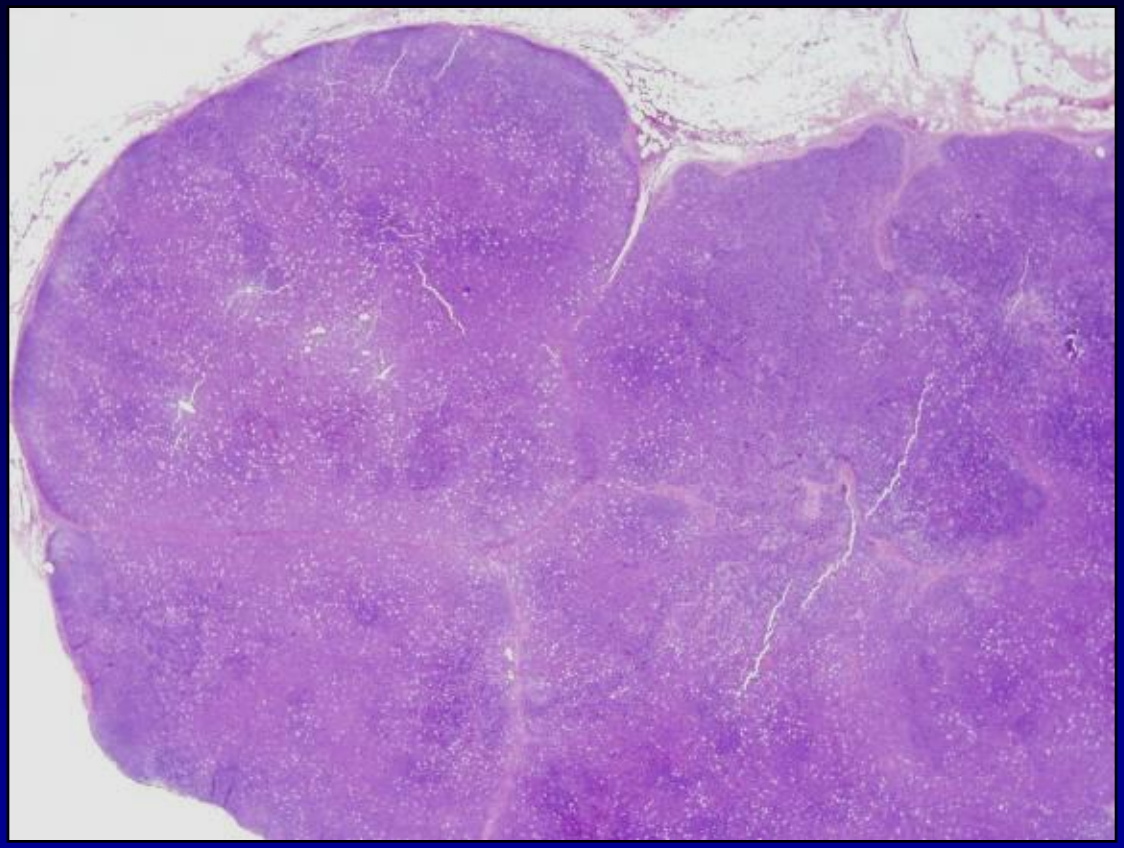
Mimics of Lymphoma



L. Jeffrey Medeiros

MD Anderson Cancer Center

Mimics of Lymphoma

Outline

Progressive transformation of GCs

Infectious mononucleosis

Kikuchi-Fujimoto disease

Castleman disease

Metastatic seminoma

Metastatic nasopharyngeal carcinoma

Thymoma

Myeloid sarcoma

Progressive Transformation of Germinal Centers (GC)

Clinical Features

Occurs in 3-5% of lymph nodes

Any age: 15-30 years old most common

Usually localized

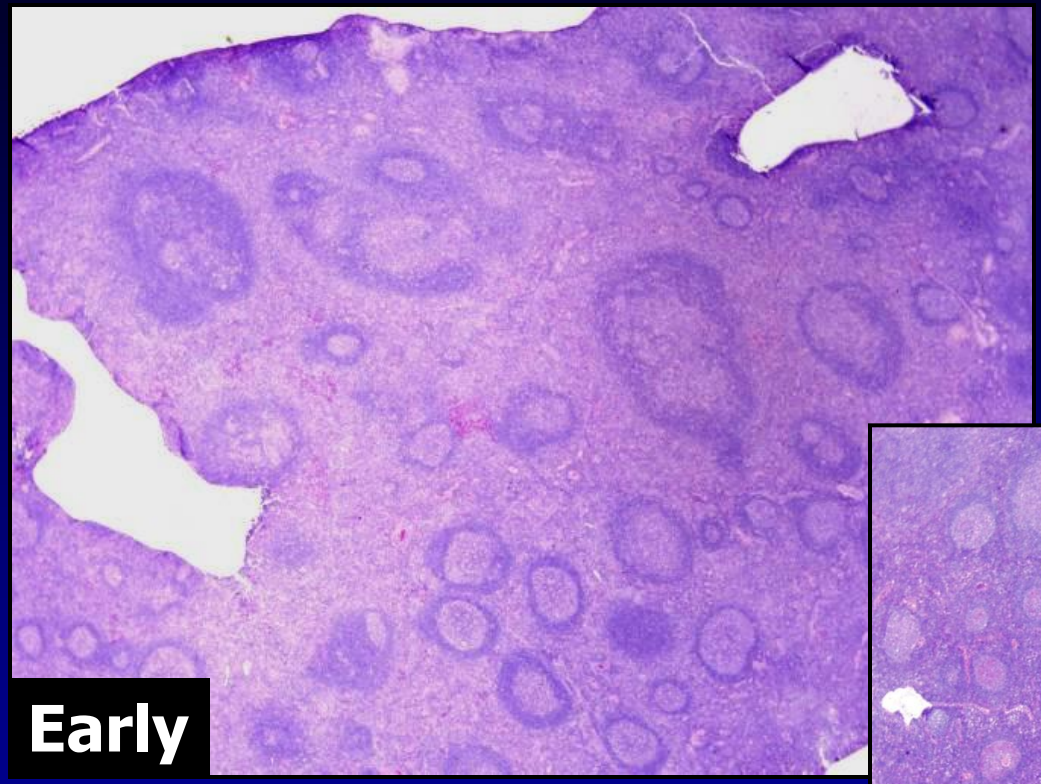
Cervical LNs # 1

Uncommonly patients can present with generalized lymphadenopathy involved by PTGC

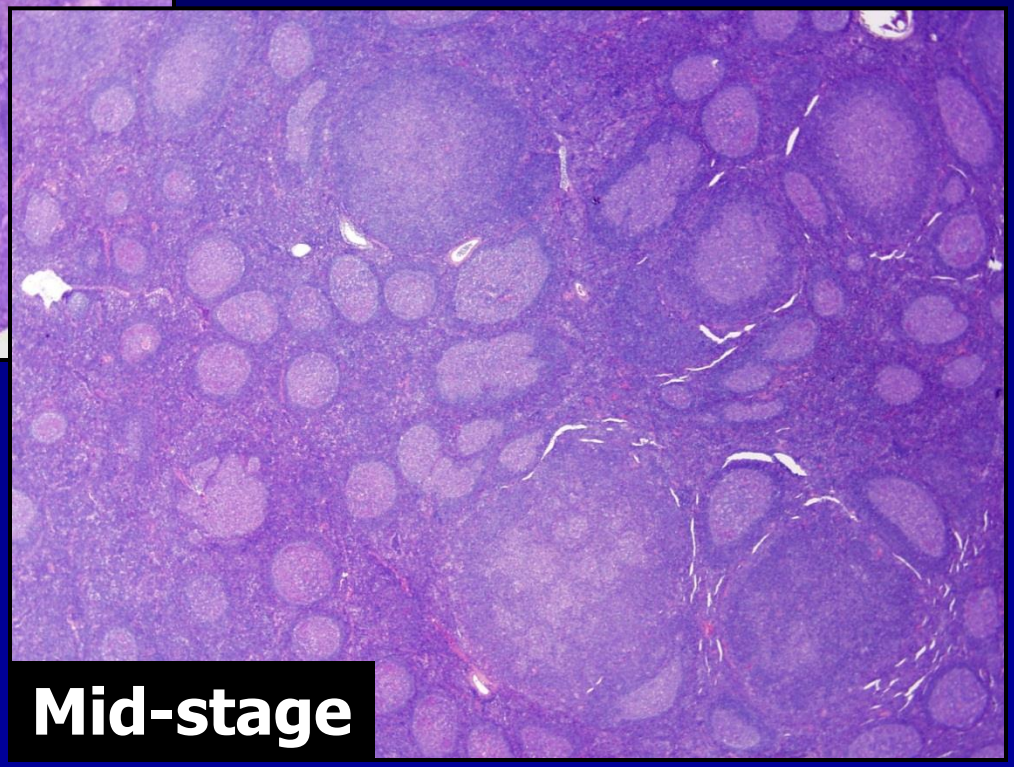
Fever and other signs suggest viral etiology

Progressive Transformation of GCs

Different Stages



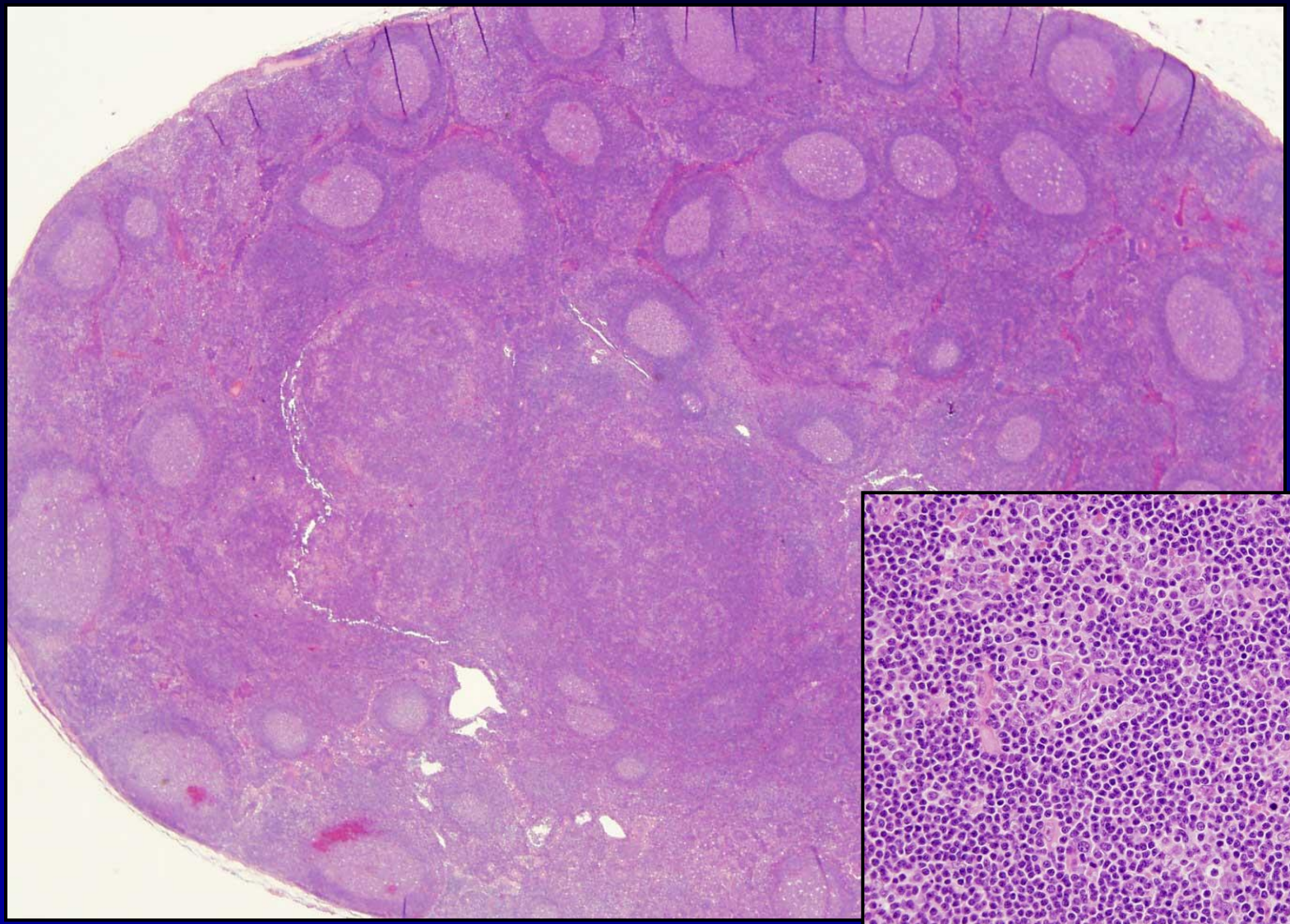
Early



Mid-stage

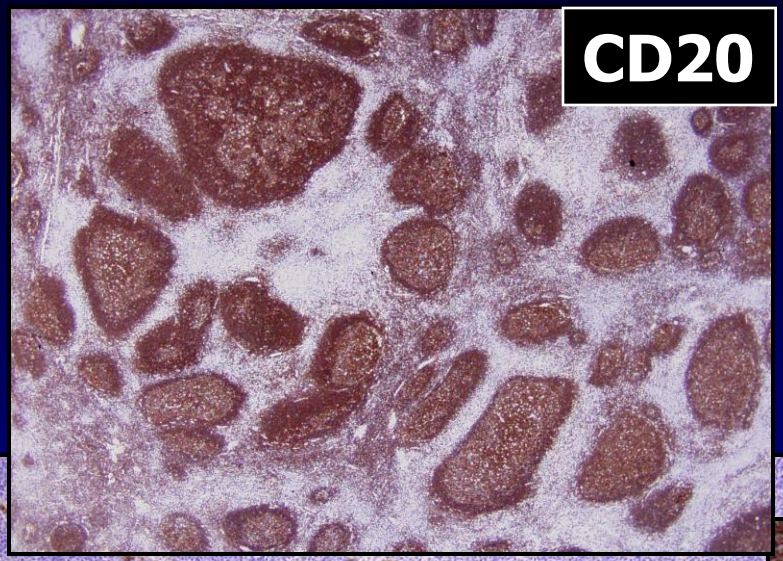
Progressive Transformation of GCs

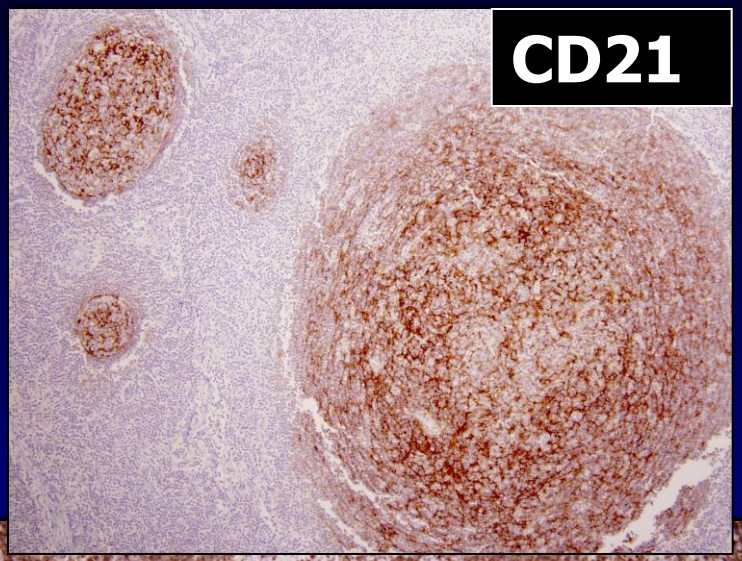
Later Stage

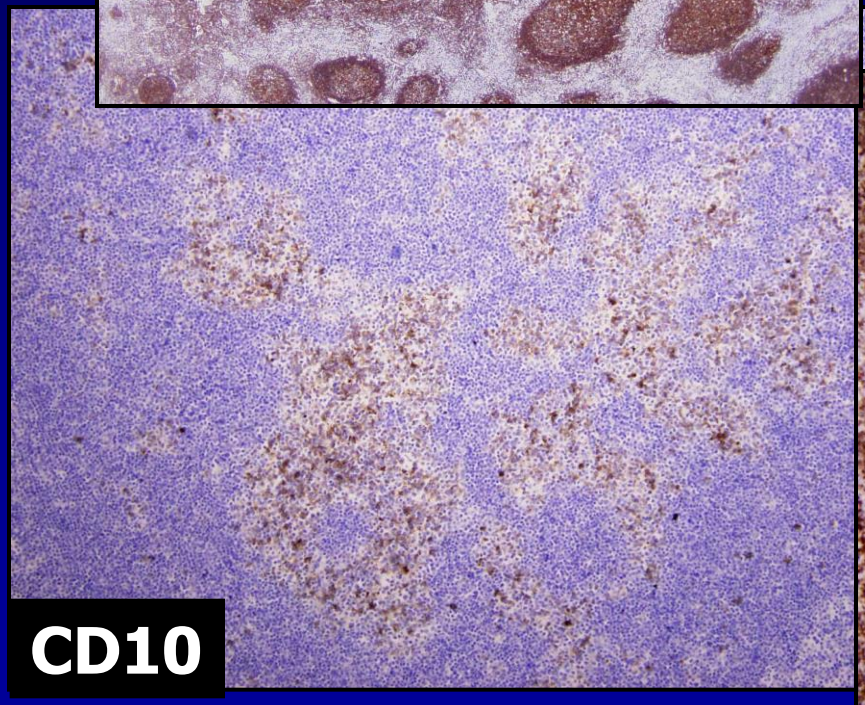


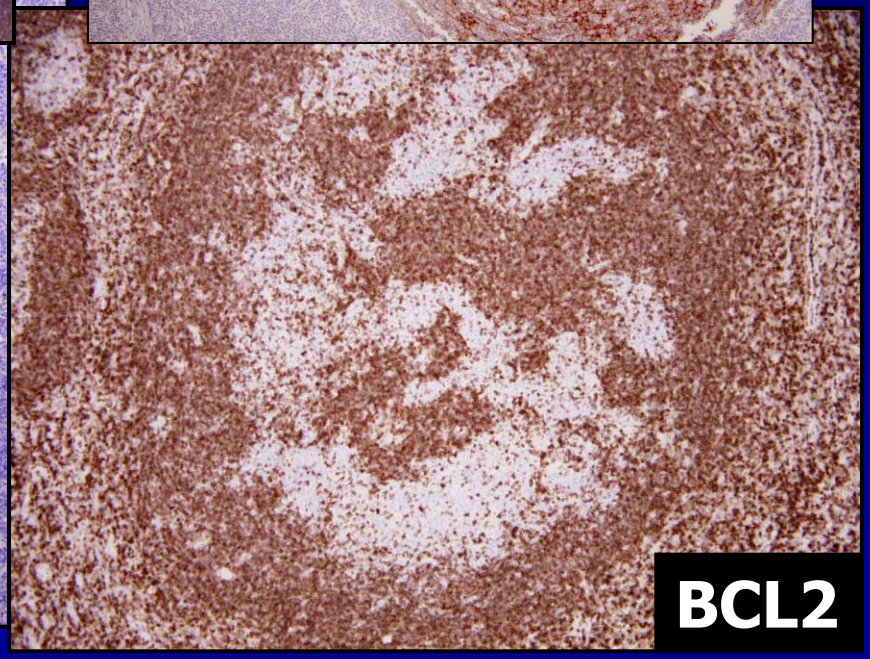
Progressive Transformation of GCs

IHC Findings









Progressive Transformation of GCs

Histologic Features

Often involves small area of LN

Large nodules (3-5 times normal)

Early stage: Irregular shape

Blurring between GC and MZ

Later stages: GCs break apart

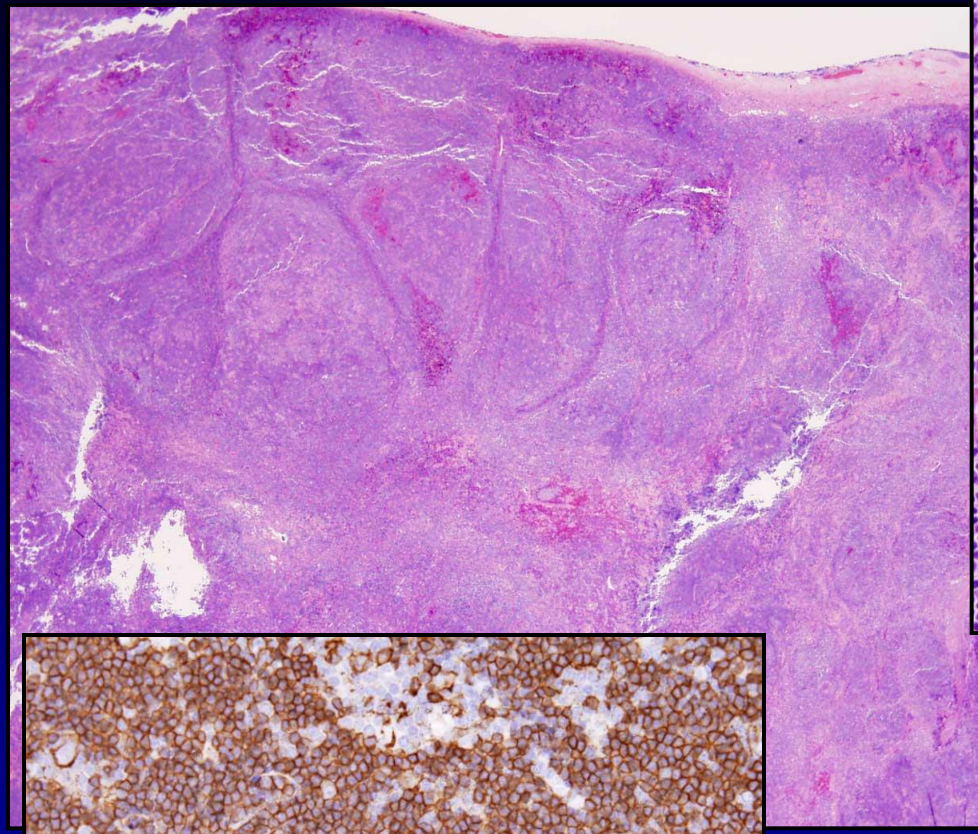
Usually associated with follicular hyperplasia

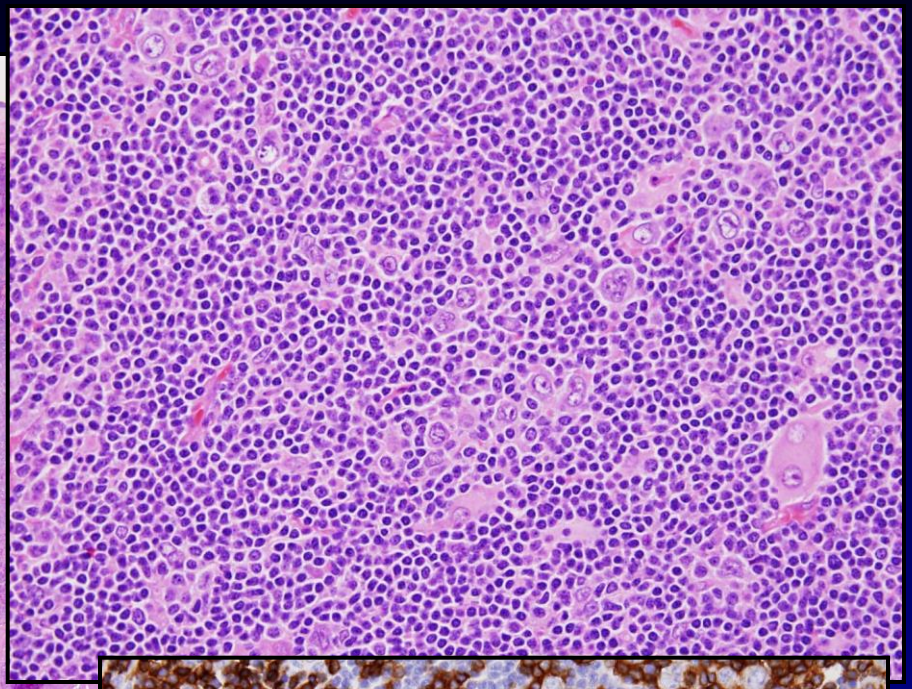
Architecture is not replaced

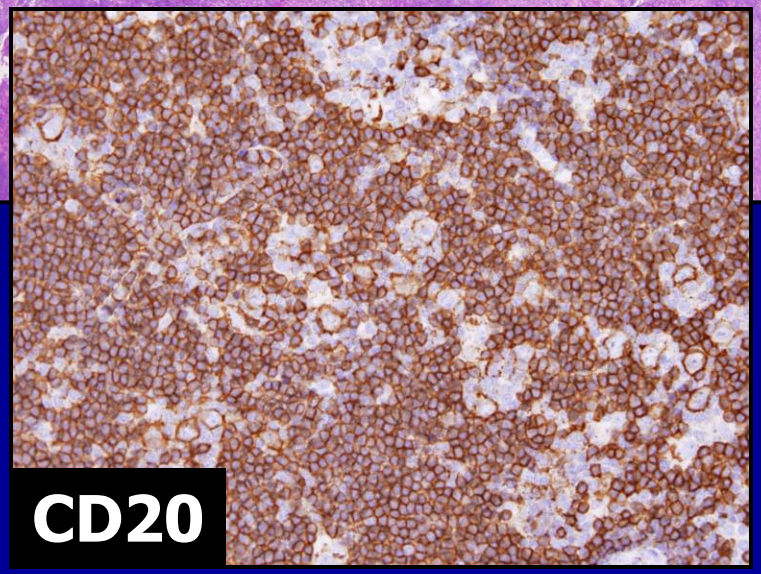
Differential Diagnosis of PTGC

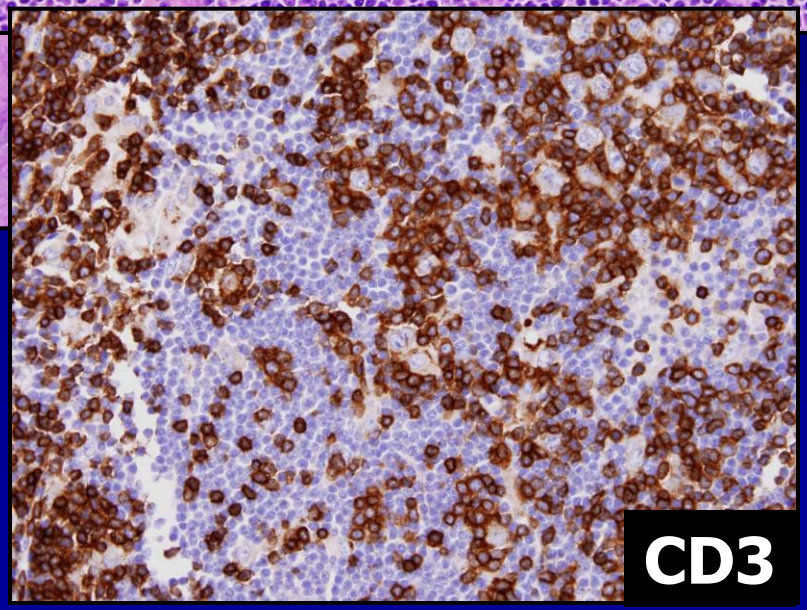
NLPHL	**Nodules replace architecture** **LP (L&H) cells are present**
Lymphocyte-rich classical HL, nodular variant	**Nodules replace architecture** **Small residual germinal centers** **RS+H cells (CD15+ CD30+ LCA-)**
Follicular lymphoma	**Numerous follicles** **Back-to-back** **Into perinodal adipose tissue** **Uniform population of neoplastic cells**

