PATHOLOGIC EVALUATION: LYMPH NODE WITH LARGE CELL LYMPHOMA

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Large cell lymphomas

- Large cells in lymphomas defined as cells which are larger than
  - endothelial cell nucleus
  - histiocyte nucleus
  - >2 x small lymphocyte
- It can arise from different lineage
  - B cell lineage
  - T cell lineage
  - Histiocytic lineage

Large cell lymphoma- B cell origin

Diffuse large B cell lymphoma , NOS	
Morphological variants	Centroblastic Immunoblastic Anaplastic Other rare variants
Molecular subtype	Germinal centre B cell subtype Activated B cell subtype
Other lymphomas of large B cells	
T-cell/histiocytie-rich large cell lymphoma	
Primary diffuse large B cell lymphoma of the CNS	
Primary cutaneous diffuse large B cell lymphoma , leg type	
EBV positive diffuse large B cell lymphoma, NOS	
Diffuse large B cell lymphoma associated with chronic inflammation	
Lymphomatoid granulomatosis	

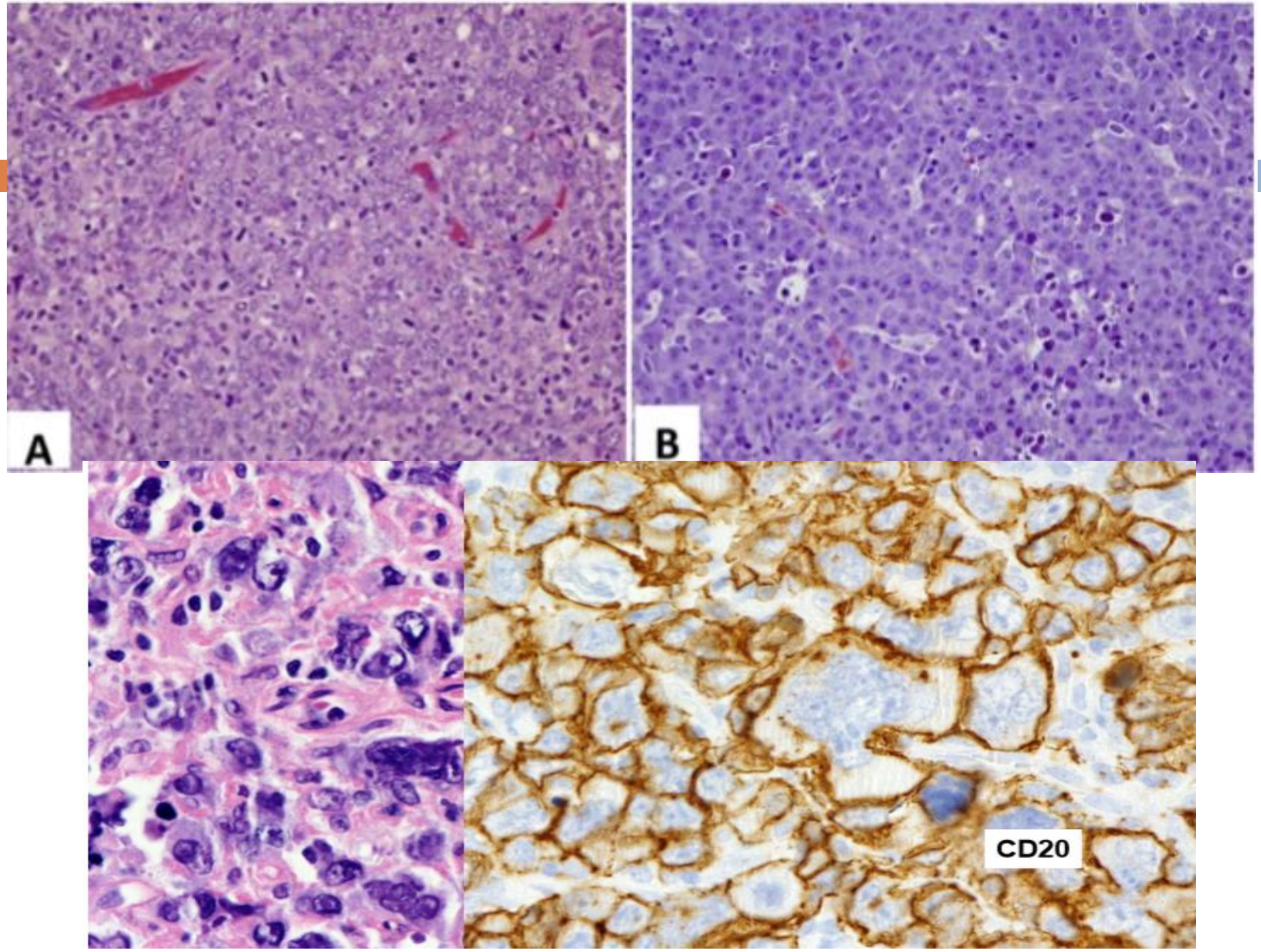
Large B cell lymphoma with IRF4 rearrangements
Primary mediastinal (thymic) large B cell lymphoma
Intravascular large B cell lymphoma
ALK+ large B cell lymphoma
Plasmablastic lymphoma
HHV-8 positive diffuse large B cell lymphoma
Primary effusion lymphoma
High grade B cell lymphoma
High grade lymphoma with MYC and BCL2 and/or BCL6 rearrangements
High grade lymphoma, NOS
B cell lymphoma , unclassifiable
B cell lymphoma, unclassifiable, with features intermediate between diffuse large B cell lymphoma and classic Hodgkin lymphoma

Large cell lymphoma- T cell origin

- ALK+ anaplastic large cell lymphoma
- ALK- anaplastic large cell lymphoma
- Peripheral T cell lymphoma
- Angioimmunoblastic T cell lympoma

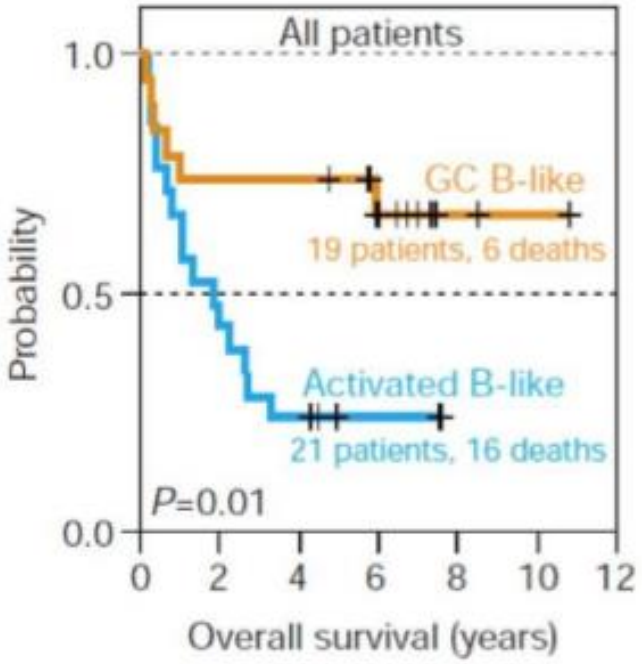
DLBCL, NOS

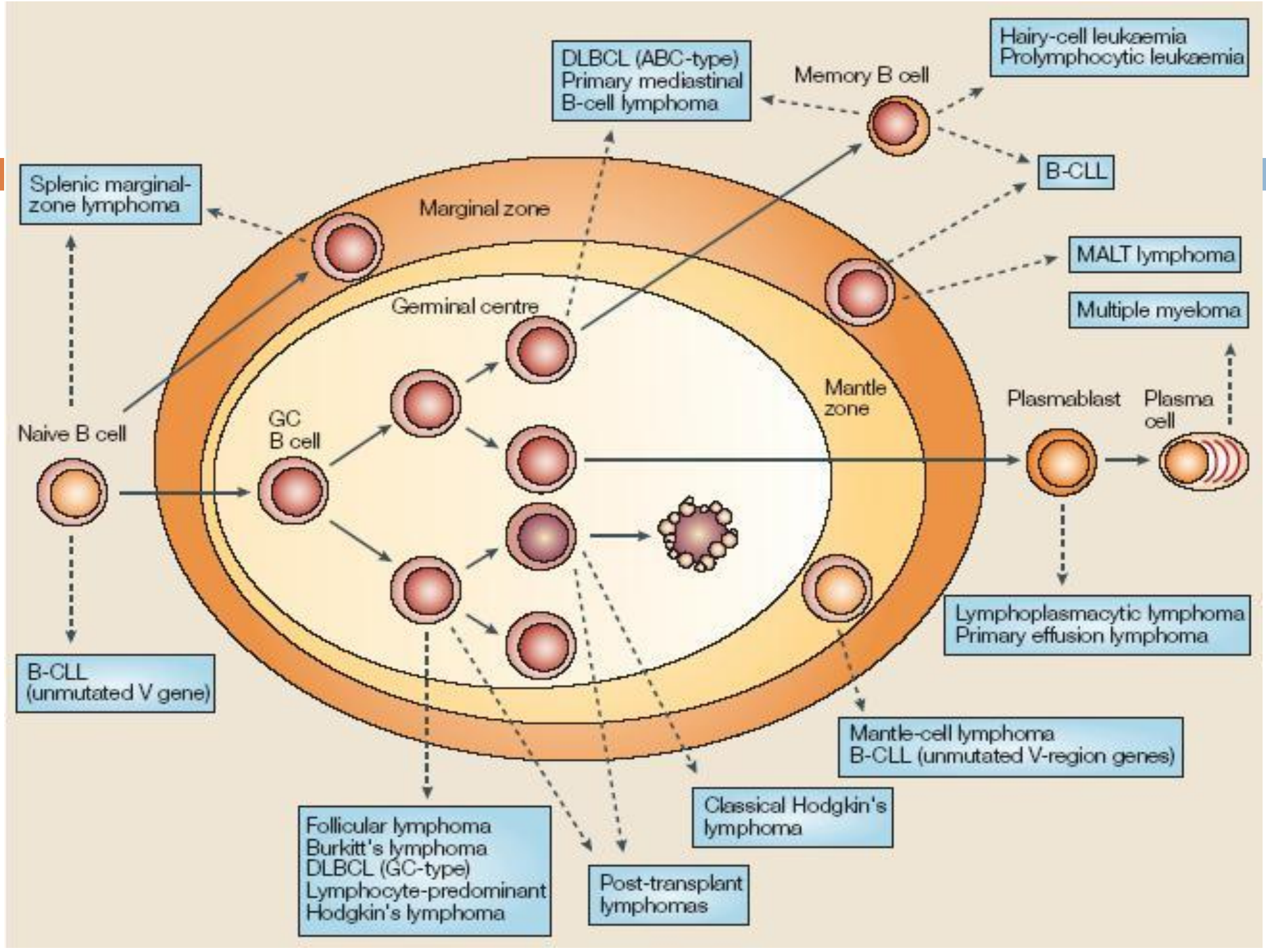
Morphological variant	Centroblastic	Immunoblastic	Anaplastic
1 . Incidence	Most common		
2. Morphology	Large Cells with round to oval nuclei, vesicular chromatin with peripherally arranged 2-3 nucleoli	When >90% cells are immunoblastic with centrally located prominent nucleoli and basophilic cytoplasm	Large oval or polygonal cells with bizzare pleomorphic nuclei
3.Prognosis	Relatively better	poor	worse
4.Characterstics		Associated with MYC translocations	CD 30 and EMA positive in many cases


