

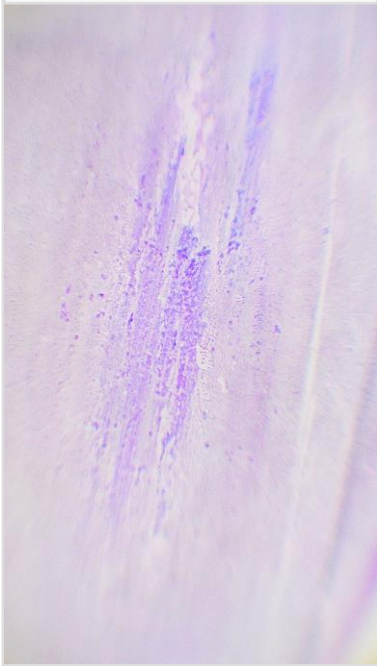
# Pitfalls of Hematopathology Diagnosis in Limited Specimens

**Margaret Williams, MD**

Assistant Professor, University of Utah & ARUP Laboratories

FEBRUARY 2023

FNA



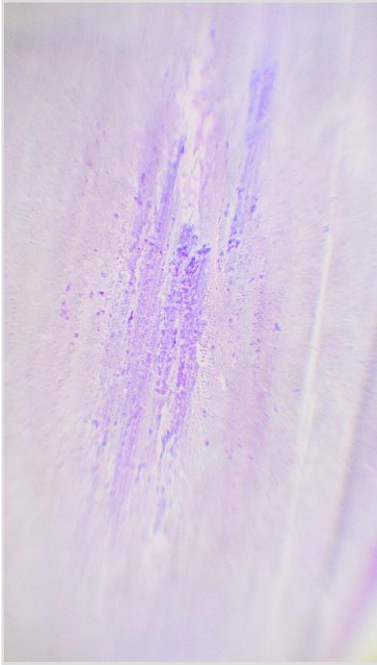
Core



Excision

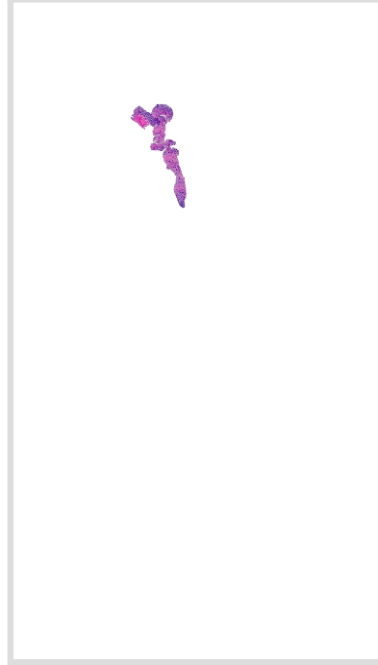


FNA



+

Core



Excision



# Agenda

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Literature Identified Pitfalls

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Clinical Cases

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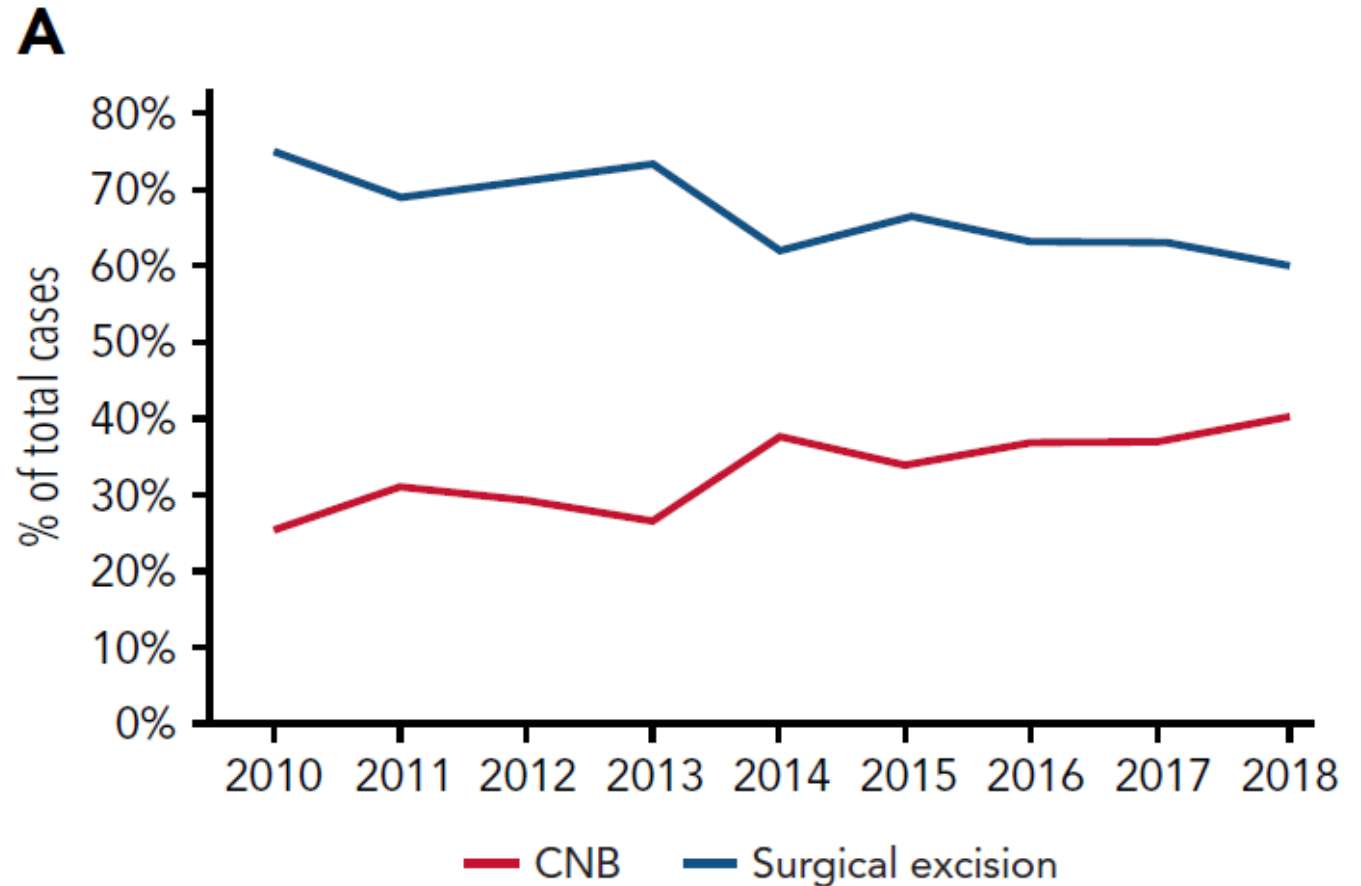
Can we make any recommendations?

# ■ Quick Lit Review

Over your practice, have you seen a trend in the frequency of core needle biopsy vs surgical excision of lymph nodes?

# Trends in Specimen Procurement

- Core needle biopsy becoming more common
- 25% to 40% in French Study
- 28% to 61% in a US study 2003 - 2009



Syrykh et al 2022, PMID: 35797472  
PMID: 21411774

# How good are FNA/CNB?

Triaging between  
benign, solid tumor, and  
lymphoma

Make a diagnosis of  
lymphoma with all  
relevant  
prognostic/theranostic  
assessments



# How good are FNA/CNB?

- CNB allowed for full diagnosis and characterization of a process in 56.8-92.3% of cases
  - » Adequate for treatment to begin
  - » Adequate to give a specific WHO classification diagnosis
  - » Diagnoses covered – including benign entities

PMID: 35797472, 33080089, 21411774, 34003078, 36395467, Ye et al 2020

# What are the trickiest diagnoses?

- Trend across studies where CNB were inadequate or discrepant from subsequent excisional biopsy
  - » T-cell lymphomas
  - » Classic Hodgkin Lymphoma
  - » B-cell lymphoma
    - Follicular lymphoma grading and transformation to diffuse large B-cell lymphoma
    - Low-grade B-cell lymphomas versus reactive processes

PMID: 35797472, 33080089, 21411774, 34003078, 36395467

# What are the trickiest diagnoses?

- Trend across studies where CNB were inadequate or discrepant from subsequent excisional biopsy
  - » Cases where the neoplastic cells are rare compared to the background
  - » Cases where architecture is essential for classification
  - » Cases with heterogeneity within the lymph node

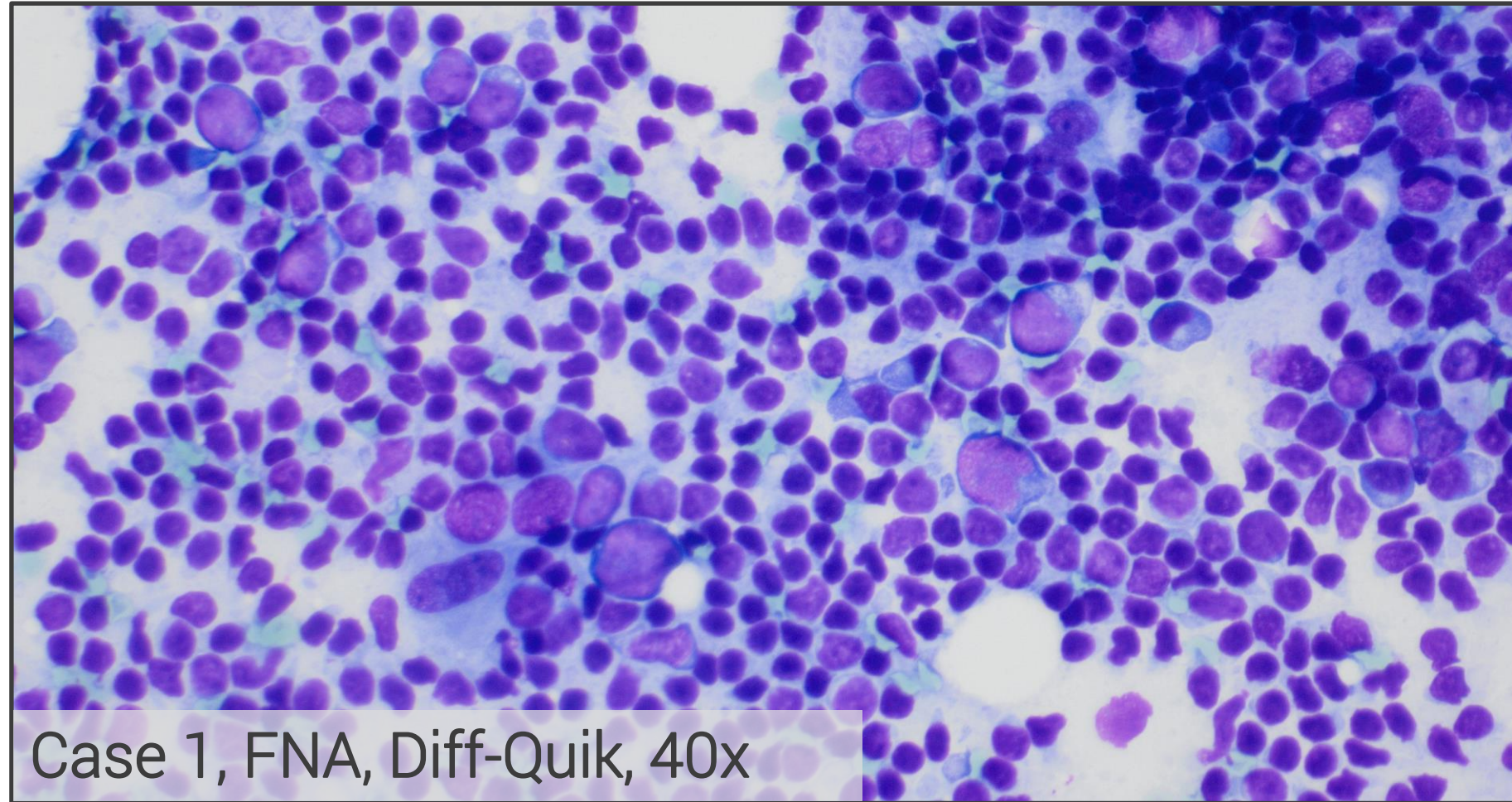
PMID: 35797472, 33080089, 21411774, 34003078, 36395467