Nodular Lymphocyte Predominant HL





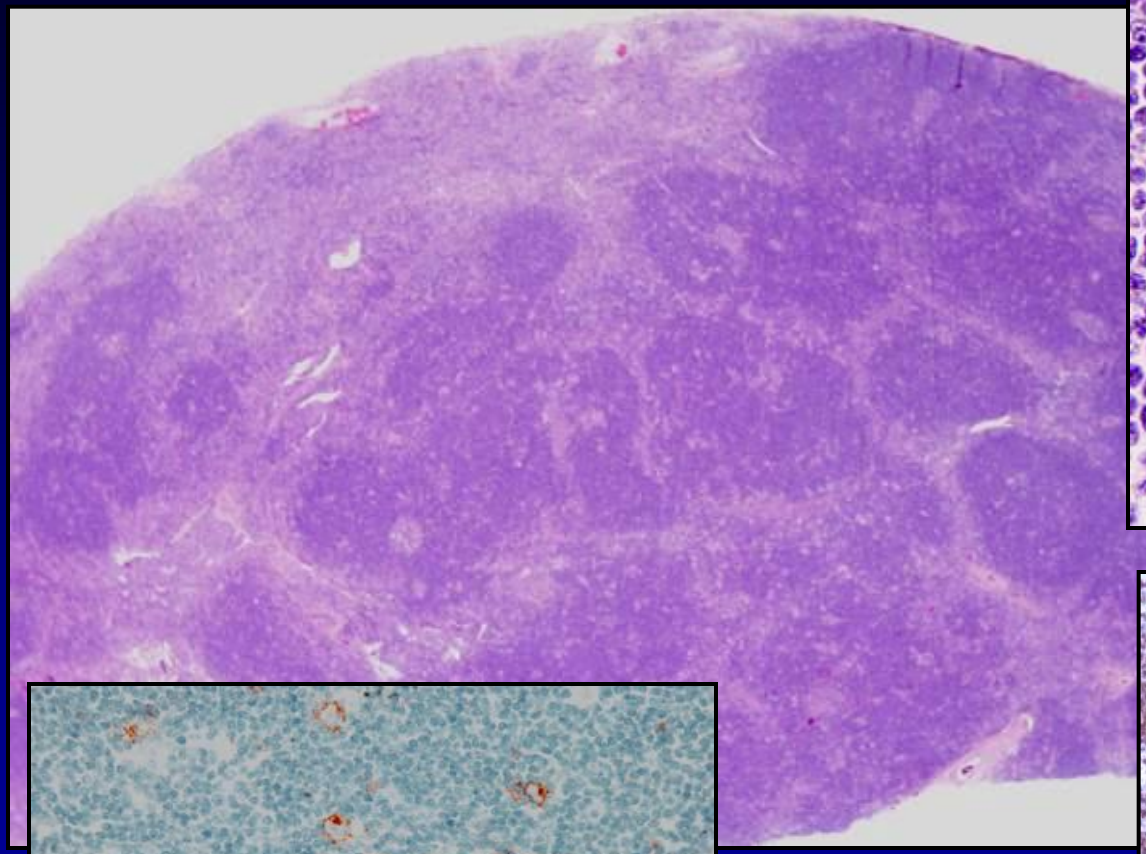


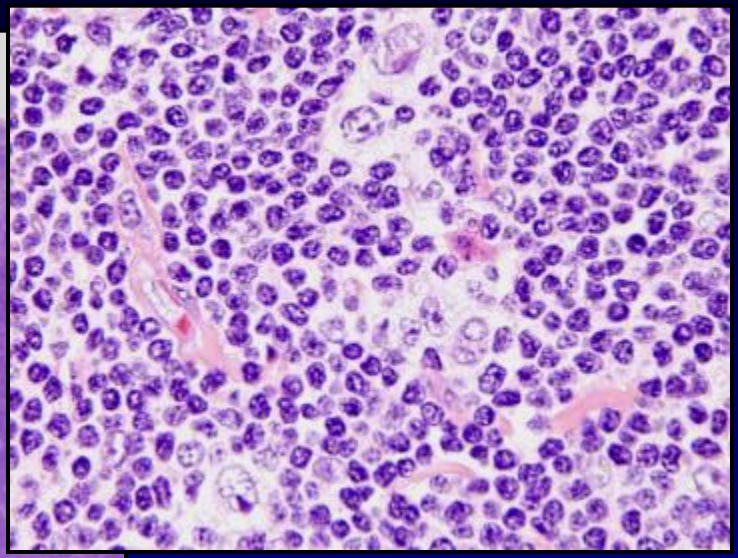


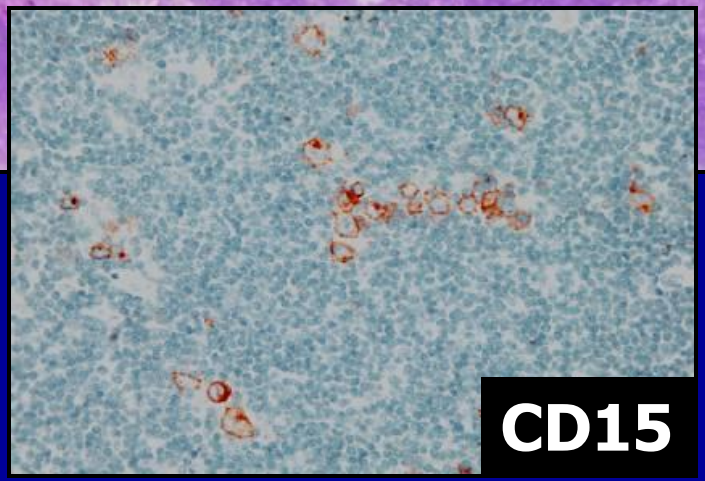
NLPHL

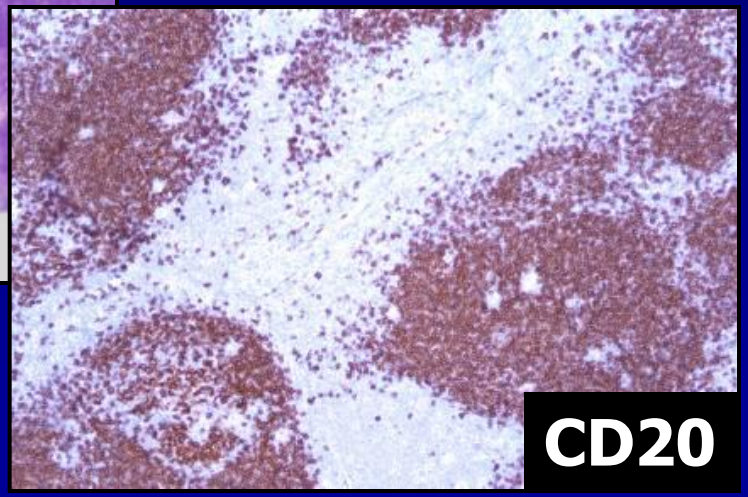
Lymphocyte-rich Classical HL

Nodular variant





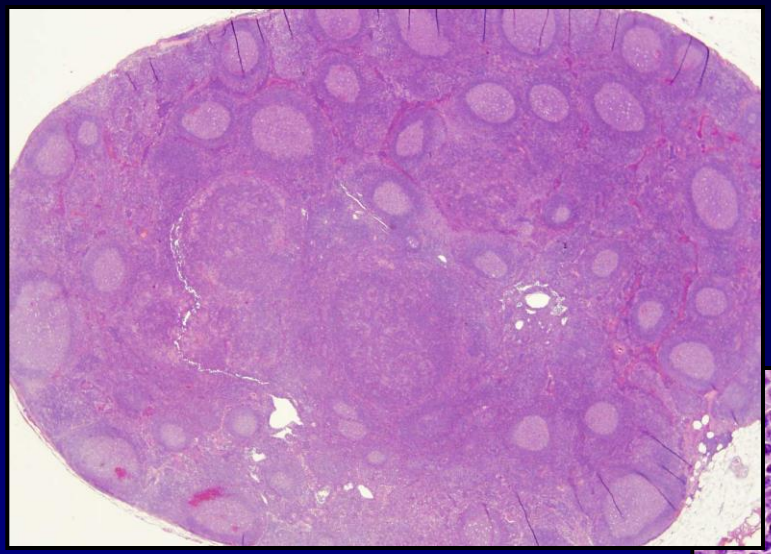


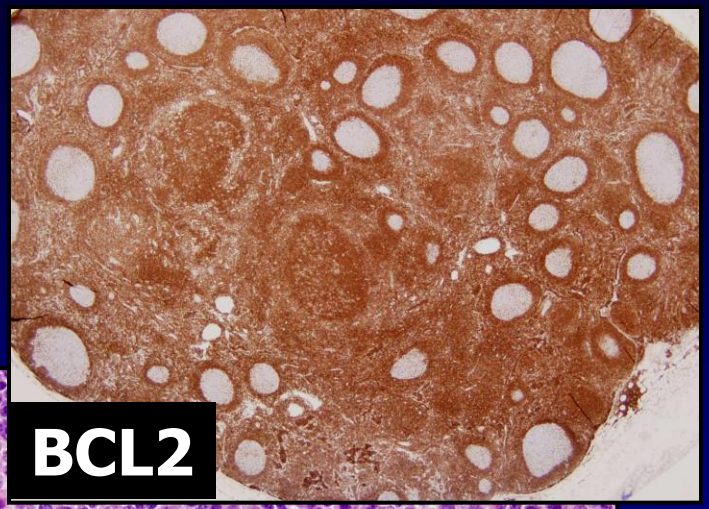


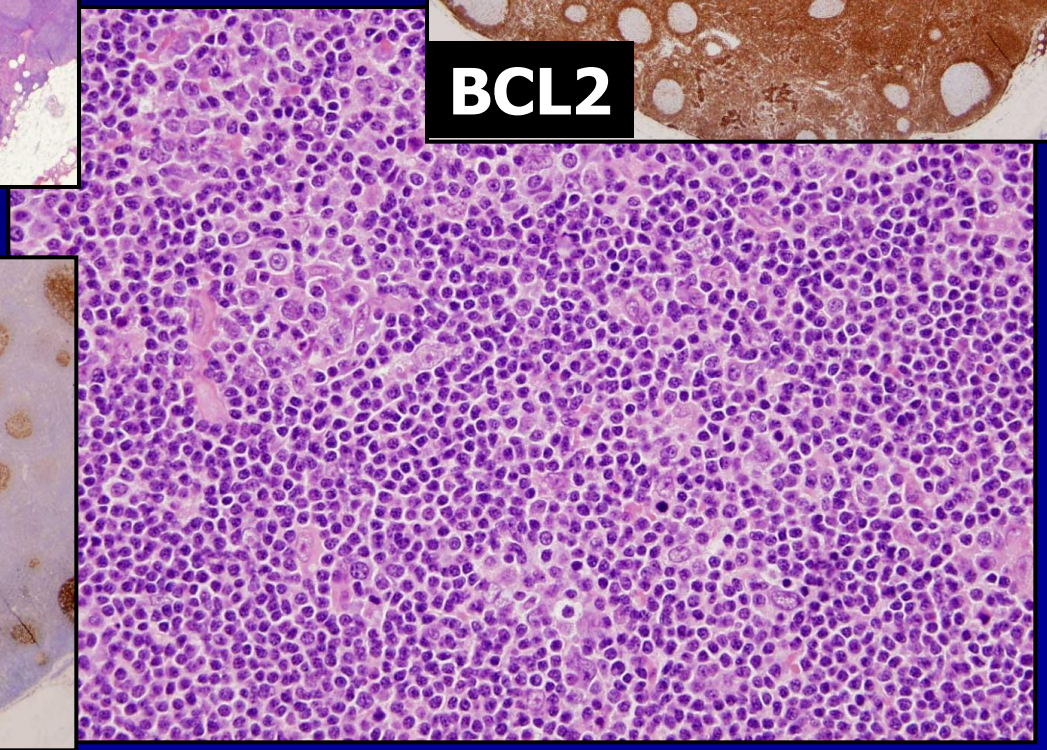
LRCHL

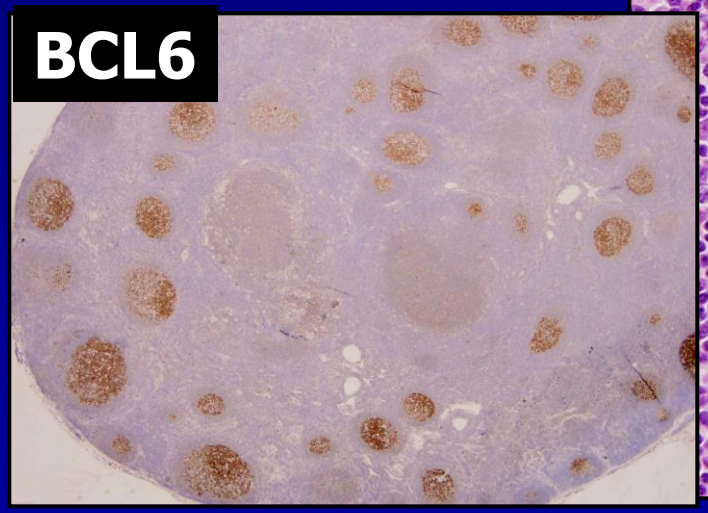
Progressive Transformation of GCs

BCL2+ is not evidence of follicular lymphoma









Practical Questions

Is PTGC associated with future risk of NLPHL?

Statistically no but …

Do I comment on possible relationship to NLPHL in the pathology report?

Never

Is PTGC one lesion?

Probably not - may be more than 1 type

Infectious Mononucleosis

Basic Facts

Caused by Epstein-Barr virus (HHV-4)

Spread by contact with human secretions

Age of contact depends on living conditions

Poor - < 3 years

Good - 10-19 years

Incubation period is 2-5 weeks

First week	Humoral antibody response
Second week	Cellular immune response

Infectious Mononucleosis

Clinical Features

Fever, pharyngitis, lymphadenopathy (50%)

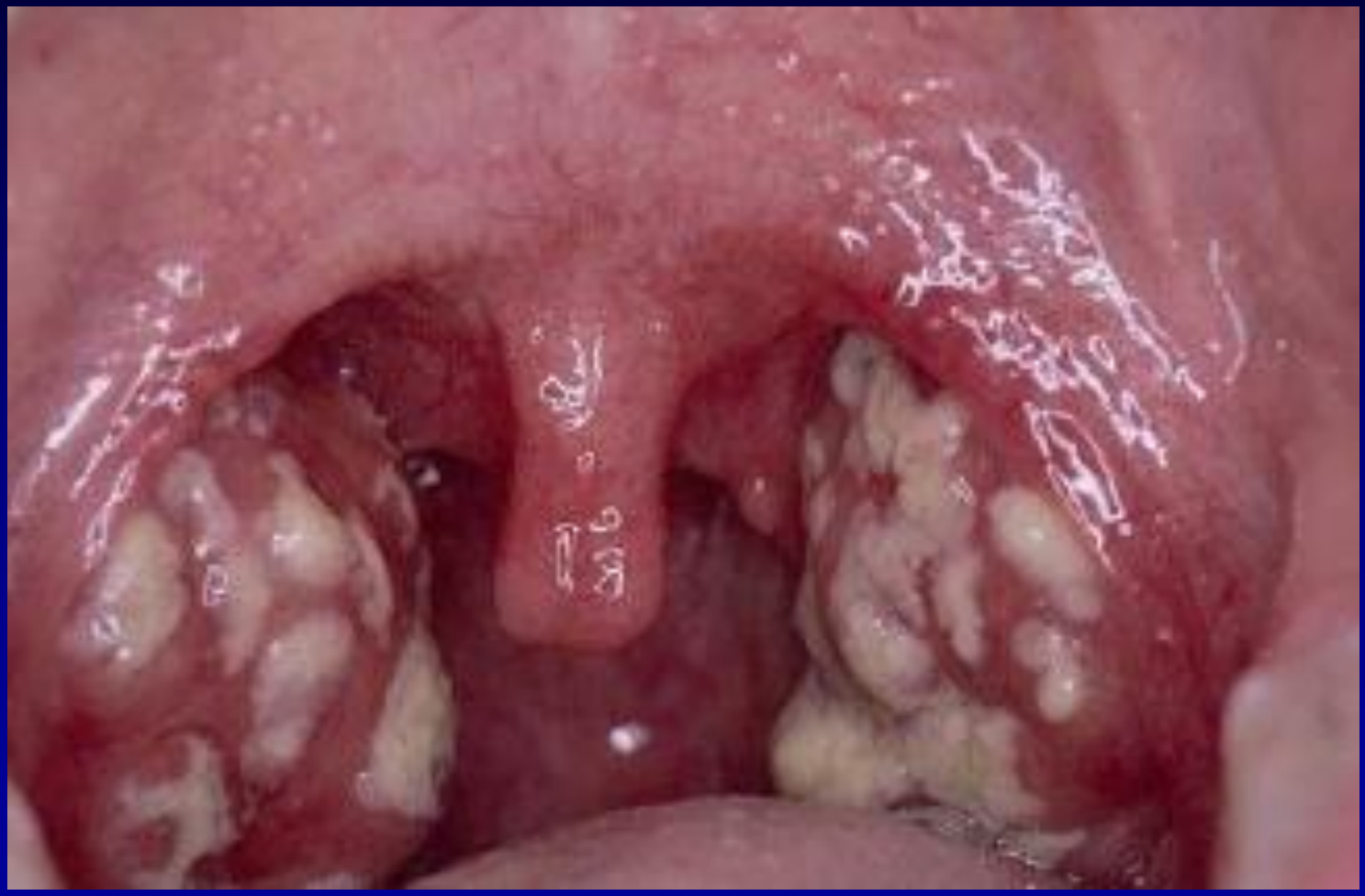
Lymphocytosis with atypical lymphocytes

Less common:

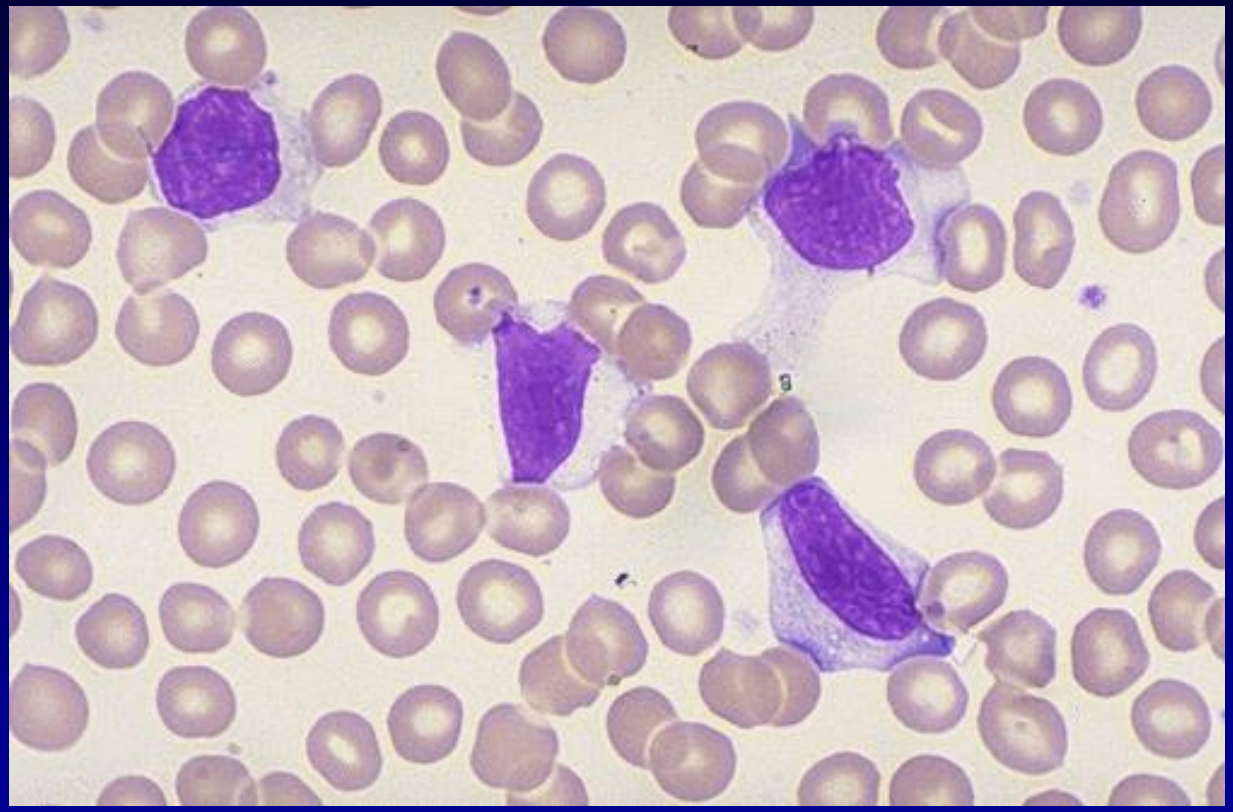
- Hepatosplenomegaly
- Tonsillitis
- Thrombocytopenia
- Anemia
- Skin rash

