Benign Mimics of Hematologic Neoplasms

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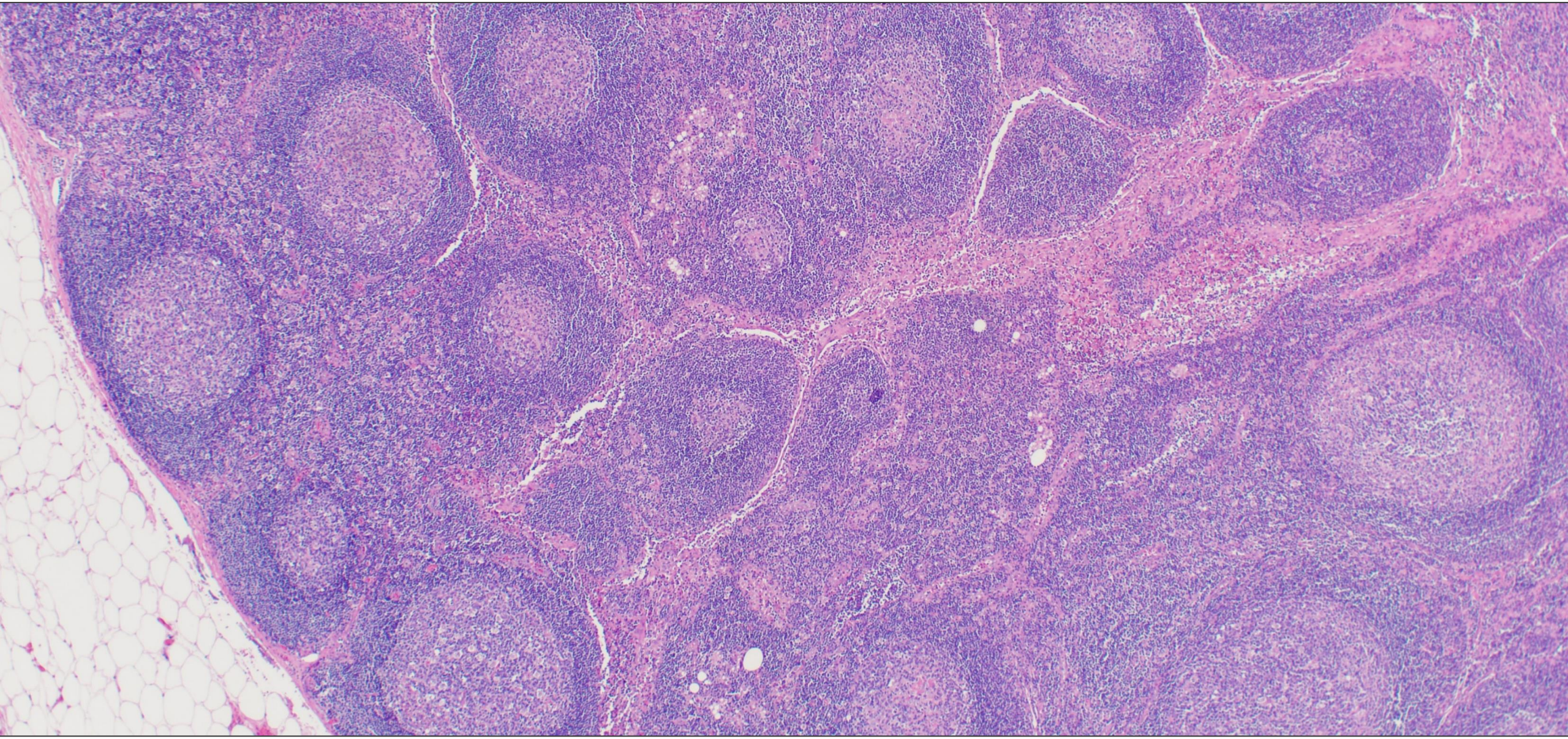
Objectives

- Review an approach to the morphologic assessment of lymph nodes
- Formulate a comprehensive differential diagnosis for common patterns of lymph node involvement
- Compare and contrast clinically relevant benign entities to their neoplastic counterparts
- Emphasize the importance of thorough morphologic evaluation in lymph node pathology

LYMPH NODE ARCHITECTURE



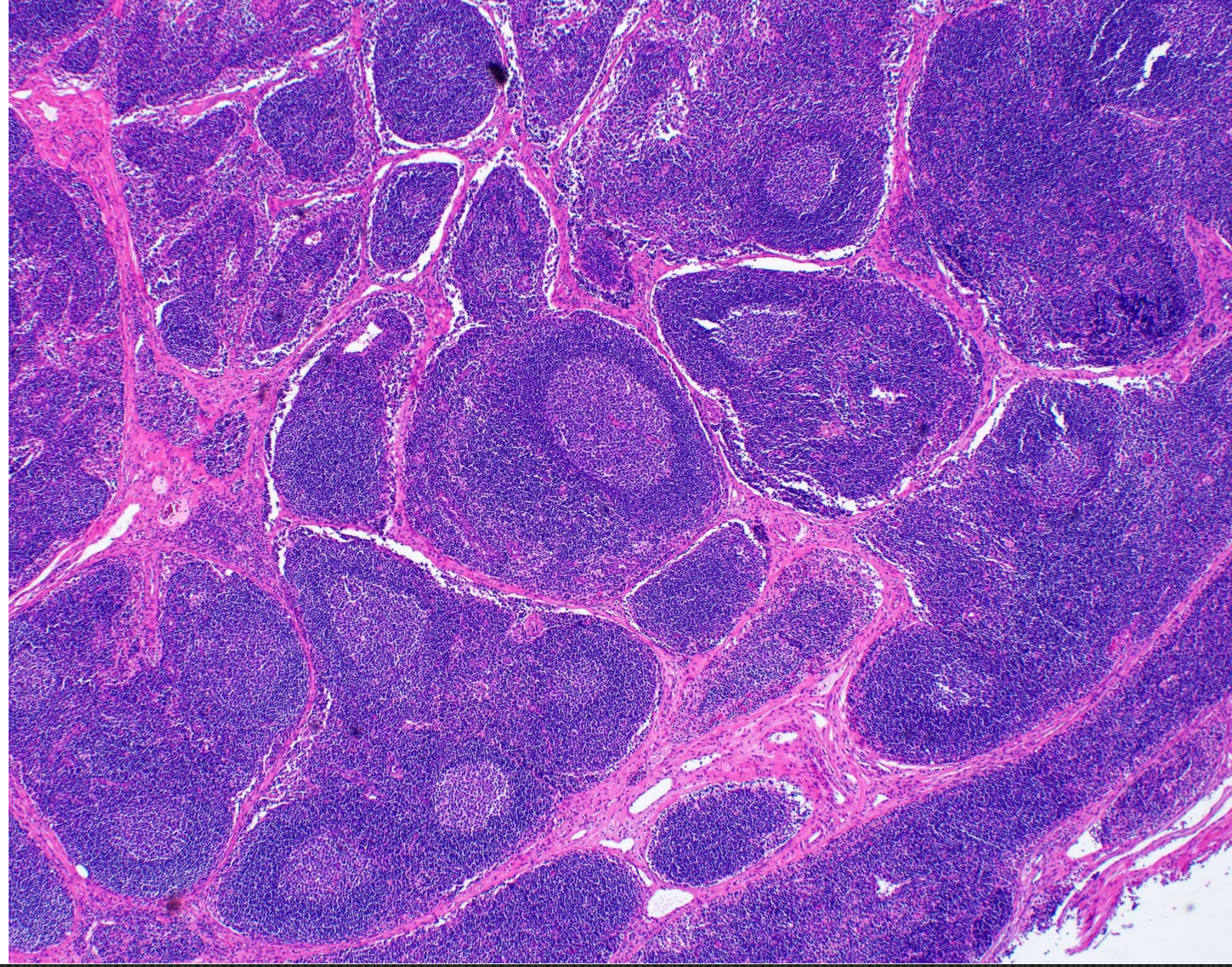
Patterns of benign lymphadenopathies

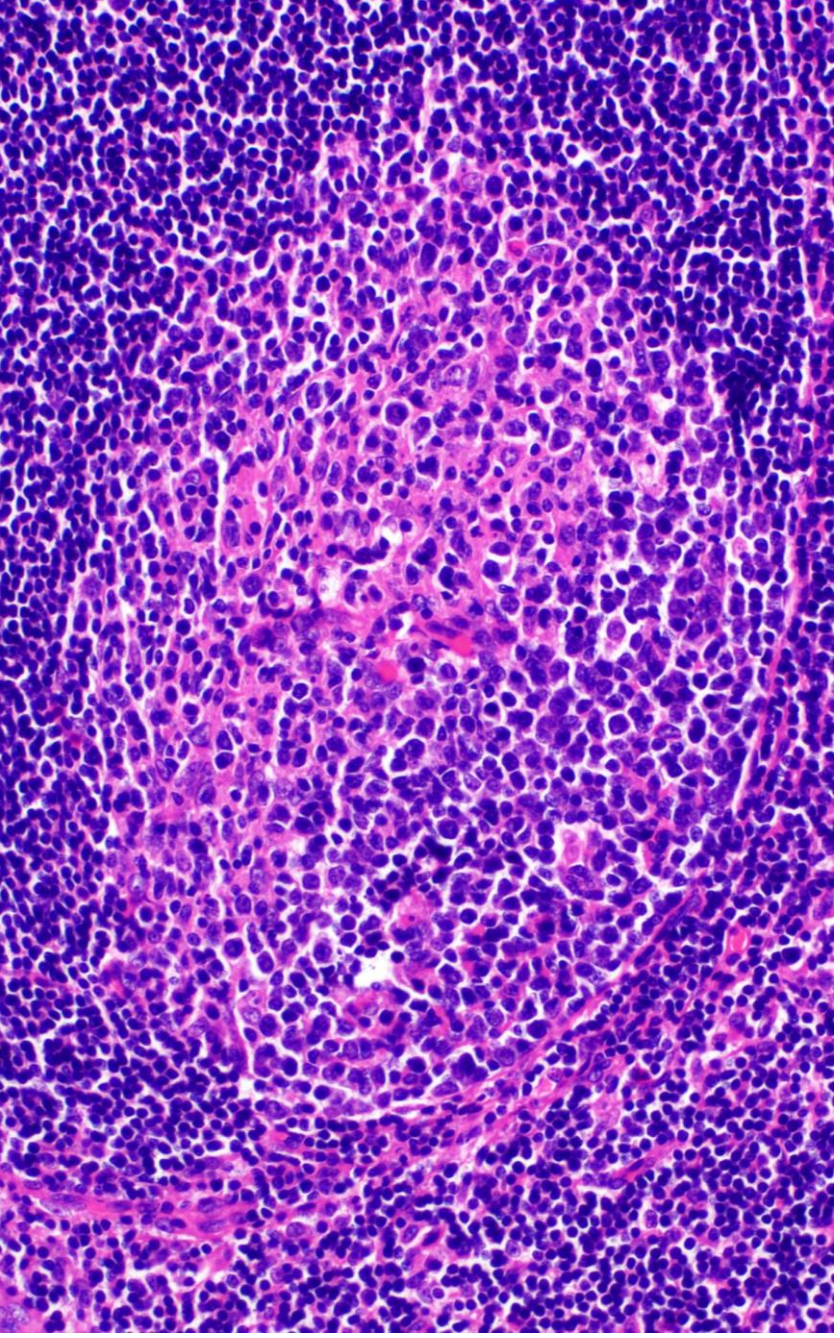
Follicular pattern	Paracortical/mixed pattern	Sinus pattern	Other patterns
• Follicular hyperplasia • Progressive transformation of germinal centers • Castleman disease, hyaline-vascular type • Rheumatoid arthritis • Toxoplasmic lymphadenitis	• Non-specific paracortical hyperplasia • Dermatopathic lymphadenopathy • Kimura disease • Toxoplasmic lymphadenitis • Kikuchi disease • Viral lymphadenitis • Drug-induced • IgG4-related disease	• Rosai-Dorfman disease • Sinus histiocytosis • Vascular transformation of sinuses	• Granulomatous lymphadenitis • Necrotizing • Foreign substances


Pony Express Station, Dugway, UT

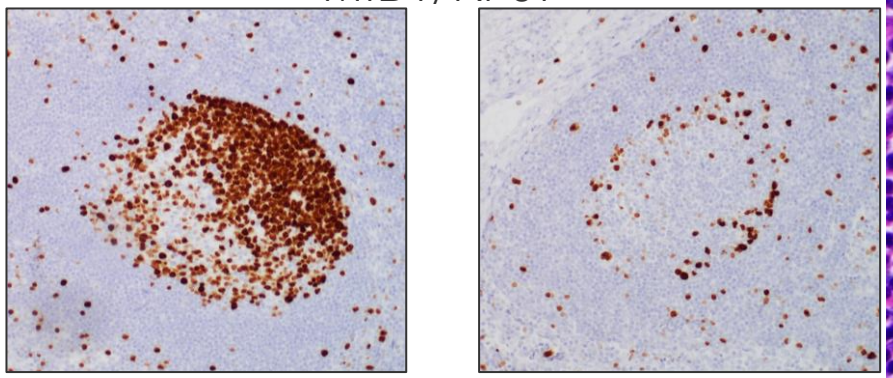
CASE #1

A middle-aged woman with incidentally found renal hilar lymph node during nephrectomy

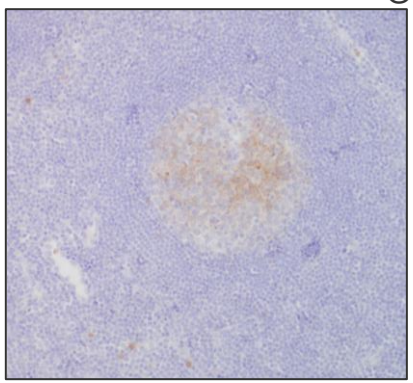


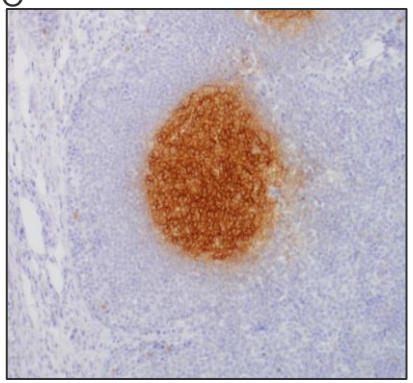


MIB1/Ki-67

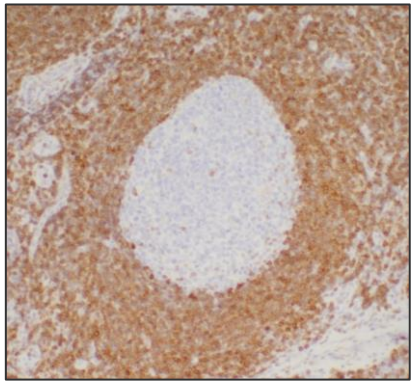


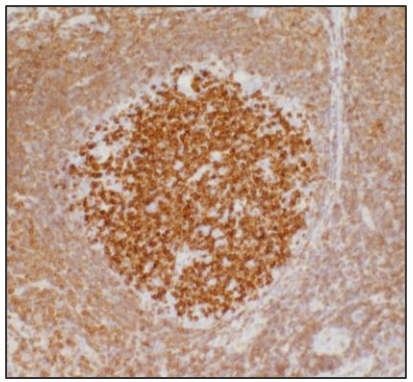
CD10

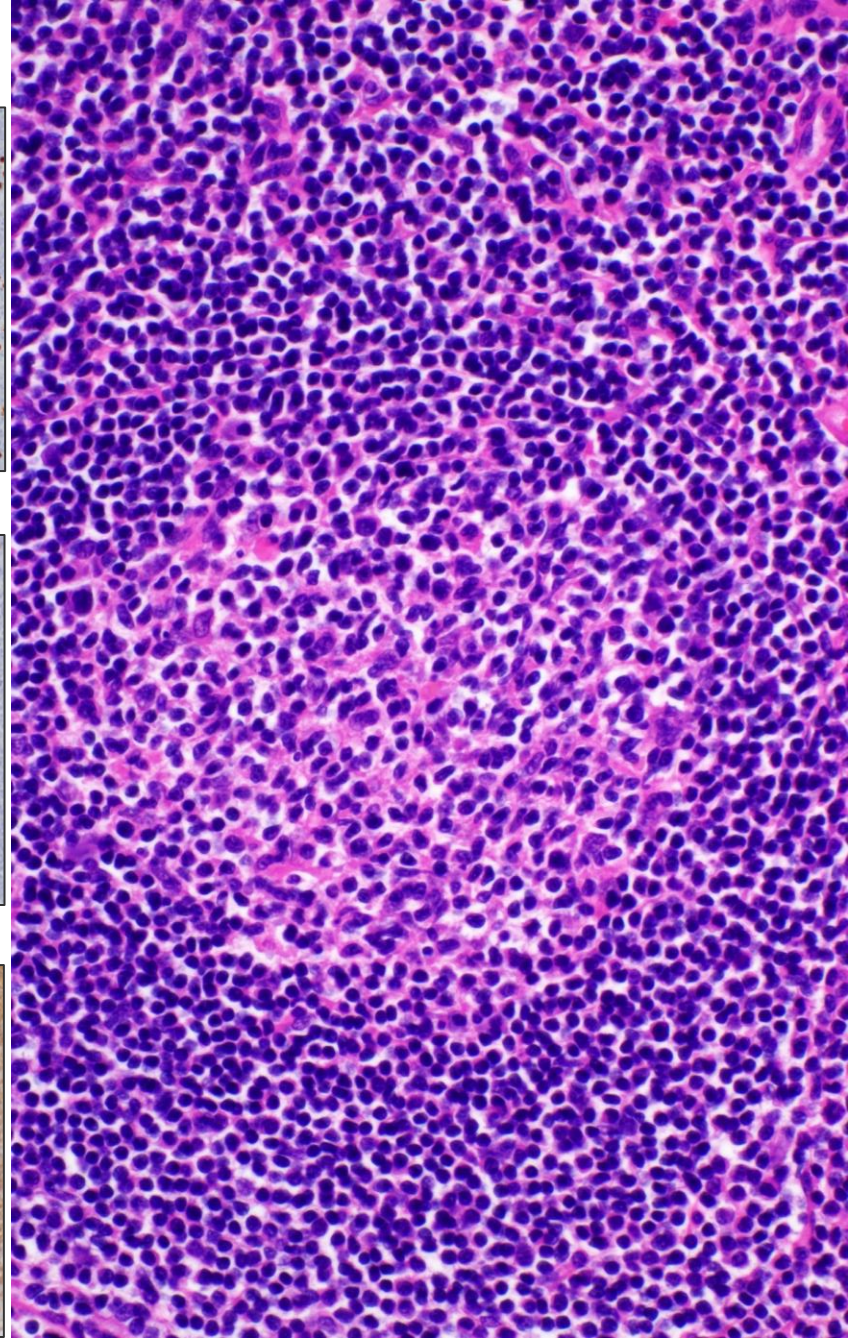




BCL2







Summary

- Incidental moderately enlarged lymph node
- Preserved architecture
- Two types of secondary follicles with germinal center B-cells
  - » BCL6+, CD10 weaker+, BCL2-, high MIB1
  - » BCL6+, CD10 strong+, BCL2+, low MIB1

