Immunodeficiency and Viral-Associated Lymphoproliferations

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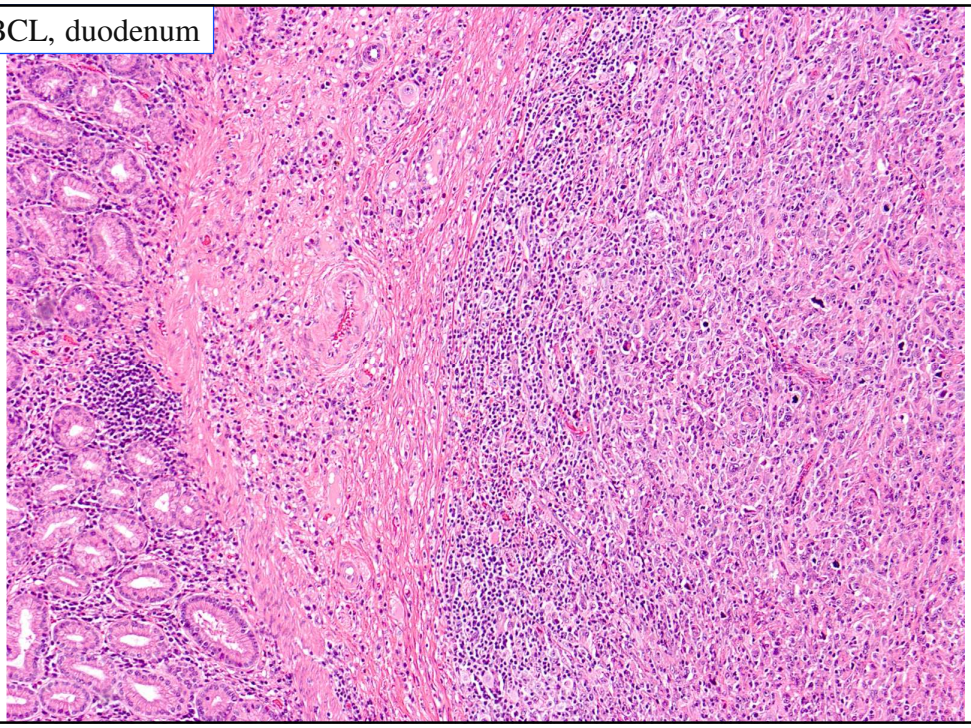
To be discussed, using 2022 WHO Classification of Haematolymphoid Tumours

- EBV+
  - EBV+ DLBCL
  - DLBCL associated with chronic inflammation (DLBCL-CI)
  - Fibrin-associated DLBCL (FA-DLBCL)
  - Plasmablastic lymphoma
  - Extranodal NK/T-cell lymphoma
- KSHV/HHV8+
  - KSHV/HHV8+ multicentric Castleman disease (Dr. Natkunam)
  - Primary effusion lymphoma
  - KSHV/HHV8+ DLBCL
  - KSHV/HHV8+ germinotropic LPD
- LPDs and Lymphomas associated with immune deficiency/ dysregulation
- Primary DLBCL of immune-privileged sites

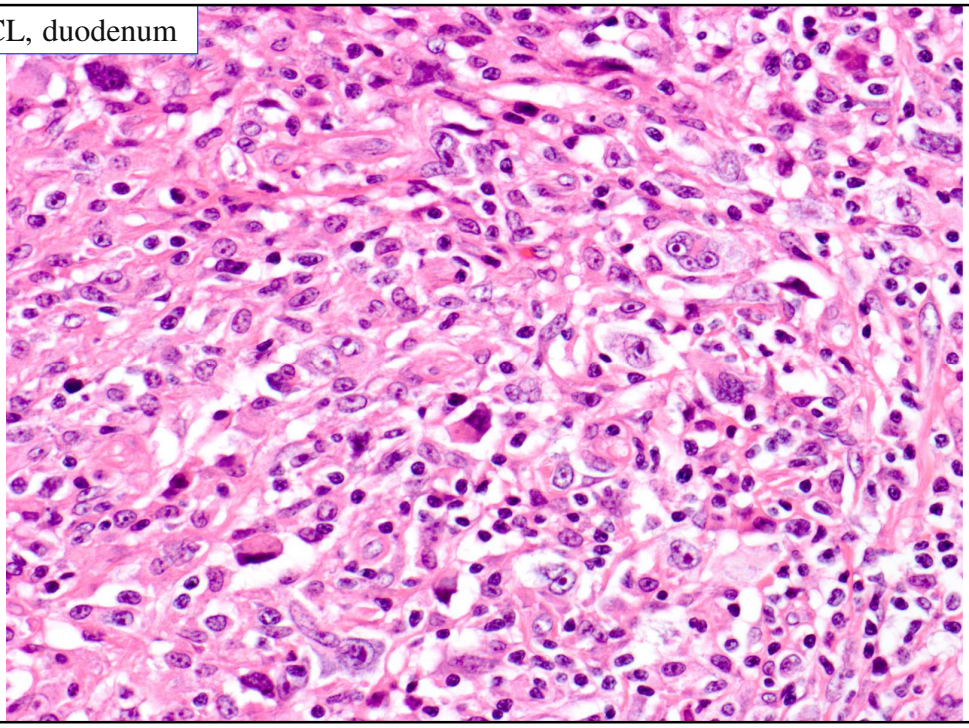
EBV+ DLBCL

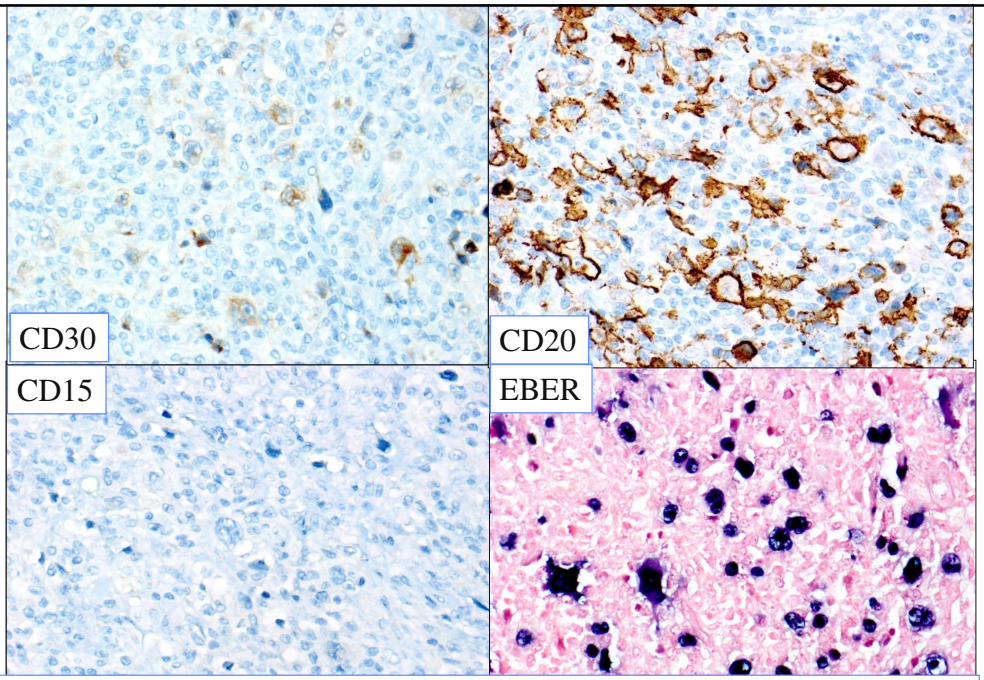
- Formerly, EBV+ DLBCL of the elderly, EBV+ DLBCL, NOS
- No prior lymphoma or specific immunodeficiency
- Related to decreased immunity of aging
- Rule out other specific EBV+ LPDs
- Most patients > 50 years old; M > F
- Extranodal (tonsils, GI, skin, marrow…) and/or nodal involvement
- Polymorphous: Large B cells/IBs/ RS-like, with small lymphocytes, plasma cells, histiocytes
- Monomorphous: Resembles EBV-negative DLBCL
- CD20 and/or CD79a+
- CD10-, BCL6+ or -, MUM1+ (non-GCB)
- CD30+/-, CD15-/+, EBER+, LMP1+
- Alterations in NFκB, WNT and IL6/JAK/STAT pathways
- Mutated gene set: *CCR6, CCR7, DAPK1, TNFRSF21, CSNK2B* and *YY1*, specific?
- Differential:
  - Other EBV+ LPDs
  - EBV-negative DLBCLs (always do EBER in DLBCL in older patients)
  - Classic Hodgkin lymphoma (sites involved, PMNs in background, CD15 help with differential)

EBV+ DLBCL, duodenum



EBV+ DLBCL, duodenum





EBV+ DLBCL: site, lack of eos, immuno are against Hodgkin lymphoma

DLBCL Associated with Chronic Inflammation

- EBV+ DLBCL
- Prototype: Pyothorax-Associated Lymphoma (PAL), in TB patients with artificial pneumothorax, subsequent pyothorax
- Other settings:
  - Longstanding venous stasis ulcers
  - Chronic osteomyelitis, +/- draining sinuses, pathologic fracture
  - Associated with implants, surgical mesh
- Often forms large mass in association with chronic suppurative inflammation
- May be locally invasive, may spread beyond primary site
- Centroblasts, immunoblasts +/- plasmablastic features
- CD20+, CD79a+, most cases; CD30 often positive; variable CD138
- Non-GC B-cell immunophenotype (MUM1+, CD10-, BCL6-/+)
- Occasional aberrant T antigen expression

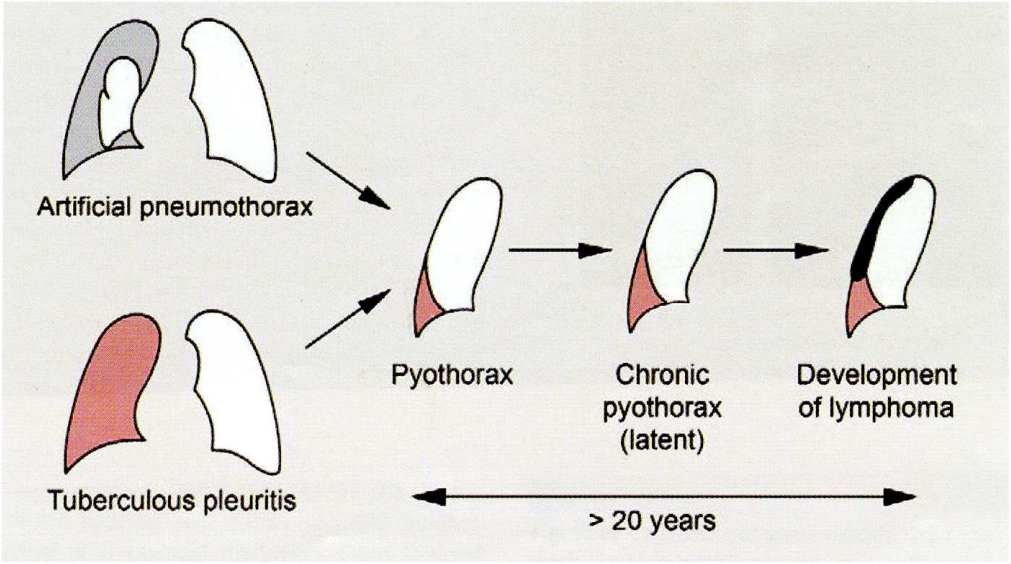


Fig.10.95 Development of pyothorax-associated lymphoma.

