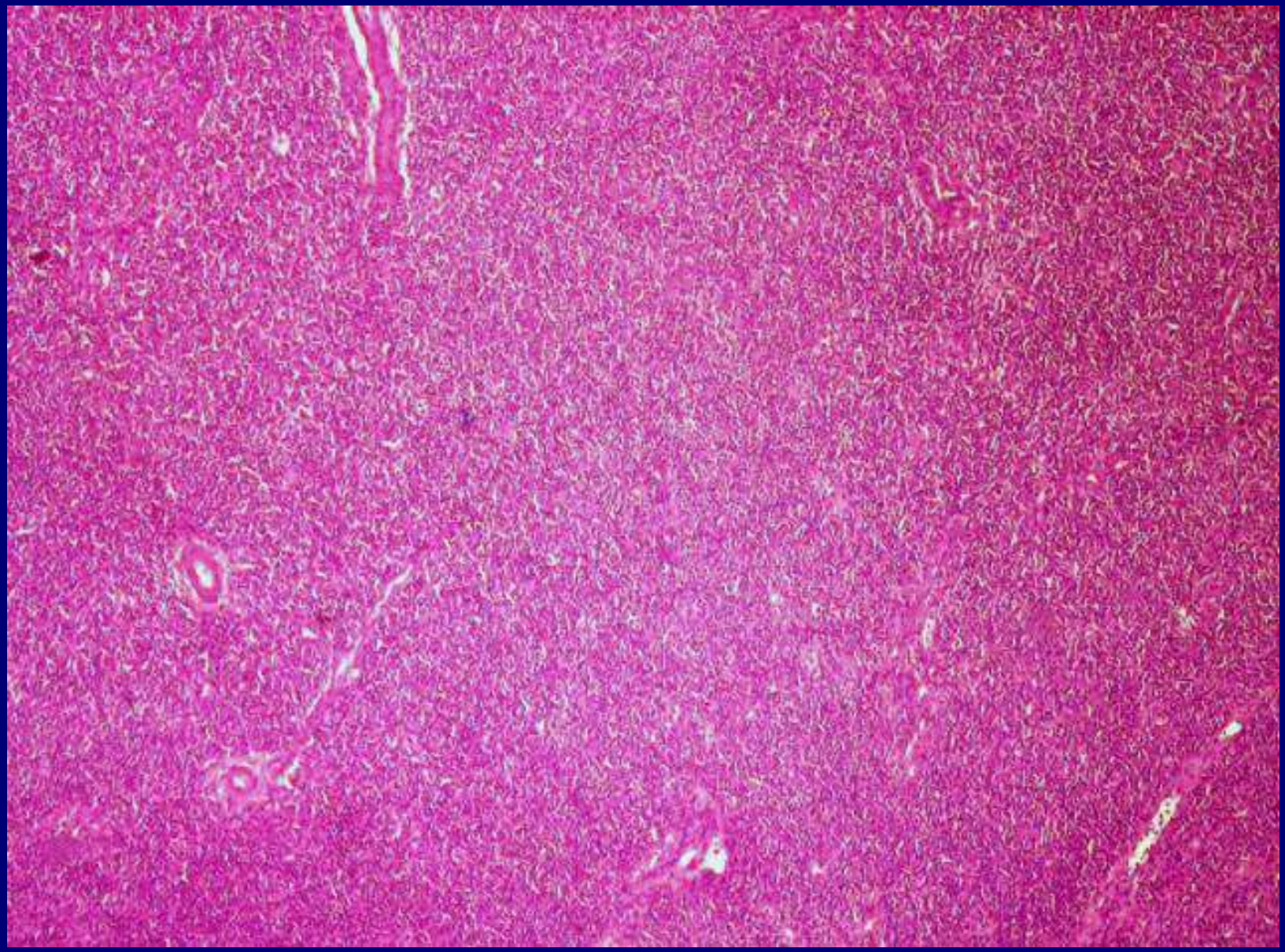
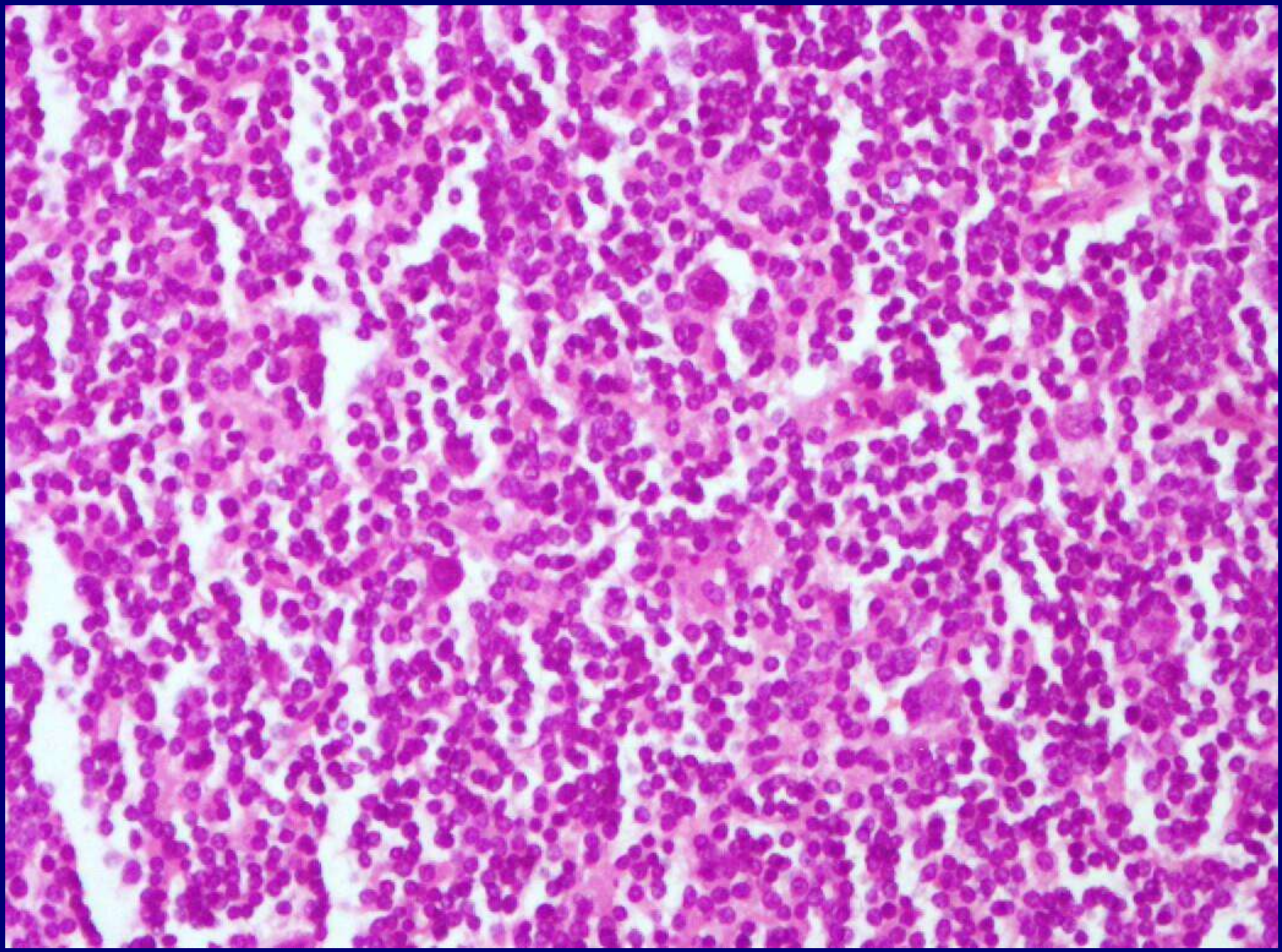
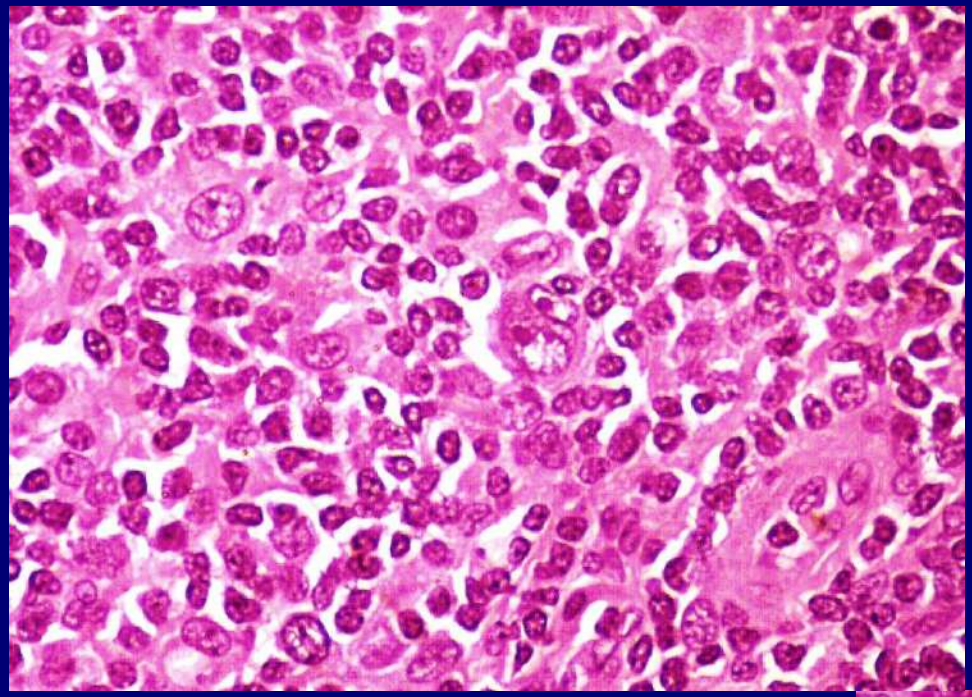
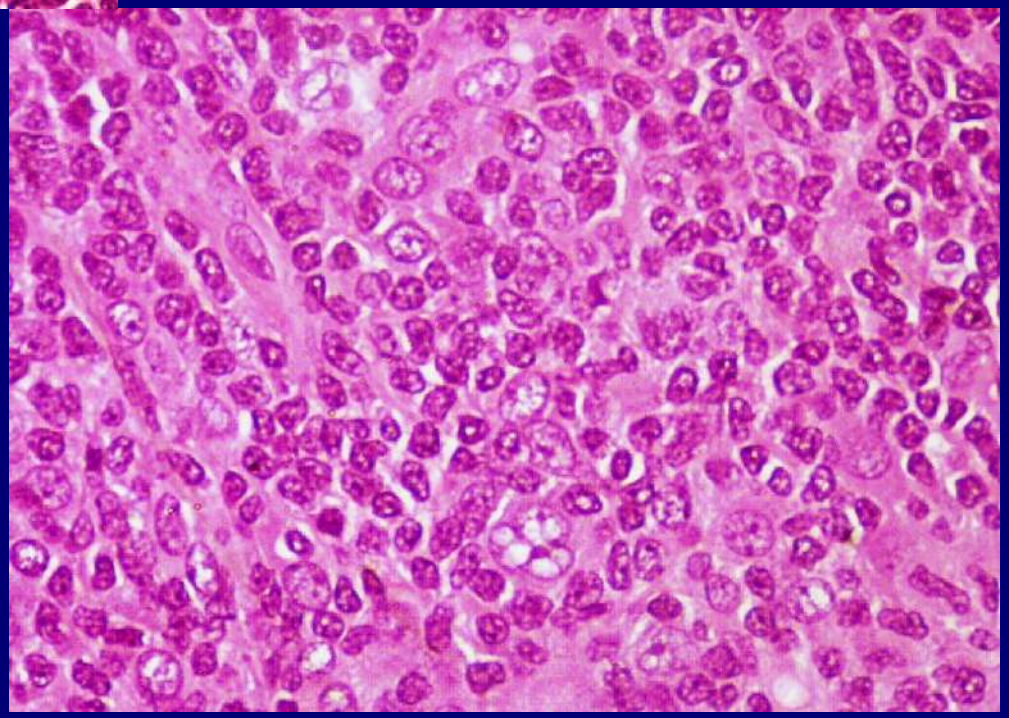
case1

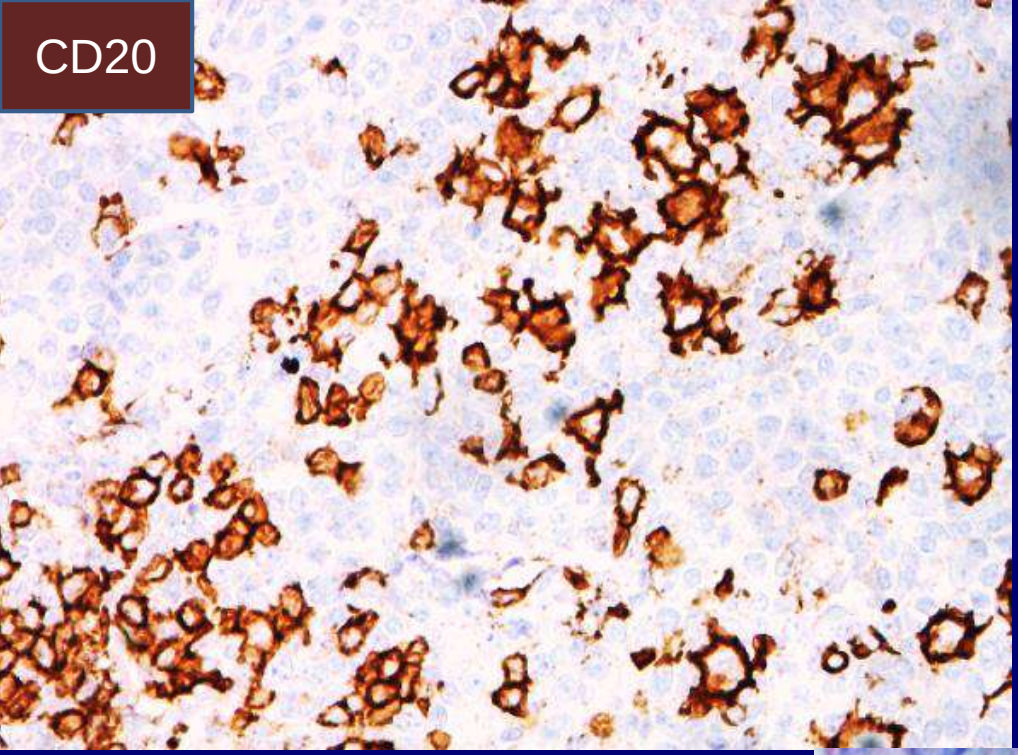
1. 36, Male
2. Generalized Lymphadenopathy
3. PET CT suggests BM involvement

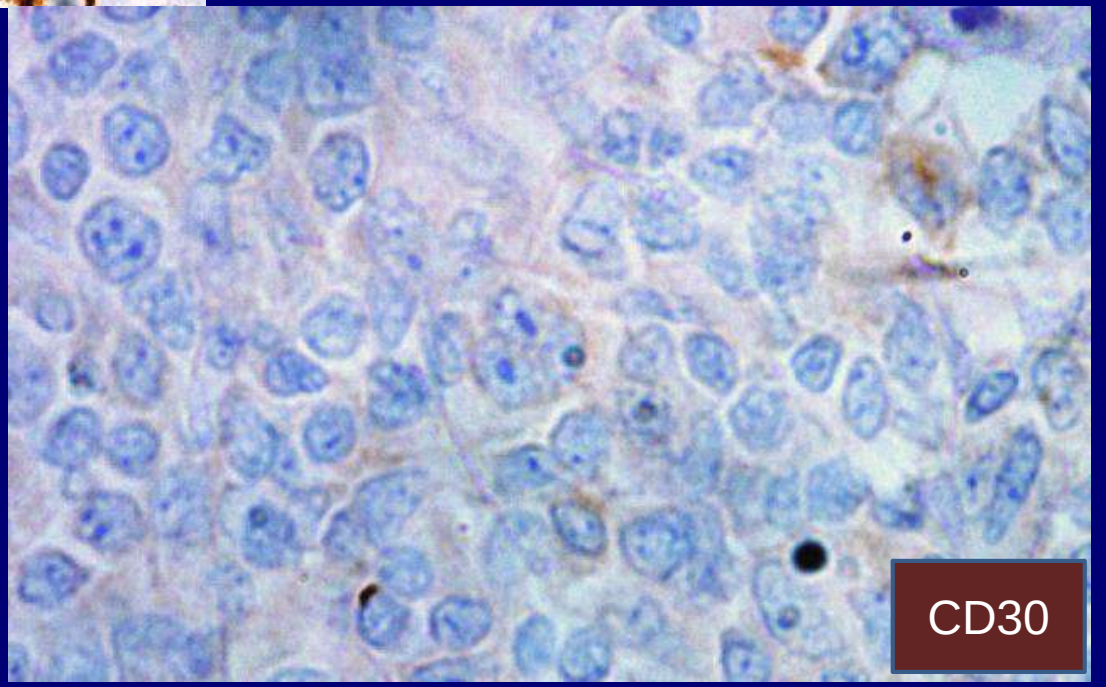


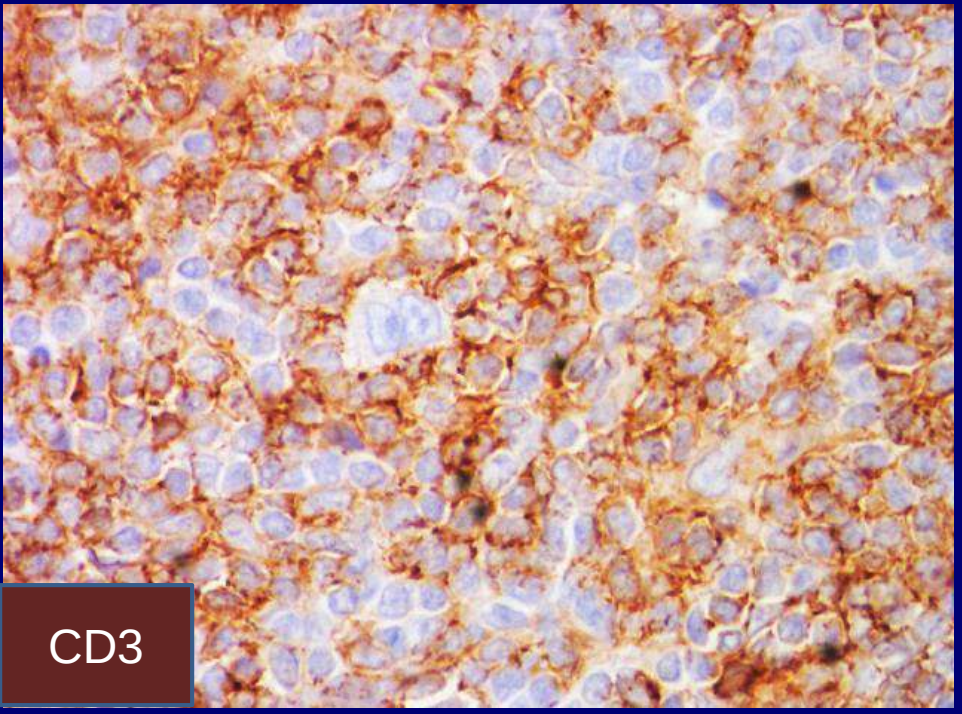




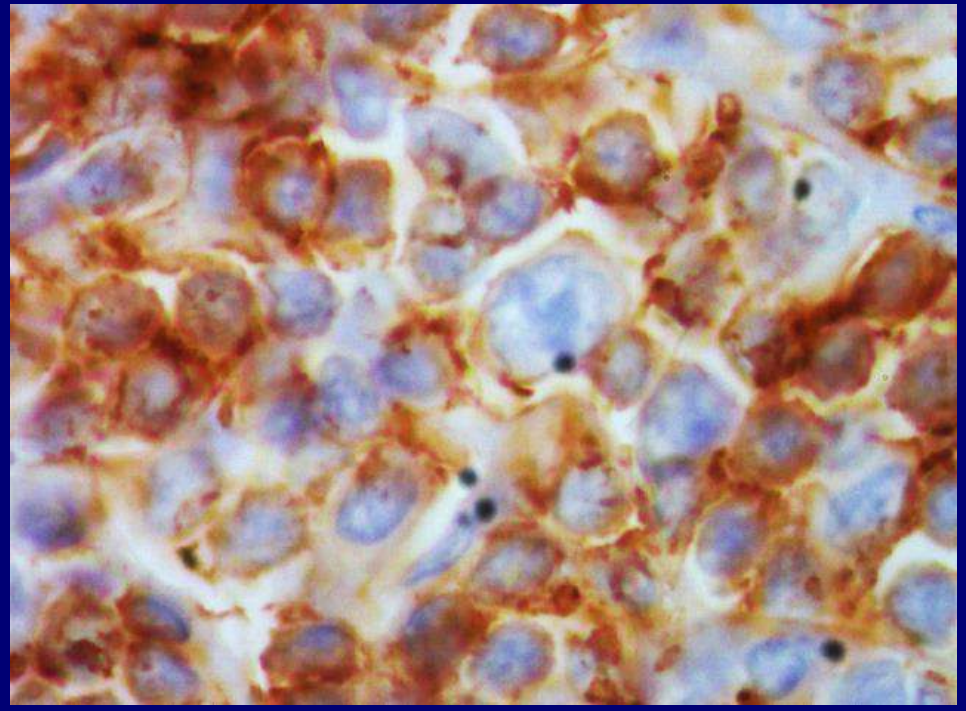


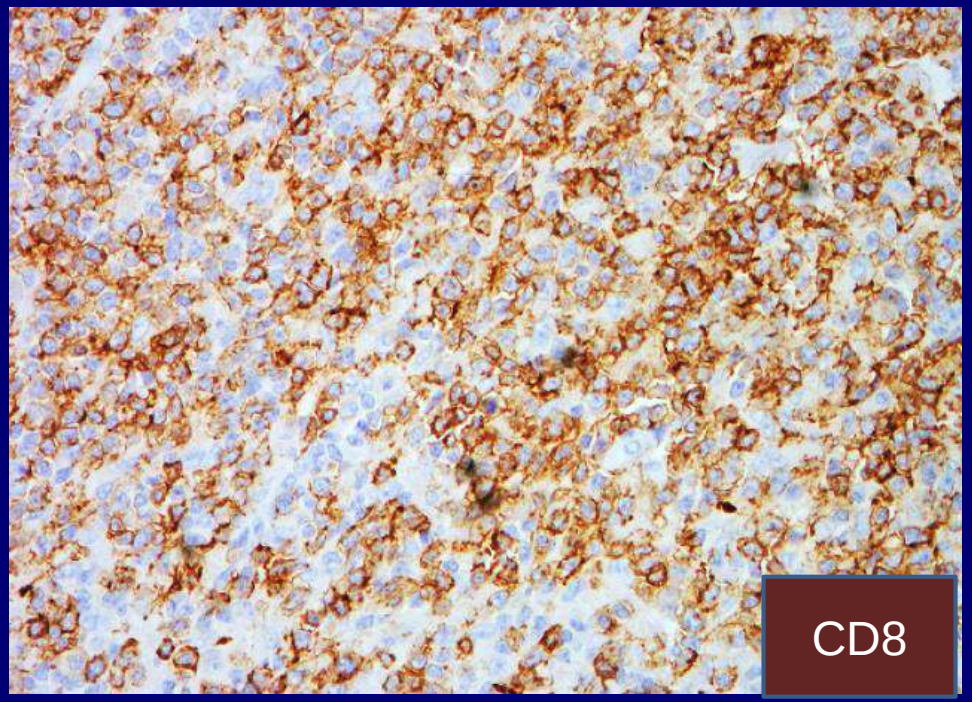

CD20


CD30



CD3





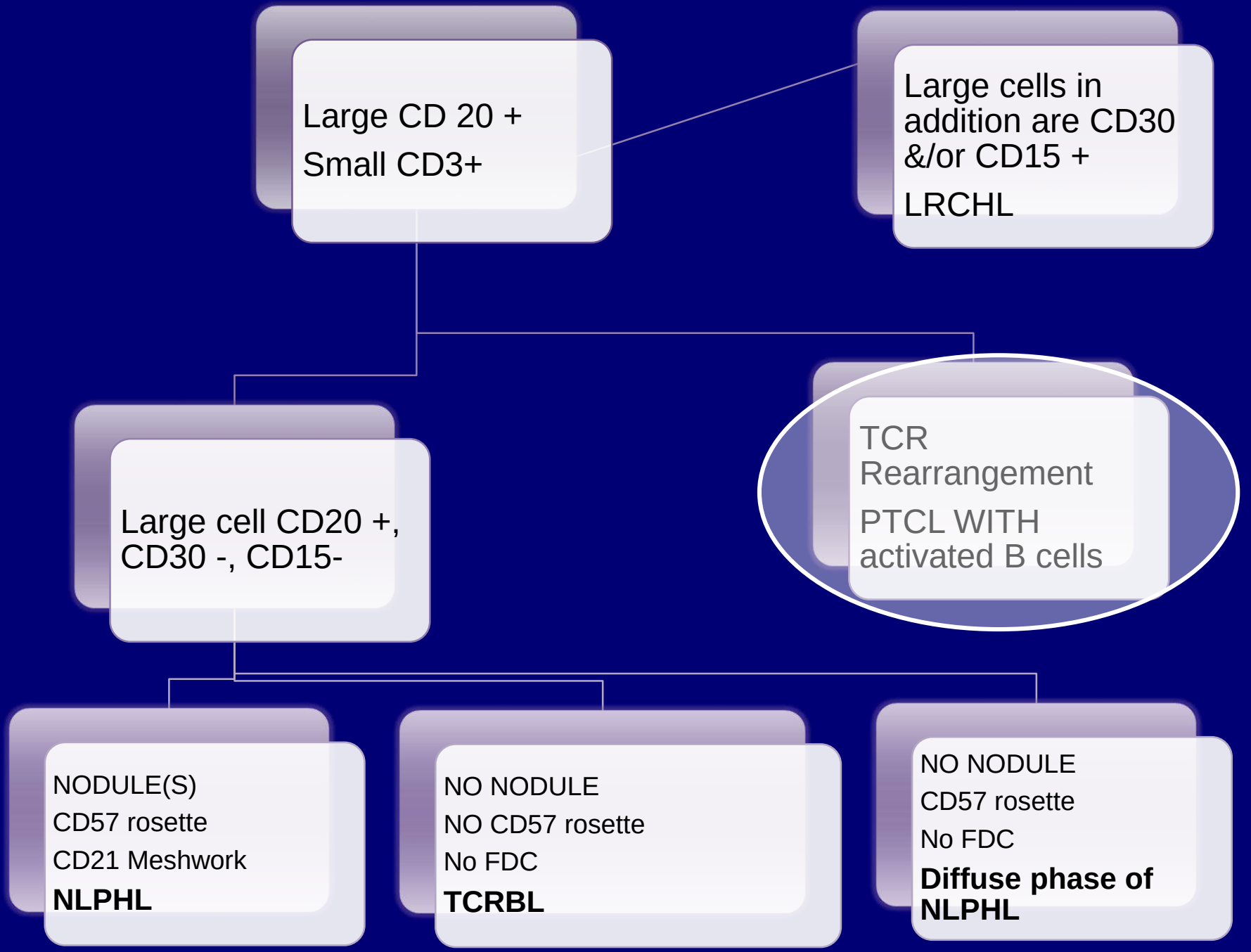
CD8

1. NO CD23 MESHWORK
2. CD57 RINGING

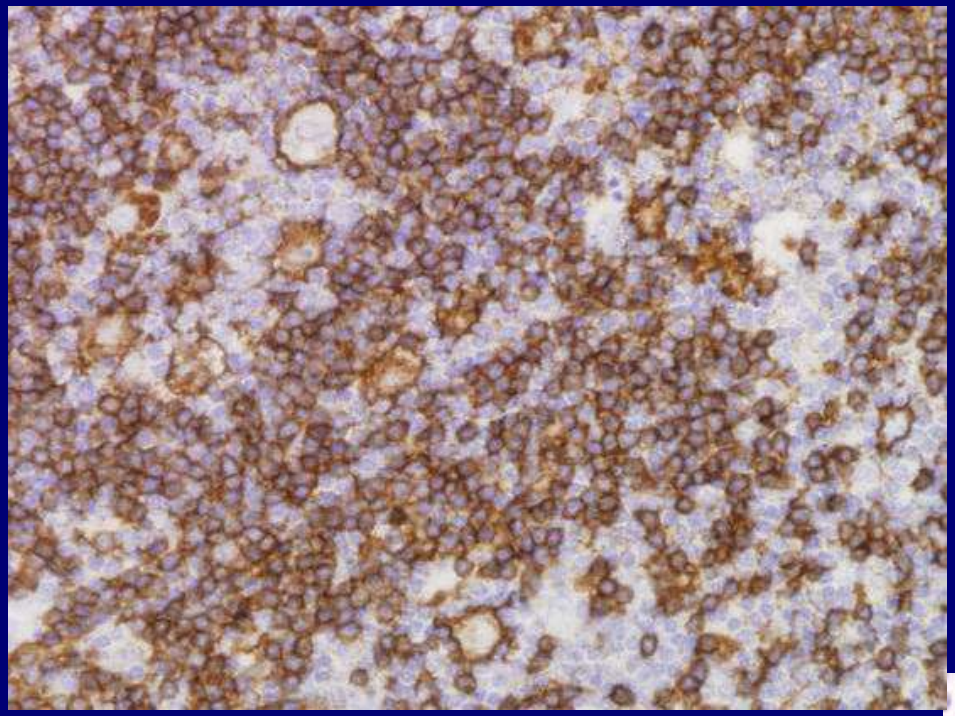
DIAGNOSIS?