A
B
CD20

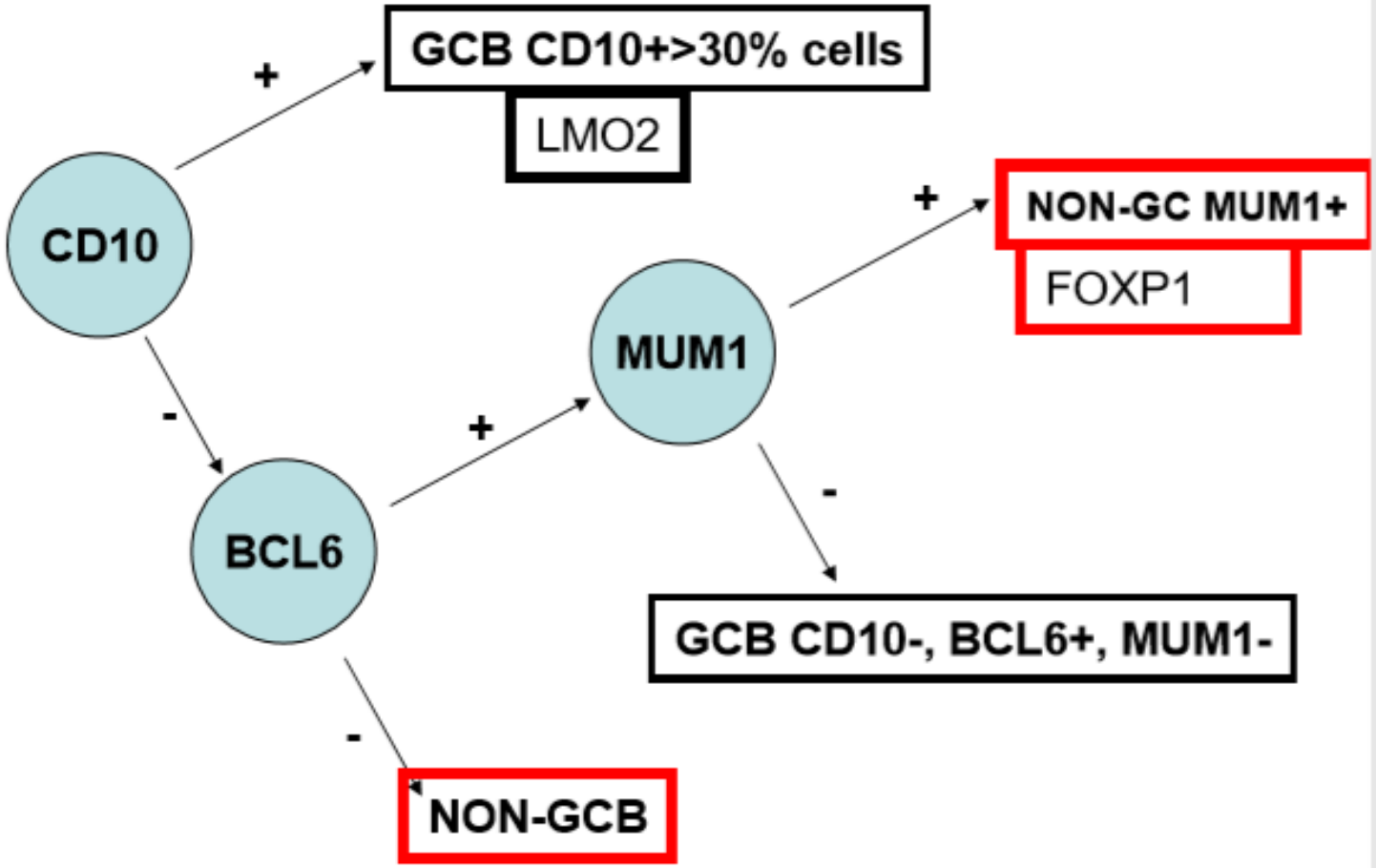
DLBCL, NOS- Cell of origin classification

- Molecular subtype
  - Germinal centre like
  - Activated B cell type
- Highly predictive of outcome
- Gene expression profiling is best method
- Not available for routine testing
- IHC determination for cell of origin has been done
- Immunohistochemistry panel- CD20,CD3,CD5, CD10, CD45, BCL2, BCL6 MUM1, cMYC, Ki-67




DLBCL (ABC-type)
Primary mediastinal
B-cell lymphoma
Memory B cell
Hairy-cell leukaemia
Prolymphocytic leukaemia
Splenic marginal-
zone lymphoma
Marginal zone
B-CLL
MALT lymphoma
Germinal centre
Multiple myeloma
Mantle
zone
Plasmablast
Plasma
cell
Naive B cell
GC
B cell
Lymphoplasmacytic lymphoma
Primary effusion lymphoma
B-CLL
(unmutated V gene)
Mantle-cell lymphoma
B-CLL (unmutated V-region genes)
Classical Hodgkin's
lymphoma
Follicular lymphoma
Burkitt's lymphoma
DLBCL (GC-type)
Lymphocyte-predominant
Hodgkin's lymphoma
Post-transplant
lymphomas

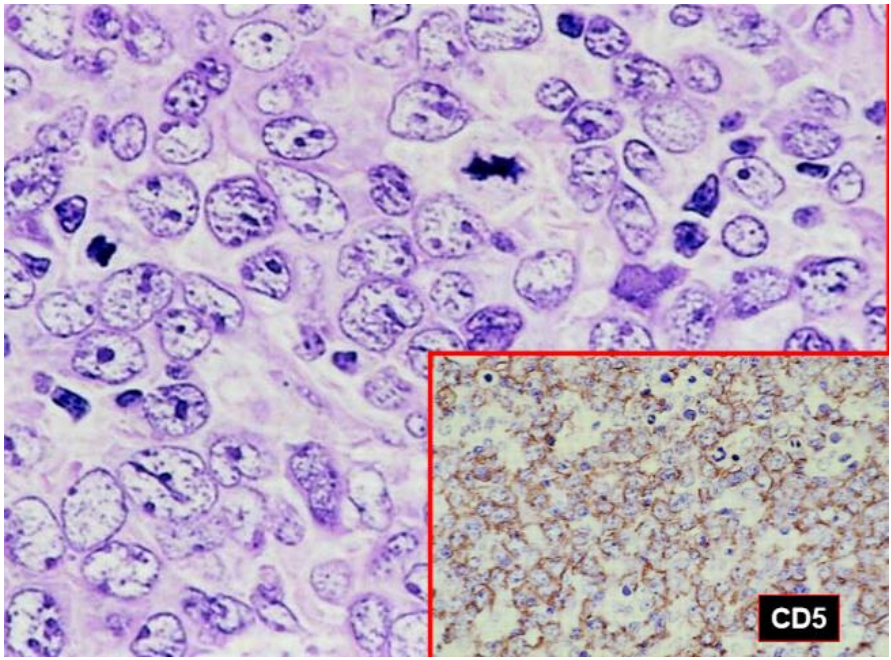
Subgrouping by Hans classifier



Blood, 103:275-82, 2004

CD 5 + DLBCL

- Higher age distribution (66 years)
- Female predominance
- Advanced disease
- Common in HIV patients
- Aggressive clinical course
- D/D
  - Mantle cell lymphoma
    - Blastoid variant
    - Cyclin D1 positive
  - CLL/SLL transformation
    - History of low grade lymphoma



Double expressor DLBCL

- Increased expression of MYC or BCL 2 proteins by IHC in presence or absence of translocations
- Criteria for positivity
  - 40% MYC expressing cells
  - >50% BCL2 expressing cells
- Found in 30-40% cases of DLBCL
- Poor prognostic factor, not a separate entity
- They are mainly NGC type

High grade lymphoma

- Replacing " B-cell lymphoma unclassifiable with features intermediate between DLBCL and BL" (WHO 2008)
- Older age, aggressive and extensive clinical course(BM, extranodal, LDH)
- Two new categories
  - HGBL with MYC and BCL2 and /or BCL6 rearrangements (HGBL-DH)
  - HGBL , NOS

HGBL-DH

- Presence of MYC and BCL2 and/or BCL6 rearrangements
- Inclusion
  - DLBCL with DH/TH genetic constitution
  - BCL-U(WHO 2008) with DH/TH genetic constitution
  - BCL- Blastoid morphology with DH/TH genetic constitution
- Features
  - MYC/BCL2 DH or MYC/BCL2/BCL6 TH mainly GCB type DLBCL
  - MYC/BCL6 DH mainly ABC type DLBCL

FISH testing for HGBL-DH

1. Test all DLBCL
2. Test on GCB-type DLBCL
   - Missed *MYC/BCL6* DHL
3. MYC-immunohistochemistry (IHC) first
   - MYC-IHC+ (cut-off 40%) → 88% of rearrangement identified by FISH
4. MYC-IHC + Ki-67-IHC (>80%)
   - Many DHL/THL have lower Ki-67 proliferation index