DLBCL with Chronic Inflammation

- Long-standing, severe CI (> 10 years; median, 20 years)
  - Tend to occur in closed spaces
  - Local immune dysregulation, decreased immune surveillance, decreased T-cell cytolytic response
    - » IL-6: promotes cellular proliferation
    - » IL-10: immunosuppressive, helps evade immune surveillance
    - » Downregulation of HLA class 1 antigens
    - » Mutations of cytotoxic T-lymphocyte epitopes in EBNA3B
  - Promotes EBV+ B-cell proliferation, leading to lymphoma
  - *TP53* deletion, MYC amplification, NFkB activation due to *TNFAIP3* deletion
  - Aggressive lymphomas; patients often die of lymphoma or co-morbidity

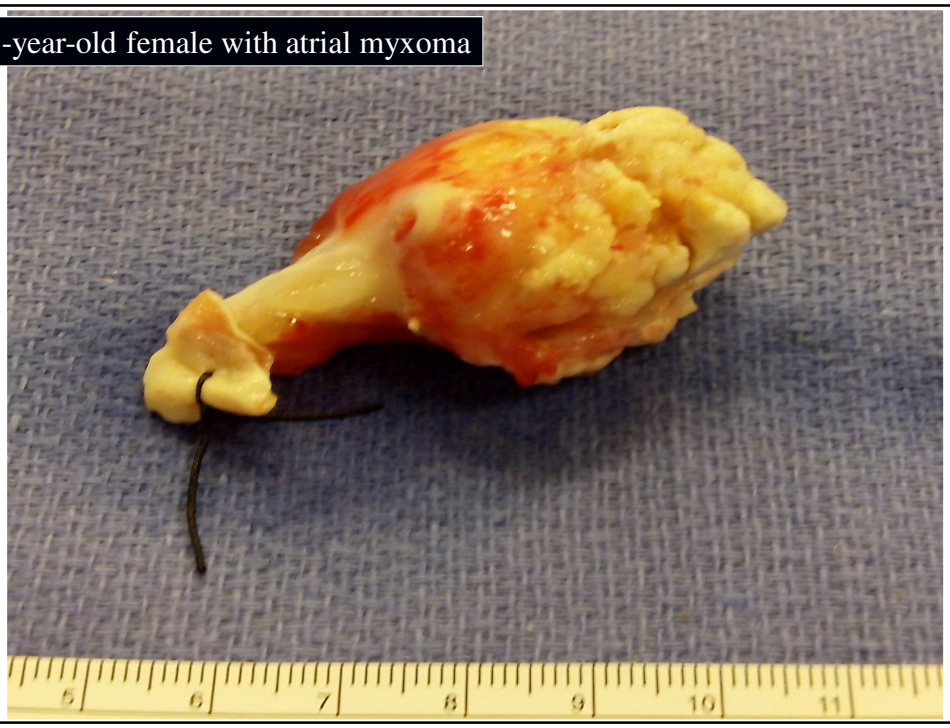
Fibrin-Associated DLBCLs

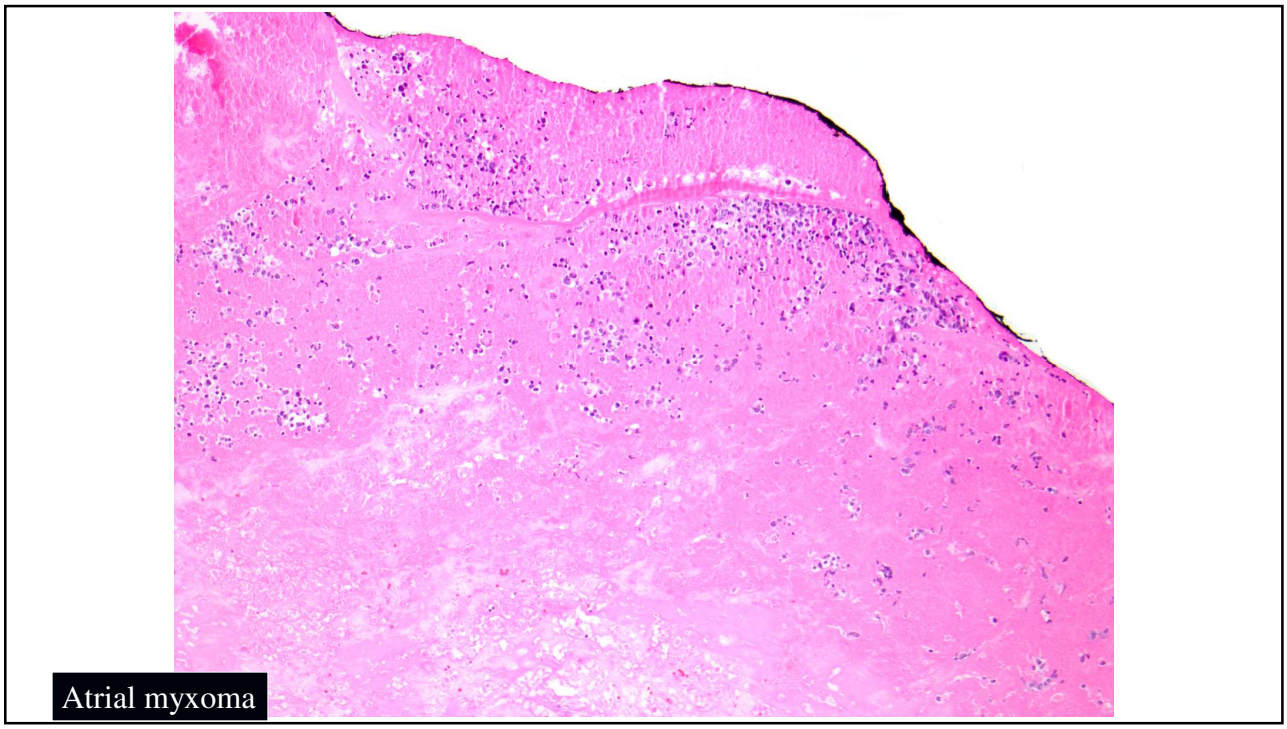
Initially grouped with DLBCL-CI, but now recognized as distinct entity *In contrast to DLBCL-CI:*	Microscopic clusters of large B cells floating in fibrin/debris and/or lined up along inner wall of cyst
Incidentally found DLBCL in a confined space	EBV+ (rarely negative) large B cells, often pleomorphic, some plasmacytoid
No mass, no invasion of normal tissue	Non-GC phenotype, CD30+/-, Ki67 high Occasional aberrant T antigen expression
Localized No acute inflammation	Treatment: variable: Resection only vs Rituxan + combination chemo
Etiology: local immune escape shielding EBV+ B cells from immune surveillance	Outcome: excellent No deaths directly due to lymphoma When incompletely resected, recurrence can occur

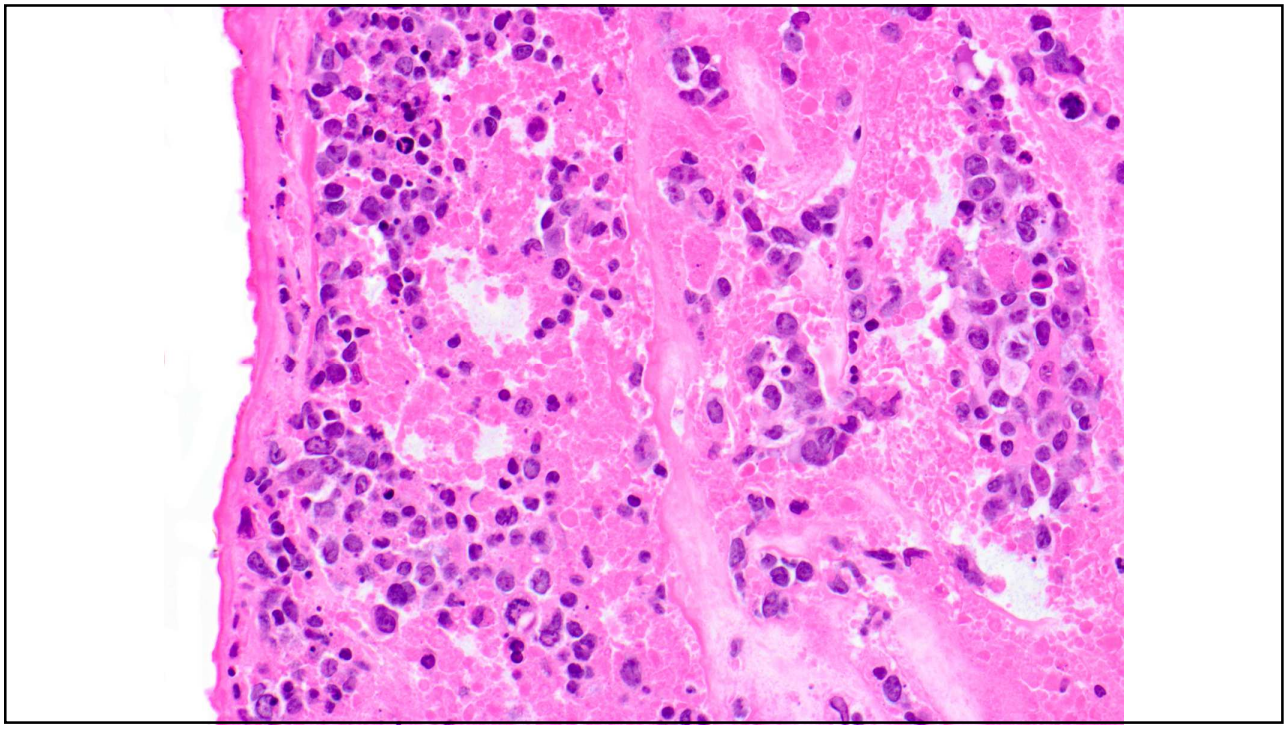
Fibrin-Associated DLBCLs

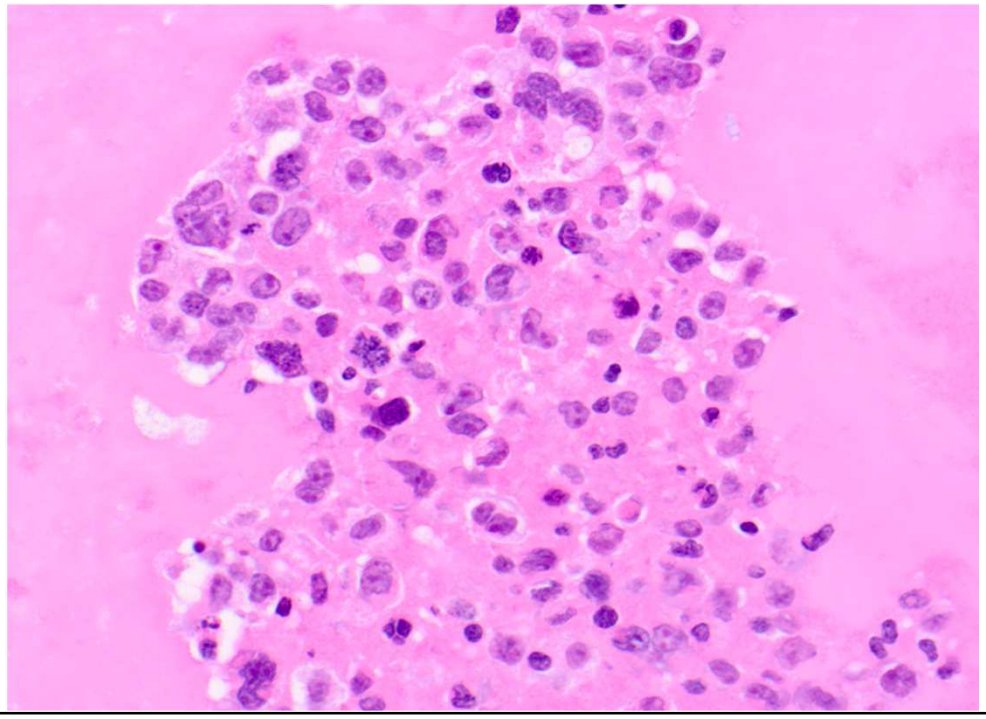
Foreign body-associated lymphomas	Lymphomas in restricted spaces
Cardiac replacement valves Dacron vascular graft Surgical mesh implant Breast implants	Atrial myxoma Cysts / pseudocysts Long-standing hydrocele Ovarian cystic teratoma Hematomas

