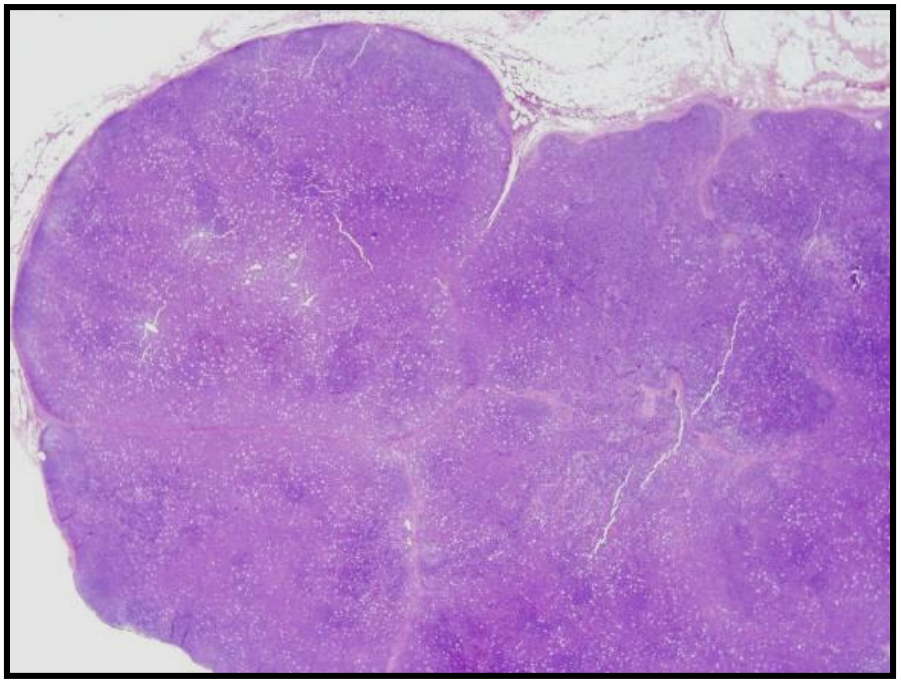
Mimics of Lymphoma



L. Jeffrey Medeiros, M.D.
MD Anderson Cancer Center

Outline

Infectious mononucleosis

Kikuchi-Fujimoto lymphadenitis

Castleman disease

Seminoma

Nasopharyneal carcinoma

Thymoma

Myeloid sarcoma

Infectious Mononucleosis

Basic Facts

Caused by Epstein-Barr virus (HHV-4)

Spread by contact with human secretions

(Saliva to oral epithelium to B-cells)

Age of contact depends on living conditions

Poor - < 3 years

Good - 10-19 years

Incubation period is 2-5 weeks

M. A. Epstein

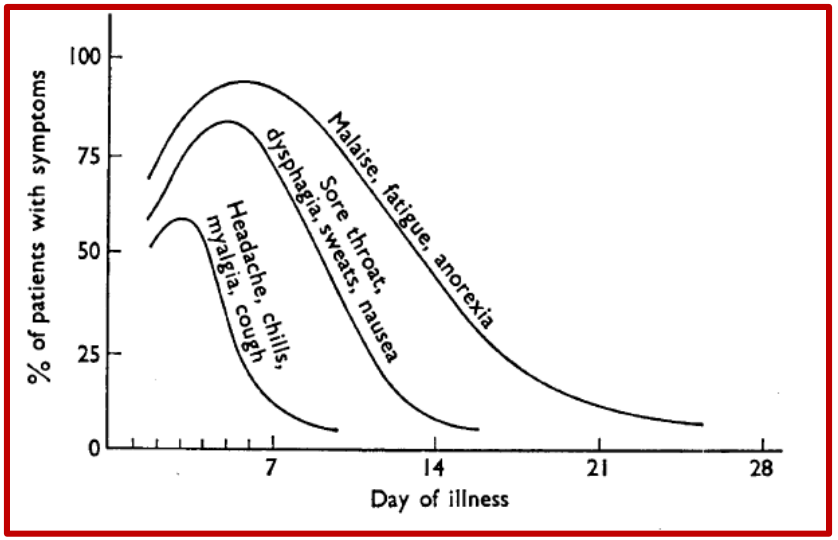
Yvonne Barr

First week **Humoral antibody response**

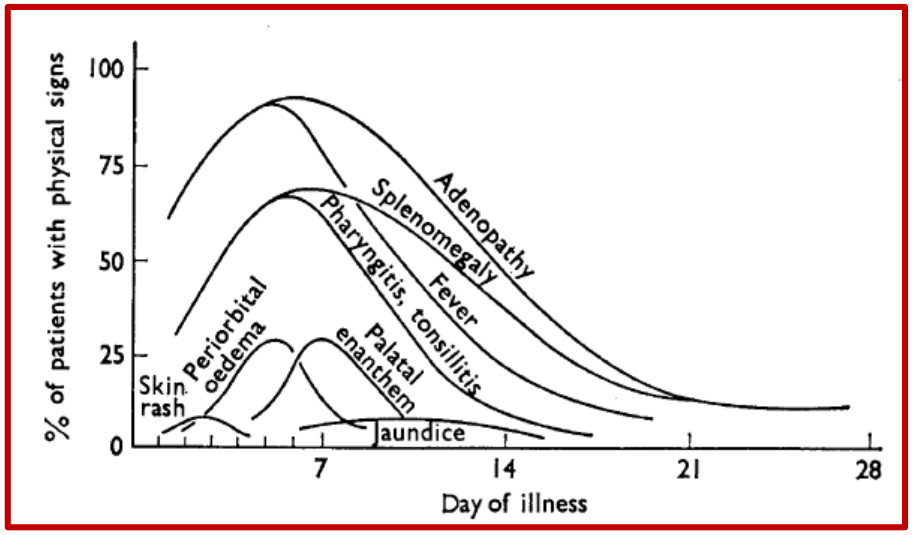
Second week **Cellular immune response**

Infectious Mononucleosis

Symptoms



Physical Findings



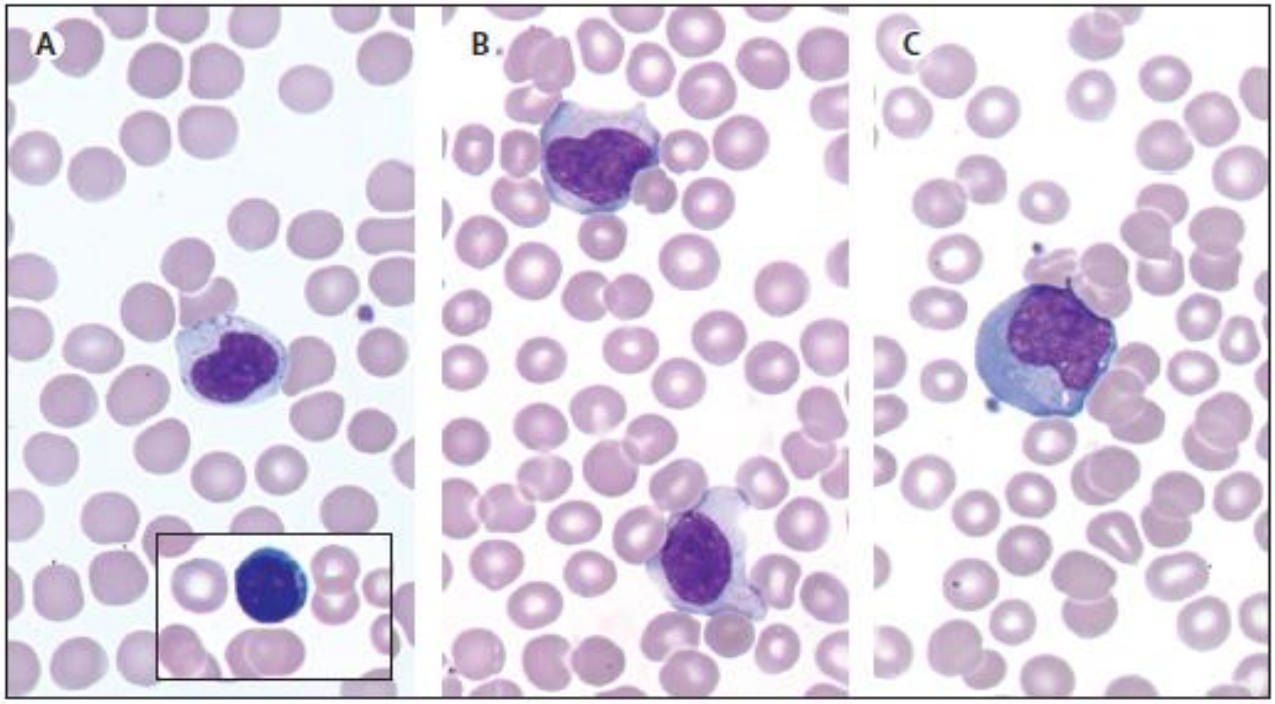
Laboratory Findings

Thrombocytopenia

Anemia

PB lymphocytosis with atypical lymphocytes

Infectious Mononucleosis
Lymphocytosis (Downey Cells)



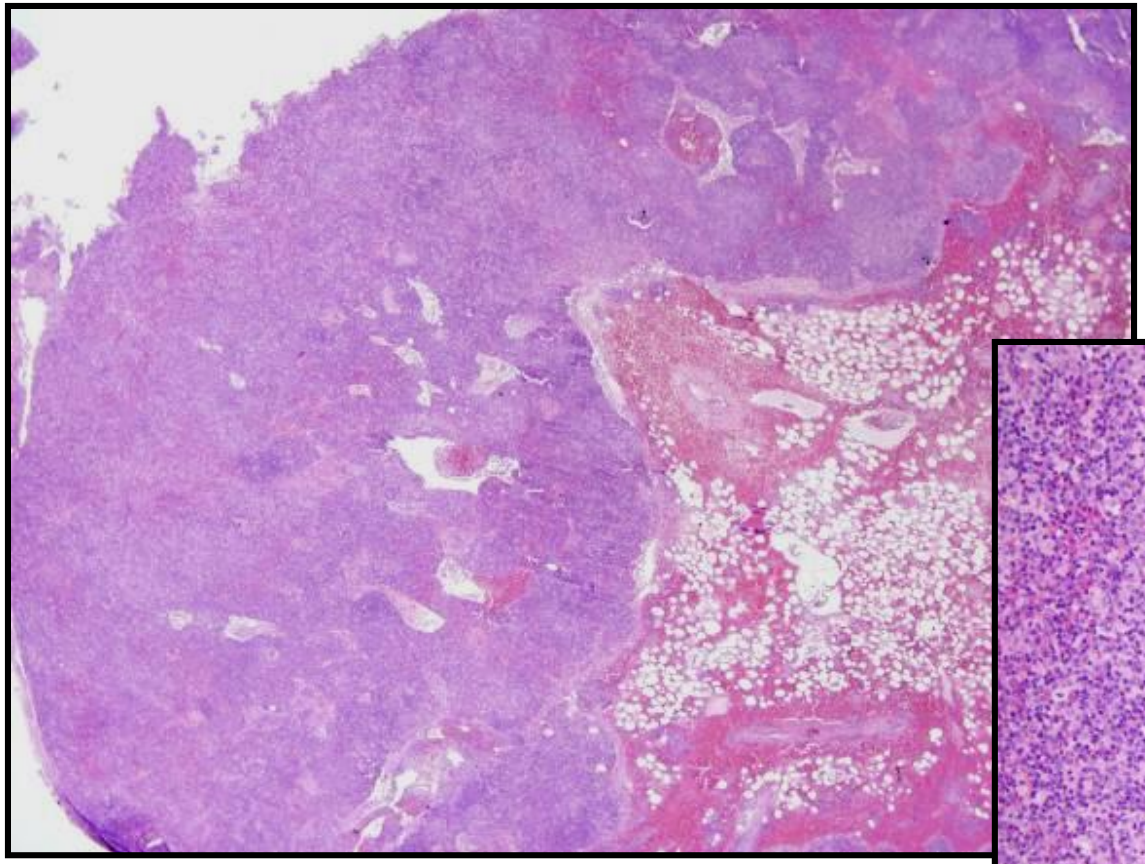
Type 1 **Type 2** **Type 3**

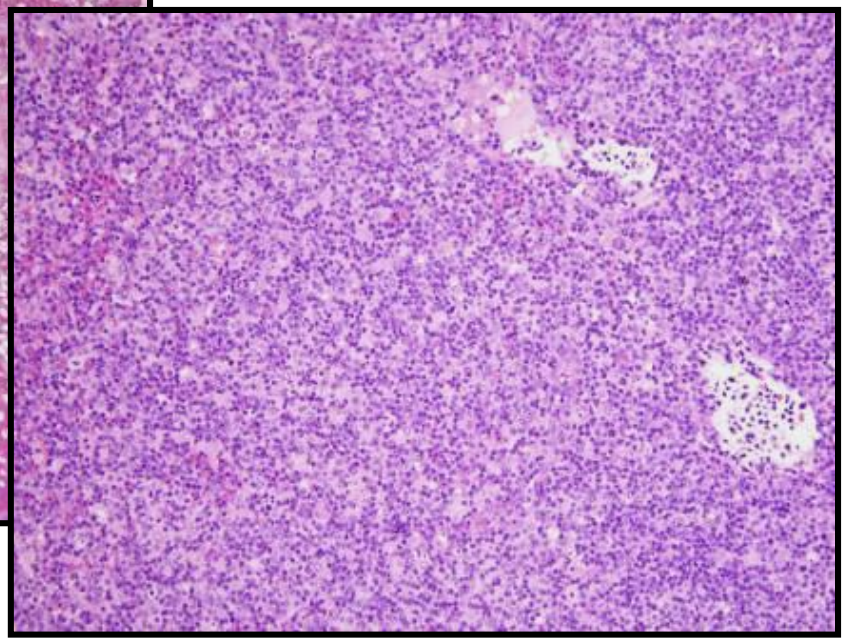
Hal Downey, PhD (1877-1959)

Lancet 395: 225, 2020

Infectious Mononucleosis

Acute EBV+ Lymphadenitis

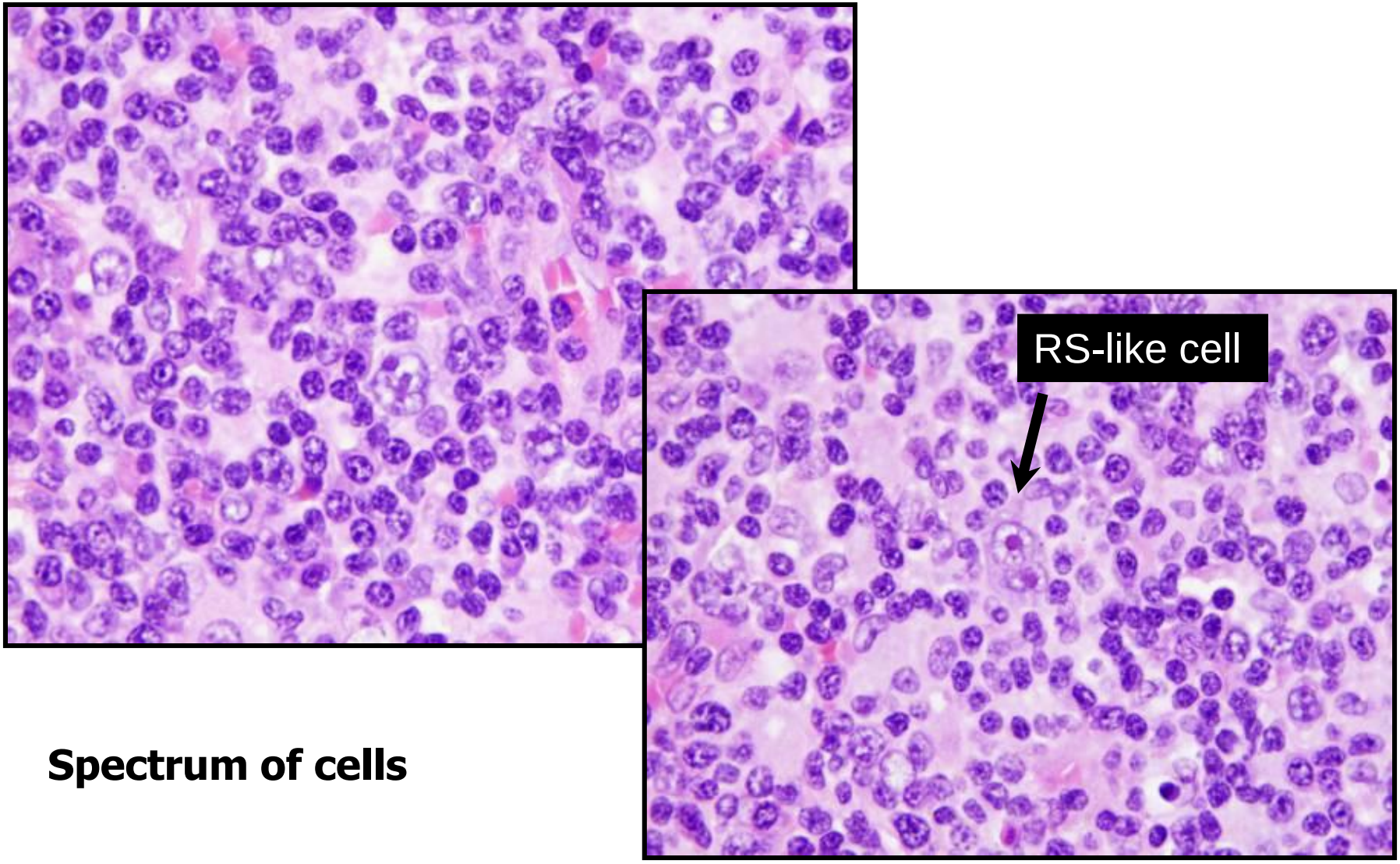




This case is not too difficult

- **Small lymph node**
- **Architecture is partially preserved**

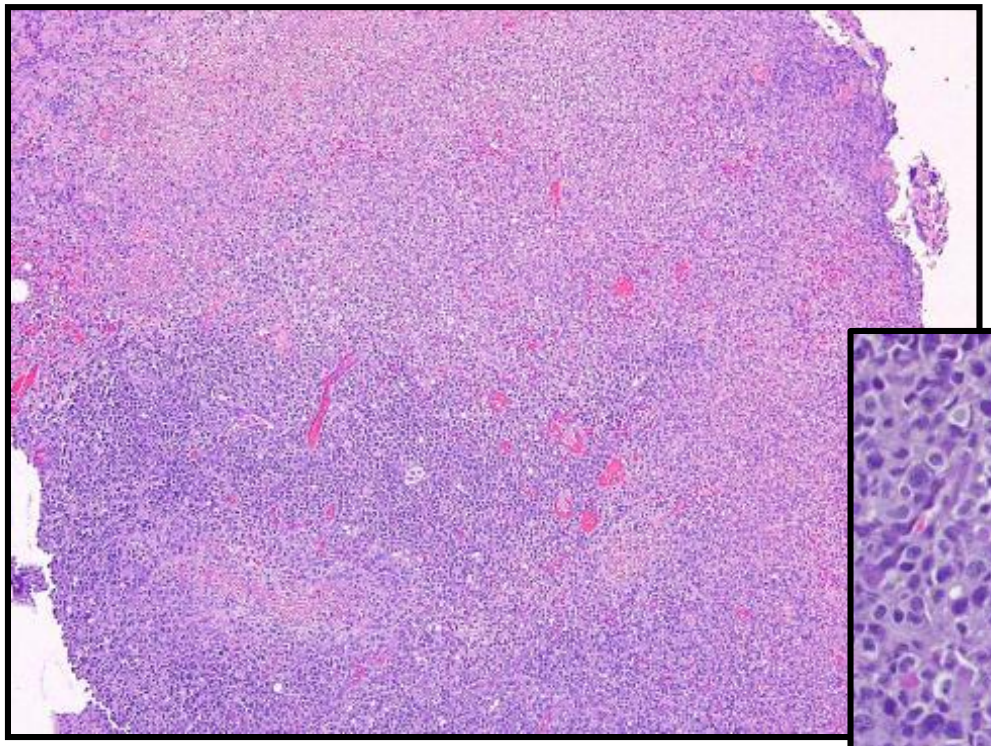
Acute EBV+ Lymphadenitis (Inf Mono)