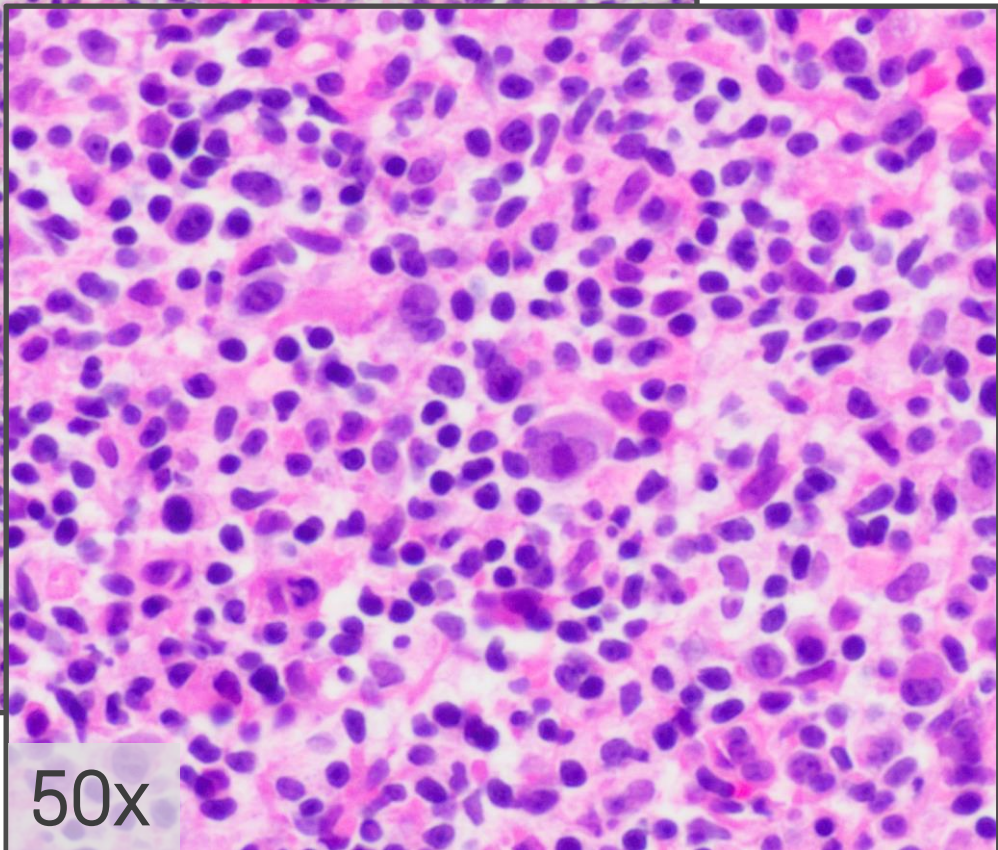
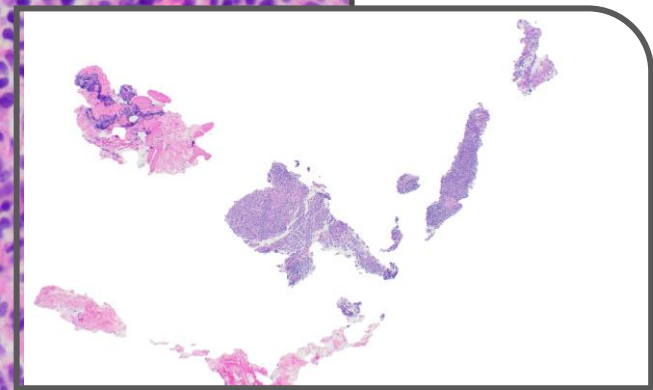
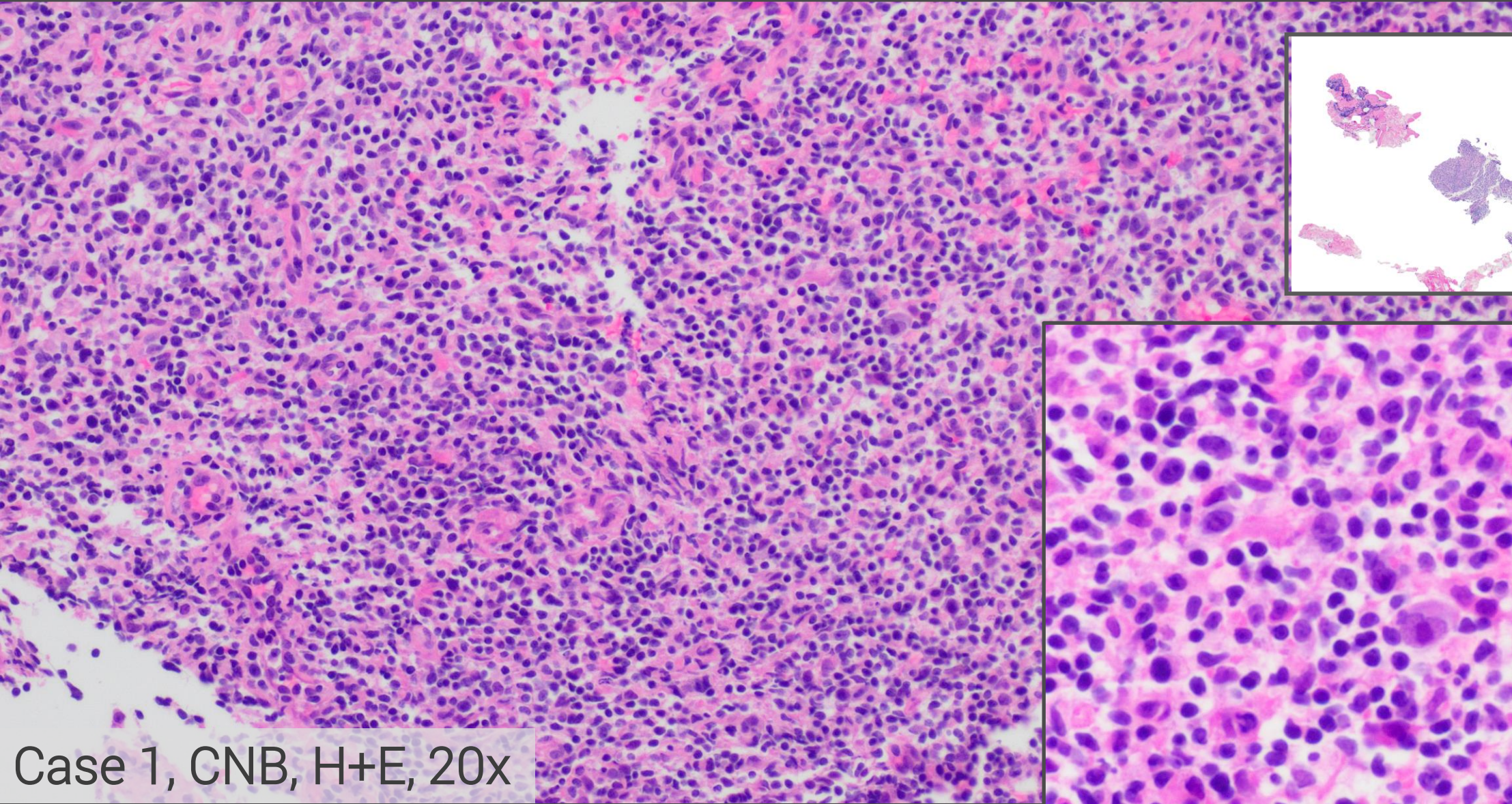
# ■ Case 1

