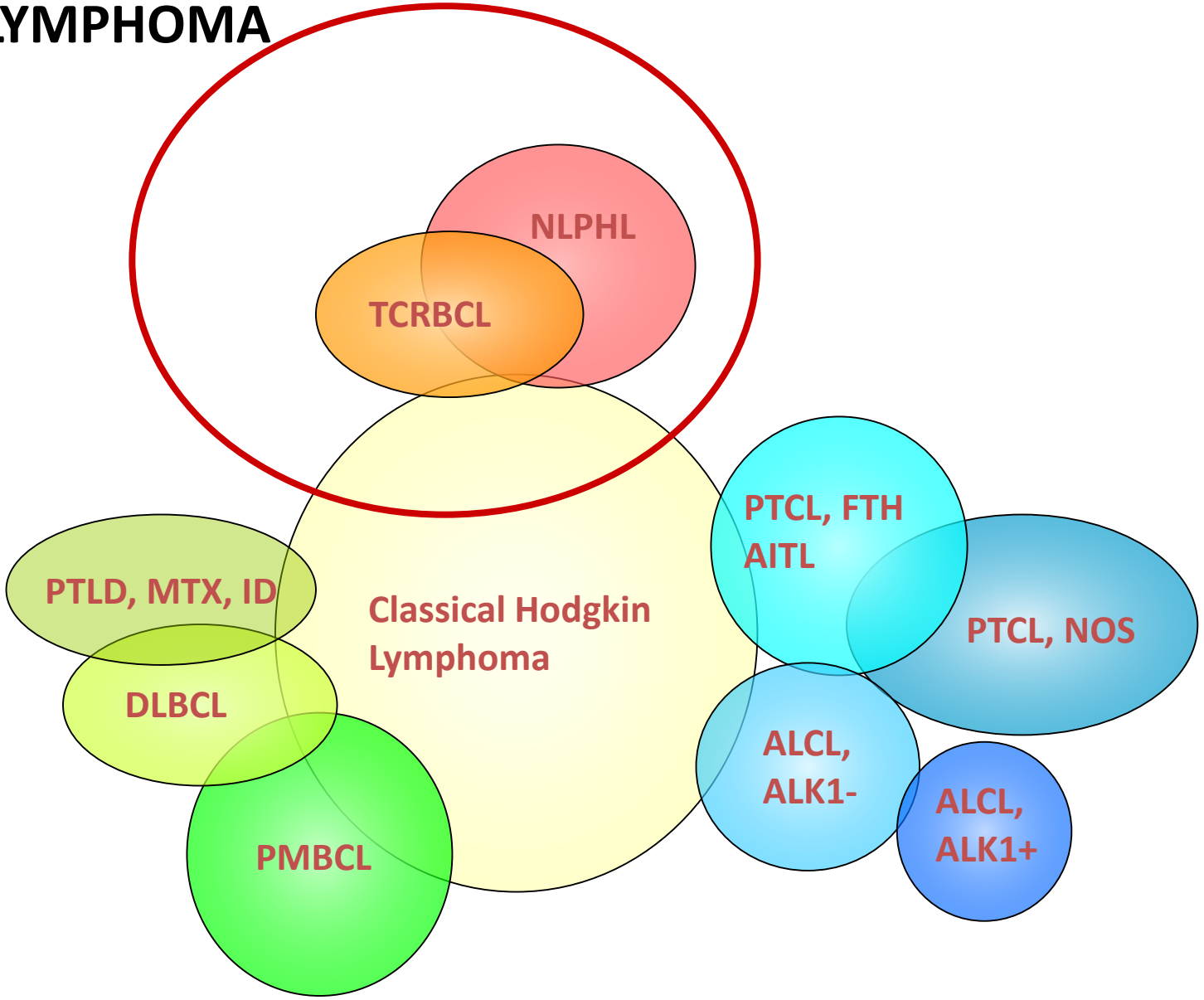
HODGKIN LYMPHOMA



de Jong 2016

2016 Revision of WHO Classification of Lymphoma

- Hodgkin lymphoma
- Indolent B cell lymphoma
- Aggressive B cell lymphoma
- T cell lymphoma

Monoclonal B lymphocytosis

- Monoclonal B-cell populations in peripheral blood up to 5 x10^9/L present for >3 months
  - CLL phenotype (75%)
  - Atypical CLL phenotype
  - Non-CLL phenotype (CD5-ve)
- Seen in up to 3.5-12% healthy individuals
  - Age <40yrs negligible
  - 90yrs 50-75%
- Virtually all cases of CLL are preceded by MBL

Monoclonal B Lymphocytosis

	CD19	CD5	CD23	CD20
CLL	+	+	+	dim
Atypical CLL*	+	+	+/-	bright
Non-CLL	+	-/dim	-	+

*For atypical CLL cases need to exclude mantle cell lymphoma

Monoclonal B lymphocytosis Non-CLL

- CD5 dim in 20%
- Some have 7q abnormalities
  - 17% may progress to splenomegaly
  - Possibly related to splenic marginal zone lymphoma

Monoclonal B lymphocytosis

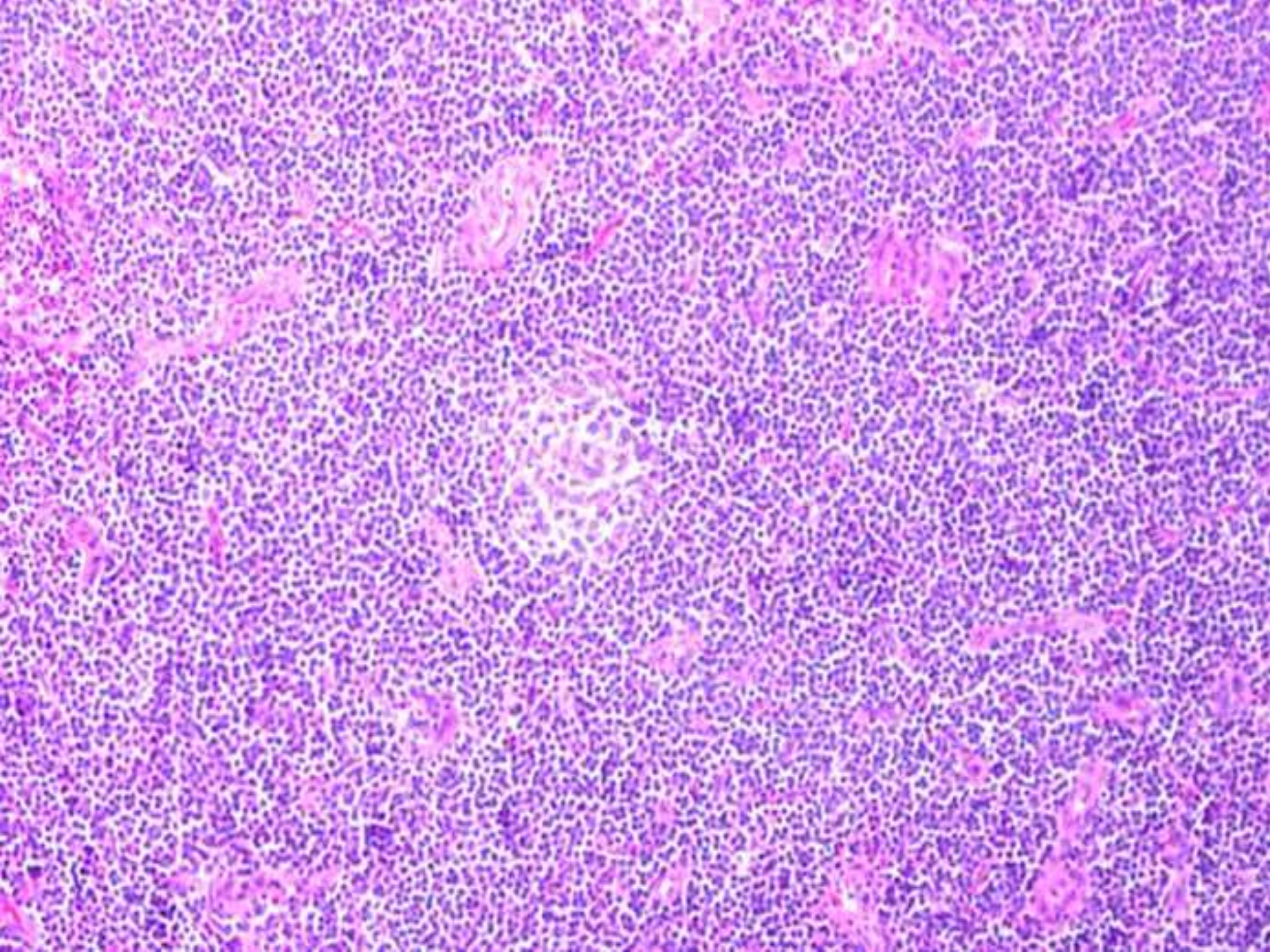
- Low count MBL
  - PB CLL <0.5 $x10^9/l$
  - Limited (if any) risk of progression to CLL
  - Does not require routine follow up
- High count MBL
  - Very similar phenotype/molecular features as Rai stage 0 CLL
  - IGVH mutated cases more frequent in CLL
  - Requires routine follow up (yearly)

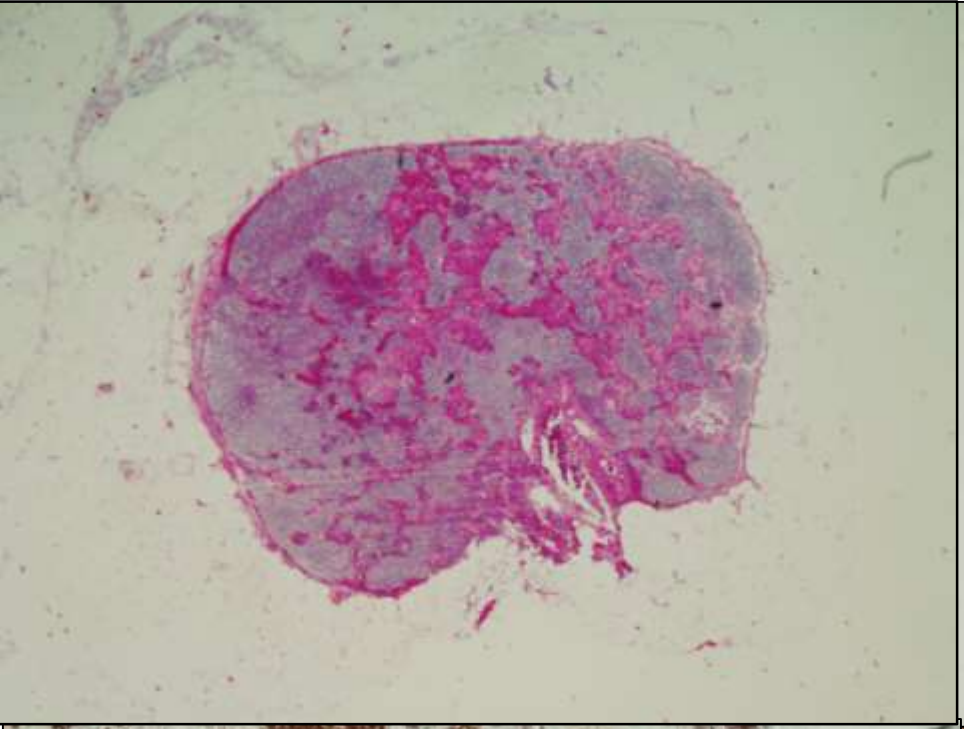
Monoclonal B lymphocytosis

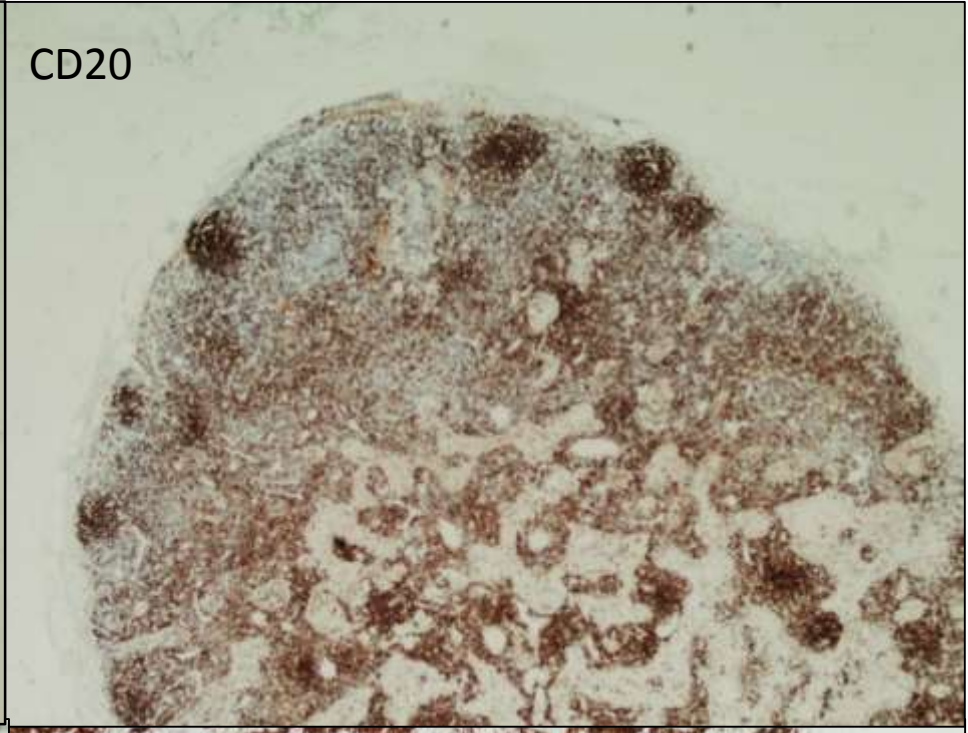
- CLL not diagnosed if monoclonal B-cell populations in peripheral blood with $<5 \times 10^9/l$ even with cytopaenias or disease related symptoms