Rarely IM can occur in the elderly

Infectious Mononucleosis
Tonsillitis

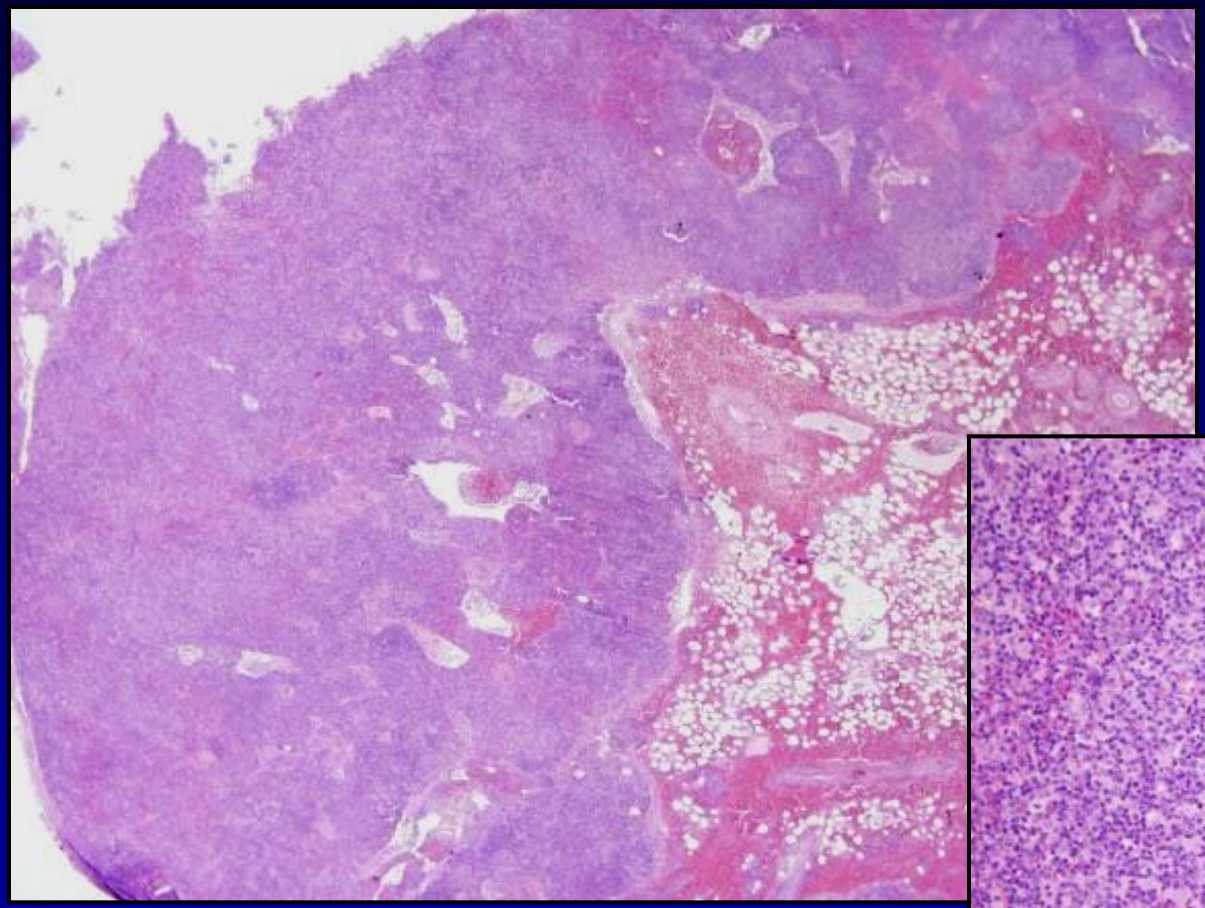


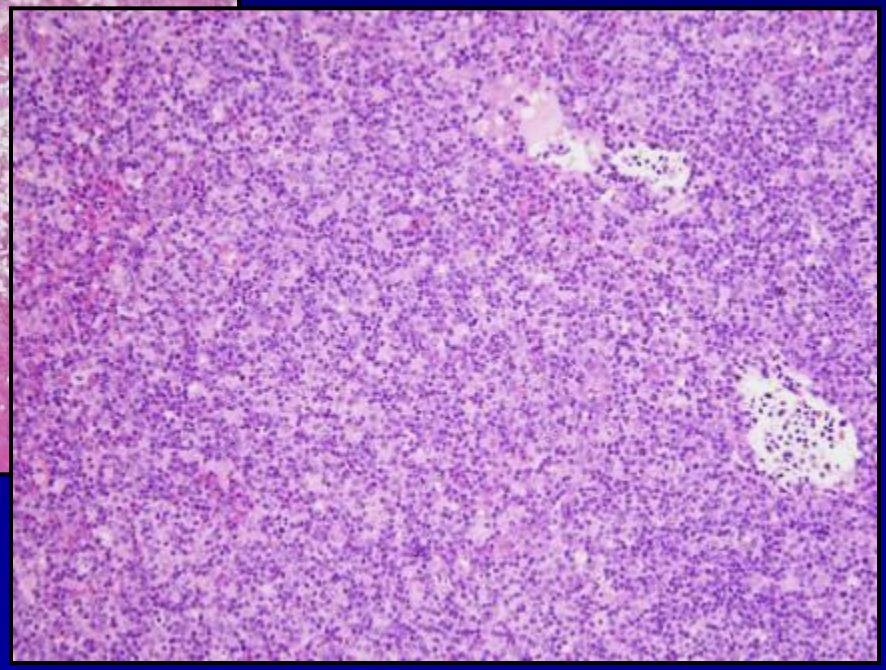
Infectious Mononucleosis
Lymphocytosis



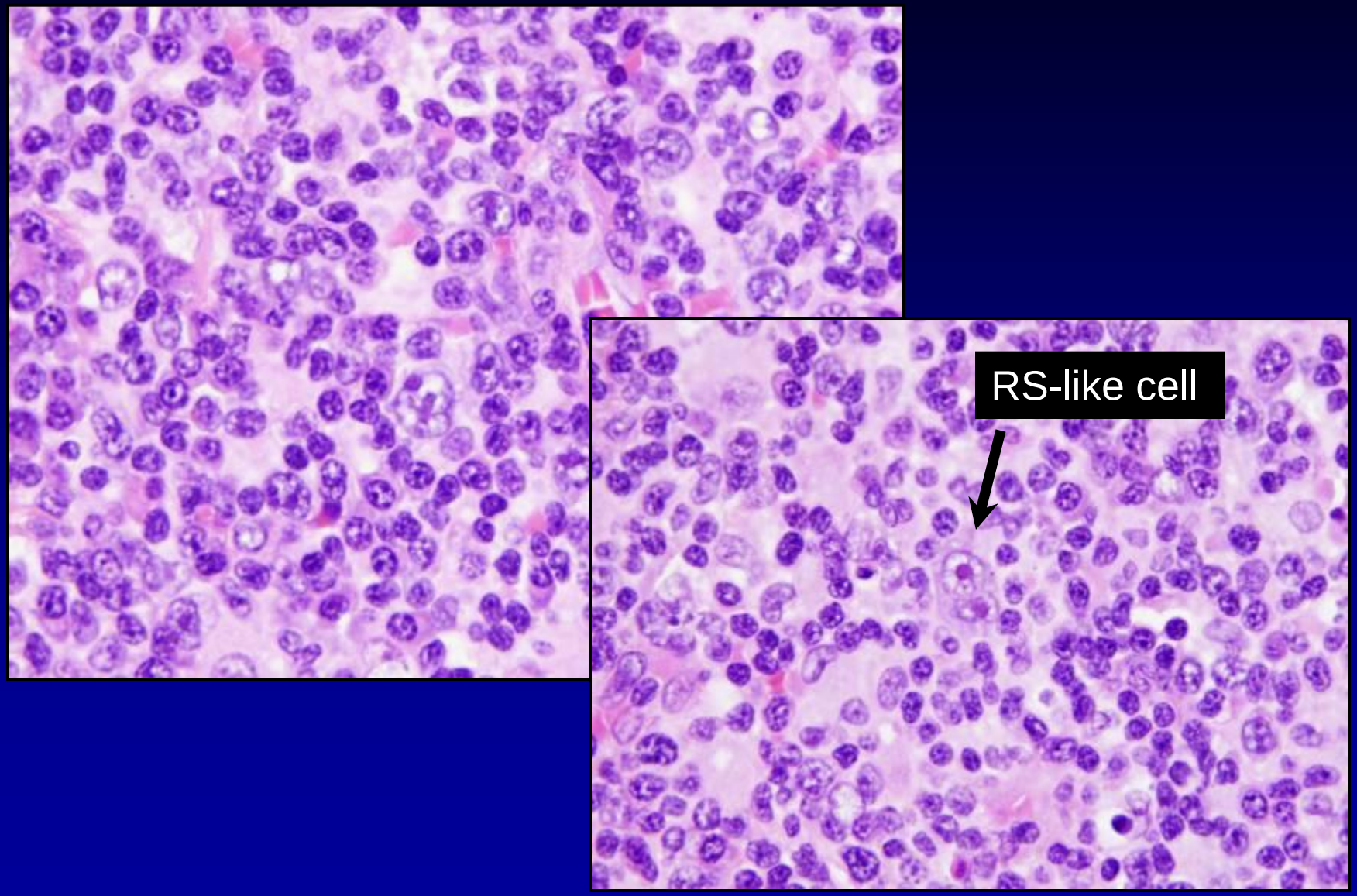
Hal Downey, PhD
(1877-1959)

Infectious Mononucleosis

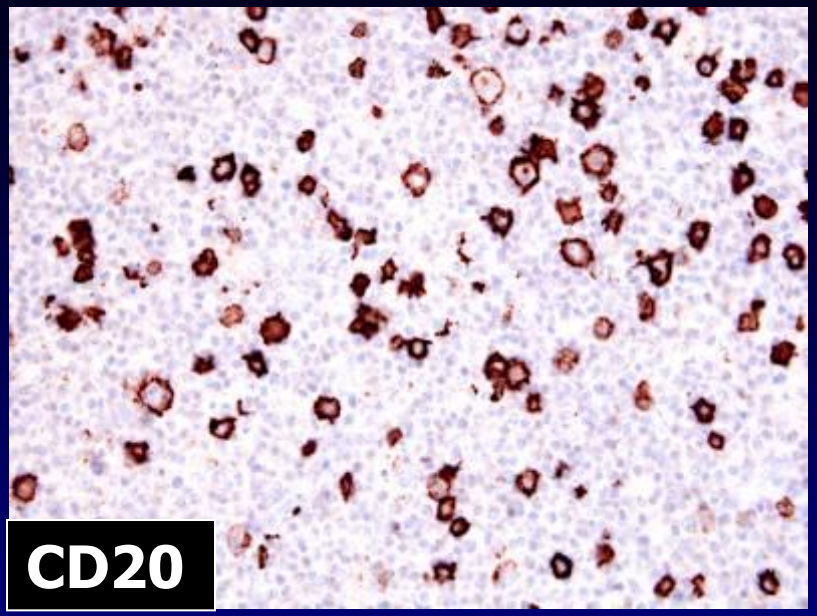


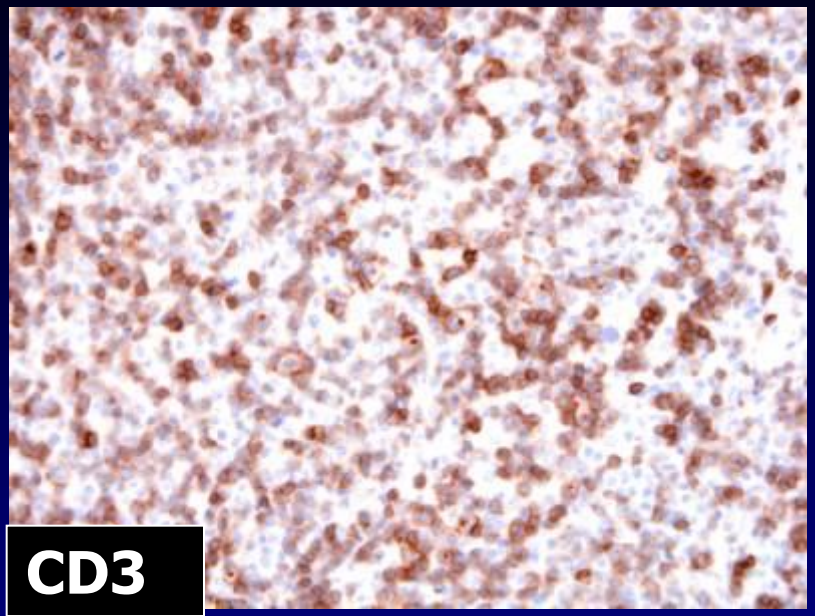


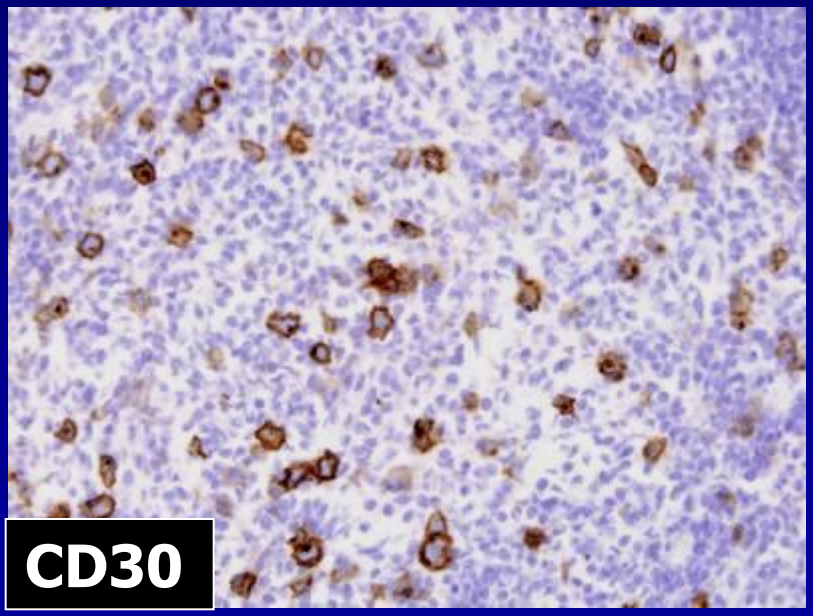
Infectious Mononucleosis

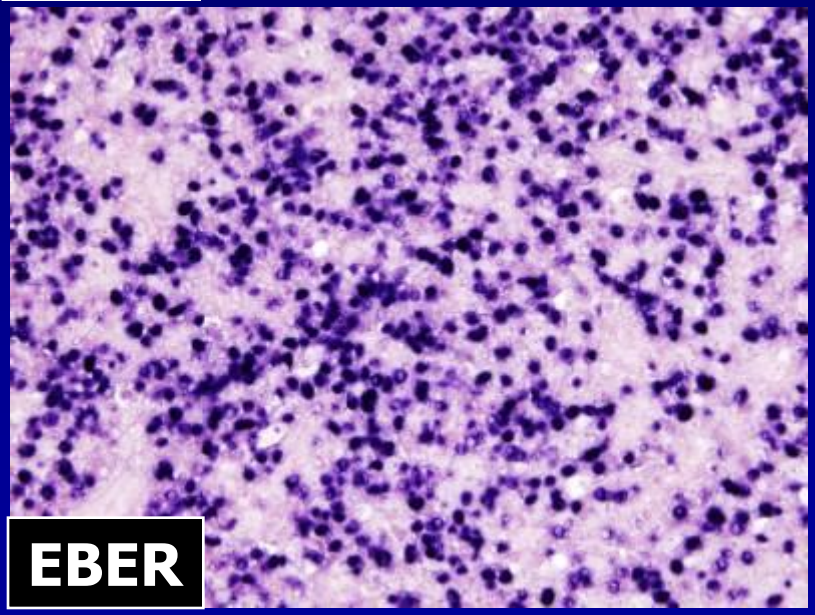


Infectious Mononucleosis









Infectious Mononucleosis

Histologic Features

- Marked expansion of the paracortex
  - Often some preservation of architecture
  - Spectrum of cells
  - Many immunoblasts
  - RS-like cells +/-
  - Necrosis common
  - Many EBER+ cells
- Follicular hyperplasia is common

Differential Diagnosis of Infectious Mononucleosis

CMV lymphadenitis	Can resemble IM histologically CMV inclusions +/- EBV absent
Large B-cell lymphoma	Architecture replaced Monotonous cell population EBV negative (usually) Monoclonal
Anaplastic large cell lymphoma	Sinusoidal (common) Hallmark cells, ALK+ Monoclonal
Classical Hodgkin lymphoma	No spectrum of cell types RS+H cells: CD15+ LCA-

Kikuchi-Fujimoto Lymphadenitis

Clinical Features

First described in 1972 in Japan

A.K.A. histiocytic necrotizing lymphadenitis

Median age 30 years (wide range)

Female predominance

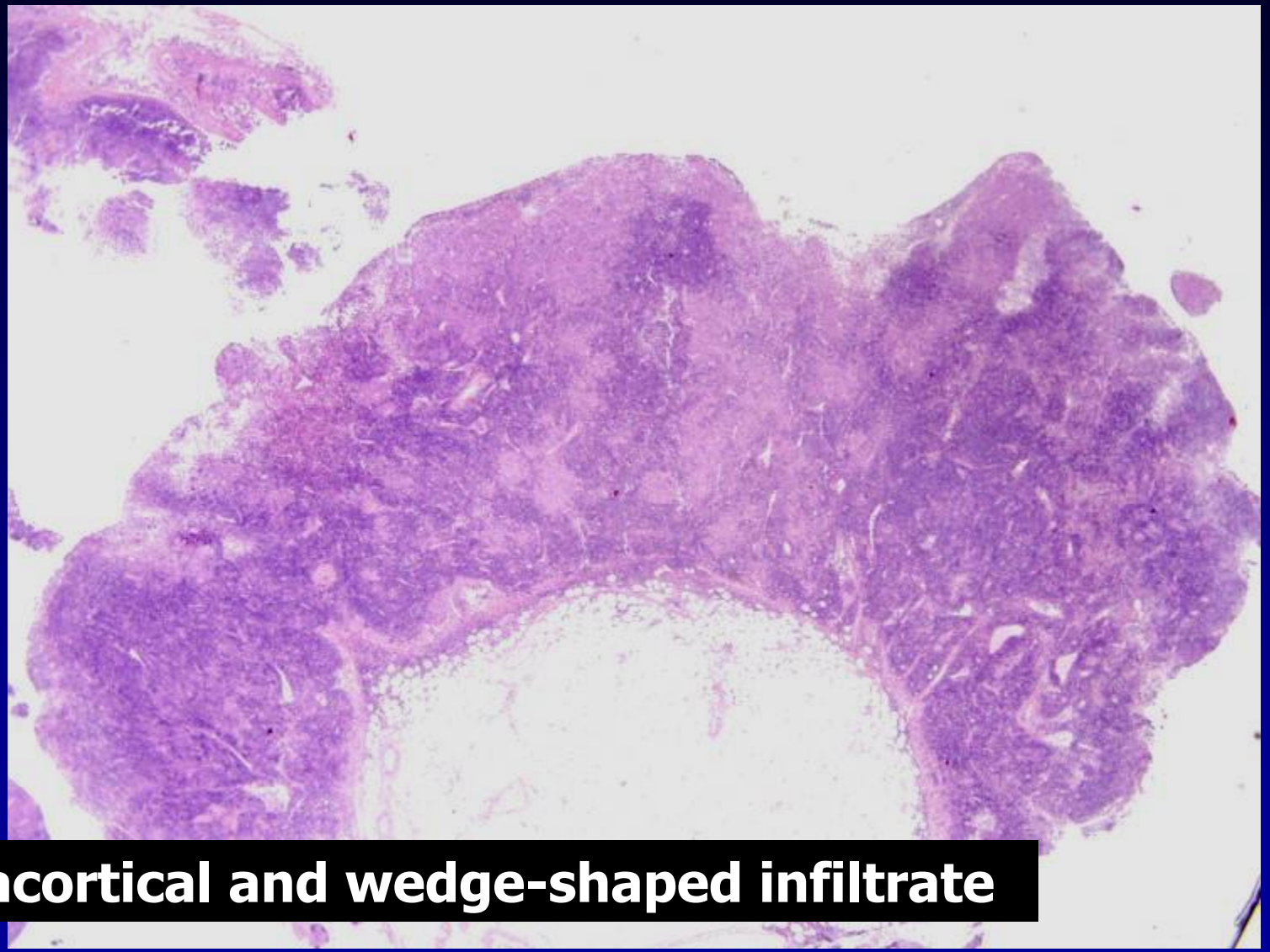
Cervical LNs # 1

Patients present with:

- Moderate fever, chills
- Myalgias +/-

Masahiro Kikuchi, MD

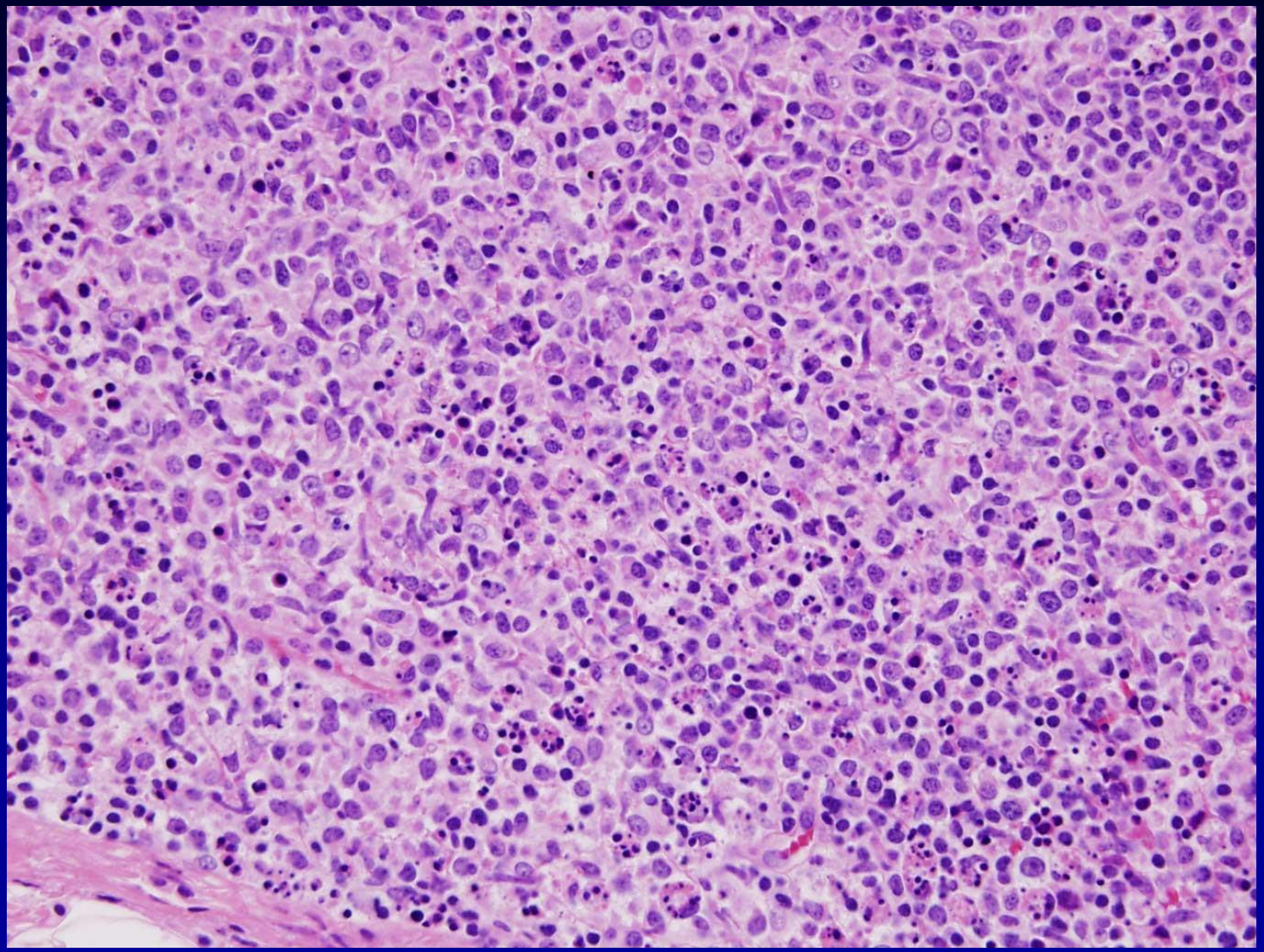
Kikuchi-Fujimoto Lymphadenitis



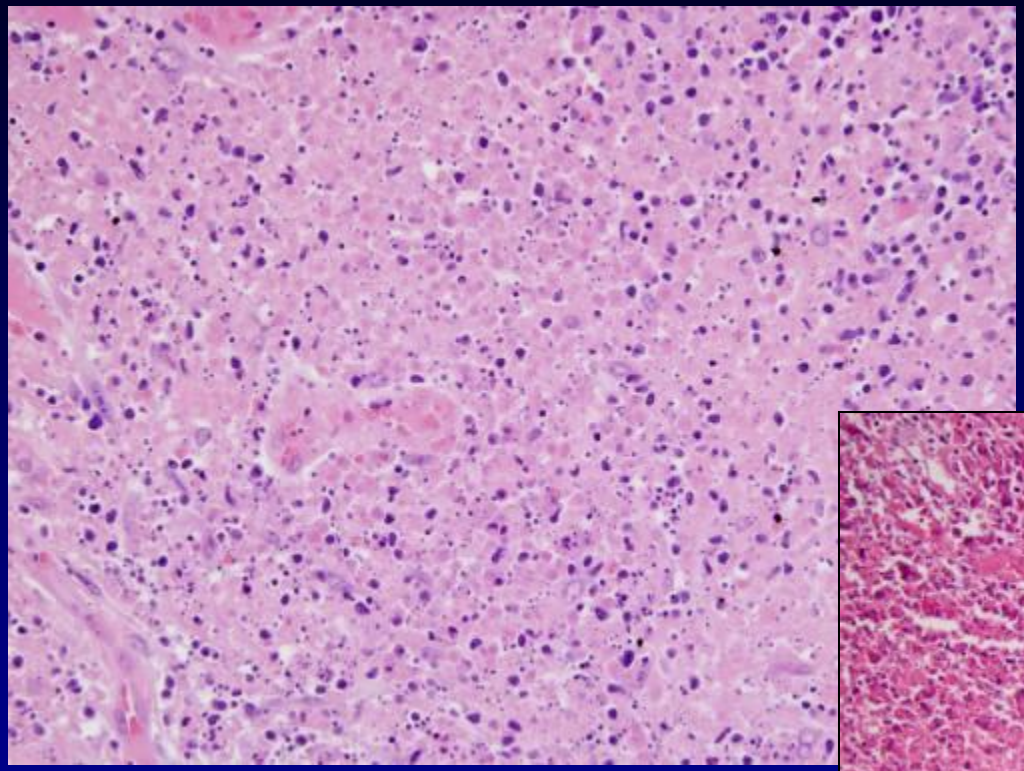
Paracortical and wedge-shaped infiltrate

Kikuchi-Fujimoto Lymphadenitis

Proliferative Phase

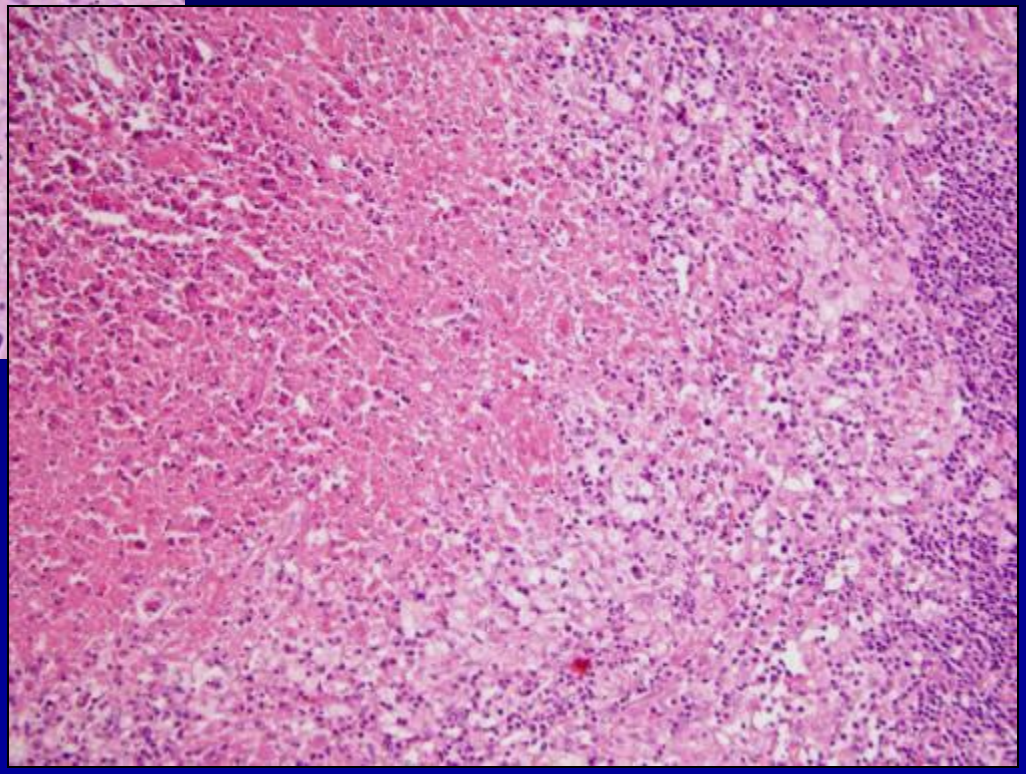


Kikuchi-Fujimoto Lymphadenitis



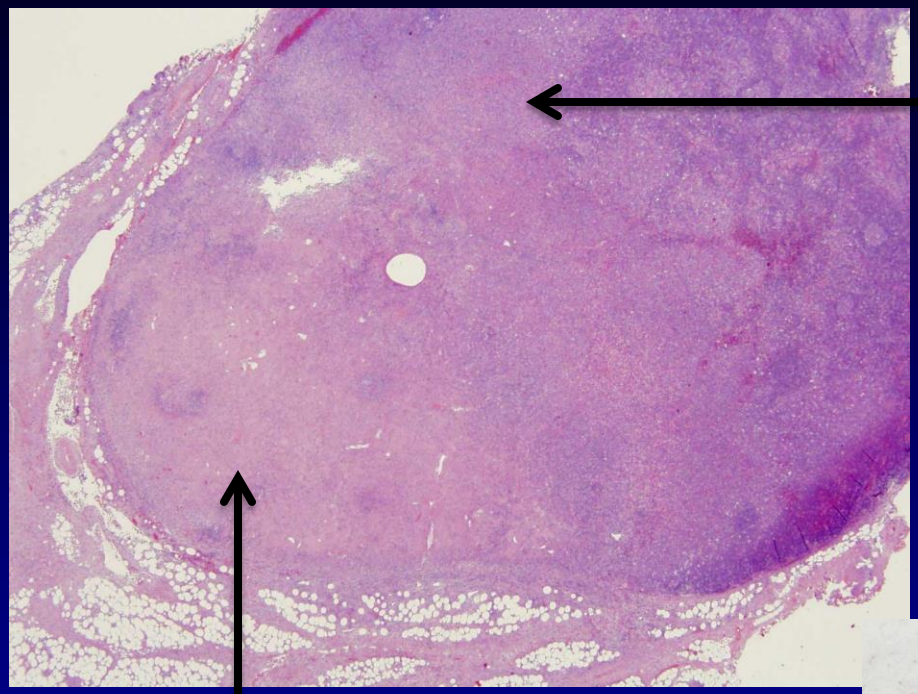
Necrotizing

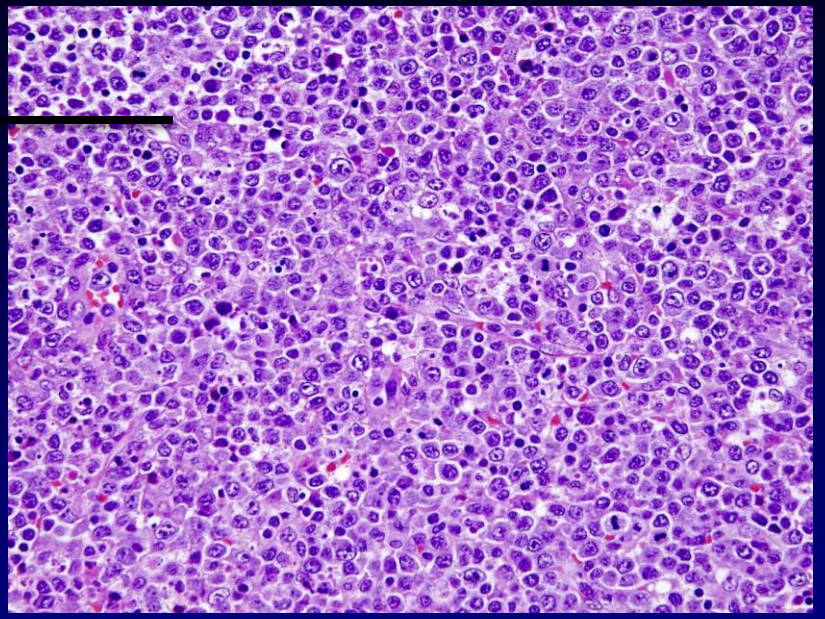
Necrotizing and Xanthomatous

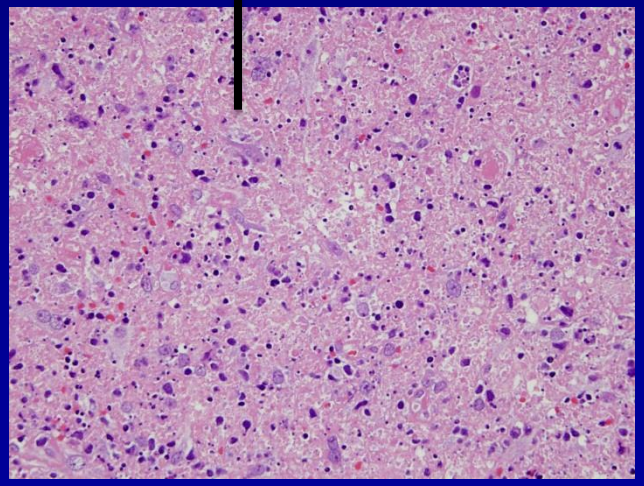


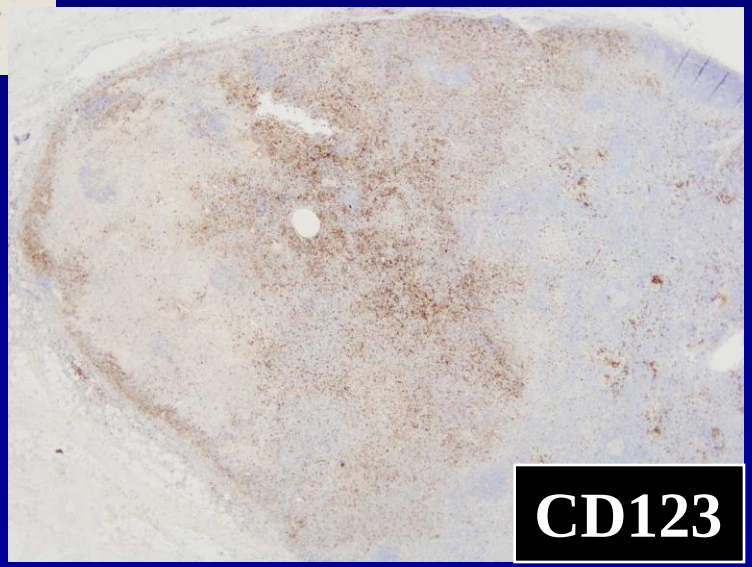
Kikuchi-Fujimoto Lymphadenitis

Necrotic and proliferative stages









Kikuchi-Fujimoto Lymphadenitis
Histologic Features

Overall architecture preserved

Paracortical; Patchy necrosis + / -

Increased histiocytes; often C-shaped

Increased plasmacytoid dendritic cells (CD123+)

