Approach to the lymph node

Pathcast June 30, 2020

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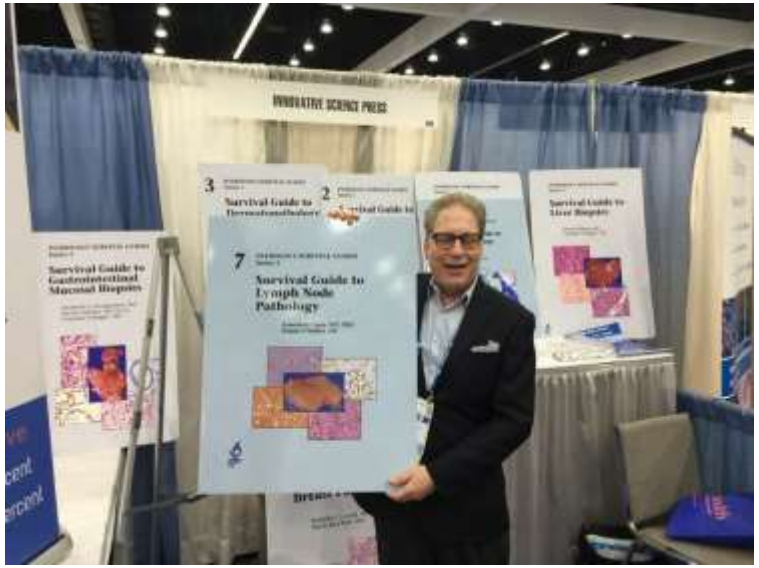
Staff Hematopathologist



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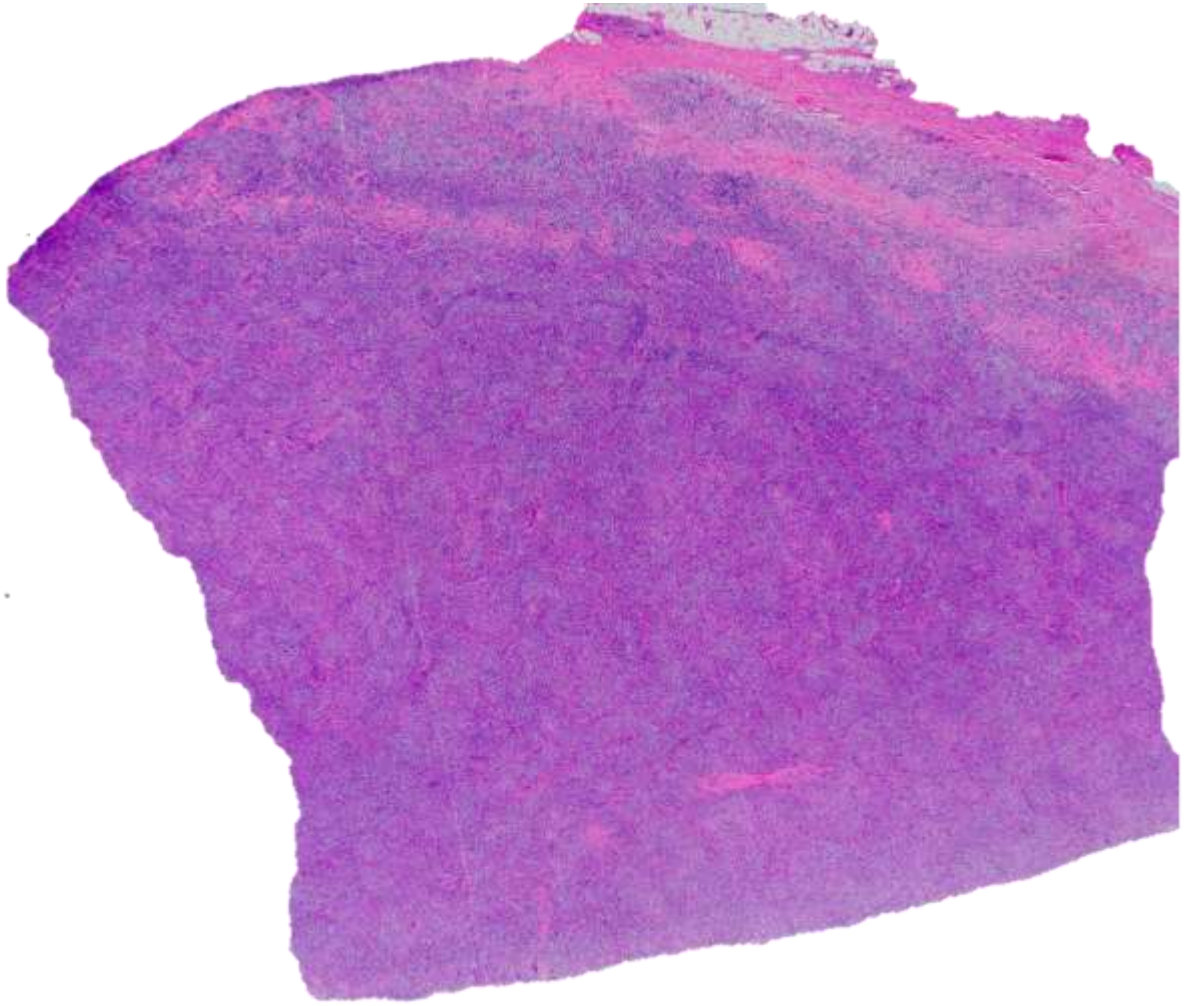
The approach and several images in this presentation are from Dr. Dennis O'Malley and are presented in more detail as part of our Survival Guide to lymph node pathology. Out in September!!!

@evemariecrane

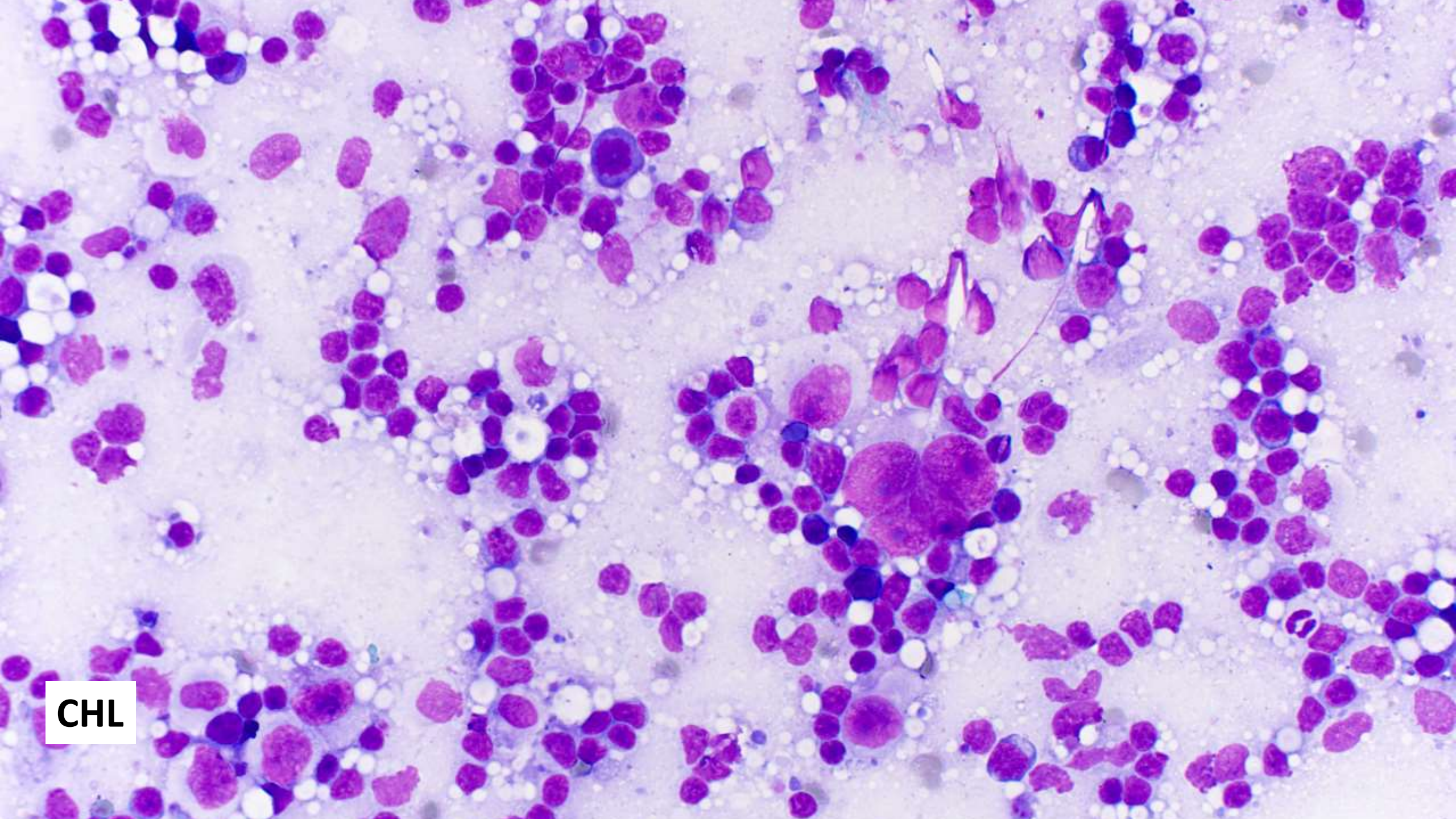
Objectives

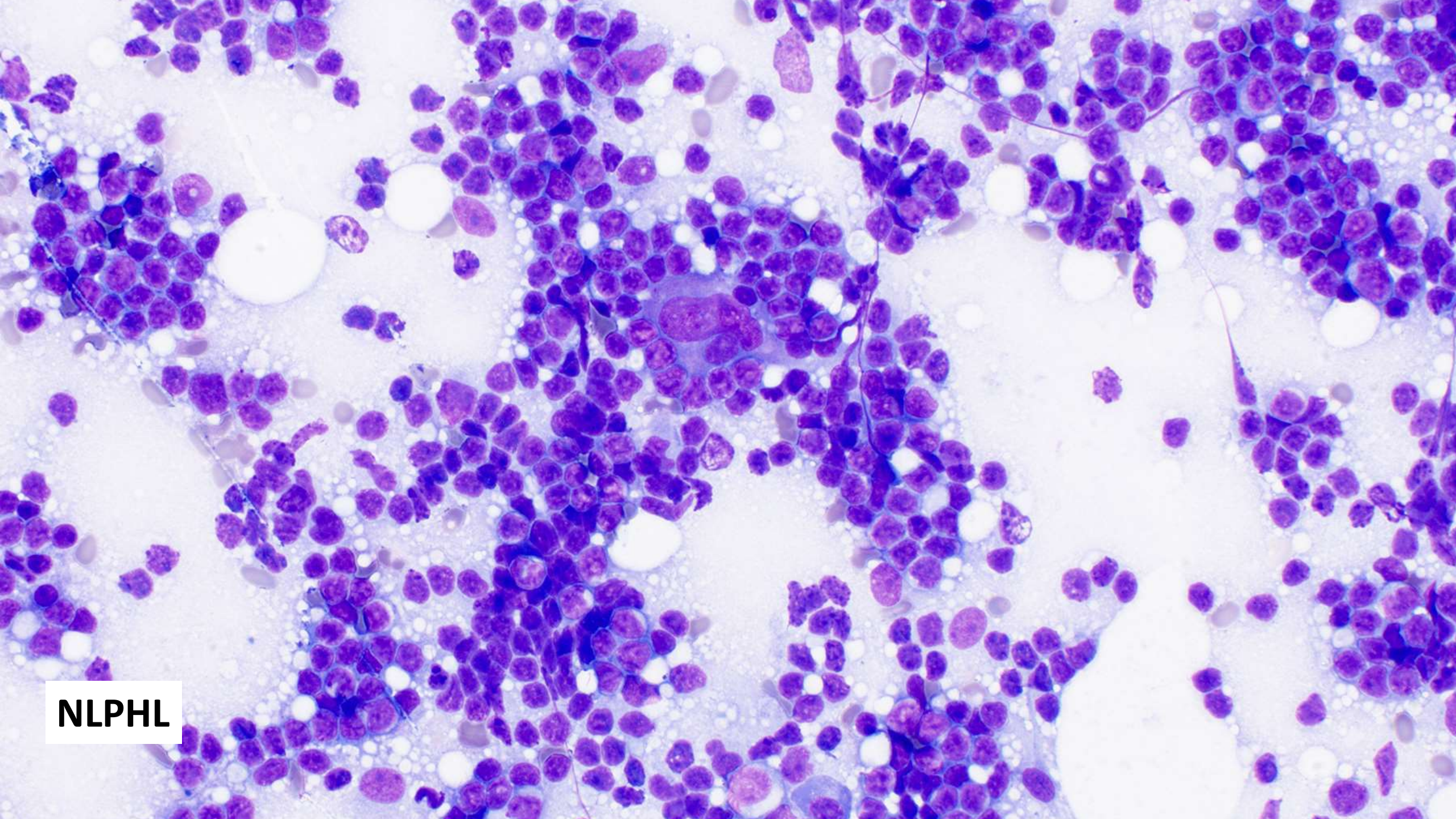
- Gross evaluation and ancillary testing
- Formulate a differential diagnosis:
  - Compartment based approach– is there something abnormal?
  - Pattern based approach– narrow differential
- Staining strategies
- Special sites

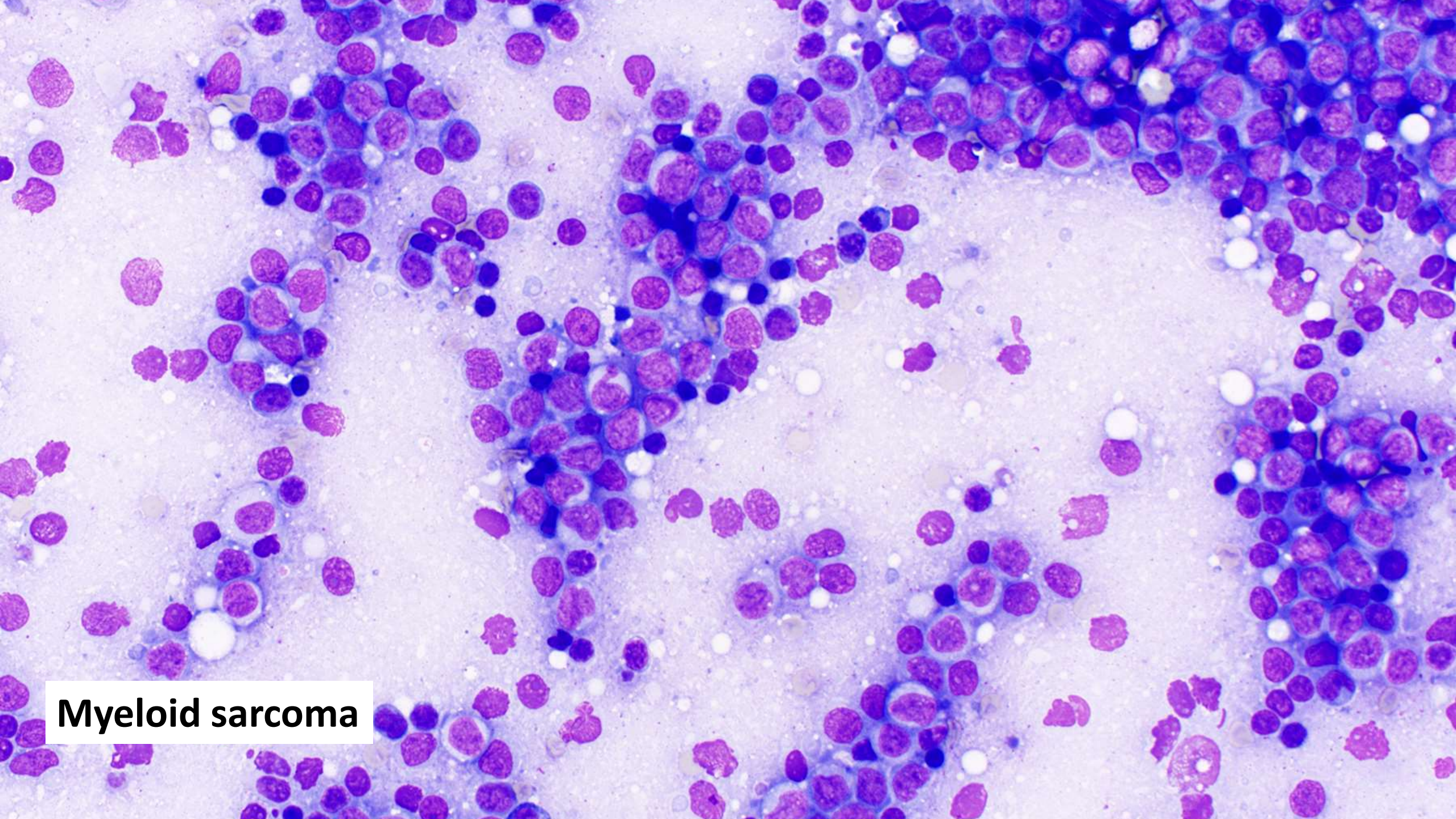


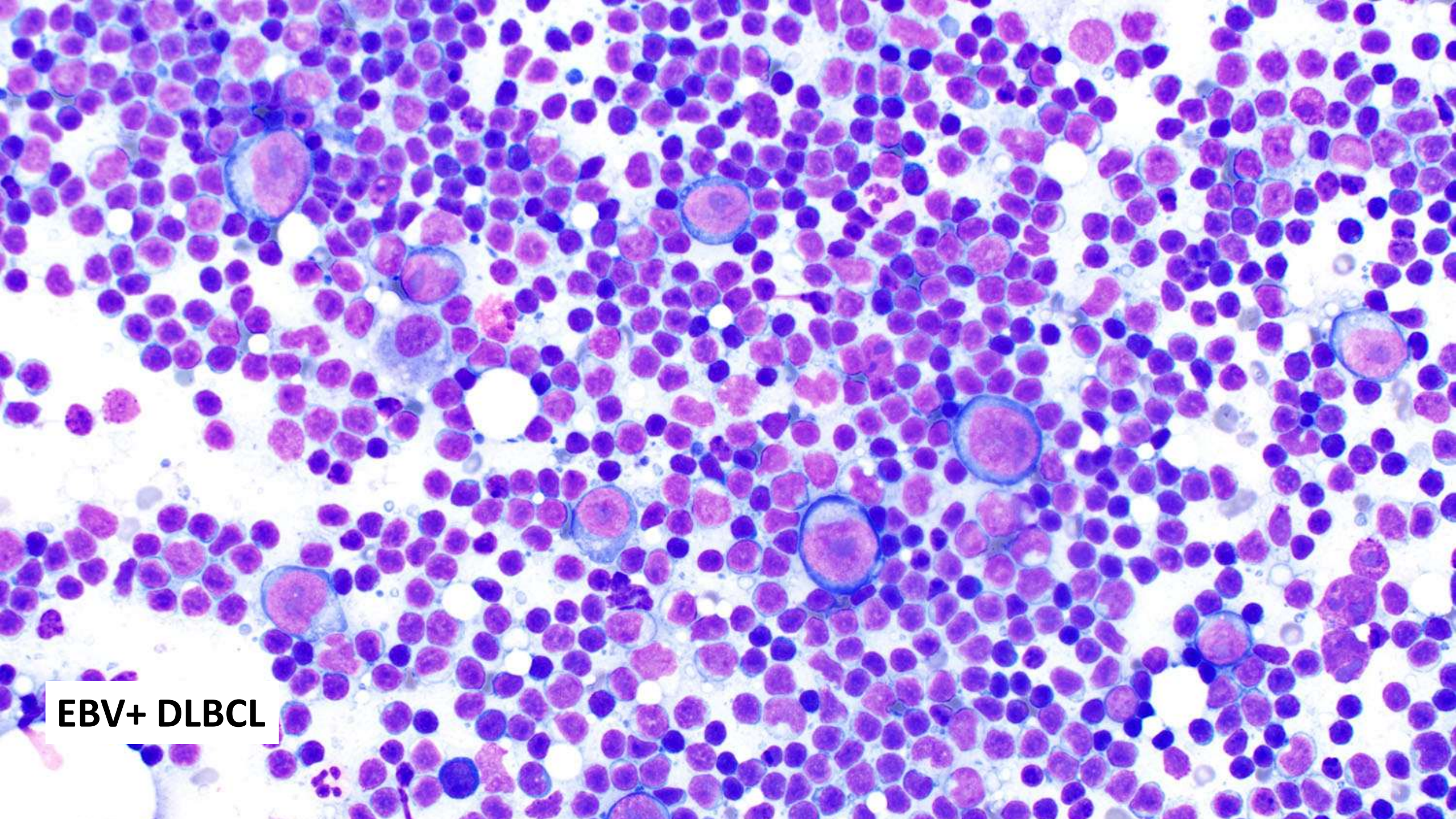
Grossing a lymph node

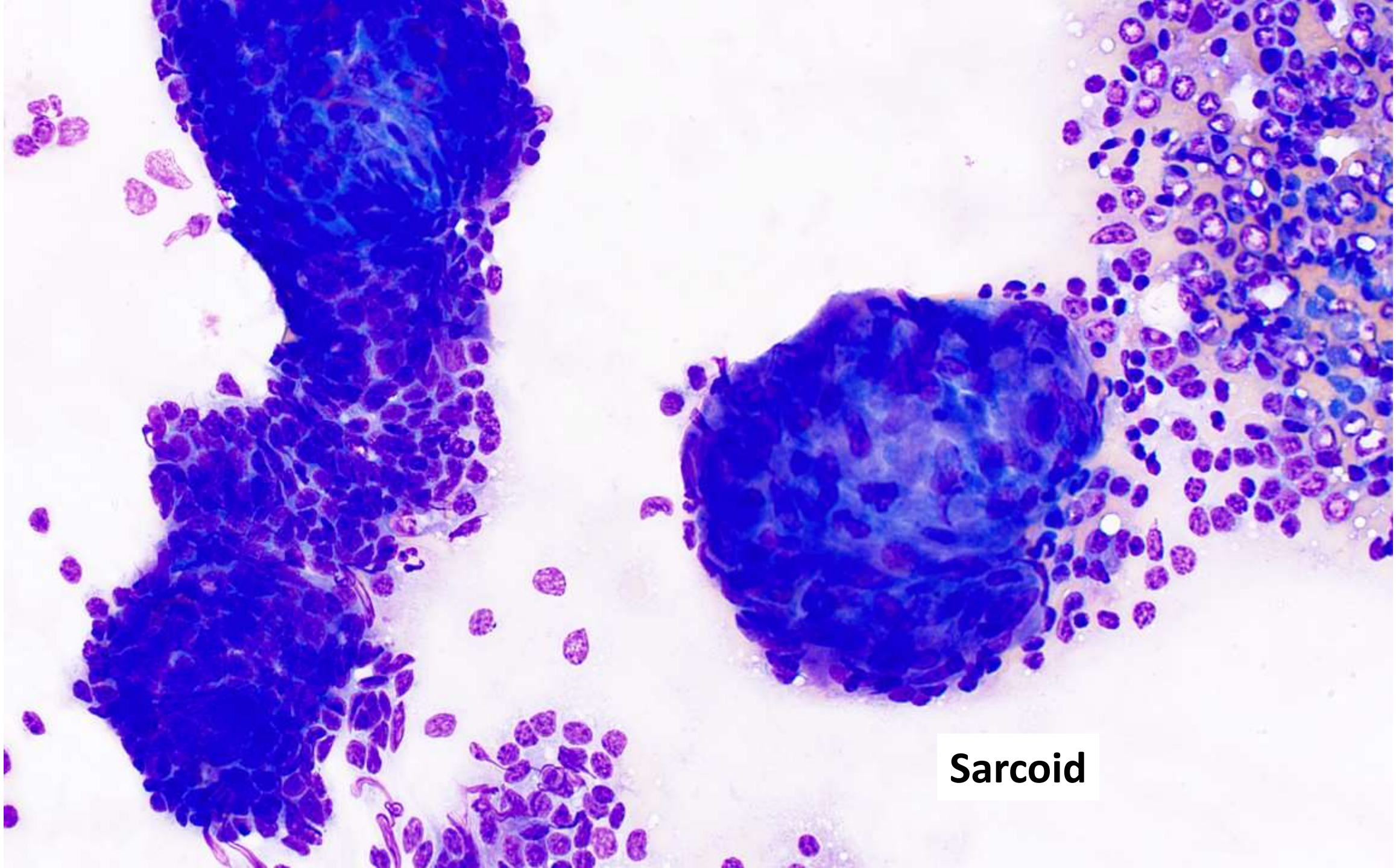
1. Review clinical history
2. Touch prep!!
   - Except tiny needle cores..
3. For further processing, take into consideration
   - Size of the specimen
   - Differential diagnosis, based on touch prep and history
   - Utility of cytogenetics?
   - Likelihood of malignancy? → Save some for frozen, biobank, etc. if possible


CHL


NLPHL


Myeloid sarcoma


EBV+ DLBCL

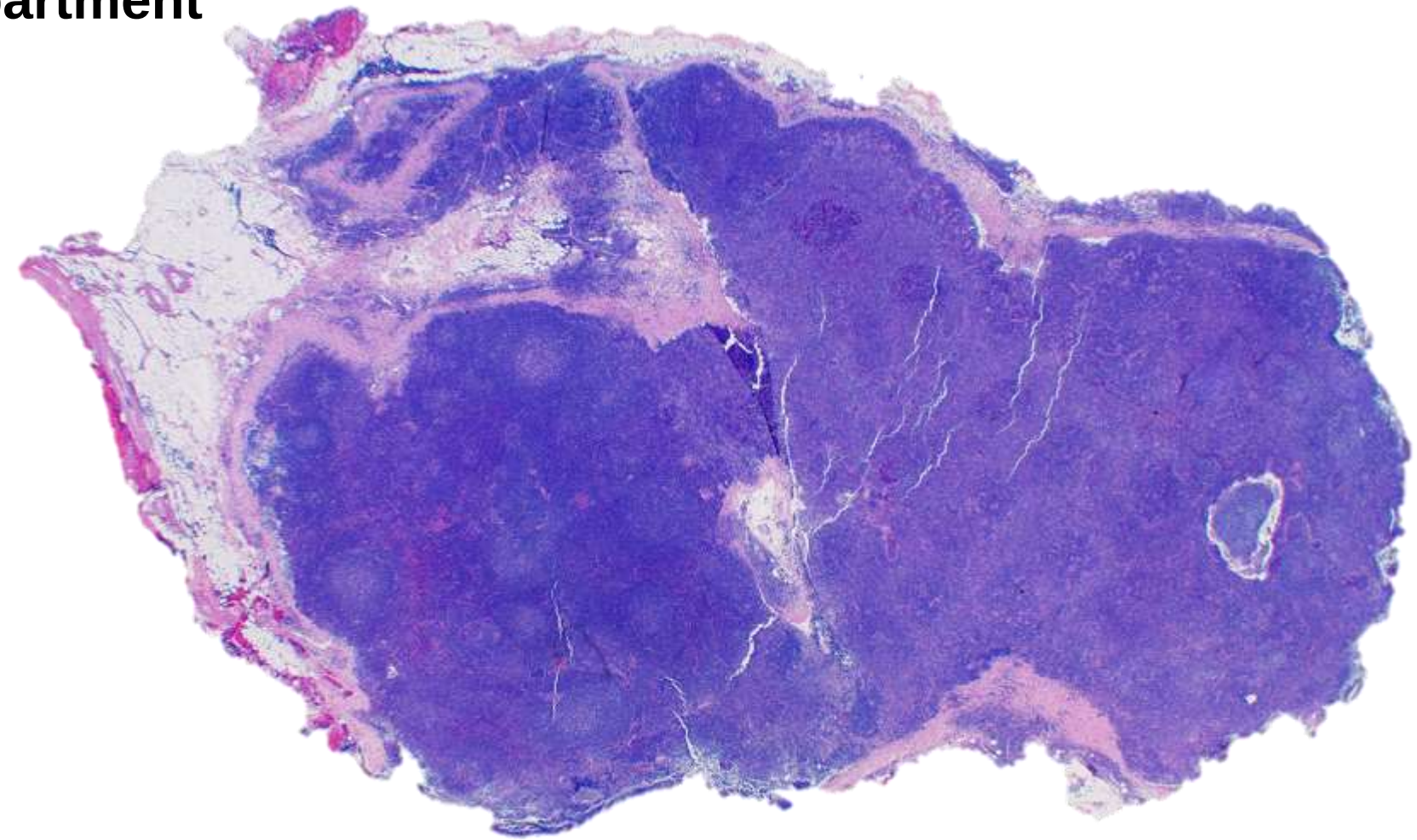

Sarcoid

Priority for evaluation

1. **Morphology**
   - **Whole cross-sections of the LN**
   - **Leave surrounding fat and soft tissue in place**
2. **Flow cytometry**
   - **Cut 2-3 small pieces of tissue (~0.3x0.3x0.3cm) from different areas**
3. **Cytogenetics**
   - **Cut 2-3 small pieces of tissue from different areas**
   - **~1cm all together**
4. **Tissue for research**

Lymph node: Compartment approach

- **Begin at low magnification to assess pattern**
- **Examine each compartment**
  - **Capsule**
  - **Sinuses**
  - **Vasculature**
  - **Paracortex**
  - **Follicles**



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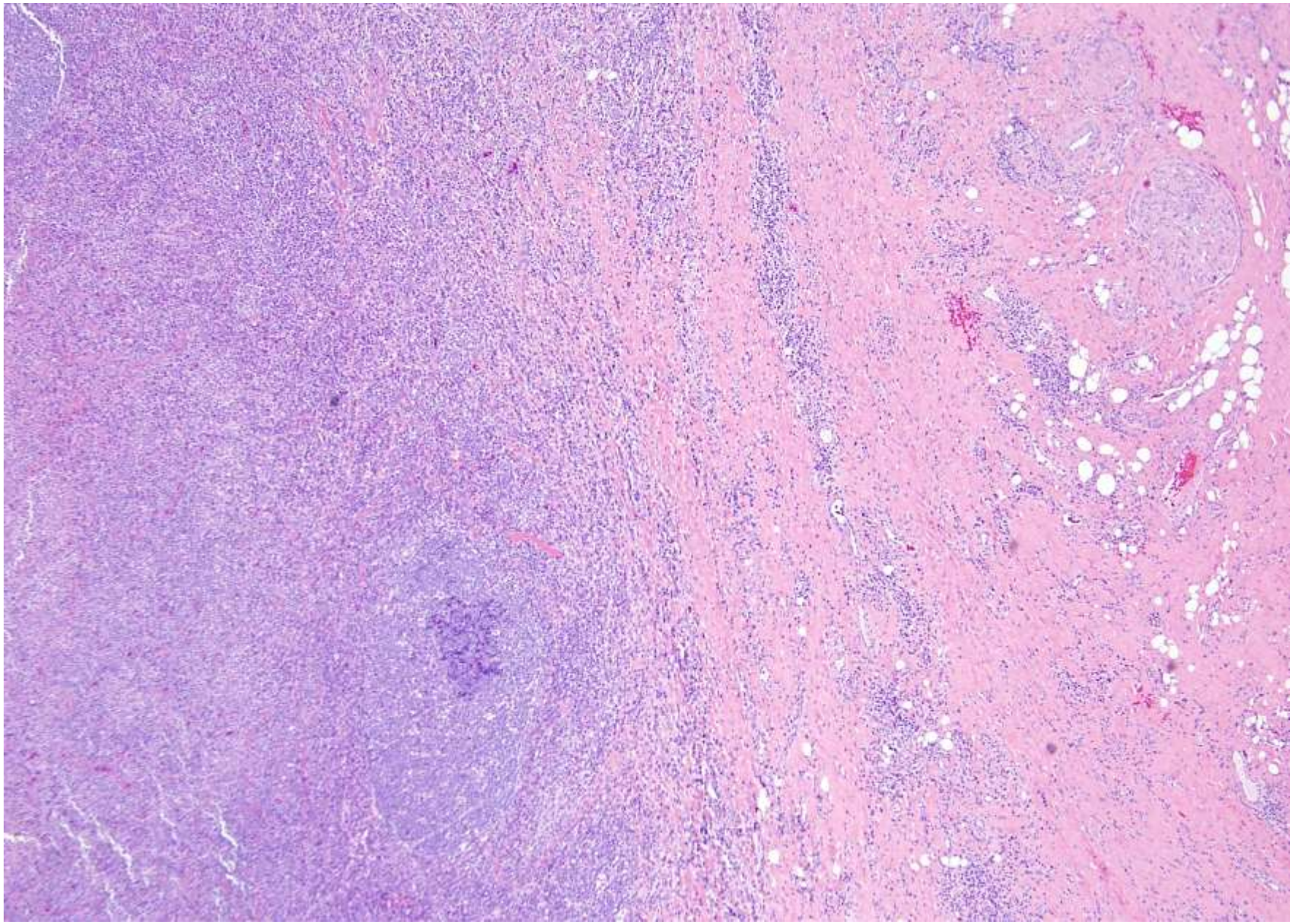
Abnormal capsular findings