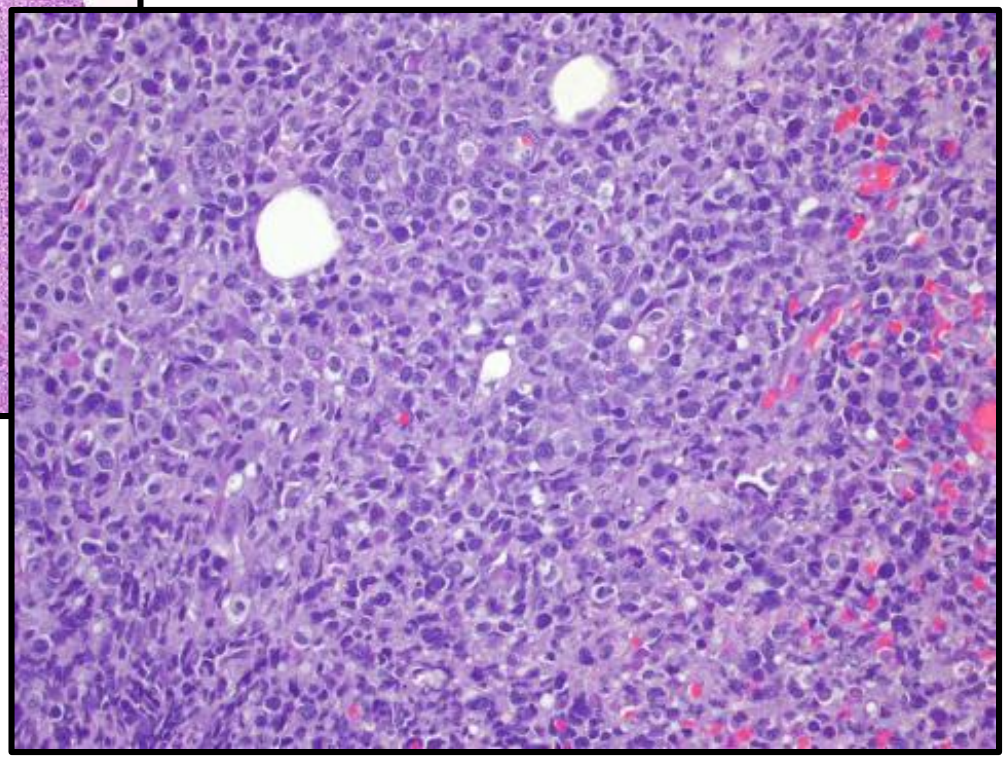


Spectrum of cells

Acute EBV+ Lymphadenitis (Inf Mono)

Looks Like Large Cell Lymphoma



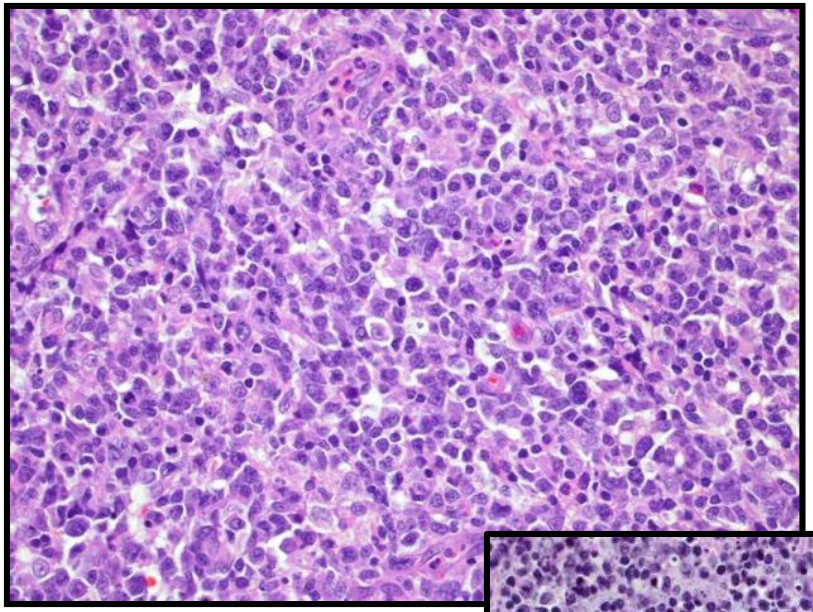


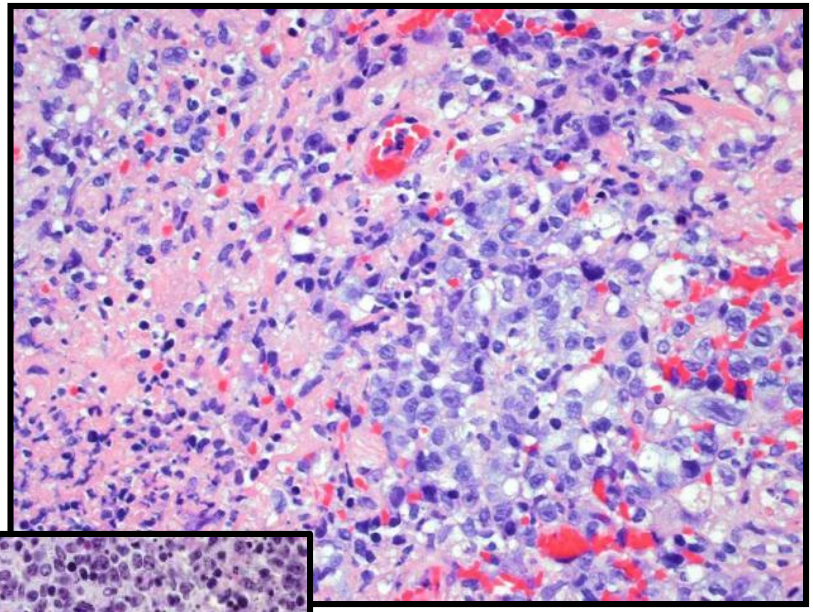
Tougher case

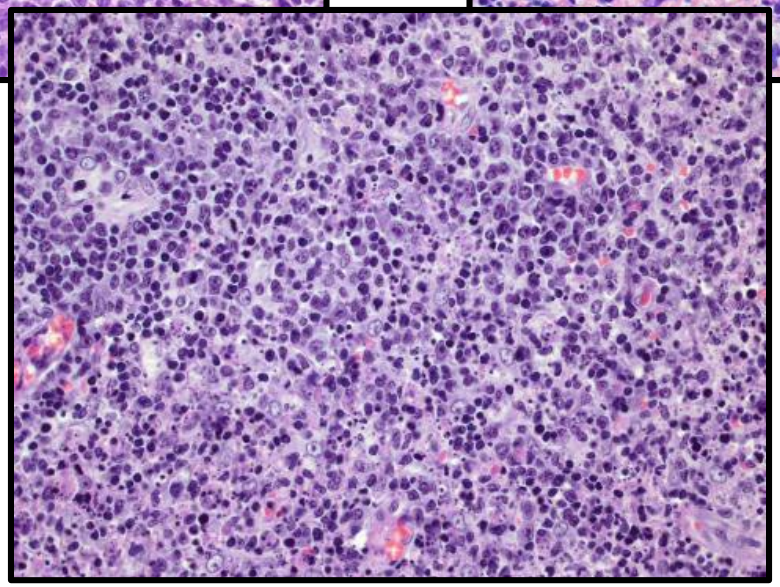
- **No architecture**
- **Necrosis**
- **Many large cells**

Acute EBV+ Lymphadenitis (Inf Mono)

3 More Cases that Mimic Lymphoma







Acute EBV+ Lymphadenitis (Inf Mono)

Histologic Features

Marked expansion/distortion of the architecture

- **Partial preservation in some cases (when lucky)**

Spectrum of cells

- **Many immunoblasts**
- **Histiocytes, plasmacytoid lymphs, plasma cells**
- **Reed-Sternberg-like cells +/-**

Follicular hyperplasia is common

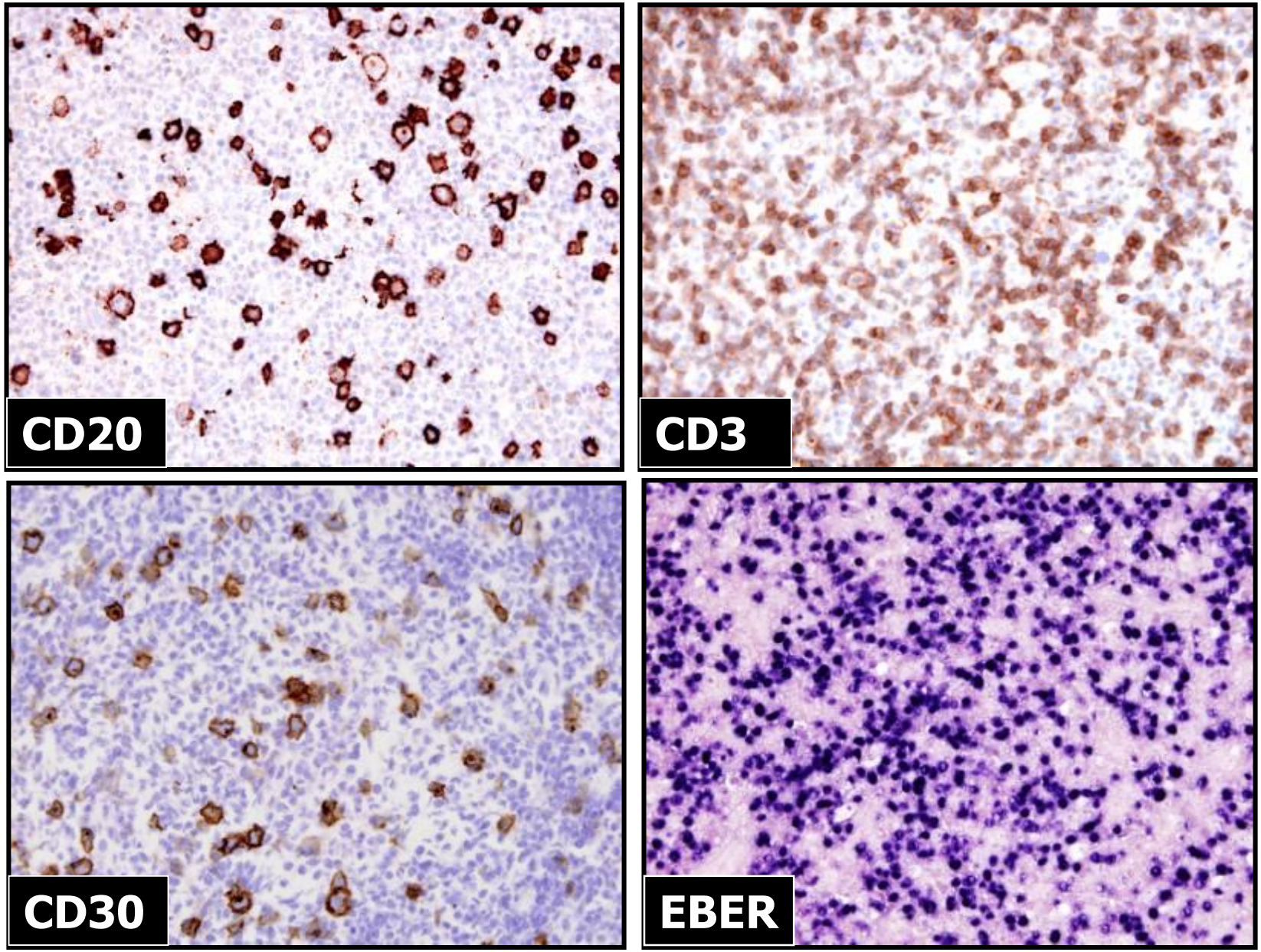
Necrosis is common

Capsular infiltration +/-

Vasculitis +/-

Acute EBV+ Lymphadenitis (Inf Mono)

Immunohistochemistry and In Situ Hybridization



Acute EBV+ Lymphadenitis (Inf Mono)

Differential Diagnosis

CMV lymphadenitis	**Resembles inf. mono. histologically** **CMV inclusions +/-** **EBV absent**
Large B-cell lymphoma	**Architecture replaced** **Monotonous cell population** **EBV negative (usually)** **Monoclonal**
Anaplastic large cell lymphoma	**Sinusoidal (common) or diffuse pattern** **Hallmark cells, ALK+** **Monoclonal**
Classical Hodgkin lymphoma	**No spectrum of cell types** **RS+H cells: CD15+/- CD45-, EBV +/-**

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

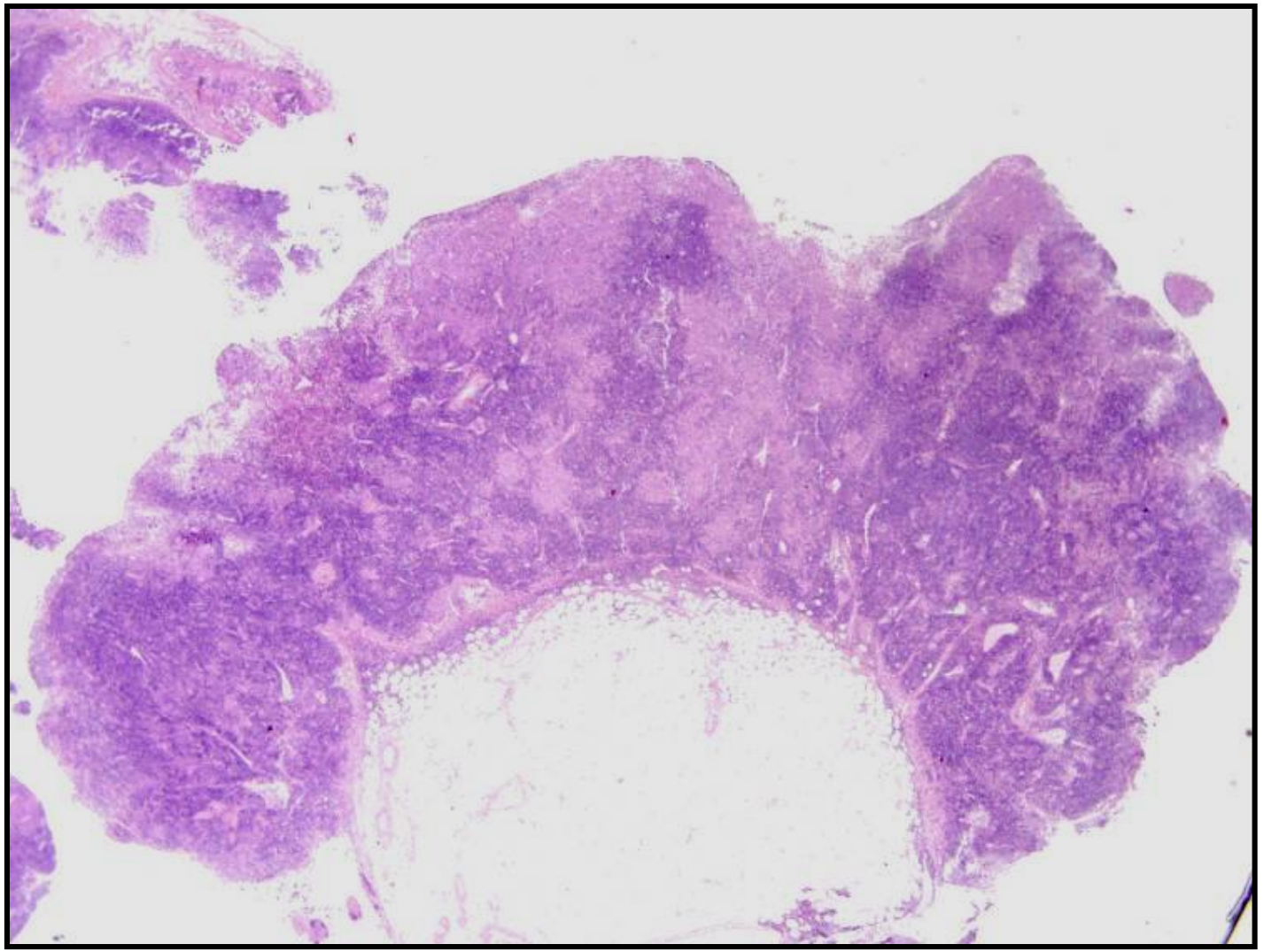
Patients present with:

- **Moderate fever, chills**
- **Myalgias +/-**

Masahiro Kikuchi, MD

Kikuchi-Fujimoto Lymphadenitis

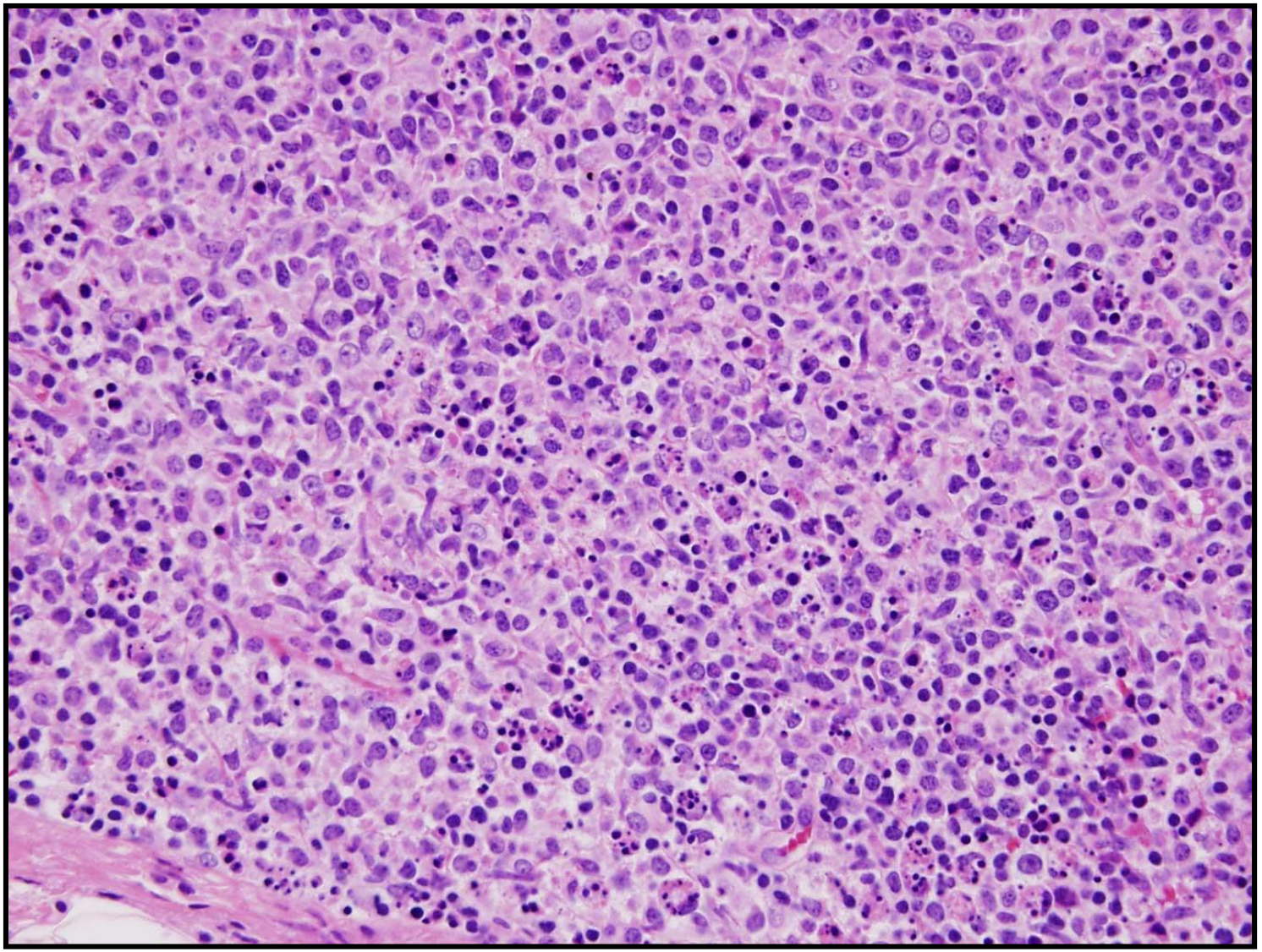
Histologic Features



Paracortical and wedge-shaped infiltrate

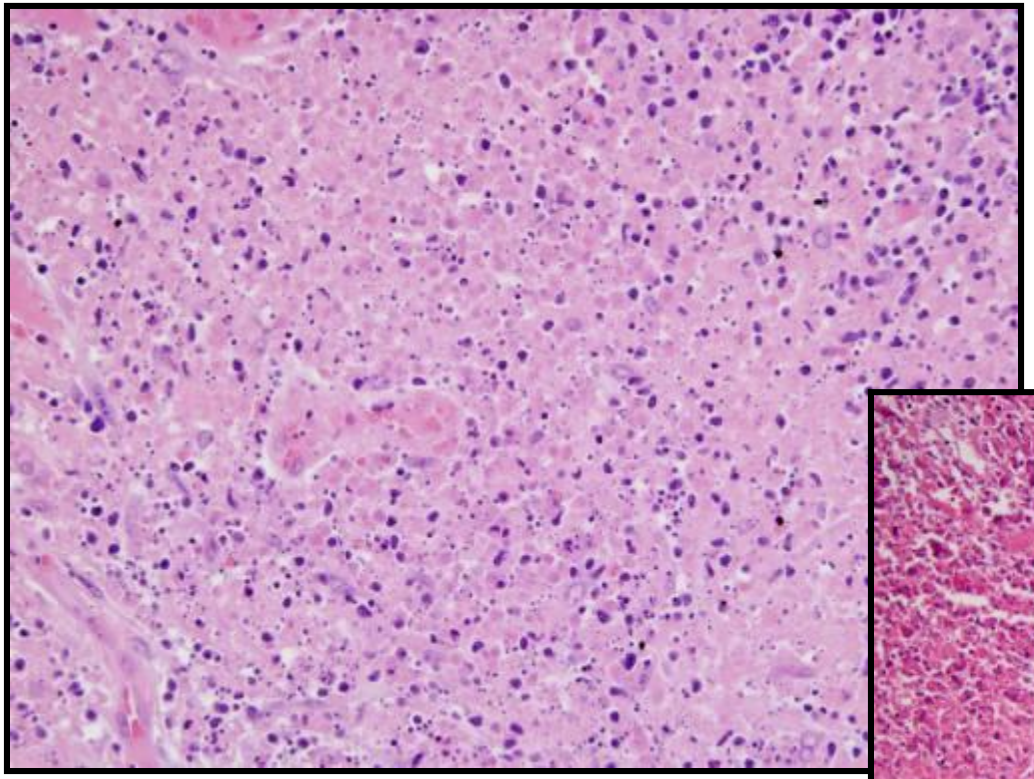
Kikuchi-Fujimoto Lymphadenitis

Proliferative Phase

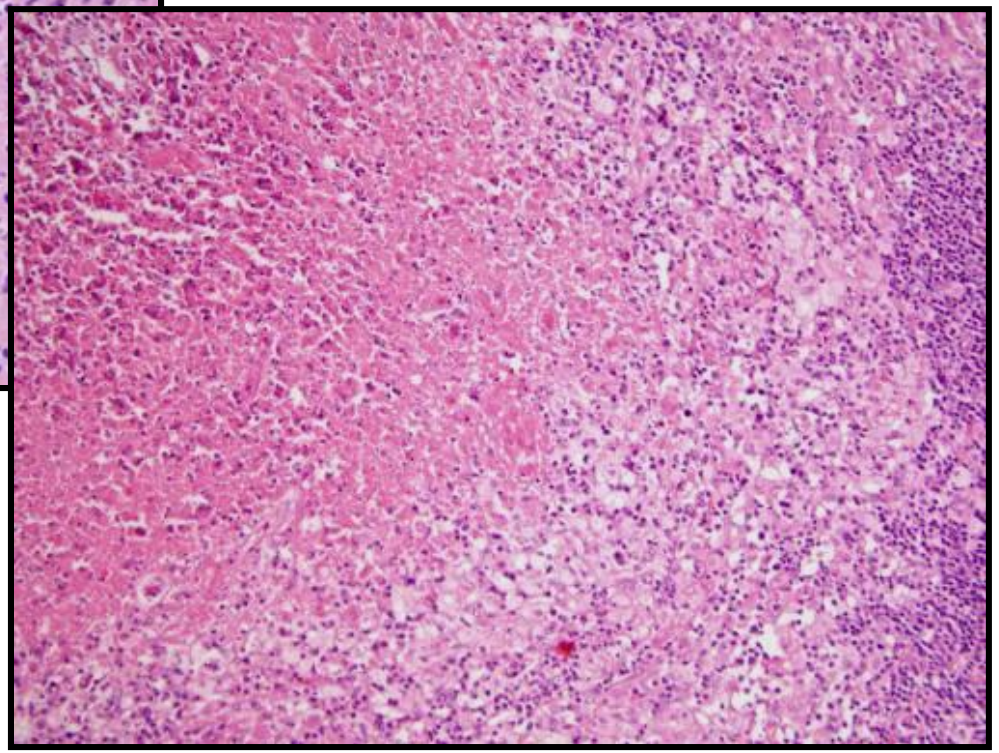


Kikuchi-Fujimoto Lymphadenitis

Necrotizing and Xanthomatous Phases



Necrotizing



Necrotizing and Xanthomatous

Kikuchi-Fujimoto Lymphadenitis

Histologic Features

Overall architecture preserved

Paracortical; patchy necrosis + / -

Increased histiocytes; often C-shaped

Increased plasmacytoid dendritic cells

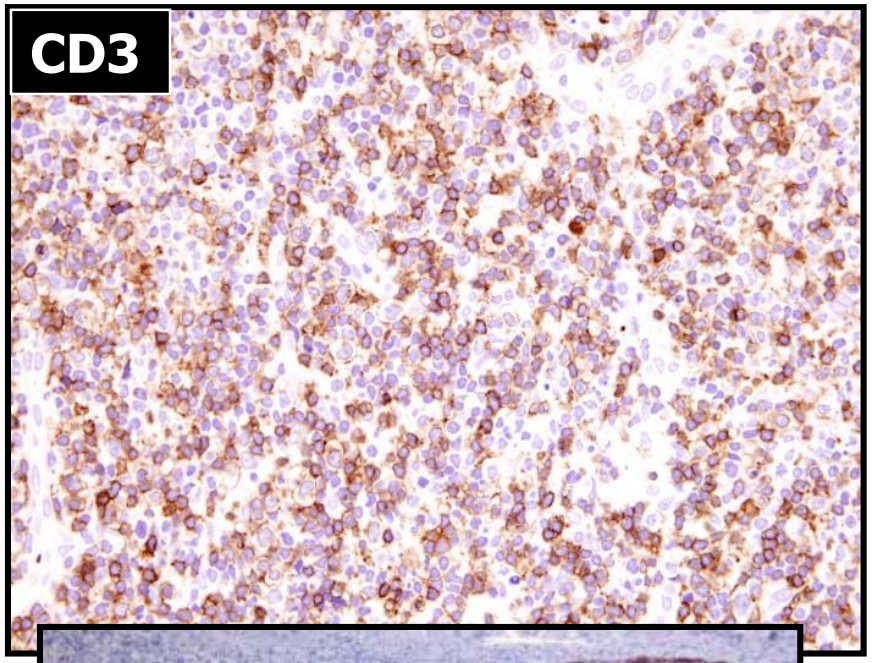
No granulocytes; no (or rare) plasma cells

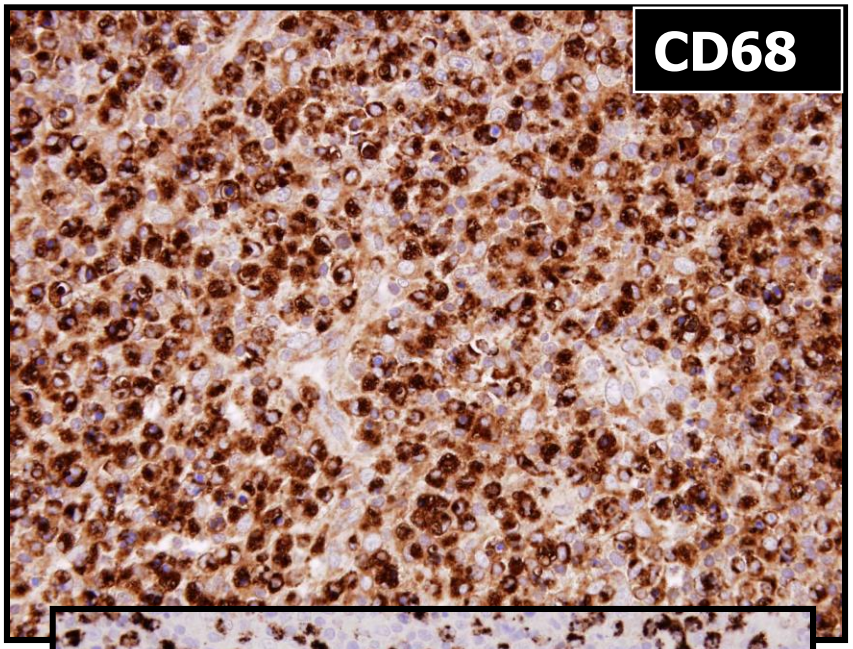
Follicular hyperplasia +/-

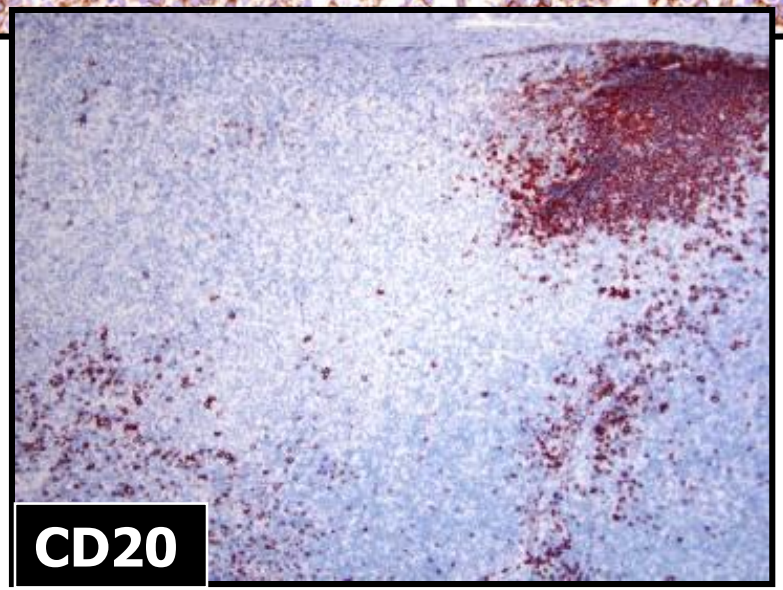
3 phases: Necrotizing
Proliferative
Xanthomatous

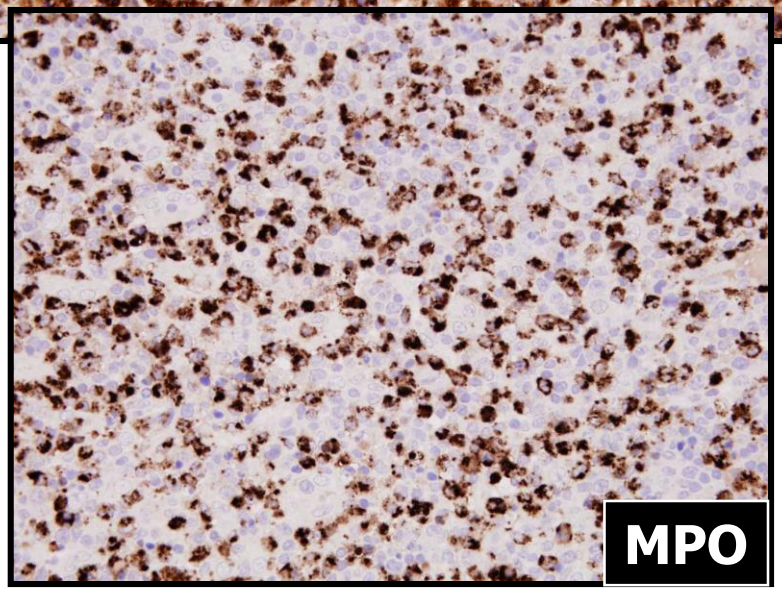
Kikuchi-Fujimoto Lymphadenitis

Immunohistochemistry









Kikuchi-Fujimoto Lymphadenitis

Immunohistochemistry

Numerous histiocytes

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

Plasmacytoid dendritic cells

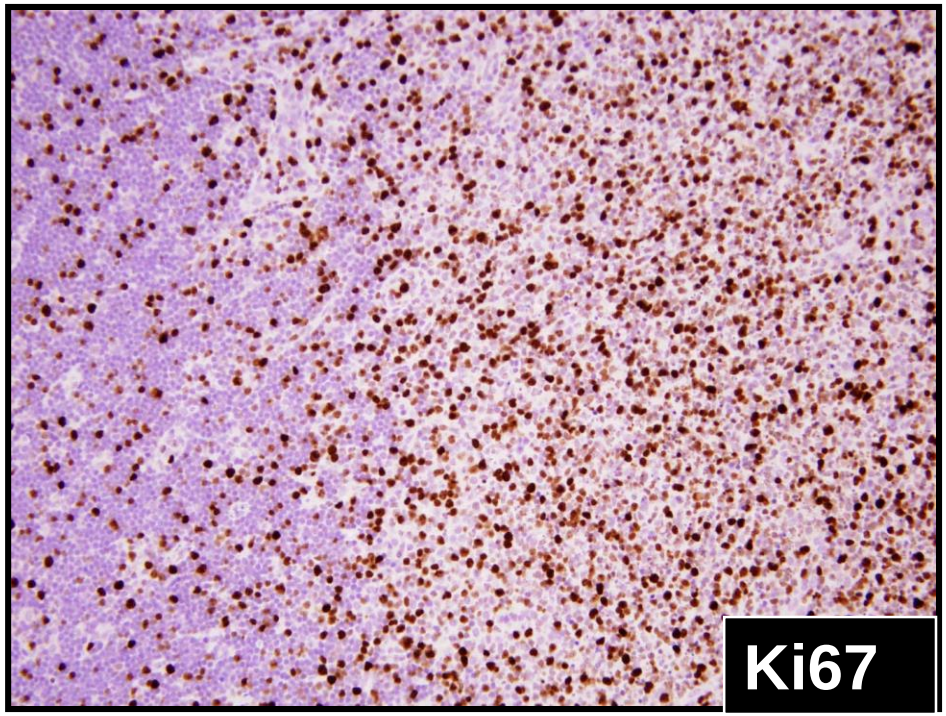
- **CD123+, TCL1+**

Many T-cells

- **CD8 > CD4**

CD30+ immunoblasts

Ki-67 high



Kikuchi-Fujimoto Lymphadenitis

Differential Diagnosis

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

Classification

Clinical

Unicentric

Multicentric

Pathological

Hyaline-vascular variant

Plasma cell variant, HHV8-

Plasma cell variant, HHV8+

HIV, Endemic

Plasma cell variant, HHV8-

Idiopathic, TAFRO

POEMS

Dr. Benjamin Castleman (1906 - 1982)