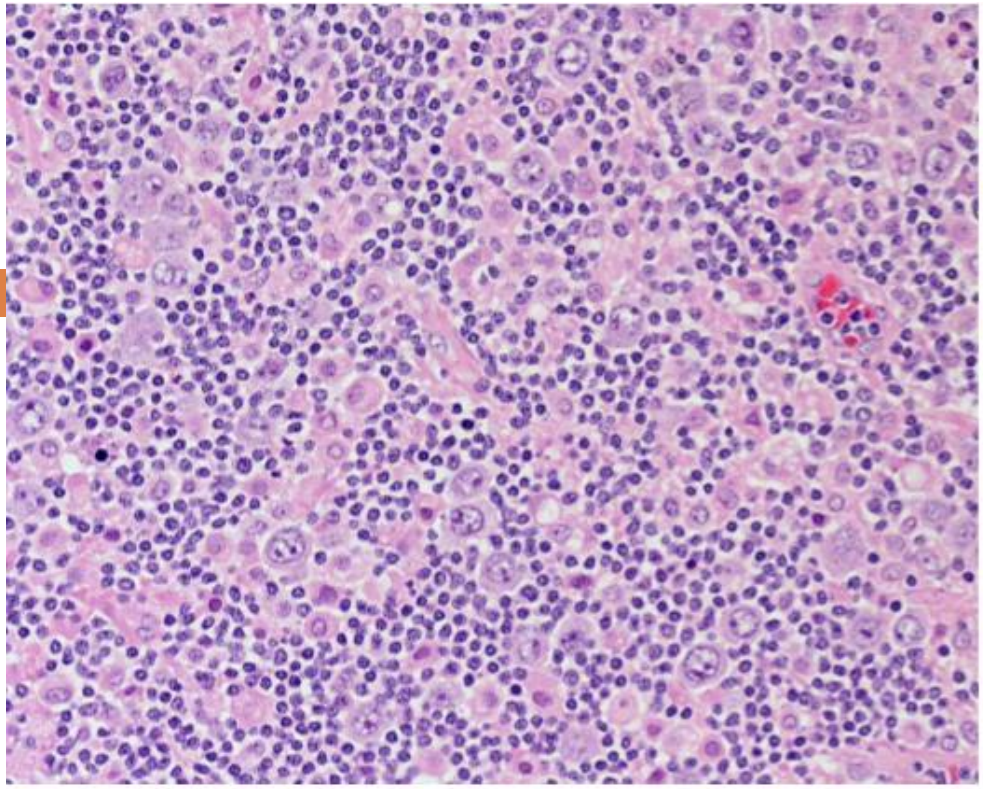
Blood. 2017;129(3):280-288

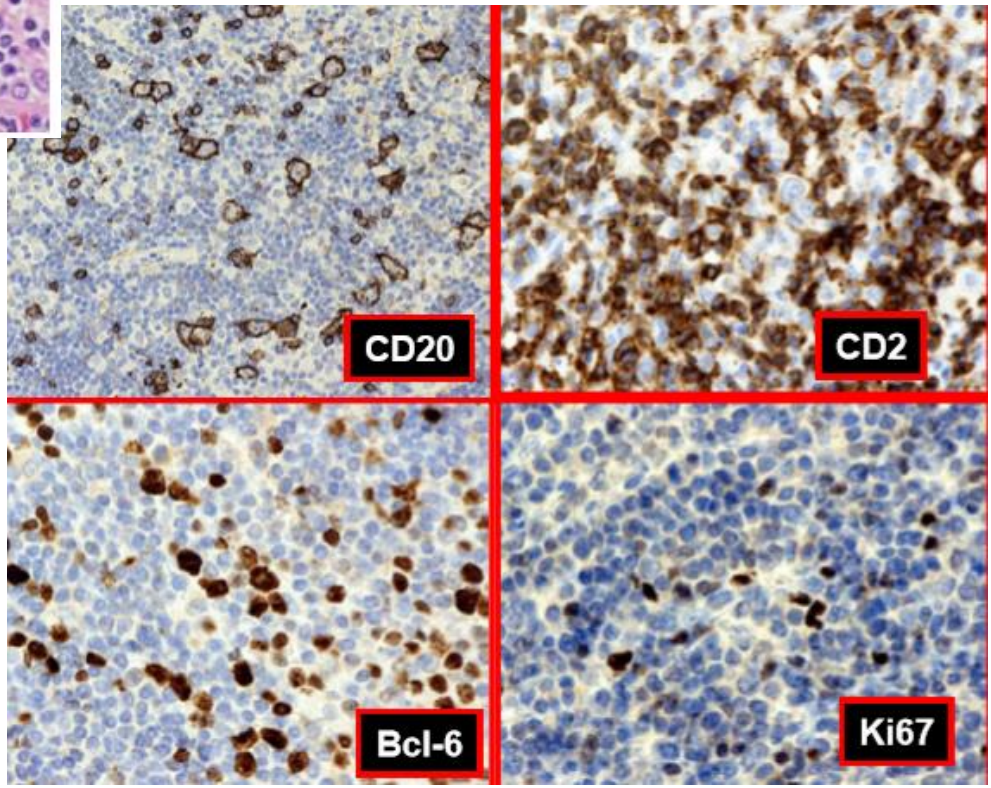
B cell Lymphoma, Unclassifiable

- Features intermediate between diffuse large B cell lymphoma and classic Hodgkin lymphoma
- A/C grey zone lymphoma composed of large cells in diffuse sheets
- Include cases
  - With morphology as PMBL with CD 15 positive or CD20 negative
  - With CHL morphology CD 20 and LCA positivity along with CD 30 and CD15 positive
- Poor prognosis

T cell rich B cell lymphoma

- Minor component of large malignant B-cells in a T-cell/histiocyte rich background
- Mainly high stage ,Bone marrow, liver spleen involved at diagnosis in up to 60% cases
- Refractory to therapy
- Large cells may be RS like, centroblast/immunoblast like, or resemble L&H cells should be distinguished from TCRHBCL like NLPHL



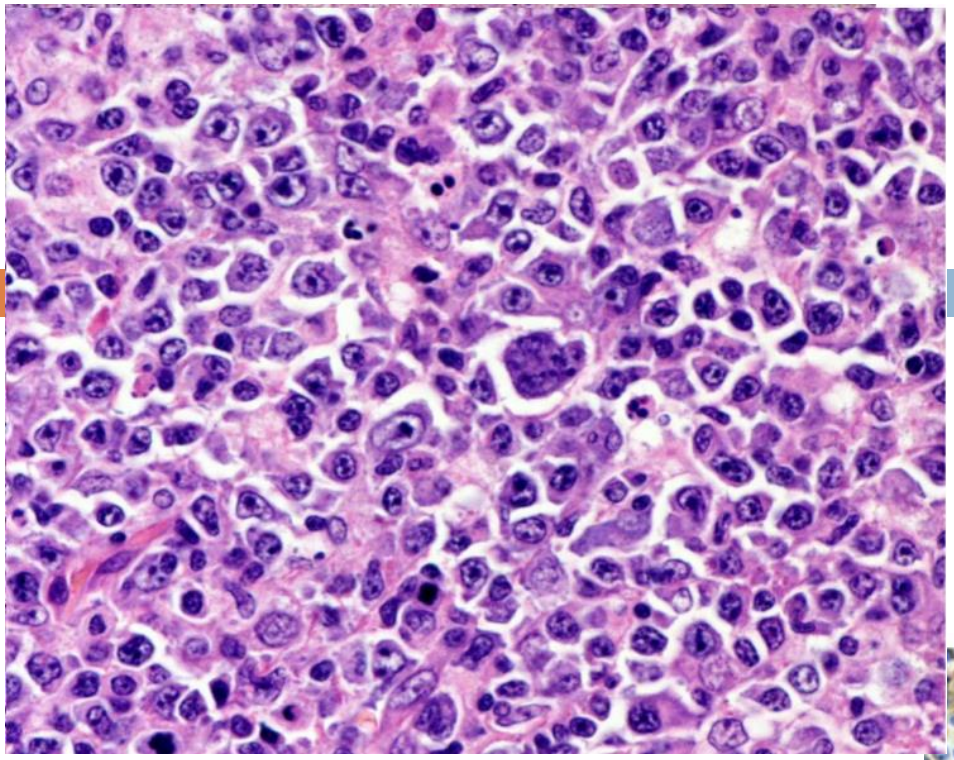

CD20
CD2
Bcl-6
Ki67

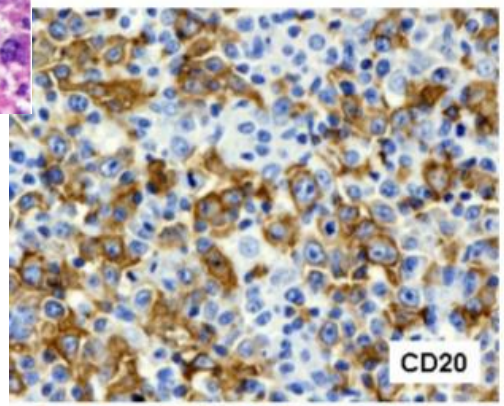
NLPHL(TCRBCL like) and THRBCL

	NLPHL	THRBCL
Malignant cells	LP cells	Scattered B cells
Morphology	Although diffuse but single nodule should be present	Diffuse
Reactive backgroud cells	B cells	T cells
IHC	Large cells Pan B markers and background cells are PD 1 positive rosette around large cells	Large cells Pan B markers but background cells are Pan T positive (CD8>CD4)
Follicular dendritic meshwork	Residual present(CD 21/23 positive)	absent
EBER	absent	rare

EBV+ DLBCL, NOS

- Previously called EBV +DLBCL of elderly
- Mostly NGCB type
- Positive for MUM1 and CD30 and negative for CD10 and BCL6
- EBER marker are consistently positive.
- 70% are extranodal
- Poor prognosis
- More refractory to initial therapy