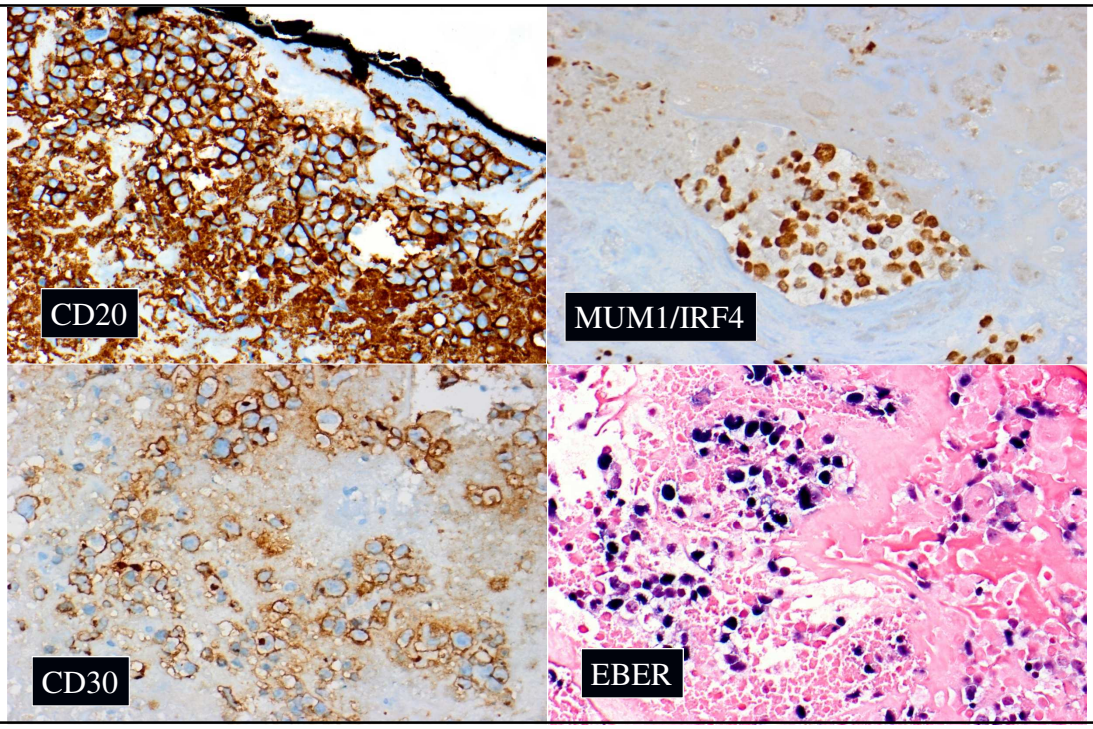
55-year-old female with atrial myxoma

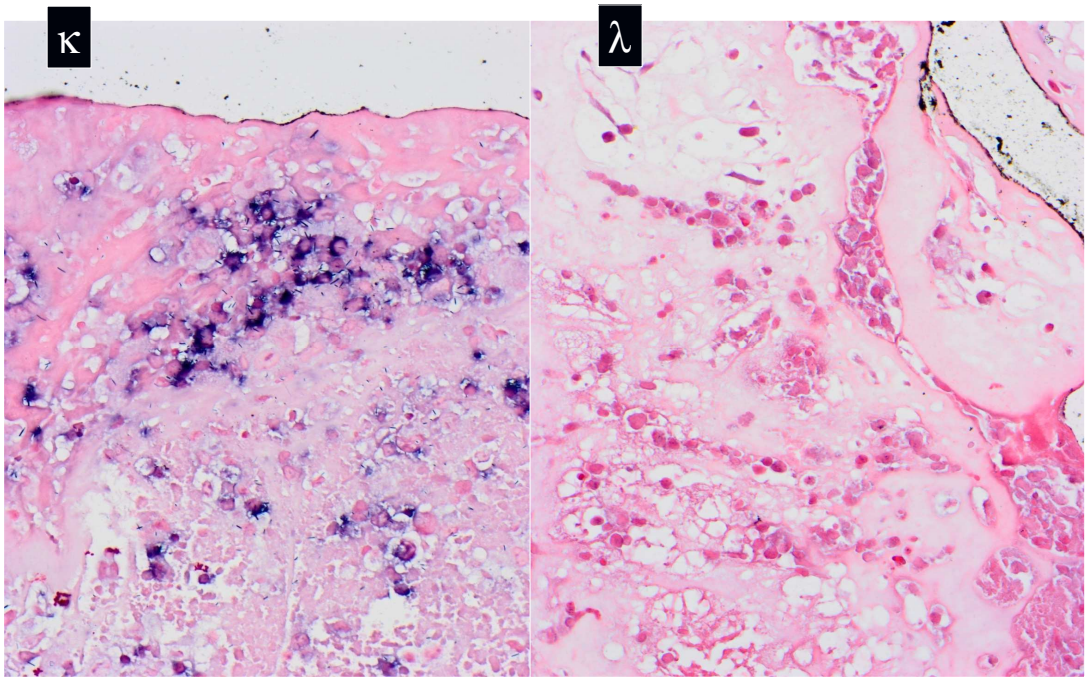



Atrial myxoma






CD20
MUM1/IRF4
CD30
EBER



WHO Classification

WHO 2008

- Diffuse large B-cell lymphoma associated with chronic inflammation

WHO 2017

- Diffuse large B-cell lymphoma associated with chronic inflammation
  - –Fibrin-associated diffuse large B-cell lymphoma

WHO 2022

- Diffuse large B-cell lymphoma associated with CI
- Fibrin-associated DLBCL

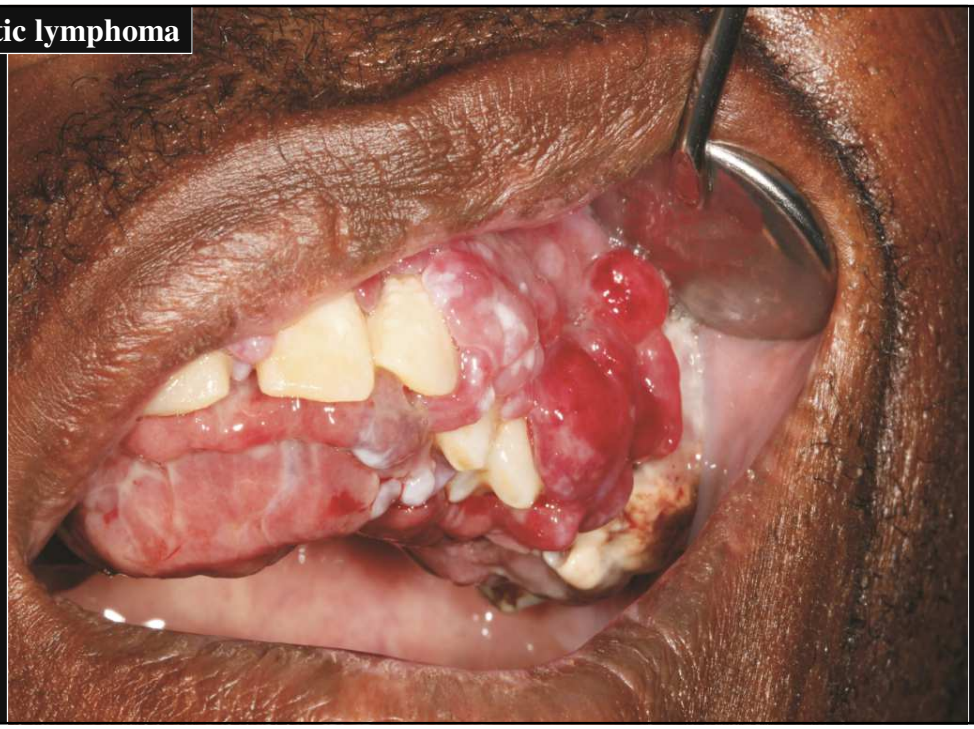
PLASMABLASTIC LYMPHOMA

- Rare lymphoma, poor prognosis
- Proliferation of large neoplastic cells with morphology of immunoblasts/plasmablasts and immunophenotype of plasma cells
- First described in HIV+ patients, arising in oral cavity
- Strong association with immunosuppression, EBV
- Majority of patients are HIV+
  - Median age, fifth decade, M >> F
  - Rarely, HIV+ children develop PBL
- HIV-negative PBL patients
  - Older, less striking male predominance
  - Post transplantation (cardiac transplant most common in one study)
  - Other iatrogenic immunosuppression
  - Older adults with immunosenescence of aging
  - Rare cases of plasmablastic transformation of low-grade BCL