Hyaline-vascular Castleman Disease
Clinical Features

~ 75% of all cases of unicentric CD

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

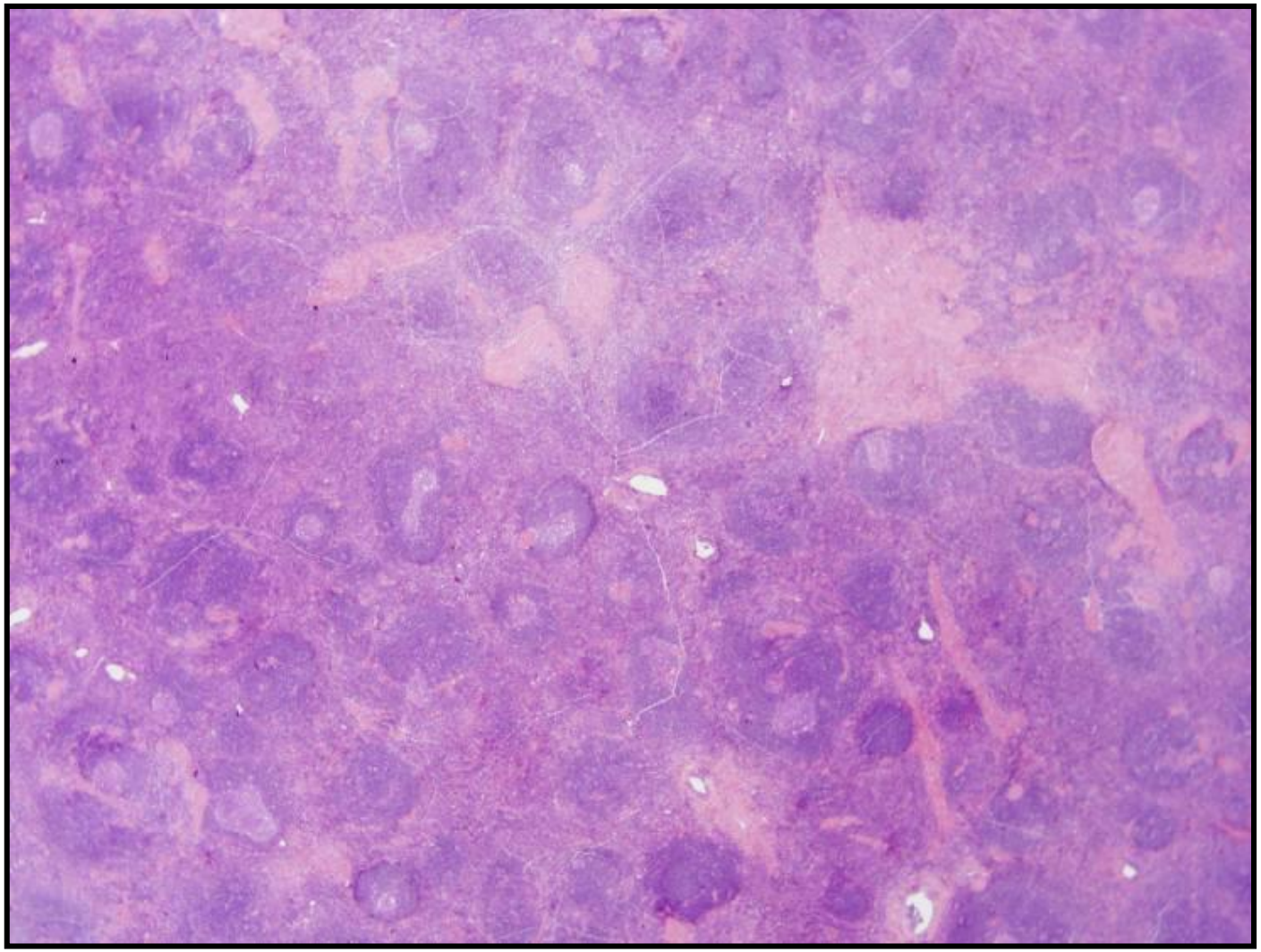
Follicular

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

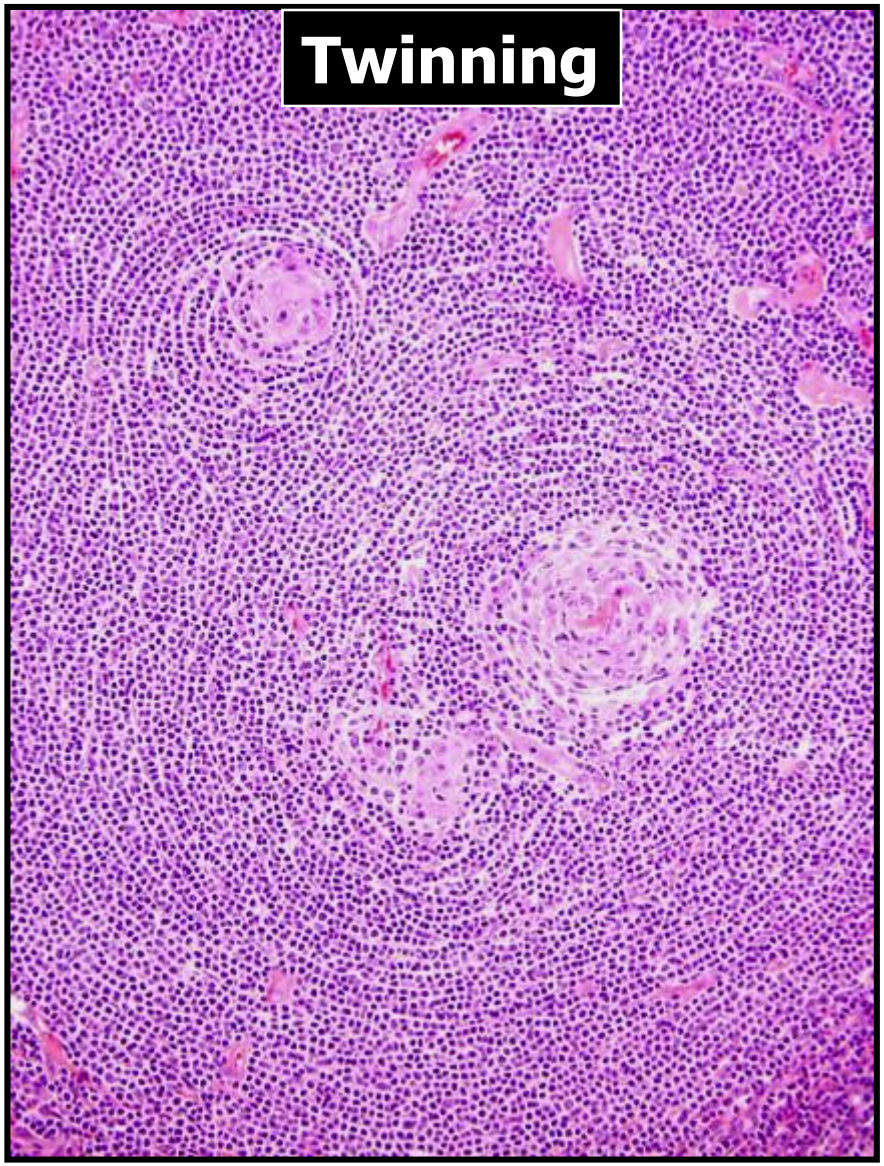
Interfollicular

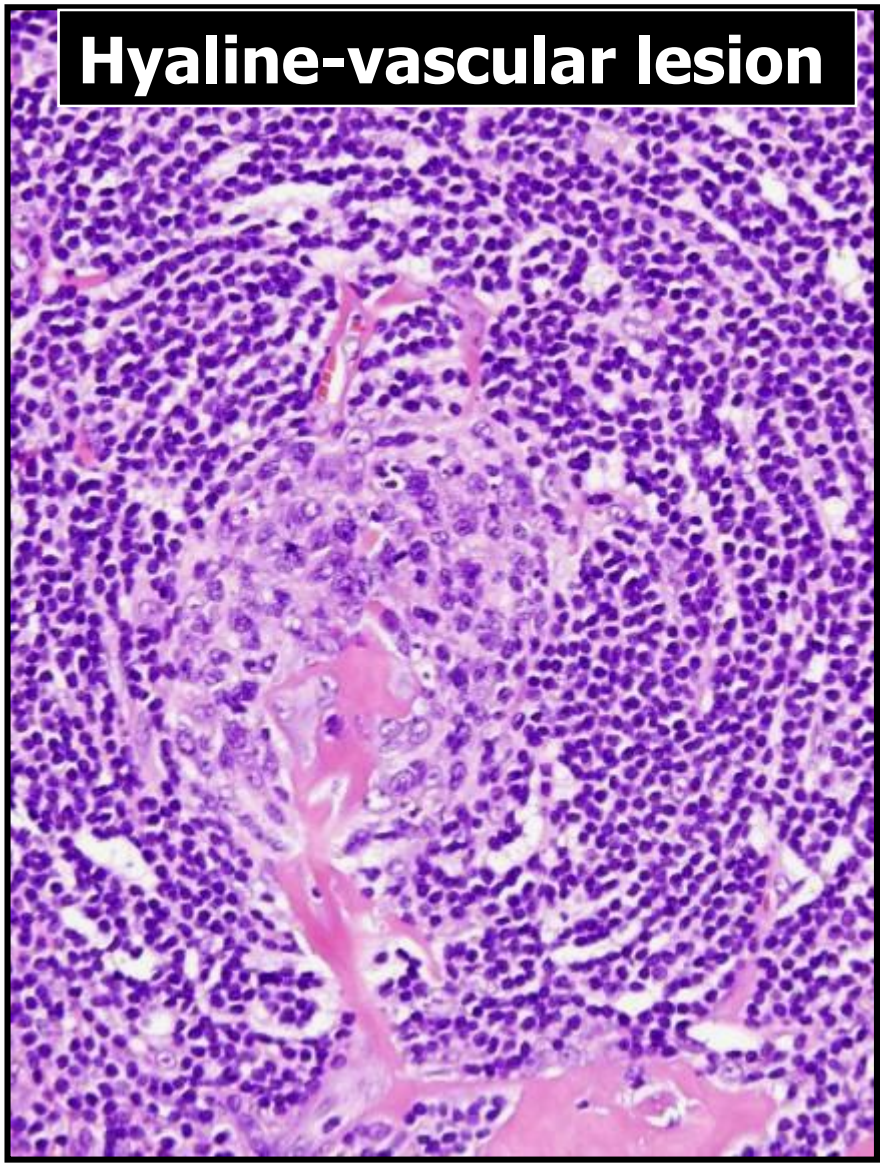
- This can be predominant (stroma-rich)
- Numerous high endothelial venules
- Actin+/-, CD68+, CD21+/-

Hyaline-vascular Castleman Disease



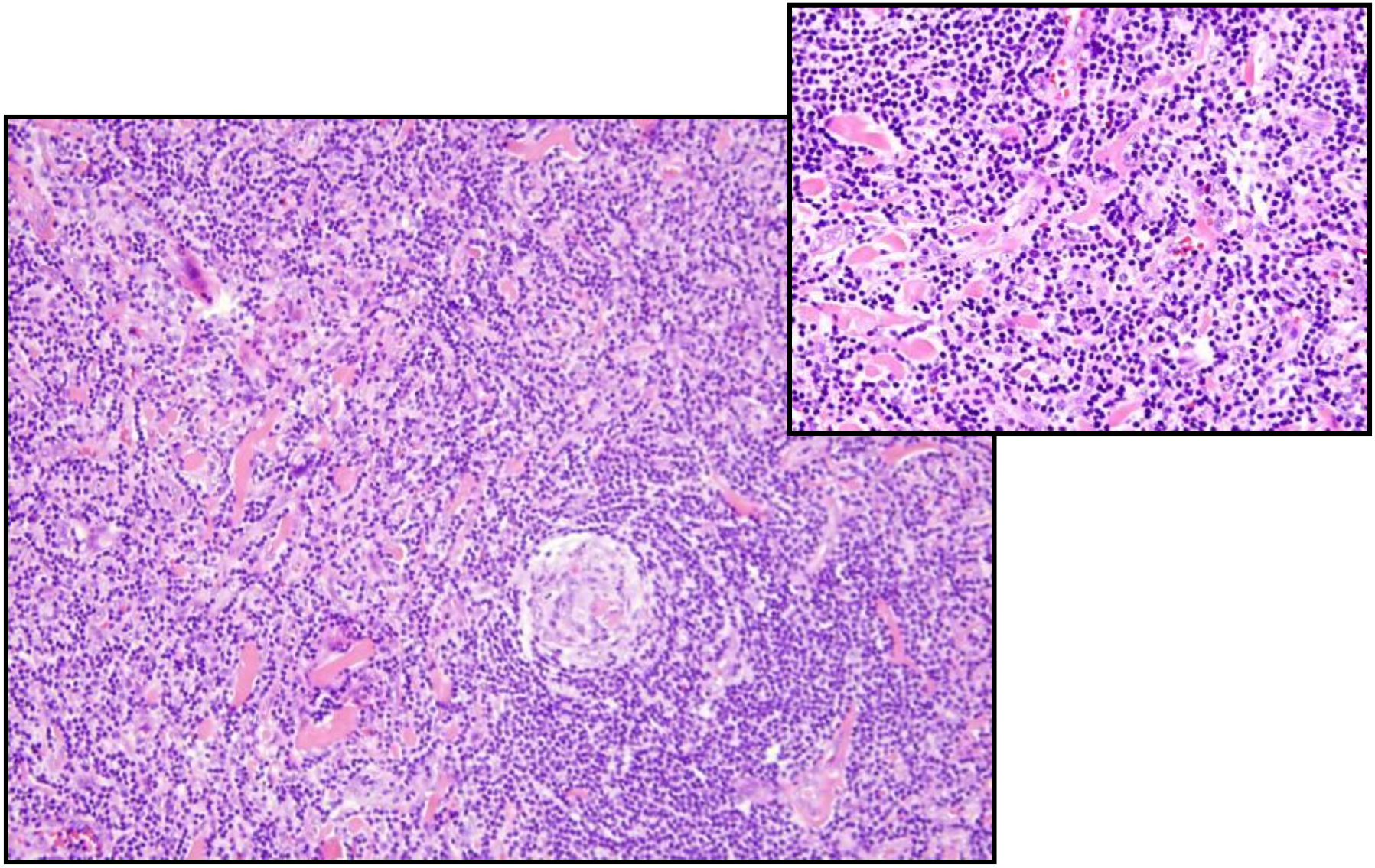
Hyaline-vascular Castleman Disease





Hyaline-vascular Castleman Disease

Stroma-rich



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 *TRG or TRB* rearrangements

Hyaline vascular CD may be a neoplasm of stromal cells

Mod Pathol 27: 823, 2014

Hyaline-vascular Castleman Disease
Differential Diagnosis

Follicular hyperplasia	**No hyaline-vascular lesions** **No lymphocyte depletion** **No interfollicular vascularity**
Follicular lymphoma	**Many follicles** **Uniform cell population** **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

~25% of cases of unicentric CD

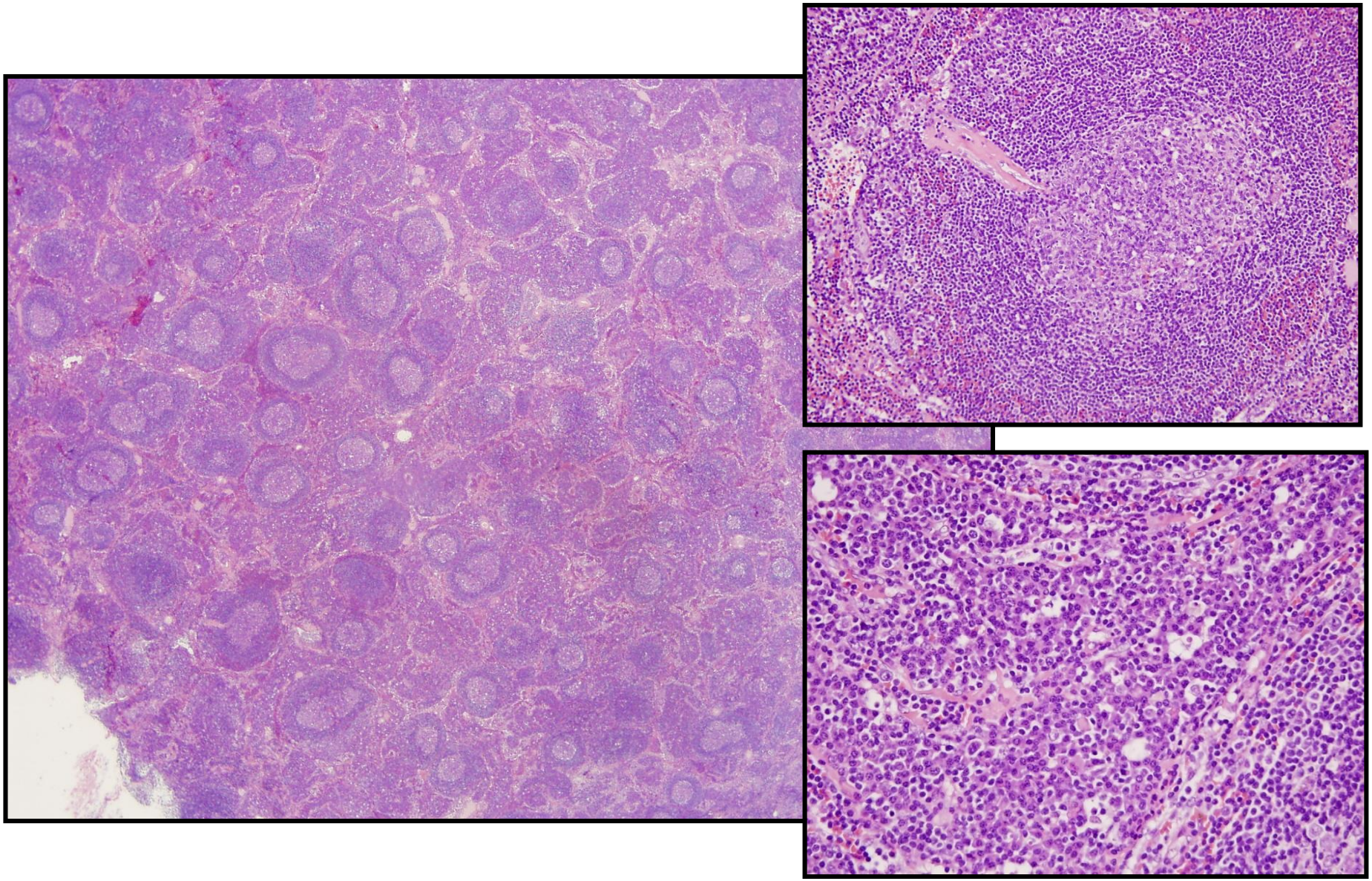
Almost any age

Small lymph node(s) at one site

Systemic symptoms in a small subset

? Misclassified multicentric cases

Plasma Cell CD (Unicentric)



