KRISTIN HENRY

IMPERIAL COLLEGE LONDON
at
CHARING CROSS HOSPITAL

ADIAP XX INTERNATIONAL CONGRESS, November 24-26 2008, AGIERS

VIRUS ASSOCIATED LPD, Tuesday November 26th 10h.30-11h.30 2008

VIRUSES AND MALIGNANT DISEASE

Viruses are aetiologically linked to 20% of all human malignancies

Viruses and LPD*

Epstein Barr Virus

First virus shown to be implicated in a human tumour - Burkitt lymphoma
Then shown in many other LPDs (and epithelial neoplasms}
Many immunodeficiency- associated LPD also associated with EBV infection
Conversely, many EBV- associated LPD arise in immunodeficient patients
B-cell lymphomas are most common but HL and T-cell lymphomas also

Other oncogenic viruses

HTLV 1 and ATLL
HHV8 and Plasmablastic lymphoma; PEL
Hepatis C virus and splenic MZL

*LPD include non-malignant lymphoid proliferations as well as lymphomas

ONCOGENIC VIRUSES: common factors

- Tumours occuring in clusters in time and space
- Tumours more commonly occuring in youth*
- Immunosuppressed patients - favours viral oncogenesis
- Oncogenic DNA viral genome directly incorporated into host DNA
- Oncogenic RNA viral genome transcribed into DNA by reverse transcriptase prior to incorporation (oncogenic retrovirus)

* NB. Age related EBV-associated LPD

EPSTEIN BARR VIRUS

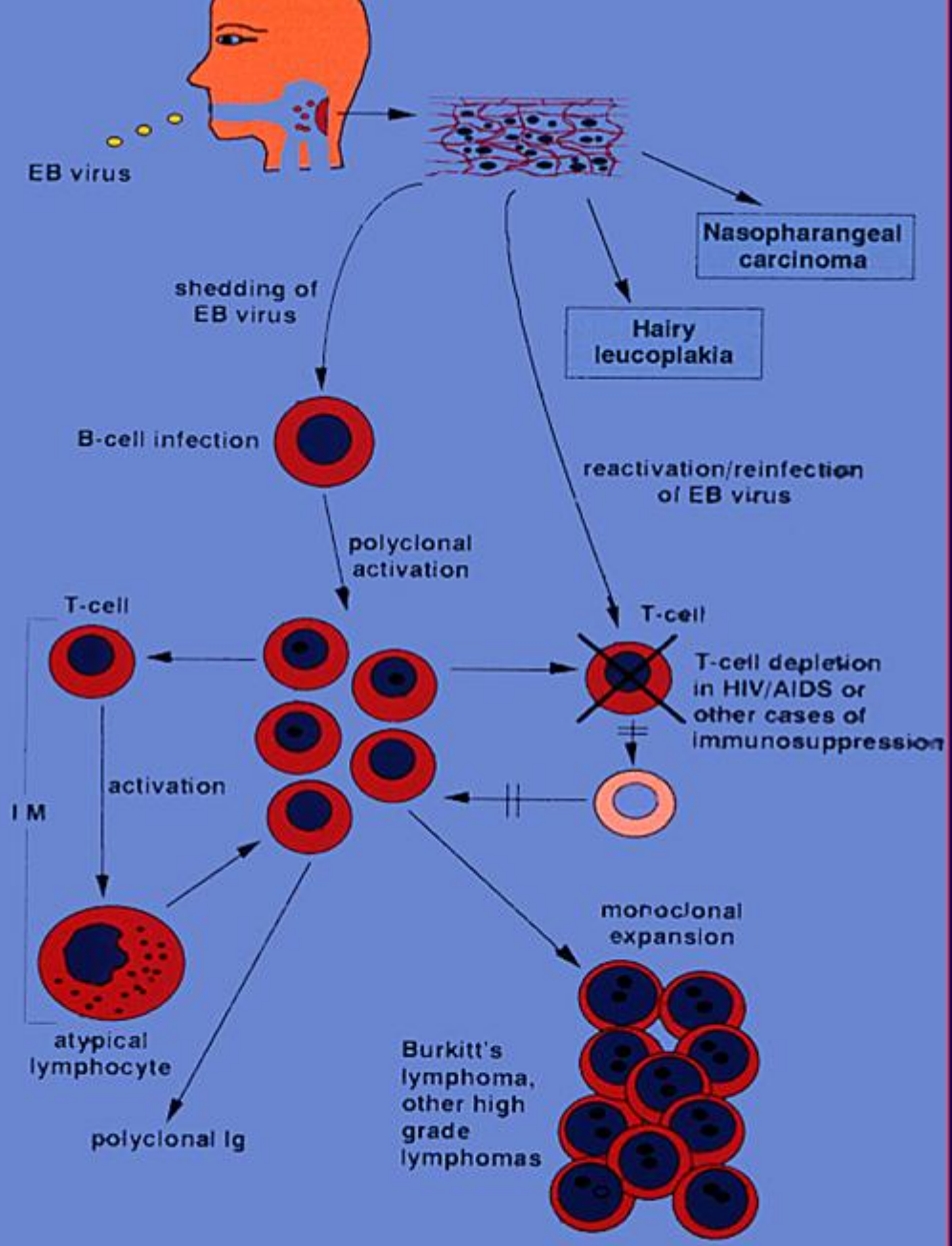
EPSTEIN BARR VIRUS (EBV)

- EBV: lymphotropic virus with a worldwide distribution; exists as type A and type B
- Resting B-cells (memory B-cells) infected in childhood and adolescents; EBV gains access to B-cells via CD21 R and escapes recognition by cytotoxic Tcells
- IM is a self limiting LPD representing a pathological response to EBV
- EBV uses viral proteins which mimic growth factors, transcription factors, anti-apoptotic factors to usurp control of cellular mechanisms that regulate cellular pathways
- EBV encoded RNAs (EBERs) are present in all infected cells but expression of EBV latency proteins (EBNAs, LMPs) differ in different types of LPD
- EBNA 1 is required for survival of infected cells and is found in all EBV associated LPD and other malignancies
- EBNA 2 is a transforming protein which can immortalise and cause non-malignant transformation of any GC derived B cell in absence of T-cell control

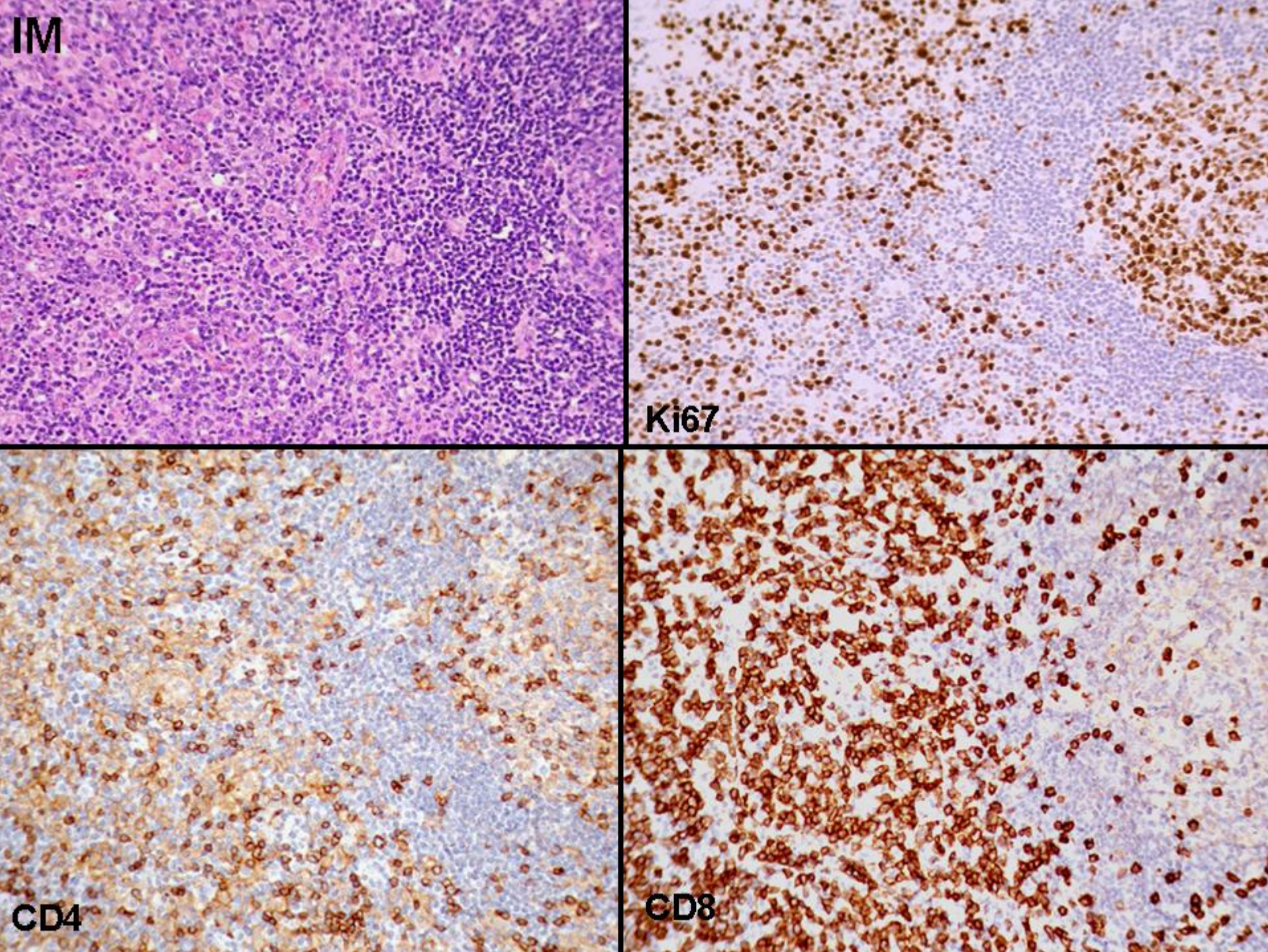
EBV LATENCY PATTERNS

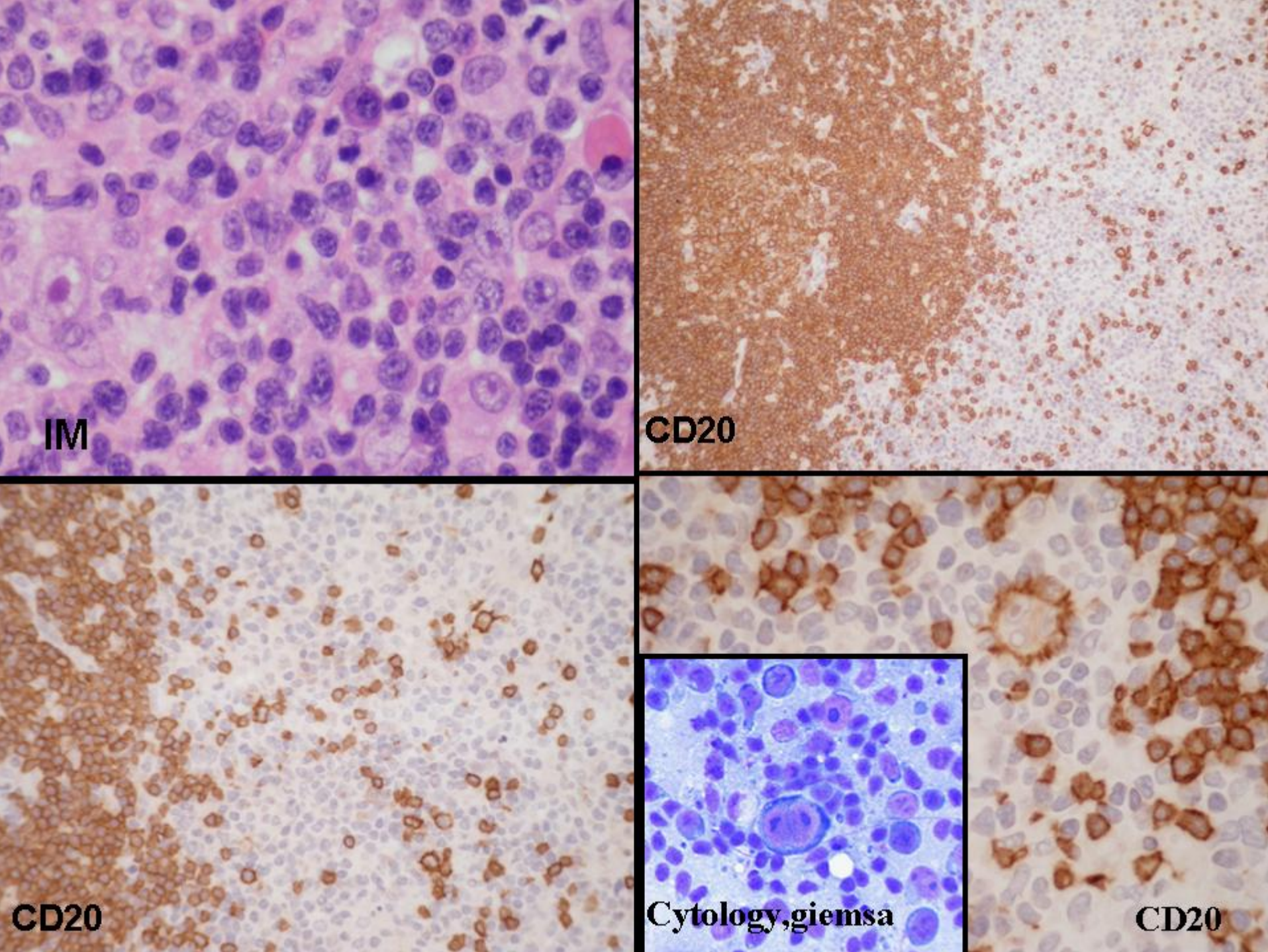
PATTERN*	GENE EXPRESSION	DISEASE
Latency I (restricted)	EBNA 1+ve EBNA 2-ve LMPs –ve	BL
Latency II (restricted)	EBNA 1+ve LMPs+ve EBNA 2-ve (rarely EBNA 2+ LMPs -)	IM, HD, EBV+ TCL
Latency III (full pattern)	EBNAs 1-6 +ve LMPs 1, 2A & 2B+ve	LBCL & IAL-TCL PTLD, other I LPD

* EBERs1 & 2 (EBV encoded RNAs) expressed in all diseases

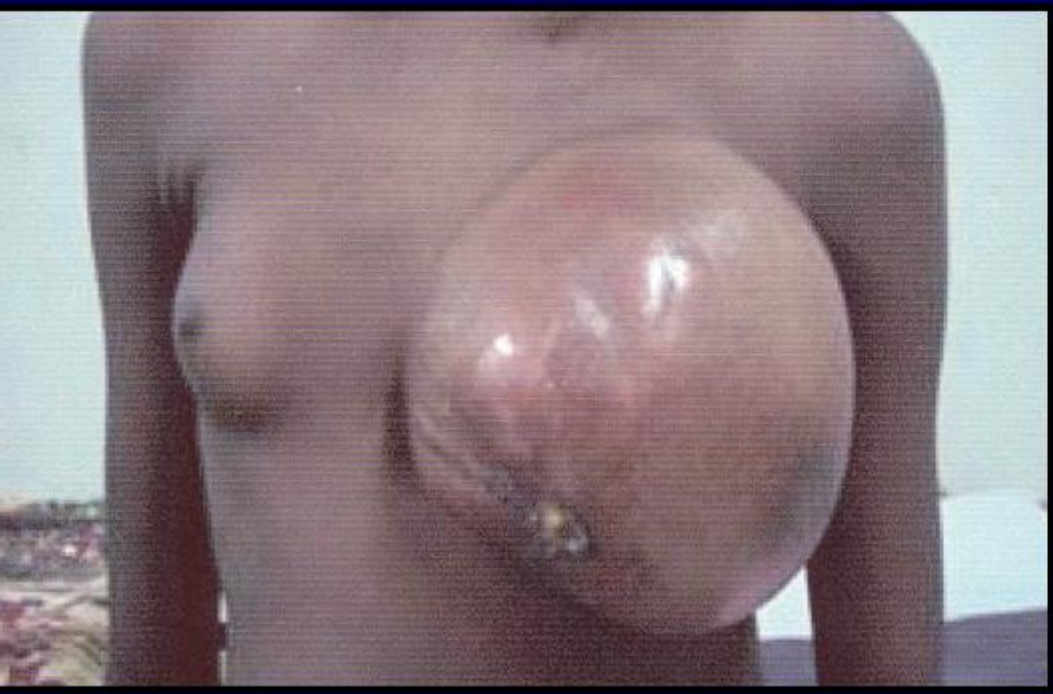


SCHEMATIC RECONSTRUCTION OF EFFECTS OF EB VIRUS IN NORMAL AND IMMUNODEFICIENT INDIVIDUALS


IM
Ki67
CD4
CD8


IM
CD20
CD20
Cytology,giemsa
CD20

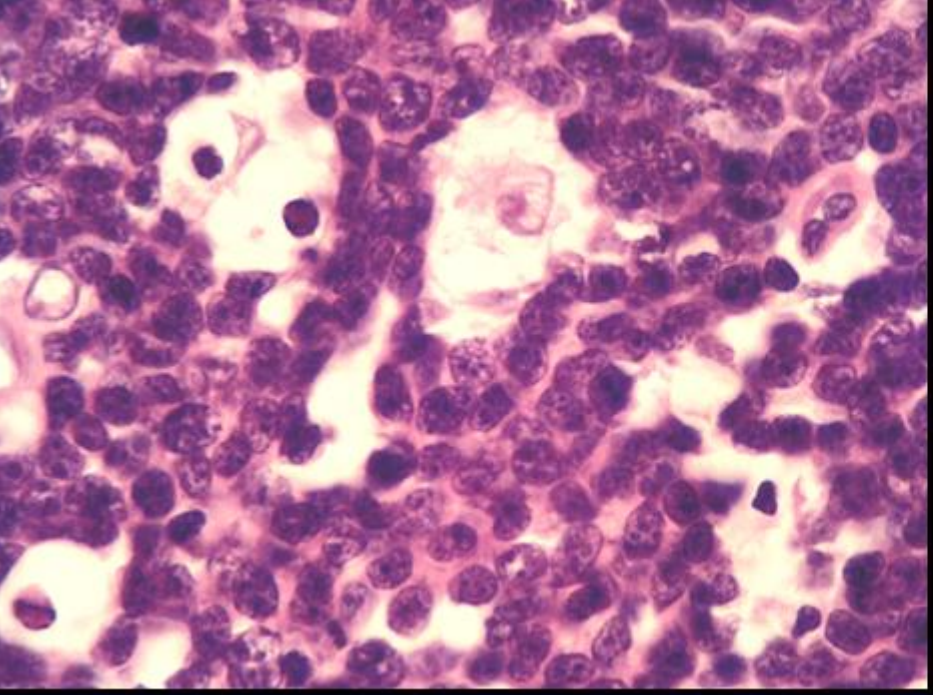
Burkitt lymphoma

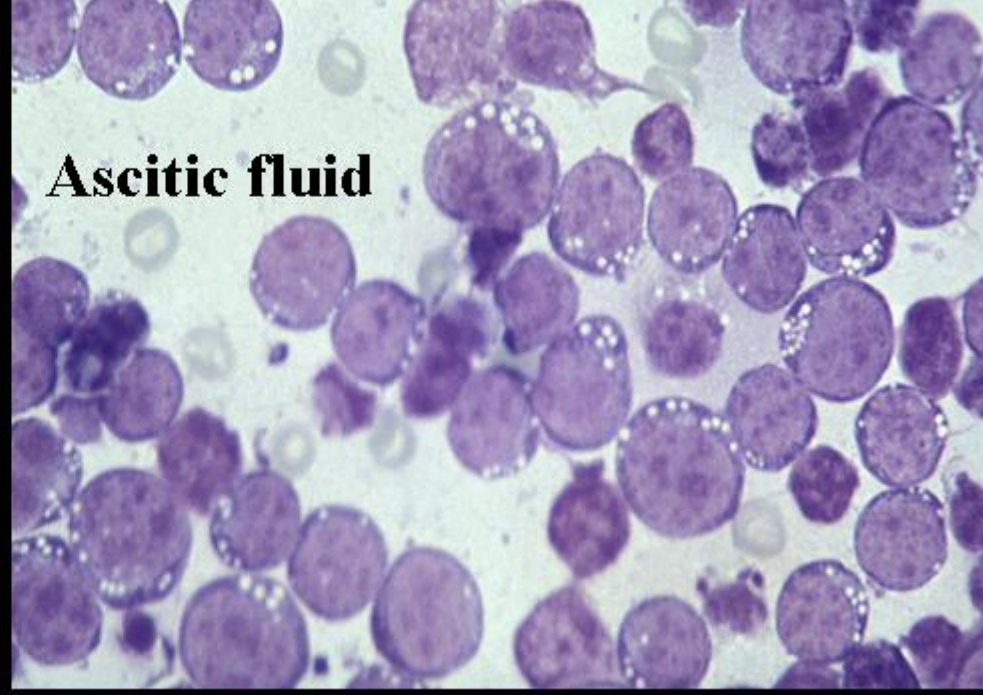


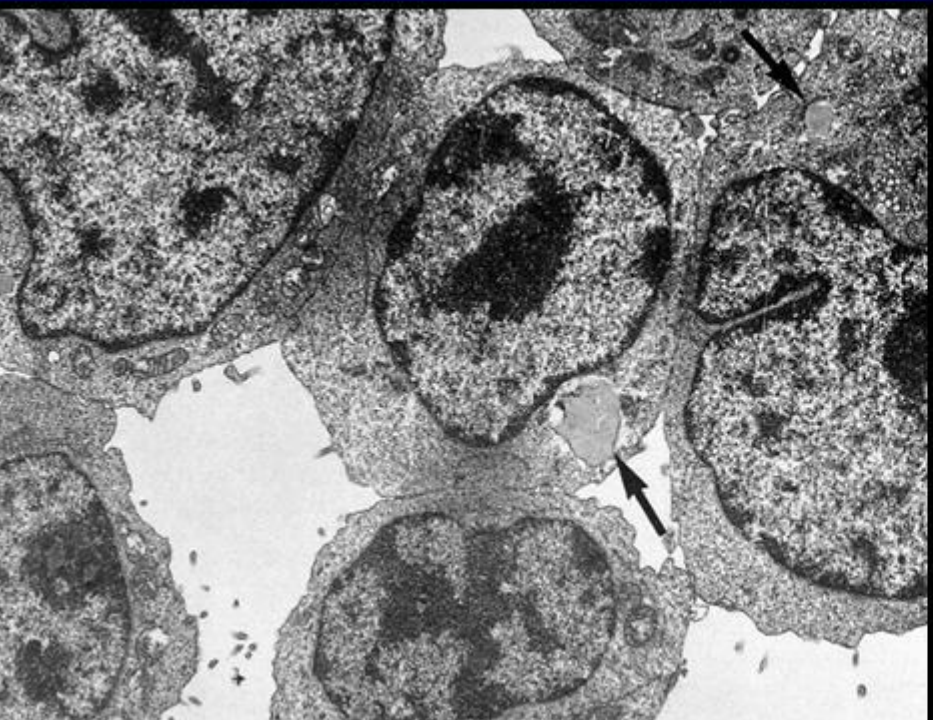
17 yr old girl from Sudan

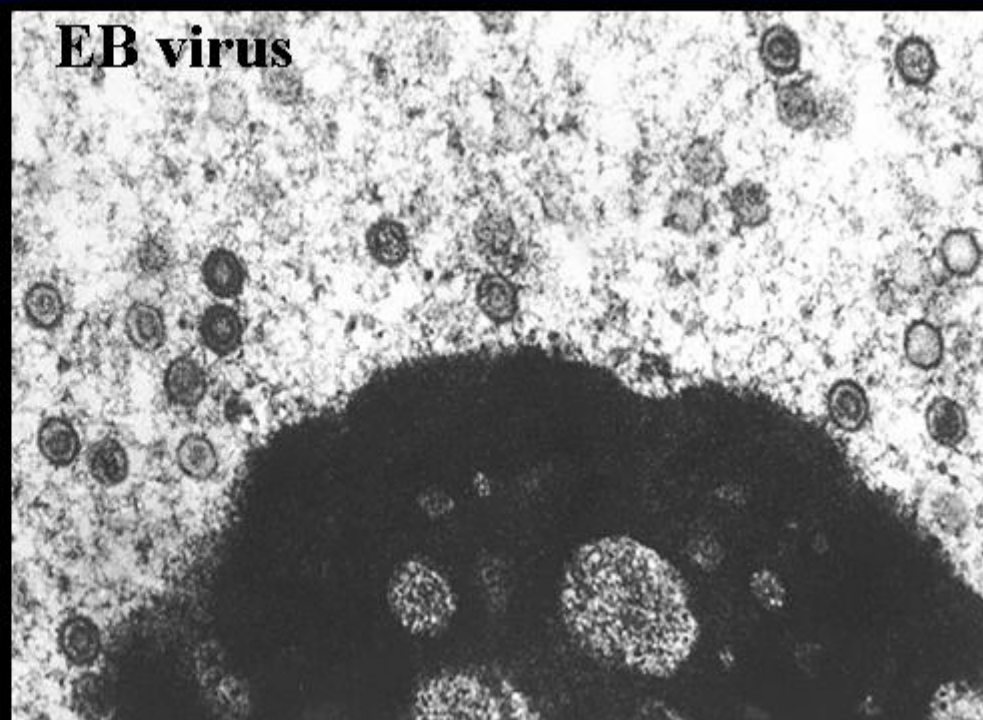
After treatment

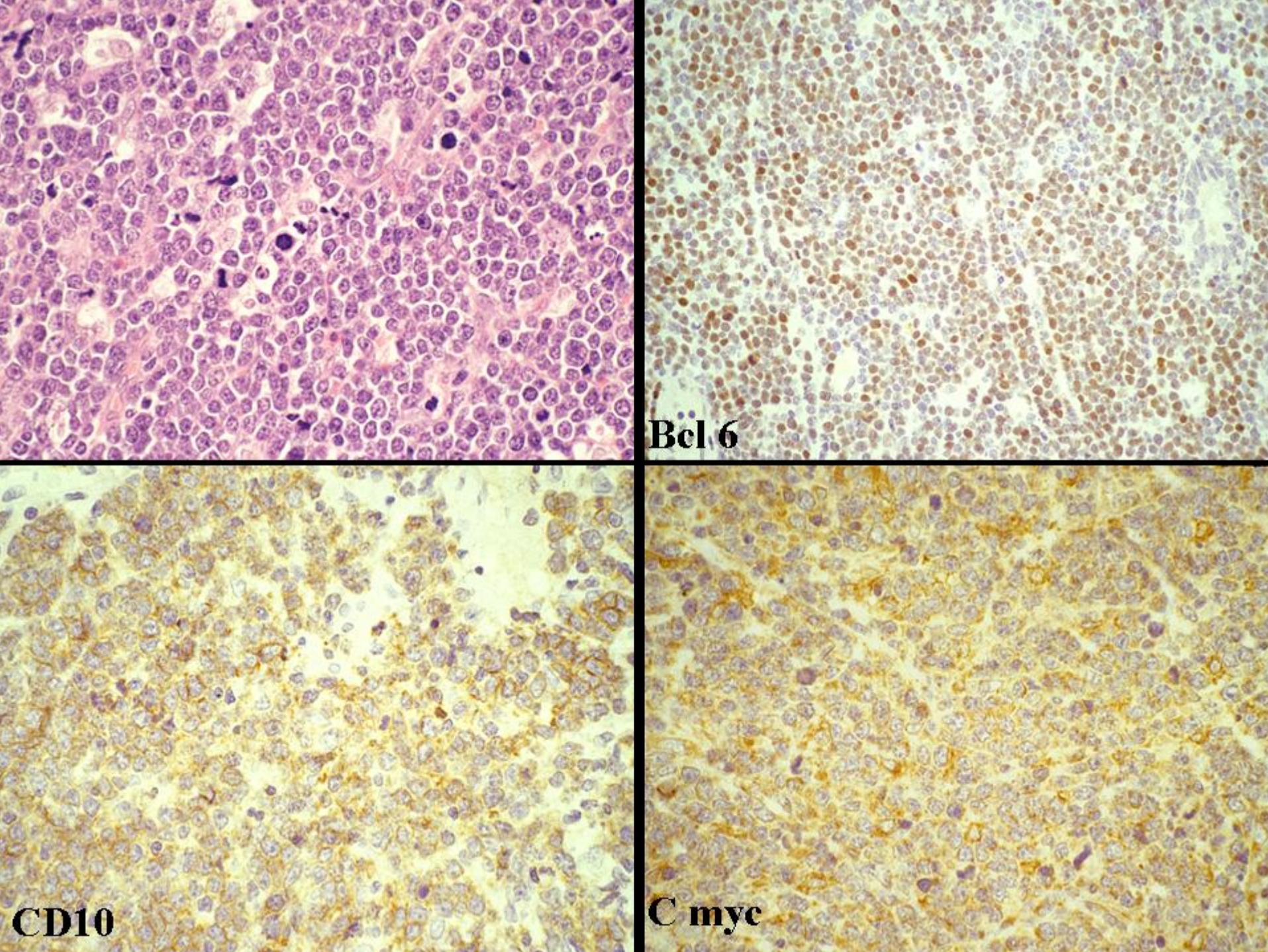
Elhaj AM, Mohamadani AA and Sanhouri K(2004). Burkitt's lymphoma of the breast and ovary: case report




Ascitic fluid




EB virus

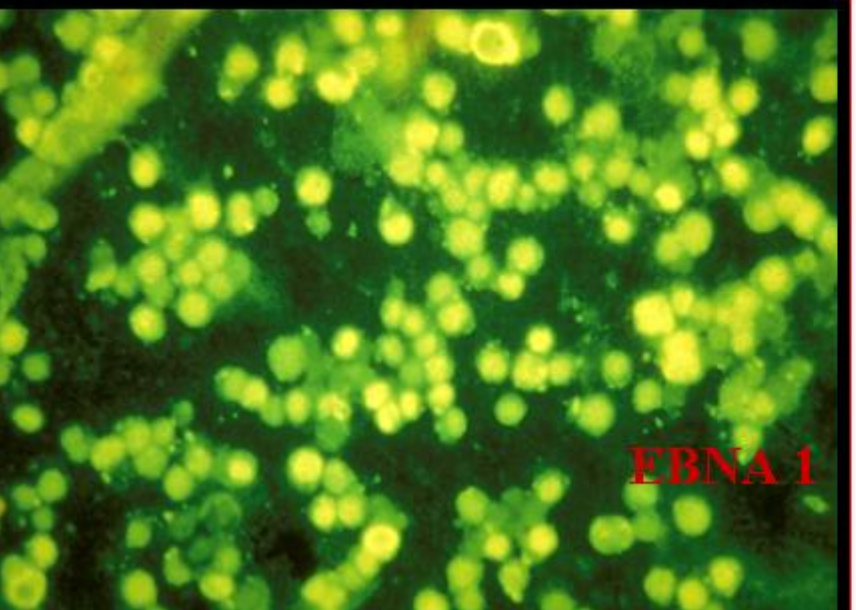

Bcl 6
CD10
C myc

Burkitt lymphoma

Immunophenotype
sIgM+; pan B+; CD10+; Bcl6+

Genotype
IgH and IgL genes rearranged; t(8;14) and variants t(2;8) and t(8;22) with rearrangement of c-myc gene

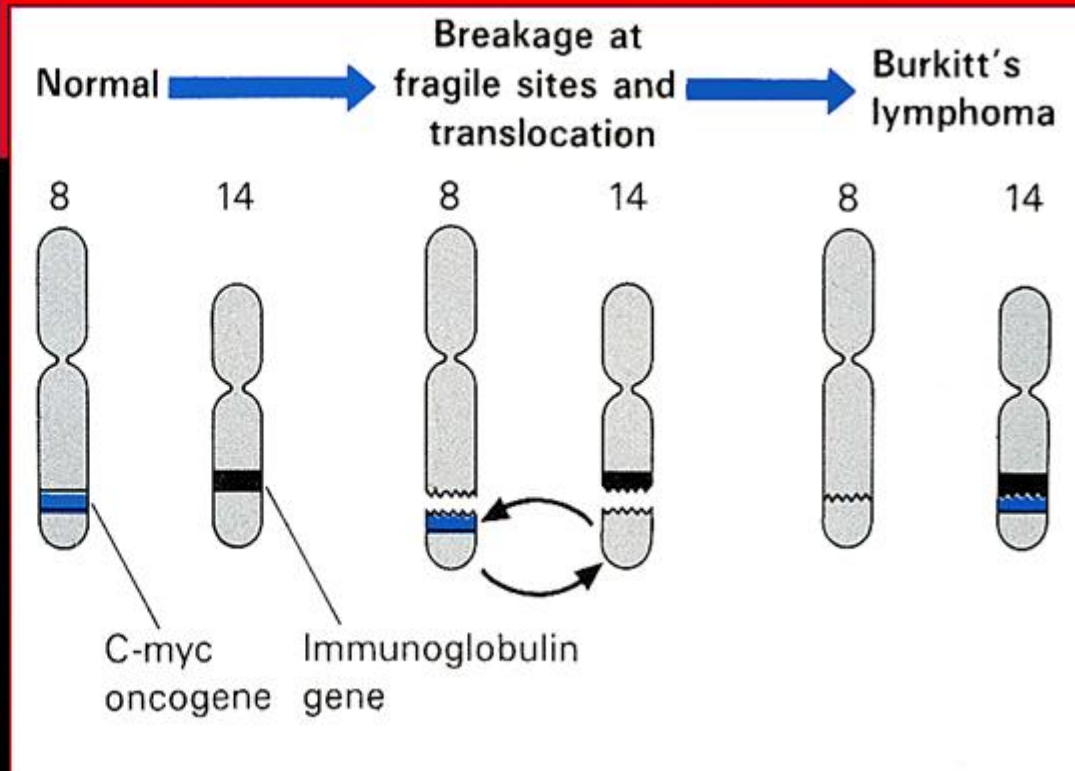
Latency pattern 1
EBNA 1+ve
EBNA 2-ve, LMP-ve



Cytogenetics t(8:14) - less commonly t(8:22) and t(2:8)

Translocation of the c-myc oncogene from chromosome 8 to chromosome 14 in juxtaposition with one of the Ig heavy chain genes activity transcribed in the B-cells of Butkitt's lymphoma

Therefore expressing a c-myc, an oncogene which binds to DNA directly stimulating synthesis



	African Burkitt's lymphoma	Sporadic Burkitt's lymphoma
Mean age (years)	7	11
Sex(M/F)	1:1	2:1
Association with EBV	95%	15%
Commonest sites of involvement	Jaw & abdomen gonads: breast	Ileocecal region
Bone marrow involvement	Rare (7%)	Commoner (20%)
Central nervous system involvement	17% initially; 60% at relapse	Uncommon

VIRUSES and ASOCIATED TUMOURS

B- cell LPD

EBV: BL, DLBCL (HIV+ & -ve), IALPD, LYG

HHV8: MCD, plasmablastic lymphoma, PEL

T- cell LPD

EBV: NK/TCL nasal type, ALCL, (Cutaneous T cell lymphoma)

HTLV 1: Adult T- cell leukaemia/lymphoma

HL

EBV: HIV+ & -ve

Kaposi sarcoma

HHV8: Endemic and sporadic; HIV+ve & -ve-

OTHER TUMOURS

EBV- HLH, NPCa, Gastric Ca, Br Ca, leimyosarcoma in ID

HBV; HcCa

HPV: Cervical Ca, head& neck Ca, anal Ca

SV40: mesotheliomas, lymphomas, bone and brain tumours

IMMUNODEFICIENCY

Congenital (primary)

Acquired (secondary)

Ageing

CONGENITAL IMMUNODEFICIENCY STATES

COMBINED IMMUNODEFICIENCY

Severe combined immunodeficiency (SCID)

eg. X linked SCID (Swiss type)

Mixed/moderate immunodeficiency

eg. Ataxia Telangiectasia (AT) *

Wiscott Aldridge Syndrome (WAS -X linked)

Common variable immunodeficiency (CVID)

SELECTIVE T-CELL DEFECT

eg. Thymic aplasia (di George syndrome)

SELECTIVE B-CELL DEFECT

eg. X linked agammaglobulinaemia (XLA)

hyper- IgM syndrome

X LINKED LYMPHOPROLIFERATION SYNDROME
(Duncan's syndrome, XLP)**

AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME (ALPS)

* autosomal mode of inheritance

** inherited defect of EBV immunity

LPD AND PRIMARY IMMUNODEFICIENCY SYNDROMES (PID)

- Most at risk of LPD:
  CVID, SCID, WAS , AT, ALPS and XLP
- Most LPDs present in childhood in extranodal sites
- Types of lymphomas similar to those in immunocompetent patients - B-cell lymphoma the most common
- Polymorphic lymphoid proliferations similar to those in post-transplant also occur
- Fatal IM develops in XLP (Duncan's syndrome) and SCID
- In WAS, increased frequency of LYG
- In AT most LPD are T-cell lymphomas/leukaemias

AQUIRED IMMUNODEFICIENCY STATES

- MALNUTRITION
- METABOLIC: eg. diabetes
- COMMON VARIABLE HYPOGAMMAGLOBULINAEMIA
- NEOPLASIA: eg. lymphomas;thymoma ⟶ hypogammaglobulinaemia
- CONNECTIVE TISSUE and AI DISEASES: eg; RhA, SS
- INFECTIVE: eg. HIV ⟶AIDS; HTLV
- IATROGENIC: Immunosupressive and cytotoxic therapy
  Transplantation
  Transfusions, blood and blood products
  Splenectomy

WHO 2001
IMMUNODEFICIENCY ASSOCIATED LYMPHOPROLIERATIVE DISORDERS (ILPD)

Lymphoproliferative diseases associated with primary immune disorders

Human immunodeficiensy virus- related lymphomas

Post-transplant lymphoproliferative disorders

Methotrexate-associated lymphoproliferative disorders

Age related EBV-associated LPD

Oyama T, Ichimura K, Suzuki R et al.(2003) Senile EBV+ B-cell lymphoproliferative disorders: A clinicopathological study of 22 patients. Am J Surg pathil 27: 16-26

IMMUNODEFICIENCY DISEASE ASSOCIATED LYMPHOPROLFERATIVE DISORDERS

LPD include non-malignant lymphoid proliferations as well as lymphomas

B-cell lymphomas are most common but HL and T-cell lymphomas also occur.

