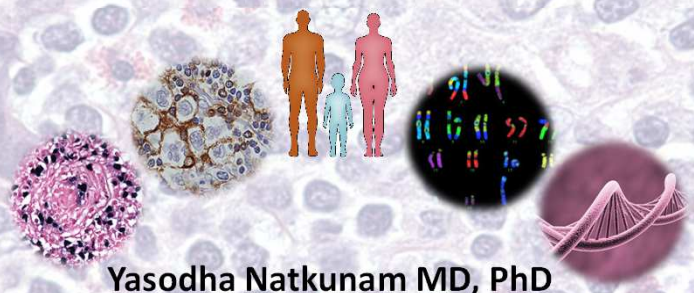
Reactive Lymphadenopathies including Castleman Disease



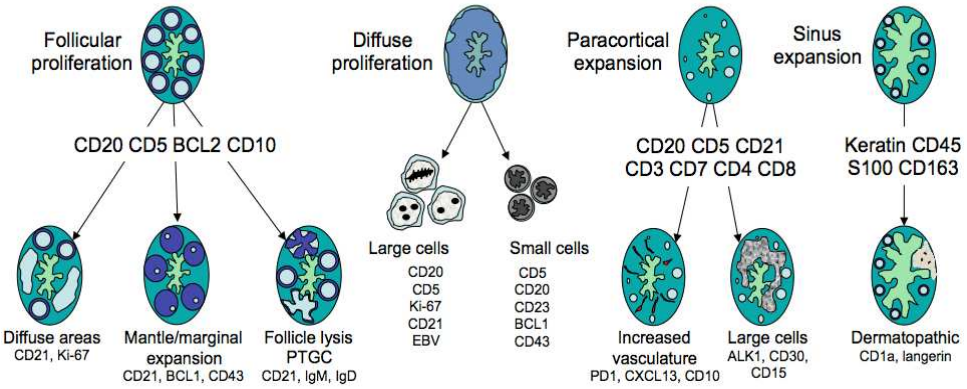
Yasodha Natkunam MD, PhD
Ronald F. Dorfman MBBCh FRCPath Professor of Hematopathology
Stanford University School of Medicine

Objectives

- Approach to the diagnosis of reactive lymphadenopathies
- Selected case examples that mimic lymphoma
- Castleman disease and its myriad manifestations

Approach to Lymph Node Diagnoses

- Recognition of a predominant pattern in lymph nodes at low power
- Awareness of the differential diagnosis to guide ancillary studies

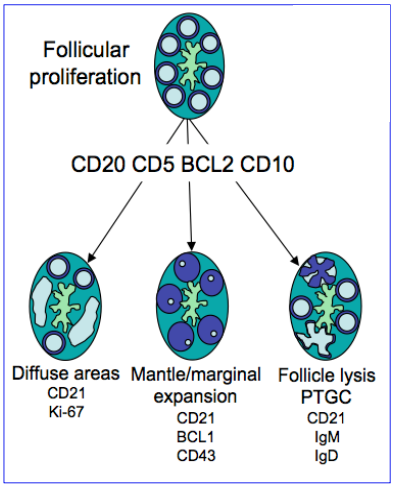


Anderson & Natkunam 2010

Reactive Lymphadenopathies

Pattern	Entity/Etiology	Differential Diagnoses
Follicular/Nodular	Florid follicular hyperplasia Progressive transformation of GCs Castleman disease Infectious: Toxoplasmosis, Syphilis, HIV	Follicular lymphoma NLPHL
Diffuse/Mixed	Autoimmune lymphoproliferative syndrome IgG4-related disease Indolent TdT proliferations	PTCL, B/T-ALL
Paracortical	Infectious mononucleosis (EBV), CMV Immunoblastic proliferations Autoimmune lymphoproliferative syndrome T-zone Hyperplasia	DLBCL, PTCL, Polymorphic PTLD Classic Hodgkin lymphoma
Sinusoidal	Dermatopathic lymphadenitis Reactive histiocytic proliferation Vascular transformation	Histiocytoses: LCH, RDD Anaplastic large cell lymphoma Metastatic carcinoma, melanoma
Necrotizing	Kichuchi lymphadenitis Systemic lupus erythematosus Infectious: Cat-scratch disease, Herpes	PTCL, DLBCL and CHL with associated necrosis

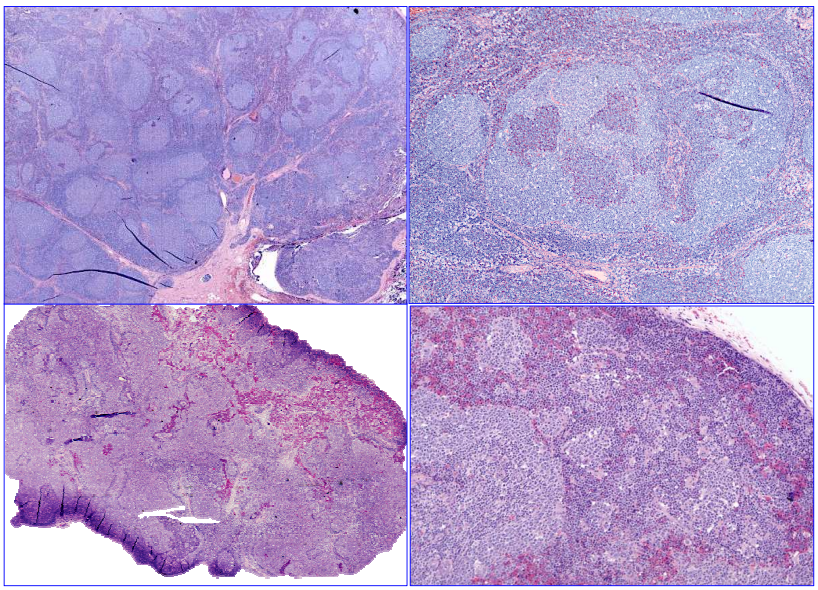
Follicular/Nodular Proliferation



Entity/Etiology	Differential Diagnoses
Florid follicular hyperplasia Progressive transformation of germinal centers Castleman disease Infectious etiologies Toxoplasmosis Syphilis HIV lymphadenopathy	Follicular lymphoma Other B-cell lymphomas with nodular growth (MZL, MCL) Nodular lymphocyte predominant Hodgkin lymphoma

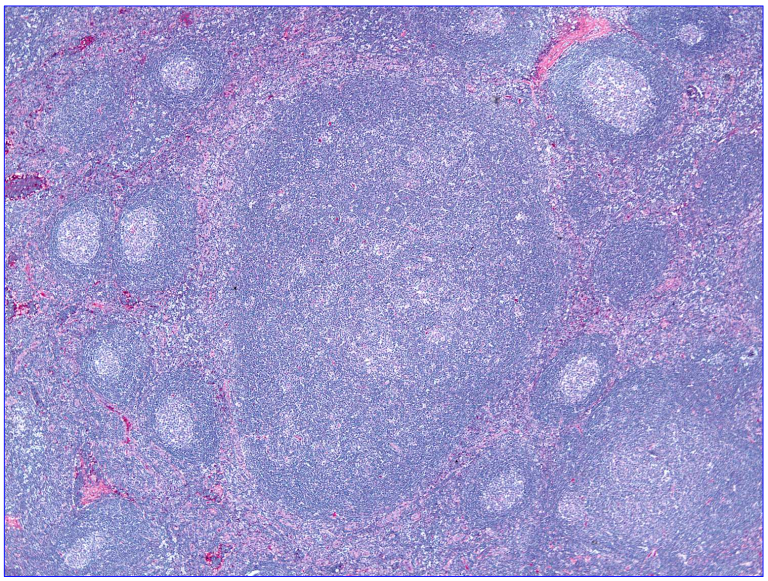
HIV Lymphadenopathy

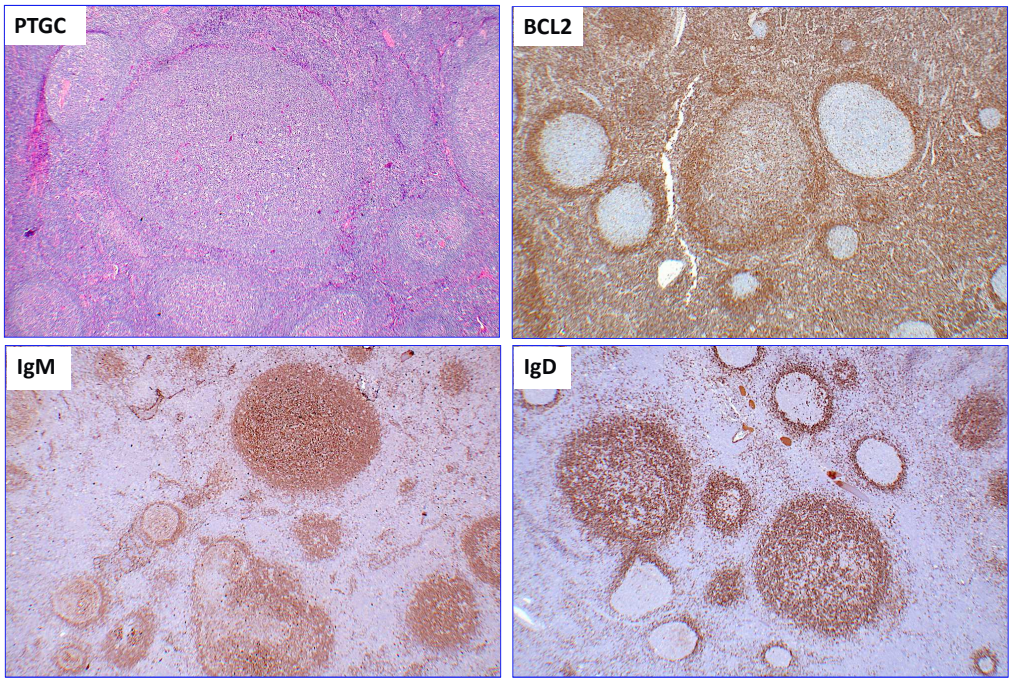
- HIV+ patients can have persistent lymphadenopathy
- Range from florid follicular hyperplasia, follicle lysis, lymphocyte depletion, epithelioid granulomas, capsular fibrosis, MCD
- Histologic features may be seen in combination with infectious organisms, especially with severity of HIV/AIDS



Progressive Transformation of Germinal Centers

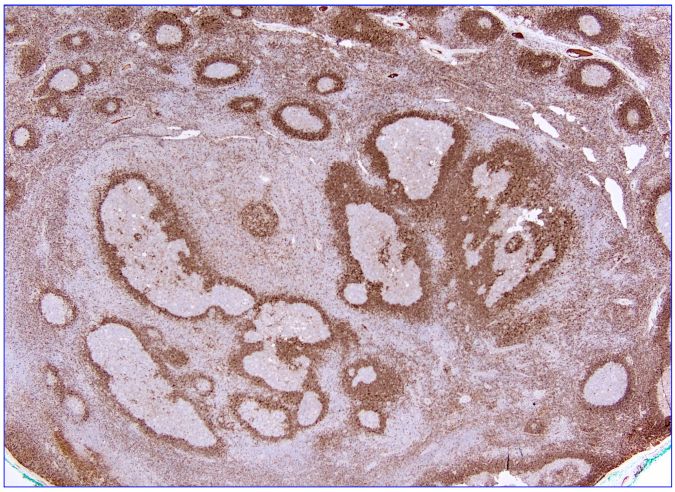
- Reactive lymphadenopathy of unknown etiology
- Isolated large follicle(s) with involution of mantle zone B-cells in a background of reactive follicular hyperplasia
- Clusters of residual germinal centers
- May be seen in association with lymphomas, especially **NLPHL**





IgD in PTGC

Useful to outline the internal and external boundaries of PTGC follicles

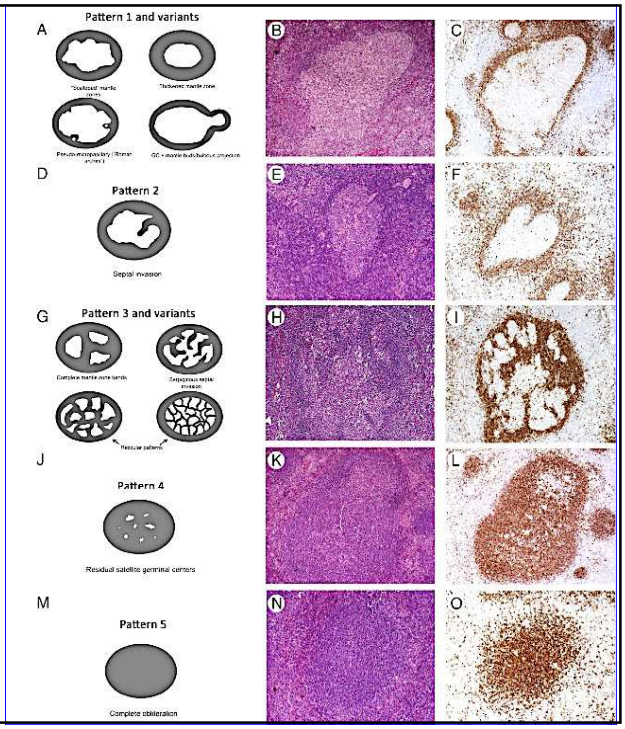


Immunoarchitectural patterns of progressive transformation of germinal centers with and without nodular lymphocyte-predominant Hodgkin lymphoma☆,☆☆