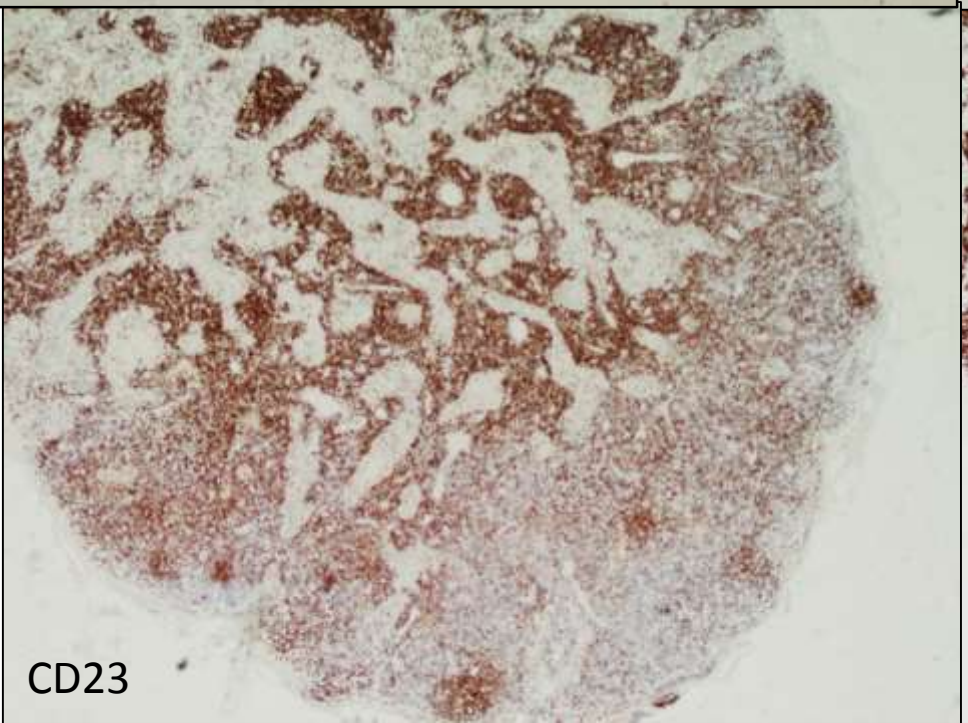
Tissue-based MBL

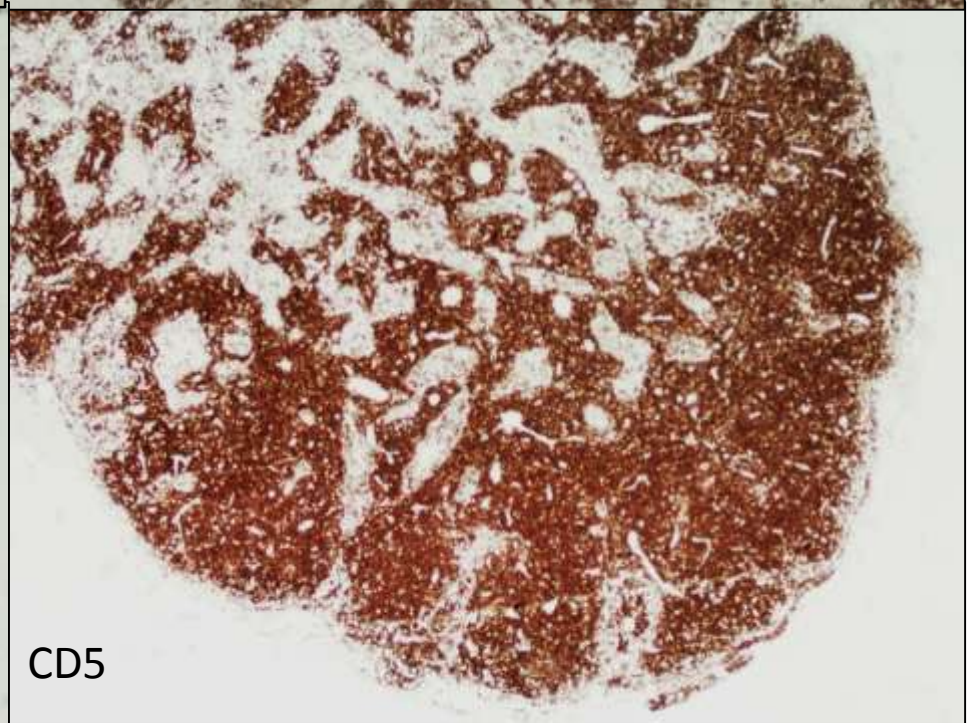
- Cases of minimal lymph node involvement by SLL
- Cases with no proliferation centres
- Adenopathy < 15mm
- No significant risk of progression to SLL






CD20


CD23

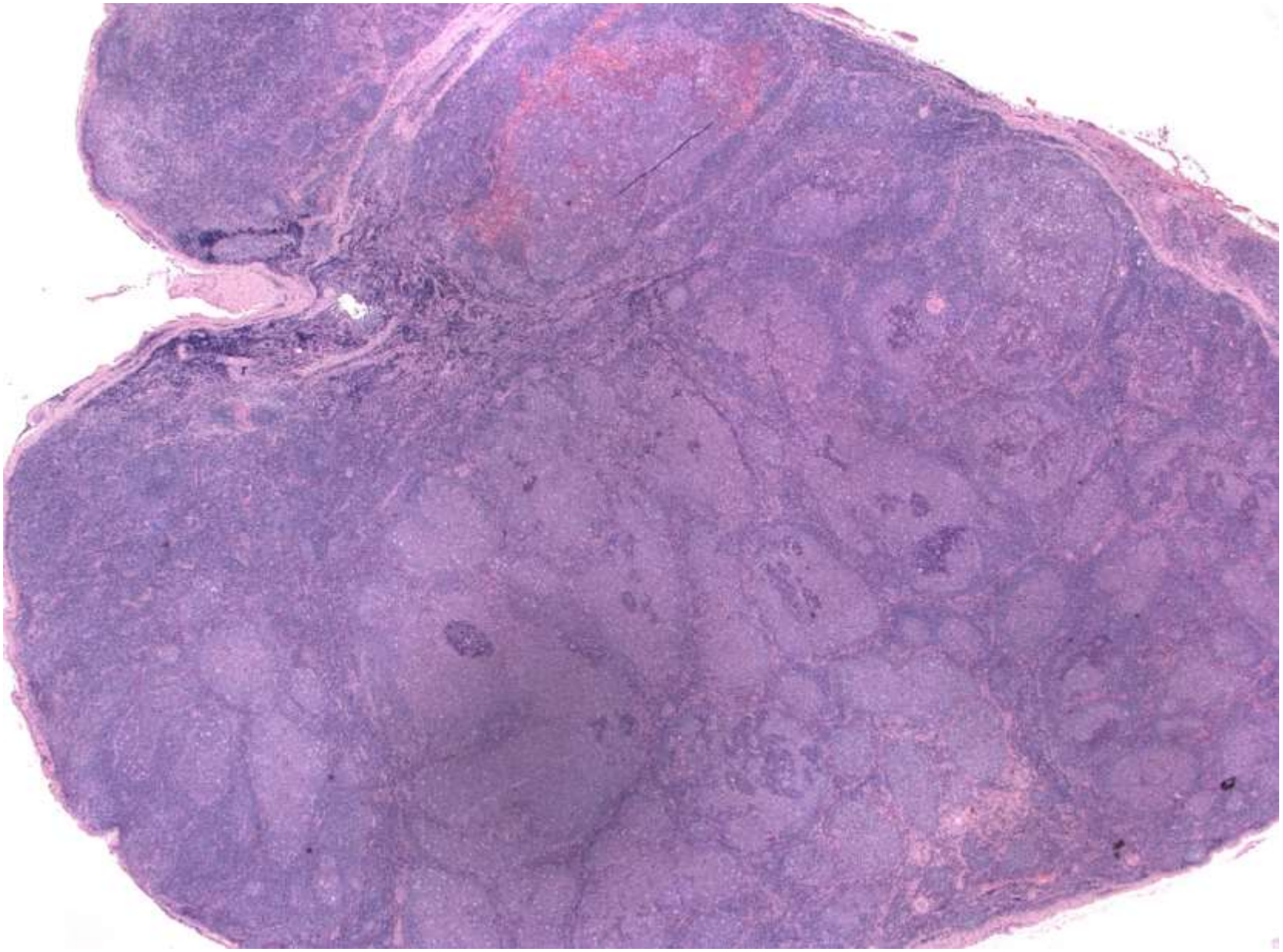

CD5

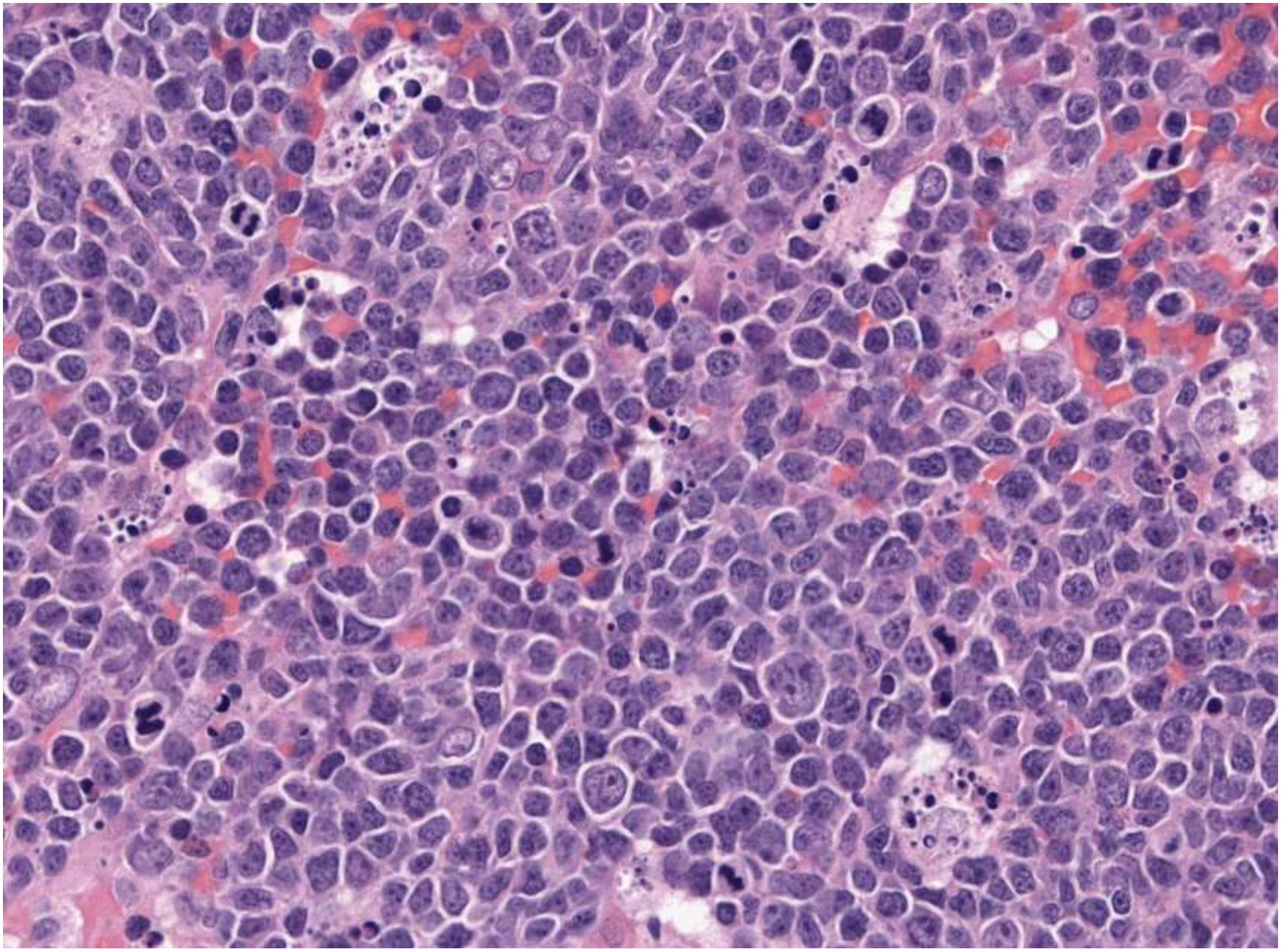
Paediatric Follicular lymphoma

- Definite entity
- Now known as Paediatric-TYPE FL
- Not used if diffuse areas
- Median age 15-18yrs
- M:F 10:1

Paediatric Follicular lymphoma

- Large expansile, highly proliferative follicle centres
- “Blastoid” morphology
- Cases of grade 1-2 have been reported
- BM involvement not reported





Paediatric Follicular lymphoma Diagnostic Features

- Morphology
  - At least partial effacement of nodal architecture (Req)
  - Pure follicular growth pattern (Req)
  - Expansile follicles
  - Intermediate sized blasts
- Immunohistochemistry
  - BCL6+
  - BCL2-/weak (in the absence bcl-2 rearrangent)
  - Proliferation >30%
- Genetics
  - No BCL2, BCL6, IRF4 or aberrant Ig rearrangment
  - No amplification of BCL2
- Clinical
  - Stage I-II (Req)
  - Age <40
  - M>>F