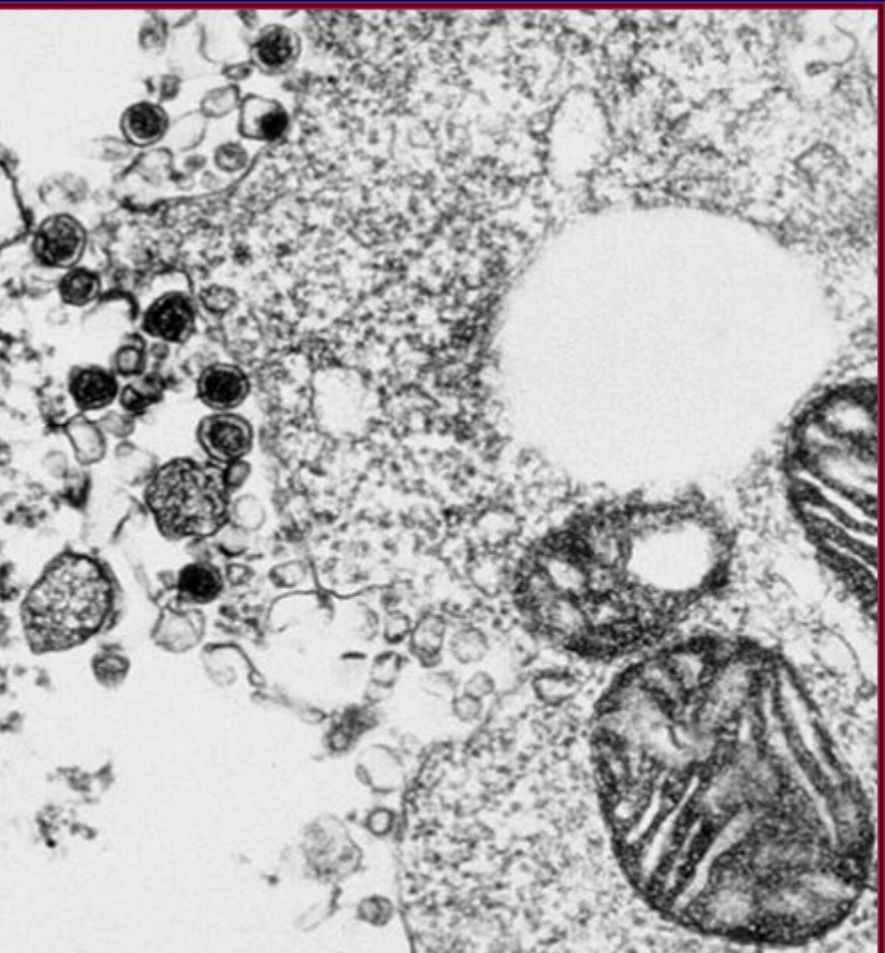
Many ID associated LPD also associated with EBV infection

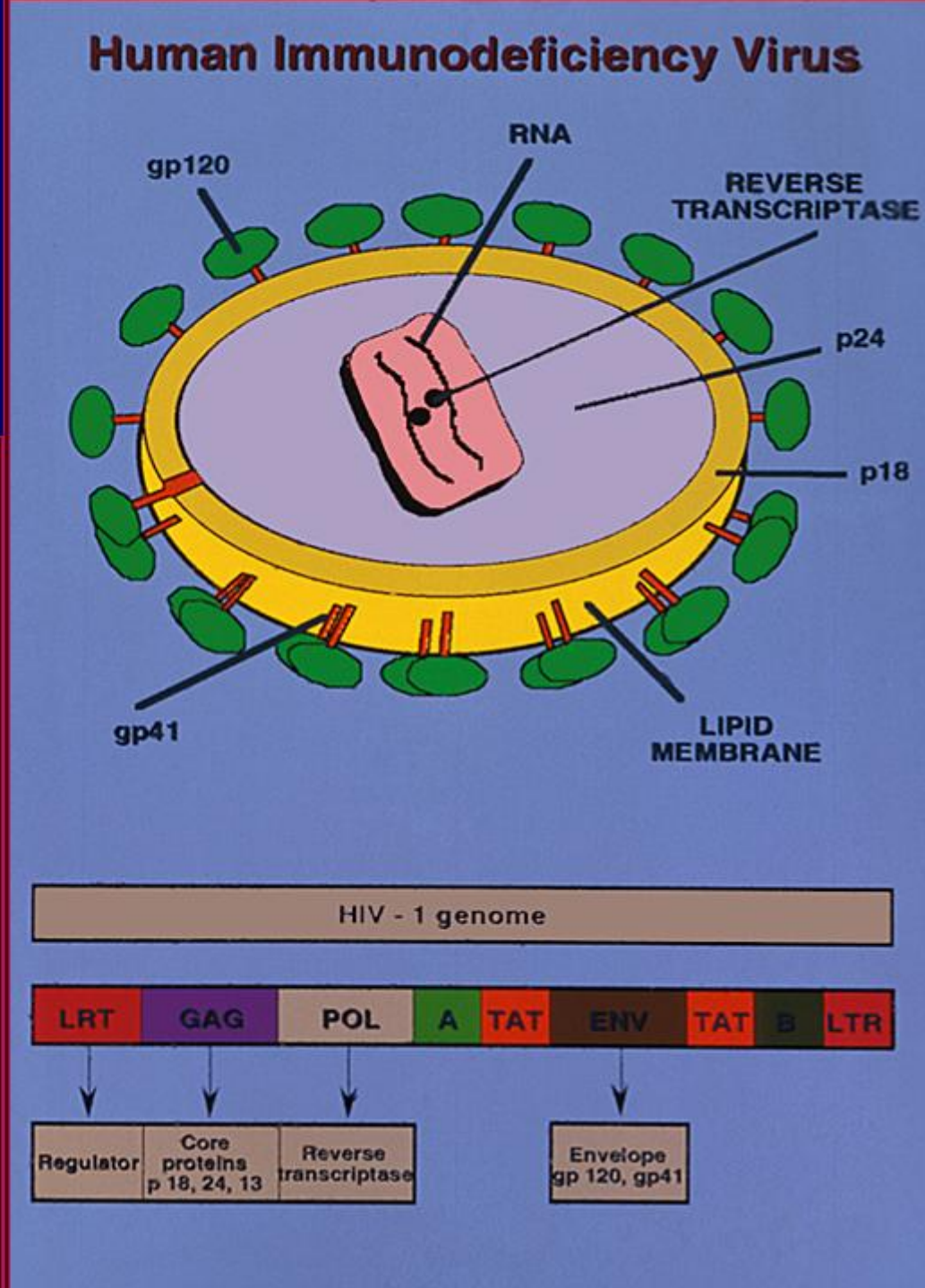
Conversely, many EBV associated LPD arise in immunodeficient patients

ACQUIRED IMMUNODEFICIENCE ASSOCIATED LPD

HIV

Not directly oncogenic but because immune status is altered HIV 'opens the door' to oncogenic viruses





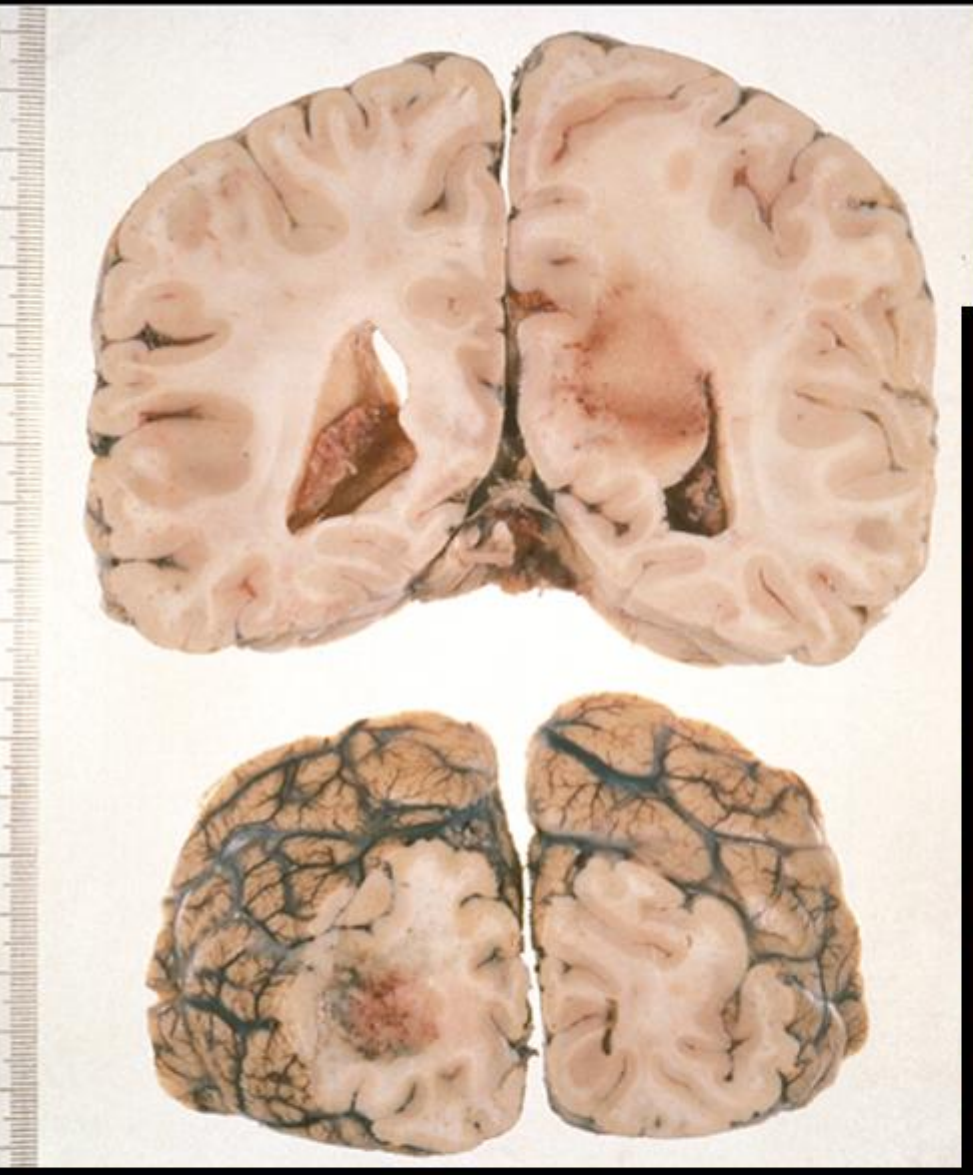
HIV +ve LYMPHOMAS

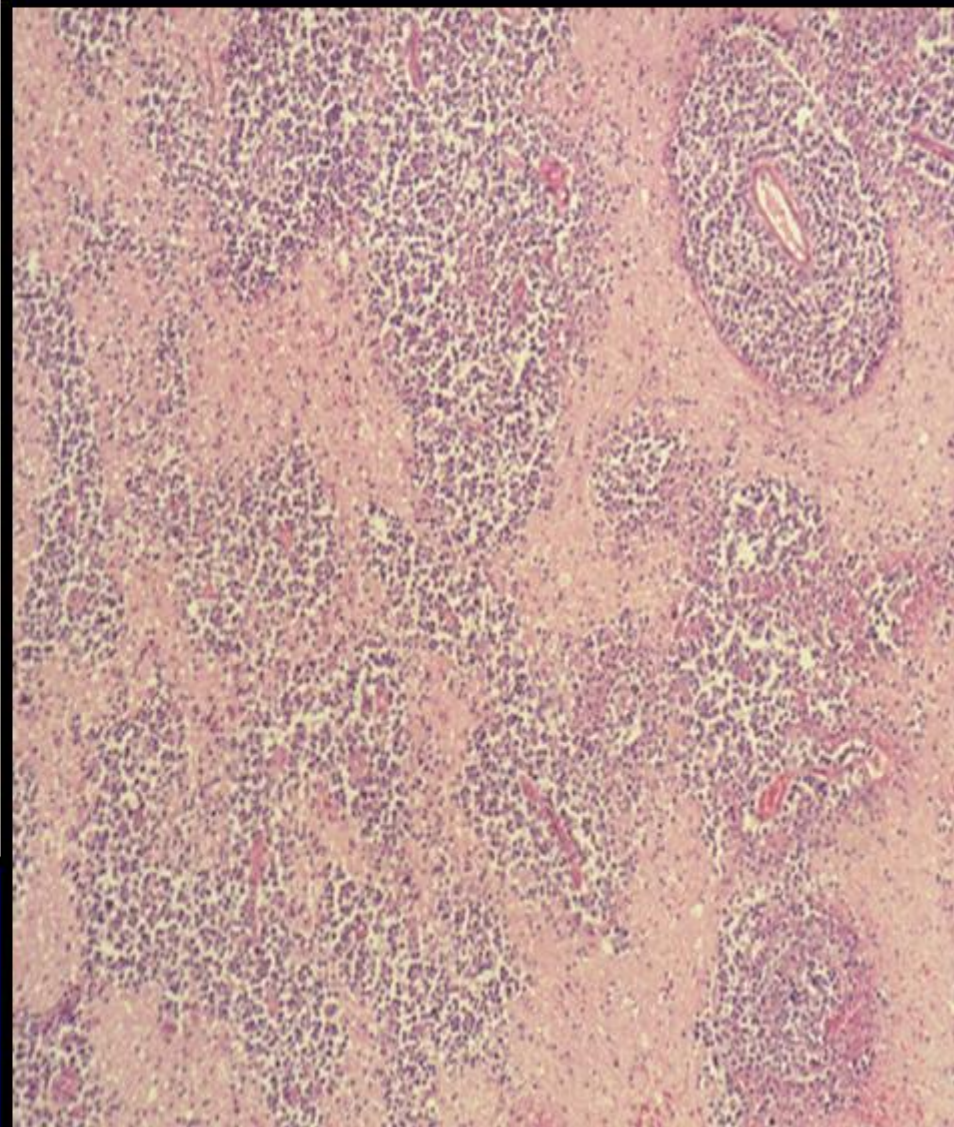
Primary site	No.
Lymph node	18
Mouth/pharynx	9
Soft tissue	8
CNS	7
GIT	6
Liver	4
Perianal	3
Skin	3
Bone Marrow	2
Lung	1
Salivary gland	1
Bone	1
TOTAL	63

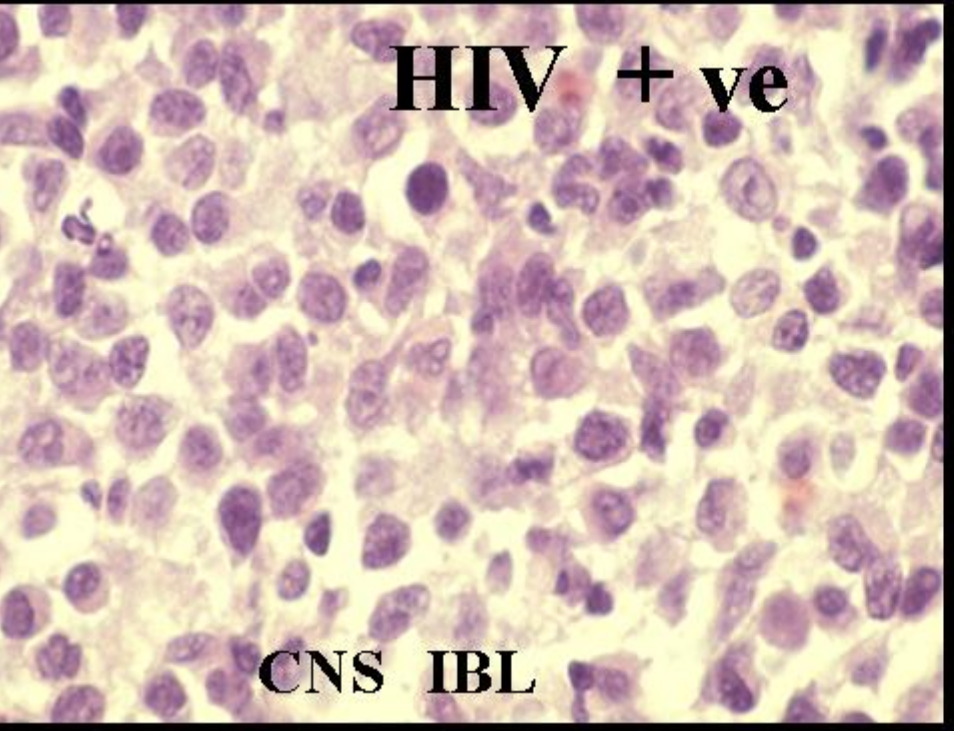
Lymphoma type:	No.	%
BCL	57	90.4
DLBCL	28	
BL/BL like	25	
Pl.blastic	2	
Uncl.	2	
TCL	4	6.4
NOS	2	
ALC	2	
HL	2	3.2
NS	2	
	63	

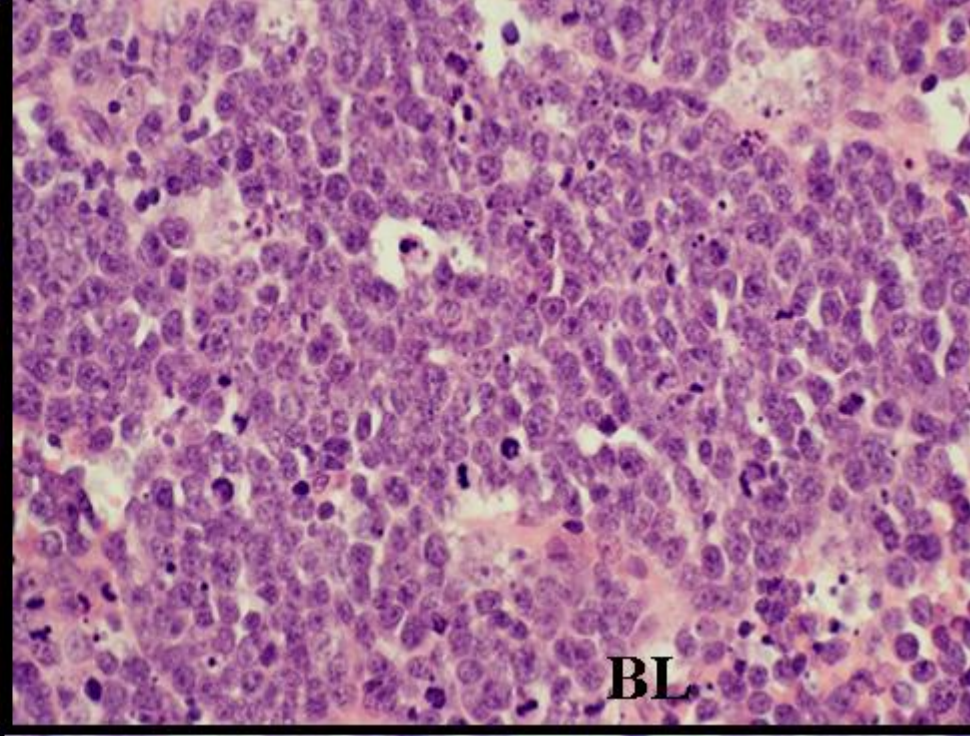
Henry K et al. 1990 AIDS - related lymphomas

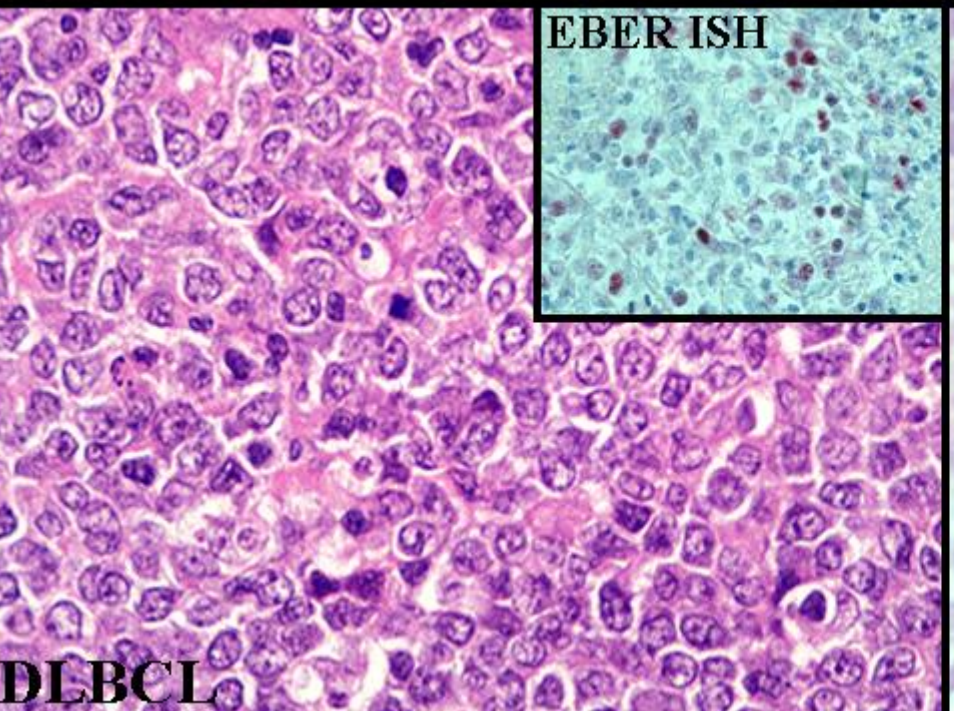
CNS DLBCL

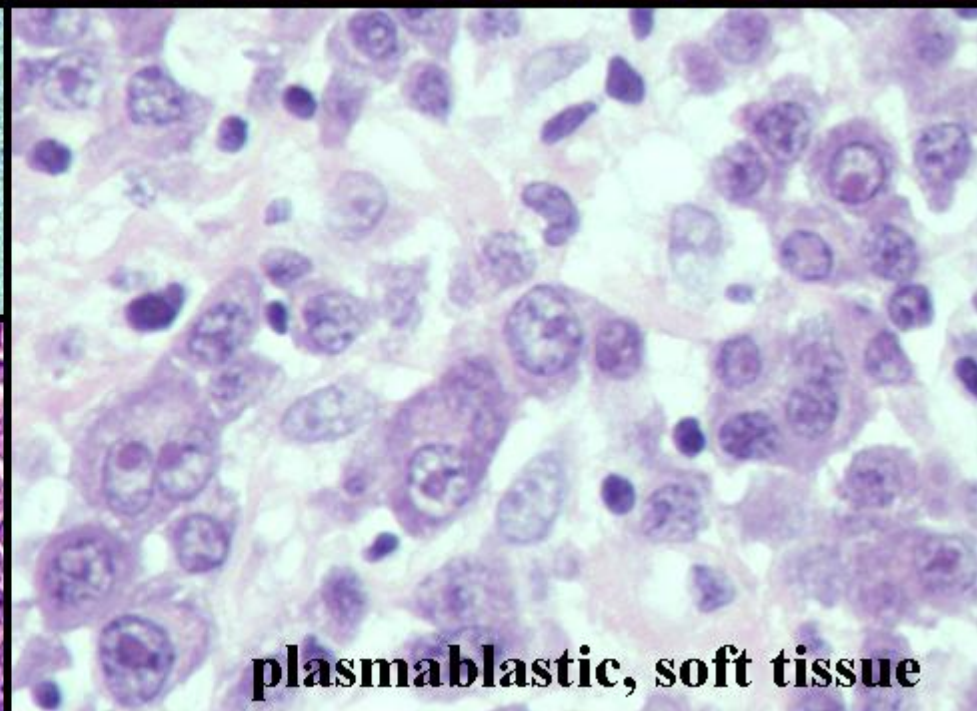





HIV + ve
CNS IBL


BL


EBER ISH
DLBCL


plasmablastic, soft tissue

Plamablastic lymphoma

Thought to be restricted to HIV infection and immunodeficiency

Initially thought to affect only oral cavity and jaws; now recognised as occurring at other sites including skin

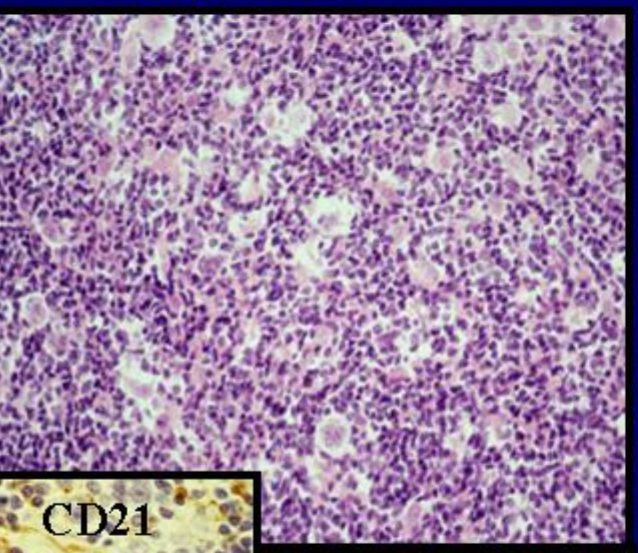
Clue to recognition is awareness of morphology of plasmablasts

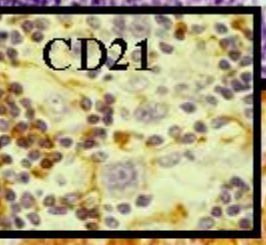
If not, IHC may cause confusion since B-cell markers lost (CD20 and often CD79a)

HODGKIN LYMPHOMA

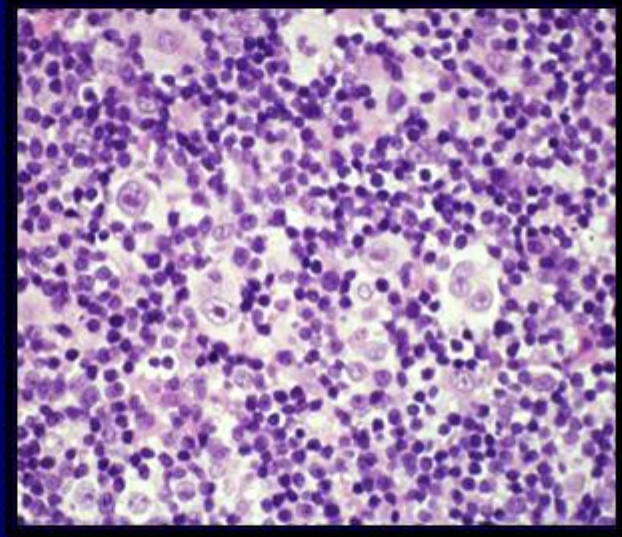
IALD

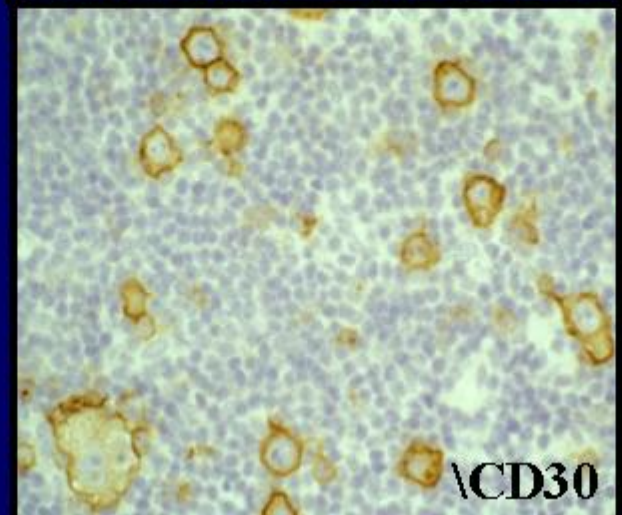
HL LP nodular

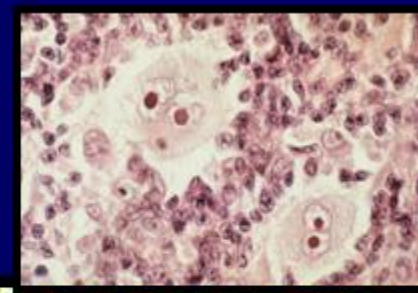


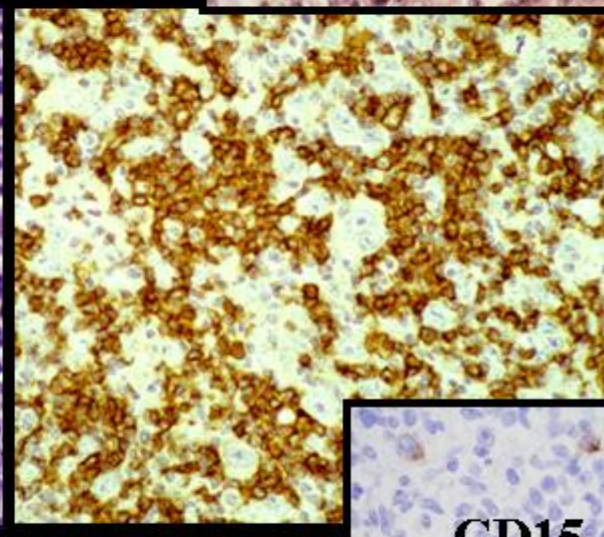


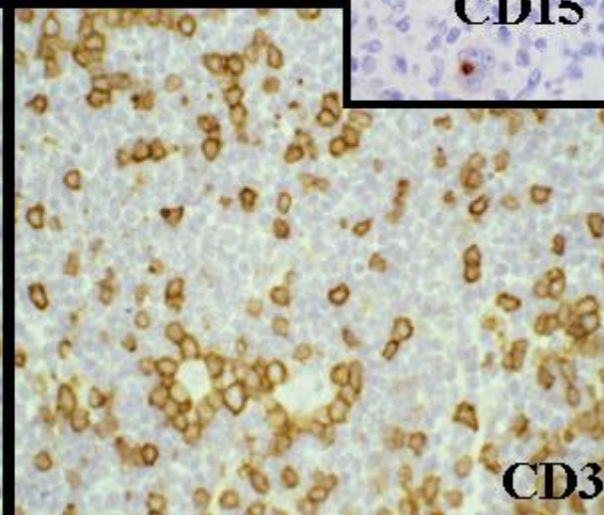
Classical HL: NS, MC, LD











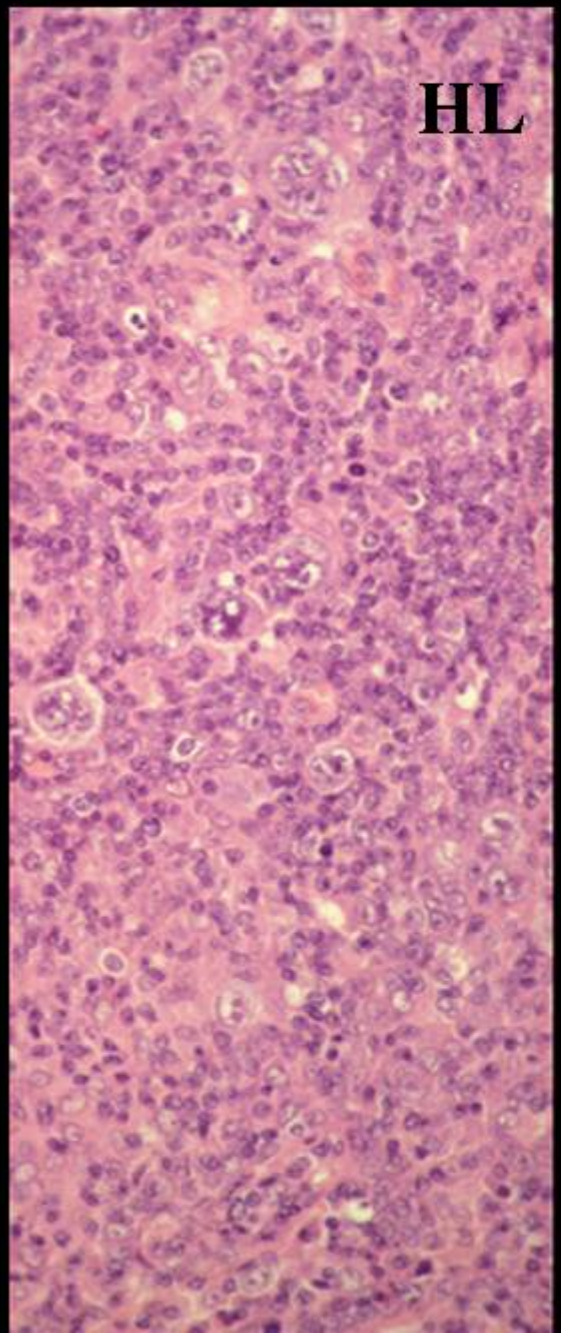
HL and EBV expression

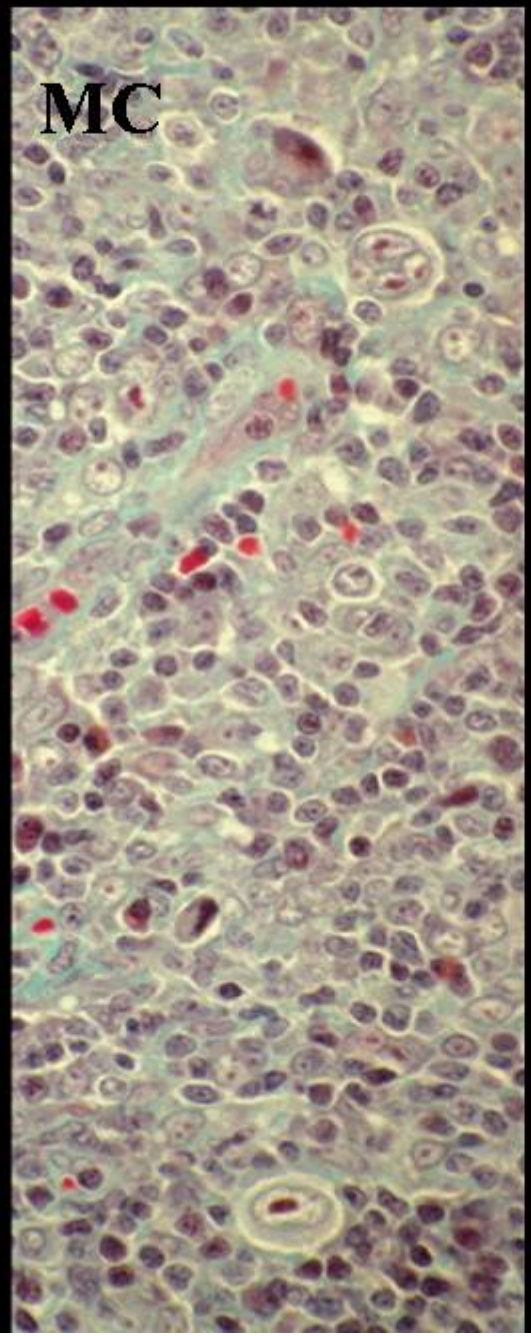
NLP HL	100% -ve
NS	15%-50% +ve
MC	up to 100% +ve

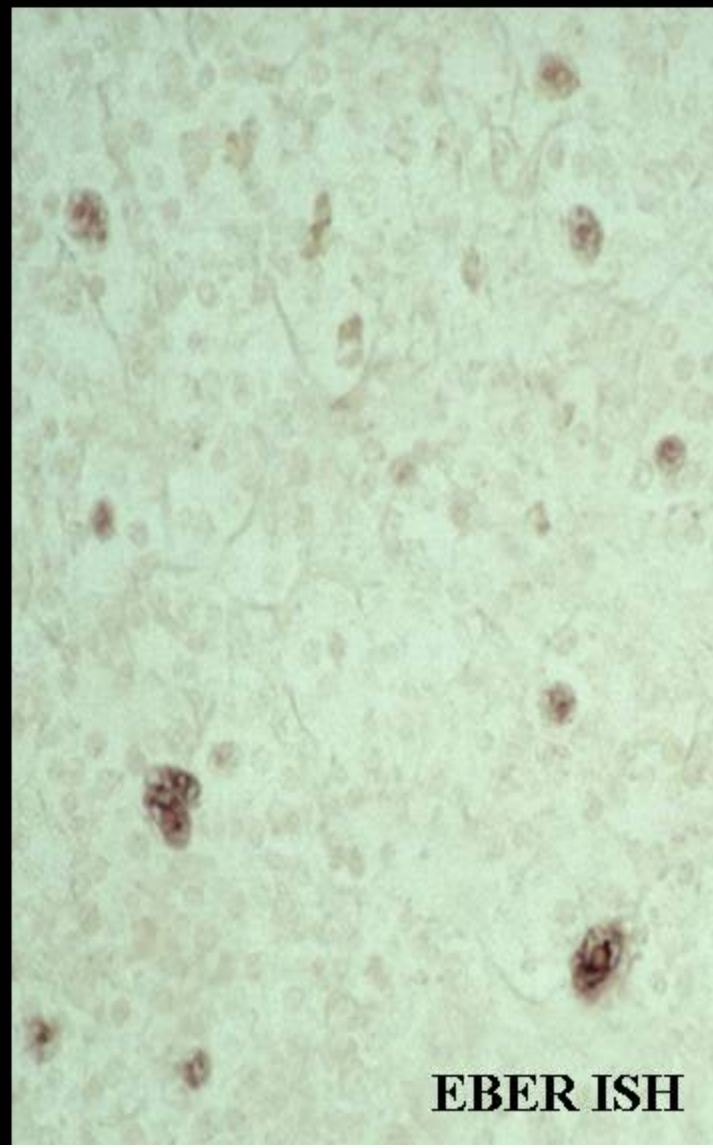
Latency type II pattern, ie. EBER +
EBNA 1+
LMP 1&2 +