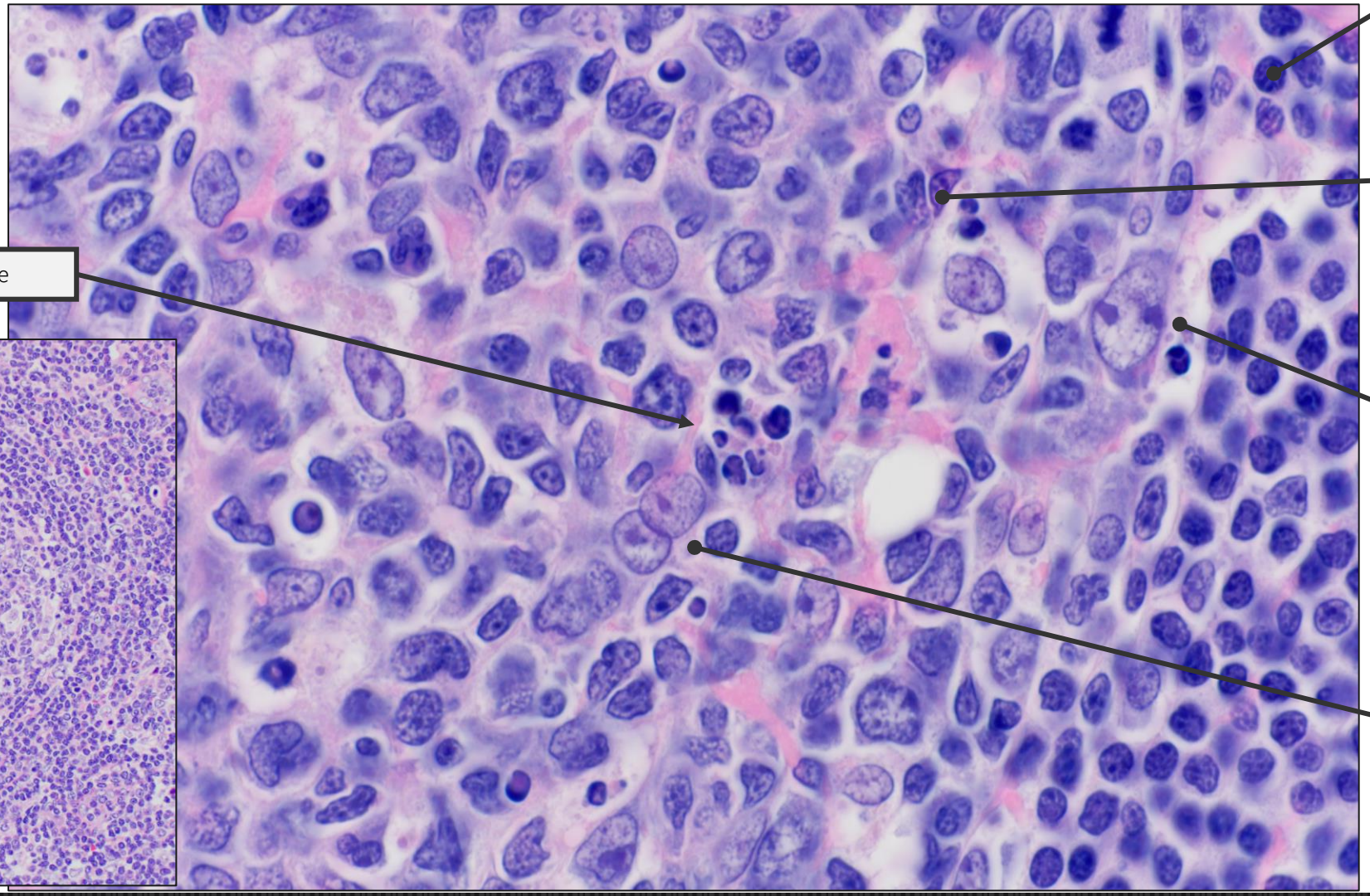
Diagnosis: In situ follicular neoplasia (follicular lymphoma in situ), partial involvement with background follicular hyperplasia

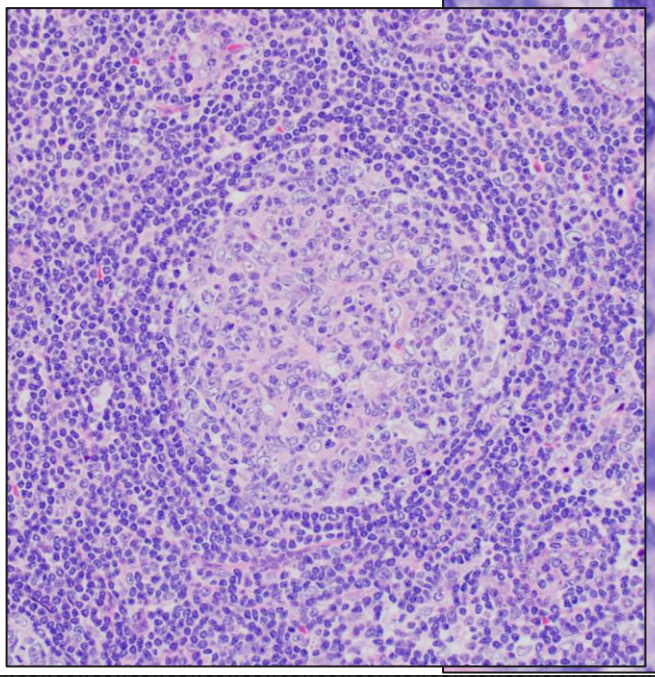
General

- Vague definition: “an increase of secondary follicles or germinal centers per unit area”

Hypertrophy – the follicles are increased in size, often irregularly shaped

Morphology



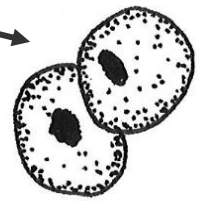


"tingible body" macrophage

small noncleaved cell

small cleaved cell
CENTROCYTE

large noncleaved cell
CENTROBLAST



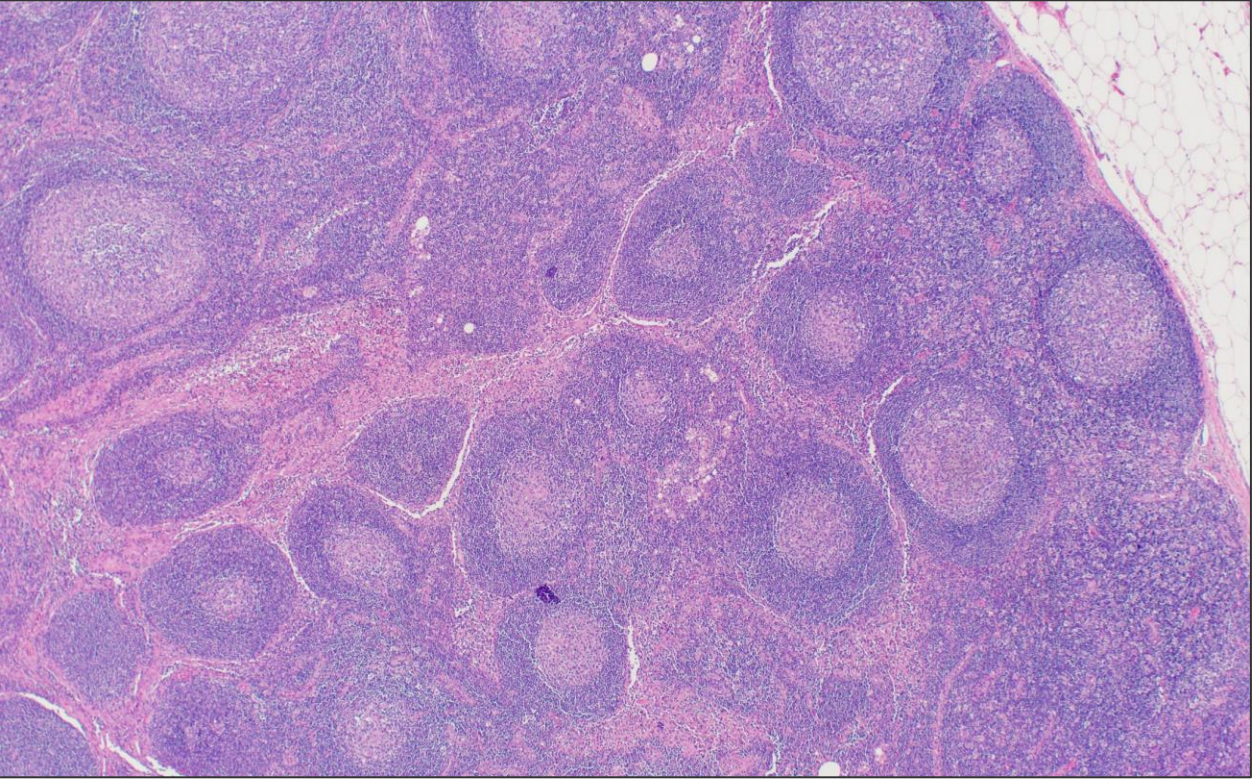
follicular dendritic cells
"kissing" nuclei

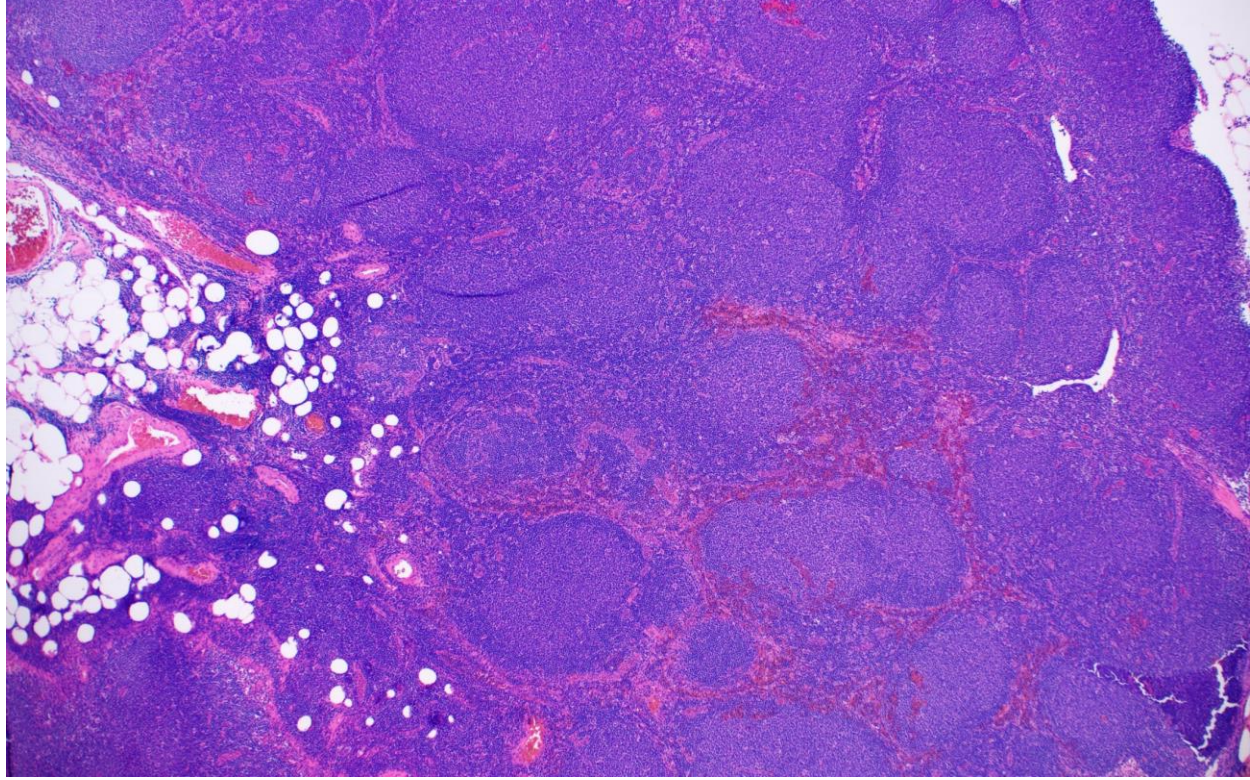
FH vs FL

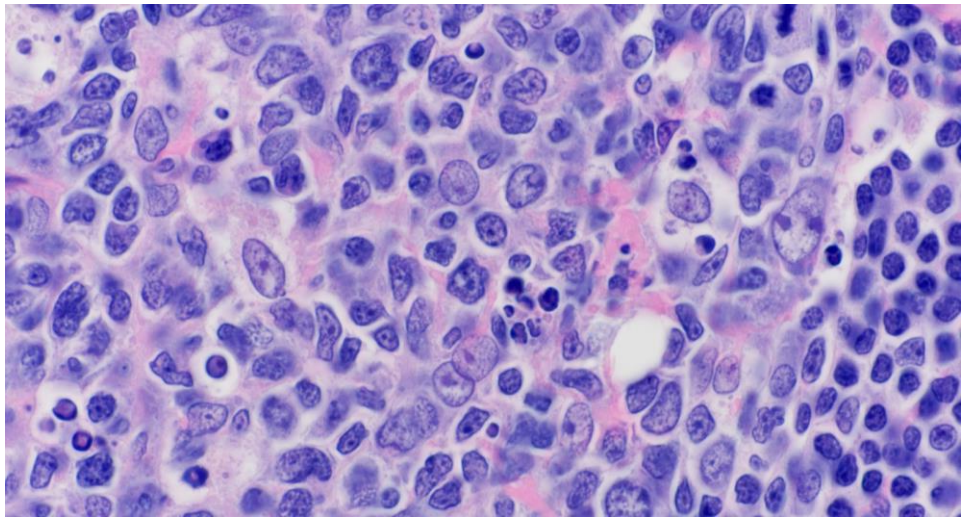
Feature	Follicular hyperplasia	Follicular Lymphoma
Clinical picture	Localized LAD in a younger patient	Localized or generalized LAD in an older patient
Density of follicles	Low, interfollicular areas are preserved	High, “back to back”
Shape and size of follicles	Variable	Monotonous
Follicles in the perinodal tissue	Rare	Common
Localization of follicles in the LN	More numerous in the periphery (cortical)	Throughout the LN
Cellular composition of the GC	Polymorphic	Polymorphic to monomorphic
Tingible body macrophages in GC	Numerous	Rare
Mitotic figures in the GC	Numerous	Decreased
GC polarization	Evident	Lost
Mantle zones	Distinct	Indistinct or absent
Diffuse nodal effacement	Absent	Can be present

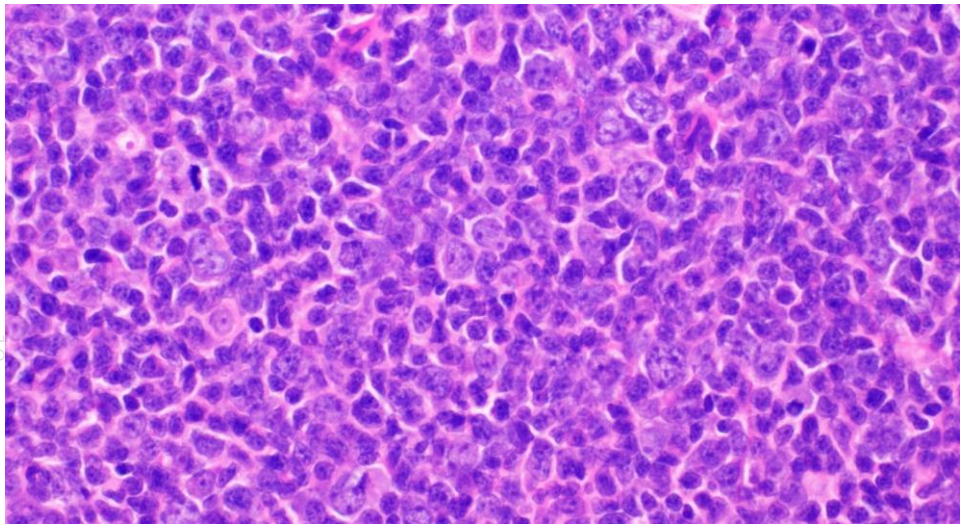
CAVEATS

- No single morphologic finding distinguished between FH and FL
- Density of follicles on low power is the most reliable H&E feature
- Presence of diffuse areas of nodal effacement strongly argues against FH
- Florid FH can show many features of FL: perinodal extension, relative increase in centroblasts, attenuated mantle zones









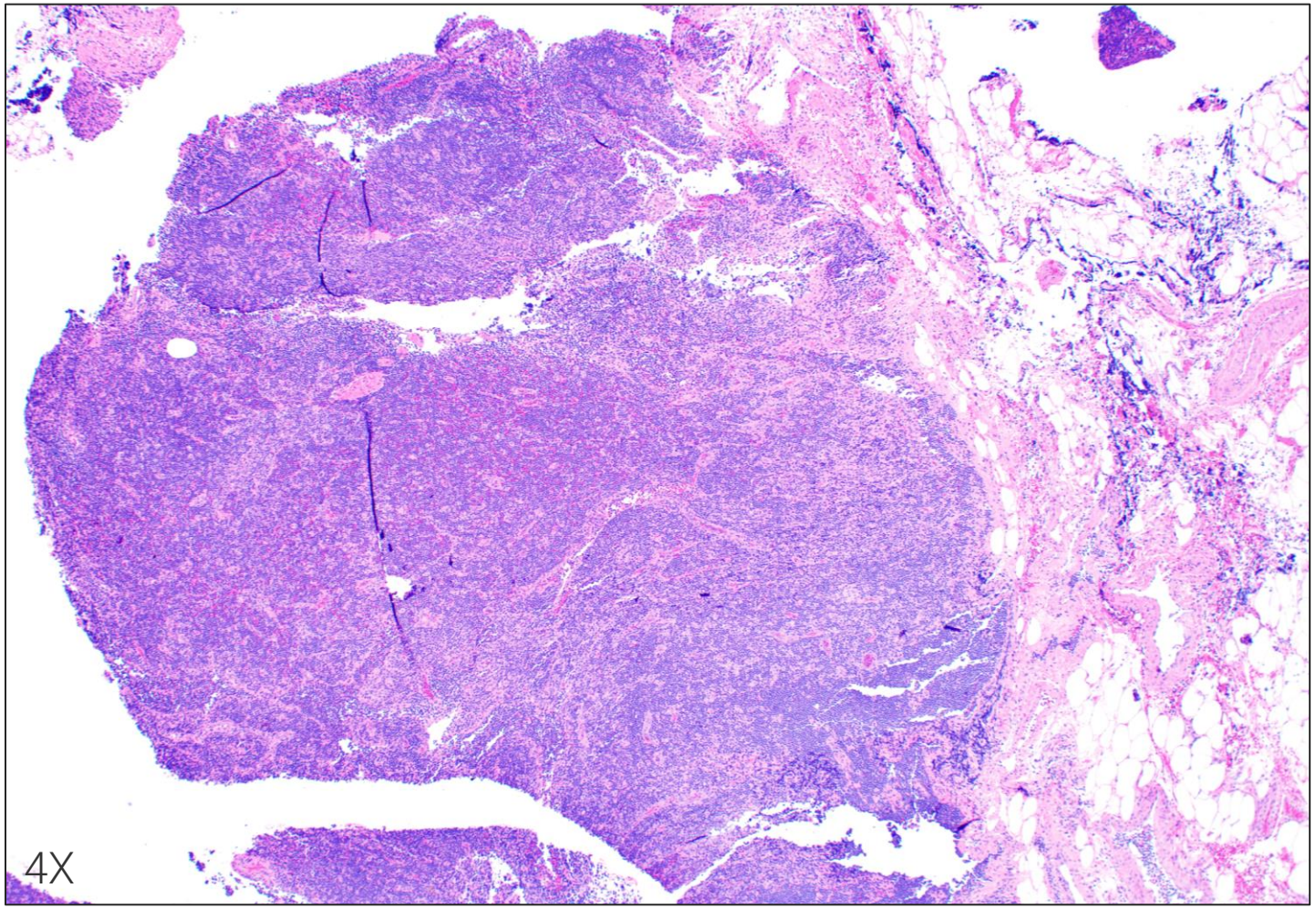
FH vs FL

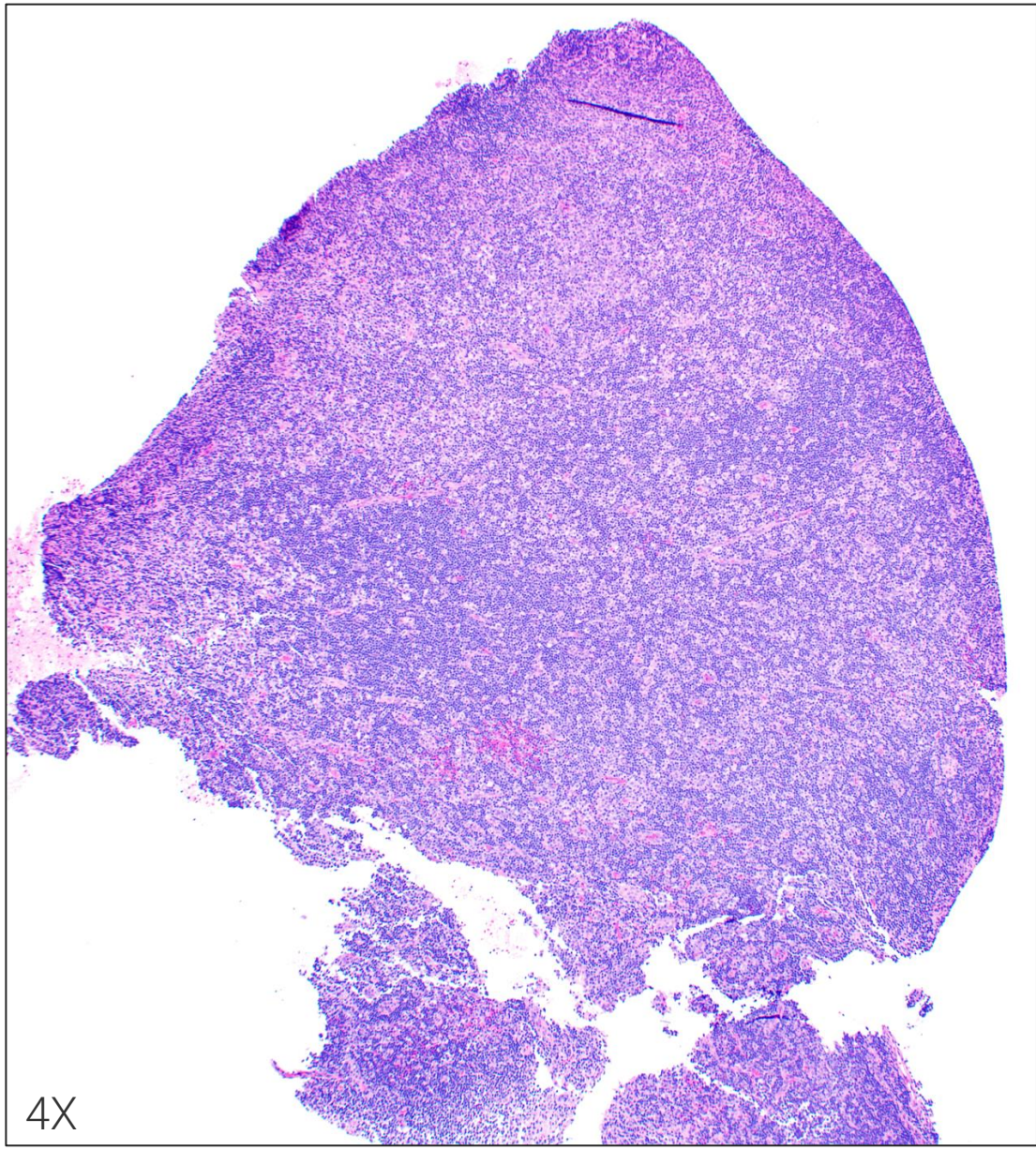
Feature	Follicular hyperplasia	Follicular Lymphoma
BCL2 expression by IHC	Germinal center B cells are NEGATIVE - beware of follicular helper T-cells - B-cells in primary follicles are BCL2+, correlate with BCL6 and CD10 - watch out for PTGC, mantle zone B-cell are BCL2+	Neoplastic cells are POSITIVE - a subset of FL can be negative (high grade, pediatric type) - FL in situ can show only scattered + cells
Light chain restriction	Negative - can be present especially in younger boys with florid FH	Positive
BCR clonality studies	Negative - positive clonality in younger patients with florid FH - oligoclonal pattern may be seen in immunologic disorders - viral infections can also have positive clonality	Positive - can be negative in 20% of cases due to somatic hypermutation
t(14;18) IGH-BCL2	Negative	Positive - can be negative in 10% FL – more so in high grade FL - negative in pediatric type FL
Proliferative index on GC (Ki-67)	High, highlights polarization	Low in low grade, increases in high grade, lost polarization