Must be distinguished from conventional follicular lymphoma, grade3 in adult

Large B Cell Lymphoma with IRF4 Rearrangement

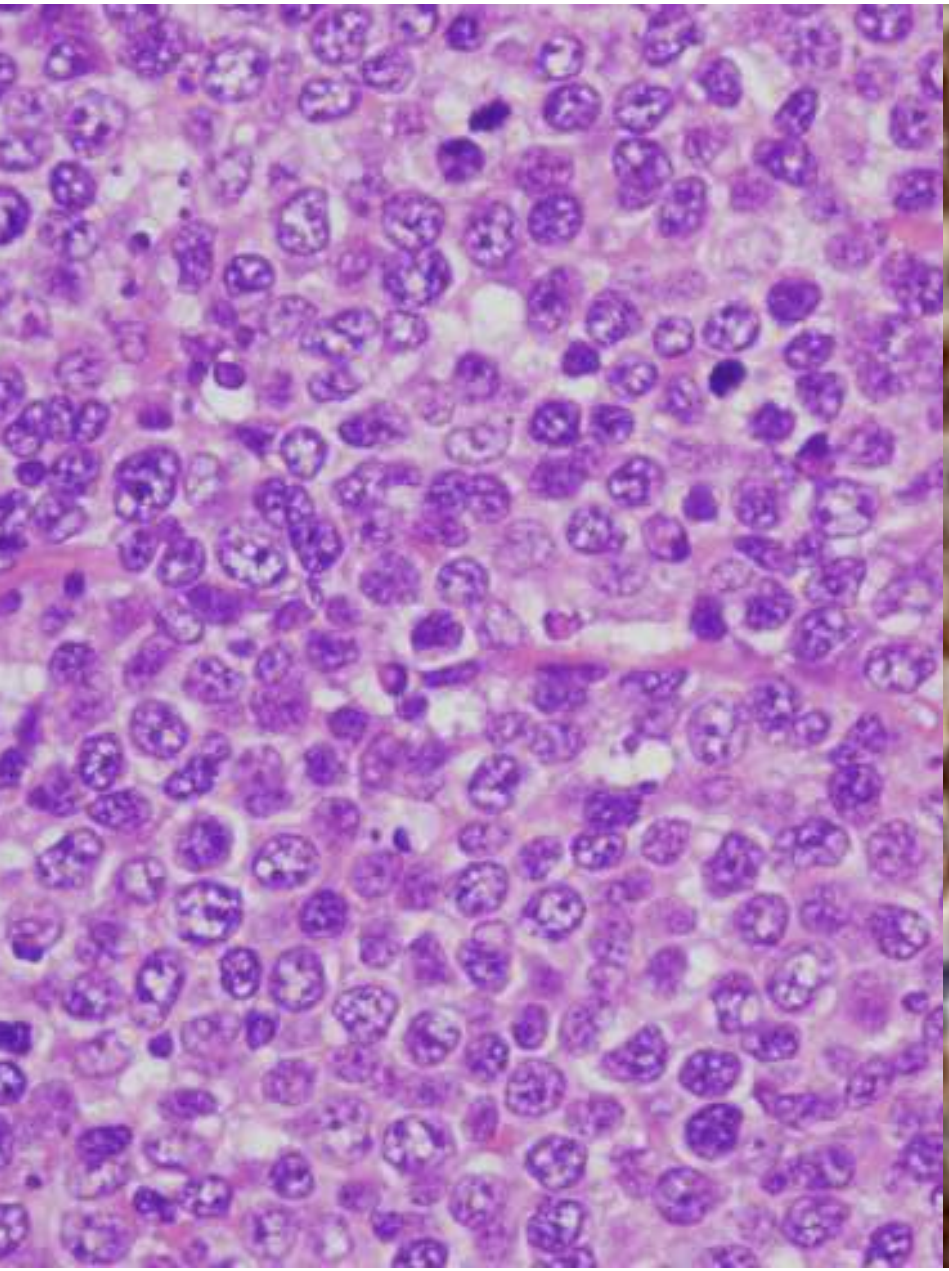
- New provisional entity

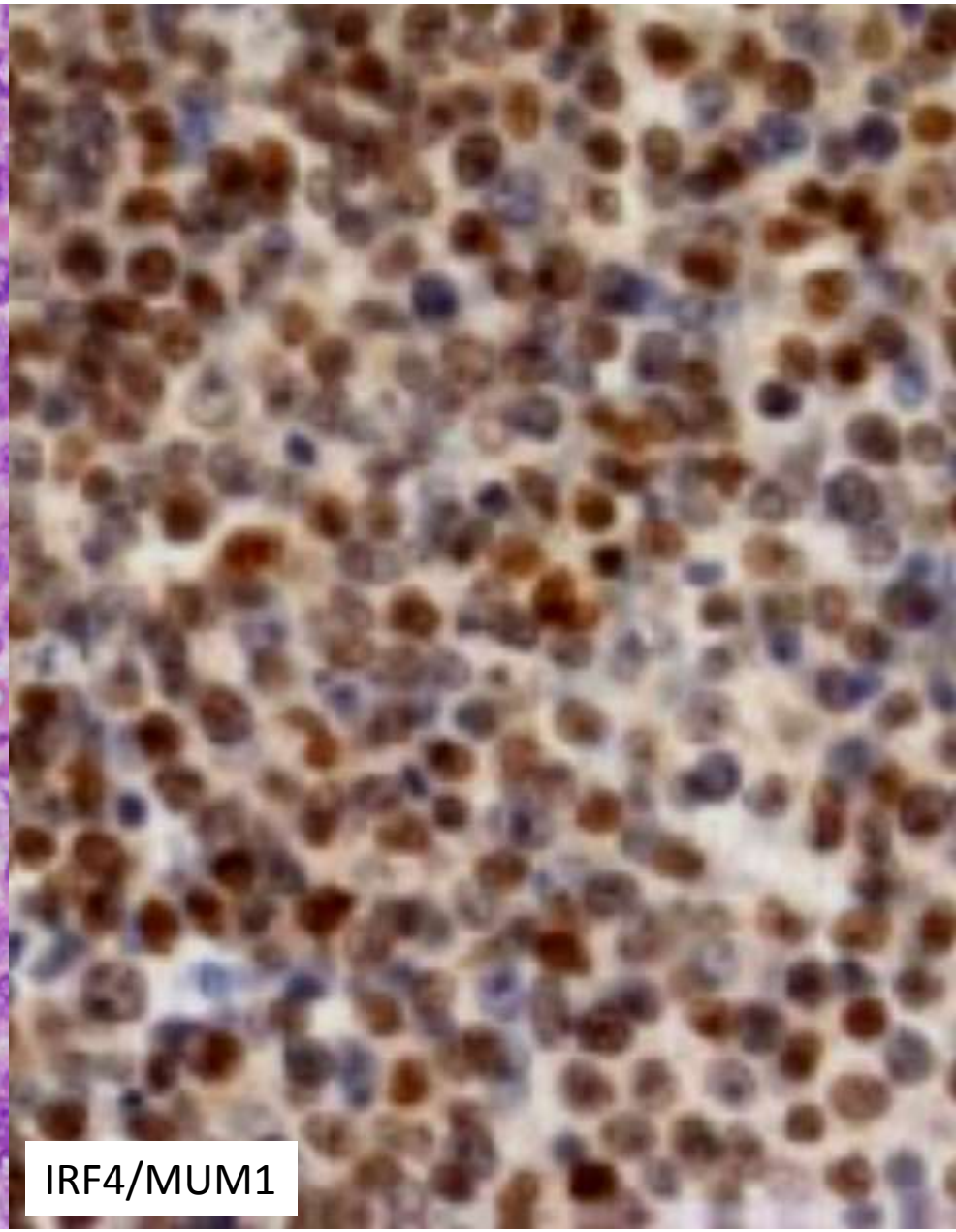
Large B Cell Lymphoma with IRF4 Rearrangement

- 0.05% of all DLBCL
- Clinical
  - M:F 1:1
  - Most Children
    - 71%, Median 10yrs; Range 4-28yrs [Salaverria et al BLOOD 2011]
  - Can present in adults
    - 29%; Median 61yrs: Range 31-79yrs [Salaverria et al BLOOD 2011]
- Most present in
  - Cervical lymph nodes
  - Waldeyer's ring
  - GIT

Large B Cell Lymphoma with IRF4 Rearrangement

- Histology
  - Large closely packed follicles
  - Centroblasts (grade 3B) or intermediate sized bastoid cells
    - Clumped chromatin
    - Small basophilic nucleoli
  - Attenuated mantles
  - Mitoses infrequent, no starry sky pattern
  - May have follicular, follicular and diffuse or pure diffuse growth pattern




IRF4/MUM1

Large B Cell Lymphoma with IRF4 Rearrangement

- Strong IRF4/MUM1 expression
- Usually BCL6 expression
- Lack BCL2 & CD10 in 50% cases
- Minority CD5+
- Must be distinguished from CD10-, IRF4/MUM1+ conventional FL (occur in older patients)

Large B Cell Lymphoma with IRF4 Rearrangement

- Genetics
  - Lack BCL2 rearrangement (in spite of protein expression
  - IRF4 rearrangement absent in some
  - BCL6 alterations (including chromosomal breaks and mutations) can be seen

- More aggressive than paediatric FL but still good prognosis

Large B Cell Lymphoma with IRF4 Rearrangement

- Outcome
  - Salaverria et al BLOOD 2011
    - All treated with chemotherapy (irrespective of growth pattern)
    - 16/17pts <30yrs alive and well (median follow up 105m)
  - Liu et al Am J Surg Pathol 2013
    - Included 2 pts treated with tonsillectomy alone
    - Disease free with up to 32m follow-up

GI Follicular lymphoma

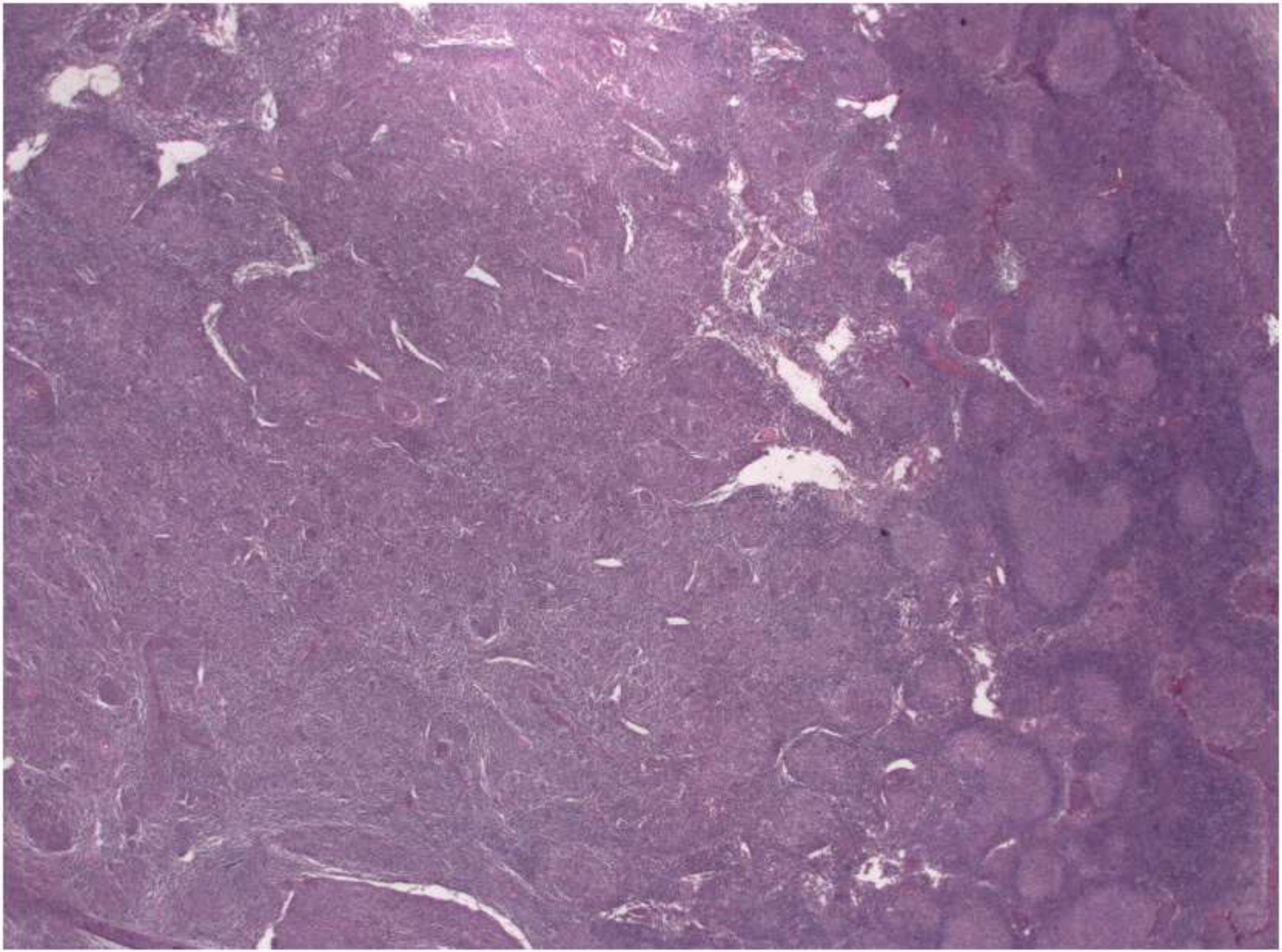
- Duodenal-type FL
  - Most in 2nd part of duodenum
    - Multiple polyps
  - Involvement of distal SI in 80-85%
  - Distinct from other GI FL
  - Some features like ISFN
  - Some features in common with MALT lymphoma
  - Good prognosis

Testicular Follicular lymphoma

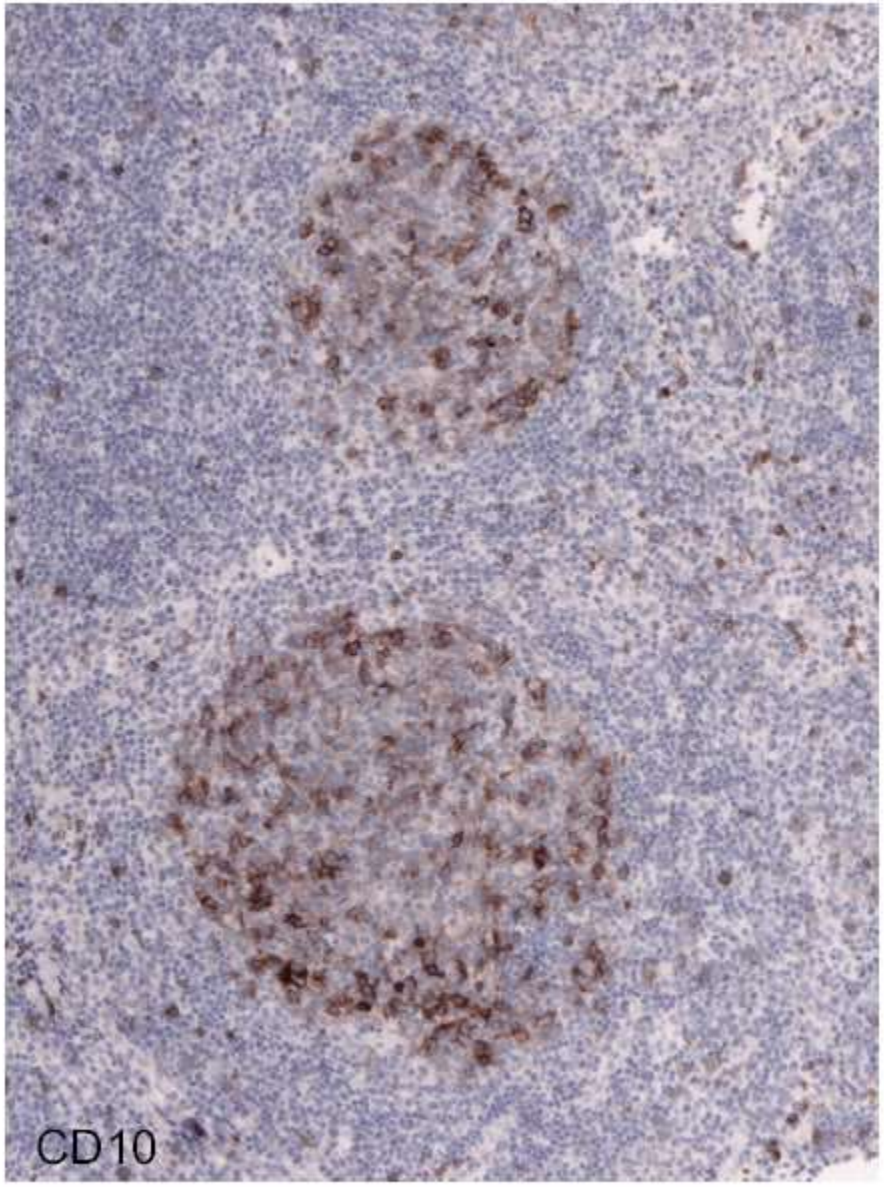
- Increased frequency in children
- Histology
  - Typical grade 3a histology
- Lack BCL2 translocation
- Good prognosis
  - Can be treated with surgery alone