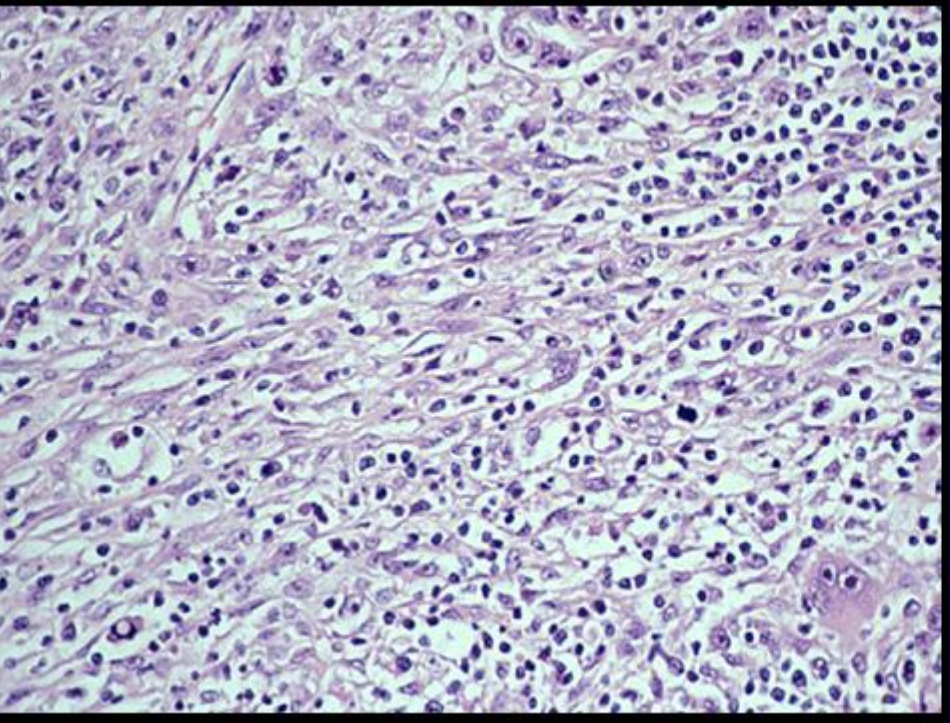
Highest % expression in children and adults > 50yrs

100 % expression on HIV +ve patients

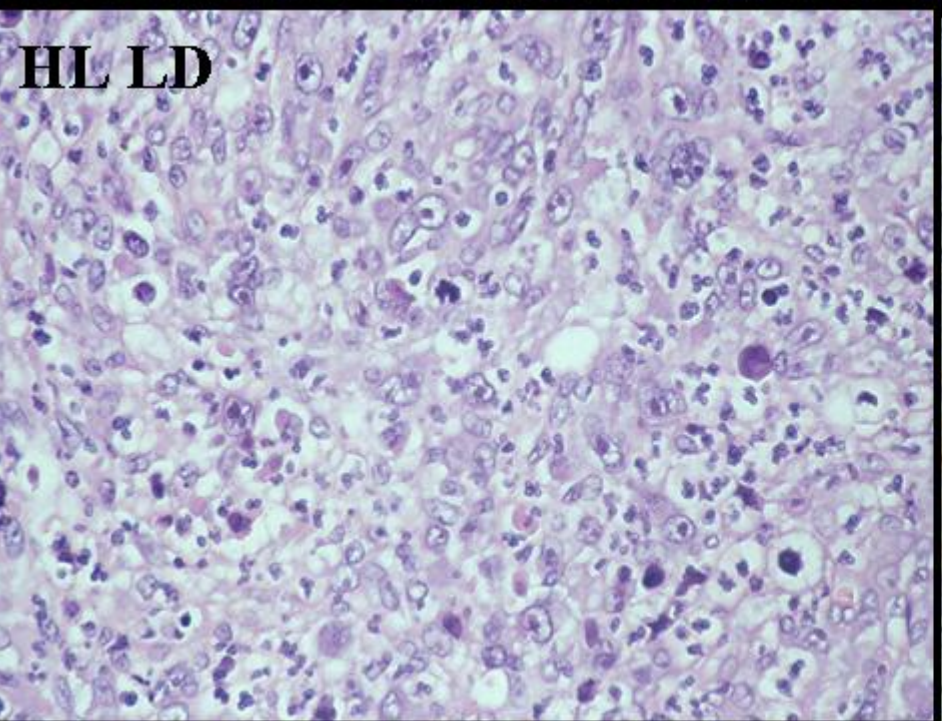

HL

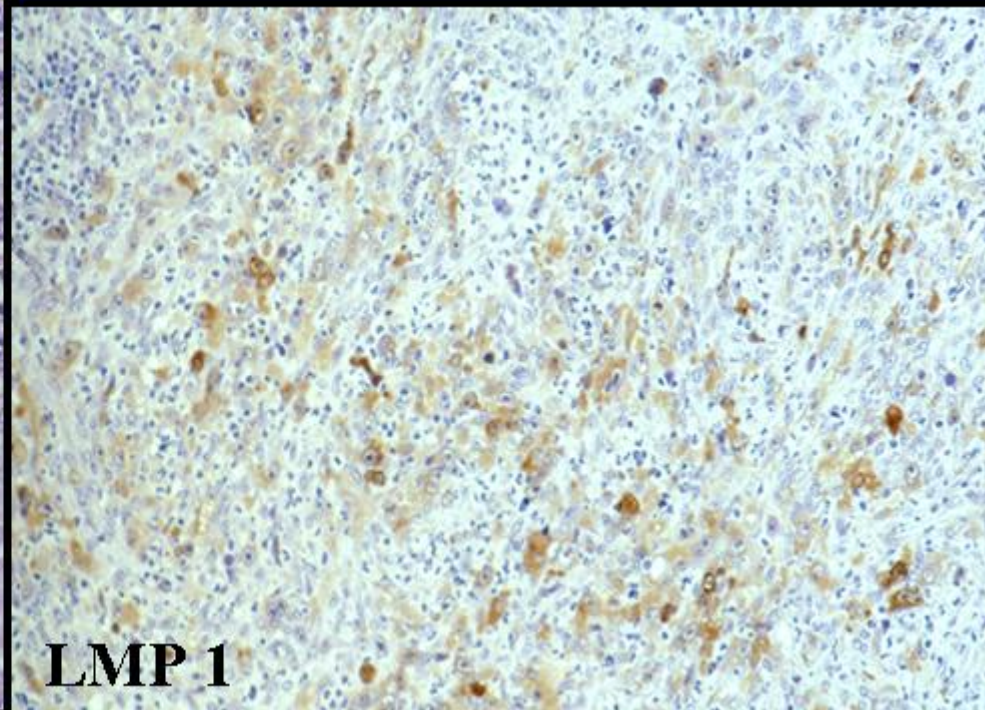

MC

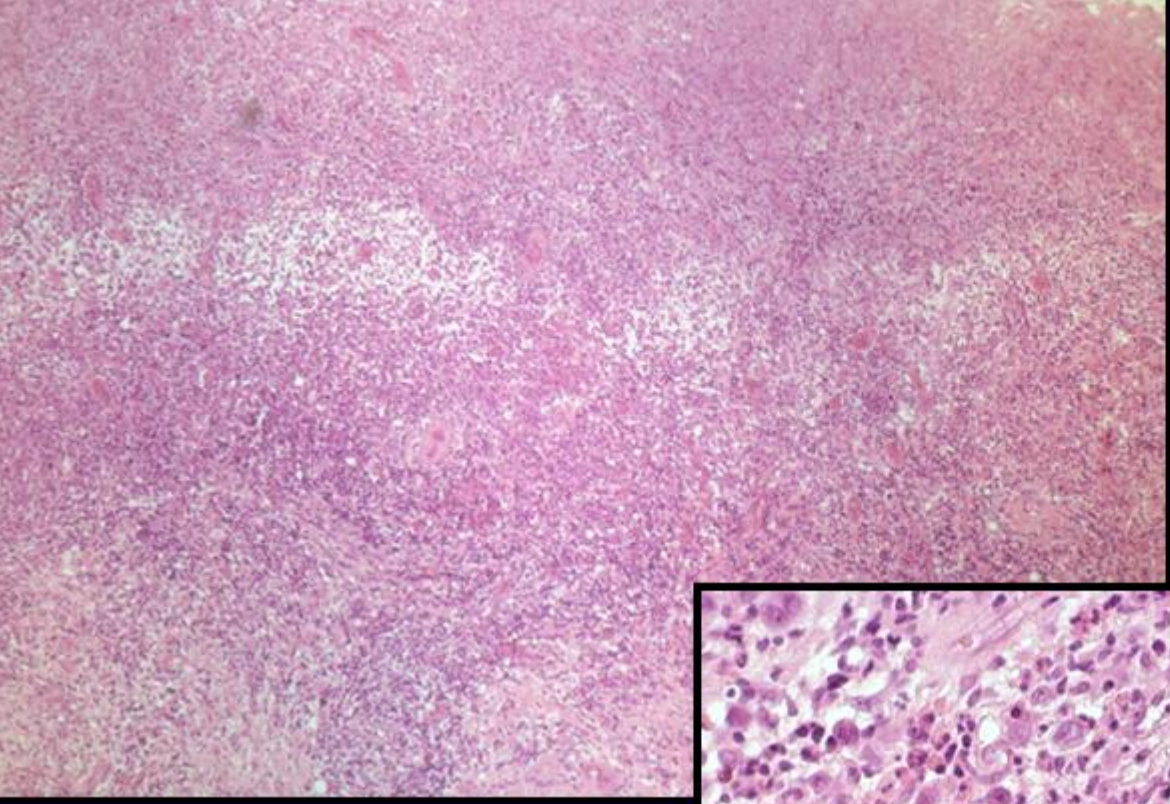

EBER ISH



HL LD
Latency pattern II
EBNA 1+, LMPs+

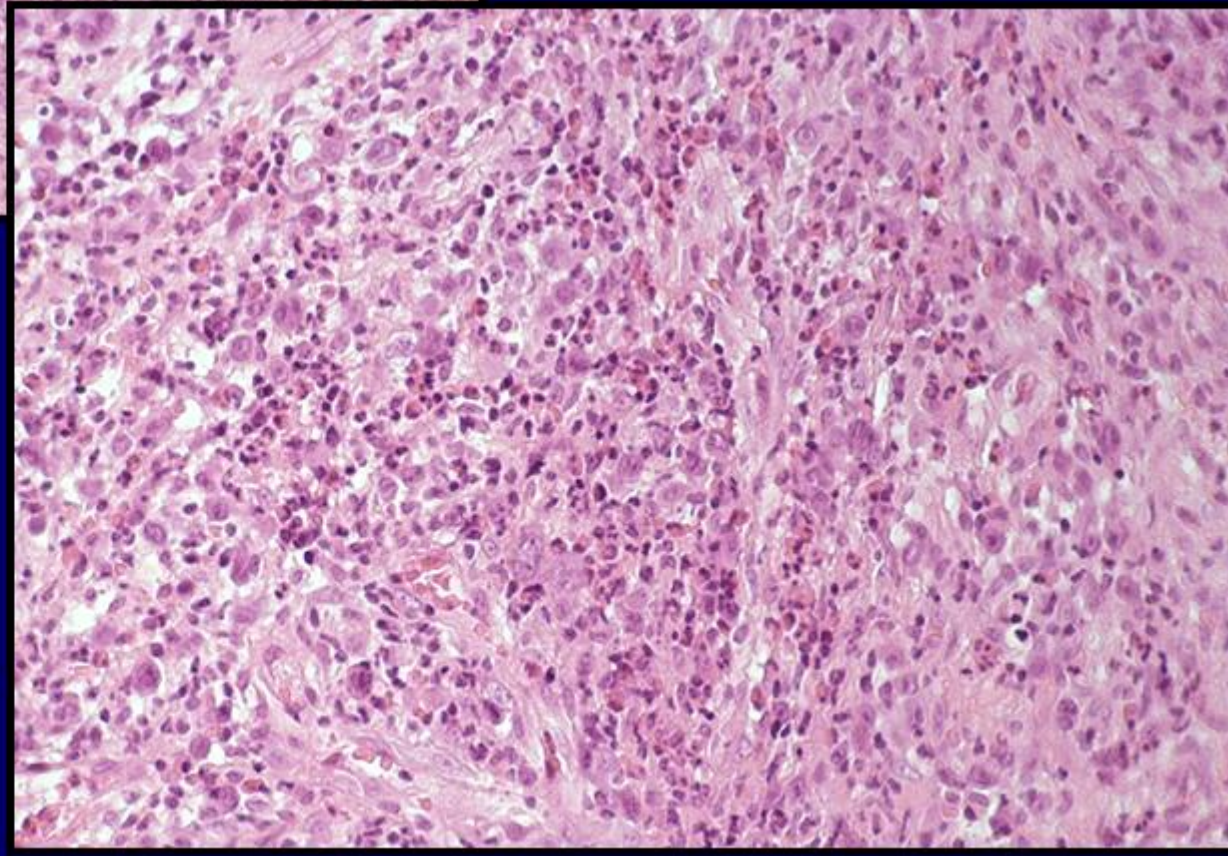






HIV +ve

Hodgkin like LBCL oral mucosa



Immunophenotype:

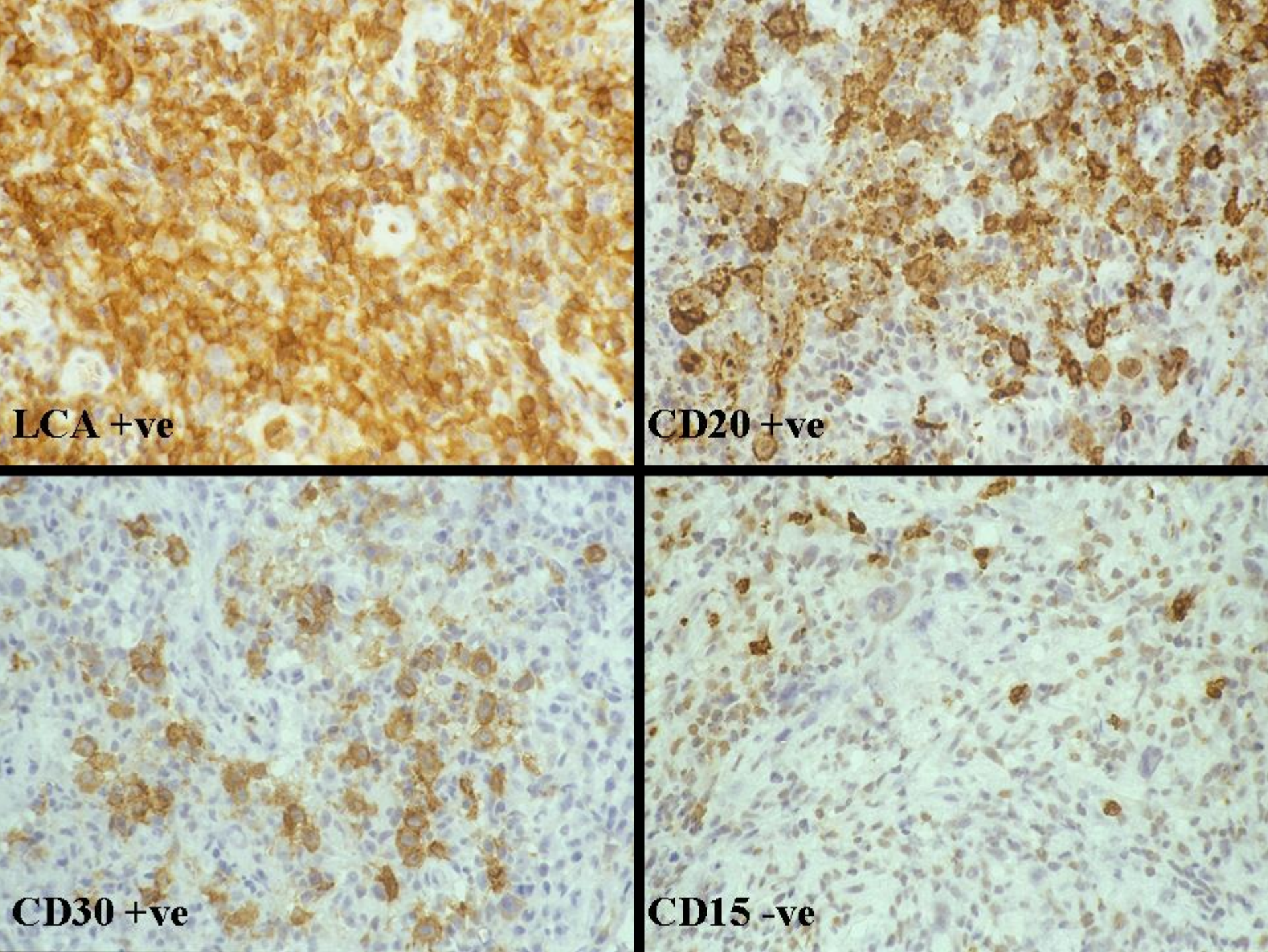
Activated B-cells

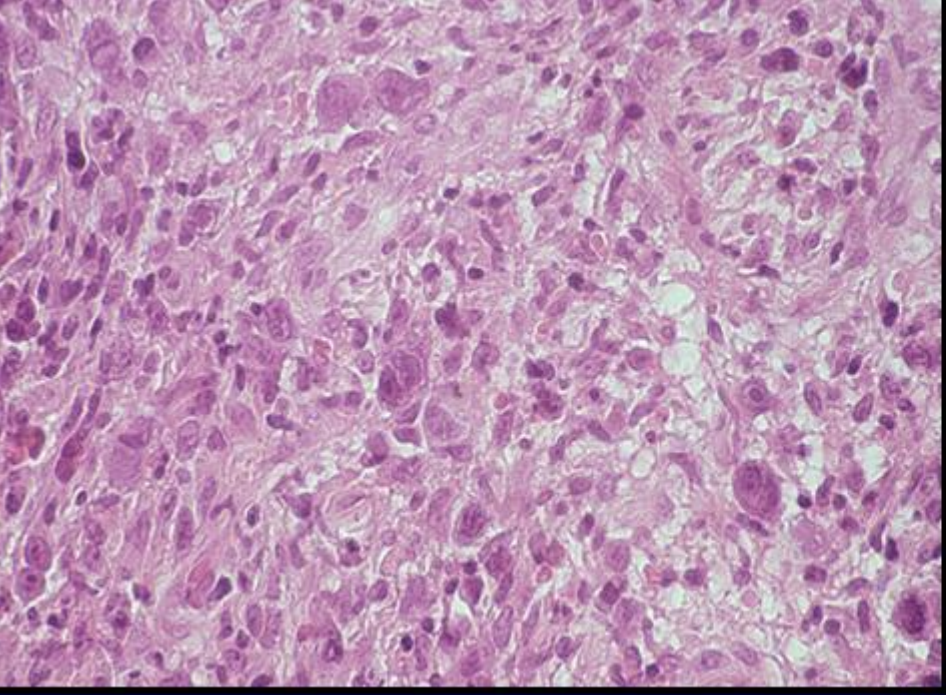
LCA+ CD20/79a+ CD30+

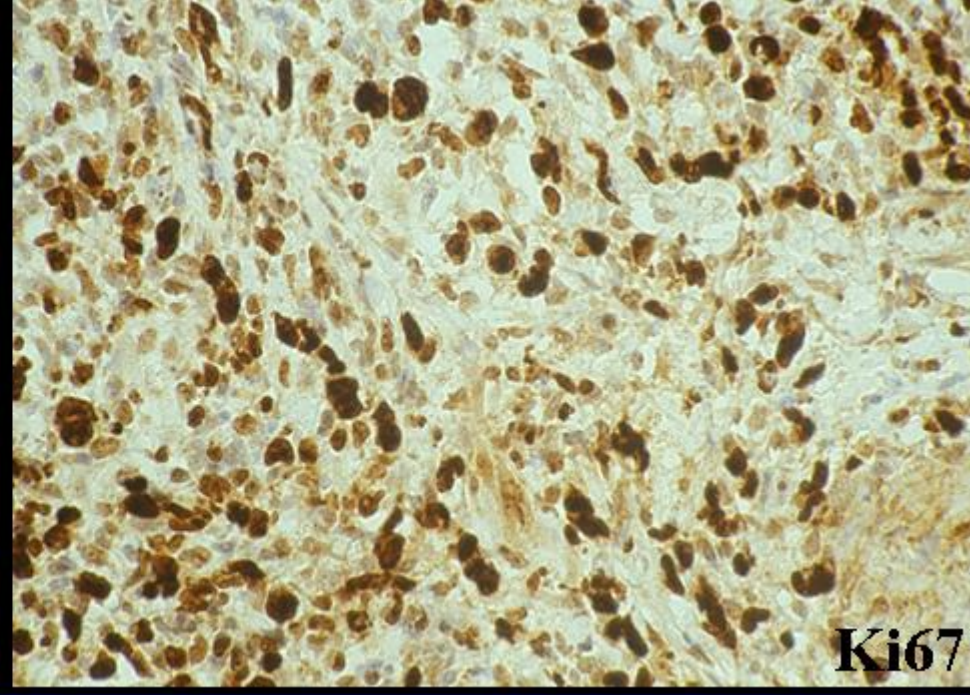
CD 15 –

Latency pattern III

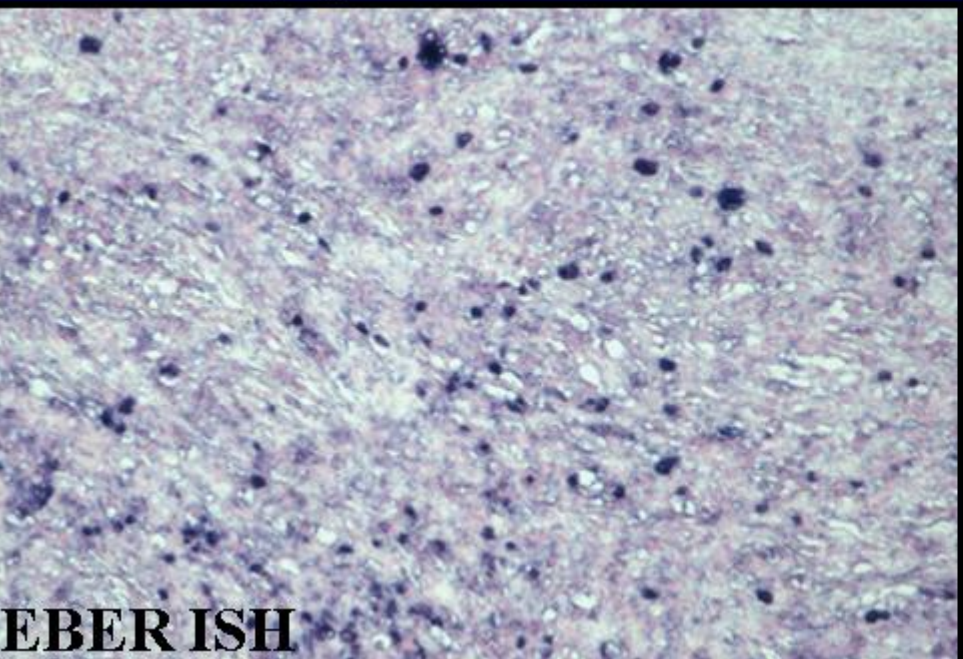
(bystander cells also EBV+)

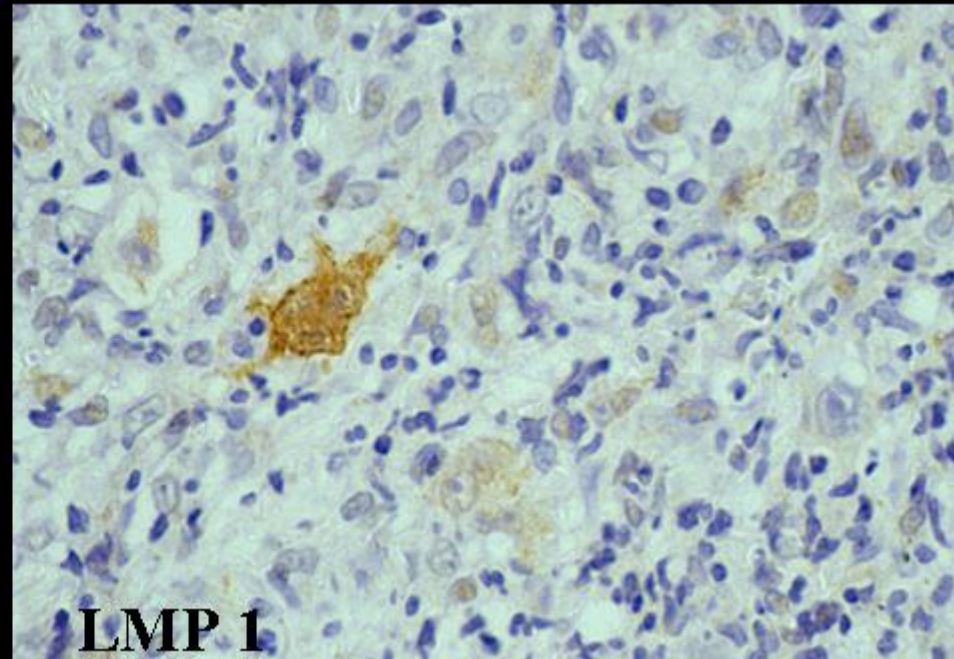

LCA +ve
CD20 +ve
CD30 +ve
CD15 -ve





Latency pattern III, EBNA 1-6+ve, LMP 1, 2a, 2b +ve





HHV8 (KSHV) and ASSOCIATED DISEASES

Kaposi's sarcoma

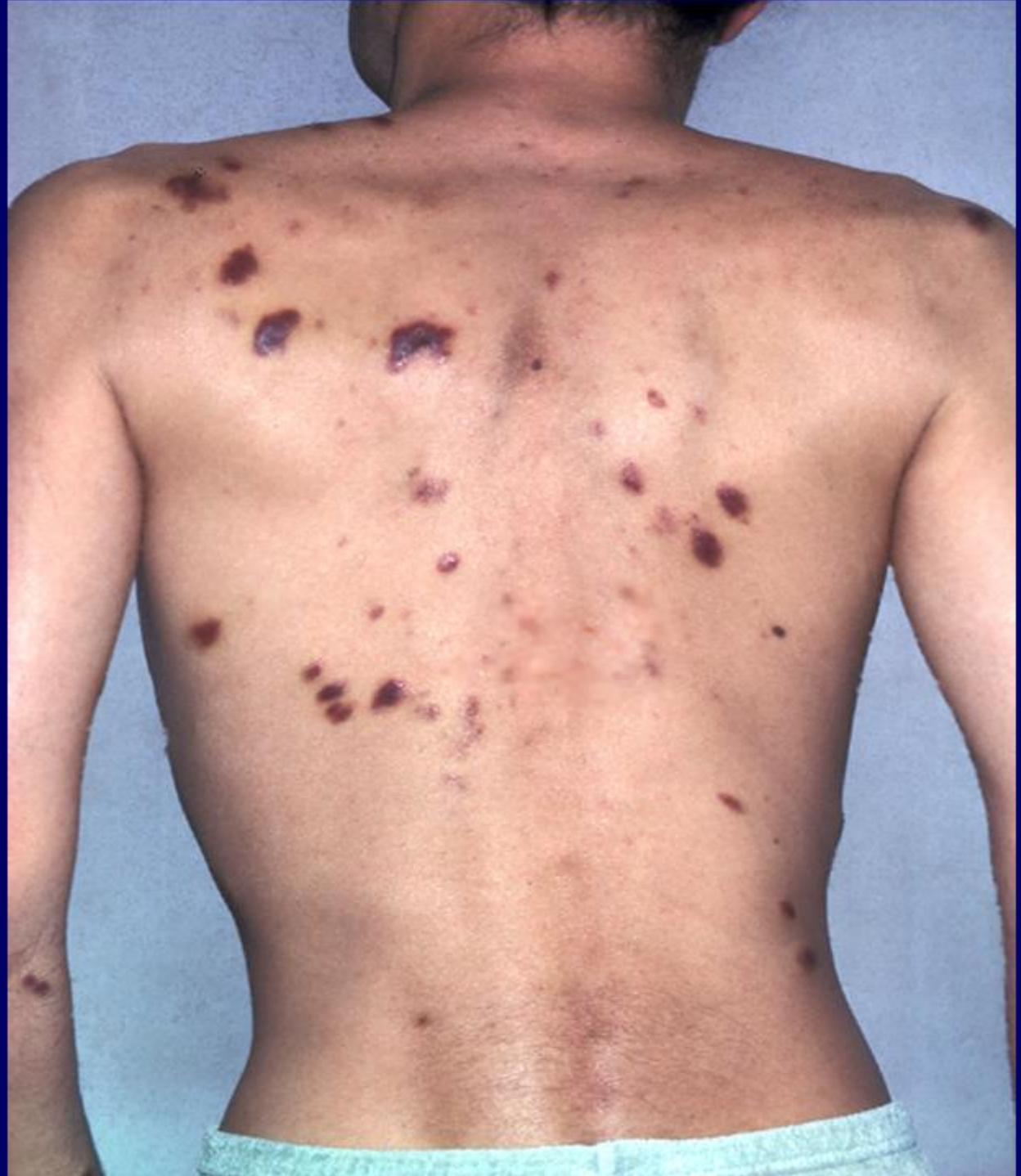
Classical – Eastern Europe
Endemic – parts of Africa
HIV and AIDS
post- transplant

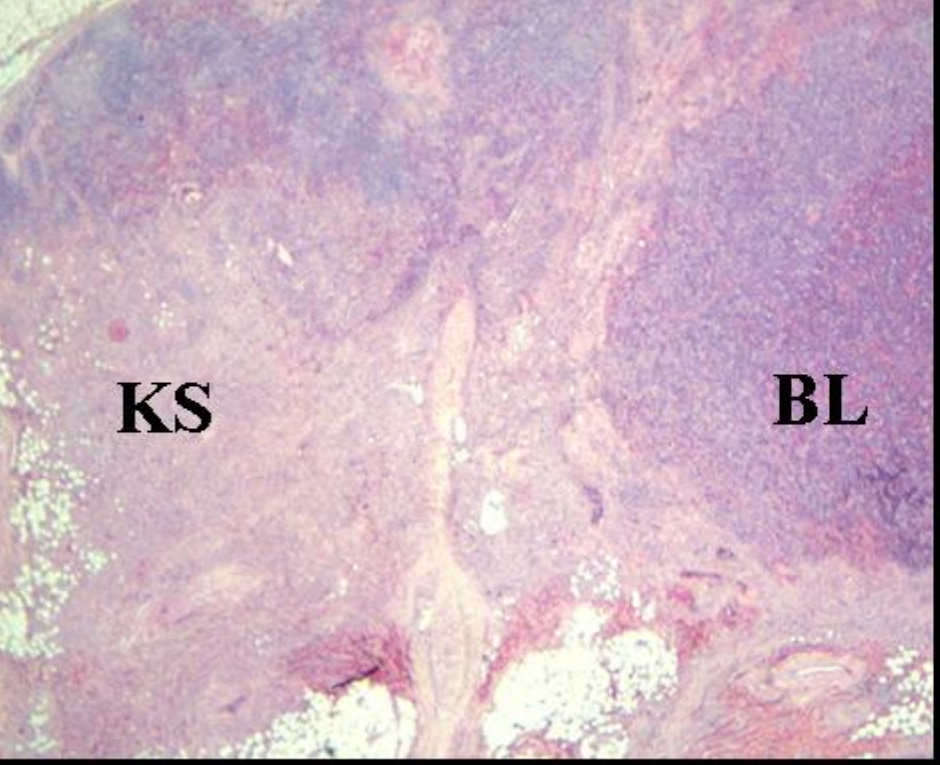
Multicentric Castlemans disease (MCD); HIV+ve and –ve cases

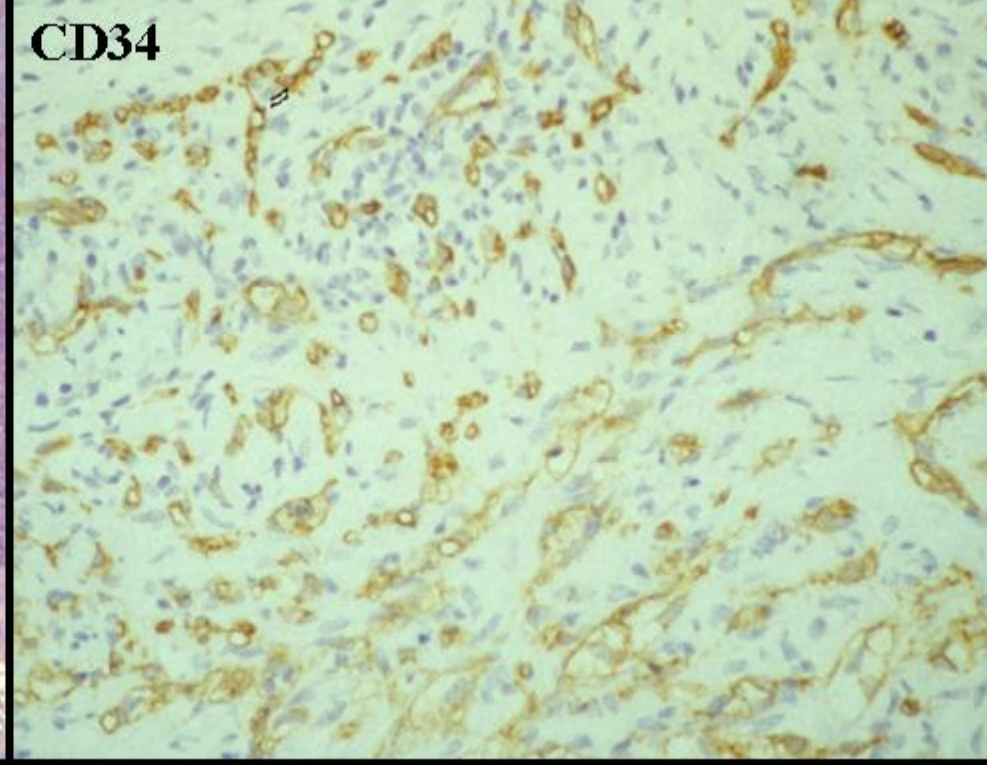
Primary effusion lymphoma (PEL)