Sylvia Hartmann MD[a,*,1], Ria Winkelmann MD[a,1], Ryan A. Metcalf MD[b], Jitsupa Treetipsatit MD[c], Roger A. Warnke MD[b], Yasodha Natkunam MD, PhD[b,1], Martin-Leo Hansmann MD[a,1]

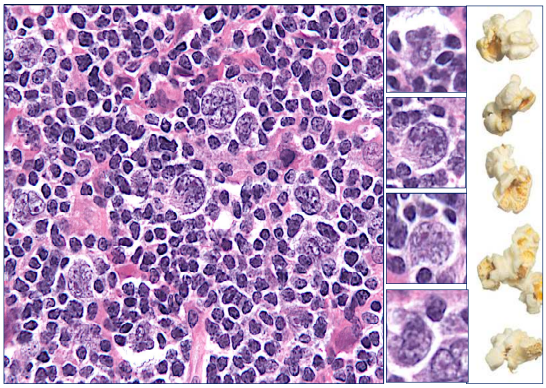
- A study of 160 cases
  - 93 PTGC: never developed NLPHL
  - 23 synchronous PTGC + NLPHL
  - 44 metachronous PTGC + NLPHL
- Patterns 5 associated with progressive dismantling of germinal centers
- Pattern 5 resembles a naïve B follicle
- Pattern 5 more common in synchronous PTGC + NLPHL

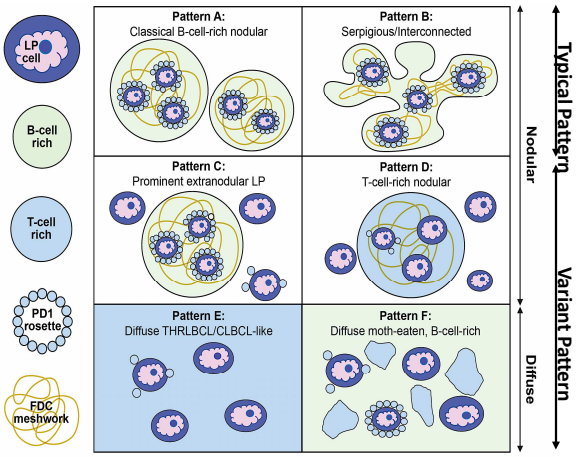
Hartmann et al, Hum Pathol 2015



Nodular Lymphocyte Predominant Hodgkin Lymphoma

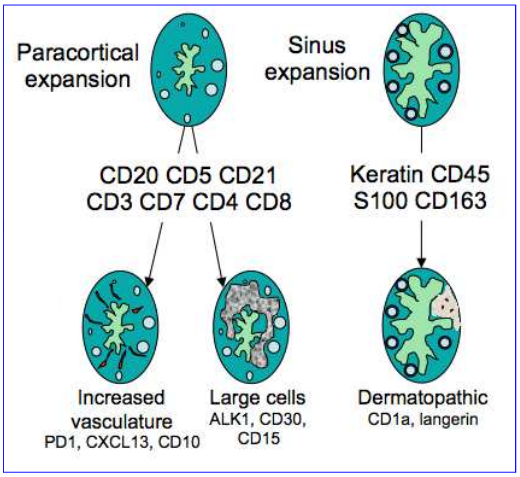
- Nodular architecture and scattered large neoplastic LP cells
- May overlap or co-exist with PTGC





Fan et al, Am J Surg Pathol 2003
Younes et al. Cancers 2021

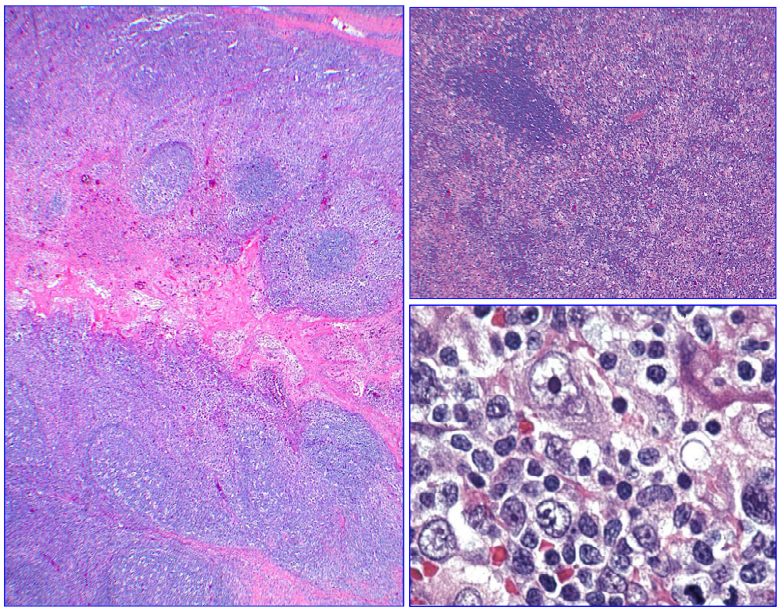
Paracortical Expansion

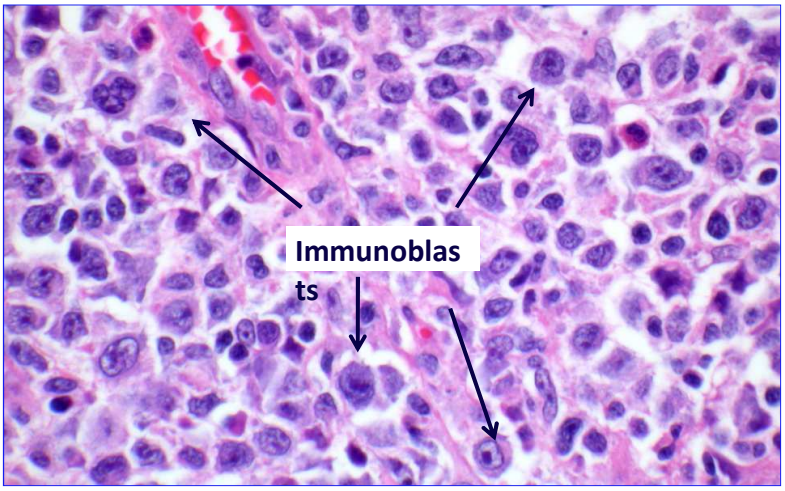


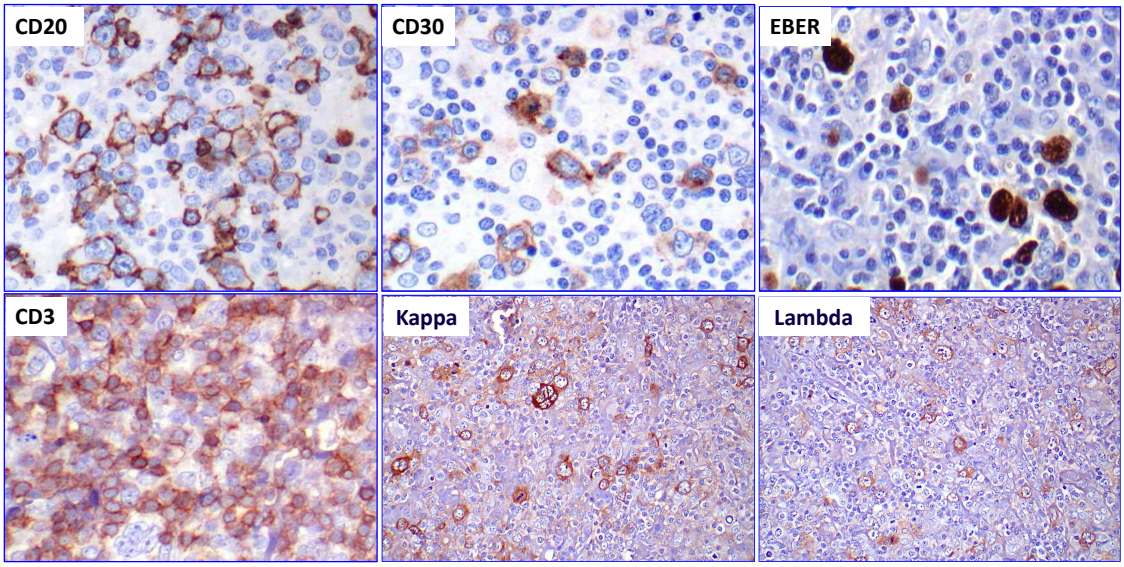
Entity/Etiology	Differential Diagnoses
Infectious mononucleosis CMV lympadenitits Immunoblastic proliferations Autoimmune lymphoproliferative syndrome T-zone Hyperplasia	DLBCL, PTCL Polymorphic PTLD Classic Hodgkin lymphoma

Case 1

- 19-year-old Filipino man with intermittent high fever and unilateral cervical lymphadenopathy
- No history of immunodeficiency
- Monospot test negative
- Cervical lymph node excision performed





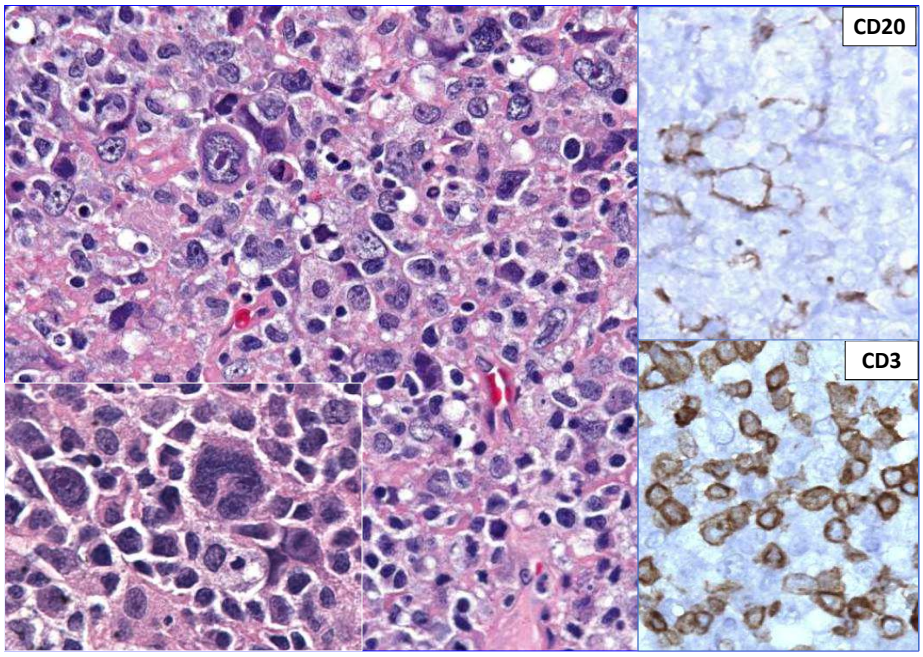


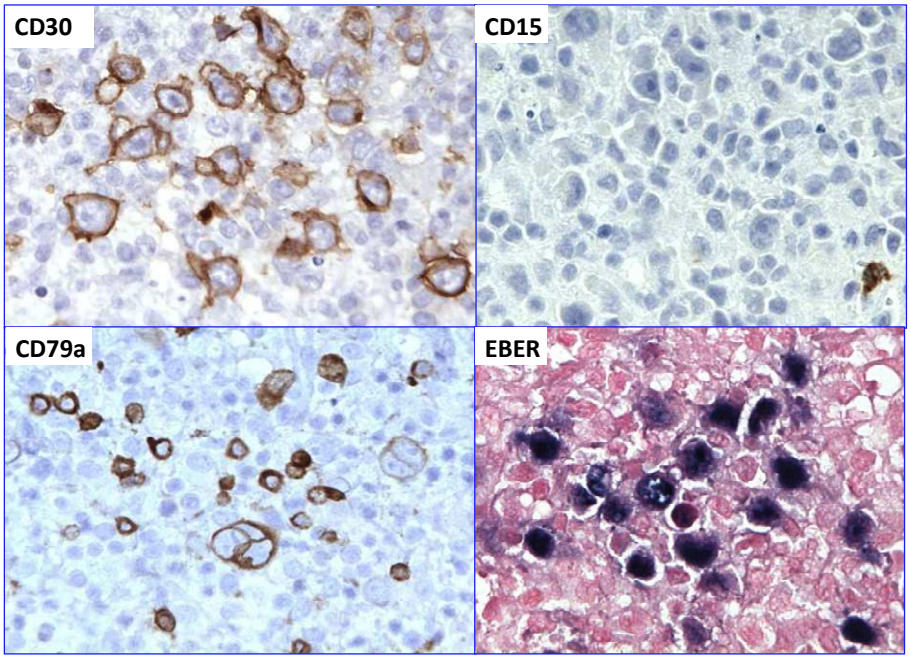
Case 1: Differential Diagnosis

- **EBV+ Classic Hodgkin Lymphoma**
  - CHL: EBV is in large cells; CD30+ CD15+ CD20-
  - EBV lymphadenitis: EBV+ cells range in size from small to large; CD30+ CD15- CD20+ CD3+
- **EBV+ Diffuse Large B-Cell Lymphoma**
  - May have sheet-like growth or T/histiocyic-rich background
  - Variability in CD20 and other B-marker expression
  - Often numerous CD30+ B cells
- **Non EBV-driven immunoblastic proliferations**
  - Drugs: methotrexate, dilantin
  - Viral: HSV, CMV
  - IgG4-related disease
- **Immunodeficiency-associated LPD**
  - Infectious mononucleosis-like hyperplasia
    - Architectural preservation with polytypic light chain expression
  - Polymorphic lymphoproliferative disorder
    - Architectural destructive with full spectrum of B-cell maturation and immunoblasts/HRS-like cells
  - EBV+ Mucocutaneous ulcer
    - Well circumscribed ulcer in mucosal and cutaneous sites including GI tract
    - Rarely involves the lymph node