# Case 1

27-year-old male  
with left  
supraclavicular  
lymphadenopathy  
for a month

No other symptoms

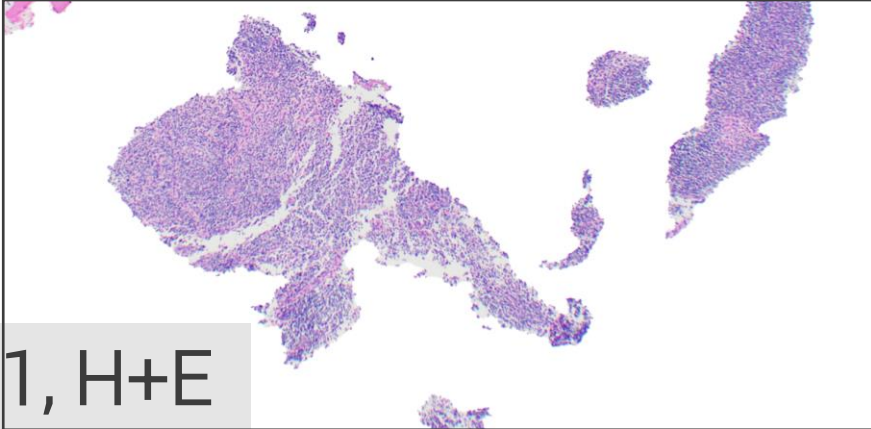




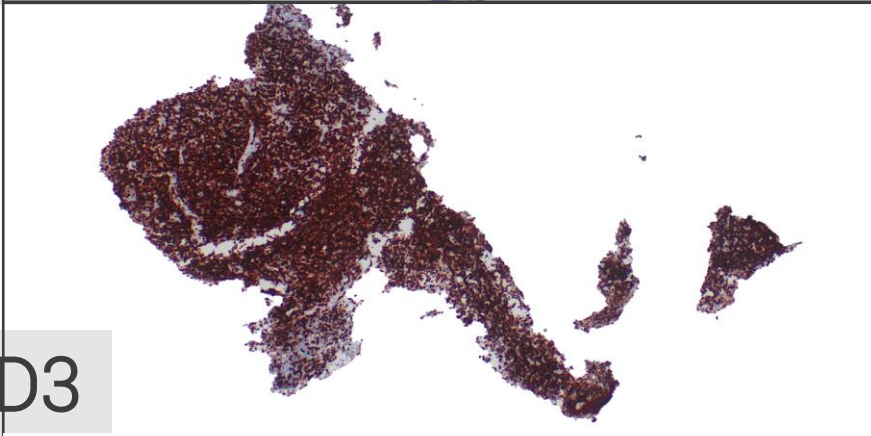
Case 1, CNB, H+E, 20x

50x

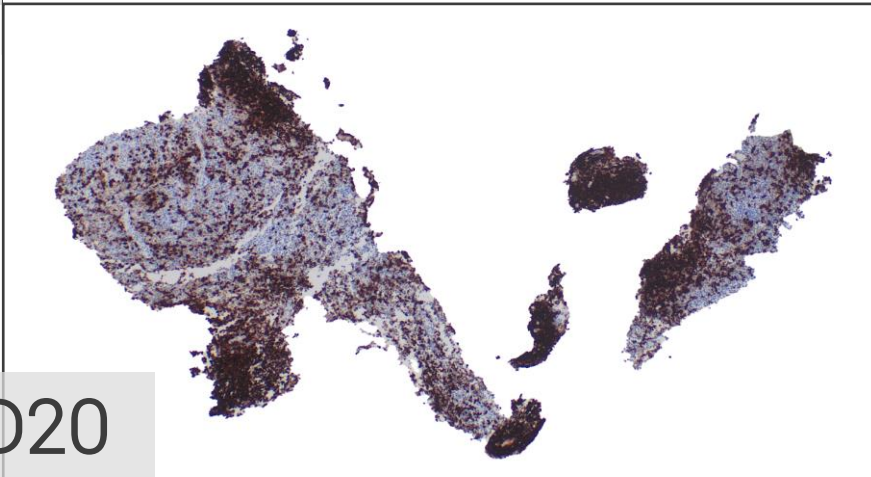
Case 1, H+E



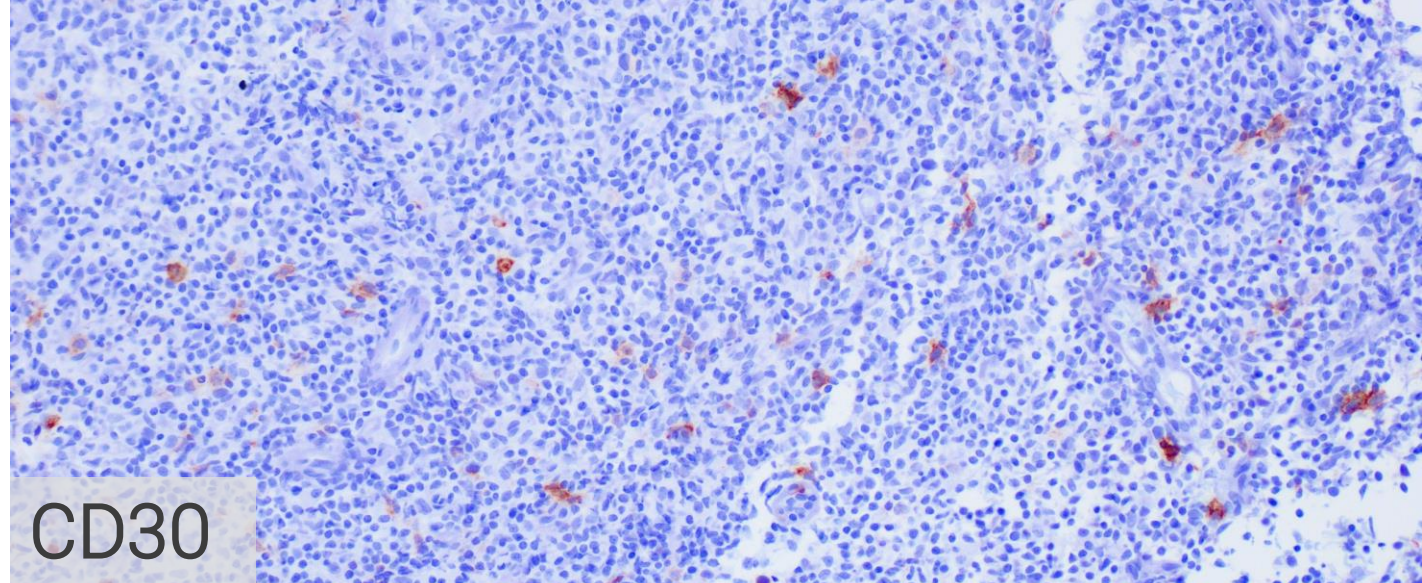
CD3



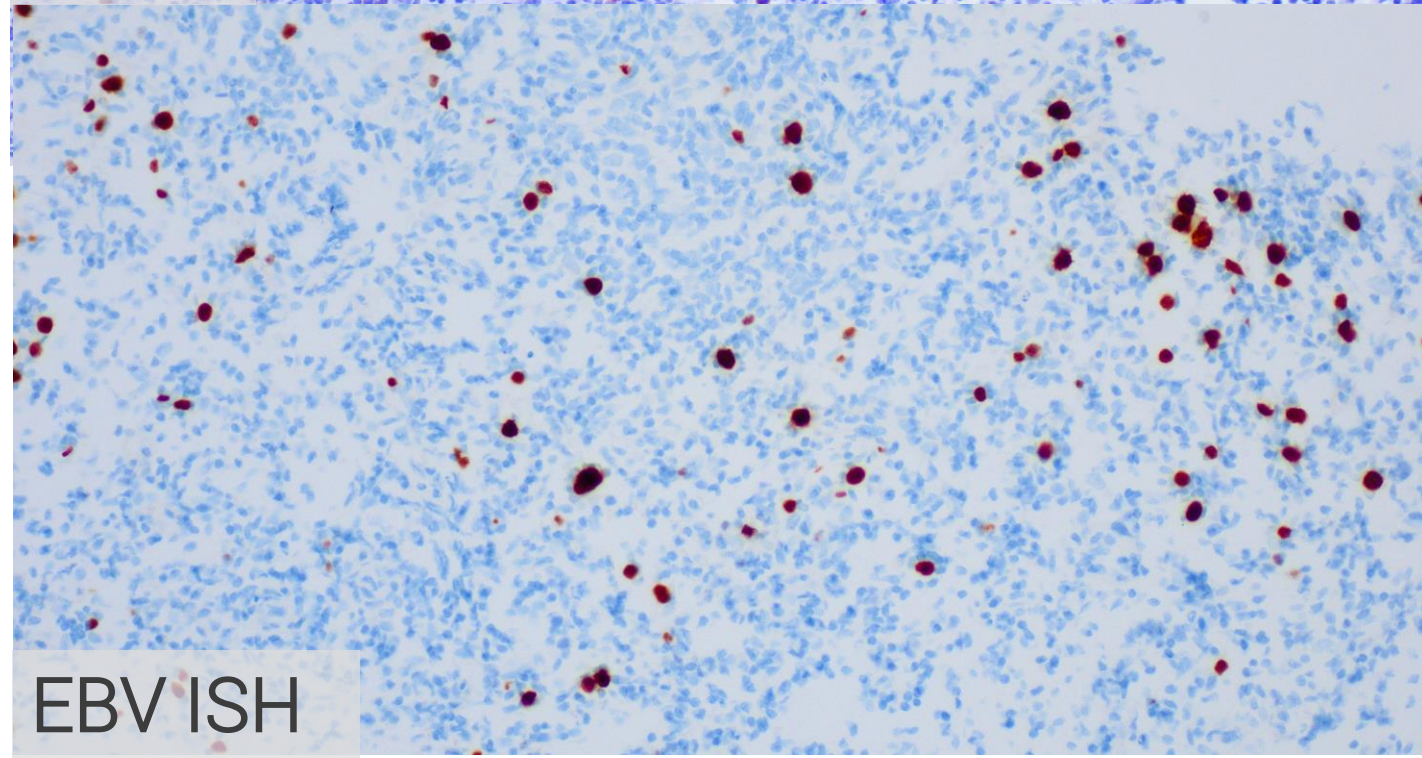
CD20



CD30



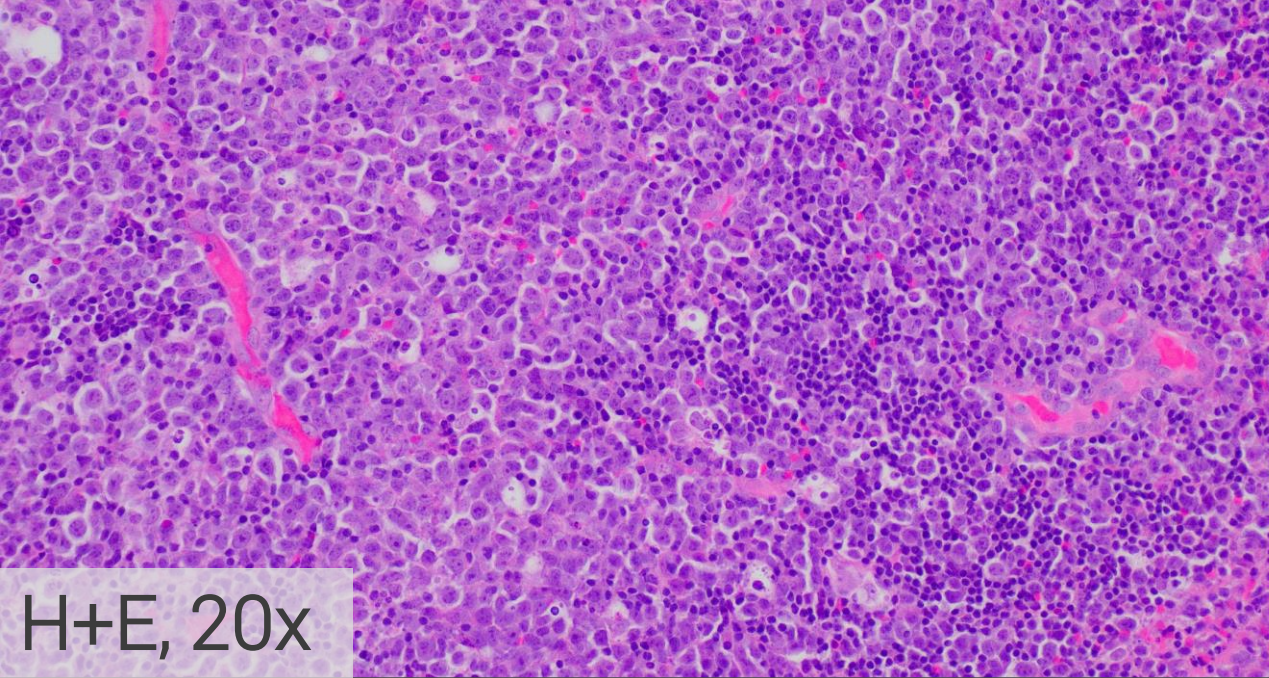
EBV ISH



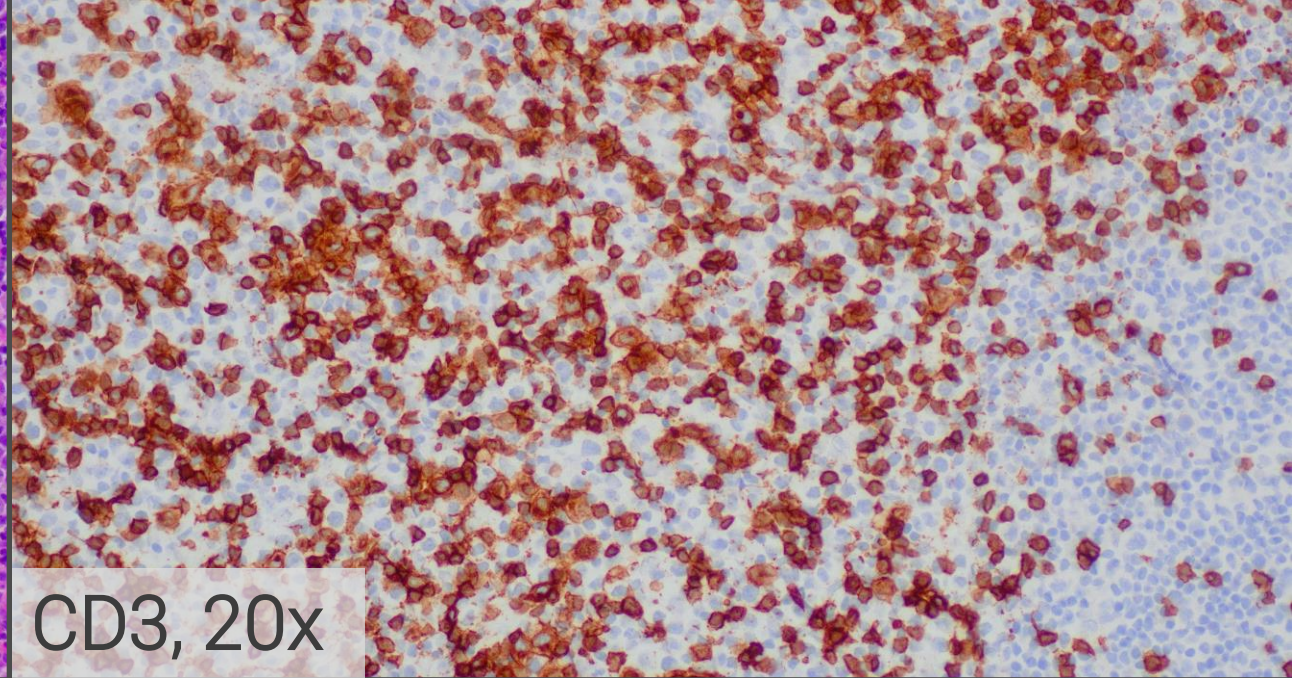
# Case 1

- Diagnosis: EBV Lymphadenitis
- “Please correlate clinically and with serologic testing for EBV. If these findings are not consistent with the clinical impression, consider excisional biopsy of this lymph node for further evaluation.”