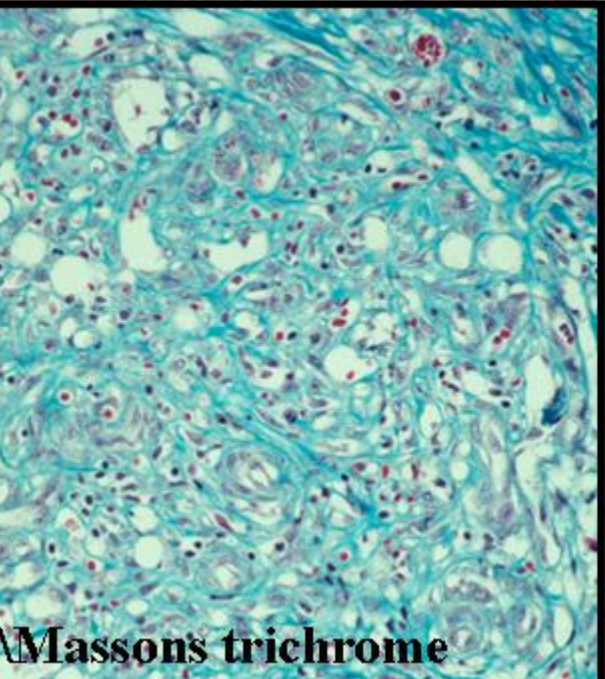
Plasmablastic lymphoma in MCD

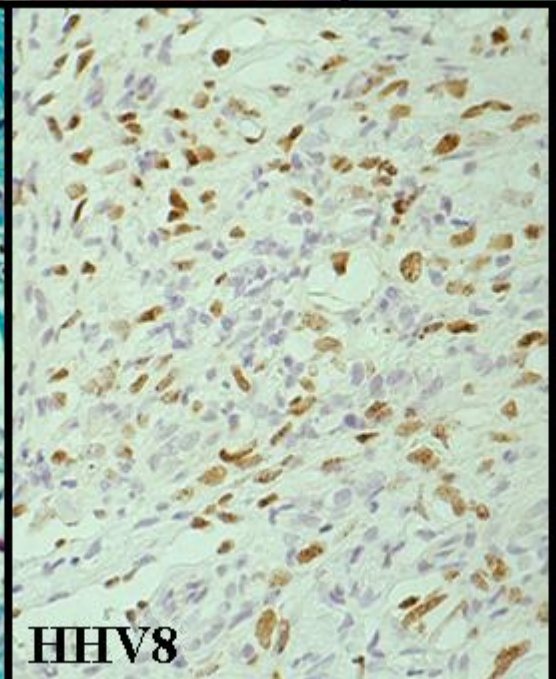
KS

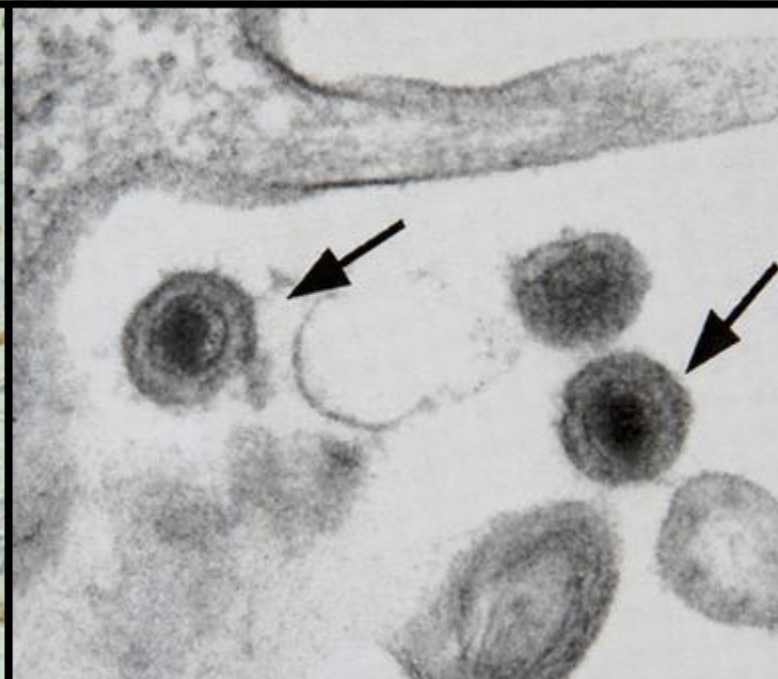



KS
BL

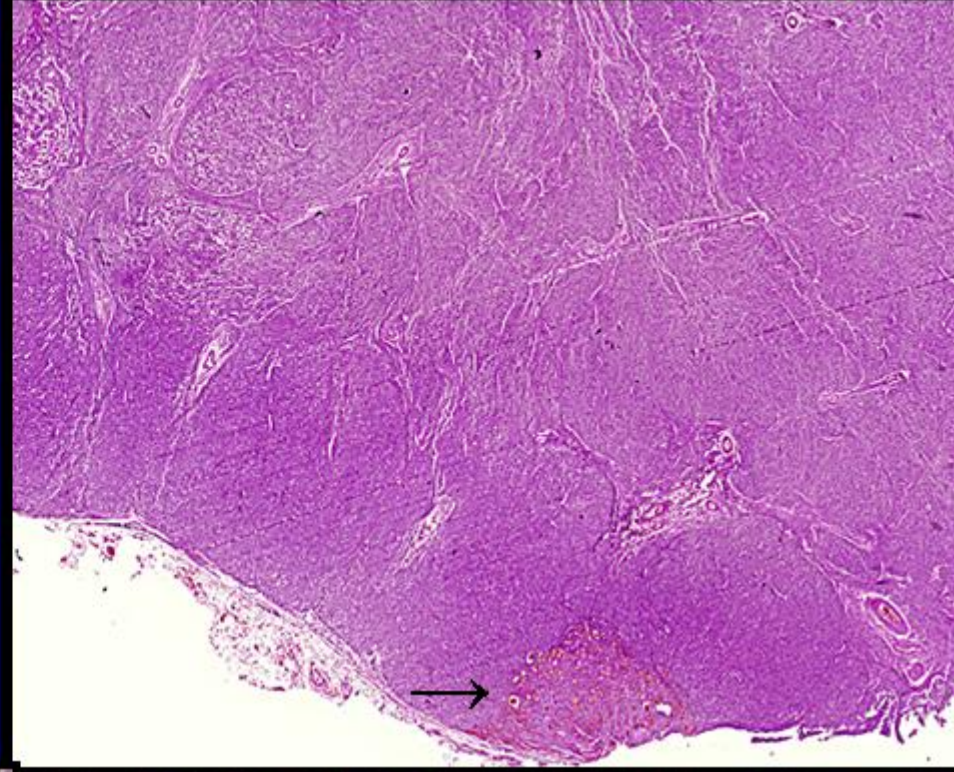

CD34

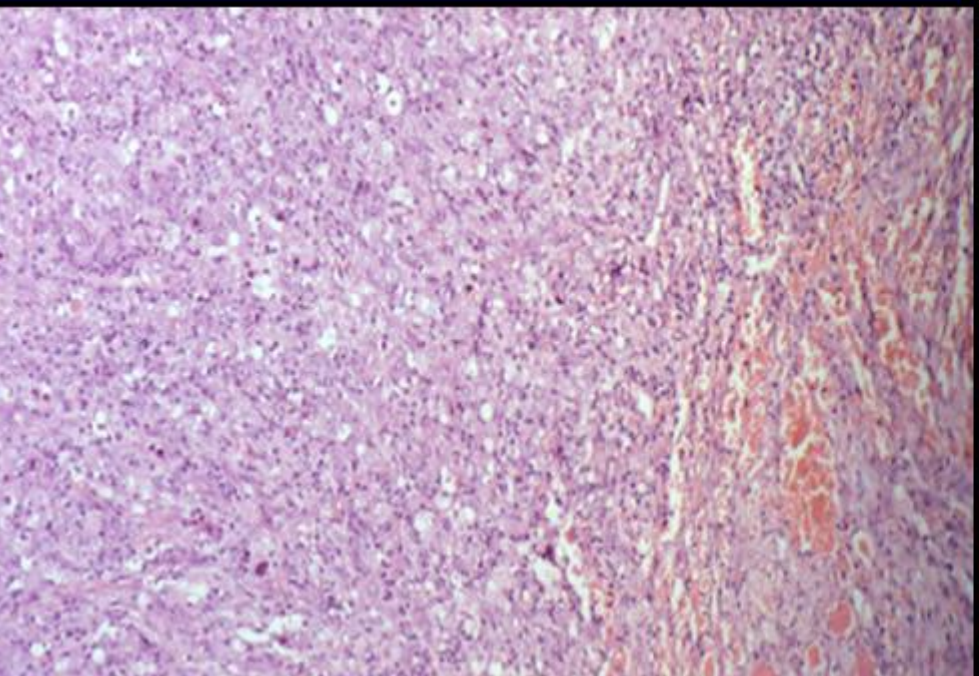

Massons trichrome

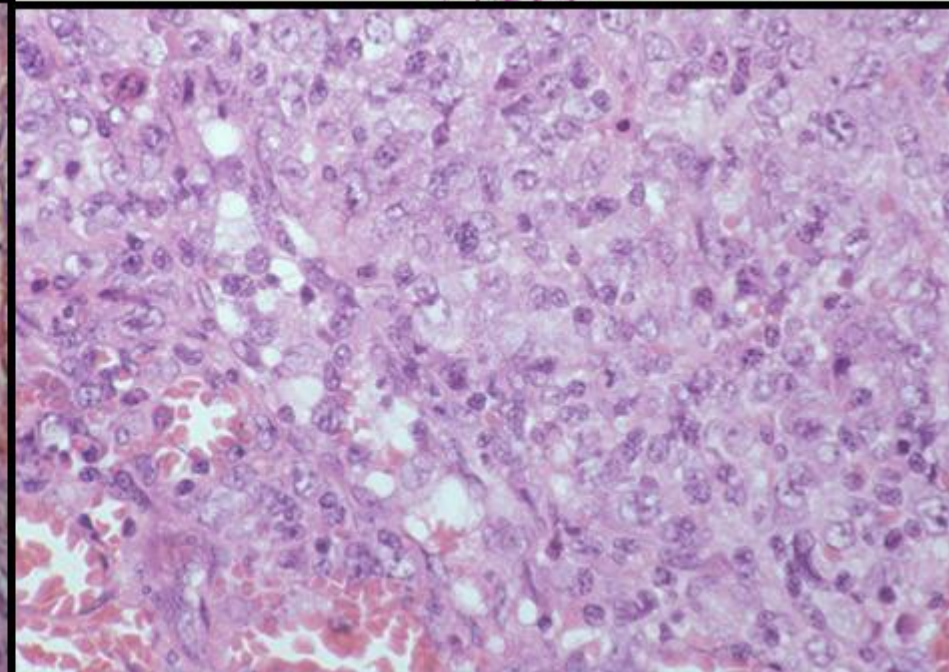

HHV8

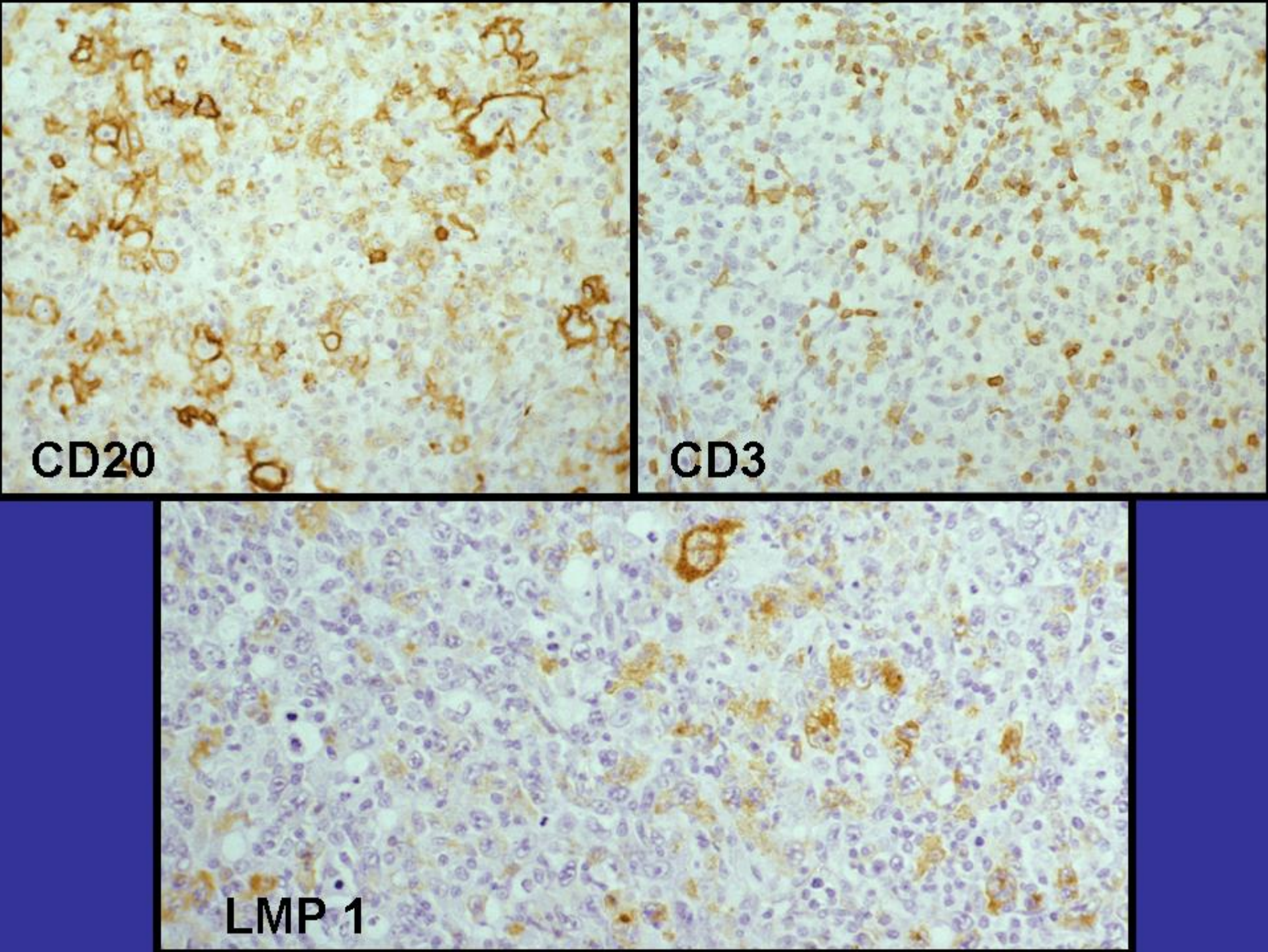


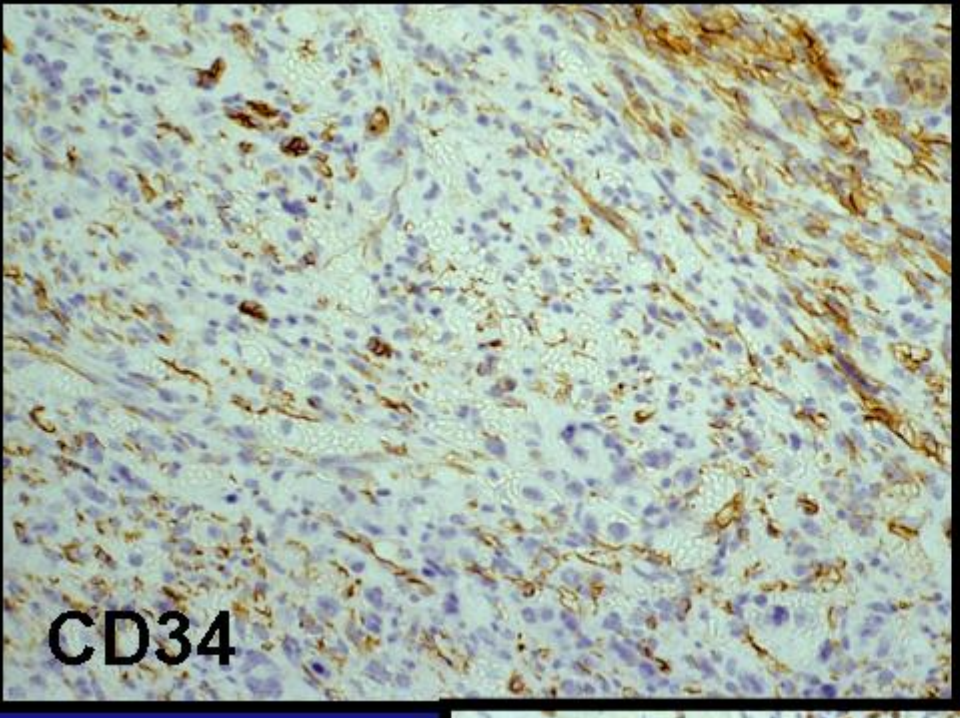
DLBCL + KS

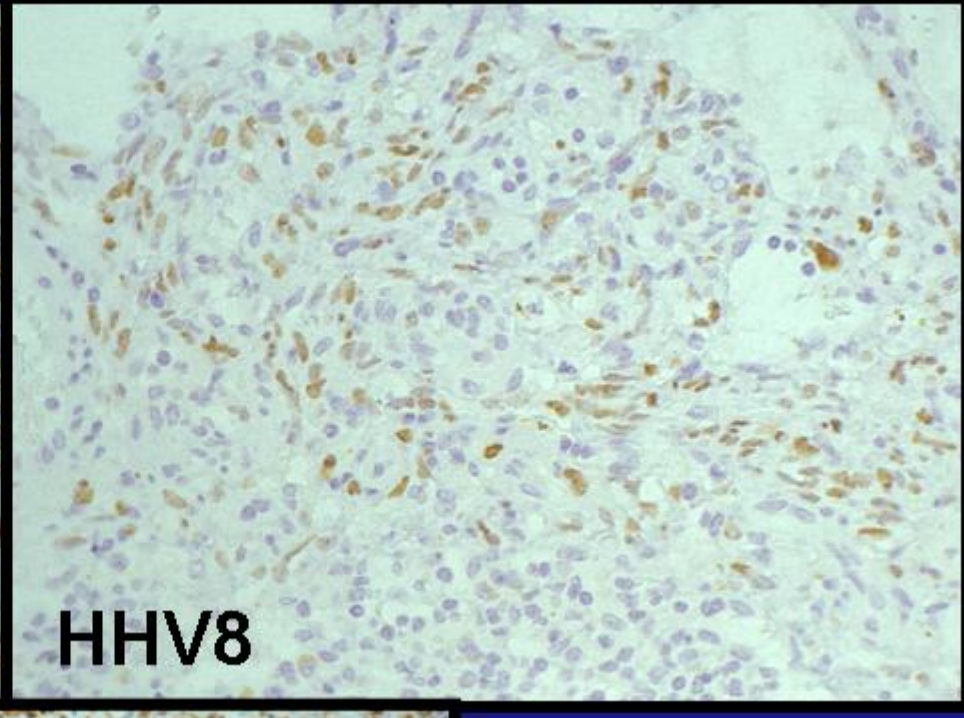


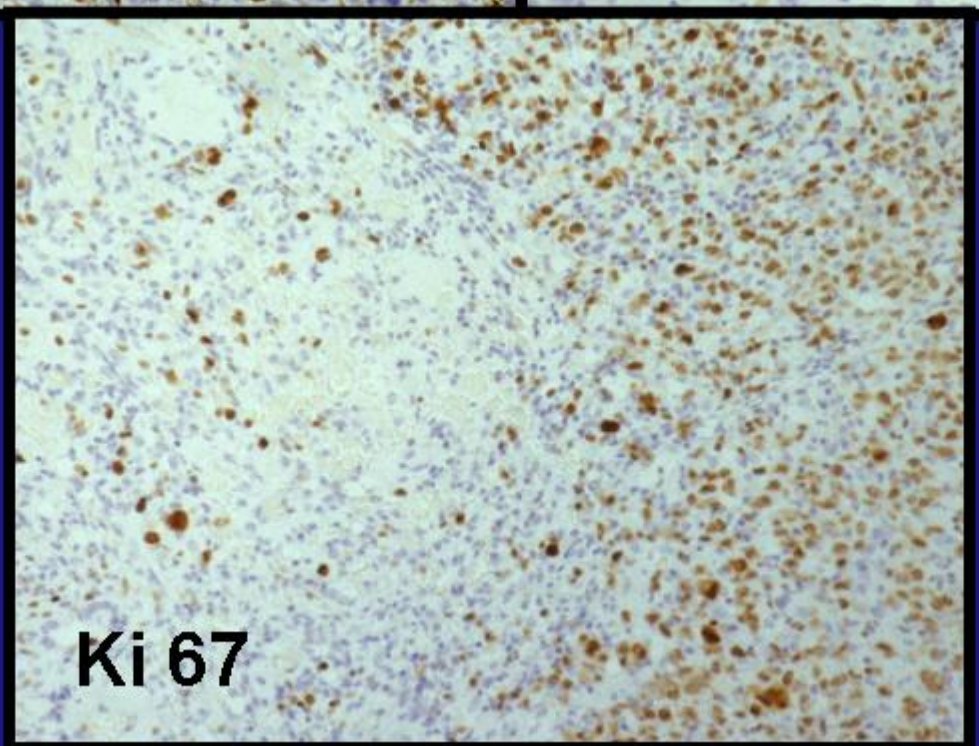





CD20
CD3
LMP 1


CD34


HHV8


Ki 67

HHV8 AND IL6

- Il 6: acute phase protein produced by hepatocyte
- HHV8 encodes a viral IL 6 (vIL 6) → plasmacytosis & angiogenesis
- vIL 6 is expressed in cells around GCS in MCD monotypic for λ light chains and may B-cell proliferation → monoclonal expansion and PblL

HHV8 (KSVH)

Human rhadnovirus (gamma-2 herpes virus)

Unlike EBV, not widespread in general population

Prevalence: 2-5% oh healthy donors except in endemic areas
10-25% in Medit. countries, 30% in African areas including Egypt
If donor sero+ve for HHV8, 23% develop KS (cf. 0.7% if sero-ve)
80-95% in classic KS patients
40-50% of HIV+ve patients without KS

Transforming virus requiring co-factors, eg. immunosuppression; cytokines

Gains access to host cells by binding to proteoglycans of cell surface allowing penetration and fusion of HHV8 viral envelope with plasma membrane

Detected by latent and lytic proteins eg. pAb to vIL6

Co-exists with EBV

CASTLEMANS DISEASE (CD)

Hyaline vascular (HVCD) –ussually single node

Plasma cell (PCD) – often more than one node (site)

Muiticentric Castlemans disease (MCD) - generalised

CASTLEMANS DISEASE

Lymph node	HVCD	PCCD
Lymphoid follicles	Sometimes very large; occasionally irregular	Normal to increased size
Germinal cetres	Absent/ small/burnt out; consist mainly of FDC	Usually very active; FDC may be increased
Mantle zones arrangement	Concentric rings of B-cells separated by FDC	Usually normal
Polykaryocytes	Present	May be present
Interfollicular area	Mainly T-cells; few PCs Numerous PMs	Mainly PCs*; few T-cells May be PMs
Vessels	Very numerous; show hyalinisation	Usually increased

PM plasmacytoid monocyte (DR2 cells)

* IL6 production

MULTICENTRIC CASTLEMAN'S DISEASE

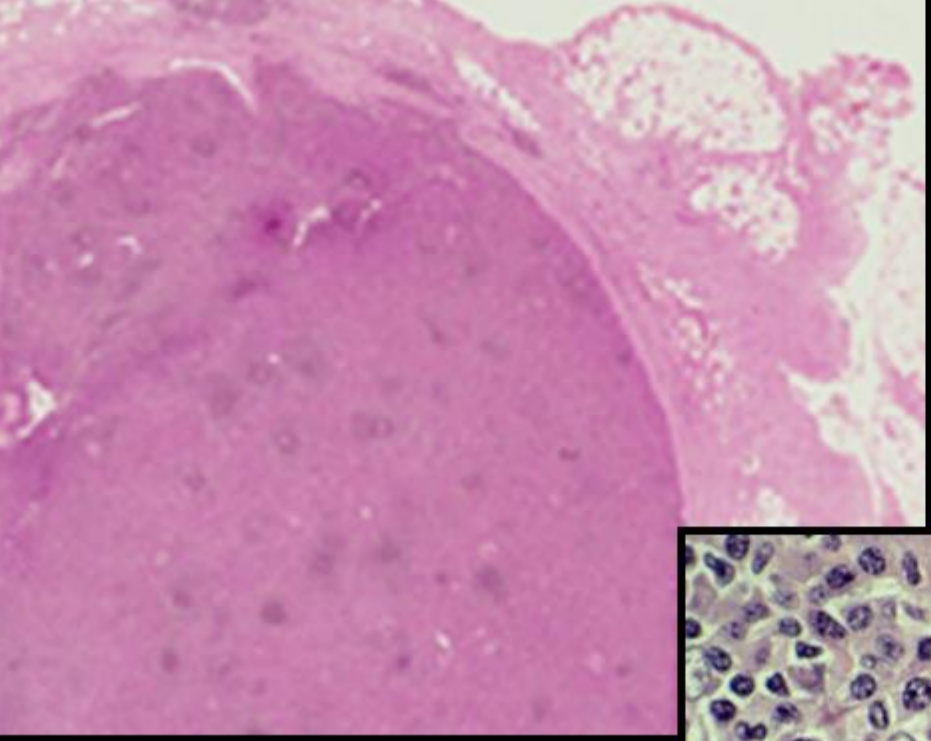
- A poorly understood lymphoproliferative disorder related to immune dysregulation
- Usually a polyclonal non-neoplastic disorder
- Plasma cell type associated with generalised lymphadenopathy and systemic symptoms and immunological disorders.
- >95% of MCD cases occur in HIV+ patients
- MCD may:

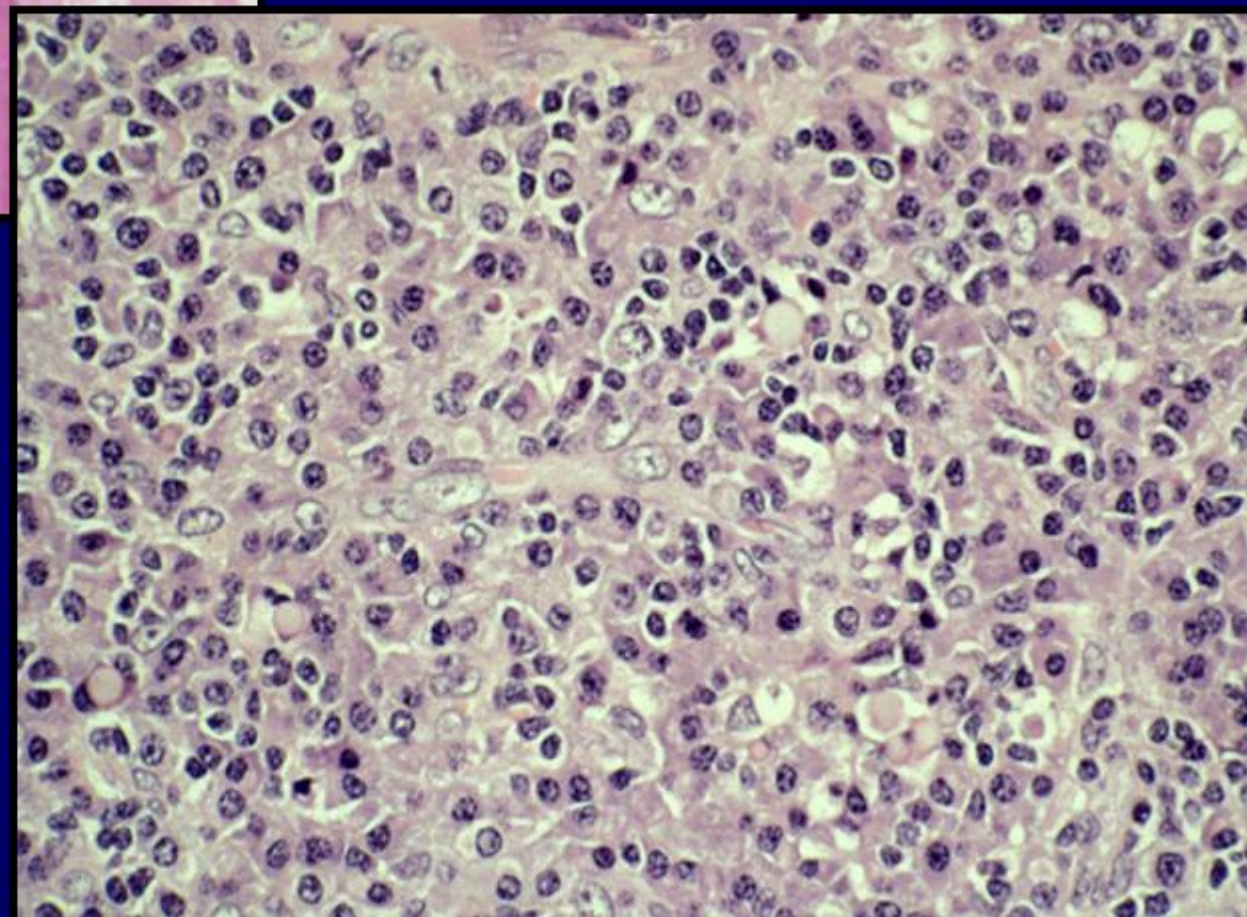
  Progress to NHL eg. plasmablastic lymphoma (PblL)

  Be associated with HHV8 (KSHV) & KS and PEL may co-exist.