Case 1: EBV+ Lymphadenitis, consistent with Infectious Mononucleosis

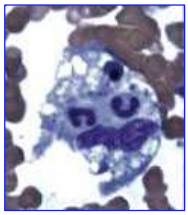
- The patient was followed without treatment
- Five months later, he presented with fever, prominent cervical lymphadenopathy, splenomegaly and cytopenias
- Repeat cervical lymph node biopsy performed
- Bone marrow biopsy was performed

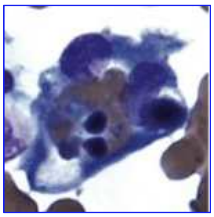




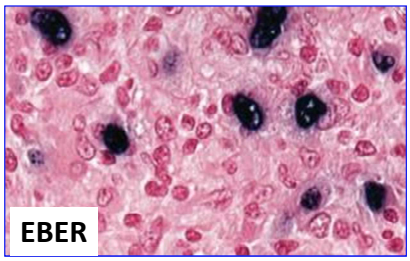
Additional workup

- EBV viremia (11,700 copies/ml)
- Normal karyotype
- *BCR* and *TCR* rearrangements were performed on both cervical LN biopsies
  - 1st negative B & T
  - 2nd oligoclonal B
- Flow cytometry
  - No clonal B cell or aberrant T-cell populations

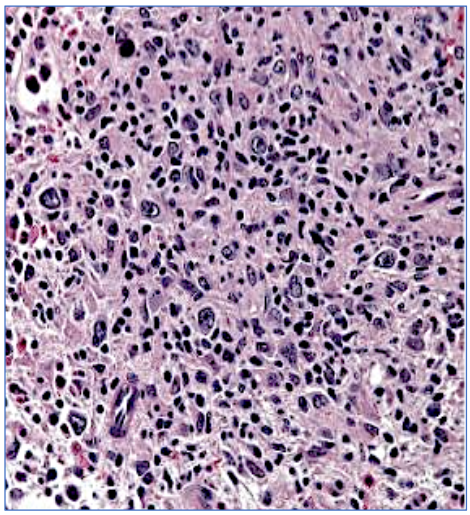




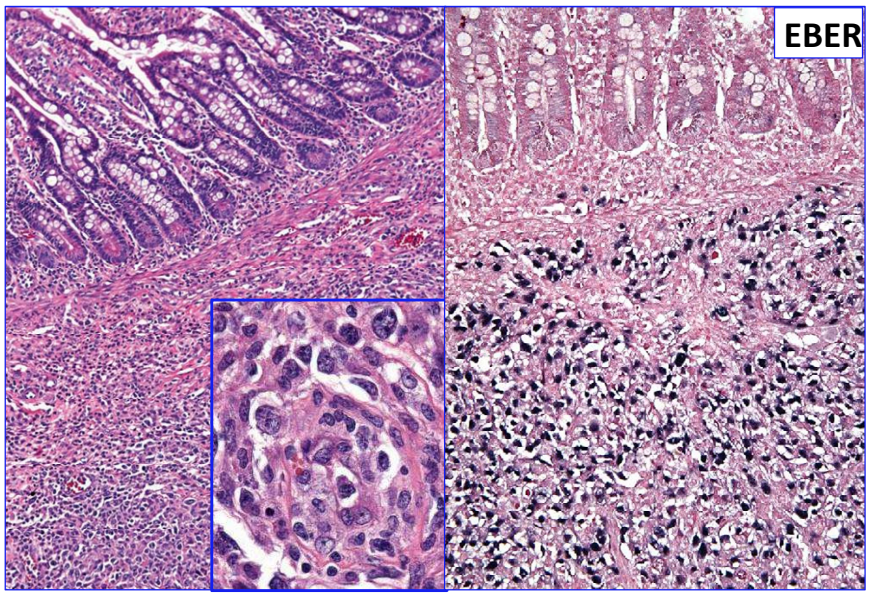
Met 6/8 HLH criteria including fever, splenomegaly, cytopenias, elevated ferritin, elevated soluble IL-2 receptor, hemophagocytosis in the bone marrow



Bone Marrow Findings



Jejunal Perforation

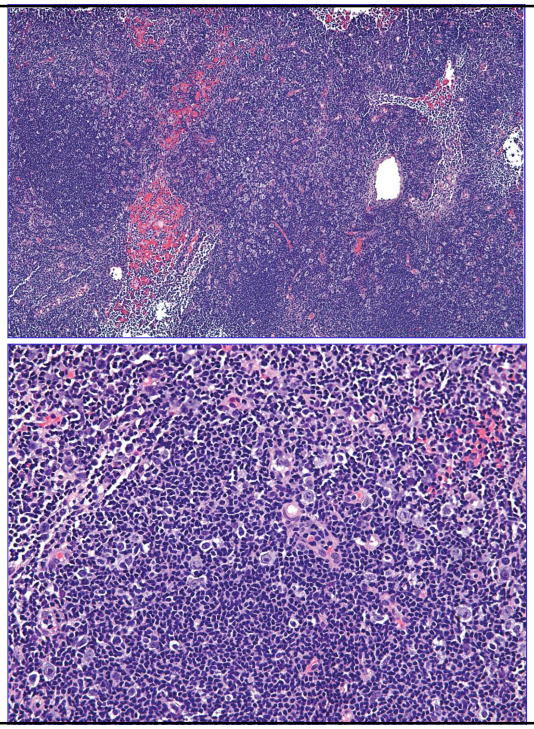


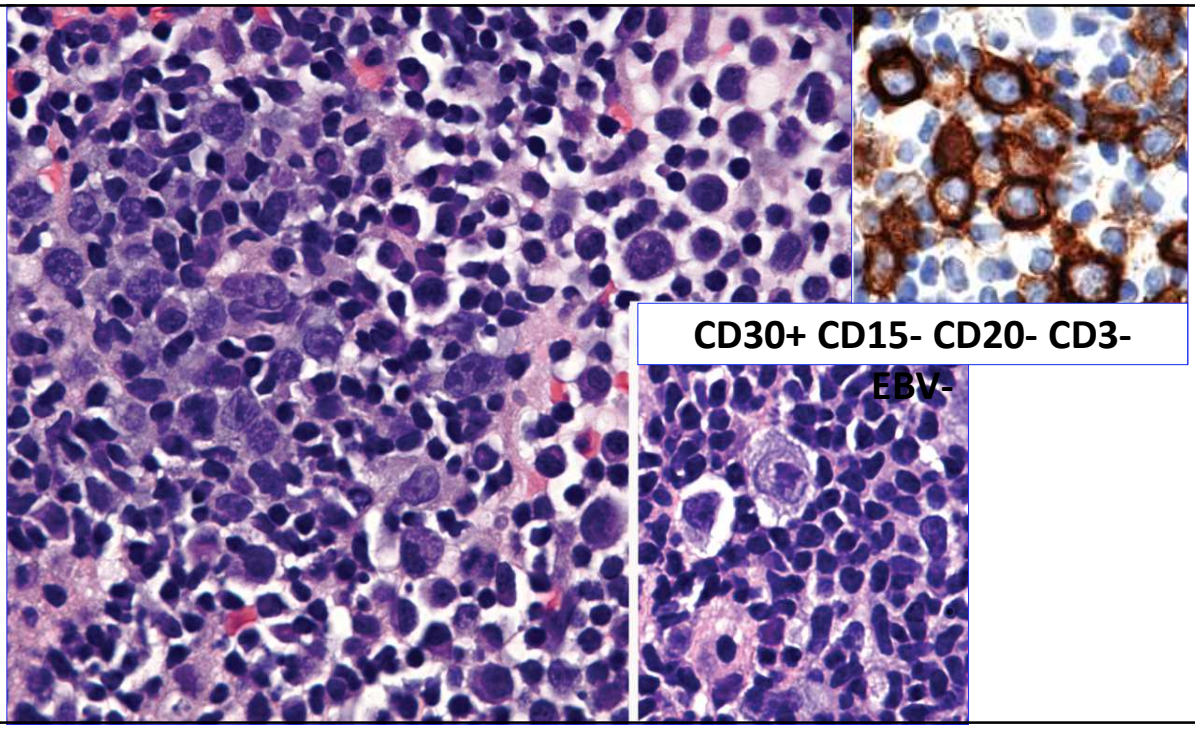
Case 1: Summary

- **EBV+ Diffuse Large B-Cell Lymphoma, complicated by Hemophagocytic Lymphohistiocytosis**
  - Rituximab and etoposide followed by R-CHOP
  - Two months later, septic shock from Klebsiella bacteremia with massive GI bleed, and masses in liver and spleen
  - Exploratory laparotomy showed a perforated jejunum with peritonitis
  - Despite aggressive management, patient expired
- ***Rare*** complication of infectious mononucleosis
  - Defective host immune response to EBV in some populations
    - In-born or acquired immunodeficiency (unknown in this patient)
  - Awareness that IM-like lesions may rarely evolve into aggressive lymphomas
    - Repeat biopsy and workup helpful (although flow and molecular were limited)

Case 2

- 53-year old woman with localized axillary lymphadenopathy
- A needle core biopsy showed partially effaced architecture and prominent paracortical expansion
- Mixed inflammatory infiltrate including eosinophils, histiocytes and plasma cells





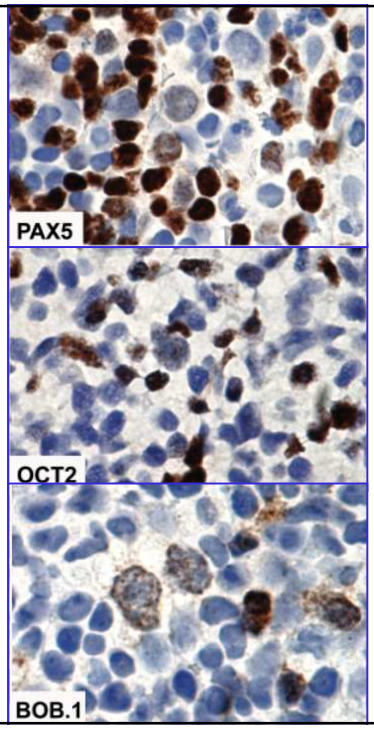
CD30+ CD15- CD20- CD3- EBV-

B-Cell Transcription Factors

- Loss or partial expression of B-cell transcription factors PAX5, OCT2, BOB1
- A diagnosis of Classical Hodgkin Lymphoma was favored

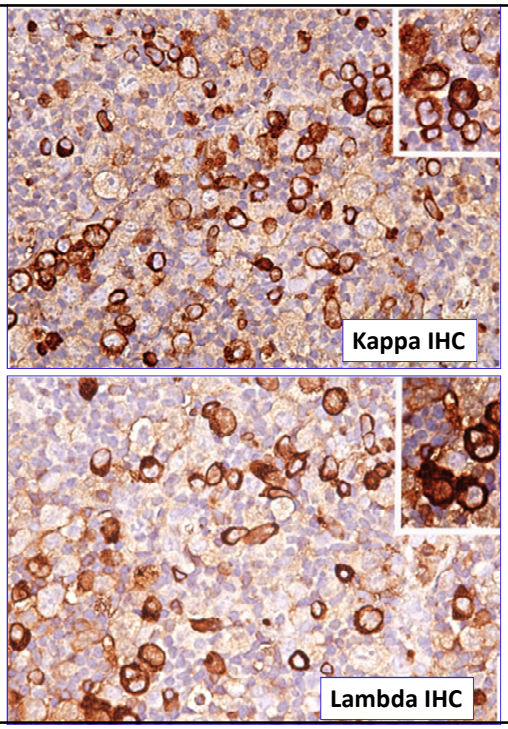
But…

- Patient was asymptomatic with no fever or other constitutional symptoms
- CT scans of chest and abdomen and bone marrow with flow cytometry were negative



Case 2 continued

- One month later, another enlarged axillary lymph node was excised and showed reactive follicular hyperplasia
- Three months later, all lymphadenopathy resolved
- Patient was alive with no evidence of disease at 3-years
- **Dx: Reactive immunoblastic proliferation**



Variable Expression of B-cell Transcription Factors in Reactive Immunoblastic Proliferations

Marker	< 30% Loss	30-70% Partial	> 70% Full
CD45RB	37.5%	25%	37.5%
CD20	39%	16%	45%
CD3	94%	0%	6%
CD30	42.5%	15%	42.5%
CD15	0%	0%	0%
PAX5	55%	15%	30%
OCT2	4%	22%	74%
BOB.1	0%	7%	93%
MUM1/IRF4	0%	10%	90%
EBV/EBER	76%	12%	12%