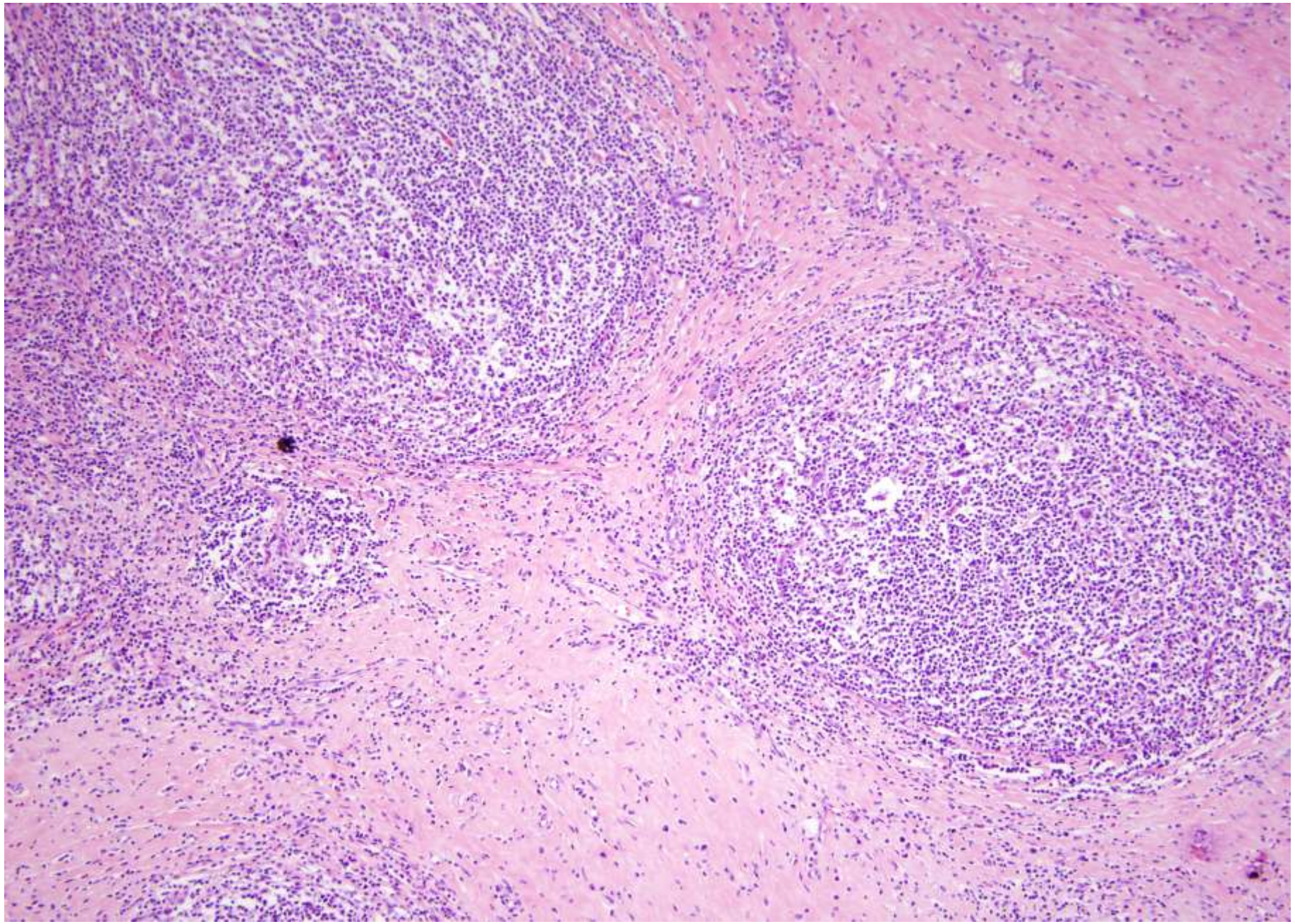
Thinning	• Rapid expansion of nodal parenchyma by malignant process
Thickening	• Chronic inflammatory process • Indolent B-cell lymphomas • Nodular sclerosis classic Hodgkin lymphoma
Extracapsular extension	• Often associated with lymphomas, although can be seen in some benign disorders
Inclusions	• Glandular elements (e.g. benign breast glands in axillary nodes) • Clusters of nevus cells (e.g. nodal nevi)

Thickened, fibrotic capsule syphilis

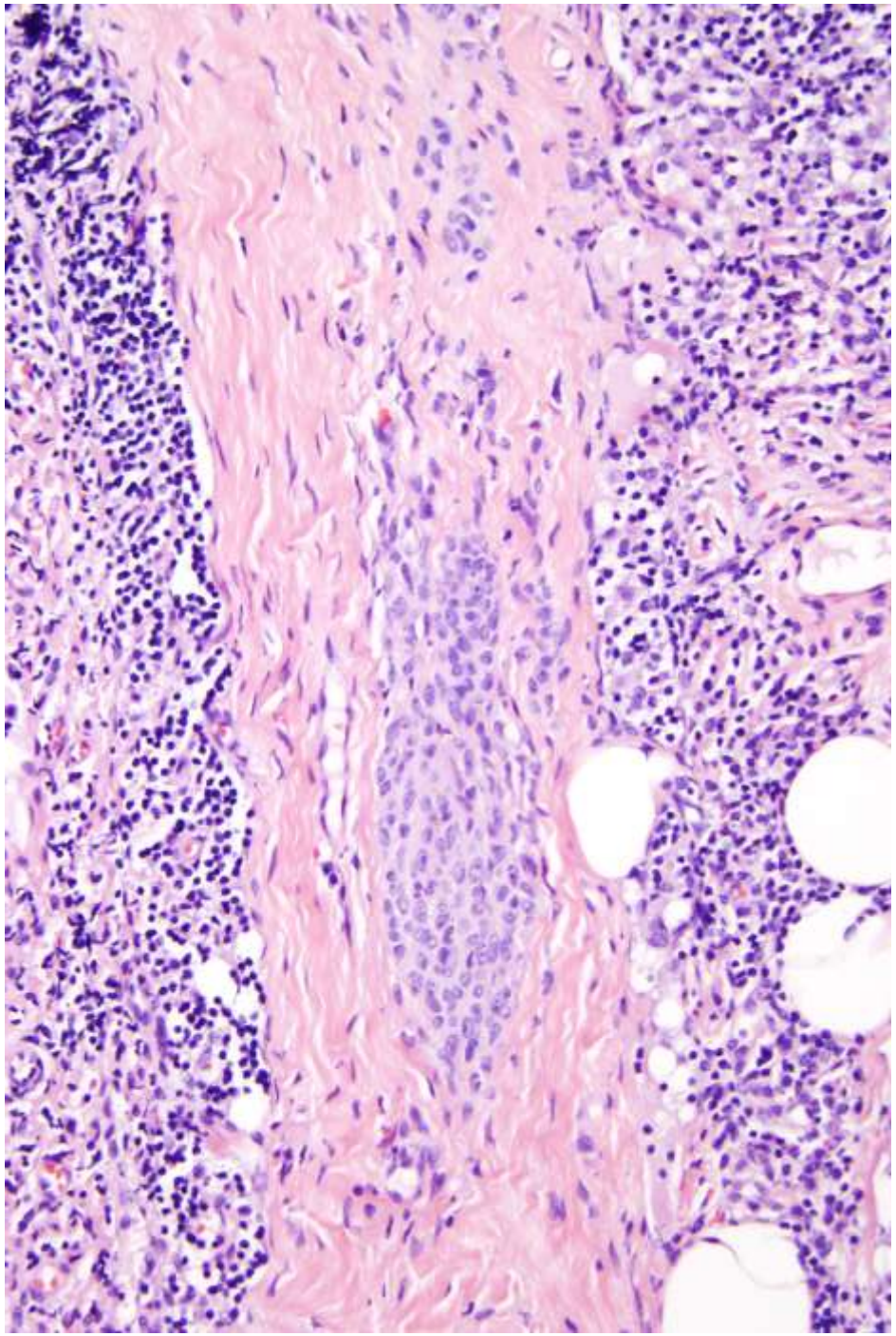
“luetic lymphadenitis”

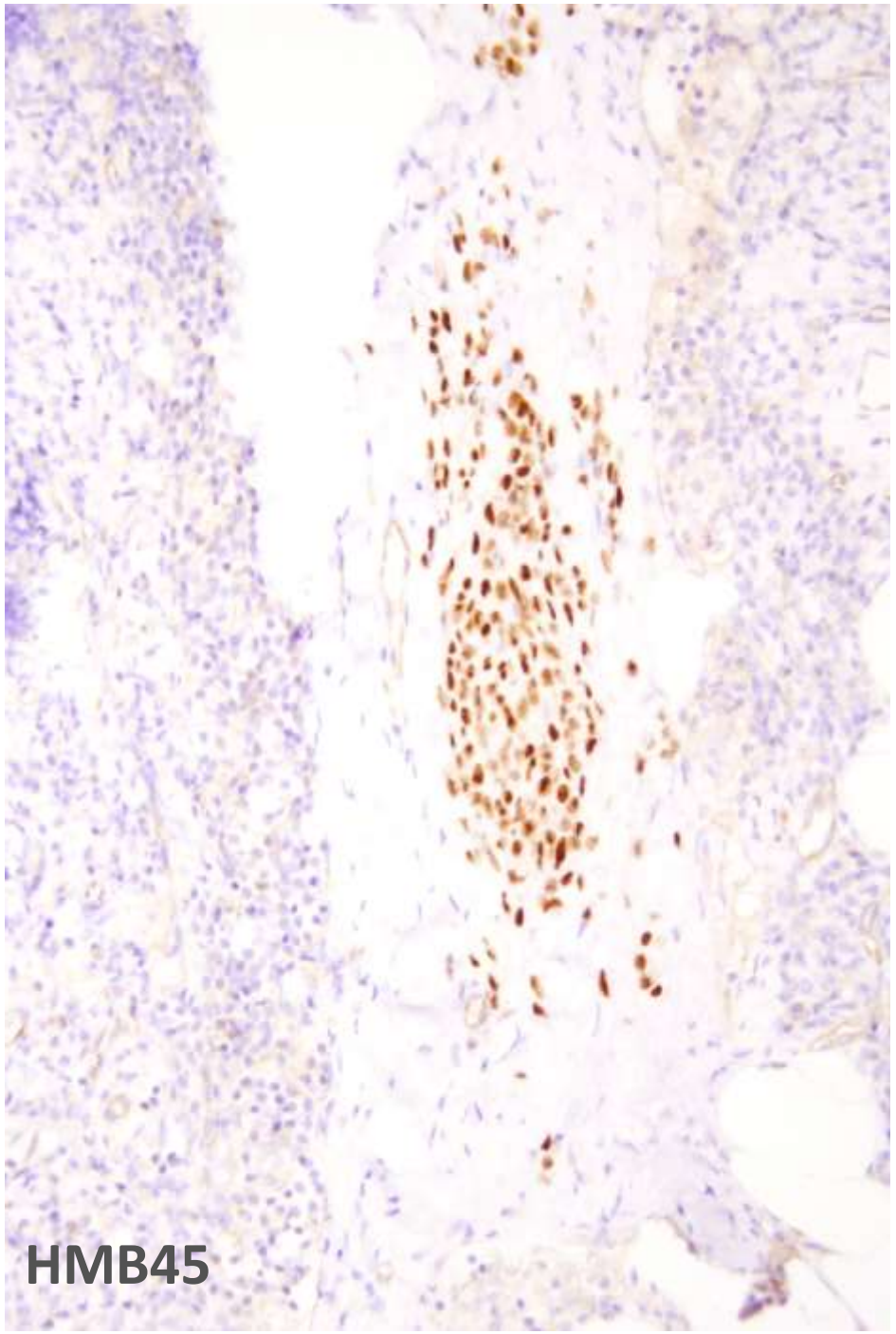


Classic Hodgkin lymphoma, nodular sclerosis subtype



Nodal nevi

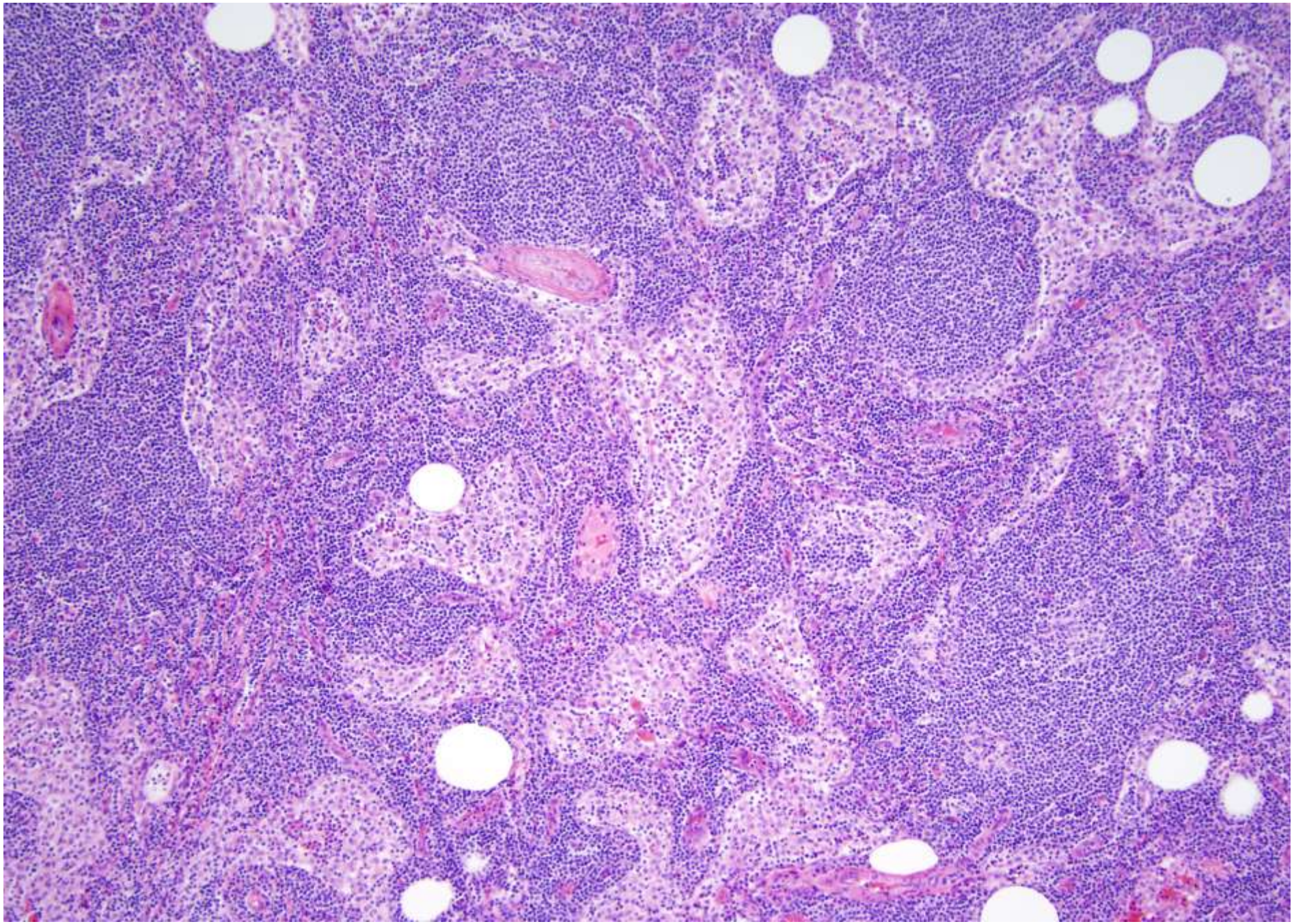




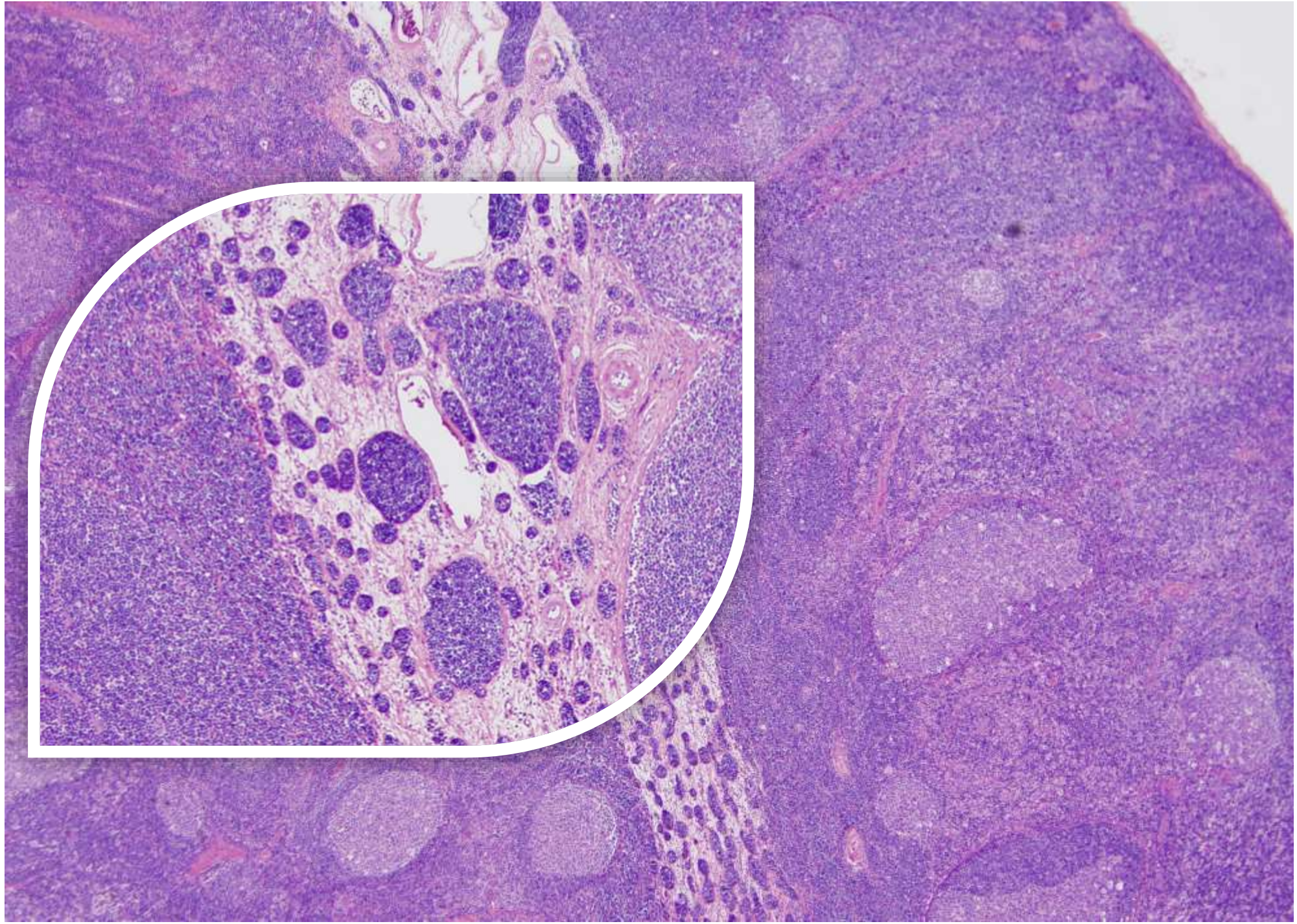
Abnormal findings in lymph node sinuses

Sinus histiocytosis	• Rosai-Dorfman disease
“Lymphocyte trafficking”: sinus expansion by lymphocytes	• Reactive conditions with increased circulating lymphocytes, e.g. viral infection, activated lymphocytes/immunoblasts also present • If cytologic atypia, lymphoma/lymphoid leukemia should be considered
Malignancy	• Metastatic disease • Anaplastic large cell lymphoma, can mimic metastatic carcinoma with a sinus pattern

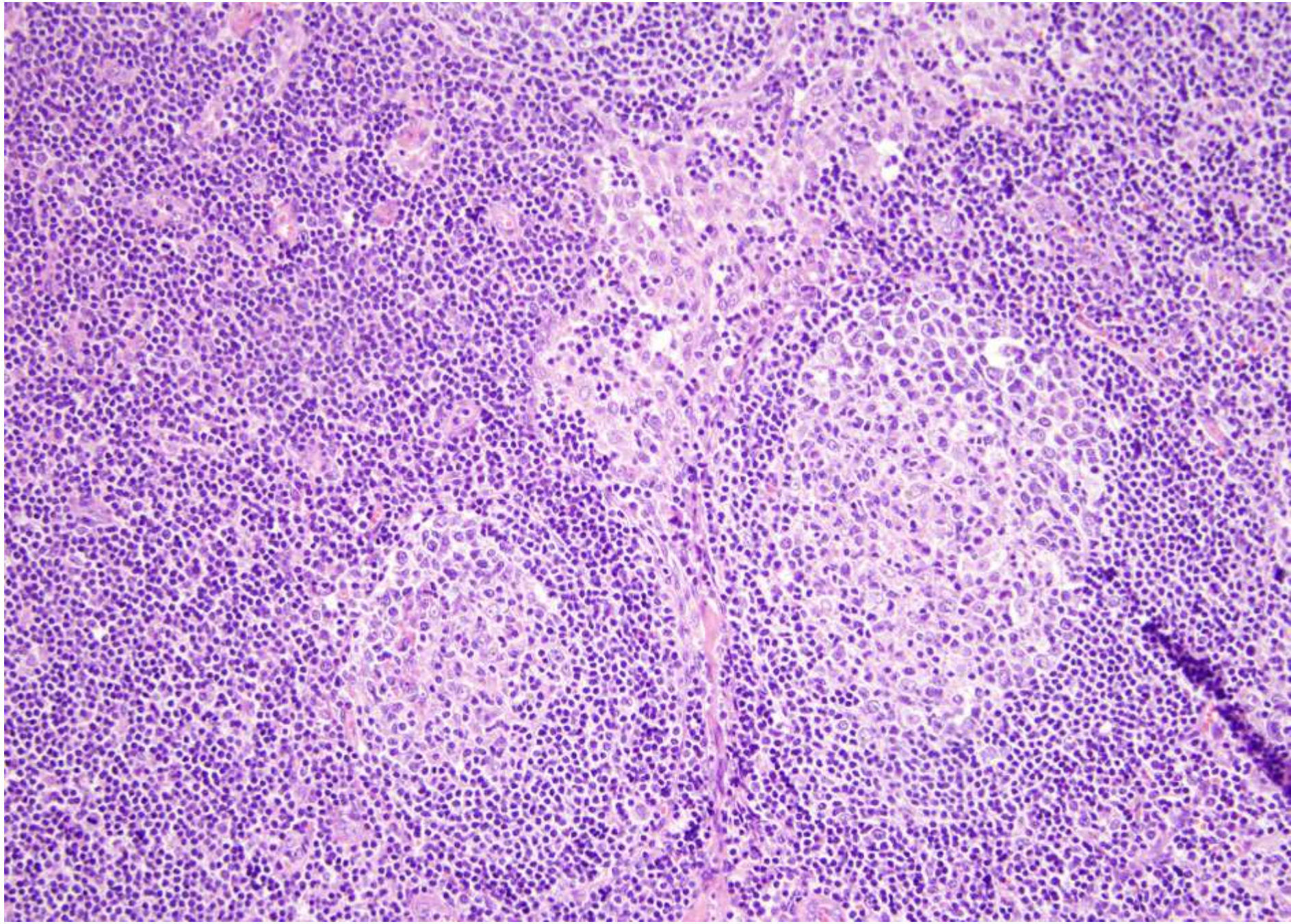
Lymph node sinuses



Increased lymphocytic trafficking, dilating lymphatics



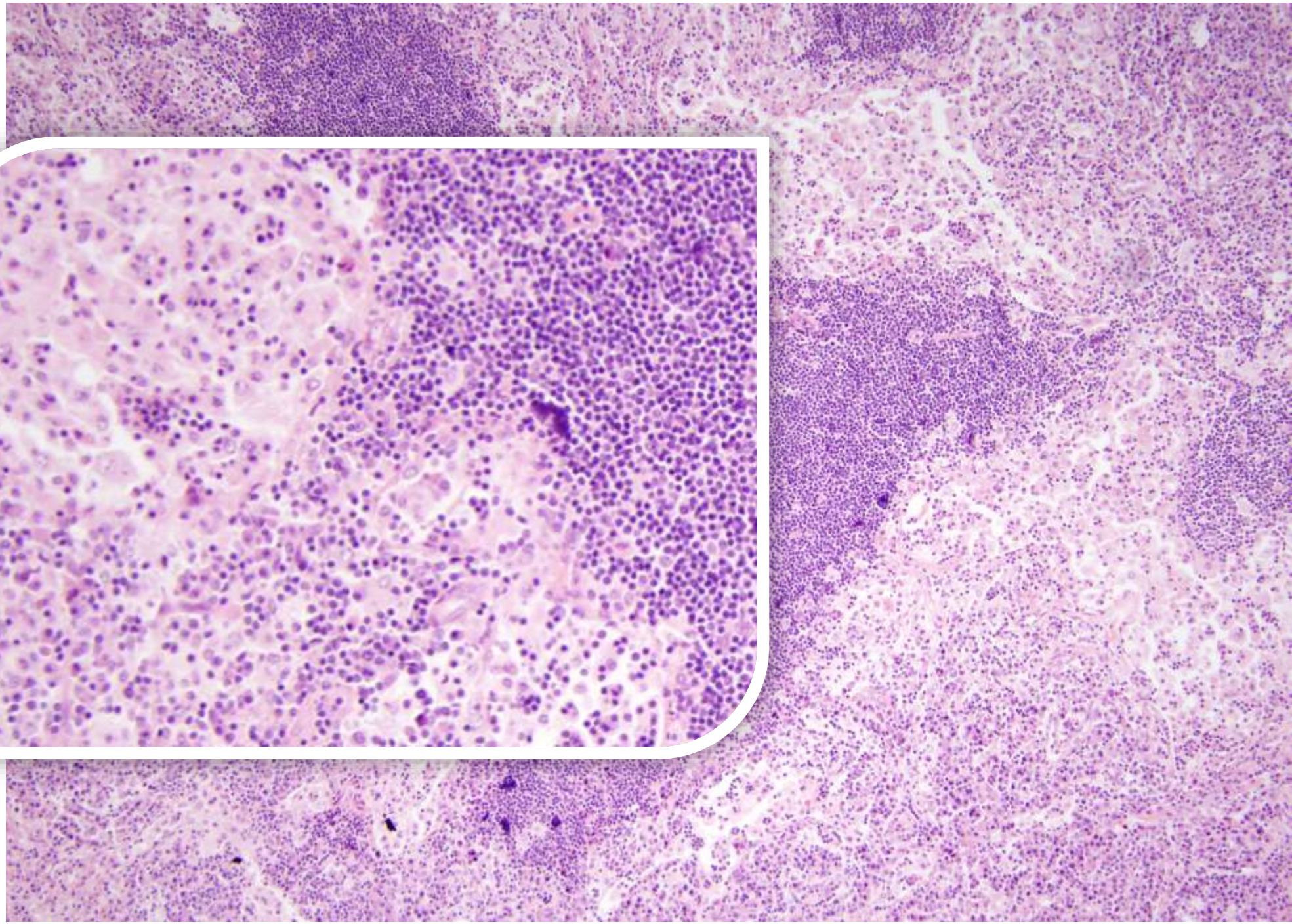
Sinus histiocytosis



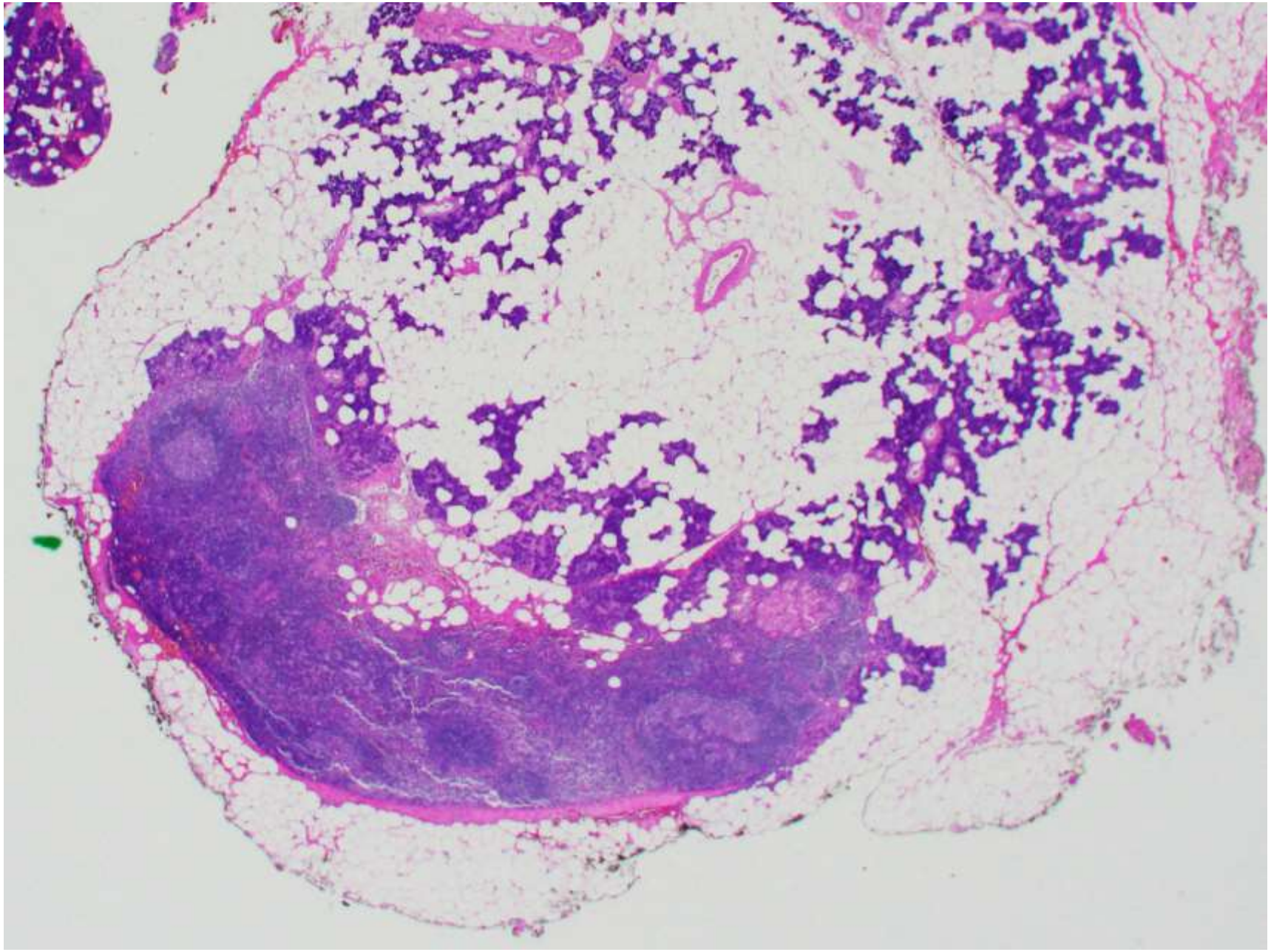
Rosai Dorfman Disease

aka
sinus histiocytos
with massive
lymph-
adenopathy

Emperipolesis

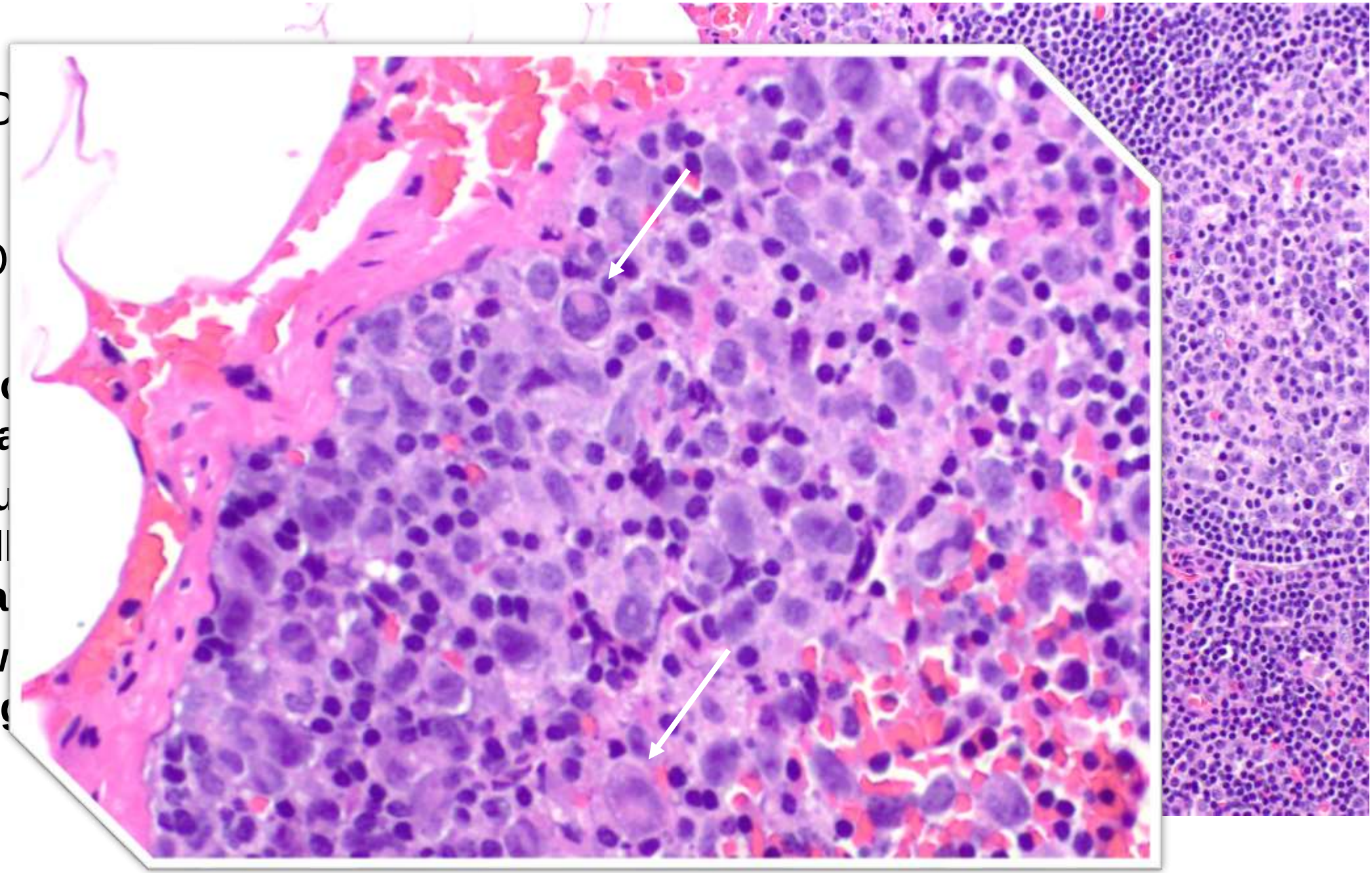


Boring lymph node?