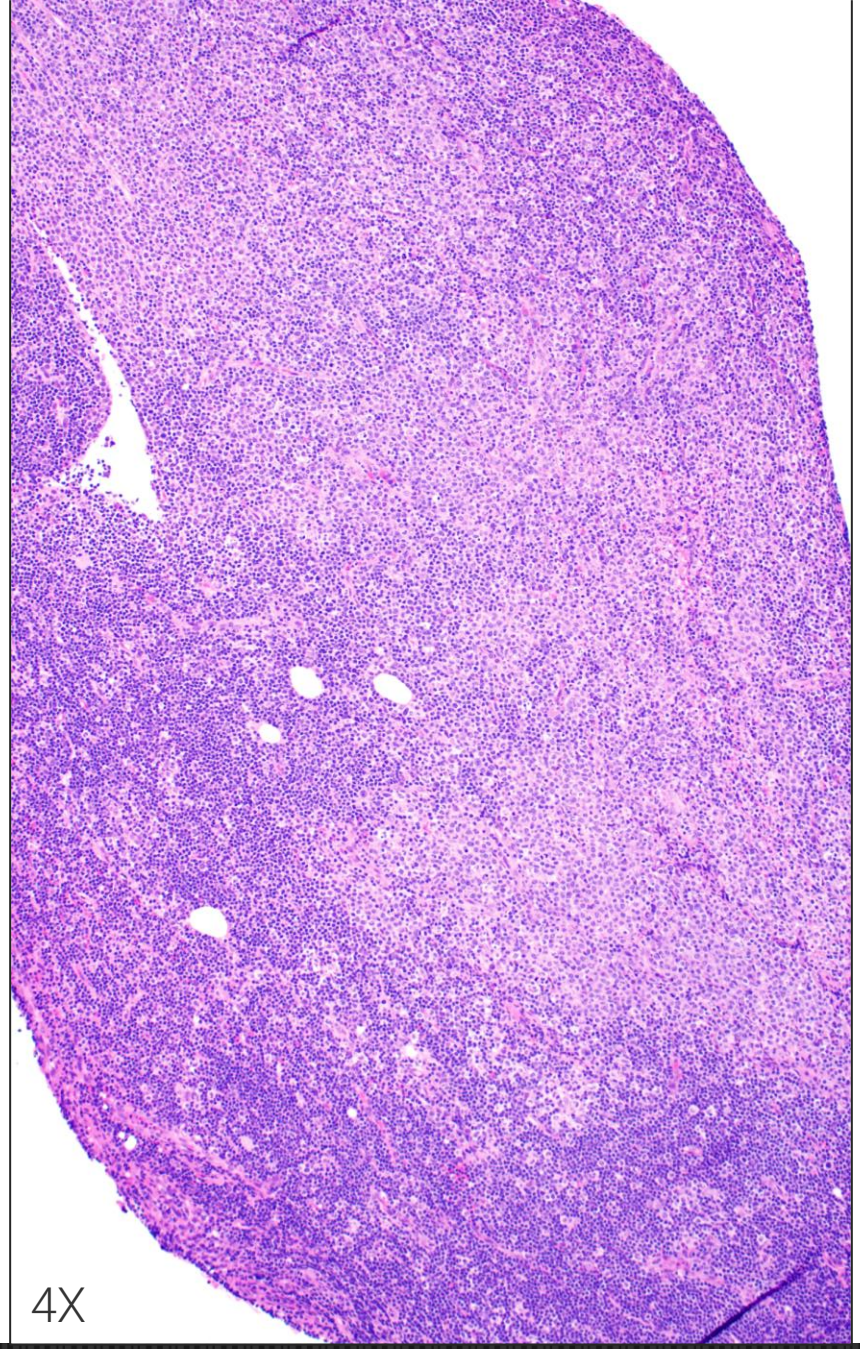

The Great Salt Lake, UT

CASE #2

A middle-aged woman with infra-auricular tender lump
- gradual enlargement for 7 months, s/p antibiotics
- previous FNA – benign lymph nodal tissue



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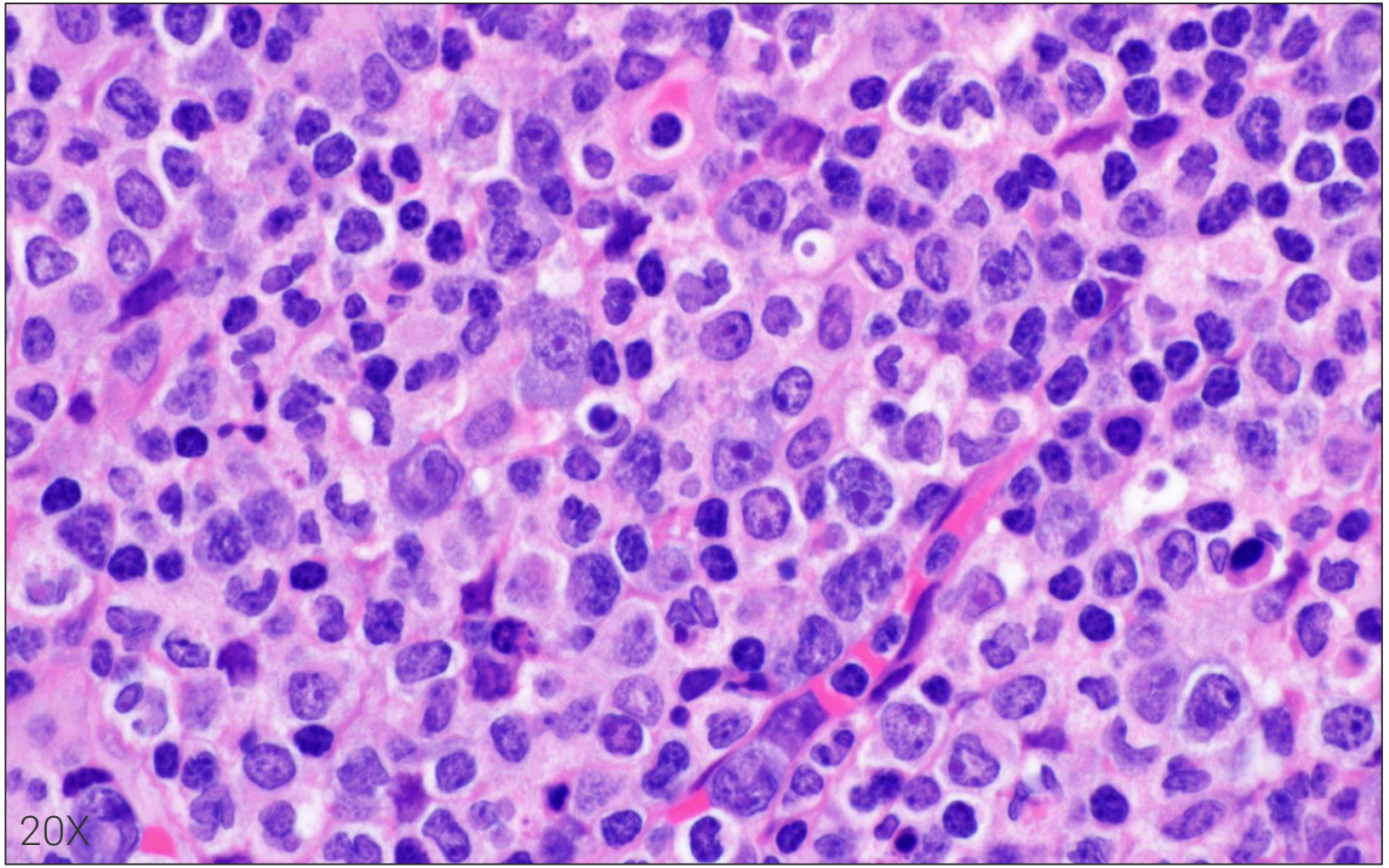
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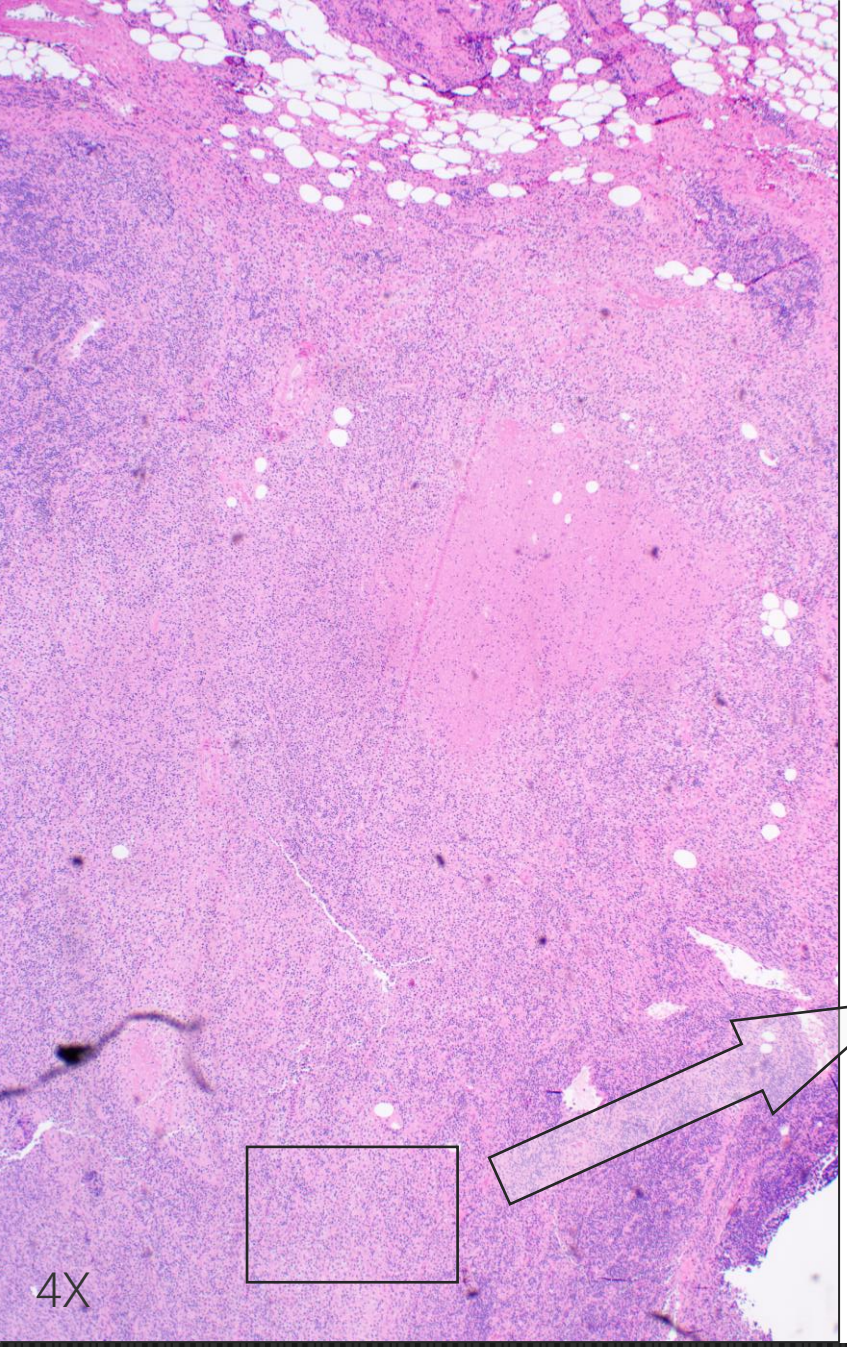
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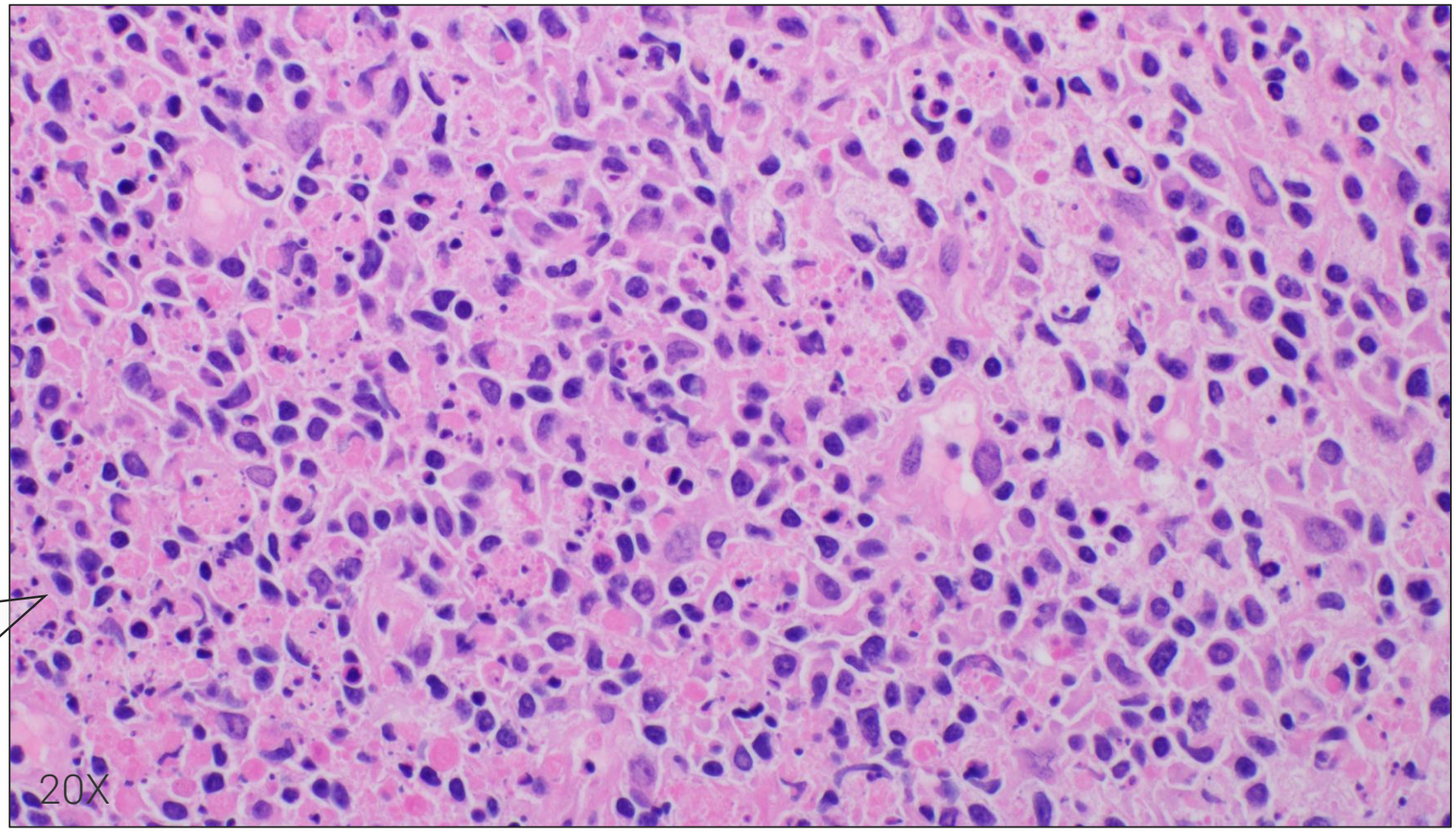
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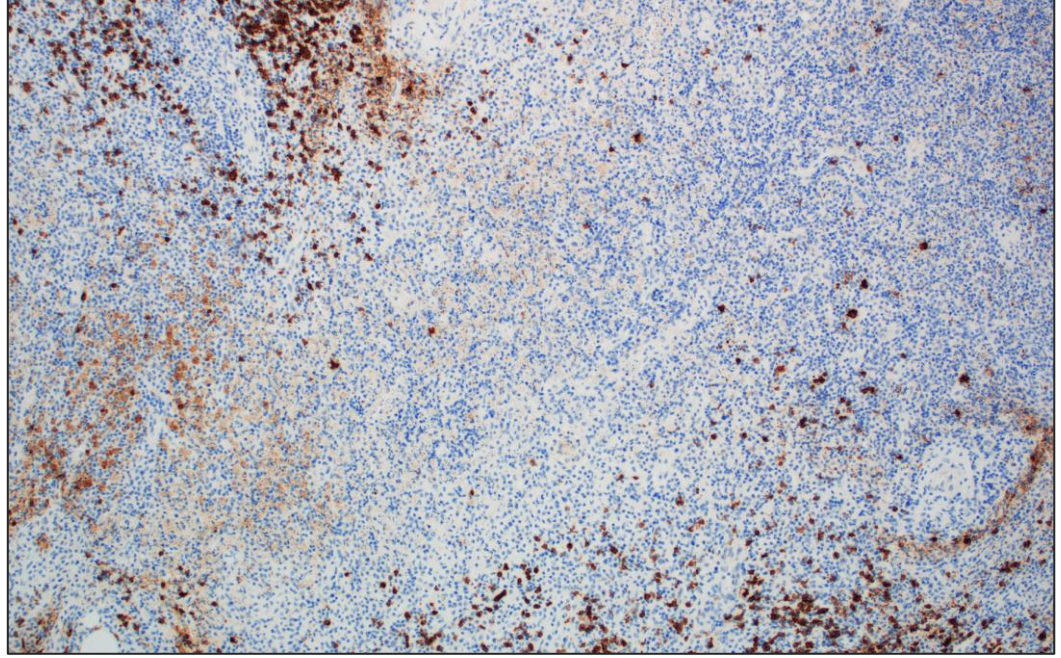
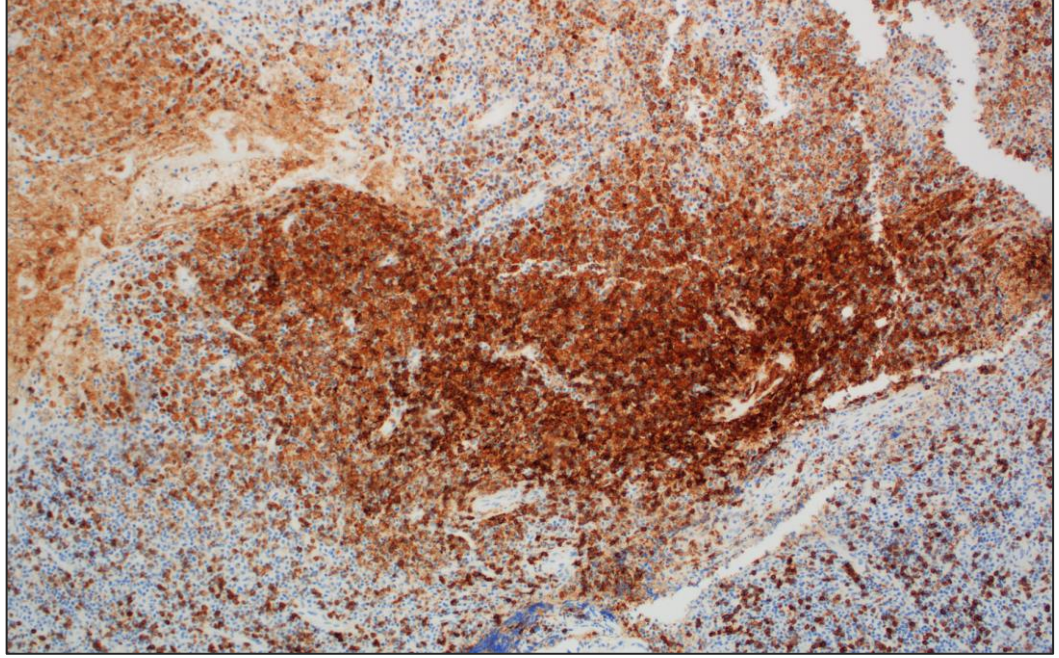
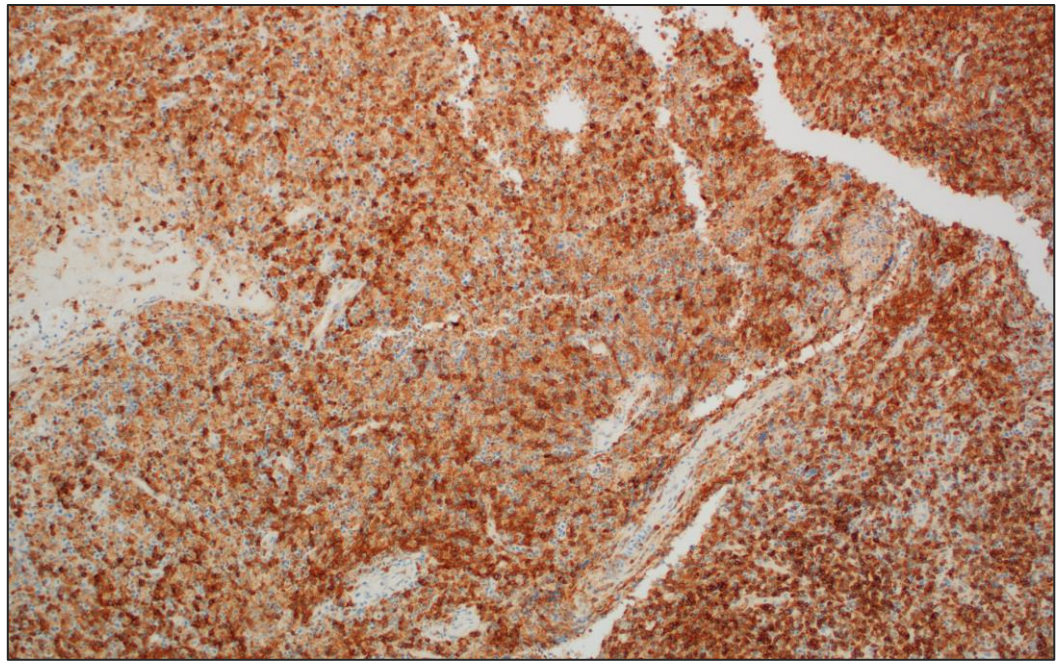
CD20