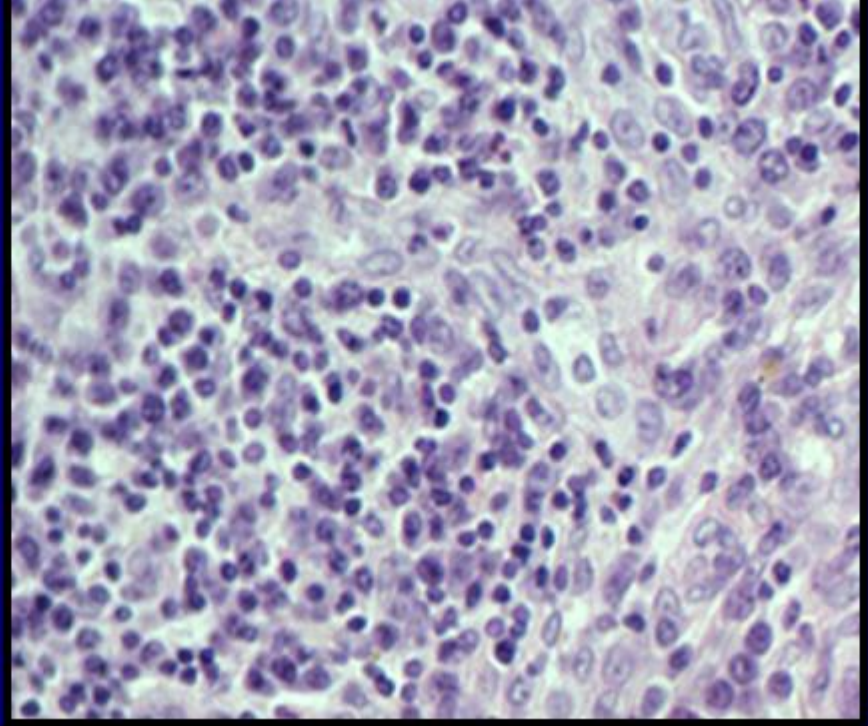
  Be associated with POEMS syndrome

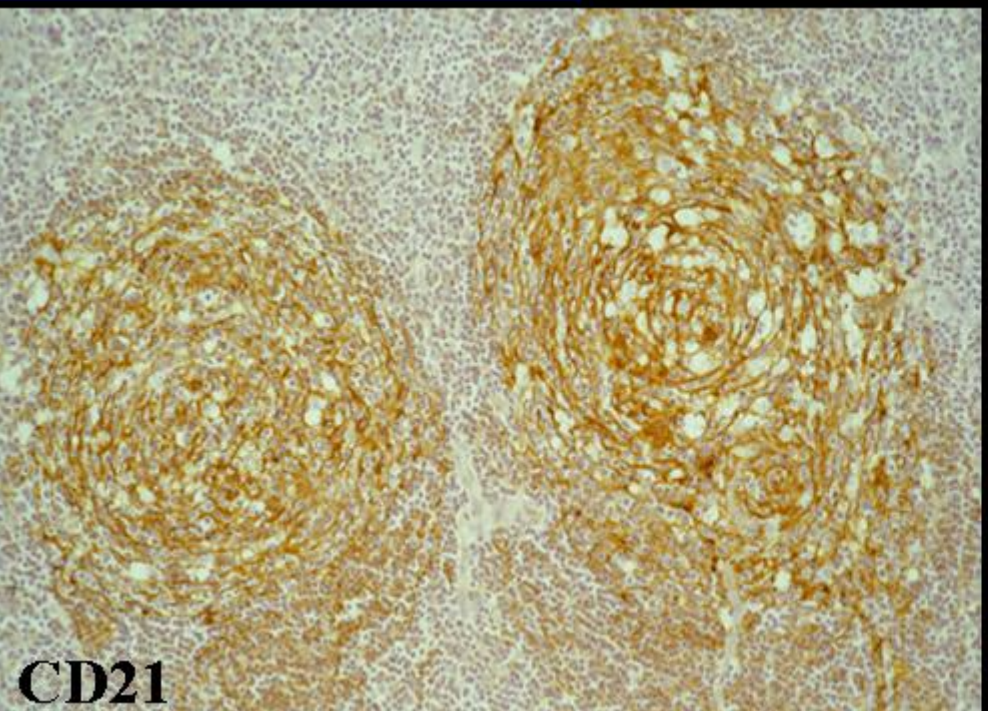
Castleman's disease plasma cell subtype

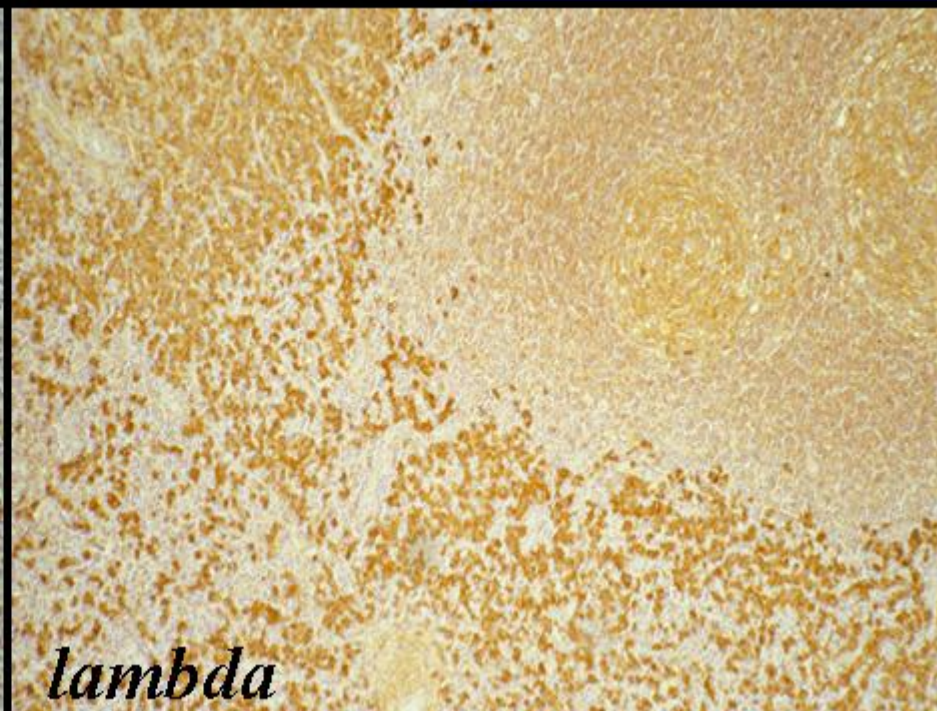


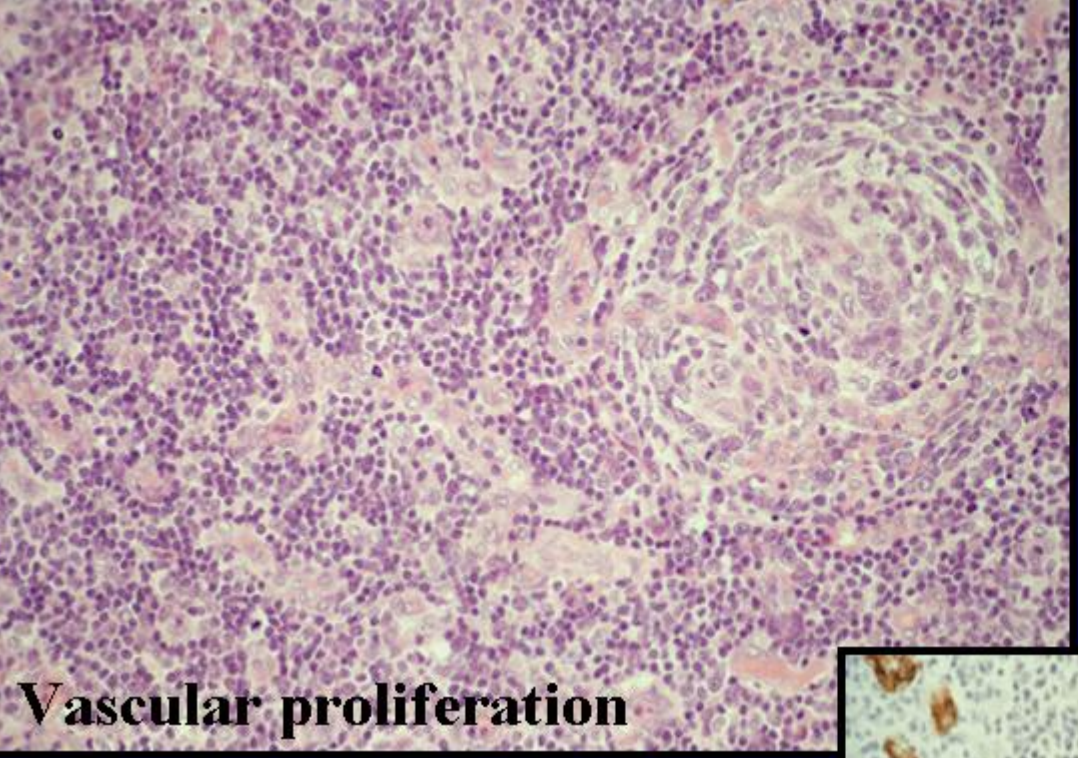


CD PC subtype



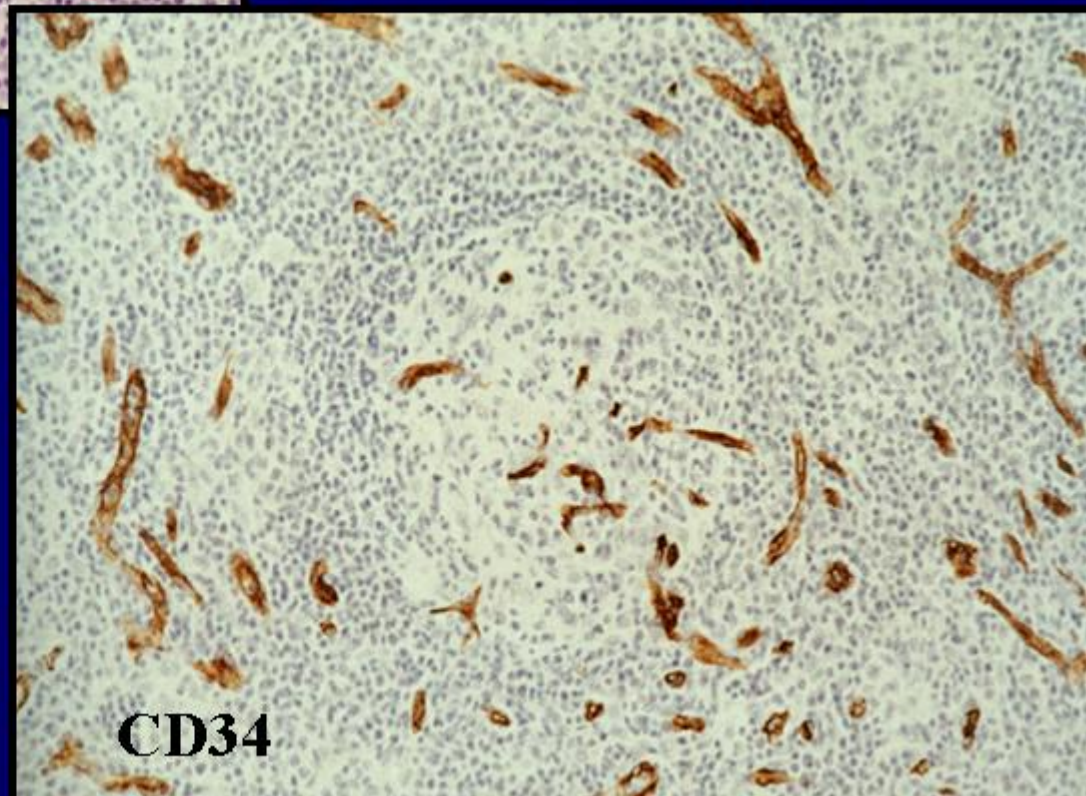




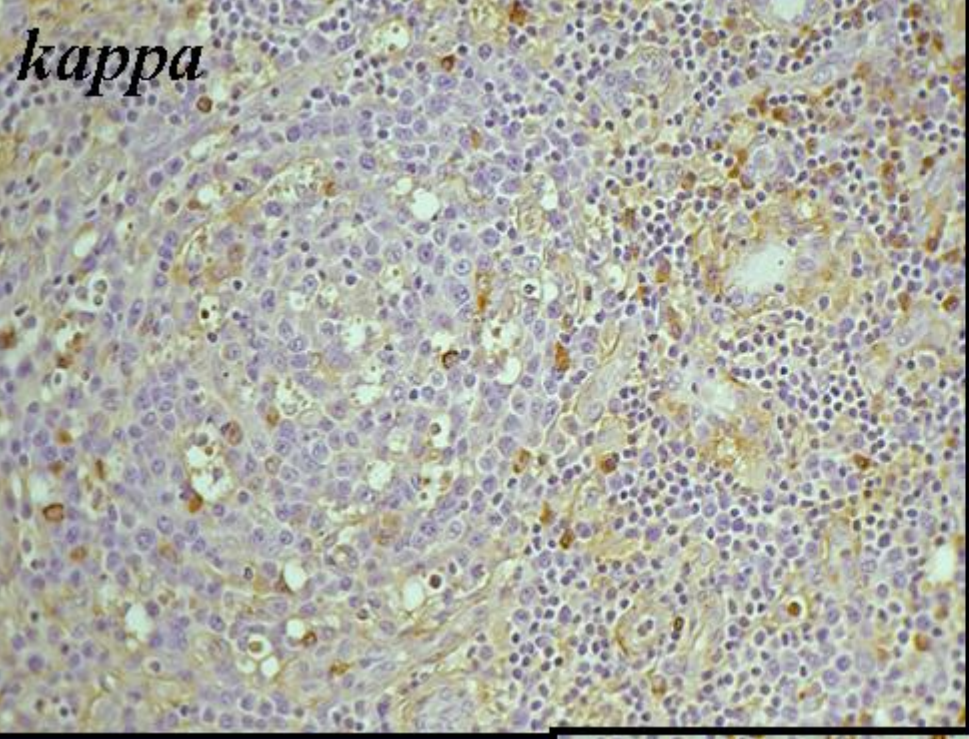


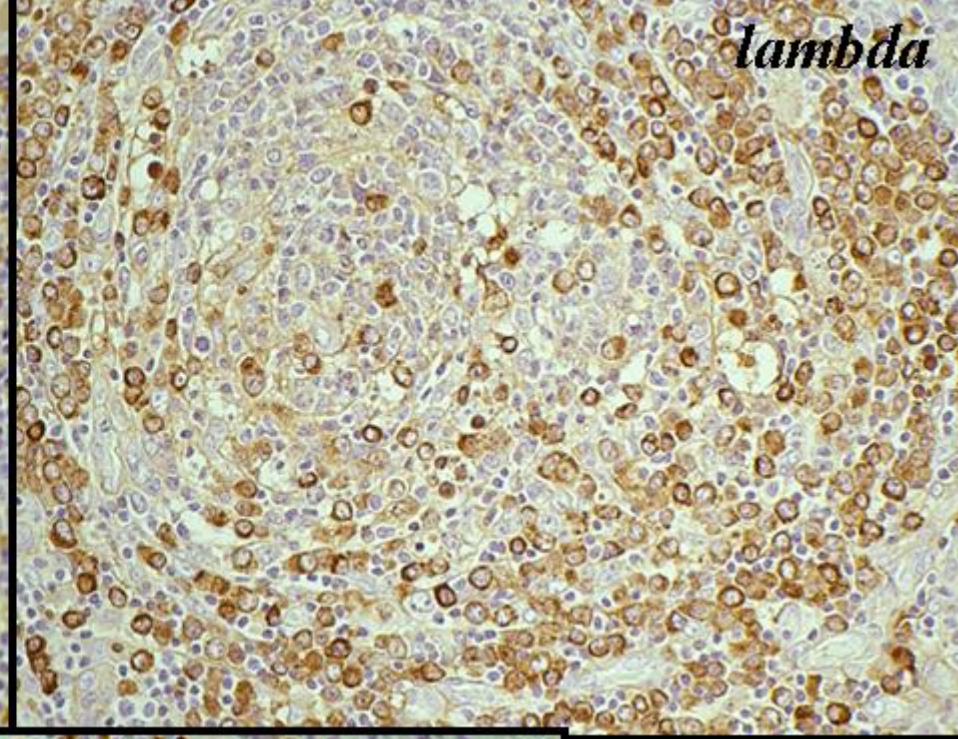
Vascular proliferation

MCD HIV+ve

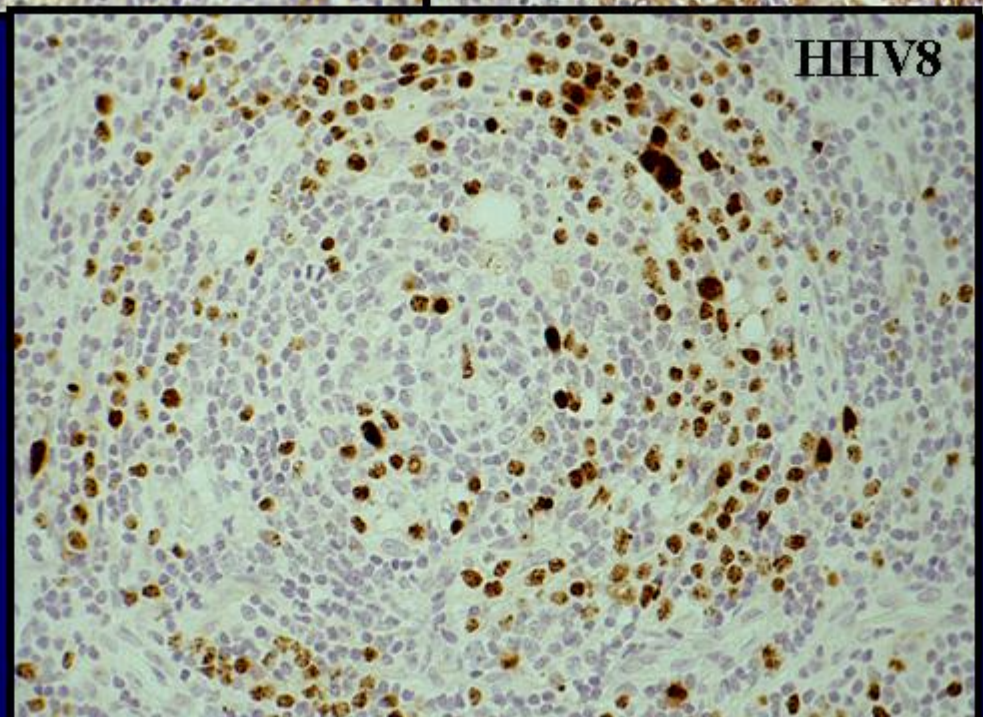


CD34



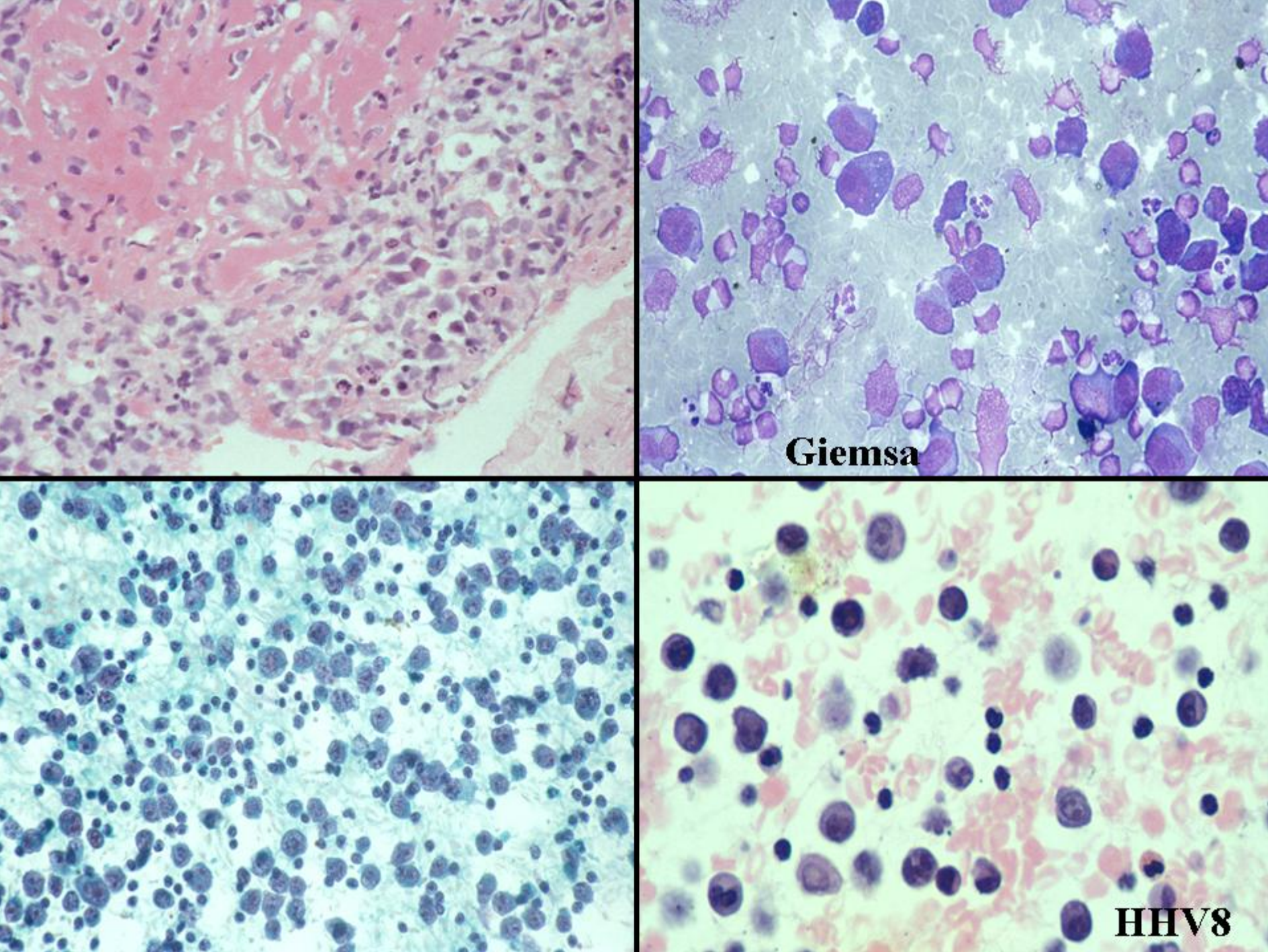


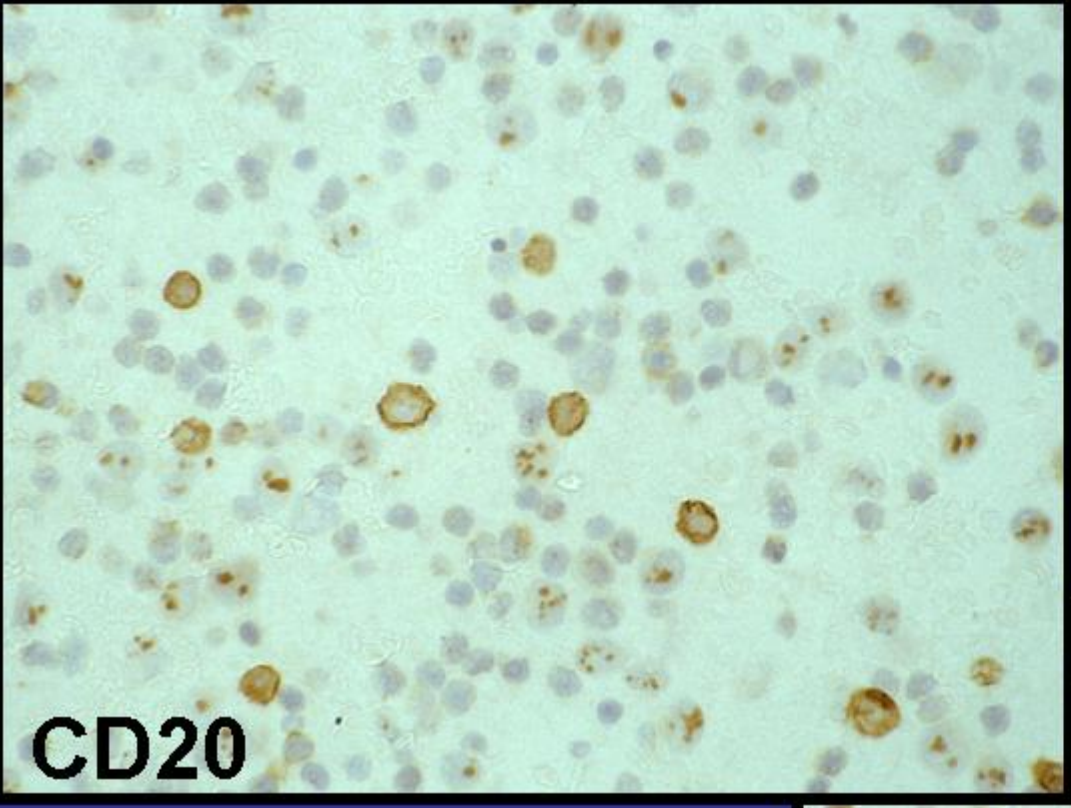
MCD HIV+ve

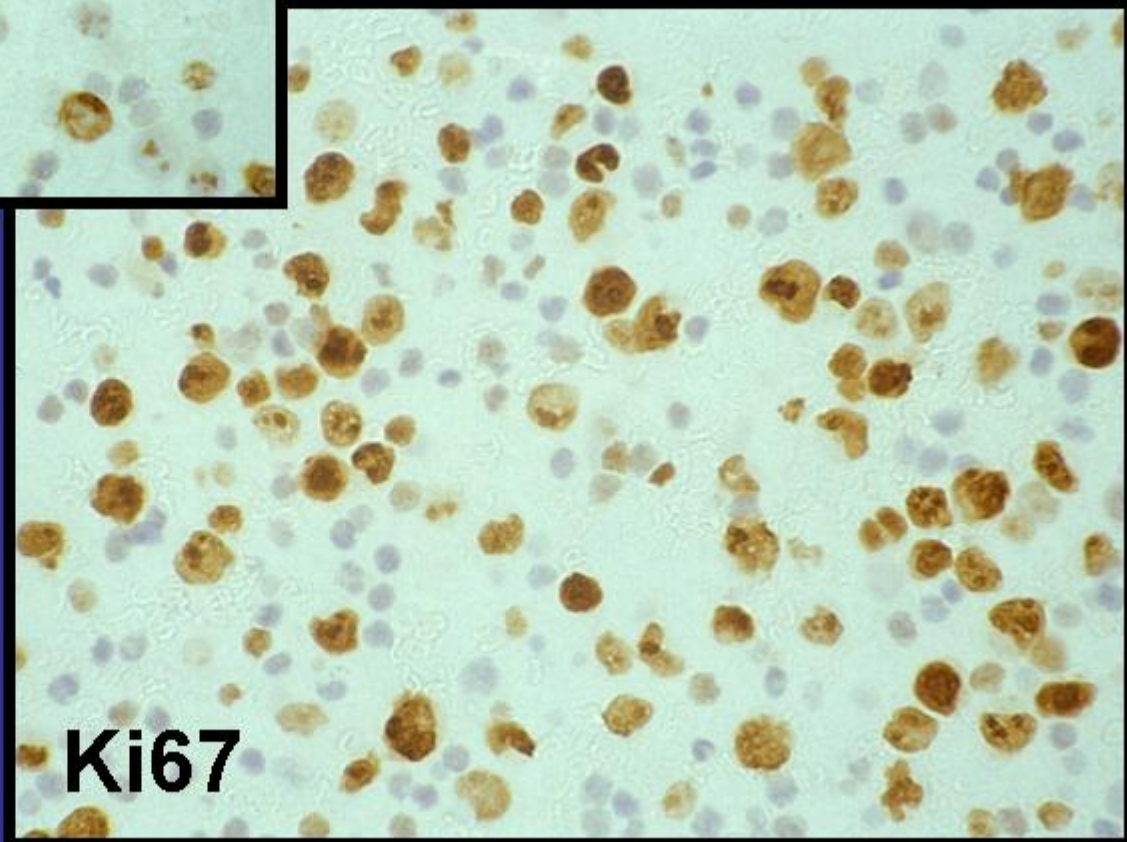


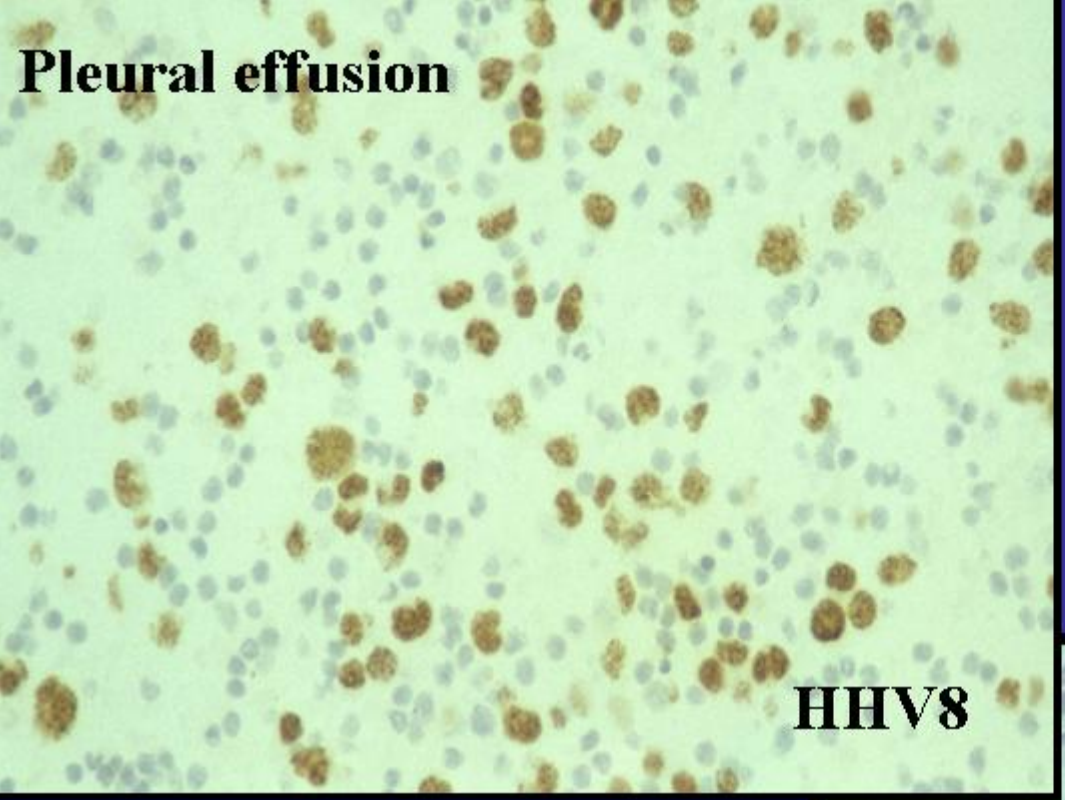
PRIMARY EFFUSION LYMPHOMA- PEL (Body cavity-based lymphoma)

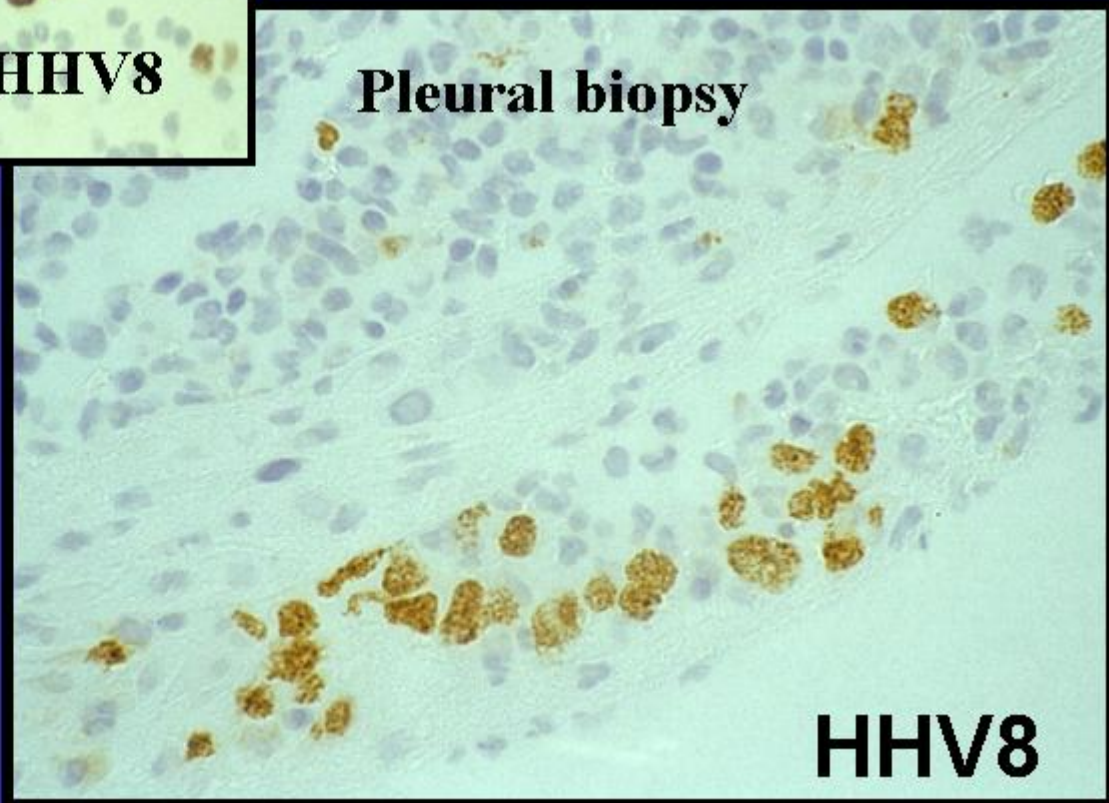
- **INCIDENCE:** 3% of all AIDS related lymphomas (cf 0.4% of HIV-ve LCL) Assoc. with both KS & HIV+ve MCD. Co-infection with EBV.
- **PRESENTATION:** lymphomatous effusions in pleural or peritoneal cavities. Occasionally as a solid tumour mass.
- **MORPHOLOGY:** large cells with features resembling those in immunoblastic and anaplastic lymphomas. Sometimes plasmablastic.
- **LINEAGE:** B-cell, post GC B-cells (Ig genes hypermutated).
- **PHENOTYPE:** CD45+, 1 or more activation- associated Ags eg. CD138, CD30 CD20 & CD79a usually-ve; may be κ or λ +ve. HHV8+ve.
- **GENOTYPE:** clonal Ig gene re-arrangement 97%; lack Bcl 2, ras and p53 gene alterations and C myc re-arrangement


Giemsa
HHV8


CD20


Ki67


Pleural effusion
HHV8


Pleural biopsy
HHV8

WHO CLASSIFICATION of CATERGORIES OF PTLD[1]

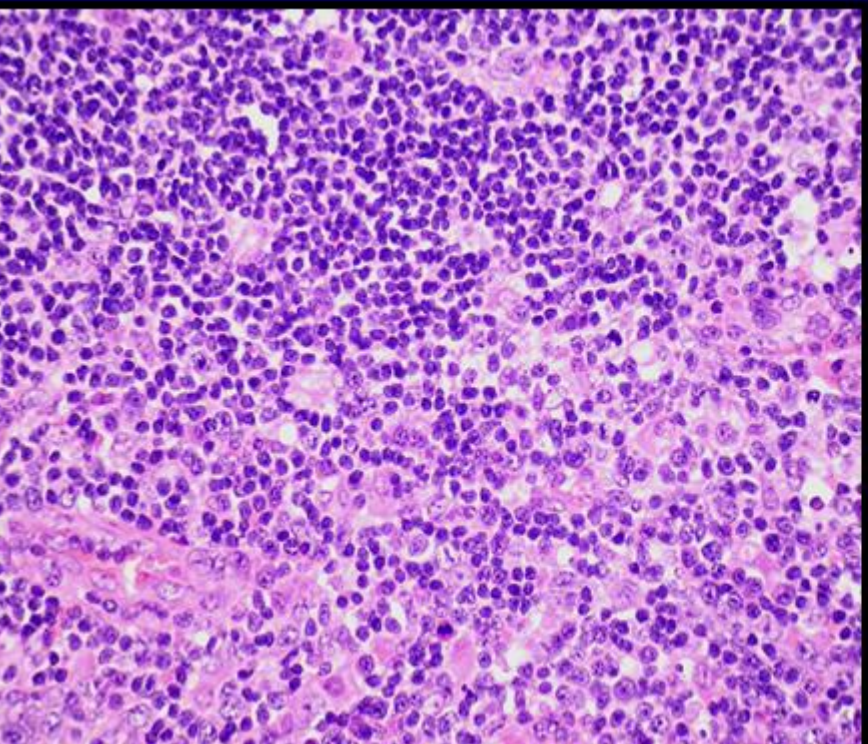
1. Early lesions
   - reactive plasmacytic hyperplasia
   - infectious mononuclosis (IM) -like
2. Polymorphic PTLD*
3. Monomorphic PTLD
   - B- cell lymphomas
     - diffuse large B-cell lymphoma
     - Burkitt/Burkitt-like lymphoma
     - plasma cell myeloma and plasmacytoma-like lesions
   - T- cell lymphomas
     - peripheral T-cell lymphoma, NOS; other types
4. Hodgkin lymphoma (HL) and HL-like PTLD

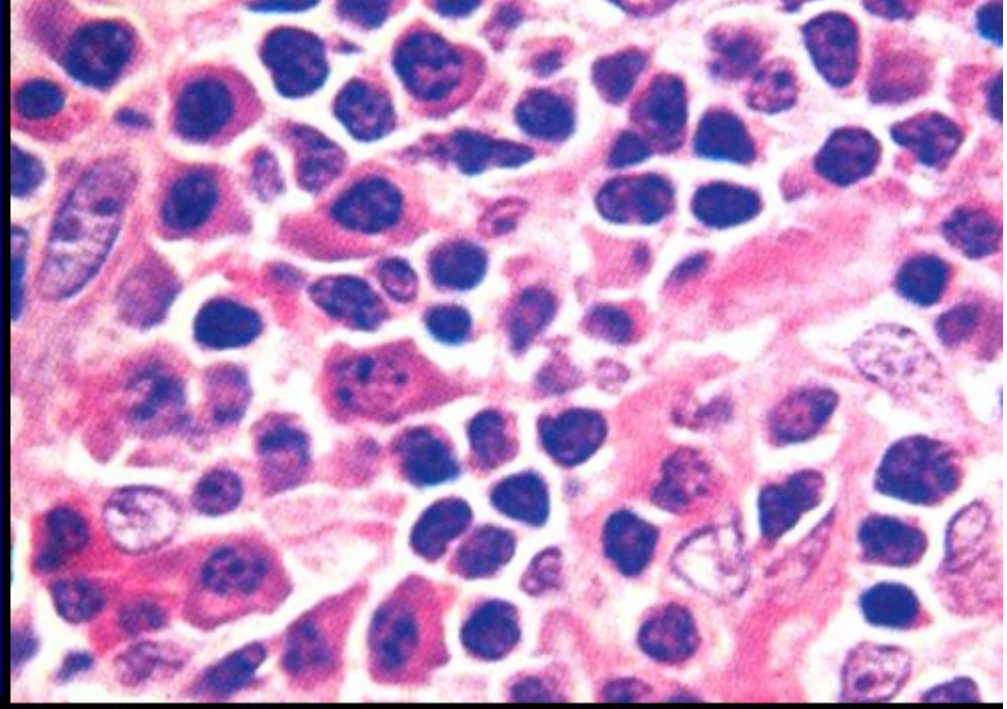
*clonal or polyclonal

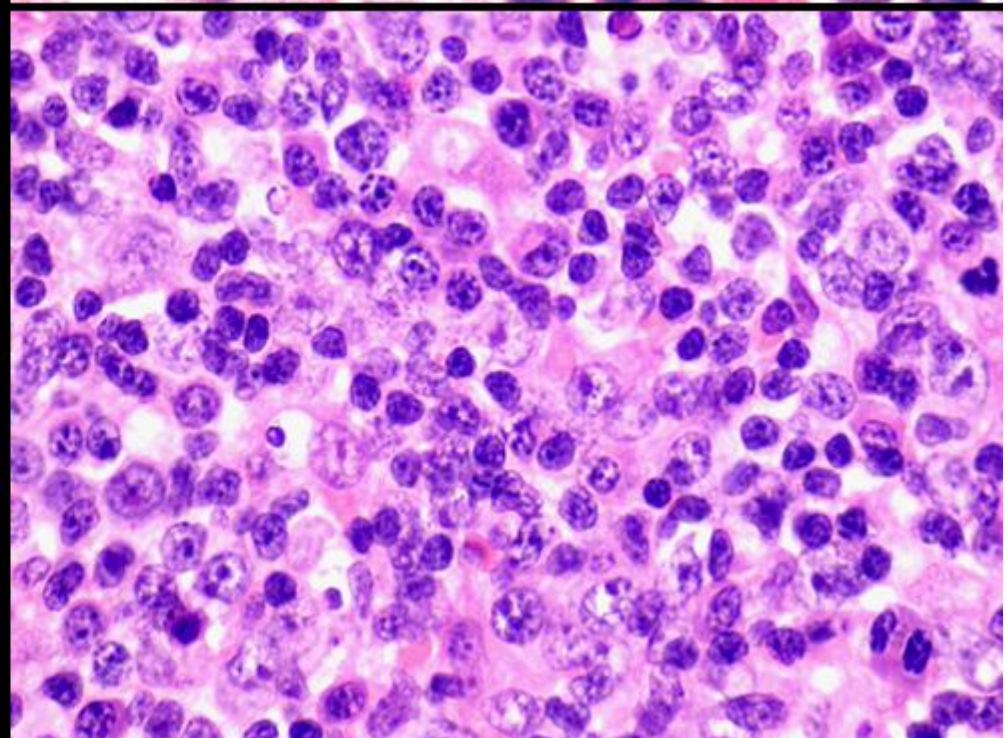
PTLD-early lesions

eactive plasmacytic hyperplasia (PCH)