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

Rheumatoid arthritis	**Grossly smaller** **No H-V lesions**
Multicentric CD	**Multiple LN groups** **~50% HHV-8+, HIV+** **~50% idiopathic**
Plasmacytoma	**Replaces of LN** **Monoclonal**

Multicentric Castleman Disease

Clinical Features

Usually associated with systemic symptoms

Often associated with HIV infection

Lymphadenopathy – 100% of patients

Hepatosplenomegaly, effusions, skin rash +/-

Laboratory

- **Elevated ESR, anemia, thrombocytopenia**
- **Polyclonal hypergammaglobulinemia**

Multicentric Castleman Disease

HHV8(+)/HIV

Interfollicular sheets of plasma cells

Atypical plasma cells/plasmablasts

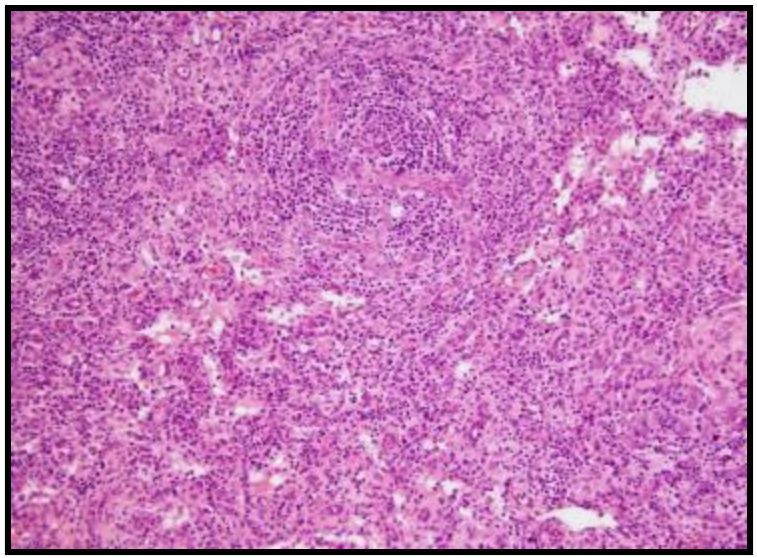
Follicles show H-V changes

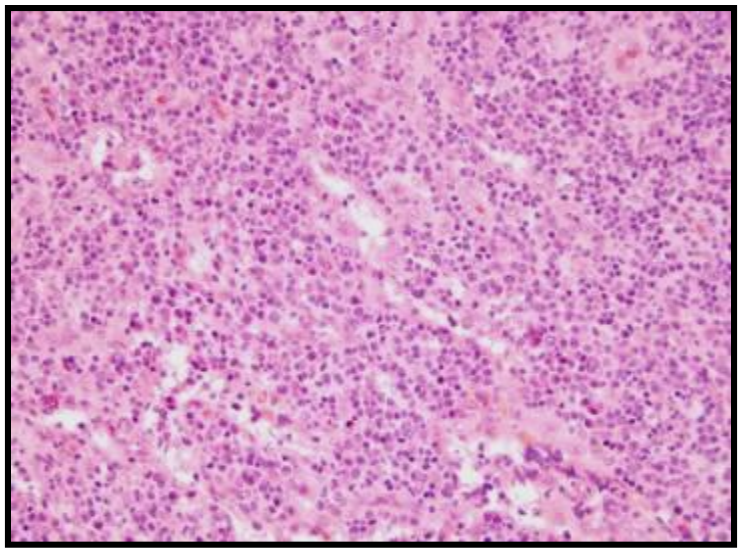
Blurring of boundary between germinal centers and mantle zones

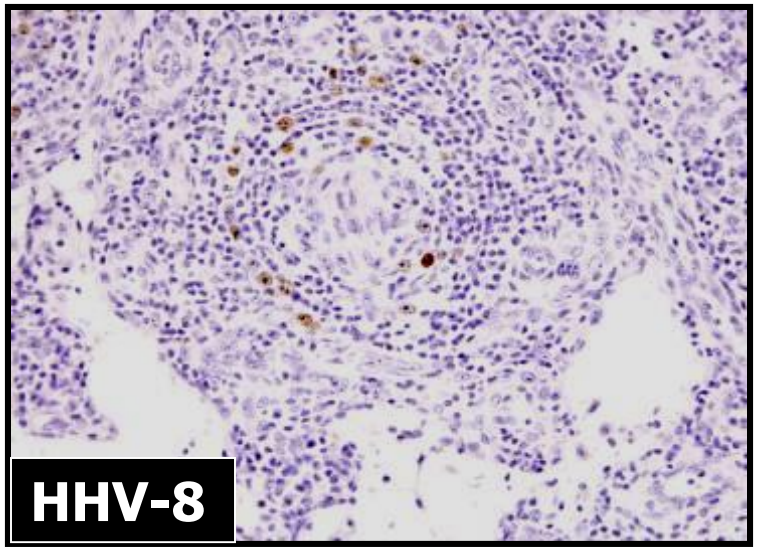
Plasma cells can be monotypic lambda

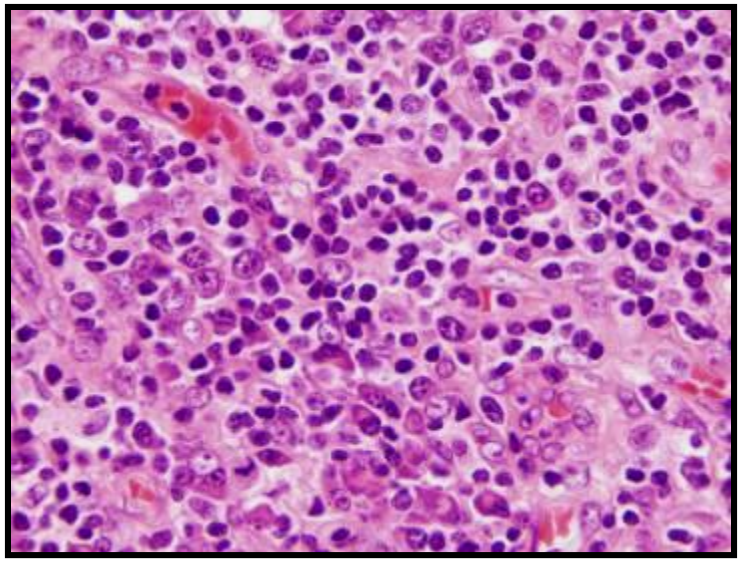
Multicentric Castleman Disease

HHV8 Positive (HIV+)









Multicentric Castleman Disease
HHV8 Negative/Idiopathic

Interfollicular sheets of plasma cells

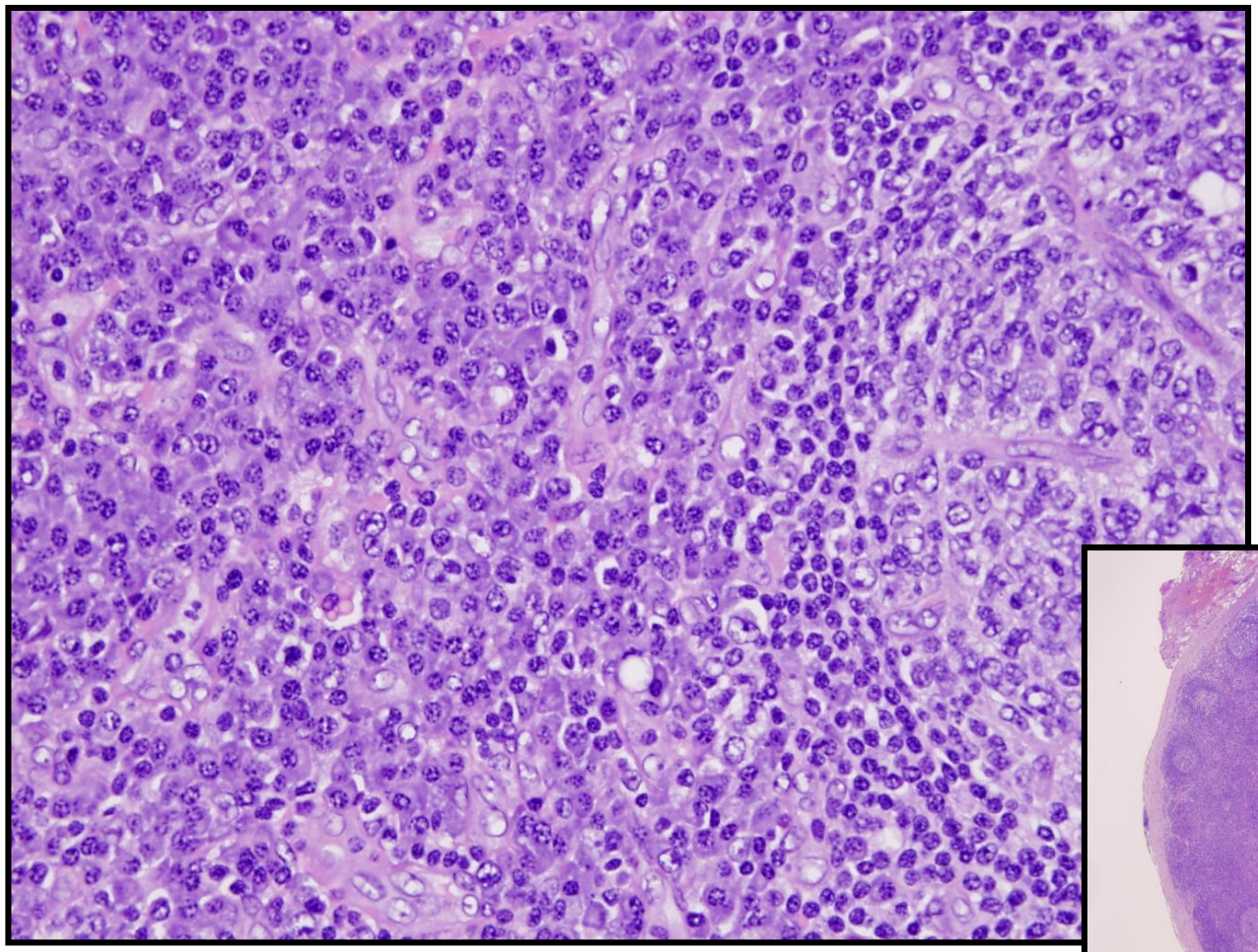
+/- Follicles with H-V changes

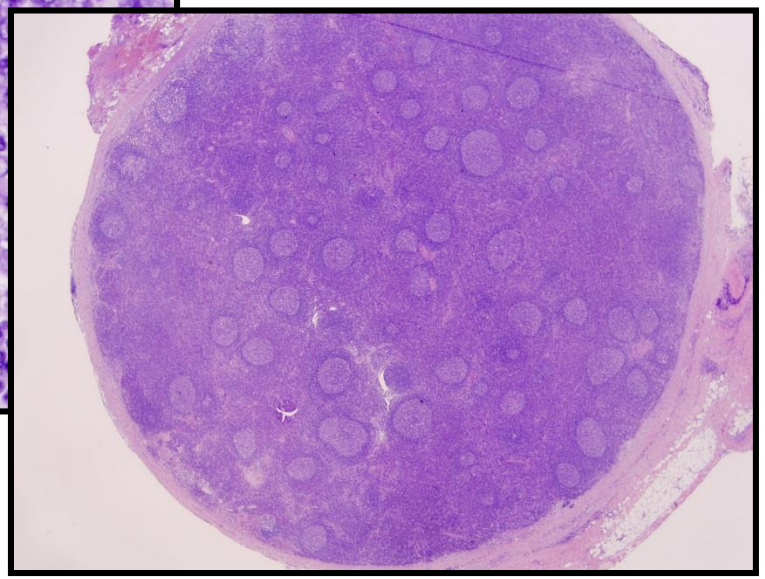
No atypical plasma cells/plasmablasts

Plasma cells can be monotypic (lambda)

Multicentric Castleman Disease

Idiopathic





Multicentric Castleman Disease
Differential Diagnosis

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**

TAFRO Syndrome

Thrombocytopenia, Anasarca, Fever, Reticulin fibrosis in BM, and Organomegaly

Variant of idiopathic multicentric Castleman disease (CD)

Etiology unknown; adults; median age in 6th decade

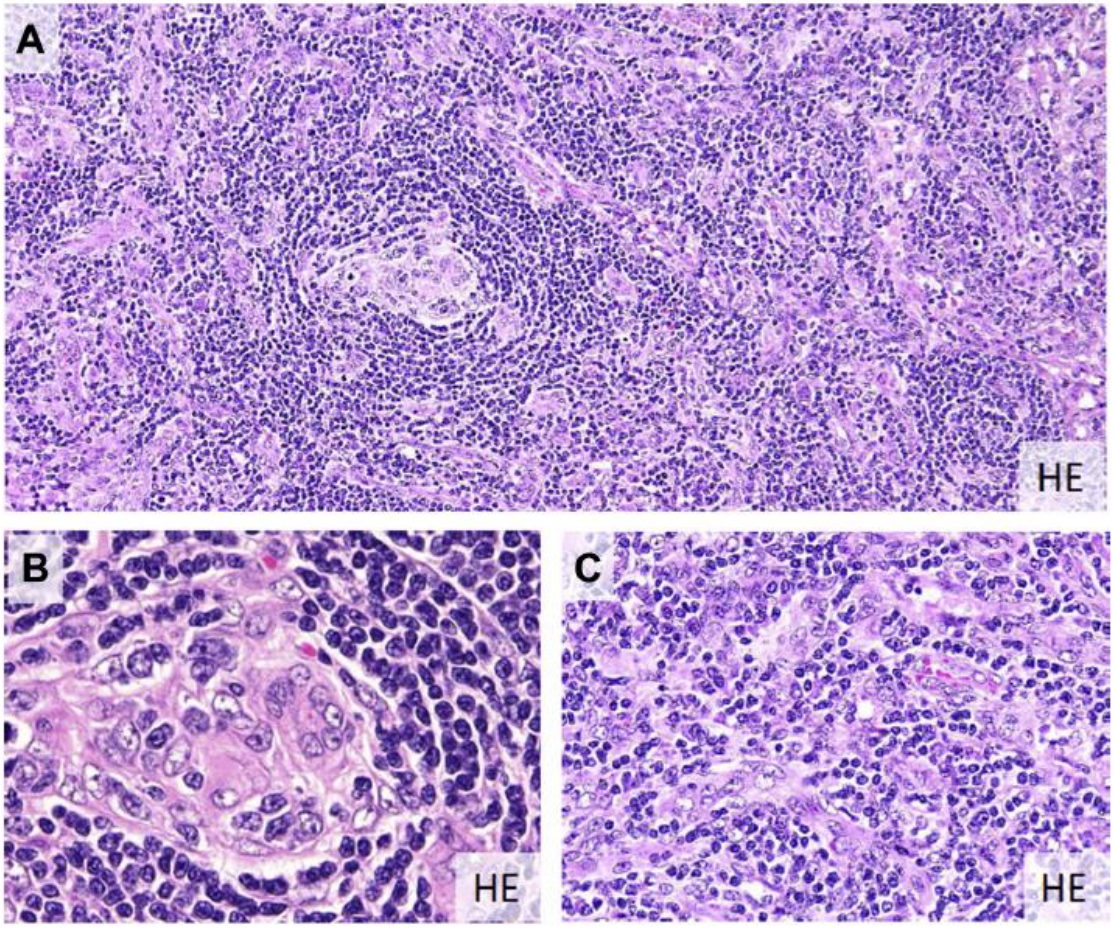
Symptoms related to cytokine storm, but not IL-6