ALCL invo
sinuses,
intraparo

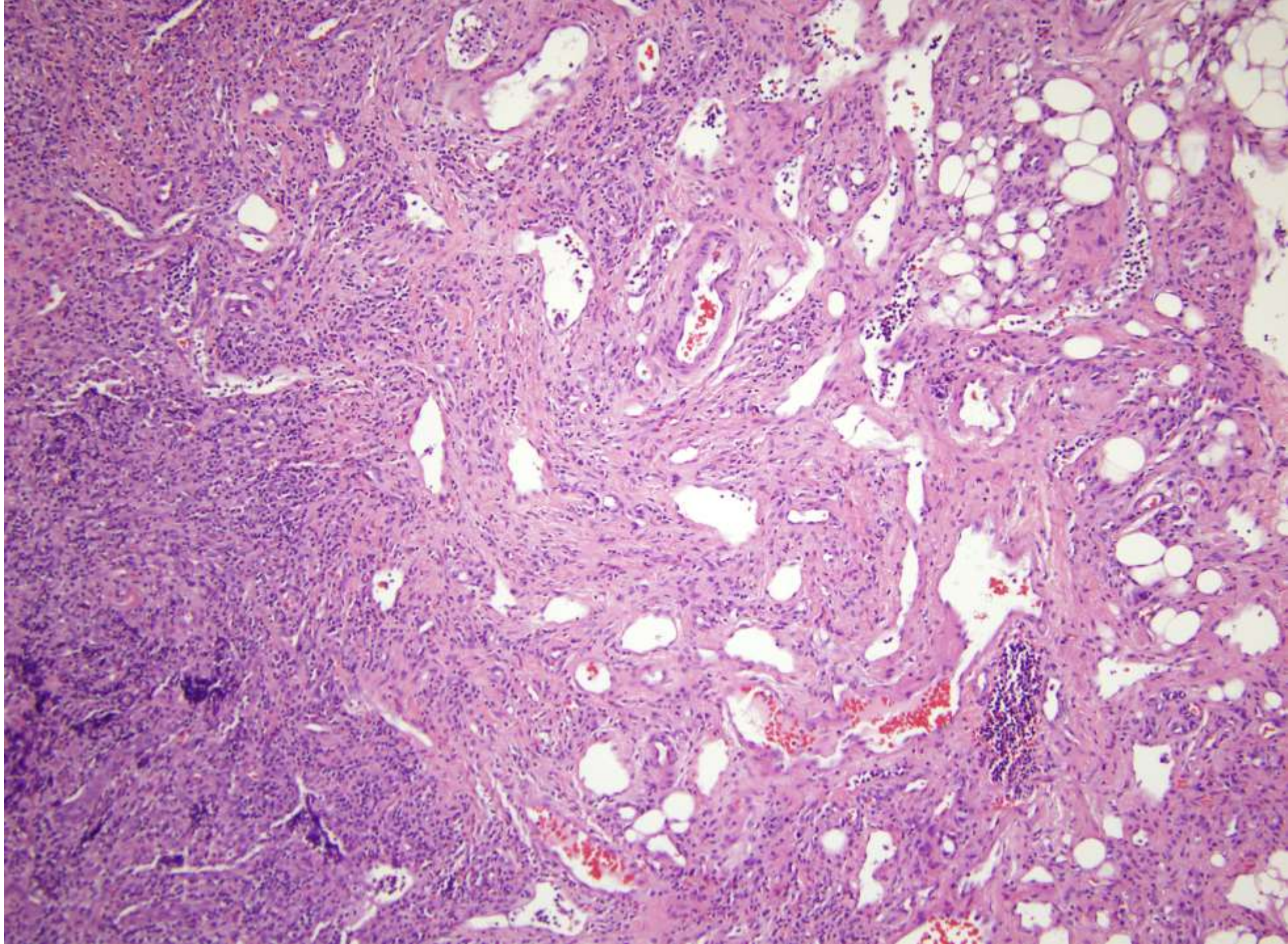
- **May mimi**
  carcinoma
- **Often sinu**
  or interfoll
  growth pa
- **May show**
  cohesive g



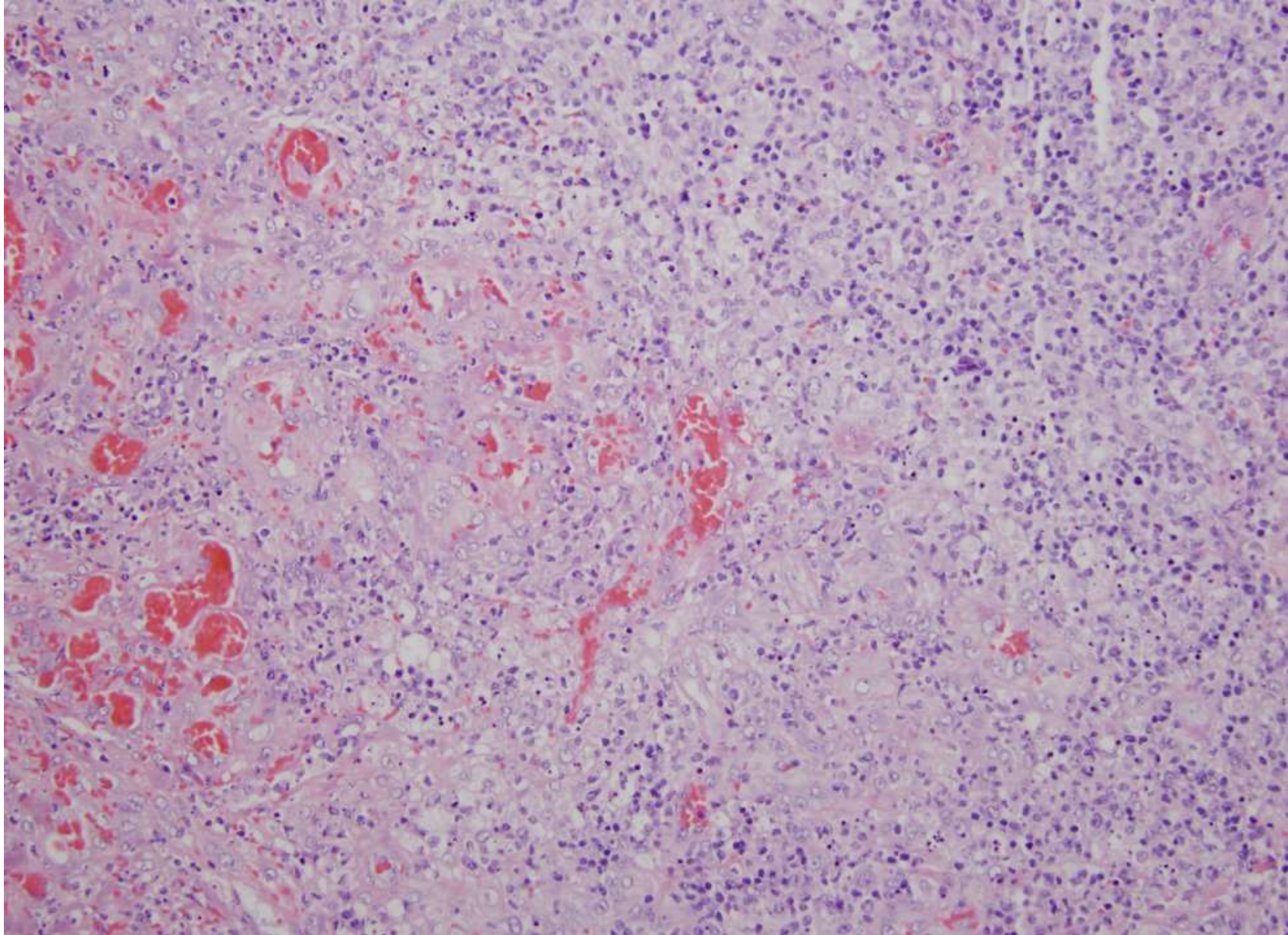
Abnormal vascular findings and associated pathology

Prominent hilar vessels	• "Vascular transformation of sinuses", usually associated with blockage of efferent lymphatics (or veins) resulting in proliferation of hilar vessels
Plump high-endothelial venules	• Angioimmunoblastic T cell lymphoma
Increased vascular elements	• Angioimmunoblastic T cell lymphoma • Bacillary angiomatosis • Less commonly B cell lymphoma
Vascular hyalinization	• Inflammatory conditions • Hyaline-vascular Castleman disease
Vascular neoplasms	• Hemangioma • Angiomyolipoma • Kaposi sarcoma

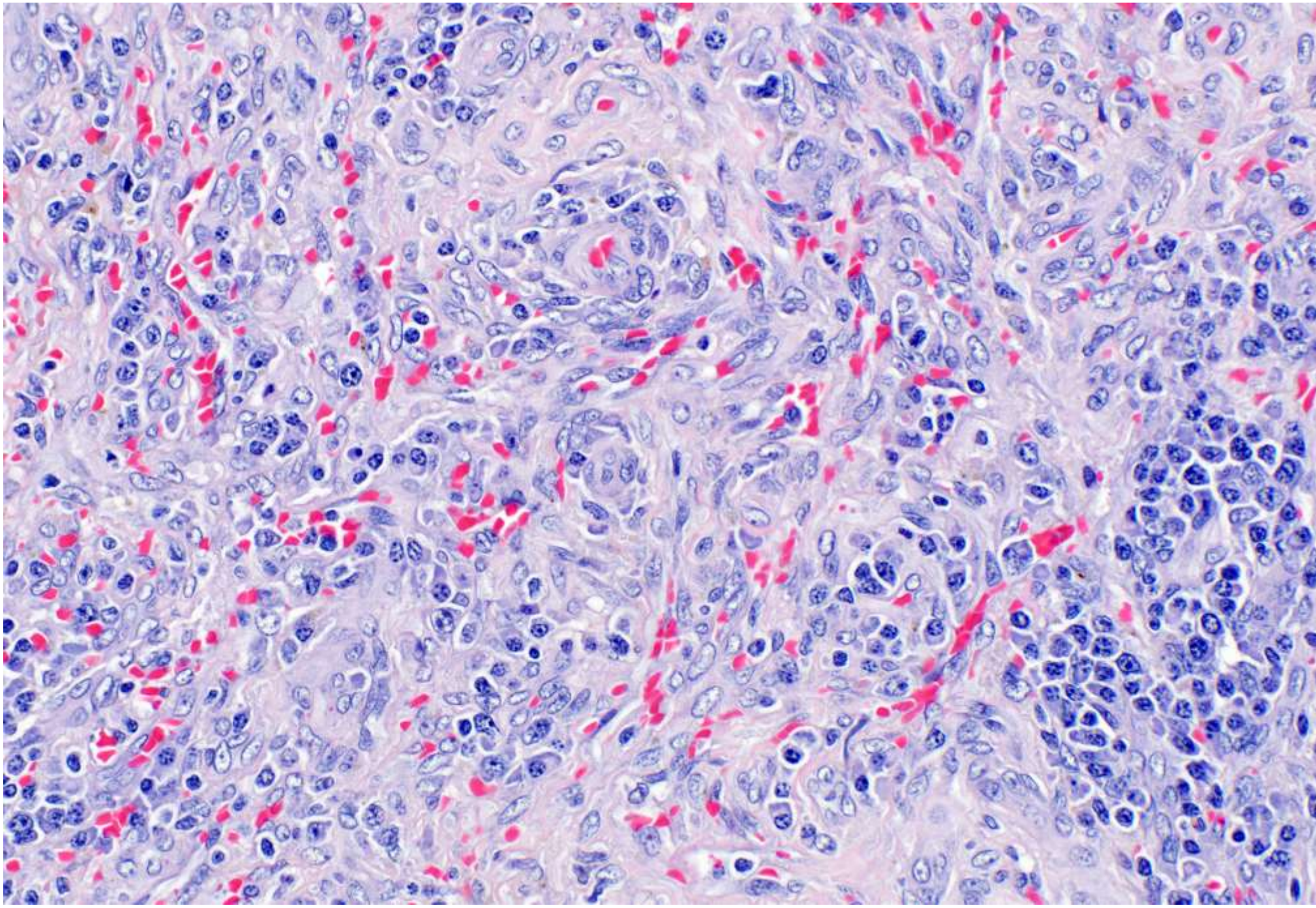
Vascular transformation of the sinuses



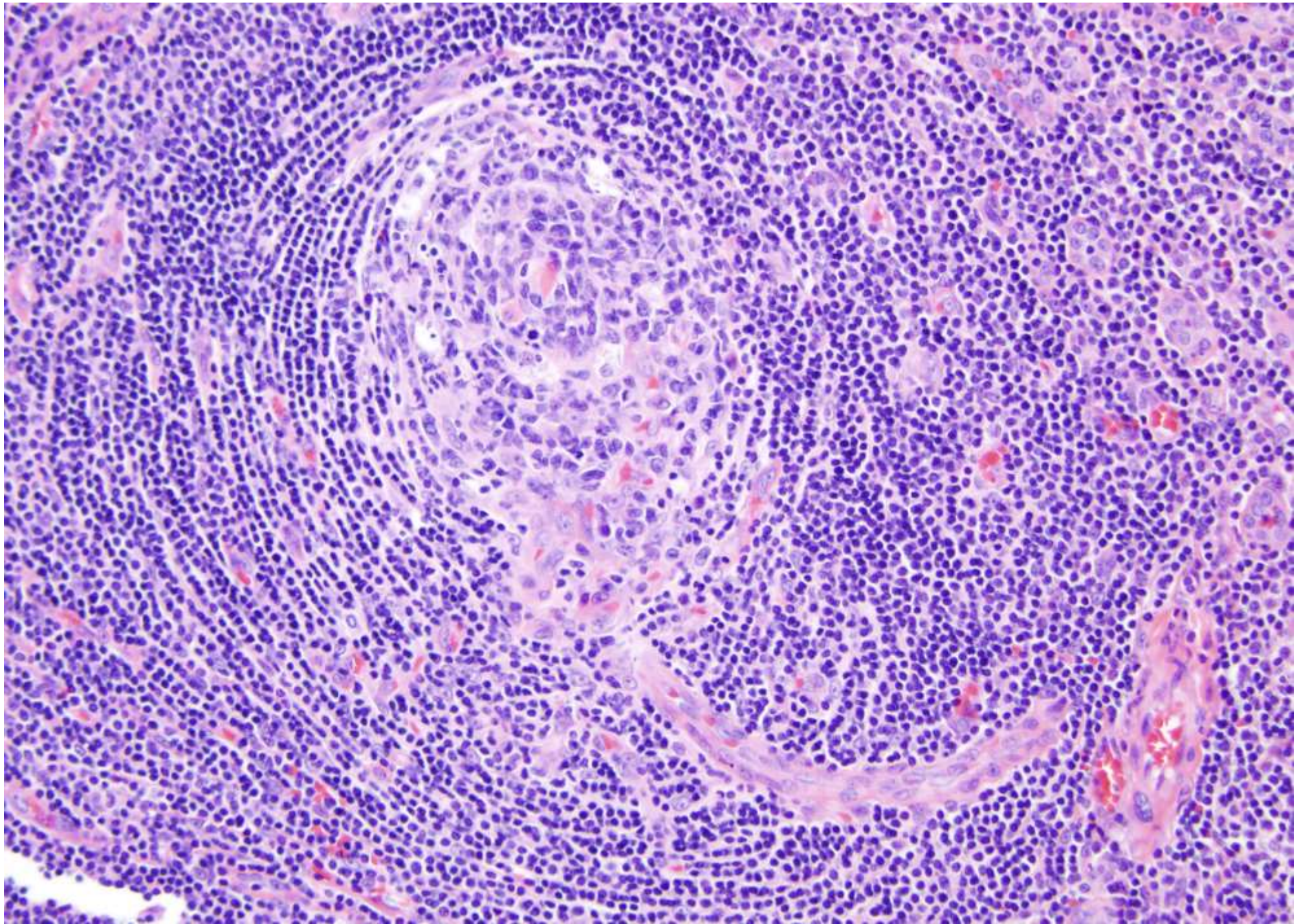
Bacillary angiomatosis



Kaposi sarcoma

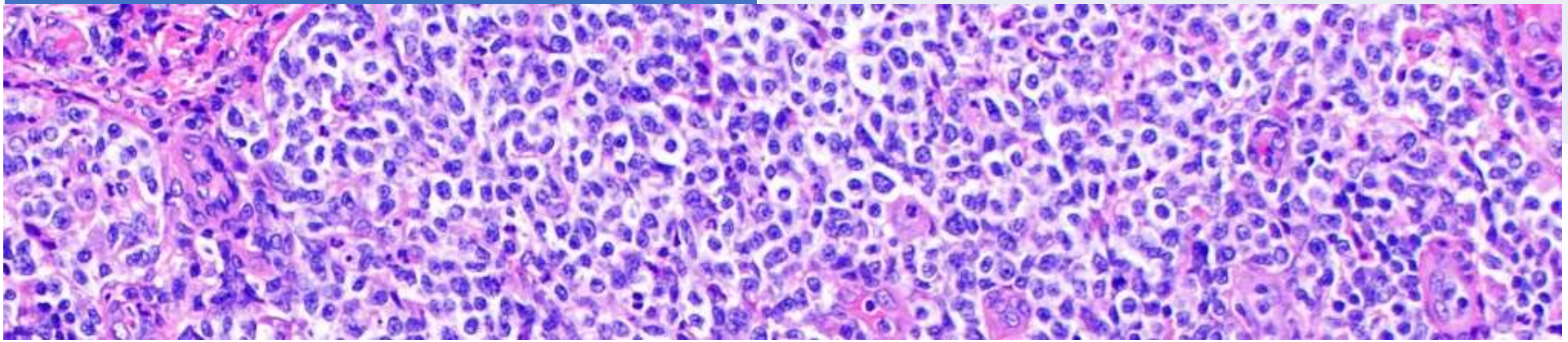


Hyaline vascular Castleman disease

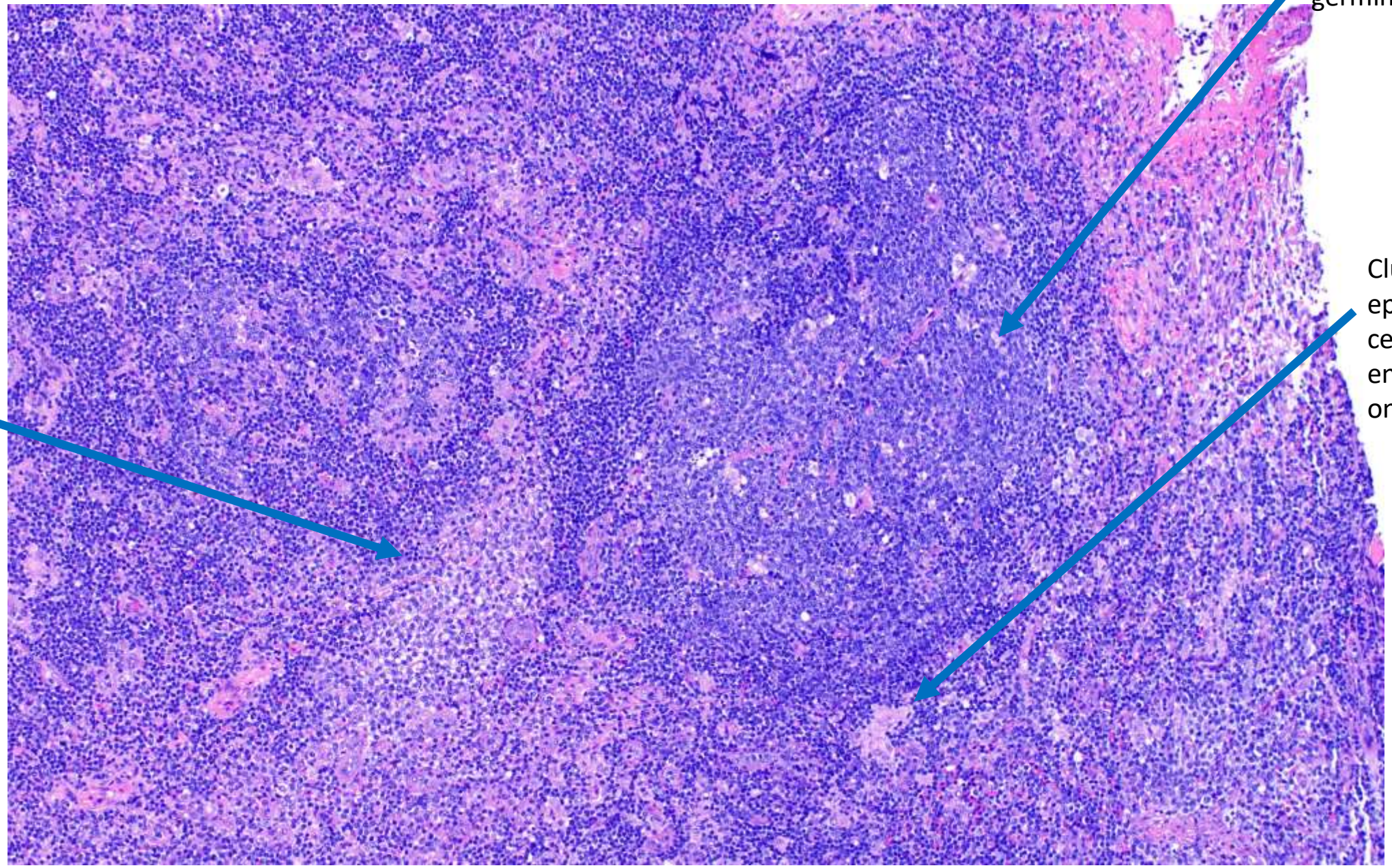


Pathology associated with increased monocytoid B-cells

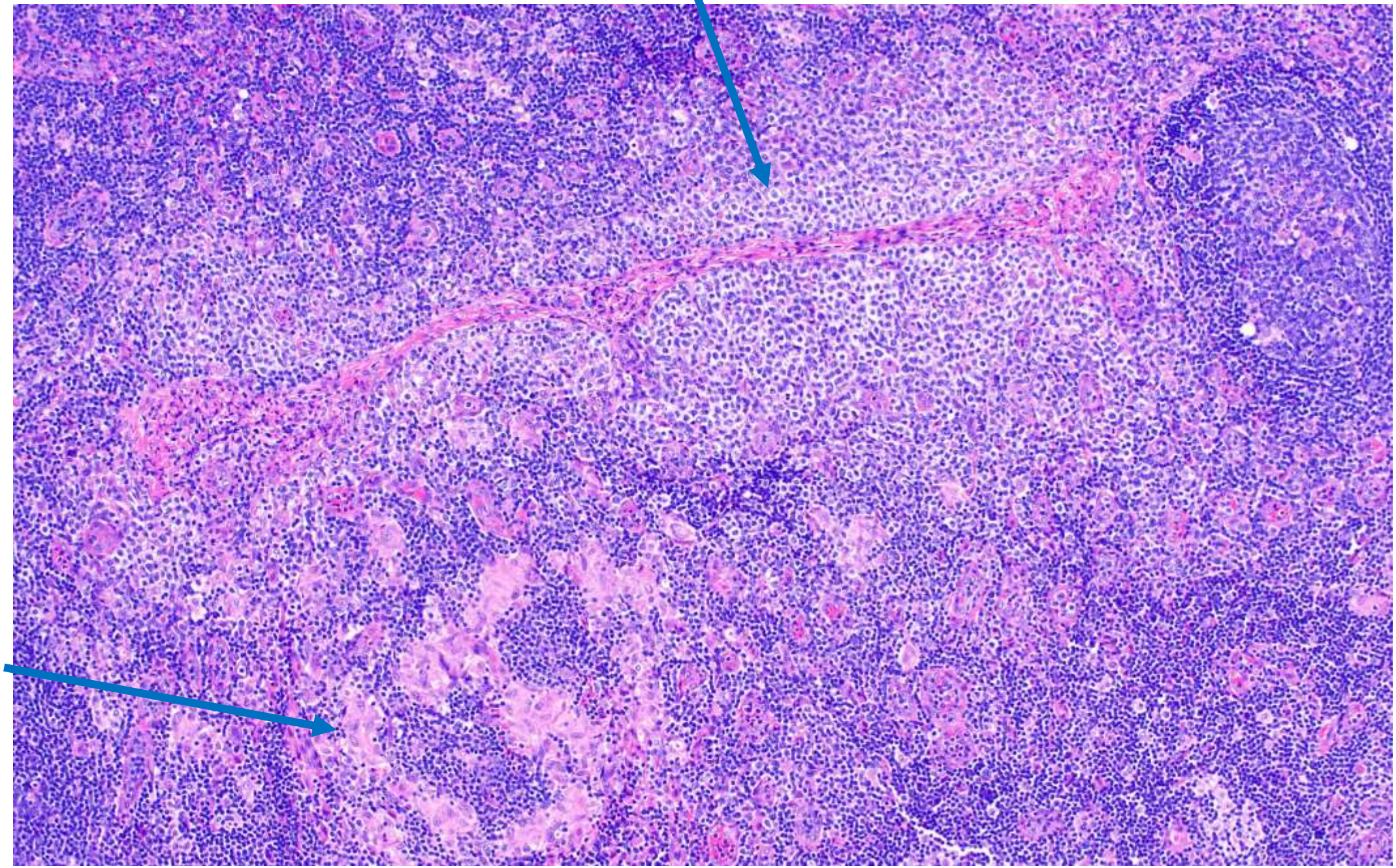
Reactive conditions	Malignancy
• Viral lymphadenitis • EBV • CMV • HIV/AIDS • Toxoplasma lymphadenitis	• Marginal zone lymphoma • Lymphoplasmacytic lymphoma • Mimicking monocytoid B cells: certain T cell lymphomas (AITL)



Characteristic triad of Toxoplasma lymphadenitis:



Area of monocytoid cells along vessel

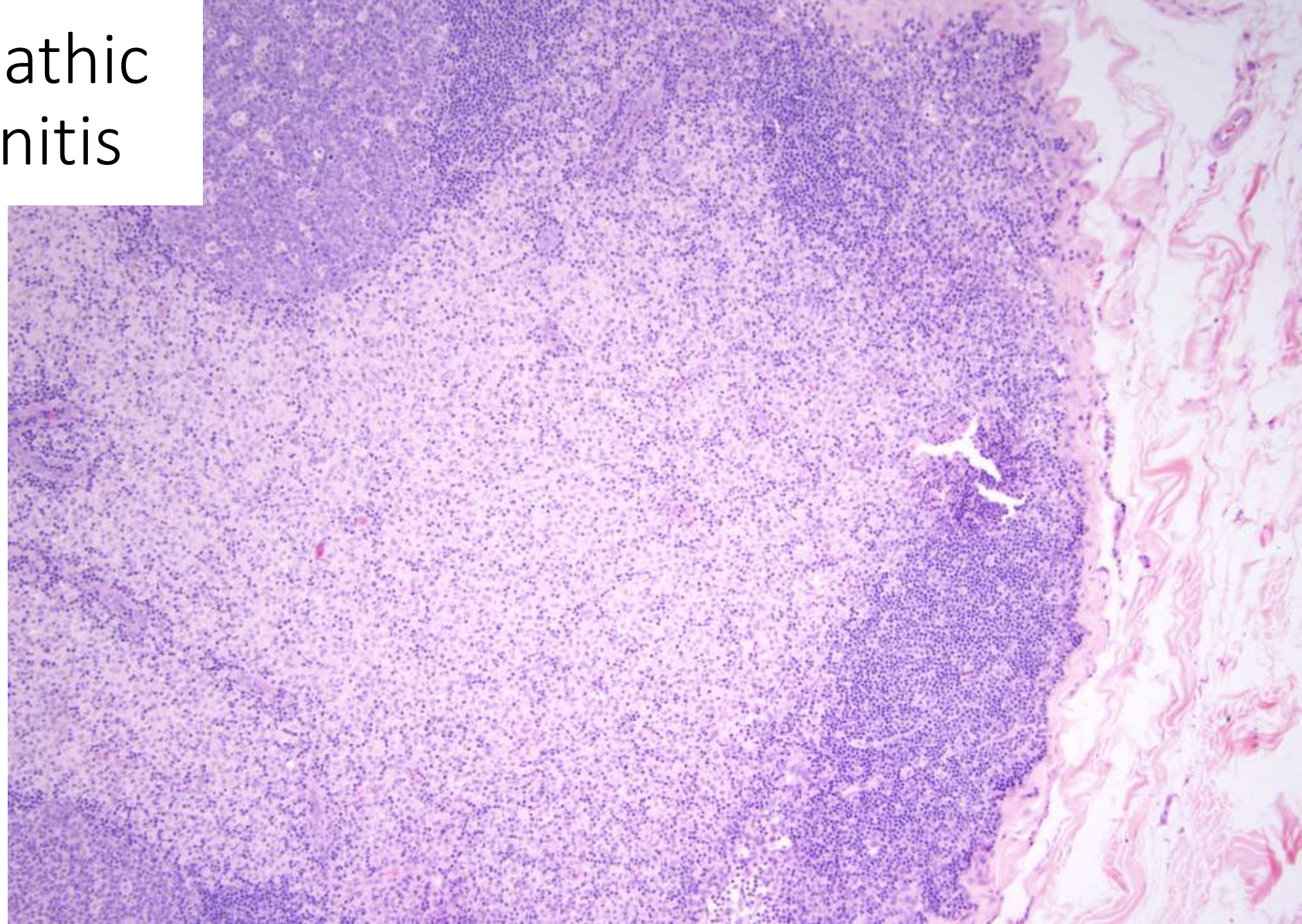


Epithelioid histiocytes better seen here

Paracortical expansion

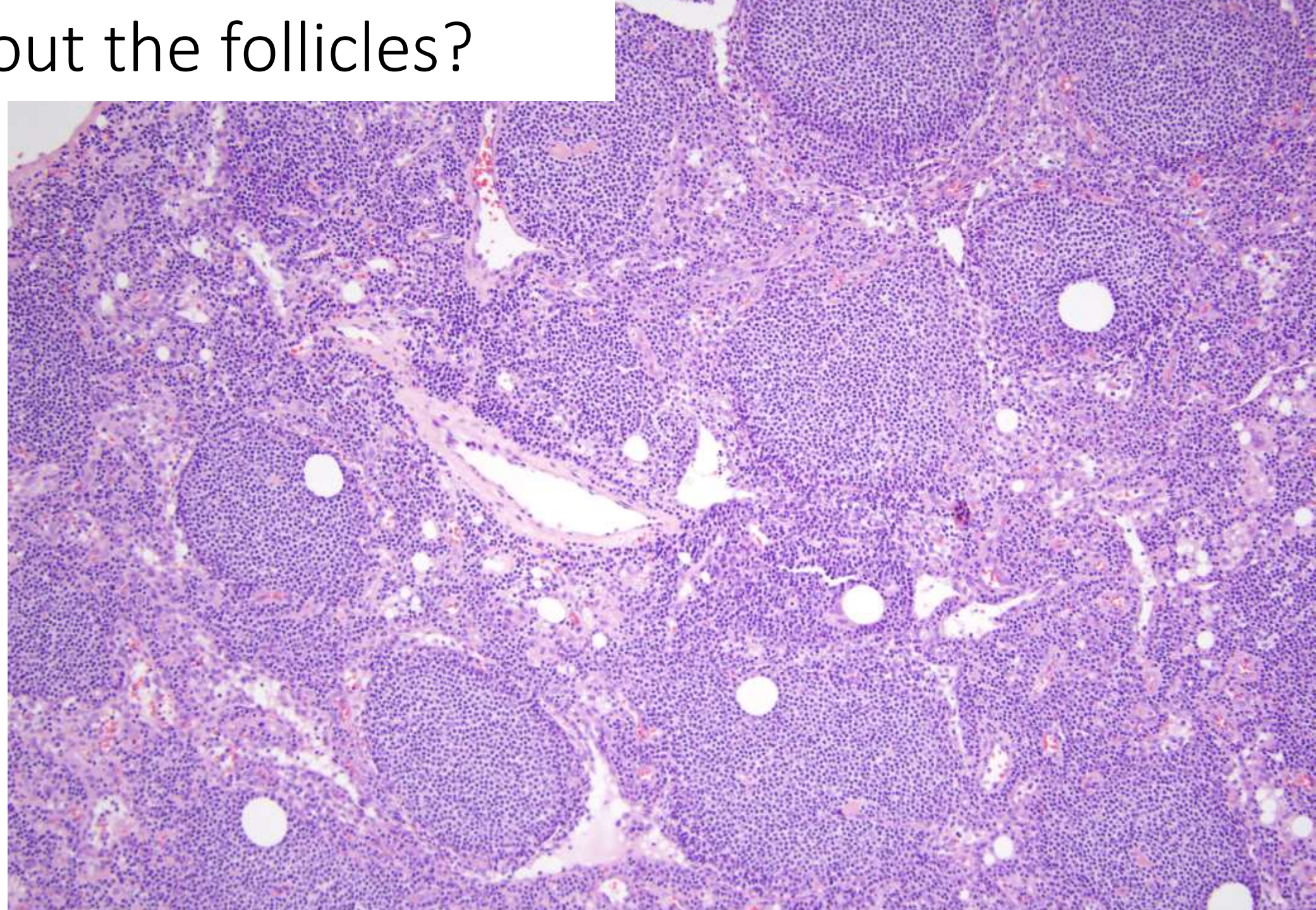
Reactive conditions	Malignancy
• Viral infection • Dermatopathic	• MZL • LPL • Early involvement by CLL/SLL • T-cell lymphomas

Dermatopathic lymphadenitis



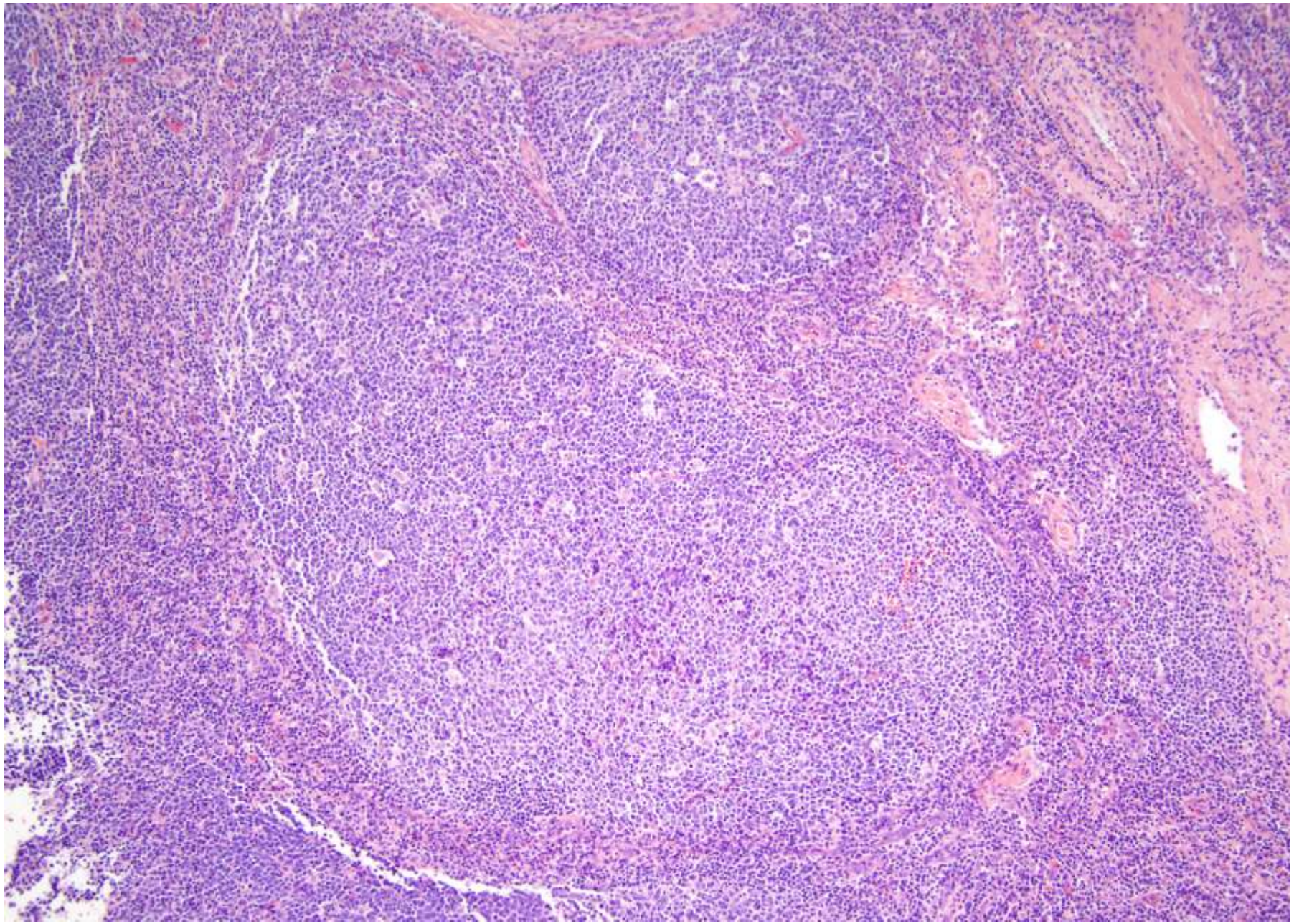
What about the follicles?