No granulocytes; no (or rare) plasma cells

Follicular hyperplasia +/-

3 phases: Necrotizing
Proliferative
Xanthomatous

Kikuchi-Fujimoto Lymphadenitis

Immunophenotype

Numerous histiocytes

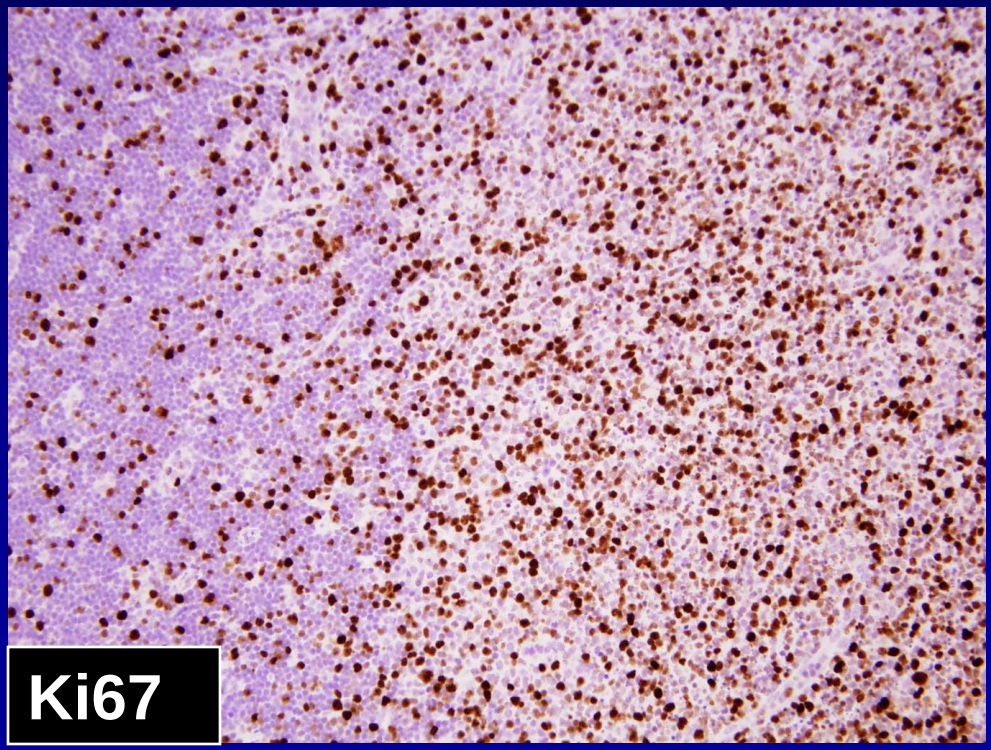
- **CD68+, CD123+, lysozyme+, MPO+**

Many T-cells

- **CD8 > CD4**

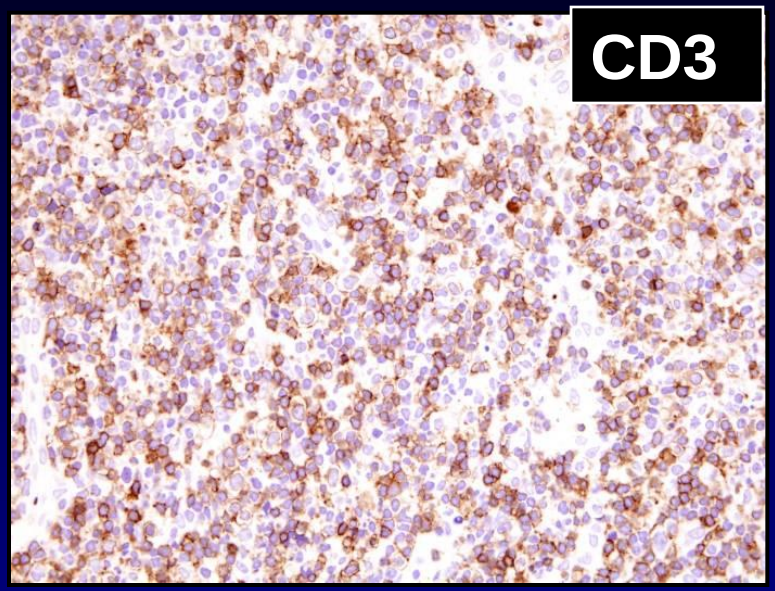
CD30+ immunoblasts

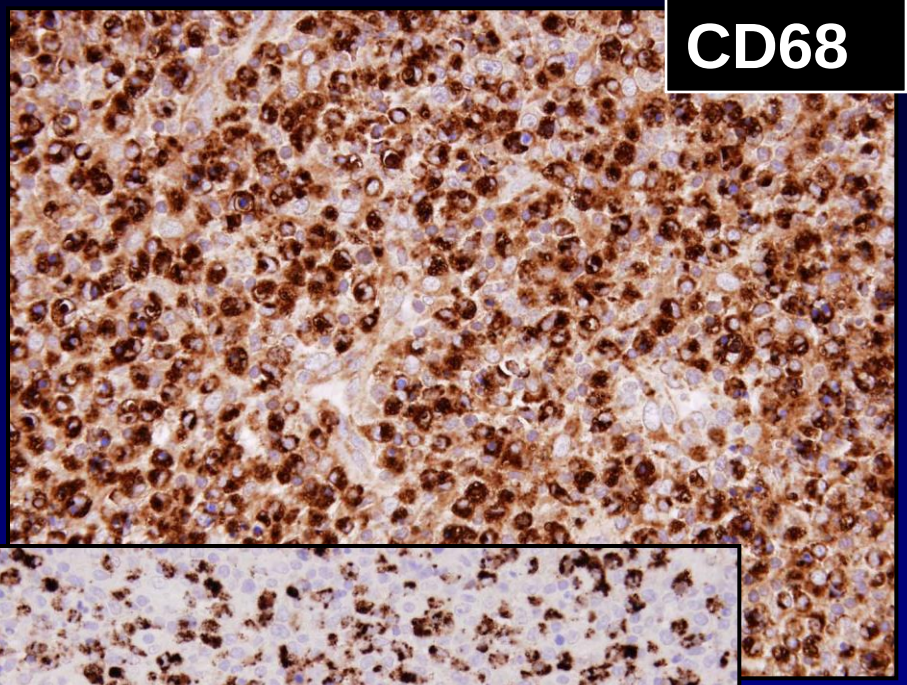
Ki-67 can be high

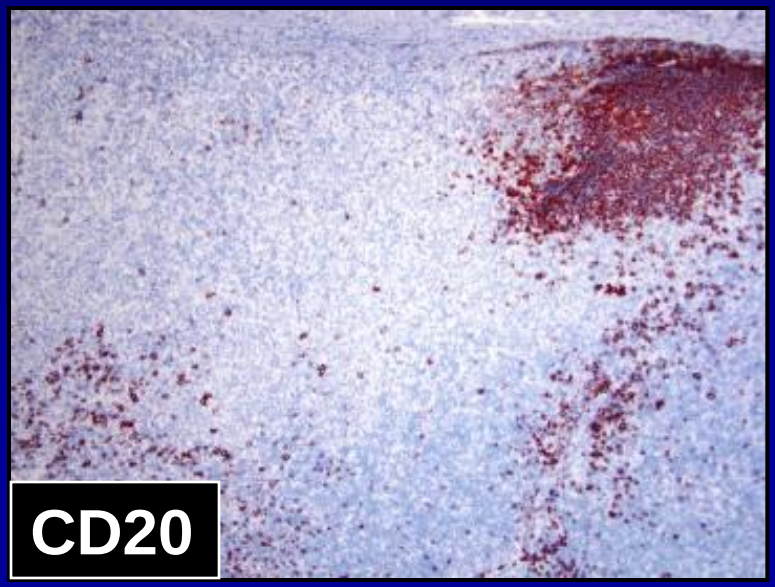


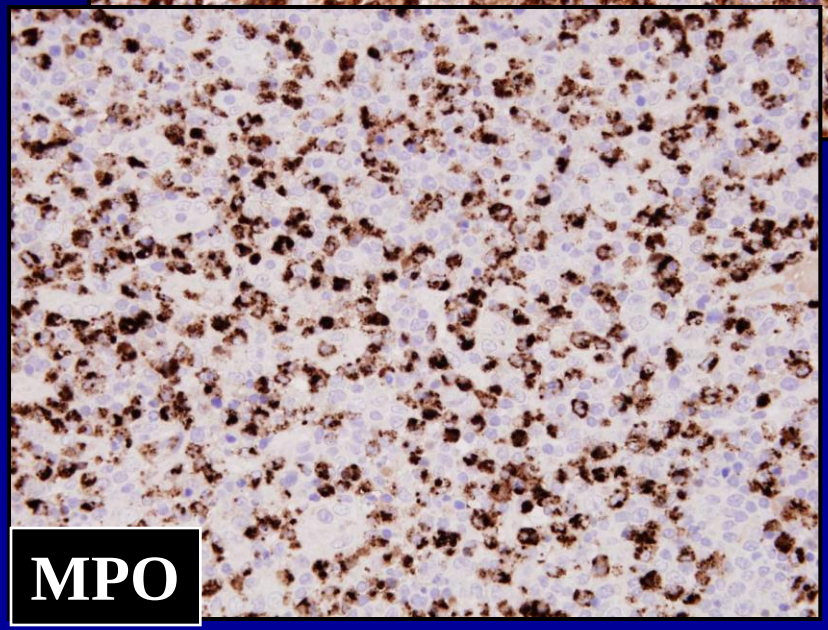
Kikuchi-Fujimoto Lymphadenitis

IHC Findings









Differential Diagnosis of Kikuchi-Fujimoto Lymphadenitis

SLE lymphadenitis	Can be identical to K-F Hematoxylin bodies +/-
Infectious lymphadenitis	Different quality of necrosis (coagulative with polys)
Infarcted lymphoma	Ghosts of tumor cells Immunostains highlight dead cells
Large B-cell lymphoma	Only proliferative phase of K-F Immunophenotype helps

Castleman Disease

Clinical	Pathological
Unicentric	Hyaline-vascular variant
	Plasma cell variant (HHV-8-)
Multicentric	Plasma cell variant (HHV-8+)

Dr. Benjamin Castleman (1906 - 1982)

Hyaline-vascular Castleman Disease
Clinical Features

90% of all cases of unicentric CD

Almost any age (8-70 yrs)

Usually asymptomatic

Small or very large mass (up to 16 cm)

Usually above the diaphragm

- Mediastinum is # 1 site

Surgical excision is optimal therapy

Hyaline-vascular Castleman Disease

Histologic Features

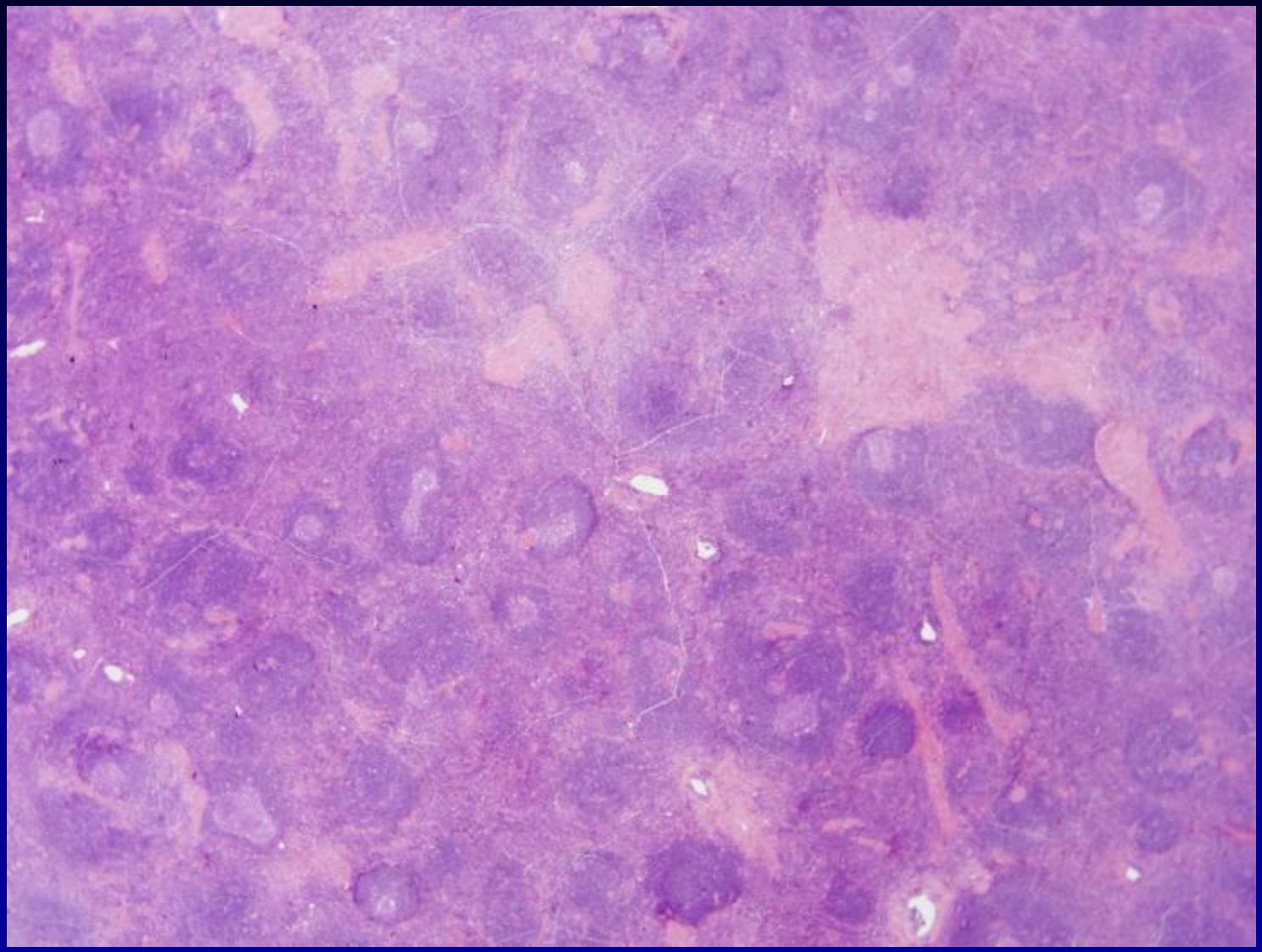
Follicular

- Large follicles
- "Twinning"
- "Onion-skin" mantle zones
- Lymphocyte depletion of germinal centers
- Hyaline-vascular lesions

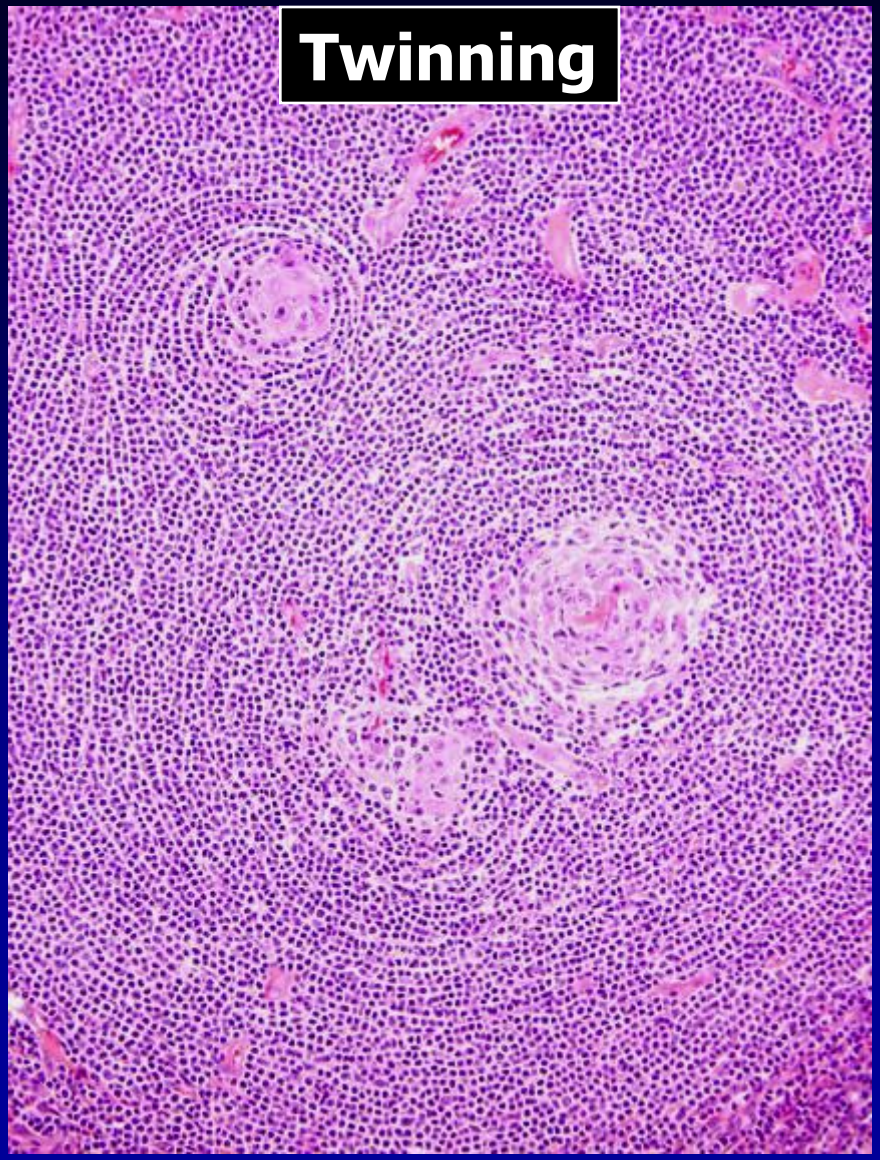
Interfollicular

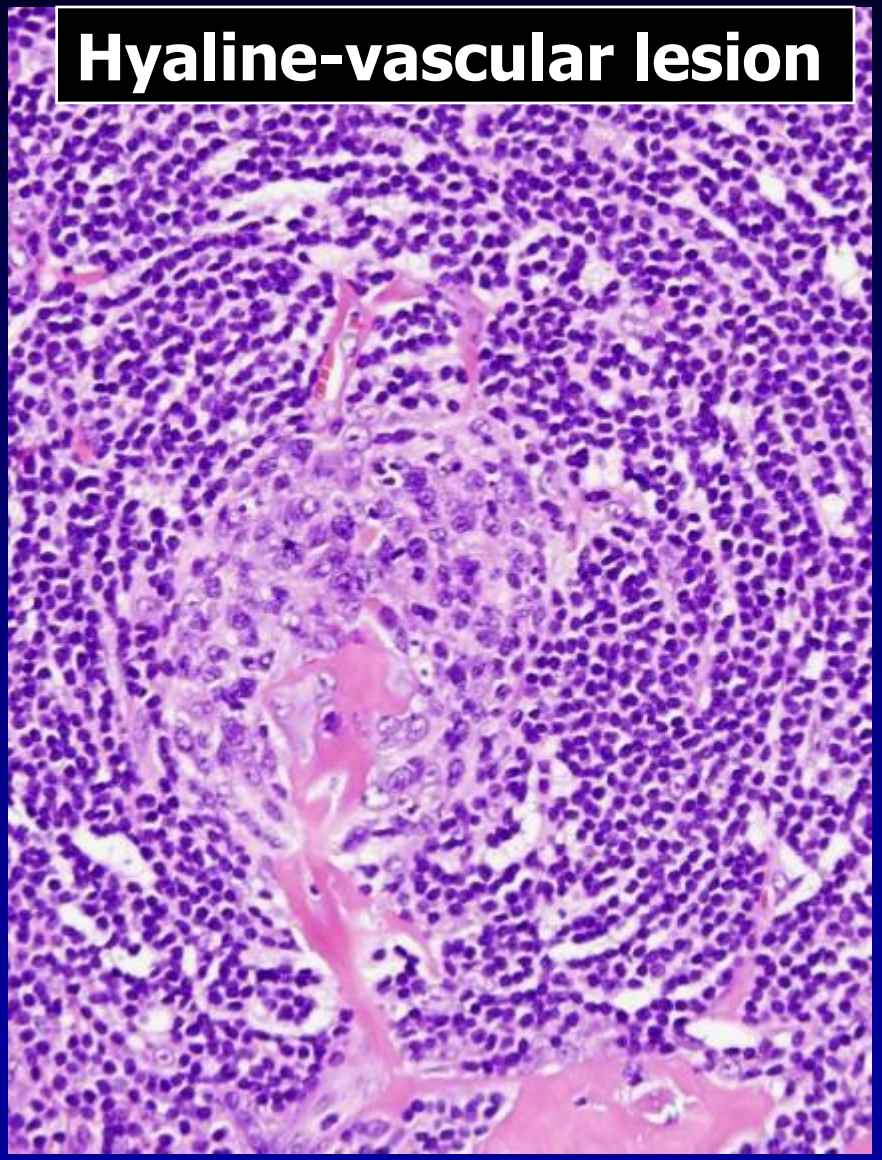
- This can be predominant (stroma-rich)
- Numerous high endothelial venules
- Actin+, CD68+, CD21+