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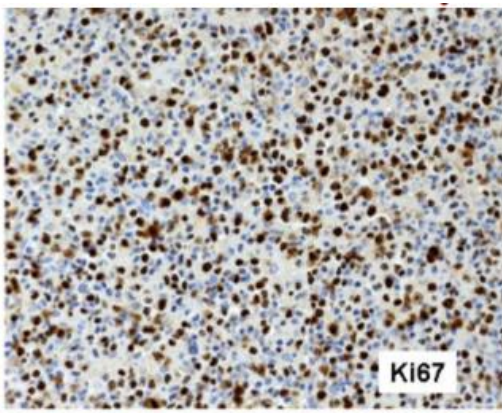
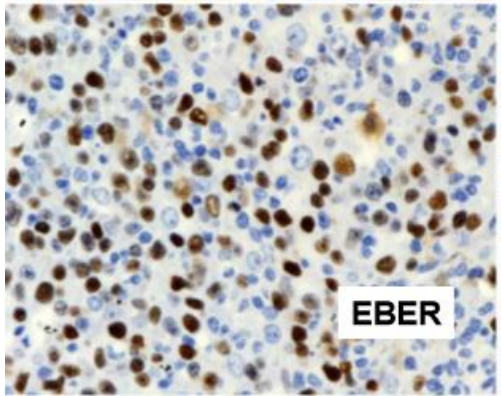
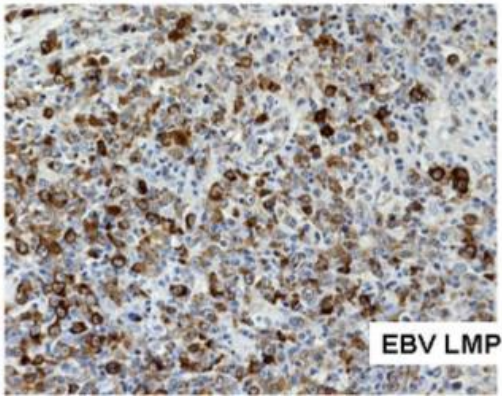
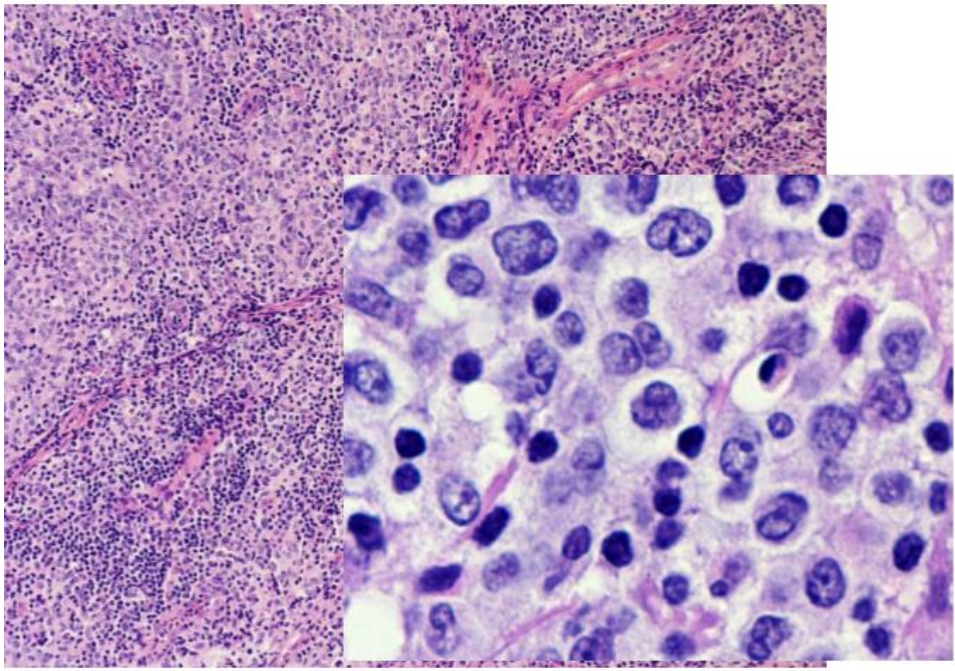

Ki67


EBER


EBV LMP

Primary mediastinal LBCL

- Arising in mediastinum from thymic B cell
- Female predominance, often bulky disease
- Aggressive, but more favorable prognosis than previously thought with intensive chemotherapy
- Immunohistochemistry
  - CD30 in 80%
  - CD23 in 70%
  - MAL in 70%
- lack BCL2, BCL6 or MYC rearrangements

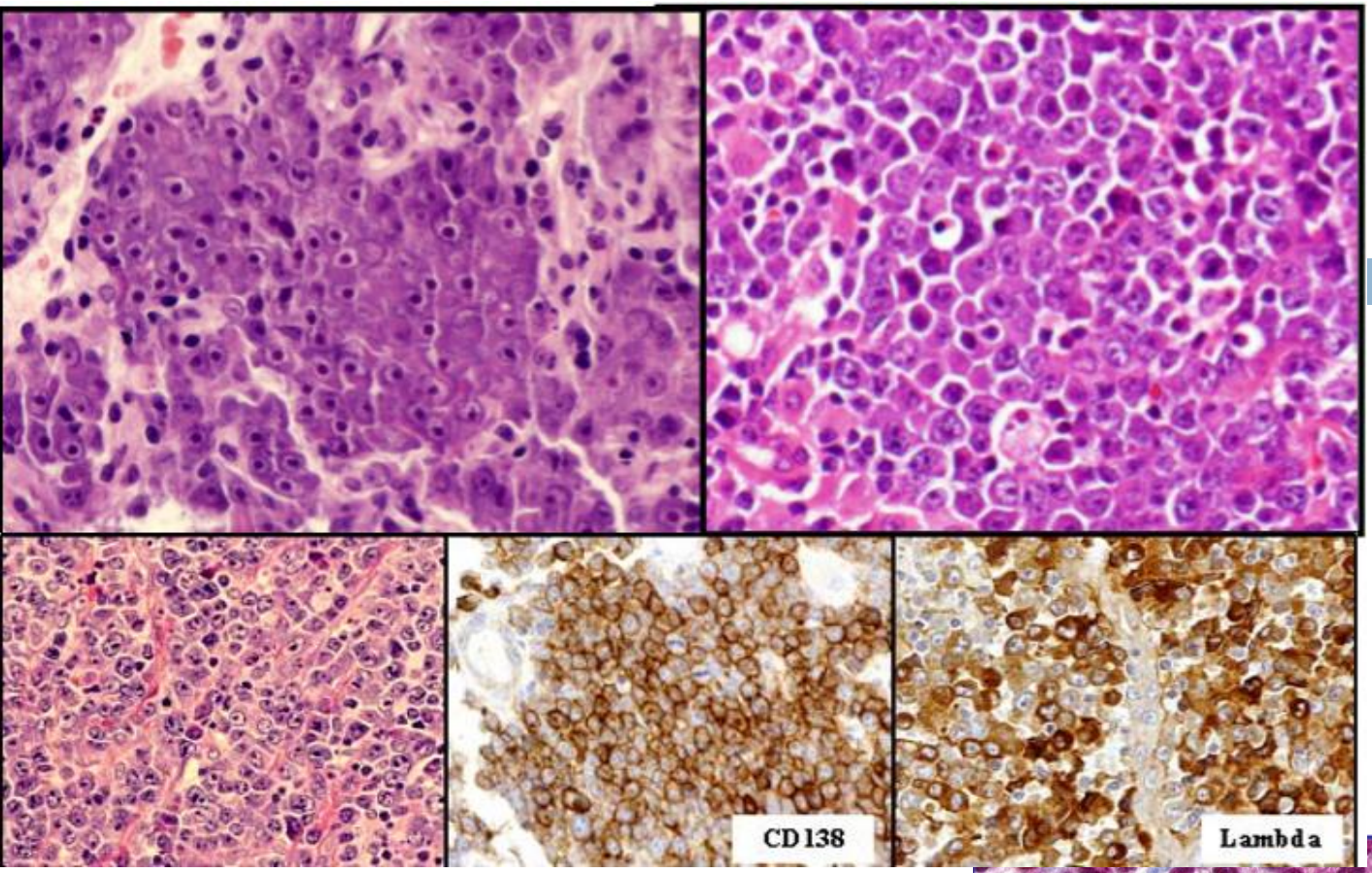


Plasmablastic lymphoma

- Diffuse large B cells which resemble B immunoblasts
- Aggressive clinical course
- Associated with HIV
- More are at stage IV at diagnosis
- Majority are EBV+, KSHV-/+
- Frequent Myc/IgH rearrangements
- CD45-, CD20-, PAX 5 -
- CD 79a in 50-85%
- CD38, CD138, MUM1, EMA are positive

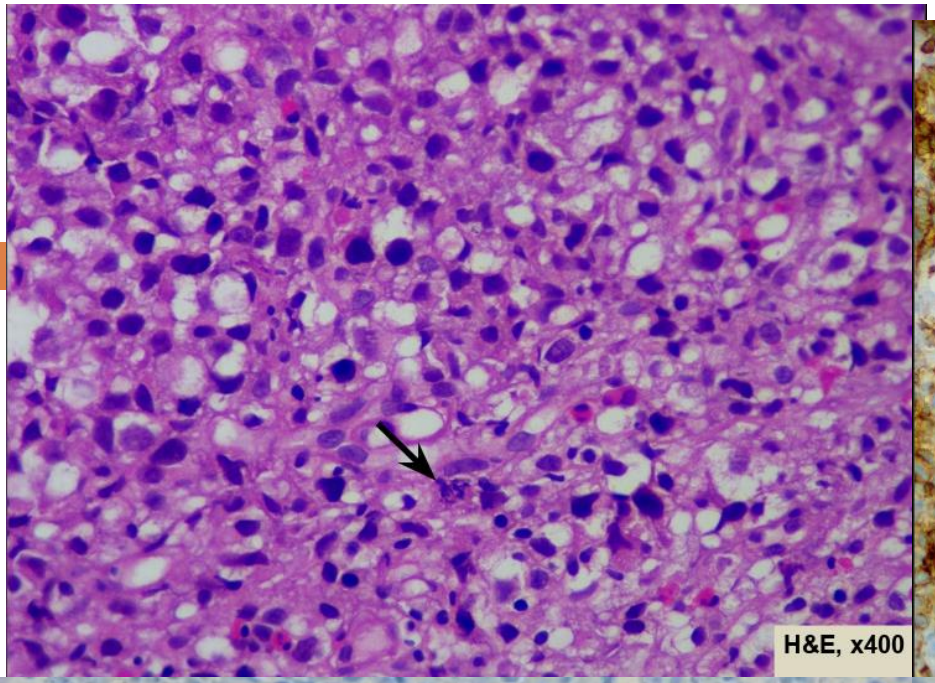
Differential diagnosis

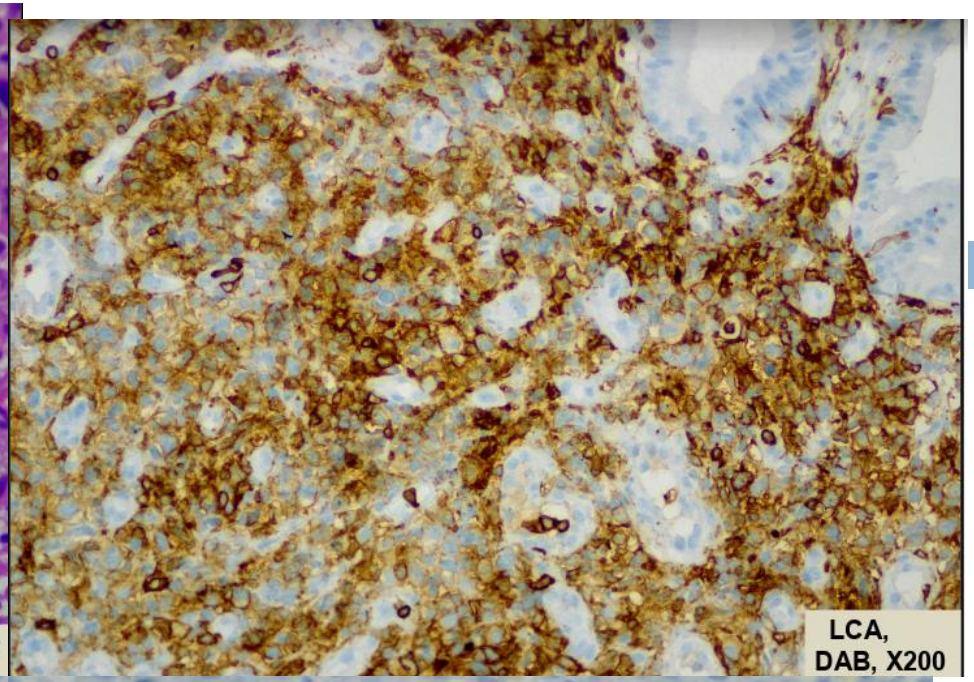
	Plasmablastic lymphoma	Plasmablastic myeloma
CD38	+	+
CD138	+	+
MUM1	+	+
CD79a	+(40%)	-/+
CD 56	-	+
EBV	+	-
ki67	>90%	+/-