Primary follicles in gallbladder fat



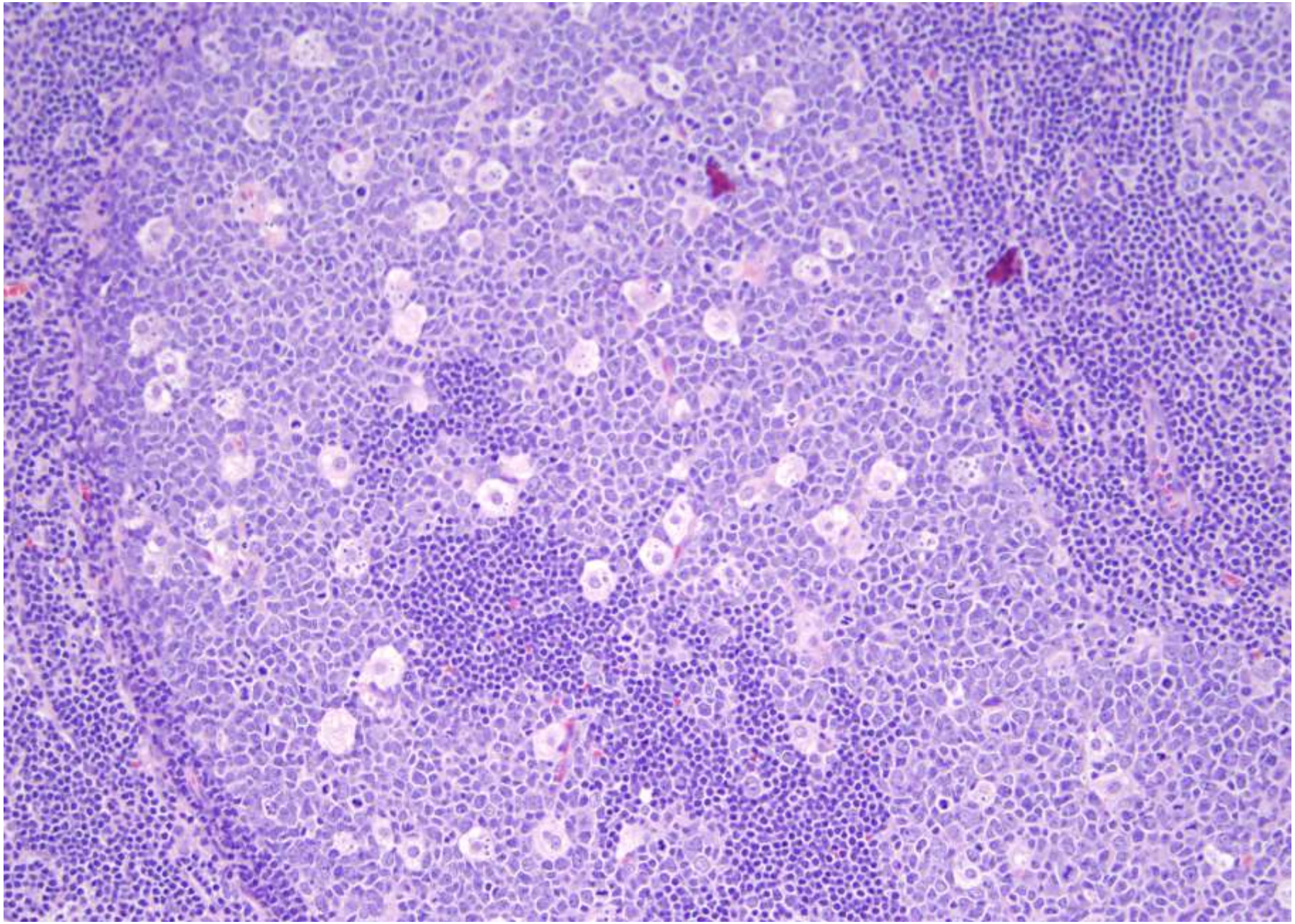
Florid follicular hyperplasia in the setting of HIV

Reduced mantle zones

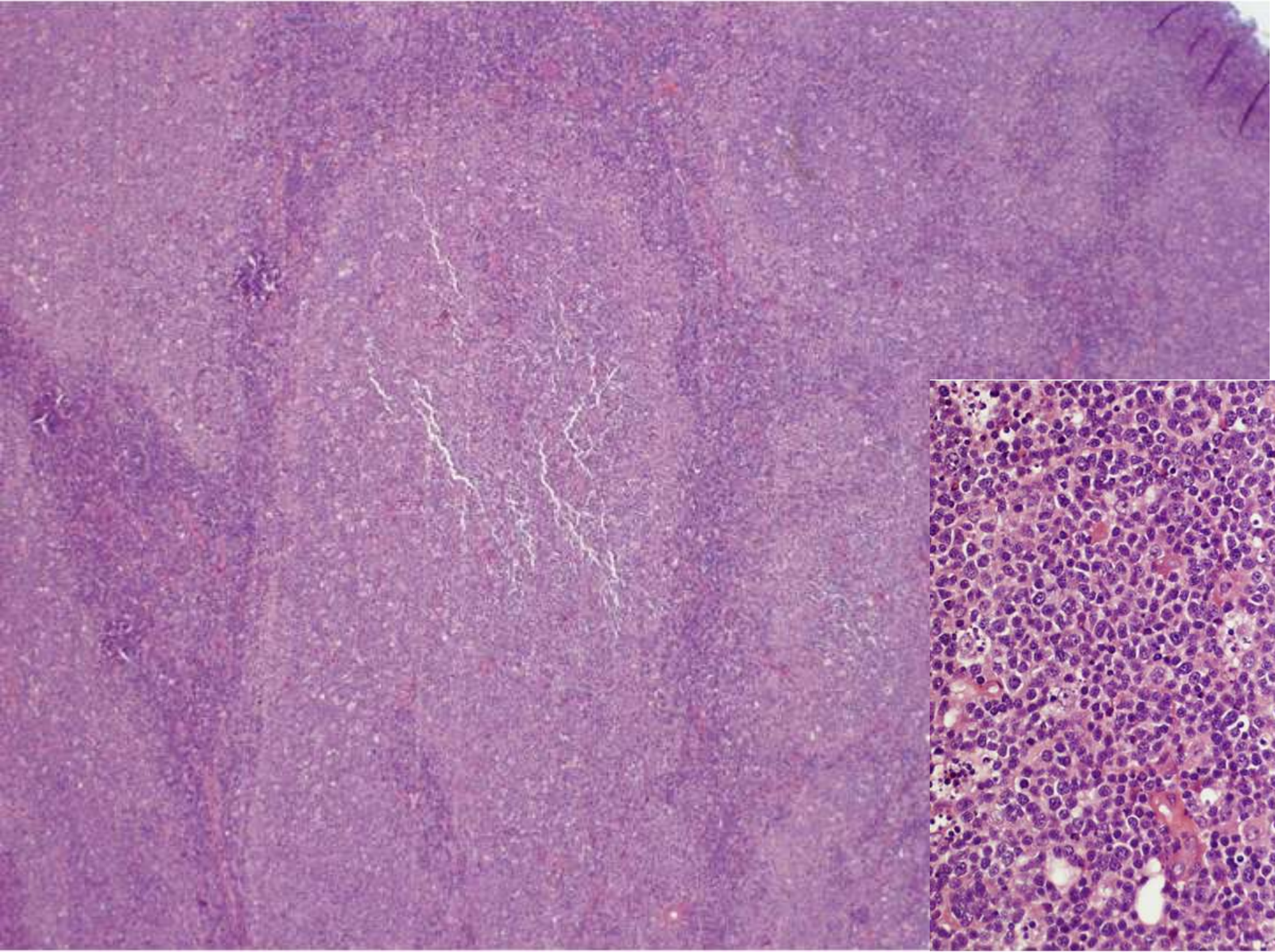


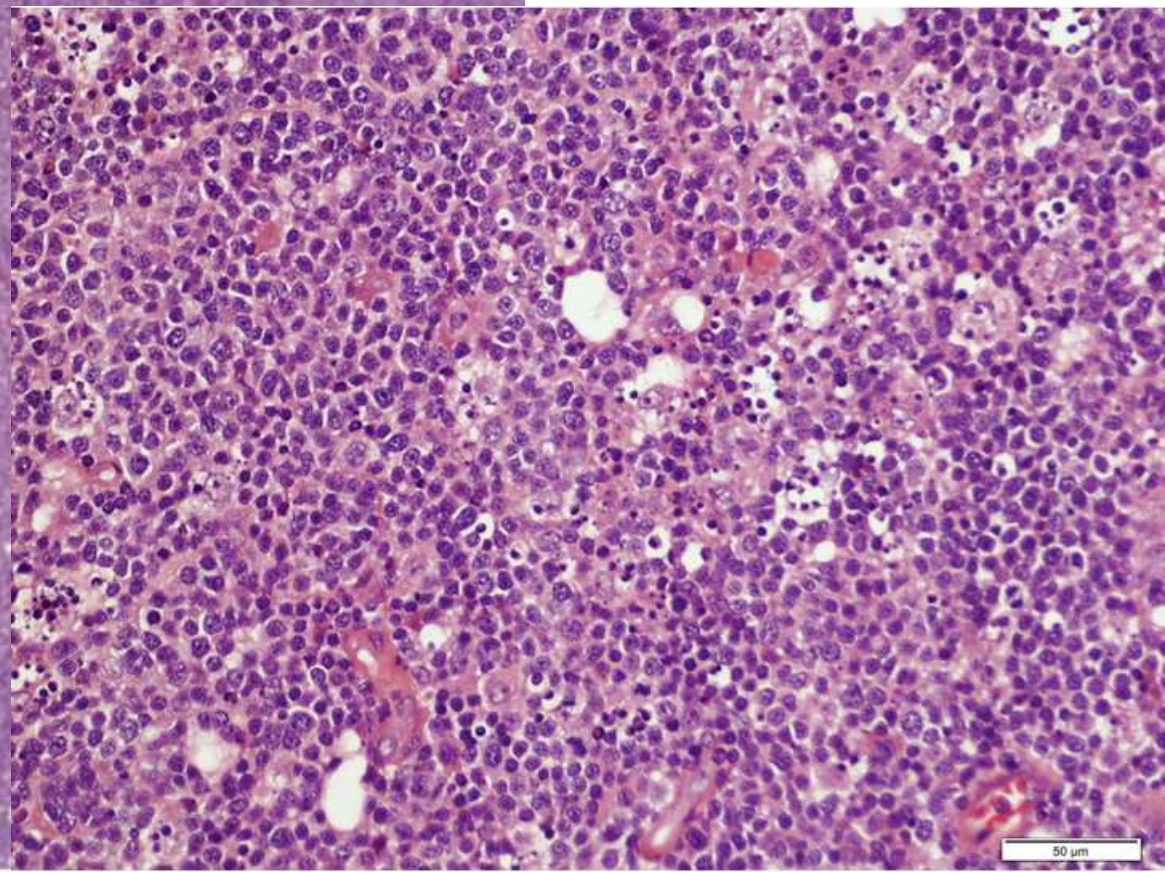
Follicular hyperplasia

Tingible body macrophages



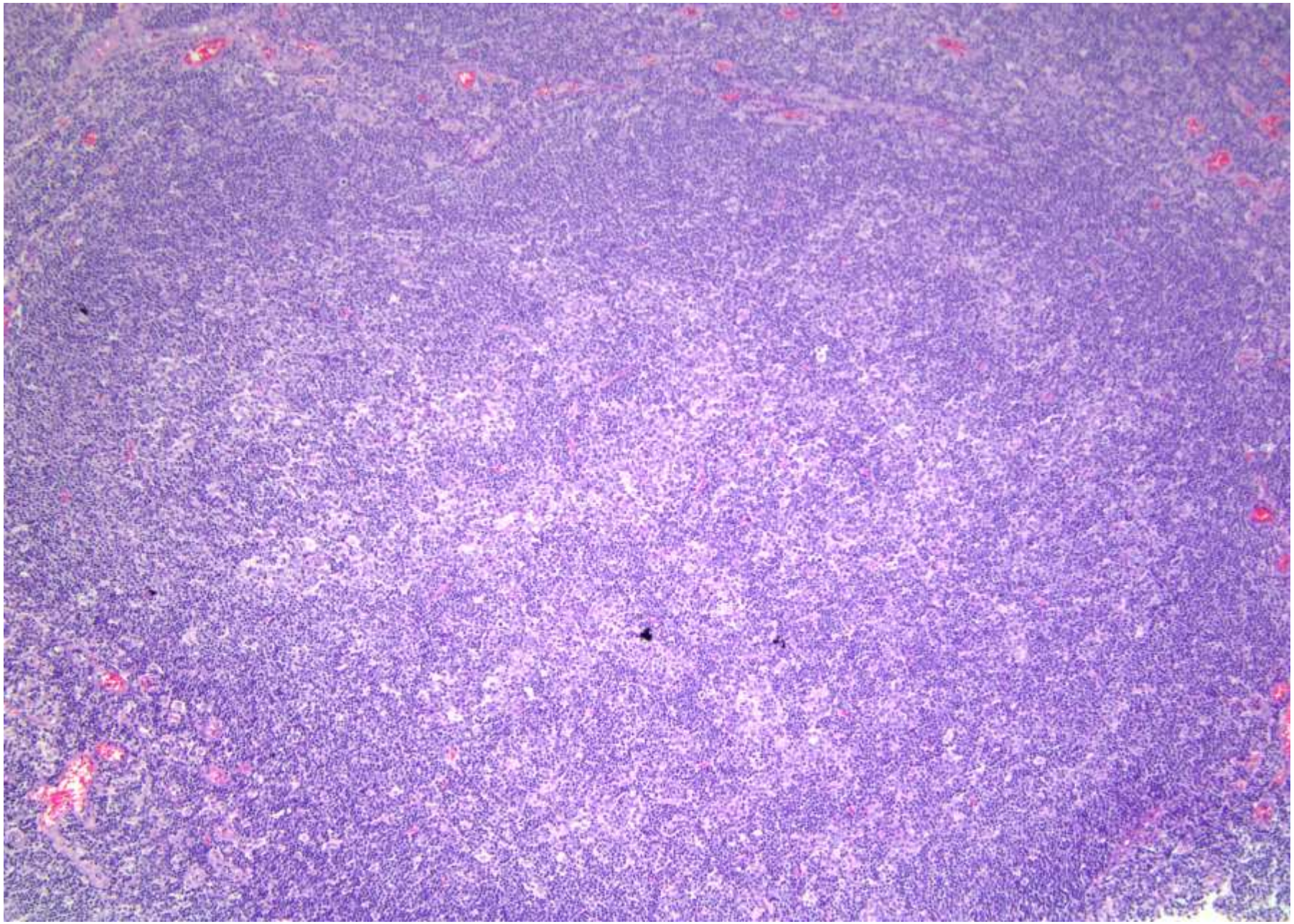
Pediatric follicular lymphoma

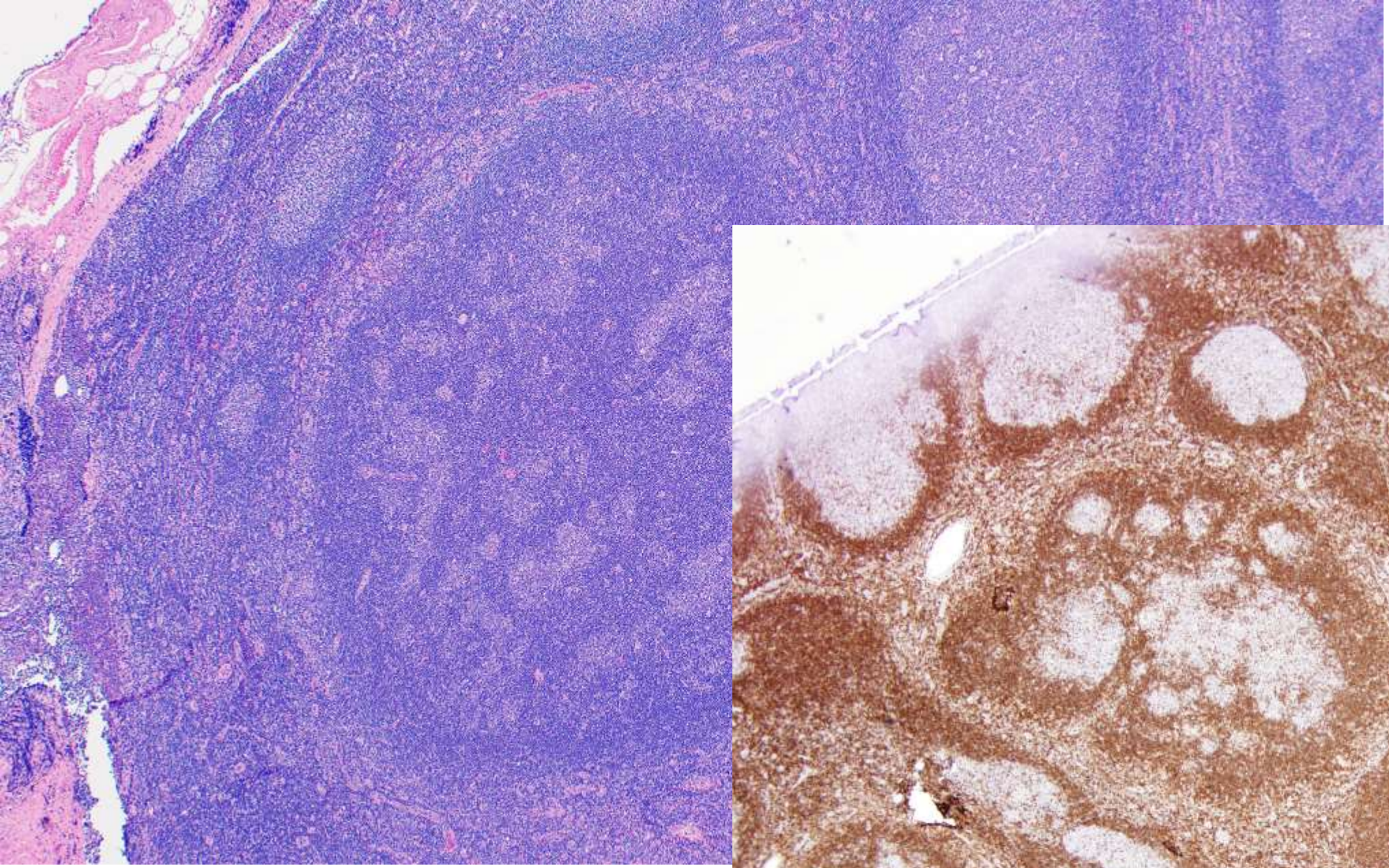




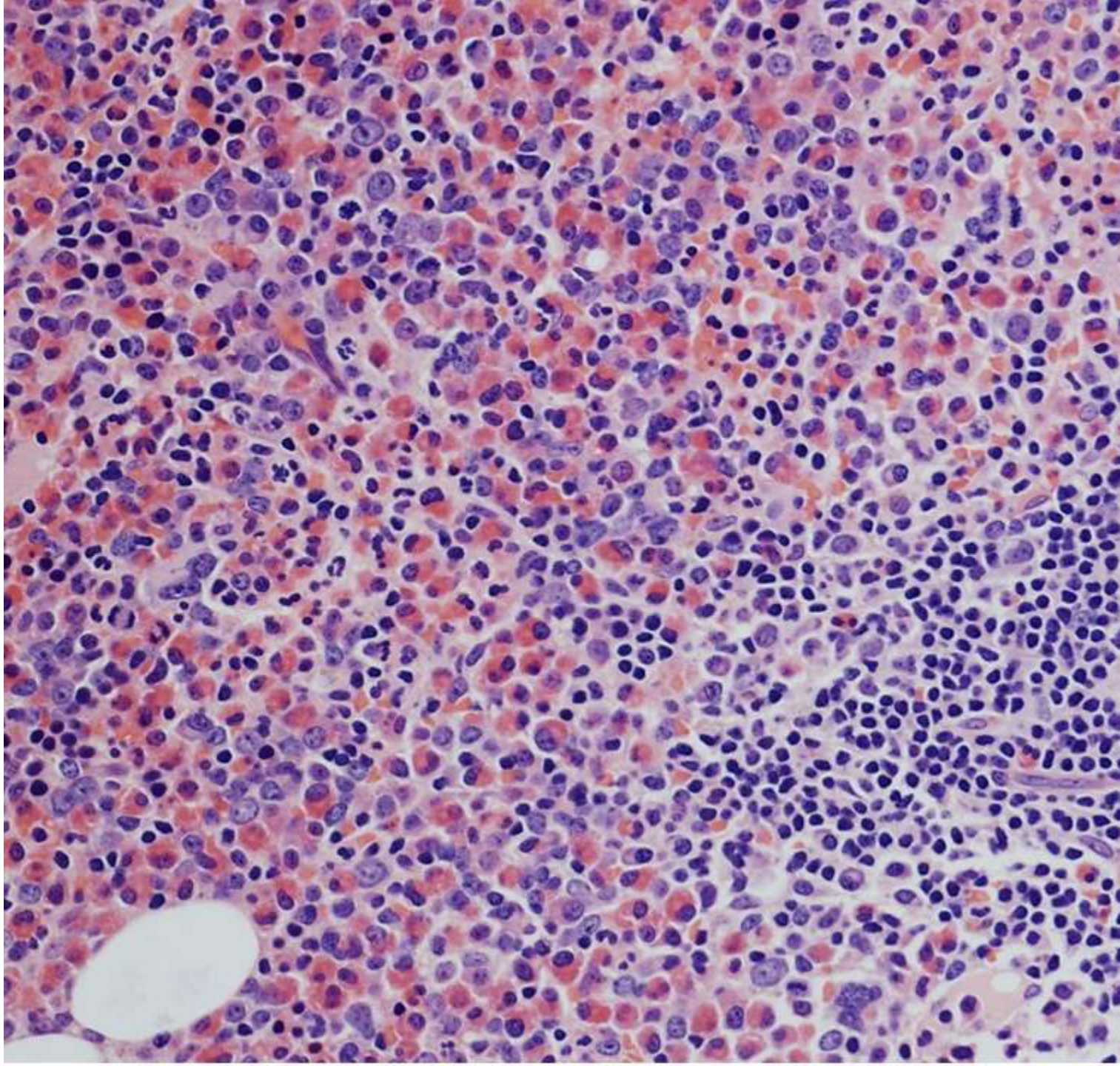
Progressive transformation of germinal centers

Inward expansion of mantle zone cells with partial disruption of the germinal center





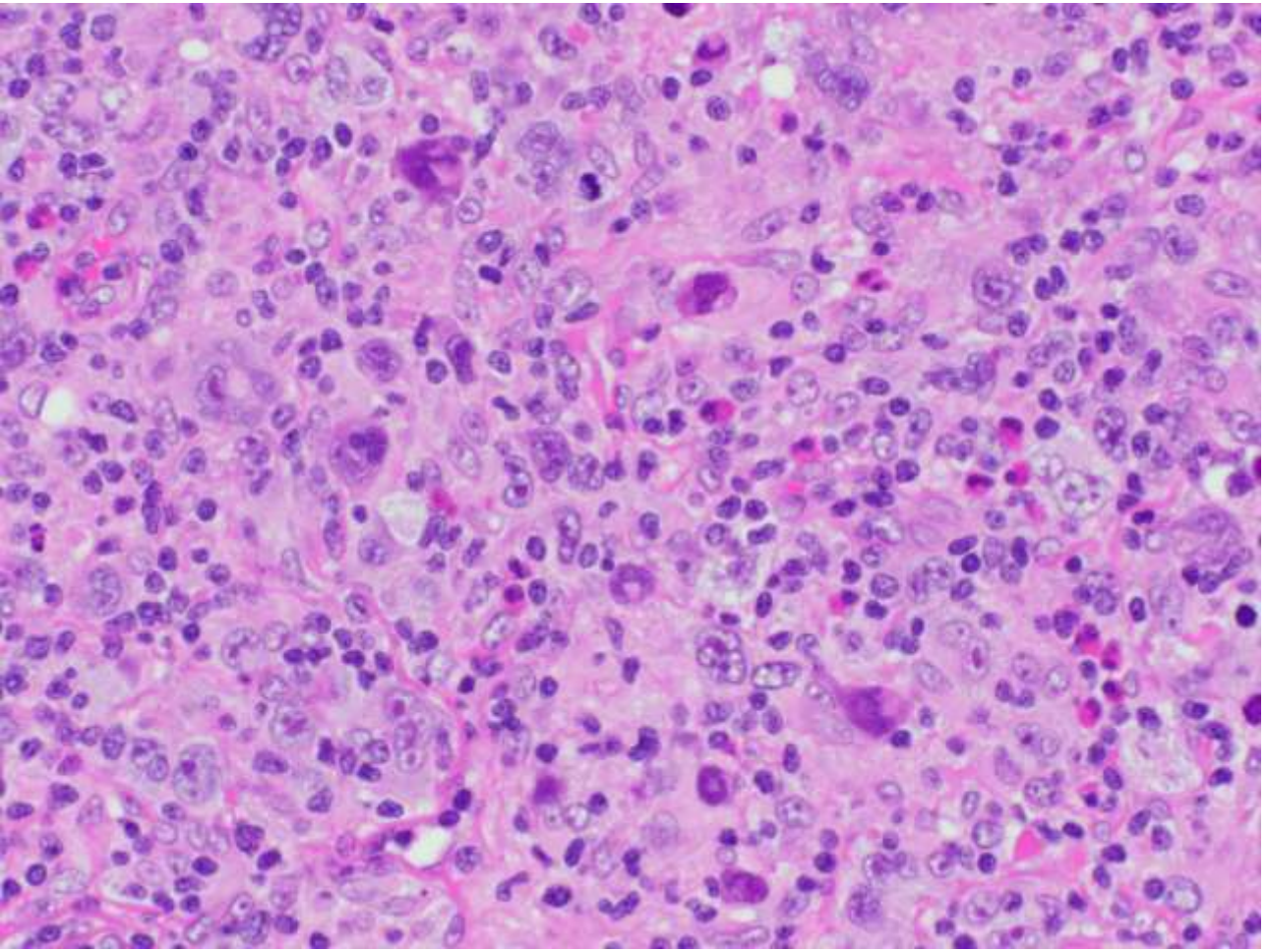
Clues from expanded or atypical cell populations



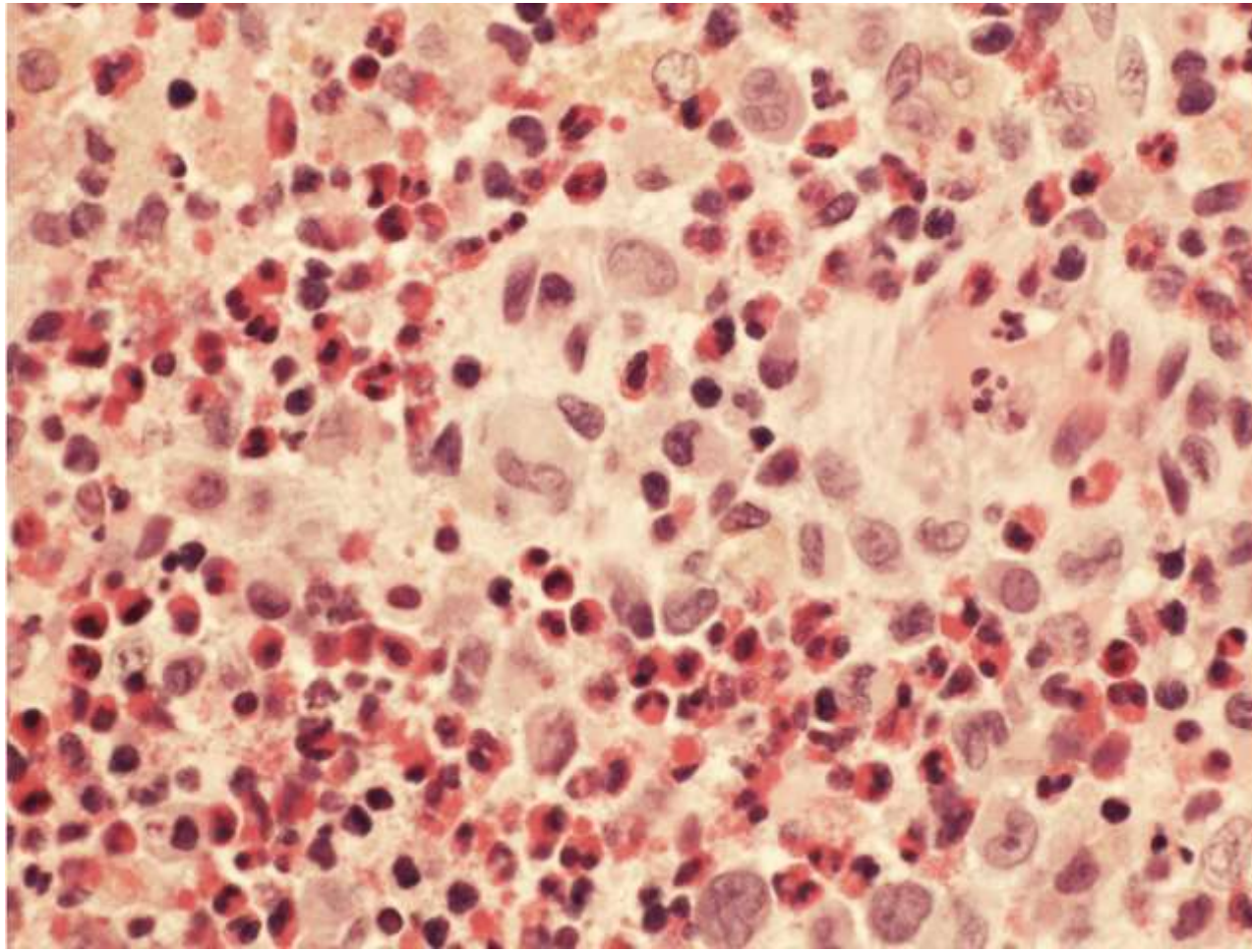
Increased eosinophils

Non-neoplastic conditions	Malignancy
• Kimura disease • Parasitic infections • Drug reactions • Certain vasculitides	• CHL • T-cell neoplasms • Systemic mastocytosis • Certain myeloid malignancies • Langerhans cell histiocytosis