- No definite nodule
- CD 20 + large neoplastic cells. Singly and small clusters
- CD30 Negative
- Background had sparse population of B cells. Not Bereft of B cells
- NO FDCs
- CD 57 rosette present

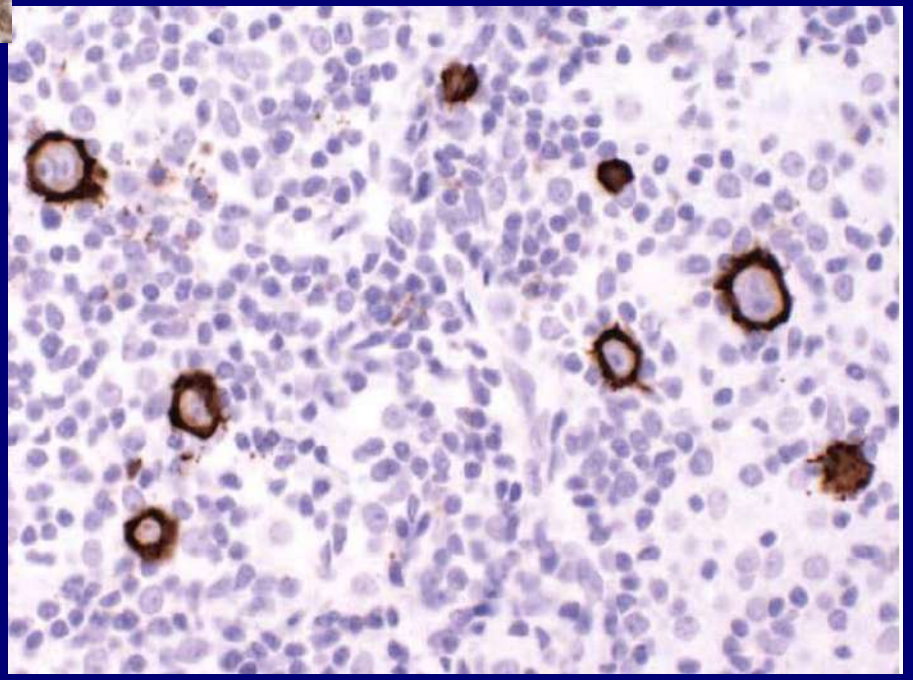
PREVIOUS DIAGNOSIS OF NLPHL X 3 yrs back


Large CD 20 +
Small CD3+
Large cells in addition are CD30 &/or CD15 +
LRCHL
Large cell CD20 +, CD30 -, CD15-
TCR Rearrangement
PTCL WITH activated B cells
NODULE(S)
CD57 rosette
CD21 Meshwork
NLPHL
NO NODULE
NO CD57 rosette
No FDC
TCRBL
NO NODULE
CD57 rosette
No FDC
Diffuse phase of NLPHL

1. Previous NLPHL
2. CD57 rosette
3. Still some B cells. (B cells are replaced by T cells in later stage and as the neoplasm becomes more diffuse.)
4. Similarly FDCs are lost as NLPHL becomes diffuse or of long standing.
5. CD 57 rosette however, is most likely too be retained
6. **The most appropriate diagnosis in this case is NLPHL with TCRBL like morphology** (WHO accepted entity)
7. **De novo.**
   - **No Nodule**
   - **T cells in background**
   - **No CD 57 rosette**
   - **No FDC- consider TCRBCL**



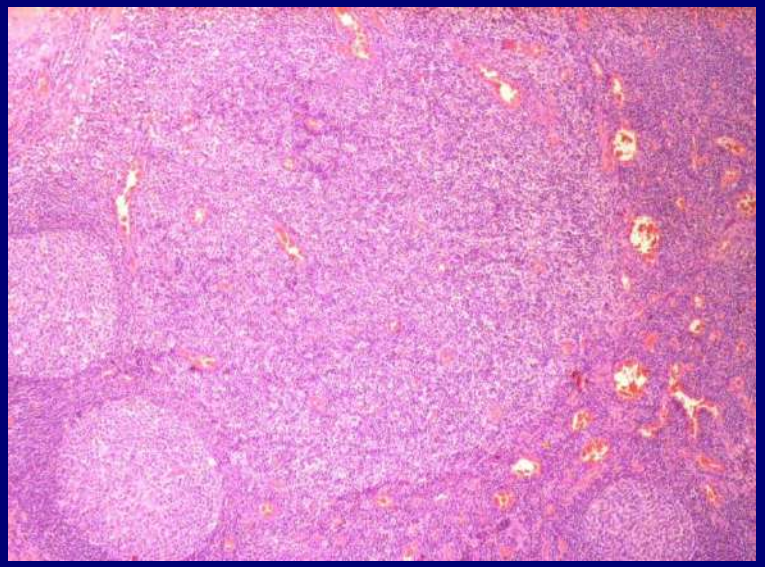
Lots of Reactive B cells in NLPHL

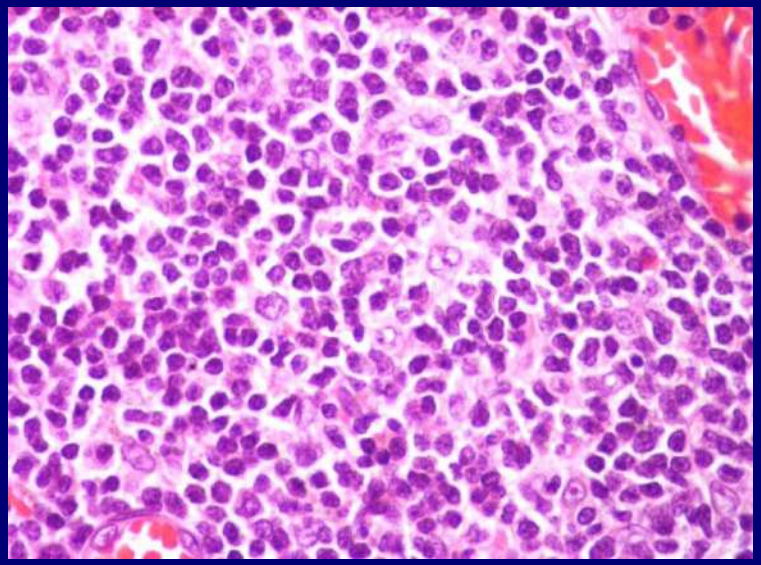


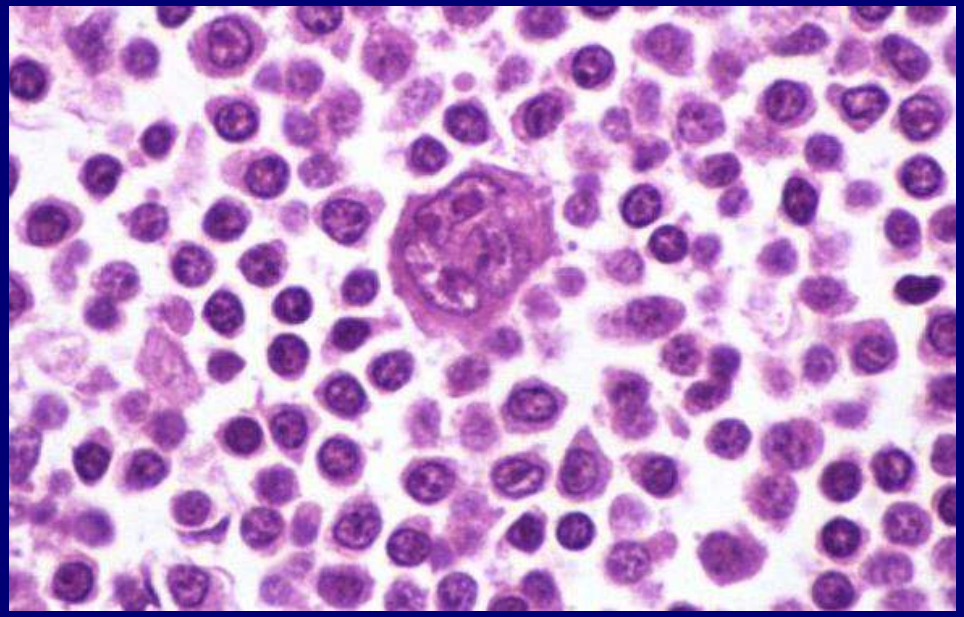
Lack of Reactive B cells in TCRBCL

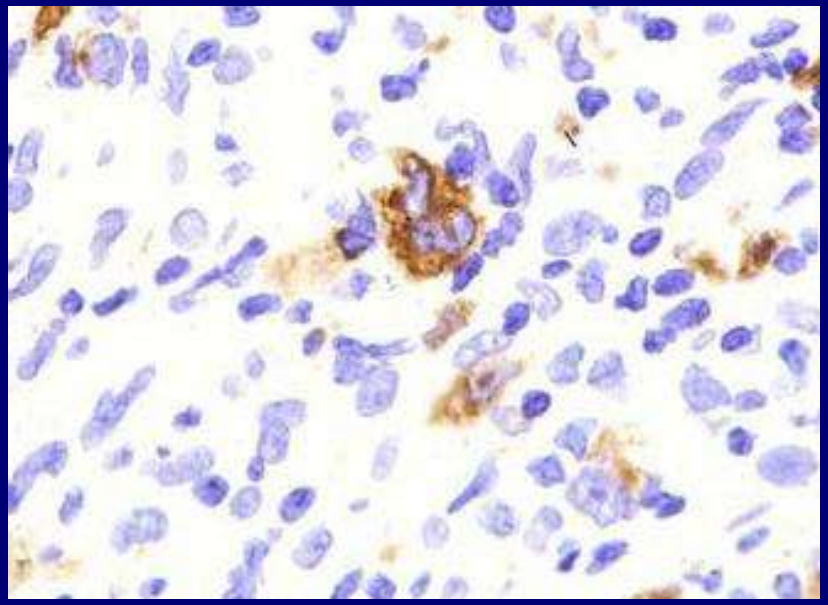
Other D/D

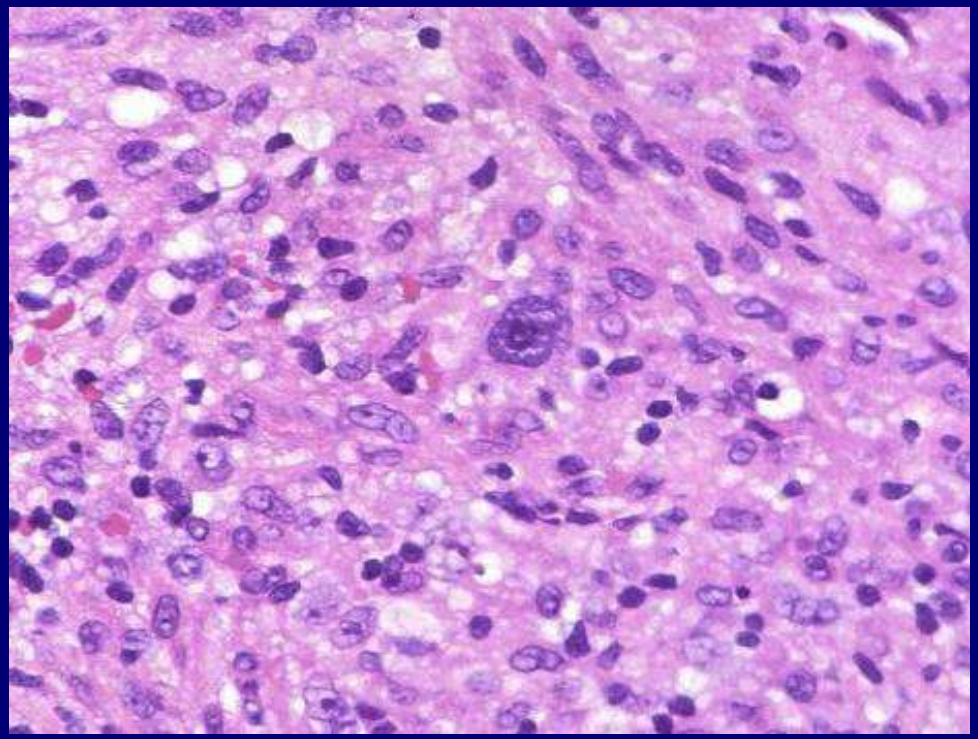
1. Progressive transformation of germinal centers(PTGC)
   - Follicular hyperplasia but no effacement of architecture.
   - The PTGC are a few amongst many reactive follicles and not uniformly large
   - No LP cells; OCT-2 can be helpful
2. CLL with large Dysplastic cells
3. Lymphocyte Rich Classic HL(LRCHL)











1. In rare cases of B-CLL/SLL, there are scattered Reed-Sternberg-like cells, which can show activated B cell like RS cell
2. These large cells are EBV+ (EBER+, LMP1+)
3. B cell phenotype with co expression of CD5 & CD23

Classical Hodgkin lymphoma (cHL)

1. Characterized by presence of RS cells and variants
2. Classified into

Classical (cHL)

Nodular Sclerosis:

1. Young adults. More in females
2. Requires intact immune system
3. Cytokine milieu which is distinct
4. GEP akin to PMBCL

MC/ LD

1. Represent a spectrum
2. Share many features related to incidence, pattern of spread, and association with immunodeficiency. HIV and EBV association
3. More in males

LRCHL

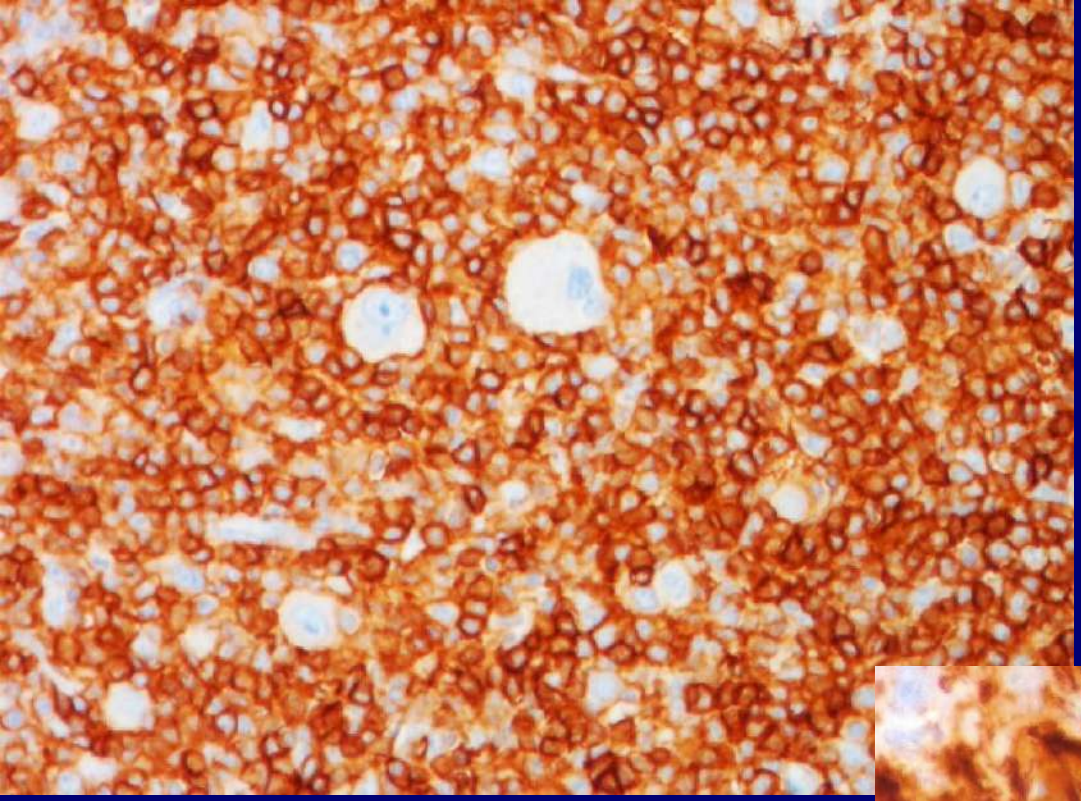
1. Least common and least understood
2. Older age
3. Excellent prognosis

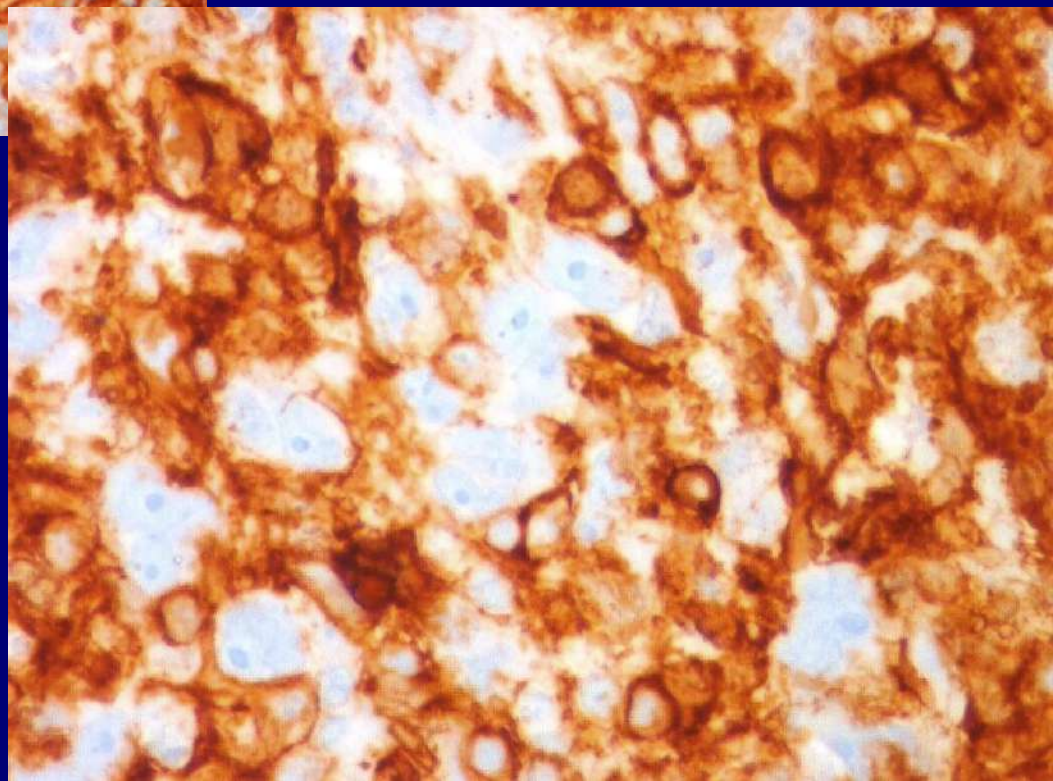
Levy A, Armon Y, Gopas J, et al. Is classicalal Hodgkin's disease indeed a single entity? *Leuk Lymphoma. 2002;43:1813–1818.*

Classical Hodgkin Lymphoma

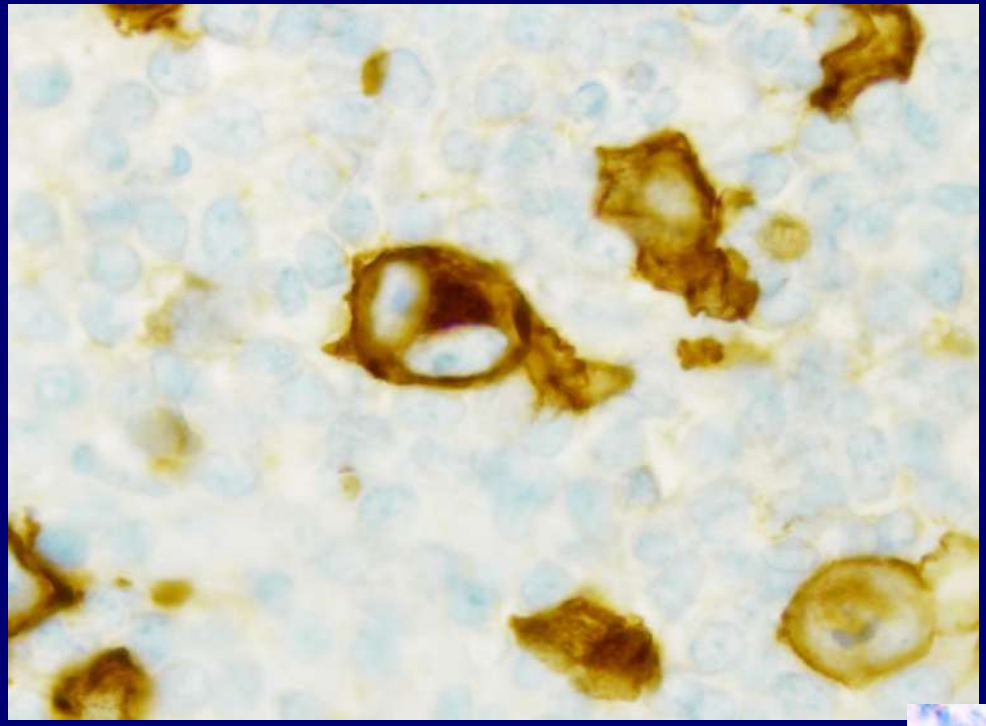
1. **RS cell / Hodgkin cells/ lacunar cells** define the disease.
2. Cells similar in morphology can be seen in several reactive and neoplastic conditions. **Milieu is to be considered**.
3. **Immunophenotypic attributes** to support

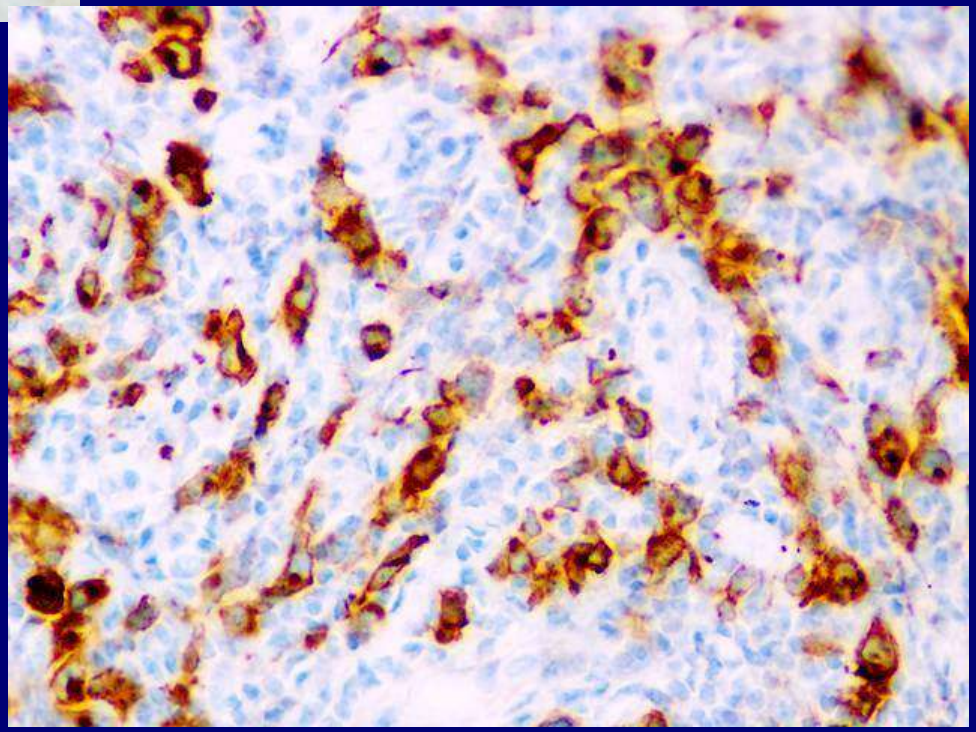
- CD45 (<5% +) : Useful . Difficult to interpret.
- CD30 (98% +).
- CD15 (85% +).
- CD20 (20% + heterogeneous- variable staining from absent to weak to moderate to strong. Few cases ~5% show uniform strong staining. ??? Cause trouble
- PAX-5 (90% + weak). Very useful. Immediate separation from ALCL
- CD3 (<5% +)