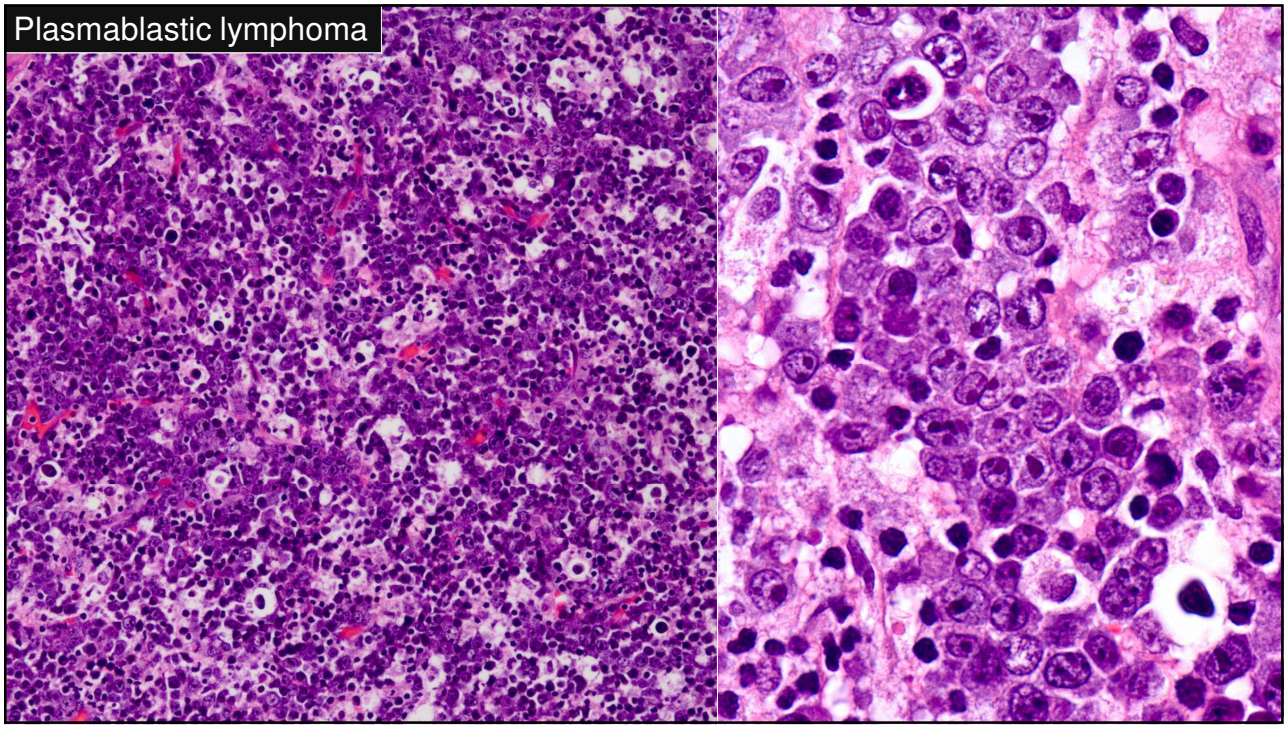
Plasmablastic Lymphoma

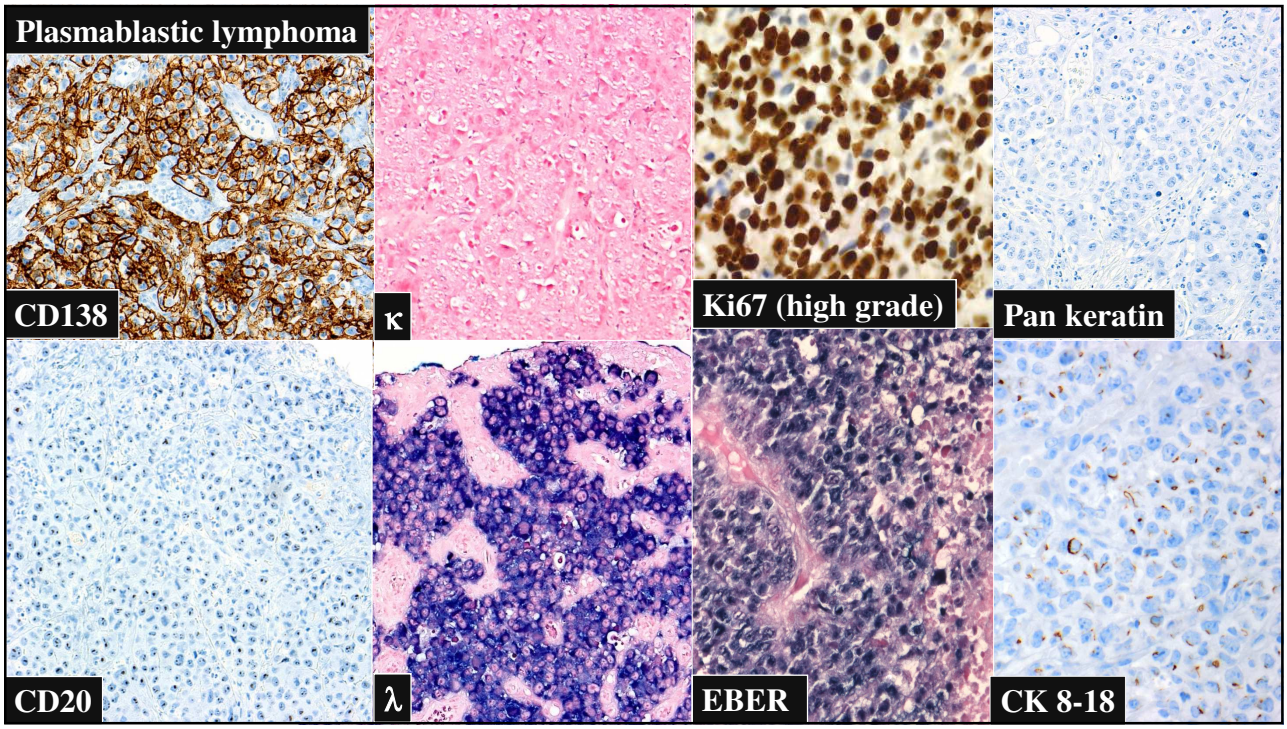
- Histology:
  - Diffuse proliferation of immunoblasts, plasmacytoid immunoblasts, plasmablasts +/- plasmacytic differentiation
  - Frequent mitoses, starry sky pattern +/- necrosis
- Immunophenotype
  - Usually +: CD138, CD38, MUM1, Blimp1, cIg, MYC
  - Variable: CD45, CD79a, CD56, CD10, CD30
  - Usually negative: Pax5, BCL6
  - Negative: CD20, ALK, HHV8
  - High proliferation index
  - Rarely, aberrant expression of keratin
- EBV, Cytogenetics, Molecular genetics
  - EBER+ in 60 – 70% of cases
  - Almost all HIV+ cases are EBV+
  - *MYC* translocation in ~ 50% of cases, fewer have *MYC* amplification
  - Complex karyotype
  - Downregulation of BCR signaling program, upregulation of genes associated with plasma cell differentiation
- Sites
  - Oral cavity, other extranodal sites
  - Lymph nodes, minority
  - Stage III/IV disease, majority

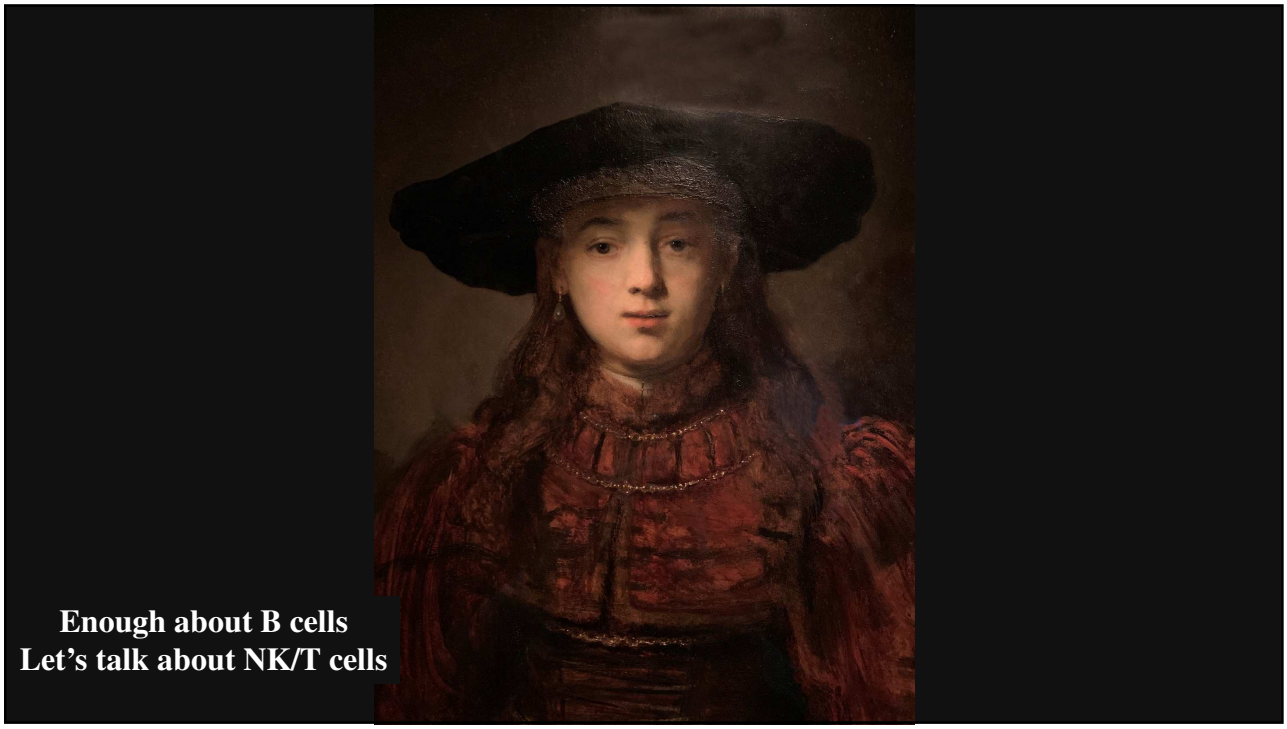
Plasmablastic lymphoma



Plasmablastic lymphoma

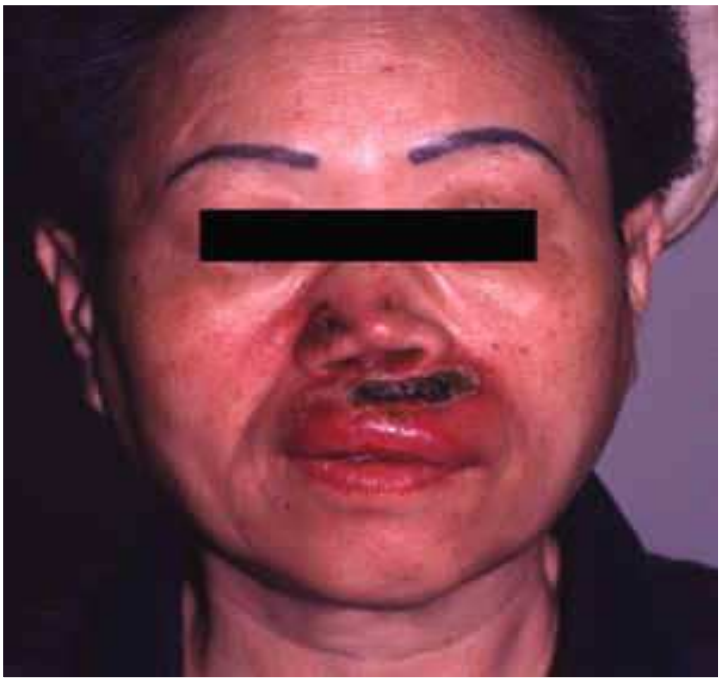



Plasmablastic lymphoma
CD138
κ
Ki67 (high grade)
Pan keratin
CD20
λ
EBER
CK 8-18

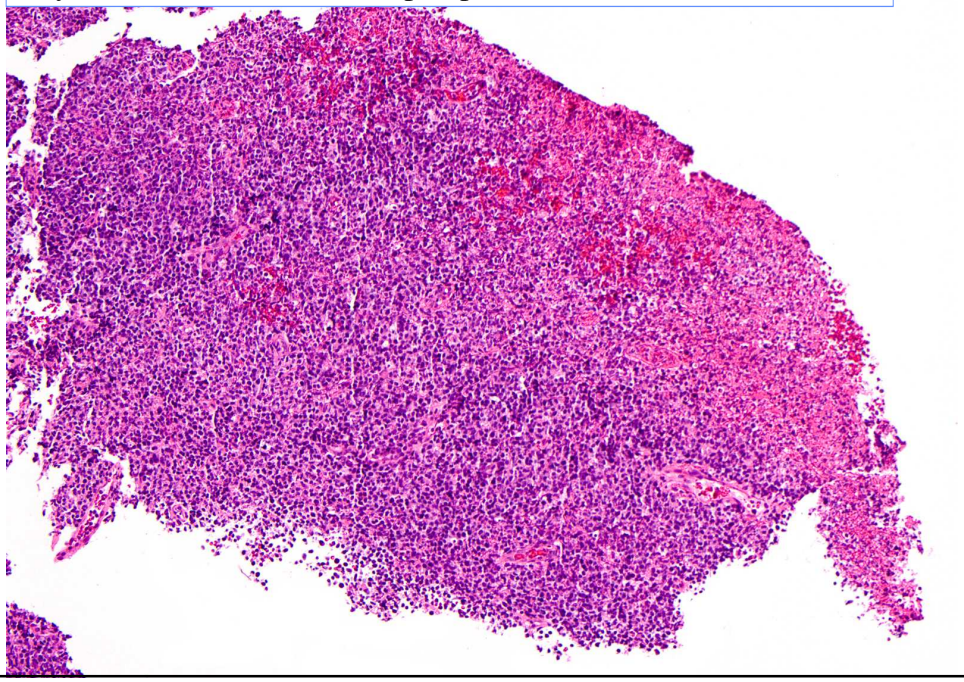

Enough about B cells
Let's talk about NK/T cells

Extranodal NK/T-Cell Lymphoma

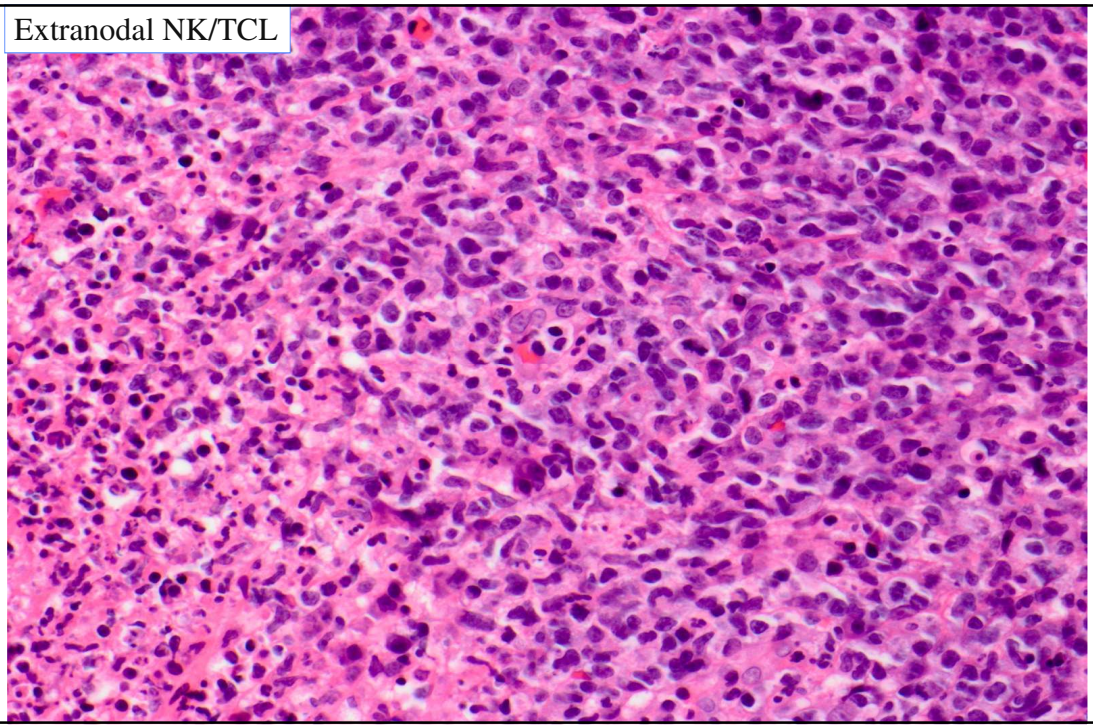
- Formerly extranodal NK/TCL, *nasal type*
- Adults, rarely children; Asians, native Americans>Caucasians
- Destructive lesion, nasal cavity or adjacent sites (80%)
  - Invasion of palate, orbit, sinuses or spread to more remote sites can occur
- Other sites: skin, GI tract, testis… (20%)
- Cytology: cells may be small, medium-sized, irregular, uniform or pleomorphic or large & bizarre
- Origin: most, NK cell; minority, T cell
- sCD3-, cCD3+, CD2+, CD5-, CD56+, perforin+, TIA-1+, granzyme B+ (cytotoxic phenotype)
- TCR usually germline (NK cell), occasionally rearranged (T cell)
- EBV+
- Pathogenesis:
  - Deletion 6q21-25 (most common CG change; location of candidate TSG: *PRDM1, PTPRK, HACE1* and *FOXO3*)
  - Mutations of JAK-STAT pathway genes, epigenetic regulators, TP53; deregulated miRNAs, others
  - Immune evasion
- Poor prognosis historically; better with low stage and improved therapy
- Hemophagocytic syndrome, some cases, worse prognosis