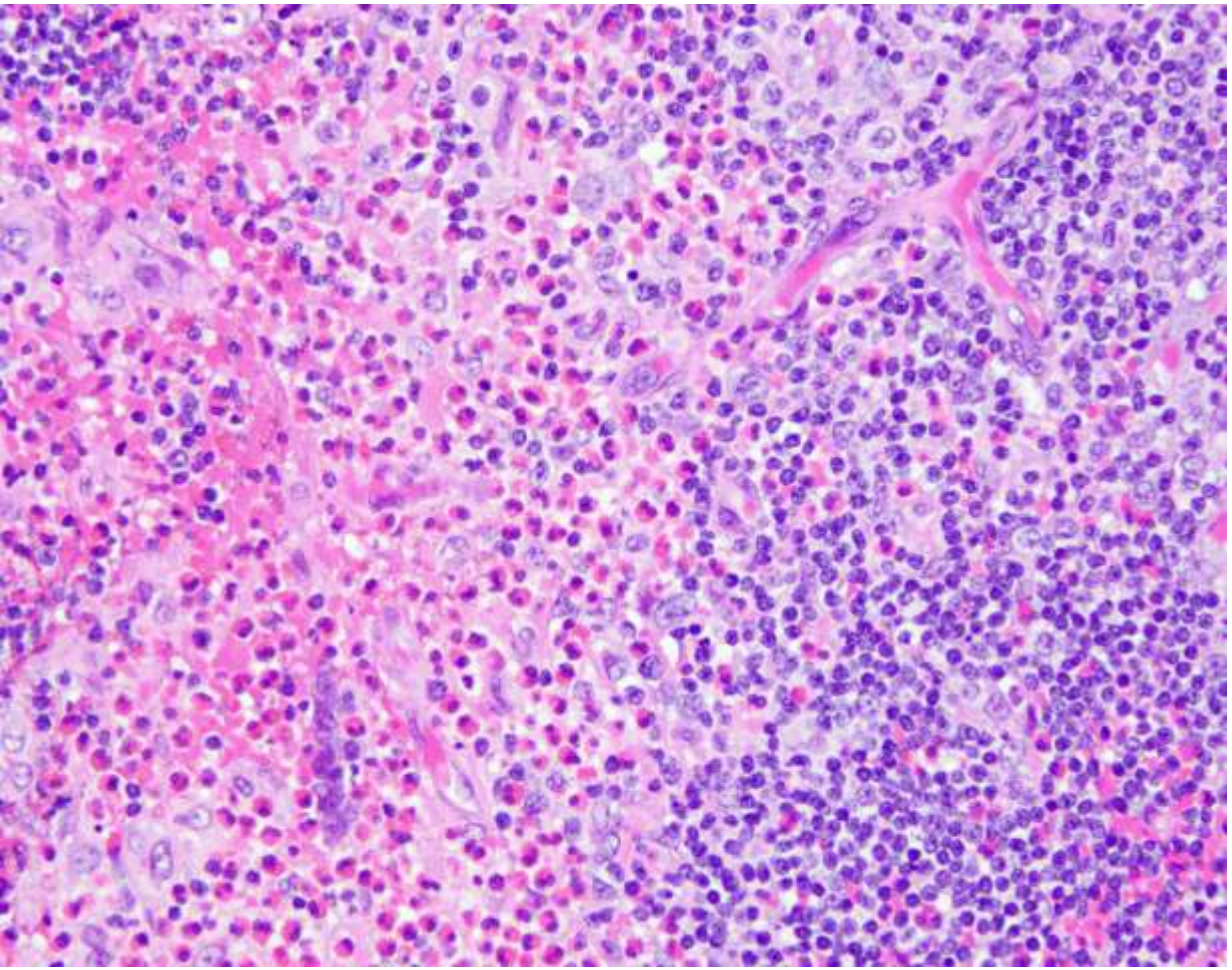
CHL

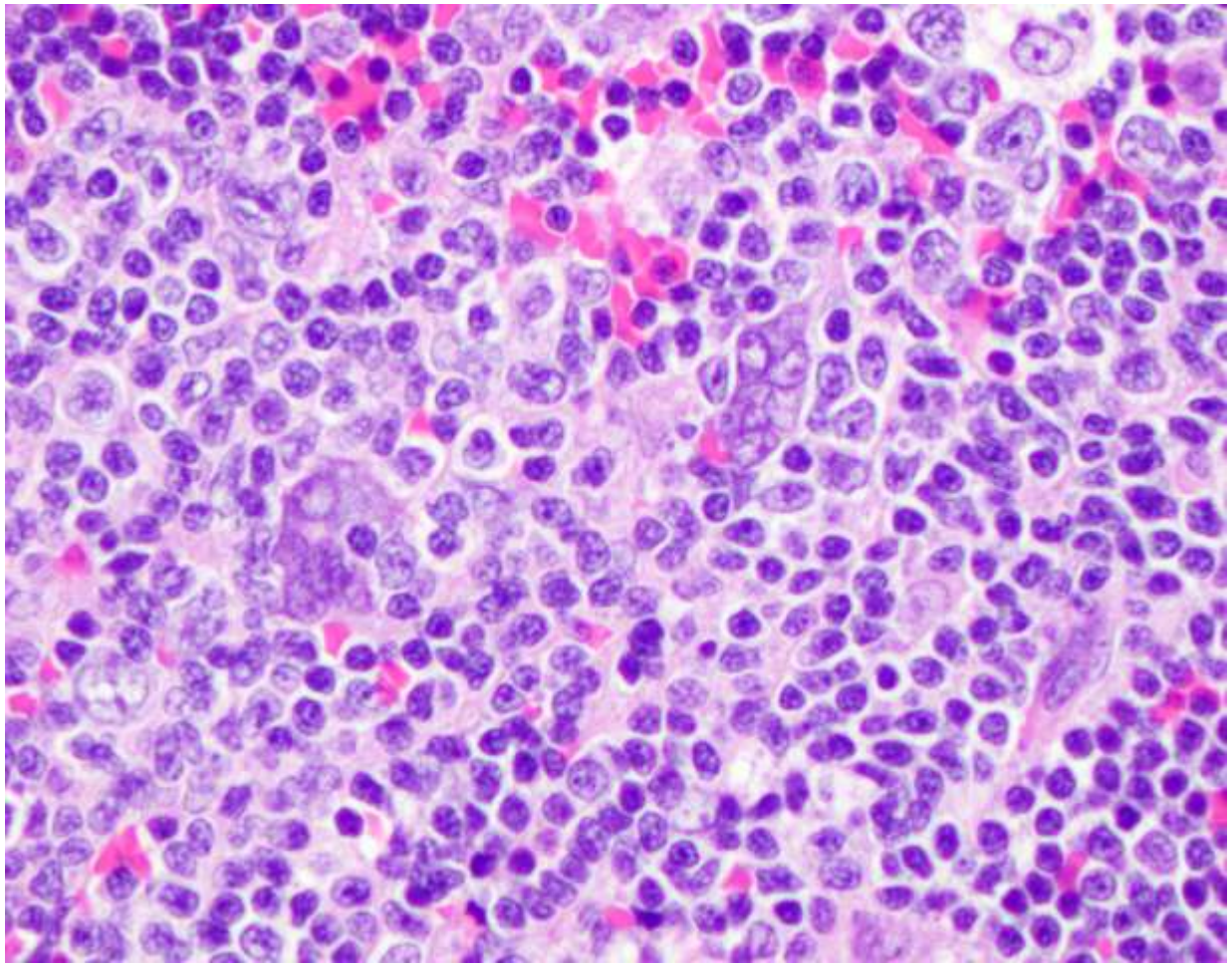


LCH



Kimura disease





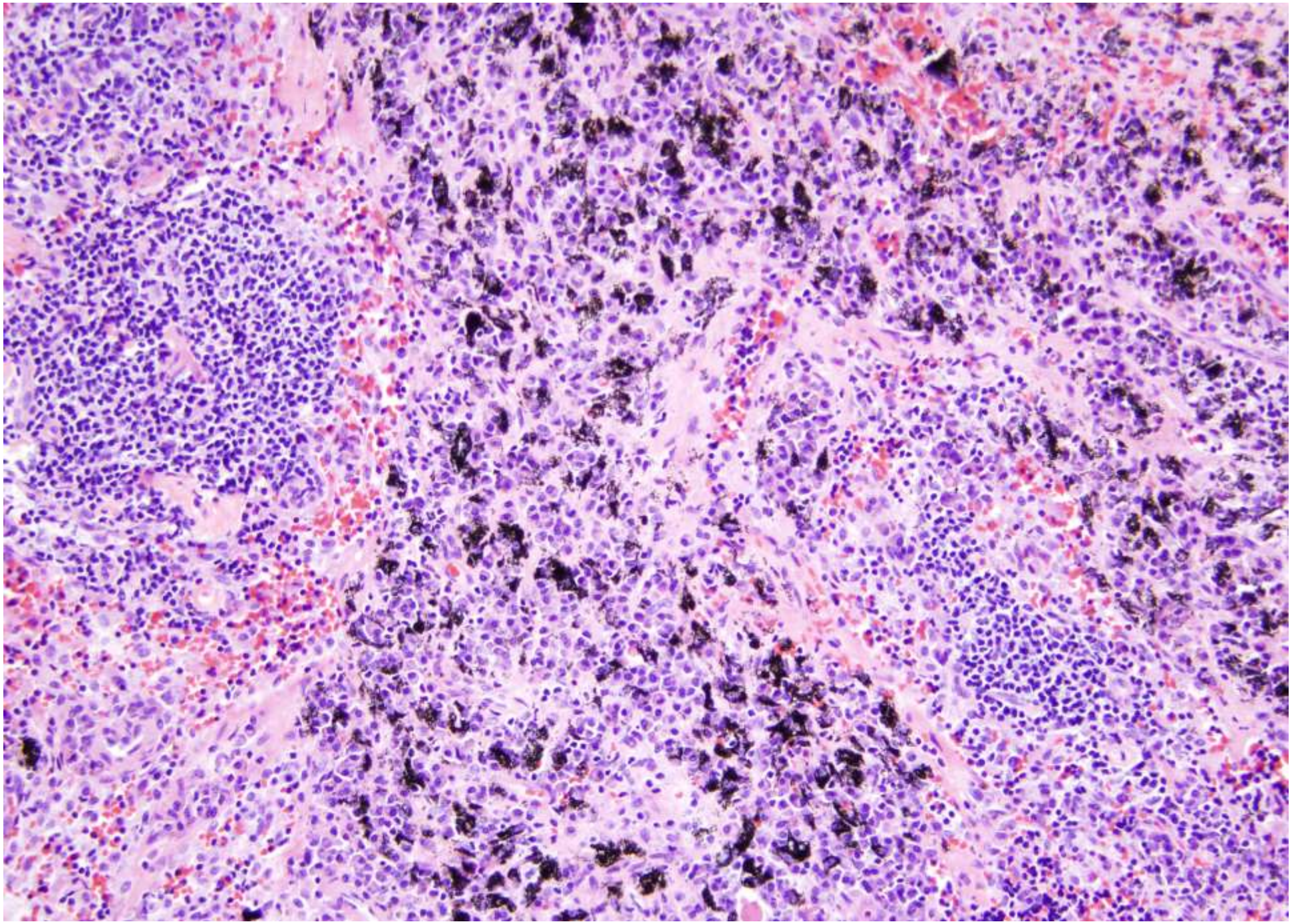
polykaryote

Images courtesy of Dr. Miguel Cantu, Weill Cornell Medicine

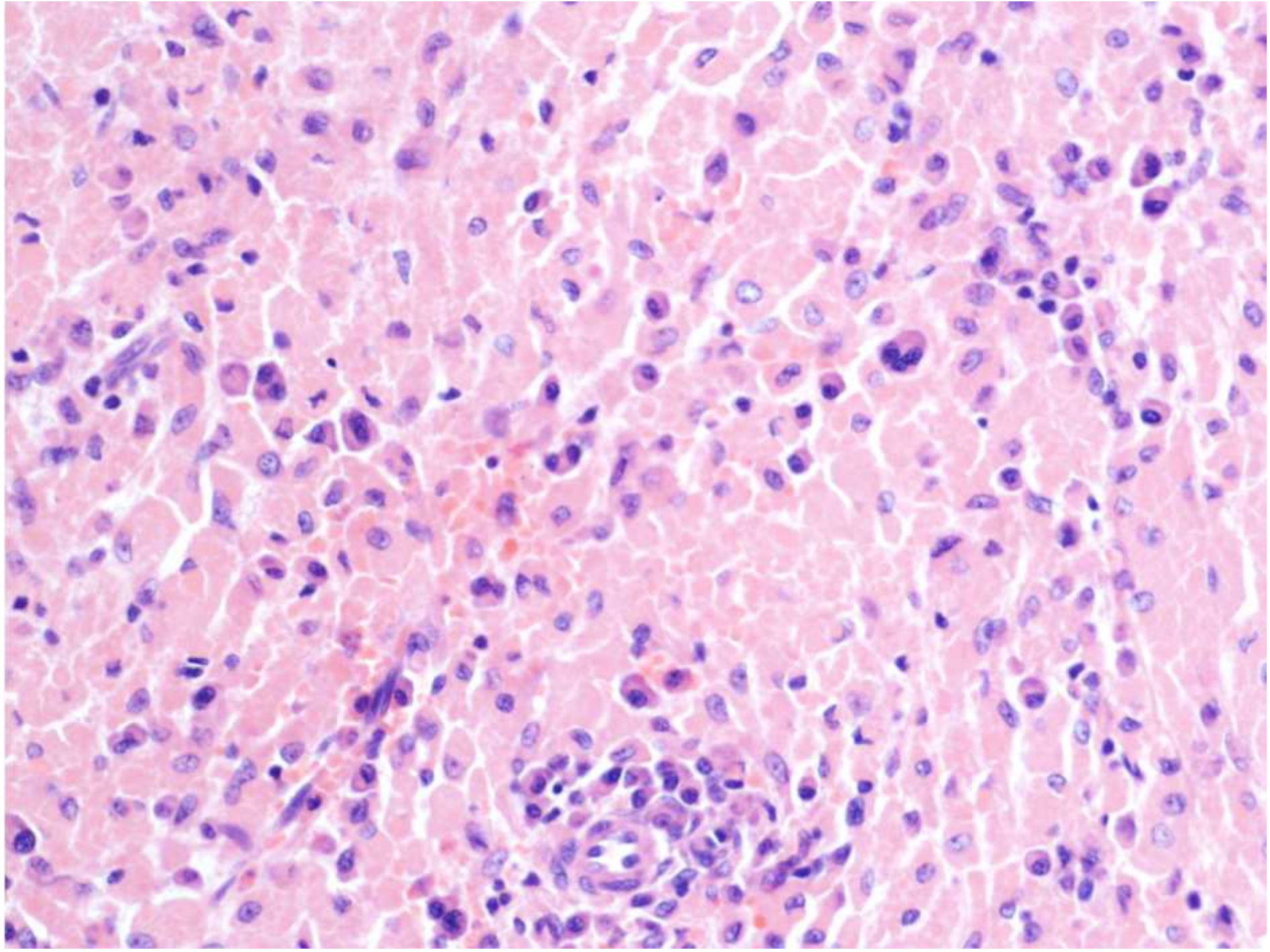
Clues from abnormal histiocytic populations

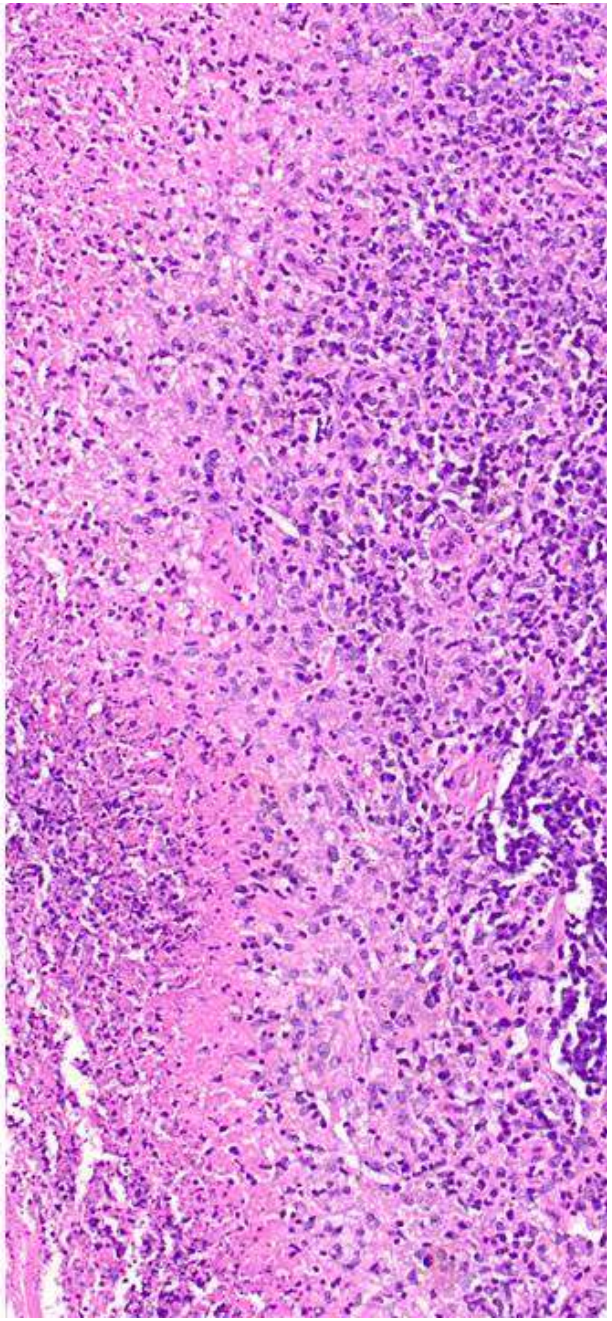
Histiocytes with unusual materials	• Accumulation of amyloid or immunoglobulin from a plasma cell disorder • Extravasated mucin from a nearby carcinoma • Debris from metal prostheses or synthetic materials • Foreign materials (e.g. injected, tattoo ink)
Epithelioid granulomas: enlarged, plump histiocytes with bland nuclei	• Infections-e.g. toxo • Systemic disorders (e.g. sarcoidosis) • Lymphomas and other neoplasms