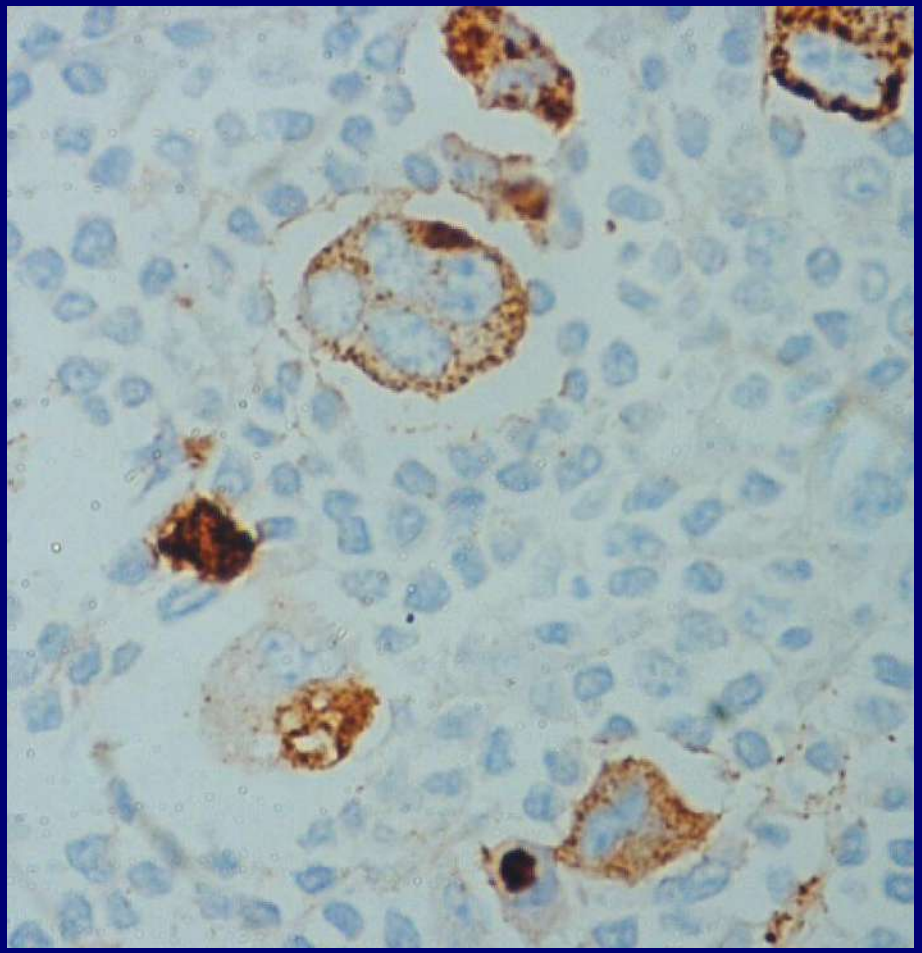


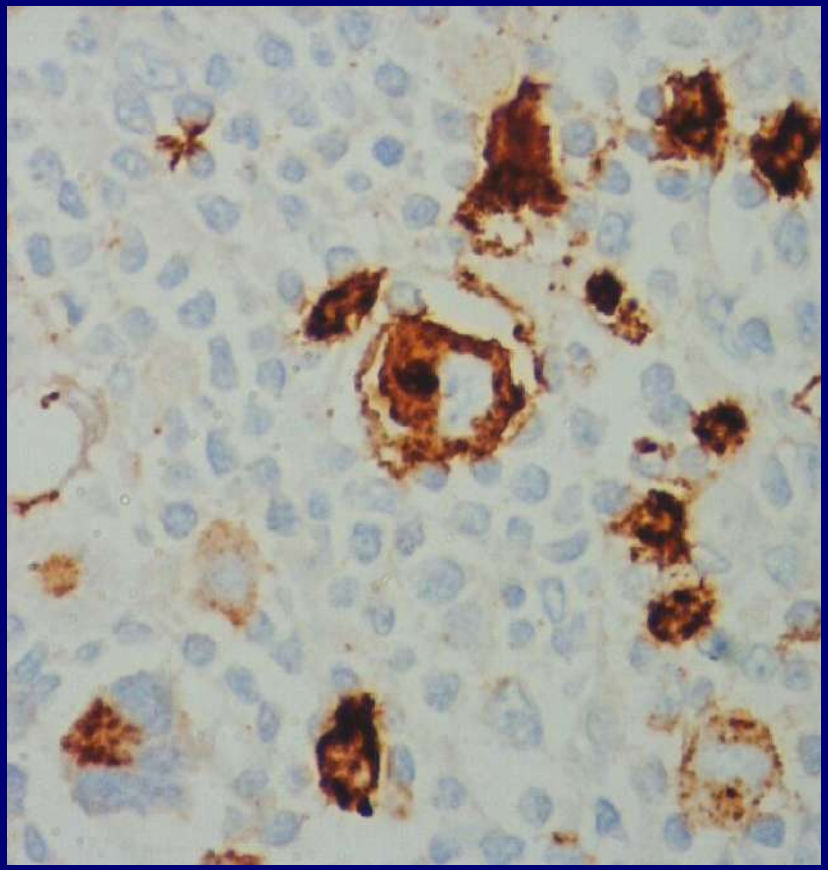
LCA difficult IHC to interpret



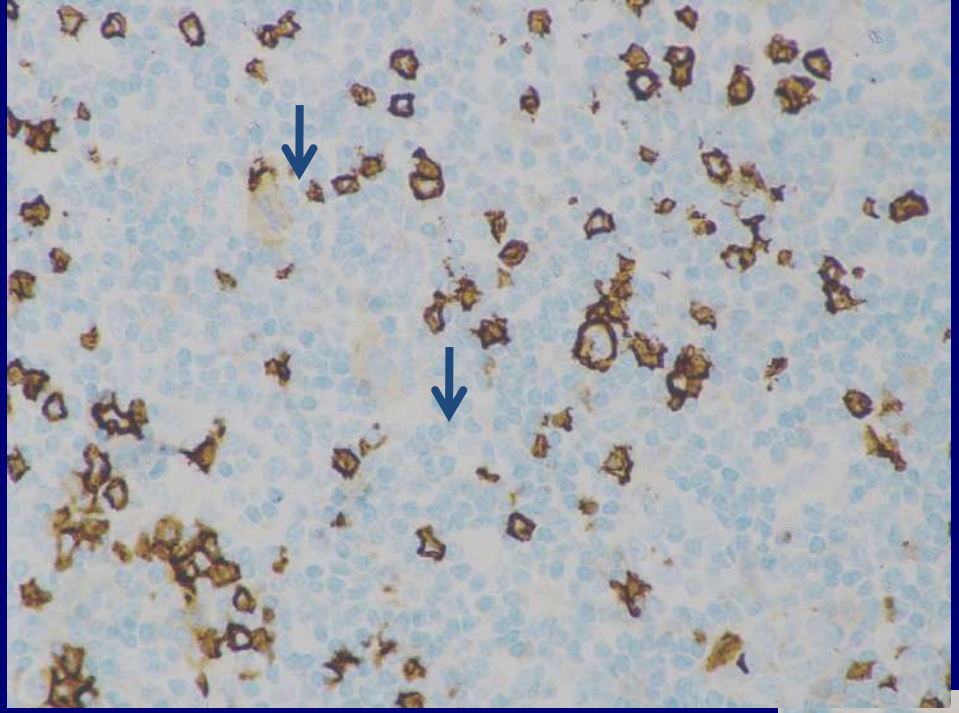


CD 30

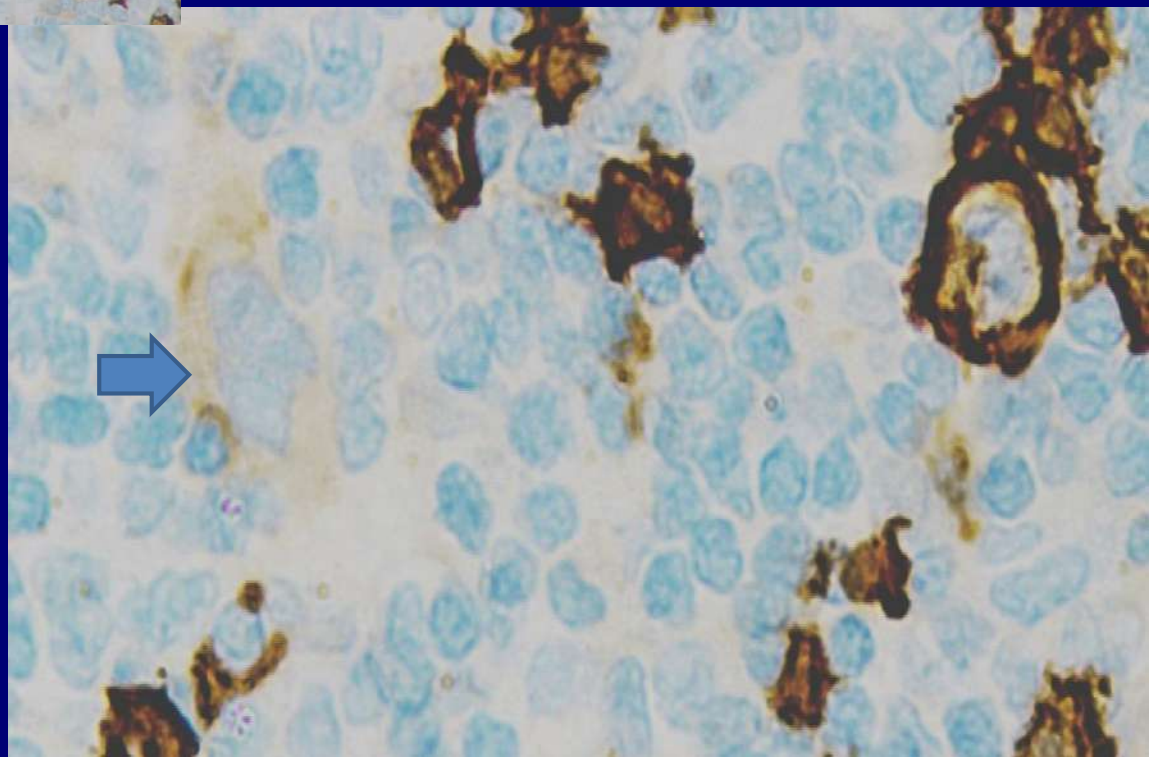


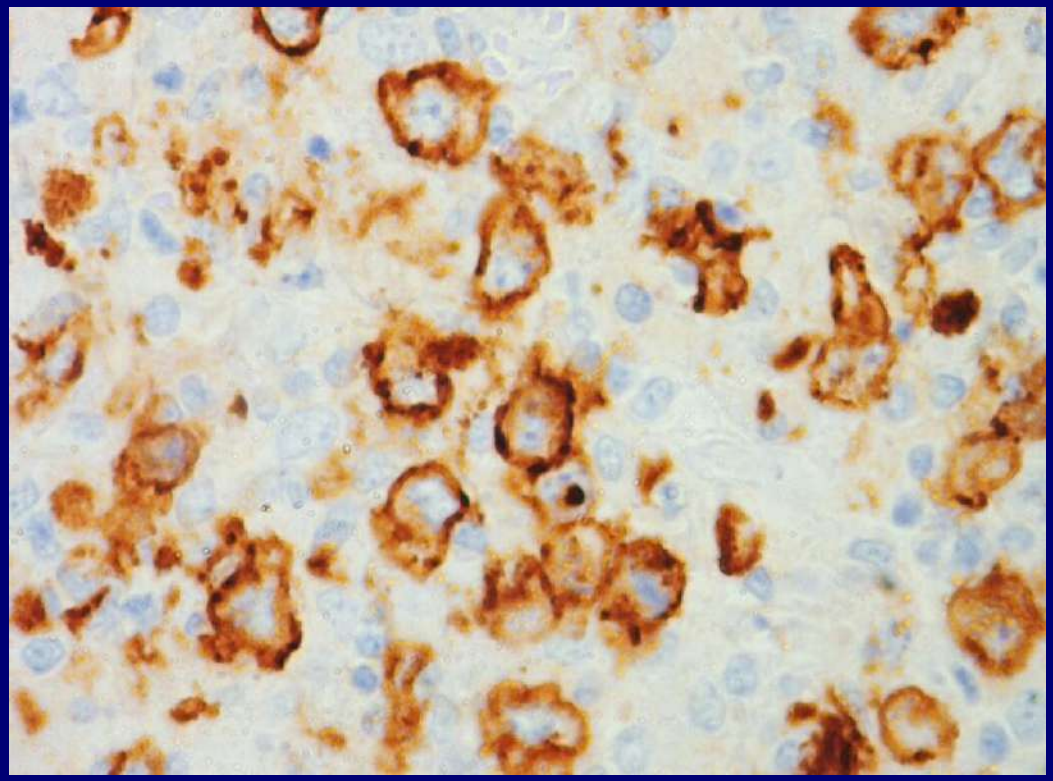


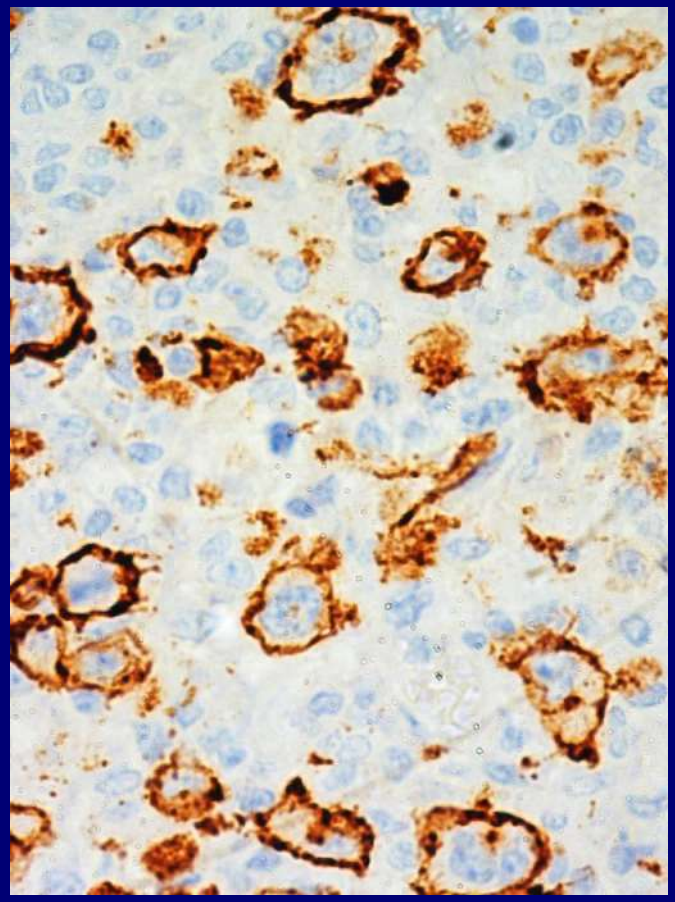
CD 15: Varying patterns of positivity



Heterogeneous CD20 staining



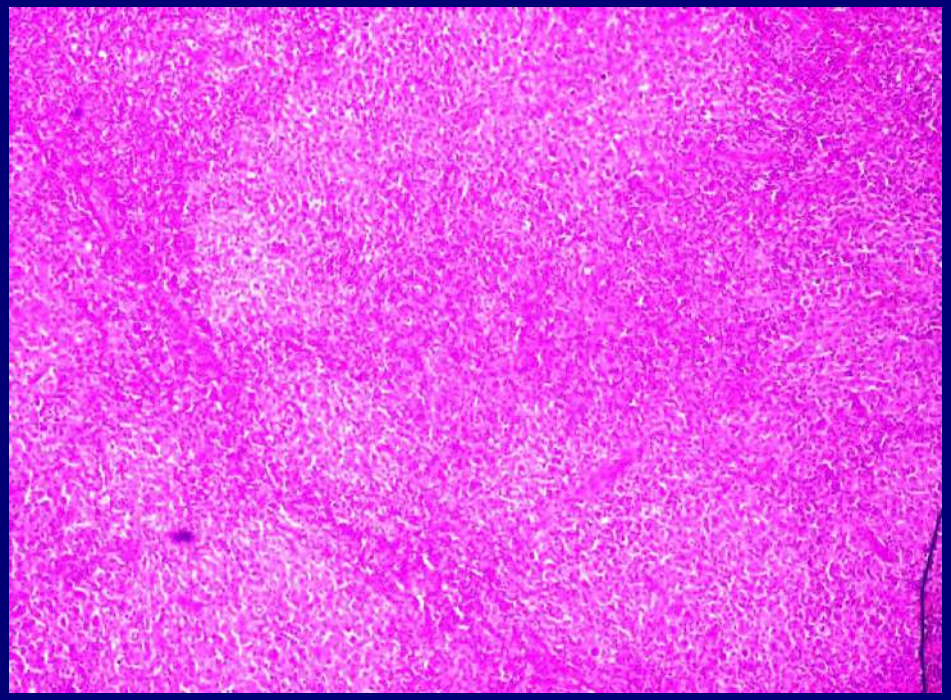


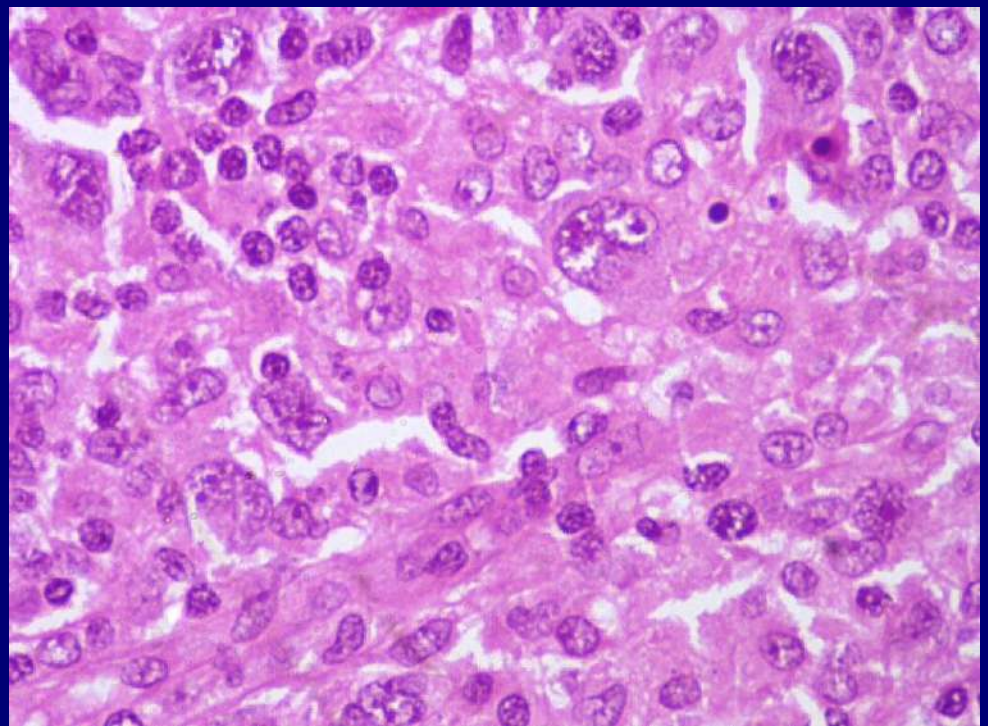


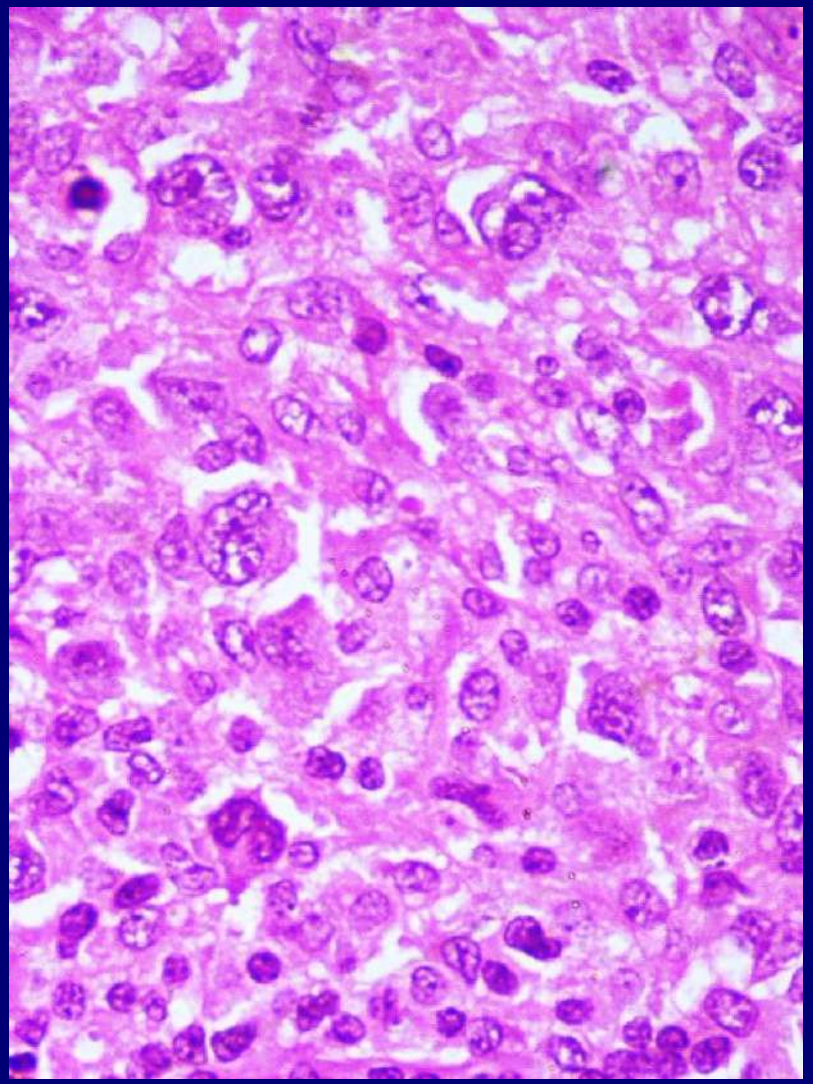
In approximately 5% cases of cHL CD 20 staining is intense and uniform. Difficult to distinguish from DLBCL.

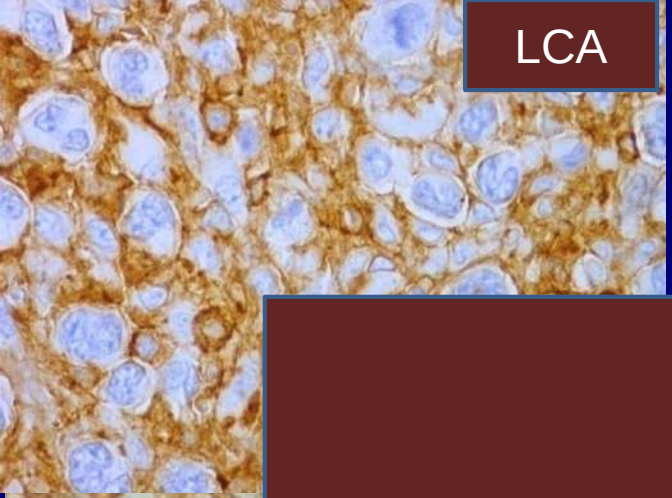
Case 2

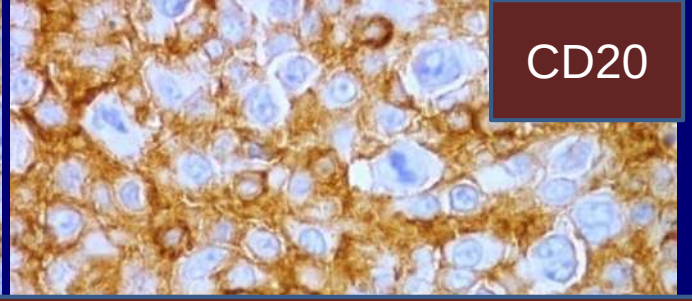
43, Male, cervical Lymphadenopathy

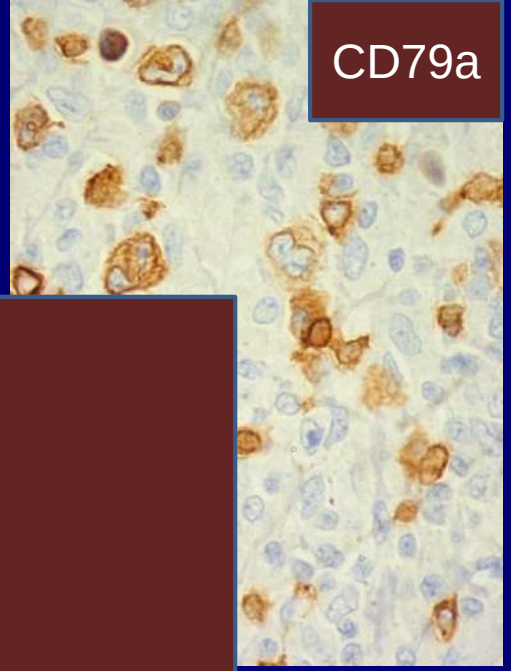


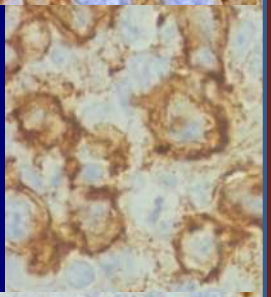


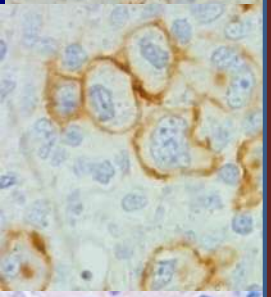




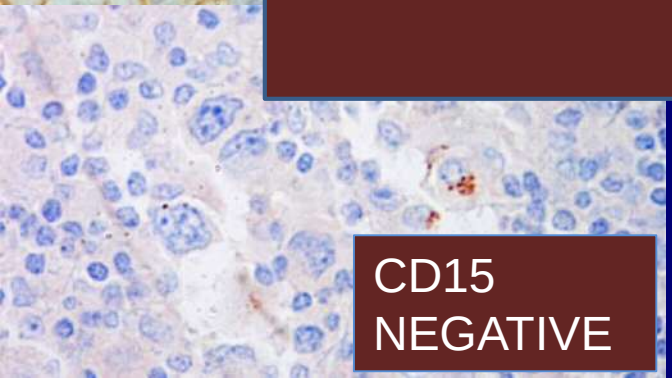


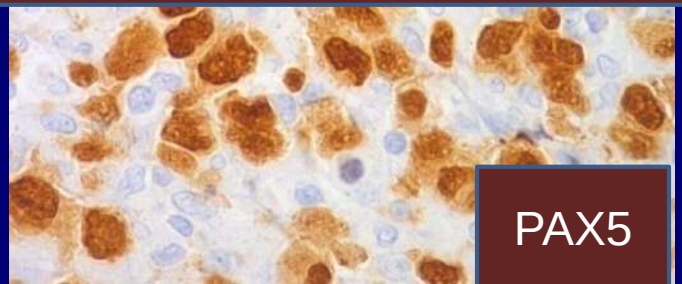


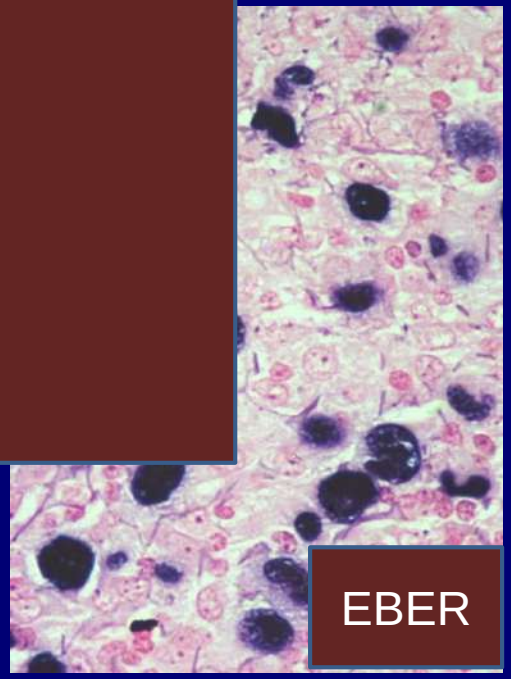




Sinusoidal DE-NOVO CD30 + DLBCL







Age: 36-82 years; mean, 63.2 years

Male to female ratio,1:1.2

Histopathology:

- Typically sinusoidal infiltrative pattern; may have foci of confluent growth
- Most cases composed predominantly of large pleomorphic cells with occasional Reed-Sternberg-like cells
- Some cases consist predominantly of large monomorphic lymphoid cells
- Necrosis and admixed granulocytes commonly present

IHC:

Positive for CD30 and CD20 or CD79a

Negative: ALK-1

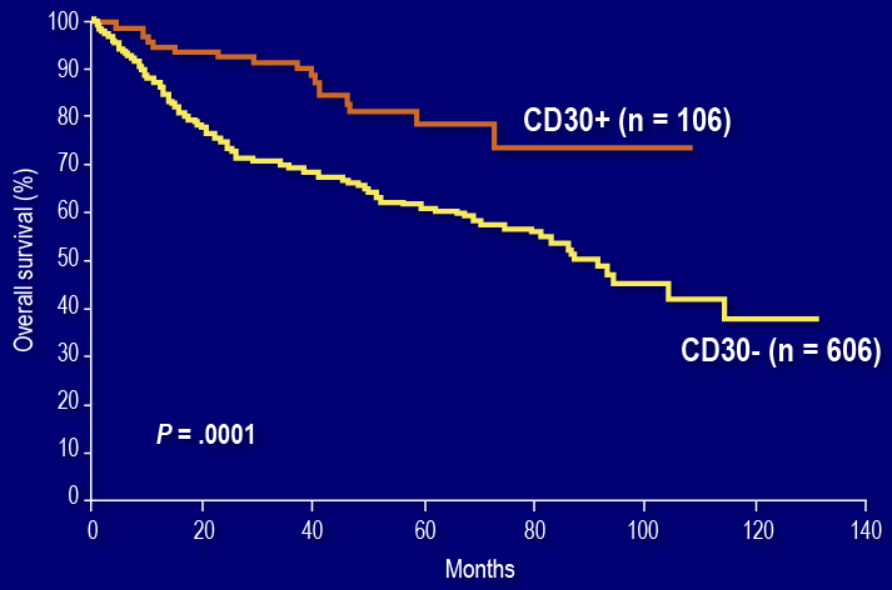
EBV present in a subset of cases. Can be GCB or ABC or EBV +

Reference:

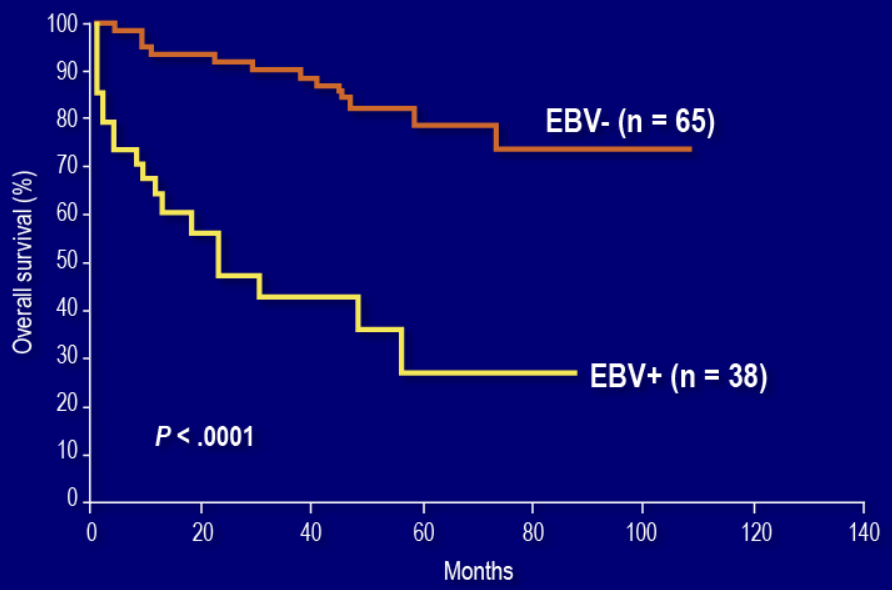
1. Hu S et al. *Blood*. 2013;121(14):2715-2724.
2. Mod Pathol. 2000 Mar;13(3):223-8.

Variable prognostic role of CD30 in DLBCL

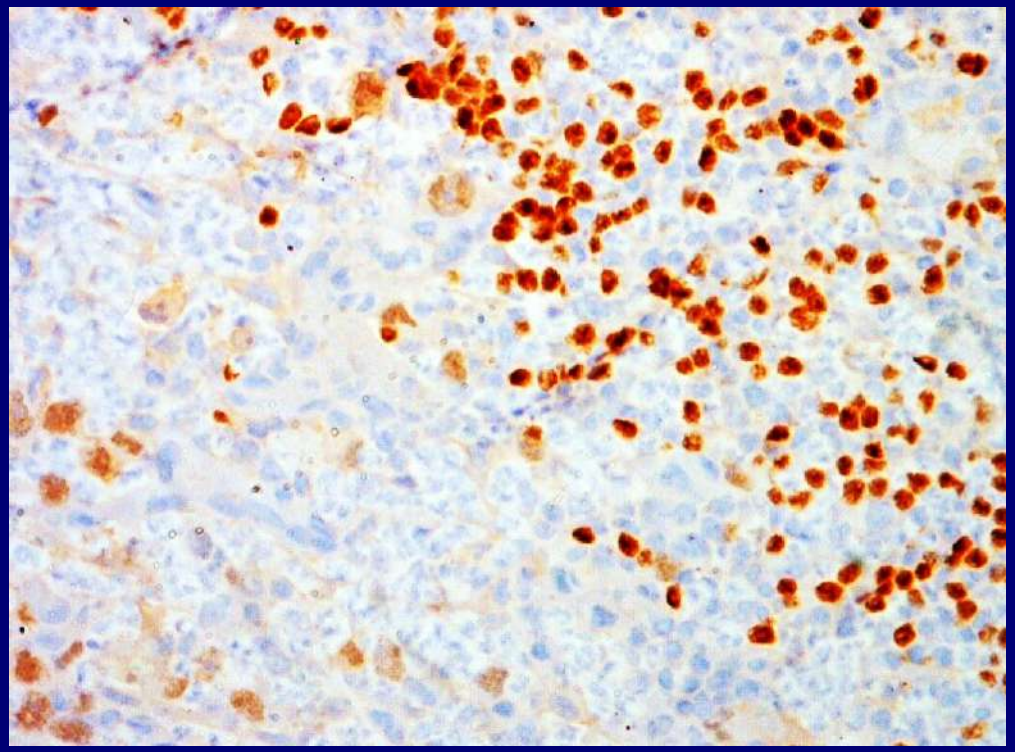
In de novo DLBCL, CD30 expression has a positive prognosis, improving OS

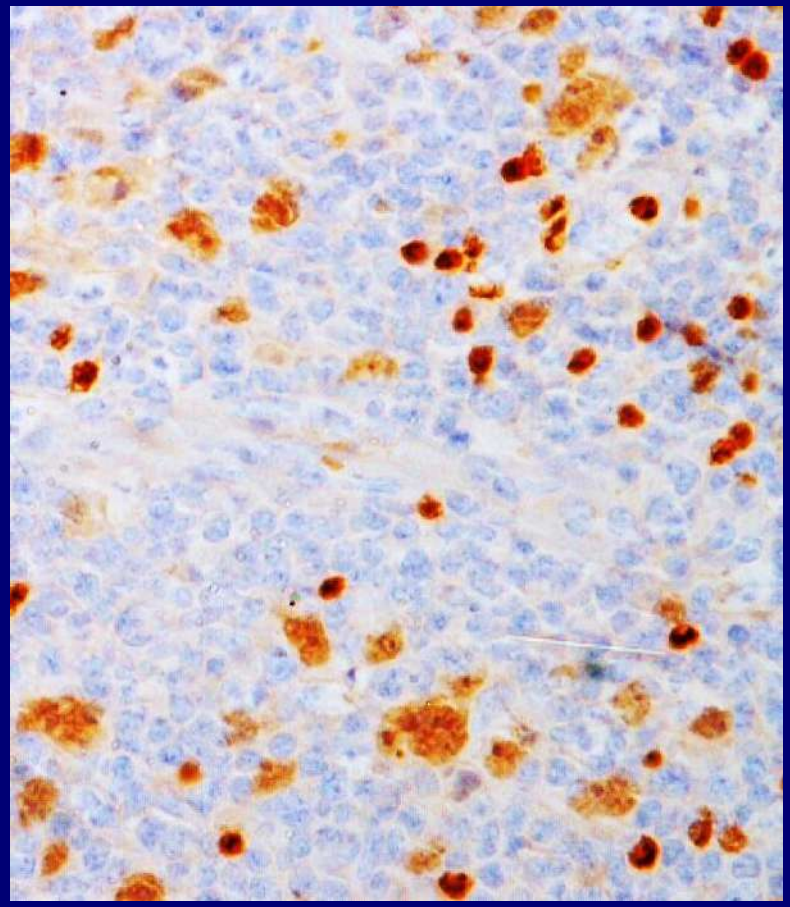


In CD30+ DLBCL, prognosis varies with EBV status, being poorer in the CD30+ EBV+ subset



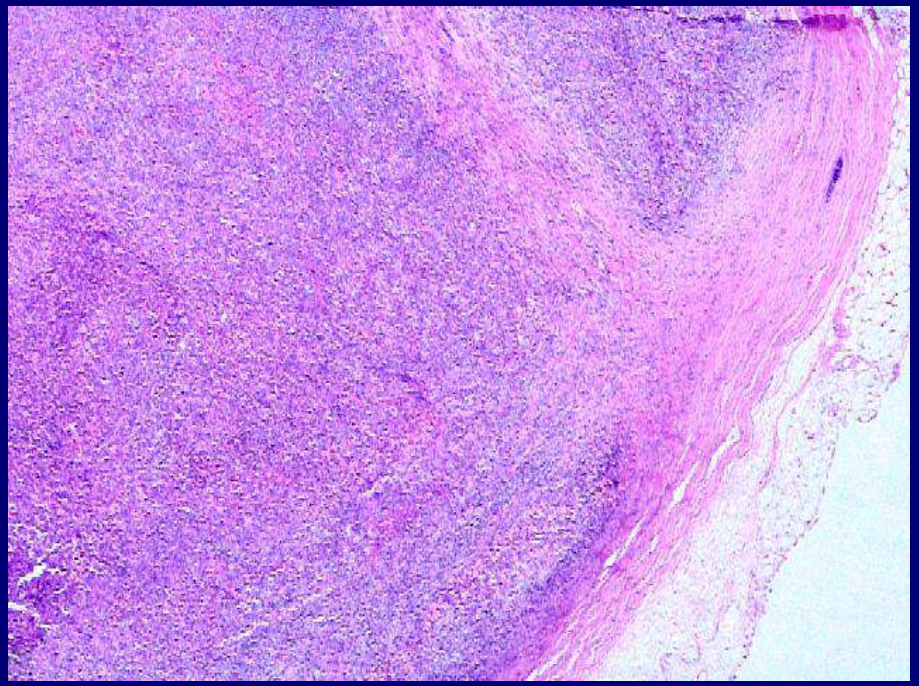
Reference: Hu S et al. *Blood*. 2013;121(14):2715-2724.

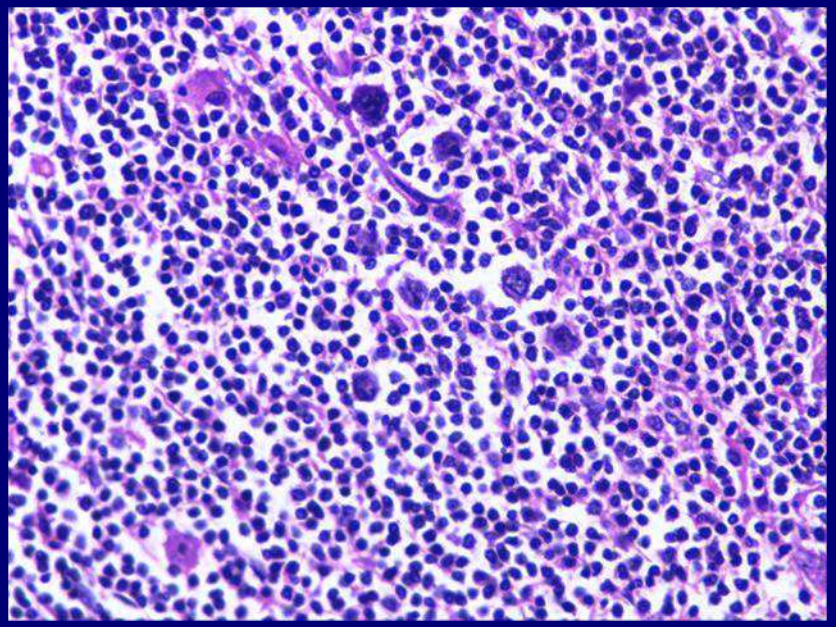


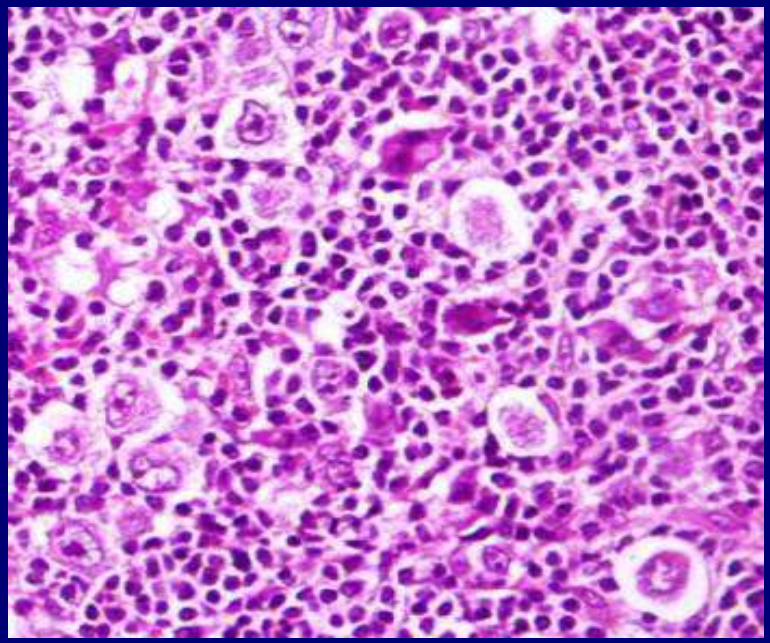


PAX 5: very useful stain. Immediately separates cHL from ALCL

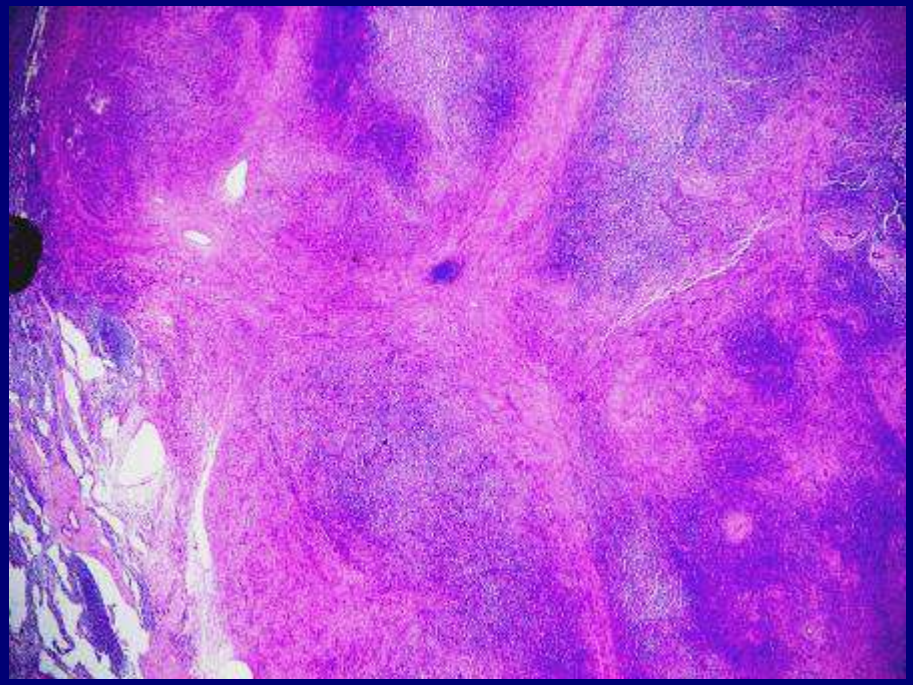
Nodular Sclerosis cHL

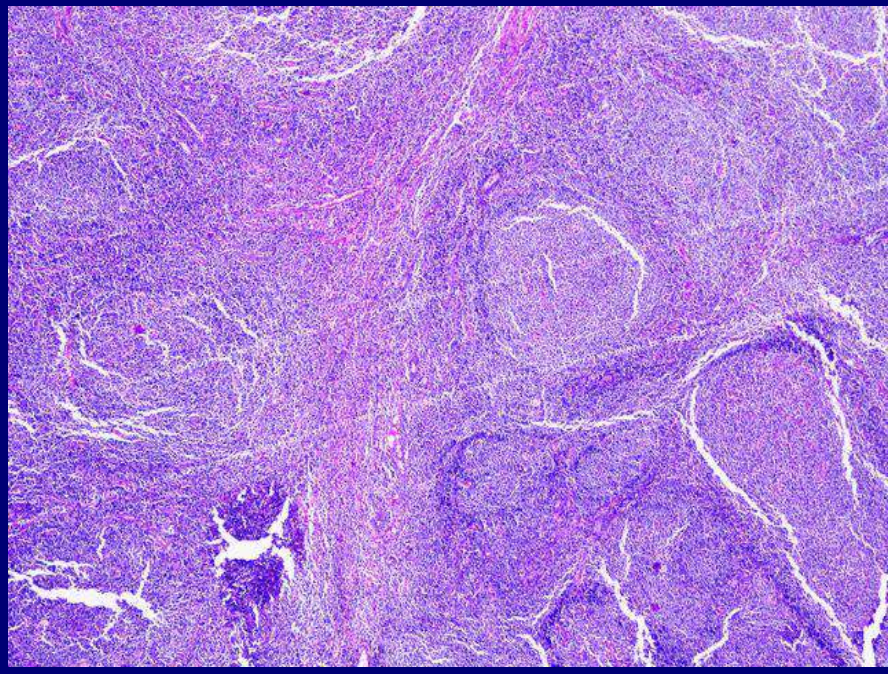


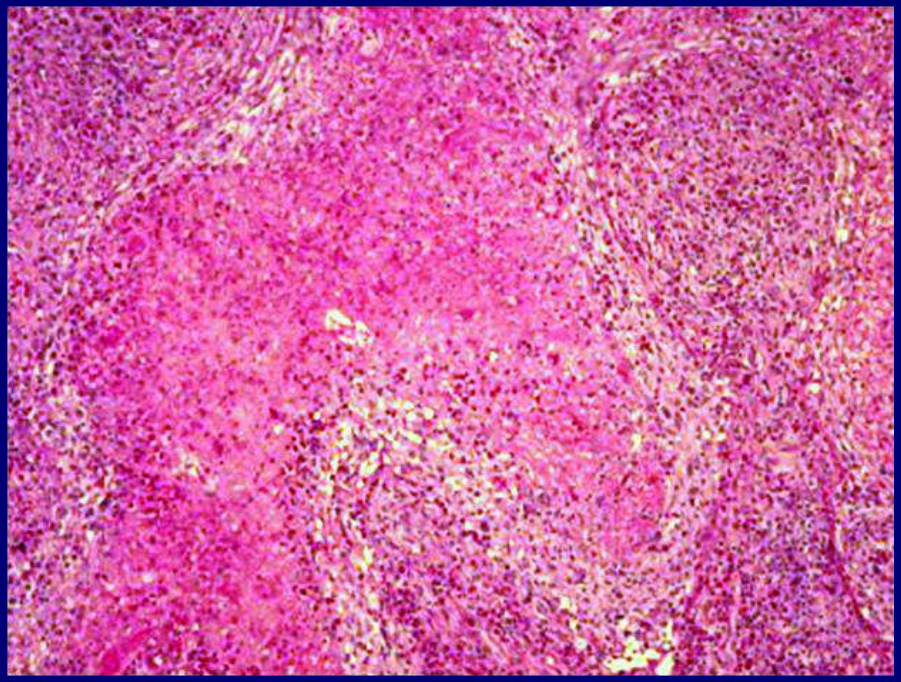


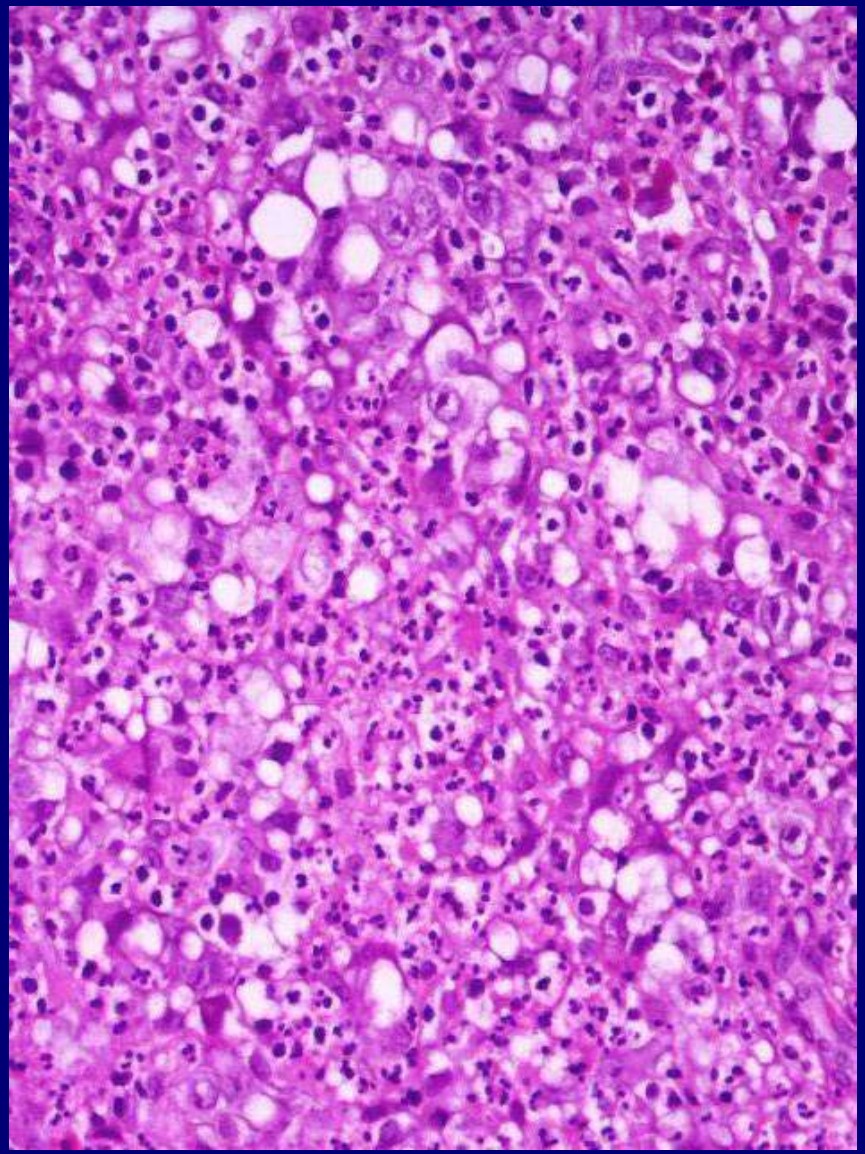


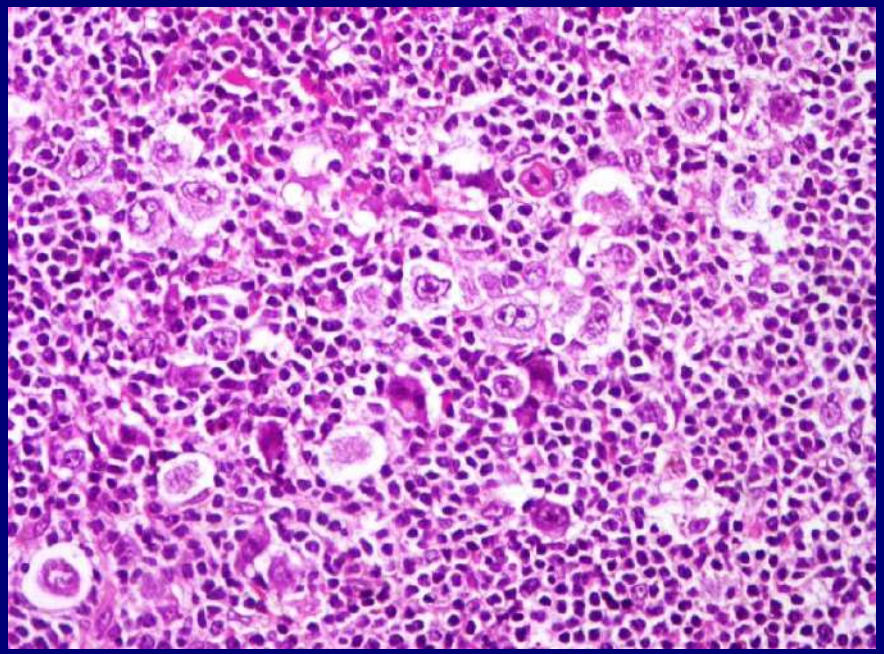
1. Thickened capsule
2. Poorly cellular fibrous band emanating from capsule surround cellular nodules .
3. At least one nodule surrounded by band of fibrous tissue must
4. Lacunar cells