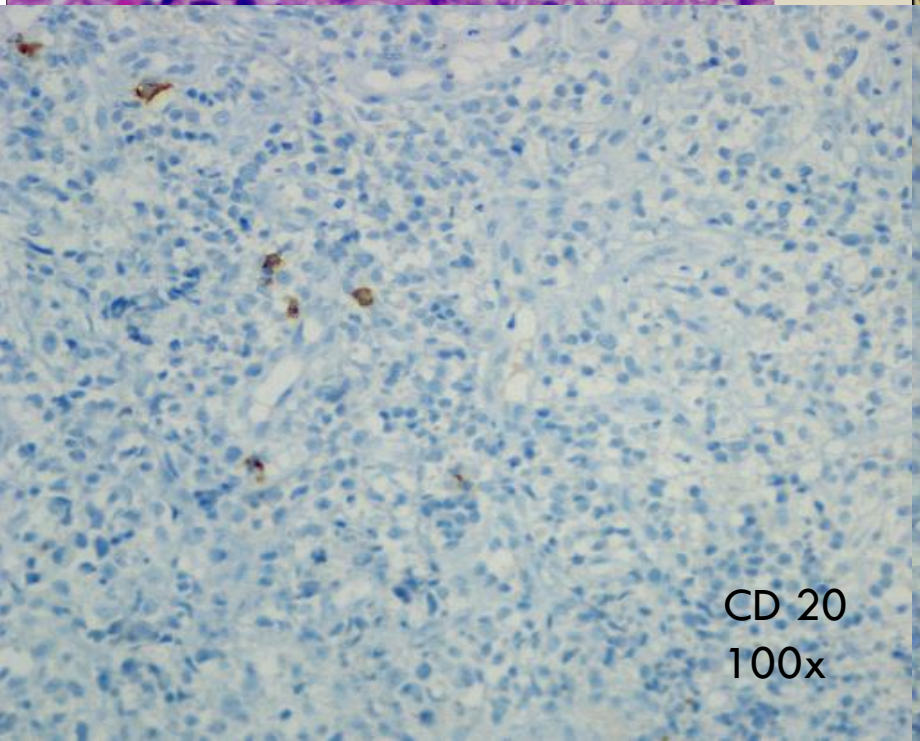

CD138
Lambda
MUM1
EMA

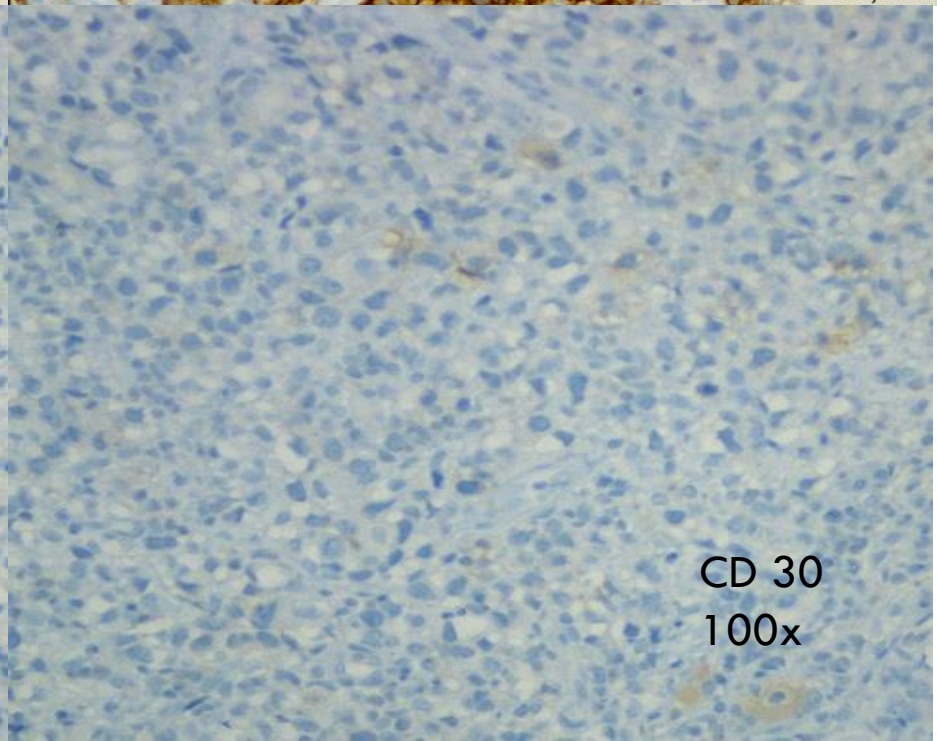
ALK + LBCL

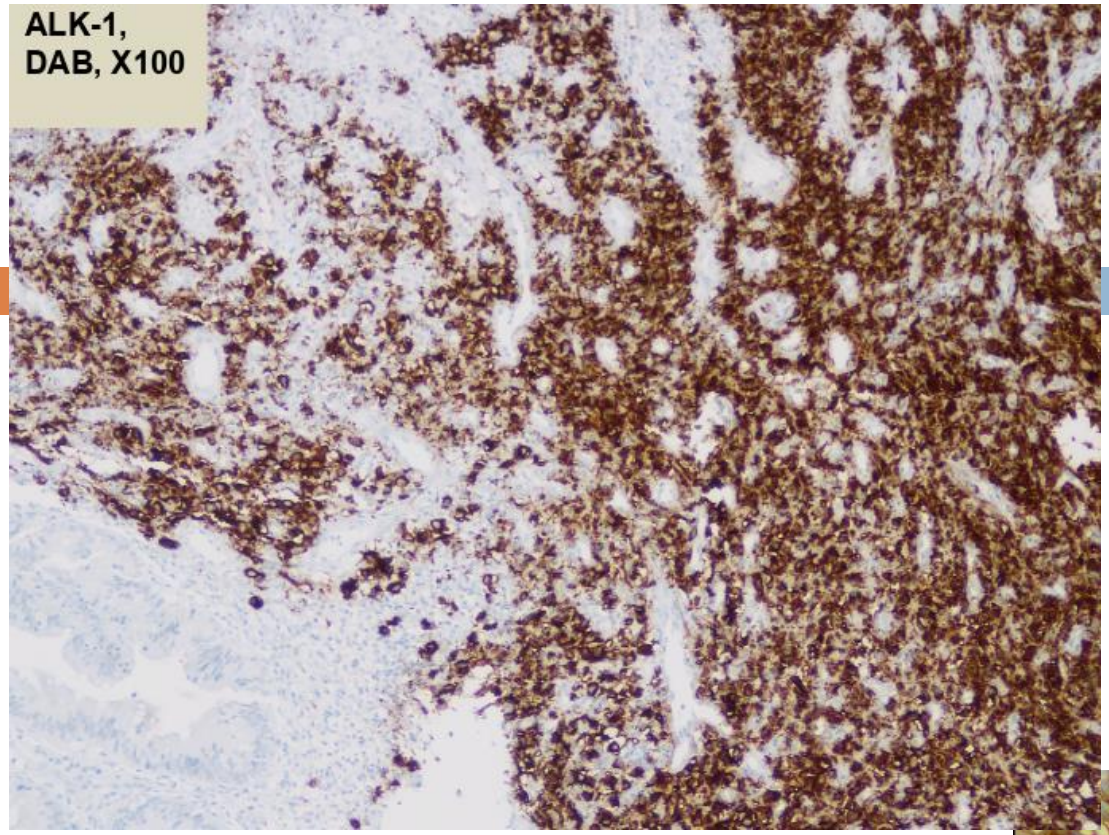
- Immunoblastic or plasmablastic morphology
- Involve subcapsular sinuses of lymph nodes
- Present with generalized lymphadenopathy
- Advanced stage
- M.C t(2;17)(p23;q23) fusion of ALK and clatherin gene cytoplasmic granular staining
- Rare t(2;5) with NPM/ALK nuclear and cytoplasmic staining