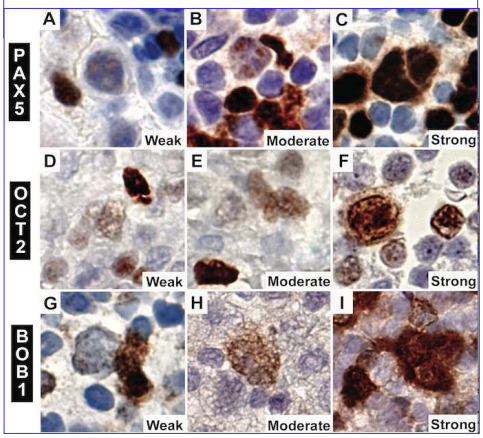
Down regulation

PAX5 in 70%> OCT2 in 26% > BOB.1 in 7%

Loss or partial expression

At least one, 48%

Two or more, 27%

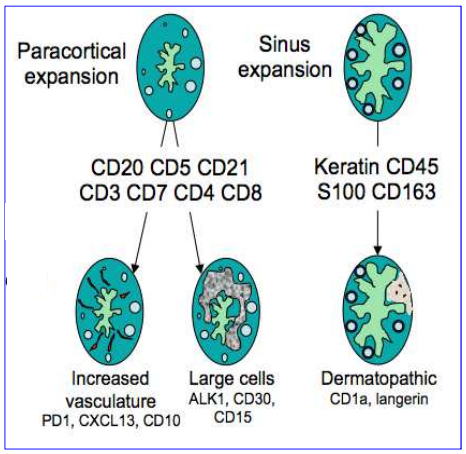


Treetipsati et al, Am J Surg Pathol 2014

Case 2: Summary

- Reactive immunoblastic proliferations can mimic Hodgkin lymphoma
- B-cell transcription factors (PAX5, OCT2, BOB1) are gradually lost as B-cells differentiate toward plasma cells (e.g. immunoblasts)
- Loss/downregulation of tx factors are useful to distinguish classic Hodgkin lymphoma from other B-cell lymphomas, but may be misleading in immunoblastic proliferations
- Multidisciplinary approach, additional biopsies, and a thorough immunophenotypic workup aided in the final diagnosis

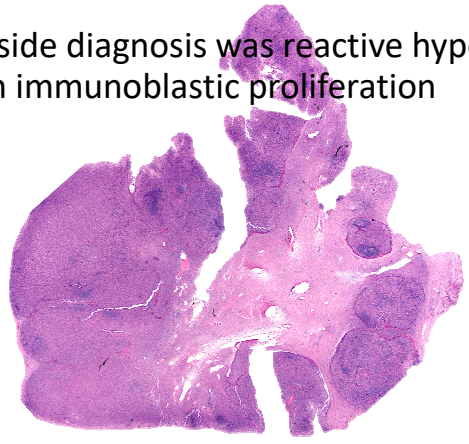
Sinusoidal Proliferation

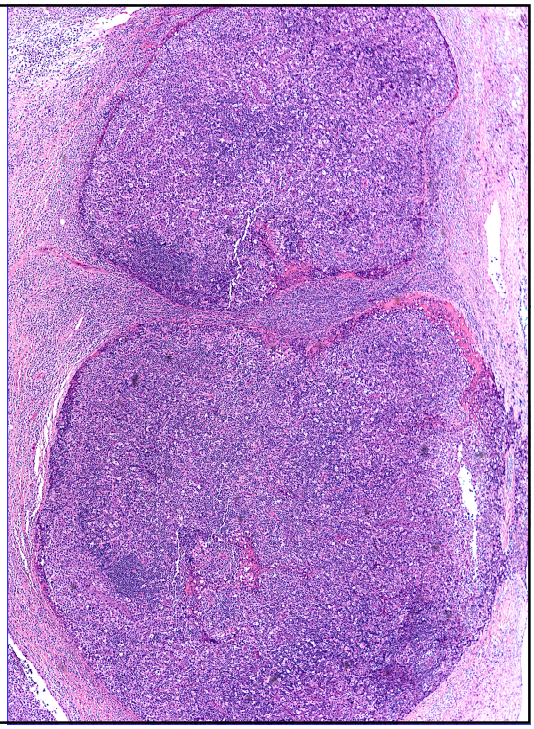


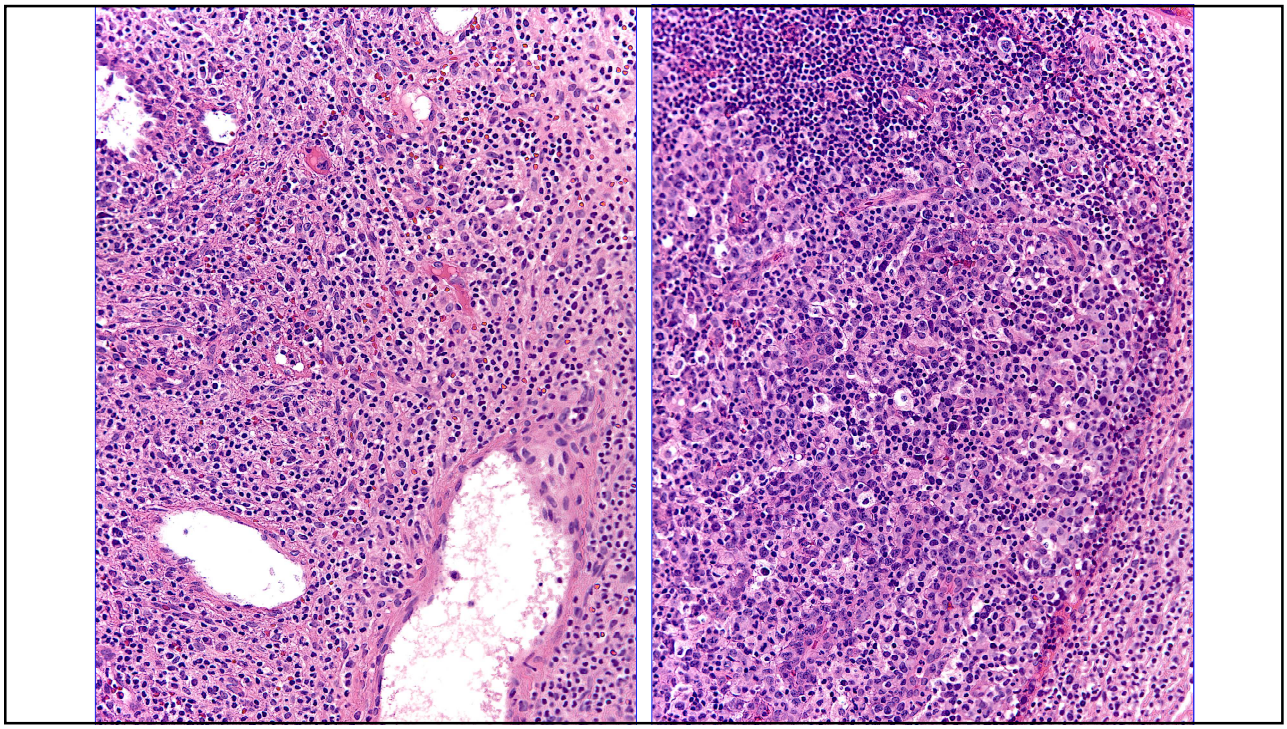
Pattern	Entity/Etiology	Differential Diagnoses
Sinusoidal	**Dermatopathic lymphadenitis Reactive histiocytic proliferations Vascular transformation**	**Histiocytoses: LCH, RDD Anaplastic large cell lymphoma Metastatic carcinoma Metastatic melanoma**

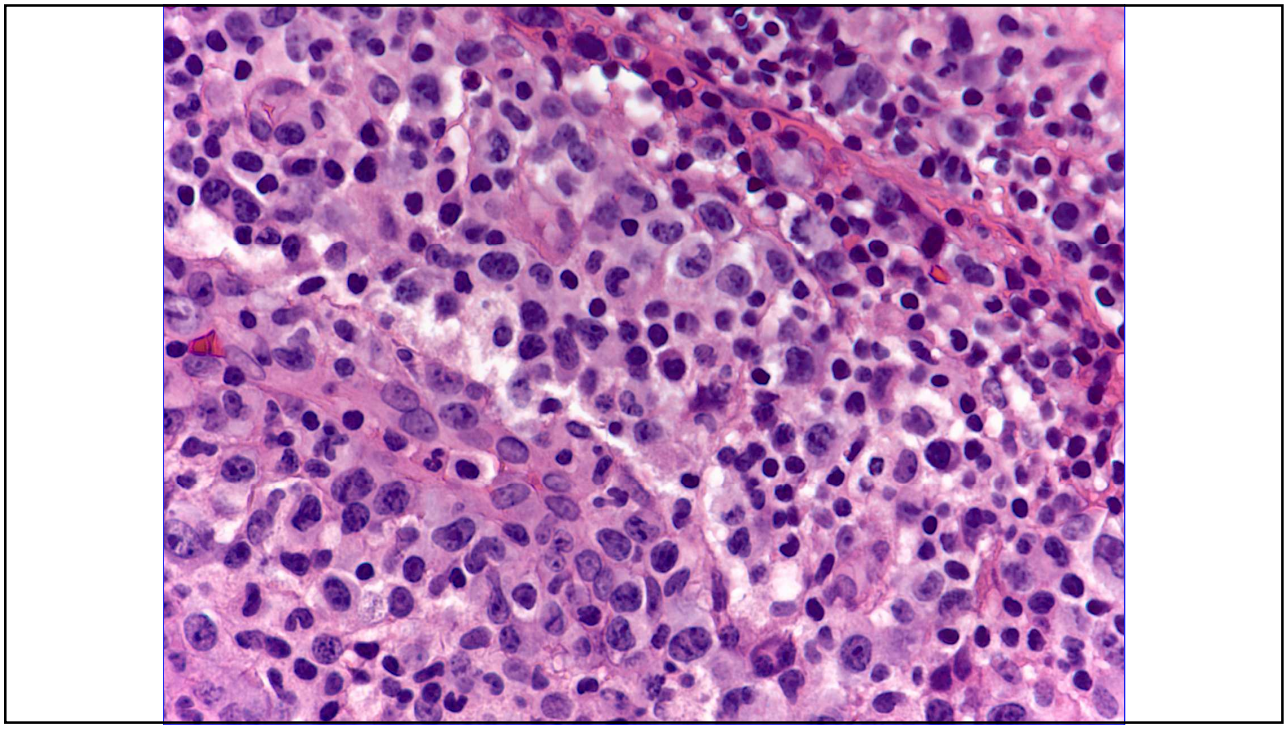
Case 3

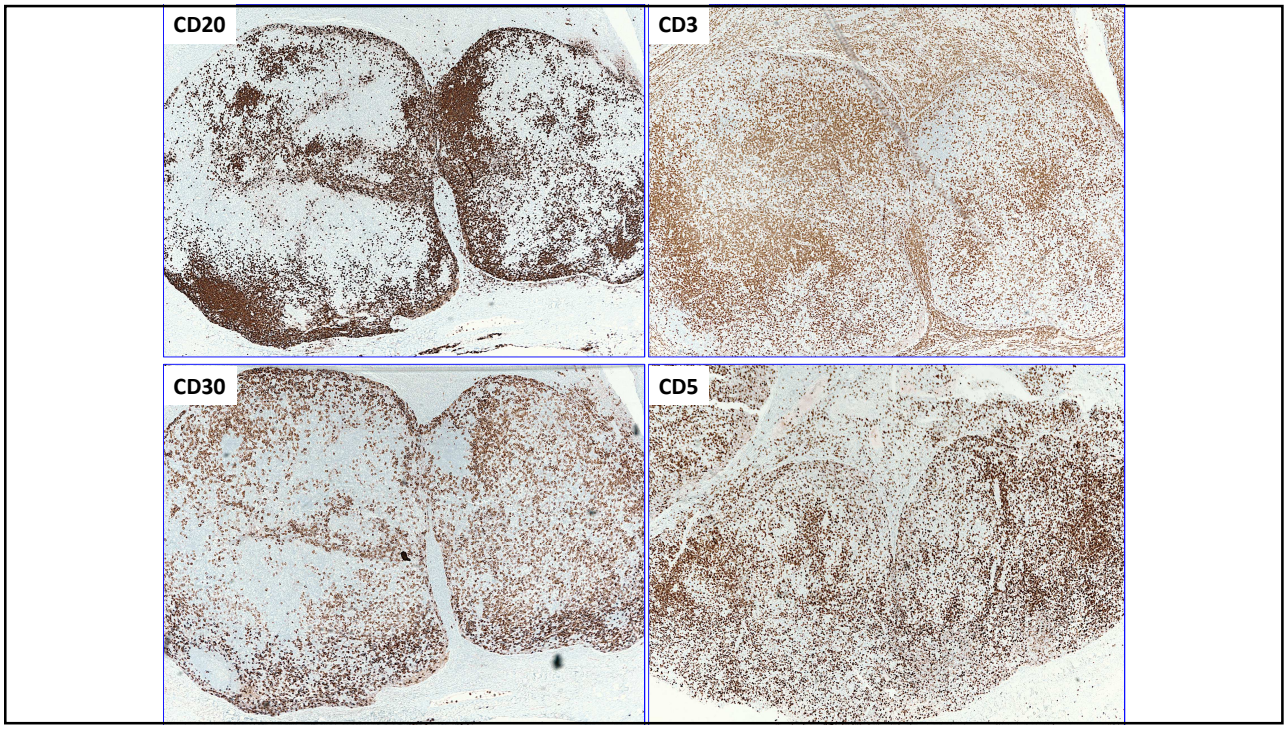
- 17-year-old boy with cervical and retroperitoneal lymphadenopathy
- Right cervical lymph node was excised
- Outside diagnosis was reactive hyperplasia with immunoblastic proliferation