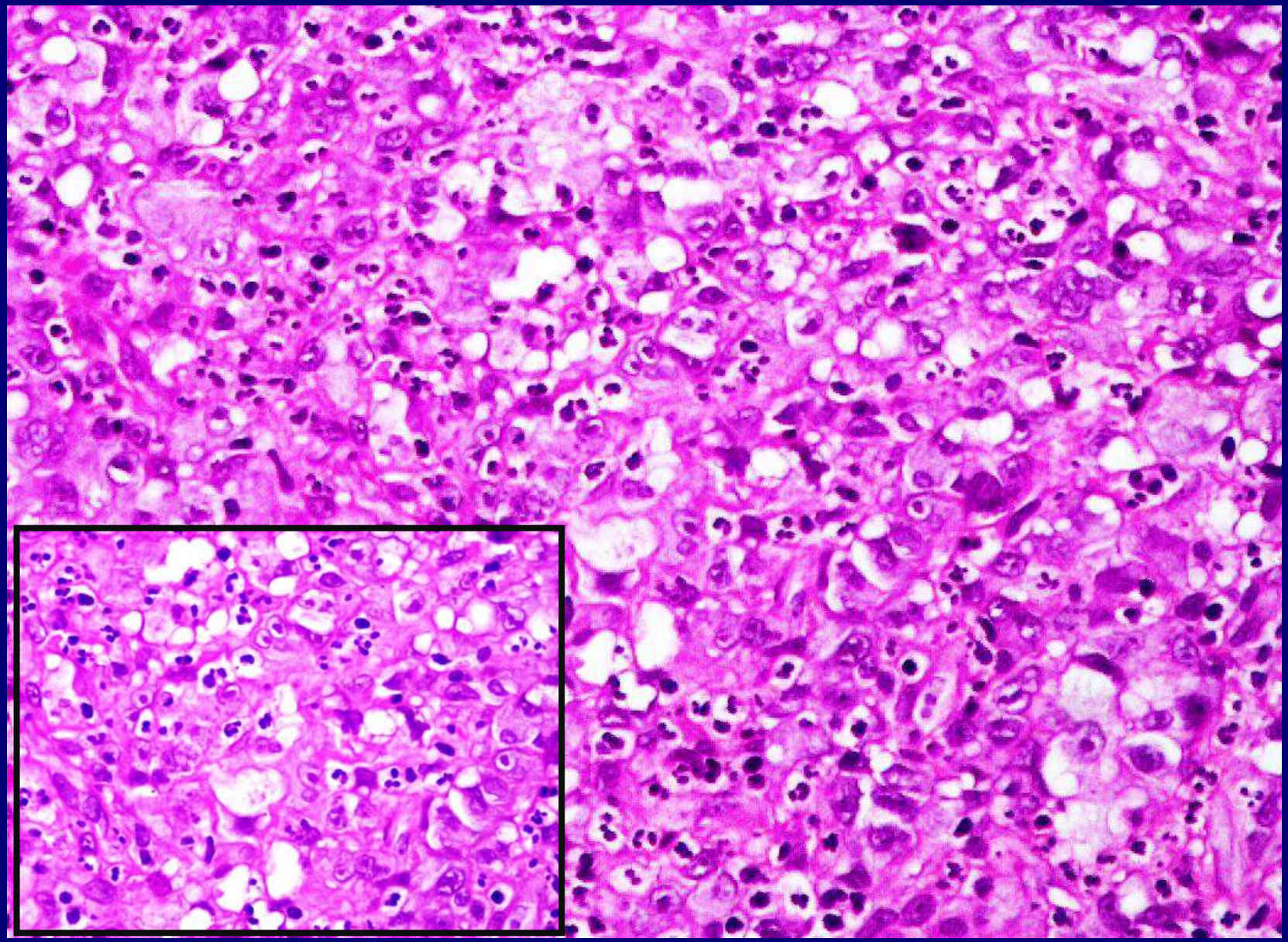








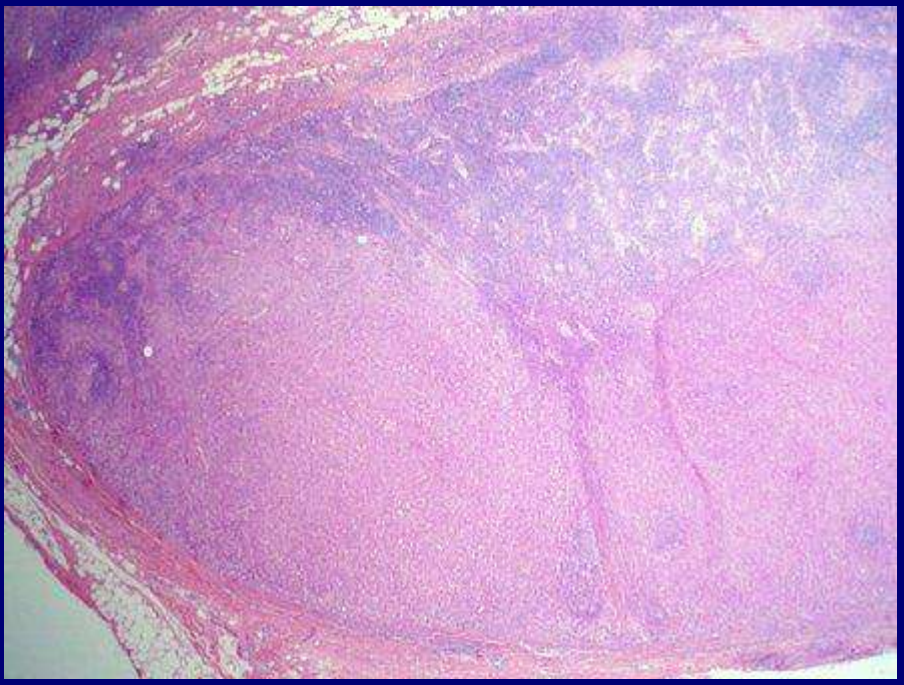


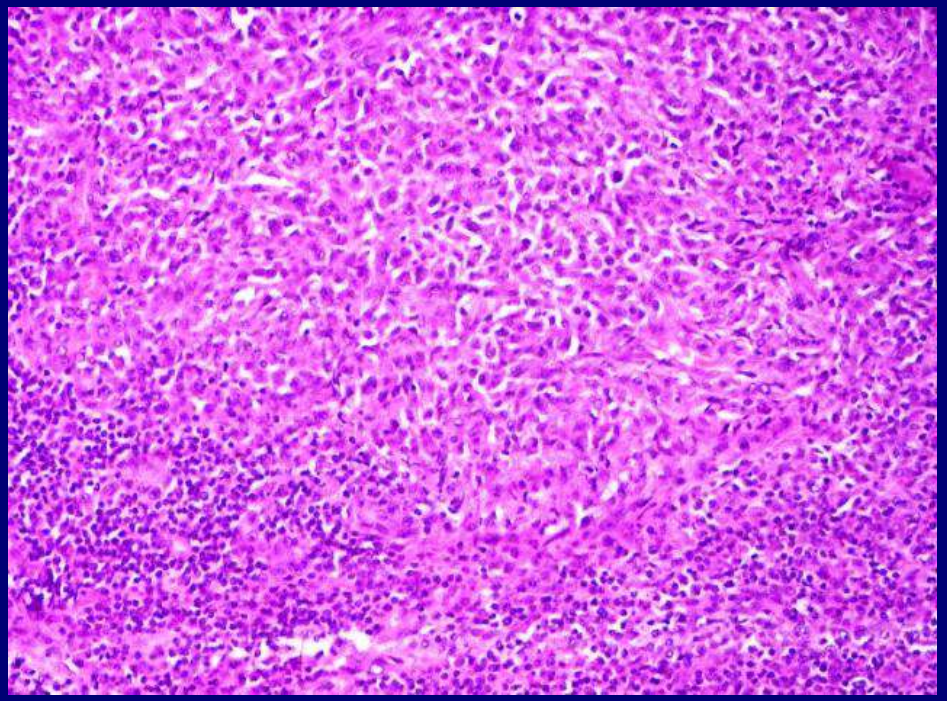


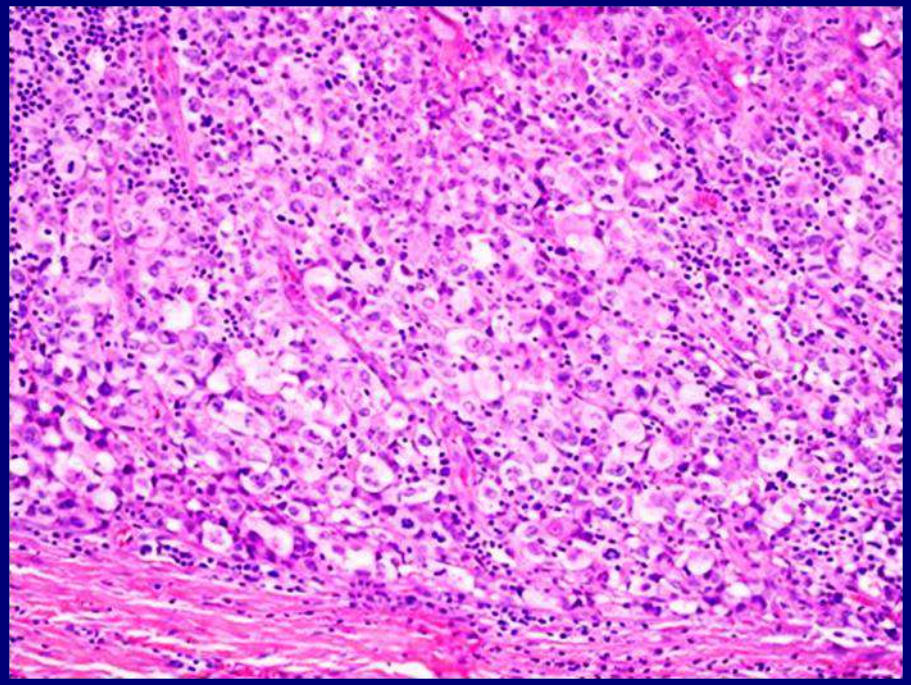
Syncytial variant of cHL→ D/D ALCL, GCT, Anaplastic Carcinoma and even a Melanoma

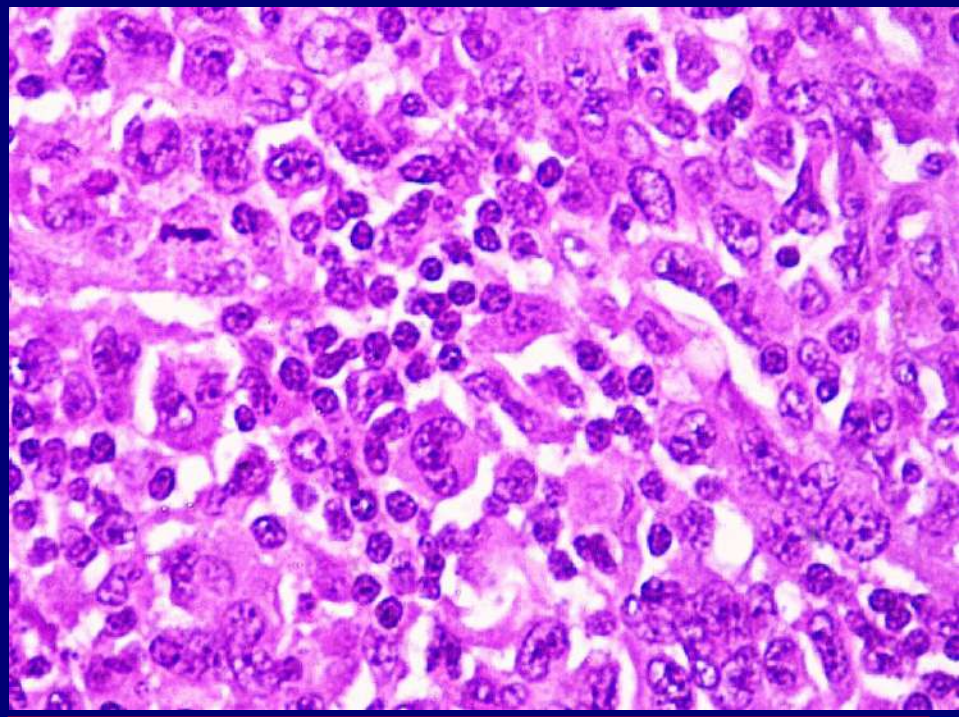
Case 3

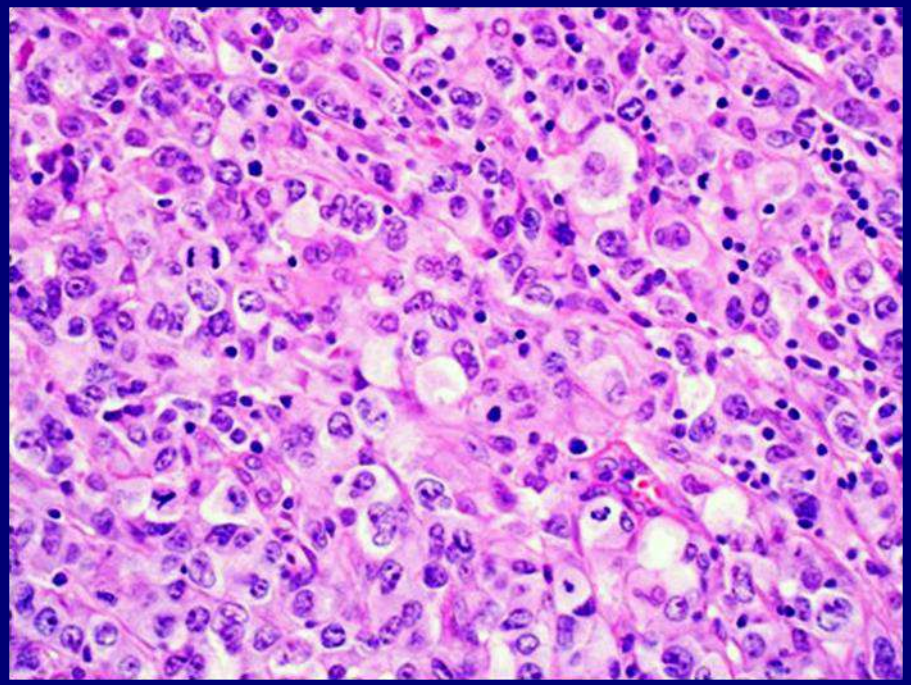
- 50/F
- C/O colicky pain upper abdomen gradually progressing x 2.5 months.
- Imaging & PET CT showed “Terminal ileum, Cecum and ascending colon mass” that is FDG avid.
- Few sub cm hyper-metabolic mesenteric LN are seen.
- Pt underwent ilio-ascending colon anastomosis in RML hospital in DEC 2011
- HPE report from referring hospital- NHL large cell type with MALT lymphoma component.
- Pt came to RGCI for further management