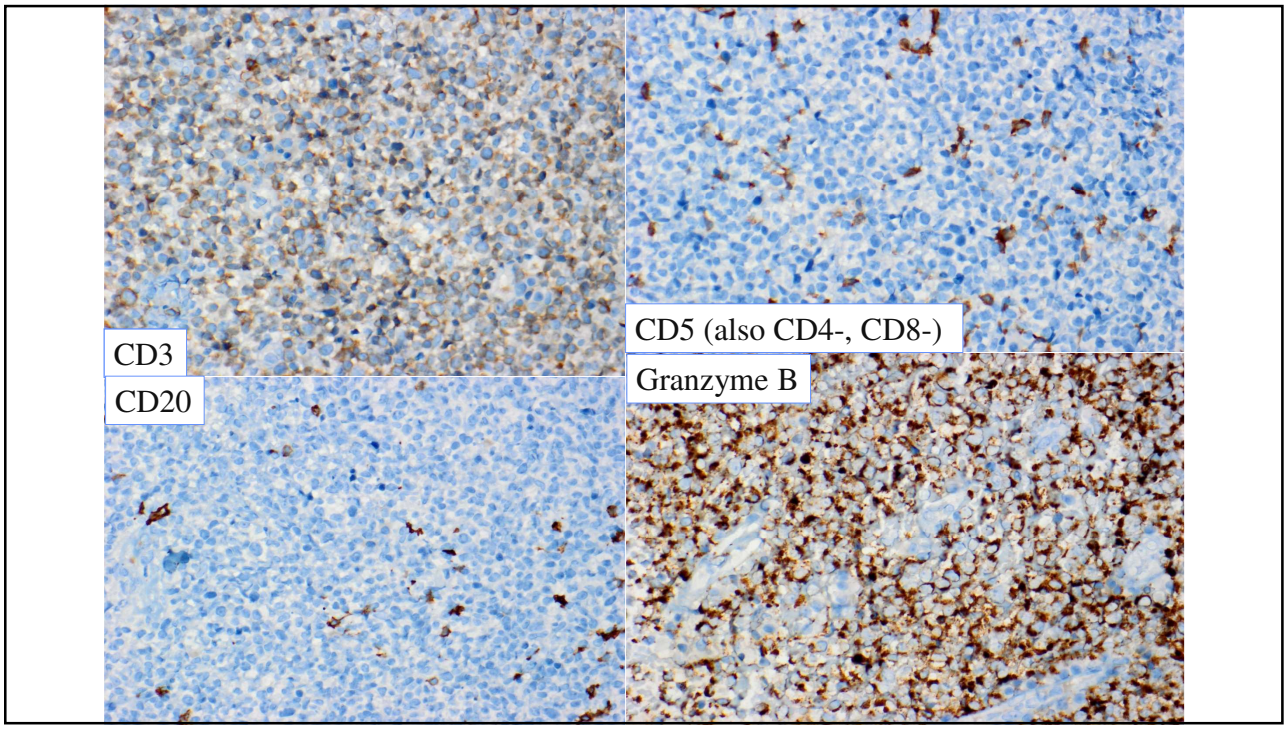


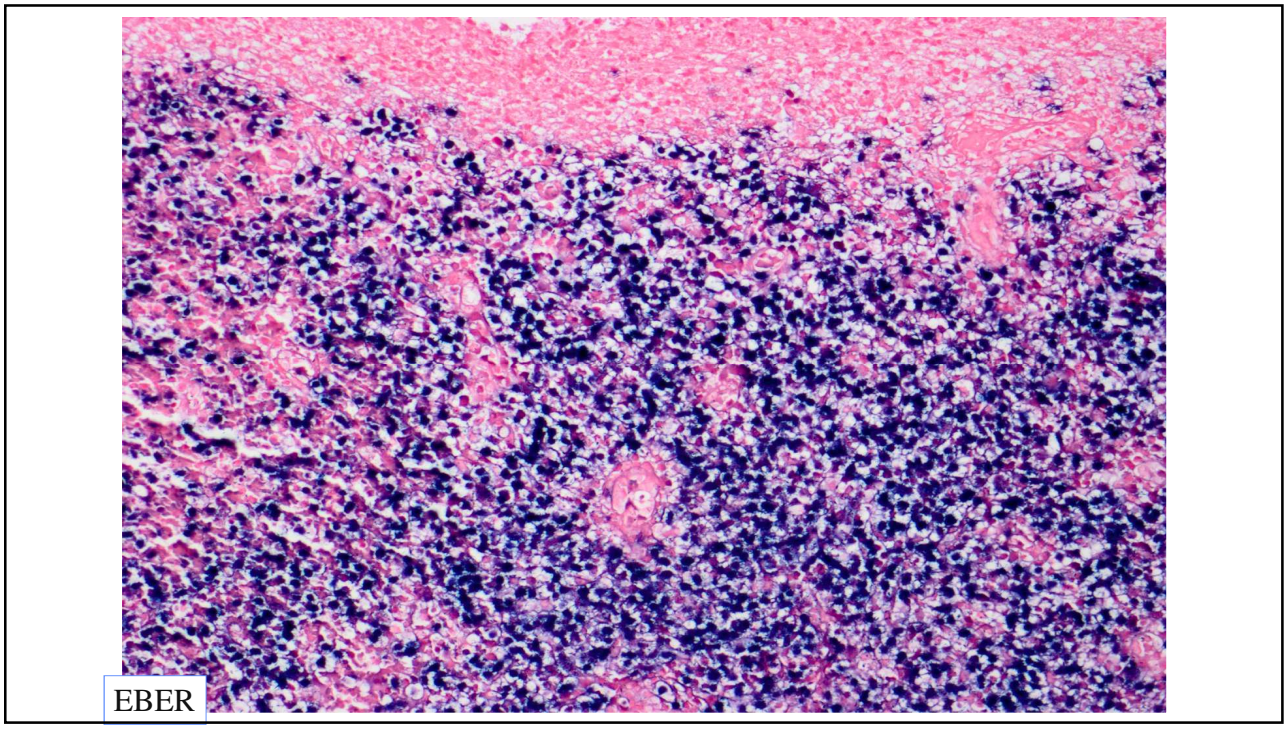
34 yo Asian man with nasal septal perforation: Extranodal NK/TCL



Extranodal NK/TCL




CD3
CD5 (also CD4-, CD8-)
CD20
Granzyme B


EBER

Primary Effusion Lymphoma (KSHV/HHV8+)

- Rare (1-4% of AIDS-related lymphomas)
- Presents as serous effusion with or without a contiguous mass
  - Pleural > peritoneal > pericardial
  - Usually only one cavity affected
- Subtype: Extracavitary PEL
  - "Solid" lymphoma in extranodal, less often nodal, site
- Most patients are HIV+, mostly young & middle-aged adults, M>F
- Small subset:
  - Post-transplant
  - Elderly

Primary Effusion Lymphoma (KSHV/HHV8+)

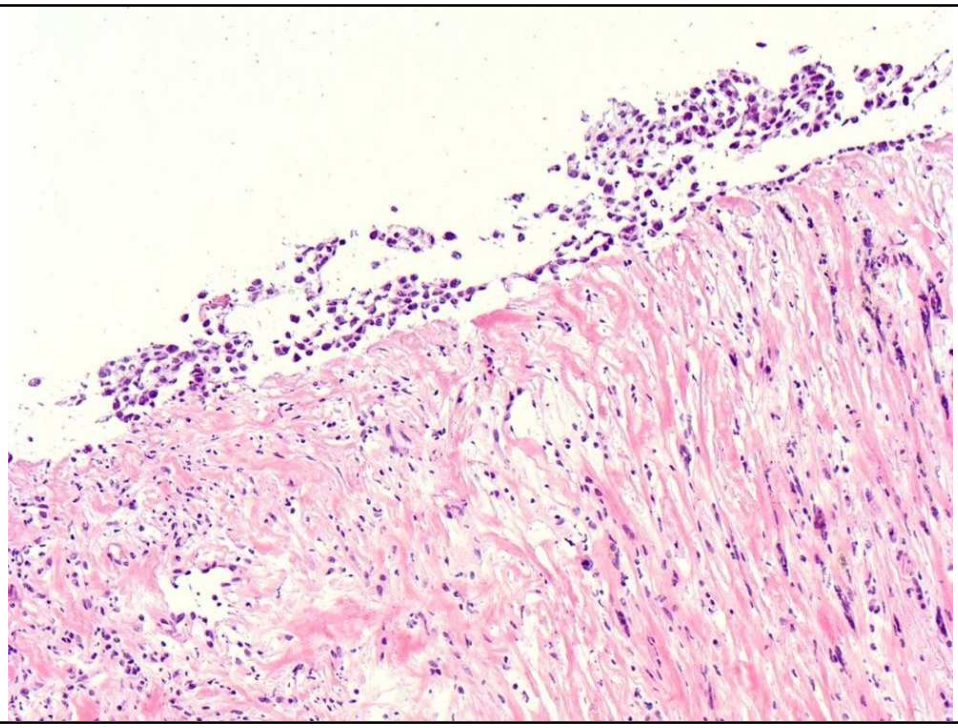
- Systemic symptoms are common
- Kaposi sarcoma: common
- Multicentric Castleman disease: minority
- Elevated KSHV viral load
- High levels of VEGF: vascular permeability, effusions