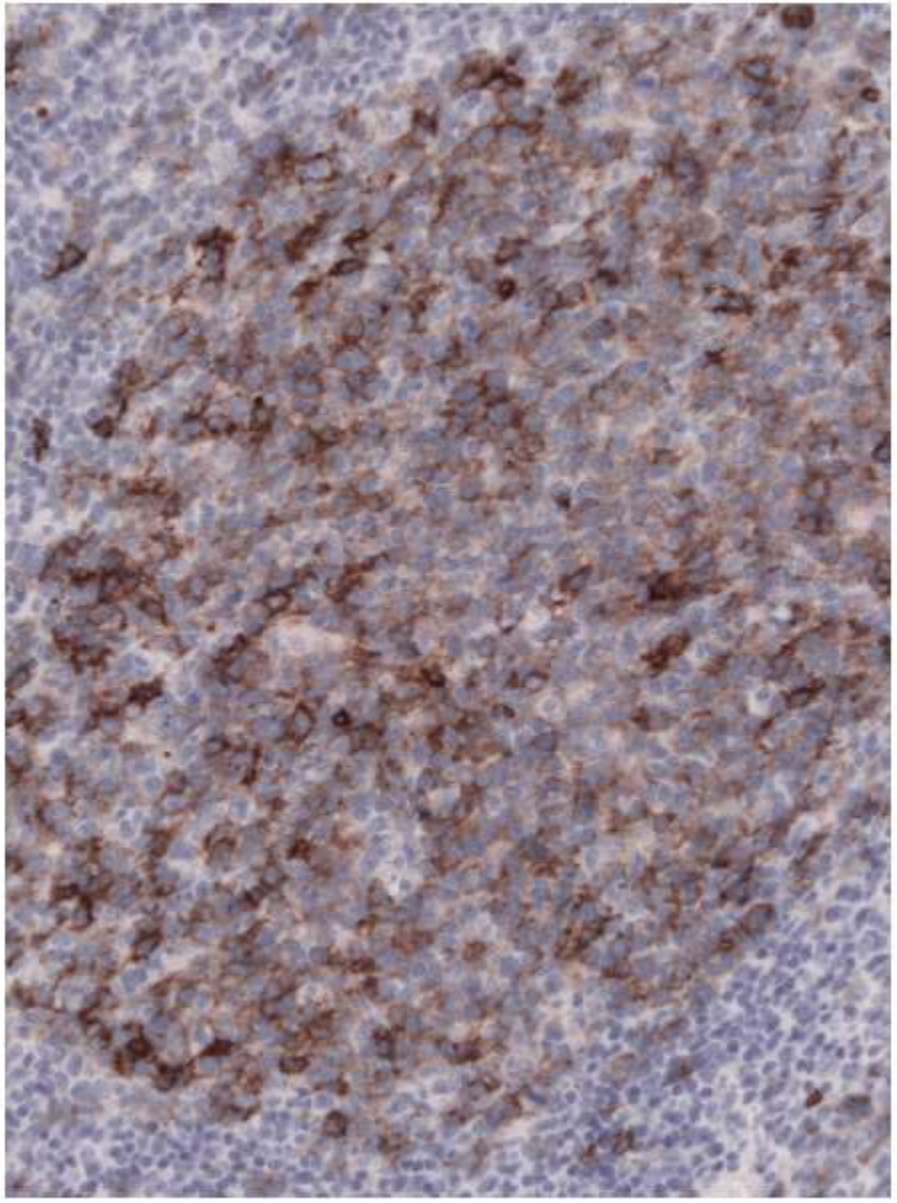
Diffuse-Appearing Follicular Lymphoma

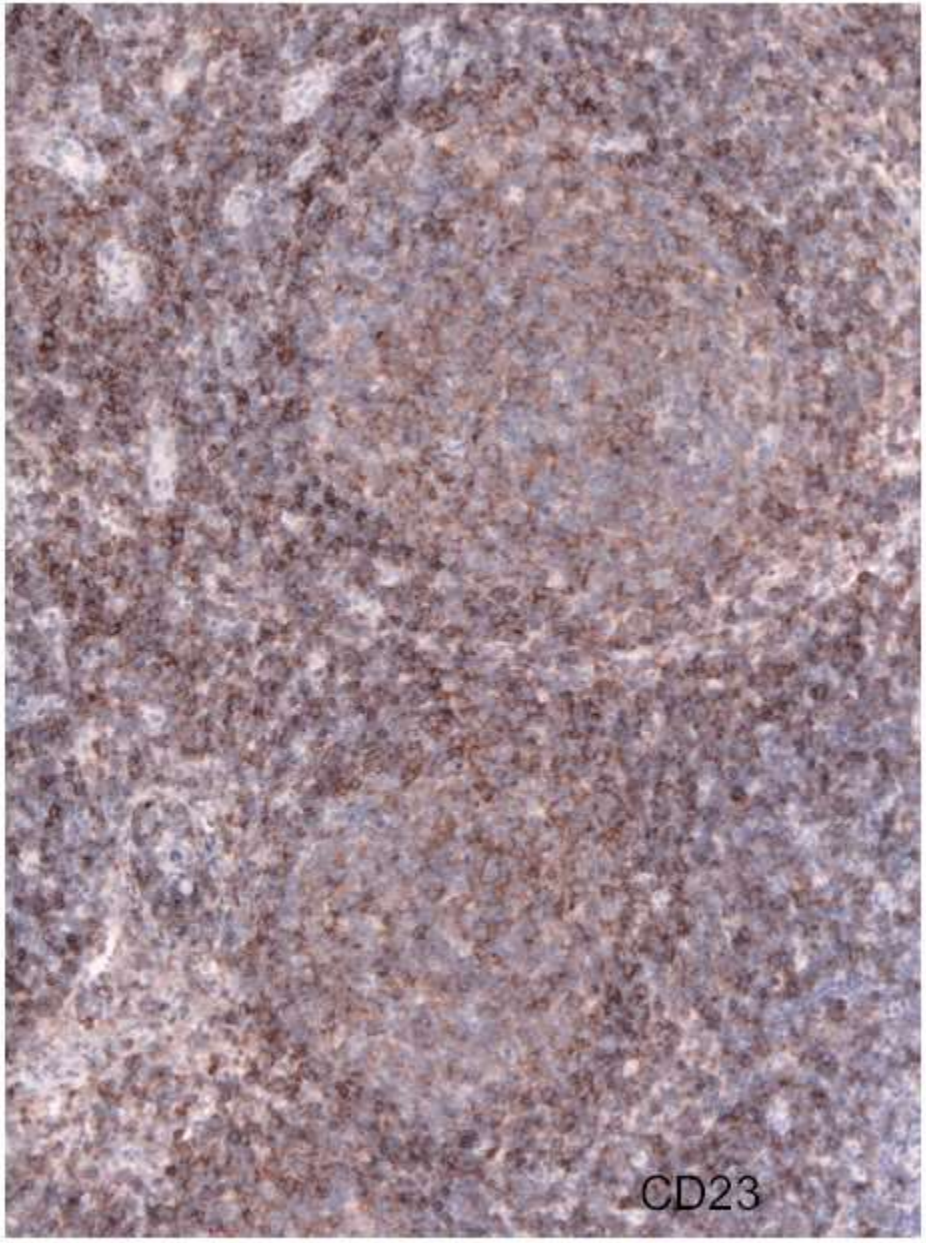
- Often large localised inguinal masses
- Largely diffuse pattern
- Low grade morphology
- Lack *BCL2* rearrangement
- Have 1p36 deletion (not specific, can be seen in conventional FL)

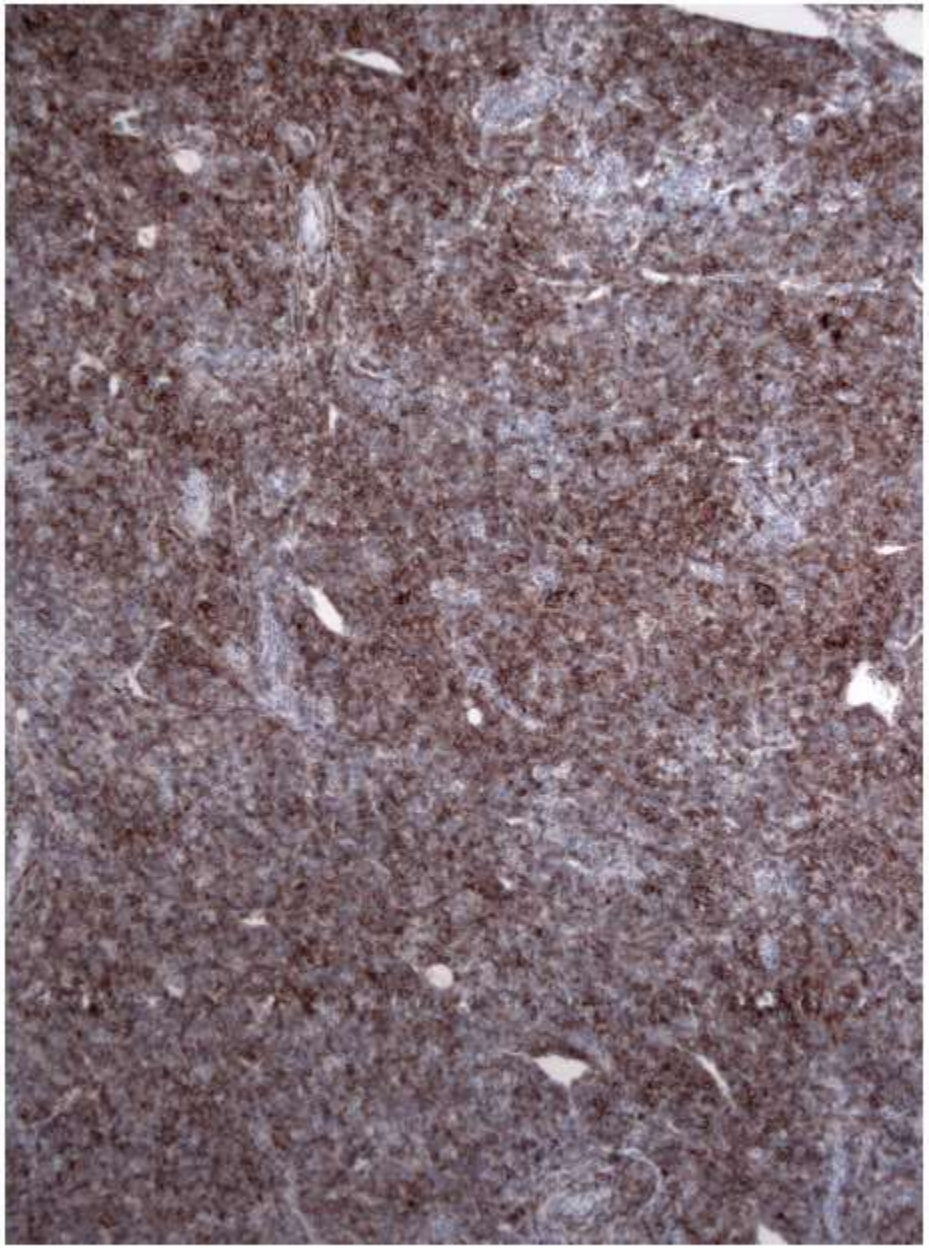


Young woman with a 3 cm inguinal lymphadenopathy

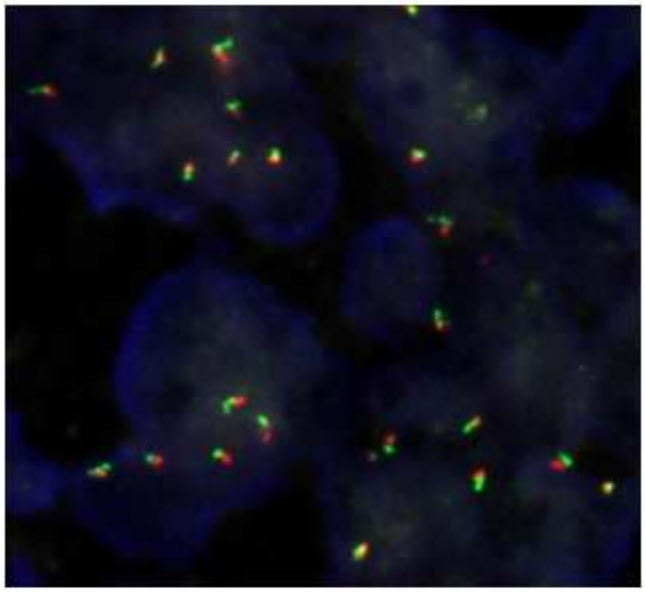

CD10



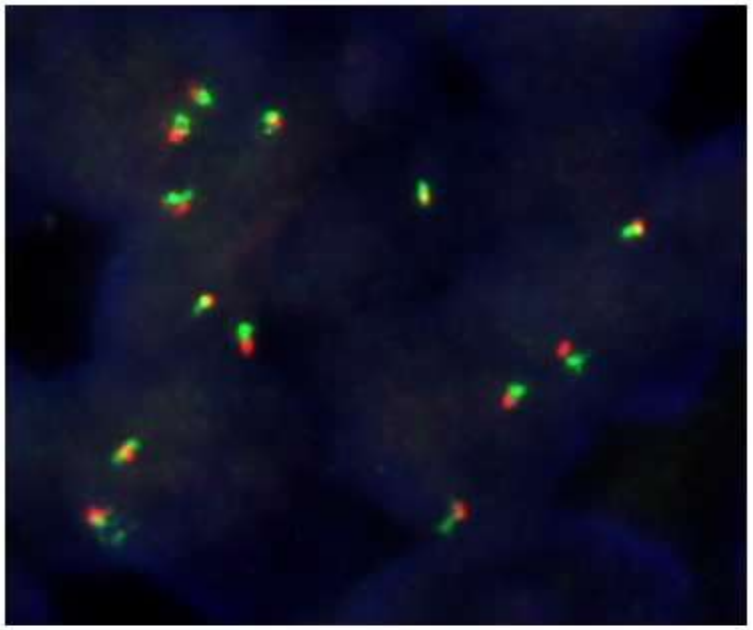




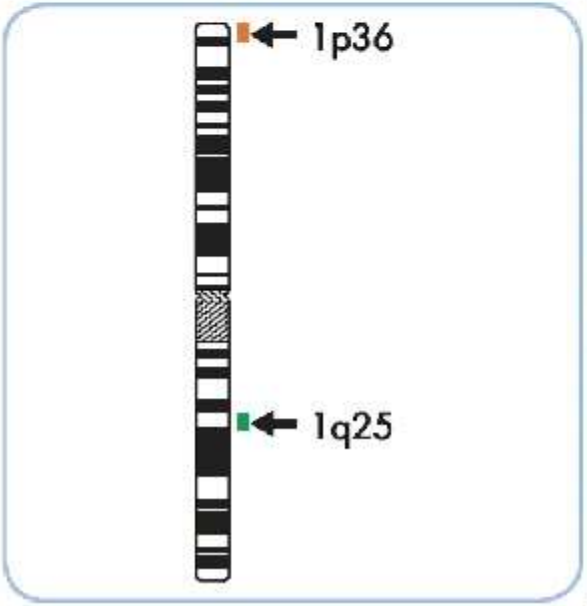
The tumor cells are CD23 positive

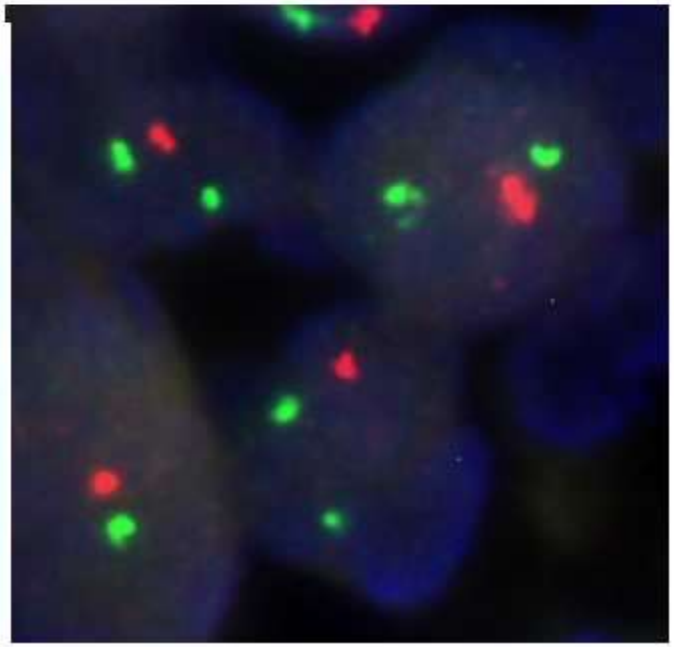


BCL2 break-apart



BCL6 break-apart



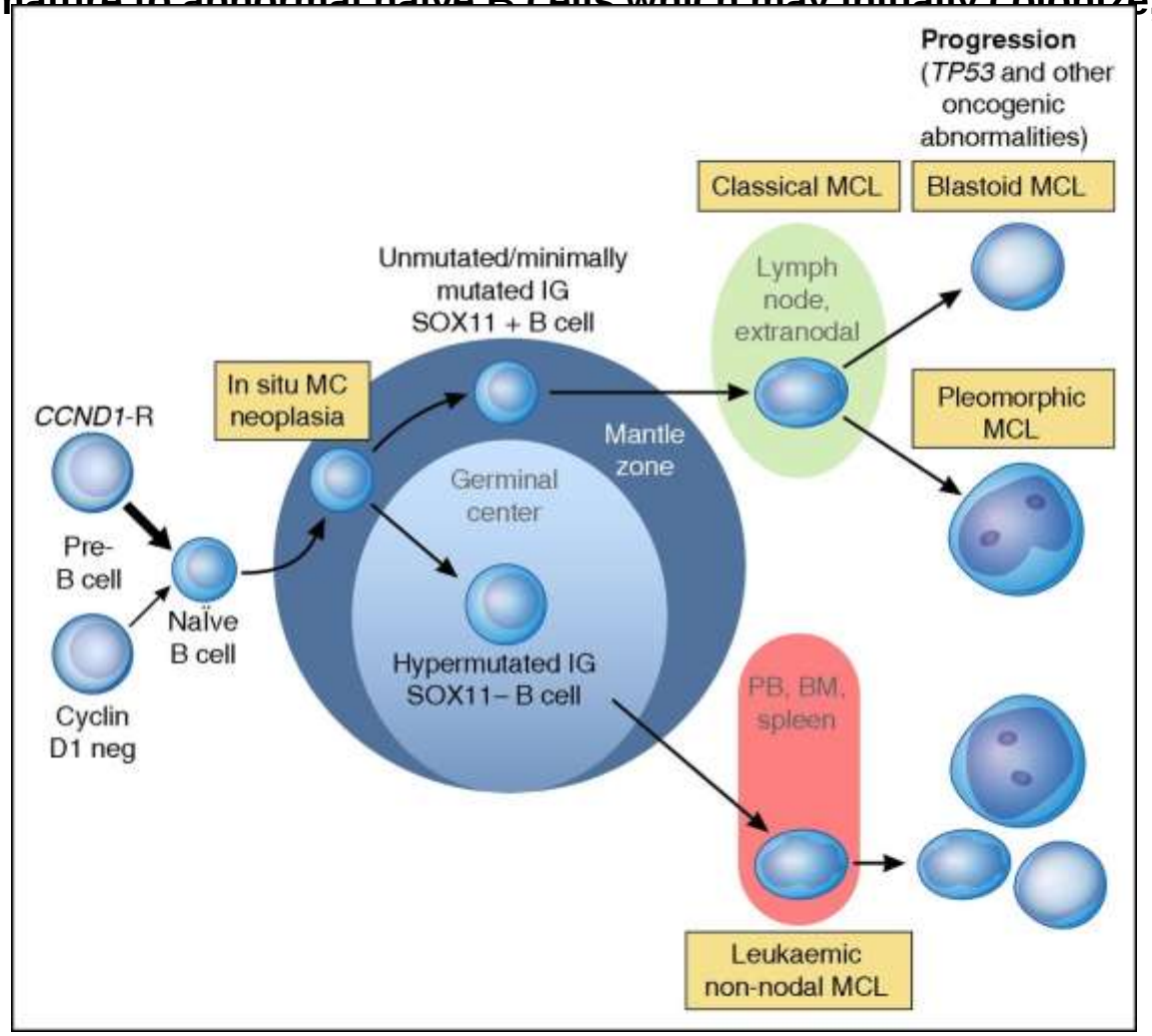


1p36 deletion (only one red signal)