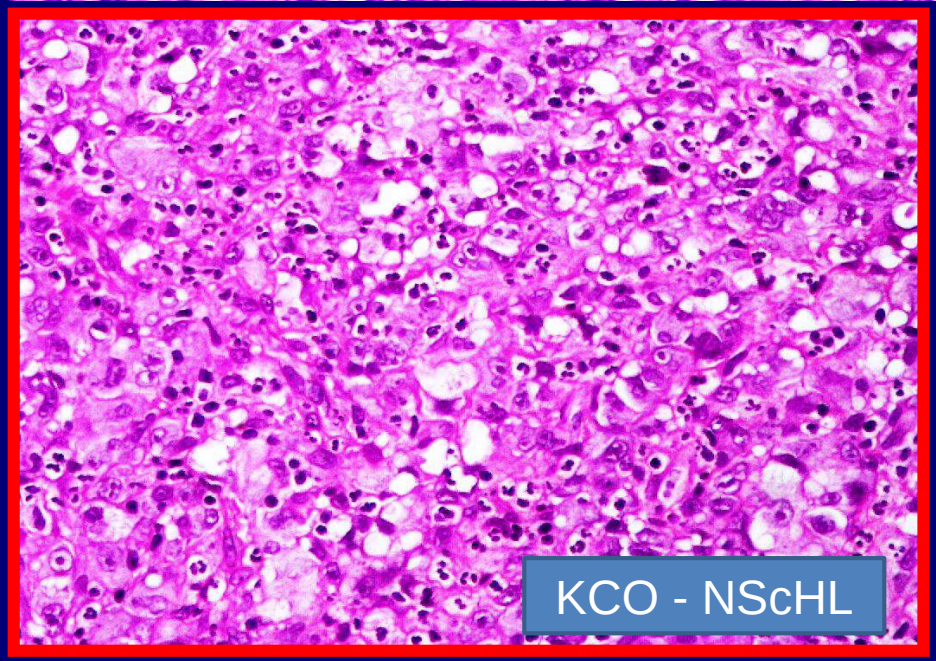




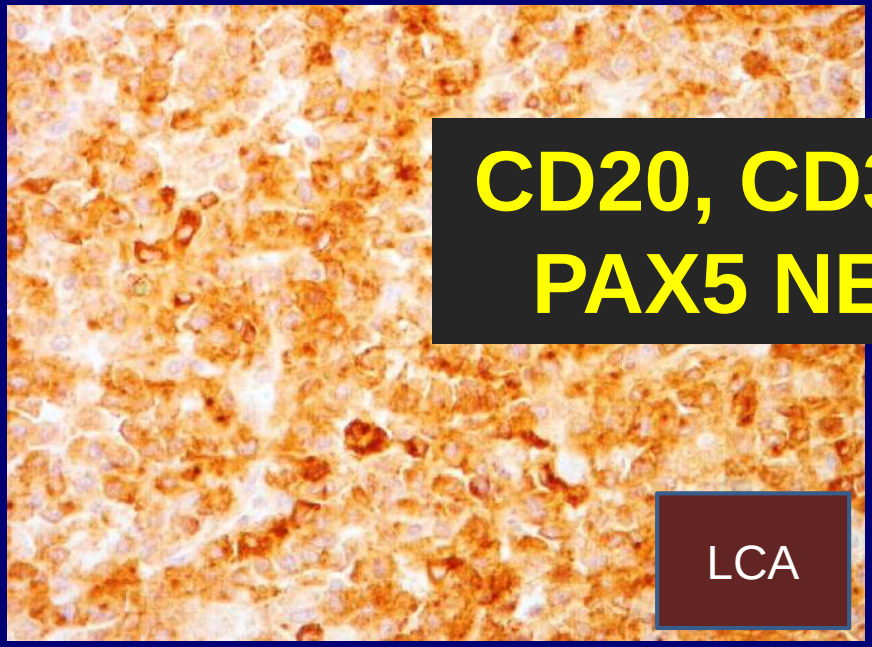


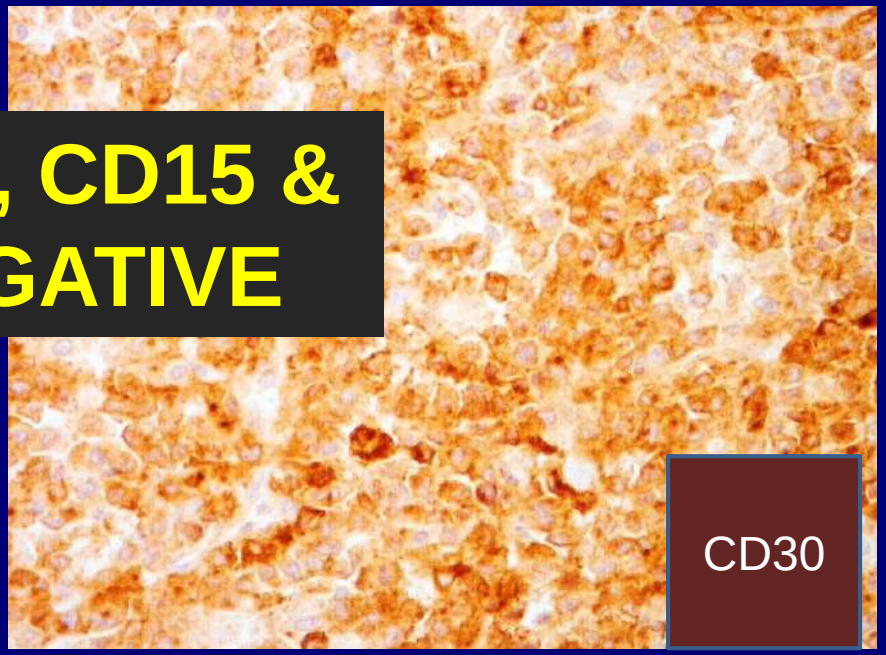


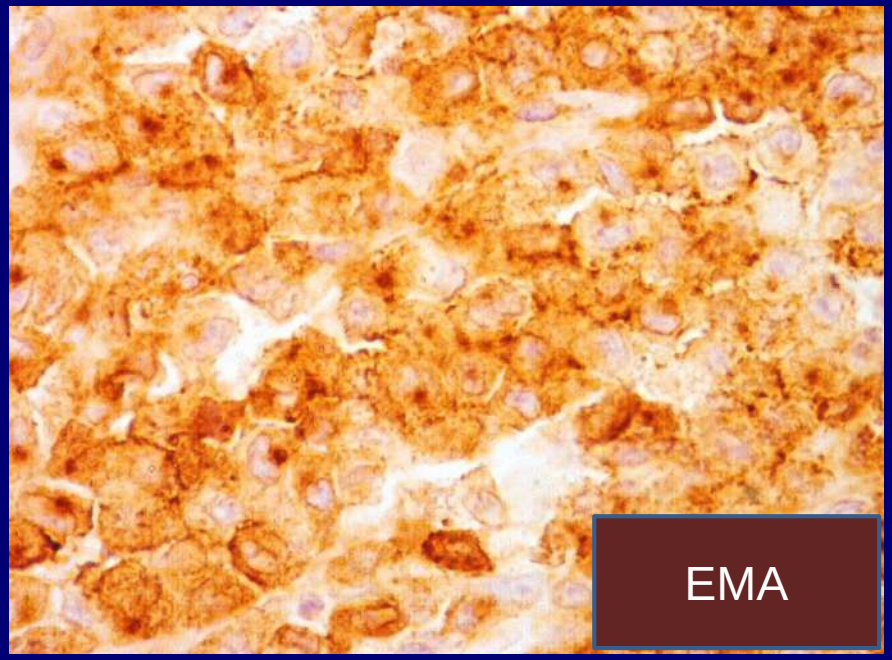


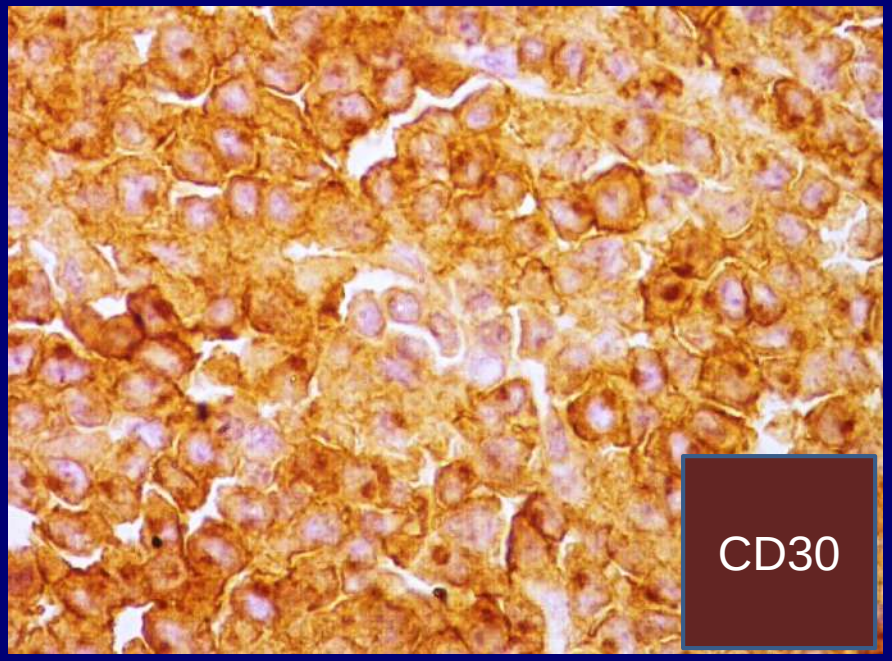

KCO - NScHL

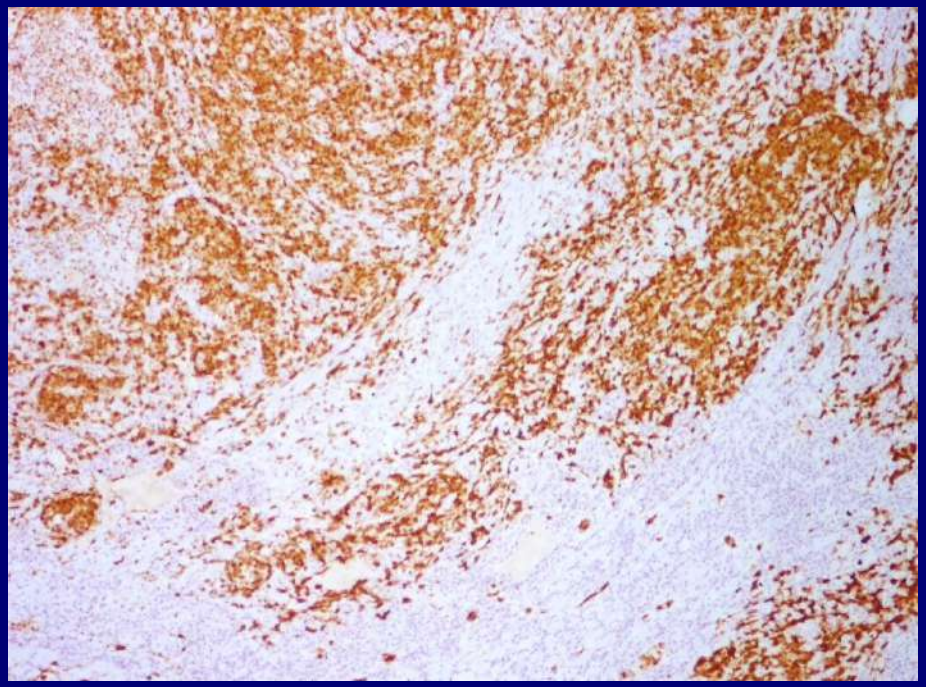
CD20, CD3, CD15 & PAX5 NEGATIVE



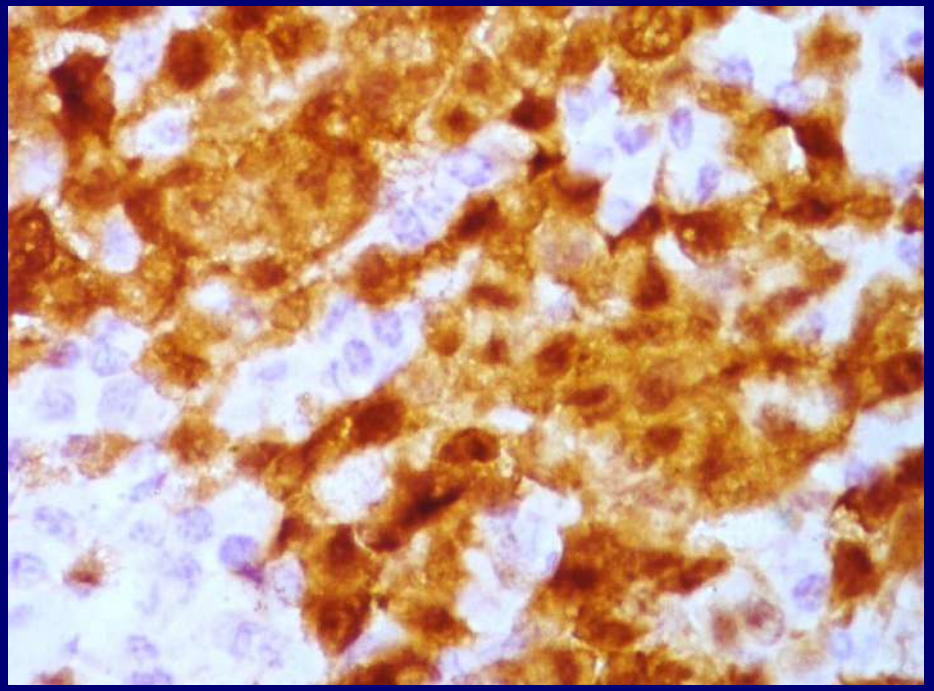






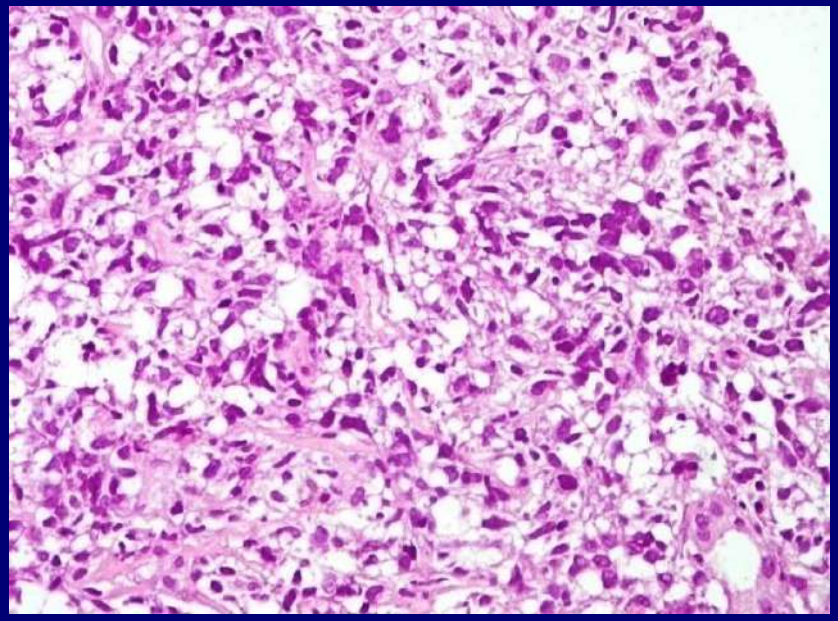


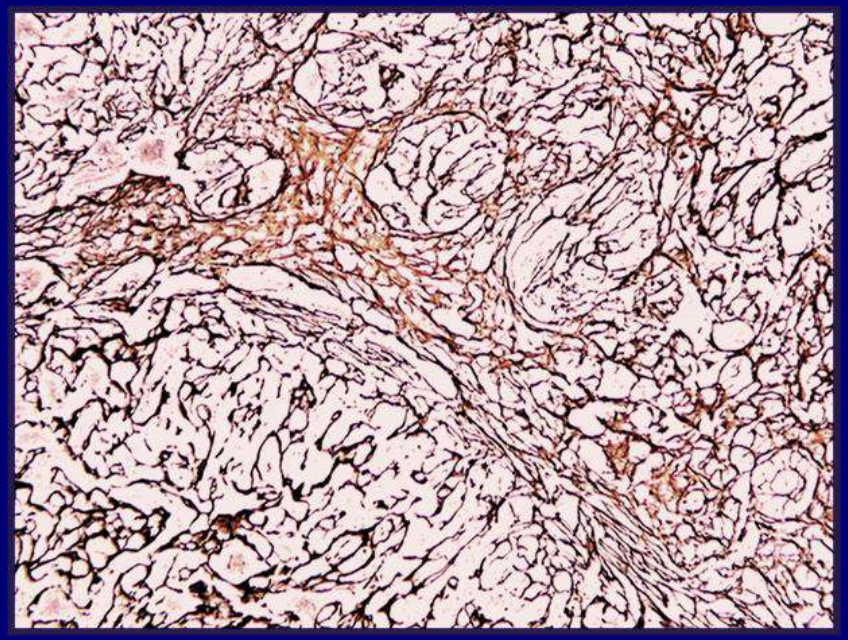
ALK1 POSITIVE

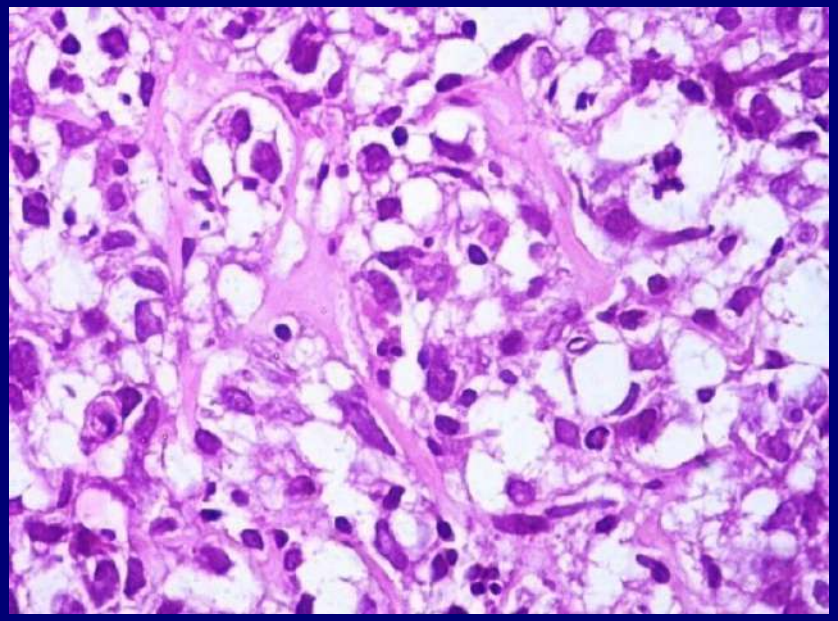


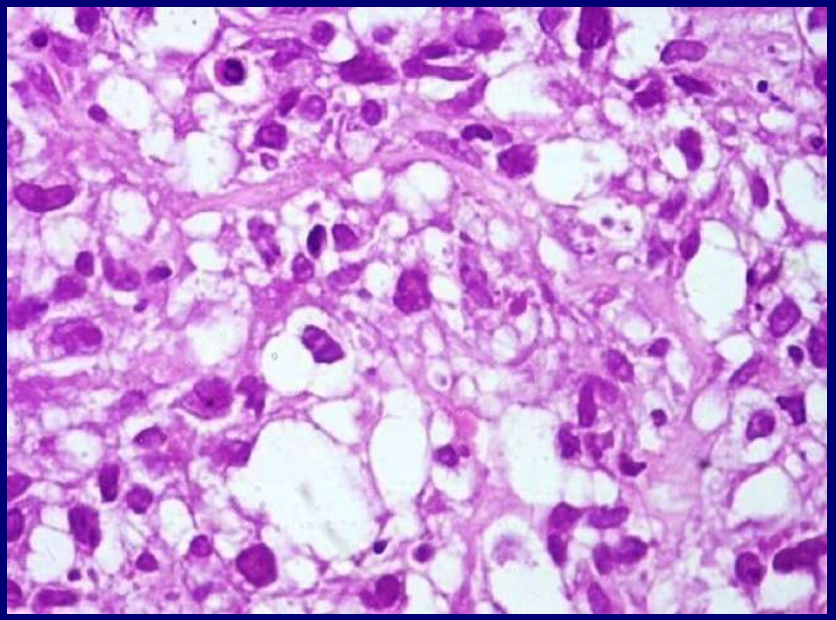
1. FINAL DIAGNOSIS: alk + ALCL.
2. Often confused with HL because of large neoplastic cells with CD30 positivity
3. High density of tumor cells. Syncytial variant however, can have high density too
4. LCA, EMA and PAX 5 important to distinguish from HL

- 21 years old
- ♀
- Cough for one month & Breathlessness for 15 days
- Chest X ray done outside had revealed a large mediastinal mass projecting on the left side
- PET-CT :
  - A predominantly necrotic soft tissue mass measuring 7.6 x 5 cm was seen with few peripheral nodular areas of hypermetabolism
- Needle biopsy

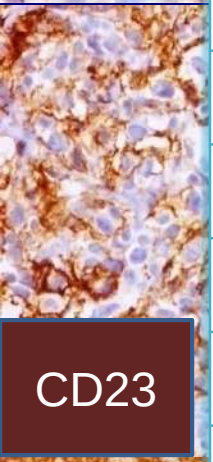


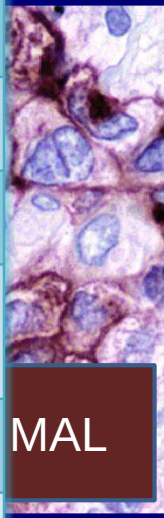






Antigen	Expression frequency
CD30	86%
CD45 and B-cell markers	100%
CD23	70%
CD15	0%
EBV	0%
Bcl6	80%
Mum 1	75%
Bcl-2	80%
BOB.1/Oct-2/PU.1	100%
MAL protein	70%
REL	100%
SIg	0%
FIG1	75%





More confounding is the "B-Cell Lymphoma, Unclassifiable, with features Intermediate Between DLBCL and Classical Hodgkin Lymphoma" – a gray zone lymphoma.

1. Lymphoma with morphologic, phenotypic, and molecular features overlapping DLBCL (PMBCL) and cHL
2. Rare; usually young adults 20-40 years, with a male predominance
3. Mediastinal mass most common, often with supraclavicular LNs; may involve only lymph nodes
4. Usually EBV –. But , several reports of EBV positive gray zone reported
5. Poor outcome, worse than either CHL or PMBL

Gray Zone NHL- BCLUc DLBCL & cHL

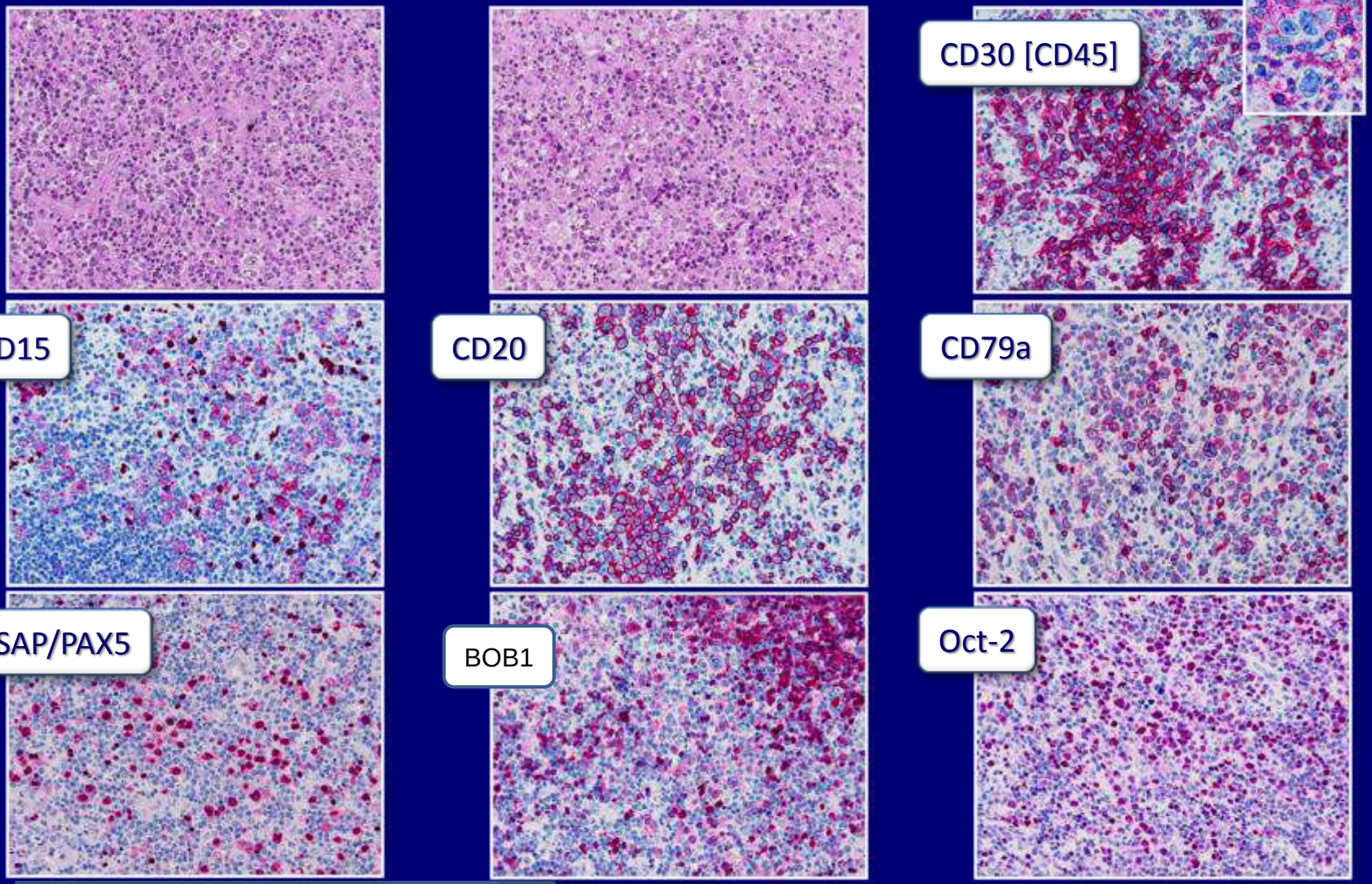
1. Morphology cHL
2. Neoplastic cell density high
3. Inflammatory milieu sparse

1. CD30+
2. CD15+
3. CD20+
4. Complete B cell program intact

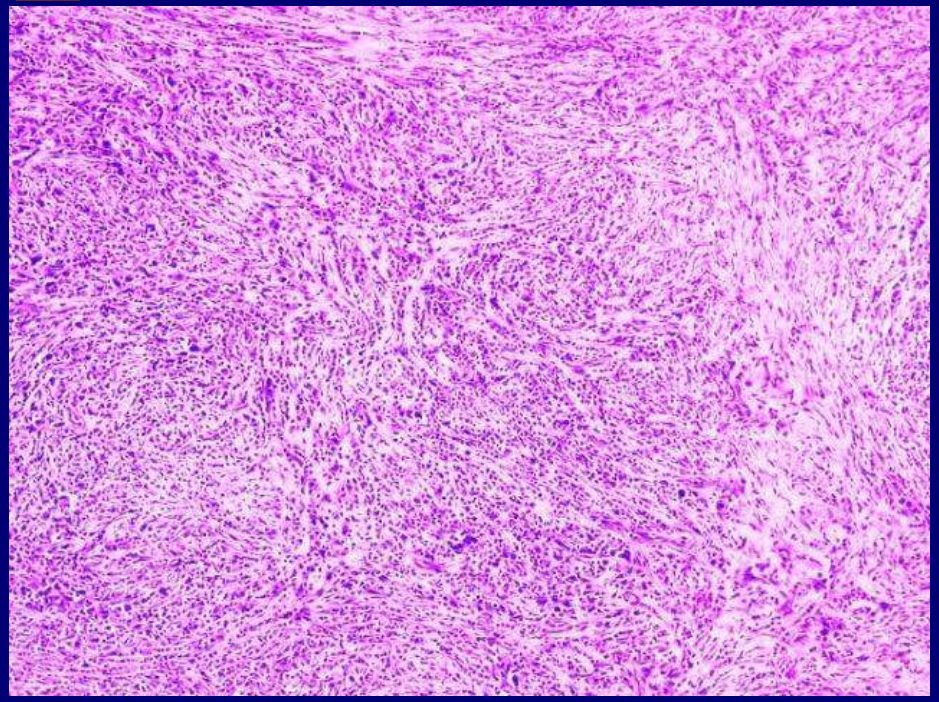
1. Morphology PMBCL
2. Lacunar or RS like cells
3. Inflammatory milieu at least focally

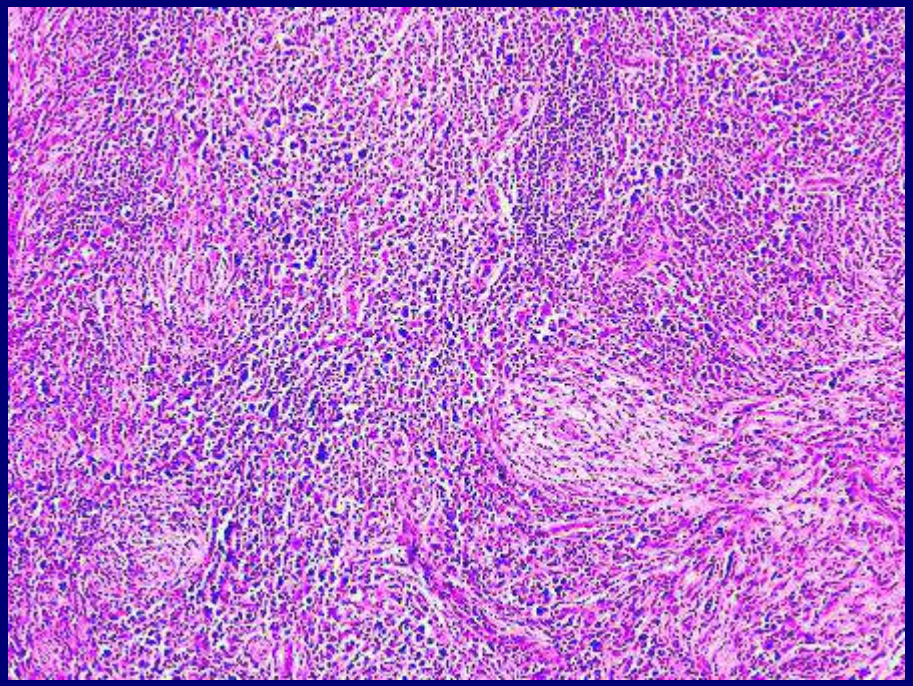
1. Strong CD15
2. Weak CD 20
3. Rest of the B cell program weakly expressed
4. EBV +

GREY ZONE LYMPHOMA: HODGKIN MORPHOLOGY & IMMUNOTYPE WITH COMPLETE B-CELL PHENOTYPE



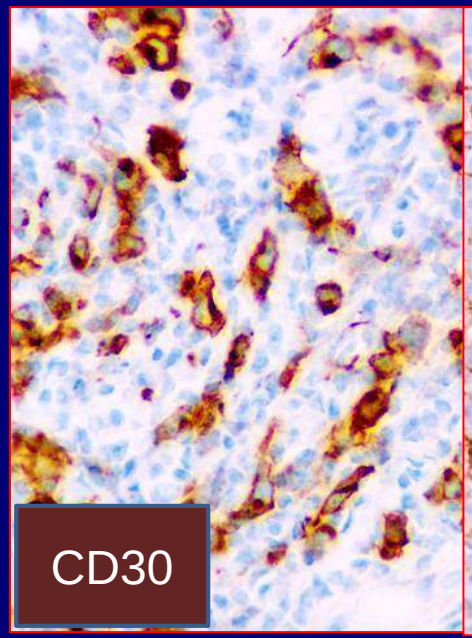
Courtesy Dr. Stefano Pileri

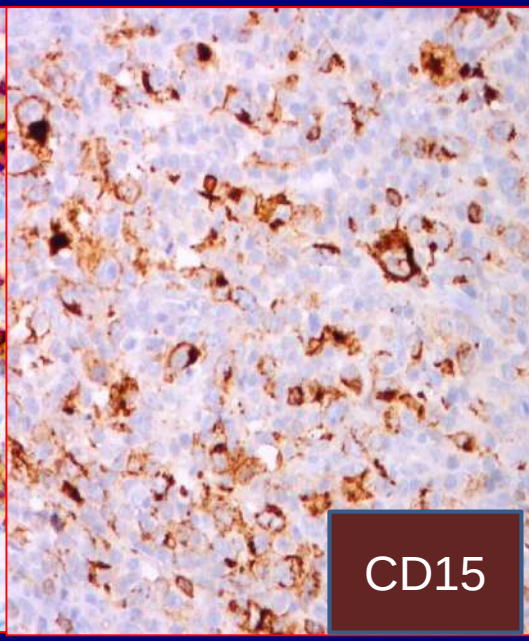




Fibrohistiocytic variant

1. Resembles pinwheels of Fibrous histiocytoma.
2. Strong CD 30 Positivity
3. **Sarcomatoid ALCL has similar morphology**





British national lymphoma investigation (BNLI) group has sub classified NS-CHL into two grades

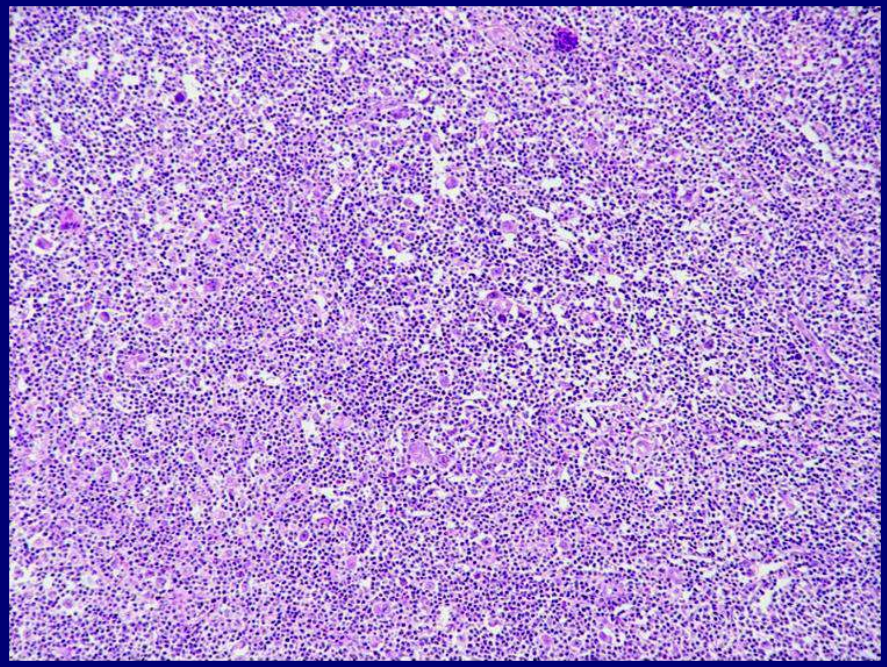
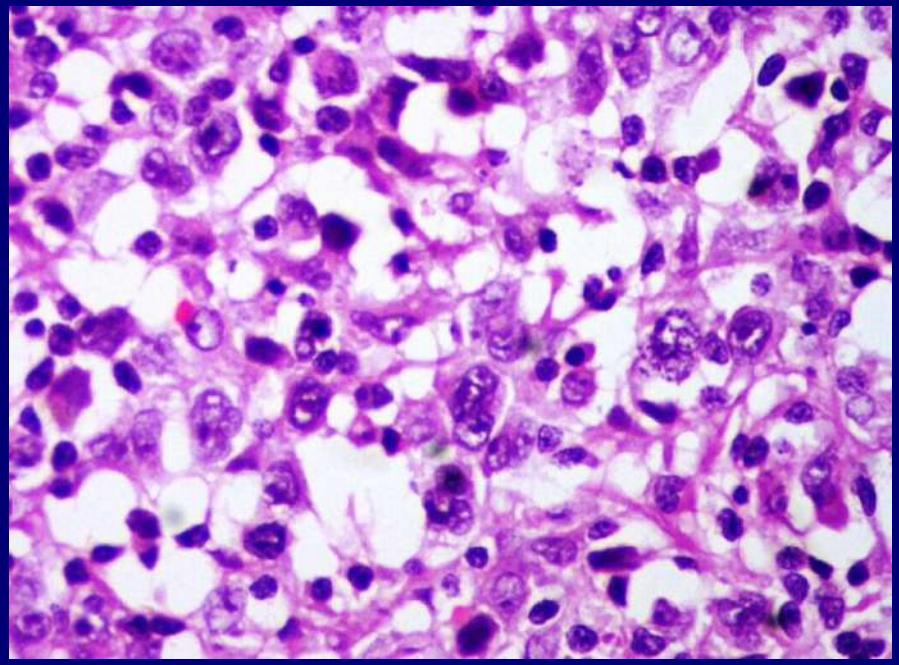
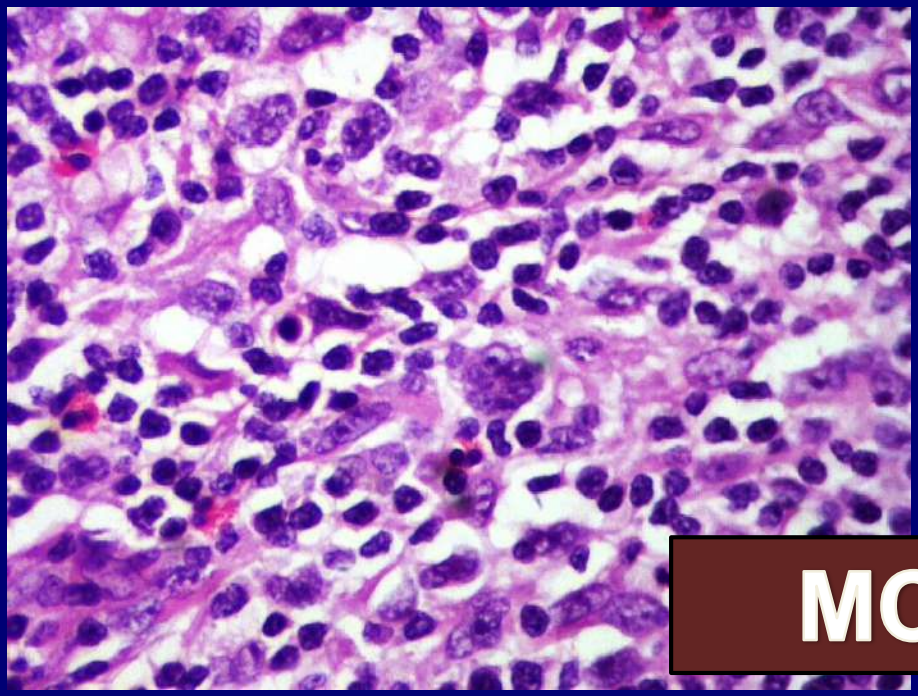
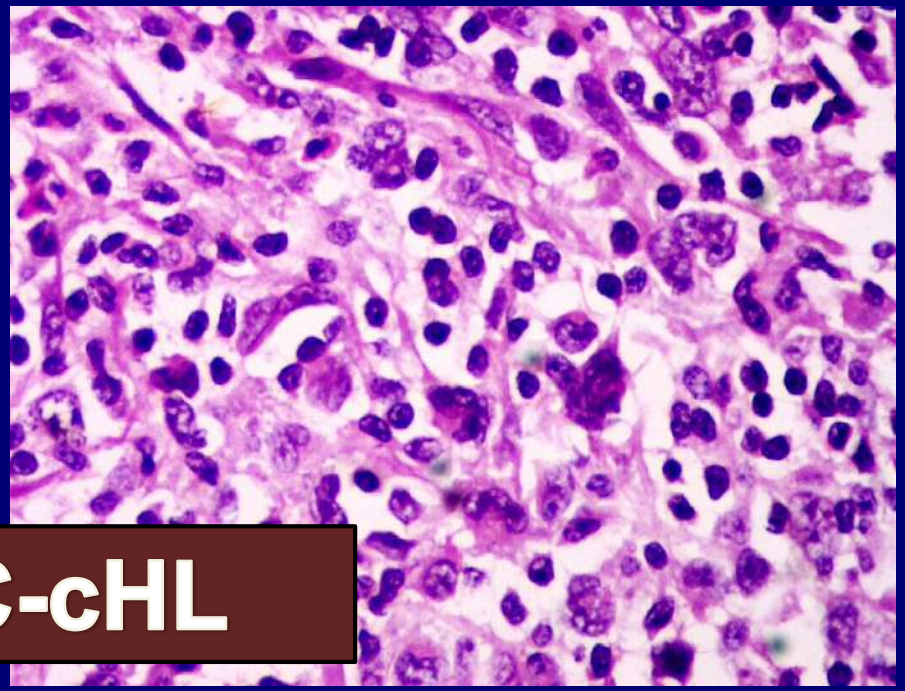
The term grade II is applied to cases showing one of the three following patterns:

I. More than 25% of the nodules have a cellular composition consistent with the pleomorphic or reticular subtype of NS-CHL/LDV

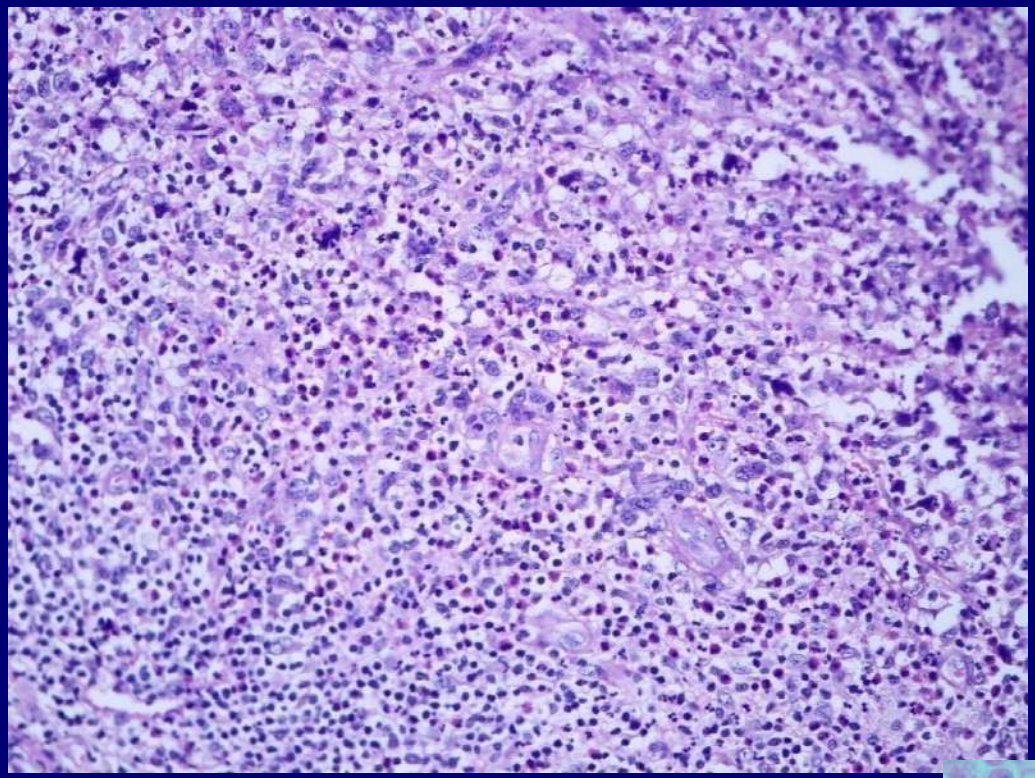
II. More than 80% of the nodules show a fibrotic or fibrohistiocytic composition.

III. More than 25% of the nodules contain numerous large bizarre or anaplastic cells, in the absence of depletion of the reactive small lymphoid component.

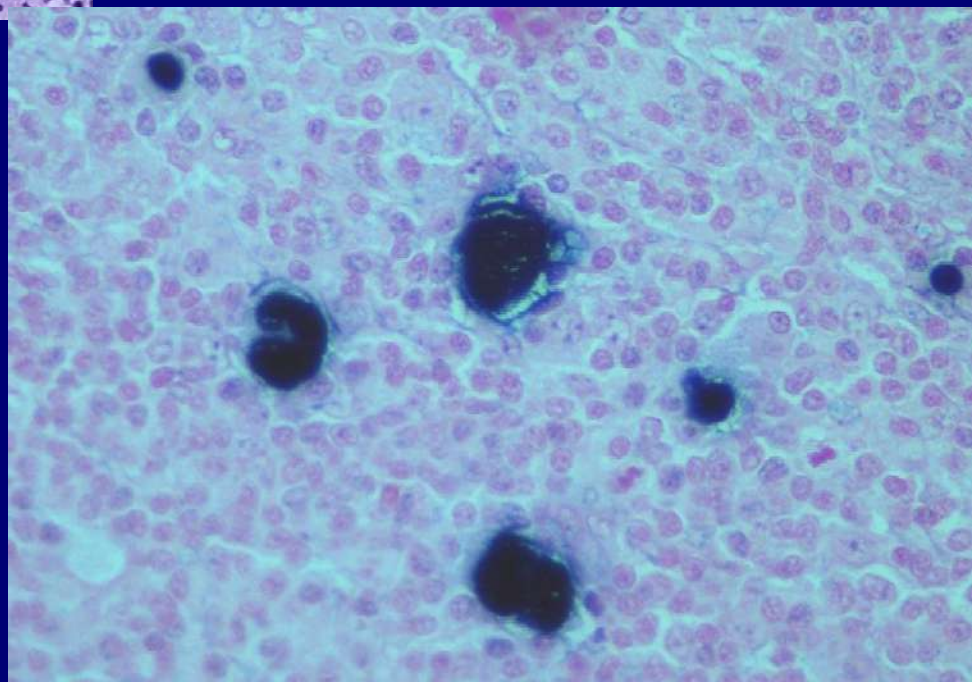
IV. WHO DOES NOT INCLUDE THE GRADING OF NS cHL

MC-cHL

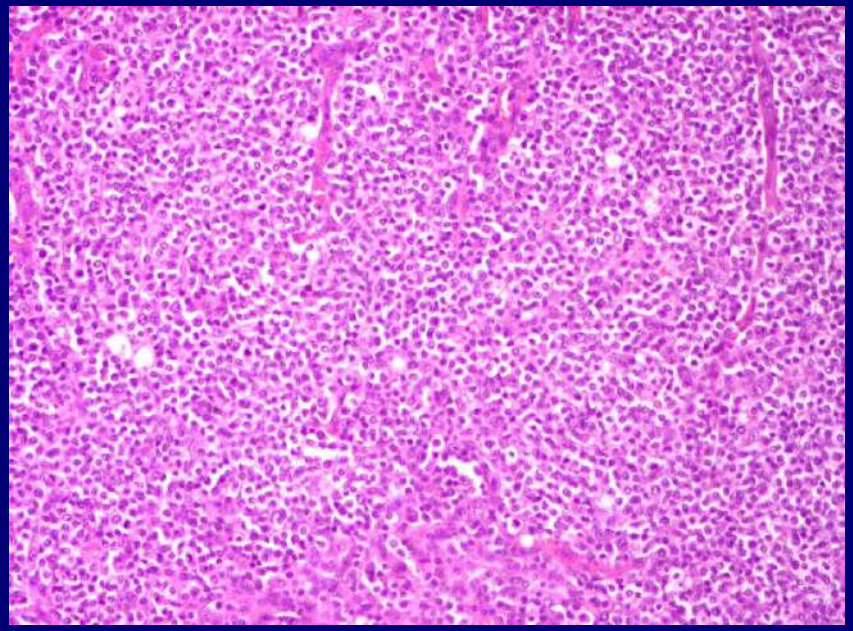
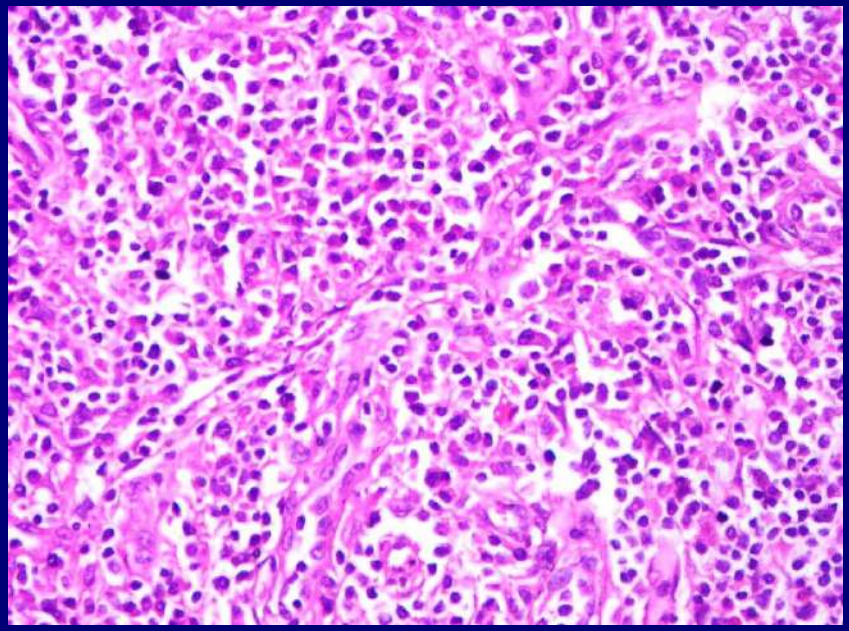
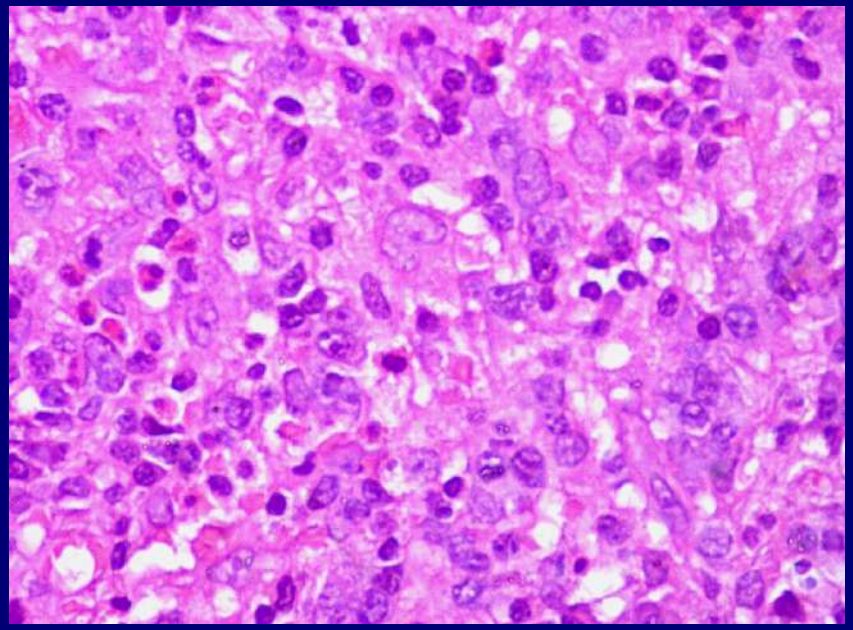
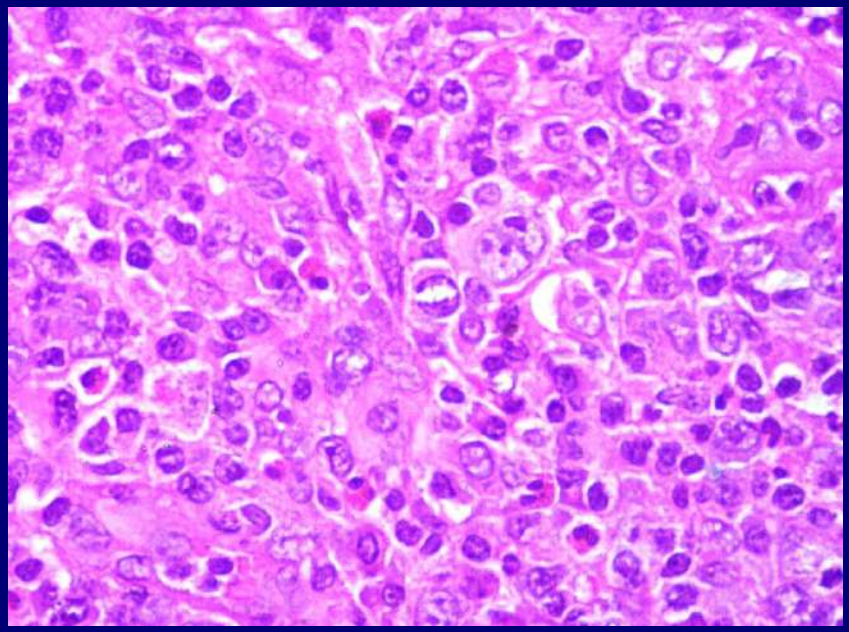


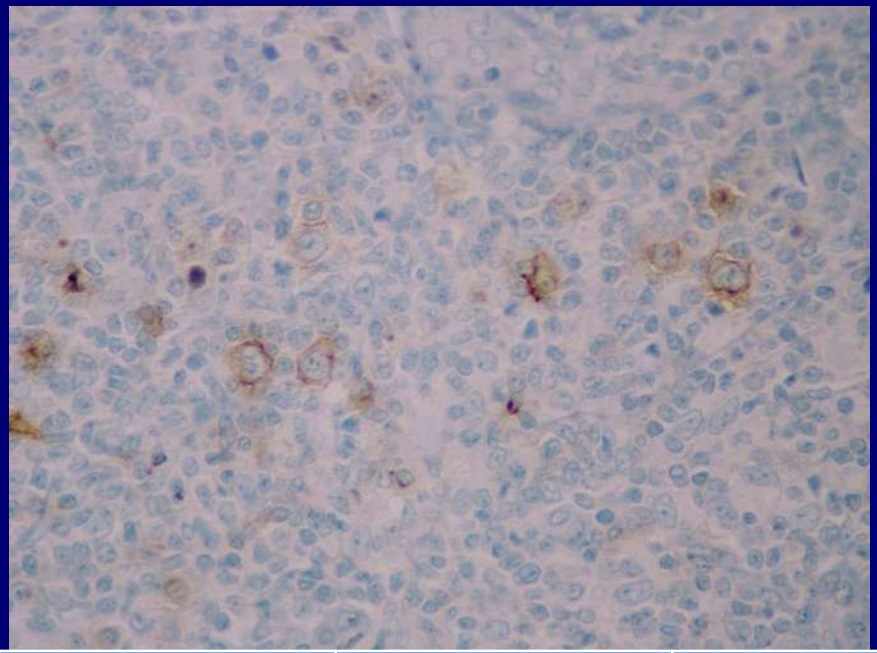
MC-cHL



Mixed Cellularity Classical Hodgkin Lymphoma: Differential Diagnosis

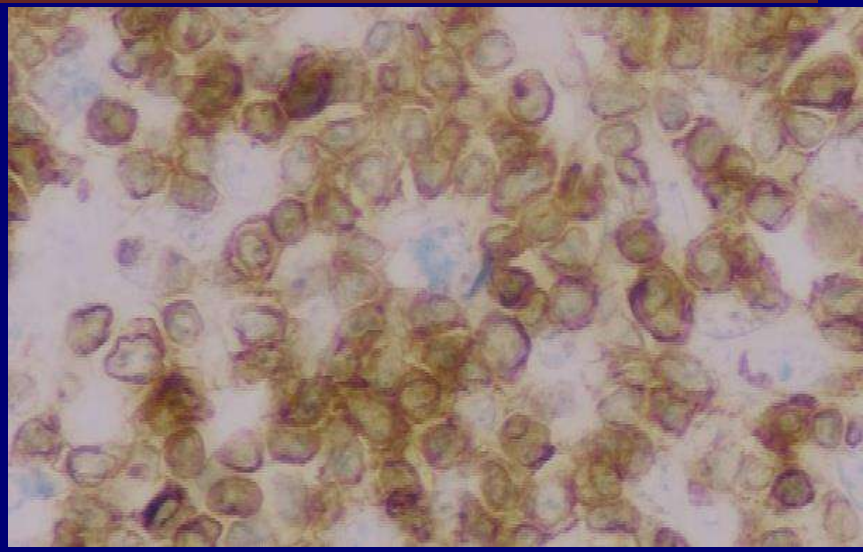
1. Peripheral T-cell lymphoma, nos – With R-S like cells
2. AITL with RS like cells
3. ALK+ anaplastic large cell lymphoma -– With lymphohistiocytic features
4. Reactive paracortical hyperplasi**a**



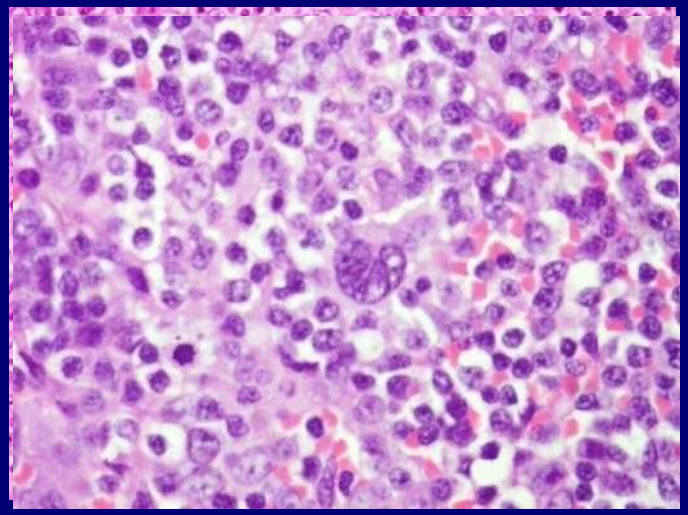
1. CD30 positive Cells in PTCL.
   ~ 30% PTCL can show CD30 expression
   - Not RS cells
   - LCA +
   - Negative for CD15, PAX 5
   - Aberrant loss of T cell Ag
   - TCR rearrangement

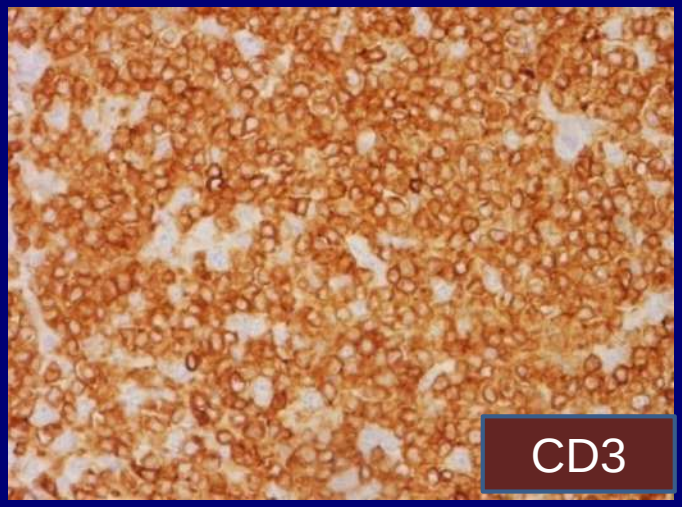
Immunotype	Mixed Cellularity Hodgkin Lymphoma	Peripheral T-Cell Lymphoma
CD30	100%	Variable. Up to 30%
CD15	85%	<5%
CD45	<5%	98%
CD3	~ 2%	98%
PAX5	99%	<5%
EBV	75%	1%

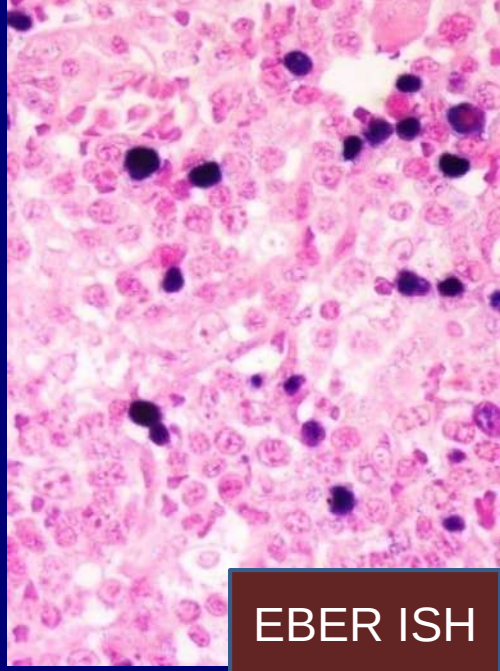


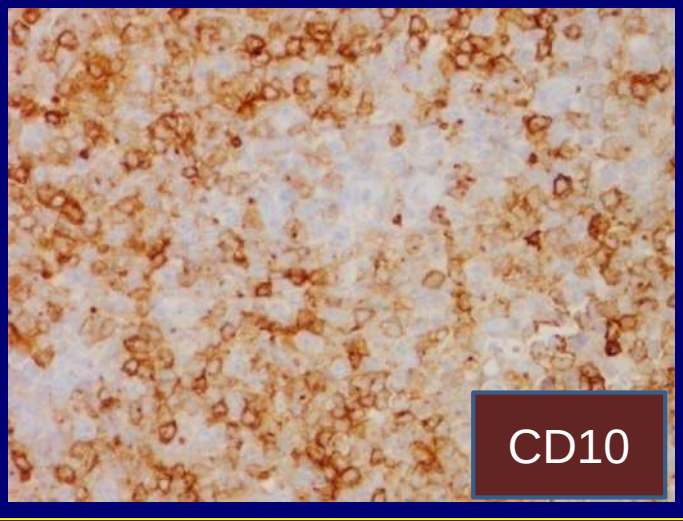
Neoplastic cells are CD3 positive .