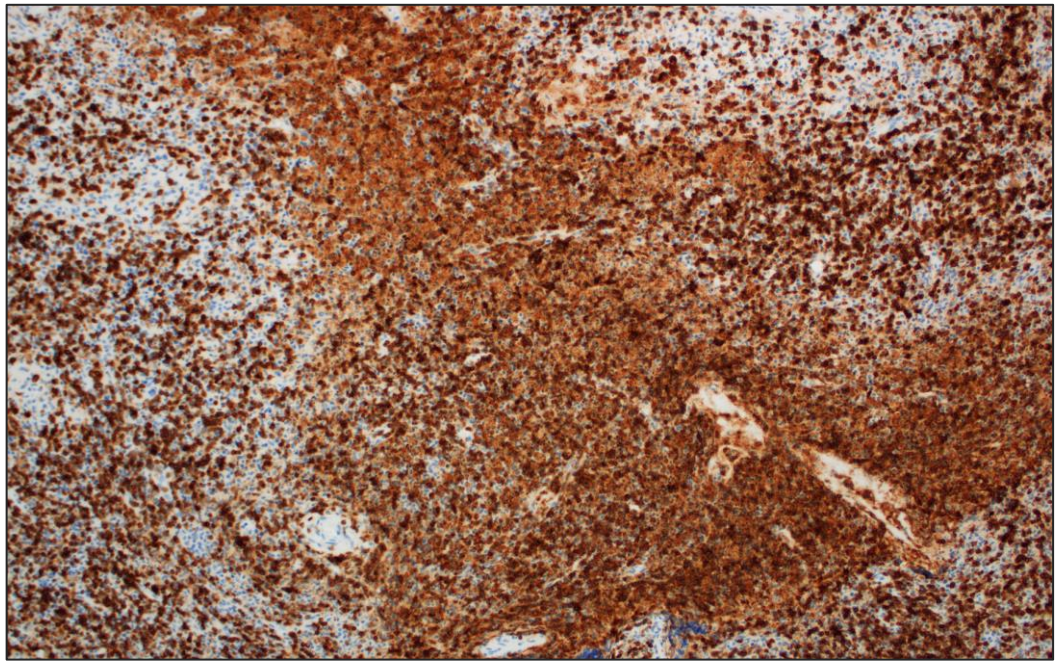
CD3



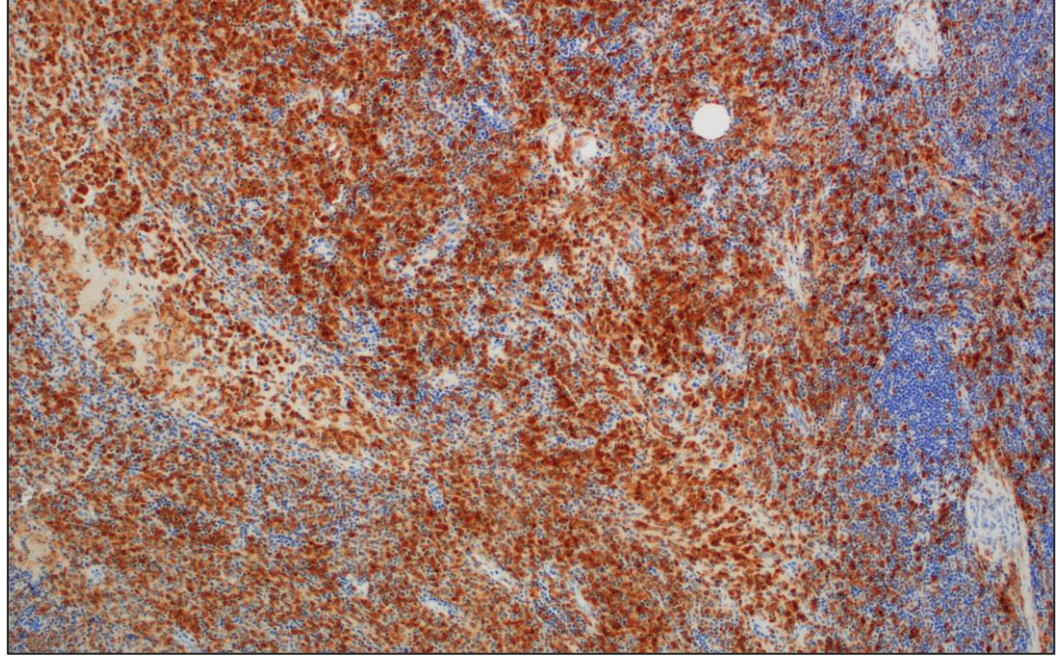
CD4



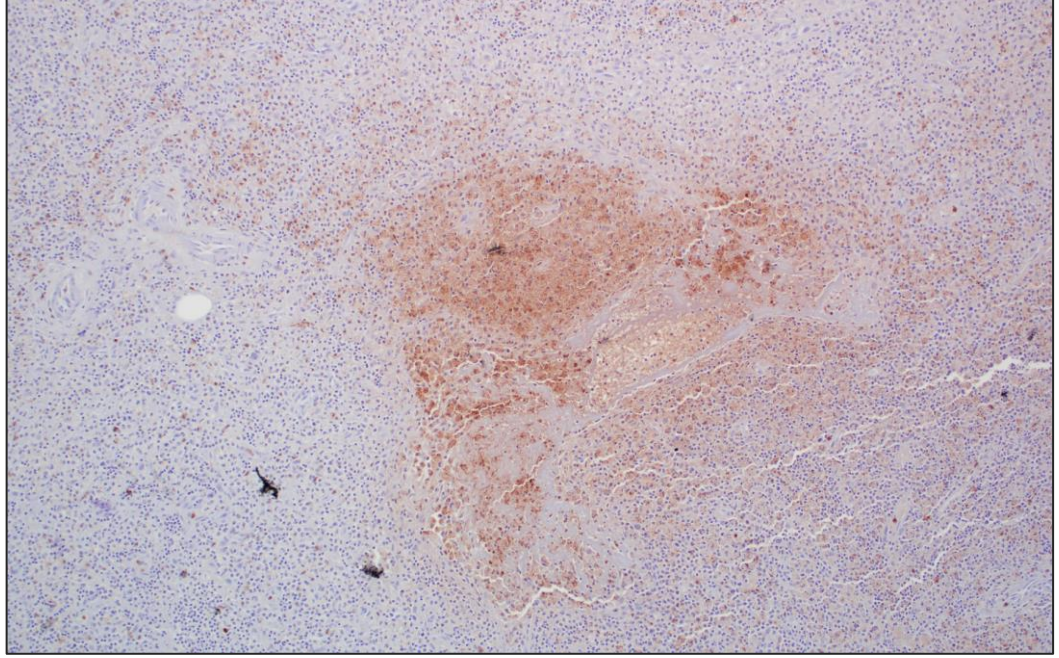
CD8



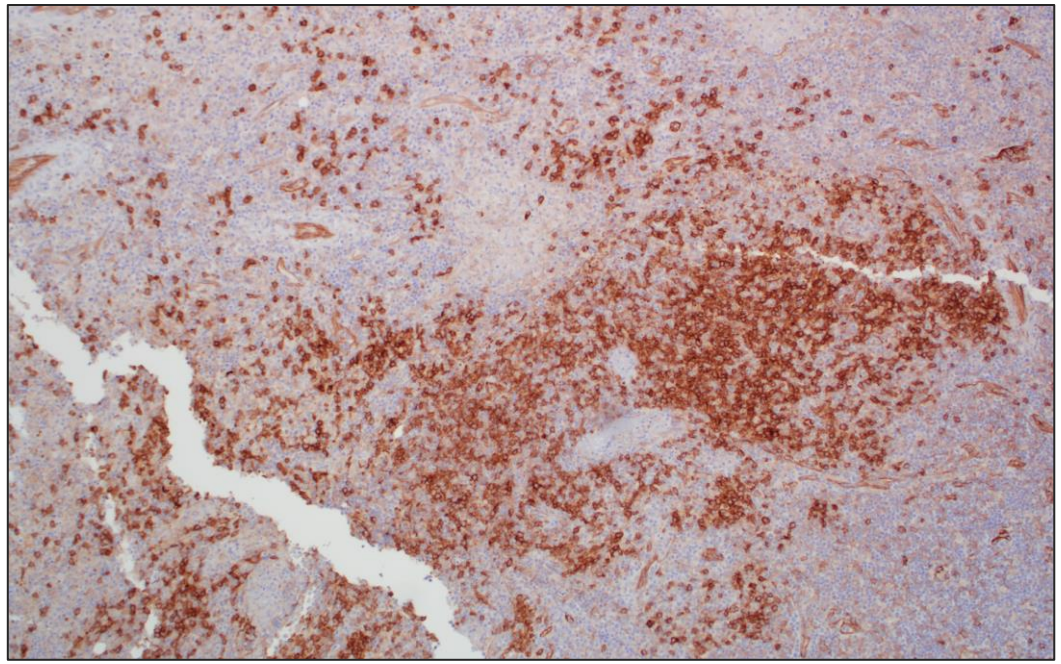
CD68



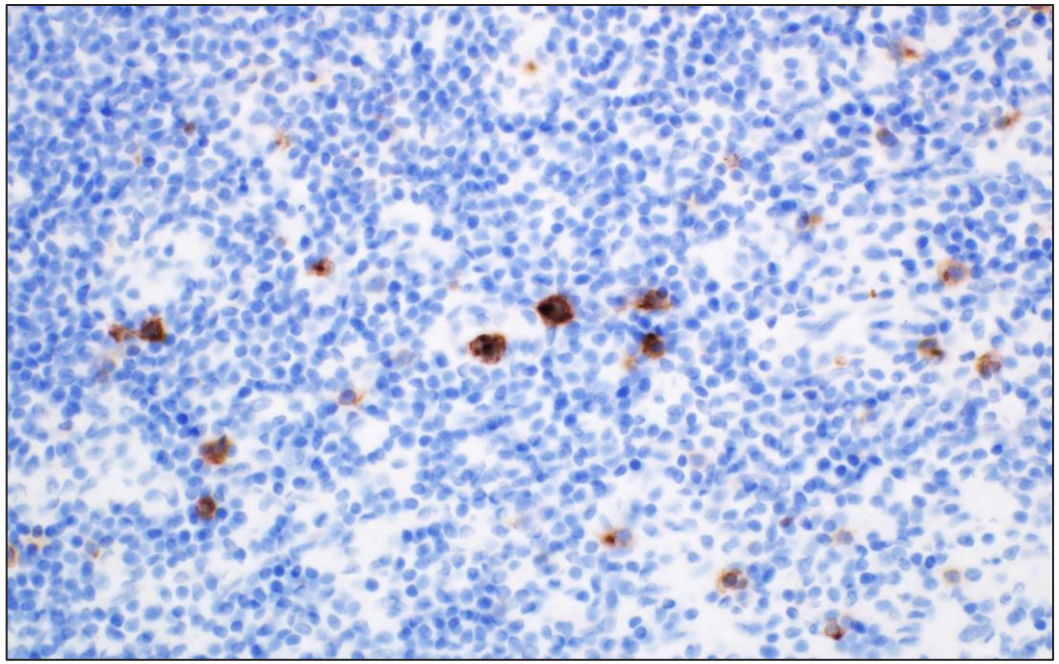
MPO



CD123



CD30



Summary

- Tender localized lymphadenopathy
- CD8+ T-cell-rich lesion with prominent histiocytic proliferation and necrosis

Diagnosis: Kikuchi lymphadenopathy

Historical perspective

- Synonyms: Kikuchi disease, Kikuchi-Fujimoto lymphadenopathy
- Described in 1972 by Kikuchi and Fujimoto
- Originally defined as histiocytic necrotizing lymphadenitis with self-limited clinical course in younger adults

Clinical aspects

- Acute or subacute regional lymphadenopathy
  - » cervical, particularly posterior cervical in 56-98% of cases
  - » variable enlargement usually 0.5-4 cm, can be over 6 cm
  - » tender or painless
  - » can be accompanied with mild fever and night sweats
- Generalized lymphadenopathy is rare (1-22% of cases)
- Deep lymphadenopathy (mediastinal, retroperitoneal, peritoneal) is very uncommon
- Extranodal involvement in rare with skin, bone marrow, and liver being the most common sites
- CBC: leukopenia and atypical lymphocytes (30% of cases)
- Imaging studies are nonspecific

Epidemiology

- World-wide distribution, more prevalent in Asian populations

- Age: mean on 21-yo, range from 19 months to 75-yo

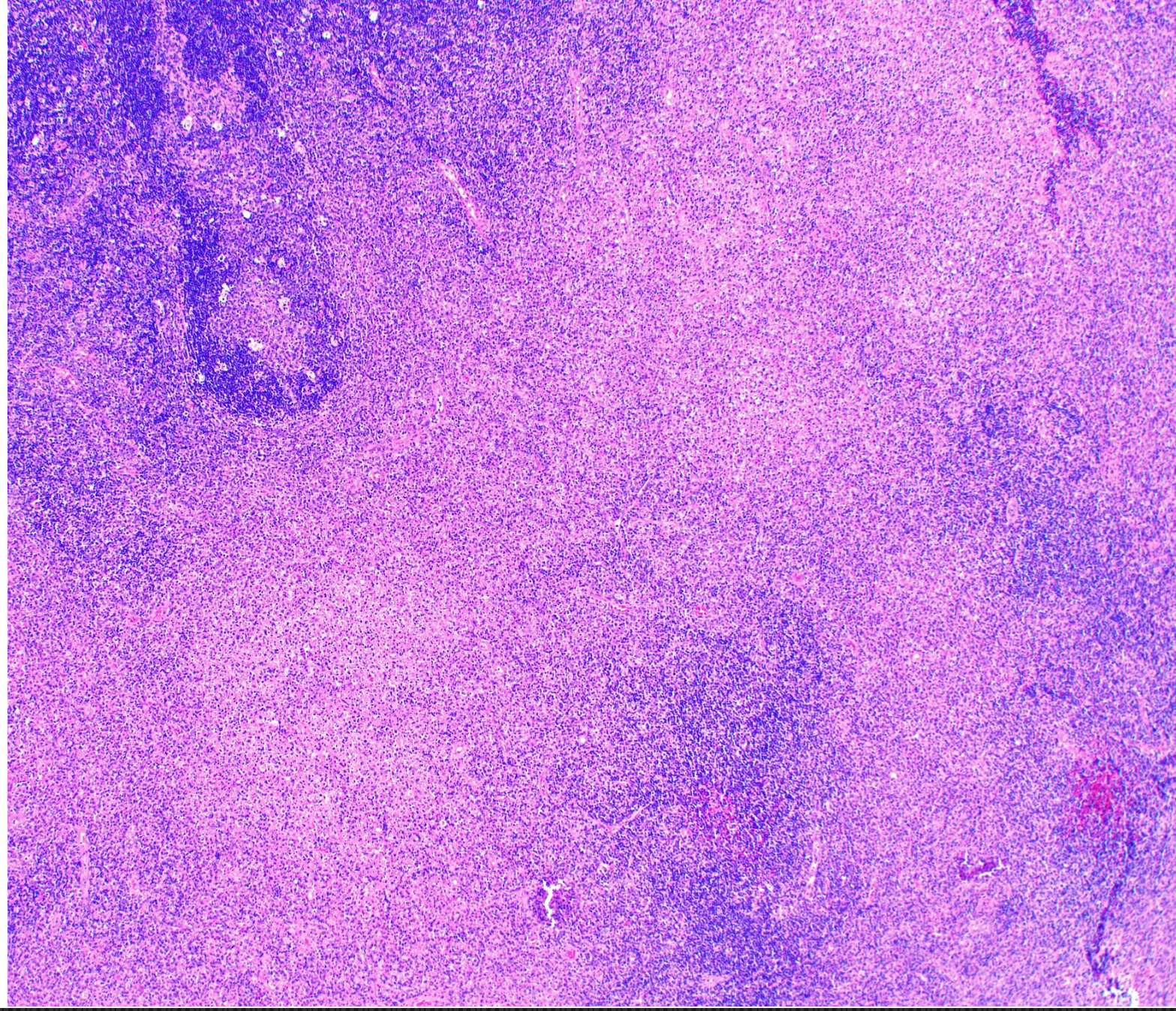
Pathogenesis

- Non-specific stimulus
  - » Viral? Role of EBV is controversial, but EBER is + in some cases
  - » Autoimmune? But serologic studies (ANA, RF) are negative