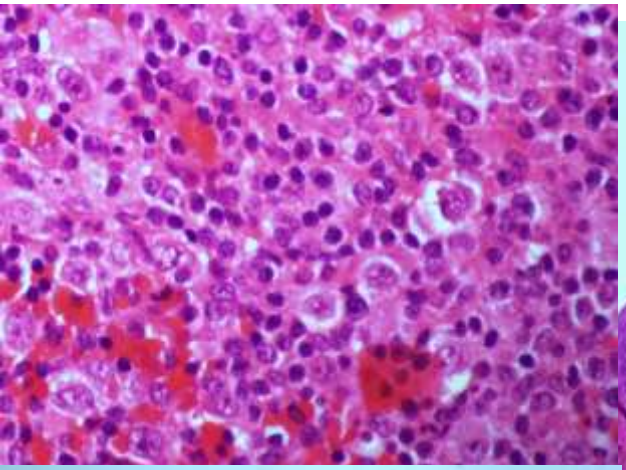
Leukaemic Mantle Cell Lymphoma

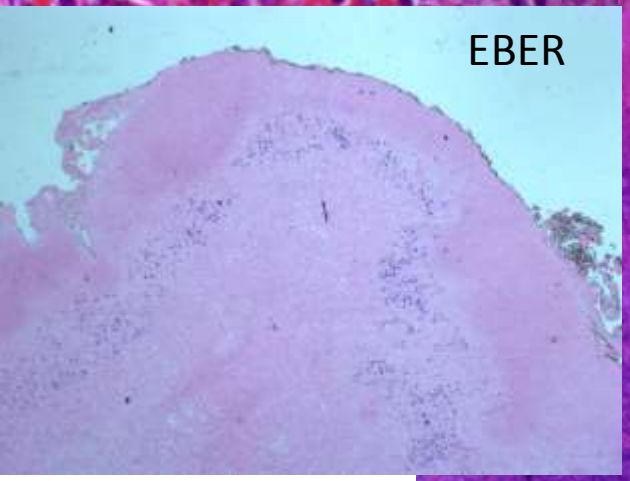
- Indolent variant
- Usually involves peripheral blood, spleen and bone marrow
- SOX11 negative
- IGHV mutated (non-naïve, passed through germinal centre)
- Secondary TP53 abnormalities may occur leading to aggressive behaviour

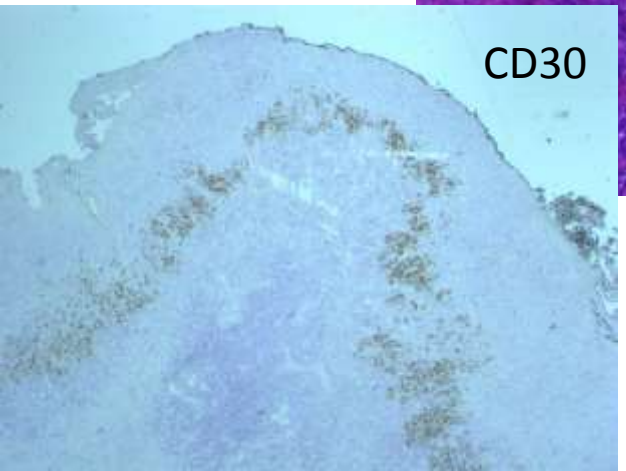
Proposed model of molecular pathogenesis in the development and progression of major subtypes of MCL. Precursor B cells usually with but sometimes without a CCND1 rearrangement mature to abnormal naïve B cells which may initially colonize, often the inner

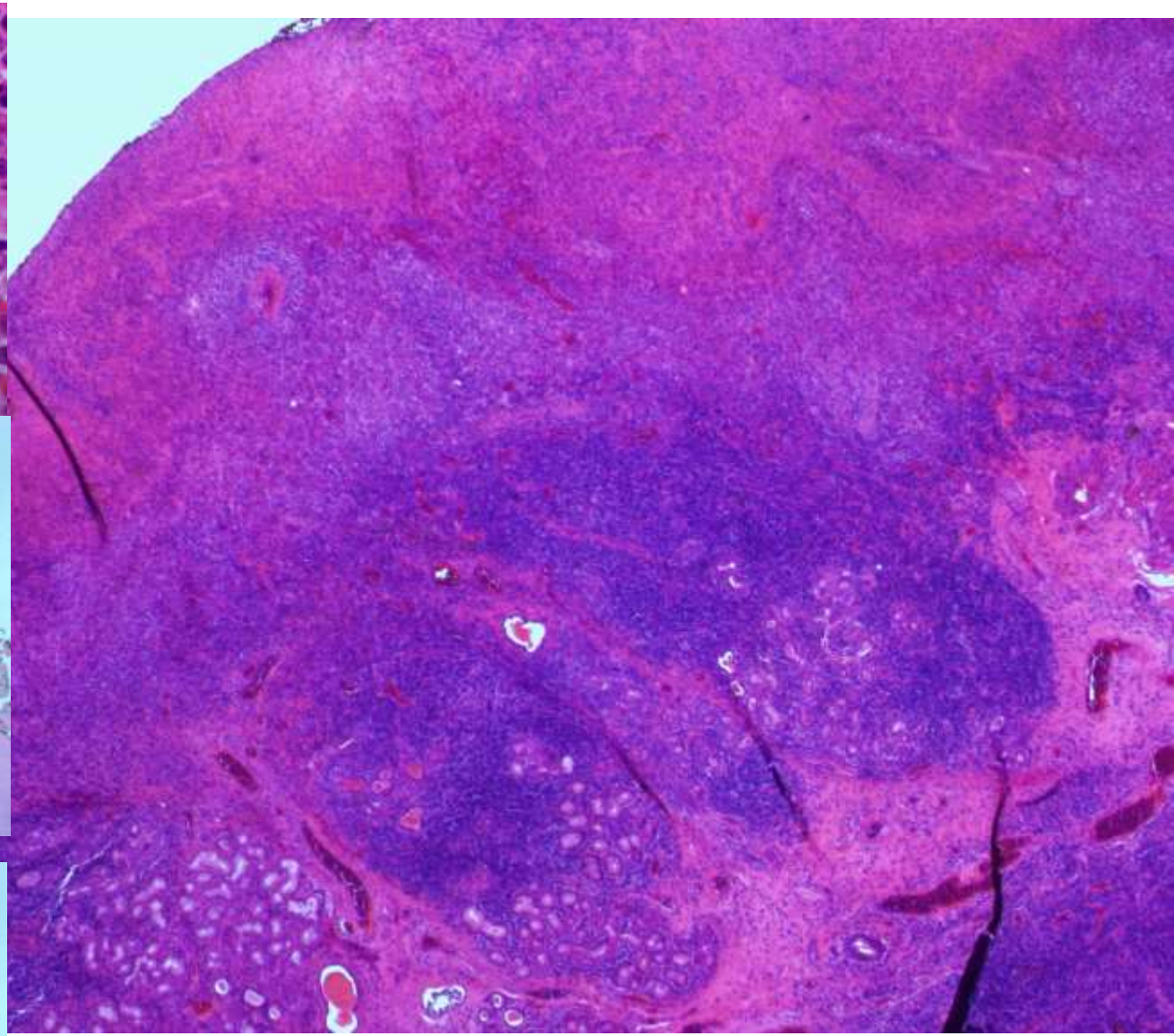


Steven H. Swerdlow et al. Blood 2016;127:2375-2390







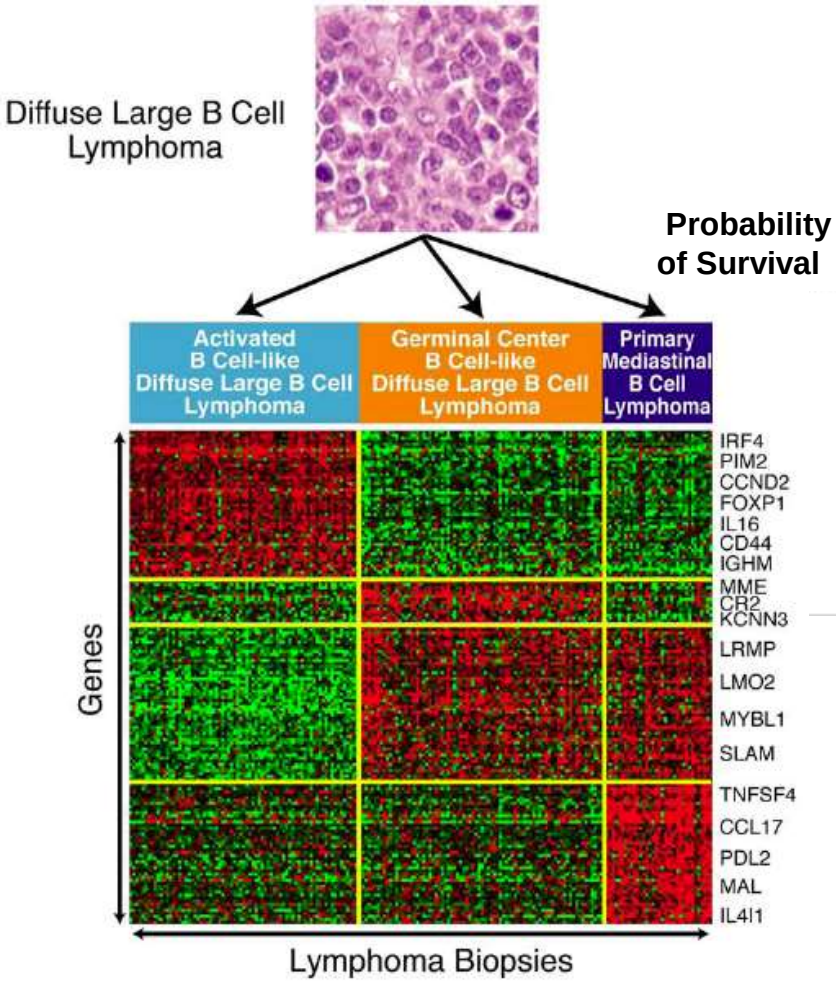


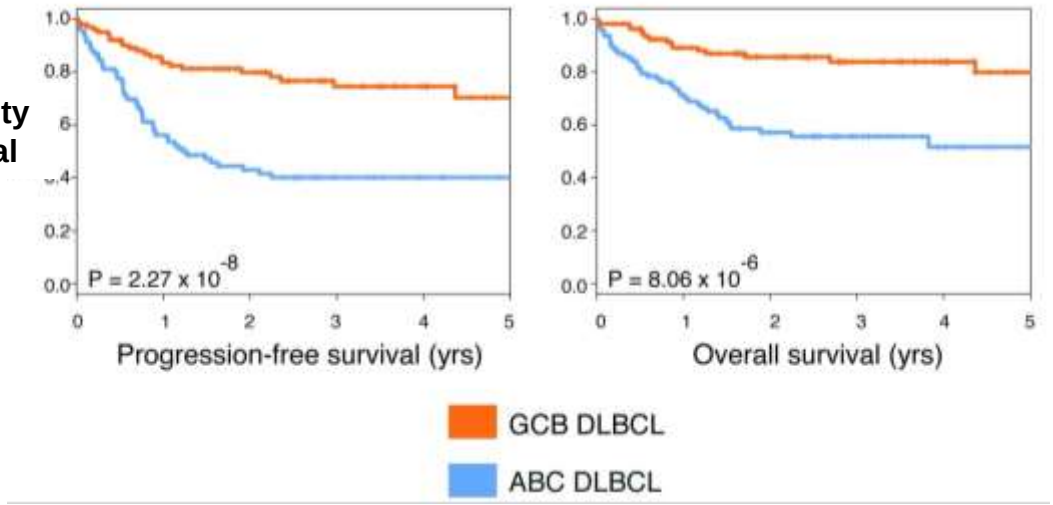
EBV+ Mucocutaneous Ulcer

2016 Revision of WHO Classification of Lymphoma

- Hodgkin lymphoma
- Indolent B cell lymphoma
- Aggressive B cell lymphoma
- T cell lymphoma

Gene Expression Profiling in DLBCL – The Gold Standard in the Definition of Sub-Diseases