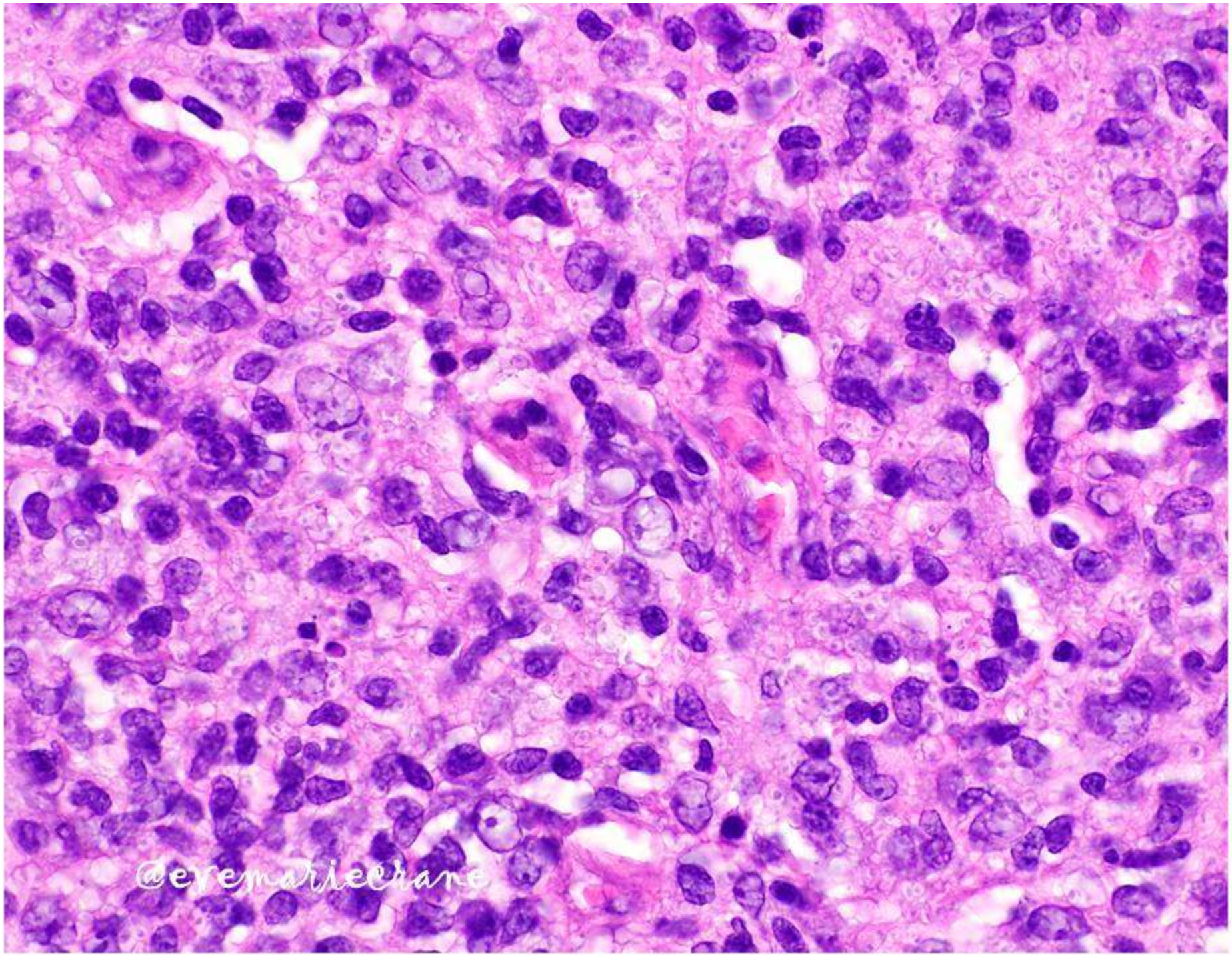
Anthracotic pigment



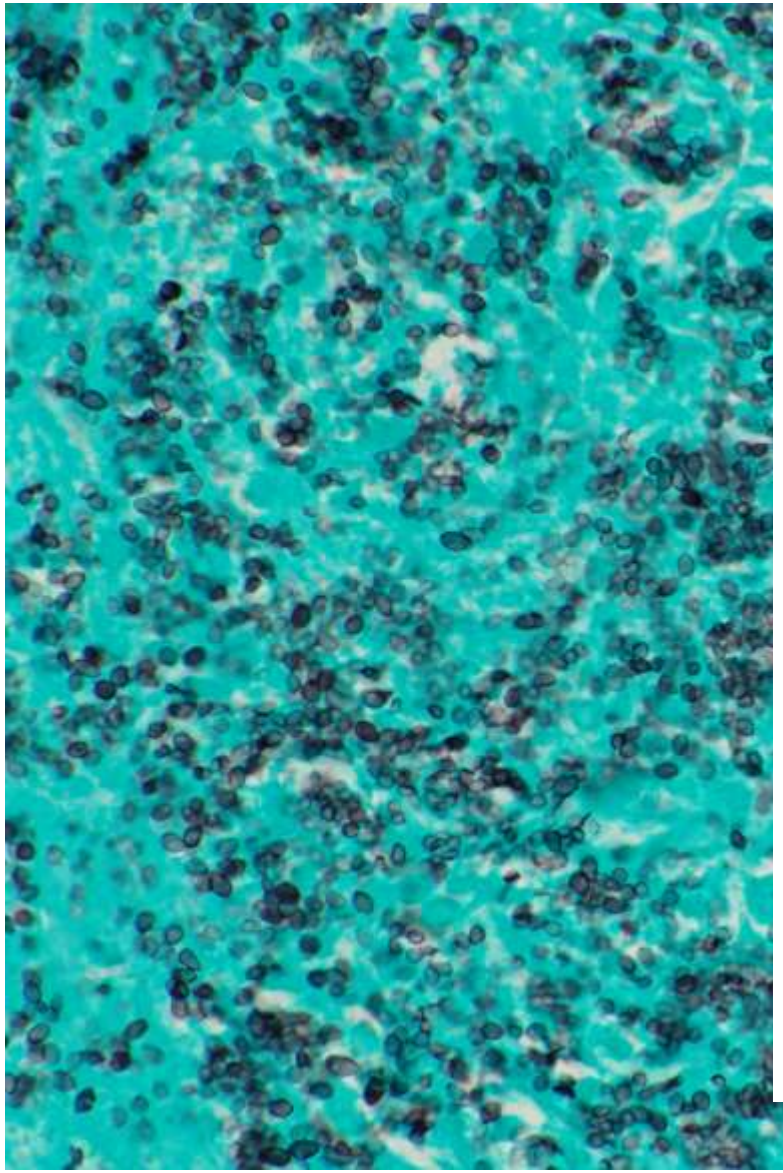
Crystal storing histiocytosis

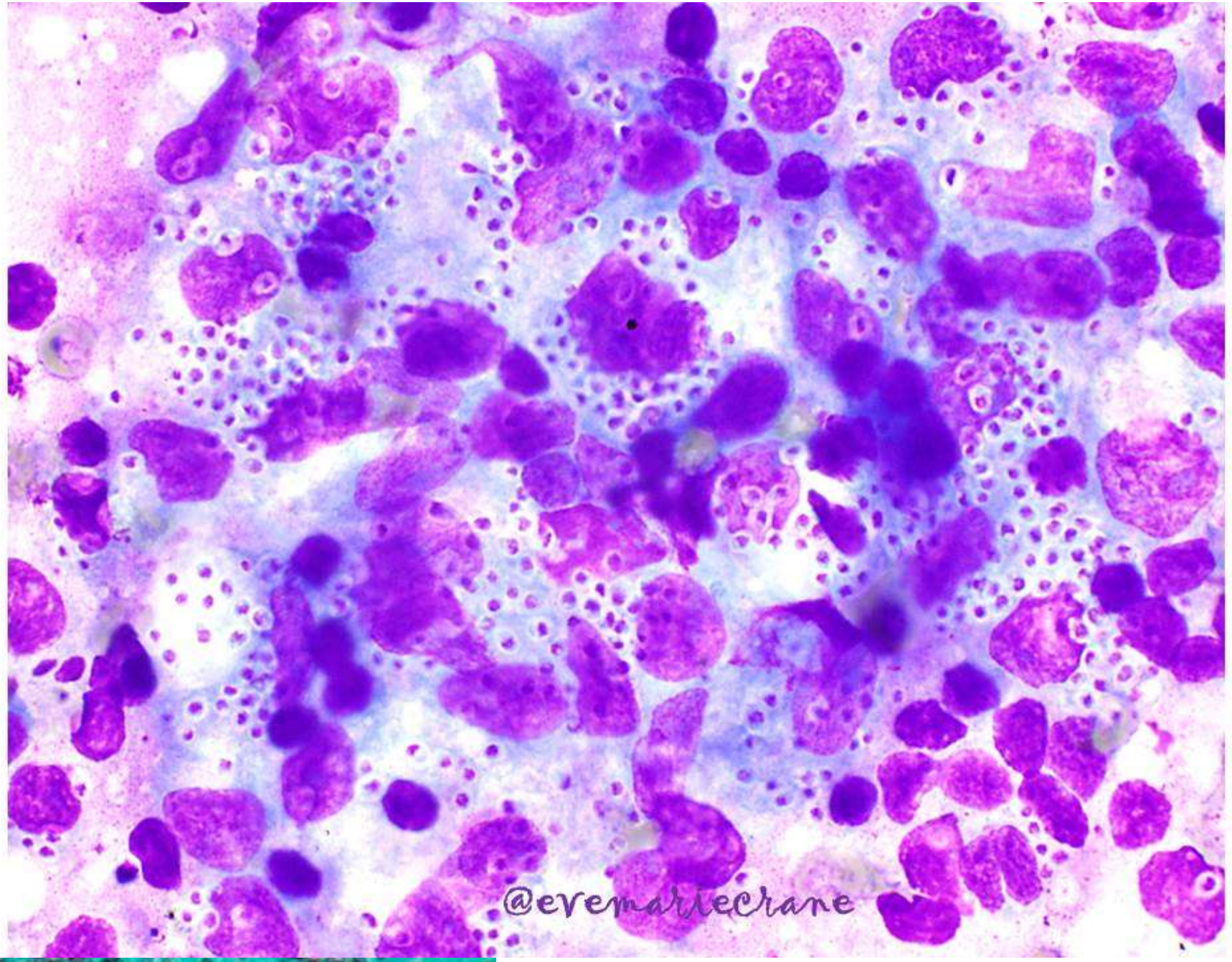




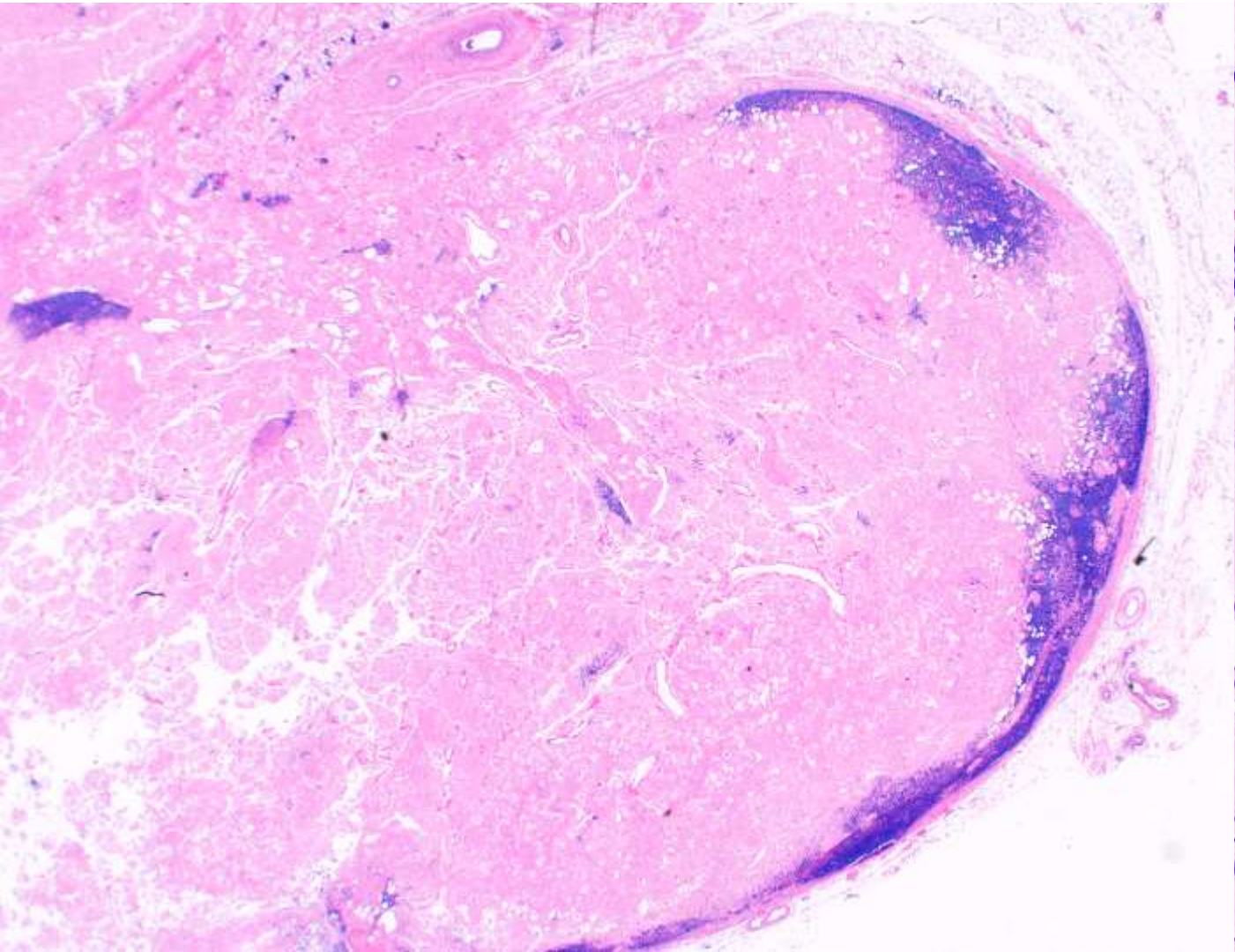

@eremarieclare

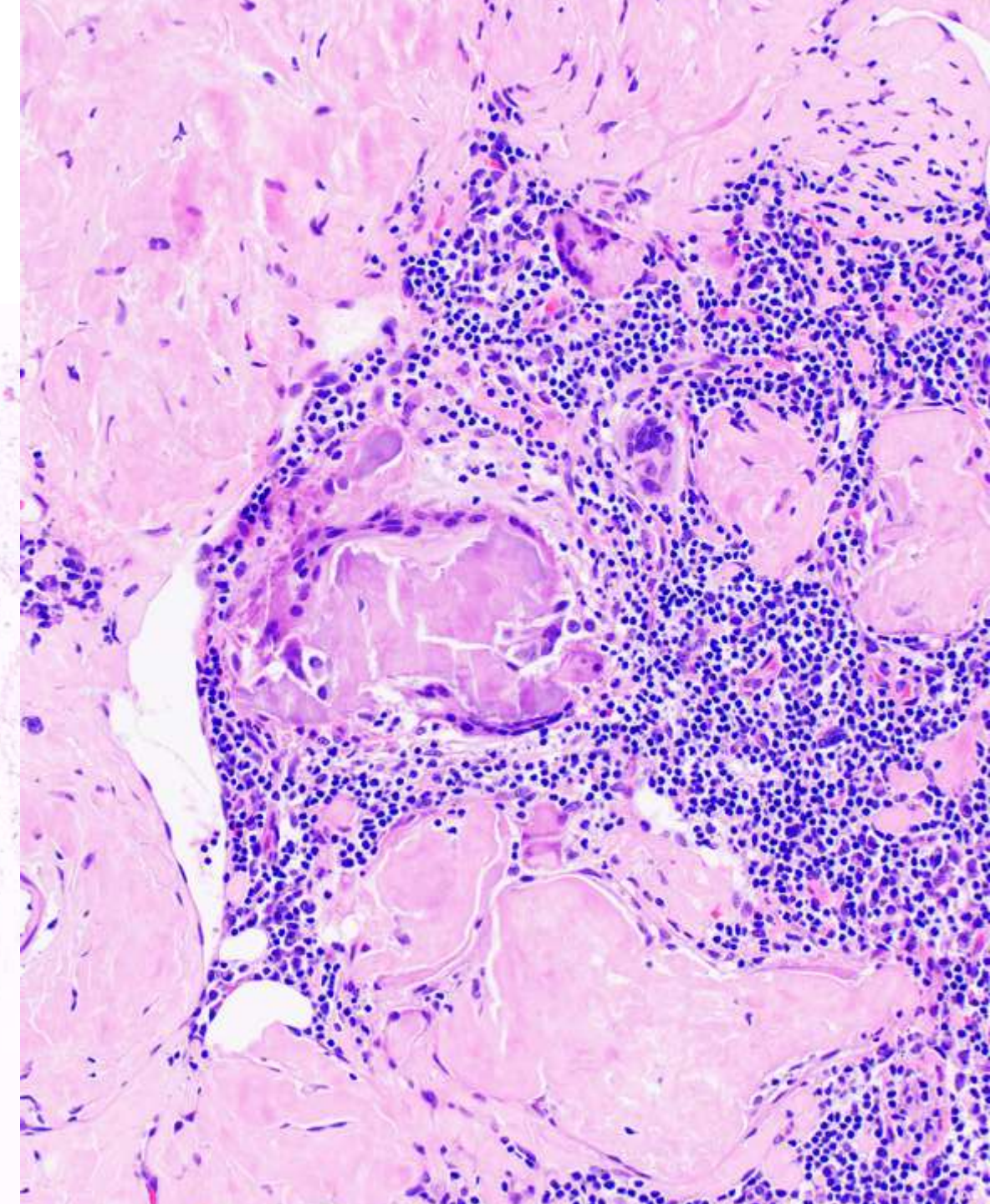
Histoplasmosis

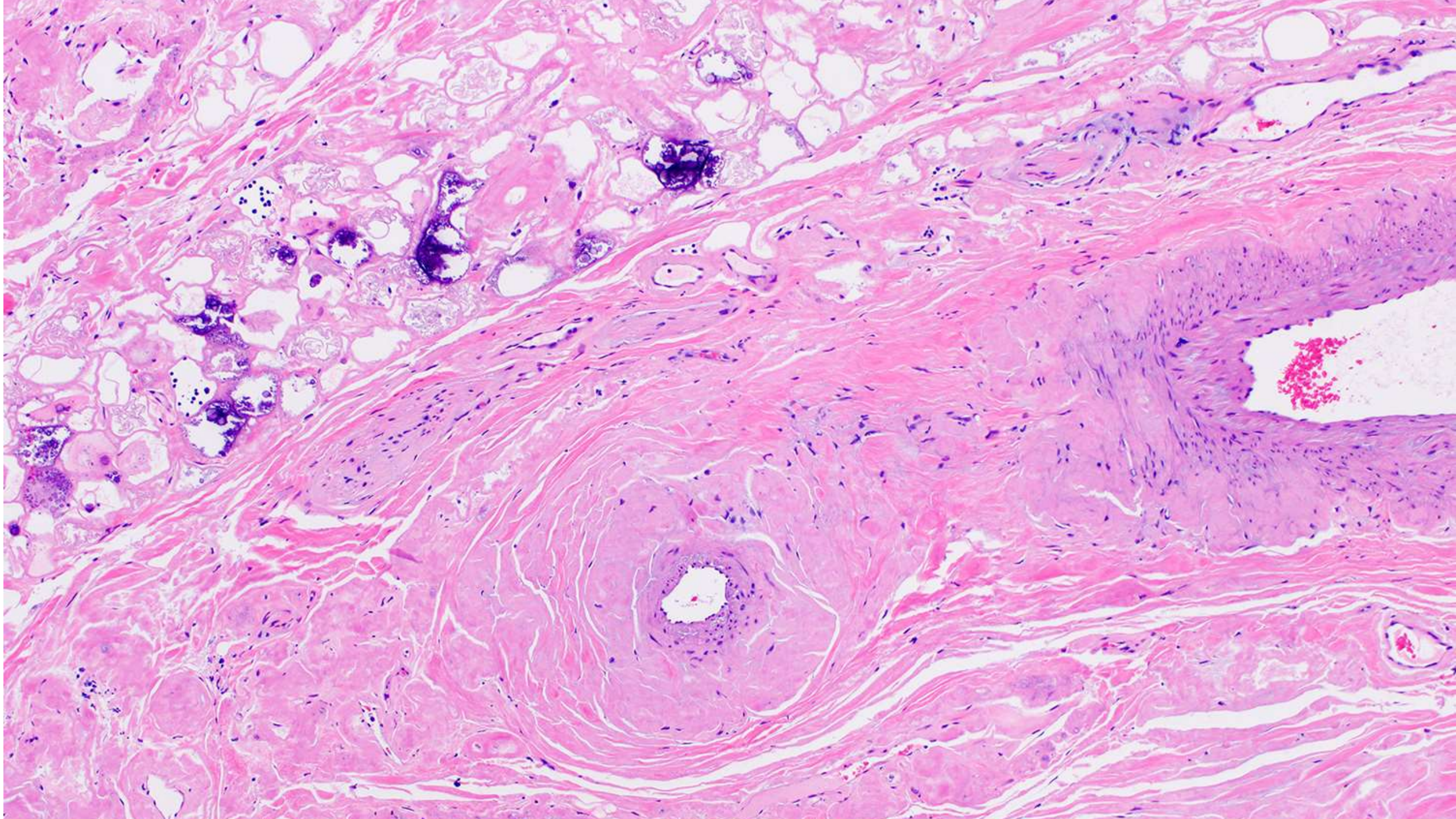


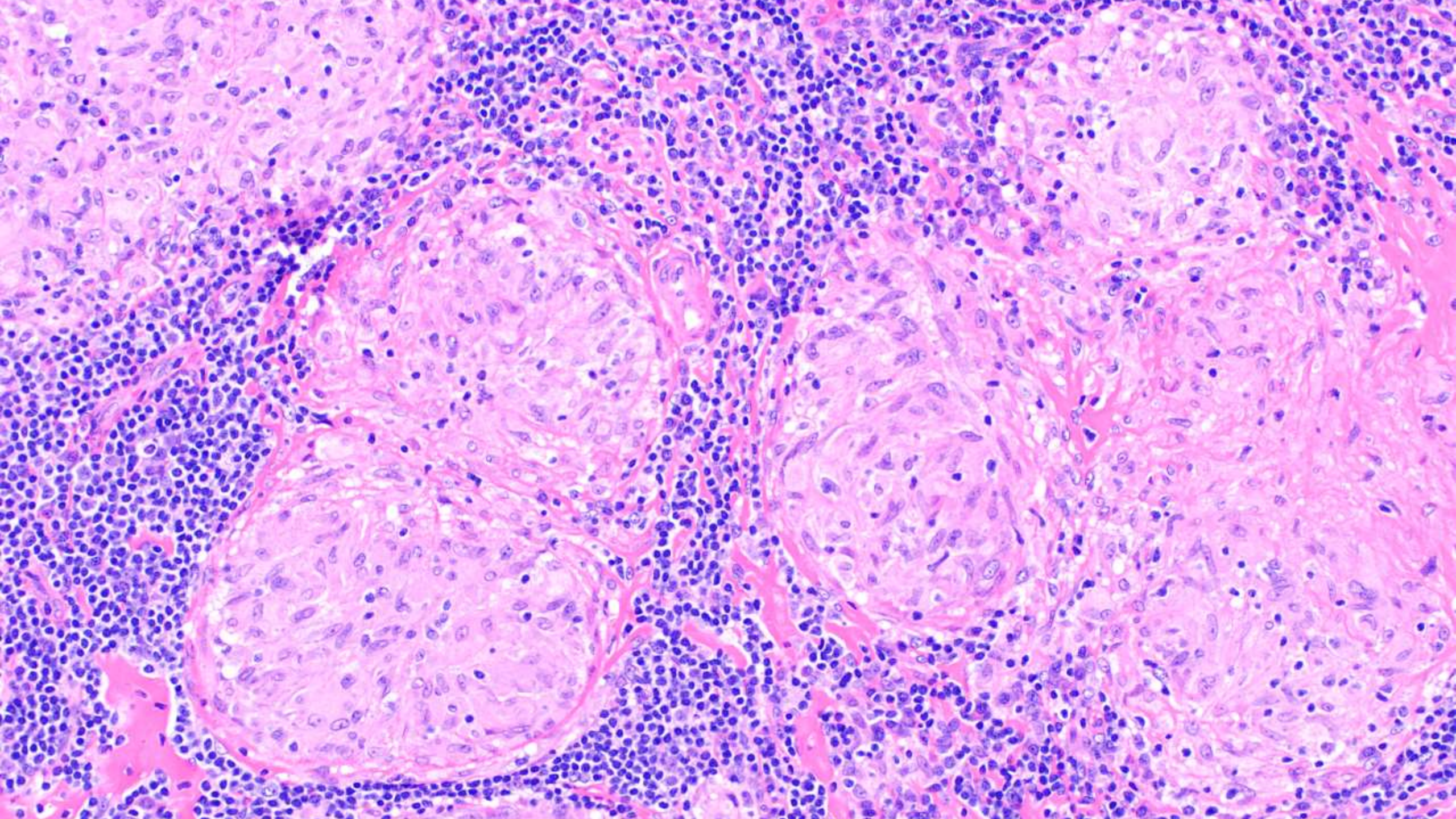


Amyloid deposition with focal giant cell reaction









Pattern-based approach

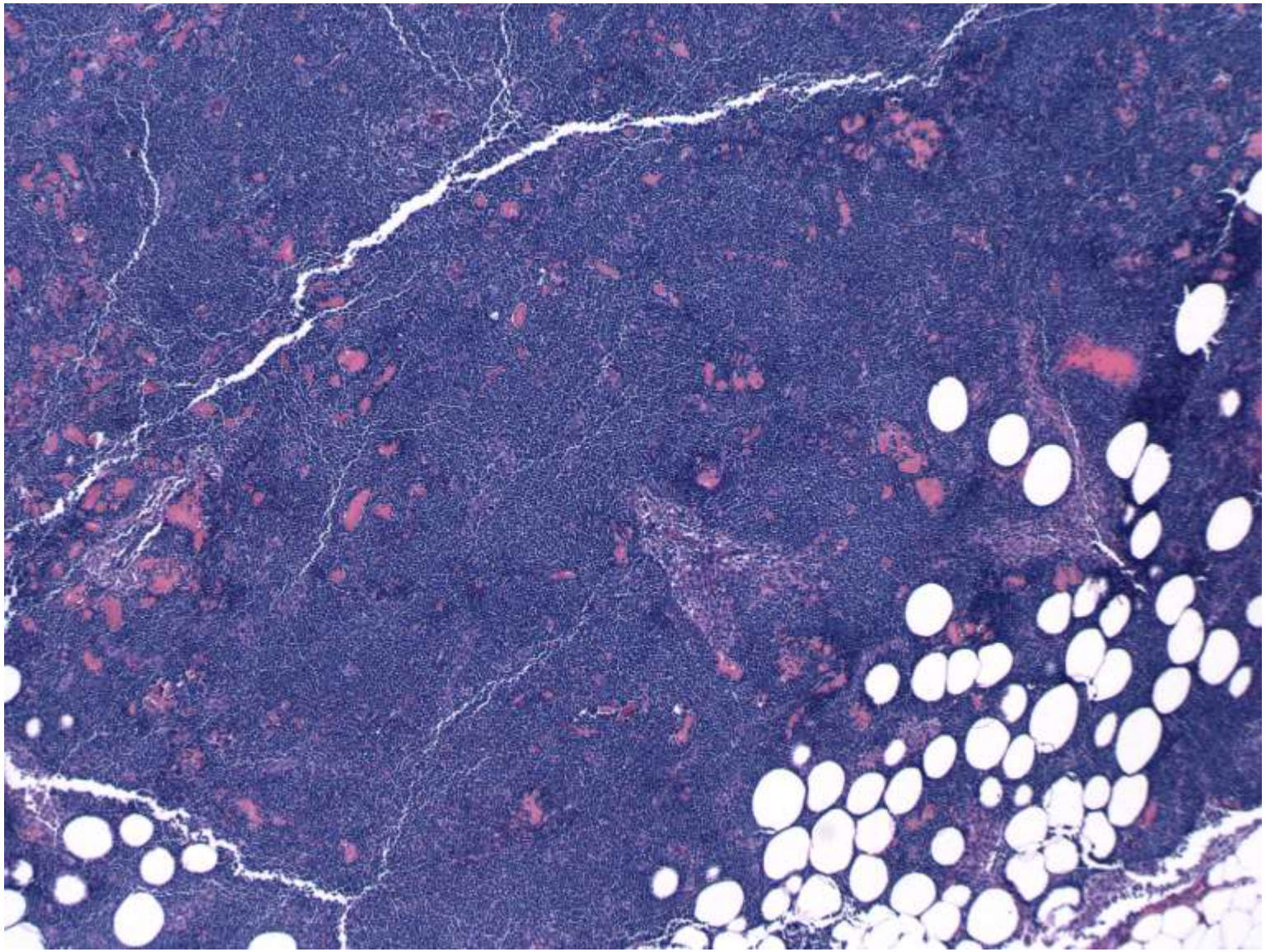
Morphologic Patterns	Examples
1. Small lymphocytes	CLL, MZL, MCL
2. Follicles	Follicular lymphoma, benign lymphoid hyperplasia
3. Follicles and some diffuse areas	Follicular lymphoma, MZL, AITL, reactive processes
4. Mixed small and large cells, no discernable pattern	T-cell lymphoma, T-cell/histiocyte-rich large B cell lymphoma, EBV+ lymphoid proliferations
5. Mixed small and large cells with localized large cells	Partial large cell transformation of low grade lymphoma

Even more patterns…

Morphologic Patterns	Examples
6. Sinus pattern	Metastatic lesions, sinus histiocytosis, ALCL
7. Polymorphous with scattered large cells	Hodgkin, EBV+ lymphoproliferative disease
8. Clusters/aggregates of large cells	High grade follicular lymphoma
9. Diffuse sheets of large cells	Diffuse large B-cell lymphoma
10. Increased stromal elements	AITL, Kaposi sarcoma
11. Interfollicular pale cells	MZL, T-cell lymphomas

Approach to staining: Simplify to 4 categories

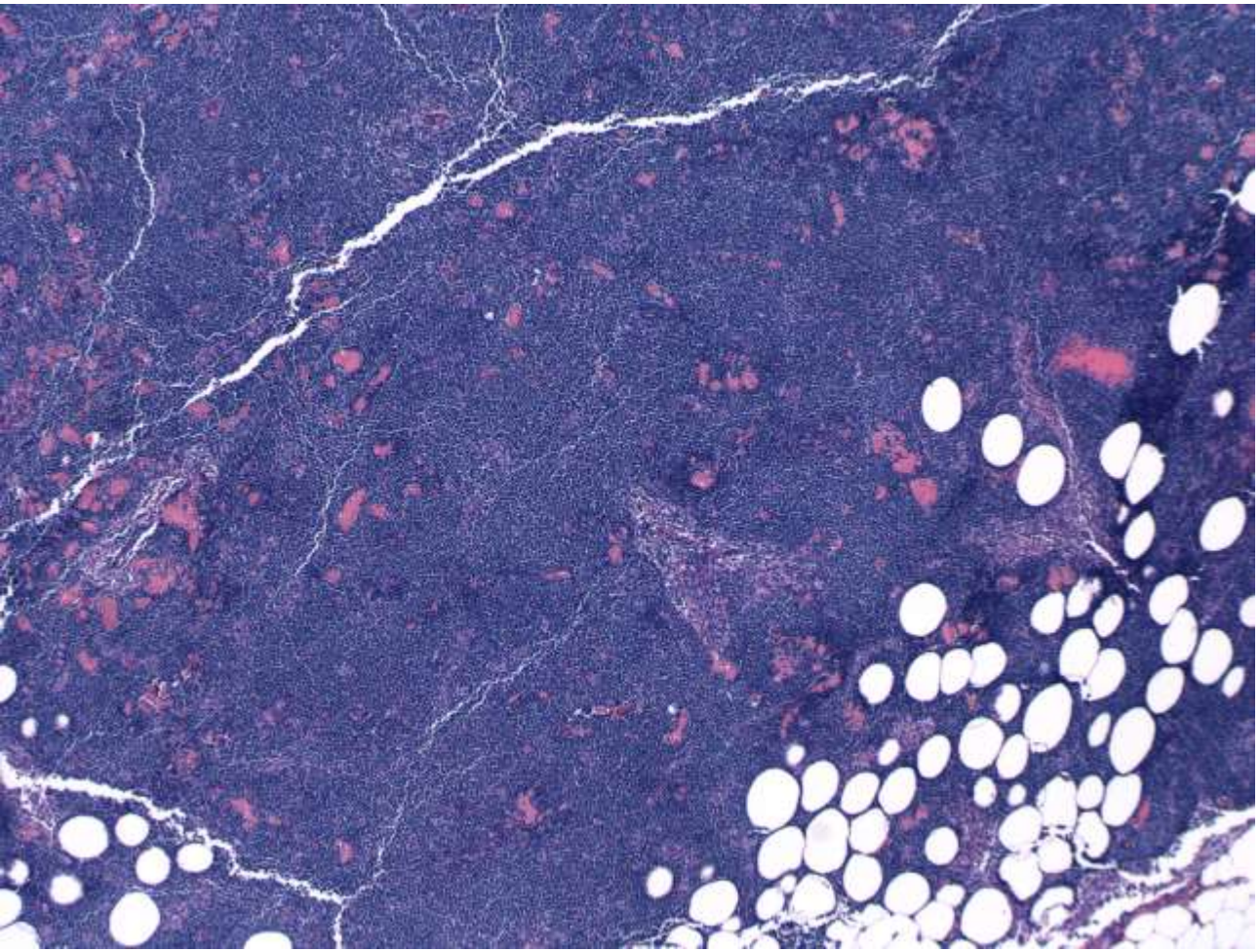
- Small B-cell
- Hodgkin
- Large cell lymphoma
- T-cell

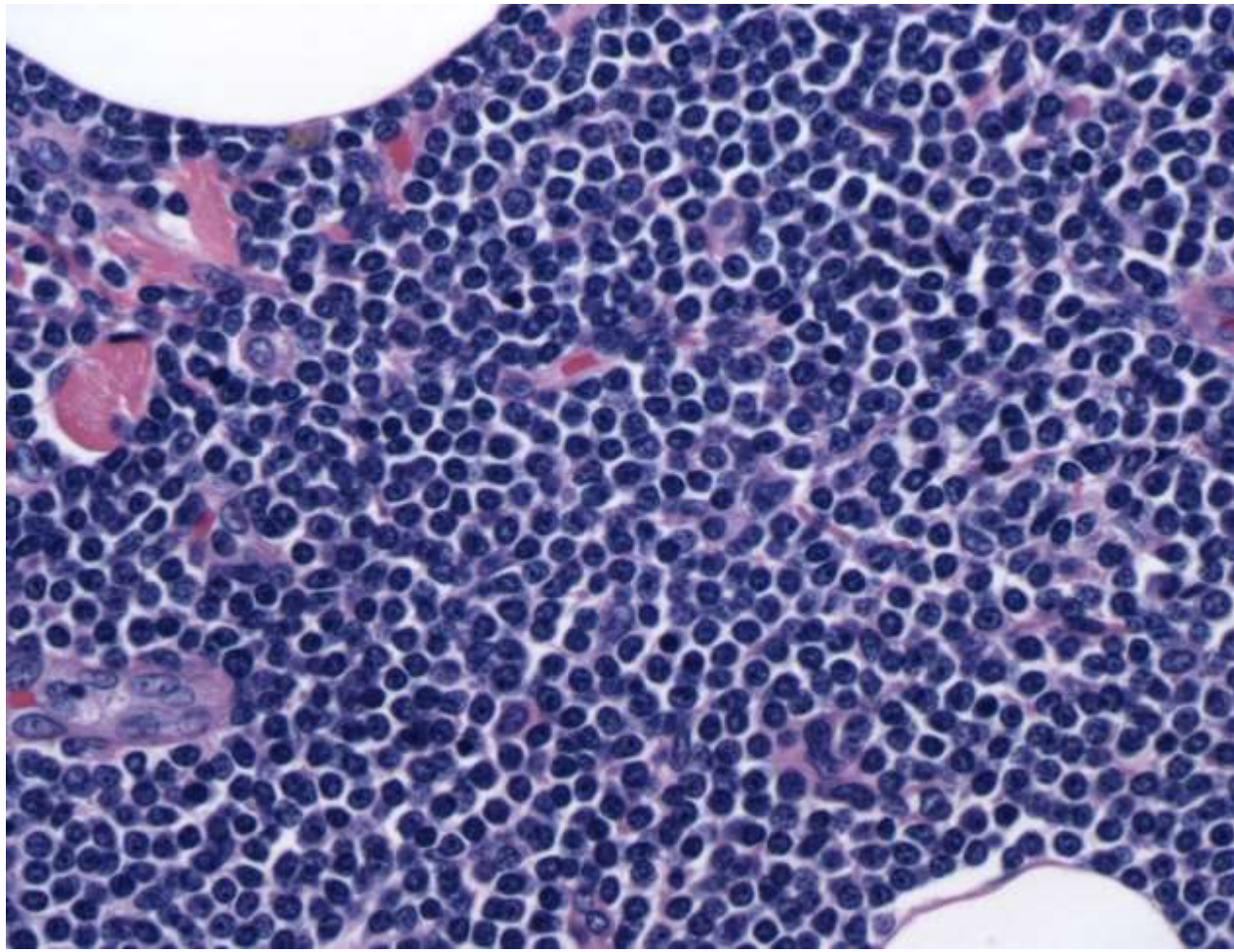


Small B-cell work up

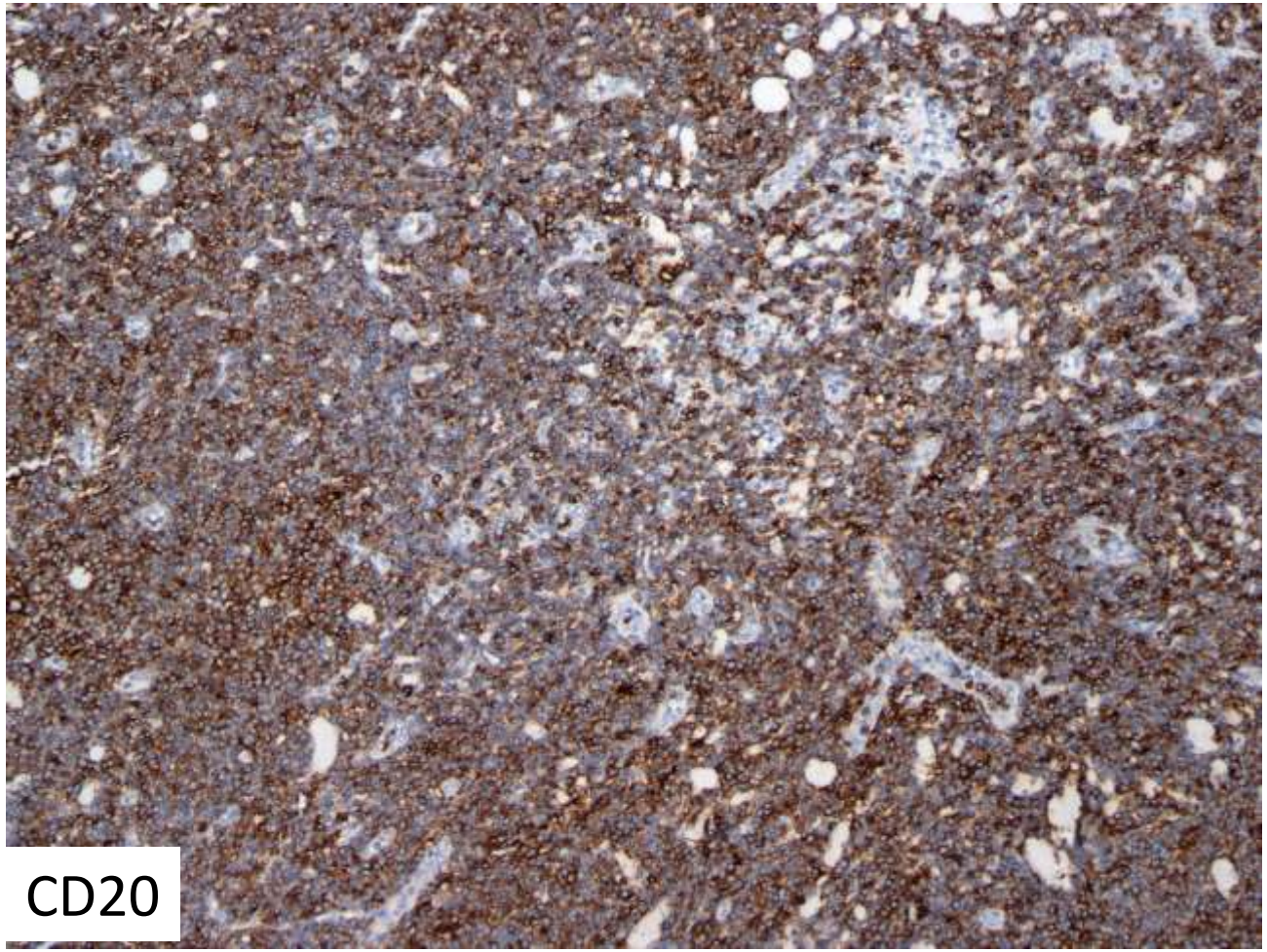
• Exclude lymphoma in benign appearing tissue • Follicles, normal or atypical • Primary follicles/ uniform small blue nodules • Diffuse proliferations of predominantly small dark blue lymphocytes	• CD3 • CD20 • CD5 • Cyclin D1, Sox11 • BCL2 • BCL6 • Ki67 • LEF1	• Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) • Follicular lymphoma (FL) • Mantle cell lymphoma (MCL) • Marginal zone lymphoma (MZL) • Lymphoplasmacytic lymphoma (LPL)

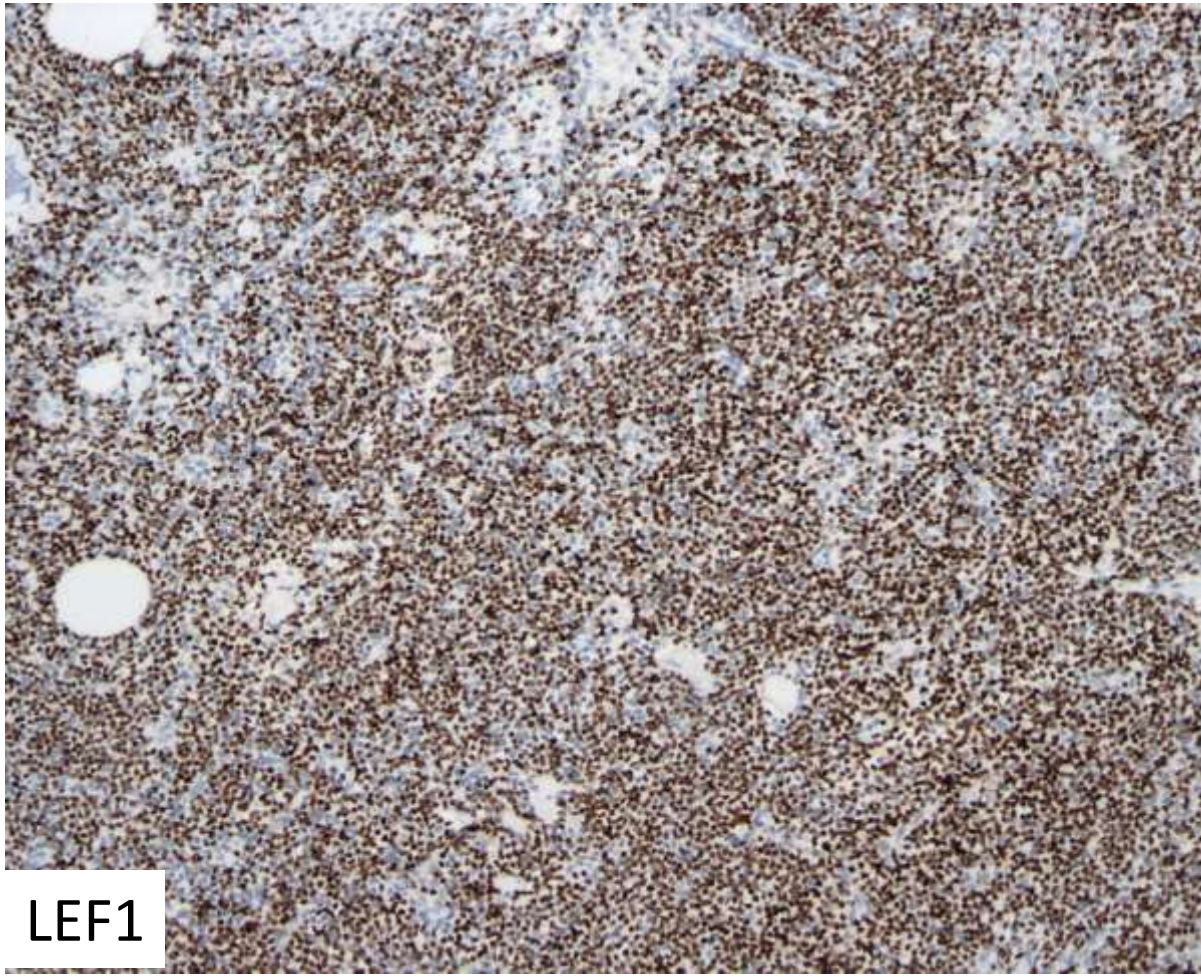
Predominantly small lymphocytes: small lymphocytic lymphoma