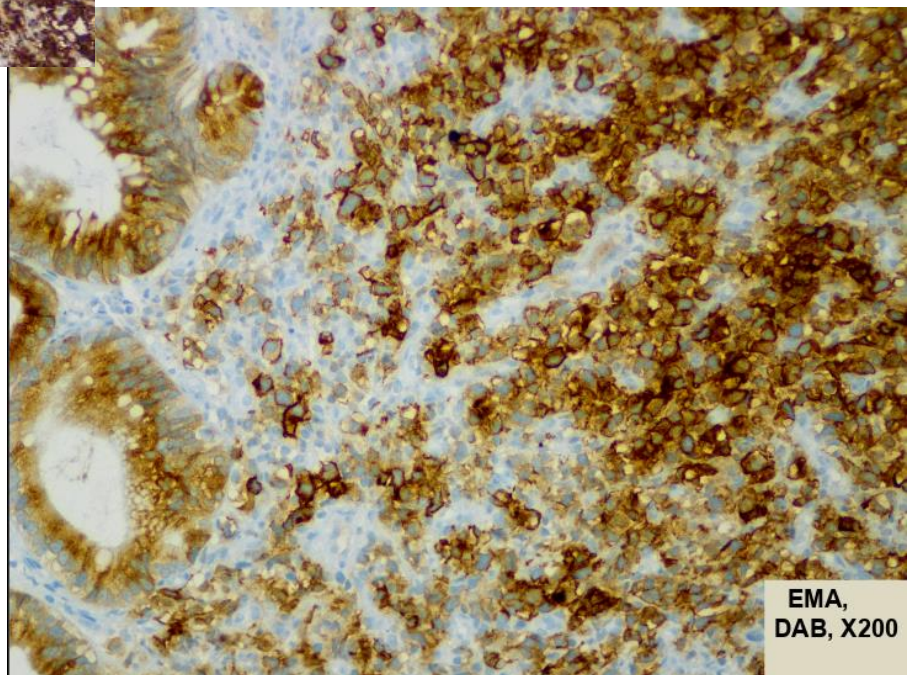

H&E, x400


LCA,
DAB, X200


CD 20
100x

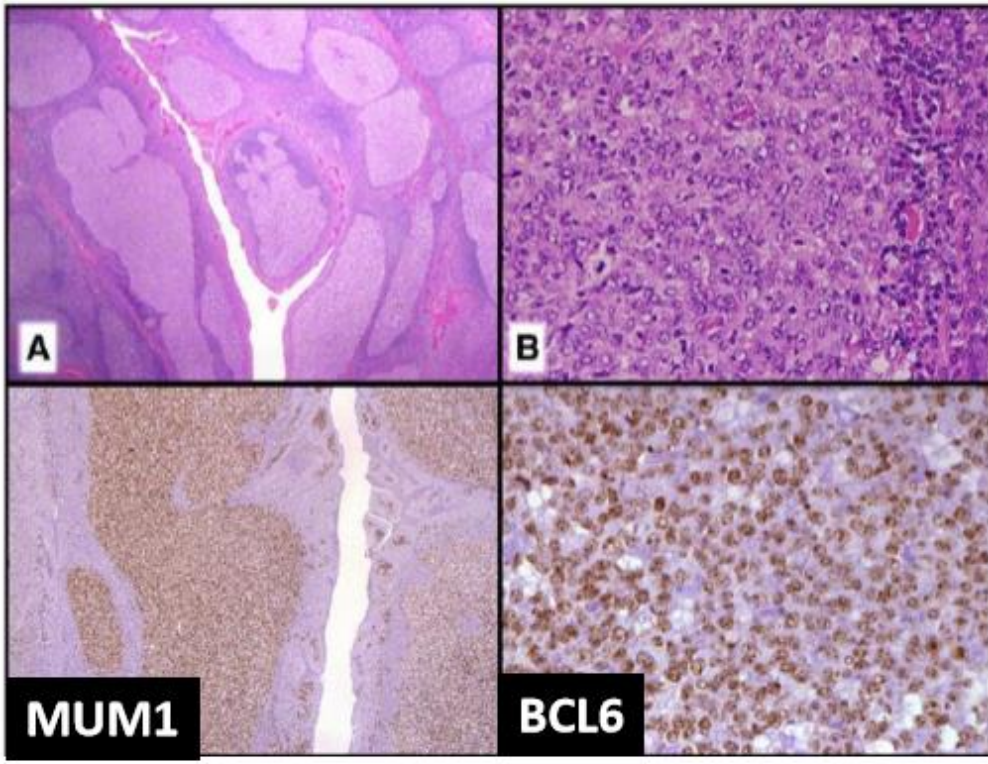

CD 30
100x


ALK-1,
DAB, X100


EMA,
DAB, X200

IRF4 –rearranged large B cell lymphoma

- Children and young adults
- Waldeyer ring, cervical LNs
- Follicular, follicular & diffuse, or diffuse
- MUM1+/BCL6+/Ki-67-high
- BCL2+, CD10+ in > 50%
- *IGH/IRF4* rearrangements common
- No *BCL2* rearrangements
- Favorable prognosis

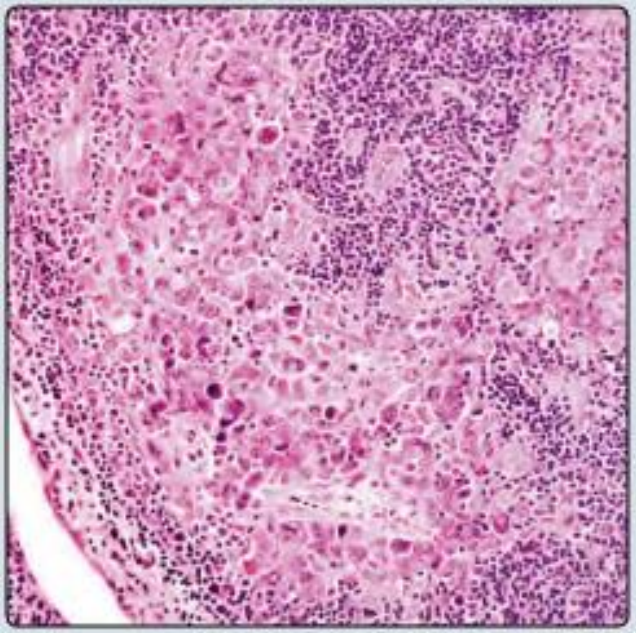


Large cell lymphoma- T cell origin

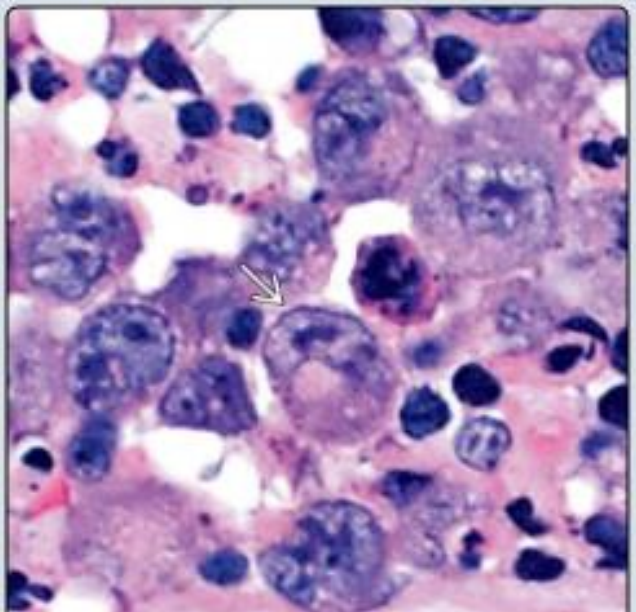
Anaplastic large cell lymphoma

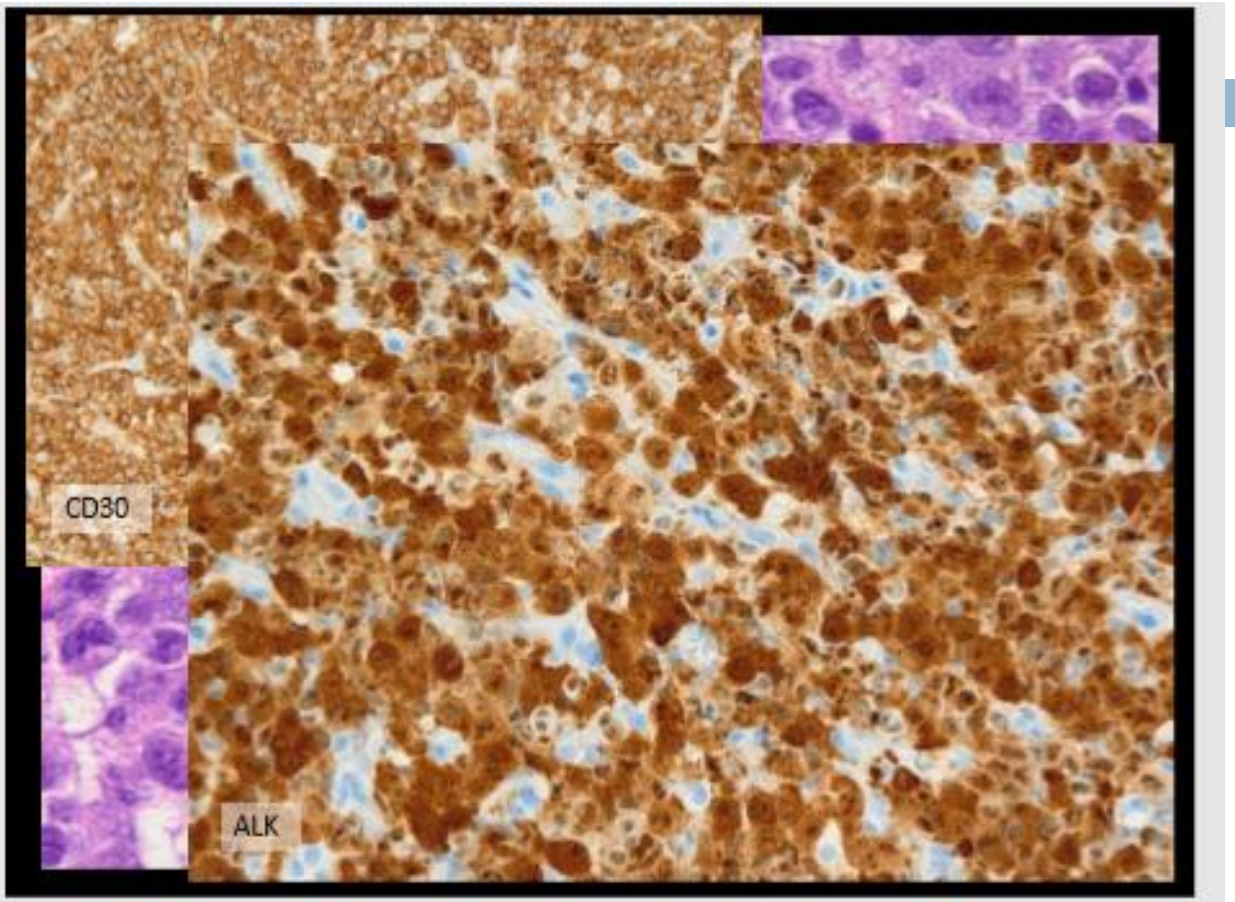
- T/null phenotype
- Aggressive disease with nodal and extranodal involvement
- Translocations involving ALK gene most commonly NPM-ALK
- Heterogenous histology with predominant sinousoidal pattern
- Hallmark cells are characteristic
- ALK positivity good prognosis