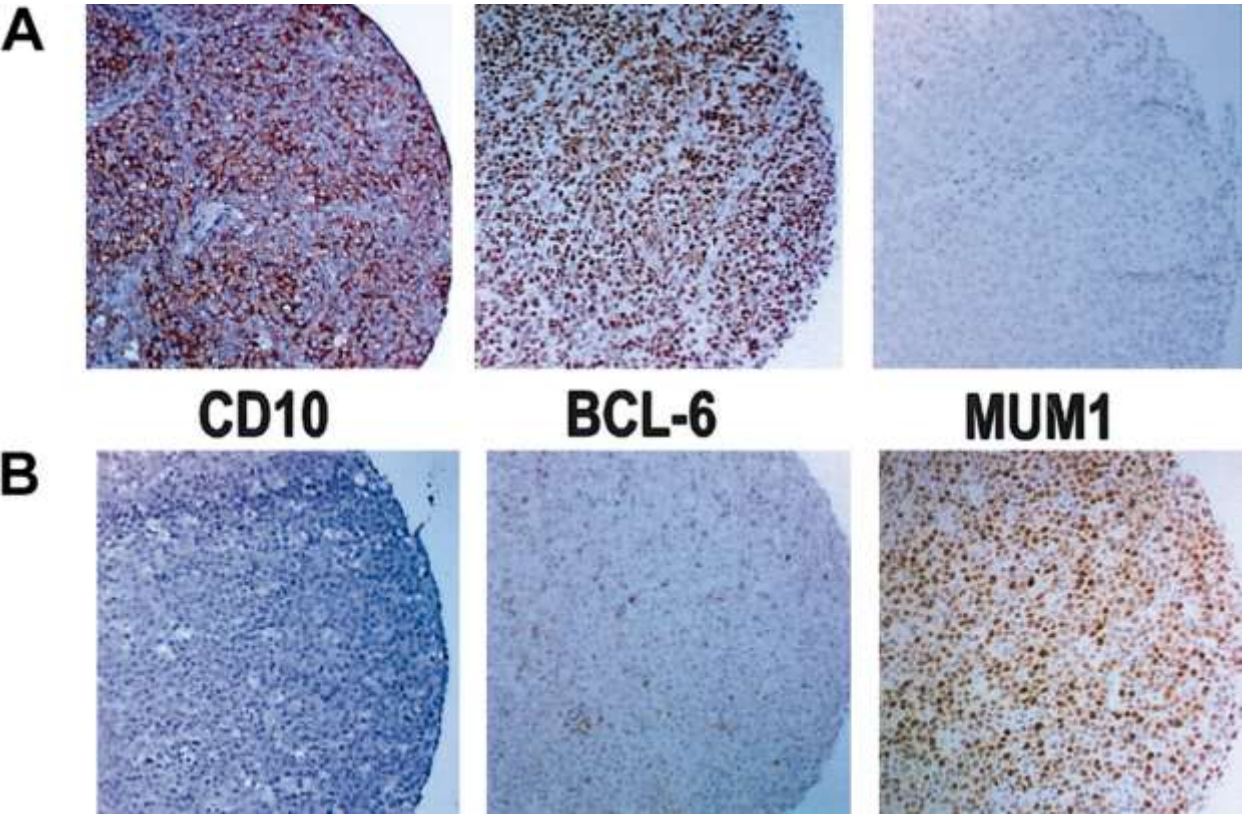




Different outcomes after R-CHOP treatment

Lenz et al. LLMPP 2008

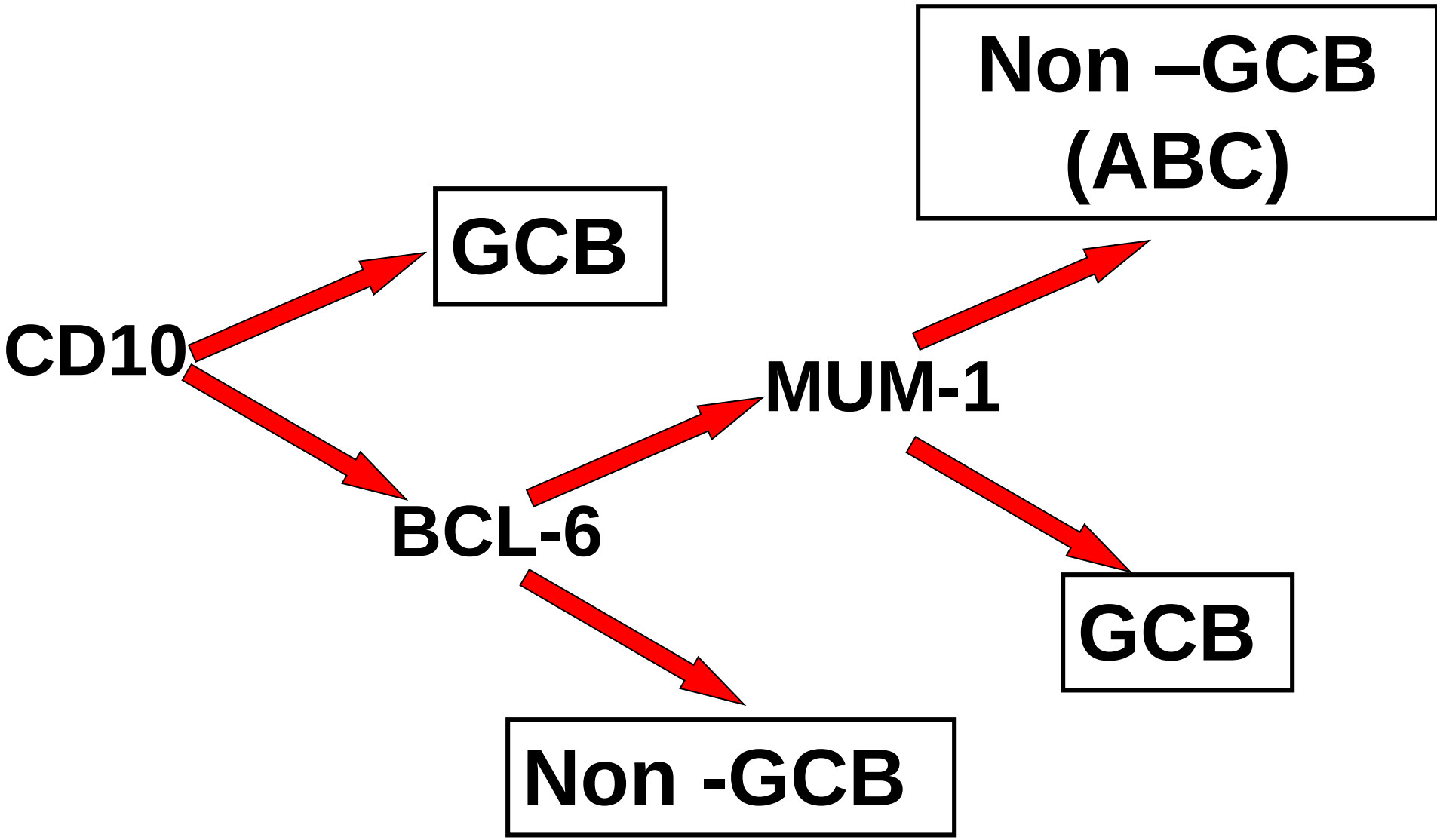
Distinct biology and pathogenesis



"Germinal centre B-cell"

Activated

Hans, C. P. et al. Blood 2004;103:275-282


Non –GCB
(ABC)
GCB
CD10
MUM-1
BCL-6
GCB
Non -GCB

Burkitt Lymphoma Without MYC Rearrangement

- Does this exist?

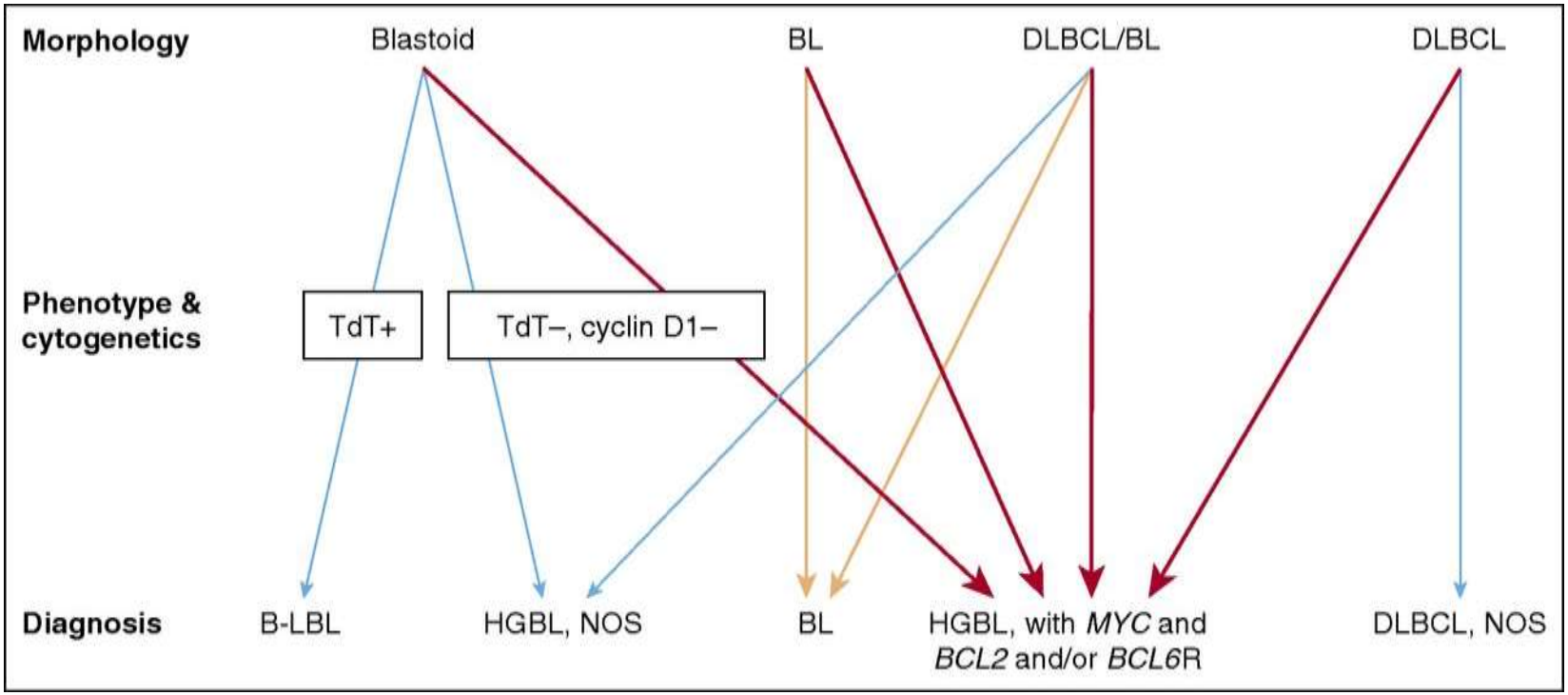
- Recent studies have identified cases that lack MYC translocation
  - Resemble Burkitt lymphoma morphologically
  - Resemble Burkitt lymphoma phenotypically
  - Resemble Burkitt lymphoma by GEP
  - Have 11q alteration with proximal gains and telomeric losses
  - More complex karyotypes compared to Burkitt lymphoma
  - Show cytological pleomorphism, frequent nodal presentation and occasionally a follicular growth pattern
  - Similar clinical course to Burkitt lymphoma

Burkitt-like lymphoma with 11q aberration (Provisional entity)

B-cell lymphoma, unclassifiable, with features intermediate between Diffuse large B-cell lymphoma and Burkitt lymphoma

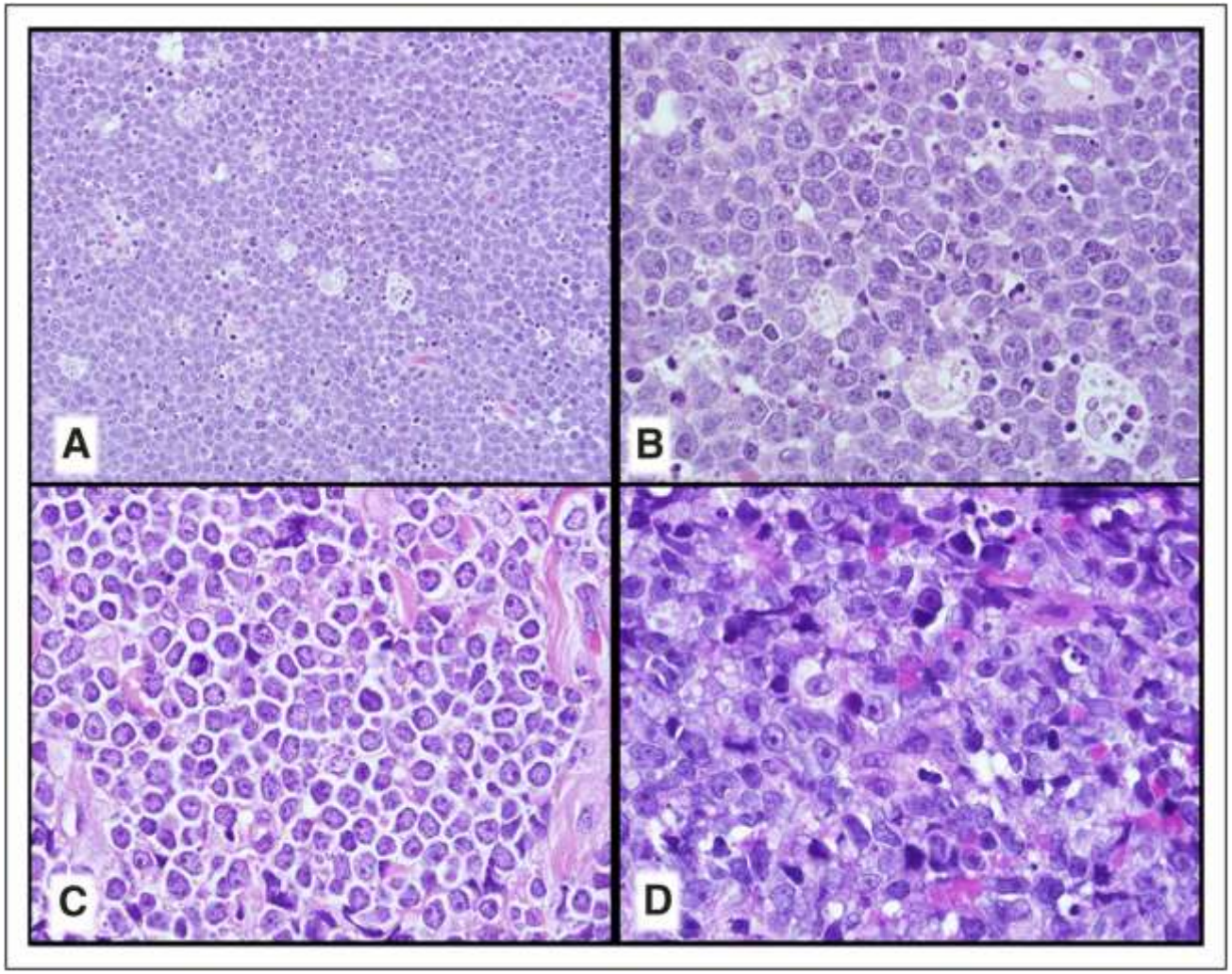
- Criteria vague
- Eliminated from revised WHO classification 2016
- All large B cell lymphomas with MYC and BCL2 and/or BCL6 rearrangments (double/triple hit) will be included in a single category
- Cases that appear blastoid or cases with intermediate morphology between DLBCL and BL but lack MYC and BCL2 and/or BCL6 rearrangements will be included in the category of **HIGH GRADE B-CELL LYMPHOMA NOS**

Diagnostic approach to HBCLs. Lymphomas that potentially fall into the HGBL categories can morphologically resemble B-lymphoblastic leukemia/lymphoma (B-LBL), BL, and DLBCL as well as lymphomas that are intermediate between DLBCL and BL (DLBCL/BL).