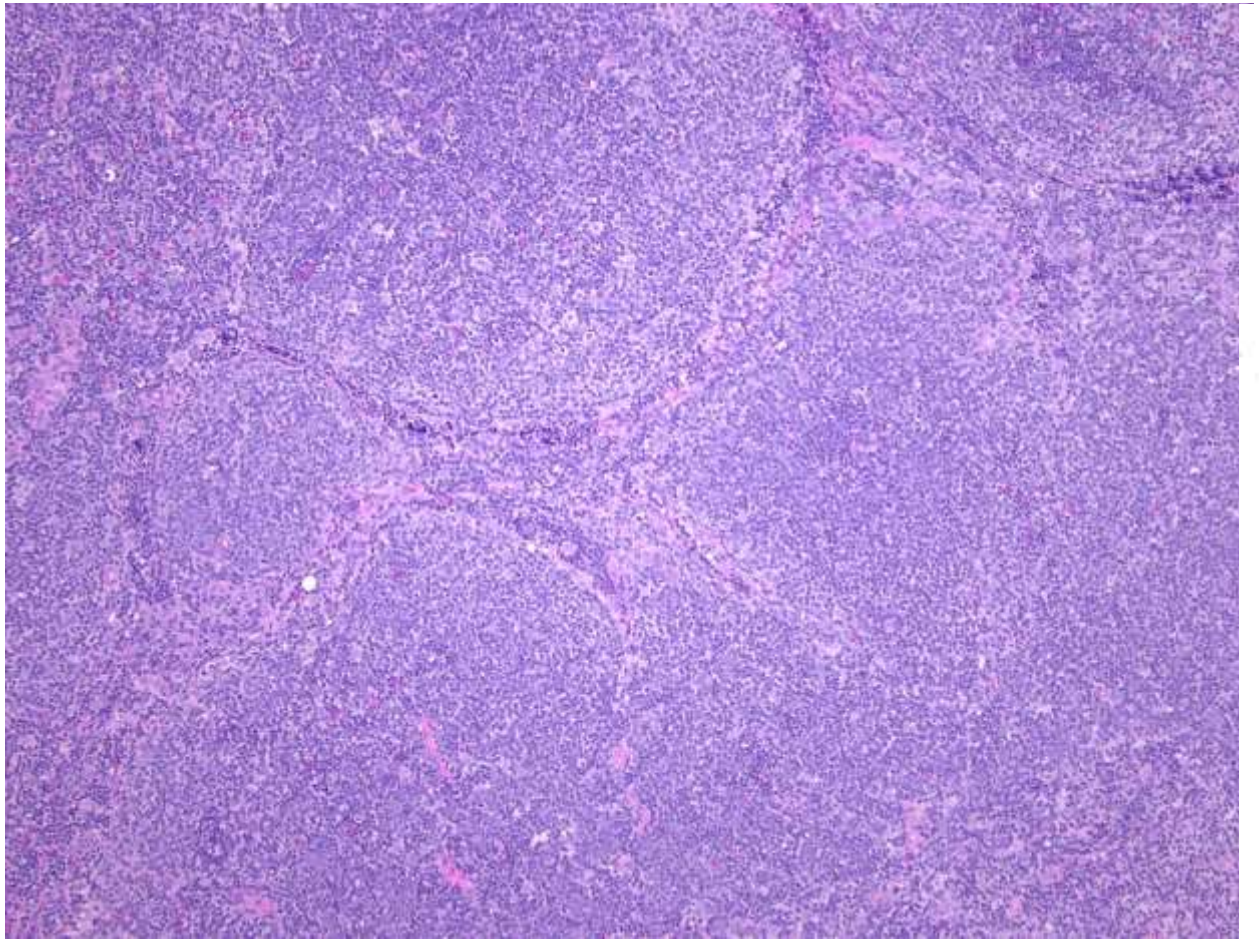


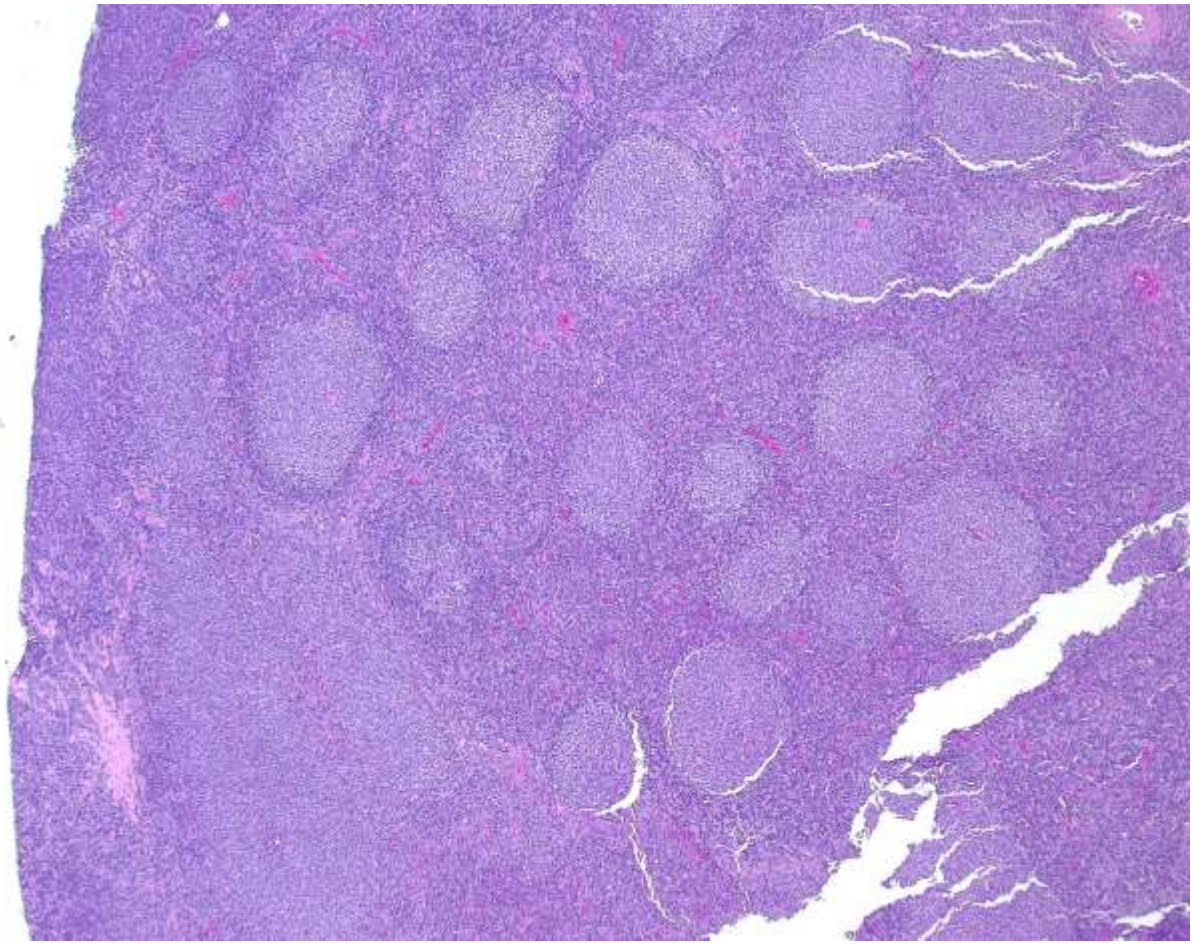
SLL in lymph node





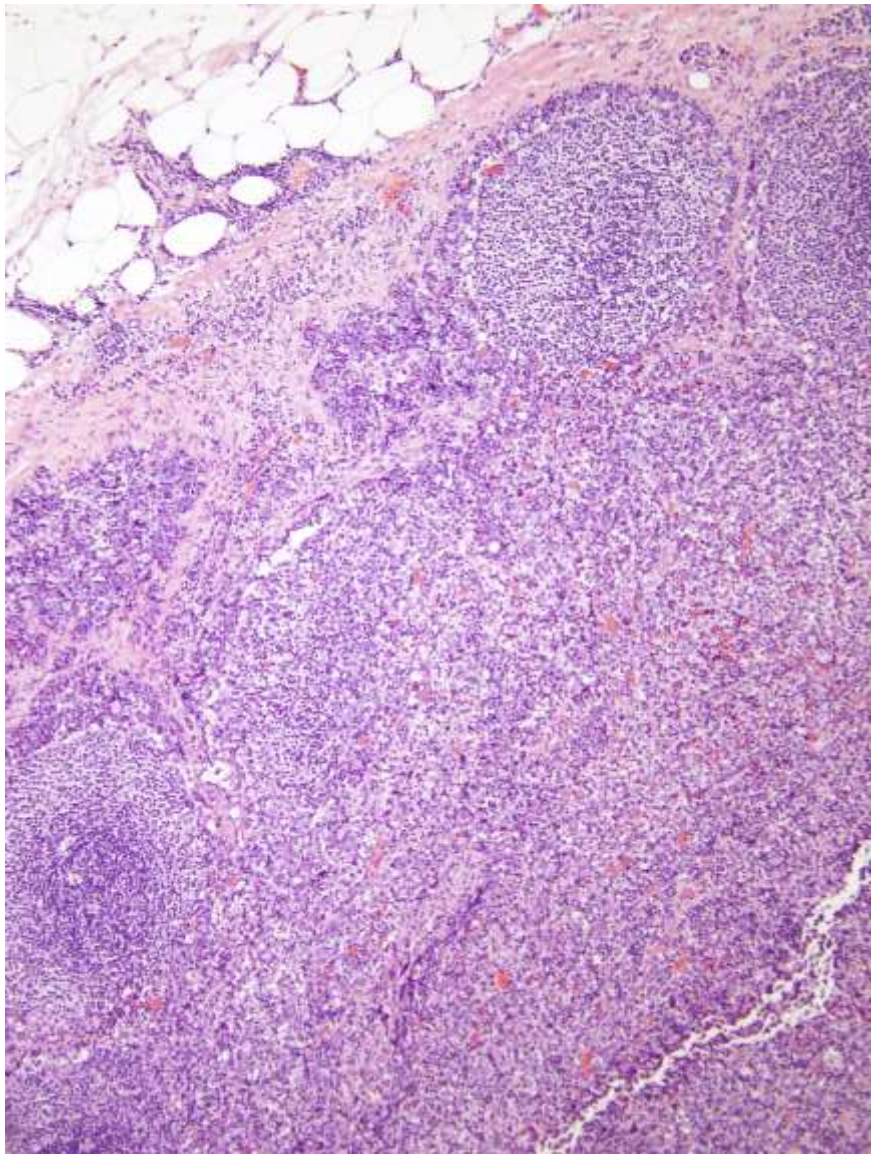
Predominantly follicles: follicular lymphoma

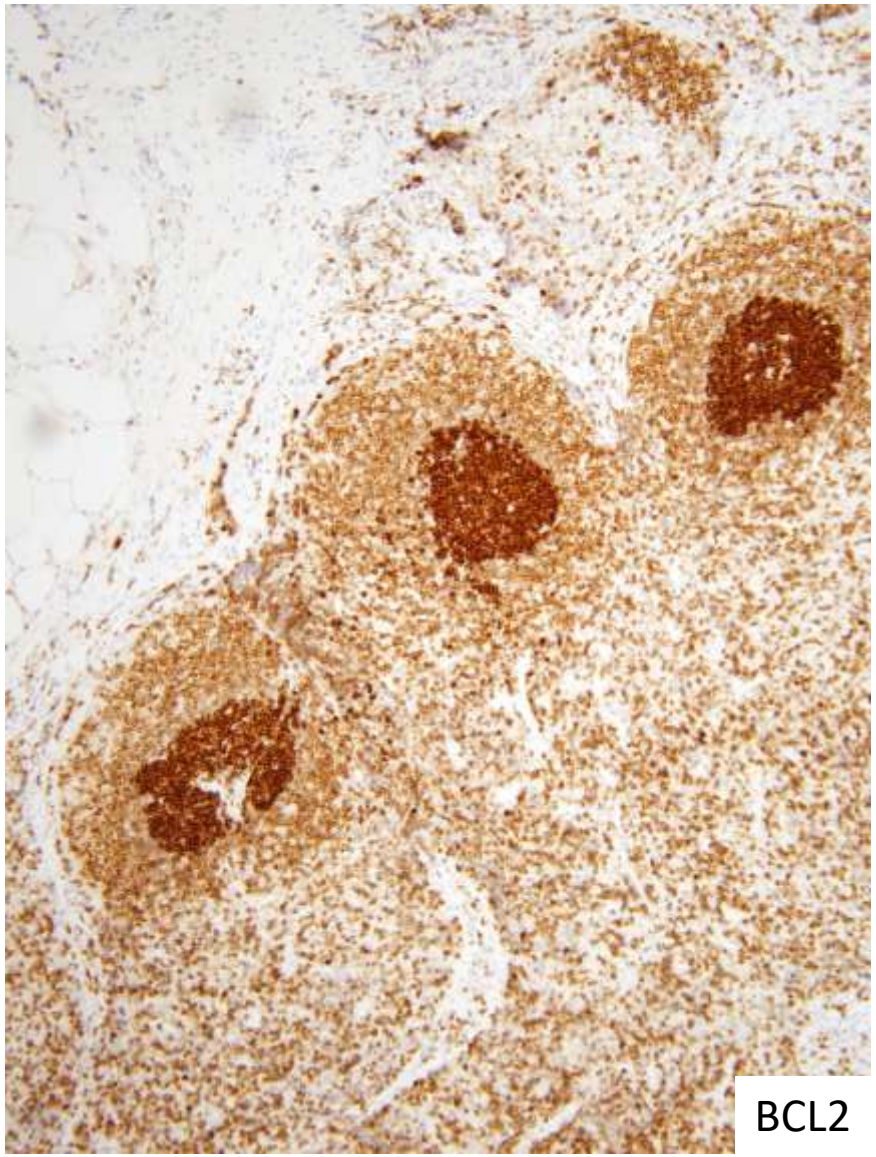




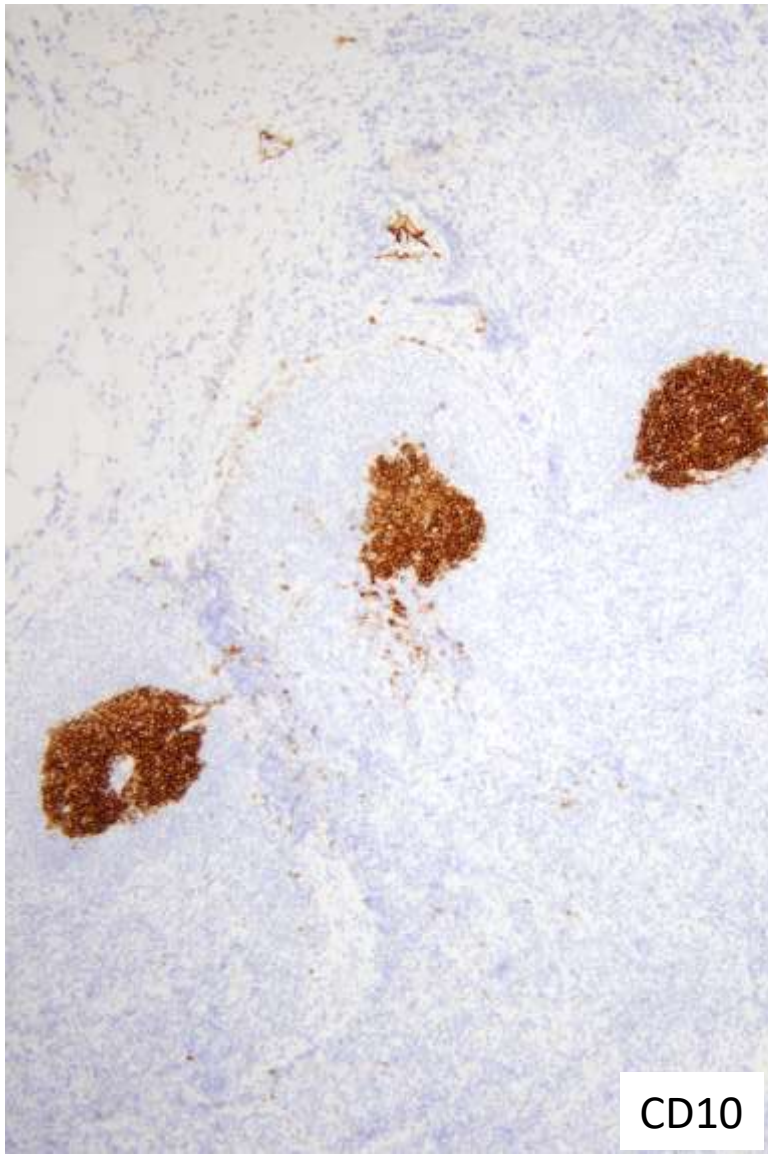
- Coexpress CD10, BCL2, BCL6
- Low grade, typically low Ki67 compared to normal reactive follicles

In situ follicular neoplasia





BCL2

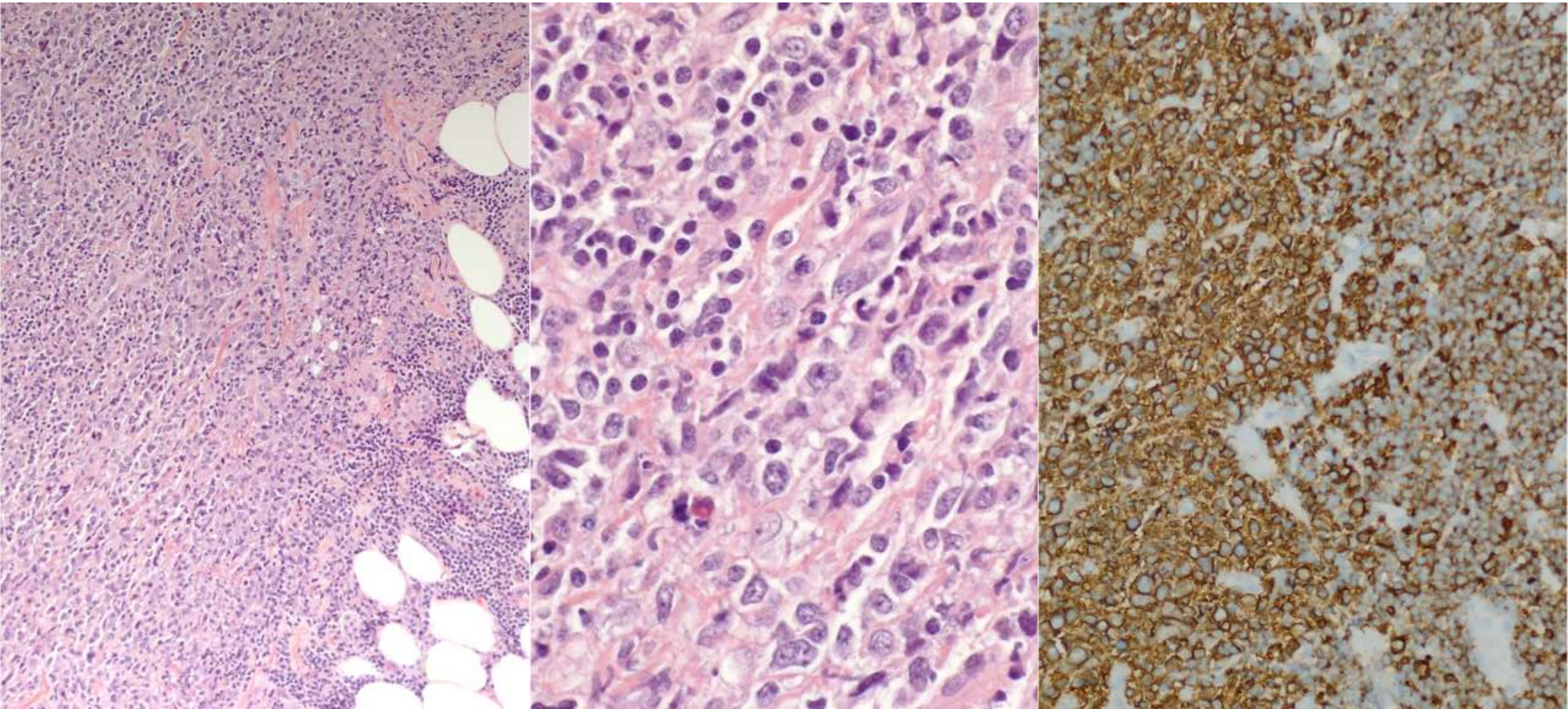


CD10

Small B-cell lymphoma Biomarkers

	Genetics/mutations	IHC/protein expression
Lymphoplasmacytic lymphoma	*MYD88* (>90%)	Increased mast cells
Hairy cell leukemia	*BRAF V600E* (virtually all)	CD103, CD11c, CD25, CD123, CD200
HCL variant	IGHV4-34 (preferential), often with *MAP2K1*	Often CD25(-), CD200(-)
Marginal zone lymphoma	Subset with translocations, *NOTCH2*	MNDA, IRTA
Mantle cell lymphoma Aggressive forms Indolent, non-nodal	t(11;14) *TP53, ATM, CDKN2A* (del 9p)	Cyclin D1 (rare cyclin D2 or D3) Sox11+; high Ki67 or mitotic rate Sox11(-), CD200+
CLL/SLL	*NOTCH1, SF3B1, TP53*, ATM, BIRC3, POT1, MYD88* del(13q), trisomy 12, del(17p)	CD5, CD23, CD200, CD20 (dim), light chain (dim); IHC: LEF1 Prognostic CD38, ZAP-70

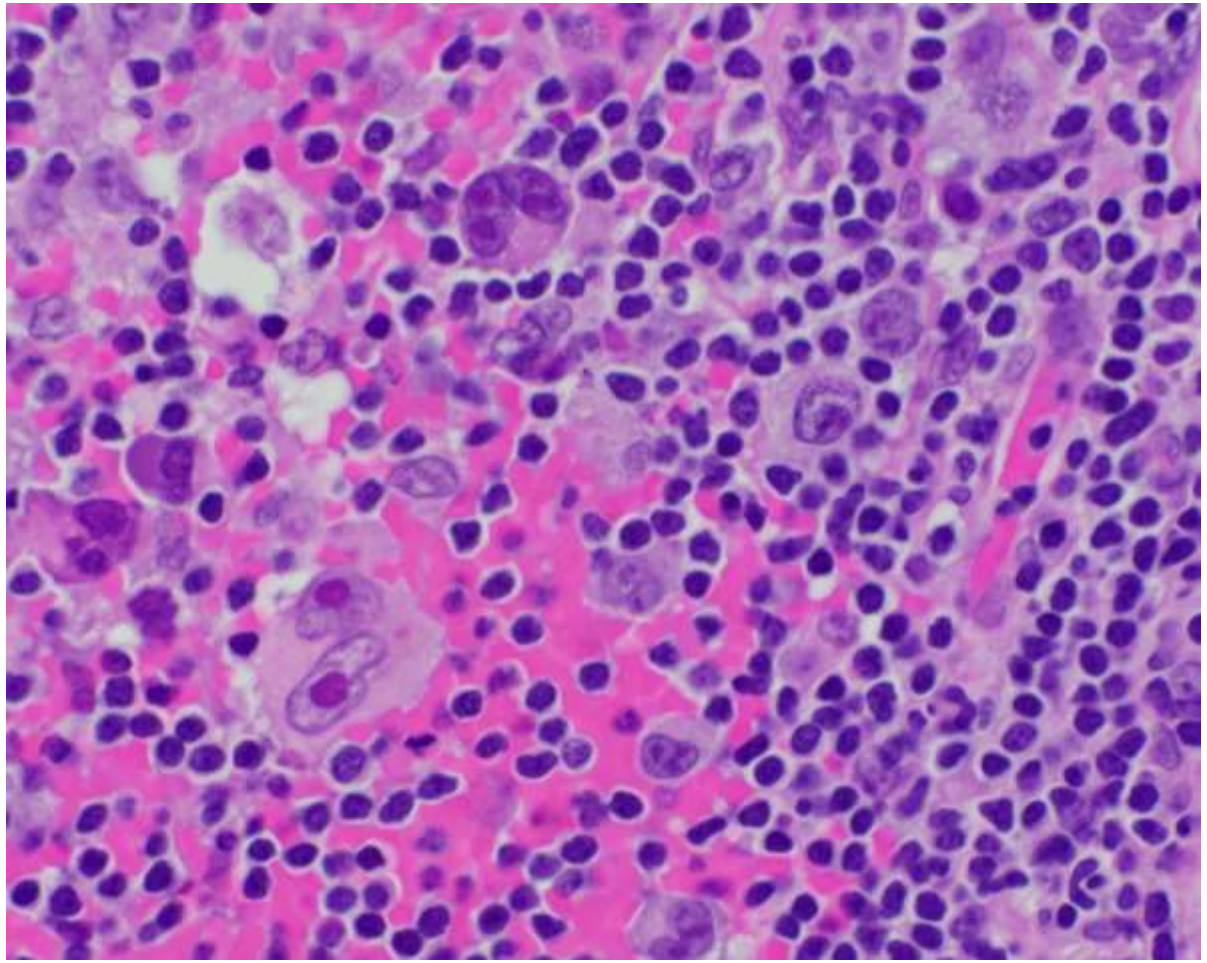
Mixed small and large cells with localized large cells: CLL/SLL with Richter transformation to DLBCL



“Hodgkin” pattern

• Bands of nodal fibrosis • Scattered very large cells/any background • Large blue nodules (NLPHL) • Mediastinal biopsies • Clinical: young/previous history	• CD3 • CD20 • CD30 • CD15 • EBER • PAX5	• CHL • NLPHL • T cell/histiocyte-rich large B cell lymphoma • Reactive processes, e.g. immunoblasts (transformed benign large lymphocytes) • Progressively transformed germinal centers (PTGC)

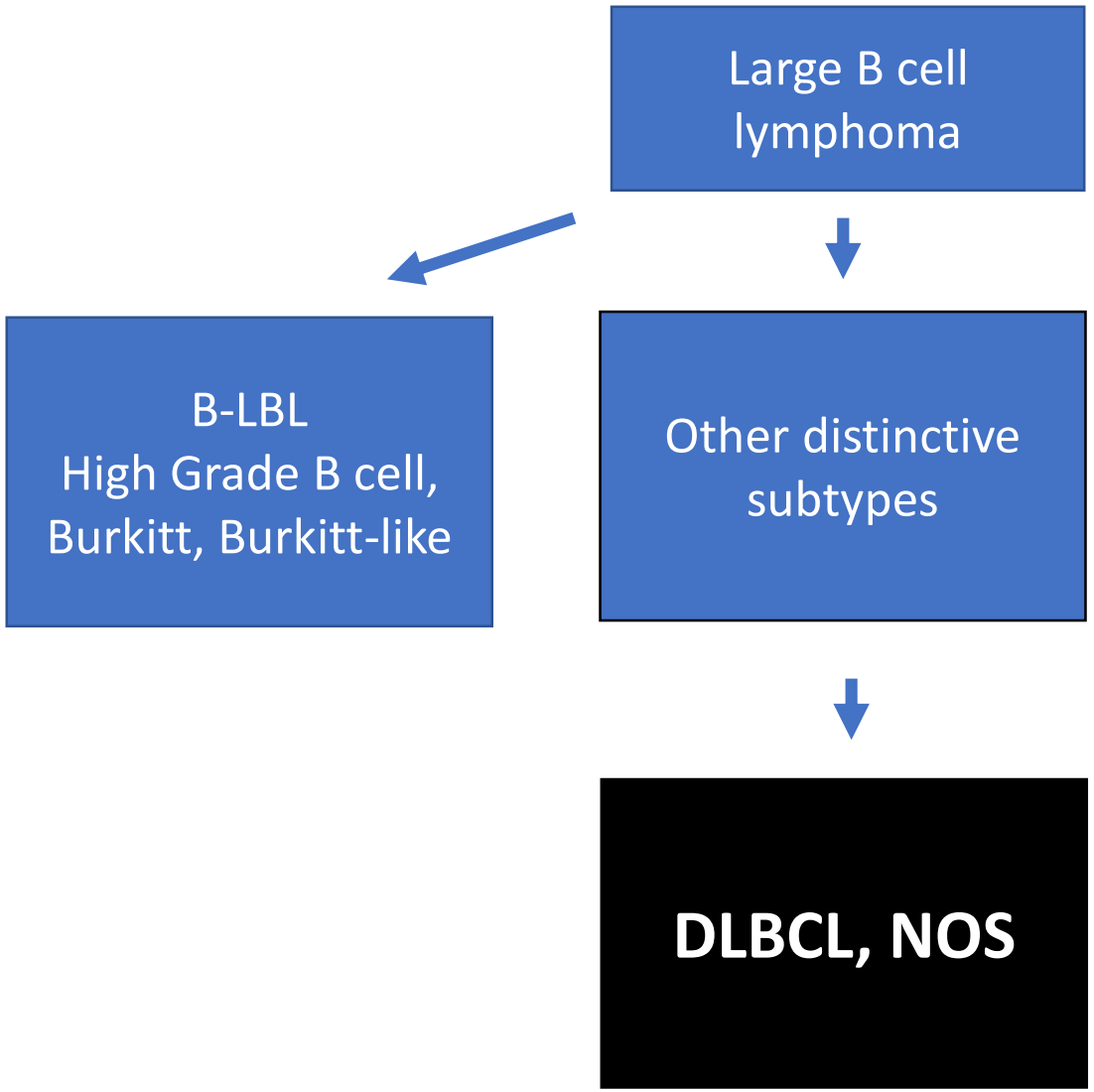
Classical Hodgkin Lymphoma



- Reed-Sternberg cells with defined immunophenotype
- Subclassify based on tumor microenvironment
  - Nodular sclerosis
  - Mixed cellularity
  - Lymphocyte-rich
  - Lymphocyte-depleted

Large cell lymphoma pattern

• Diffuse sheets of large or intermediate-sized hematopoietic cells	• CD3, CD20 • CD5, CD10 • Cyclin D1 • BCL2, BCL6 • MUM1 • CD30, C-MYC, P53 • Ki67, EBER	• Diffuse large B cell lymphoma (DLBCL) and its variants • High grade B-cell lymphoma • Burkitt lymphoma



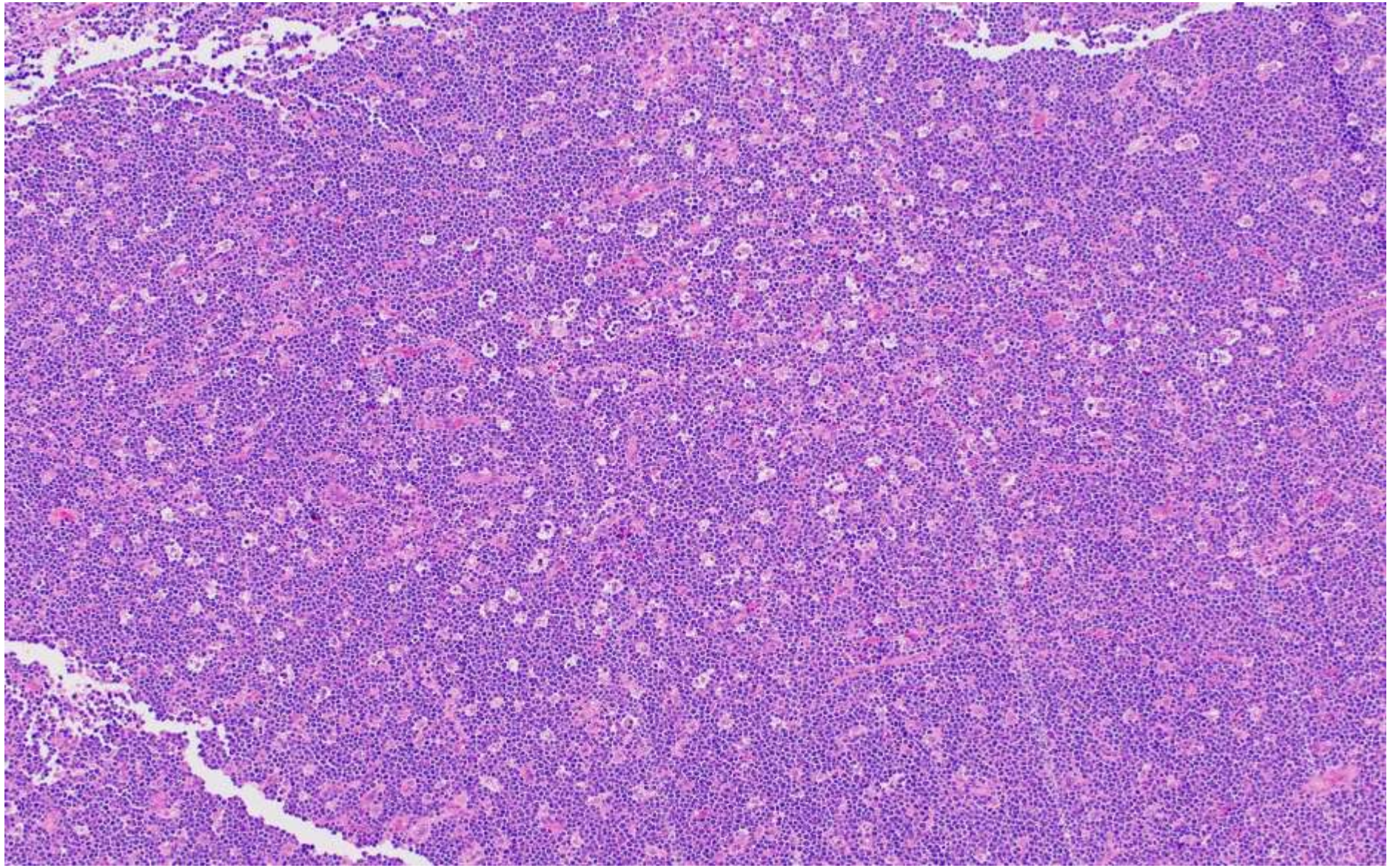
- T-cell/histiocyte-rich large B-cell lymphoma
- Primary DLBCL of the central nervous system (CNS)
- Primary cutaneous DLBCL, leg type
- EBV^{+} DLBCL, NOS*
- EBV^{+} mucocutaneous ulcer
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK^{+} large B-cell lymphoma
- Plasmablastic lymphoma
- Primary effusion lymphoma
- HHV8^{+} DLBCL, NOS
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

Adapted from Swerdlow et al. Blood 2016 127:2375-2390.