Activation of CD8+ T-cells with exuberant immune response and apoptosis

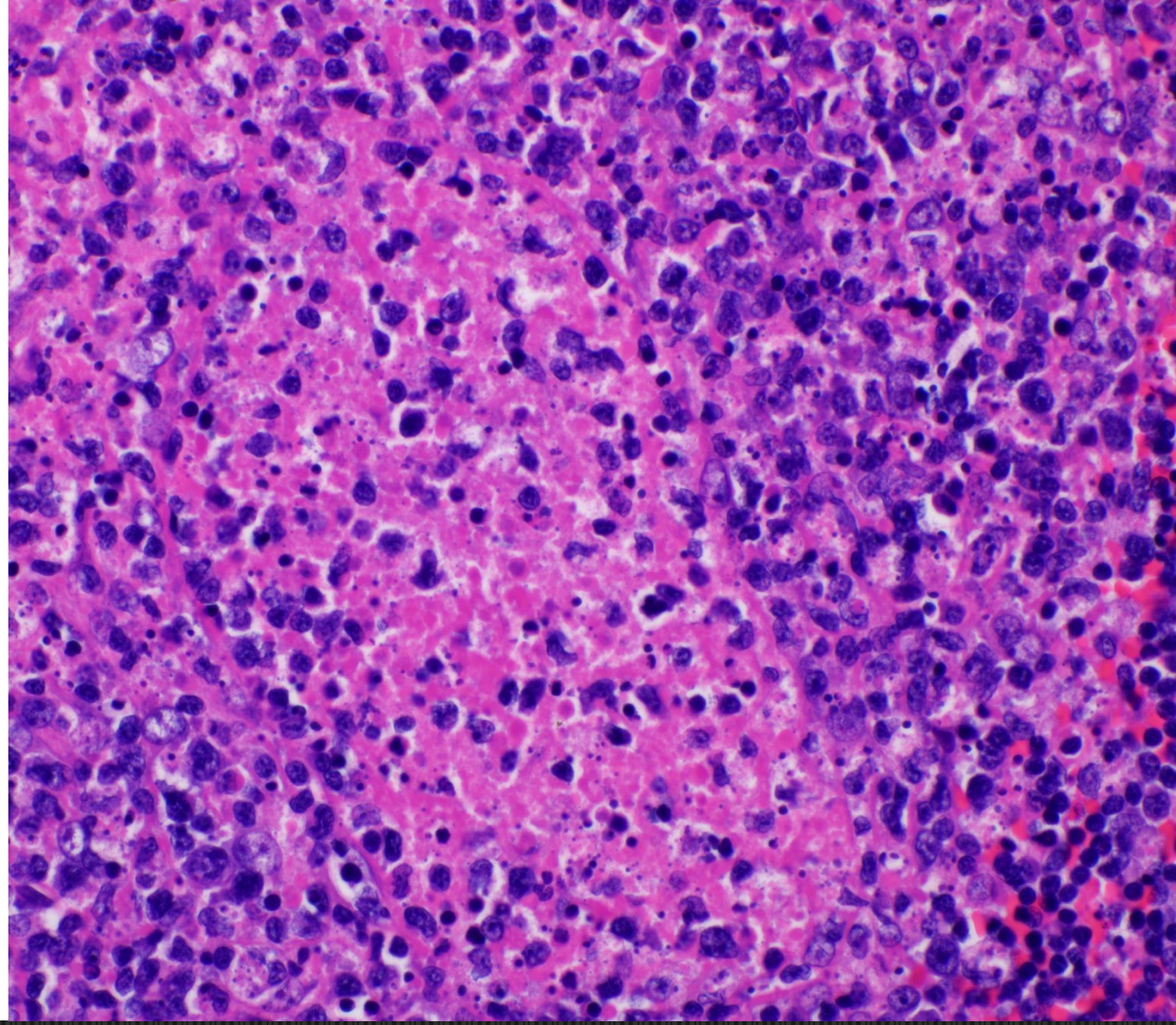
Morphology

- Intact capsule
- Extranodal extension is uncommon but possible
- Distorted architecture
  - » Paracortical expansion
  - » Reactive follicles (50%)
  - » Follicular hyperplasia (10%)
- Patchy pale-stained areas
  - » Necrosis
  - » Histiocytic proliferation
  - » Plasmacytoid dendritic cells



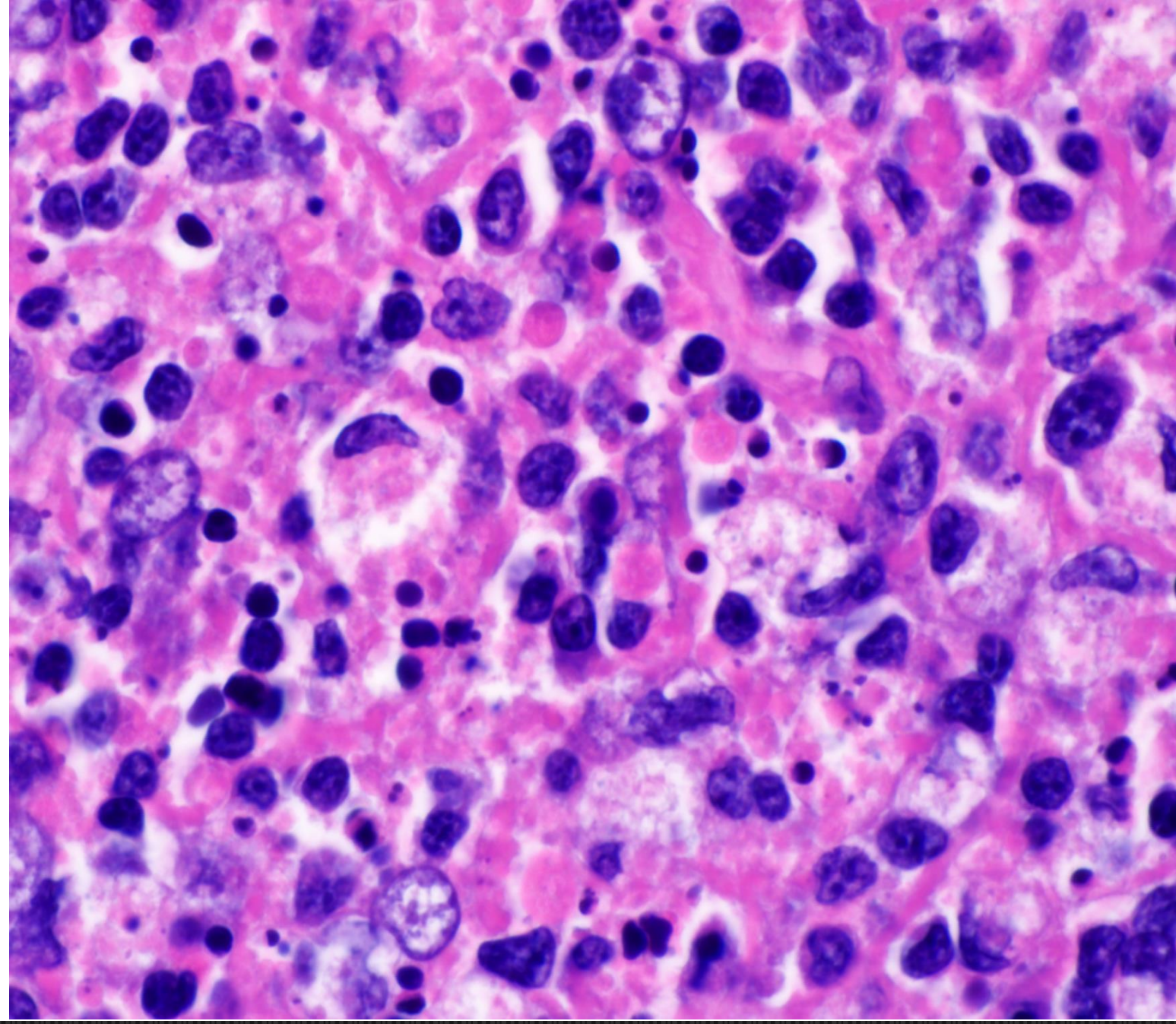
Necrosis

- Coagulative necrosis
- Prominent karyorrhexis attributed to the apoptosis of CD8+ T-cells
- Absent neutrophils



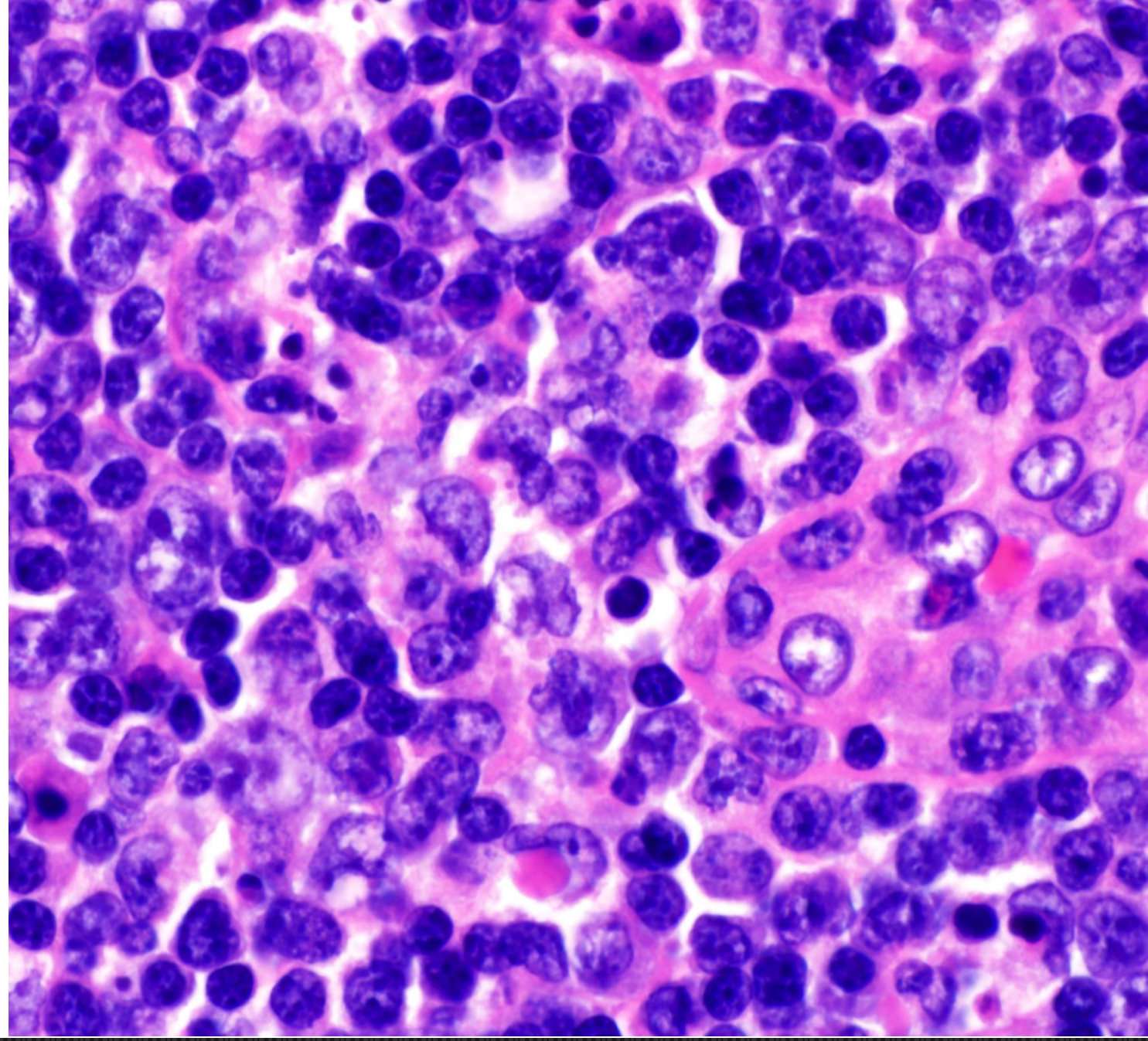
Macrophages

- "Crescent histiocytes"
  - » crescent-shaped nuclei
  - » + for lysozyme, CD68, CD163, and MPO
  - » Not specific for KD
- Tingible body macrophages
- Foamy histiocytes



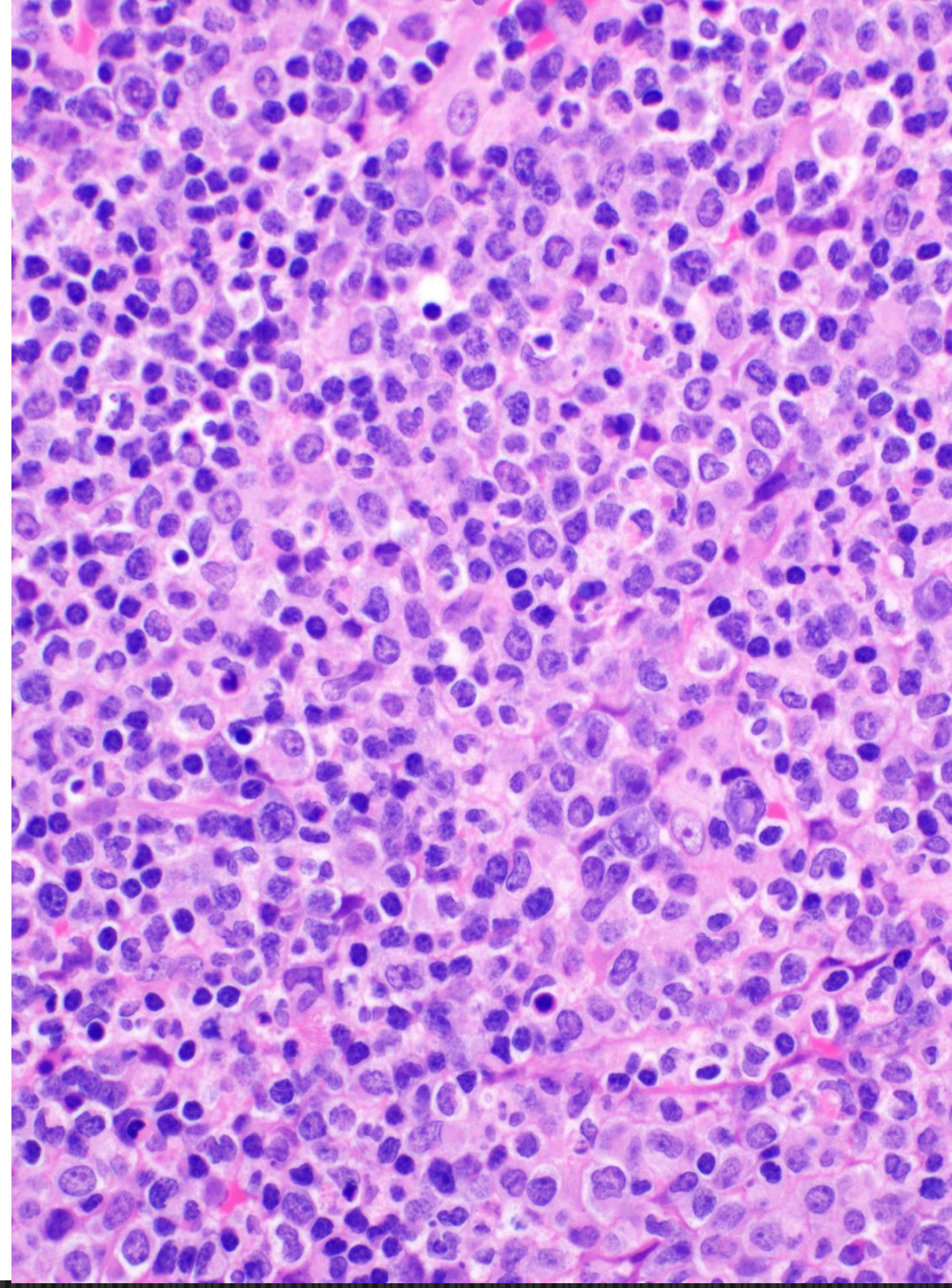
Lymphoid cells

- Small mature lymphocytes
  - » T-cells > B-cells
  - » CD8+ > CD4+
  - » TIA+ and Granzyme B+
  - » Decreased CD57 on CD8+ cells (CD57 expression is associated with replicative senescence)
- Immunoblasts
  - » Usually T-lineage (CD8+), but B-immunoblasts can be present
  - » Can be confused with malignant cells
  - » CD30+ and CD15-



Plasmacytoid dendritic cells

- Aka plasmacytoid monocytes, Lennert-Remmele cells
- Immature dendritic cells form the bone marrow
- Responsible for production of type I interferon promoting proliferation of cytotoxic T-cells
- CD4+, CD68+, CD43+, **CD123**+ (most specific and sensitive)



Histologic variants (*Tseng-tong Kuo, Am J Surg Path, 1995*)

Types	Frequency	Morphologic features	Caveats
Proliferative	30%	Mostly histiocytic proliferation Scattered nuclear debris Plasmacytoid monocytes are prominent	Macrophages can have signet ring appearance
Necrotizing	50%	Presence of any coagulative necrosis Numerous immunoblasts	Immunoblasts with unusual morphology
Xanthomatous	20%	Predominantly foamy macrophages Focal necrosis can be present	

Differential diagnosis and diagnostic problems

- Uncommon disease in the Western world with worrisome morphologic findings
  - » Up to 35% of KD cases were misdiagnosed as lymphoma (*Dorfman et al. Seminars in Diagnostic Pathology, 1988*)
- Correct diagnosis is dependent of the amount of tissue
  - » FNA shows diagnostic accuracy in 56% of cases (*Tong et al. Acta Cytol., 2001*)
  - » Excisional biopsy is mandatory in the majority of cases

Non-neoplastic	Neoplastic
• SLE/lupus lymphadenitis • Necrotizing lymphadenitis: herpetic, mycobacterial, cat scratch disease, toxoplasmosis	• B-cell lymphoma • T-cell lymphoma • Metastatic carcinoma (CD163)

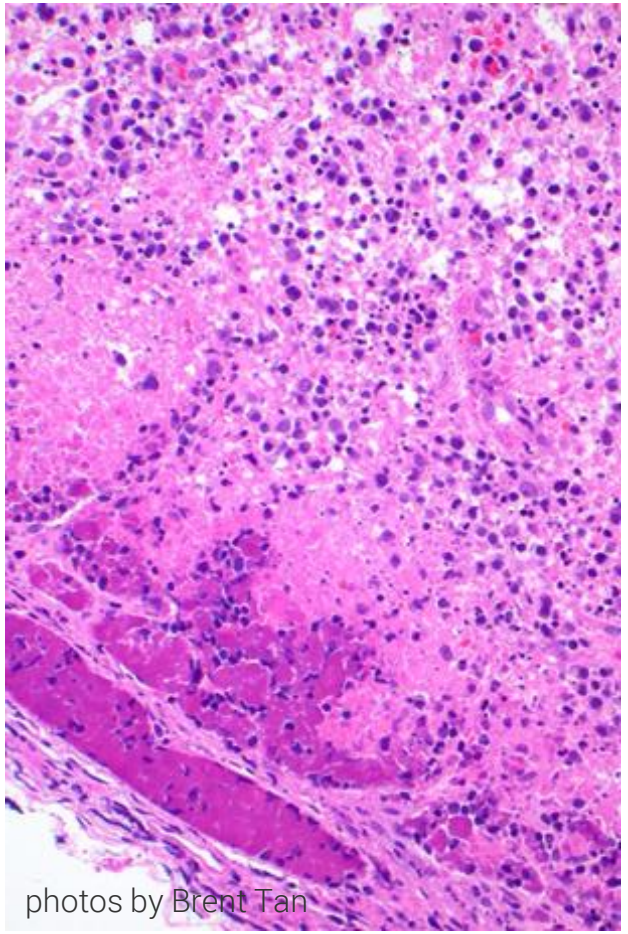
vs LYMPHOMA

Feature	Kikuchi lymphadenitis	Lymphoma
T-cells	CD8-predominant with preserved expression of other markers	Nodal mature T-cell lymphomas are CD4+ and show abnormal loss of some markers
B-cells	Clusters of B-immunoblasts	Can be very challenging
Histiocytes	The nuclei can be very atypical, but the nuclear membrane is thin IHC to confirm histiocytic profile (CD68, CD163, CD4, Lysozyme) Positive for MPO	Can be mistaken for lymphoid cells Histiocytes are not so polymorphous and MPO-negative
Clonality studies	Polyclonal TCR (Lin et al. AJCP, 2002) Polyclonal BCR with caveats	TCR positive in T-cell lymphomas

vs LUPUS LYMPHADENOPATHY

Feature	Kikuchi	Lupus
ANA	Negative	Elevation of ANA titers
T-cells (a more sensitive and specific feature)	CD8 > CD4	CD4 > CD8
Plasma cells	Rare	Abundant
Neutrophils	Absent	Present, sometimes necrotizing neutrophilic infiltrates
Histiocytes	MPO+	MPO can be +
Necrosis		Extensive necrosis favors SLE
Other findings		• Hematoxylin bodies (degenerated nuclei-ANA complexes) – "pathognomonic"(?) • Azzopardi effect (nuclear material impregnated into vascular walls) • Vasculitis