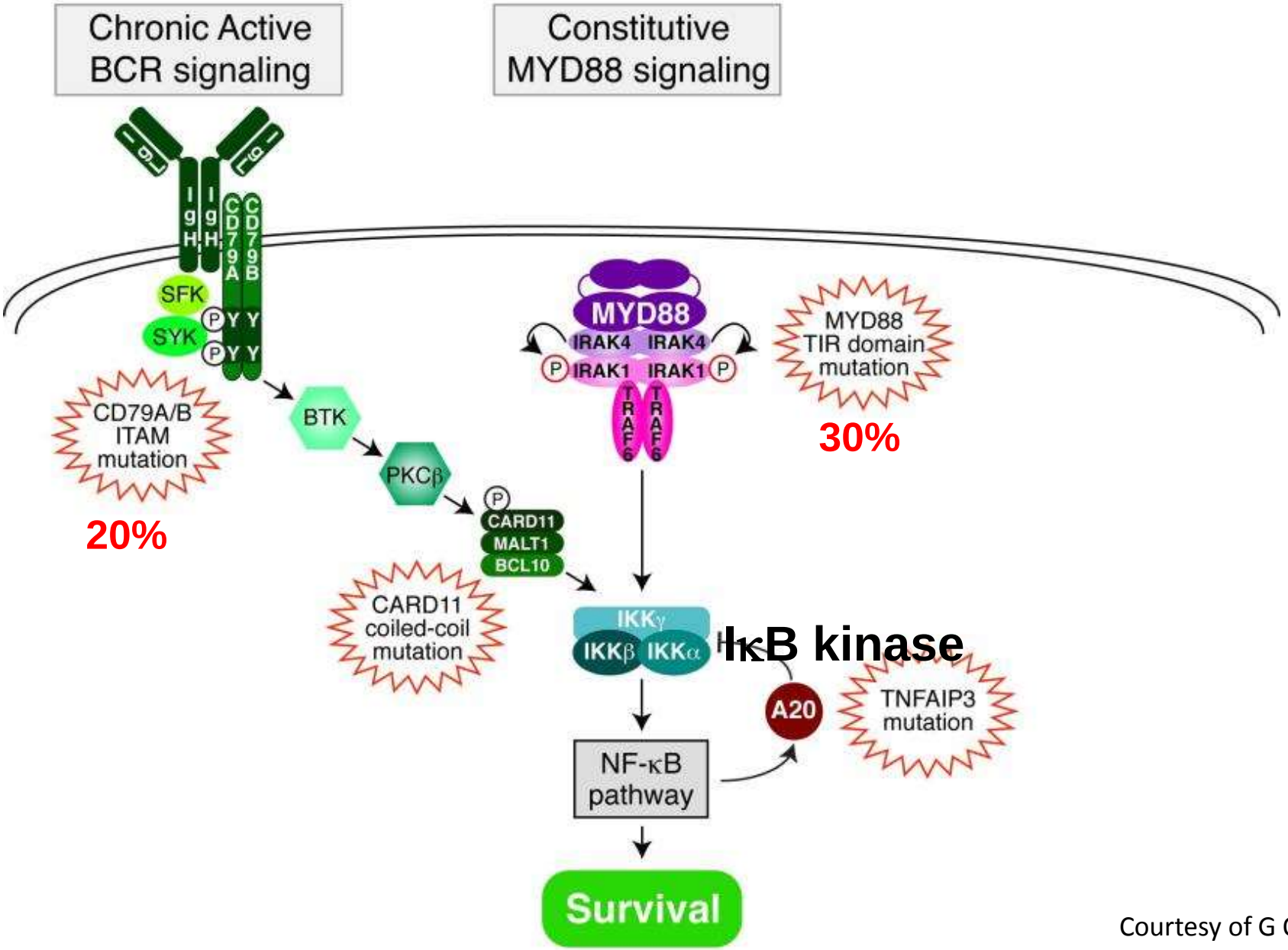
Steven H. Swerdlow et al. Blood 2016;127:2375-2390

Cytologic spectrum of HGBL, with MYC and BCL2 and/or BCL6 rearrangements.



Steven H. Swerdlow et al. Blood 2016;127:2375-2390

Oncogenic NF-kB Signaling in ABC DLBCL

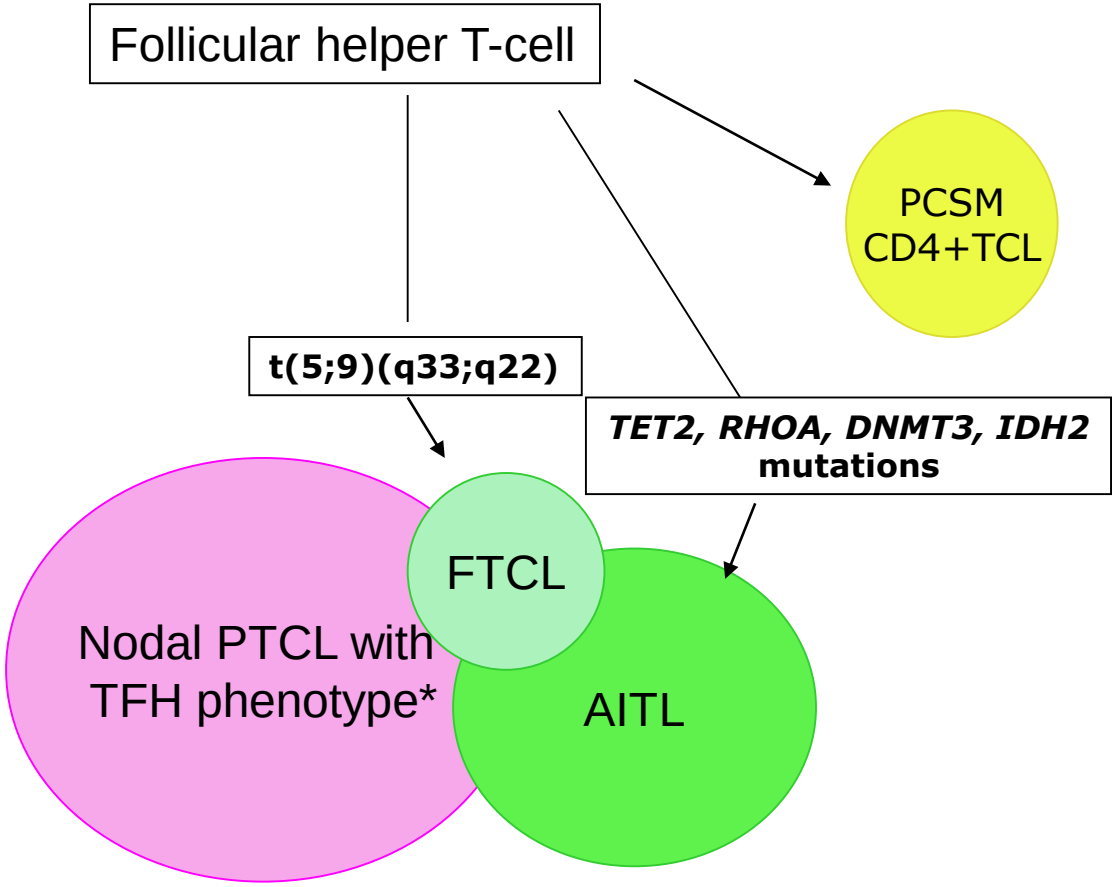


Courtesy of G Ott

2016 Revision of WHO Classification of Lymphoma

- Hodgkin lymphoma
- Indolent B cell lymphoma
- Aggressive B cell lymphoma
- T cell lymphoma

T cell lymphomas with T_{FH} phenotype



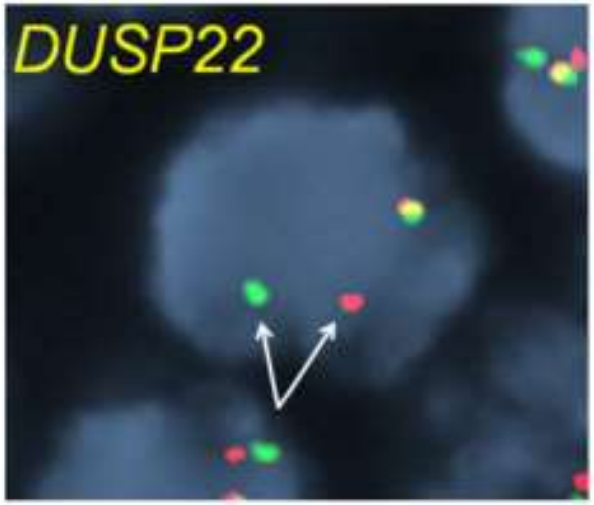
Quintanella-Martinez 2016

ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes

Edgardo R. Parrilla Castellar,[1] Elaine S. Jaffe,[2] Jonathan W. Said,[3] Steven H. Swerdlow,[4] Rhett P. Ketterling,[1] Ryan A. Knudson,[1] Jagmohan S. Sidhu,[5] Eric D. Hsi,[6] Shridevi Karikehalli,[7] Liuyan Jiang,[8] George Vasmatzis,[9] Sarah E. Gibson,[4] Sarah Ondrejka,[6] Alina Nicolae,[2] Karen L. Grogg,[1] Cristine Allmer,[10] Kay M. Ristow,[11] Wyndham H. Wilson,[12] William R. Macon,[1] Mark E. Law,[1] James R. Cerhan,[10] Thomas M. Habermann,[11] Stephen M. Ansell,[11] Ahmet Dogan,[1] Matthew J. Maurer,[10] and Andrew L. Feldman[1]

Key Points

- ALK-negative ALCLs have chromosomal rearrangements of *DUSP22* or *TP63* in 30% and 8% of cases, respectively.
- *DUSP22*-rearranged cases have favorable outcomes similar to ALK-positive ALCLs, whereas other genetic subtypes have inferior outcomes.

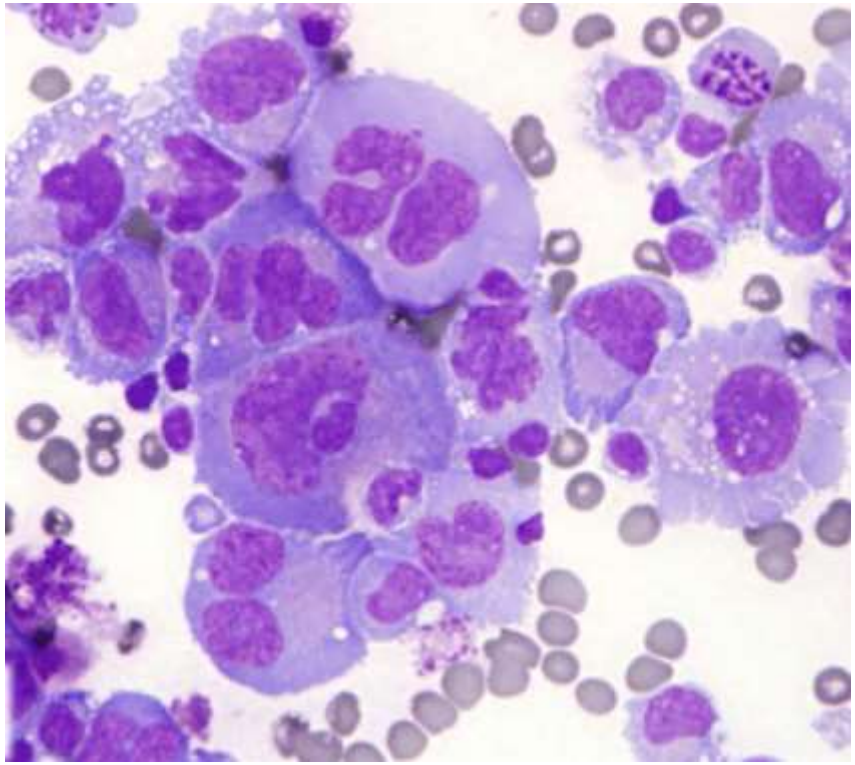


Breast Implant Associated Anaplastic Large Cell Lymphoma

- Most found in seroma fluid between implant and capsule with no mass lesion
- Can be managed conservatively with removal of implant and capsule

- Some are associated with mass lesion or invasion of capsule
- Poorer prognosis – need chemotherapy +/- radiotherapy

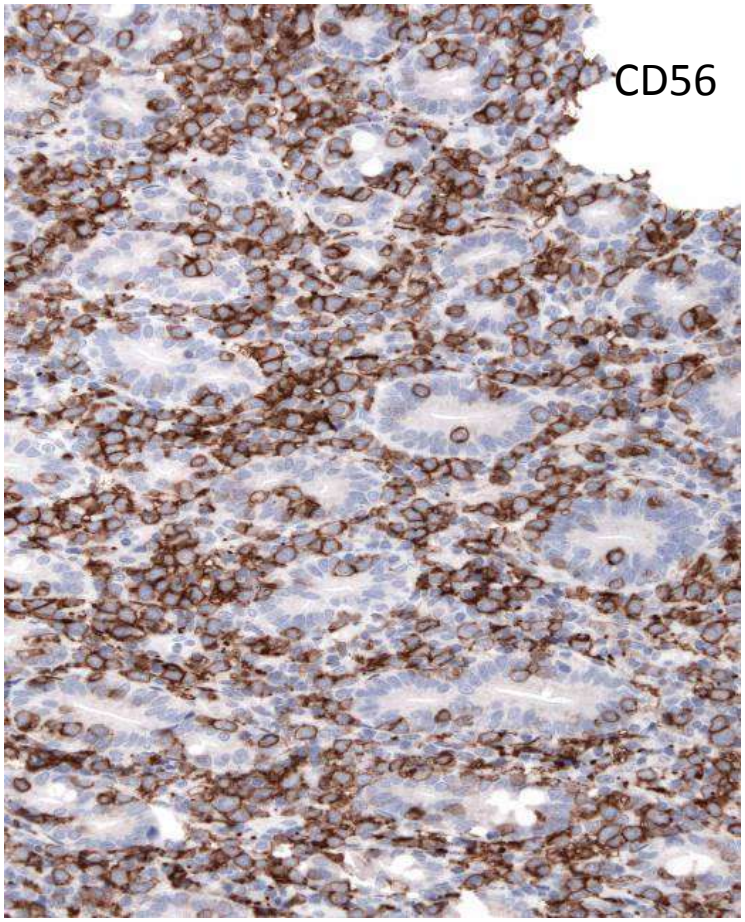
Breast Implant Associated Anaplastic Large Cell Lymphoma



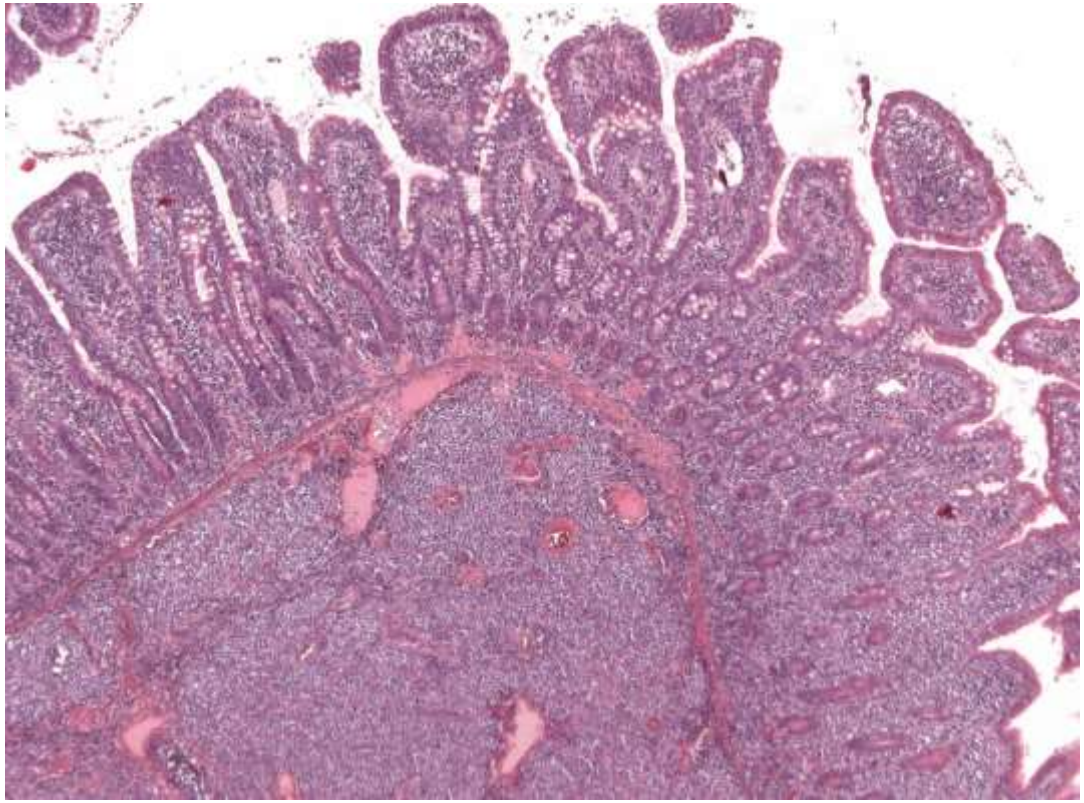
Courtesy of Letitia Quintanella-Martinez