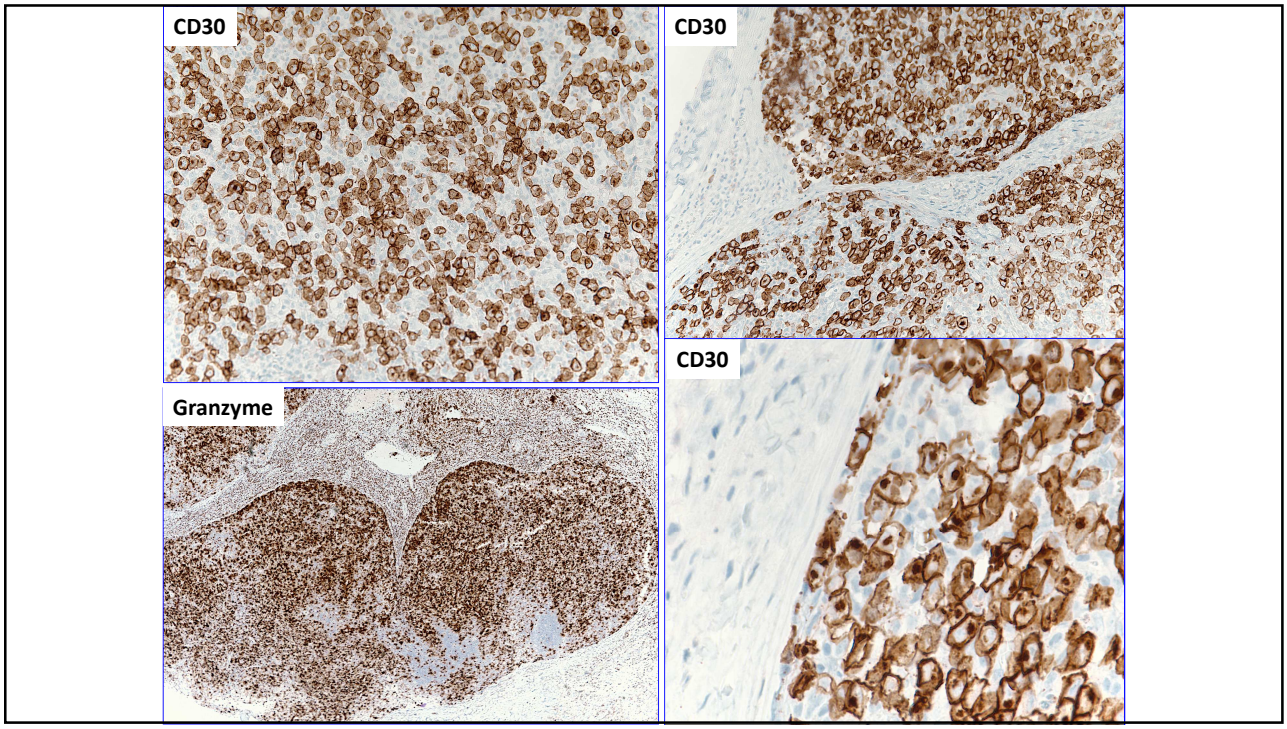




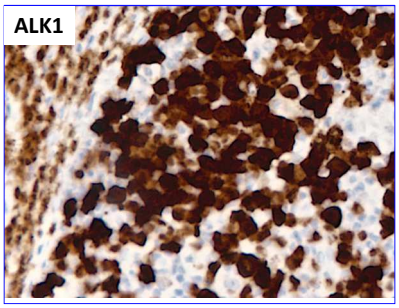


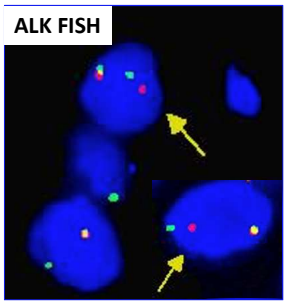



CD20
CD3
CD30
CD5


CD30
CD30
Granzyme
CD30

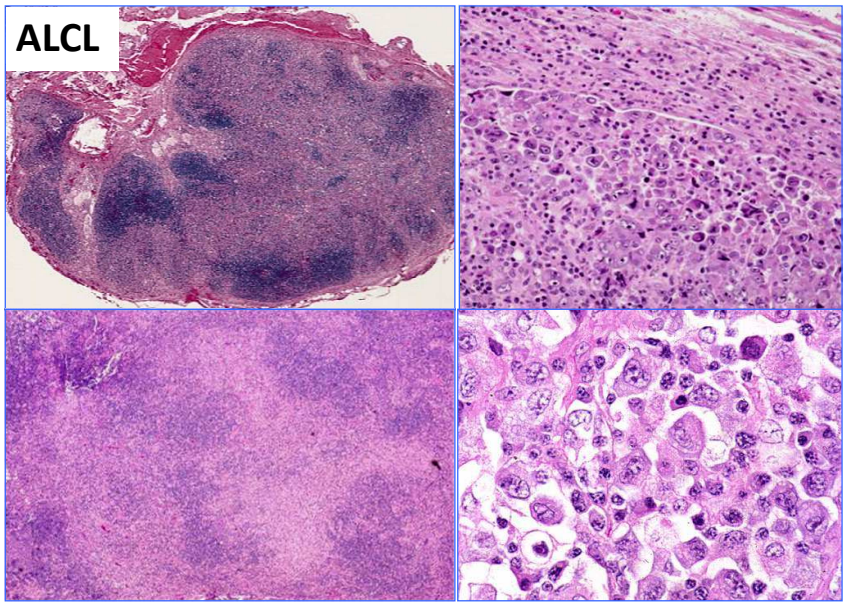
Case 3: Summary

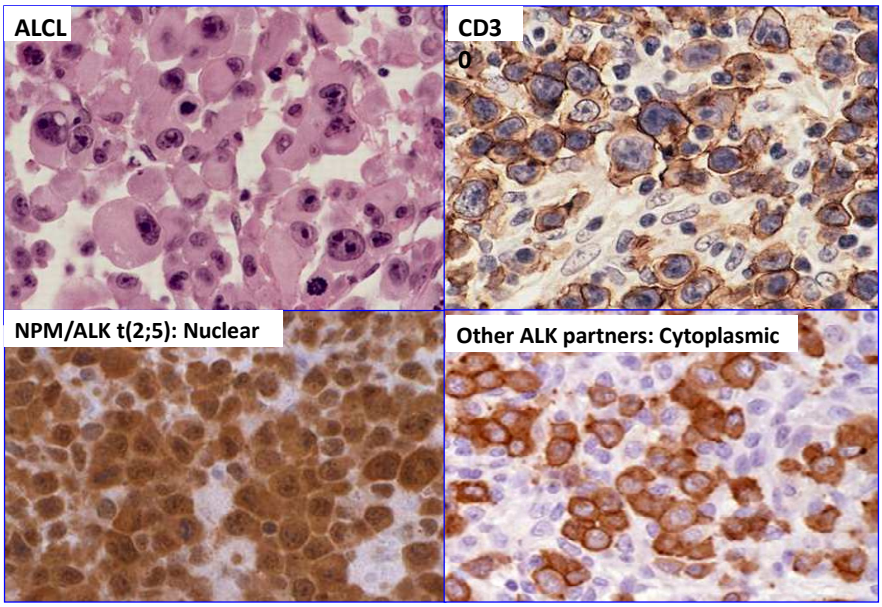




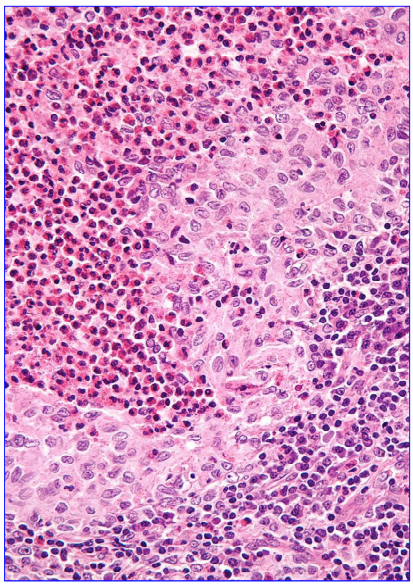
ALK+ Anaplastic Large Cell Lymphoma

- ALCL can occur in nodal and extranodal sites
- Pleomorphic large cells typical; the **small cell variant** can be a diagnostic pitfall
- A sinusoidal growth pattern overlaps with the distribution of histiocytoses and non-hematopoietic tumors such as metastatic carcinoma and melanoma

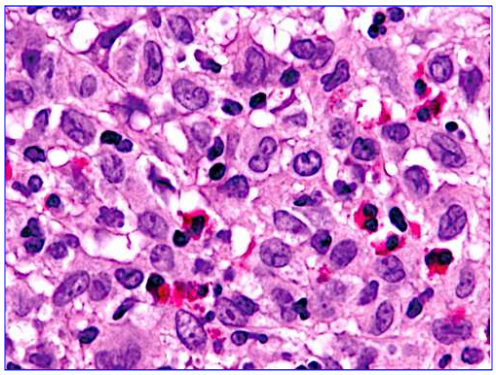


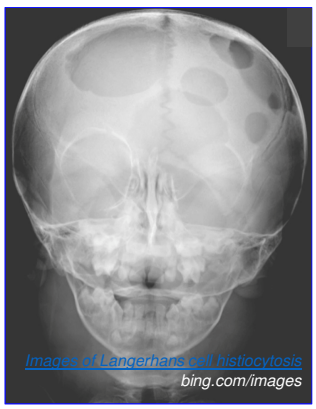


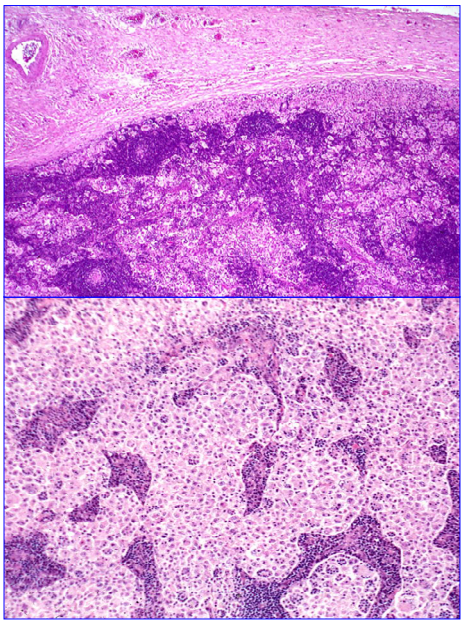
Langerhans Cell Histiocytosis



- Clonal neoplasm derived from myeloid dendritic cells
- CD1a+ CD207/Langerin+ S100+/-
- MAPK pathway gene mutations in > 85%:
  BRAF V600E, MAP2K1

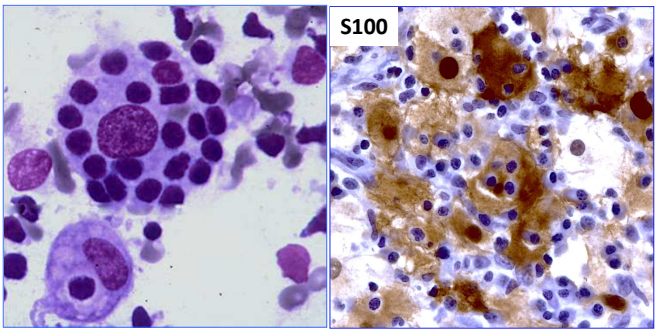






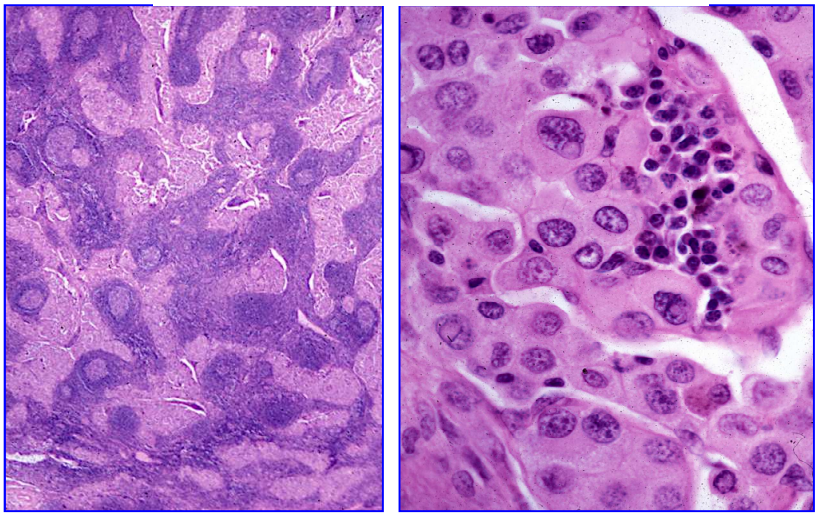
Rosai-Dorfman Disease

- Neoplasm characterized by the accumulation of large histiocytes with emperipolesis
  - S100+ CD163+ Cyclin D1+ OCT2+
- ~50% carry gain-of-function mutations in the MAPK/ERK pathway: *KRAS, NRAS, MAPK21*, *ARAF*, *CSF1R,* and rarely, *BRAF V600E*