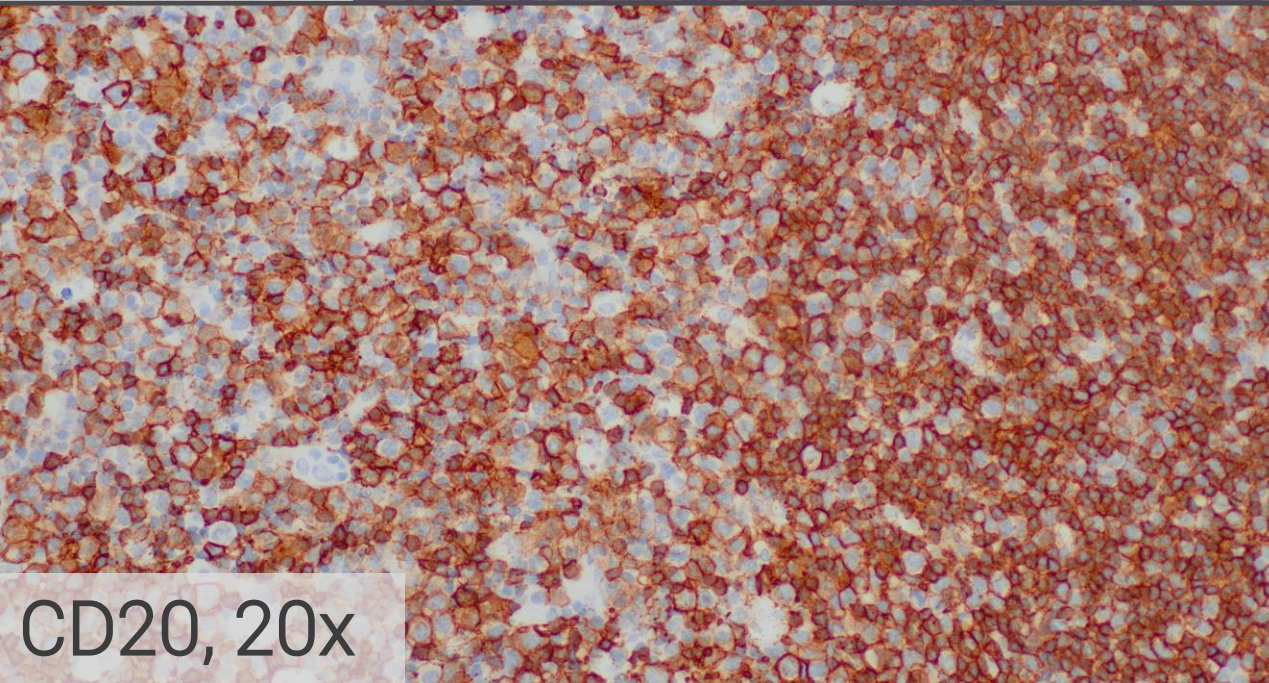




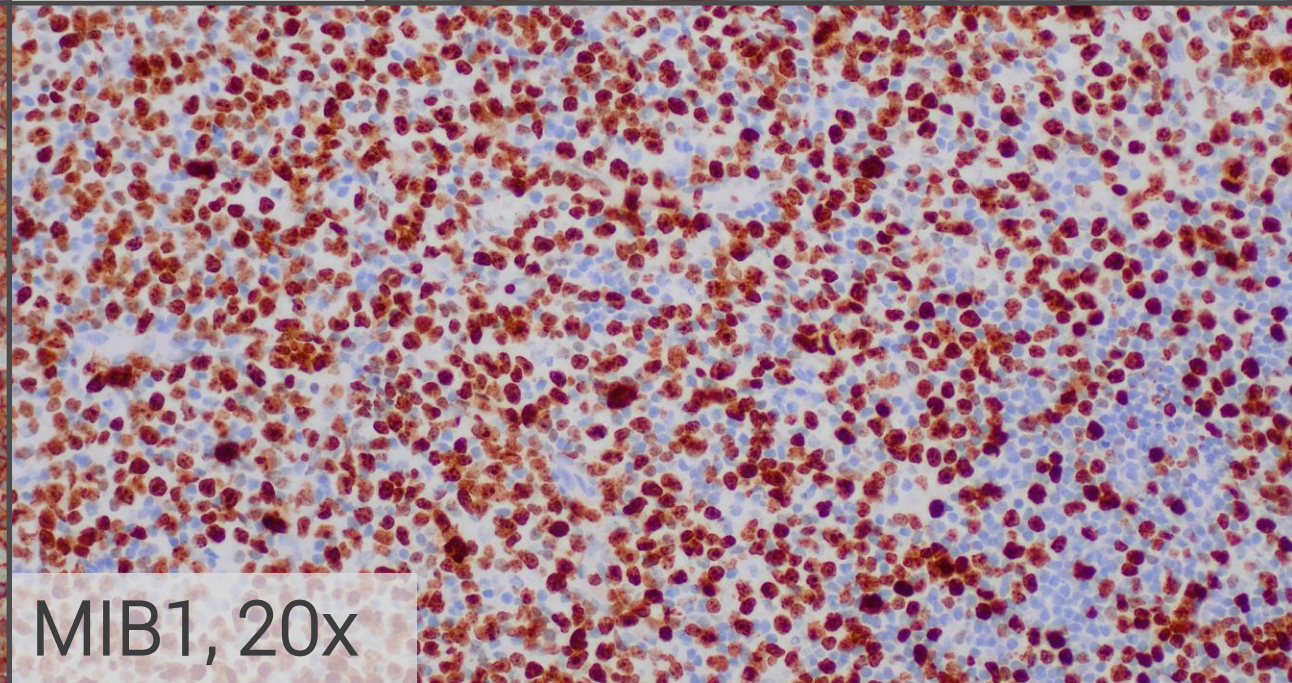
H+E, 20x



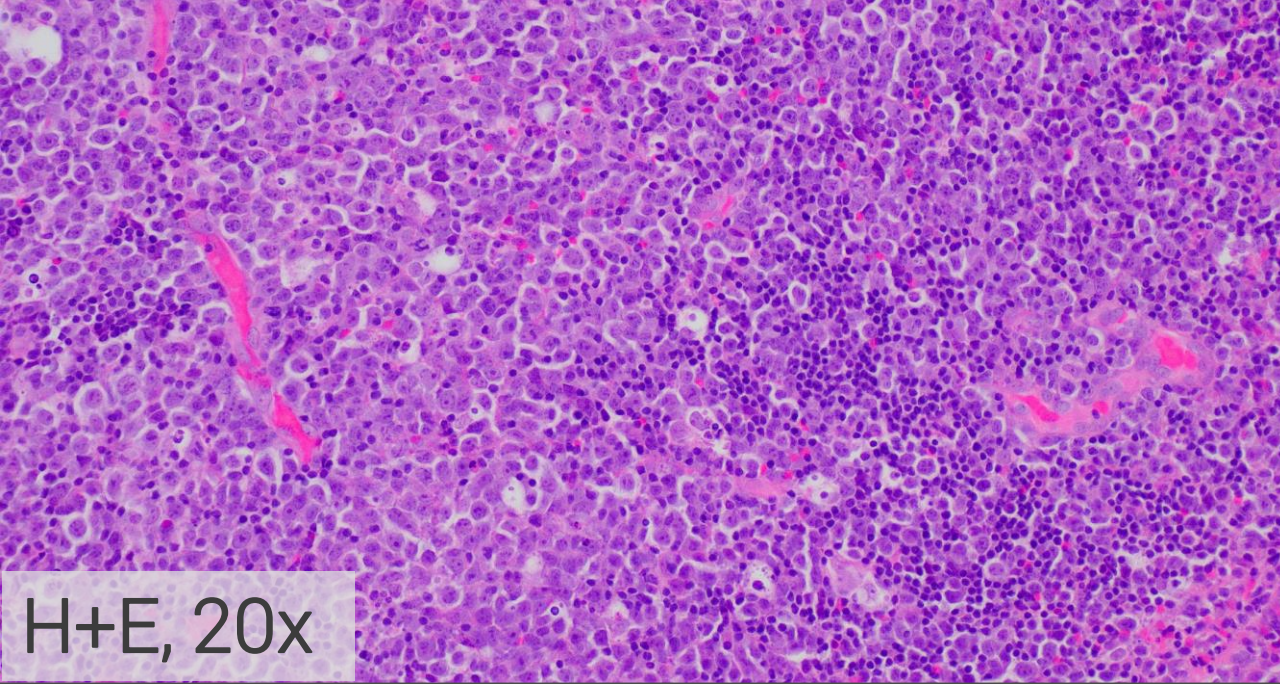
CD3, 20x



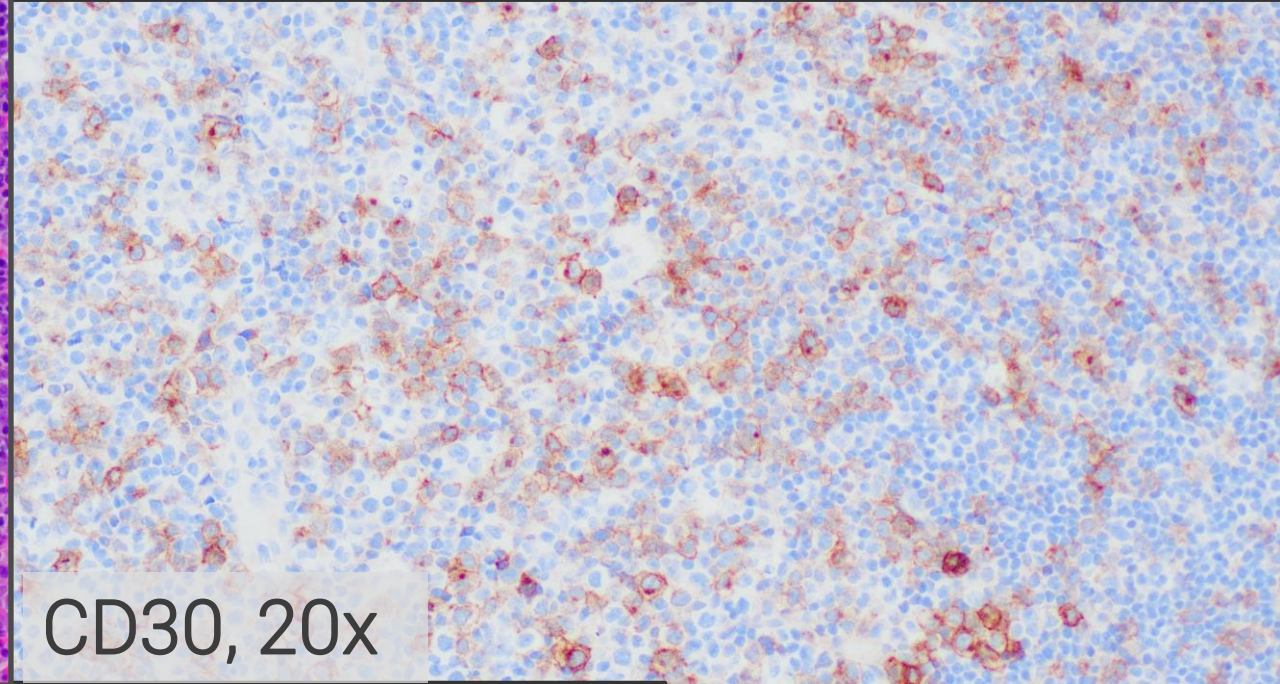
CD20, 20x



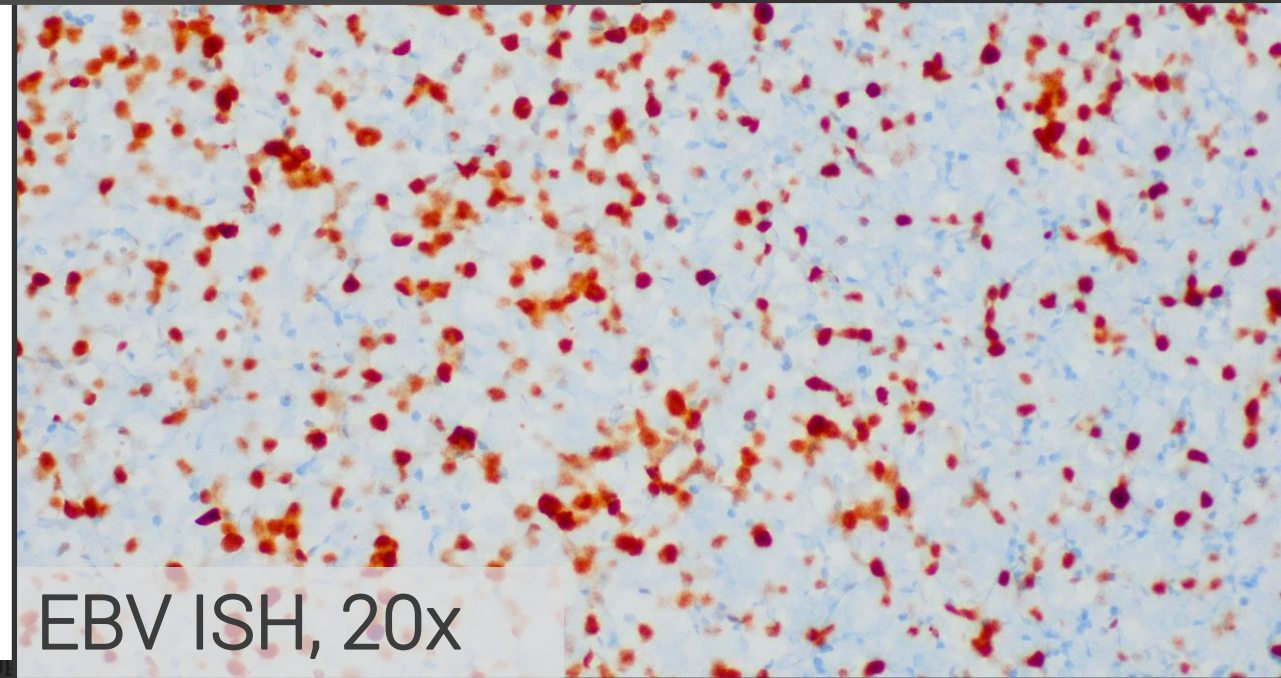
MIB1, 20x



H+E, 20x



CD30, 20x



EBV ISH, 20x

# Case 1: EBV lymphadenitis:

- Clusters to sheets of mitotically active immunoblasts
- Pleomorphic Reed-Sternberg like cells
- Larger biopsies can help to show other areas of preserved architecture
- Immunohistochemistry can help:
  - » Immunoblasts may be mix of CD20 and CD3+ cells
  - » Retained B-cell expression (CD20, OCT-2, BOB-1)
  - » CD30 should be variable and in spectrum of cell sizes

PMID: 22627742

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**Clinical correlation is essential to avoid over-calling this**

PMID: 22627742