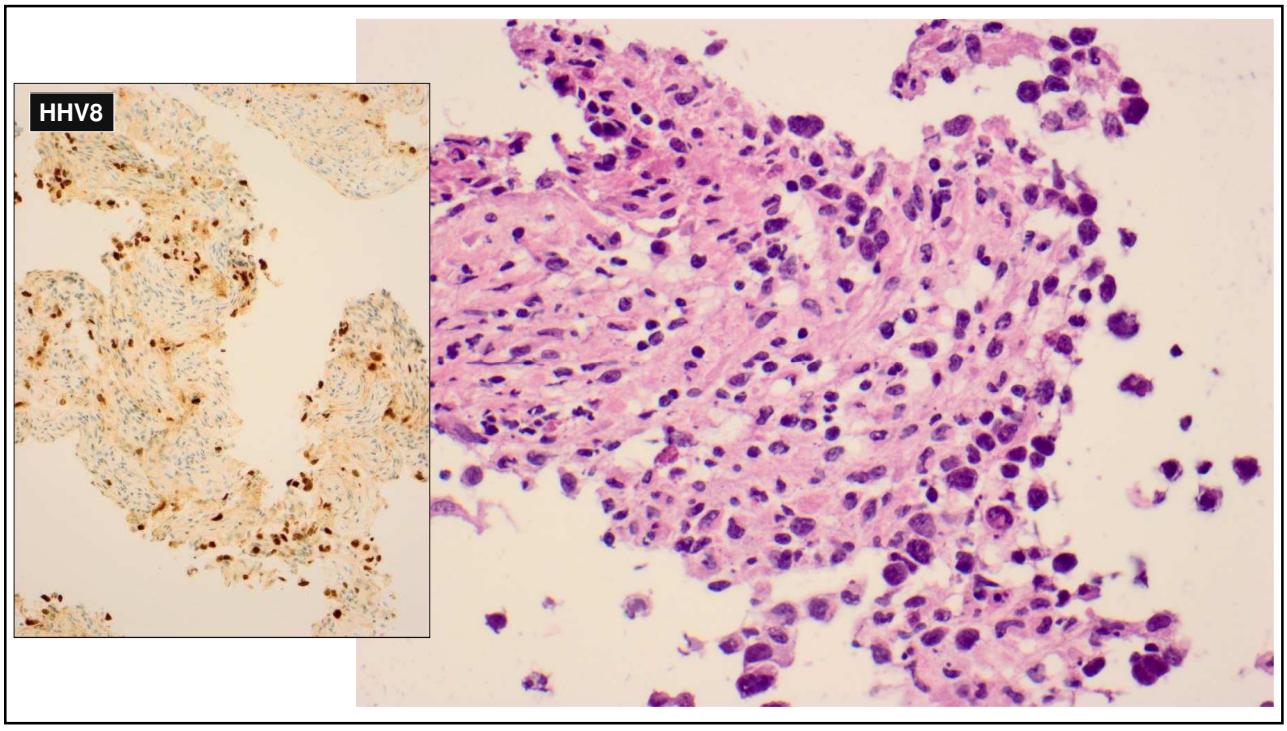
KSHV/HHV8: Characteristics

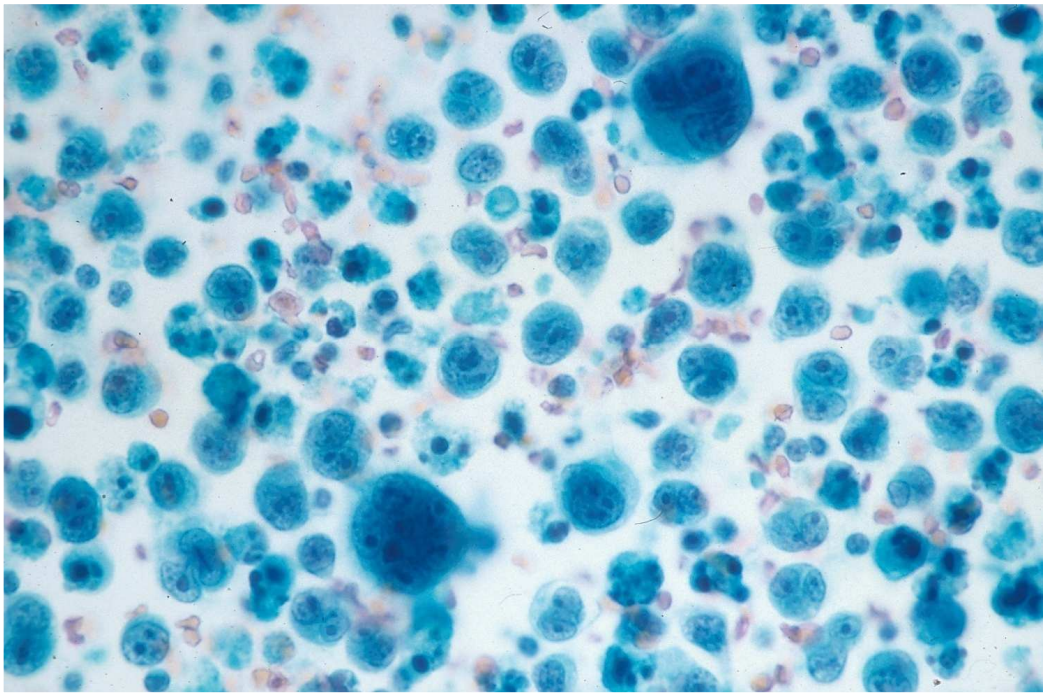
- Large double-stranded DNA genome in circular episomal form
- Tethered to host chromosome by LANA
- KSHV/HHV8 genes: effective mechanisms for evading host immune response, promoting tumorigenesis and inhibiting apoptosis
  - vIRF3 inhibits HLA transactivators, inhibiting T-cell activity
  - vFLIP activates NFkB
  - vIL-6 inhibits apoptosis by suppressing pro-apoptotic cathespsin D
- Lytic replication triggered by oxidative stress, certain cytokines or chemicals, other infectious agents such as HIV
- Dysregulated cytokine activation
  - Elevated IL6 and IL10 common
- Multiple viral genes have human homologues, e.g., vIL6

Primary Effusion Lymphoma

By definition: KSHV/HHV8+	EBV+ (~80%)
Morphology: Anaplastic, immunoblastic, plasmablastic	EBV-negative cases: more often elderly, with no specific immunodeficiency
Usually positive: CD45, CD30, EMA, CD138, MUM1/IRF4 Usually negative: CD19, CD20, Pax5, CD79a, CD10, BCL6, immunoglobulin	Genetic/ cytogenetic features: *IGH* clonal, somatic hypermutation No rearrangements of *MYC, BCL2, BCL6* No mutations of *TP53* Complex karyotype
Extracavitary PEL: more often B antigen positive	Features correspond to late stage in B-cell differentiation
Aberrant expression of T-cell antigens in some cases	Prognosis: Poor; better with ART; better for EC-PEL




HHV8



Fluid overload-associated large B-cell lymphoma: Clinical Features

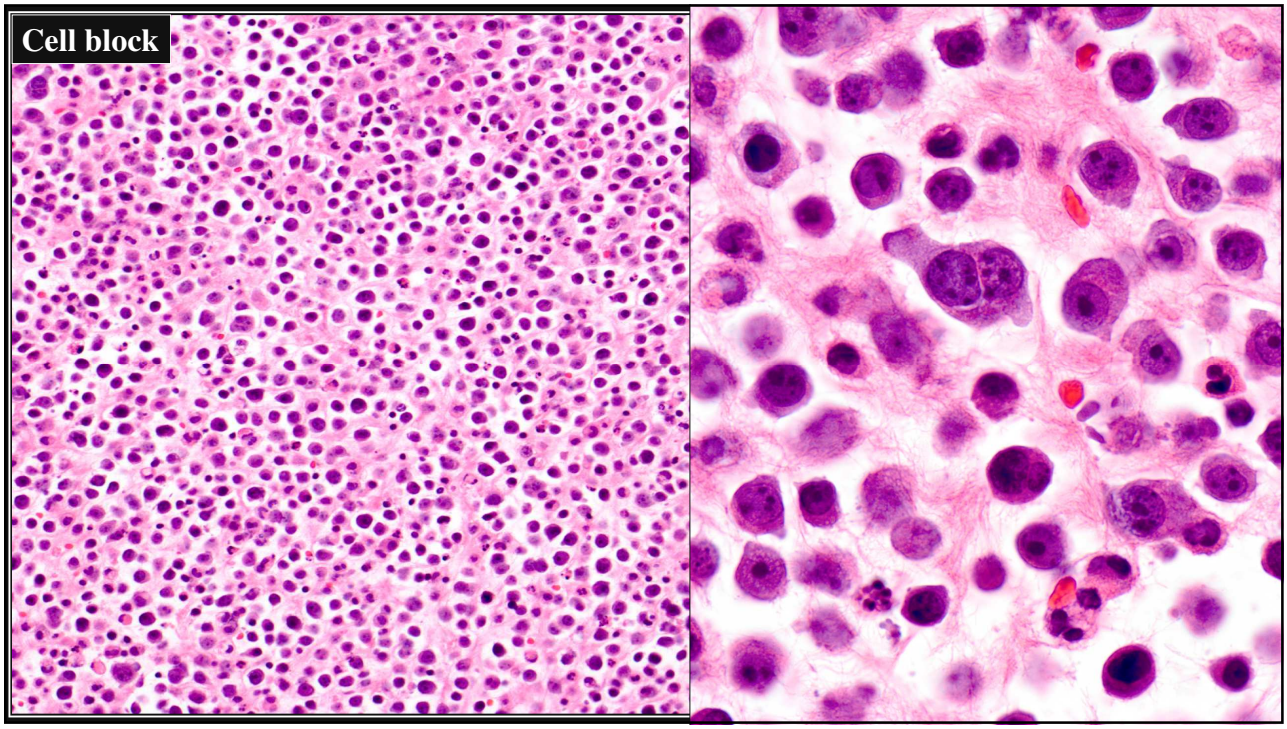
Older adults (median, ~70 years) Men slightly more affected than women	(PEL: single cavity effusions and pleural cavity only more common)
Most lack specific immunodeficiency except for age • HIV+ (8%) • Iatrogenic immunosuppression (few) • CVID (rare)	• Pericardial involvement almost always with pleural involvement • Subset with hepatitis C (25-33%): Peritoneum+ • Subset with hepatitis B
Frequent evidence of fluid overload • Cardiac or hepatic disease	Outcome: • Better than KSHV/HHV8+ PEL • Worse in immunodeficient patients • Remission in subset after draining • Death often not due to lymphoma
Pleural cavity> peritoneal cavity> multiple cavities > pericardial cavity	

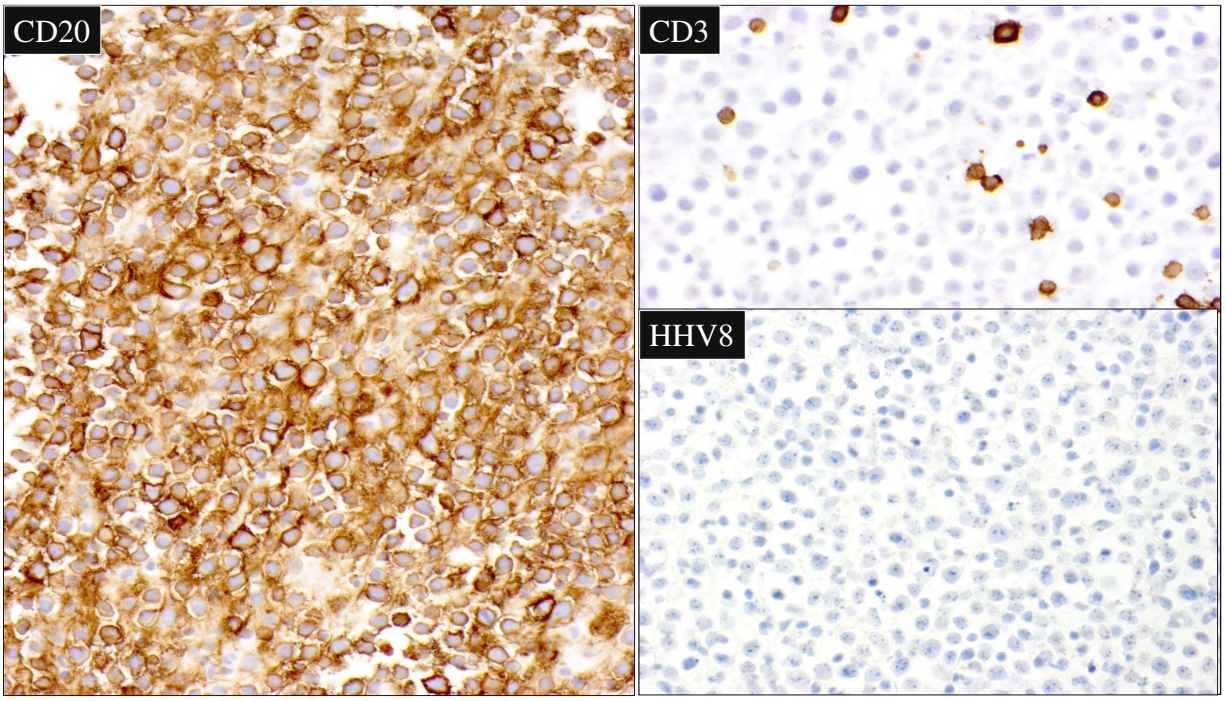
Fluid overload-associated large B-cell lymphoma: Pathology

Cytomorphology • Large cell, often pleomorphic (> 90%) • Some with plasmacytoid features	EBV • Usually negative (17-33% +) • More often positive in HIV+ or HCV+ patients
B-cell immunophenotype • Majority: non-GCB • Minority: GCB (0-15%)	Excluded • Similar cases of T-lineage • Burkitt lymphoma presenting as effusion

Fluid overload large B-cell lymphoma: Genetics

MYC	Translocation and amplification common
BCL2, BCL6	Occasionally translocated
DHL	Reported but rare
Karyotype	Abnormal, almost all cases
CGH	Frequent CNAs, ~ typical DLBCL
Mutational analysis	ABC type: mutated *MYD88, PIM1, BCL2, KLH14* GCB type, subset: mutated chromatin modifiers *CREBBP, KMT2D, MEF2B*
Other	Somatic hypermutation c/w post-GC stage





PEL and Fluid overload large B-cell lymphoma: Risk Factors

PEL (KSHV/HHV8+)	FOLBCL (KSHV/HHV8-)
HHV8	Advanced age
HIV	Effusions
EBV	EBV
Miscellaneous immunosuppression	HCV
	Miscellaneous immunosuppression

Two more KSHV/HHV8+ LPDs:

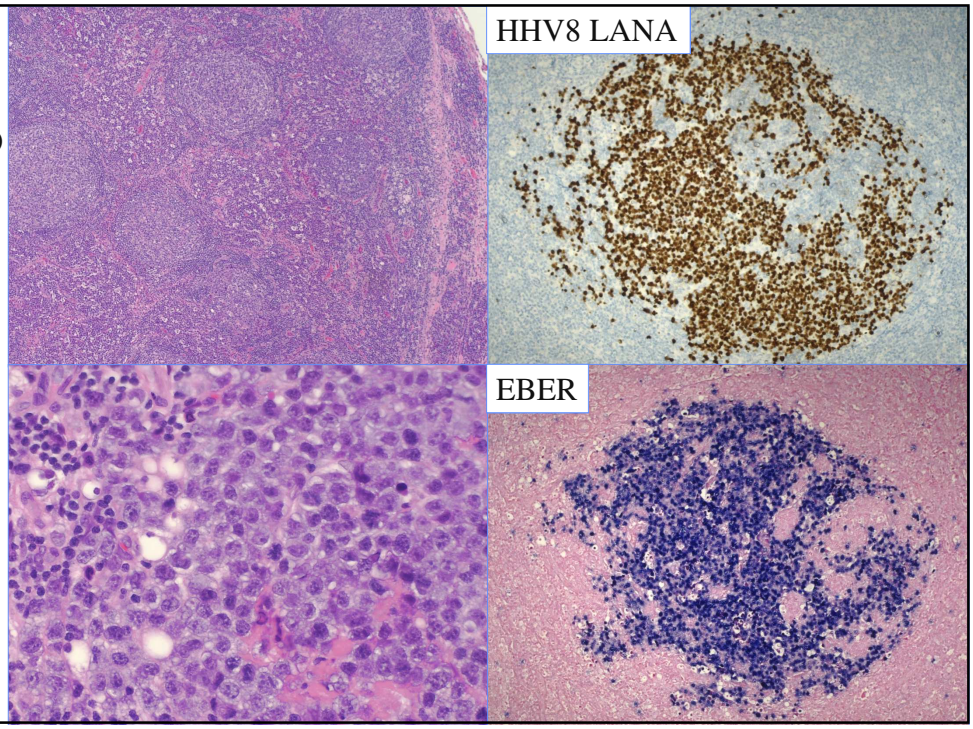
KSHV/HHV8+ DLBCL

- Occurs most often in immunodeficient patients
- Often occurs with KSHV/HHV8+ MCD
- Prognosis: poor
- In contrast to PEL,
  - Involves lymph nodes and/or spleen
  - IgM+
  - EBER usually negative

KSHV/HHV8+ germinotropic LPD

- Patients usually immunocompetent
- KSHV/HHV8+ large cells colonize follicles of LNs
- Nodal architecture intact
- EBV usually+
- Polyclonal
- Prognosis: good; some progress to aggressive disease

KSHV/HHV8+ Germinotropic LPD

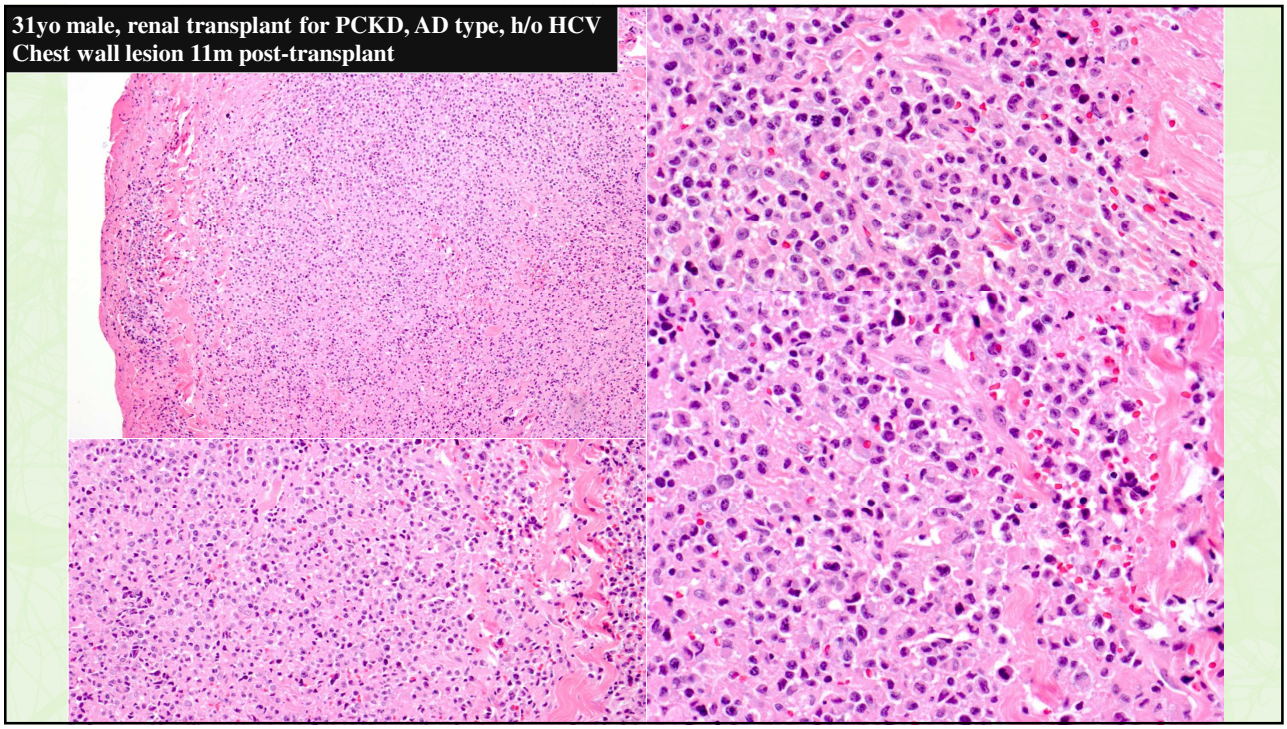


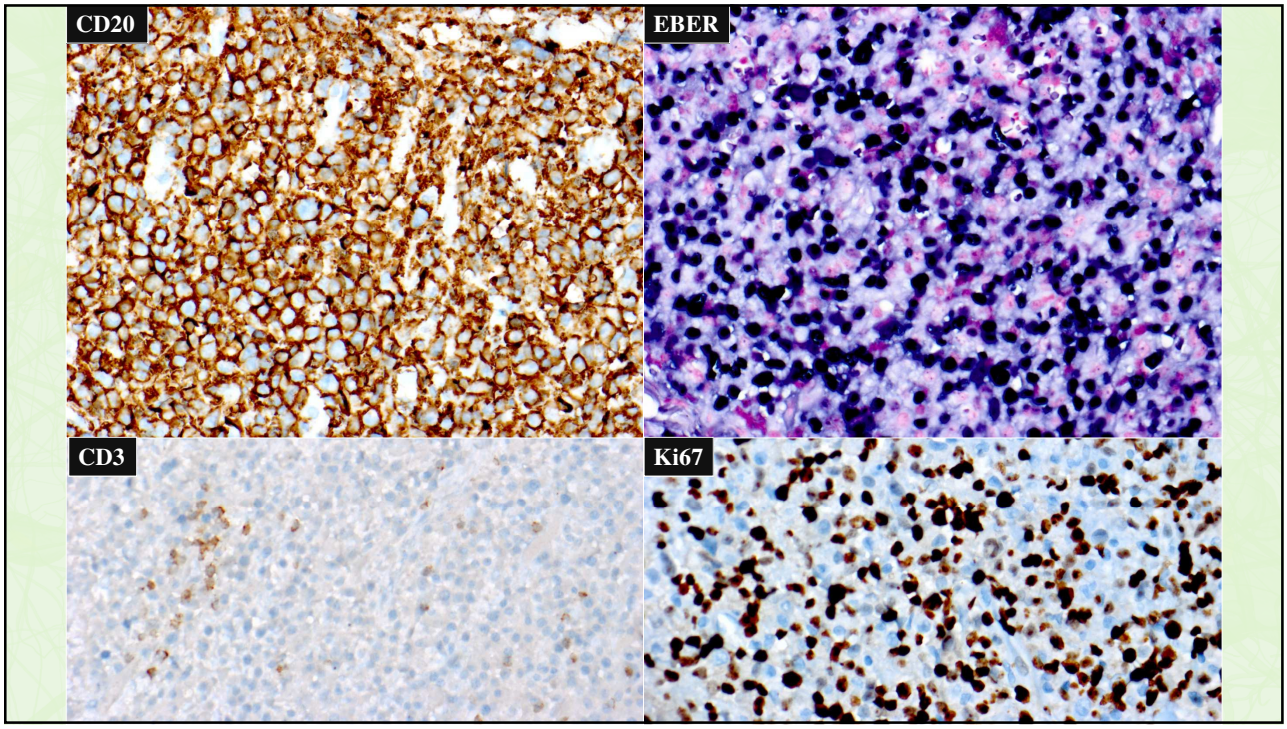
LPDs and Lymphomas associated with Immune Deficiency and Dysregulation

- Nomenclature for these disorders has changed
- Initial discussion:
  - 2015 Society for Hematopathology/European Association for Hematopathology Workshop
- New format:
  - *Diagnosis, oncogenic virus (if any), type of immunosuppression*
  - e.g., DLBCL, EBV+, post-transplant
  - Instead of monomorphic post-transplantation lymphoproliferative disorder

LPDs and Lymphomas associated with Immune Deficiency and Dysregulation

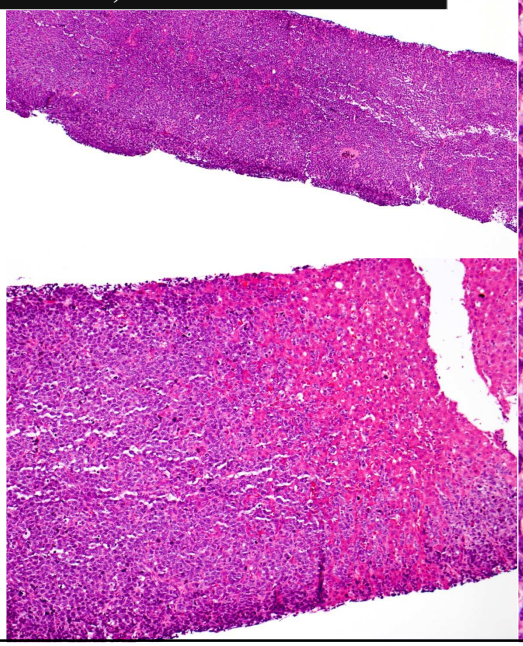
- Hyperplasias
  - Follicular hyperplasia
  - Infectious mono-like hyperplasia
  - Plasmacytic hyperplasia
- Polymorphic LPDs
  - EBV+ mucocutaneous ulcer
- Lymphomas
  - DLBCL
  - Burkitt lymphoma
  - Classic Hodgkin lymphoma
  - Low-grade B-cell lymphomas
  - T-cell & NK/T-cell lymphomas
    - » Various types

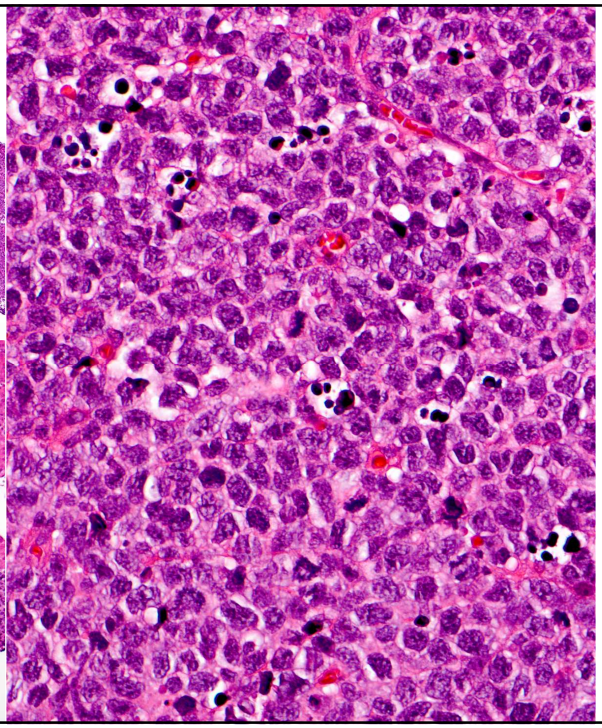

31yo male, renal transplant for PCKD, AD type, h/o HCV
Chest wall lesion 11m post-transplant