Hyaline-vascular Castleman Disease



Hyaline-vascular Castleman Disease

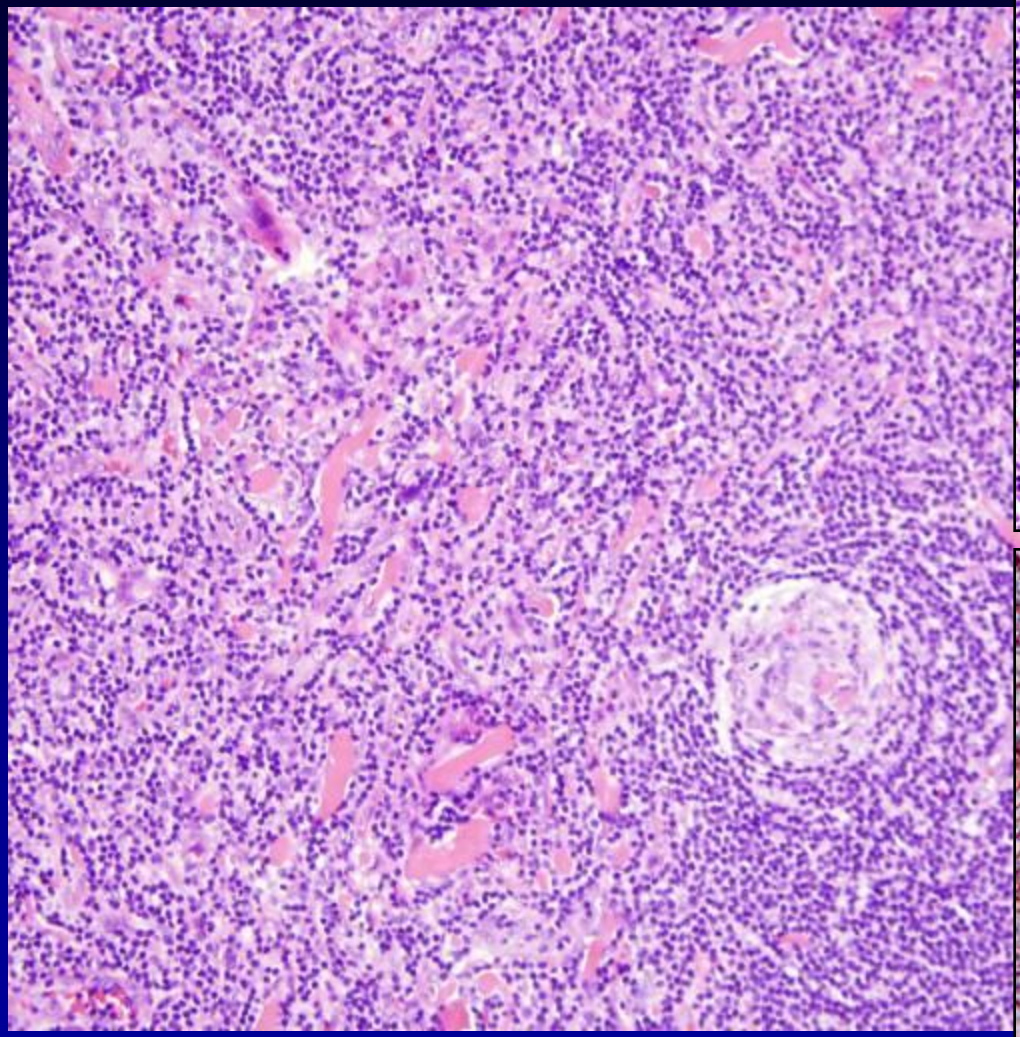


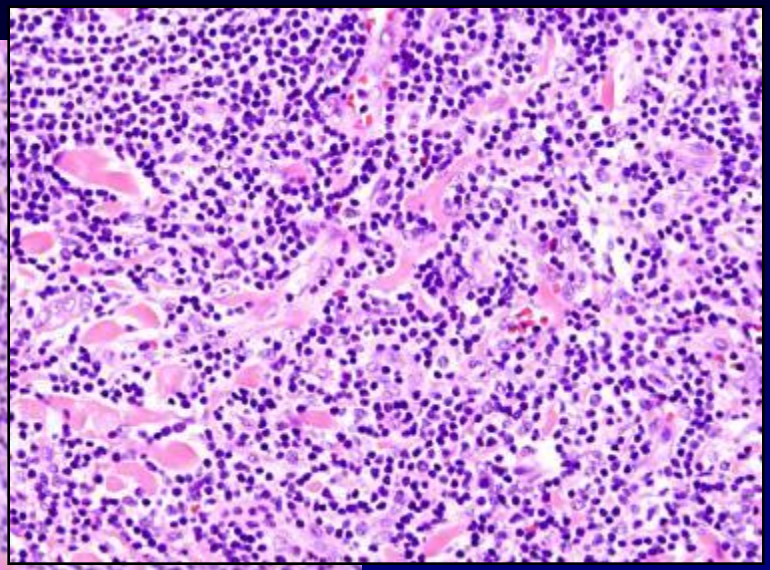


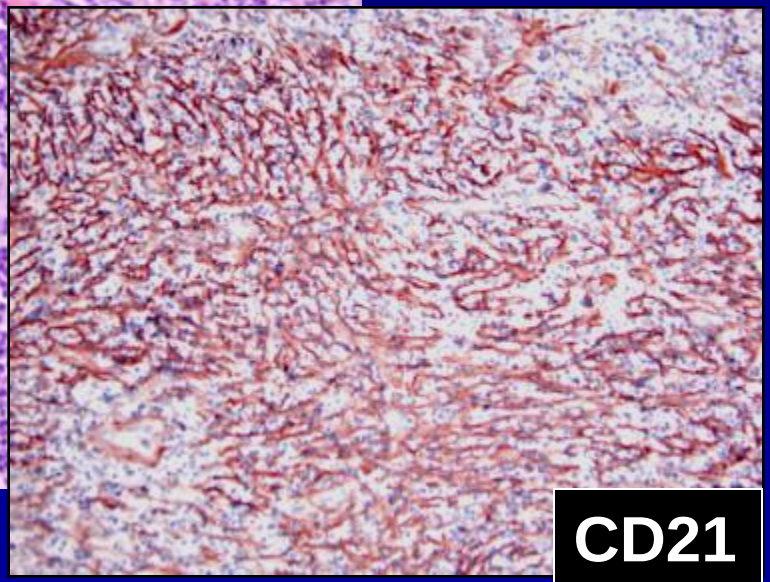
CD – hyaline-vascular variant

Hyaline-vascular Castleman Disease

Stroma Rich







CD – hyaline-vascular variant

Monoclonality and cytogenetic abnormalities in hyaline vascular Castleman disease

Kung-Chao Chang[1], Yu-Chu Wang[2,7], Liang-Yi Hung[2,7], Wan-Ting Huang[3,7], Jen-Hui Tsou[2,8], Dan M Jones[4], Hsiang-Lin Song[1], Yu-Min Yeh[5], Lin-Yuan Kao[1] and L Jeffrey Medeiros[6]

32 cases analyzed by HUMARA assay

25 / 32 cases were monoclonal

22 / 29 hyaline vascular variant
3 / 3 plasma cell variant

3 cases had clonal karyotypes

No *IGH* or *TCRG or TCRB* rearrangements

Hyaline vascular CD may be a neoplasm of stromal cells

Mod Pathol 27: 823, 2014

Differential Diagnosis of Hyaline-vascular Castleman Disease

Follicular hyperplasia	No hyaline-vascular lesions No lymphocyte depletion No interfollicular vascularity
Follicular lymphoma	Follicles are numerous and monotonous No lymphocyte depletion No interfollicular vascularity
Mantle cell lymphoma, mantle zone pattern	CD5+ cyclin D1+
Plasma cell variant CD	Marked plasmacytosis Can have H-V follicles

Plasma Cell CD (Unicentric)
Clinical Features

10% of unicentric CD

Almost any age

One or multiple small lymph nodes

Systemic symptoms in a subset
(? multicentric CD)

Plasma Cell CD (Unicentric)

Histologic and Immunophenotypic Features

Interfollicular sheets of plasma cells

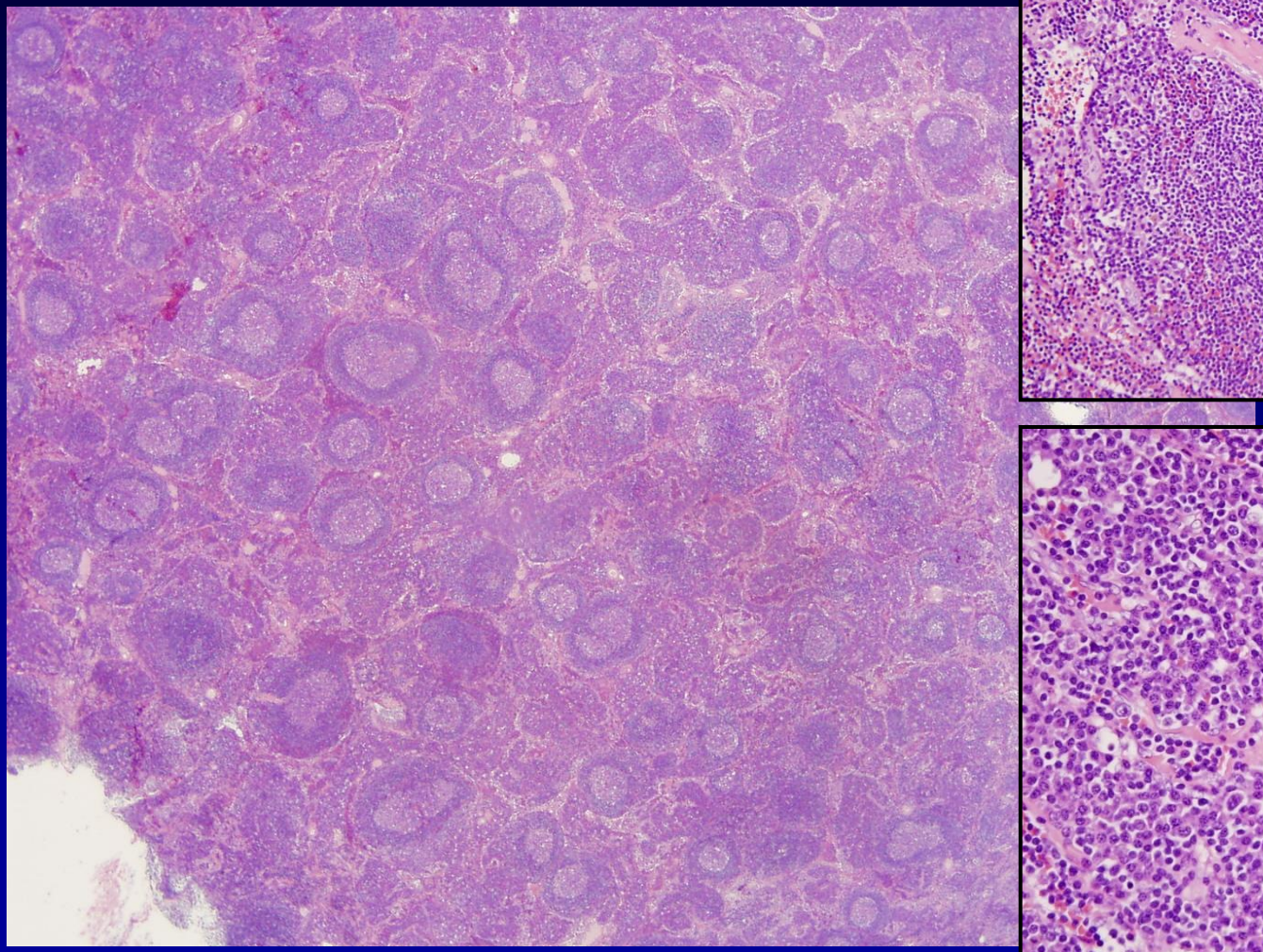
Sinuses usually patent

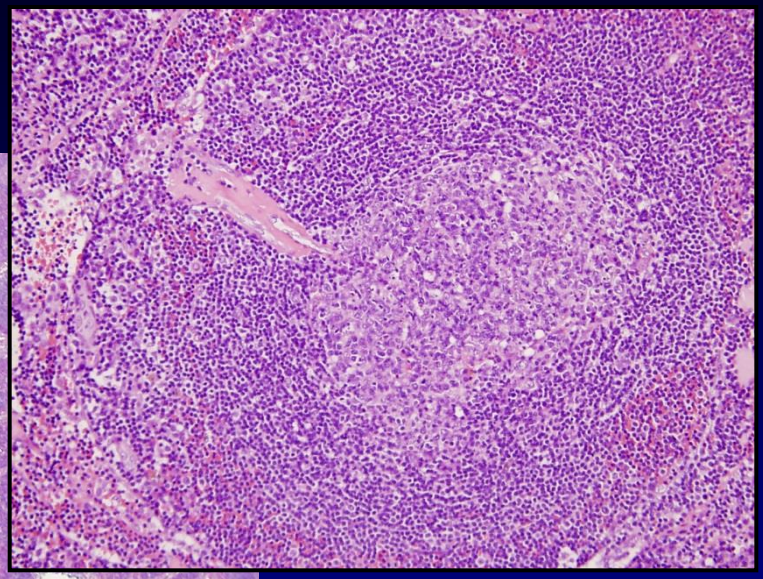
Follicles have some H-V lesions +/-

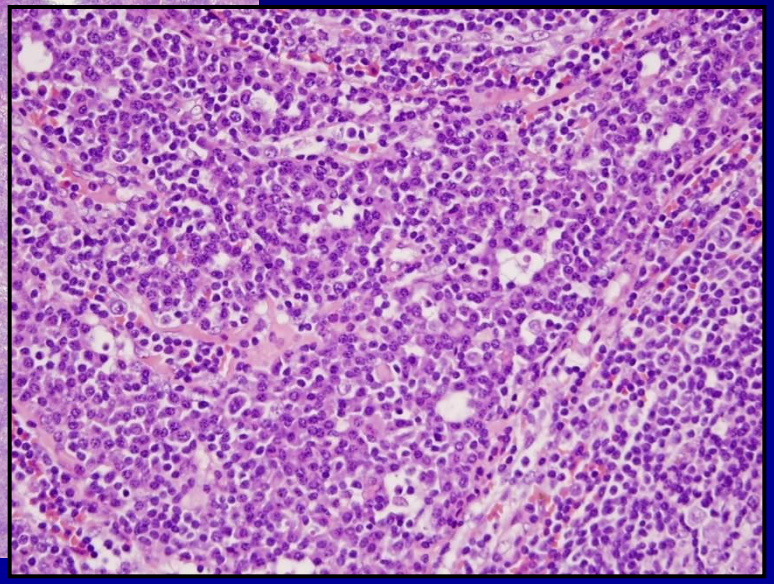
Polytypic plasma cells and B-cells

Human herpes virus 8 (KSHV) -

Plasma Cell CD (Unicentric)







Differential Diagnosis of Plasma Cell CD (Unicentric)

Rheumatoid arthritis	Grossly smaller No H-V lesions
Plasmacytoma	Replacement of LN architecture
Multicentric CD	HHV-8+ (usually HIV+)

Multicentric Castleman Disease

Clinical Features

Usually associated with systemic symptoms

Often associated with HIV infection

Lymphadenopathy – 100% of patients

Hepatosplenomegaly, effusions, skin rash +/-

<u>Laboratory</u>

Elevated ESR, anemia, thrombocytopenia

Polyclonal hypergammaglobulinemia

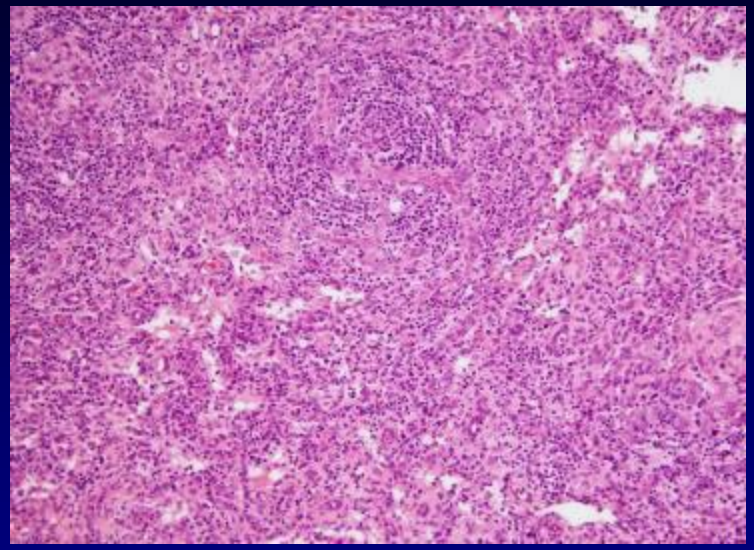
Multicentric Castleman Disease

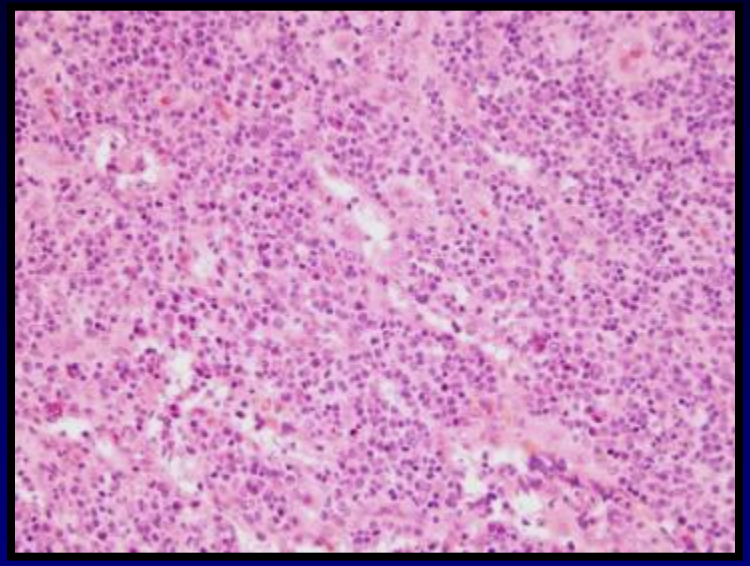
Histologic and Immunophenotypic Features

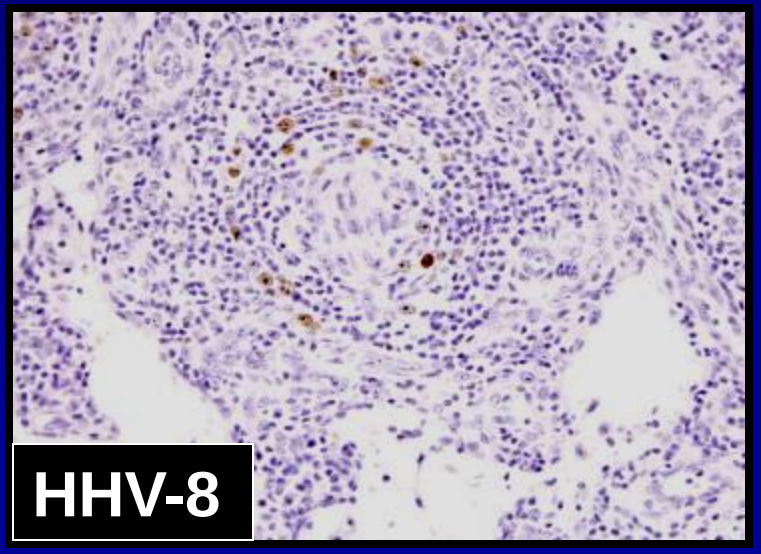
- Similar to unicentric plasma cell variant
  - Interfollicular sheets of plasma cells
  - Atypical plasma cells
- Follicles show H-V lesions
- Blurring of boundary between germinal centers and mantle zones
- HHV-8+, EBV+/-
- Plasma cells can be monotypic

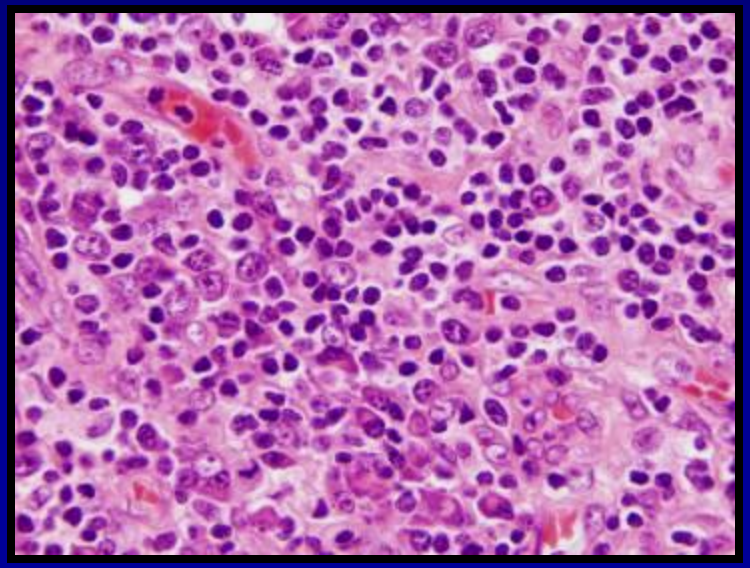
Multicentric Castleman Disease

HIV Positive



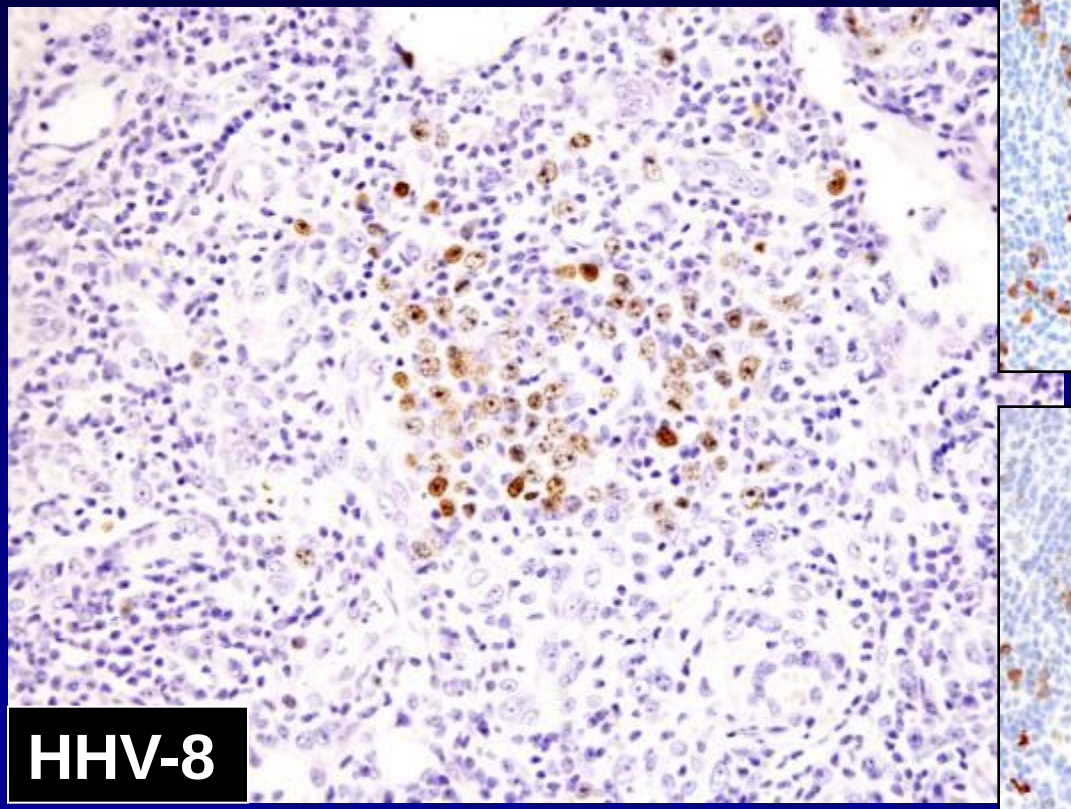


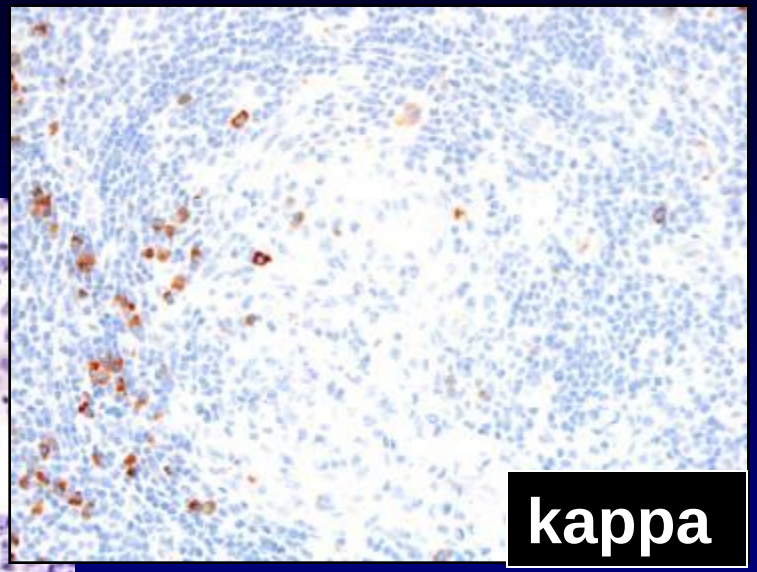


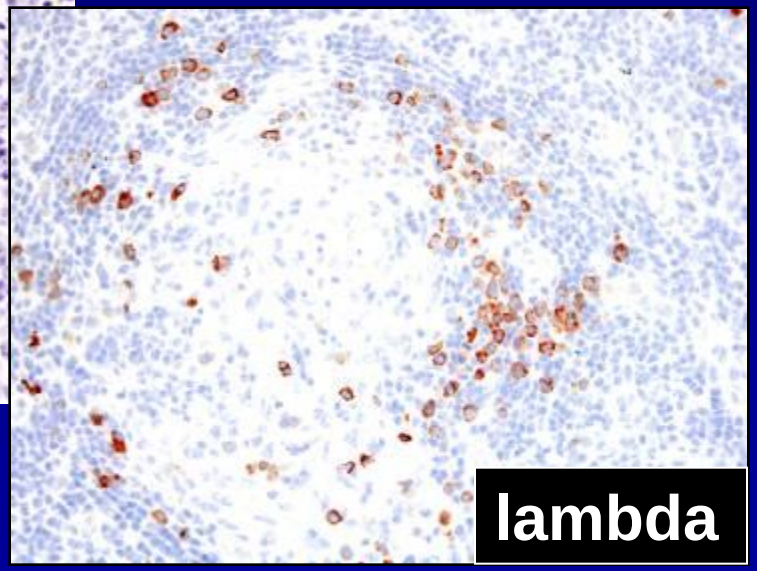


Multicentric Castleman Disease

Presence of "Microlymphoma"







Differential Diagnosis of Multicentric Castleman Disease

Unicentric plasma cell variant	Unicentric HHV-8- No HIV infection
Hyaline-vascular variant	HV lesions Big follicles Interfollicular vascularity
Peripheral T-cell lymphoma	Architecture effaced Monoclonal T-cell population

POEMS Syndrome

Polyneuropathy, **o**rganomegaly, **e**ndocrinopathy, **M** protein, **s**kin changes