nfectious mononucleosis (IM) like

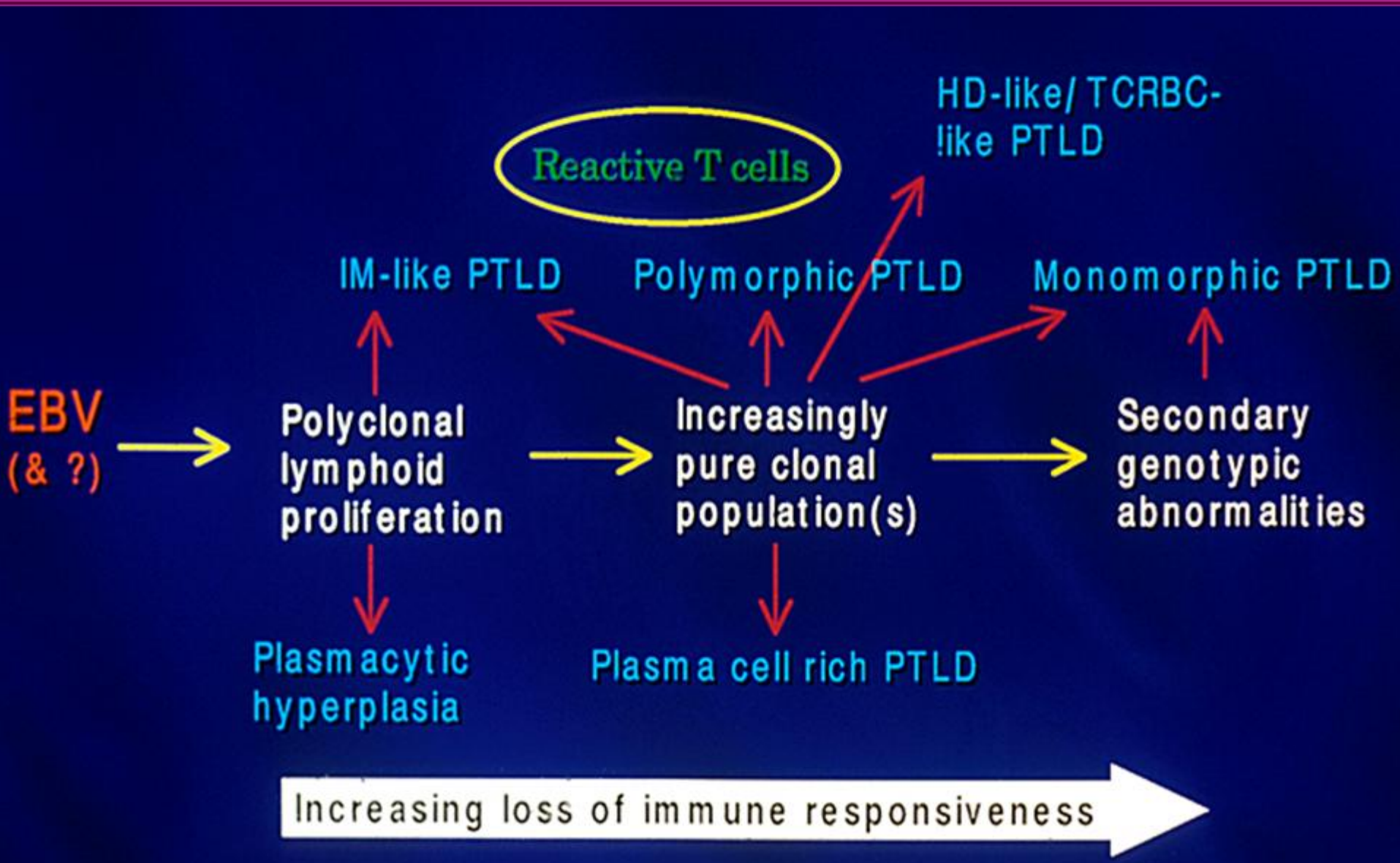


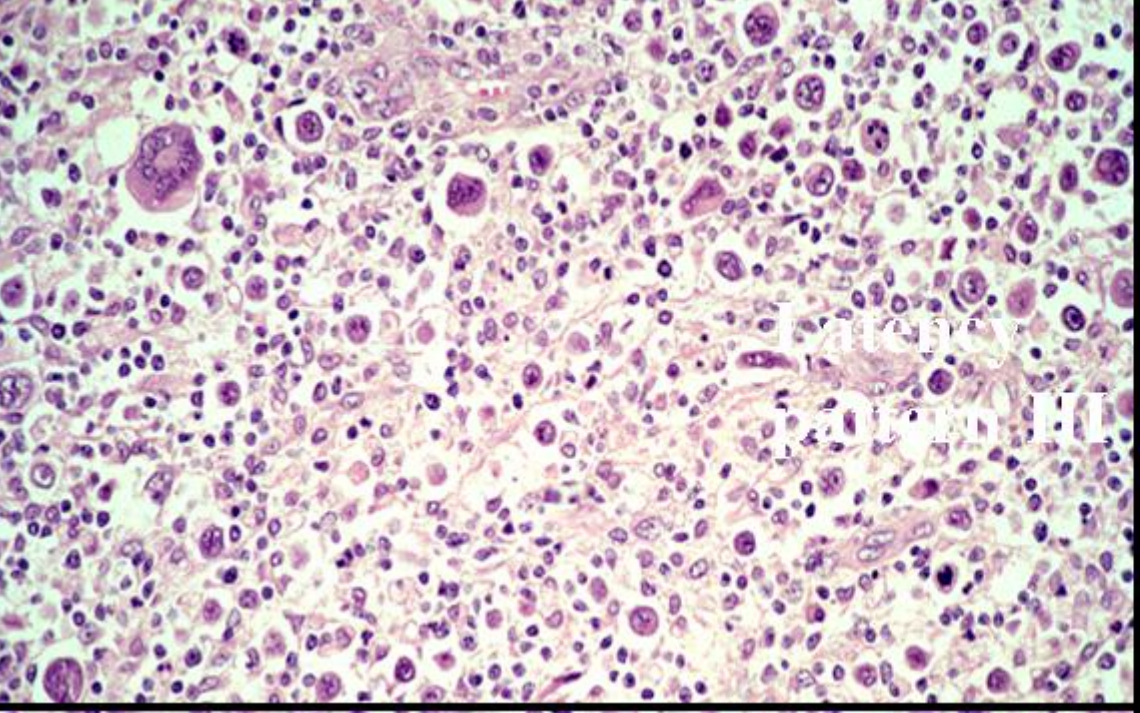


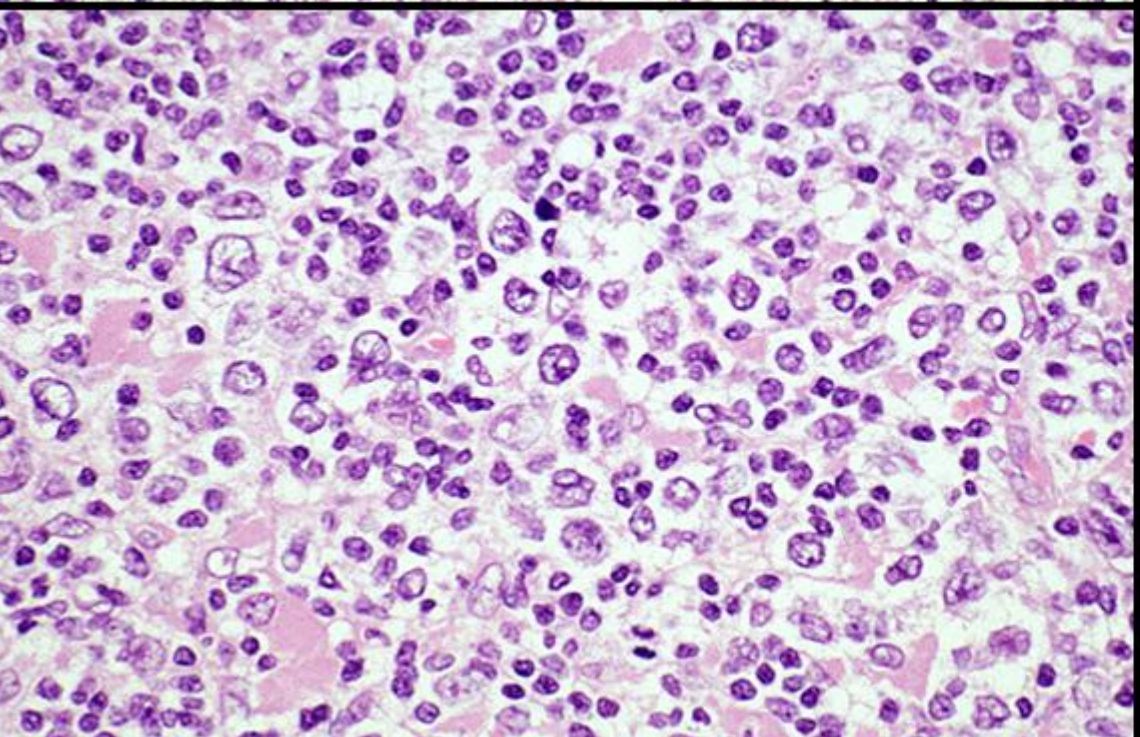


SUGGESTED MODEL OF EVOLUTION AND PROGRESSION OF PTLD

Swerdlow SH 1997

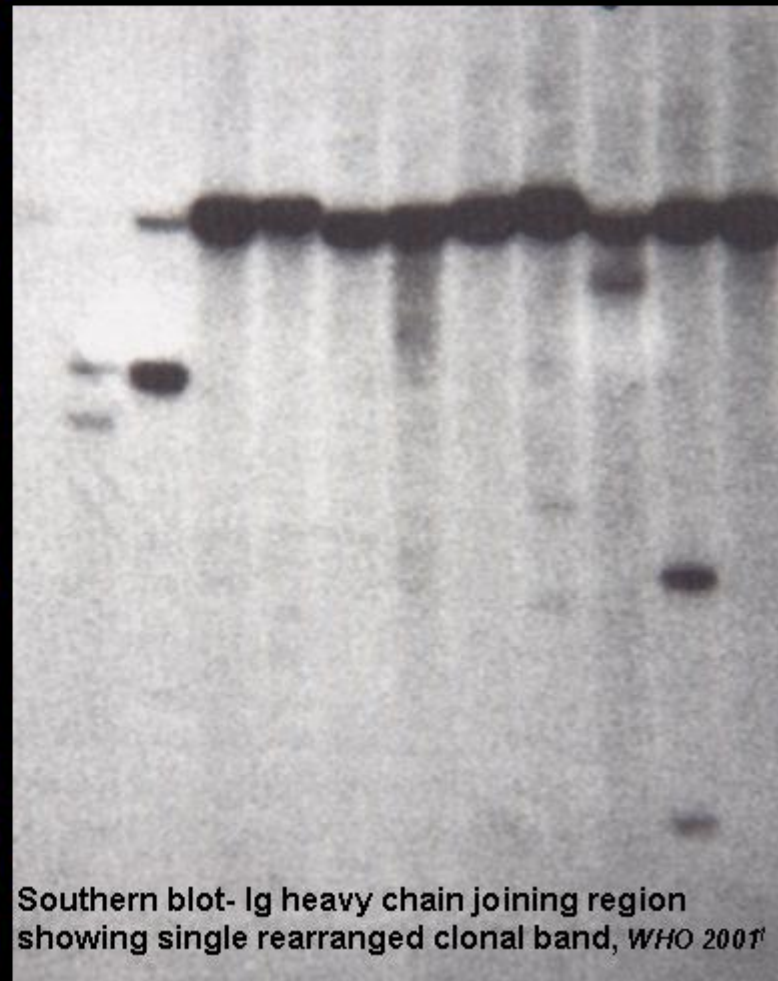




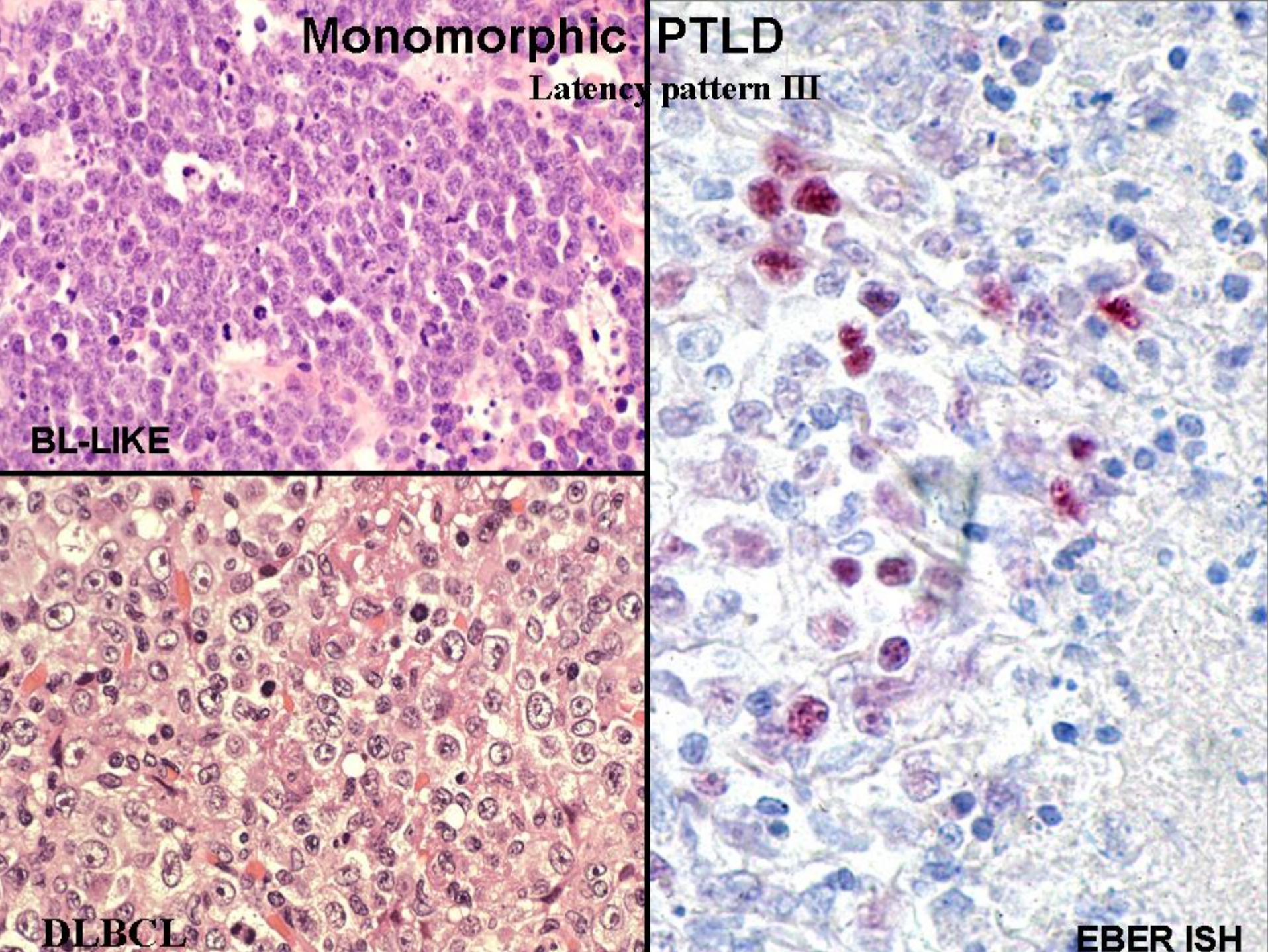


Polymorphic PTLD

Latency pattern III



Southern blot- Ig heavy chain joining region showing single rearranged clonal band, *WHO 2001*


Monomorphic PTLD
Latency pattern III
BL-LIKE
DLBCL
EBER ISH

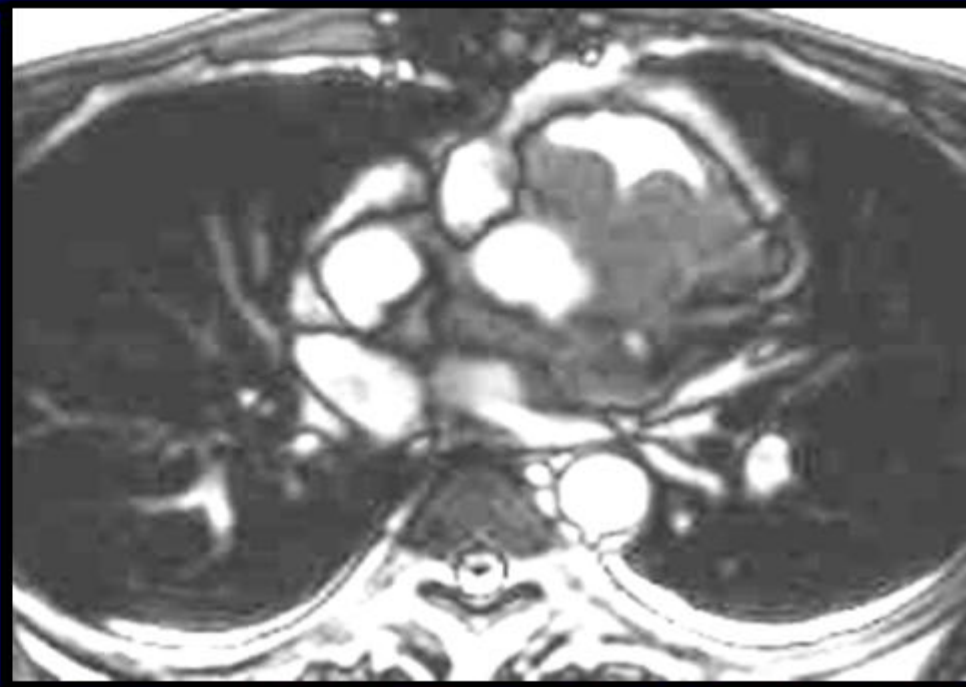
PTLD ARISING P0ST SOLID ORGAN TRANSPLANT

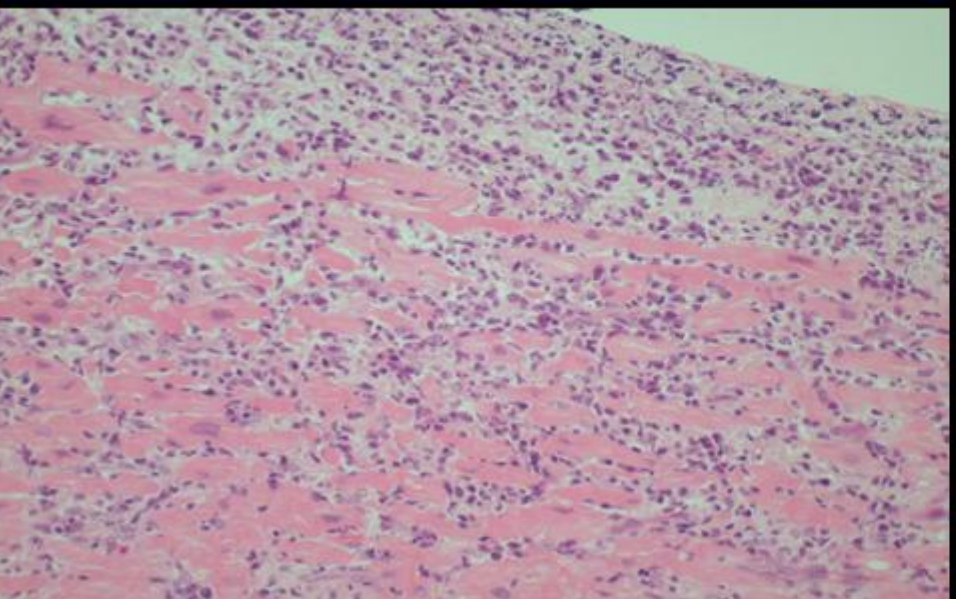
- **Incidence** – varies according to type of allograft
- **Risk factors** - young age, rejection (mismatching), T-cytolytic therapy, pre-transplant EBV seronegativity, recipient cytokine gene polymorphism
- **Site** - nodal/extra-nodal, including lung
- **Time post-tx** - majority in 1st 2 years following tx, increasing number of late occurrences (>6 years post-tx)
- **Biology** - unpredictable irrespective of morphology
- **ISH for EBV** detects EBV in >80% of early PTLD but in few PTLDs
- **Therapy** - may compromise the graft
- **Monitoring** - of infection/disease - PB EBV DNA?

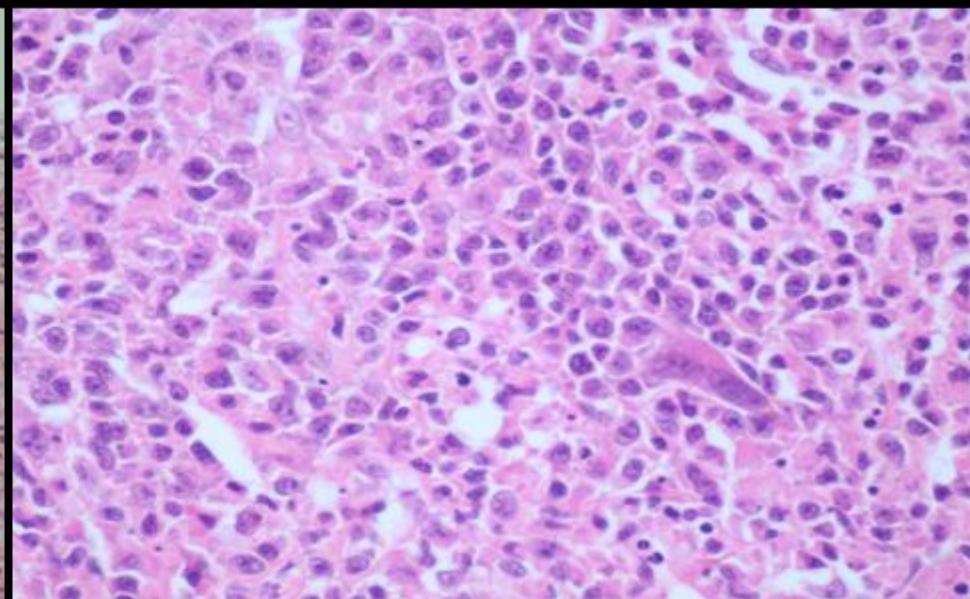
MONOMORPHIC CARDIAC PTLD- DLBCL, *courtesy Dr. M. Burke, Harefield transplant unit*

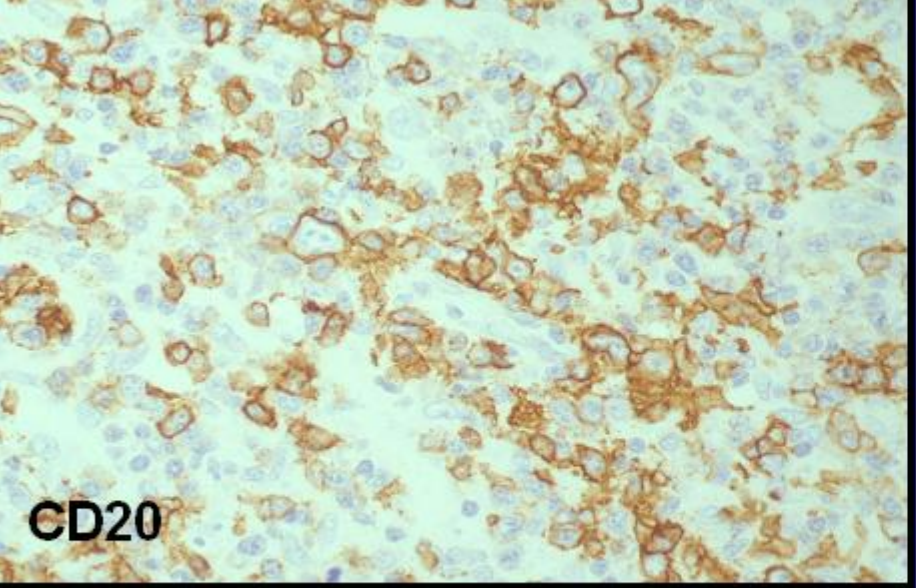
Male, 33yrs, black African Cameroonian

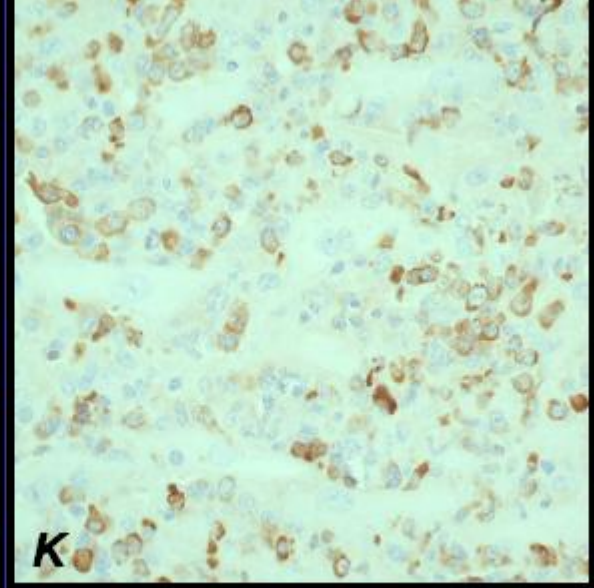
- Transplanted in March 2001 for DCM, diagnosed 1 year previously.
- Several episodes of mild or moderate acute rejection.
- Two months later treated with steroids and rATG
- Maintenance : Cyclosporine (CSA),prednisolone, mycophenolate (MF); tatacrolimus substituted for CSA
- At first annual review (March 2002) higher than normal RV pressures with gradient of 18 to 25 mm Hg between RV and PA.

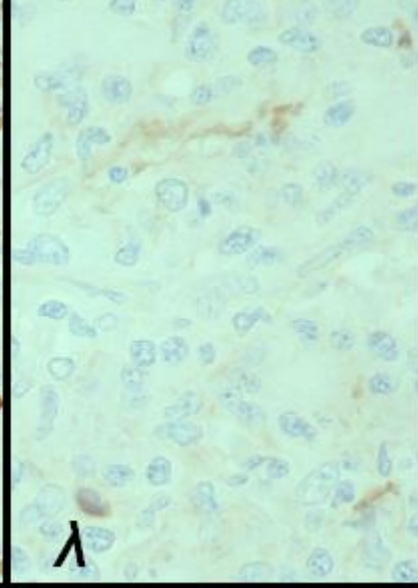


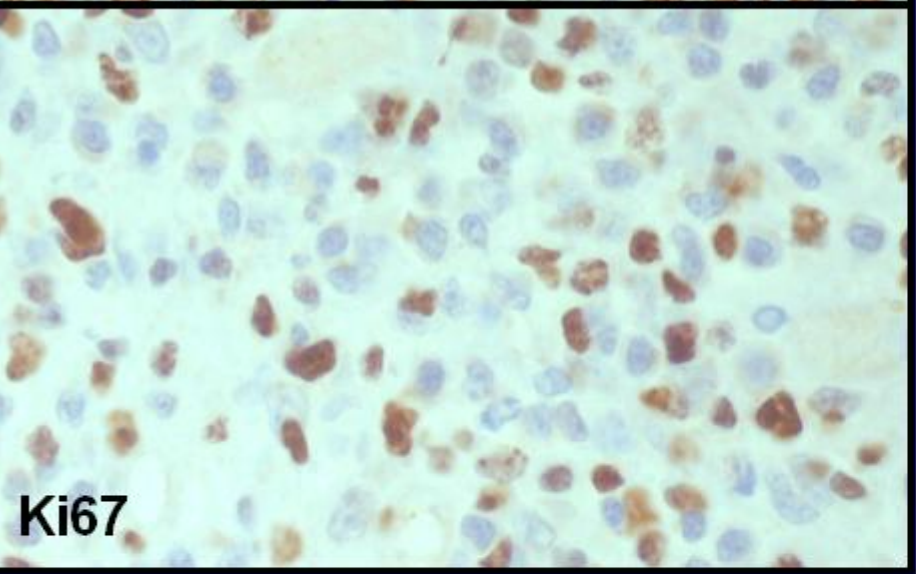


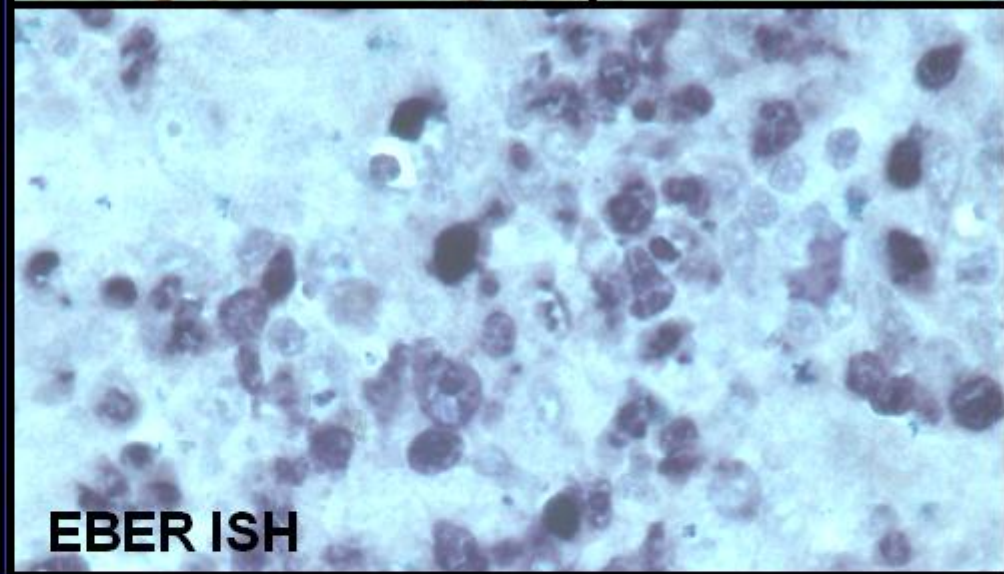












Full staging. BMA AND BMT clear; no extra cardiac disease
Retuximab x 6. Has remained well since September 2002
Serial CTs- no change other than due to de-bulking surgery

Cardiac PTLD: points of interest

Location

Differentiation from rejection

Source of EBV and PTLD

Management

LPD of donor or recipient origin?

HLA typing of tumour cells vs recipient cells

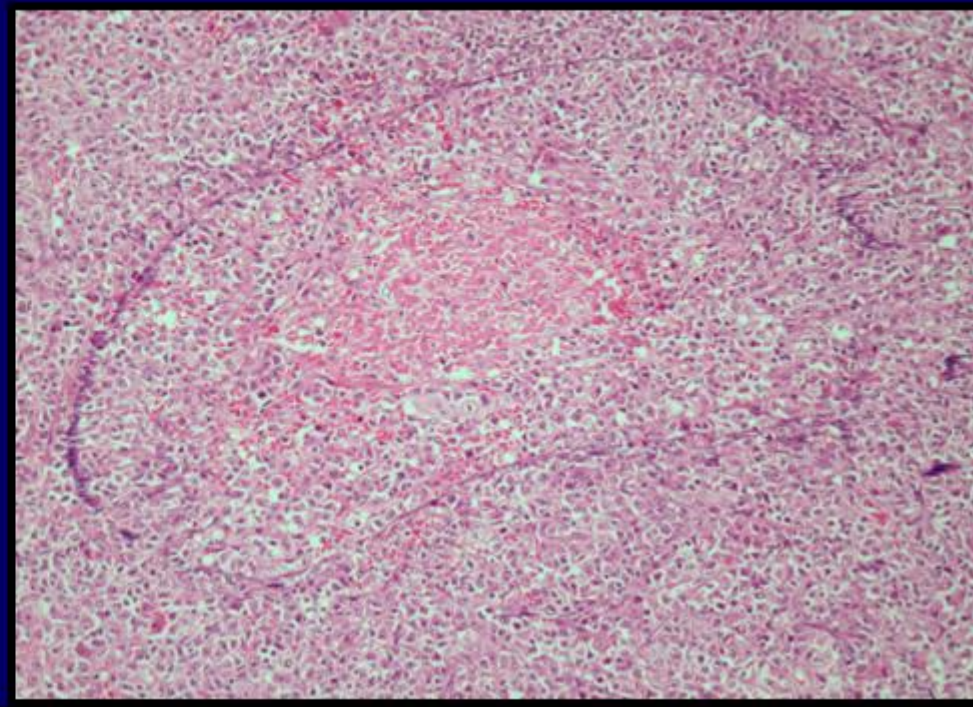
EBV of donor or recipient origin?

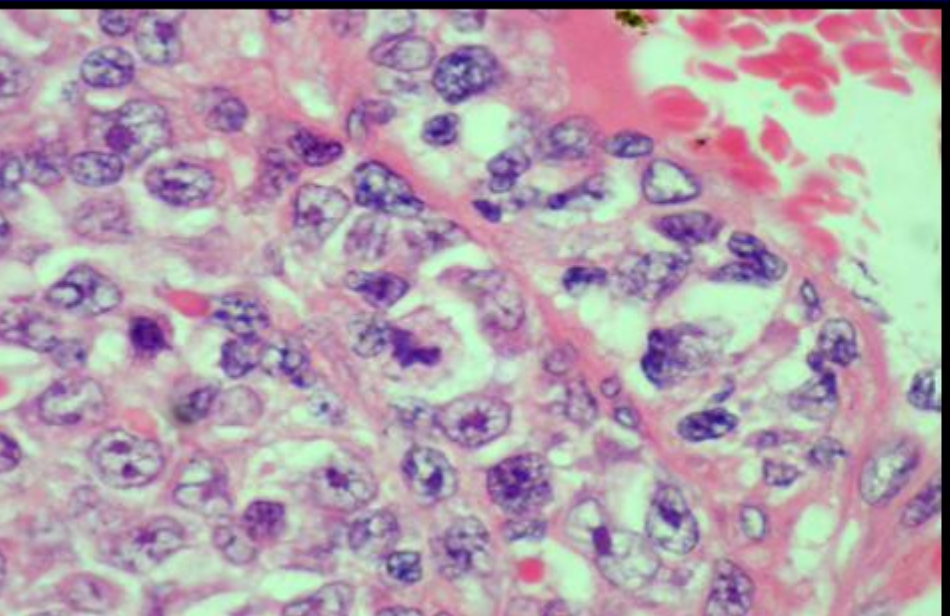
EBV in donor organs a/c LPD in seronegative recipients

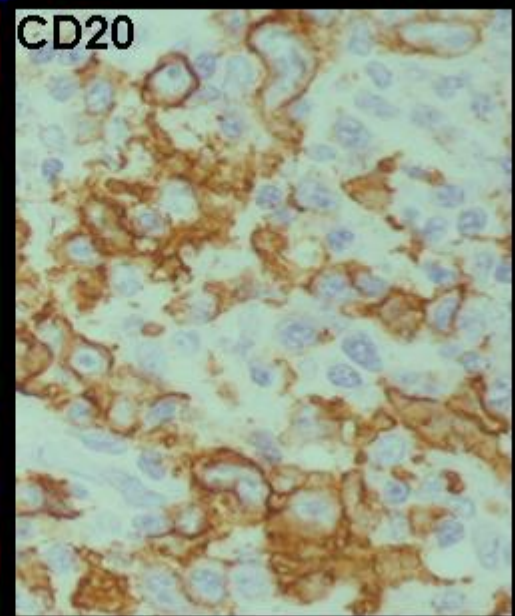
(Haque et al (1996) J Gen Virol 77(Pt 6):1169-72)

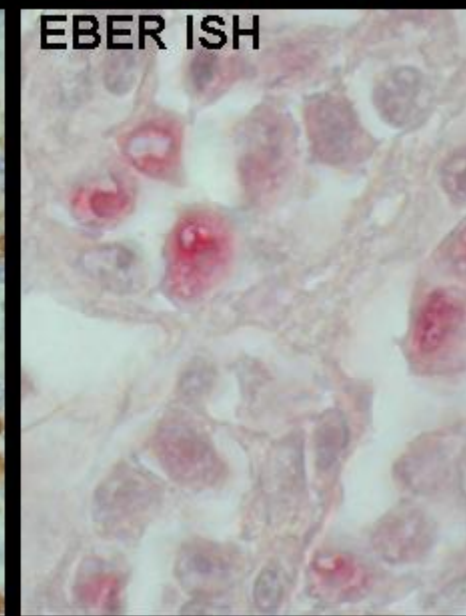
Male, 22yrs

- Double lung tx in early 1994 for cystic fibrosis
- Repeat single lung tx in late 1994 for diffuse alveolar damage/recurrent infections
- White nodule 2 cm. diam in base of explanted lung
- Staging: no extra-pulmonary disease







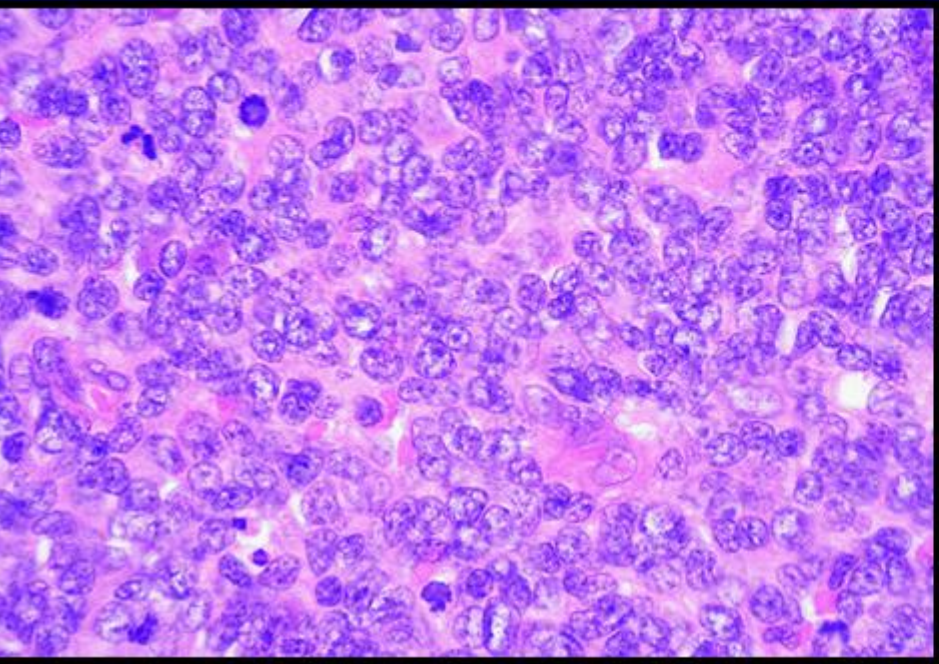


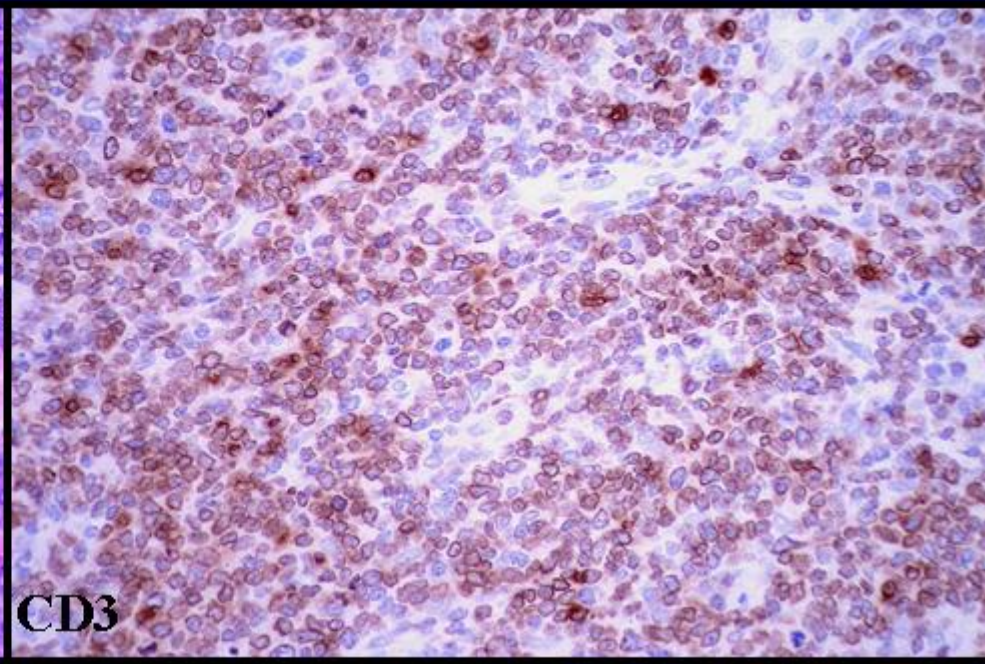
Difficulties in diagnosis of pulmonary LPD

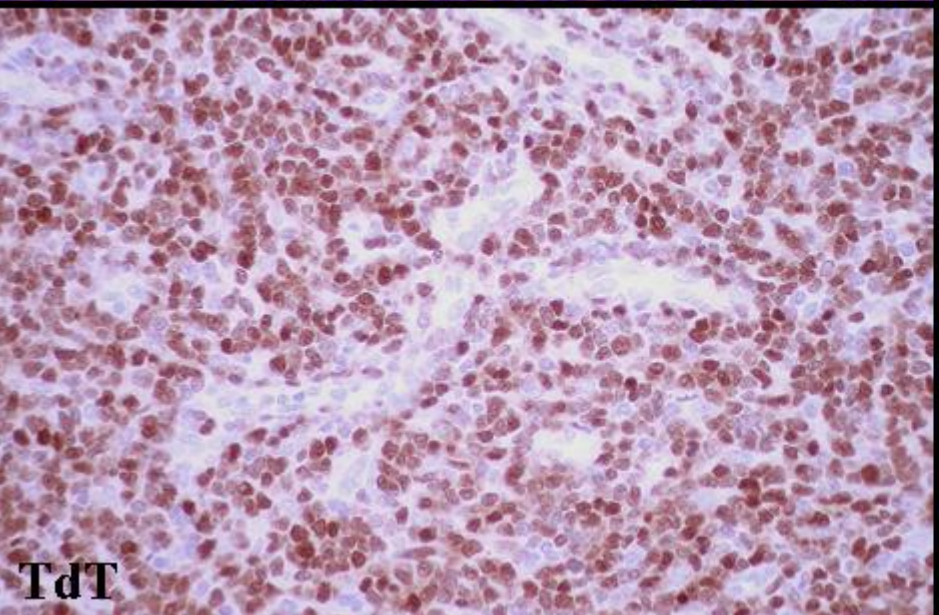
- Biopsy diagnosis - sampling error
- Tissue trauma
- Necrosis
- Assessment of clonality
- Differentiation from non-PTLD causes of pulmonary lymphoid infiltrates