# Case 1

## Core Needle Biopsy in Lymphoma Diagnosis

### *The Diagnostic Performance and the Role of the Multidisciplinary Approach in the Optimization of Results*

*Marianne de C. Gonçalves, MD, PhD,\* Claudia Regina G.C.M. de Oliveira, MD, PhD,\*  
Alex F. Sandes, MD, PhD,† Celso A. Rodrigues, MD, PhD,‡ Yana Novis, MD,§  
Públio C.C. Viana, MD,|| Márcia M.P. Serra, PhD,¶ and Maria Claudia N. Zerbini, MD, PhD#*

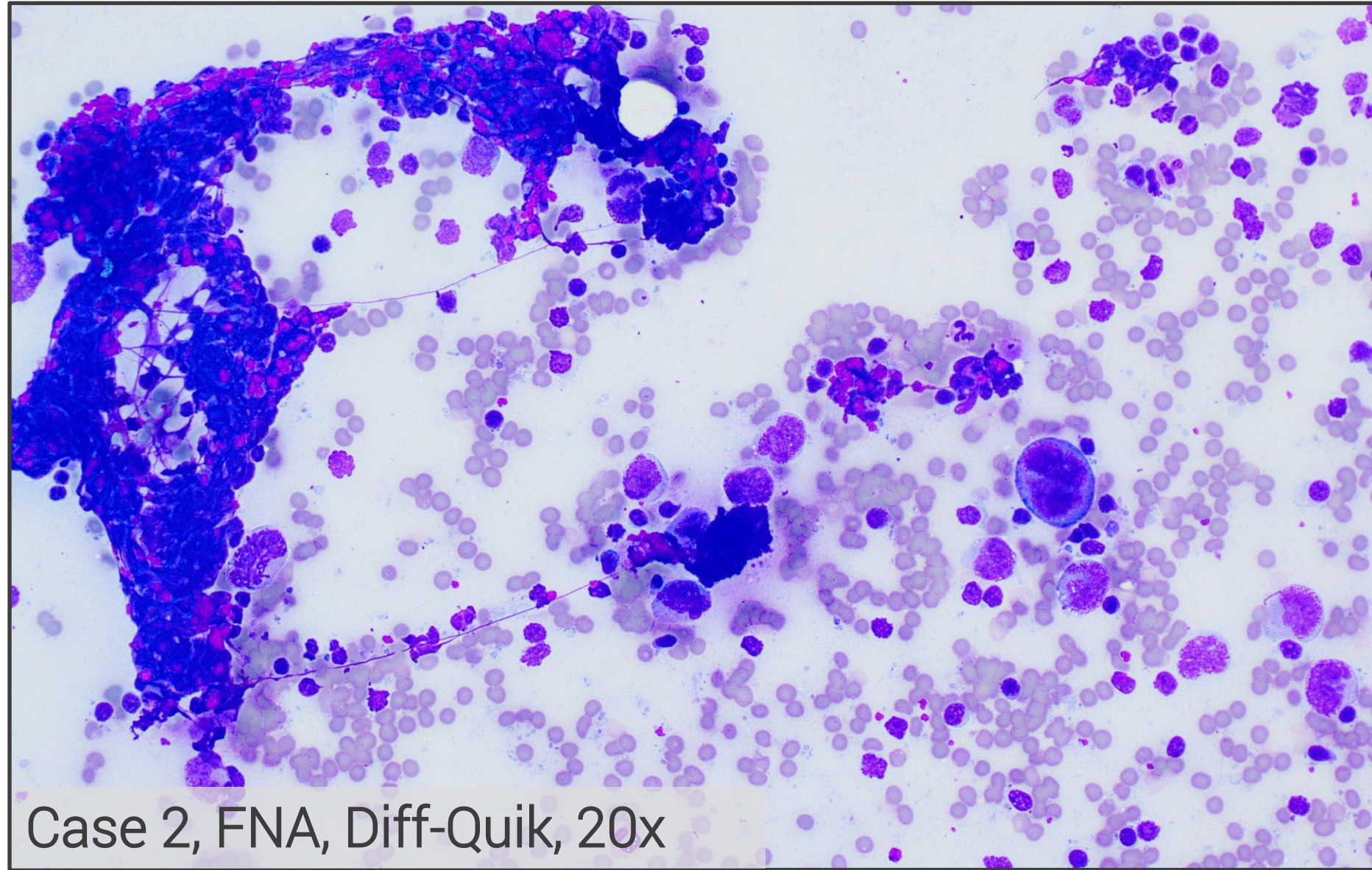
Clinical and radiologic assessments considered essential for diagnosis is significantly more core needle biopsy assessments than excisional biopsies

PMID: 36395467

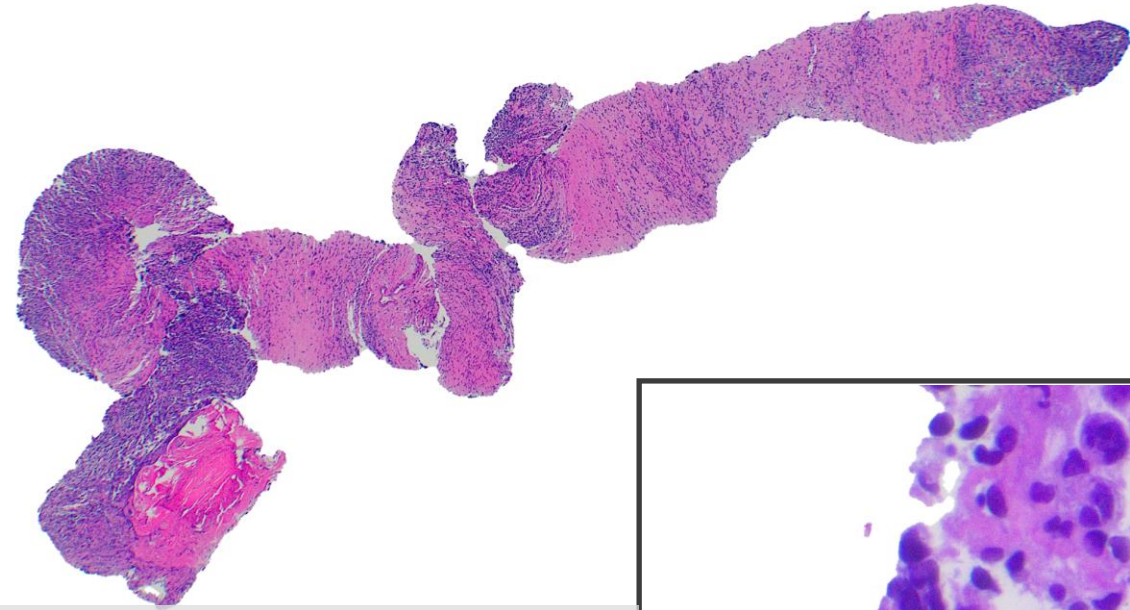
## ■ Case 2

## Case 2

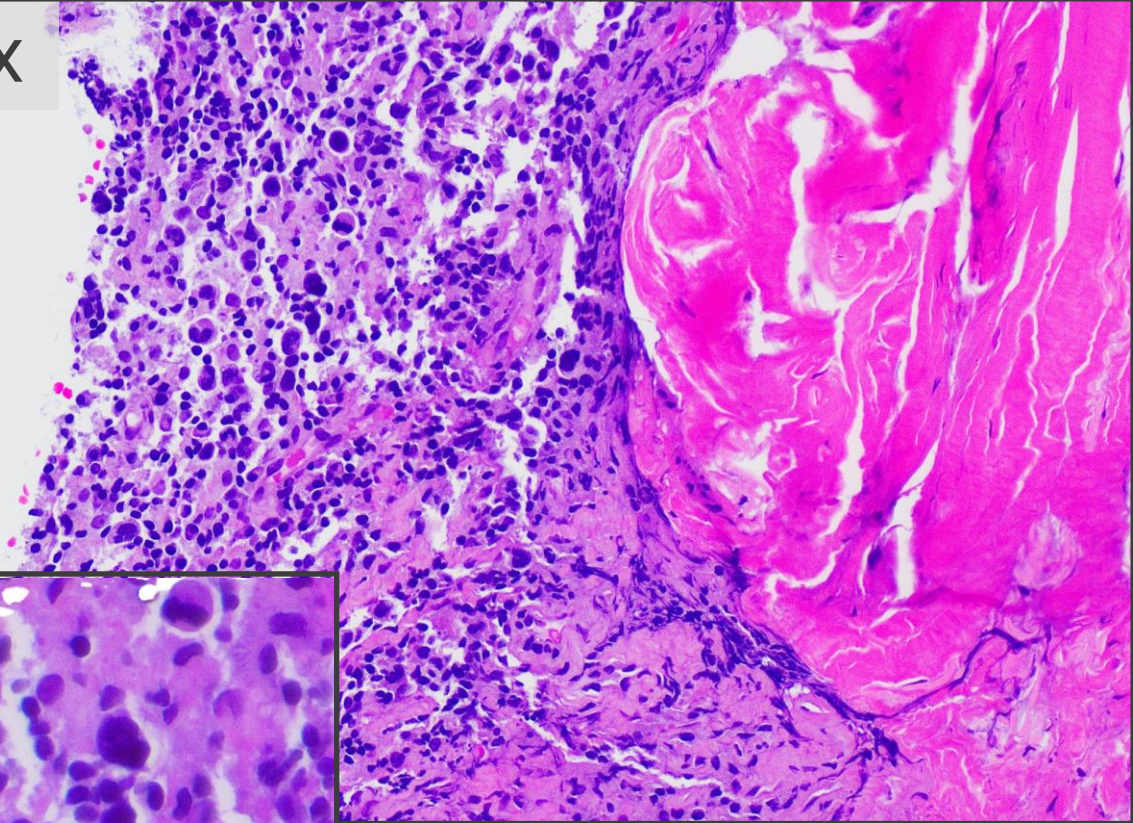
28-year-old male patient with a history of widespread intra-abdominal and pelvic lymphadenopathy with rapid growth