Paraneoplastic syndrome caused by elevated angiogenic and inflammatory cytokines

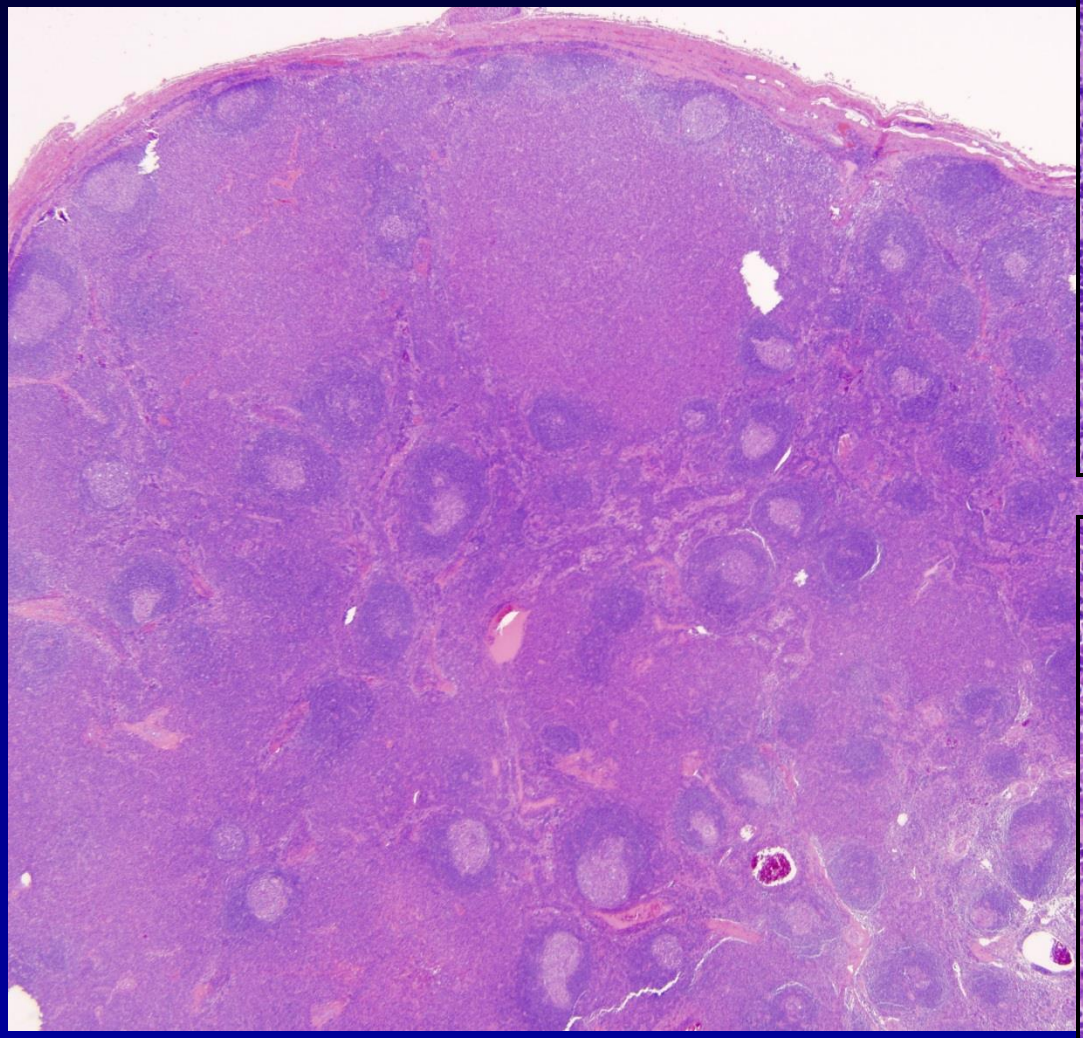
Associated with underlying plasma cell dyscrasia

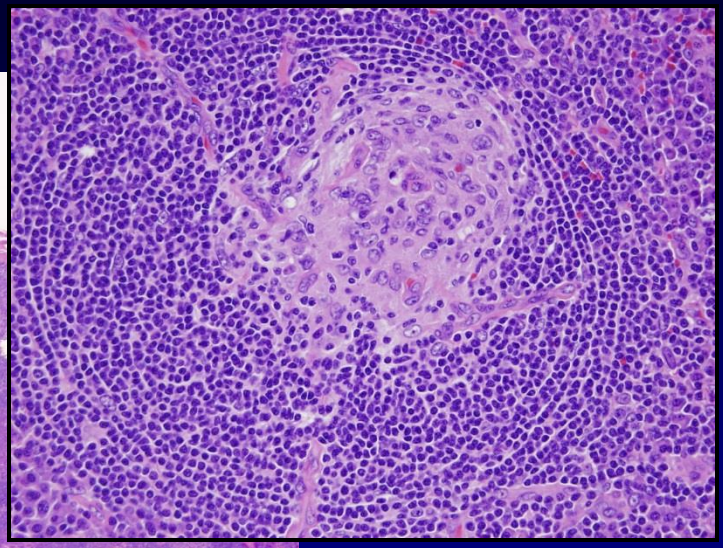
- 95% lambda
- Often osteosclerotic

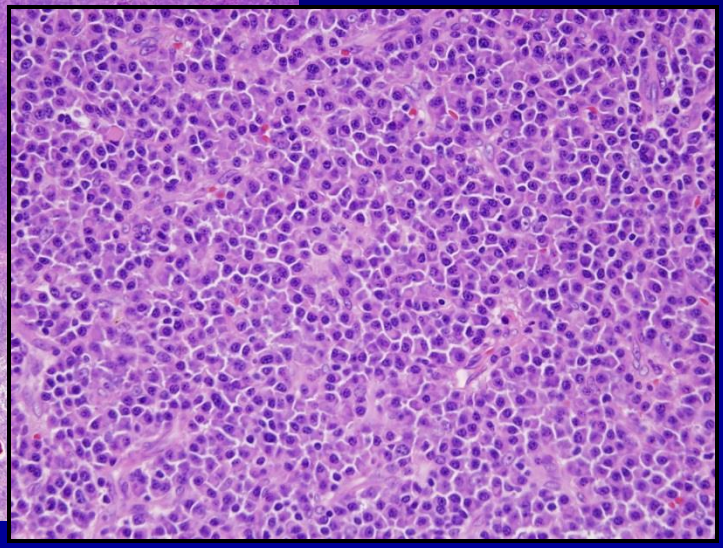
50% of patients have Castleman disease, plasma cell variant

Multicentric Castleman Disease

POEMS Syndrome







TAFRO Syndrome

Thrombocytopenia, **A**nasarca, Fever, **R**eticulin fibrosis in BM, and **O**rganomegaly

Also known as Castleman-Kojima disease

Most common in Japan

Women most often affected

? Cytokine storm attributable to IL-6 and VEGF

J Clin Exp Hematop 53: 95, 2103

Seminoma

Clinical Features

Most common germ cell tumor of testis

Age range: 30-45 years

80-90% have a palpable mass

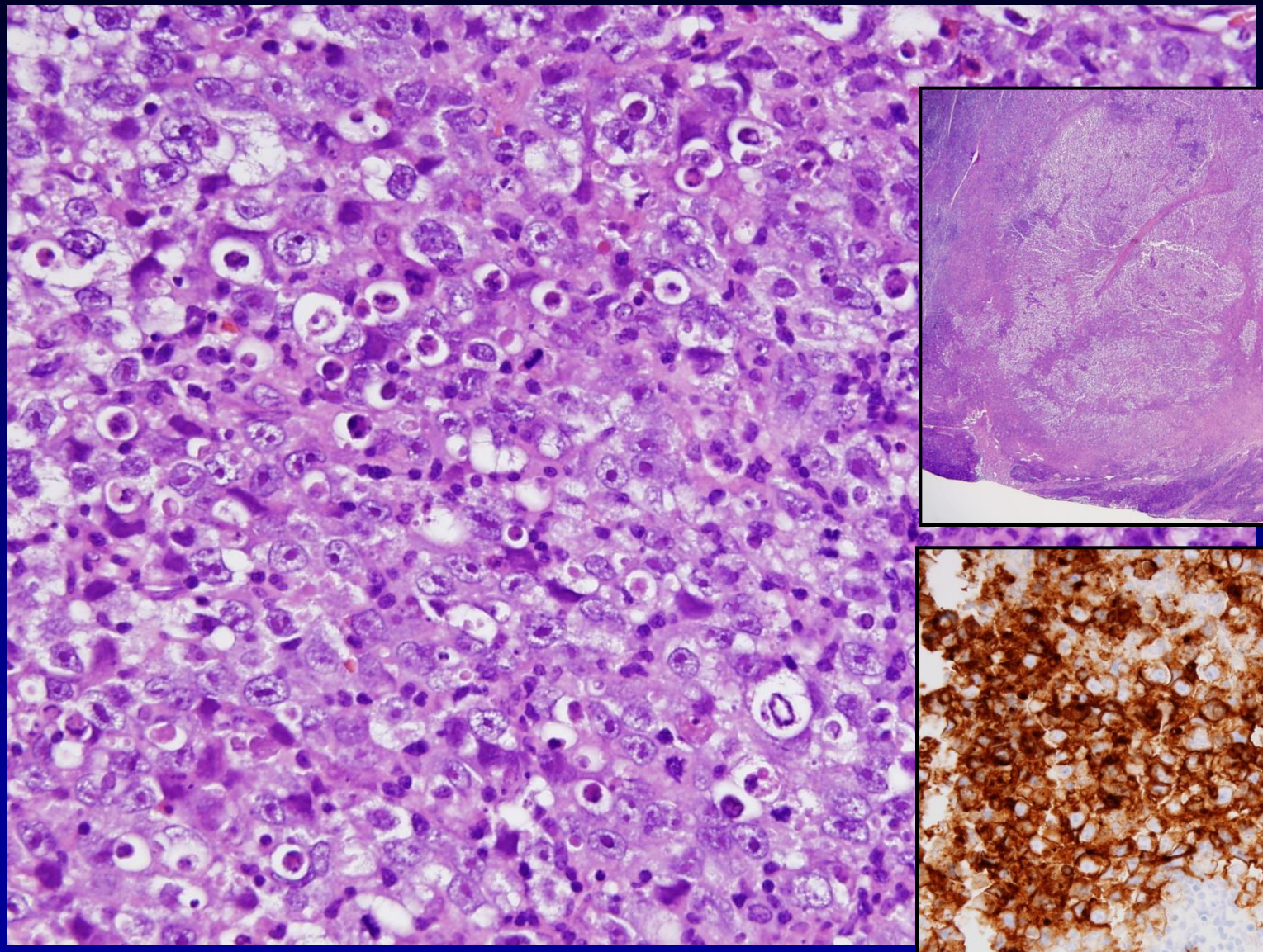
Often no symptoms; testicular pain ~20%

Laboratory tests: ↑LDH
↑HCG (~10%)
AFP negative

75% of pts have stage I (localized) disease

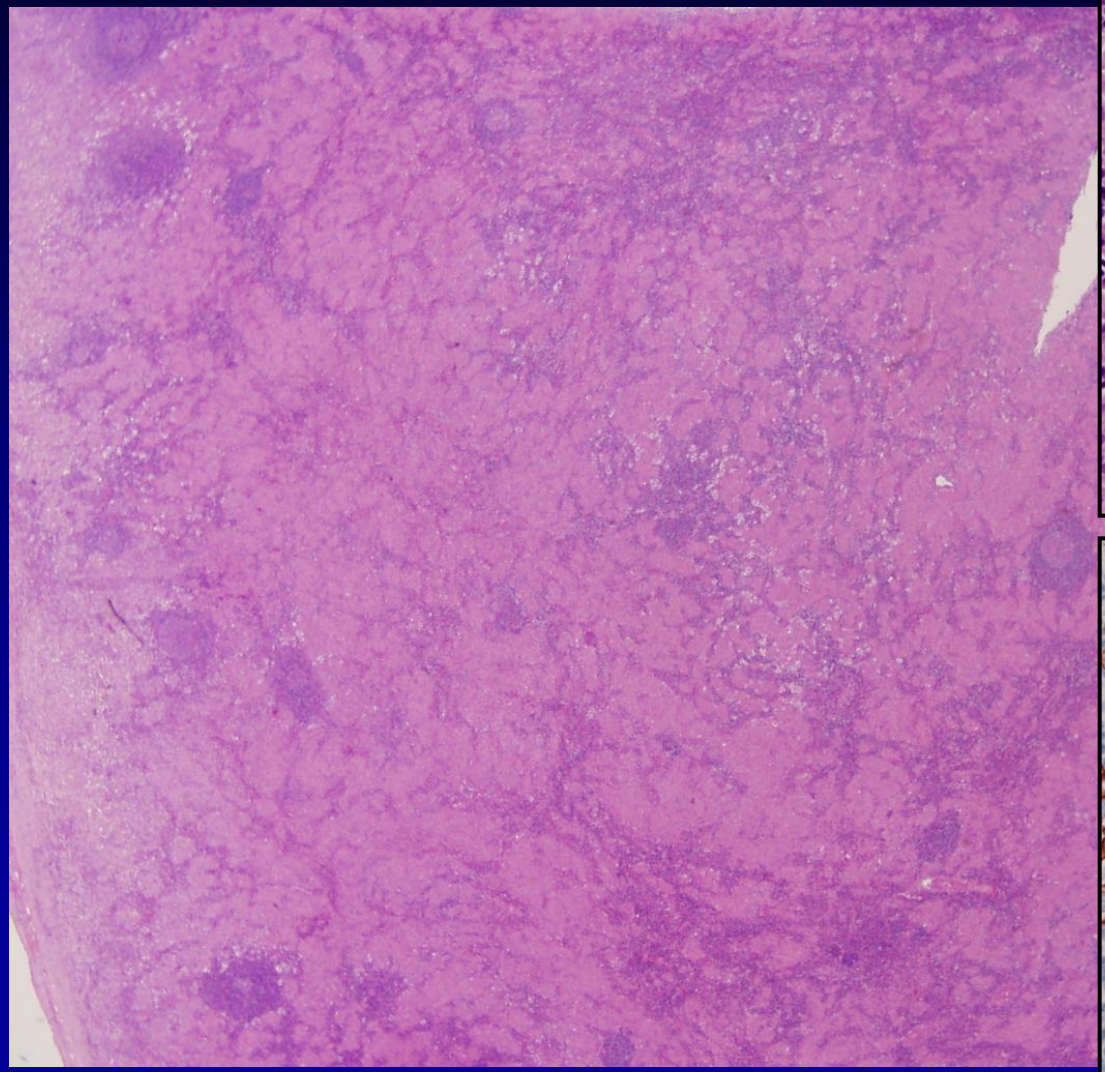
Metastases to: retroperitoneal LNs, lungs