Standard of care biomarker testing DLBCL

- Cytogenetics: High grade B cell lymphoma (MYC and BCL2 and/or BCL6)
- Cell of origin: GCB vs. non-GCB/ABC
- Double expresser: Myc and BCL-2
- Therapy:
  - CD20, rituximab
  - CD30, brentuximab
- Optional:
  - EBER avoid missing subtypes, underlying immune suppression
  - P53: over-expression with R-CHOP, worse survival

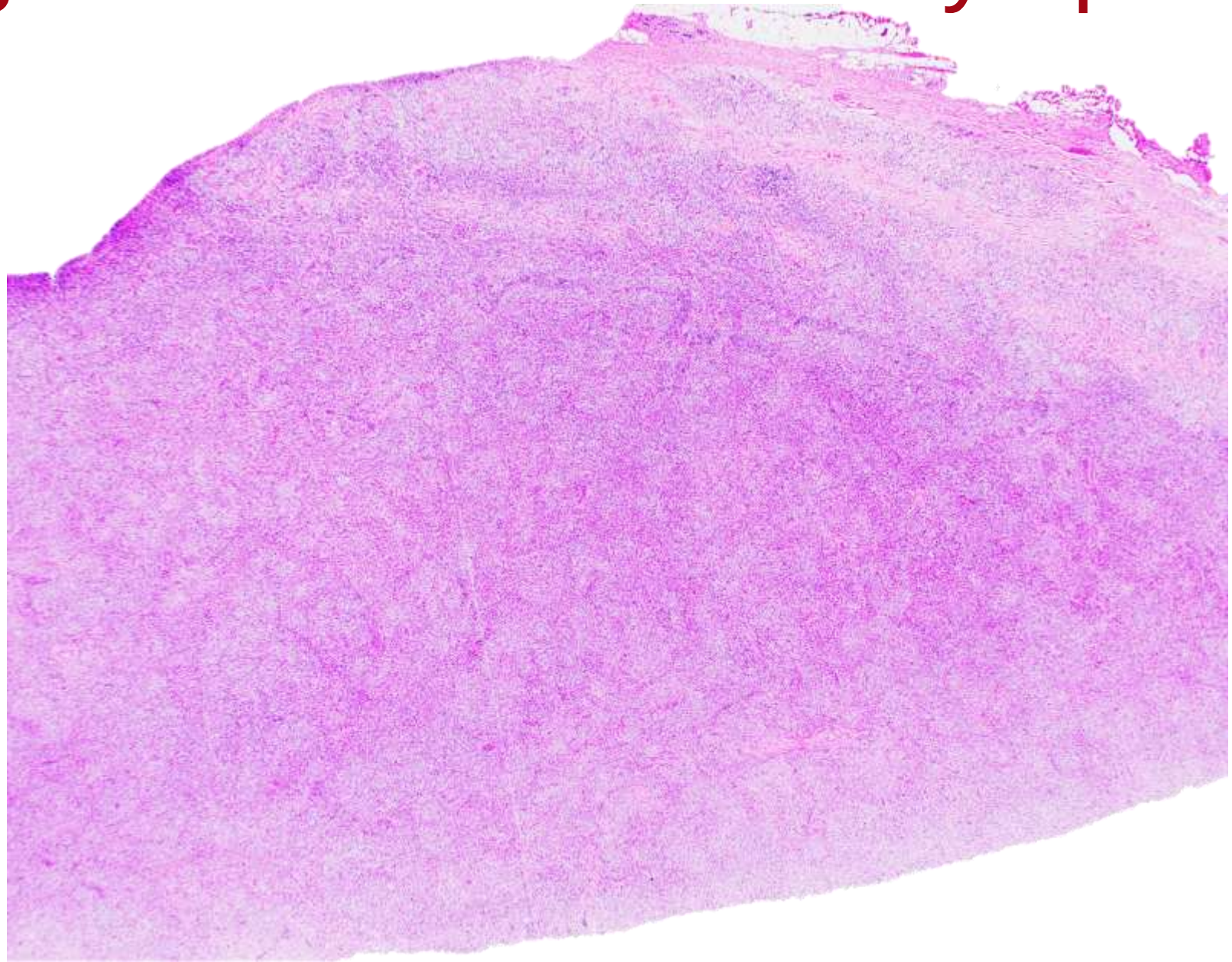
Burkitt lymphoma

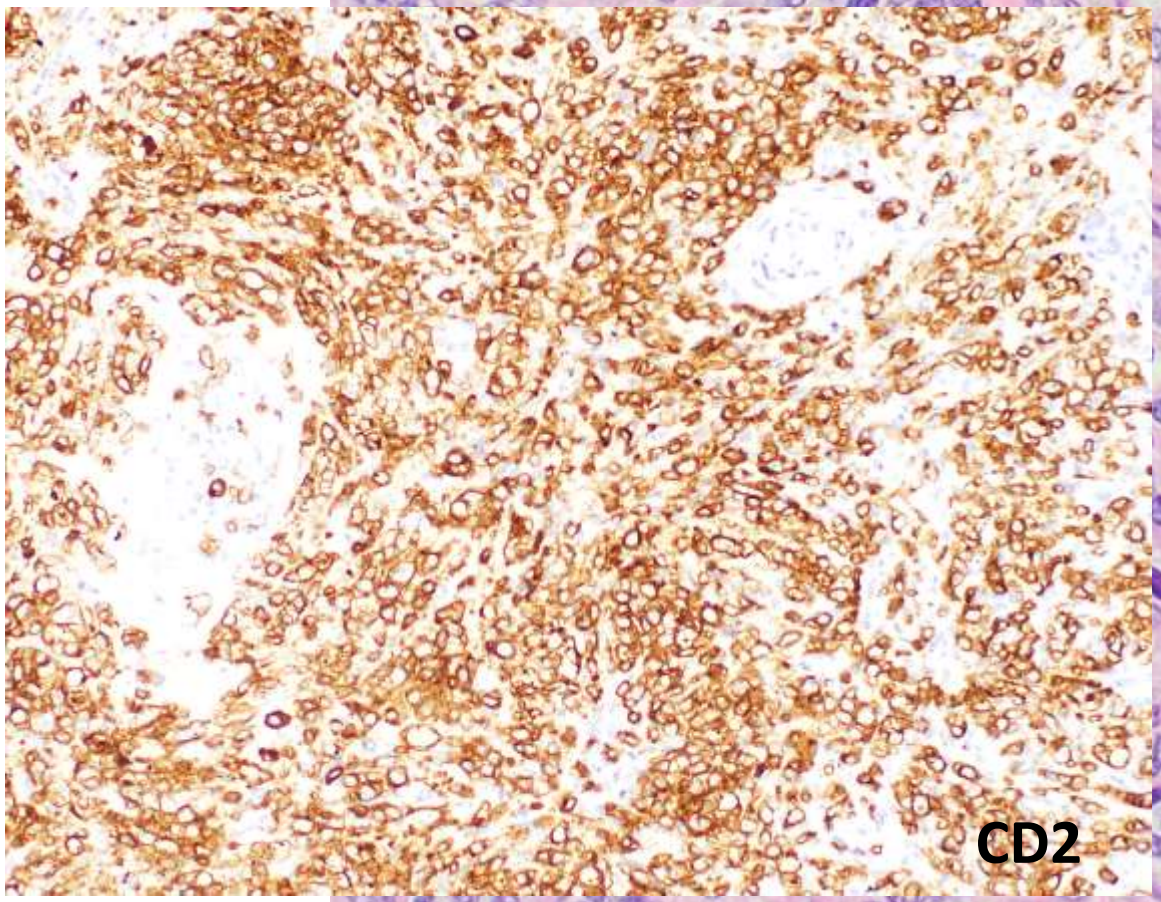


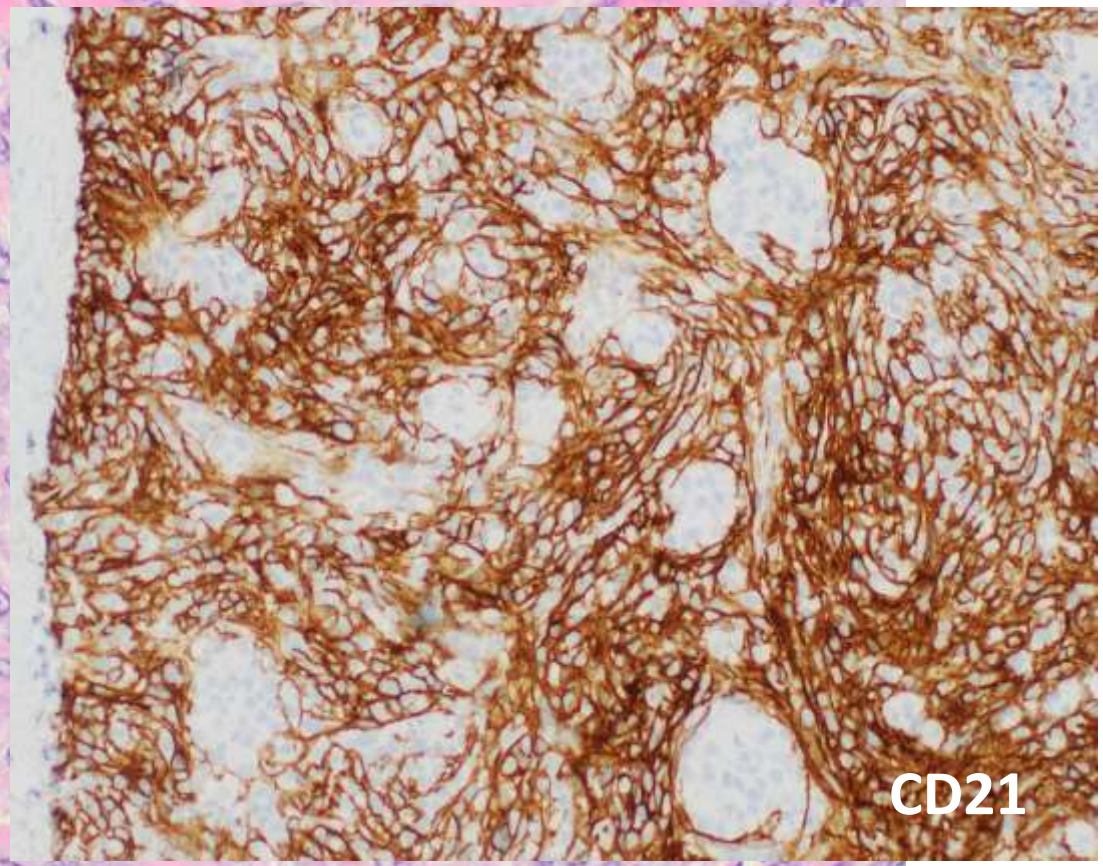
T cell patterns

• Polymorphous background with cytologic atypia • Small or polymorphous lymphocytes with increased vasculature • Increased histiocytes • Eosinophils • Increased lymphocytes with pale cytoplasm • Sheets or intrasinusoidal large/anaplastic lymphoid cells	• CD3, CD20 • CD2, CD5, CD7 • CD4, CD8 • CD56 • CD25, CD30 • CD10, BCL2, BCL6 • CD21 • PD1, Ki67 • TCR beta F1, TCR gamma/delta • TIA1, perforin, granzyme B • ALK, EBER	• AITL, other follicular helper T-cell lymphoma • Peripheral T-cell lymphoma, not otherwise specified • ALCL (ALK-positive and ALK negative subtypes) • HTLV-1 associated adult T-cell leukemia/lymphoma • Mycosis fungoides • Reactive conditions

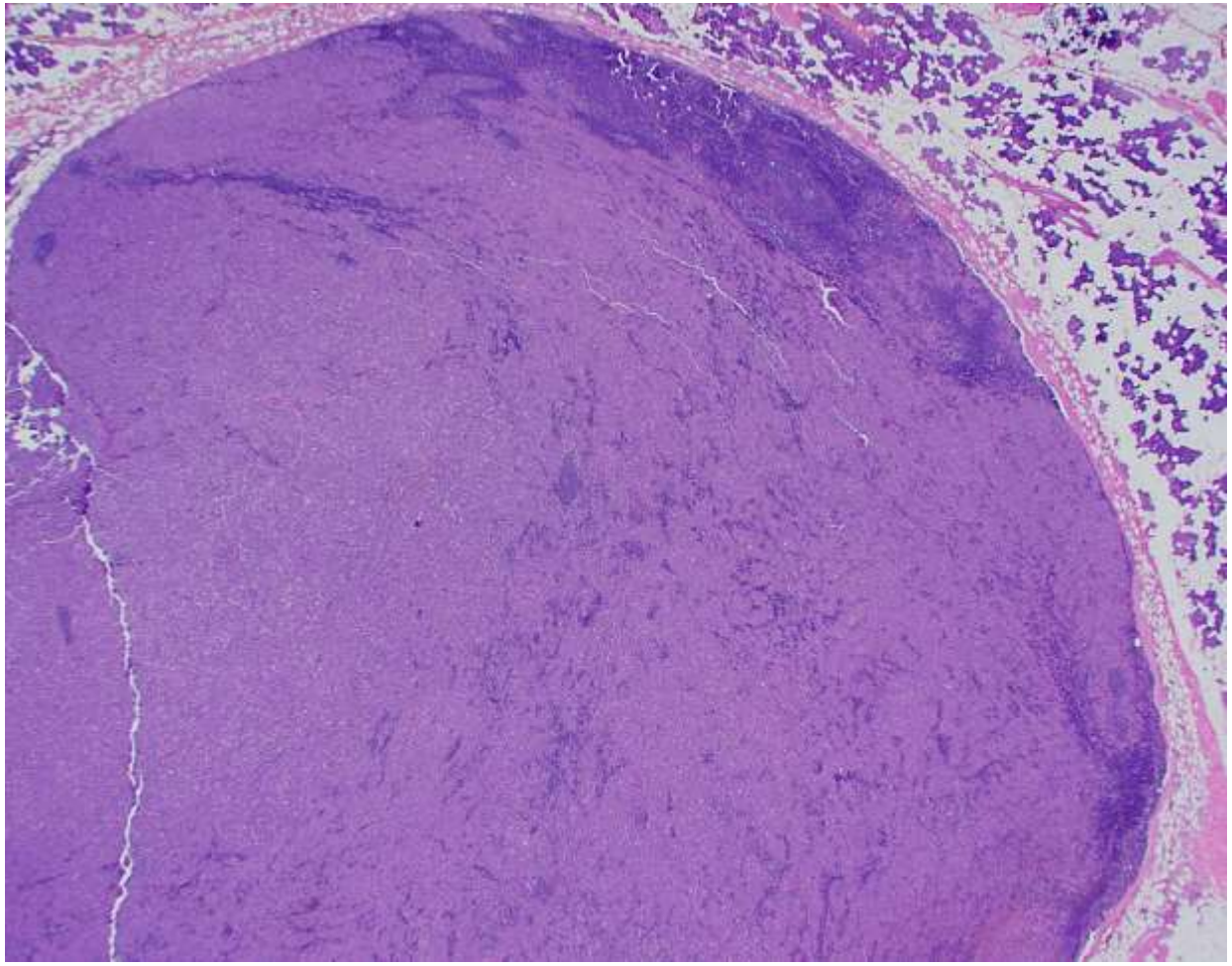
Angioimmunoblastic cell lymphoma

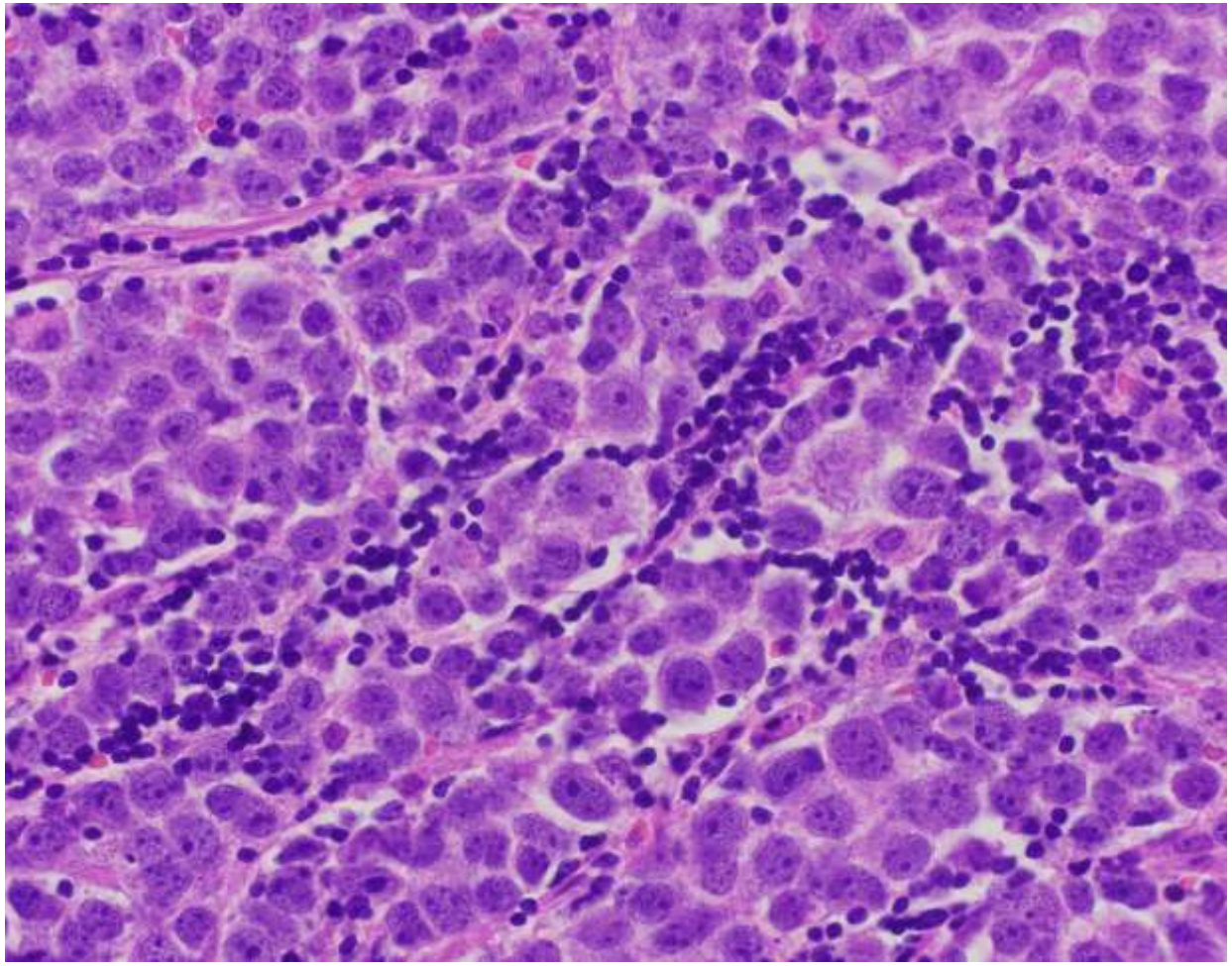



CD2


CD21

ALCL, ALK-negative

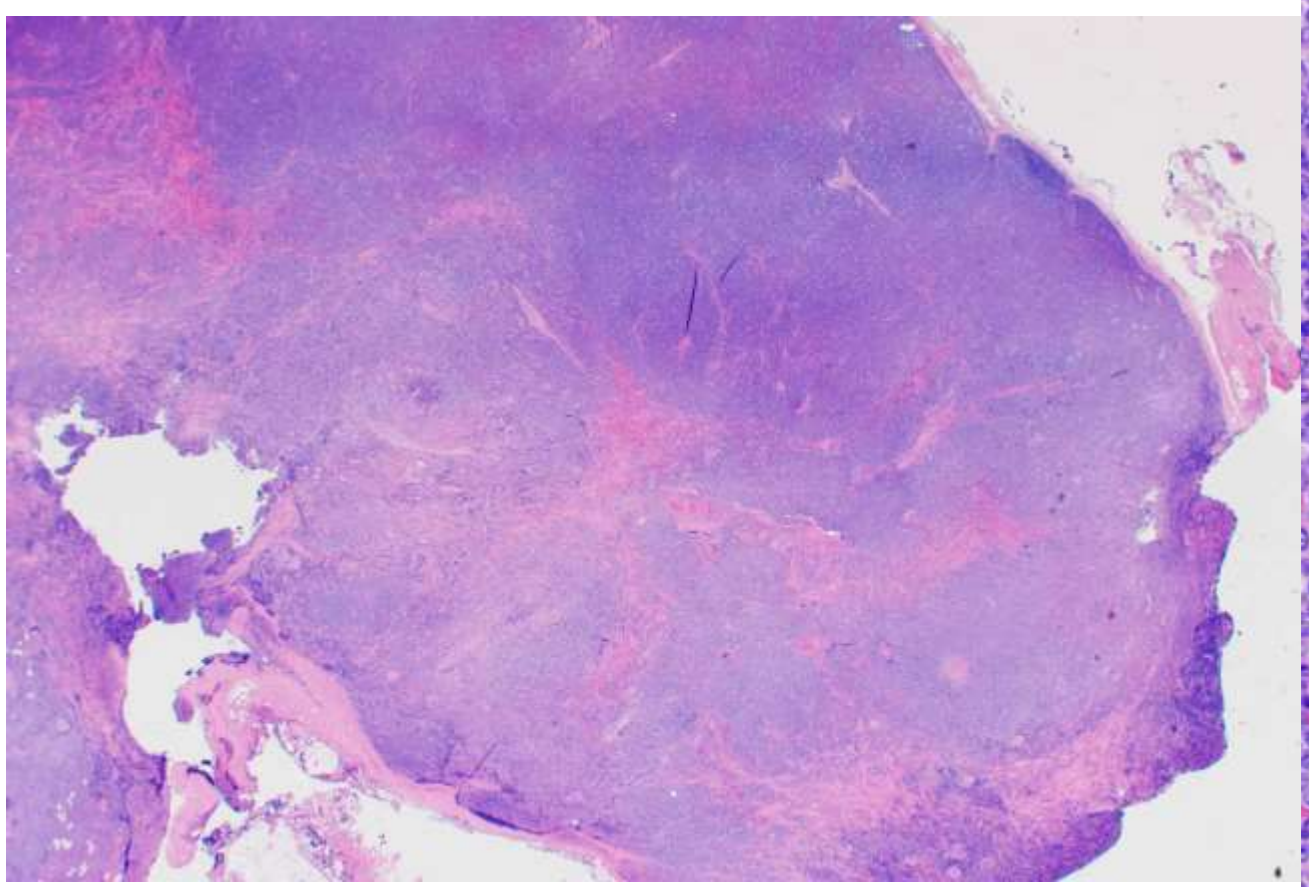


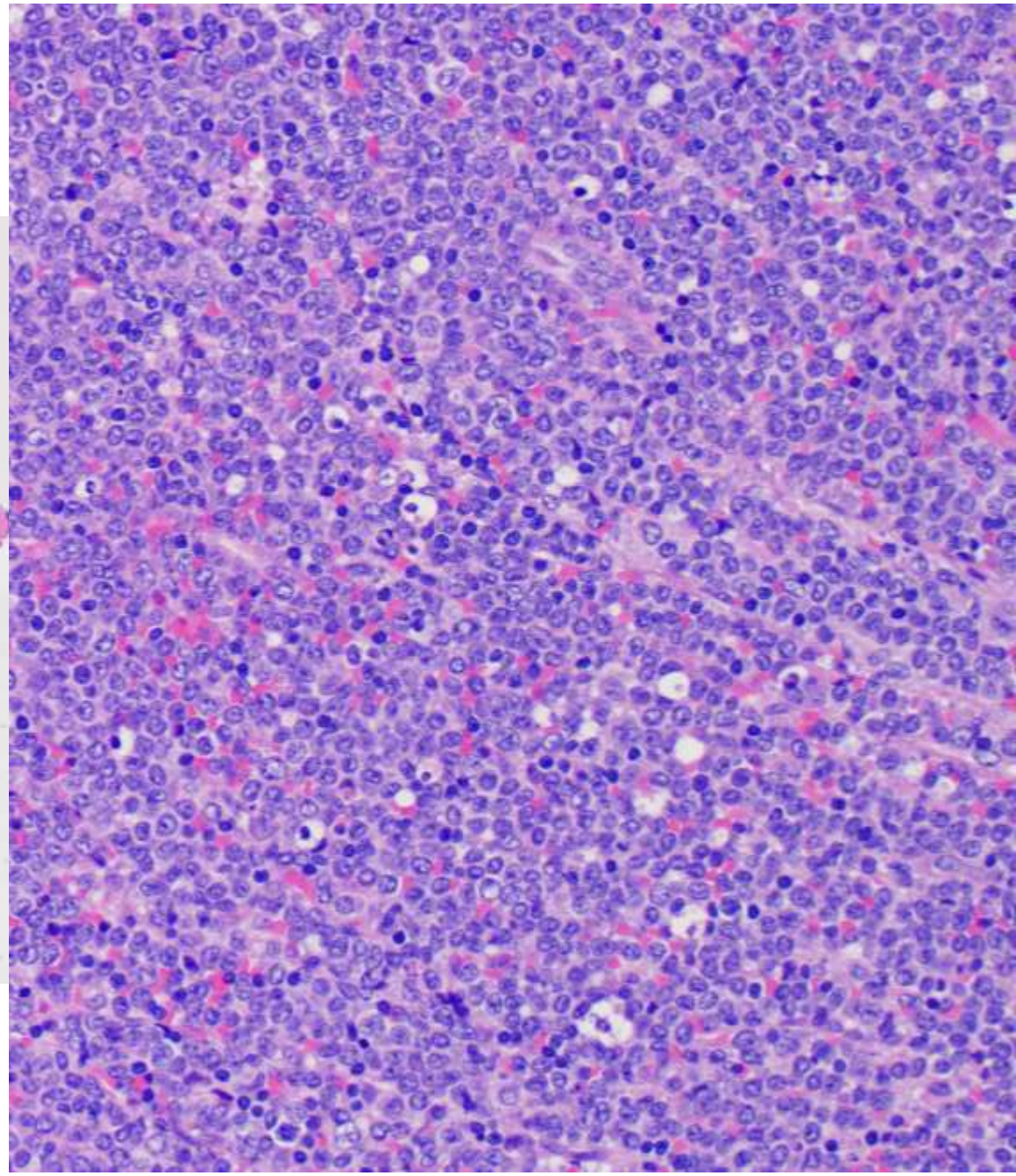


Other patterns

Necrosis	• Demonstrates a uniform pink color • Can be focal • More often interfollicular distribution	• Cat scratch disease, Kikuchi-Fujimoto disease, infarction, viral infections (e.g. EBV and herpes lymphadenitis) • CHL, diffuse large B-cell lymphoma, others • Non-hematopoietic malignancies including carcinomas
"That old bone marrow look"	• Resembles the appearance of acute myeloid leukemia in the bone marrow	• Myeloid Sarcoma • Blastic plasmacytoid dendritic cell neoplasm

Myeloid sarcoma

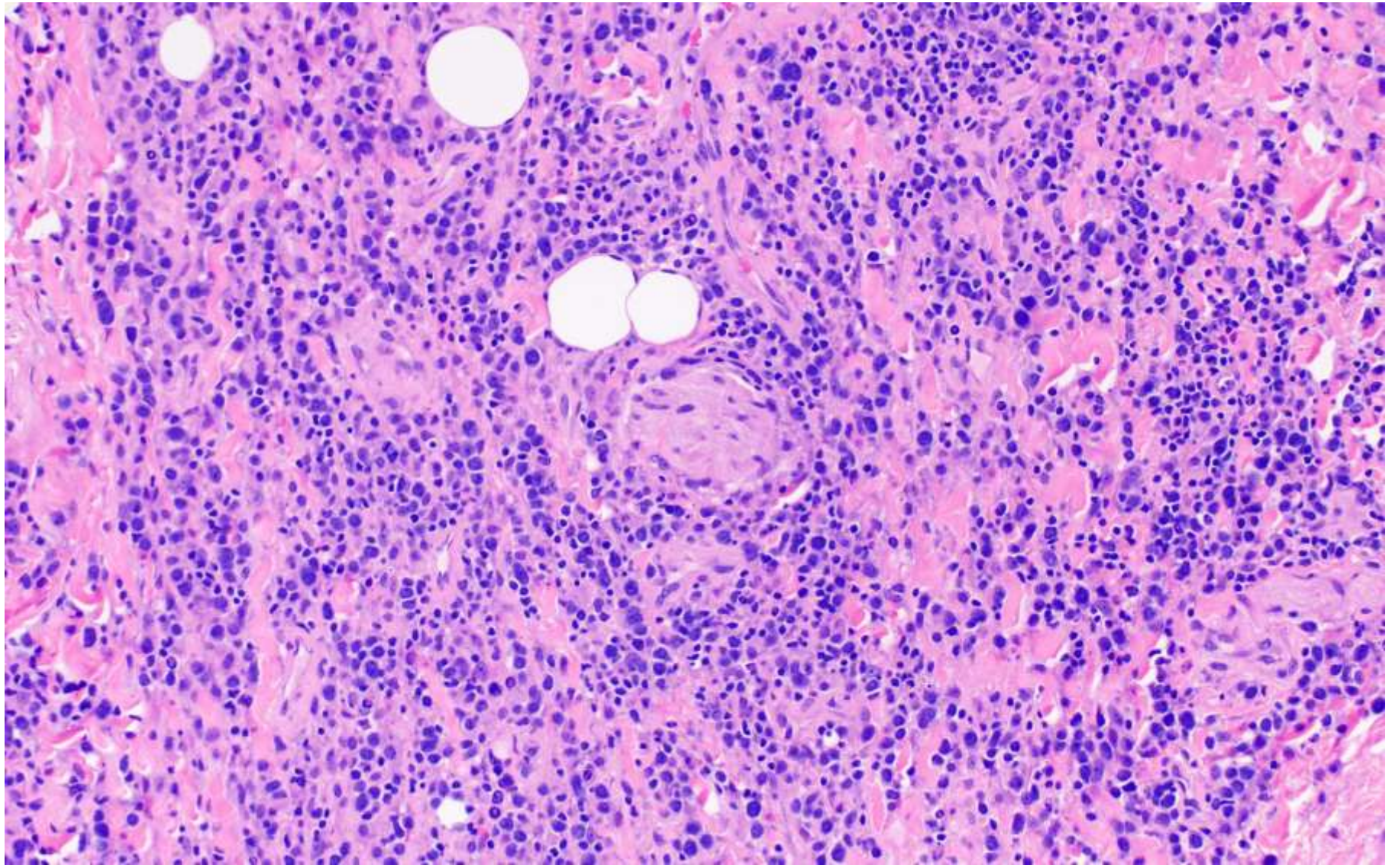


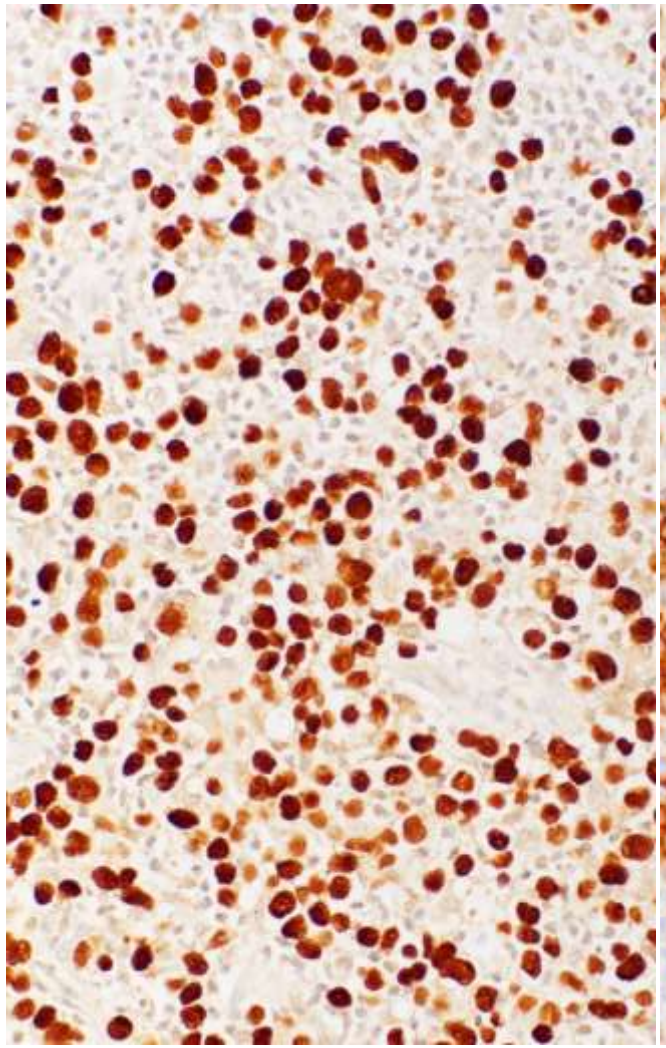


Special sites may call for special stains

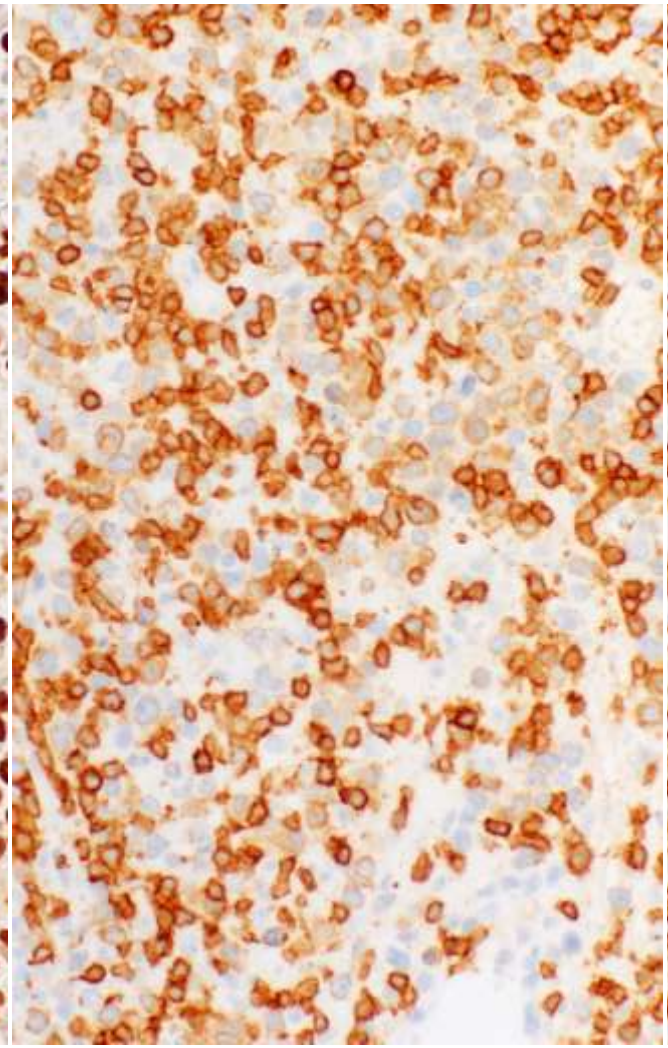
Nasopharynx	Extranodal NK/T-cell lymphoma, nasal type	CD56 EBER
Stomach	?MALT lymphoma	*H. pylori*
Small intestine	• Consider possibility of enteropathy associated T cell lymphoma, MEITL, exclude extranodal NK/T-cell • Duodenal type follicular lymphoma • Mantle cell lymphoma	• T cell markers and molecular studies for clonality, EBER • Bcl2, Bcl6, cyclin D1
Mediastinum	• CHL, primary mediastinal large B cell lymphoma, gray-zone lymphoma • Primary thymic pathology	CD30, CD15, PAX5 and CD20 TdT: immature thymic T cells Pancytokeratin: thymic epithelium
Spleen	Look for disrupted architecture	CD8: outlines red pulp sinuses

Extranodal NK/T cell lymphoma, Right Facial “Lymph Node”

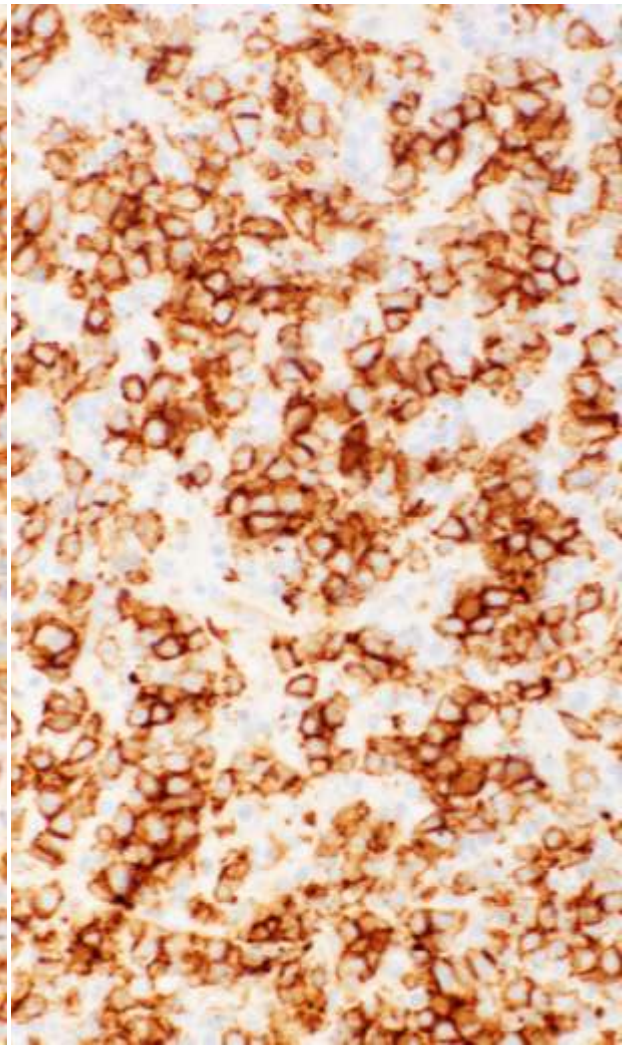




EBER



CD3



CD56

Thank you!!

- And thank you to Dr. Dennis O'Malley for shared material and insight on the approach to lymph node pathology

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