TAFRO versus idiopathic multicentric CD

Thrombocytopenia, anasarca, and low IgG levels only in TAFRO

Rinsho Ketsueki 51: 320, 2010
Hematol Oncol Clin N Am 32: 107, 2018

TAFRO Syndrome



Hematol Oncol Clin N Am 32: 107, 2018

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

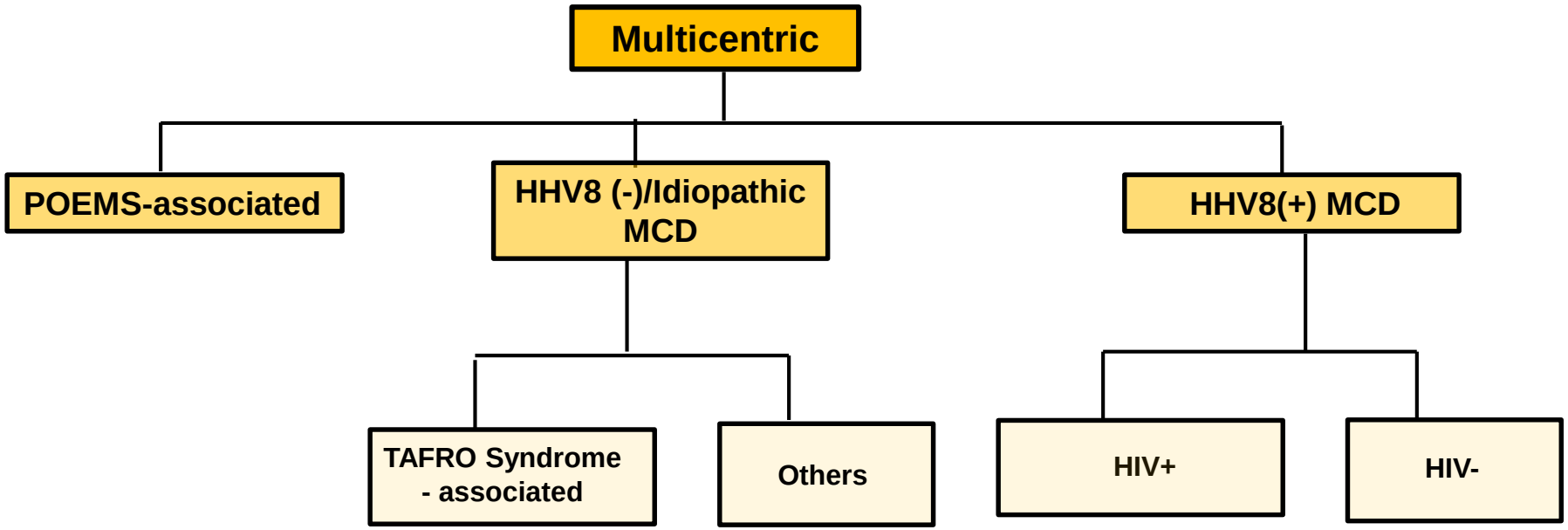
95% lambda

Often osteosclerotic

50% of patients have multicentric Castleman disease, plasma cell variant, HHV8 -

Multicentric Castleman Disease

Multiple types



Surg Pathol Clin 12: 849, 2019

Seminoma

Clinical Features

Most common germ cell tumor of testis

Age: 30-45 years

80-90% have a palpable mass

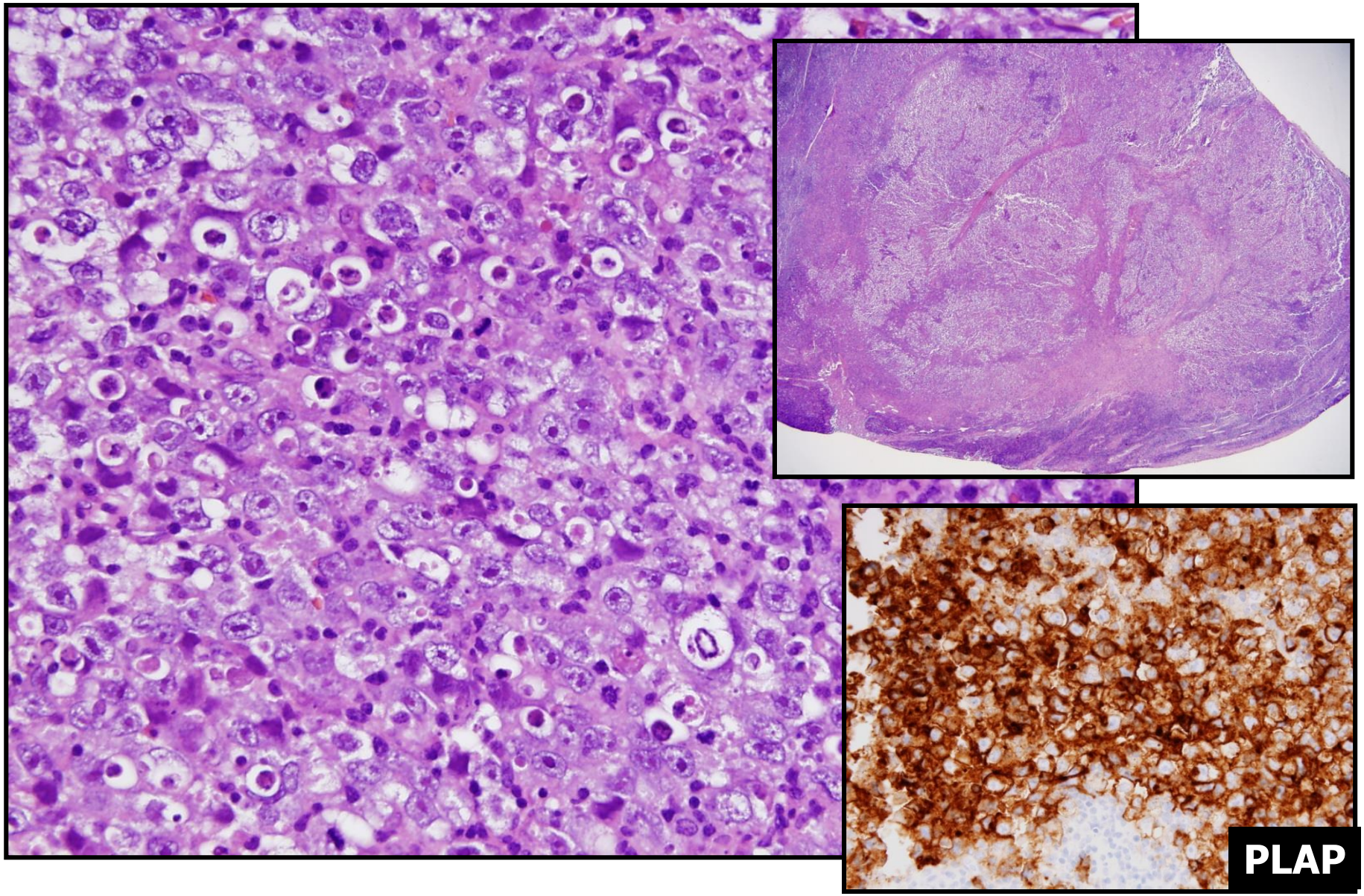
Often no symptoms; testicular pain ~20%

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

75% of pts have stage I (localized) disease

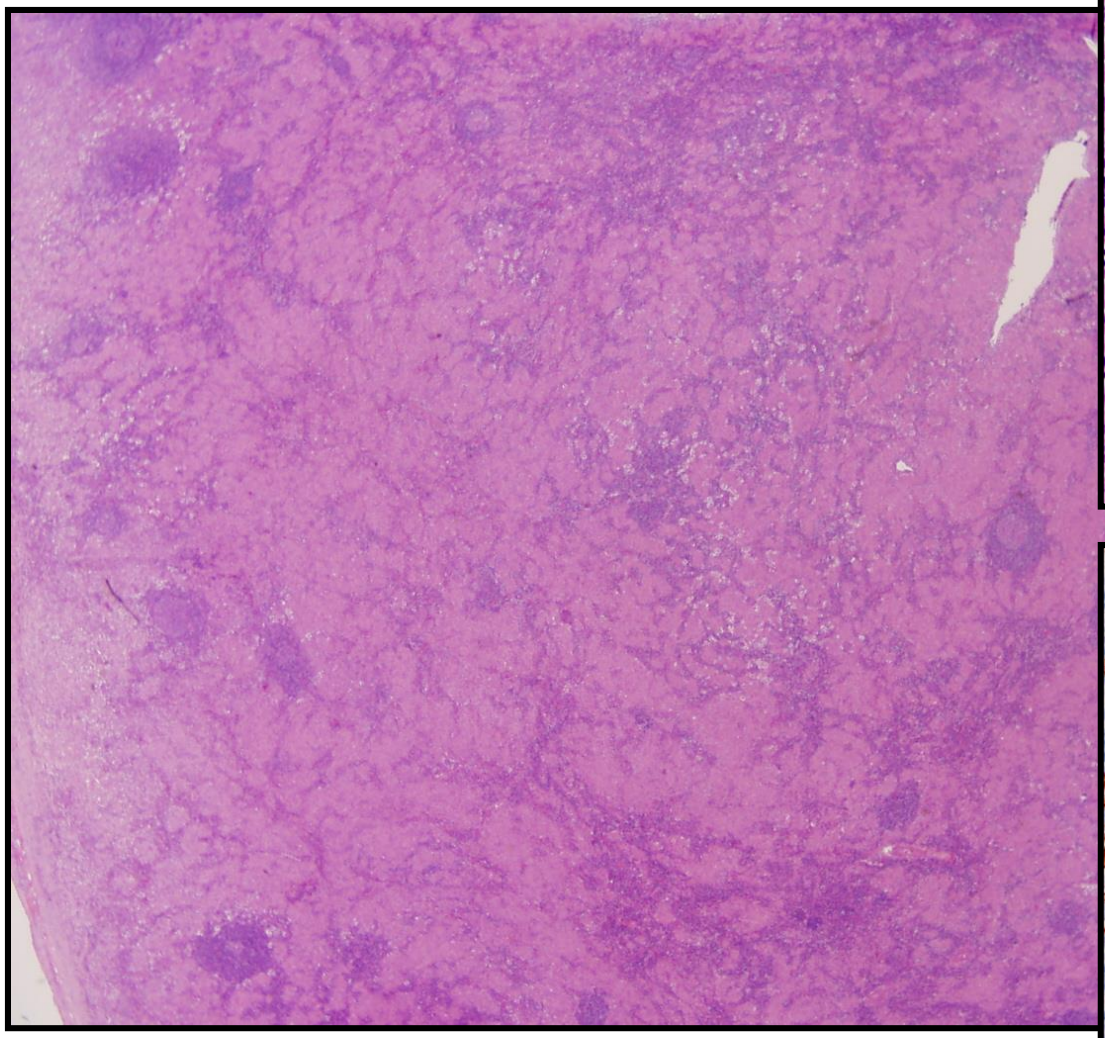
Metastases to: retroperitoneal LNs, lungs

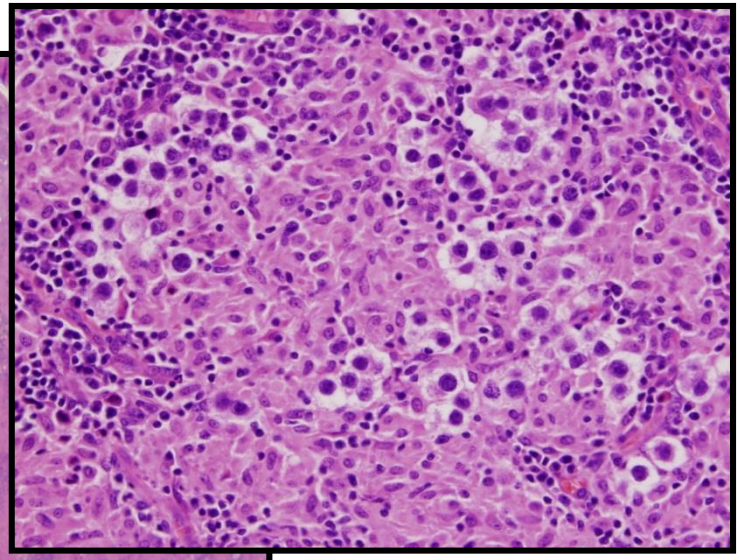
Metastatic Seminoma to LN

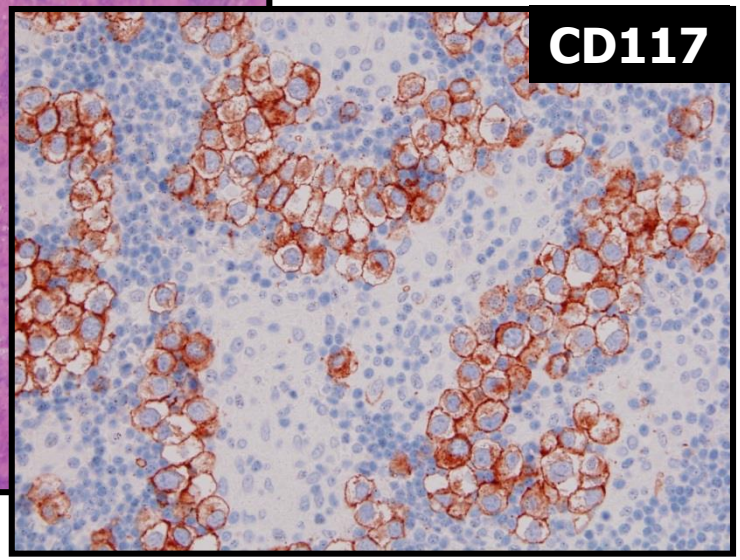


Metastatic Seminoma to LN

Many Granulomas





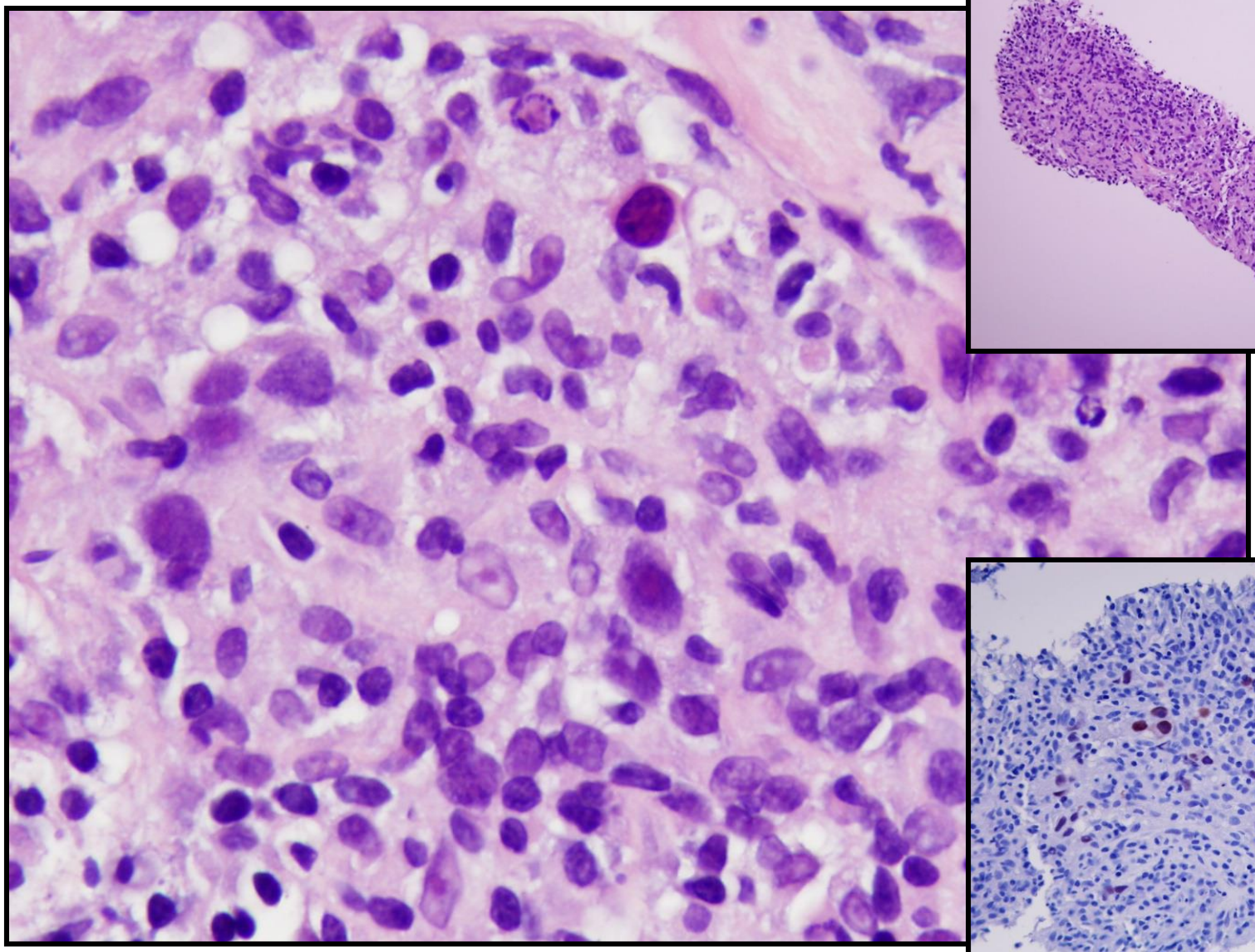


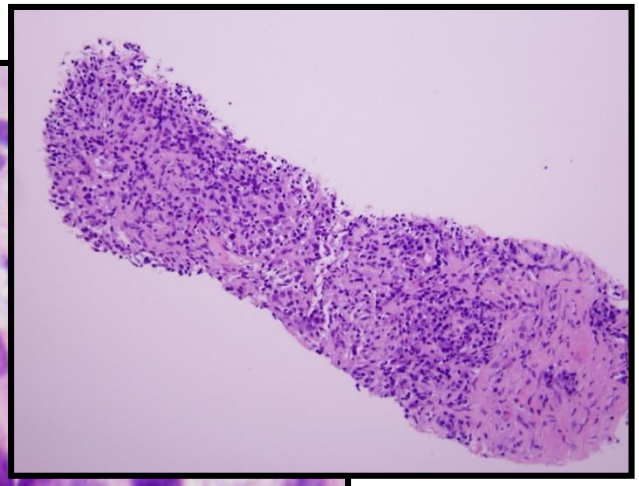
Seminoma

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

Mediastinal Mass in 18 yo





Primary Mediastinal Seminoma
Clinical Features

3-4% of tumors in the mediastinum

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

> 90% of patients are men

Usually associated with the thymus

Ectopic germ cells or thymic cells with germ cell potential?