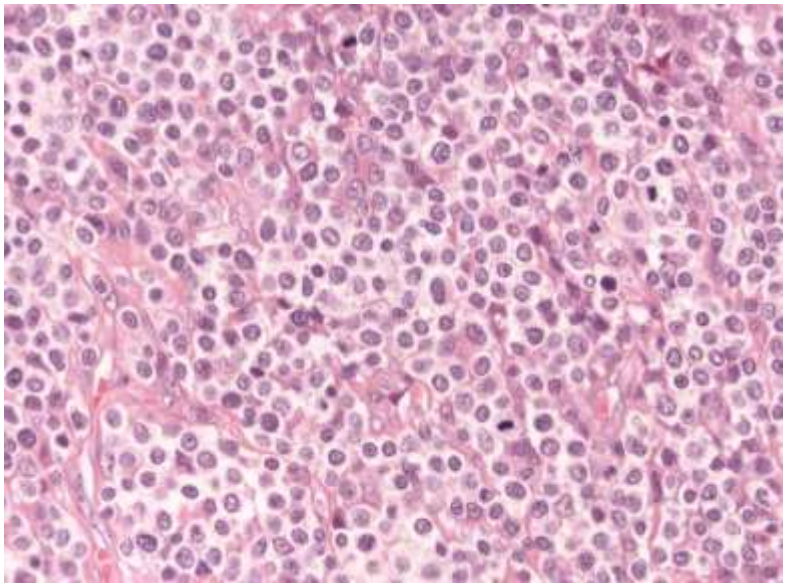
Monomorphic Epitheliotropic Intestinal T-cell Lymphoma (MEITL)

- Used to be Type II Enteropathy Associated T cell Lymphoma (Type II EATL)
- Worldwide distribution but common in Asia and Hispanics
- No link to coeliac disease
- Monomorphic infiltrate of medium sized cells with clear cytopplasm and very prominent epitheliotropism
- CD56+, CD8+
- Usually γδ T cell derived (78%)



Monomorphic Epitheliotropic Intestinal T-cell Lymphoma (MEITL)

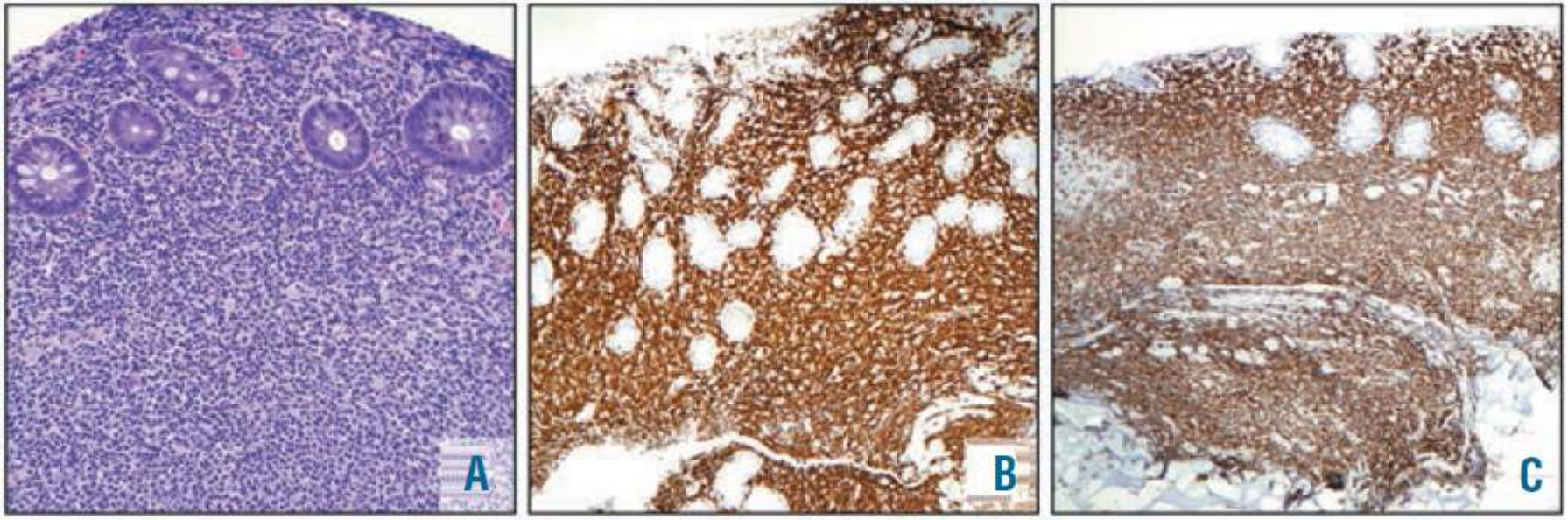




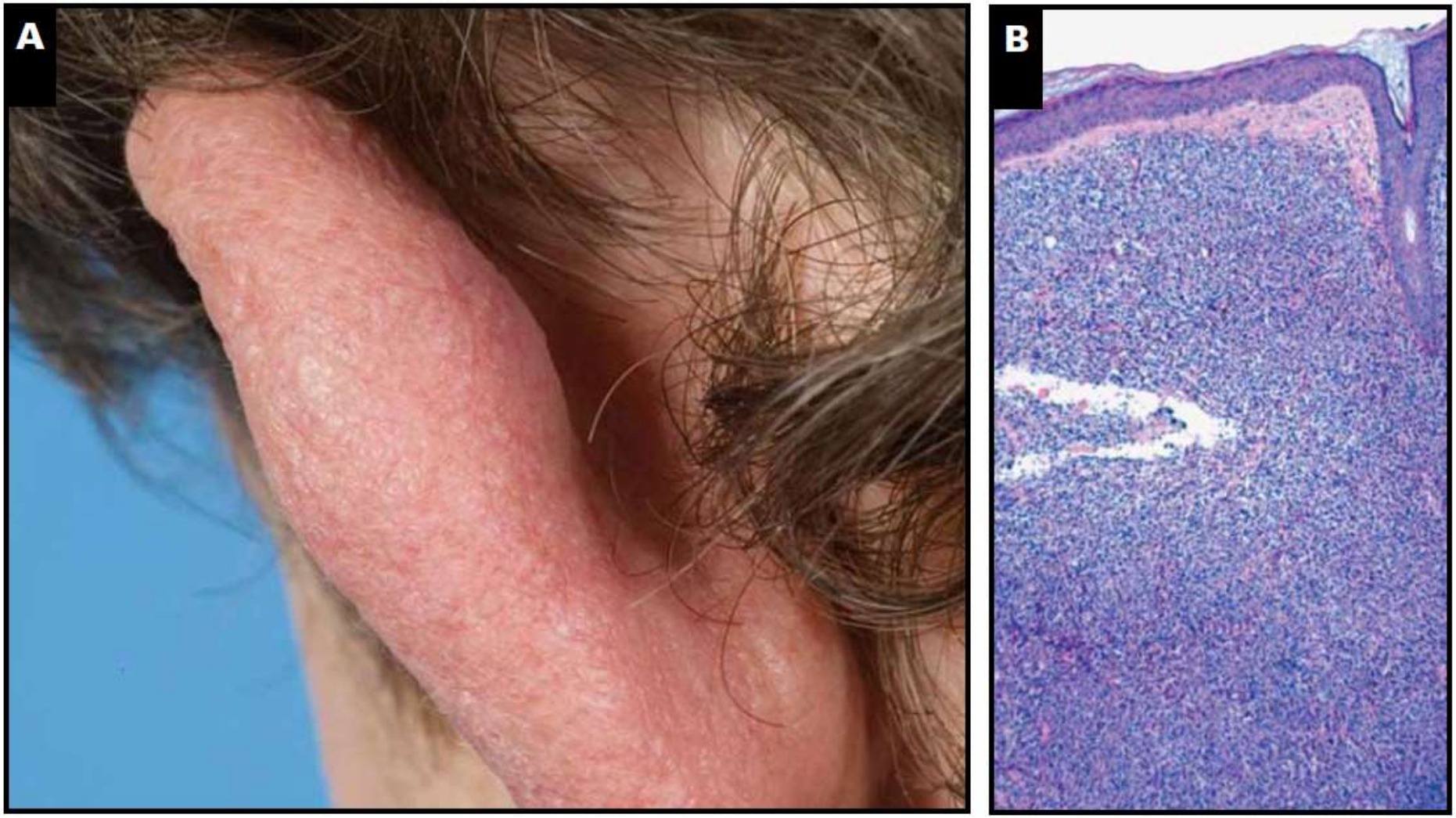
Courtesy of Letitia Quintanella-Martinez

Indolent T-cell lymphoproliferative disorder of the GI Tract

Most are CD8+ although CD4+ cases have been describe
Indolent clinical course
Poor response to chemotherapy



Courtesy of Letitia Quintanella-Martinez



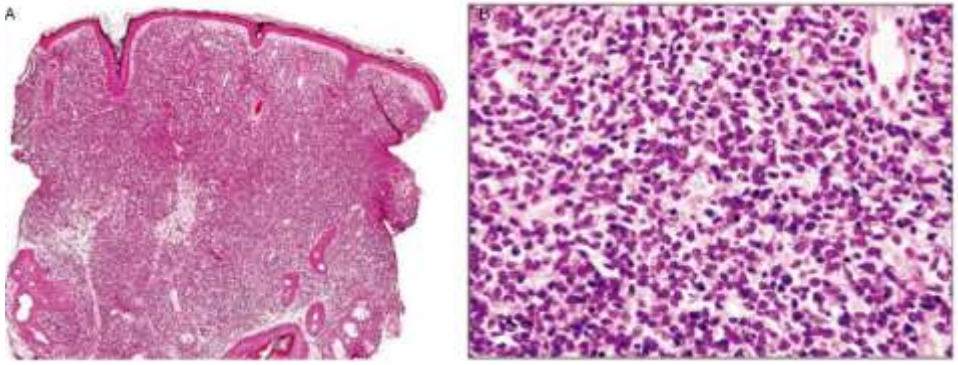
Courtesy of Letitia Quintanella-Martinez

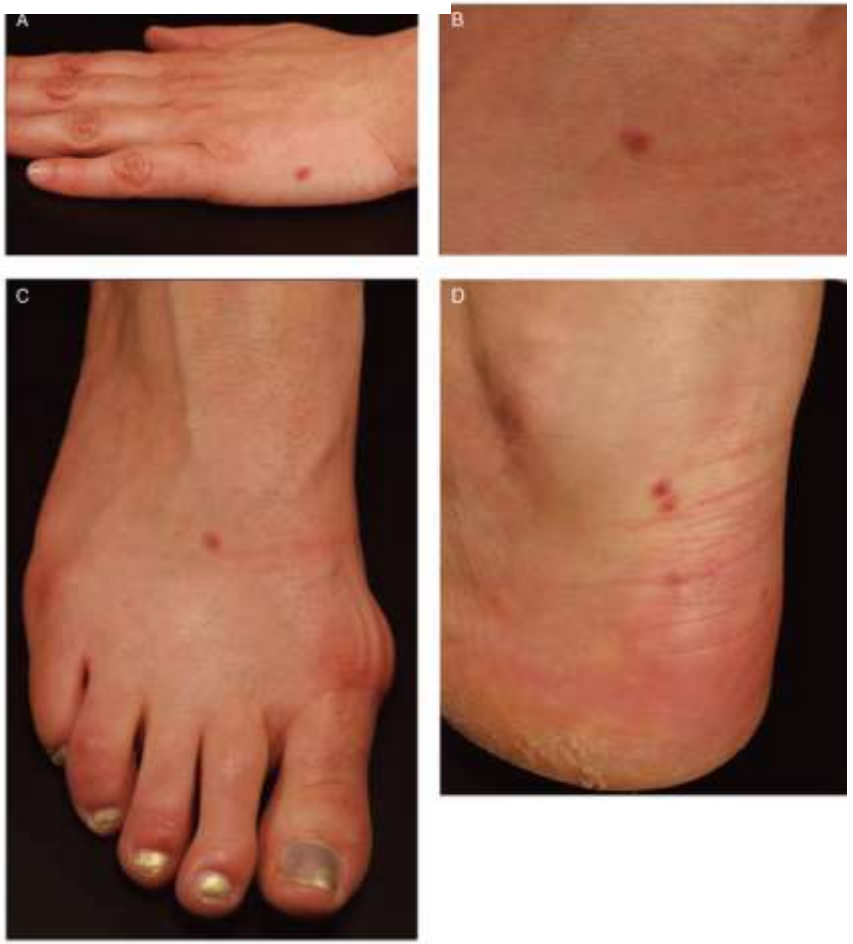
Indolent CD8+ lymphoid proliferation of acral sites: a clinicopathologic study of six patients with some atypical features

Danielle Greenblatt[1], Mina Ally[1], Fiona Child[1], Julia Scarisbrick[2], Sean Whittaker[1], Stephen Morris[1], Eduardo Calonje[3], Tony Petrella[4] and Alistair Robson[3]

Table 1. Clinical data

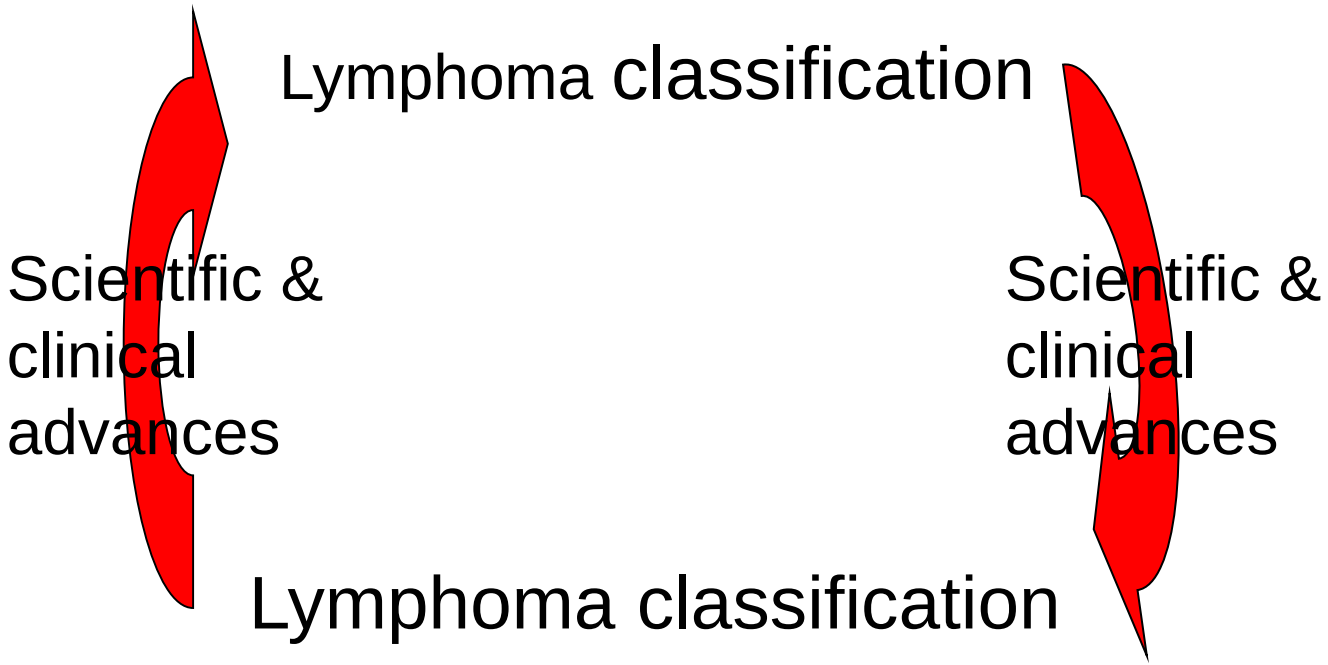
Number	Sex/age	Lesion	Location
1	F/47	Nodule and papules	Nose, hands, feet
2	F/37	Nodule	Left heel
3	F/70	Plaque	Nose
4	M/70	Ulcerated plaque	Left heel
5	F/73	Papule	Nose
6	M/68	Papule	Left ear





J Cutan Pathol 2013: 40: 248–258

Lymphoma classification cycle



HAEMATOPATHOLOGY WHAT NEXT

Revised European and American Lymphoma (REAL) Classicifation

WHO classification 2001

WHO classification 2008

WHO classification update 2016/7

WHO Lymphoma Classification 2023