Hematoxylin bodies

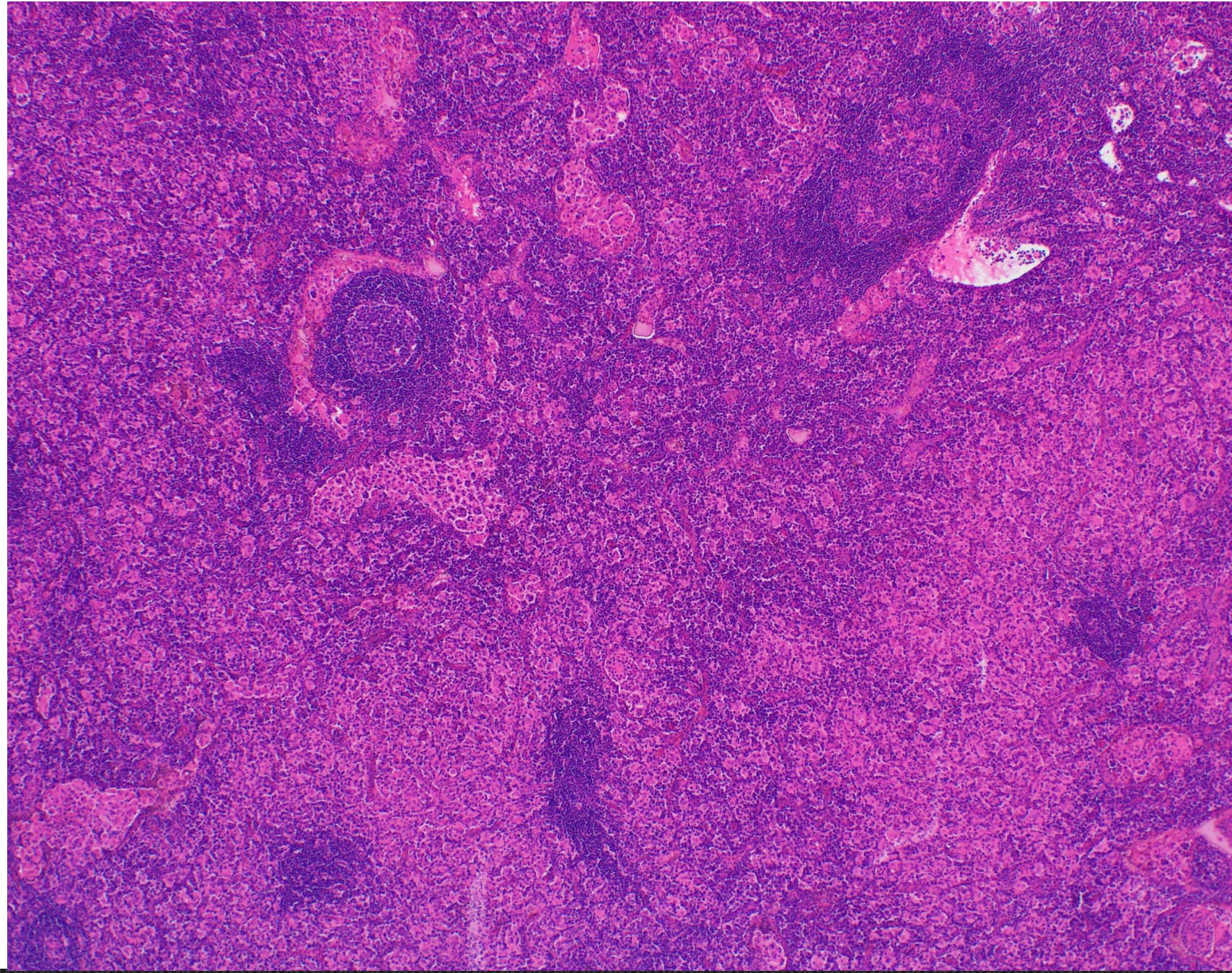


photos by Brent Tan


Mount Olympus Peak, Salt Lake City

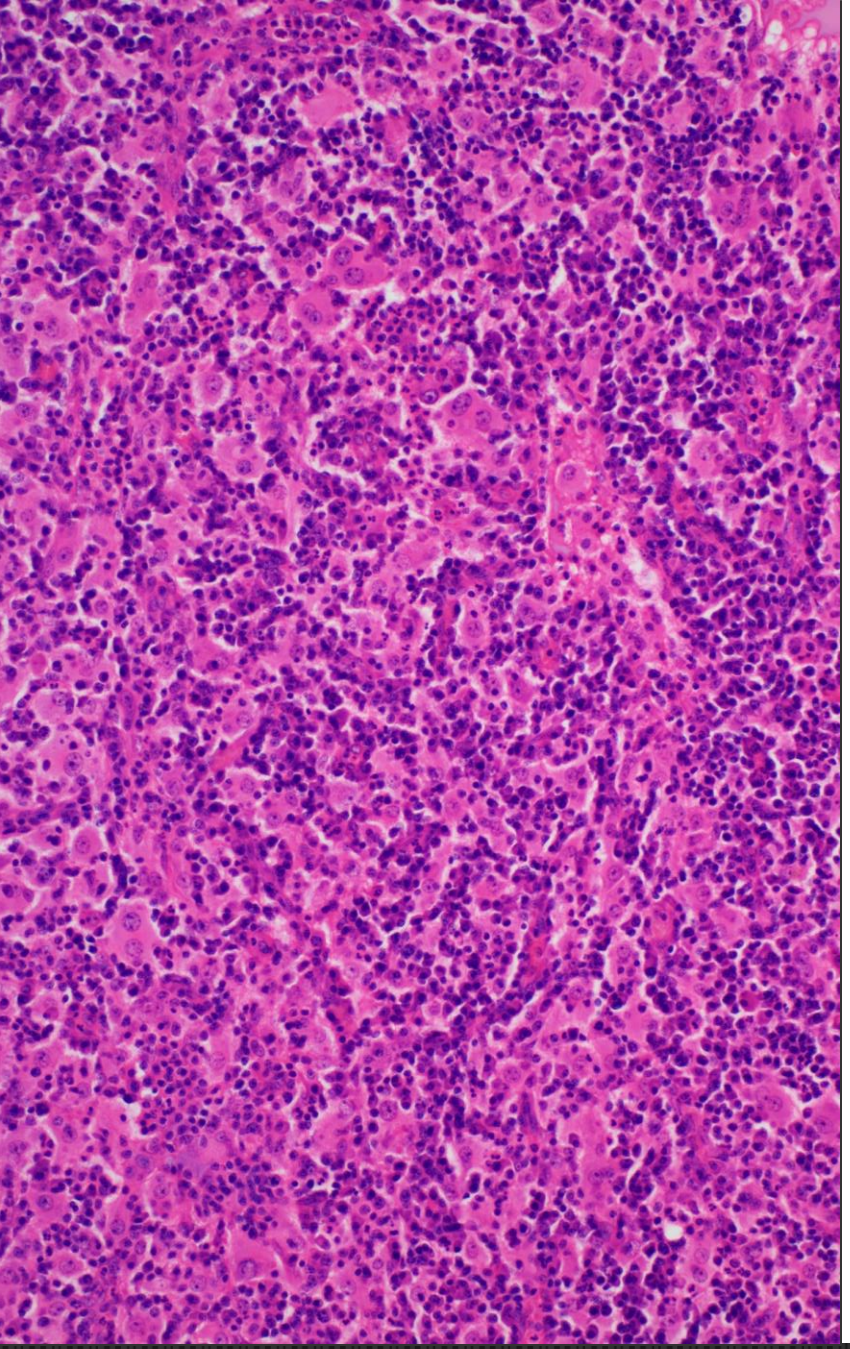
CASE #3

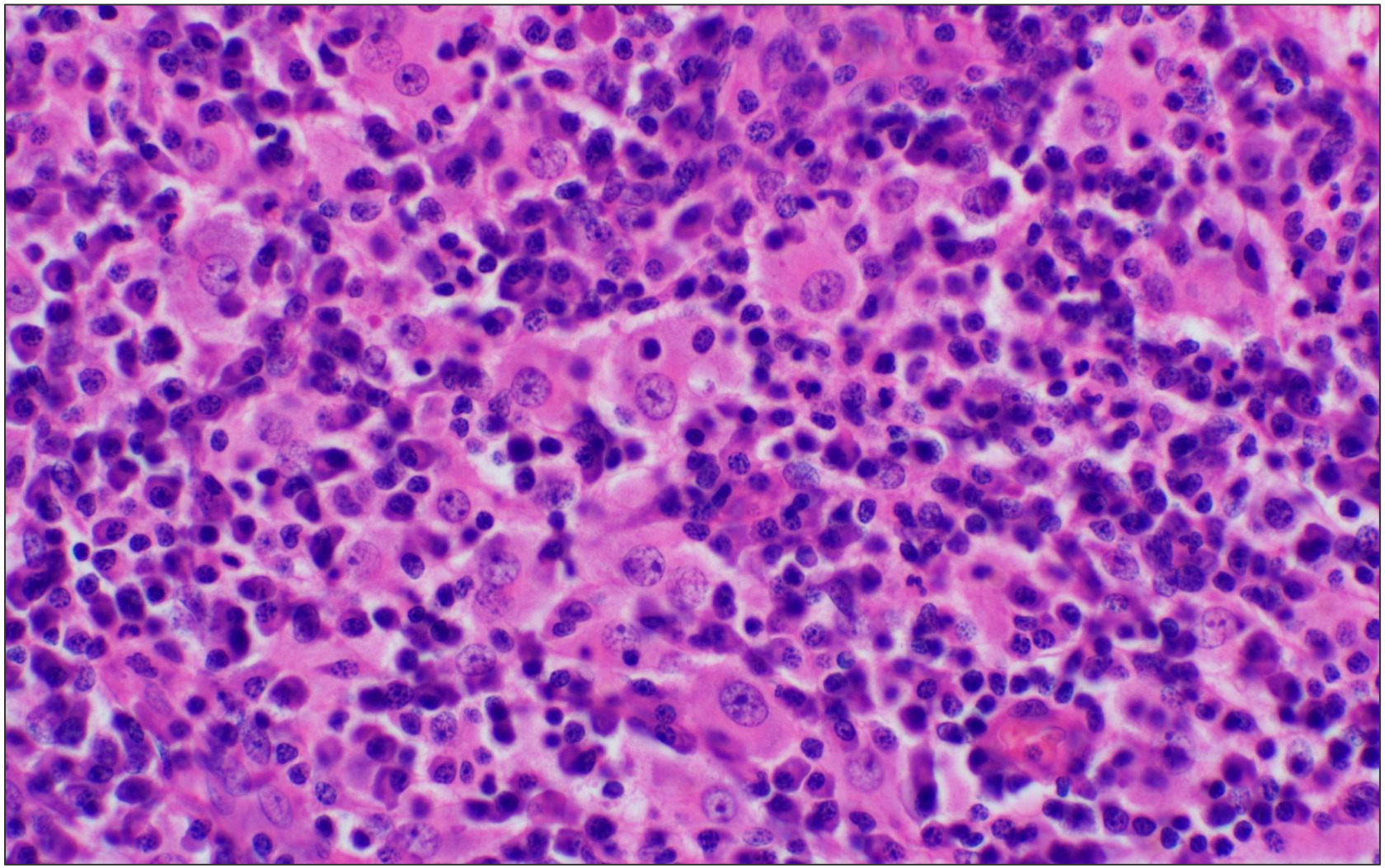
A teenage boy with a previously diagnosed type I autoimmune lymphoproliferative syndrome (ALPS) and worsening lymphadenopathy, clinically worrisome for lymphoma

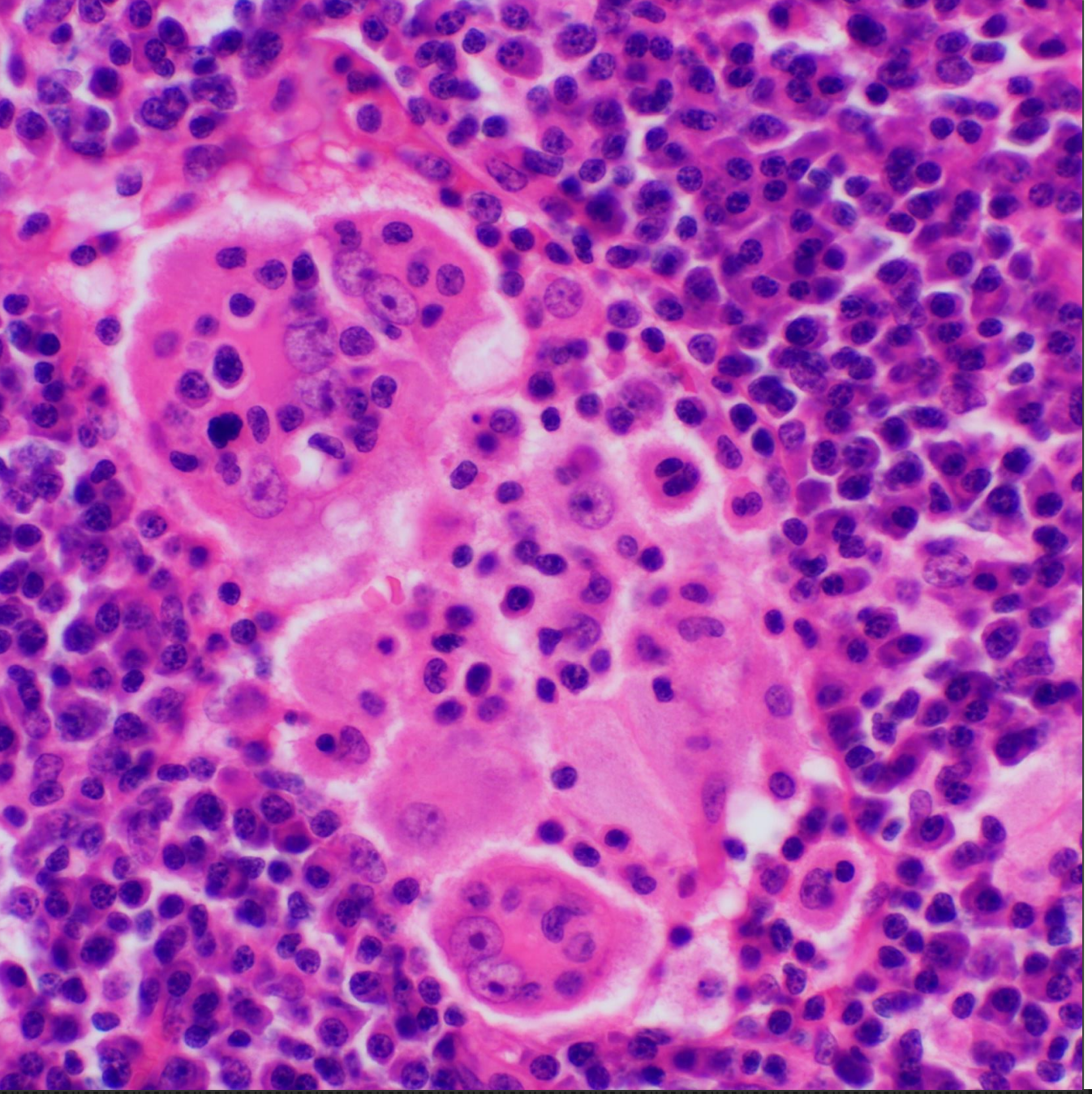


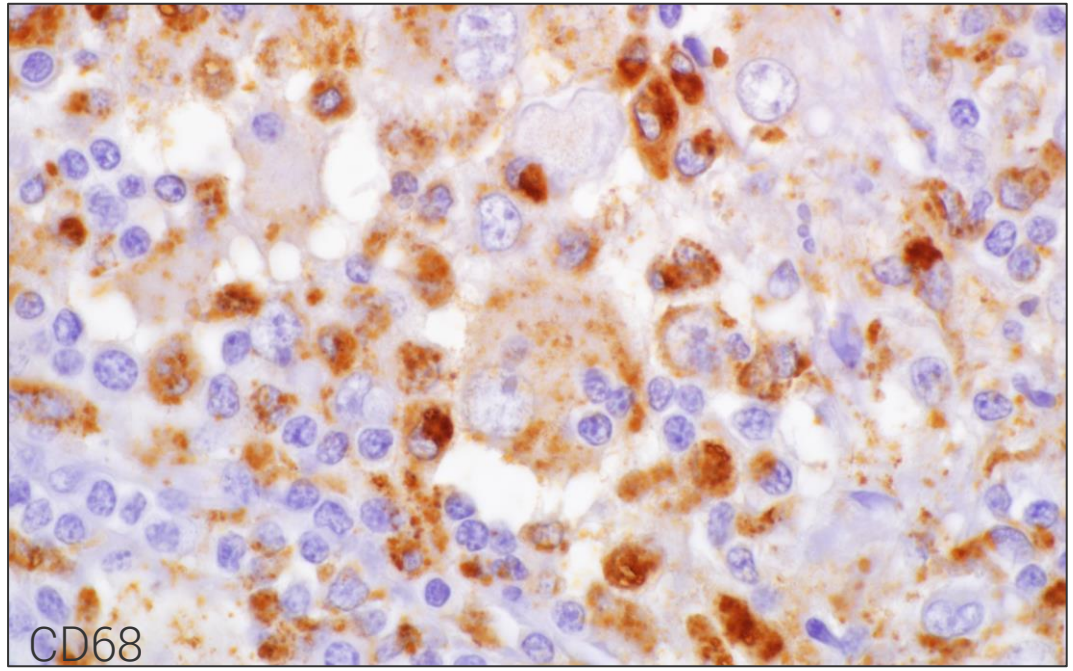
ALPS type I

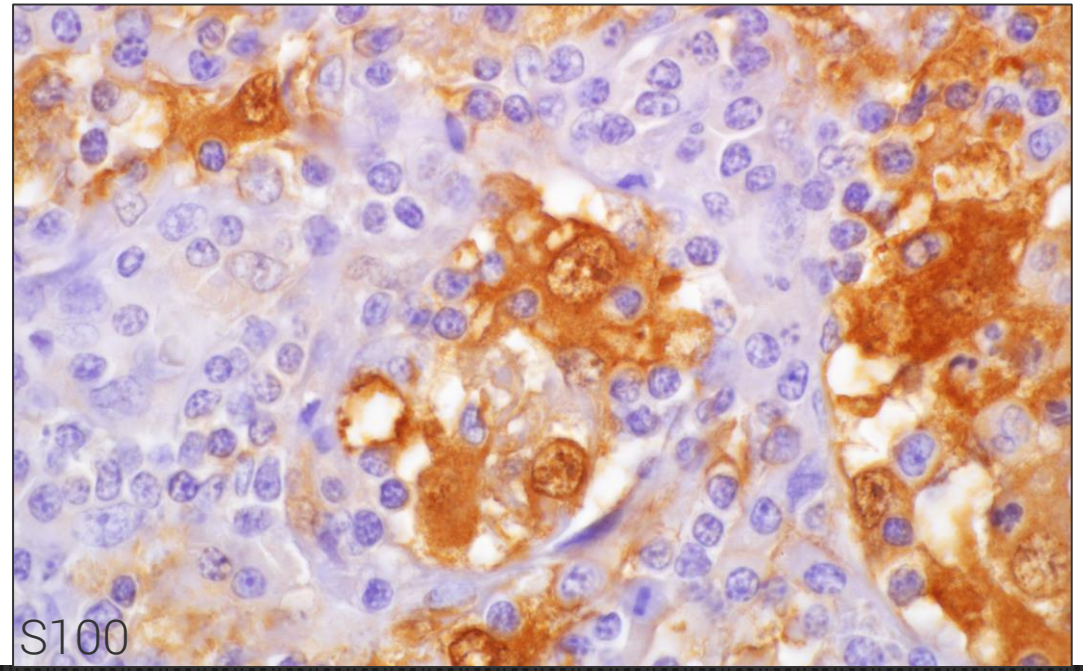
- More recently described disorder due to mutations of the *FAS* gene (CD95)
- Deficiency of Fas-induced apoptosis
- Generalized persistent lymphadenopathy
  - » Marked paracortical expansion
  - » Prominent CD30+ immunoblasts
  - » Variable follicular hyperplasia
- Autoimmune anemia, thrombocytopenia
- DN T-cells in the peripheral blood








CD68


S100

Summary

- Predominantly “sinus pattern”
- Histiocytes with unusual cytologic and immunophenotypic features
- Prominent plasma cells

Diagnosis: Rosai-Dorfman disease

Historical perspective

- Synonyms: Sinus histiocytosis with massive lymphadenopathy

- Initially described in 1965 by Dr. Paul Destombes in 4 AA patients
- 4 years later Drs. Rosai and Dorfman published 4 more cases

- Originally defined as massive lymphadenopathy with prominent sinus histiocytosis and benign albeit prolonged clinical course

Epidemiology

- World-wide distribution, more prevalent in African-Americans
- Age: mean on 20-yo, range from neonates to 74-yo
- M>F