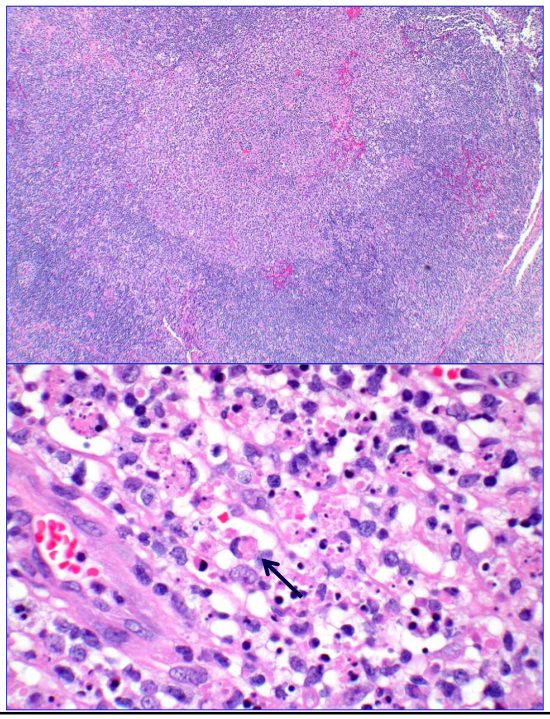
Metastatic Melanoma

S100+ SOX10+



Necrotizing Lymphadenitis

- Kikuchi lymphadenitis/Lupus
  - Necrosis/karyorrhexis without neutrophils
  - Crescent-shapes histiocytes
- Cat scratch lymphadenitis
  - Neutrophilic microabcesses
- Herpes
  - Multinucleated cells
- Caseating granulomas
  - Acid fast organisms
- Malignancy
  - Diffuse large B-cell lymphoma
  - Hodgkin lymphoma



Kikuchi Lymphadinitis

Often misdiagnosed as a T cell lymphoma

- Predominance of T-cells, CD8 > CD4; loss of CD5, CD7, CD2, CD3 in T-cells
- Immunoblasts are mostly T-cells and frequently express CD30; B-cells are usually rare

- Typically presents in head & neck LN of young pts, F>M, fever and night sweats
- Pale areas of necrosis lacking neutrophils
- Histology similar to systemic lupus erythematosus

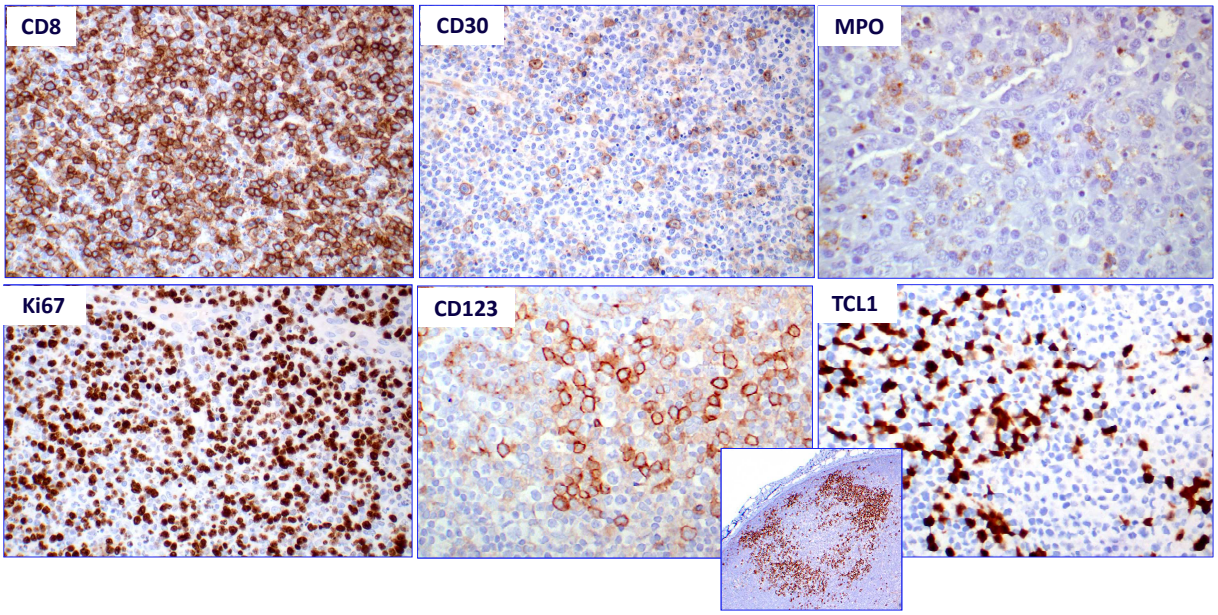
Features specific for SLE:

- Hematoxylin bodies (degenerated nuclear debris)
- Azzopardi phenomenon (degenerated nuclear material in the walls of blood vessels)

Stage	Characteristic Features
Proliferative	• **Early phase** • **Paracortical expansion with immunoblasts** • **Plasmacytoid dendritic cells** • **Histiocytes** • **Karyorrhectic debris**
Necrotic	• **Late phase – a majority present at this stage** • **Paracortical foci of necrosis without neutrophils** • **Crescentic histiocytes: CD163+ MPO+ CD68+** • **Necrotic foci surrounded by CD123+ TCL1+ plasmacytoid dendritic cells**
Xanthomatous	• **Least common and final healing stage** • **Foamy histiocytes** • **Fewer immunoblasts and may lack necrosis**

Wei, et al. "Aberrant Phenotypes in Kikuchi's Disease." International Journal of Clinical and Experimental Pathology 7, no. 9 (2014): 5557.

Kikuchi lymphadenitis: IHC



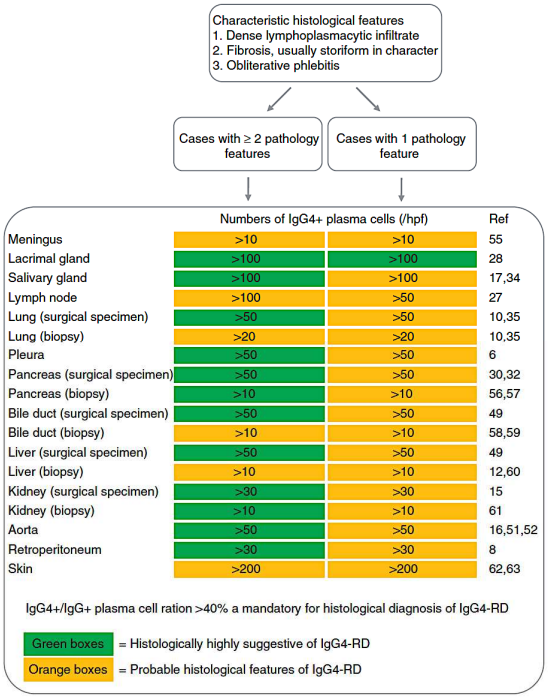
IgG4-Related Disease

- IgG4 is the least common IgG class and shows low affinity binding
  - Protective/blocking antibody in parasitic infections, asthma, allergy, eczema
- Age: middle age to elderly, M>>F
- Site: any site; pancreas, salivary gland, orbit, LN etc
  - Frequent multi-organ involvement
- Symptoms: Typically related to mass lesion; no constitutional sx
- Clinical response:
  - Excellent response to steroids; fibrosis may be less responsive
  - Relapsing/remitting course; high IgG4/IgE/eosinophilia a/w recurrence
  - May have increased risk of malignancy; causal relationship not established

IgG4-RD Diagnostic Criteria

- Diagnosis is based on 3 criteria
  - Lymphoplasmacytic infiltrate with increased IgG4+ plasma cells (>10-200 IgG4+ cells/HPF; IgG4/IgG >40%)
  - Typical extranodal sites and serum IgG4 $\geq$ 135 mg/dL
  - Characteristic histologic features
- If <3, render a descriptive diagnosis
- If only LN or other unusual sites
  - Classic laboratory findings required
  - Follow-up to see if definitive sites become involved
- Assess other organ involvement by radiology/pathology

Cheuk & Chan, AJSP 2008
Despande et al, Mod Path 2012
Bledsoe et al AJSP 2020

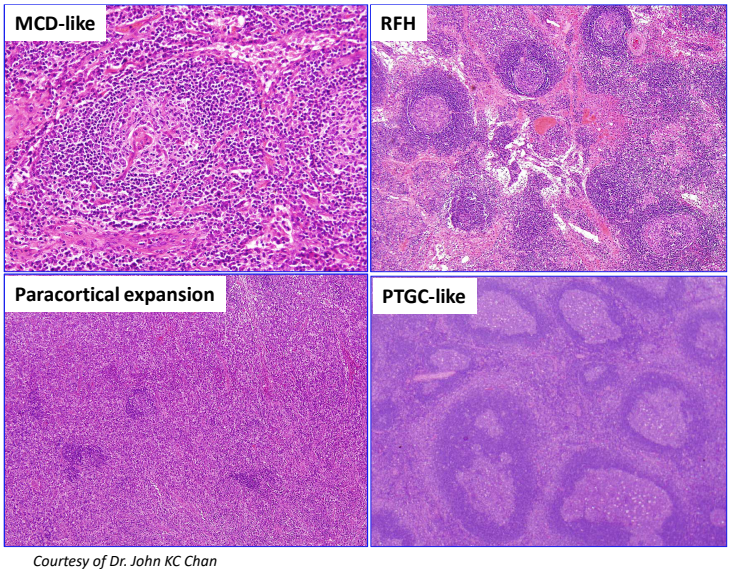


	Numbers of IgG4+ plasma cells (/hpf)		Ref
Meningus	>10	>10	55
Lacrimal gland	>100	>100	28
Salivary gland	>100	>100	17,34
Lymph node	>100	>50	27
Lung (surgical specimen)	>50	>50	10,35
Lung (biopsy)	>20	>20	10,35
Pleura	>50	>50	6
Pancreas (surgical specimen)	>50	>50	30,32
Pancreas (biopsy)	>10	>10	56,57
Bile duct (surgical specimen)	>50	>50	49
Bile duct (biopsy)	>10	>10	58,59
Liver (surgical specimen)	>50	>50	49
Liver (biopsy)	>10	>10	12,60
Kidney (surgical specimen)	>30	>30	15
Kidney (biopsy)	>10	>10	61
Aorta	>50	>50	16,51,52
Retroperitoneum	>30	>30	8
Skin	>200	>200	62,63

IgG4+/IgG+ plasma cell ration >40% a mandatory for histological diagnosis of IgG4-RD

Green boxes = Histologically highly suggestive of IgG4-RD
Orange boxes = Probable histological features of IgG4-RD

Types of IgG4-Related Disease



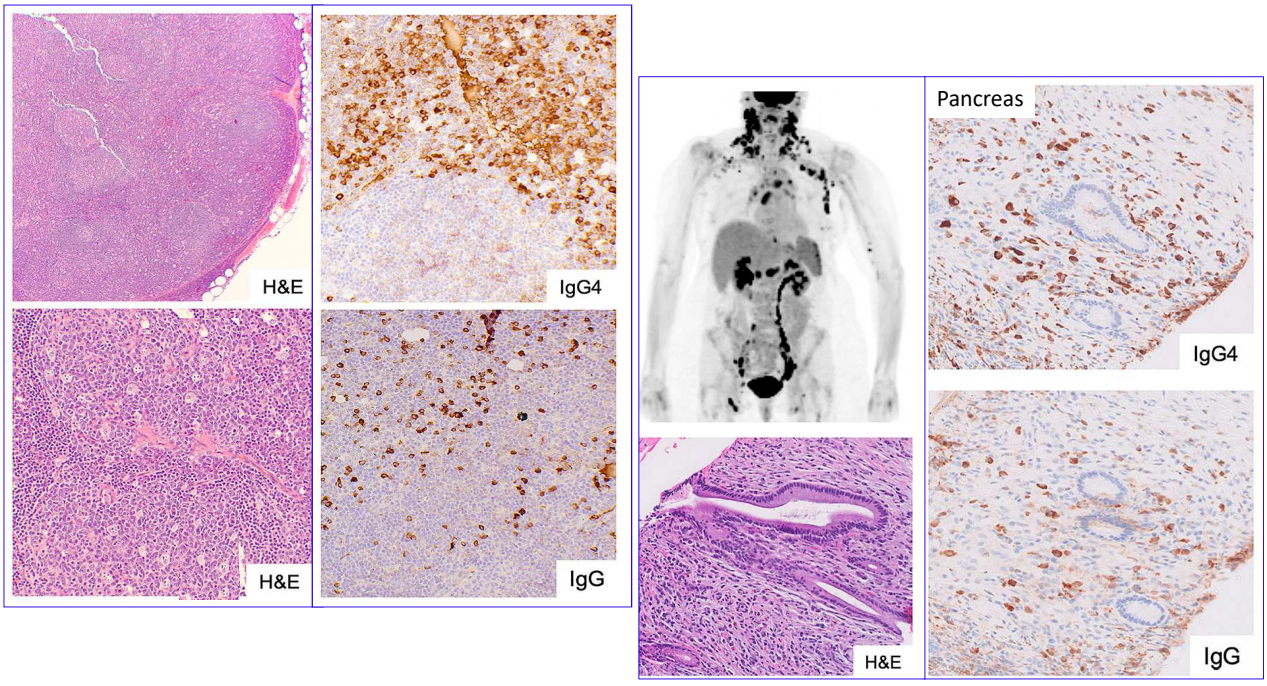
Courtesy of Dr. John KC Chan

- Type I: MCD-like
- Type II: RFH
- Type III: Paracortical
- Type IV: PTGC-like
- Type V: IPT-like
- Other types also described