ALK(+) ALCL Involving Lymph Node



ALK(+) ALCL: Hallmark Cells

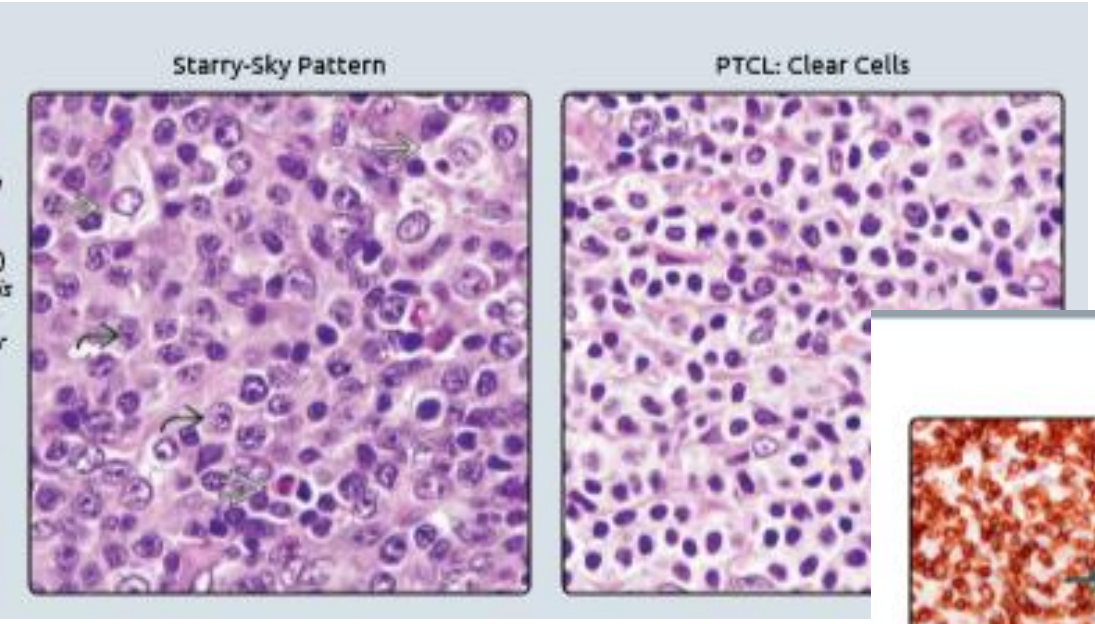


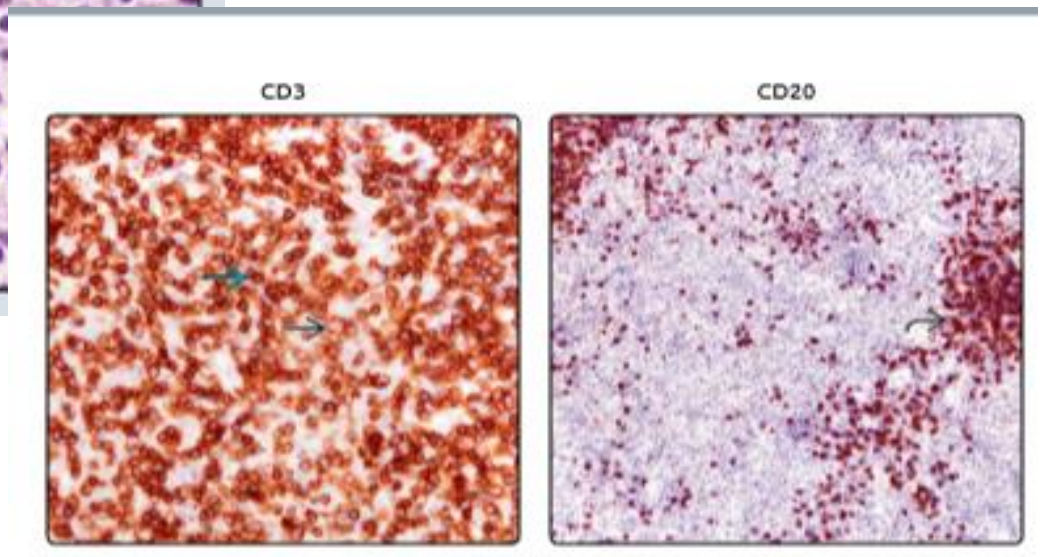


-	ALK+ALCL	ALK-ALCL
Age	25-35 years	55-60years
Extranodal involvement	60%	20%
Stage at diagnosis	III-IV	III-IV
PAX-5	Negative	Negative
CD15	-/+	+ (small subset)
CD30	+	+
CD3	- (75%)	+/-
Cytotoxic markers	+	+
CD43	+	+
EMA	+	+
Prognosis	Good	poor

PTCL ,NOS

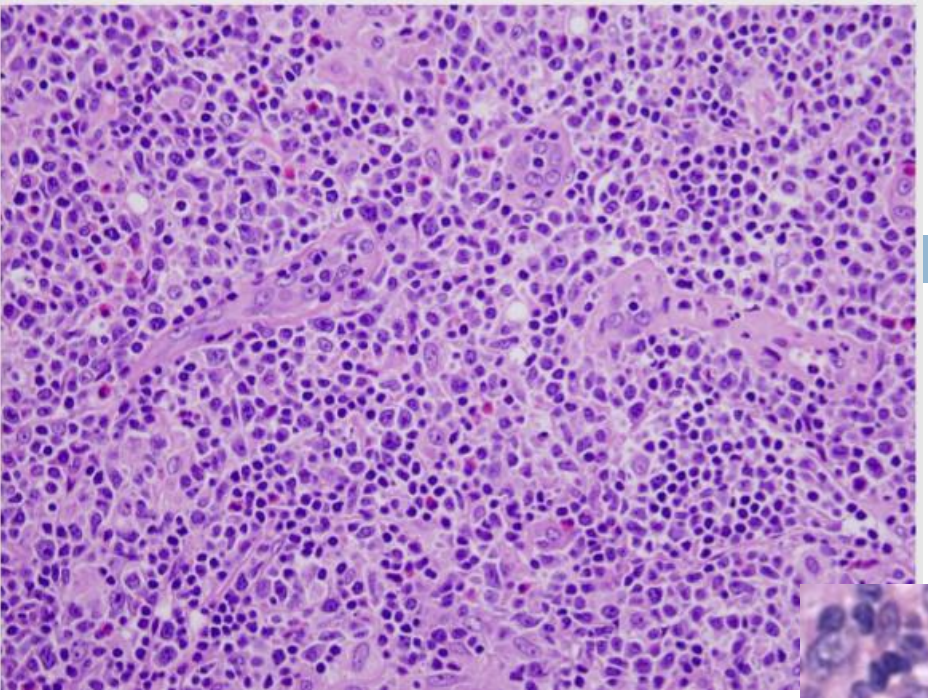
- Aggressive, poor prognosis
- Multiple large cells with pleomorphic nuclei

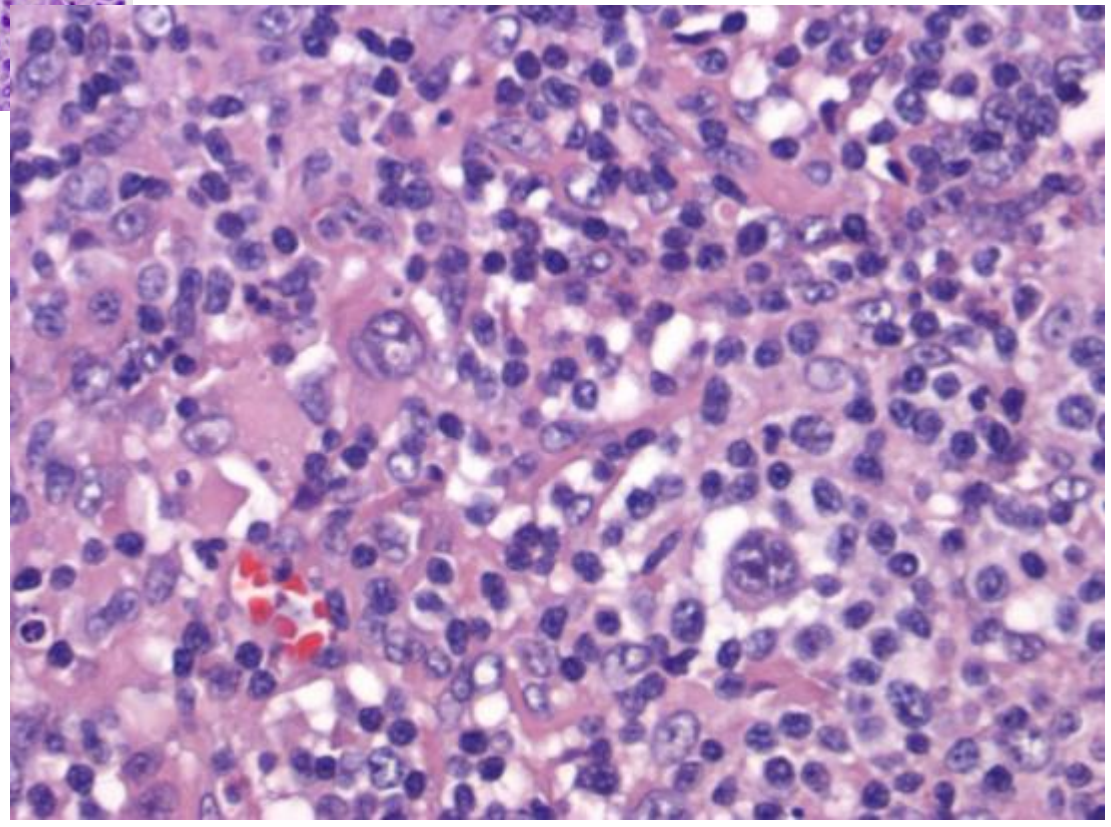




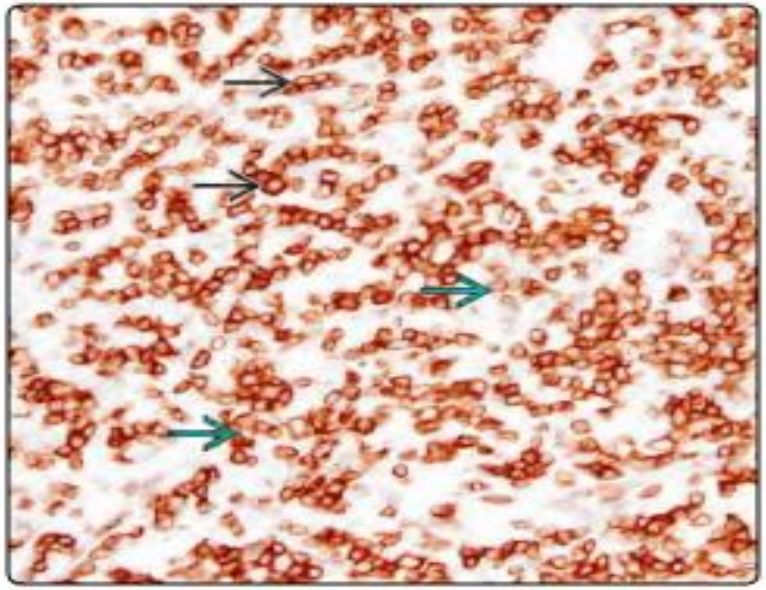
Angioimmunoblastic Lymphoma

- Generalized lymphadenopathy
- Hepatosplenomegaly
- Nodal architecture is partly effaced
- Regressed or absent follicles
- Scattered RS like cells (EBV driven large B cells)
- Prominent arborizing high endothelial venules
- Aggressive