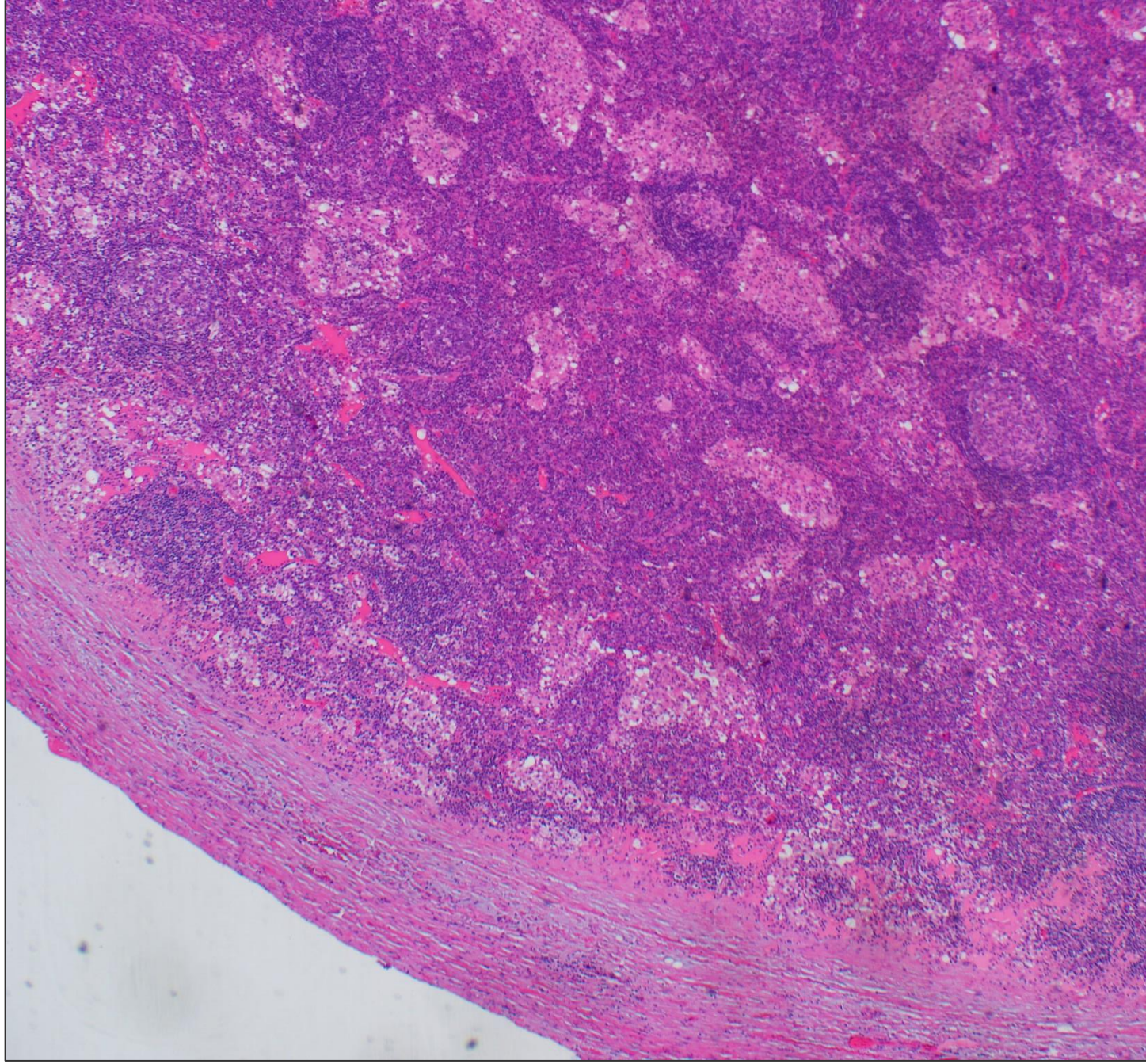
Clinical aspects

- Lymph nodes in 60% cases
  - » various regions, but more commonly cervical
  - » massive deforming enlargement
  - » painless
  - » can be accompanied with mild fever and night sweats
- Extranodal involvement in 40-45% cases
  - » predilection to head/neck region: orbit, nasal sinuses, intracranial (meninges)
  - » skin and soft tissues
- May be associated with immune/autoimmune dysregulation (Wiscott-Aldrich syndrome, ALPS) or lymphomas (NLPHL and FL among the most common)
- May persist for years
- Spontaneously resolves, but can be lethal when constricts vital structures or associated with immune disorders

ROSAI-DORFMAN DISEASE

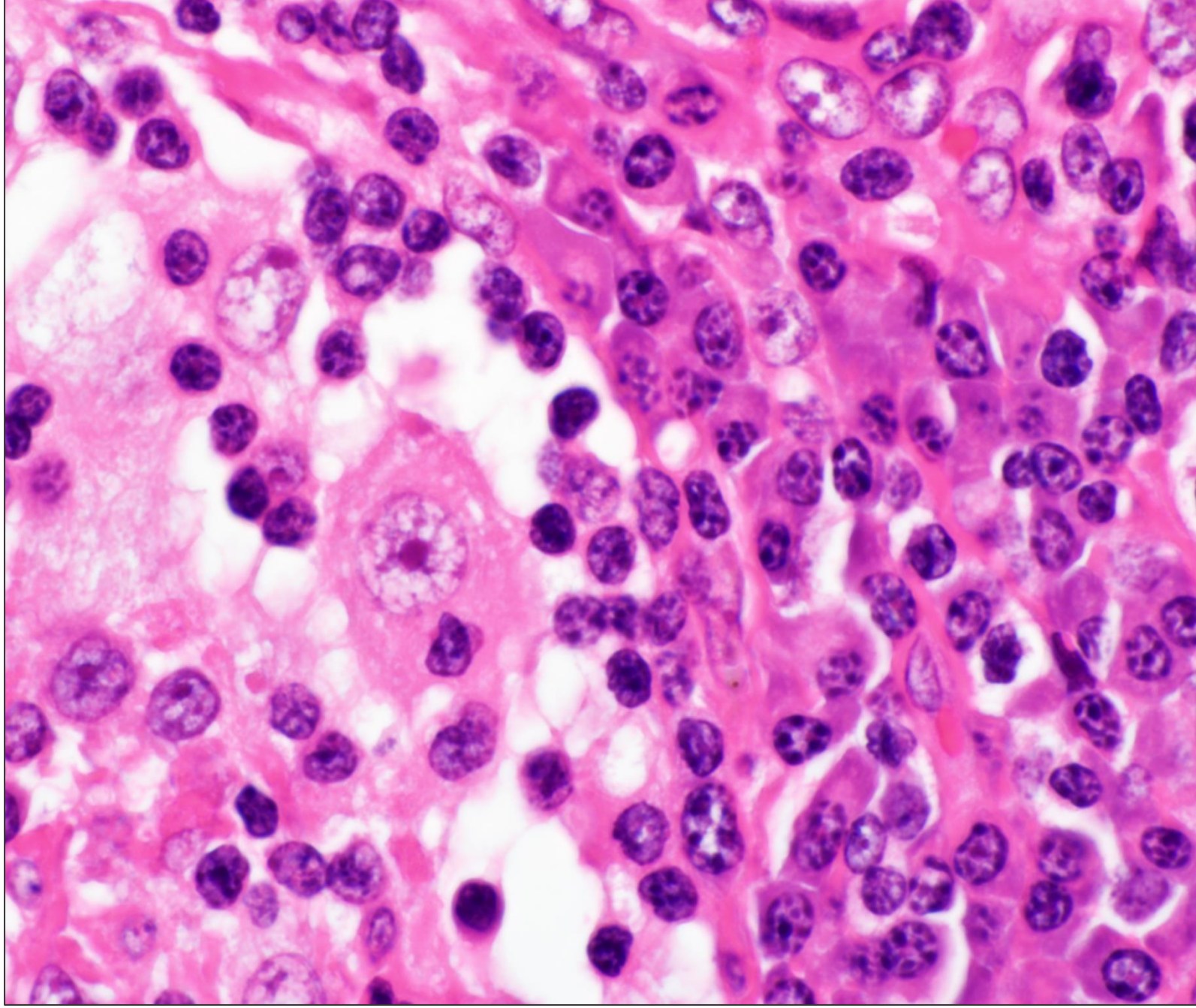
Morphology

- Thick fibrotic capsule
- Distorted architecture
  - » Reactive follicles and follicular hyperplasia
  - » Significant sinus dilation

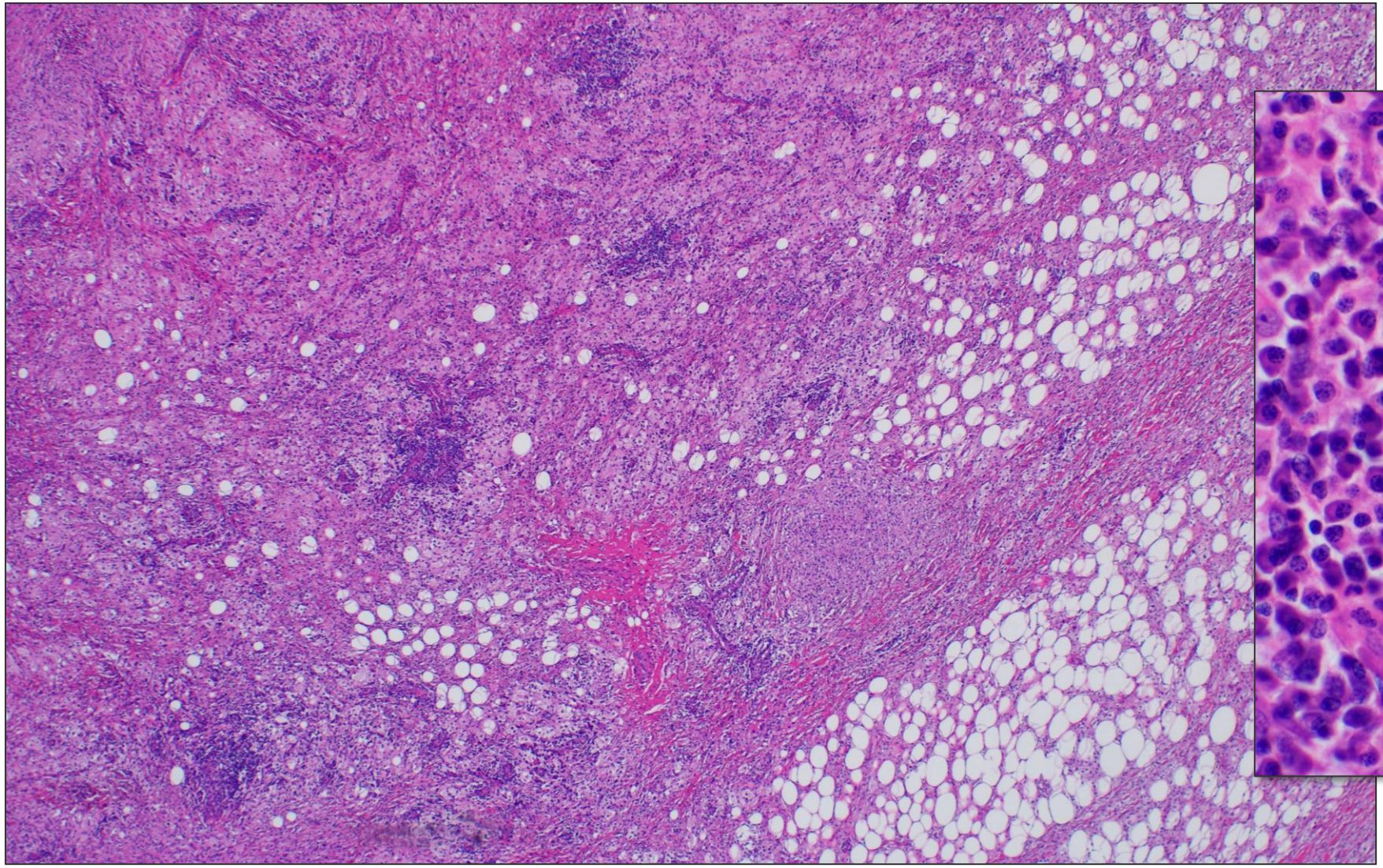


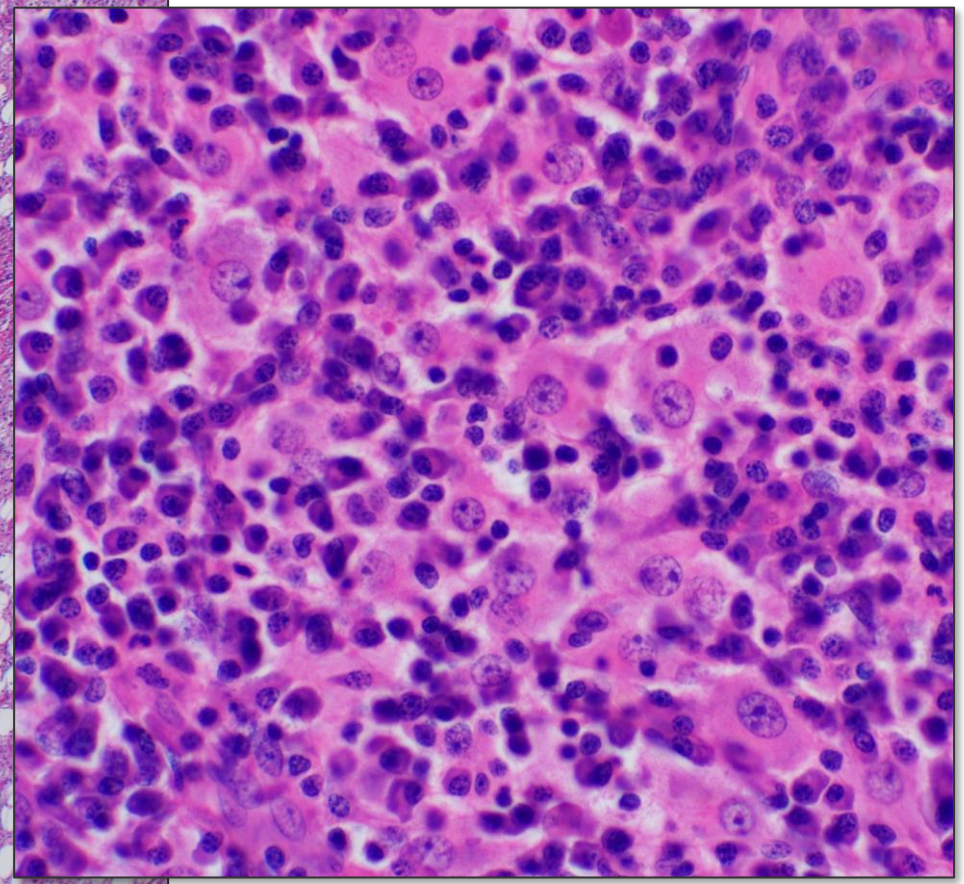
Diagnostic cells

- Histiocytes/MLSH cells
  - » Large polygonal
  - » Large round nucleus
  - » Prominent central nucleolus
  - » Abundant eosinophilic cytoplasm, can be vacuolated
  - » Emperiopolesis
  - » $CD4^{+}$, $CD68^{+}$, $CD163^{+}$, $Lysozyme^{-/weak}$, $S100^{+}$, $CD30^{-/+}$
- Plasma cells
  - » Mature, can be binuclear
  - » Polytypic



Extranodal disease





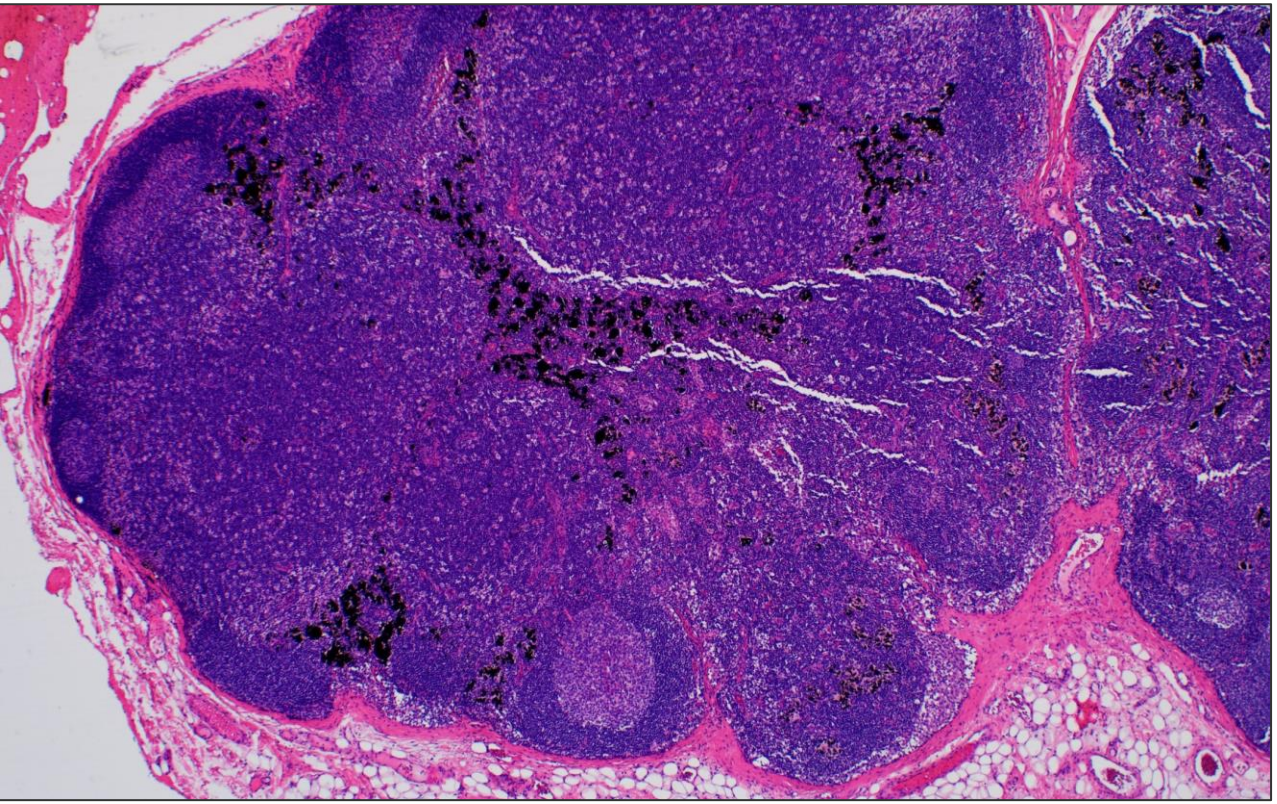
Differential diagnosis

Sinus histiocytosis	Hemophagocytic syndrome	Histiocytic neoplasms	Other neoplasms
• Nonspecific pattern • Histiocytes retain "usual" morphology • Only rare S100^{+} cells	• Can be familial or secondary to viral, malignant or other causes • Acute onset with pancytopenia and other relevant clinical and laboratory findings • Lymphoid depletion • Dilated sinuses with "usual" macrophages and intracellular RBCs, WBCs, and debris	• LCH - oblong folded coffee bean-shaped nuclei - background eosinophils • Histiocytic sarcoma - cytologic atypia, mitoses • IHC panel - Monocyte-derived histiocytes: CD68^{+}, CD163^{+}, Lysozyme$^{+/-}$ - Myeloid-derived DC: S100^{+}; LC: CD1a^{+}, Langerin^{+} - Plasmacytoid DC: CD123^{+} - Stromal derived DC: CD21^{+}, CD23^{+}, CD35^{+}	• CHL • ALCL • Lymphomas with associated RDD: FL, NLPHL • Metastatic carcinoma • Metastatic melanoma


Big Cottonwood Canyon, Salt Lake County

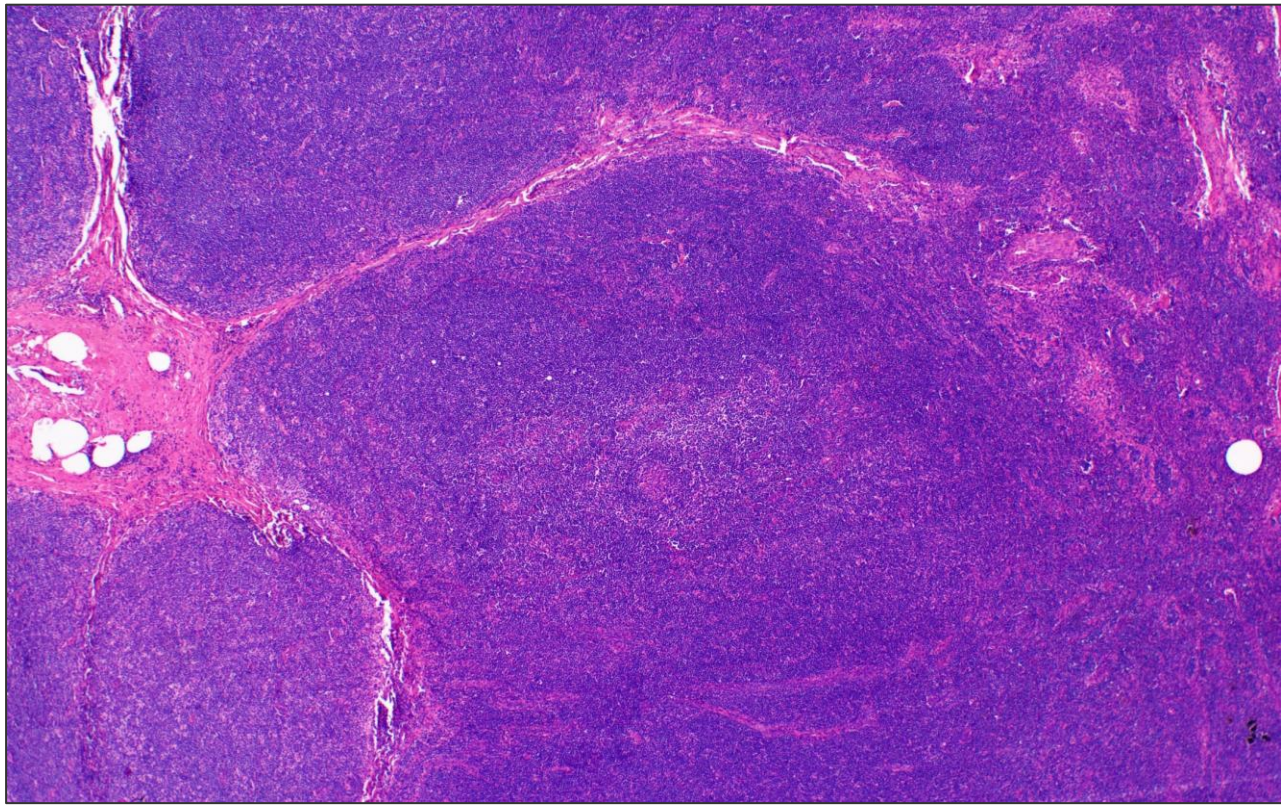
CASE #4

A young man with fever and shoulder infection; clinical suspicion for an autoimmune process. Axillary lymph node.