- IgG4+ cells can be increased in many other conditions
  - Allergy, parasitic infestation
  - Rheumatoid arthritis
  - Rosai-Dorfman disease
  - Wegener granulomatosis
  - Syphilis
  - Hyper-IL6 syndrome
  - Inflammatory component around cancer
  - NLPHL, EMZL
- Increased IgG4+ plasma cells in tissue is ***NOT*** sufficient for a diagnosis of IgG4-related disease

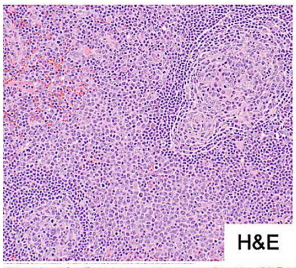
Case 4

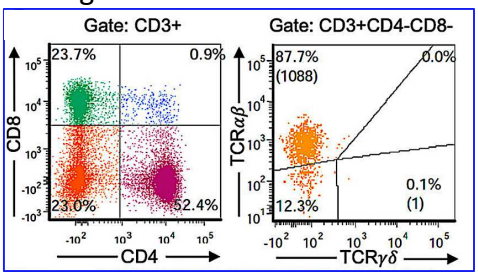
- 63-year-old woman with left axillary lymphadenopathy
- At 54y: Peripheral T-cell lymphoma, stage IIIA; CHOP + auto-SCT
- At 59y: Invasive ductal carcinoma stage IA (pT1bN0); lumpectomy + adjuvant chemo
- At 60y: Bilateral cervical lymphadenopathy with a waxing and waning course
- At 61 years: Excisional bx of a right cervical LN showed IgG4-related disease
- At 63y: PET showed extensive hypermetabolic adenopathy above and below the diaphragm, along with PET avid lesions in the pancreas and spleen, concerning for recurrent lymphoma
  - FNA/core biopsy of pancreas: Increased IgG4+ cells (>25/HPF) ; IgG4:IgG ratio >50%)
  - Serum IgG4 and IgE markedly elevated
  - Excisional biopsy of the axillary lymph node was performed

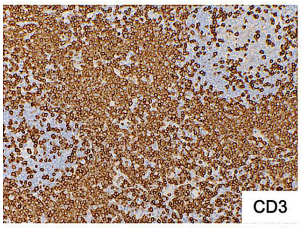


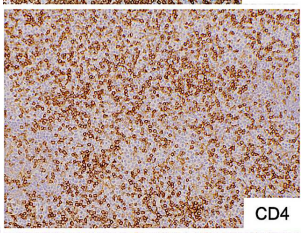
Brar et al Haematologica 2022

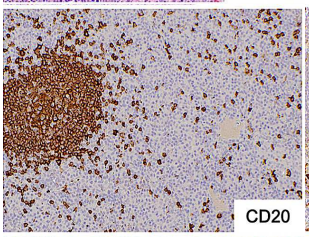
- Workup on 2nd LN
  - Flow cytometry showed an increase in αβ+DNT
  - Immunohistochemistry showed paracortical expansion of T-cells surrounding reactive germinal centers

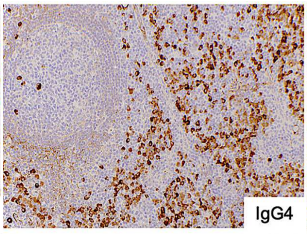


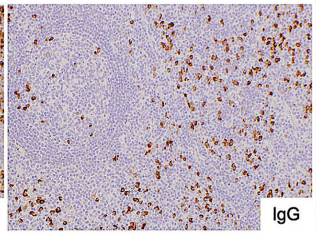


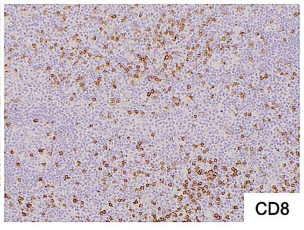












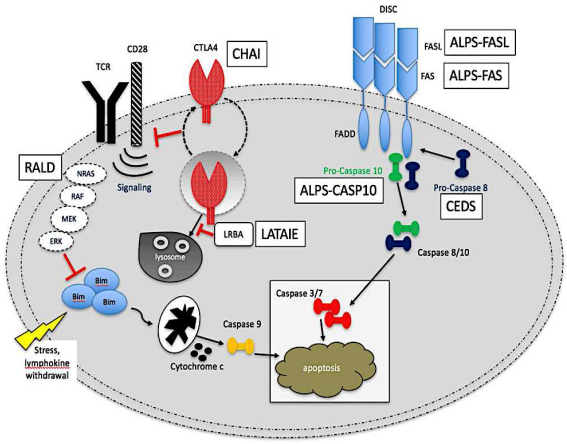
Brar et al Haematologica 2022

Case 4: Summary

- PB flow cytometry confirmed an increase in circulating αβ+DNT cells
- Elevated soluble FAS ligand (824 pg/mL) and vit B12 (>1,000 pg/mL)
- Negative for TCR β and γ rearrangements
- Pathogenic *FAS* c.841T>A (p.W281R), VAF 56% c/w germline mutation
- Patient apparently had lymphadenopathy since the age of six (!)

Autoimmune Lymphoproliferative Syndrome

- Rare genetic disorder of defective lymphocyte apoptosis leading to accumulation of CD4/CD8 double-negative αβ-T cells
- Chronic lymphadenopathy, hepatomegaly, splenomegaly, autoimmune cytopenias
- Increased risk of malignancy incl. lymphoma
  - Deficient *FAS*-dependent T-cell immune surveillance and *FAS*-deficient GC B-cells
- Germline or somatic defects in the FAS-mediated apoptosis pathway
  - *FAS* (85%, high proportion germline), *FASL, CASP10, CASP8, FADD*
  - **Typically diagnosed in early childhood; some are asymptomatic and can present in adulthood**



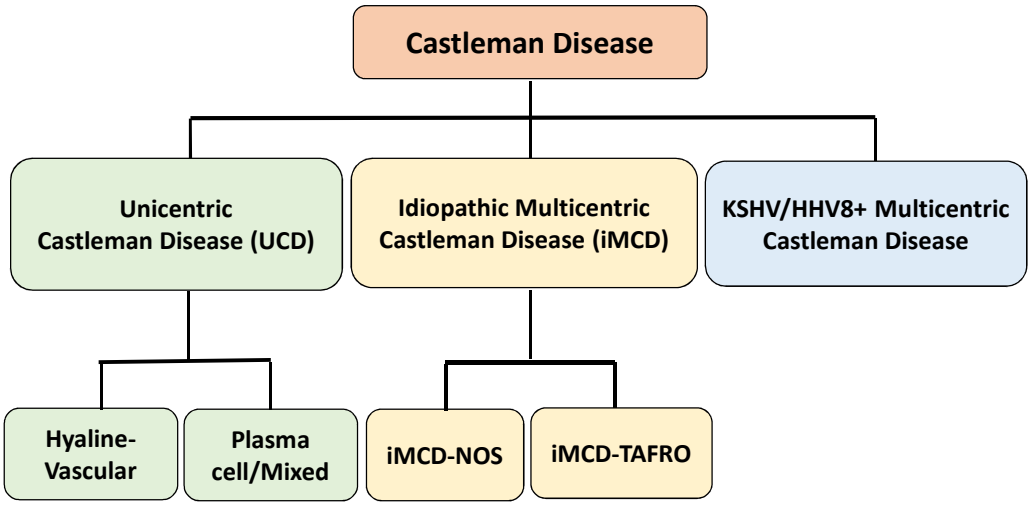
Bride K and Teachey D. Autoimmune lymphoproliferative syndrome: more than a FAScinating disease. F1000Research 2017, 6:1928; Updated 2022

ALPS: Differential Diagnoses and Pitfalls

- Lymphoid follicles with PTGC-like or Castleman-like changes and plasmacytosis may mask ALPS-related histology
- Rosai-Dorfman disease in ~25%
- IgG4-related disease in ~20%
- ALPS can mimic T- cell lymphoma
  - Atypical T-cell infiltrate with aberrant immunophenotypes
  - High proliferative index associated with atypical T-cell infiltrates
  - Can involve extranodal sites and the bone marrow
  - Detection of *FAS, FASLG, CASP8, FADD* or *CASP10* mutations and lack of *TCR* gene rearrangements are confirmatory for ALPS (these mutations can be seen in lymphomas as well)

Price et al, Blood 2014
Maric I, et al, AJSP 2005
van de Ven AAJM et al, Clin Immunol 2017
Raine JI et al, Histopathology 2022

Classification of Castleman Disease



Unicentric Castleman (UCD)

- 50-70% of CD
- Single LN or single group of LNs
- 4th decade, F>M
- Majority asymptomatic
- Complete surgical excision

Hyaline-Vascular

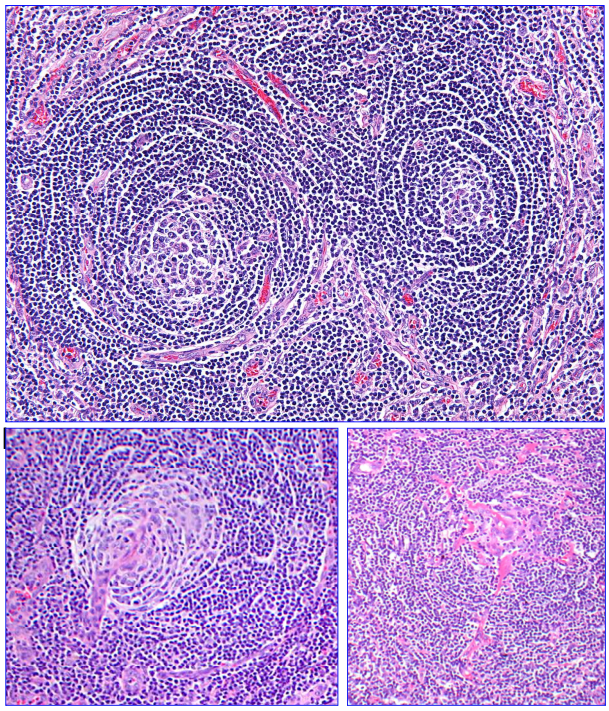
- 70-80% of UCD
- Clonal neoplasm of stromal FDC
- Regressed follicles
- Prominent stromal fibrosis
- Prominent HEV
- Few polytypic plasma cells
- *PDGFRB* mutations
- 5% autoimmune/paraneoplast sx
- Rare FDC dysplasia or sarcomas
- Compression sx – radiation

Plasma Cell/Mixed

- 20-30% of UCD
- Pathogenesis unknown
- Preserved LN architecture
- Interfollicular plasmacytosis
- Regressed or hyperplastic follicles; may have prominent vessels
- Cytokine dysregulation (IL-6) with systemic inflammatory sx – anti-IL6 or immchemotherapy

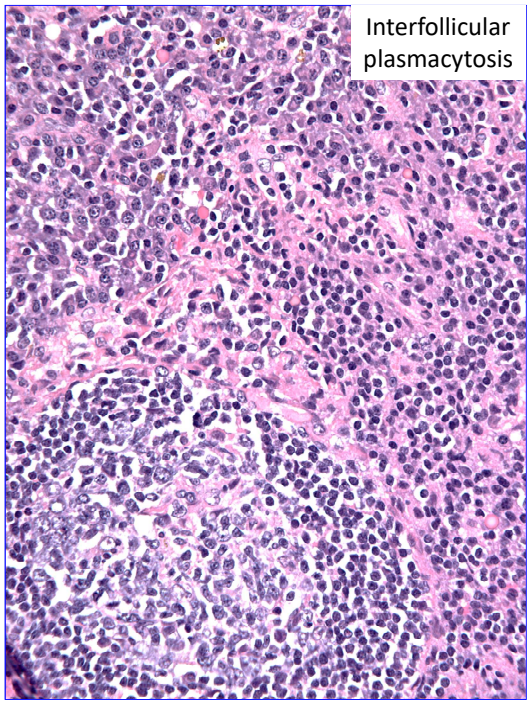
Unicentric Castleman Disease, Hyaline-Vascular Type

- Regressed follicles with onion skinning of mantle zones and vessels penetrating GCs
- Dysplastic follicular dendritic cells
- Follicles with multiple GCs ("twinning")
- Clusters of CD123+ plasmacytoid dendritic cel
- Increased TdT+ cells
- ***PDGFRB*** mutations
- Occasionally harbor KSHV/HHV8