Case 2, FNA, Diff-Quik, 20x

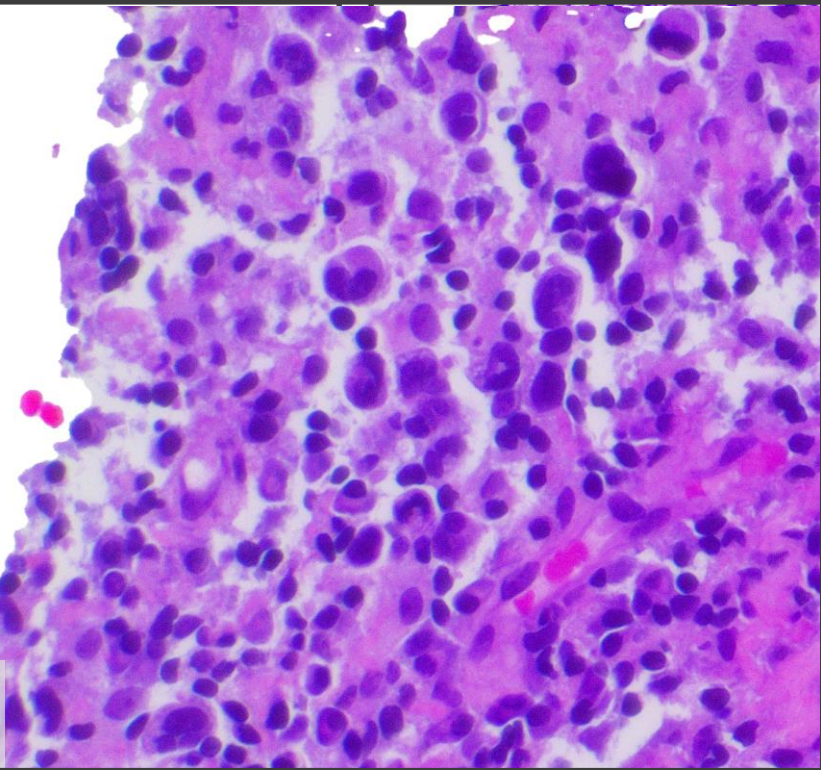


20x

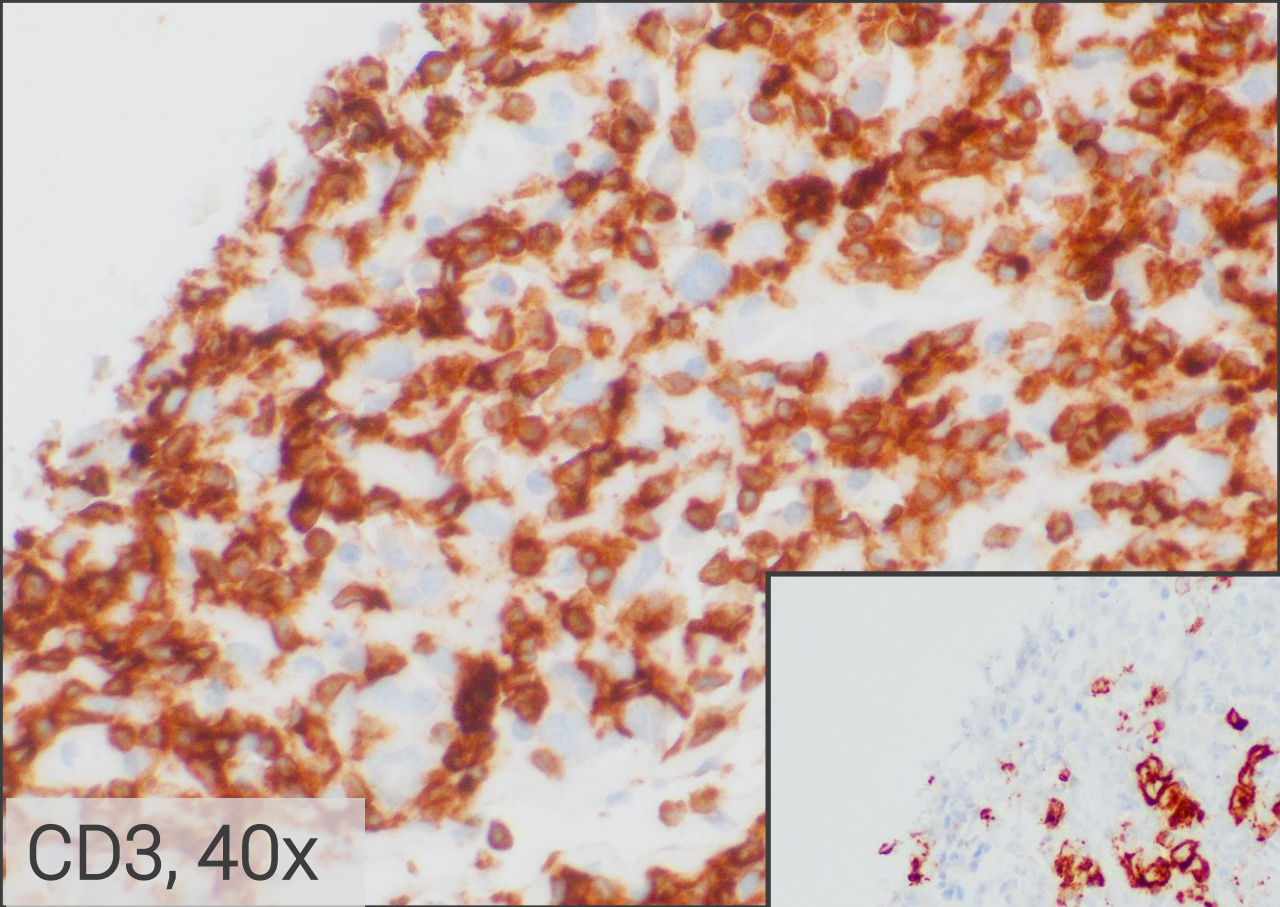


Case 2, CNB, H+E, 2x

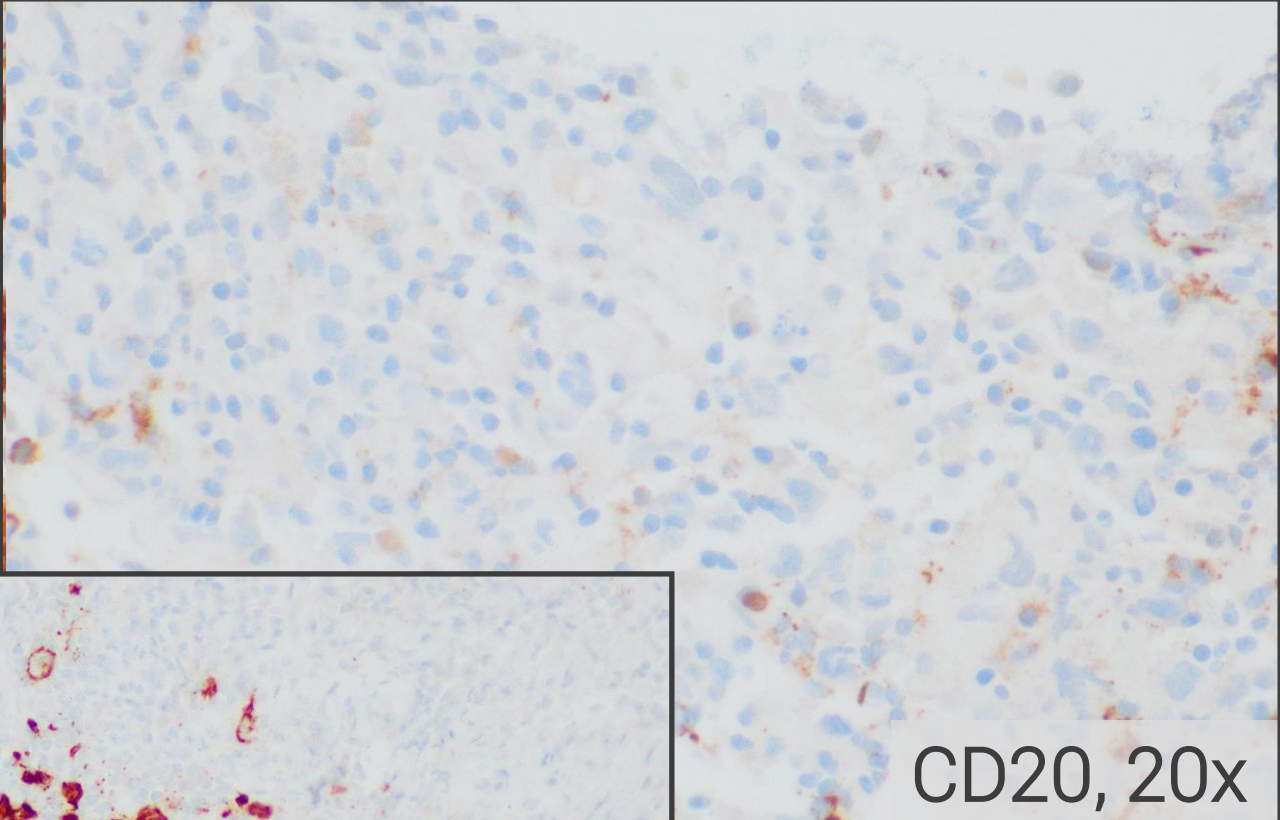
40x



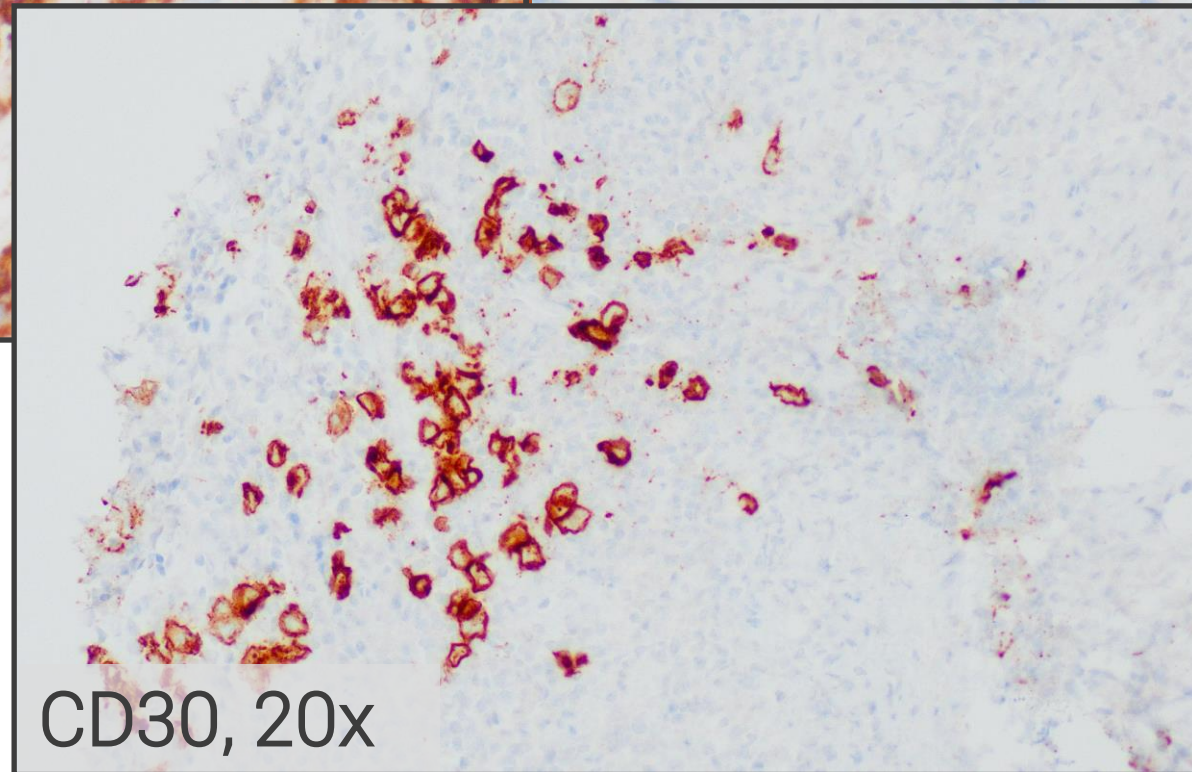




CD3, 40x



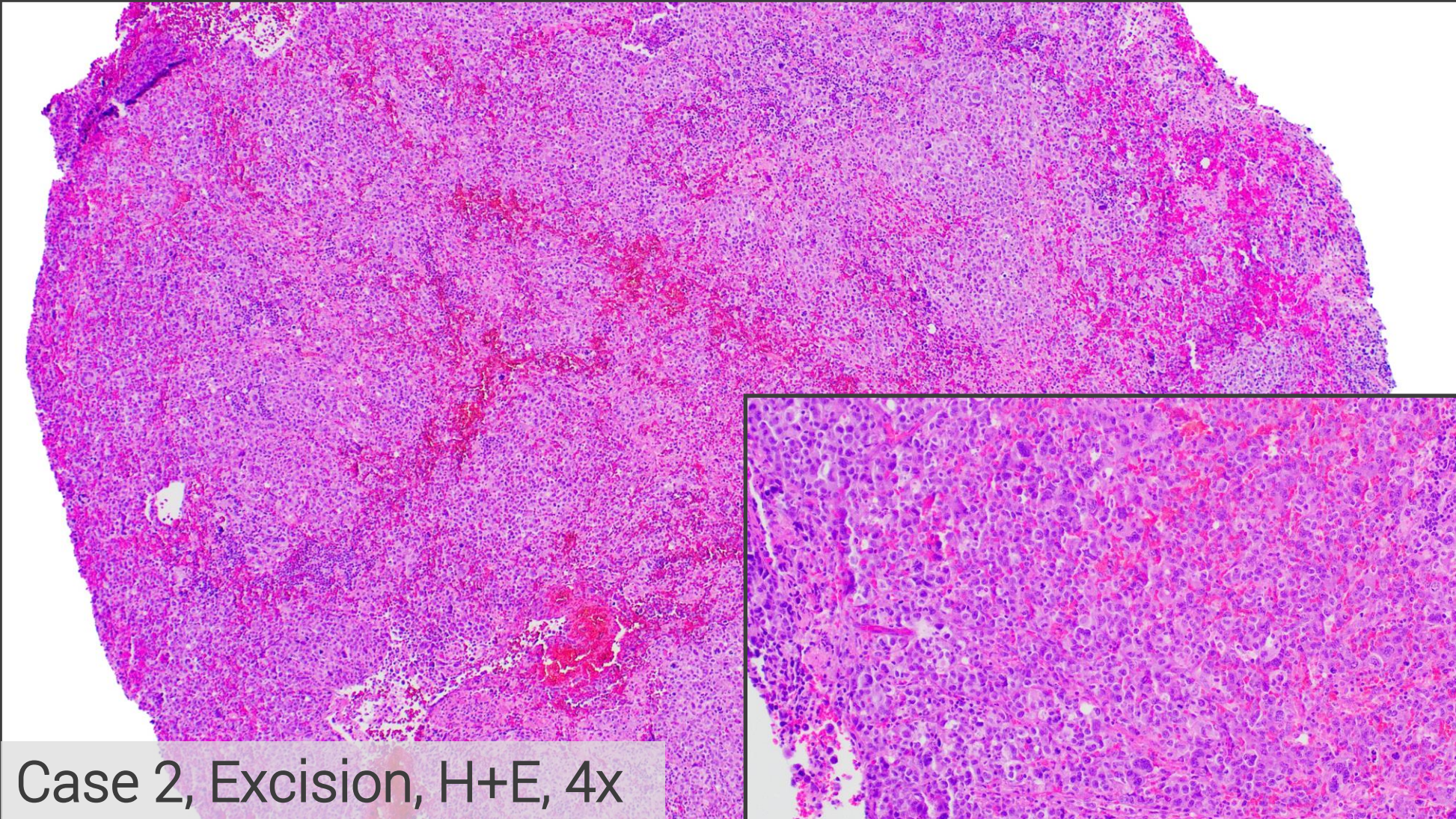
CD20, 20x



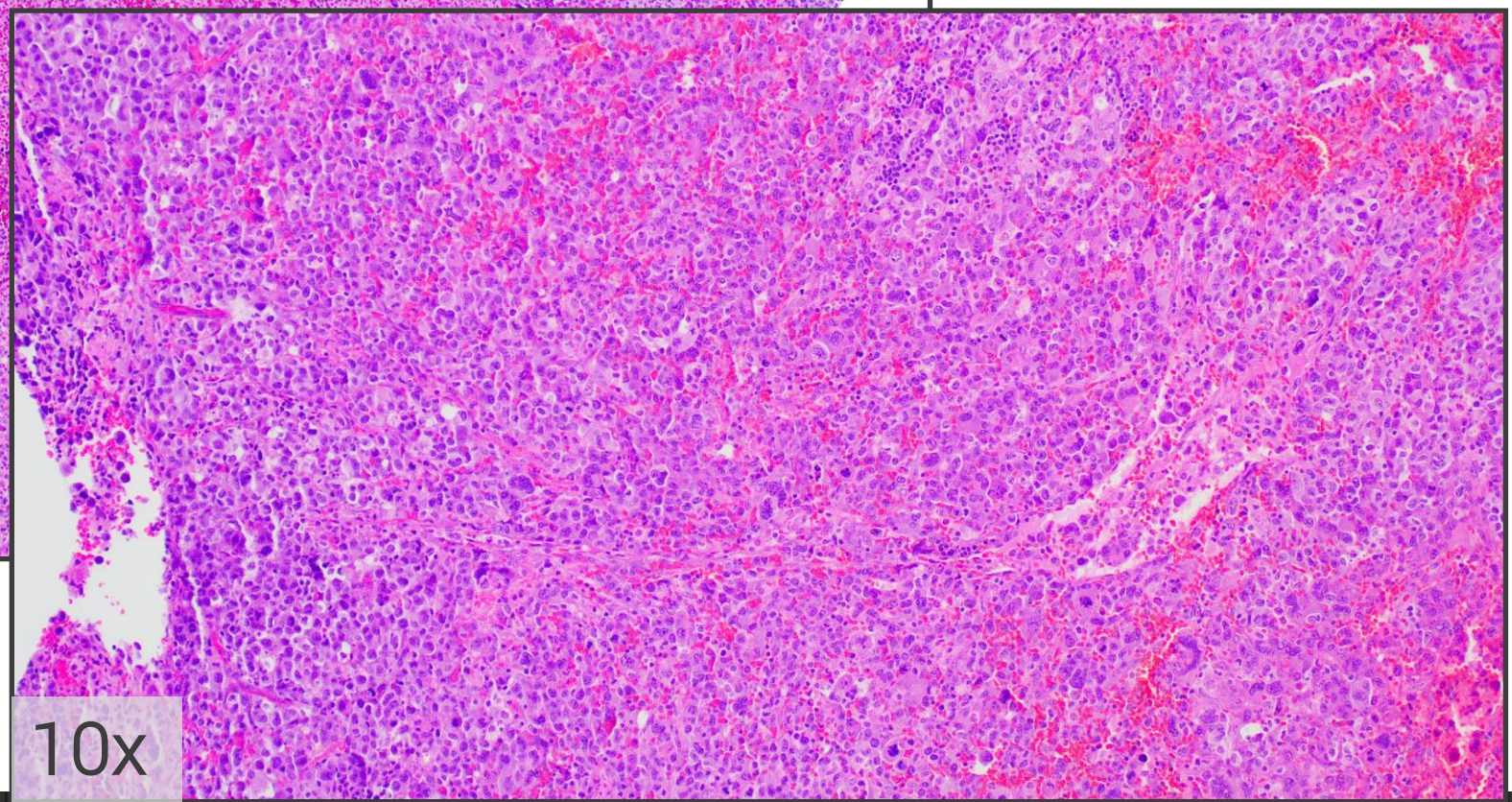
CD30, 20x

# Case 2:

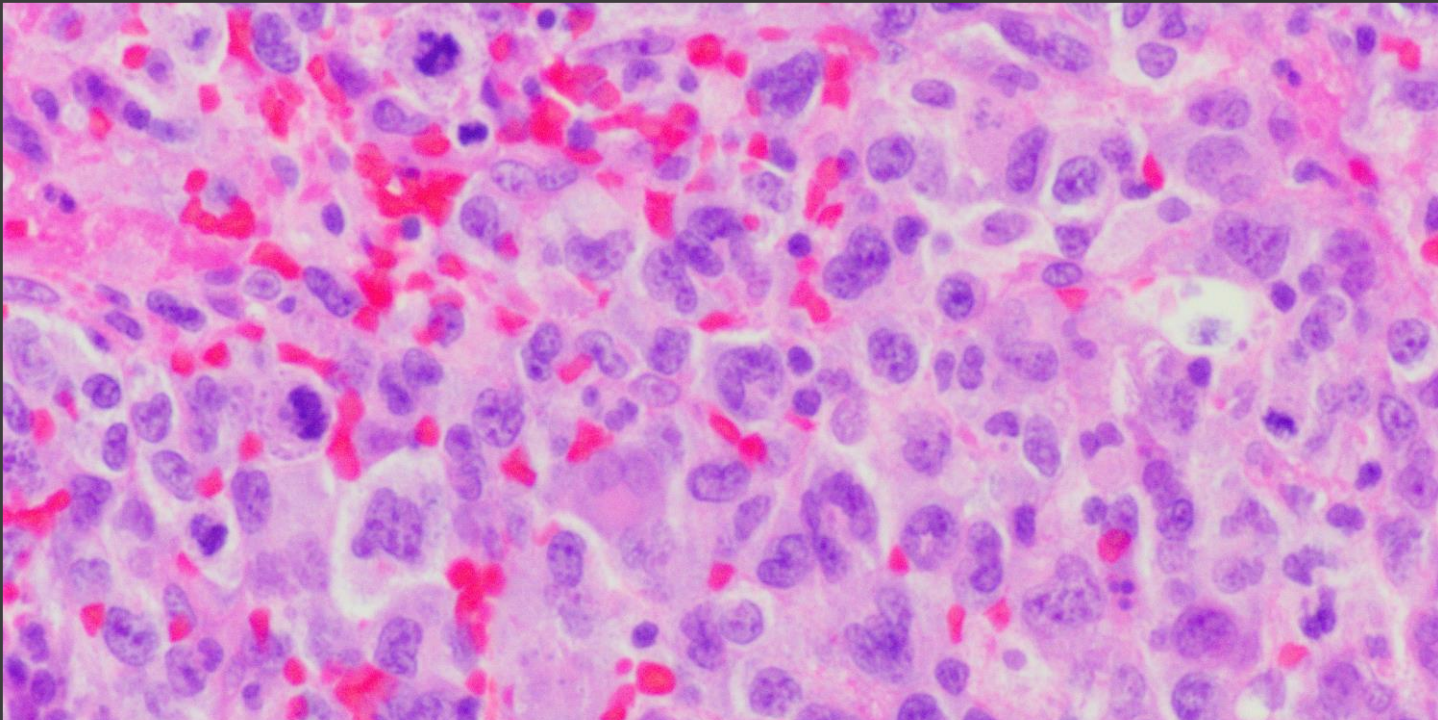
- Differential for Hodgkin-Like Cells:
  - » EBV Lymphadenitis
  - » Classical Hodgkin Lymphoma
  - » Nodular Lymphocyte Predominant Hodgkin Lymphoma
  - » T-cell Lymphomas
    - Nodal T-follicular Helper Cell Lymphomas (include angioimmunoblastic-type, follicular type, NOS)
    - Anaplastic Large Cell Lymphoma
  - » Large B-cell Lymphomas
    - Immune Deficiency/Dysregulation- Associated or EBV+ Diffuse Large B-cell Lymphoma
    - T-cell/Histiocyte-Rich Large B-cell Lymphoma
    - Mediastinal Grey Zone Lymphoma