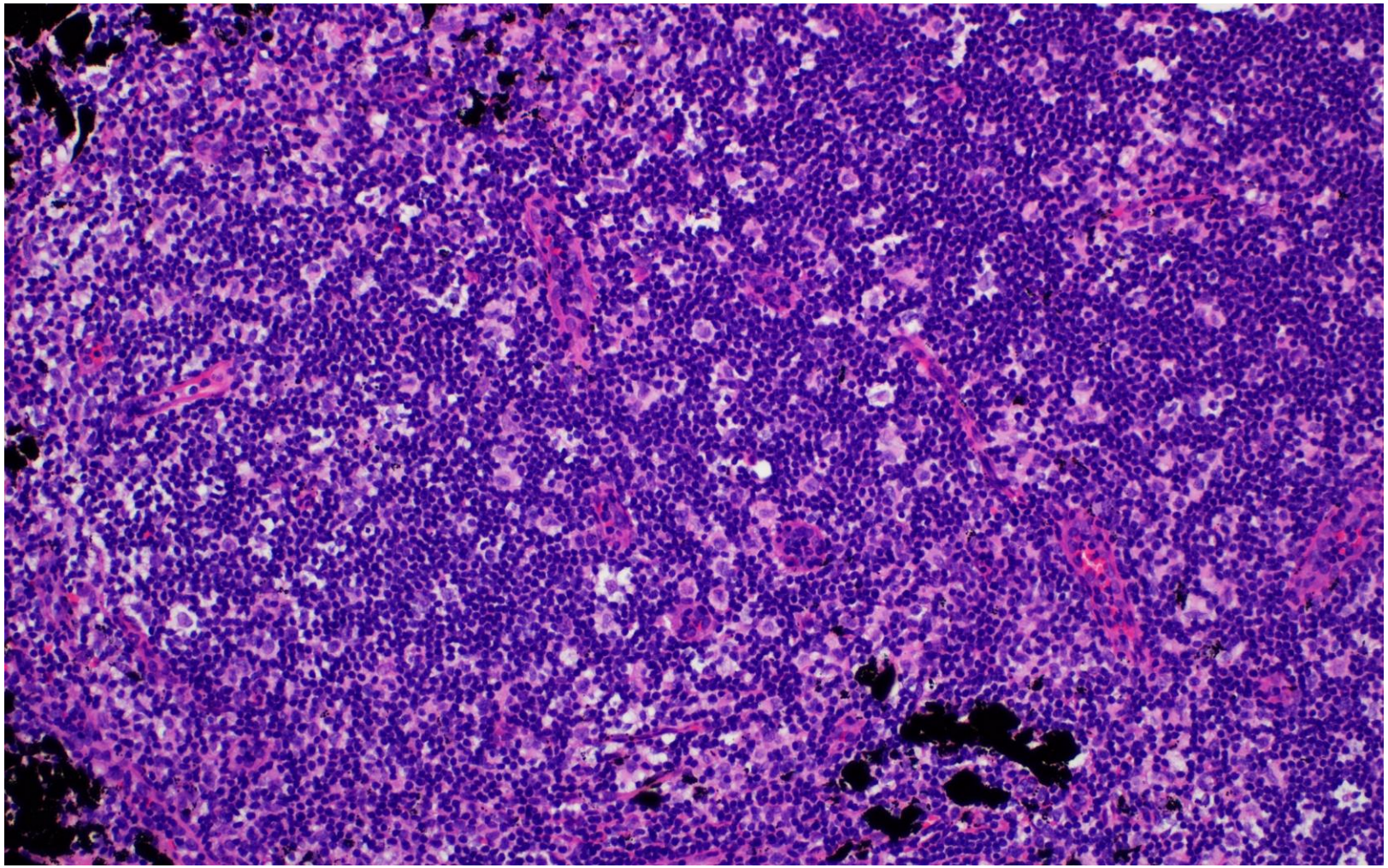


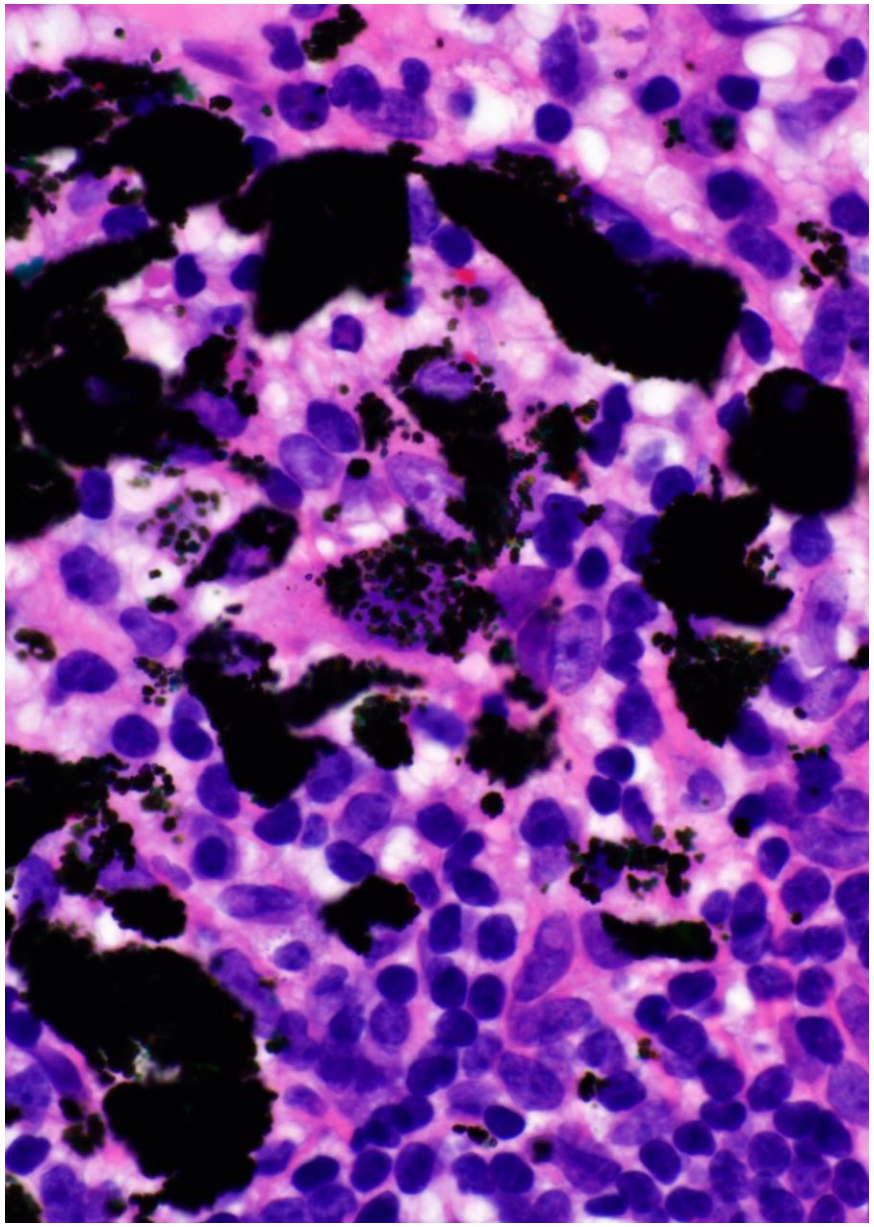
CASE #5

An elderly man with extensive skin rash and lymphadenopathy. Axillary lymph node.



CASE #4





Summary

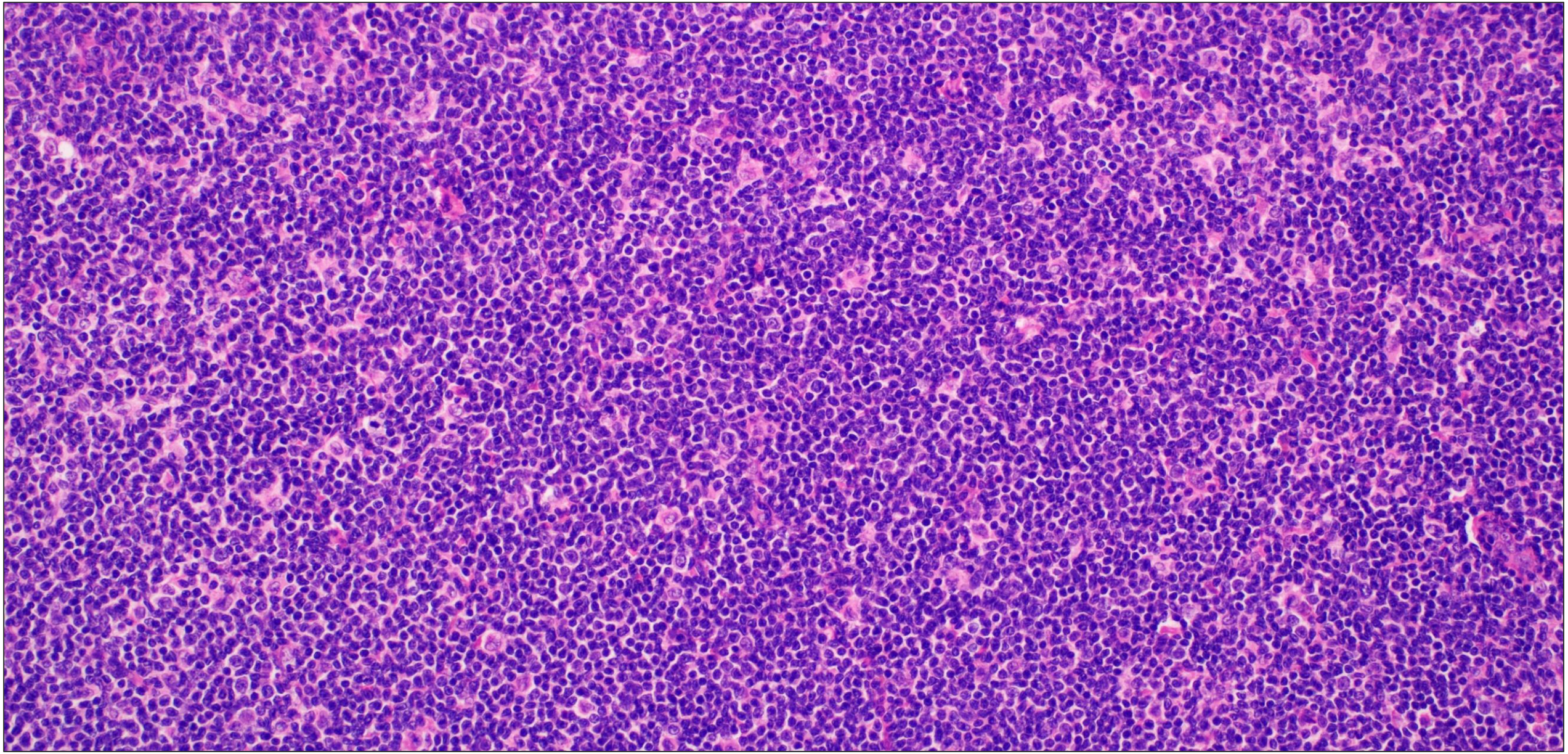
- Young male
- Enlarged axillary lymph node on the side of shoulder infection
- Review of the external examination shows extensive colored tattoos on both arms

Diagnosis: Dermatopathic lymphadenopathy

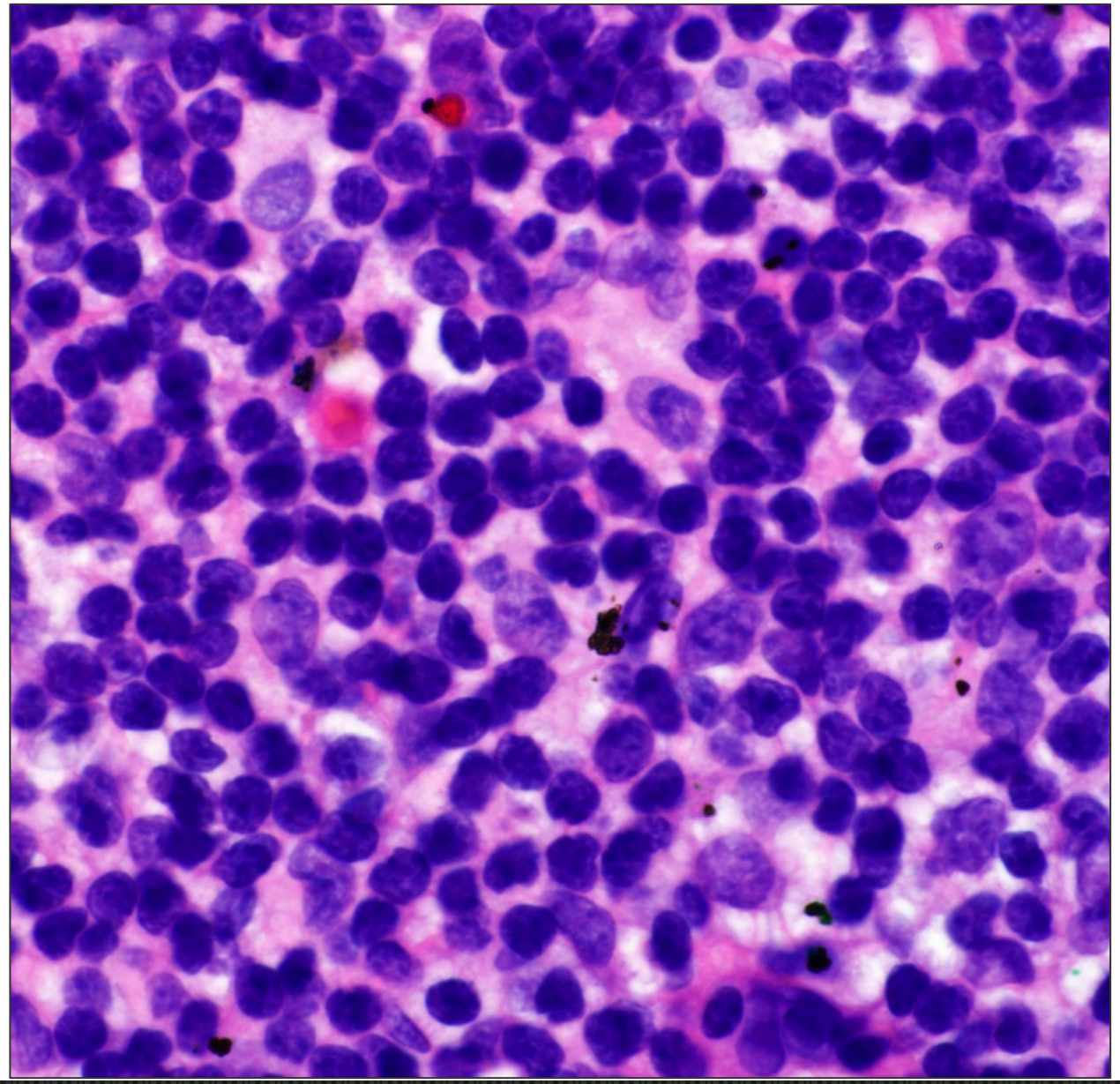
Features

- Common pattern usually associated with chronic skin diseases (!)
- Most affected lymph nodes are axillary and inguinal
- Non-tender, moderately enlarged, firm, movable lymph node(s)
- Morphology
  - » Preserved architecture
  - » Nodular paracortical expansion adjacent to the capsule/subcapsular sinus
  - » Small mature lymphocytes and admixed interdigitating dendritic and Langerhans cells (both are $S100^{+}$), and melanin-laden histiocytes
- Caveat: can be associated with skin neoplasms – squamous cell carcinoma, mycosis fungoides/Sezary syndrome

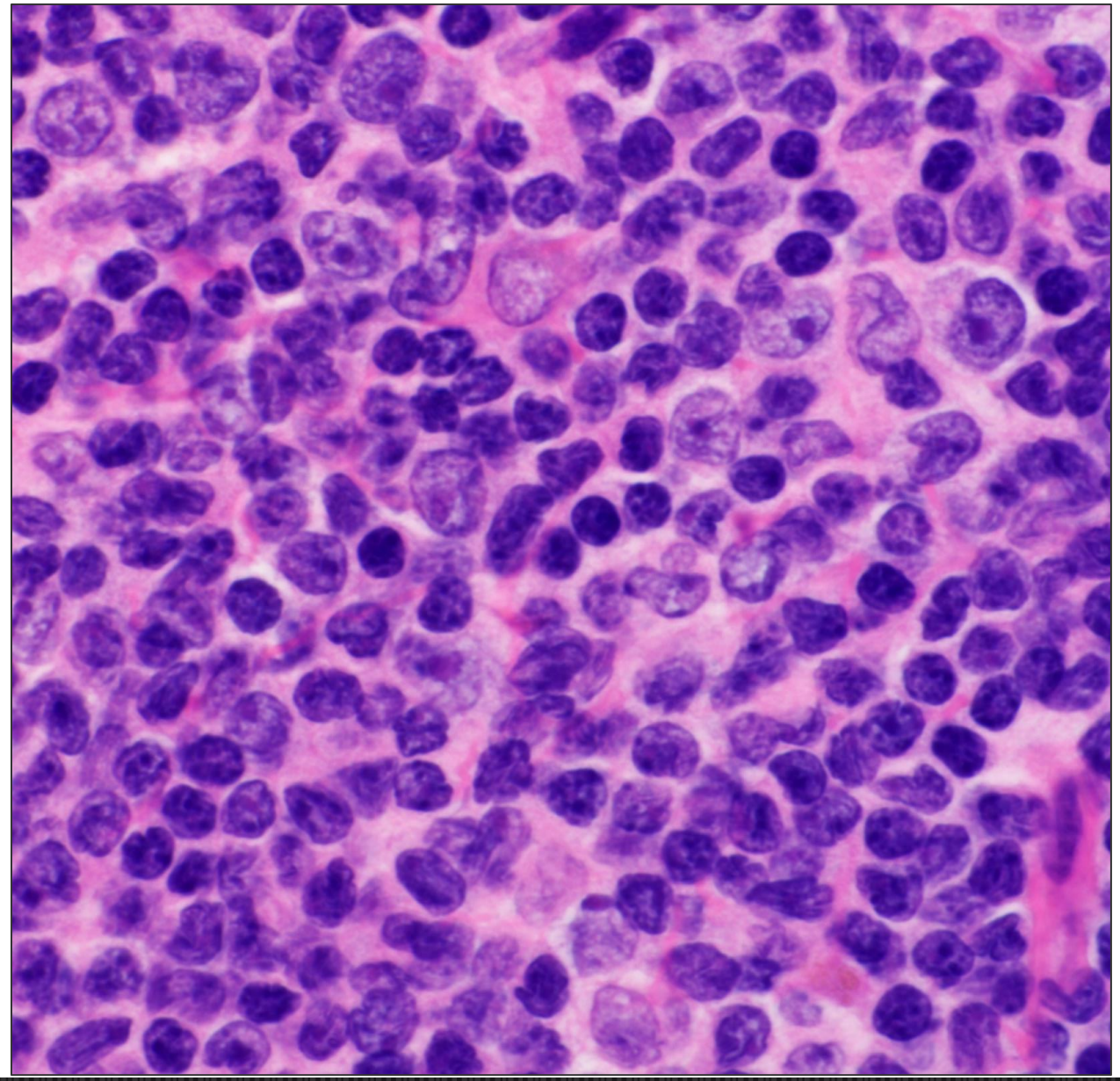
CASE #5



CASE #4



CASE #5



Summary

- An elderly man with extensive skin rash
- Enlarged axillary lymph node with architectural effacement and morphologically atypical lymphocytes
- Flow cytometry and IHC showed abnormal $CD4^+$ T-cell population (decreased CD2, CD5, and CD7, $CD26^-$). Similar population was also found in the blood, bone marrow, and skin biopsy

Diagnosis: Sezary syndrome

Take home points

- The distinction between a benign lymphadenopathy and a hematologic neoplasm can be very challenging
- Methodical evaluation of morphologic features and the correlation with clinical picture and ancillary studies are key to the correct diagnosis
- Morphology should be the cornerstone of the diagnostic process
- Quantity of available tissue often translates to the quality of the final diagnosis

Thank you

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