Unicentric Castleman Disease, Plasma Cell Type

- Follicles vary from atrophic to hyperplastic
- Interfollicular sheets of plasma cells, often lambda monotypic (Ig polytypic by PCR)
- Increased TdT+ cells
- Most patients are asymptomatic; subset with inflammatory syndrome
- Lab findings: cytopenias, hypoalbuminemia, polyclonal hypergamma globulinemia, elevated CRP and/or IL6
- Can be associated with POEMS syndrome
  - Polyneuropathy, organomegaly, endocrinopathy/edema, monoclonal proteins, skin changes



Idiopathic Multicentric Castleman Disease (iMCD)

- Clinical, histologic, lab criteria necessary for diagnosis
- Enlarged LN in ≥ 2 LN stations
- Median 50y M:F 1:1
- >80% present with systemic inflammation and organ dysfunction
- Elevated cytokines (IL6, IL2R, VEGF)
- Firstline anti-IL6 therapy, followed by steroid, immune modulators, chemo, IVIG, thalidomide

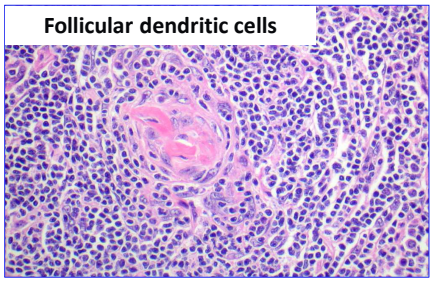
iMCD-NOS

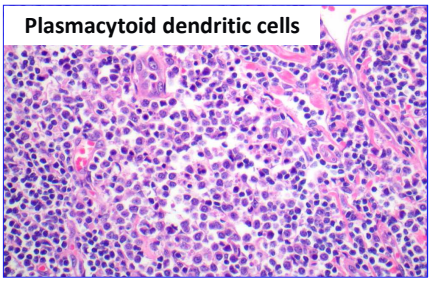
- Do not meet all 5 TAFRO criteria
- Thrombocytosis common
- Five histologic criteria (scored based on degree):
  - Regressed follicles
  - Prominence of FDC
  - Vascularity
  - Hyperplastic follicles
  - Plasmacytosis
- BM may have increased plasmacytosis, MK hyperplasia

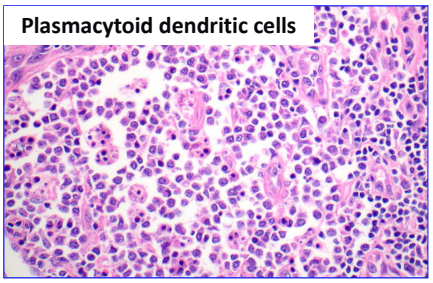
iMCD-TAFRO

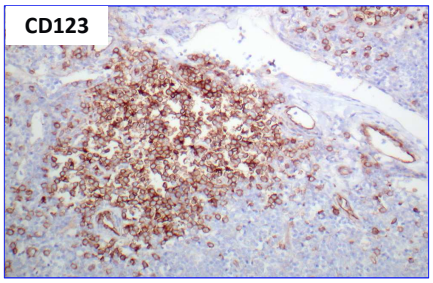
- All 5 criteria required for diagnosis:
  - **T**hrombocytopenia
  - **A**nasarca (fluid overload, effusions, edema)
  - **F**ever/systemic inflammation
  - **R**enal dysfunction/BM reticulin fibrosis
  - **O**rganomegaly (hepatosplenomegaly)
- BM hypercellularity, MK hyperplasia/clustering
- Remit/relapsing or progressive disease; may be fatal

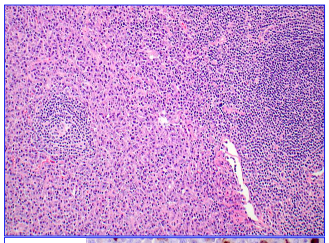
Idiopathic Multicentric CD (iMCD)

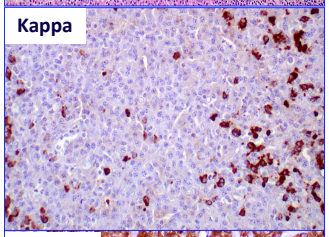


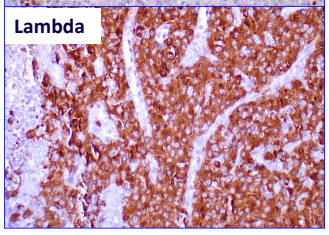








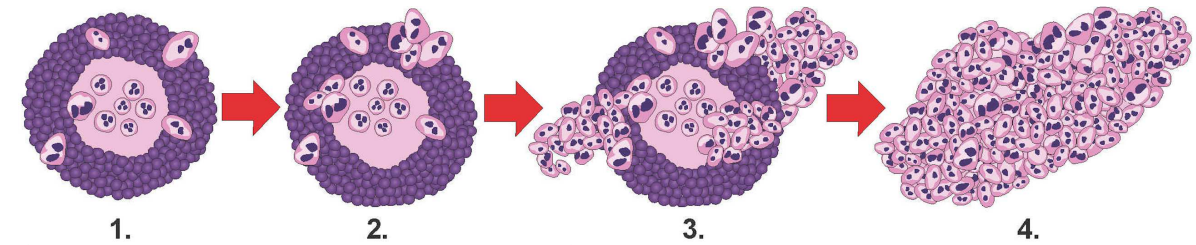




KSHV/HHV8+ Multicentric Castleman Disease

Clinical	Median age ~40, M>>F Generalized lymphadenopathy, splenomegaly, systemic inflammation, lung, GI, autoimmune hemolytic anemia, HLH "Flares" correlate with HHV8 viral load & cytokine levels (IL6, IL10, vIL6)
Histology	Abnormal follicles Plasmablasts predominantly in mantle zones forming clusters and aggregates Interfollicular plasma cell hyperplasia (polytypic) Foci of Kaposi sarcoma may be seen
IHC	B-cell antigens +/- CD20- IgM/lambda + MUM1+ Blimp1+ CD138-
Clonality	Polyclonal
HHV8	Positive
EBV	Negative
HIV	Majority positive (80%)
Prognosis	Remitting/relapsing course with increased risk of lymphoma Overall survival ~2 years; improved survival with ART + Rituximab

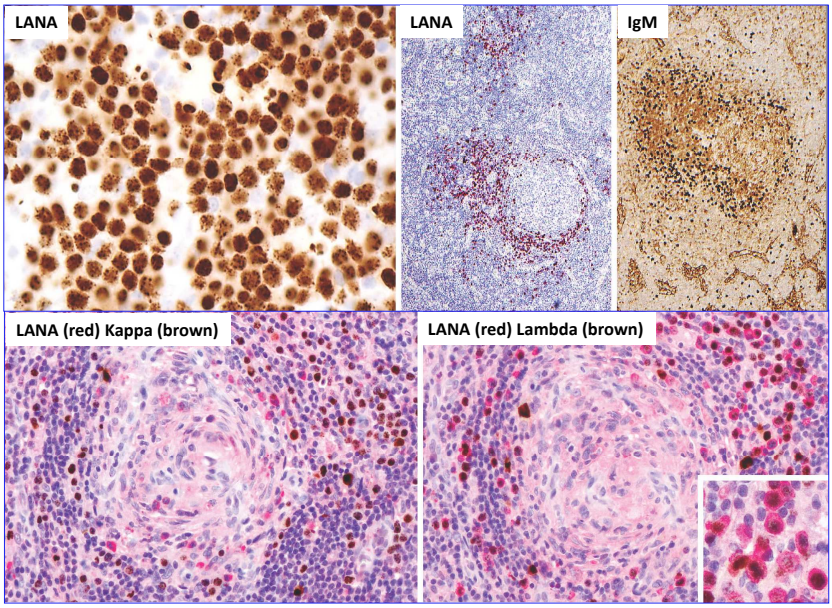
Plasmablasts in KSHV/HHV8+ MCD



1.	2.	3.	4.
Individual plasmablasts	**Small clusters of intraperifollicular plasmablasts**	**Large aggregates of plasmablasts growing independently of follicles**	**Frank large B-cell lymphoma**

Courtesy of Dr. John Goodlad
Chadburn et al. AJCP 2017

KSHV/HHV8+ MCD



Chadburn et al. AJCP 2017

Castleman Disease: Differential Diagnosis

- **HIV lymphadenitis**
  - Changes that mimic hyaline-vascular Castleman occur late in HIV
    - Plasmacytoid dendritic cell clusters are also seen in HIV lymphadenopathy
  - Increased HHV8+ plasmablasts can be seen in HIV+ patients
- **Follicular dendritic cell sarcoma**
  - Dysplastic FDC are seen in Castleman disease
  - Aggregates of FDCs and frank FDC sarcoma can arise in UCD
- **IgG4-related lymphadenopathy**
  - May mimic plasma cell variant of Castleman disease
  - Fever uncommon in IgG4-RD
  - Associated with pancreatitis, cholangitis, sialadenitis, etc.
  - Castleman may exhibit IgG4/IgG > 40% and elevated serum IgG4
    - MCD typically presents with hepatosplenomegaly, fever, night sweats
    - MCD may be HHV8+ and IgM/lambda monotypic

Castleman Disease: Differential Diagnosis

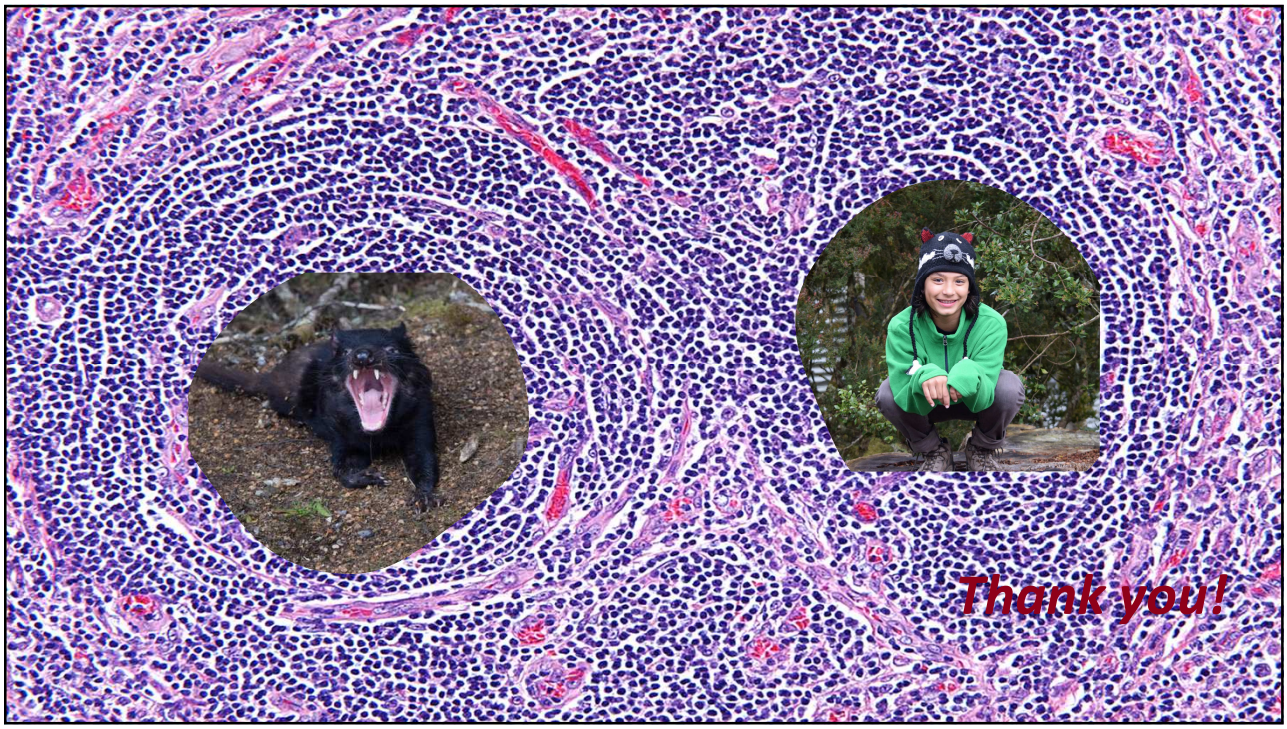
- **B-cell lymphoma**
  - B cell lymphomas may show prominent Castleman-like features
  - Lymphocyte variant hyaline vascular Castleman has expanded mantle zones that may mimic marginal zone or mantle lymphoma
  - Follicles with few tangible body macrophages may mimic follicular lymphoma

- **Angioimmunoblastic T-cell lymphoma**
  - AITL may have atrophic follicles
  - The proliferation of HEV in AITL may mimic Castleman disease
  - AITL has atypical T-cells with a TFH phenotype (CD10, BCL6, PD1)

Take-Home Points

- Clinical context, anatomic site, and disease presentation provide valuable information – using a methodical approach avoids misses
- Fibrosis, inflammation, and necrosis may mask tumor cells (e.g. mediastinum
- FNA/CNB with flow: excellent 1st choice for R/O lymphoma; broader IHC panels may be needed; seek additional sampling if initial biopsy is inconclusive
- Everything that is large and CD30-positive is not Hodgkin lymphoma
- Correlate flow and molecular data with histology and immunophenotype
- A multidisciplinary approach ensures a sound diagnosis

Acknowledgements: Drs. Roger Warnke & Brent Tan


Thank you!