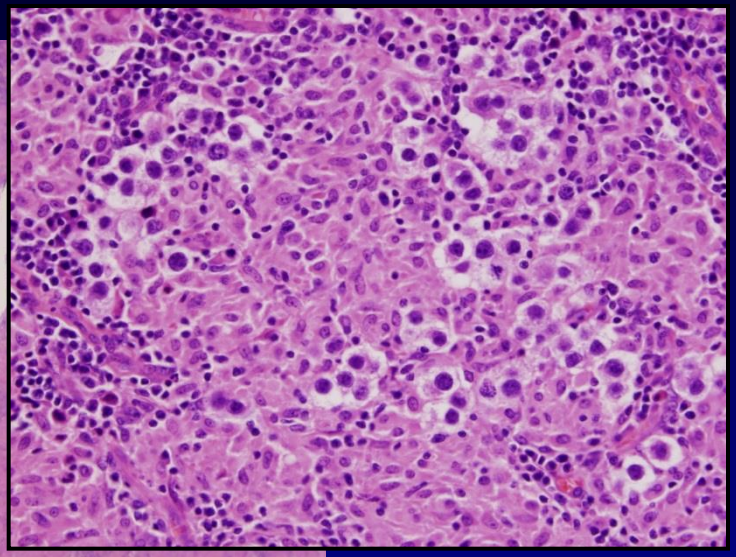
Metastatic Seminoma to LN

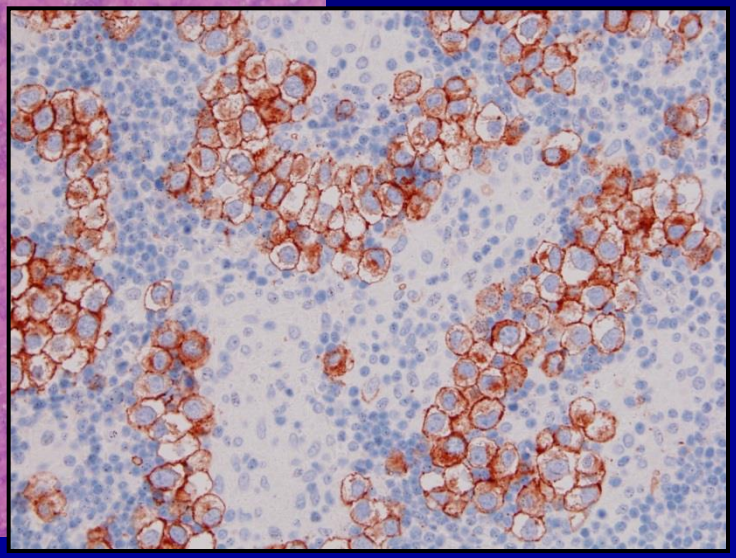


Metastatic Seminoma to LN

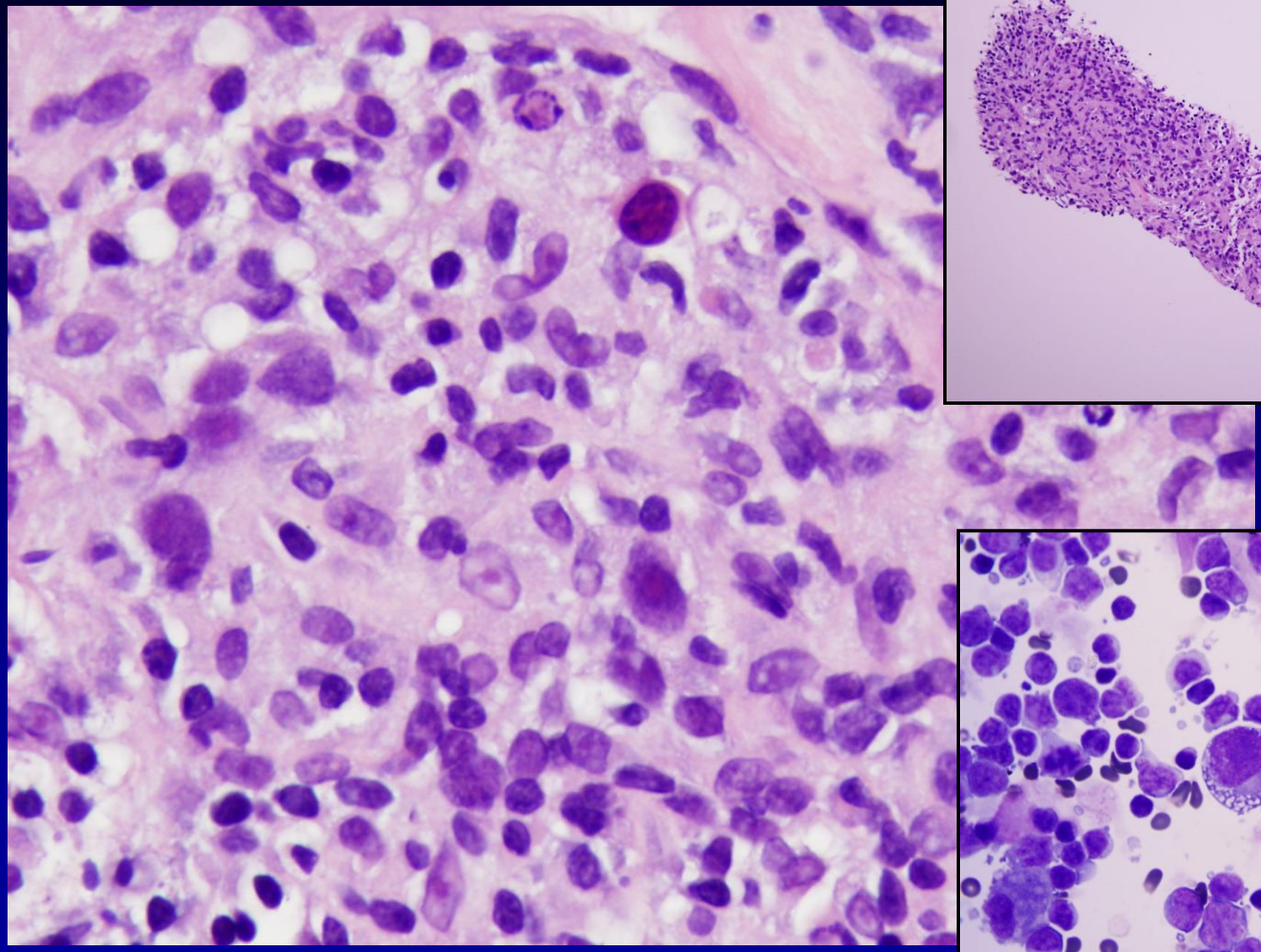
Many Granulomas

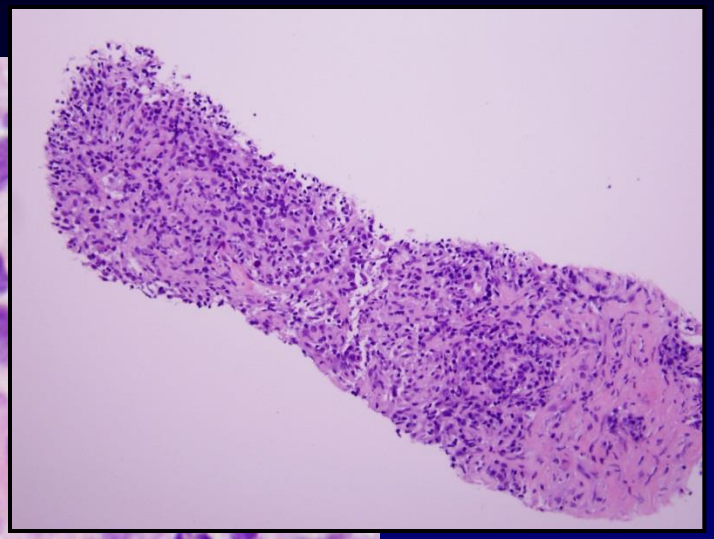


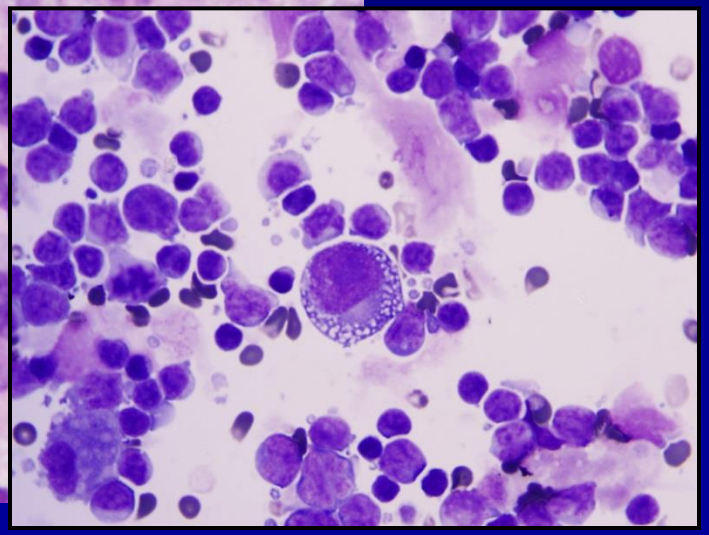




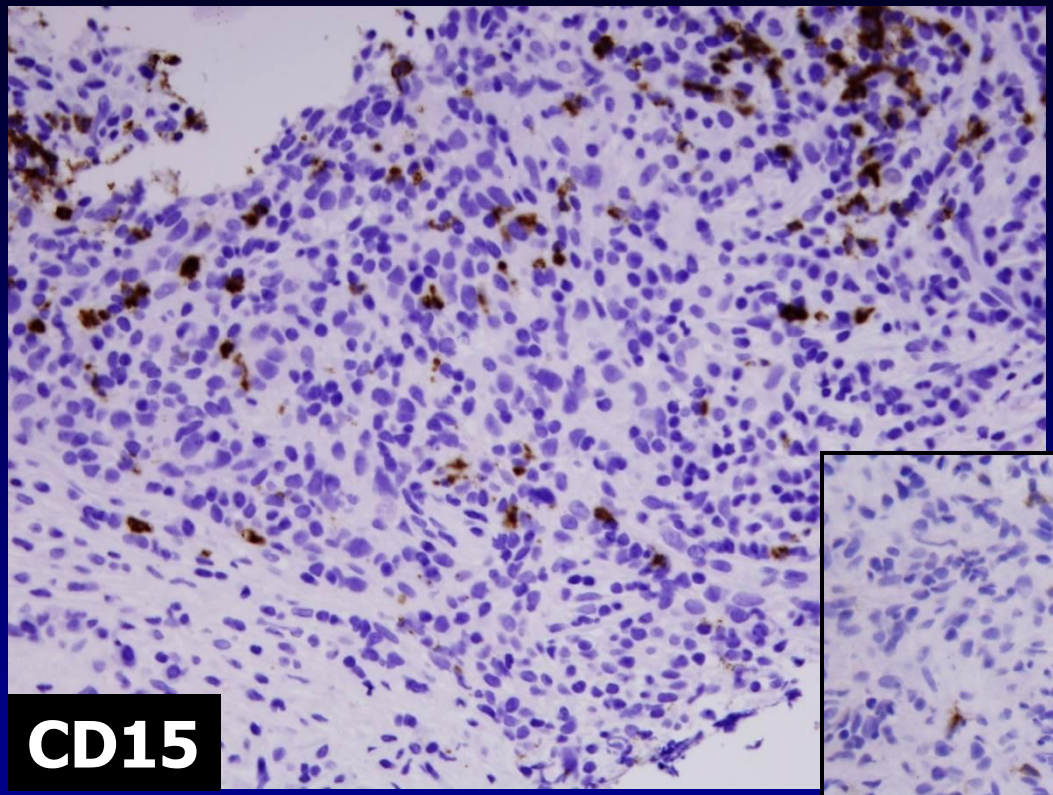
Mediastinal Mass in 18 yo

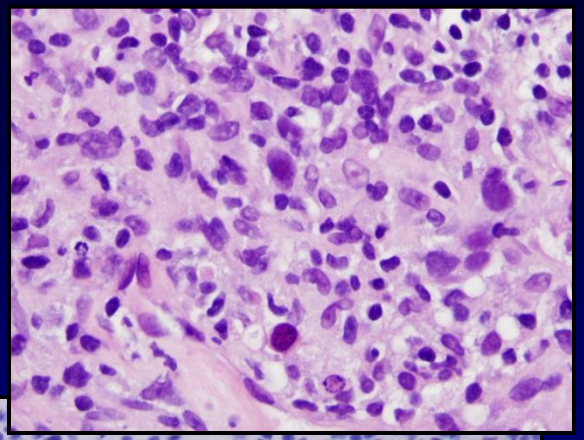


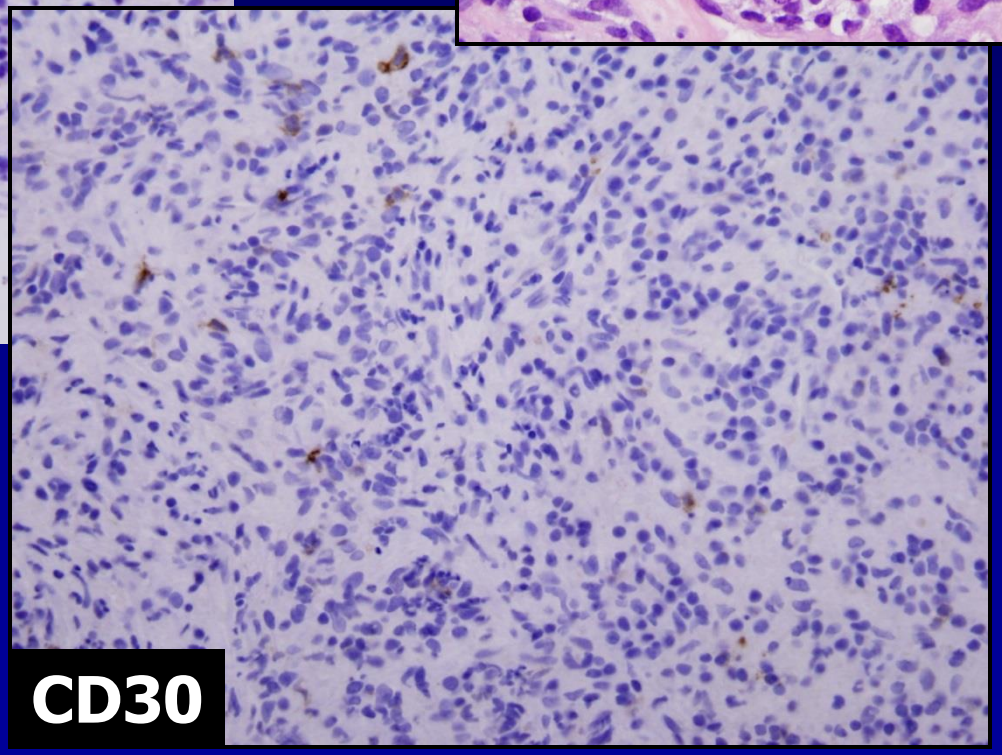




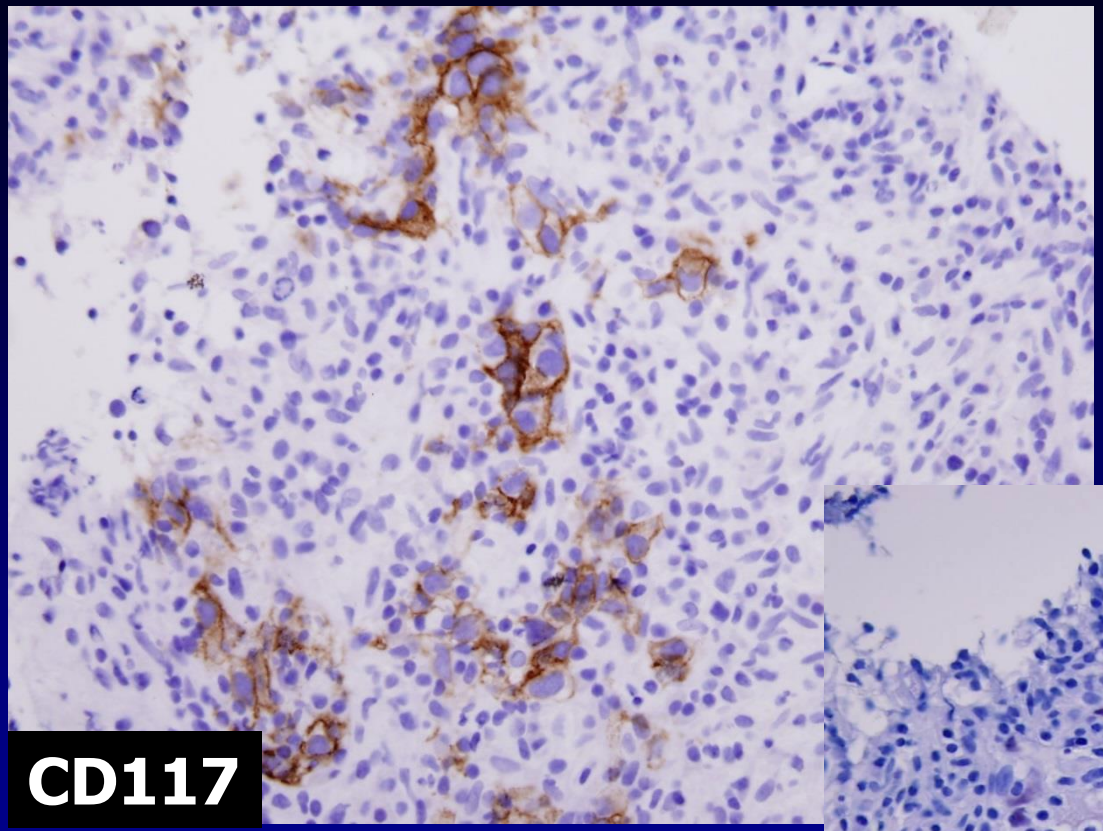
Mediastinal Mass in 18 yo



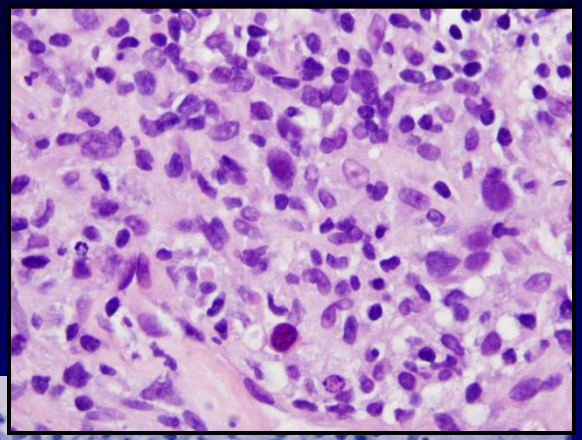


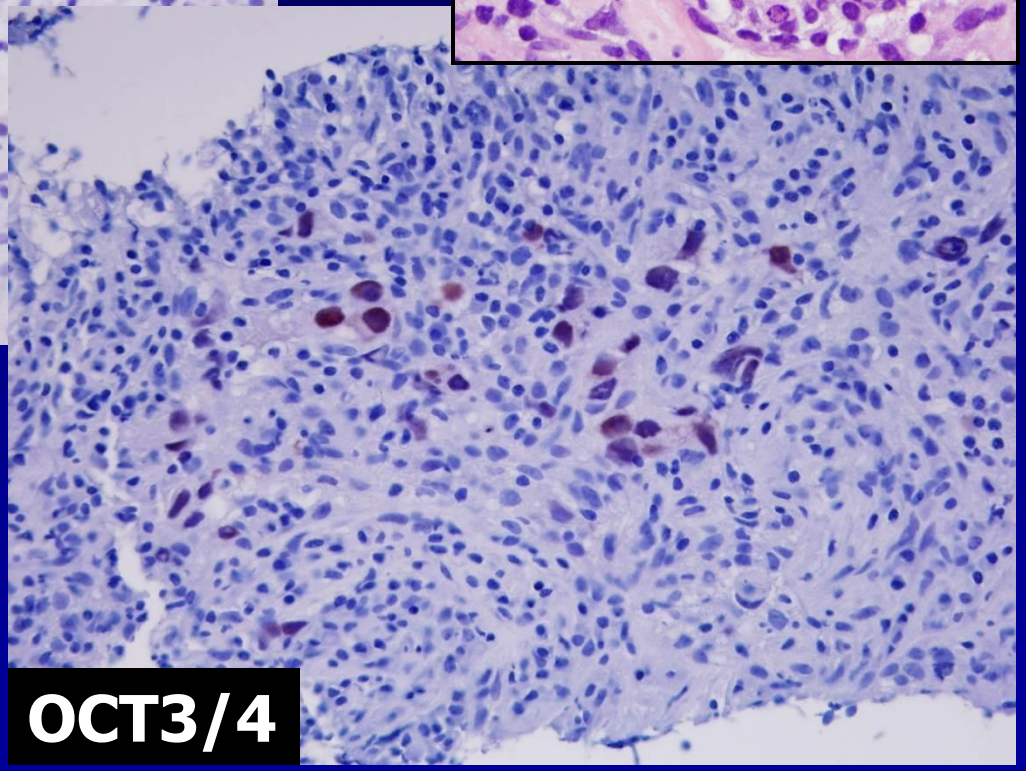


Mediastinal Mass in 18 yo



CD117





OCT3/4

Dx: Seminoma

Primary Mediastinal Seminoma
Clinical Features

3-4% of tumors in the mediastinum

Mean age: 32 years (range, 19-56)

Over 90% of patients are men, but rare women

Usually associated with the thymus

Ectopic germ cells or thymic cells with germ cell potential?

Present as mass

+/- compressive symptoms

Hum Pathol 46: 376, 2015

Seminoma
Immunohistochemistry

Antibody	Frequency
SOX17	> 95%
OCT3/4	~ 90%
SALL4	~ 90%
CAM5.2 (low mw keratin)	80-90%
PLAP	80-90%
CD117/KIT	80-90%
MAGEC2	80-90%
CD3	Negative
CD20	Negative
CD30	Negative

Differential Diagnosis of Metastatic Seminoma

Diffuse large B-cell lymphoma	Not cohesive, no abundant pale cytoplasm CD20+, CD45/LCA+
Hodgkin lymphoma	Reed-Sternberg/Hodgkin cells CD15+/-, CD30+, PAX5+
Anaplastic large cell lymphoma	Hallmark cells T-cell; ALK+
Granulomatous lymphadenitis	No tumor cells Necrotizing granulomas Evidence of organism

Nasopharyngeal Carcinoma
Clinical Features

Rare in US (72X more common in China/Taiwan)

Men > women

Median age: 30-50 yo (~15% in children)

Presentation

- Nasal symptoms
  - Obstruction, discharge, pain, cranial nerve palsies
- Asymptomatic posterior cervical mass

Metastases

- LNs, lungs, bones, liver

Nasopharyngeal Carcinoma
Pathologic Features

Two general pathologic types of NPC

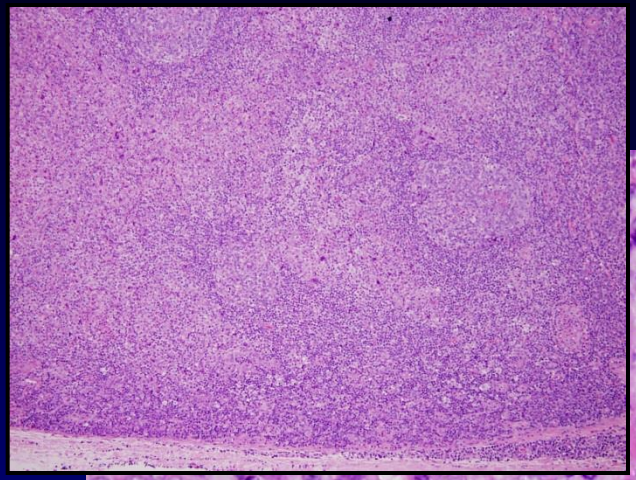
Keratinizing (linked to HPV)

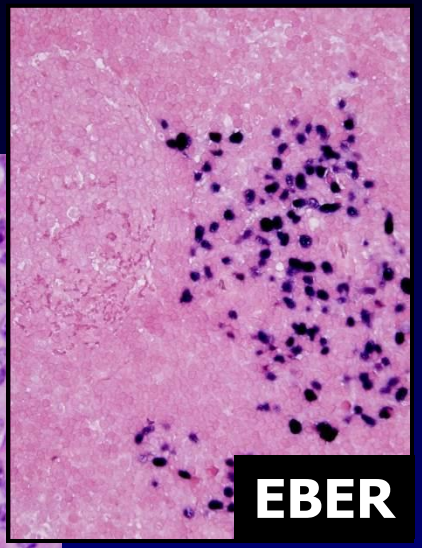
Non-keratinizing (linked to EBV)

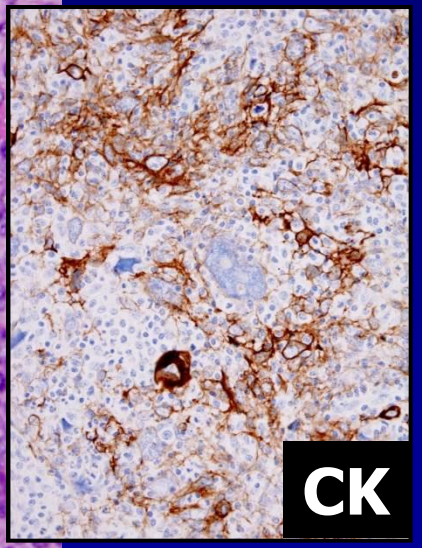
- **Differentiated**
- **Undifferentiated (lymphoepithelioma)**

Undifferentiated type more common in children

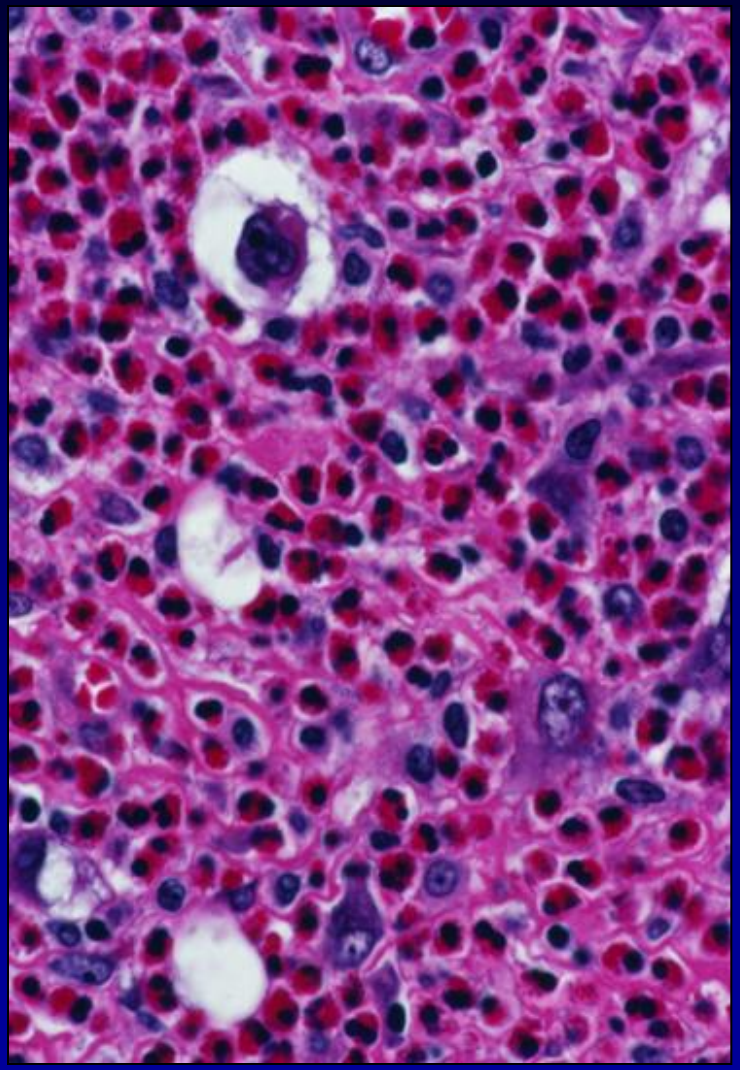
Nasopharyngeal Carcinoma Metastatic to LN

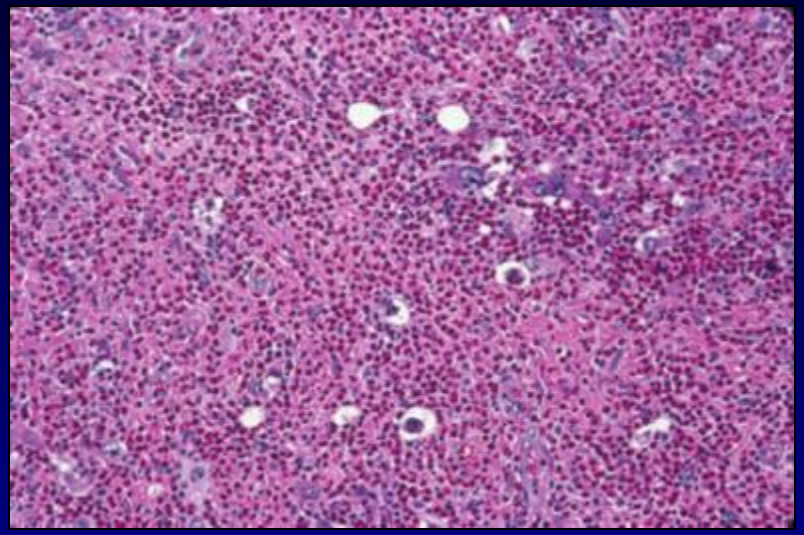


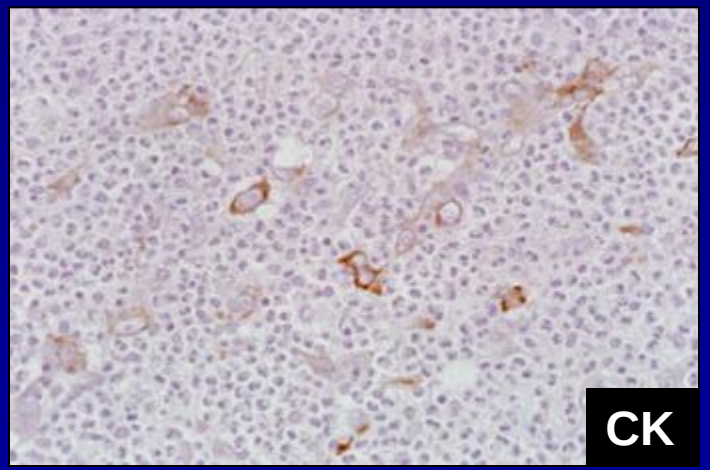




Nasopharyngeal Carcinoma Metastatic to LN
Eosinophil Rich







Arch Pathol Lab Med 116: 862, 1992

Differential Diagnosis of Metastatic Nasopharyngeal Carcinoma

Classical HL	**Fibrous band and RS/H cells** **CD15+/-, CD30+, PAX5+, CK-**
DLBCL - NOS	**Sheets of large cells** **CD20+ CD45/LCA+ CD15-**
Peripheral T-cell lymphoma	**Cytologic atypia of T-cells** **Aberrant immunophenotype common** **Monoclonal TCR gene rearrangements**

Thymoma

Clinical Features

Median age: 30-40 years (up to elderly)

Men and women equally affected

Anterior mediastinal mass

30-50% Asymptomatic

30% Local compression

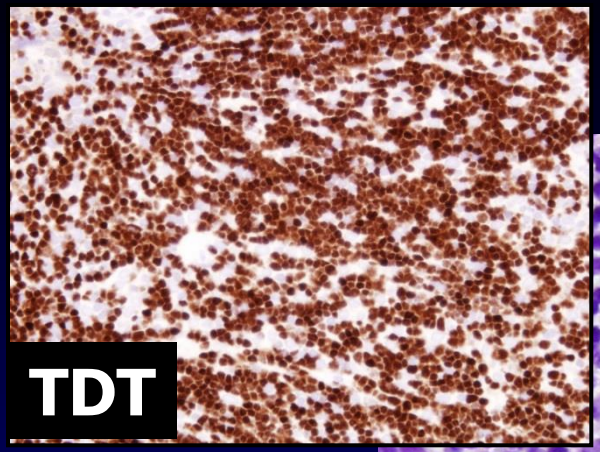
20% Myasthenia gravis

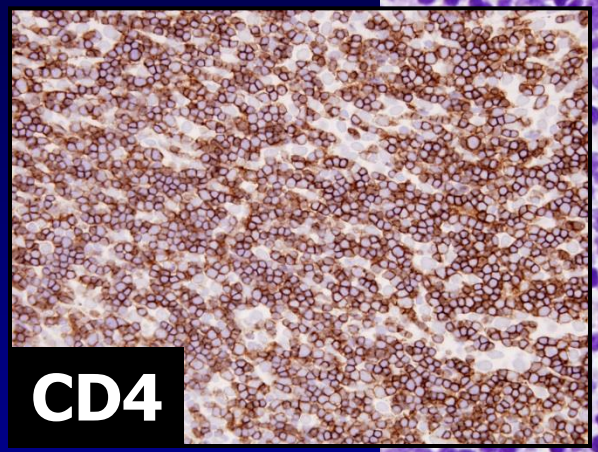
Pathology

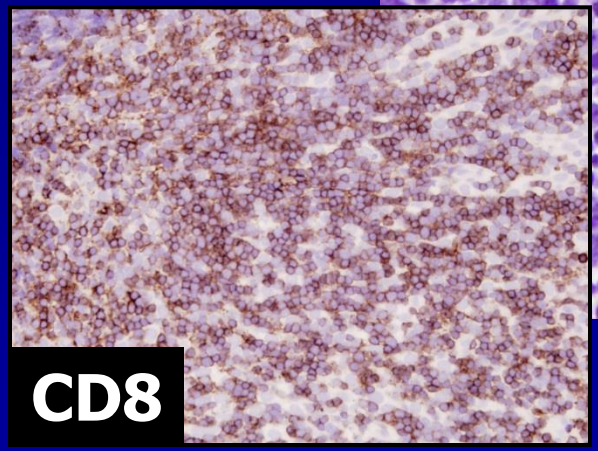
Epithelial cell rich

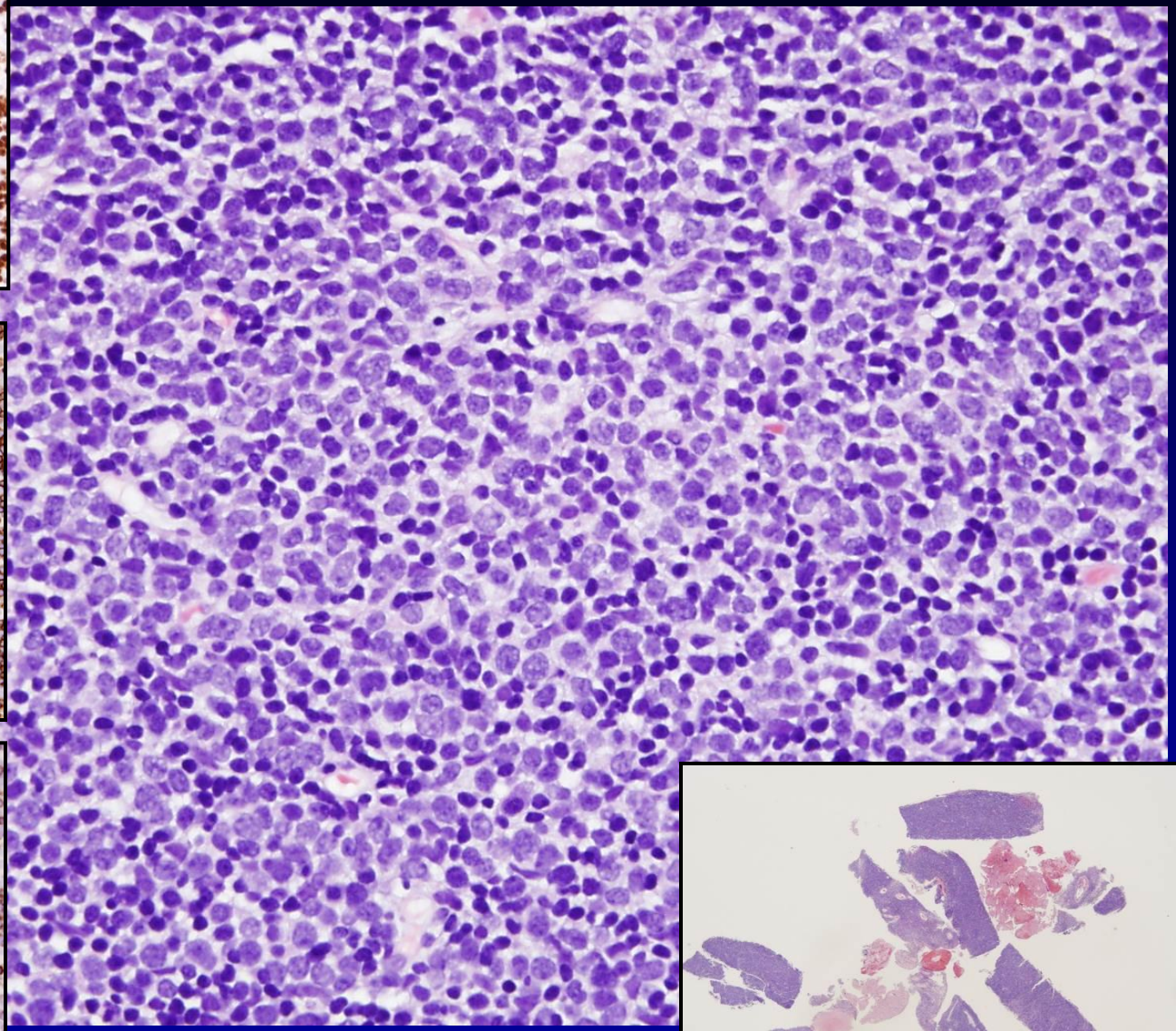
Thymocytes and epithelial cells (B1 or B2)