Present as mass

+/- compressive

Metastatic Seminoma
Differential Diagnosis

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 SE China

Men > women

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

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

Metastases
- **LNs, lungs, bones, liver**

Nasopharyngeal Carcinoma

Pathologic Features

Two general pathologic types of NPC

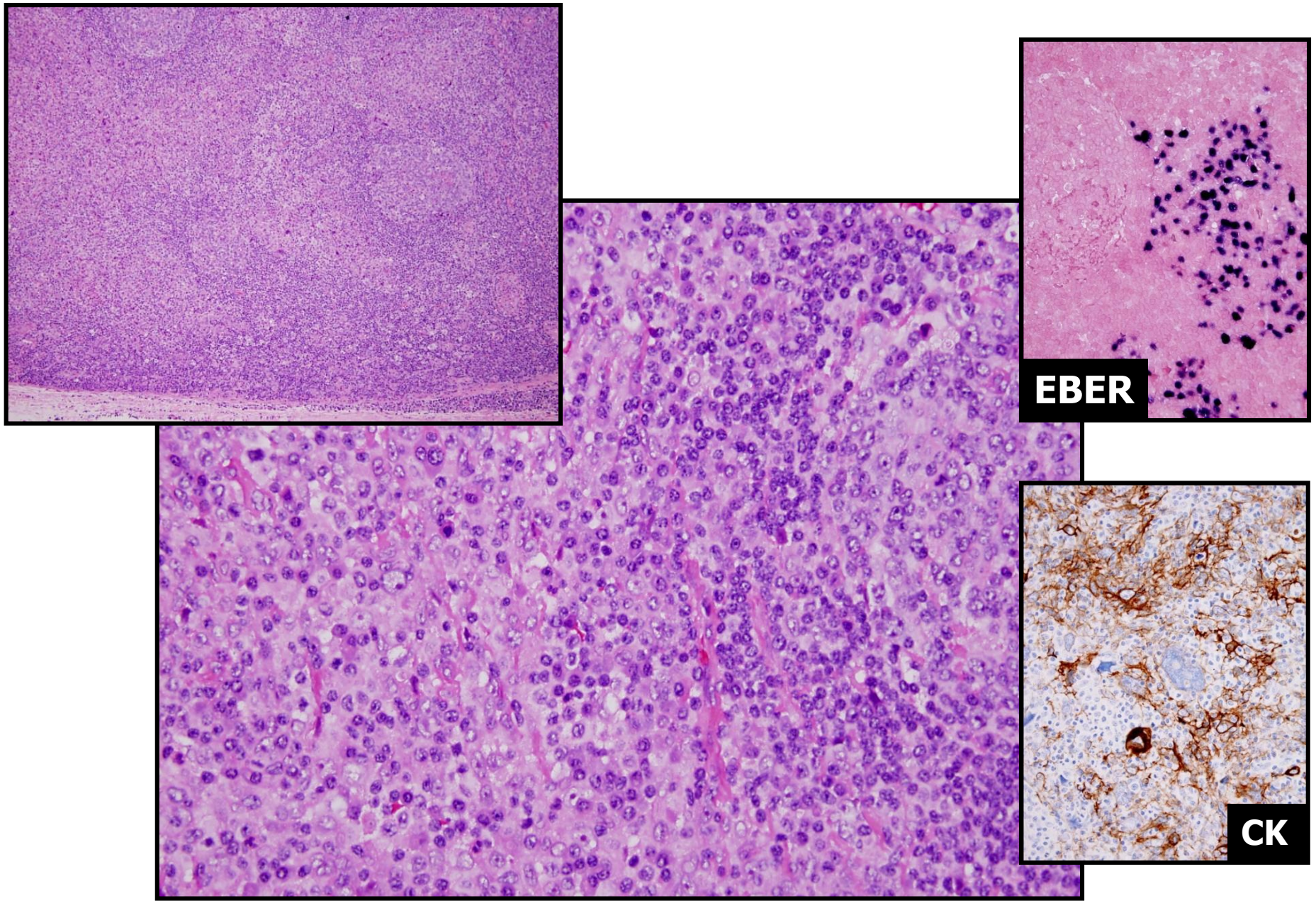
Keratinizing (linked to HPV)

Non-keratinizing (linked to EBV)

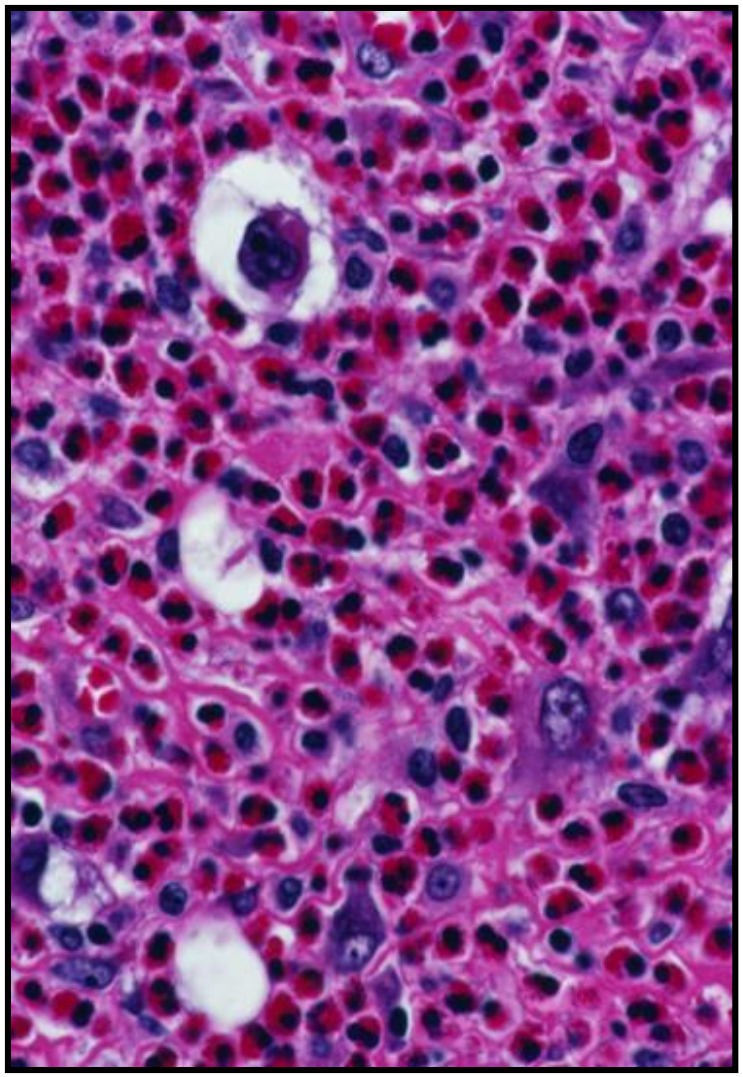
- **Differentiated**
- **Undifferentiated (lymphoepithelioma)**

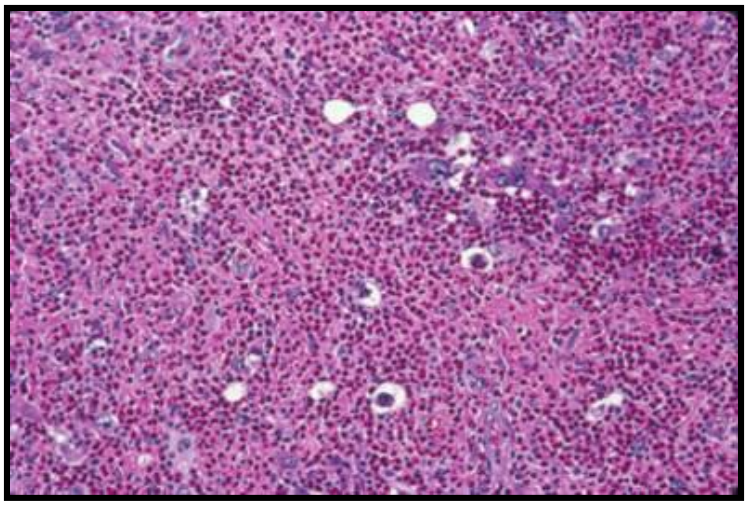
Undifferentiated type more common in children

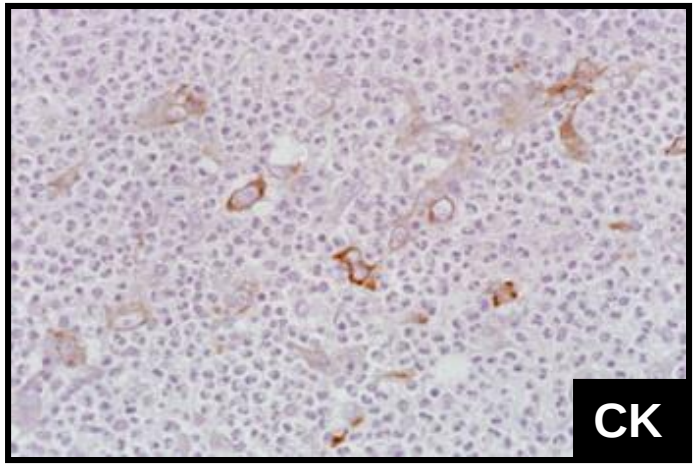
Nasopharyngeal Carcinoma Metastatic to LN



Nasopharyngeal Carcinoma Metastatic to LN
Eosinophil Rich







Zarate-Osorno et al. Arch Pathol Lab Med 116: 862, 1992

Metastatic Nasopharyngeal Carcinoma
Differential Diagnosis

Classical HL	**Fibrous bands and RS + H cells** **CD15+/-, CD30+, PAX5+** **Keratin-**
DLBCL - NOS	**Sheets of large cells** **CD20+ CD45/LCA+ CD15-** **Clonal *IGH* ,*IGK*, or *IGL* rearrangements**
Peripheral T-cell lymphoma	**Cytologic atypia of T-cells** **Aberrant immunophenotype +/-** **Clonal *TRG* and *TRB* 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

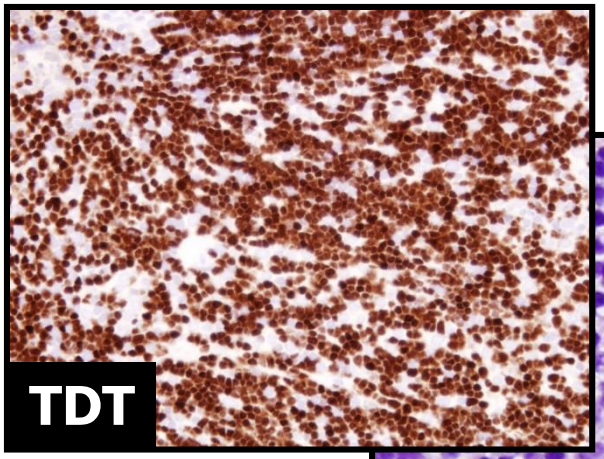
20% Myasthenia gravis

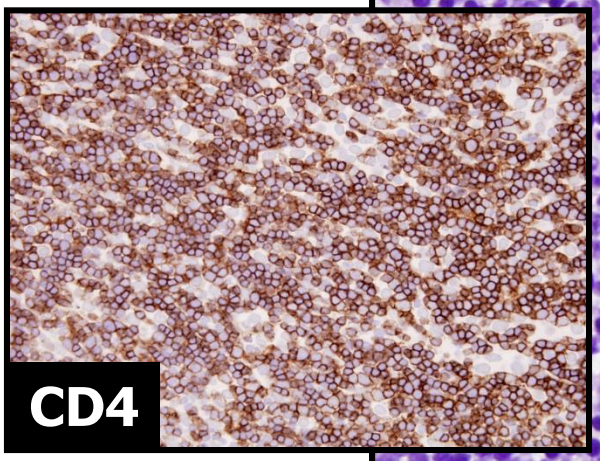
Pathology

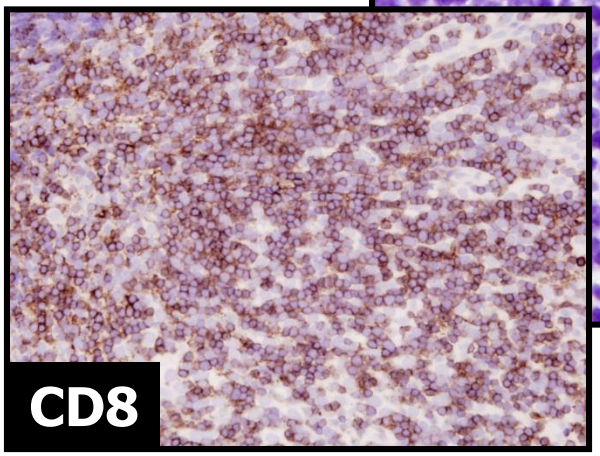
Epithelial cell rich (spindle cell or epithelioid)

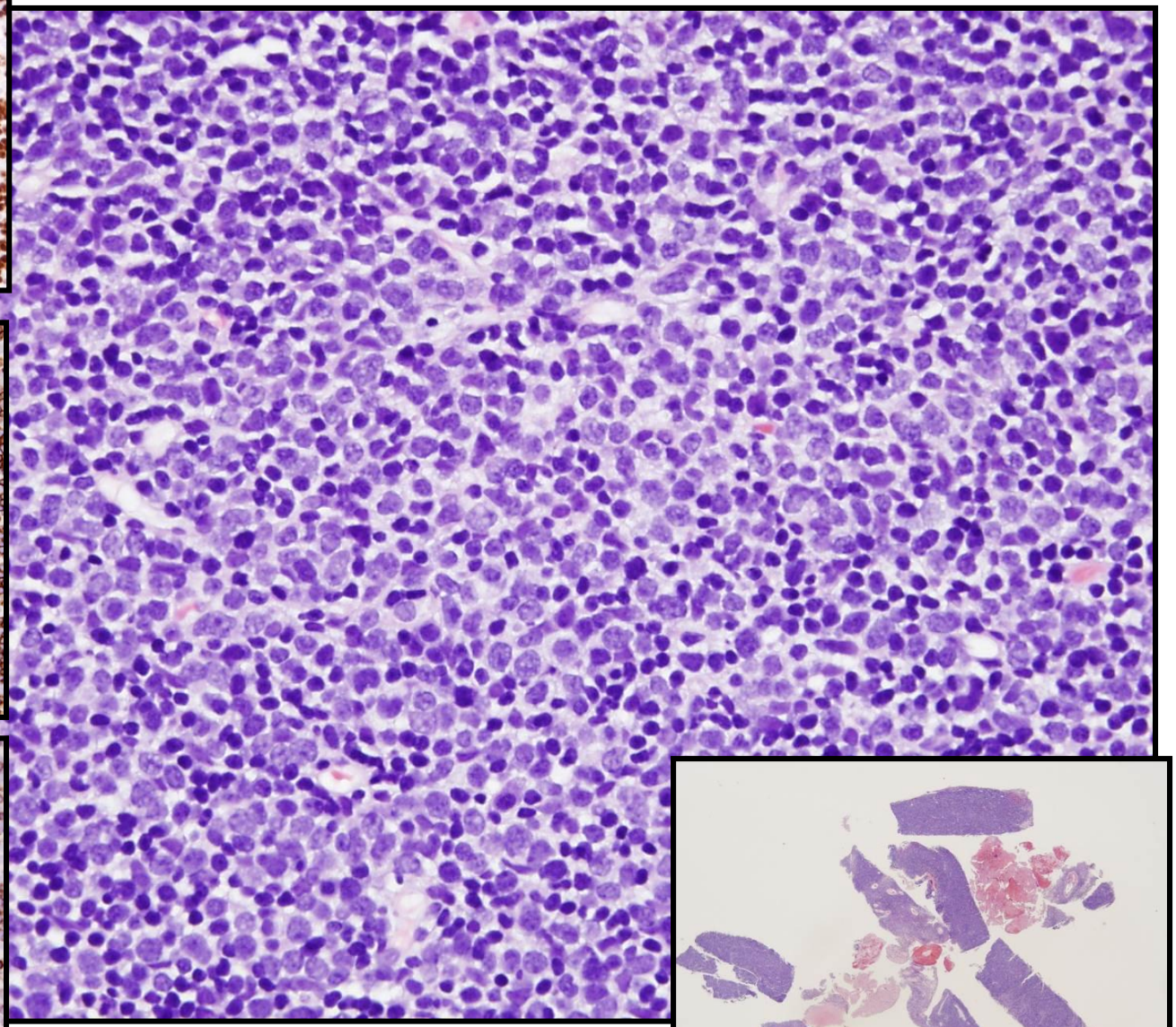
Thymocytes and epithelial cells (B1 or B2)

Thymoma

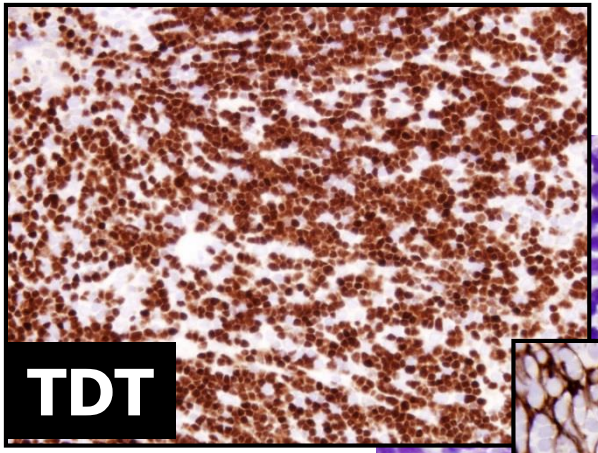


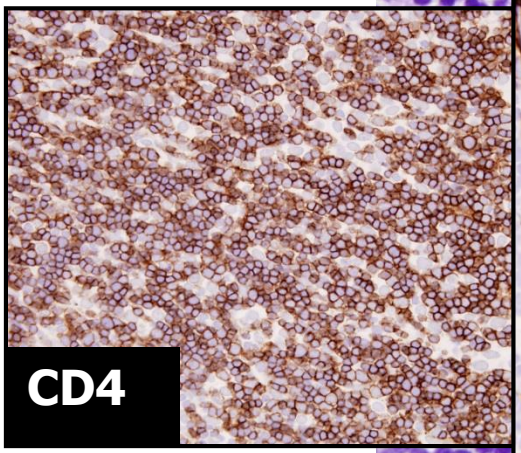


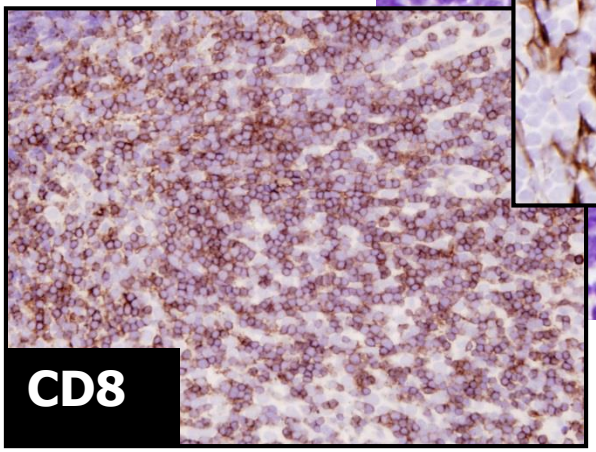


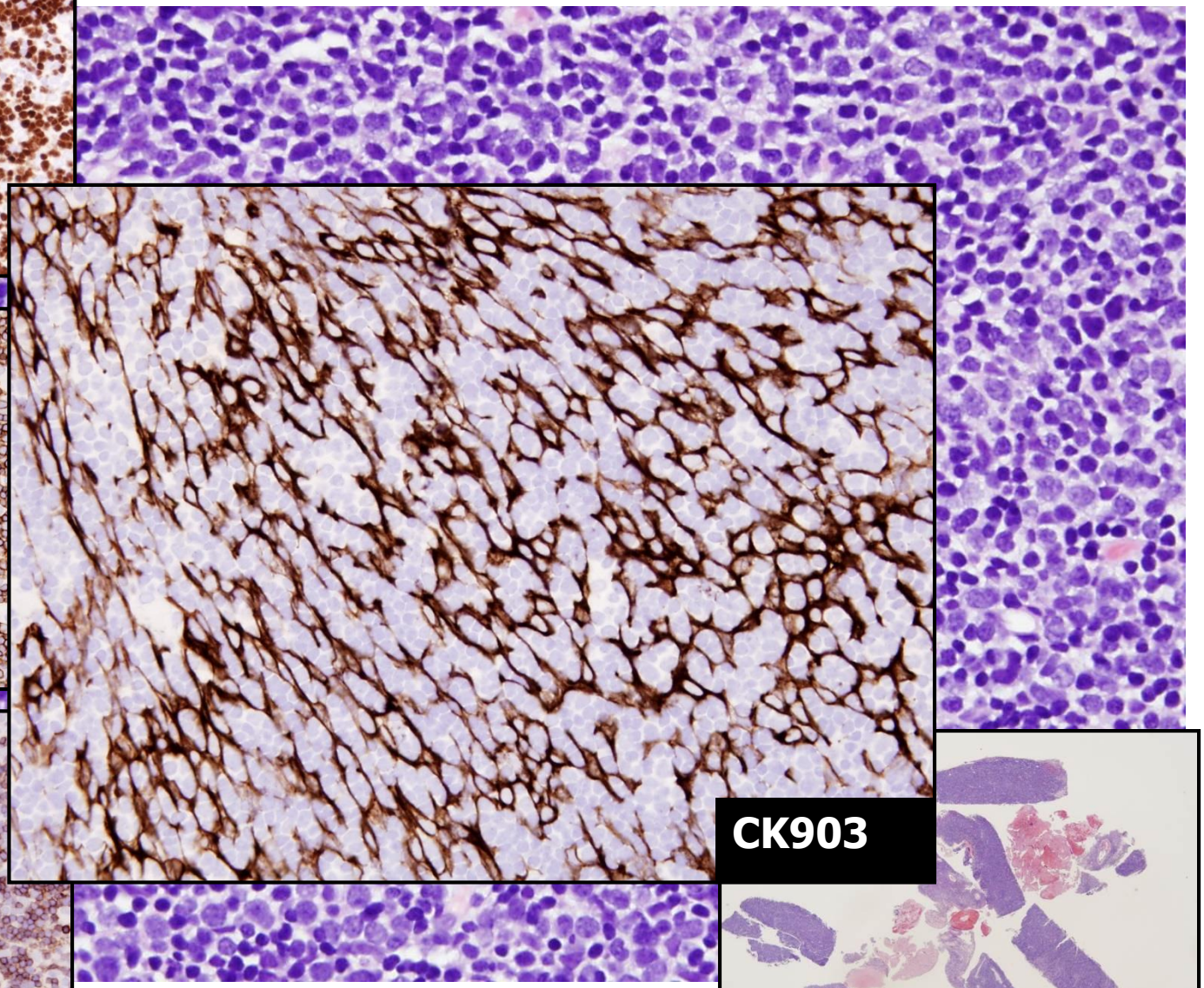


Thymoma









Thymoma

Immunophenotype

Immunohistochemistry

Thymic epithelial cells

CK5/6, CK903, pankeratin, p63

Thymocytes

Immature T-cells: TdT(+), CD4/8(+)