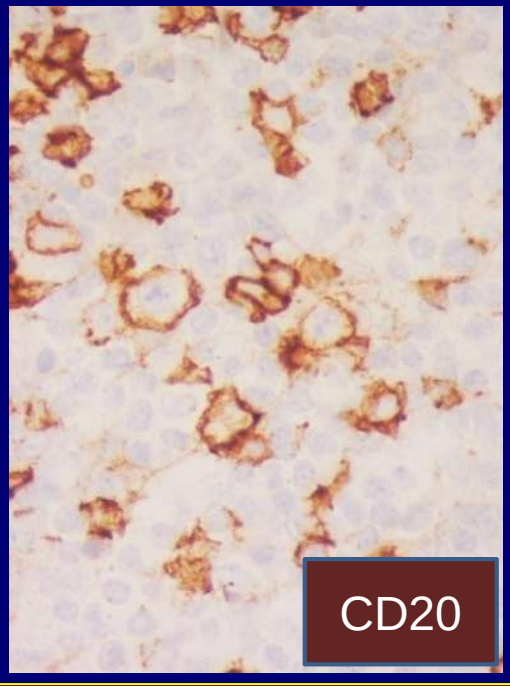
AITL WITH RS LIKE CELLS

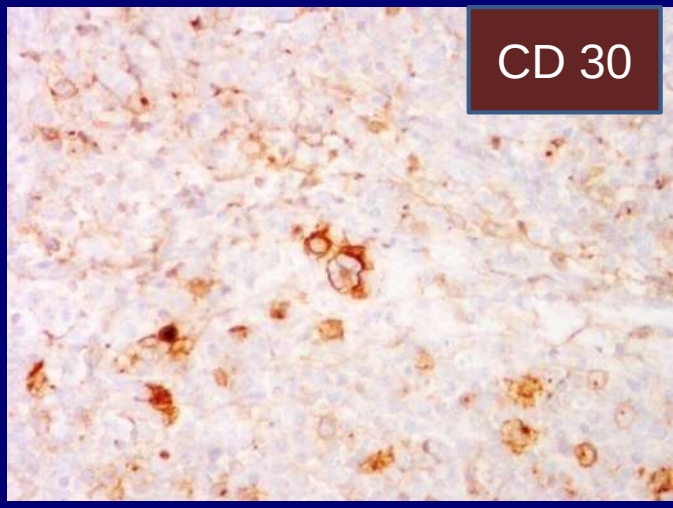








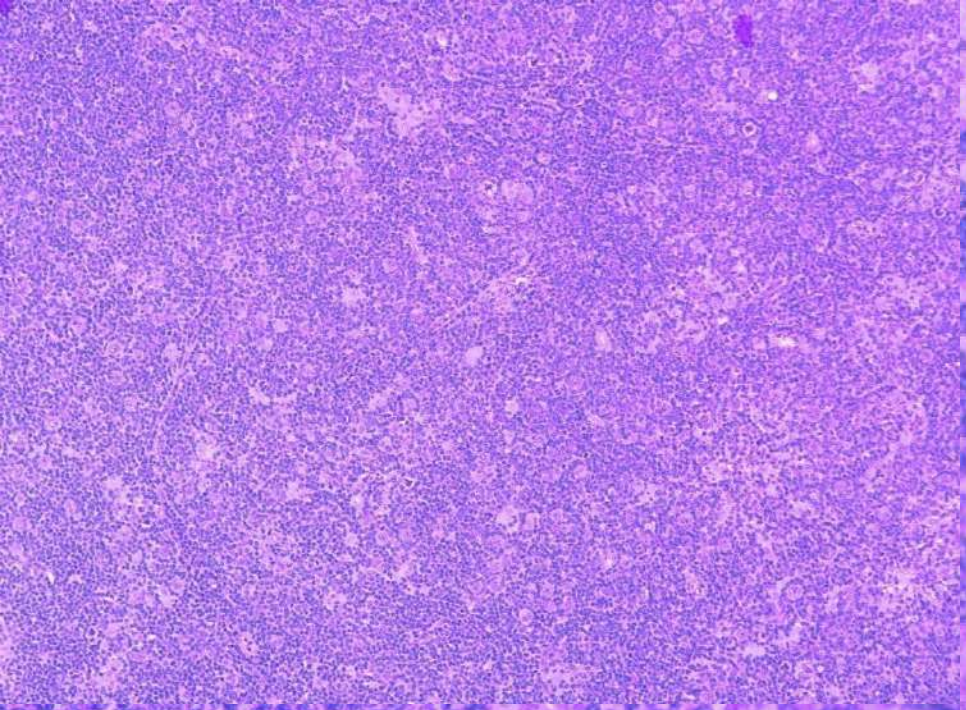
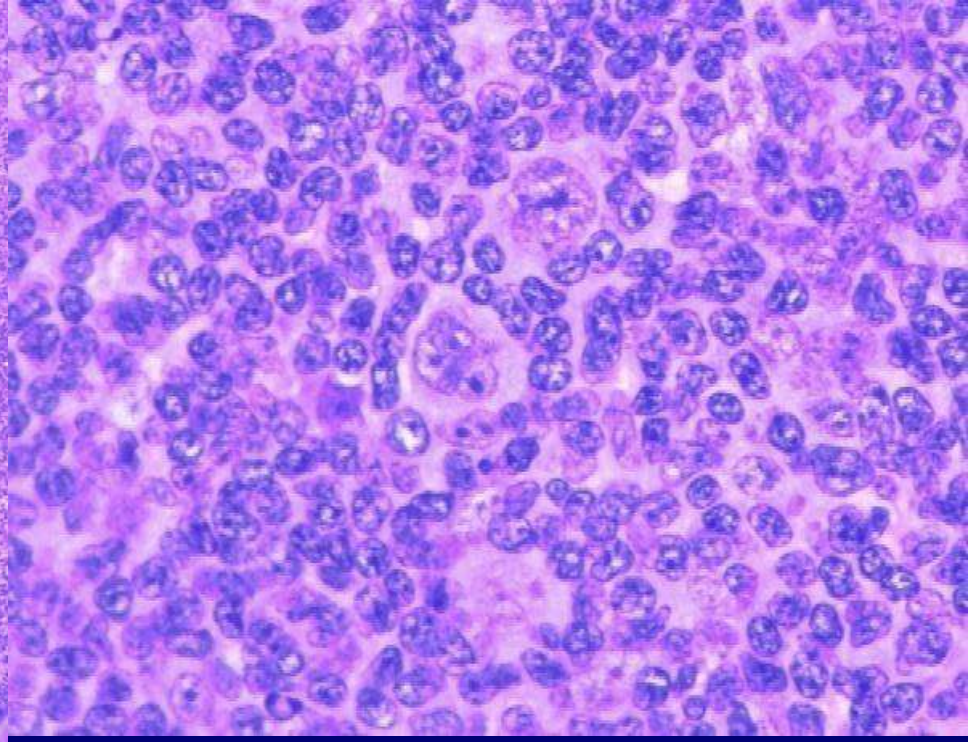
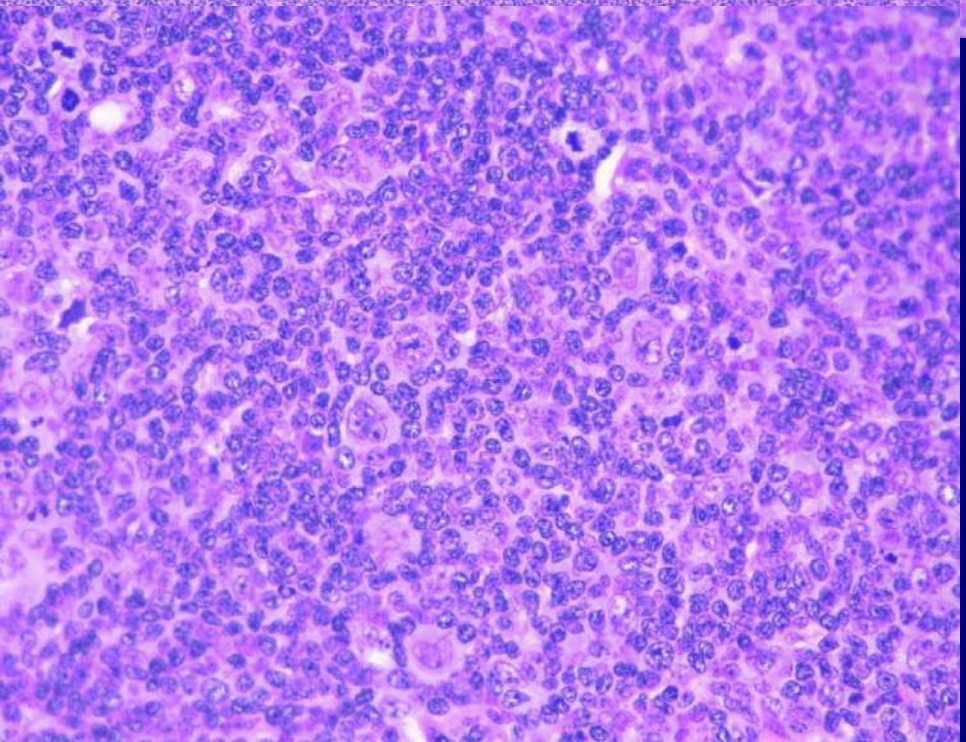
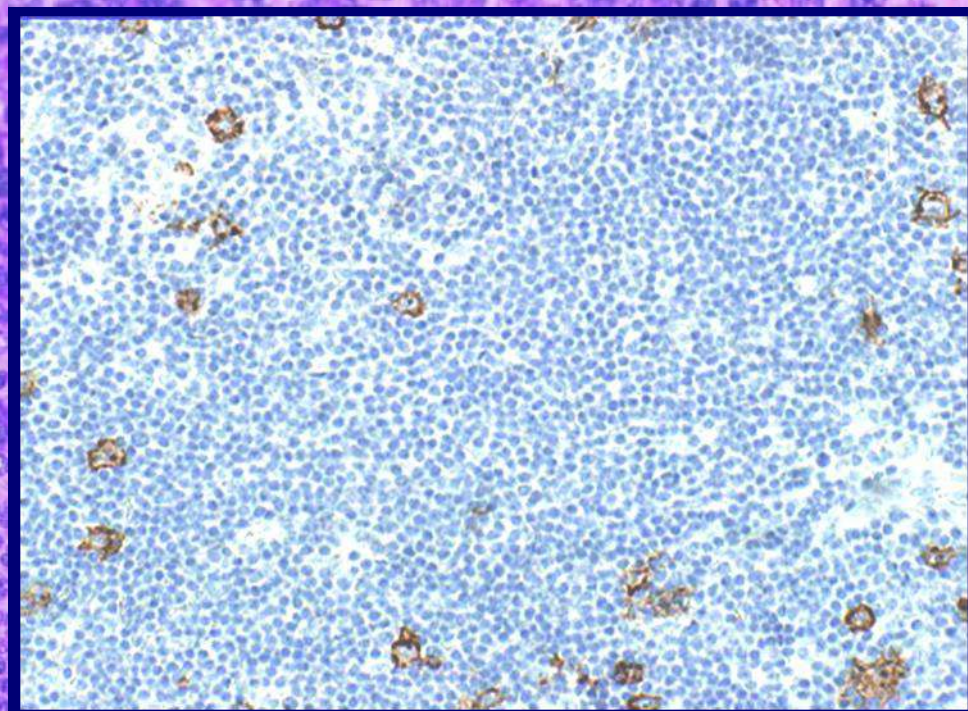


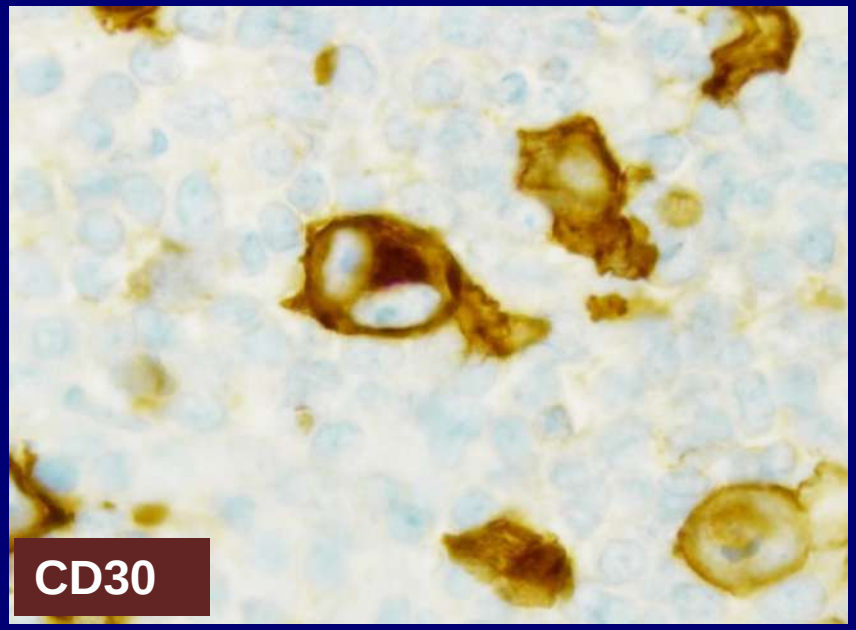


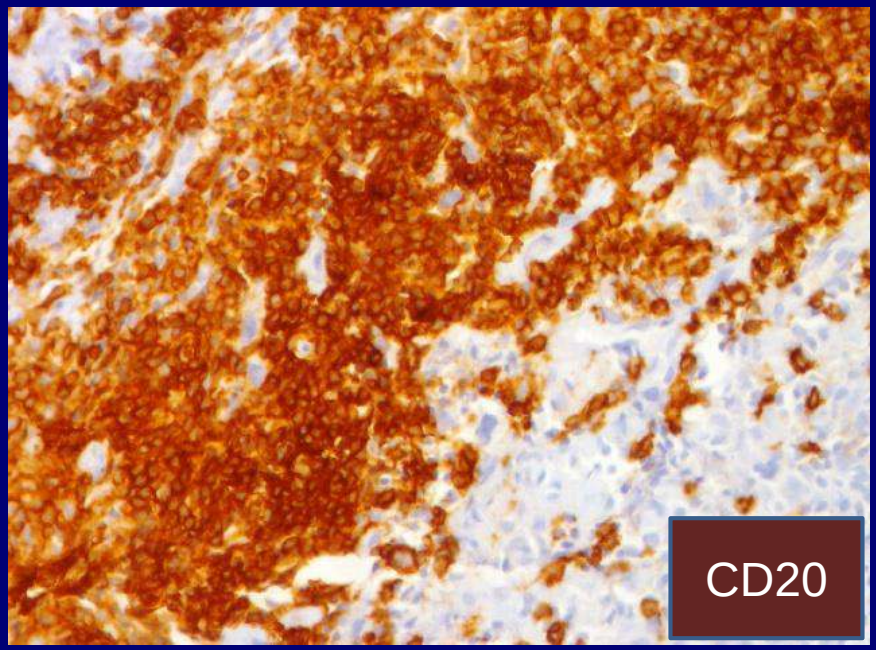
1. Identify the atypia of the background population including clear cells
2. Demonstrate THFC phenotype. Large Atypical Cells are of B lineage and can be CD 30 +

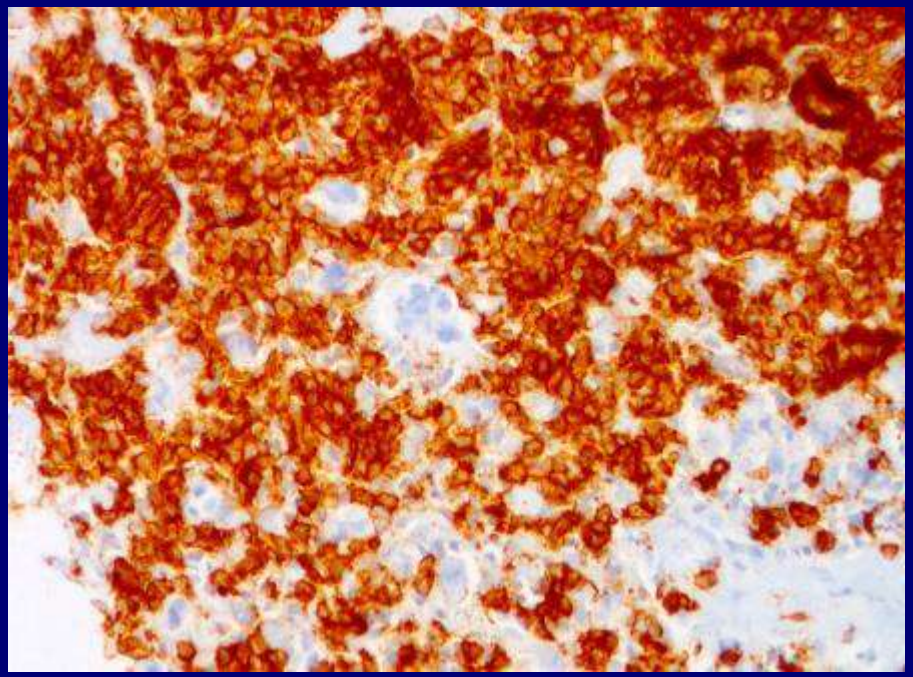
Lymphocyte Rich cHL

1. 5% of all cases
2. Distinct entity
3. Maintains fidelity in recurrences and relapses.
4. Intermediate between cHL and NLPHL
5. The LRCHL bears a clinical resemblance to NLPHL but on average affects an older group of people($\geq$50).
6. Less frequent recurrences (late recurrences, though prognostically inferior)
7. Mediastinal involvement rare but more common than NLPHL
8. Can be EBV positive

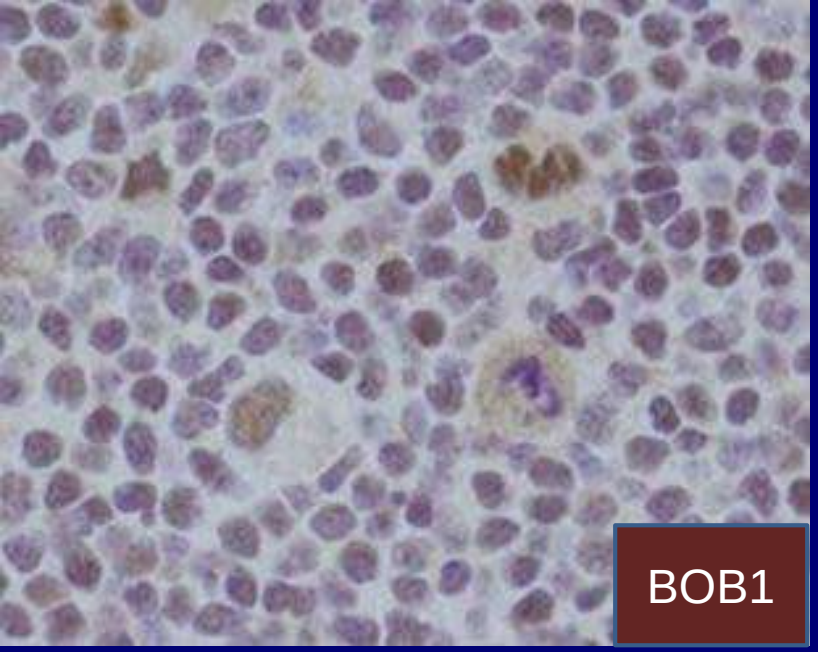







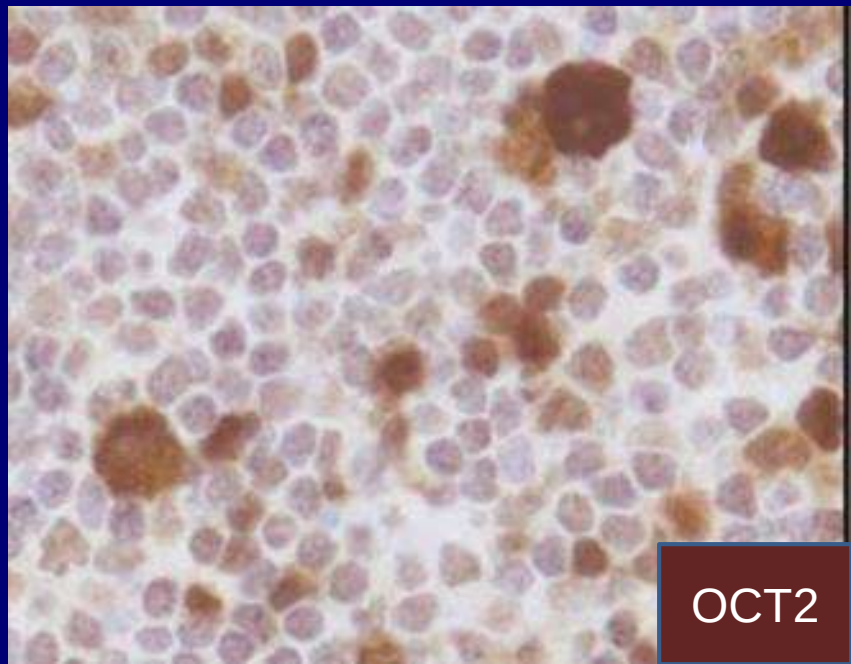




Neoplastic cells embedded in B cells (Like NLPHL)



1. **50% of LRCHL can express BOB 1 & OCT 2. 20% can also show CD57 rosettes.**
2. **LRCHL MIDWAY BETWEEN NLPHL & c HL**



D/D of Lymphocyte Rich Classical Hodgkin Lymphoma

1. NLPHL
2. TCRBL
3. Nodular SLL/CLL with large dysplastic cells

Features	TCRBL	LRClassical HL
Large cells	Variable morphology and size. Centroblast like, Immunoblast like, LP cell like, RS cell like	Reed-Sternberg cells and variants
Small lymphocytes	Often slightly activated	Usually non-activated
LCA in large cells	+	-
B cell markers	Uniformly CD20+ and CD79+; Oct-2/Bob.1+	CD20- or heterogeneous +; CD79-/+;
CD30 : CD15	-/+ : -	Oct-2/Bob.1 -, sometime one of it is positive
EBV	Always negative	Positive sometimes

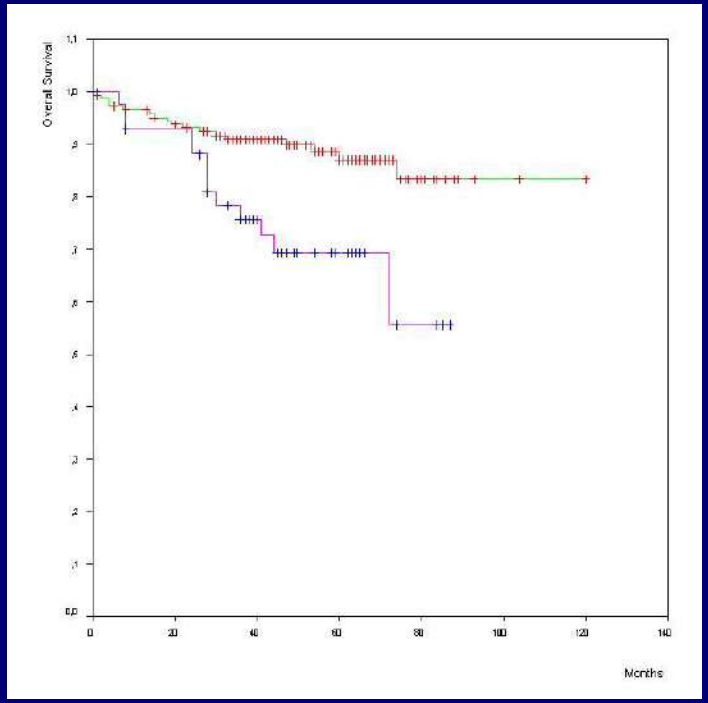
PROGNOSTIC MARKERS

Worse prognosis

1. CD68+ host cells
2. CD20+ H/RS cells
3. CD15- H/RS cells

1. Touati M, Delage-Corre M, Monteil J. **CD68-positive tumor-associated Macrophages predict unfavorable treatment outcomes in classical Hodgkin lymphoma in correlation with interim fluorodeoxyglucose-positron emission tomography assessment**. Leuk Lymphoma. 2015 Feb;56(2):332-41.
2. Tzankov A, Krugmann J, Fend F et.al. **Prognostic significance of CD20 expression in classical Hodgkin lymphoma: a clinicopathological study of 119 cases.** Clin Cancer Res. 2003 Apr;9(4):1381-6
3. L. S. Maeda, R. T. Hoppe, R. A. Warnke et.al. **Prognostic significance of CD15 expression in classical Hodgkin lymphoma (cHL): The Stanford University experience**. J Clin Oncol 28, 2010

4. **EBV+ in patients older than 60**
5. **EBV- in patients younger than 15**
6. **BCL2 expression in classical HL**



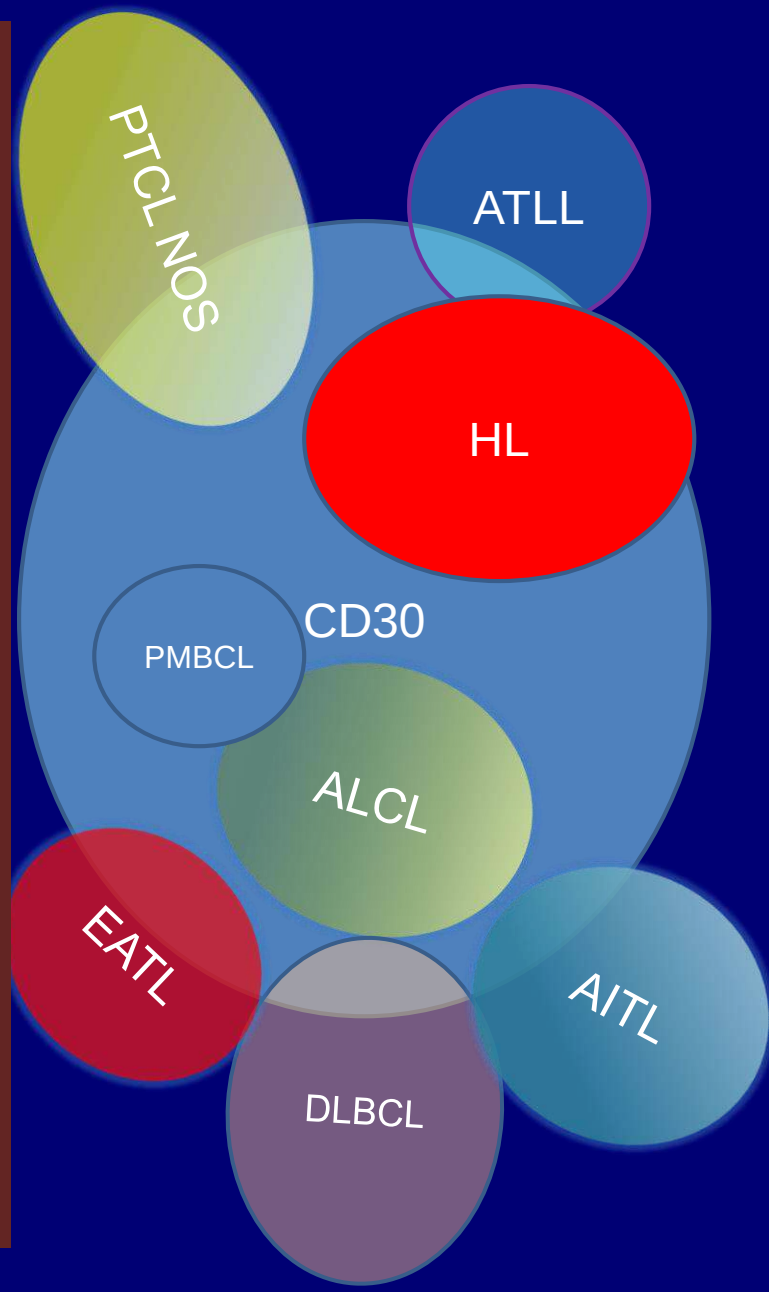
Role of EBV

1. K. J. Flavell, L. J. Billingham, J. P. Biddulph et al., "The effect of Epstein-Barr virus status on outcome in age- and sex-defined subgroups of patients with advanced Hodgkin's disease," *Annals of Oncology, vol. 14, no. 2, pp. 282–290, 2003.*
2. R. F. Jarrett, G. L. Stark, J. White et al., "Impact of tumor Epstein-Barr virus status on presenting features and outcome in age-defined subgroups of patients with classic Hodgkin lymphoma: a population-based study**,"**

Role of BCL2 overexpression on survival

1. *Blood, vol. 106, no.*7, pp. 2444–2451, 2005.
2. **Brink AA, et al. Mod Pathol1998;11:376.**
3. **van Spronsen DJ, et al. Histopathology 2000;37:420.**
4. **Rassidakis GZ, et al. Blood2002;100:3935**
5. ***Garcia, et al. Blood2003;101(2):681***

1. Classical Hodgkin lymphoma
2. Nodular lymphocyte predominant Hodgkin lymphoma (predominantly diffuse)
3. T-cell/ histiocyte-rich large B-cell lymphoma (TCRBL)
4. Reactive lymphoid hyperplasia with R-S-like cells
5. B-CLL/SLL with Reed-Sternberg-like cells
6. Peripheral T cell lymphoma



Thank You for Your Patience