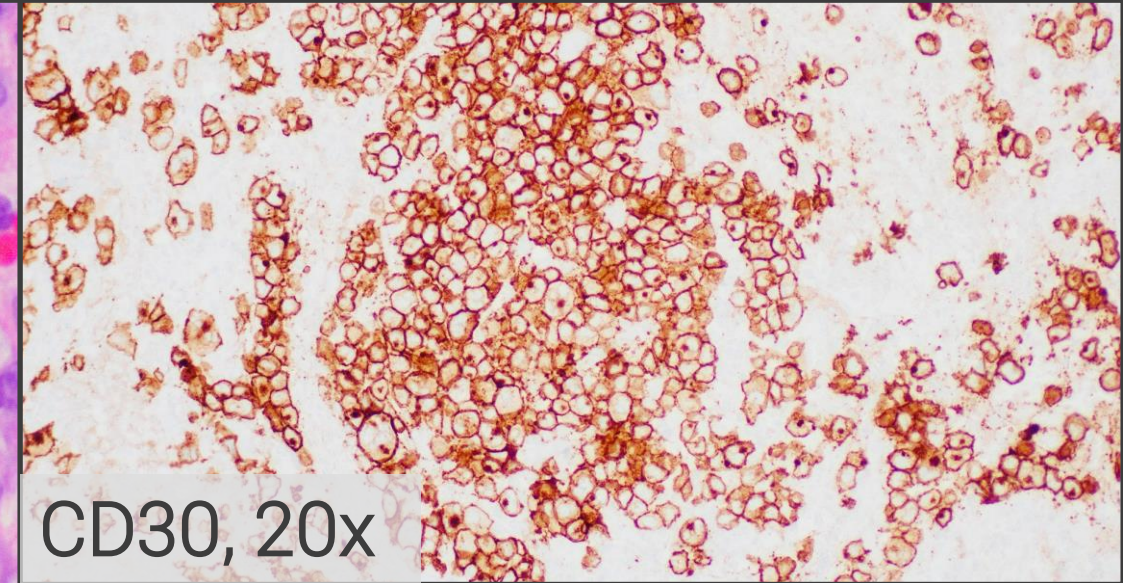
Case 2, Excision, H+E, 4x



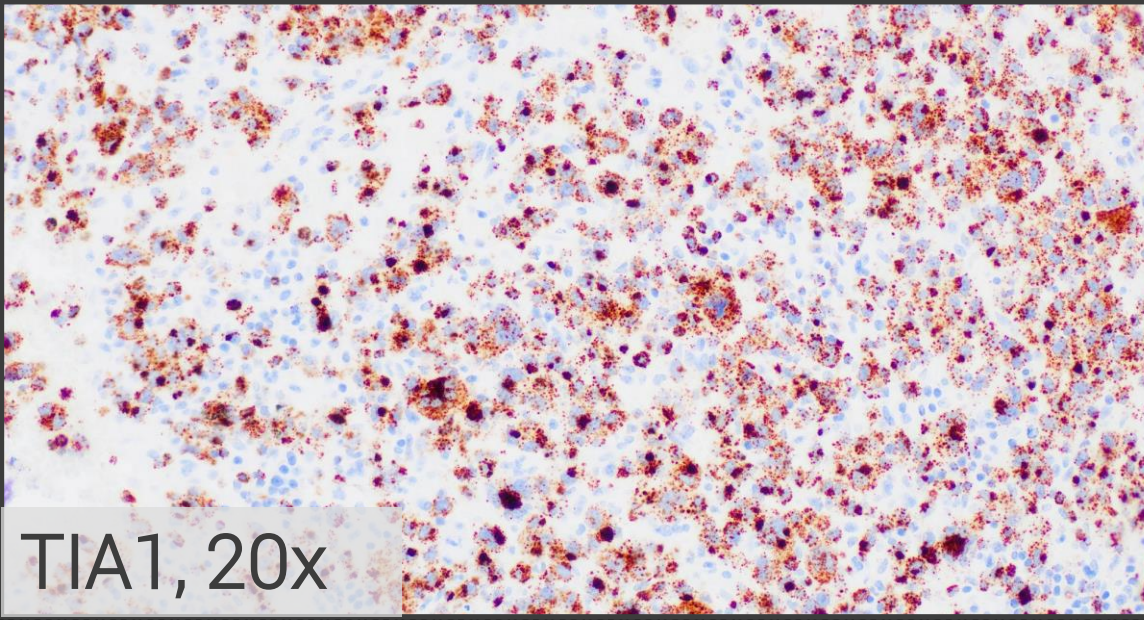
10x



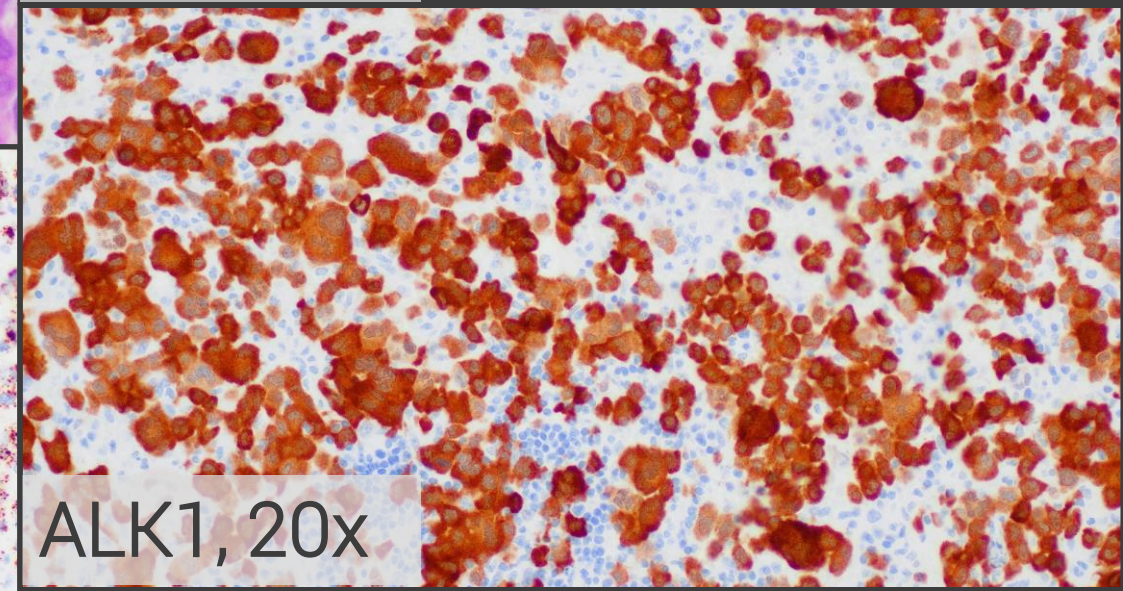
50x



CD30, 20x



TIA1, 20x

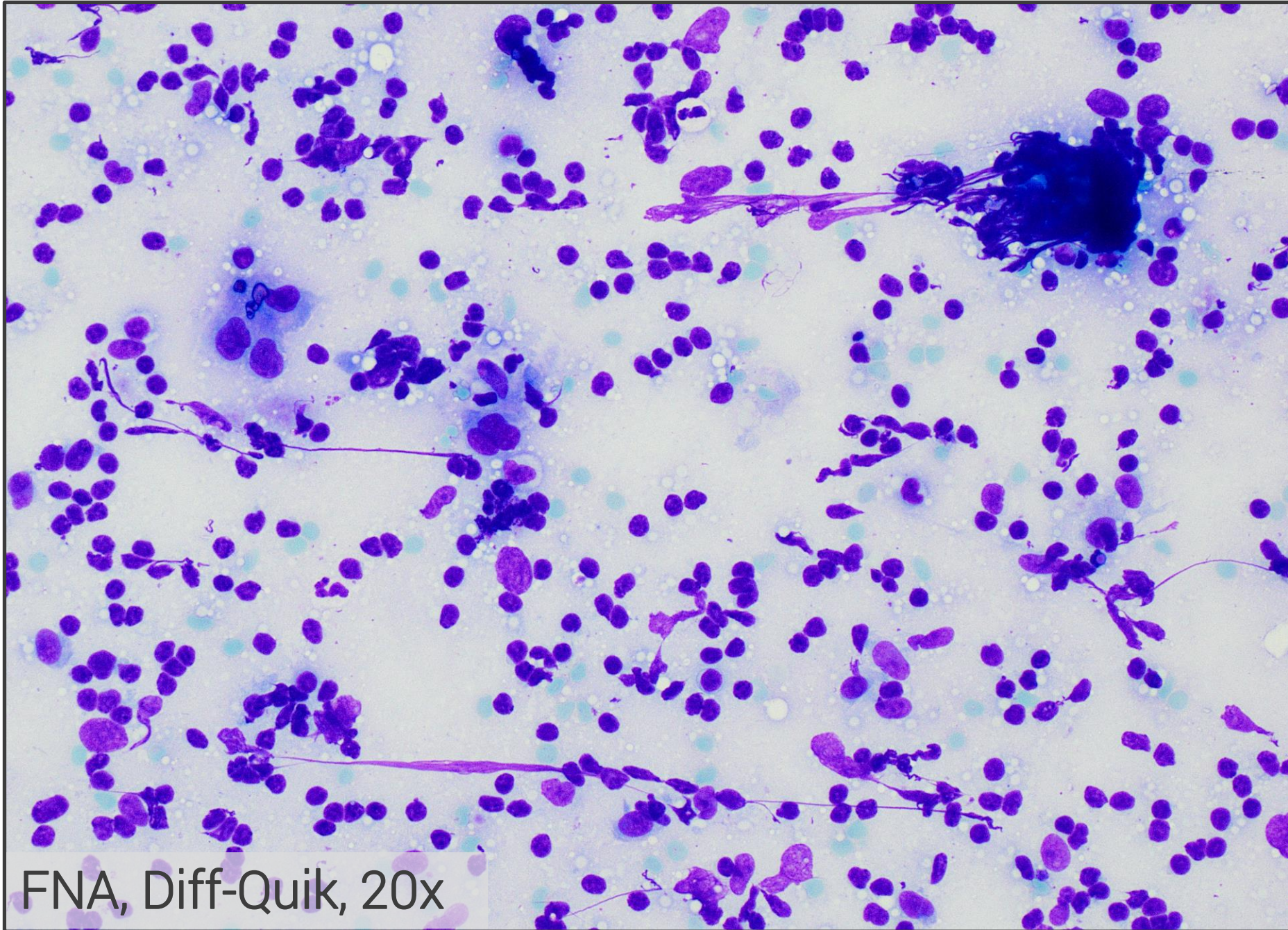


ALK1, 20x

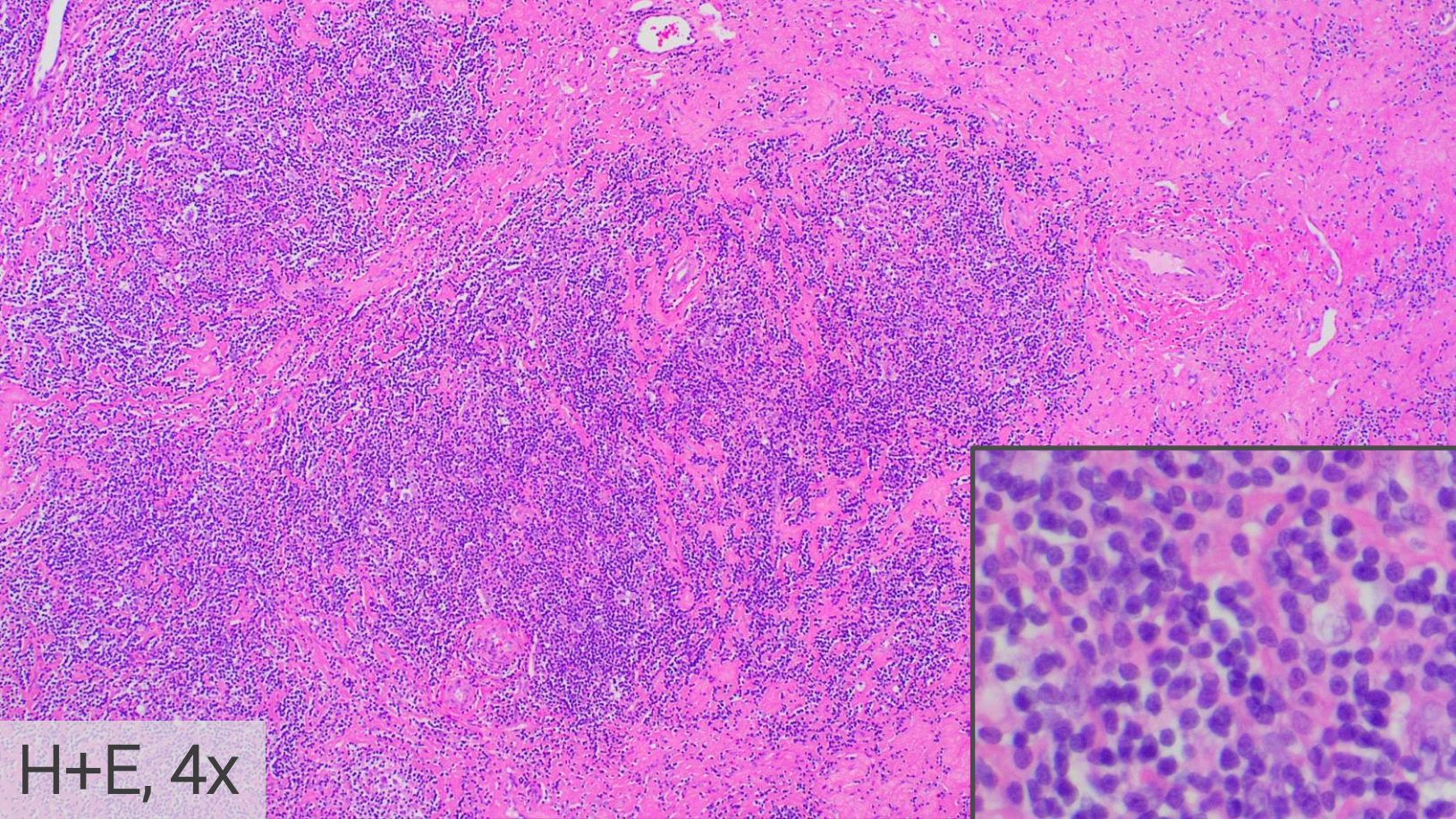
# Case 2:

- Diagnosis: Anaplastic Large Cell Lymphoma, ALK-Positive
- Morphology is key in the diagnosis of lymph nodes with Hodgkin-like cells
  - » Need adequate tissue to evaluate
  - » Immunophenotype can sometimes be challenging
    - Rare PAX5+ cases of ALCL
    - Uncommon Classic Hodgkin Lymphoma cases can express CD3 or CD5
    - Uncommon Nodular Lymphocyte Predominant Hodgkin Lymphoma cases can express CD30 and rare cases can express CD15
  - » Interpretation of molecular studies in limited core biopsies can also be challenging

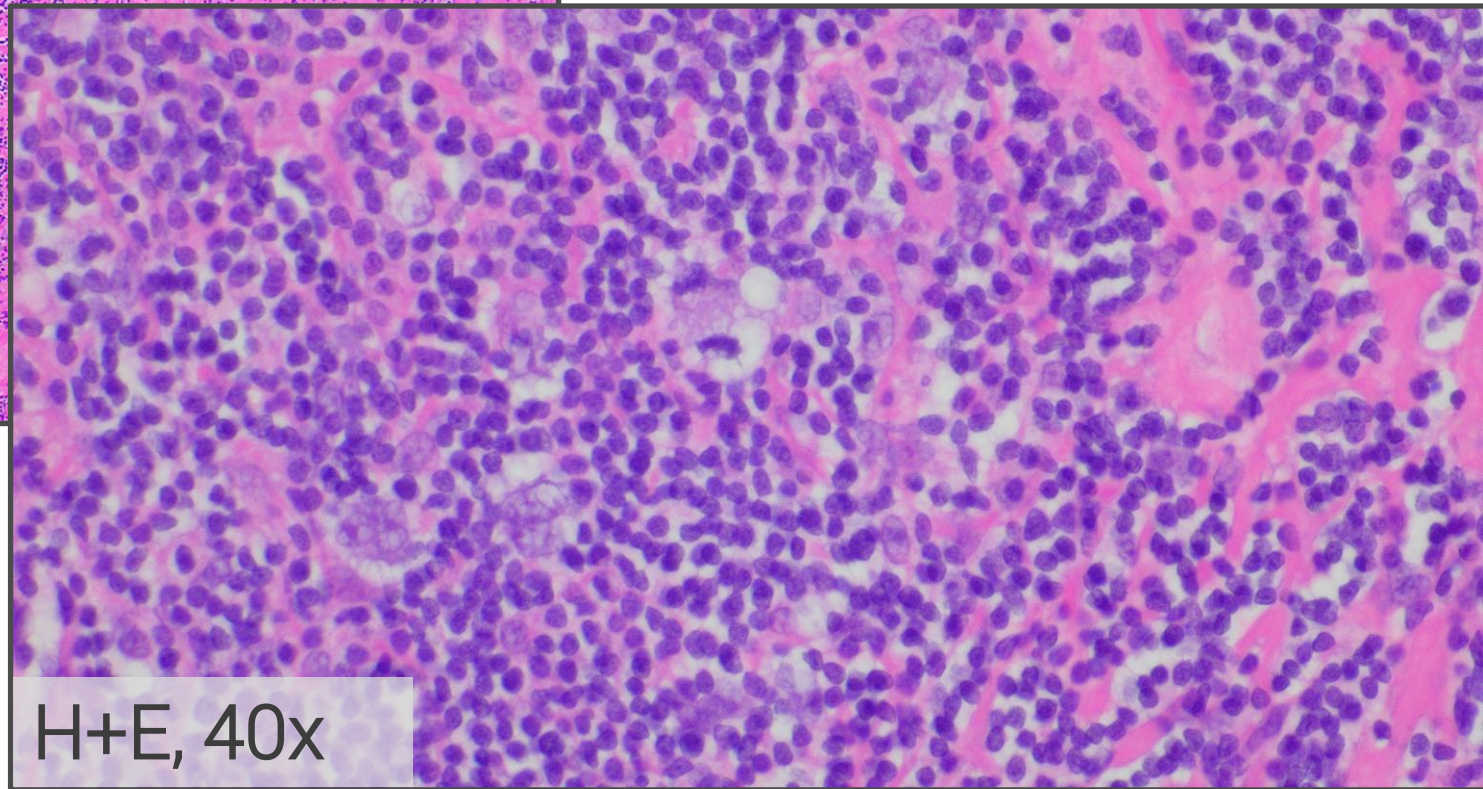
63-year-old male with waxing and waning chronic neck lymphadenopathy for over 10 years, now with hypercalcemia, large neck mass, hepatosplenomegaly, and retroperitoneal lymphadenopathy