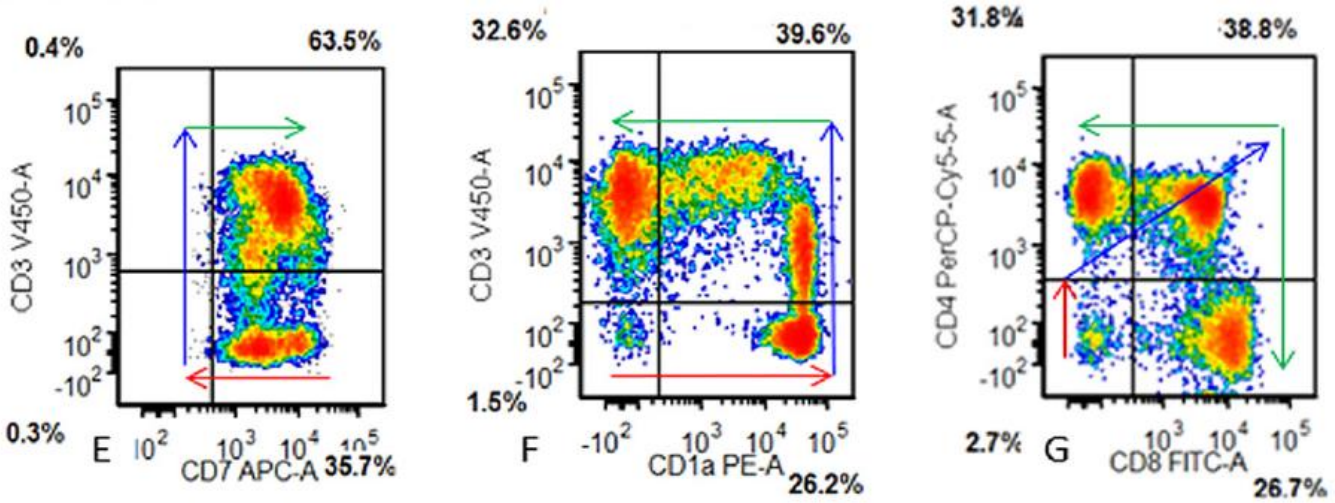
Flow Cytometry

Thymocytes show maturation (smear)

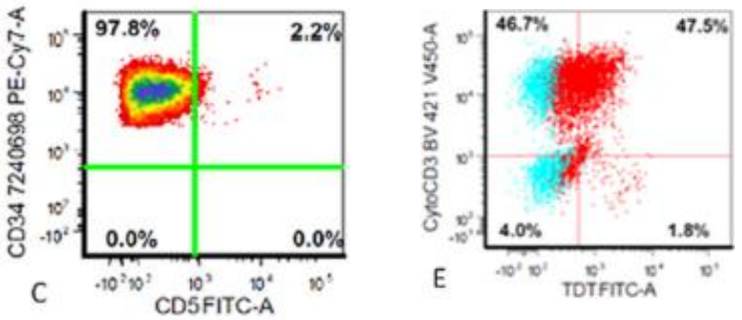
Thymoma vs T Lymphoblastic Lymphoma

Flow Cytometry

Thymoma



T-Lymphoblastic lymphoma



J Clin Pathol 72: 251, 2019

Thymoma
Differential Diagnosis

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

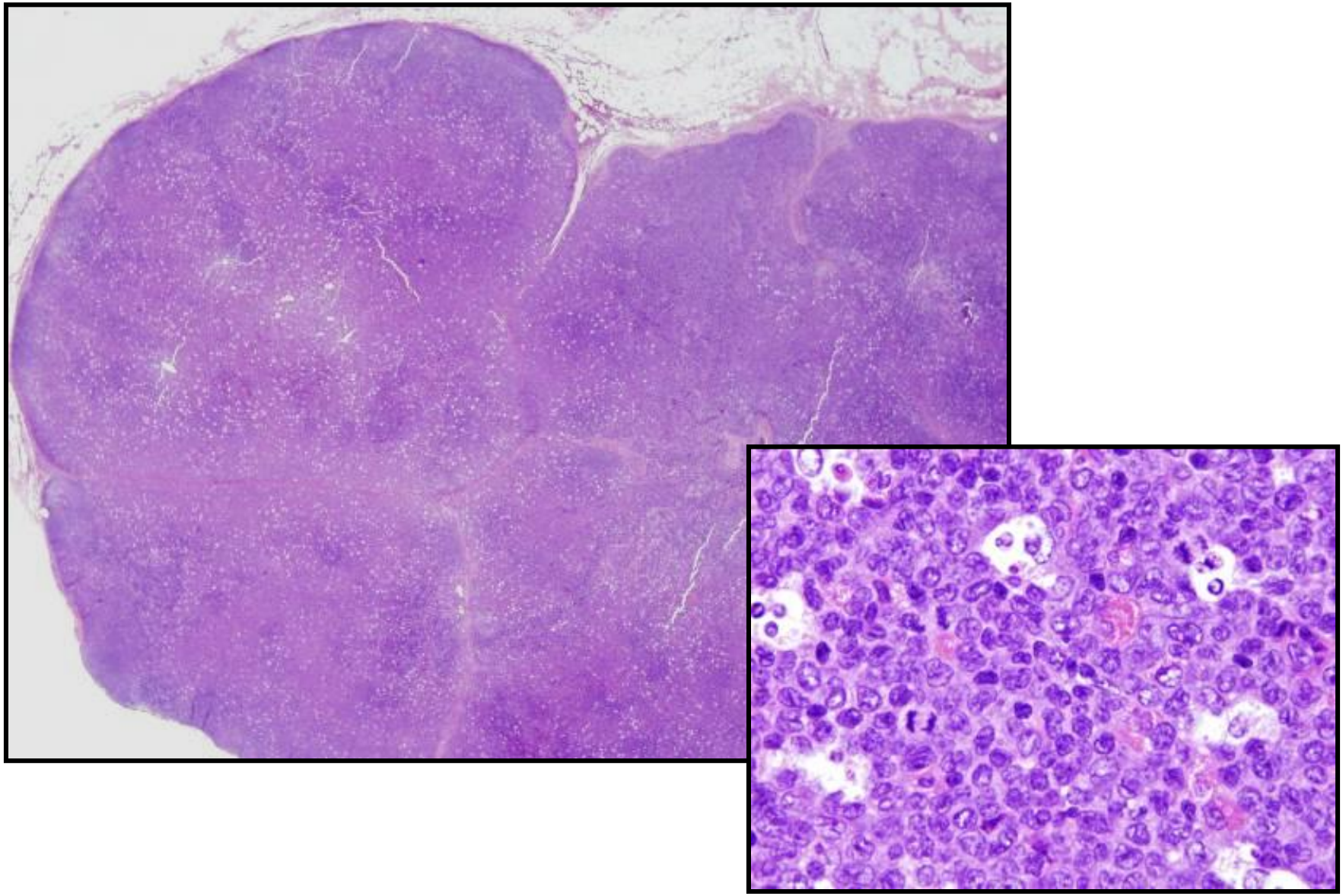
Myeloid Sarcoma
Clinical Features

Three scenarios:

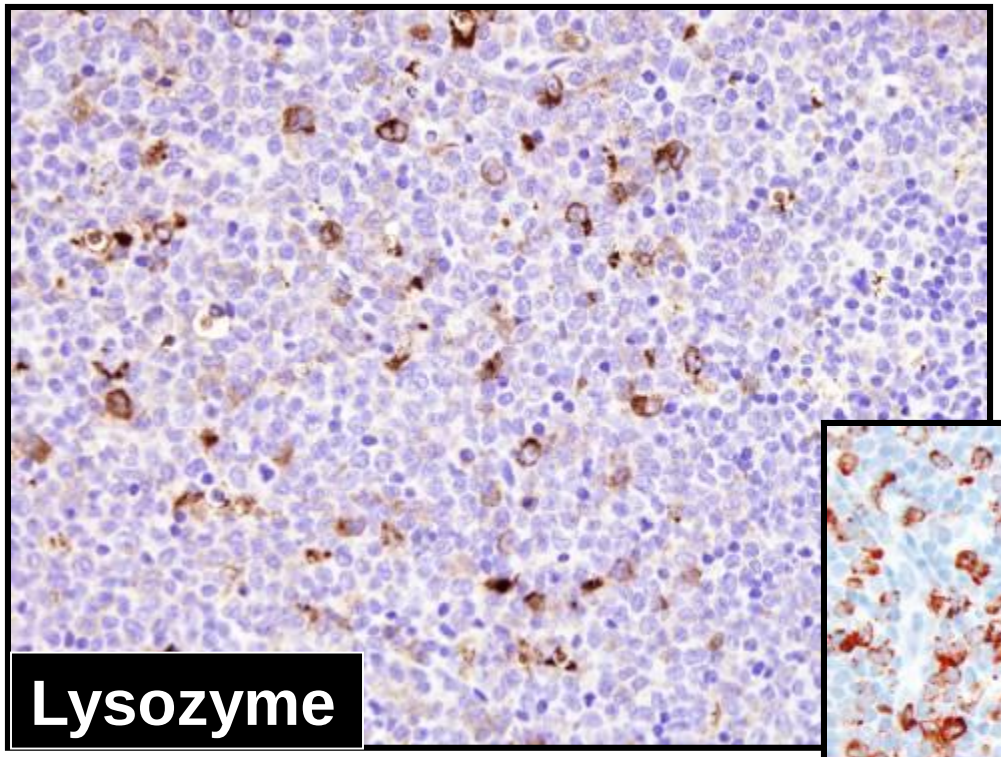
1. **Concurrent evidence of AML in blood and bone marrow**
2. **History of AML (first sign of relapse)**
3. **Precedes systemic AML**

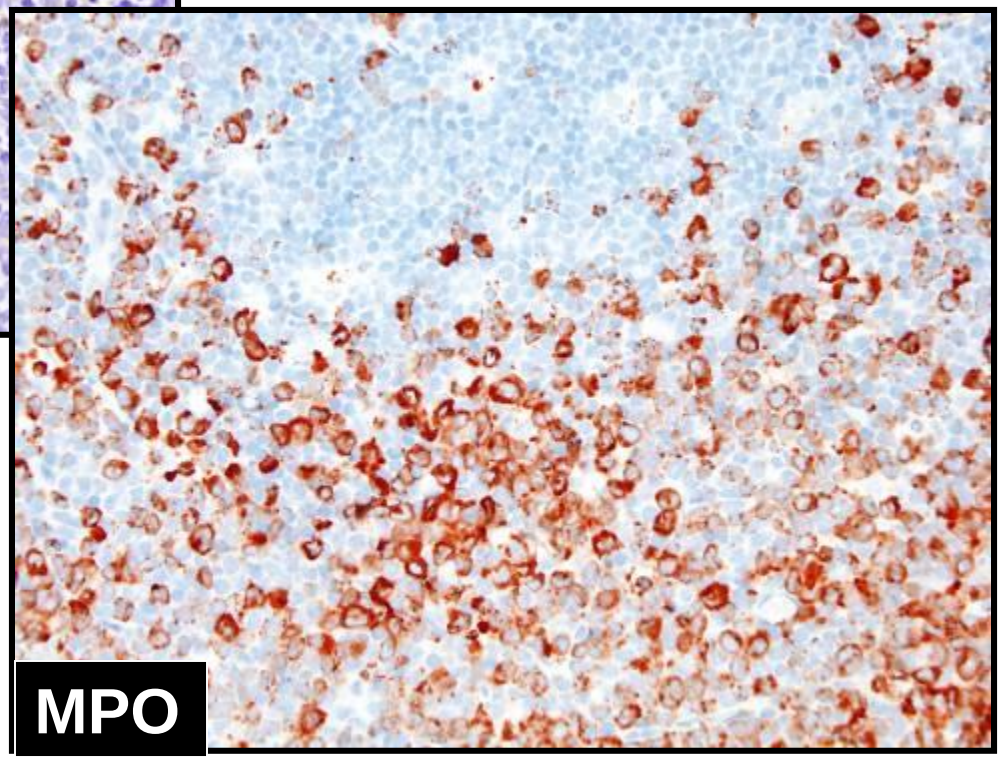
Can also occur in pts with myelodysplastic syndrome (MDS), myeloproliferative neoplasm (MPN) or MDS/MPN

Myeloid (Granulocytic) Sarcoma



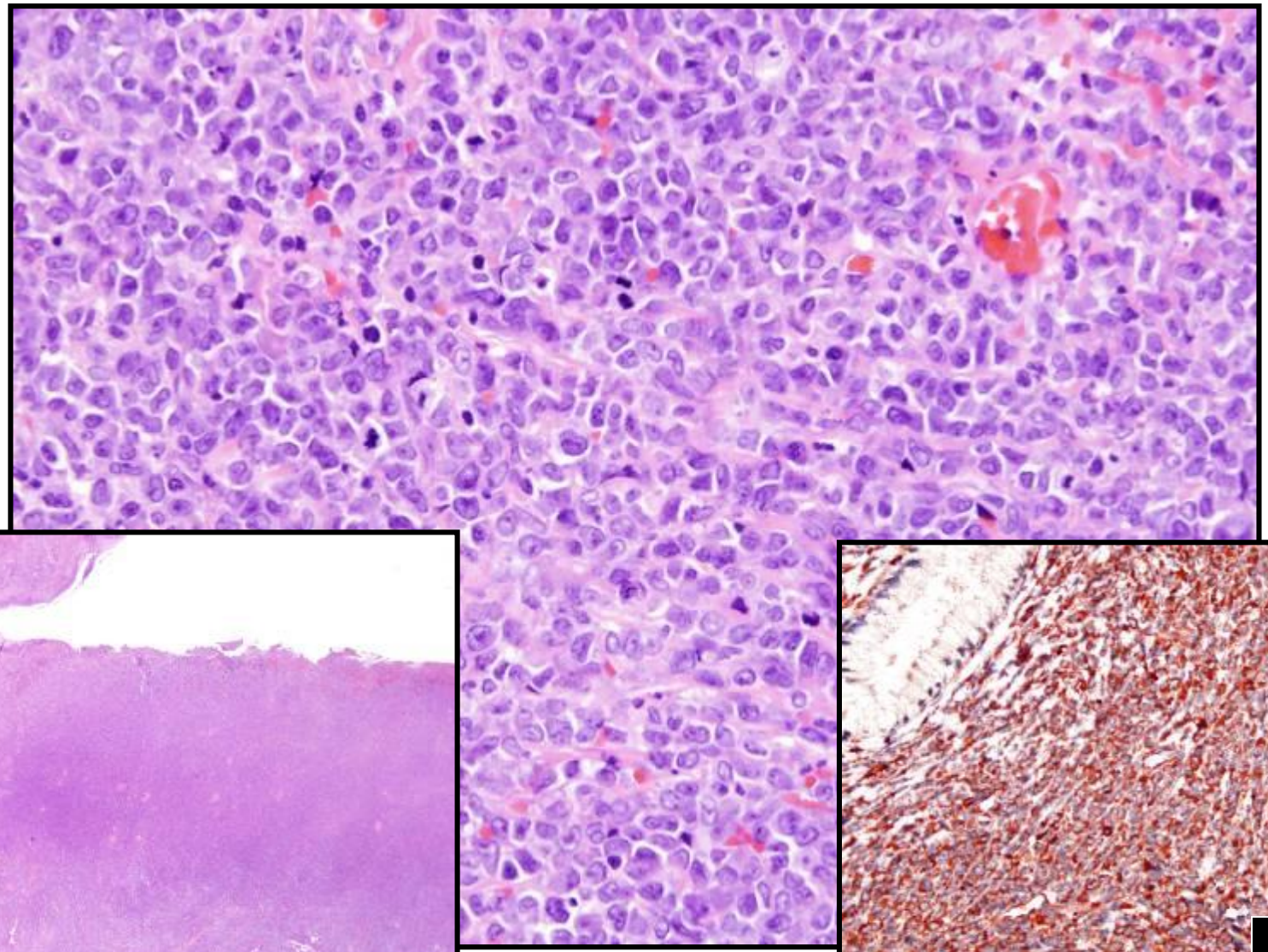
Myeloid (Granulocytic) Sarcoma





Myeloid (Monocytic) Sarcoma

Uterine Cervix



Myeloid Sarcoma
Histologic Features

Diffuse pattern

Often paracortical

Blasts or promonocytes

Immature chromatin

- **Thin nuclear membranes**
- **Small nucleoli**
- **Mitoses**

Myeloid Sarcoma
Immunohistochemistry

Antibody	Frequency
Lysozyme	>95%
CD117 (c-kit)	>95%
CD43	>95%
CD11c	90-95%
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)
CD3, CD5, CD20	Negative

Myeloid Sarcoma
Differential Diagnosis

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 -**

MD Anderson Cancer Center

1954

2014