Thymoma

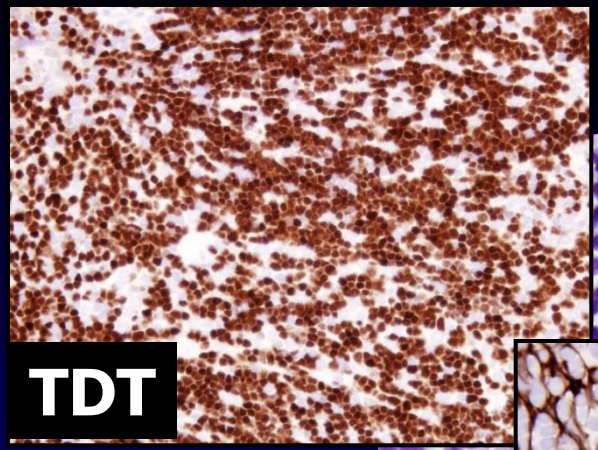


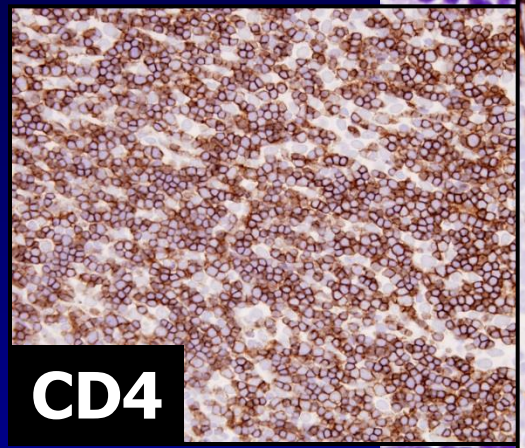


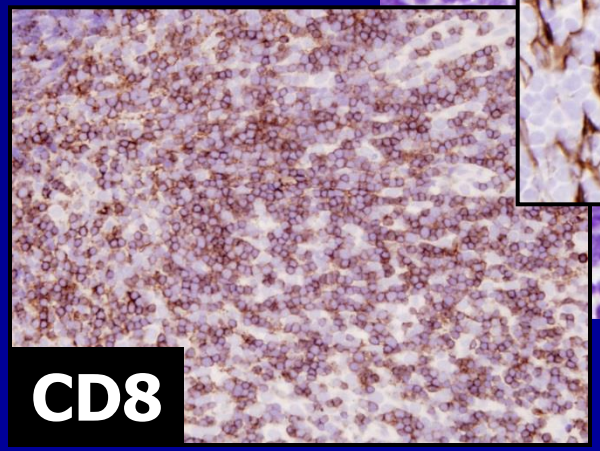


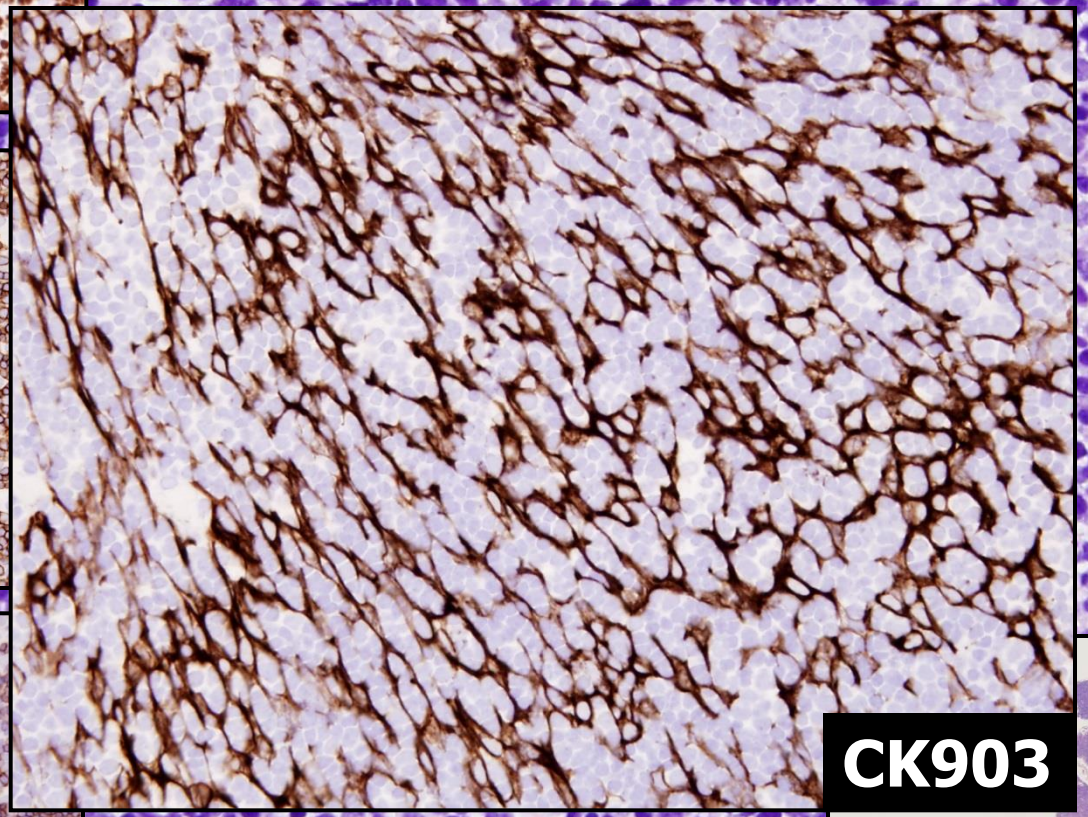


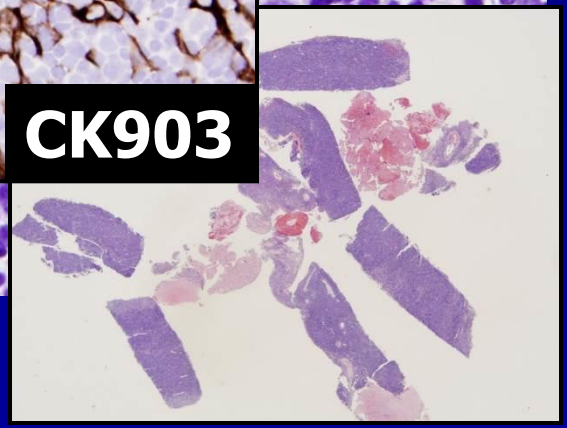
Thymoma











Thymoma

Immunophenotype

Immunohistochemistry

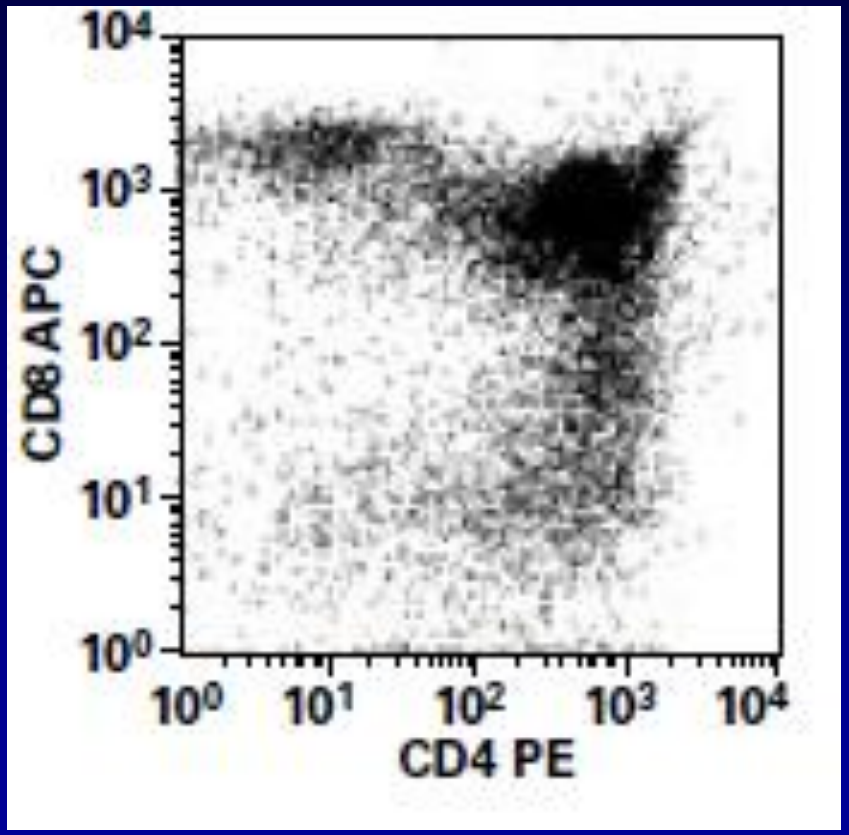
- **Thymic epithelial cells**
  - CK5/6, CK903, pankeratin, p63
- **Thymocytes**
  - T-cell, CD4, CD8, TdT

Flow Cytometry

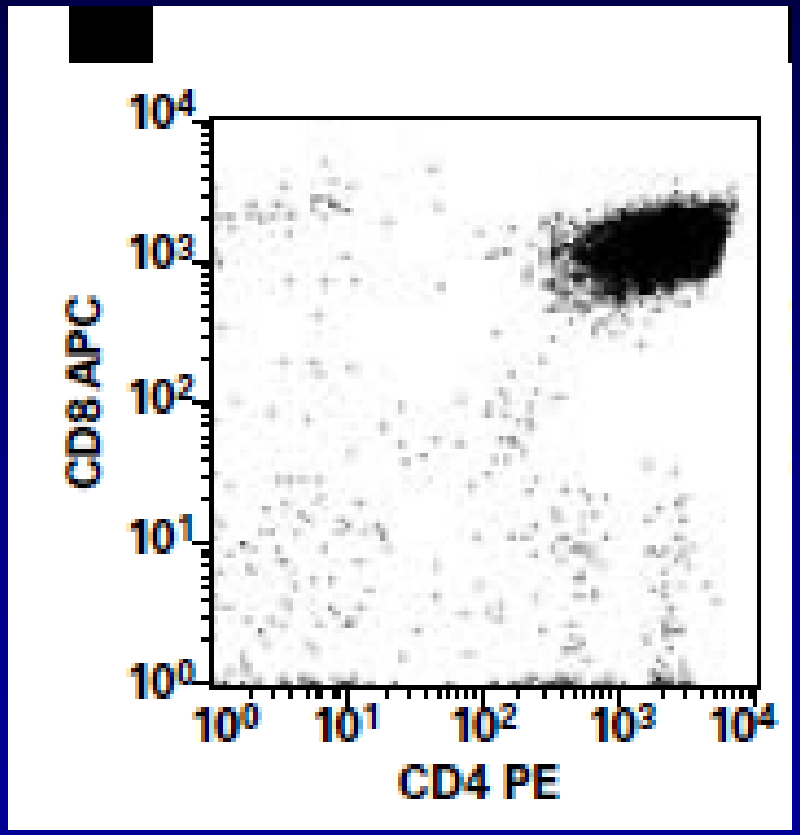
- Thymocytes show maturation (smear)

Thymoma
Immunophenotype

Thymoma



T-lymphoblastic lymphoma



Li et al. Am J Clin Pathol 121:268, 2004

Differential Diagnosis of Thymoma

T-lymphoblastic lymphoma	Younger patients Often PB and BM involvement No CK+ cells Tight clusters by flow cytometry
DLBCL - NOS	Sheets of large cells CD20+ CD45/LCA+ CD15-
Nodular sclerosis HL	Fibrous bands and lacunar cells CD15+/-, CD30+, PAX5+, CK-

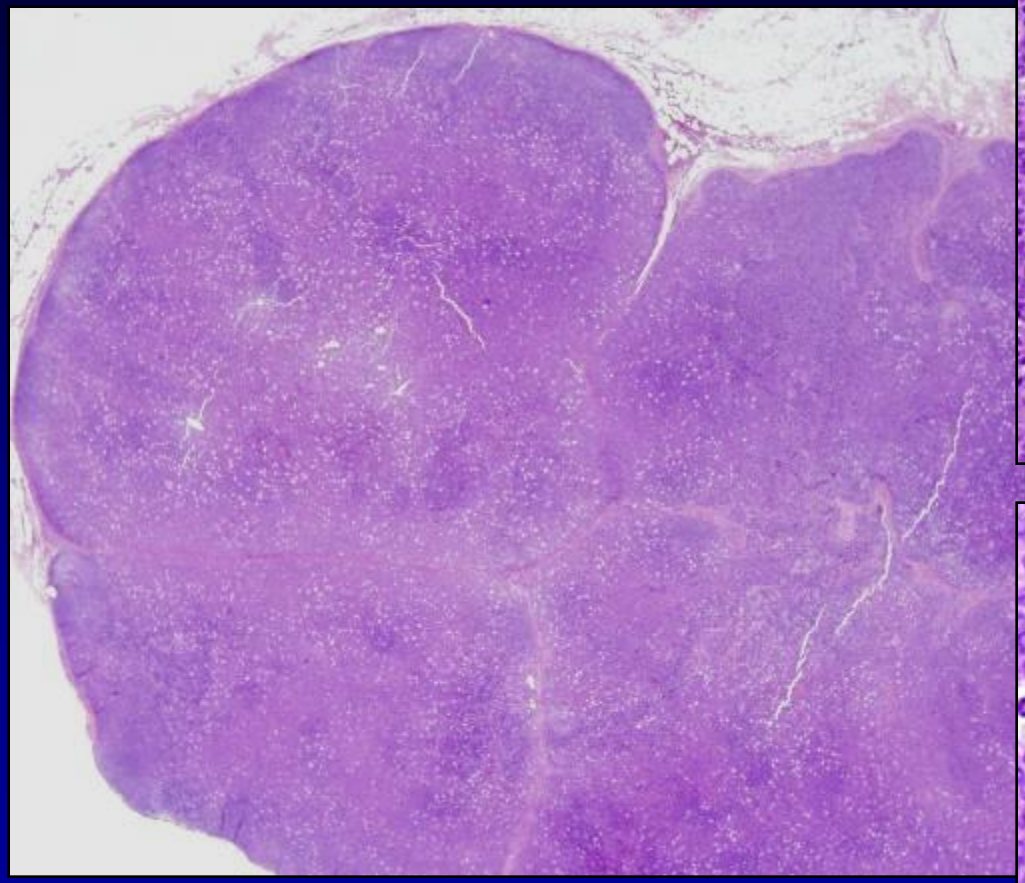
Myeloid Sarcoma
Clinical Features

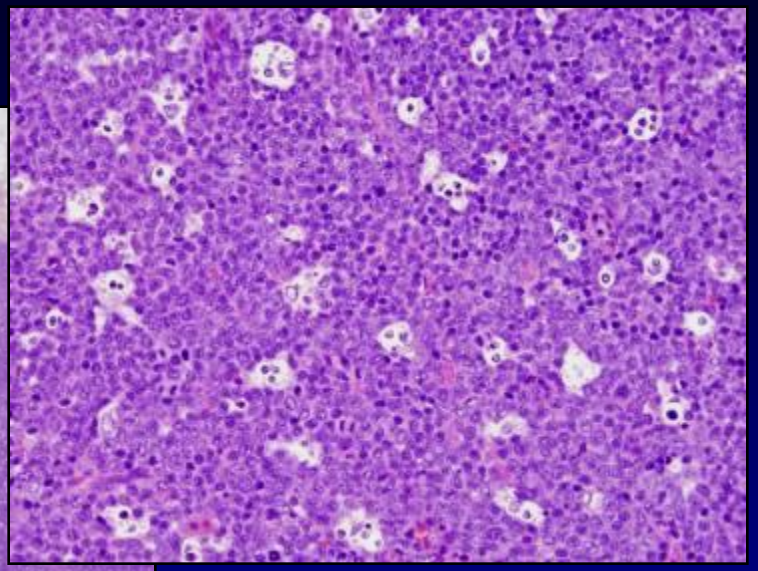
Three scenarios:

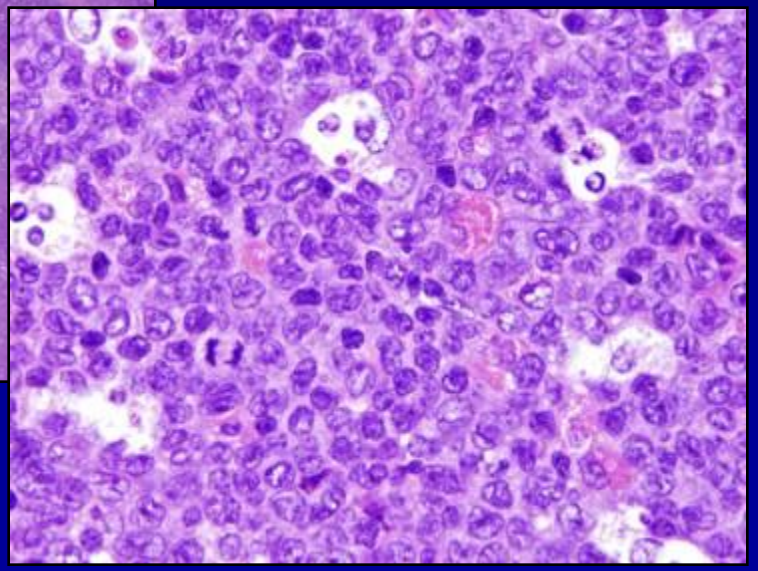
1. Concurrent evidence of AML in blood and bone marrow
2. History of AML (first sign of relapse)
3. Precedes systemic AML

Can also occur in pts with myelodysplastic syndrome (MDS), myeloproliferative neoplasm (MPN) or MDS/MPN

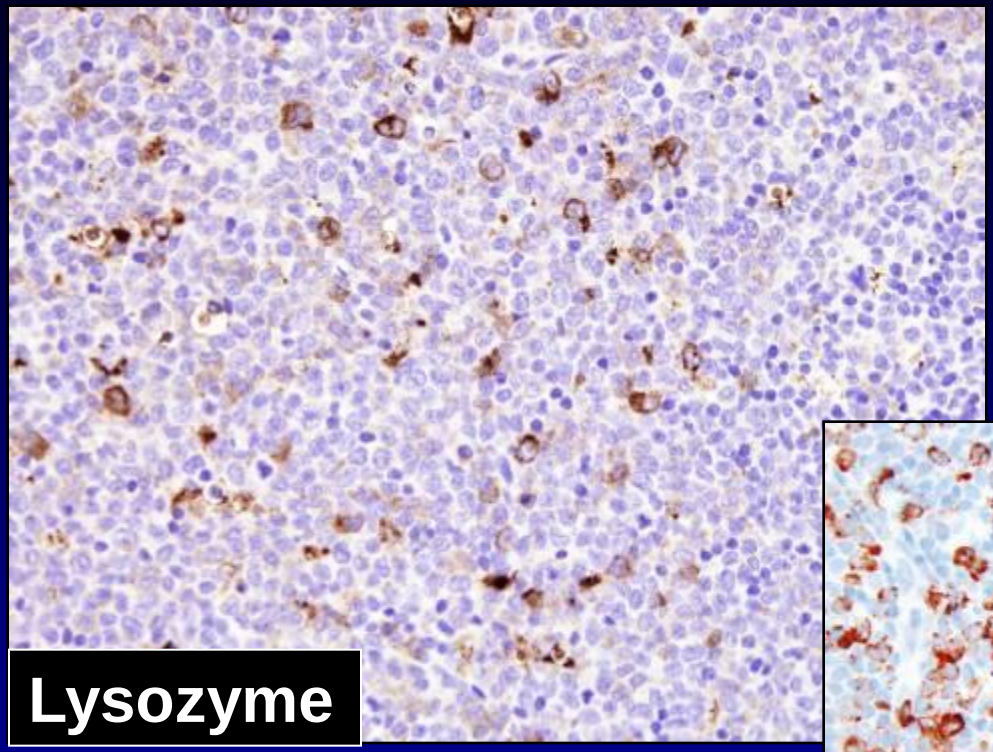
Myeloid (Granulocytic) Sarcoma

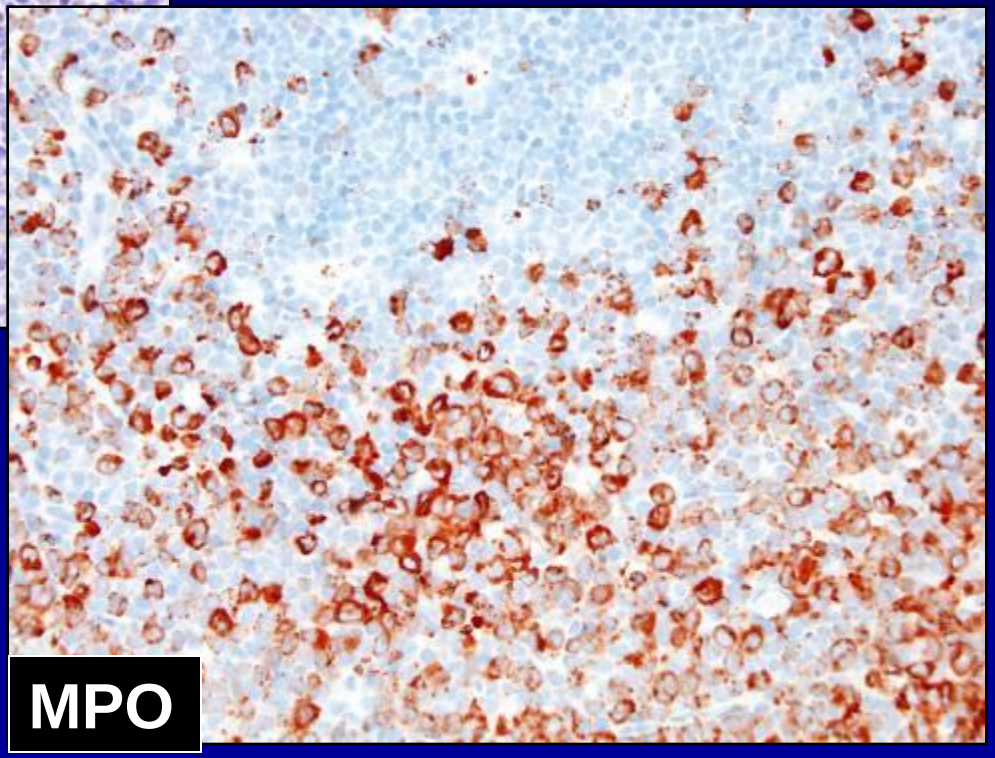






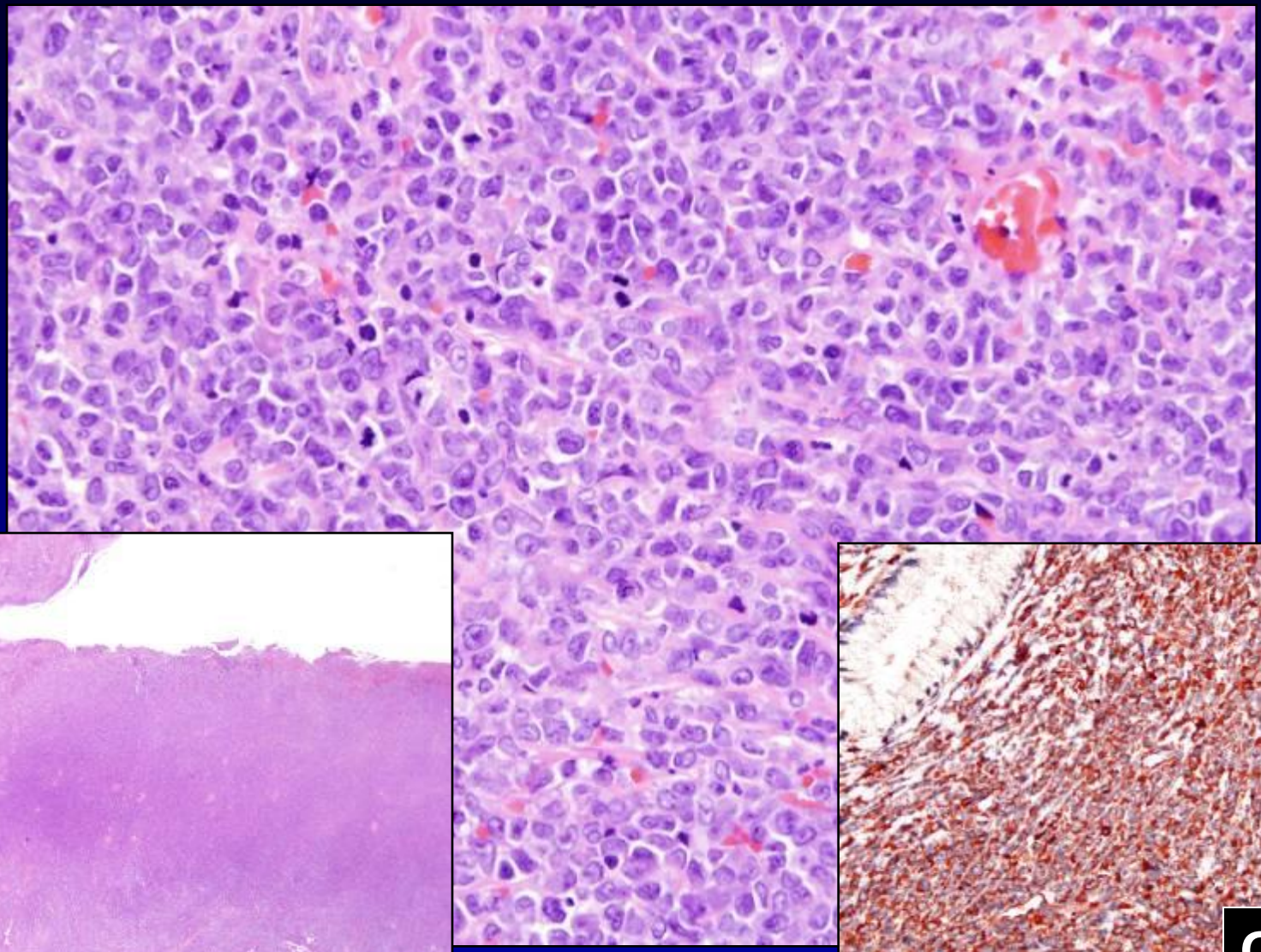
Myeloid Sarcoma





Myeloid (Monocytic) Sarcoma

Uterine Cervix



Myeloid Sarcoma
Histologic Features

Diffuse pattern
Often paracortical
Blasts or promonocytes

Immature chromatin
- Thin nuclear membranes
- Small nucleoli
- Mitoses

When You Have The Fresh Specimen
Don't Forget

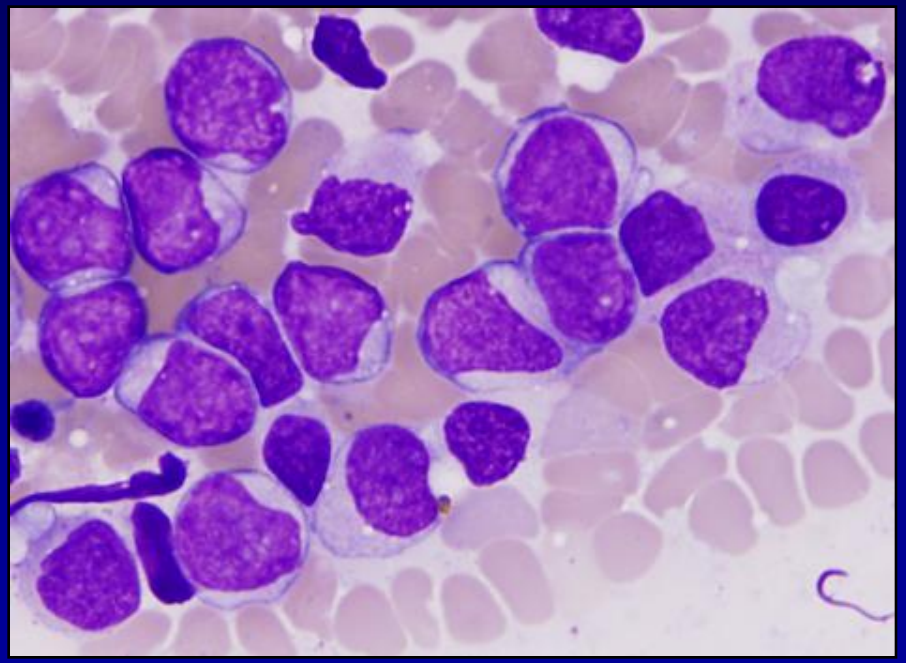
Look for the green color

Do a touch prep

Consider cytochemistry

- Myeloperoxidase
- Butyrate esterase

Triage for cytogenetics and molecular



Myeloid Sarcoma
Immunohistochemistry

Antibody	Frequency
Lysozyme	>95%
CD117 (c-kit)	>95%
CD43	>95%
Myeloperoxidase	80-90%
CD45/LCA	70-80%
CD15	40-50%
CD99	30-40%
TdT	30-40% (dim)
CD34	30-40%
CD56	30-40%
PAX5	+ in cases with t(8;21)
CD20	Rare
CD3 or CD5	Negative

Differential Diagnosis of Myeloid Sarcoma

Diffuse large B-cell lymphoma	Thicker nuclear membranes More prominent nucleoli B-cell
Burkitt lymphoma	Thicker nuclear membranes Multiple basophilic nucleoli B-cell CD10+, BCL-6+, BCL-2-
Anaplastic large cell lymphoma	Hallmark cells T-cell; ALK+
Lymphoblastic lymphoma	TdT+ Immature B- or T-cell lineage
Ewing sarcoma	CD99 +/- , keratin +/- Myeloid antigens -