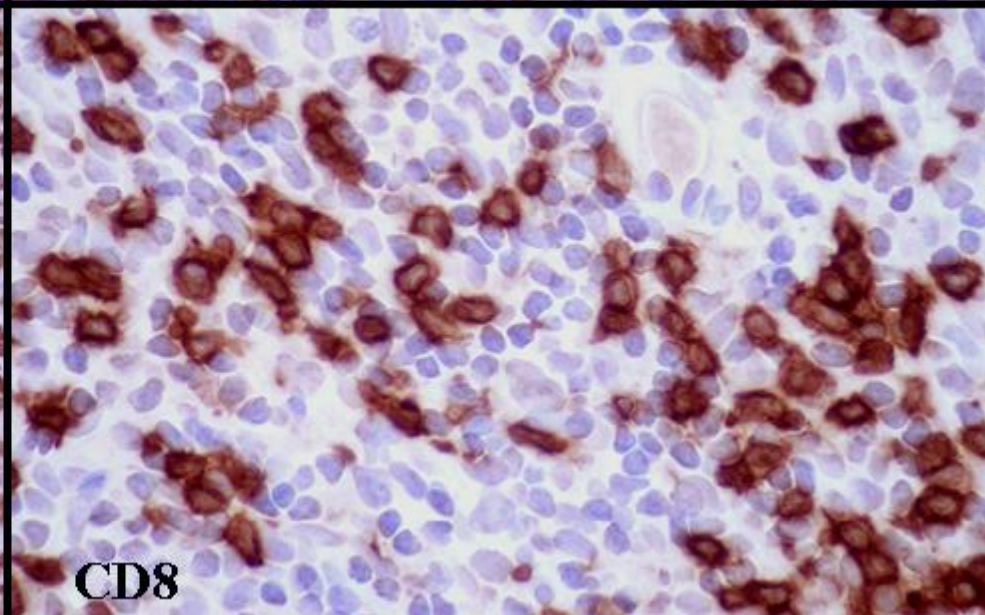
NB. acute rejection, infection

PTLD- TLB 7 years post renal transplant







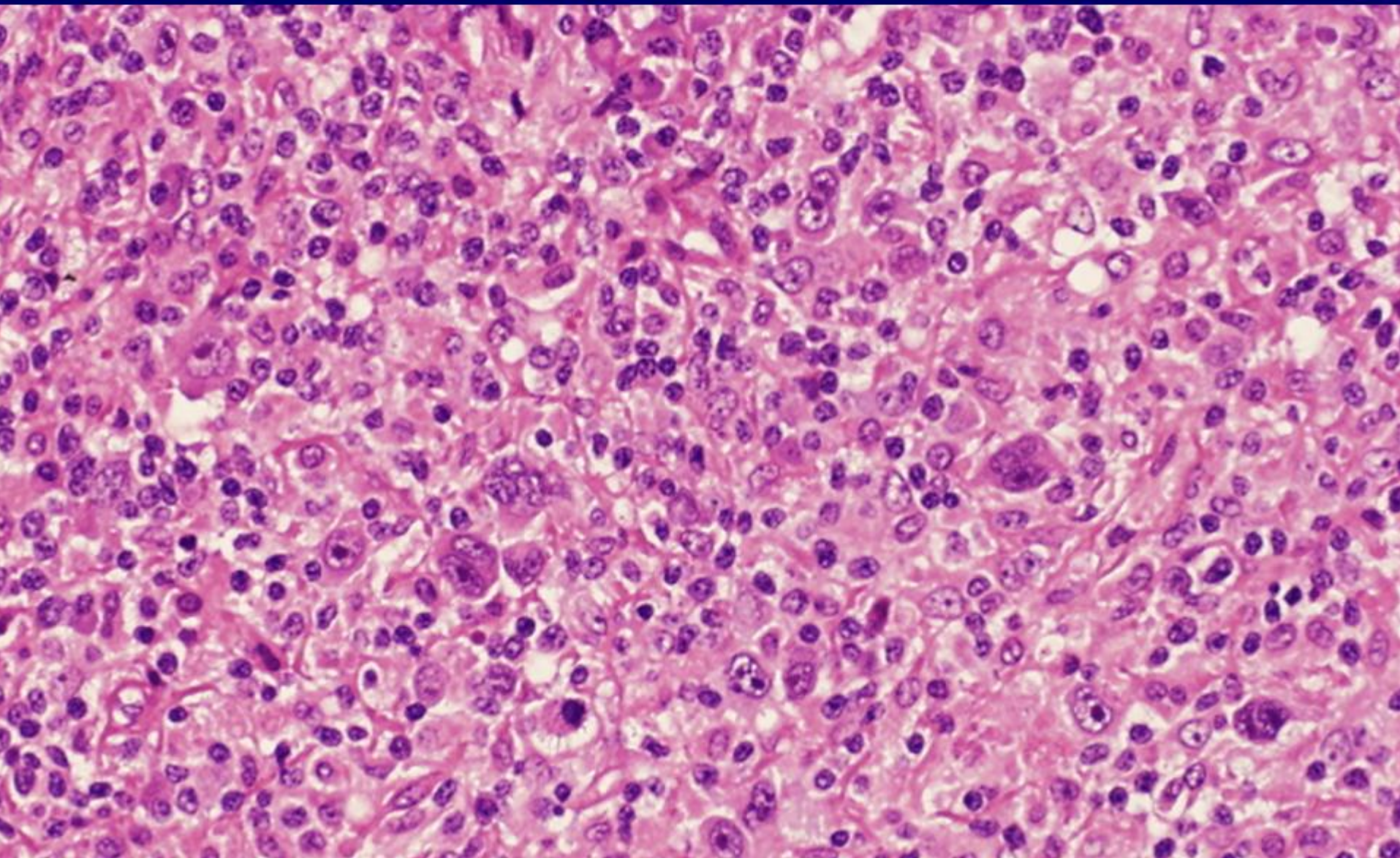


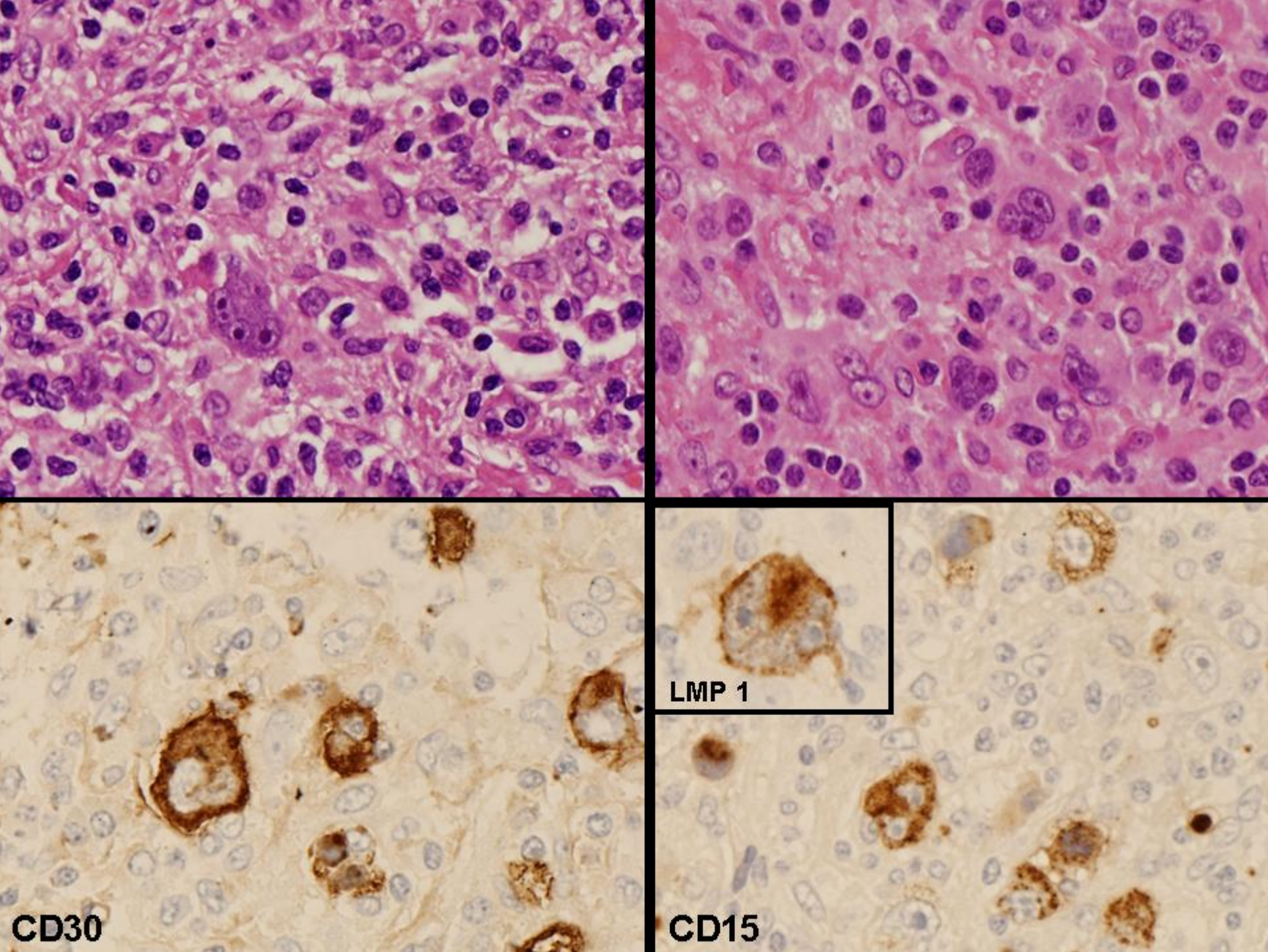
PTLD ARISING IN POST BM AND STEM CELL TRANSPLANT RECIPIENTS

- Incidence- 1-2% (rises up to 20% if multiple risk factors)
- Risk factors- young age, EBV seronegativity prior to Tx, HLA mismatch or unrelated donors, T-cell depletion of either recipient or transplant, significant GVHD
- Lowest risk (<1.3 cf. to no T cell modulation) is induction with CAMPATH-1MoAb (targets B- as well as T cells

PTLD-HL

9 years post BM transplant




LMP 1
CD30
CD15

MANAGEMENT OF PTLD

- Reduction of immunosuppression
- Anti-viral therapy
- Anti-CD 20 antibody (Rituximab)
- Alpha-interferon
- Anti-EBV cytotoxic T-cell lymphocyte therapy/infusion
- Cyt0kine inhibitor therapy
- Local radiotherapy
- Combination chemotherapy
- Surgery

AQUIRED IMMUNODEFICIENCY STATES

- Malnutrition
- Metabolic: eg; Diabetes
- Common variable hypogammaglobuliaemia
- Neoplasia: Thymoma → hypogammaglobulinaemia
  Hodgkin lymphoma, NHL
- Connective tissue and auto-immune diseases: eg; RhA, SS
- Infective: eg; AIDS
- Iatrogenic: Transplantation
  Immunosupressive and cytotoxic therapy
  Splenectomy
  Transfusions, blood and blood products

LPD AND AUTO-IMMUNE (AI) and OTHER DISEASES

Rheumatoid arthritis (RA)

Sjogren's syndrome

Dermatomyositis

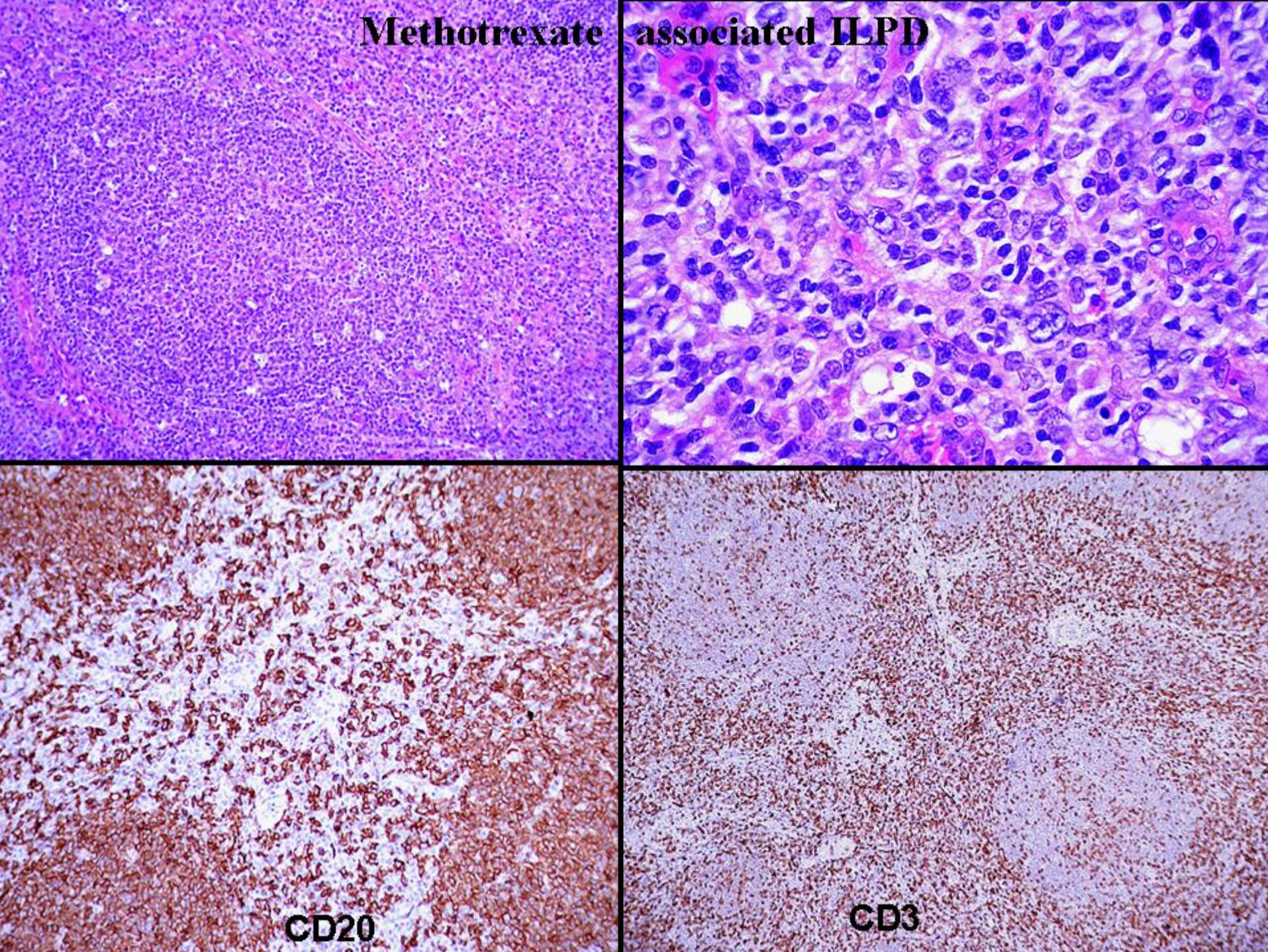
Crohn's disease

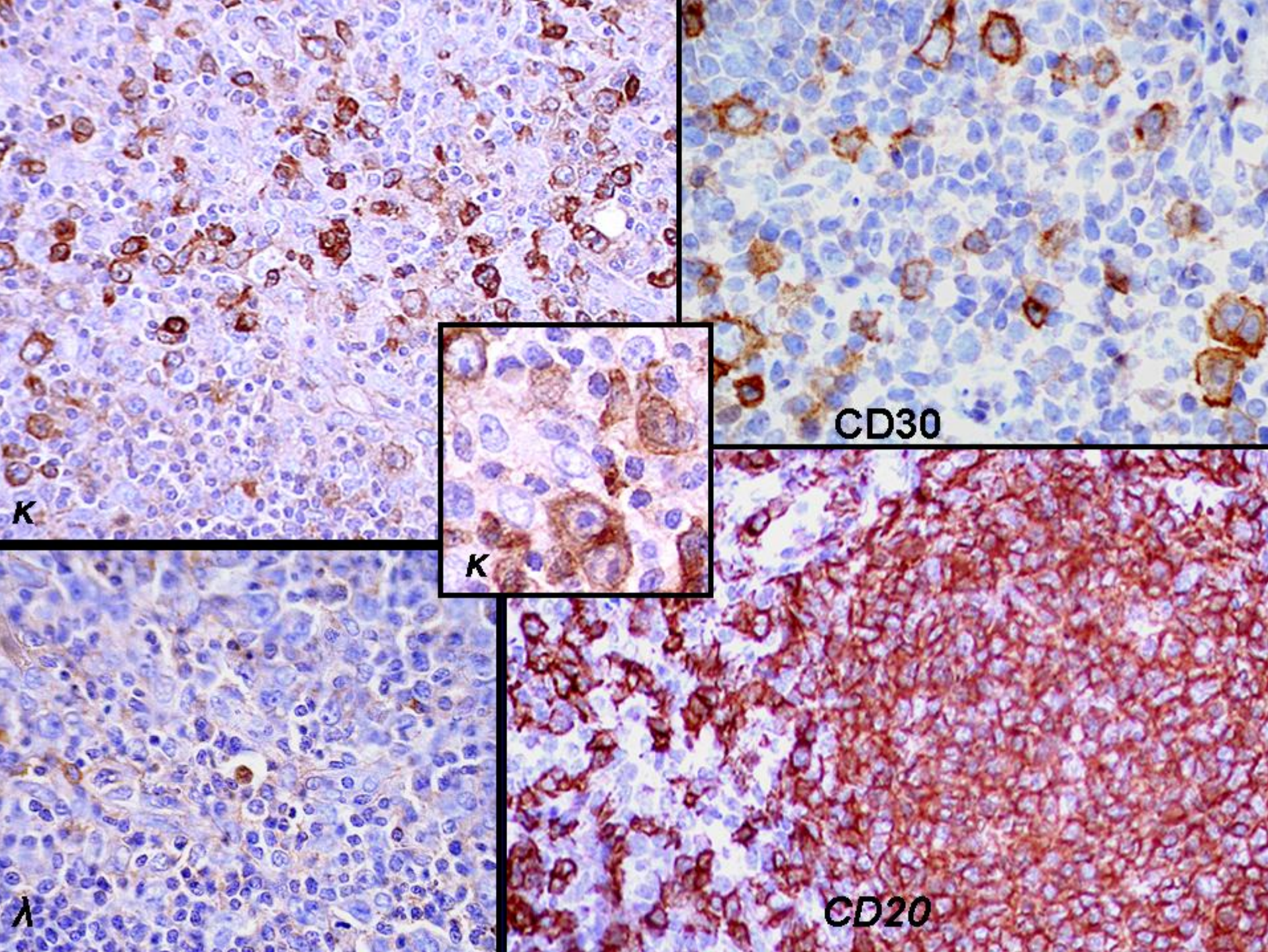
Psoriasis

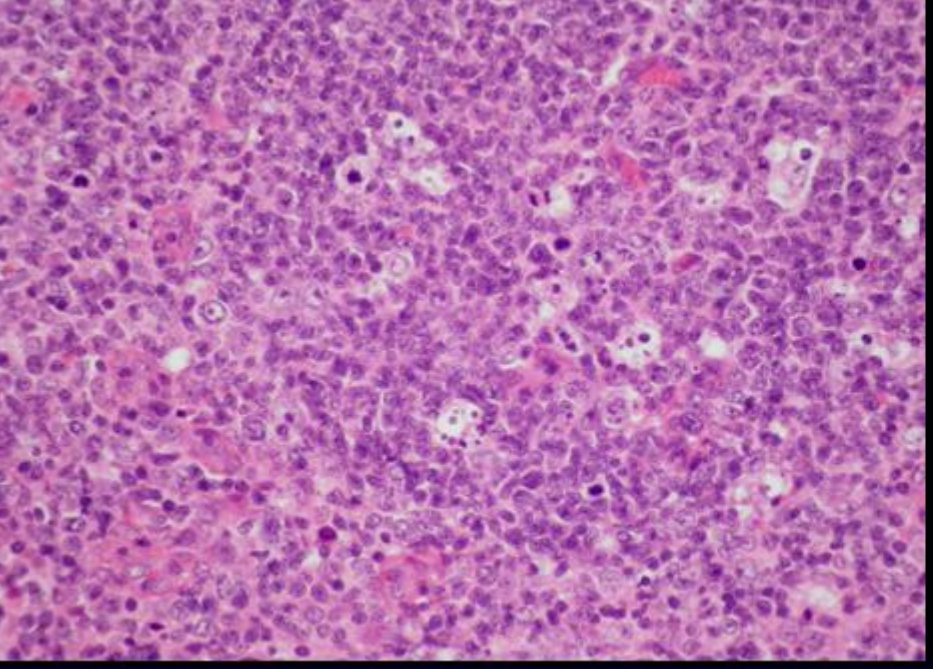
ANTI-INFLAMMATORY DRUGS IMPLICATED IN CAUSING LPD

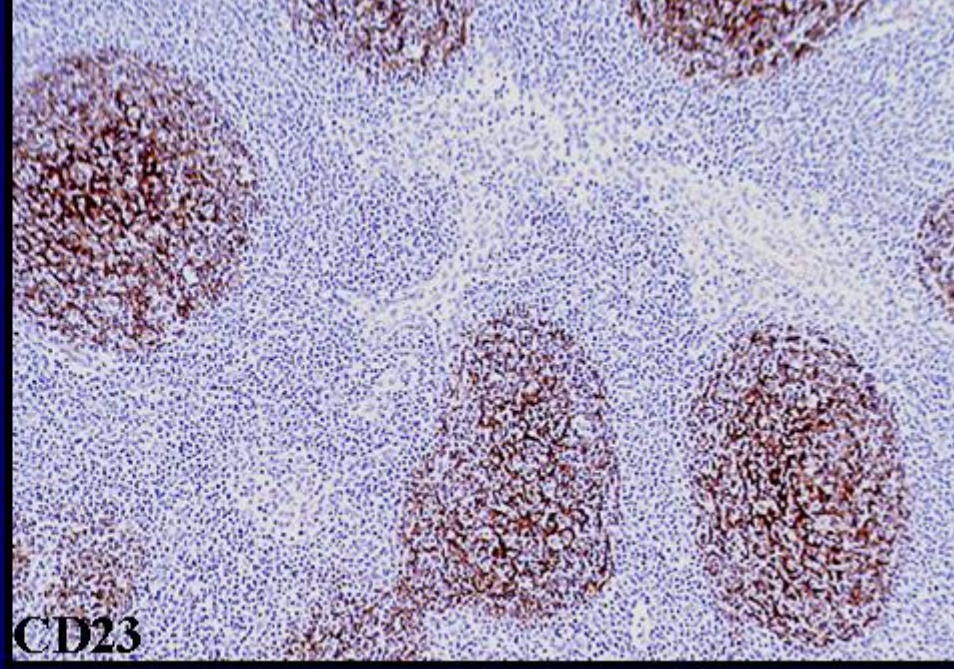
- Methotrexate
- Azothiaprine
- Cyclosporin
- Steroids
- anti-TNF/ blocking agents

  eg; infliximab, etanercept

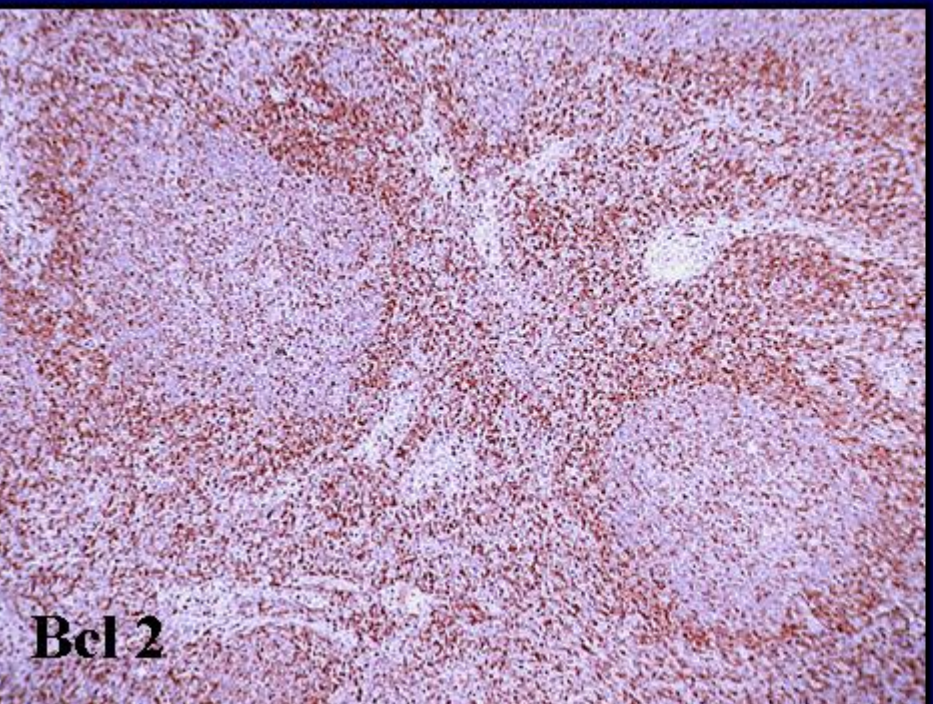

Methotrexate
associated LLPD
CD20
CD3

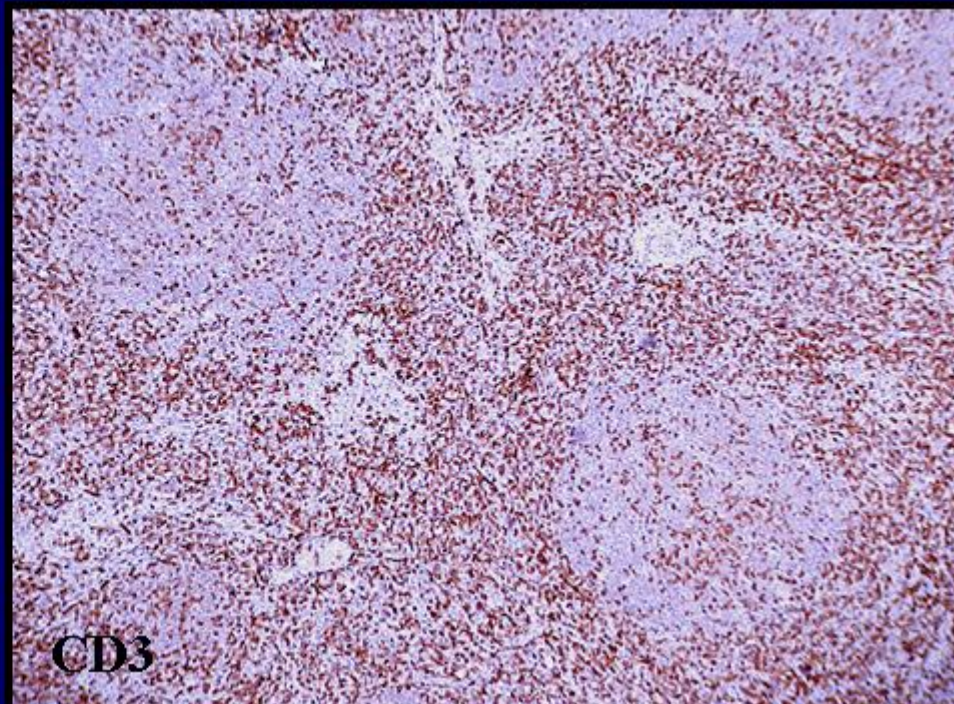

κ
κ
CD30
λ
CD20





reactive follicles





METHOTREXATE-ASSOCIATED LPD

Most commonly seen in RhA, dermatomyositis, psoriasis

Occurrence about 15 yrs from diagnosis of AI disease*

All types of lymphoma occur:

- DLBCL(35%)
- FL (10%)
- BL (4%)
- HL (25%)
- HL-like (8%)
- T-cell (4%)
- SLL, LpL& polymorphous (14%)

EBV related in 50% and dependent of type

May regress with cessation of therapy

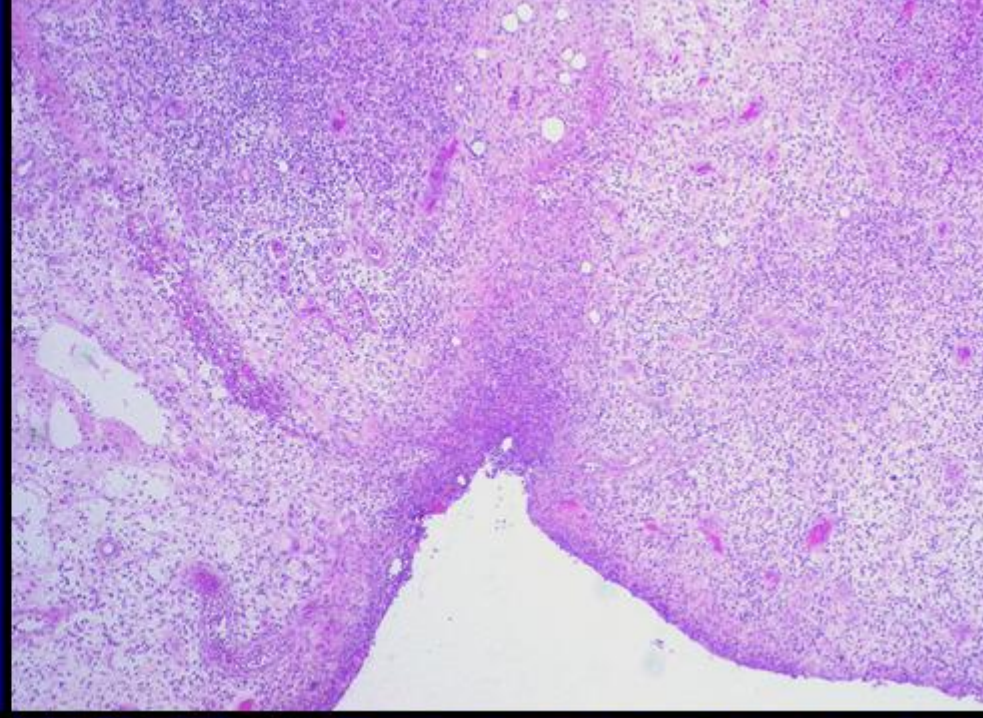
* Similar to non-methotrexate treated patients

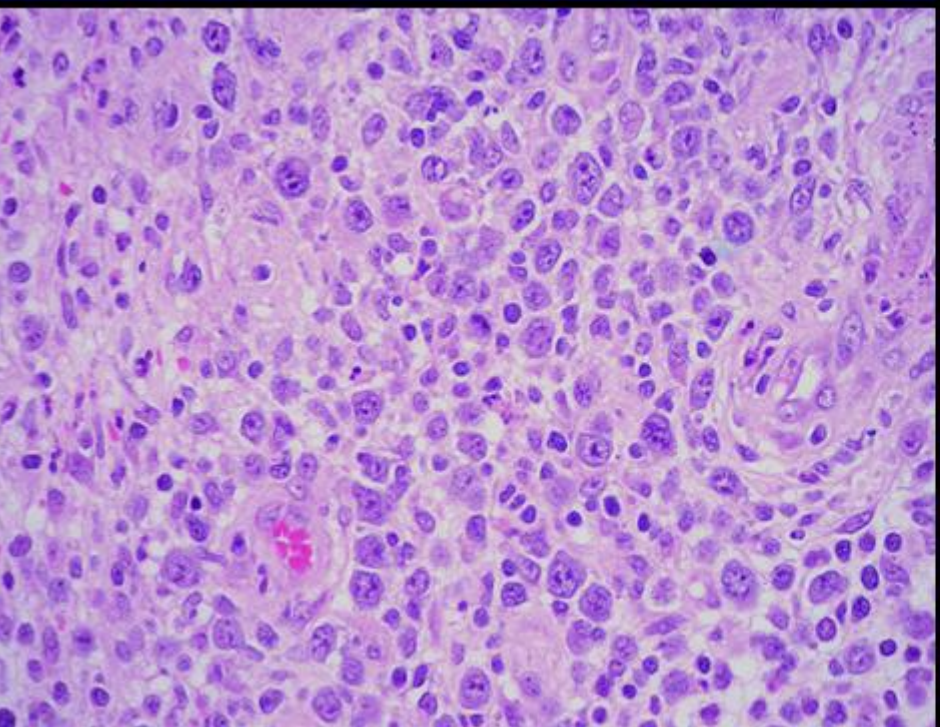
Woman aged 55 yrs

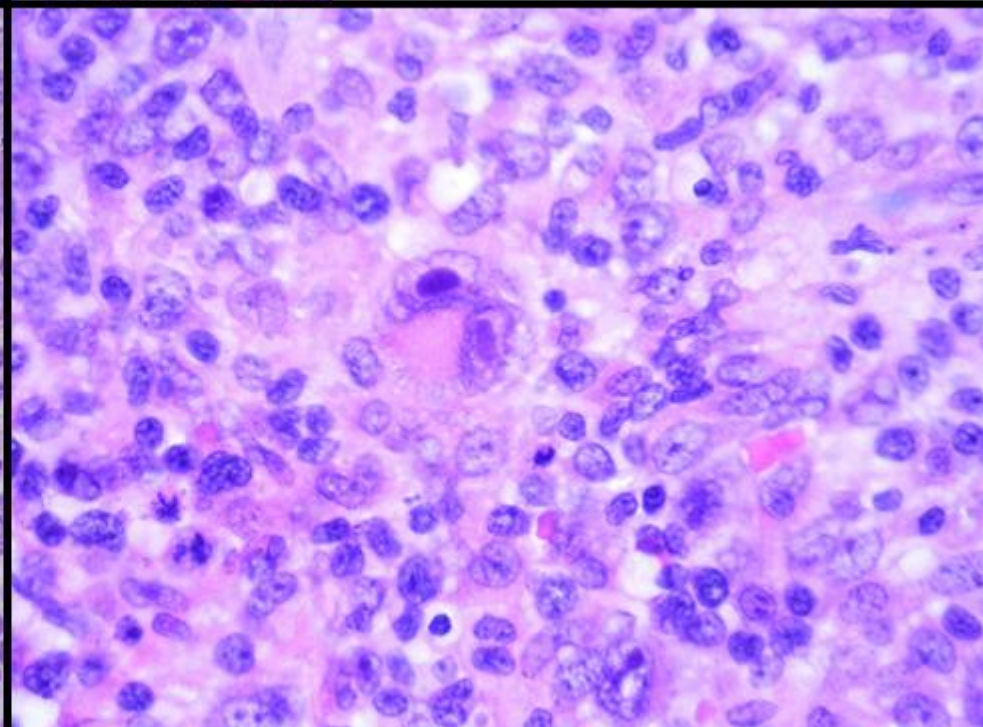
Long standing Crohn's disease

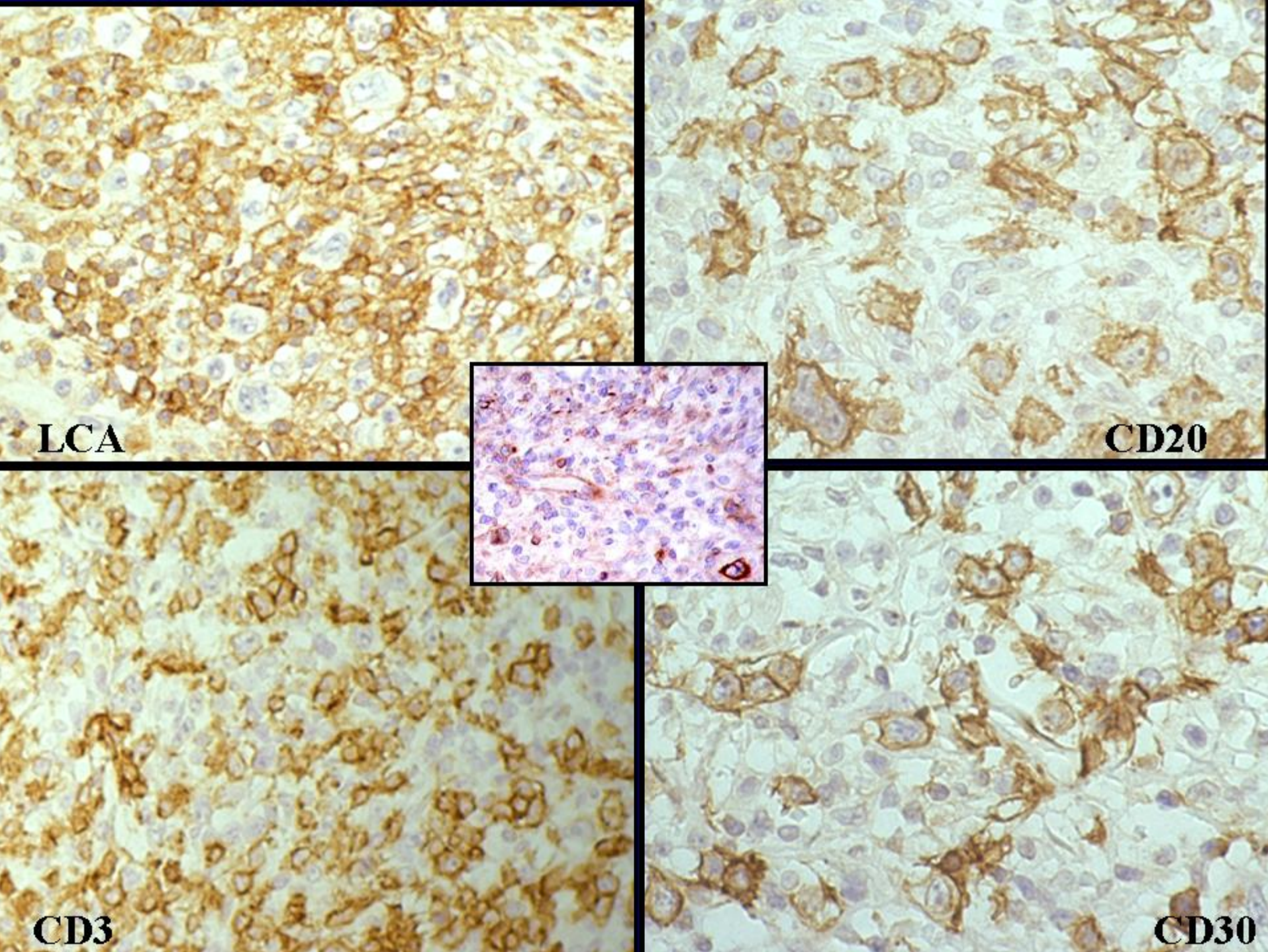
Steroids
Azothiaprine

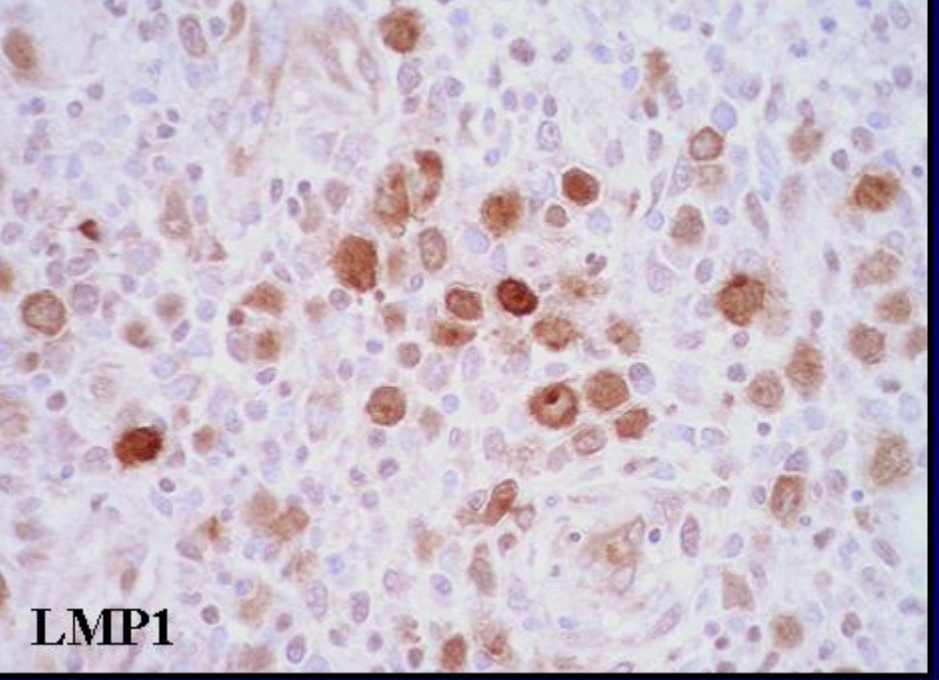
PCR: Ig - germ line configuration

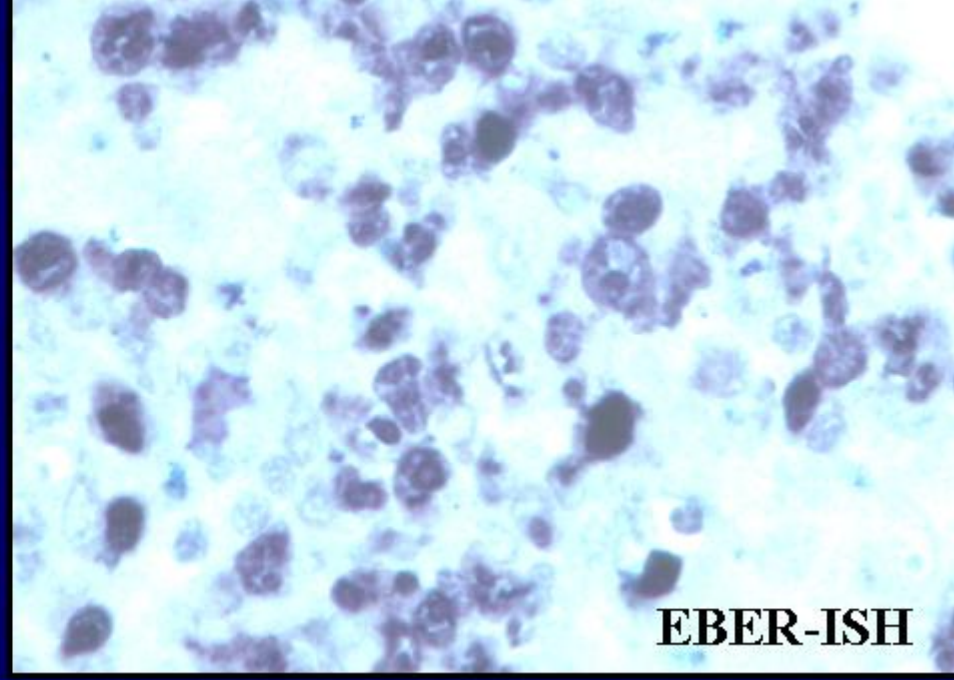







LCA
CD20
CD3
CD30





Final diagnosis: IALPD polymorphic- HL-like; EBV driven

Immunophenotype

LCA+, CD20+ve, CD30+ve, CD79a+ve CD15-ve.