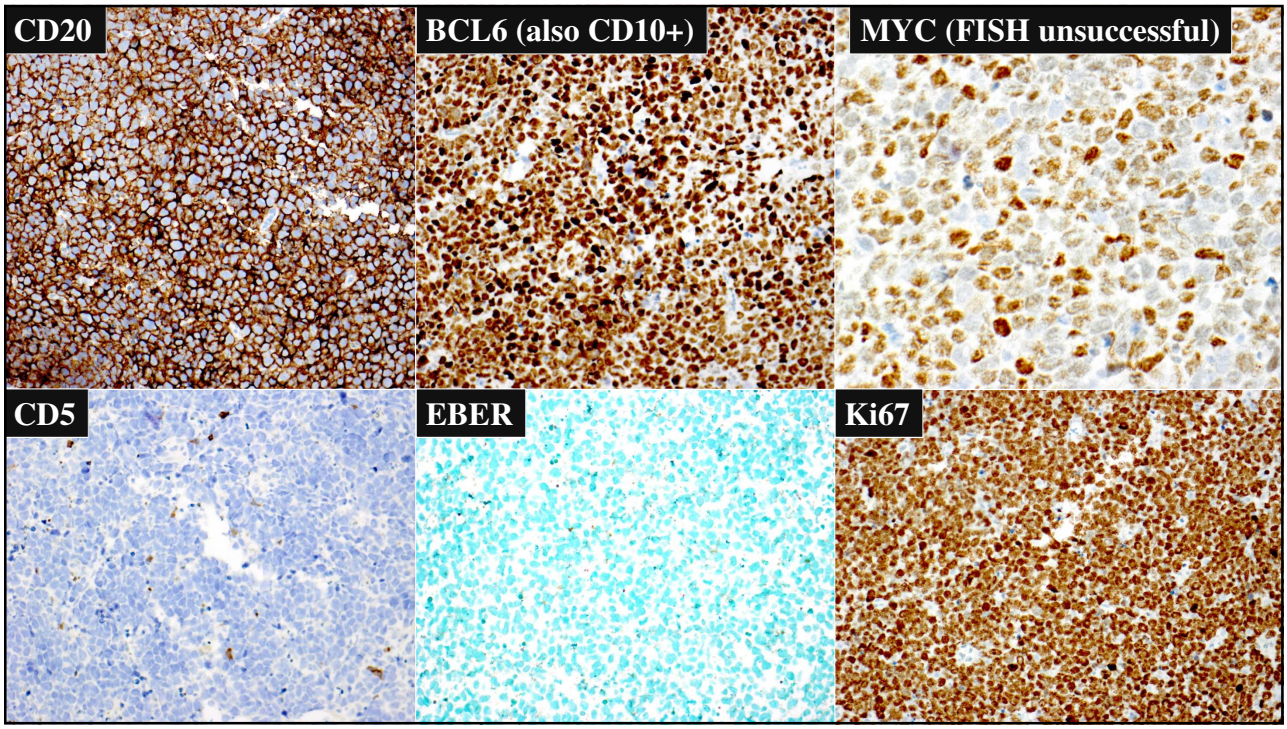

CD20
EBER
CD3
Ki67

- Prior nomenclature:
  - –Polymorphic PTLD (EBV+)
- Updated nomenclature:
  - –Polymorphic lymphoproliferative disorder, EBV+, post-transplant
- Outcome:
  - –NED, 16 months

61 yo male 37m s/p liver transplant for HCV, HCC and cirrhosis







Prior nomenclature:
Monomorphic B-PTLD, consistent with
Diffuse large B-cell lymphoma, germinal center B-cell subtype

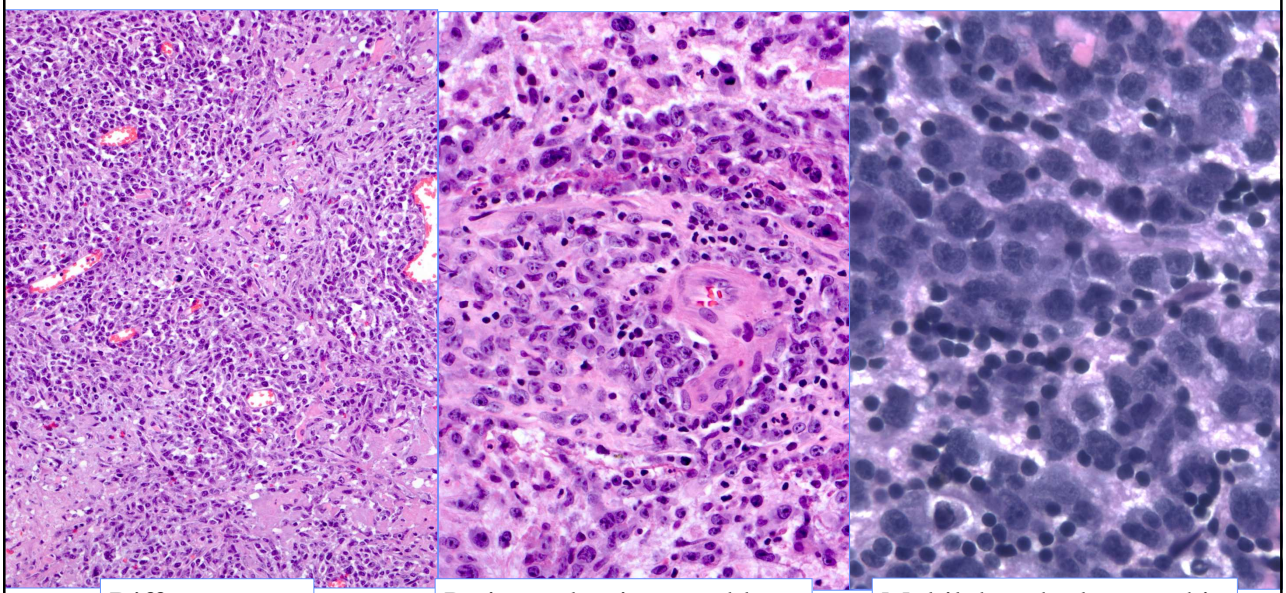
Updated nomenclature:
Diffuse large B-cell lymphoma, GCB subtype (EBV-negative), post-transplant

Hospital course
Bone marrow: extensive involvement by PTLD
1 cycle of CHOP
Leukocytosis, respiratory distress, altered mental status, renal failure c/w ATN
Died, 1 month after diagnosis of DLBCL

Primary diffuse large B-cell lymphoma of immune-privileged sites

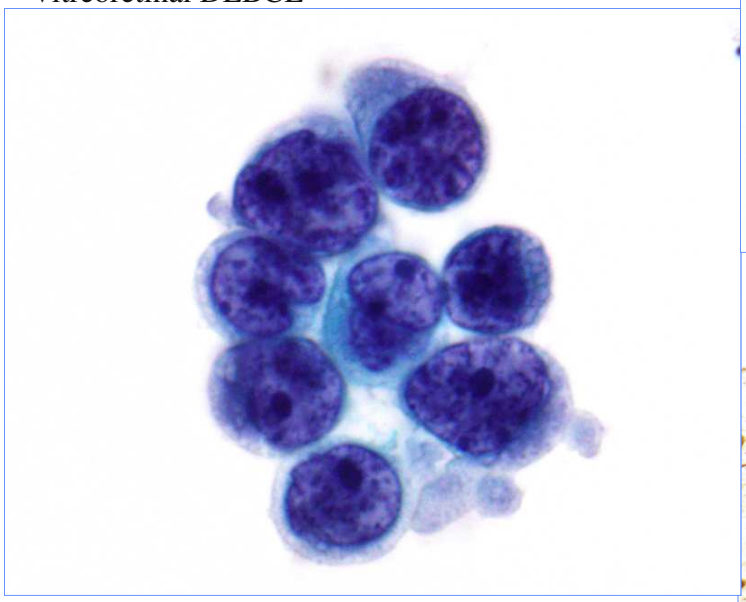
- Primary CNS, vitreoretinal & testicular lymphoma
- Arise in immune sanctuary sites
- Occur in immunocompetent patients
- Certain ovarian & breast DLBCLs and cutaneous DLBCL (leg-type) share features with lymphomas in this category
- Immunophenotype
  - Positive: pan-B-cell markers, MUM1, BCL2, IgM (non-GCB)
  - High Ki67 (>80%)
  - Typically negative: CD10, EBV
- Ongoing somatic hypermutation
- Preferential use of *IGHV4-34* gene
- Mutated *MYD88* and *CD79B* common
- Molecular changes (loss/inactivation of MHC I and II & B2M) facilitate immune escape
- Gains of 18q21 (*BCL2*, *MALT1*), 9p24.3 (*PD-L1*)
- Losses of 6q21 (*PRDM1*) and 10q.23.21 (*PTEN*)
- Frequent bi-allelic CDKN2A inactivation: deletion of 9p21 and/or epigenetic silencing

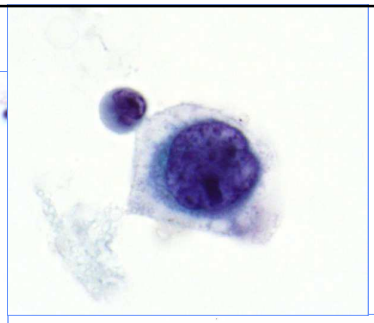
Primary CNS DLBCL



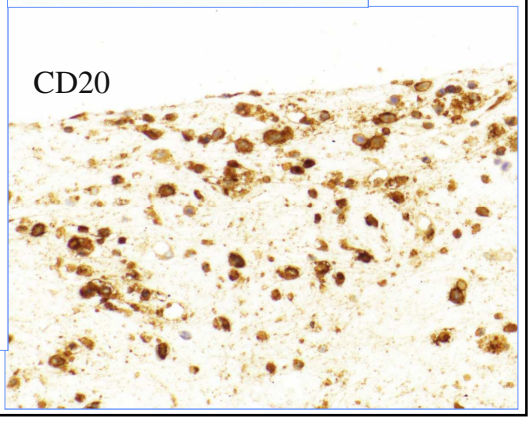
Diffuse pattern | Perivascular; immunoblasts | Multilobated, pleomorphic

Vitreoretinal DLBCL

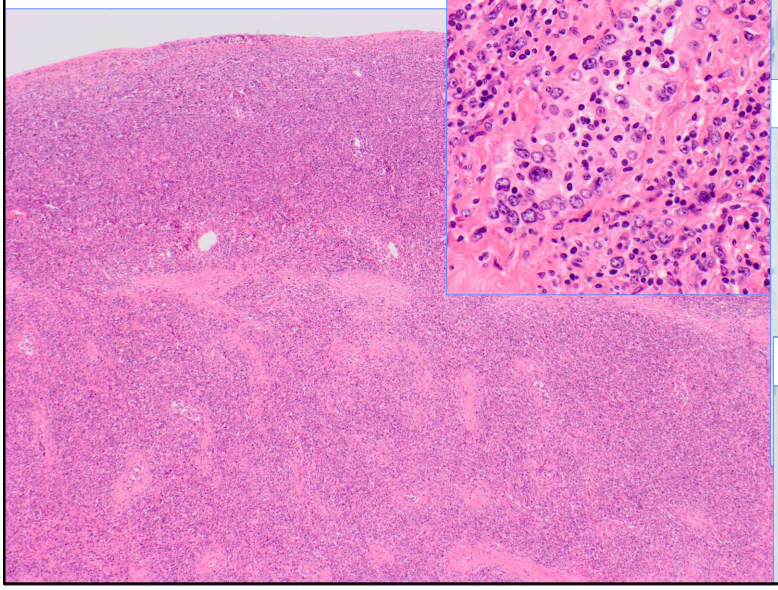




CD20

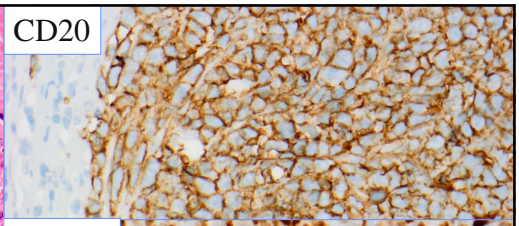


Primary testicular lymphoma

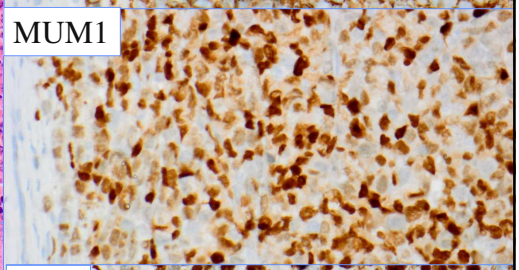


Tubule

CD20



MUM1



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