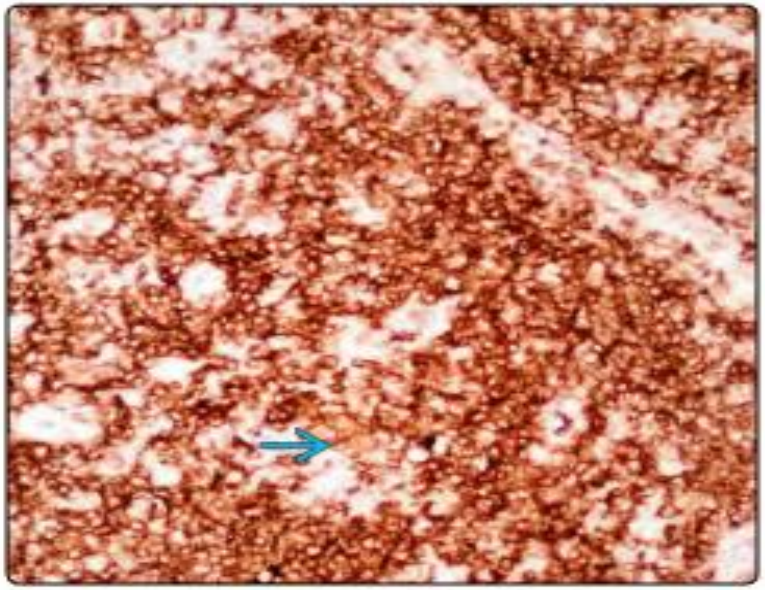




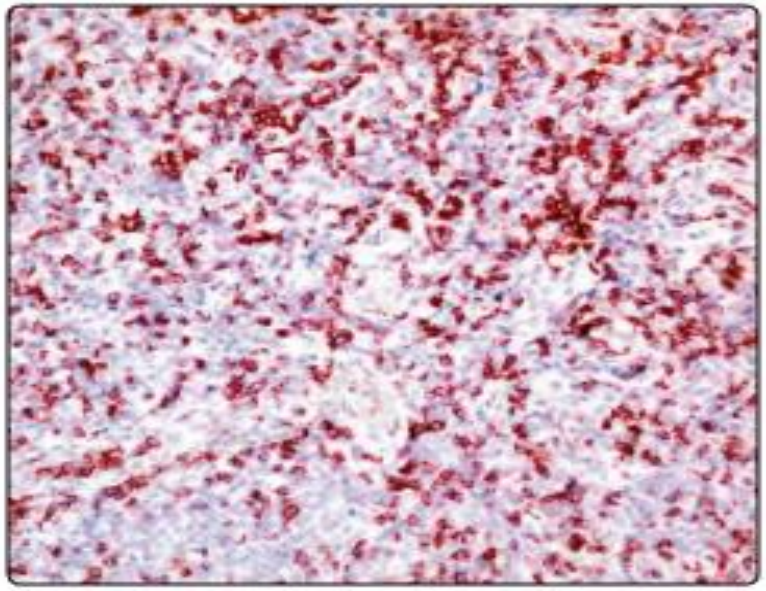
AITL: CD3



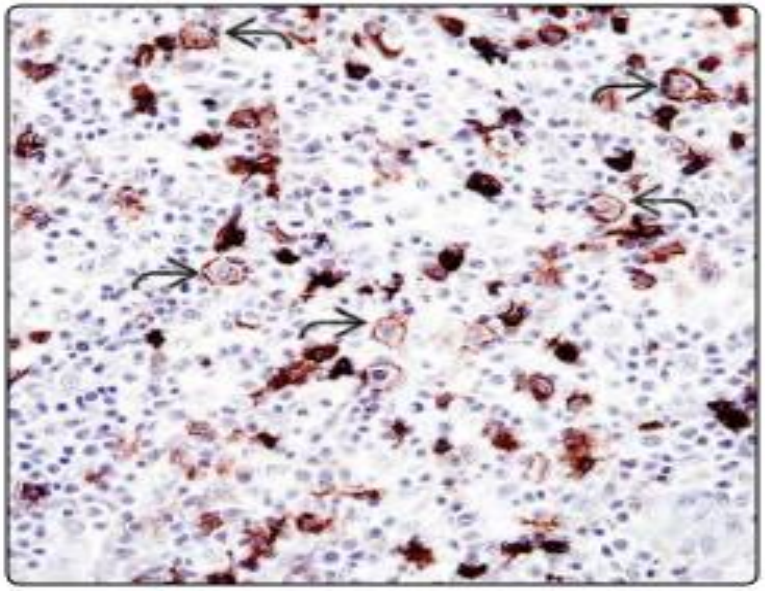
AITL: CD4



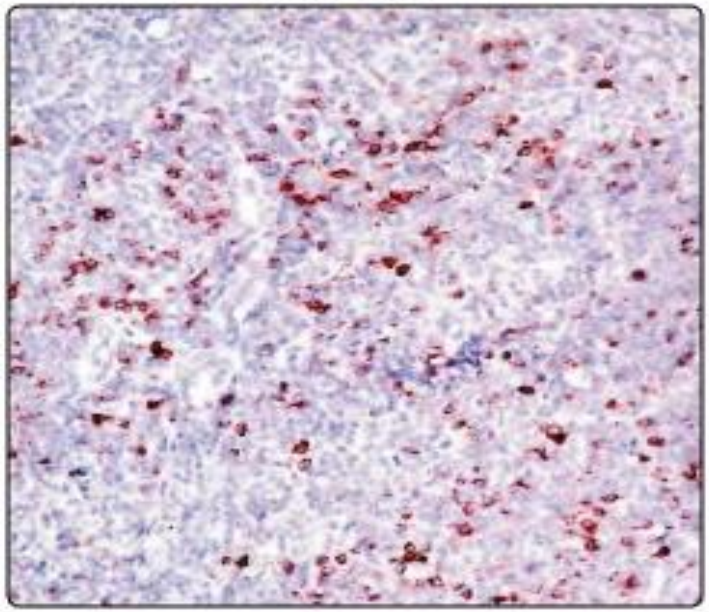
AITL: CD8



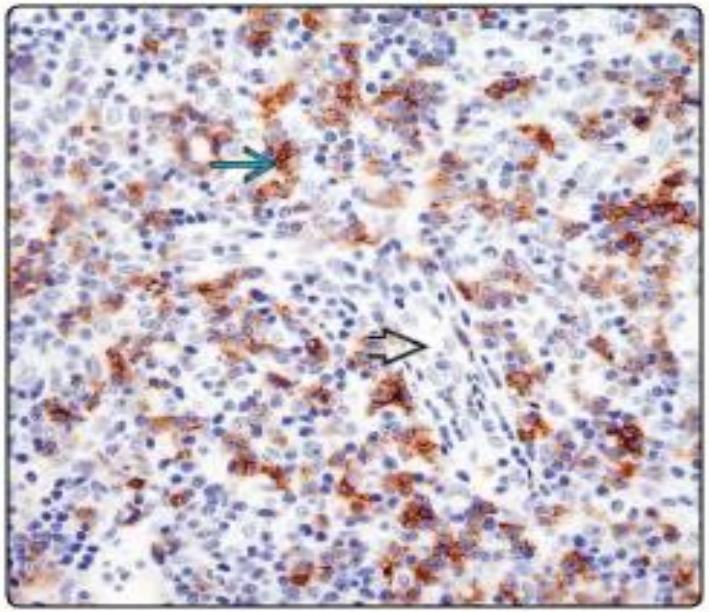
AITL: CD20



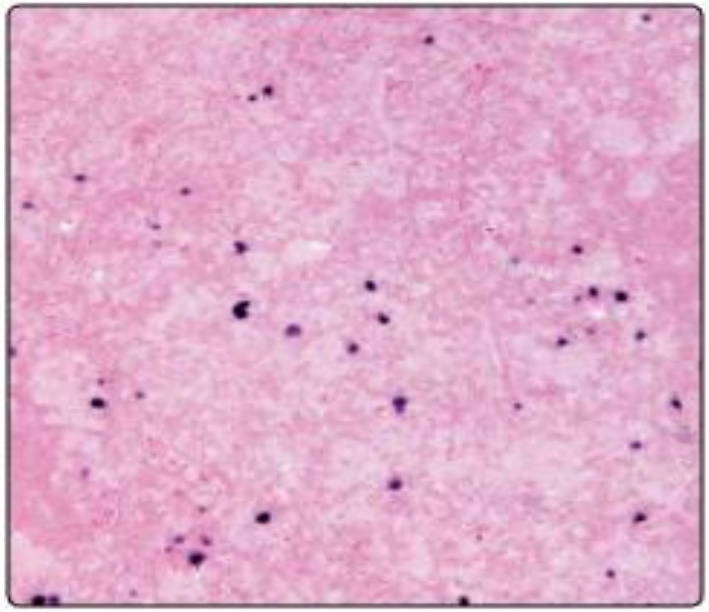
AITL: CD10



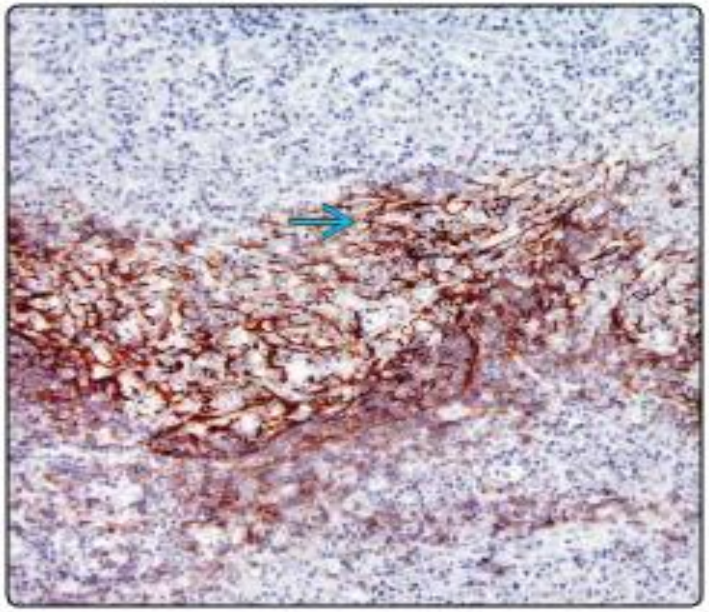
AITL: PD-1



AITL: EBER



AITL: CD21



THANK YOU

Joke of the day

I have chinese friend named Fang. At an official function ,we were having snacks.

I asked him," Fang, do you ever get fed up of people saying that all chinese look the same?"

He replied,"Fang has gone to the washroom. I am his wife".