LMP1+ve; EBER-ISH: neoplastic cells and bystander cells+

PCR germ line; no B-cell clonality

LPD AND SECOND HAEMATOLOGICAL MALIGNANT DISEASE MALIGNANCIES

Hodgkin lymphoma and 2nd malignancies

Average time to development of lymphoma 5 years

Relationship of high grade NHL to chemotherapy +/- radiotherapy

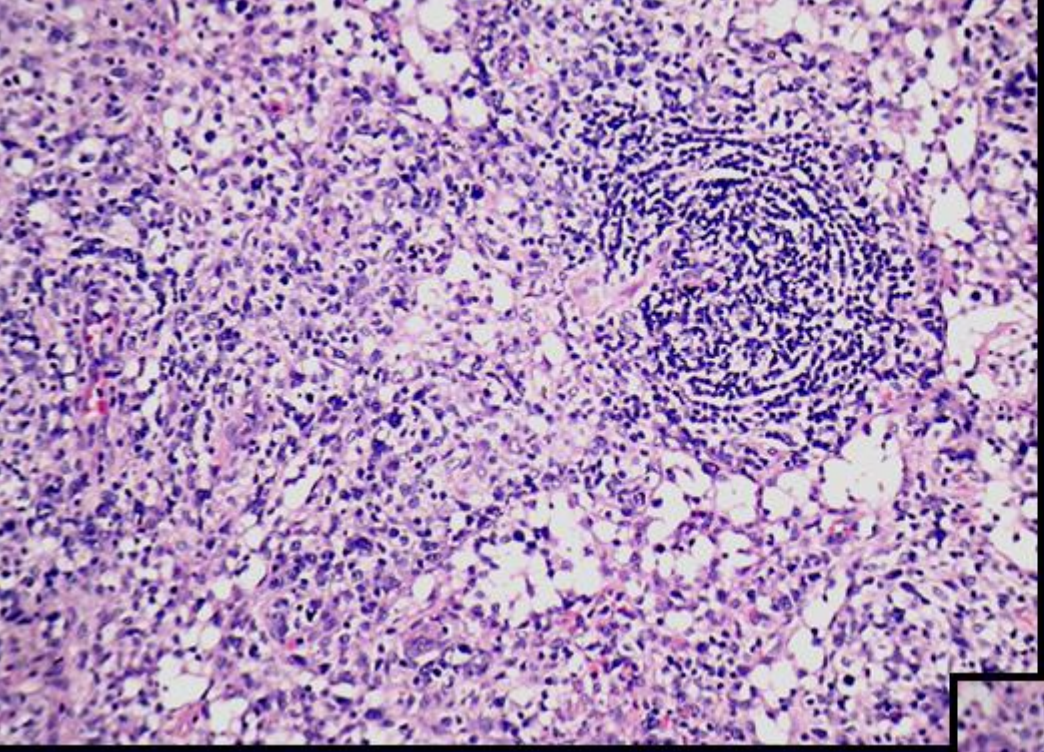
In a BNLI series of 3033 HL patients, of 70 2nd malignancies, there were 22 NHL (16 high grade, B-cell 12, T-cell 4) & 14 acute leukaemias

NHL and second malignancies

Strong relationship to t-MDS and t-AML

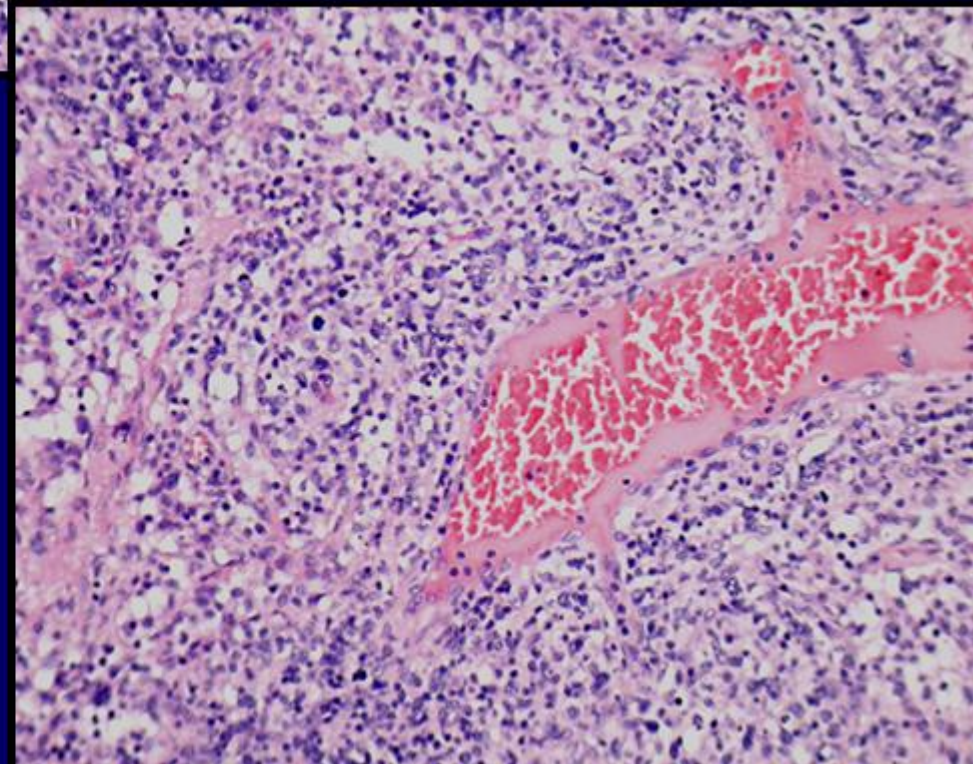
Sporadic reports of non-clonally related NHL

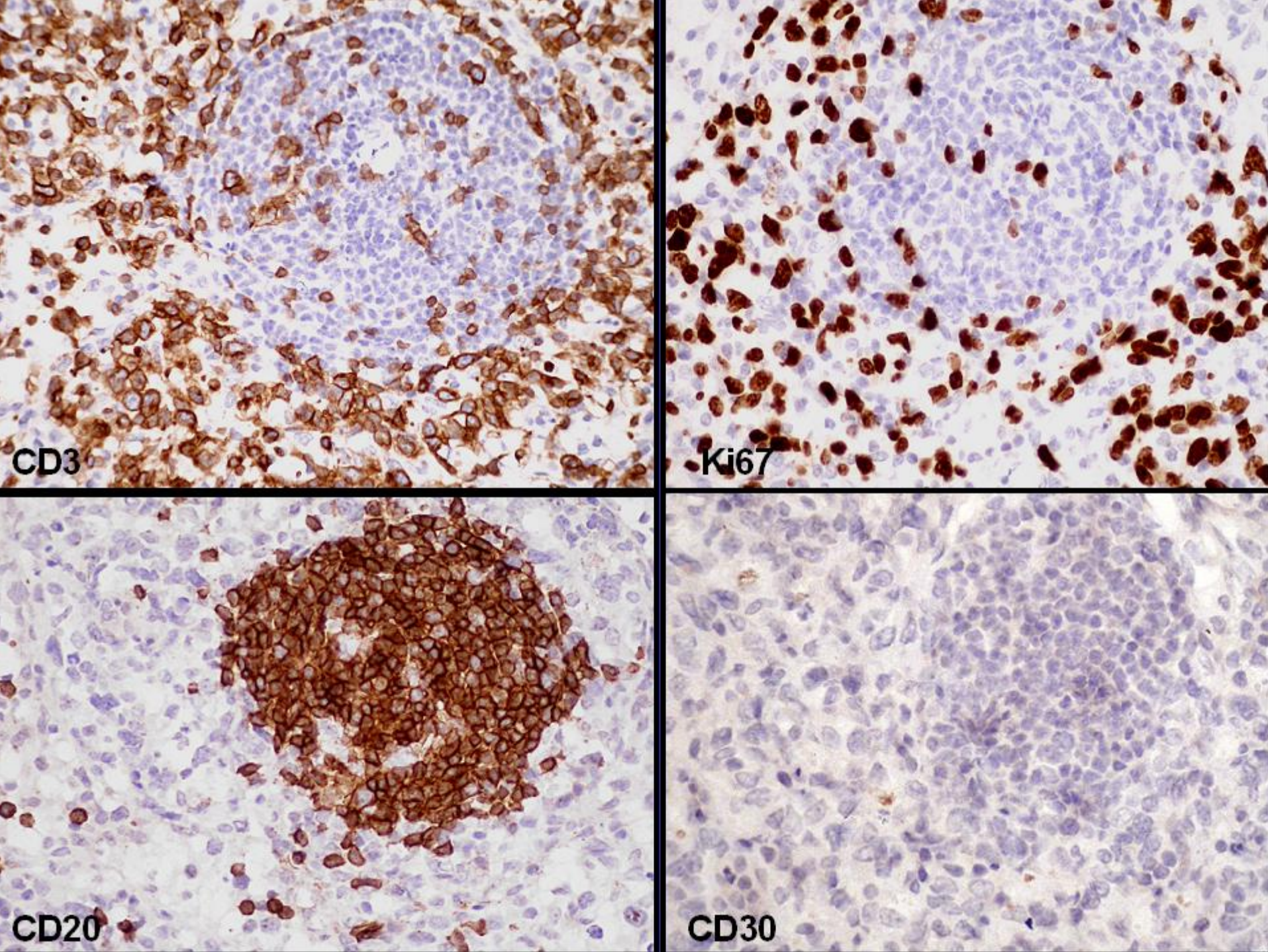
Eg. EBV associated B-cell LPD after fludarabine therapy for CLL

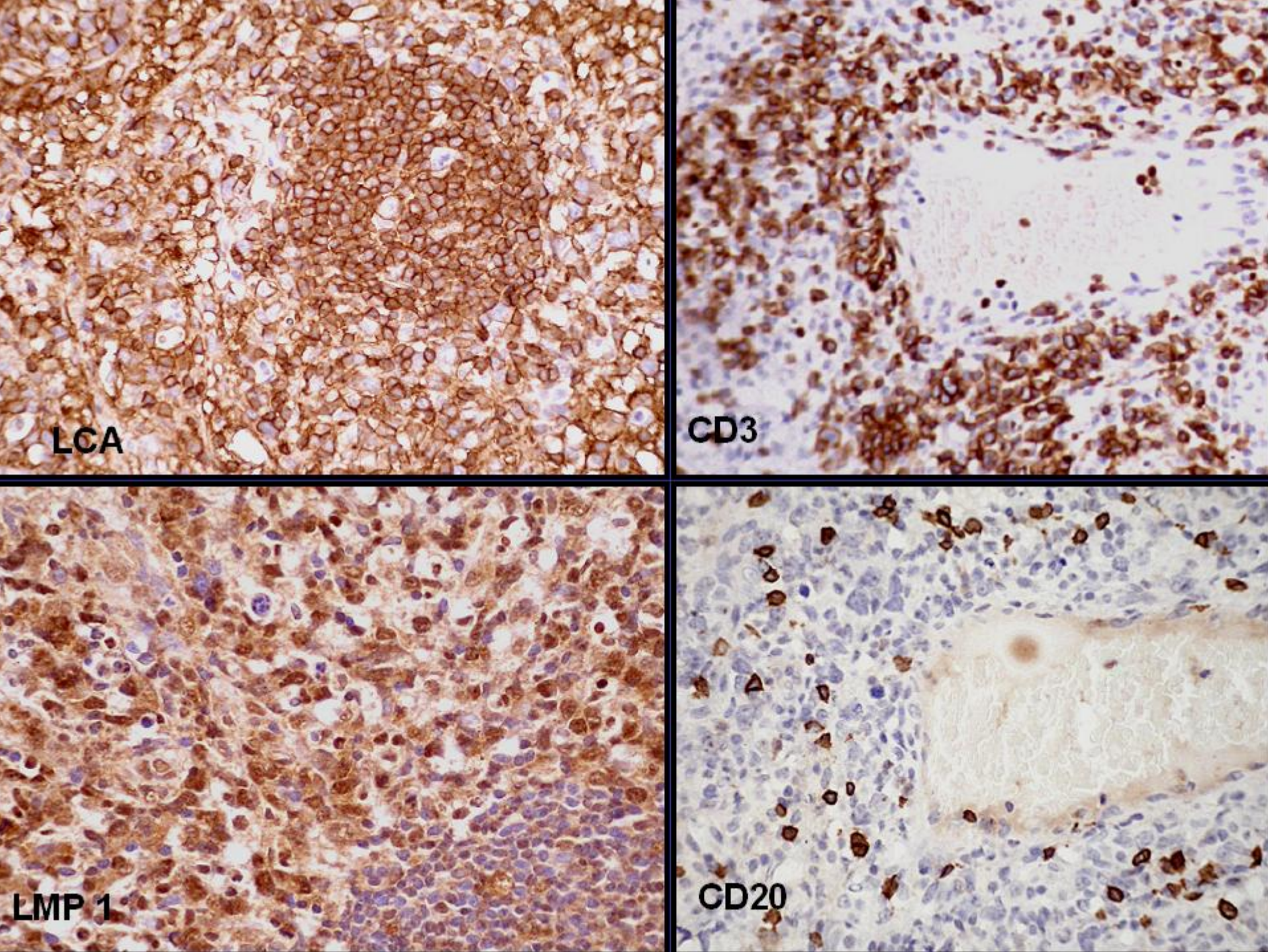


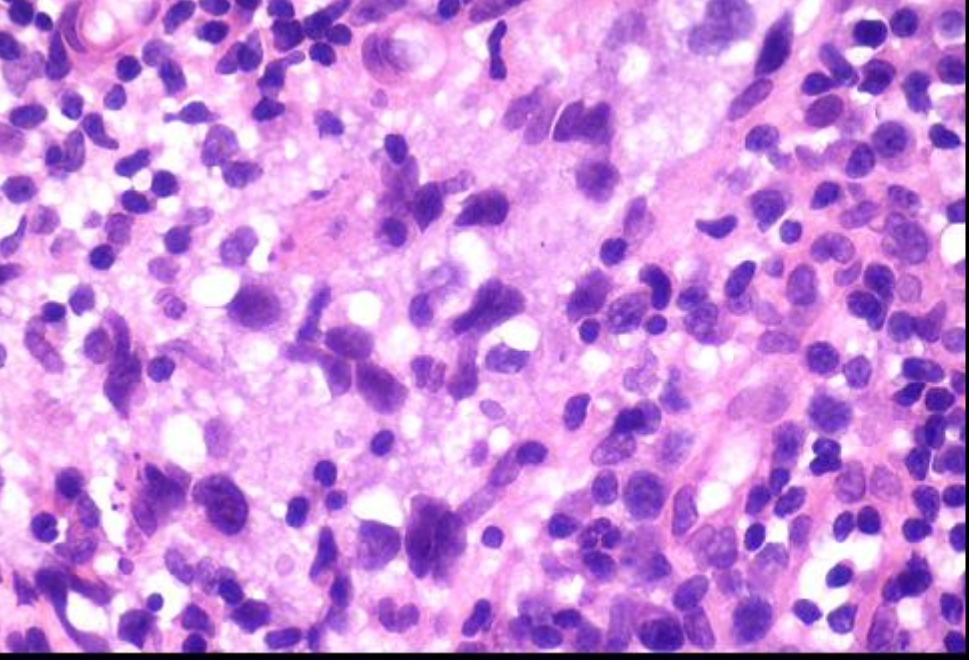
Mesenteric lymph node biopsy man aged 71yrs

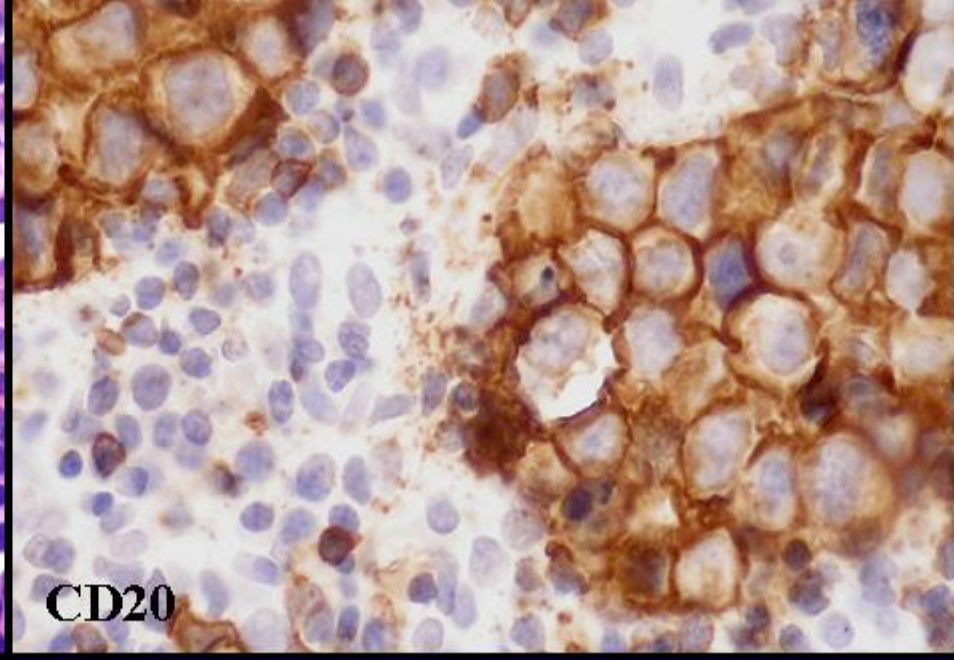
7 yrs previously DLBCL



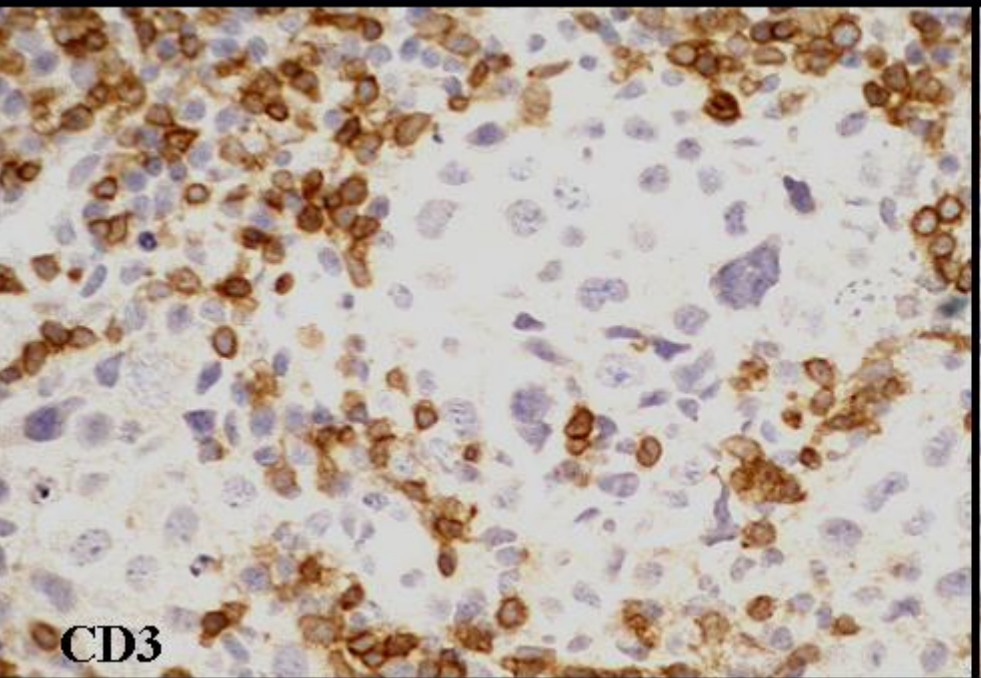

CD3
Ki67
CD20
CD30

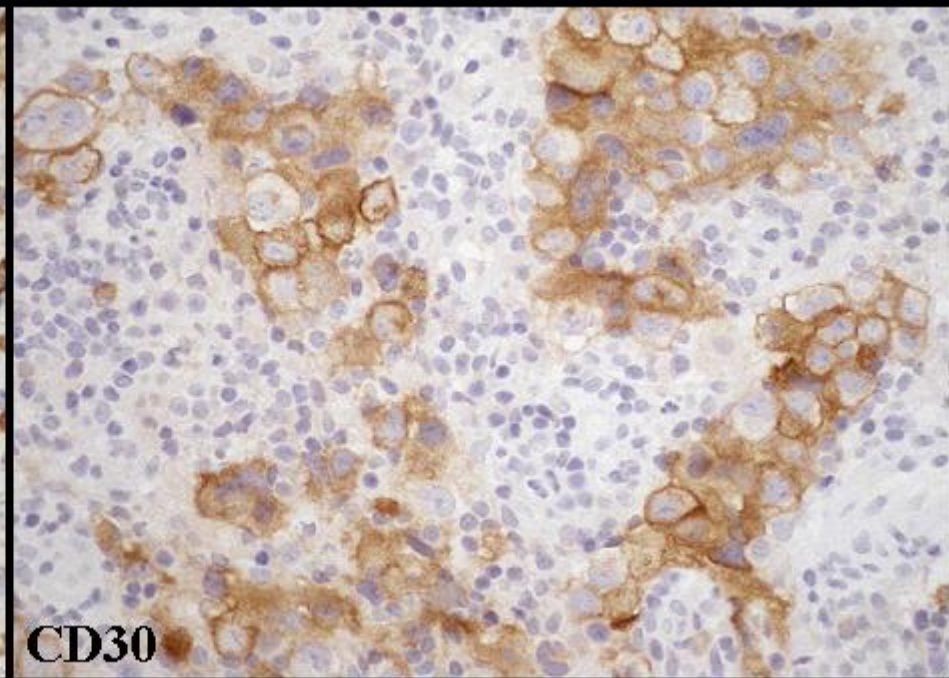

LCA
CD3
LMP 1
CD20





DIFFUSE LARGE B CELL LYMPHOMA





IMMUNOHISTOCHEMISTRY

	Inguinal LN 1997 DLBCL	Mesenteric LN 2004 TCL- NOS
LCA	+ve	+ve
CD20	+ve	-ve
CD79a	+ve	-ve
CD3	-ve	+ve
CD30	+ve	-ve
LMP 1	-ve	+ve

Man aged 71 years

Inguinal lymph node: DLBCL

Complete remission following chemotherapy + irradiation

Abdominal lymphadenopathy 7 years later

Mesenteric LN biopsy: T-cell lymphoma – NOS

EBV associated

BLOOD TRANSFUSIONS, BLOOD PRODUCTS

Transmission of Infective agents (viral) with risk of immunosuppression and/or development of LPD:

HIV
HTLV
HHV8

ADULT T CELL LEUKAEMIA/LYMPHOMA – ATLL

Incidence: **Asia Pacific regions** Japan especially Japan, Caribbean basin, S.America, parts of central Africa; occurs sporadically worldwide.

Presentation: 4 clinical variants; acute, lymphomatous, chronic, smouldering
Causes profound immunodeficiency

Morphology: Lymphoma cells medium to large size with marked nuclear pleomorphism; sometimes small or HL-like. In PB often polylobated - 'flower cells'.

Lineage: Peripheral CD4+ T-cells in different stages of activation.

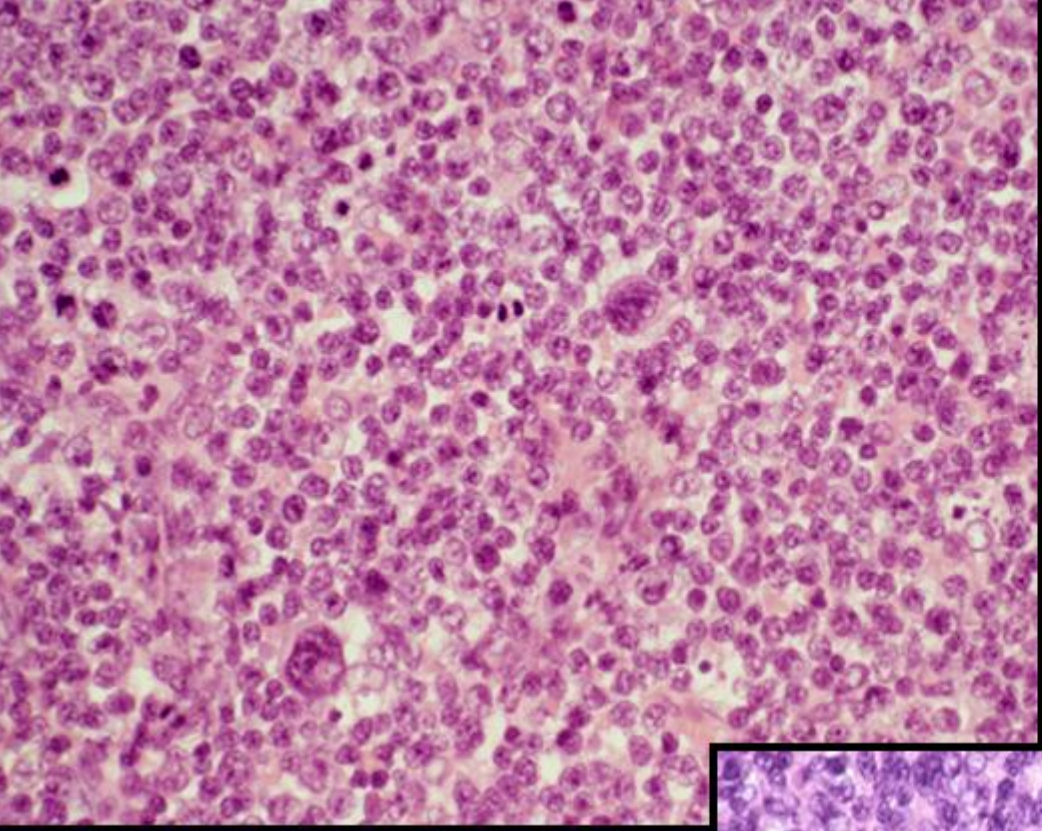
Phenotype: CD3+, CD 5+, CD4+/C8- (rarely CD8+ CD4- or CD4 & 8+)
CD30+ sometimes, ALK-

Genetics: HTLV 1 is clonally integrated and T-cell receptor genes are re-arranged but *per se* is not oncogenic; the HTLV 1 p40 tax viral protein cause transcriptional activation of genes in the HTLV 1 infected lymphocytes

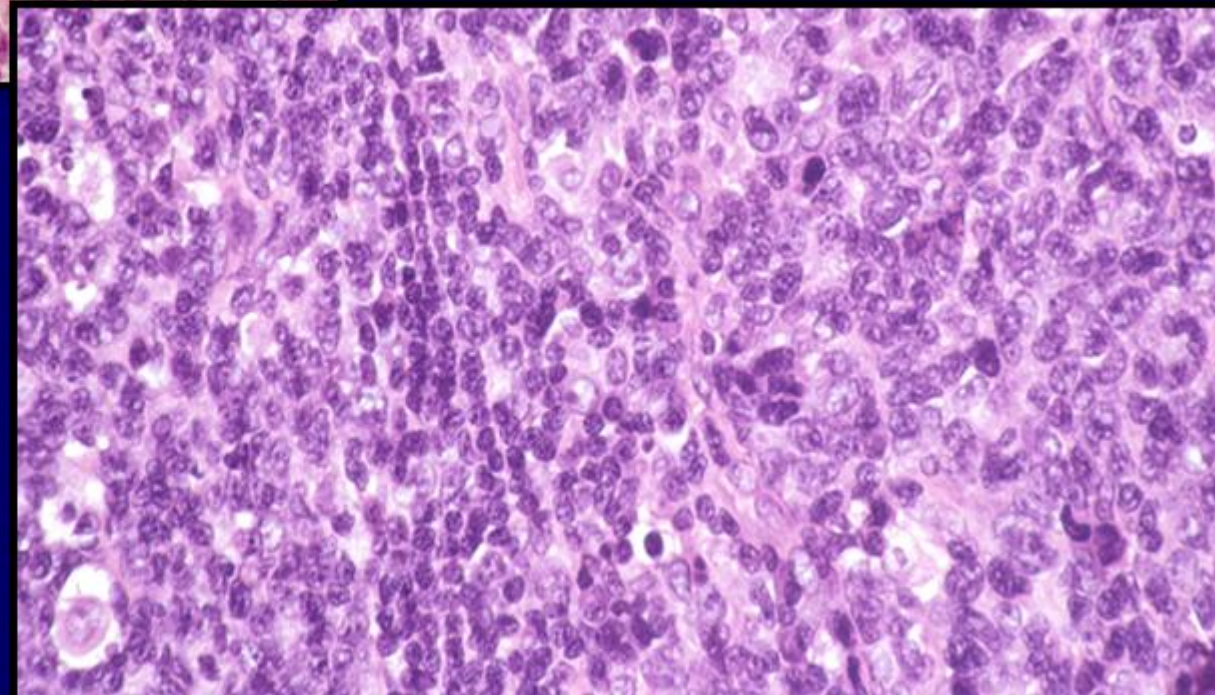
Transmission: Vertical ie. mother- to- infant ⟶ HTLV Carriers
Sexual (mainly male to female)
Parental (blood transfusion, I V drug abusers); transplant recipients especially at risk

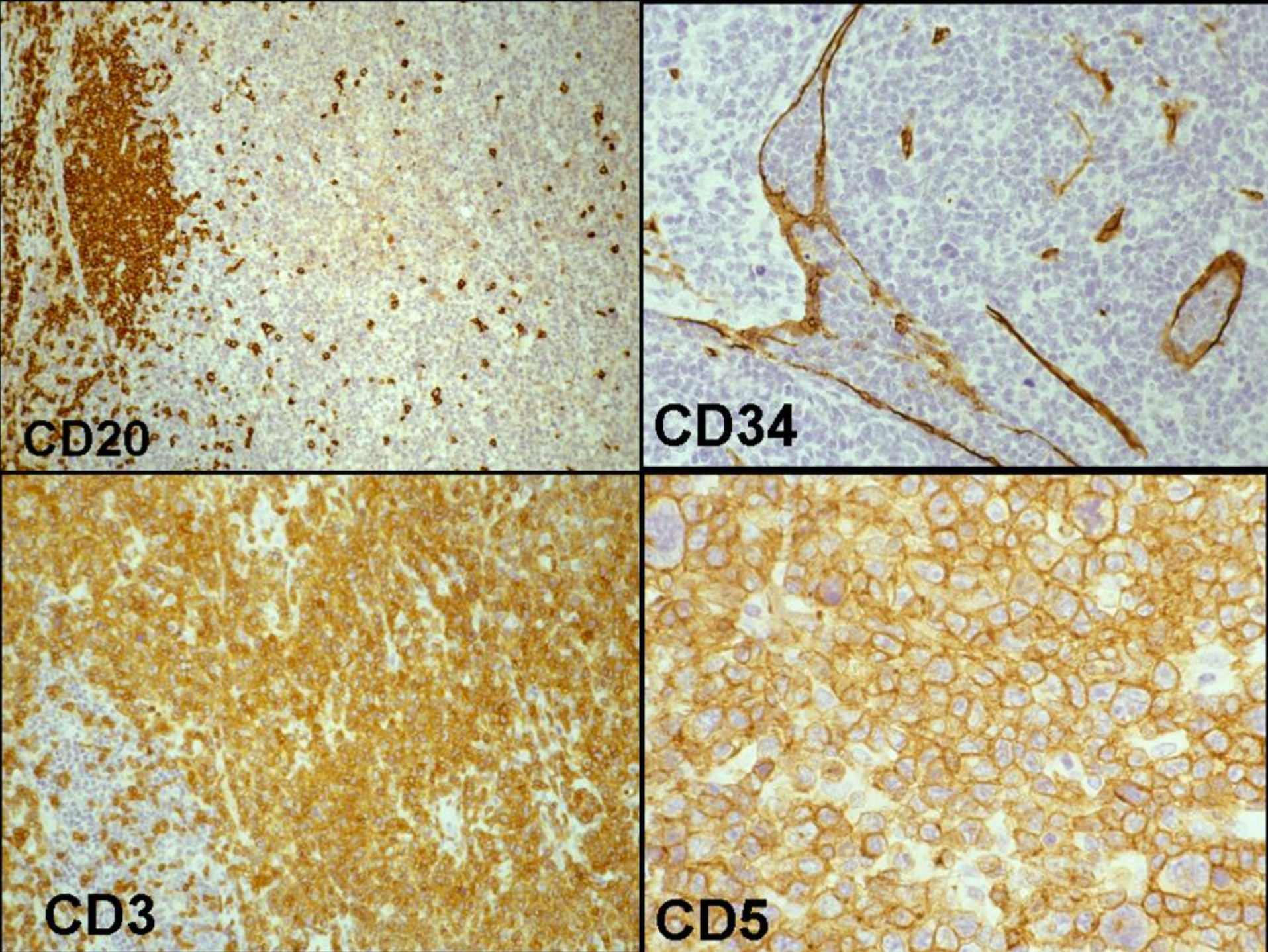
Adult T-cell lymphoma/leukaemia: clinical features (U.S. NCI series)

Clinical features	At presentation (%)	During course (%)
Leukaemia	62	100
Hypercalcemia	73	83
Lytic bone lesions	36	
Lymphadenopathy	61	85
Hepatosplenomegaly	61	
Skin lesions	61	
Bone marrow+	58	
Stage IV	100	



ADULT TCL HTLV +ve




CD20
CD34
CD3
CD5

DISEASE IS OF OLD AND NOTHING ABOUT IT HAS CHANGED

IT IS WE WHO CHANGE WHEN WE LEARN TO RECOGNISE WHAT FORMERLY WAS IMPERCEPTIBLE

Jean Marie Charcot 1825-1893
Phycisian, Salpêtrière Hospital, Paris