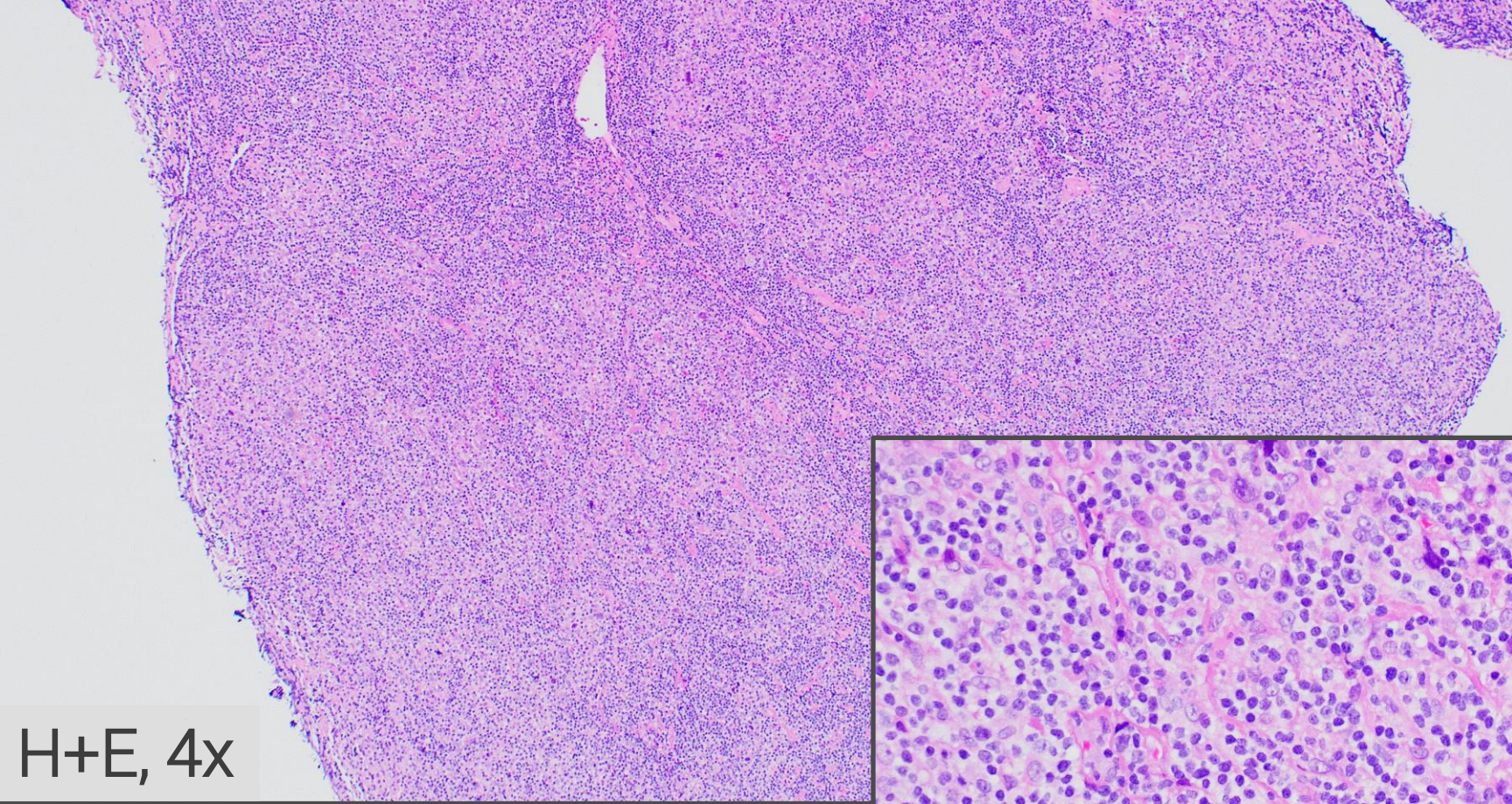
FNA, Diff-Quik, 20x



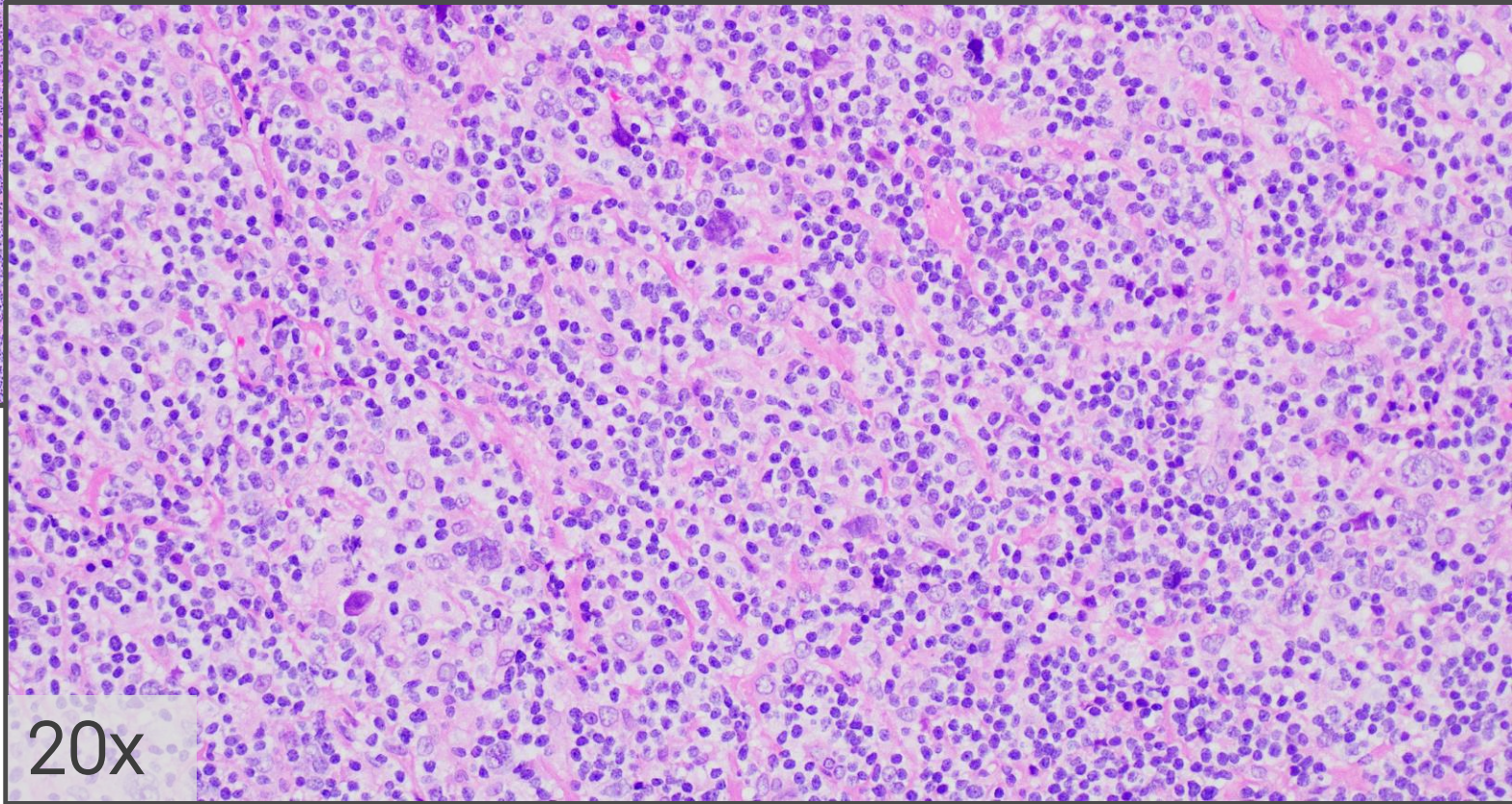
H+E, 4x



H+E, 40x



H+E, 4x



20x



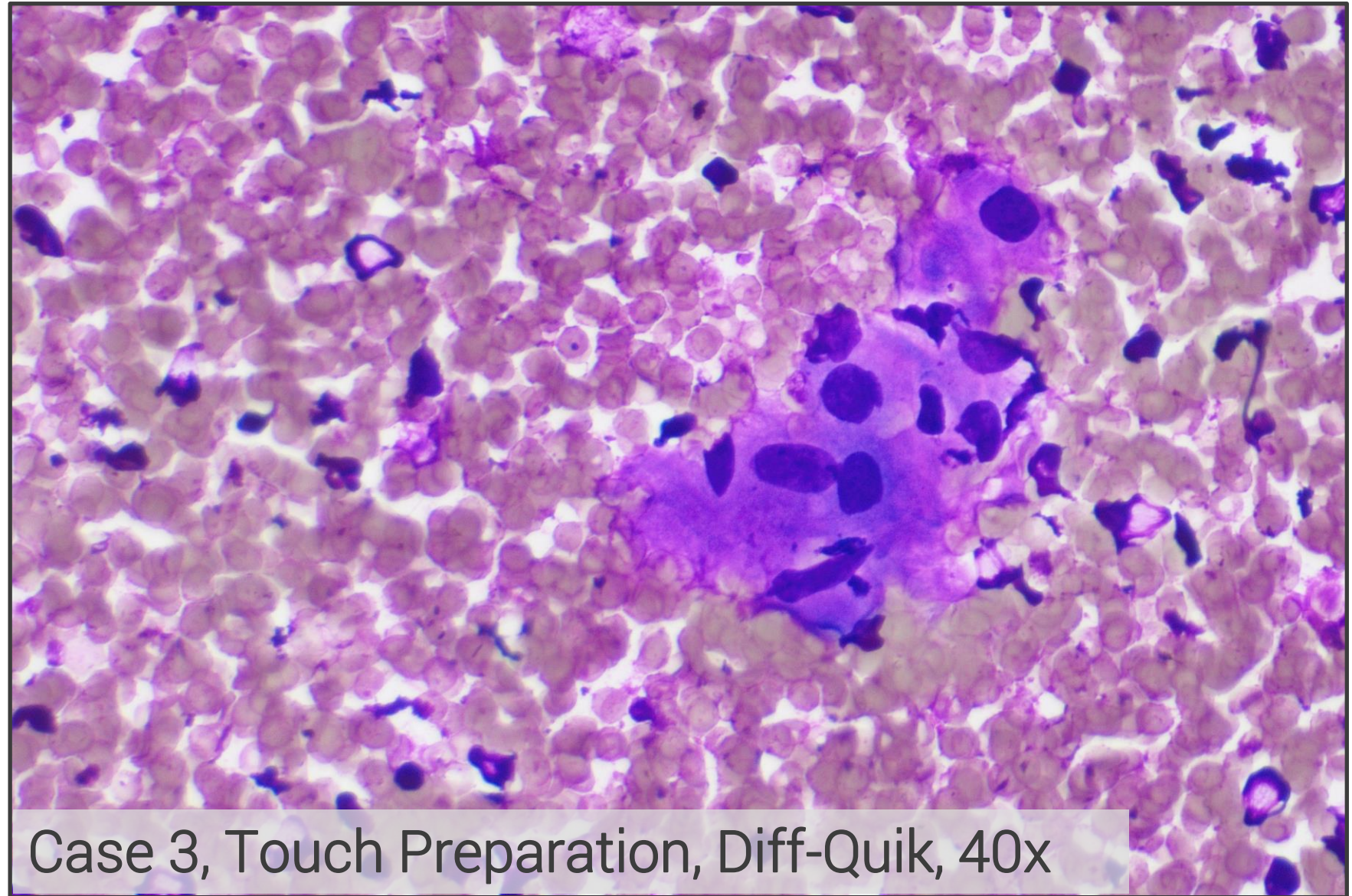
# Case 2:

- Morphology is key in the diagnosis of lymph nodes with Hodgkin-like cells
- Some tumor types with Hodgkin-like cells show significant heterogeneity
  - » Nodular Lymphocyte Predominant Hodgkin Lymphoma and T-cell/Histiocyte-Rich Large B-cell Lymphoma (TCHRLBL) are distinguished by architectural patterns which may be limited
- Clinical correlation and discussion with the treating oncologist about therapeutic implications can be helpful

# ■ Case 3

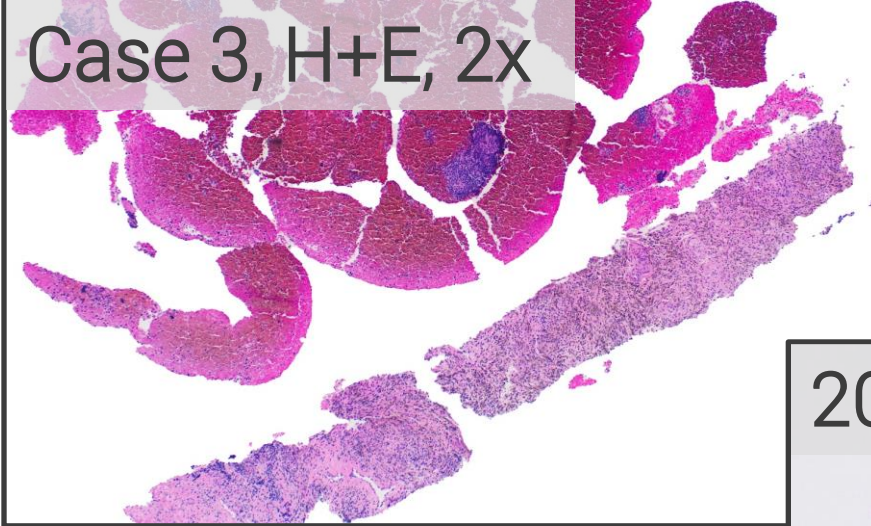
## Case 3

29-year-old male patient with several year history of cough and imaging showing bilateral hilar lymphadenopathy

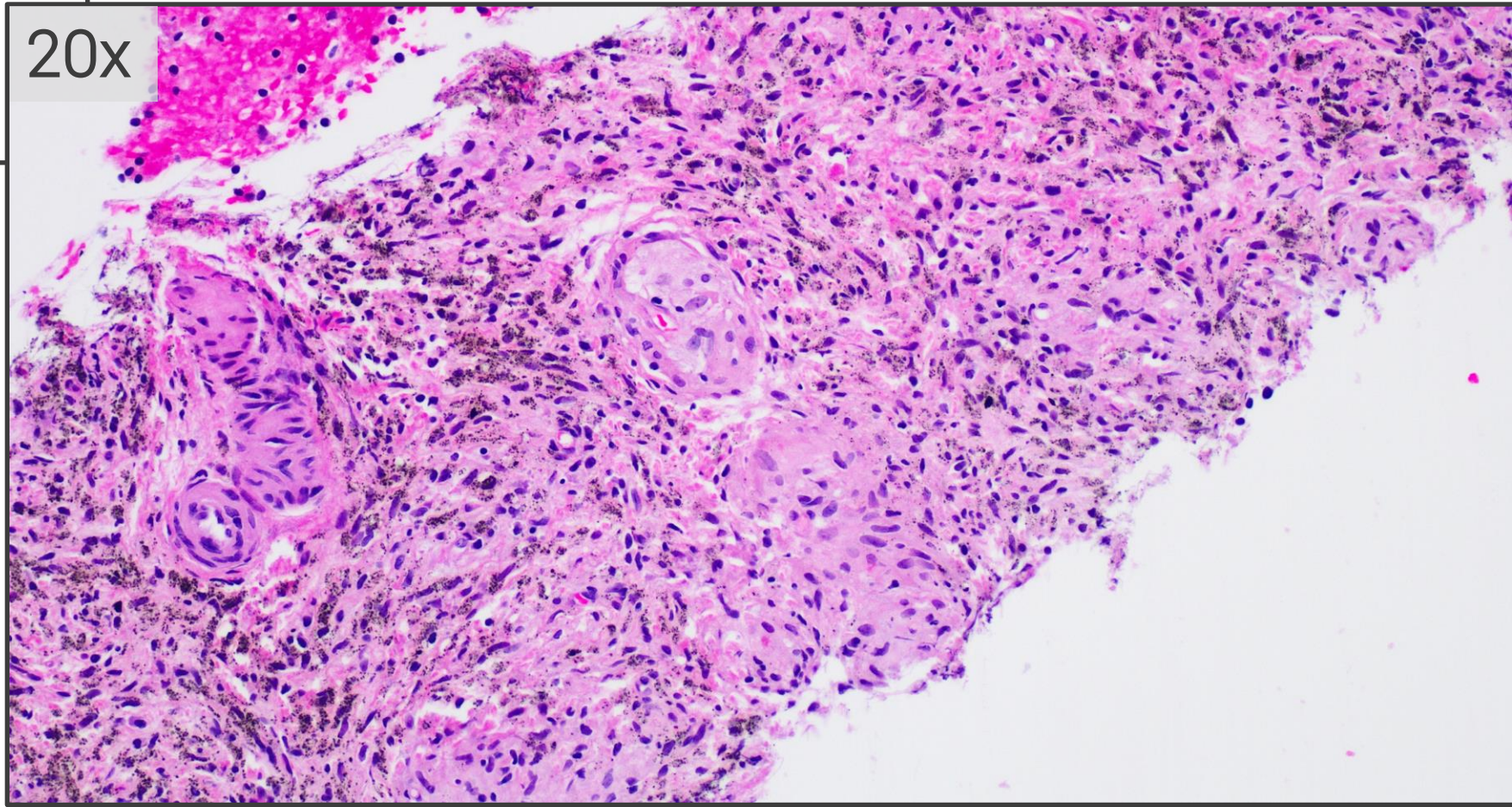


Case 3, Touch Preparation, Diff-Quik, 40x

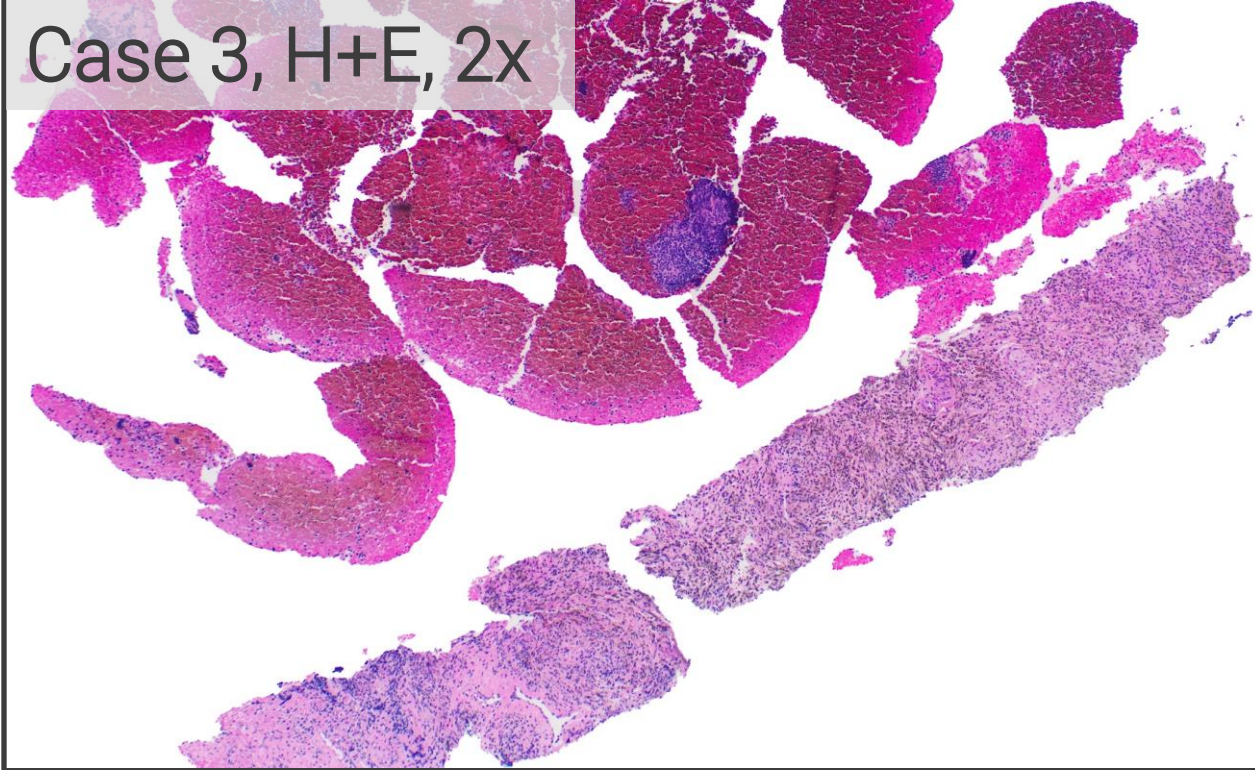
Case 3, H+E, 2x



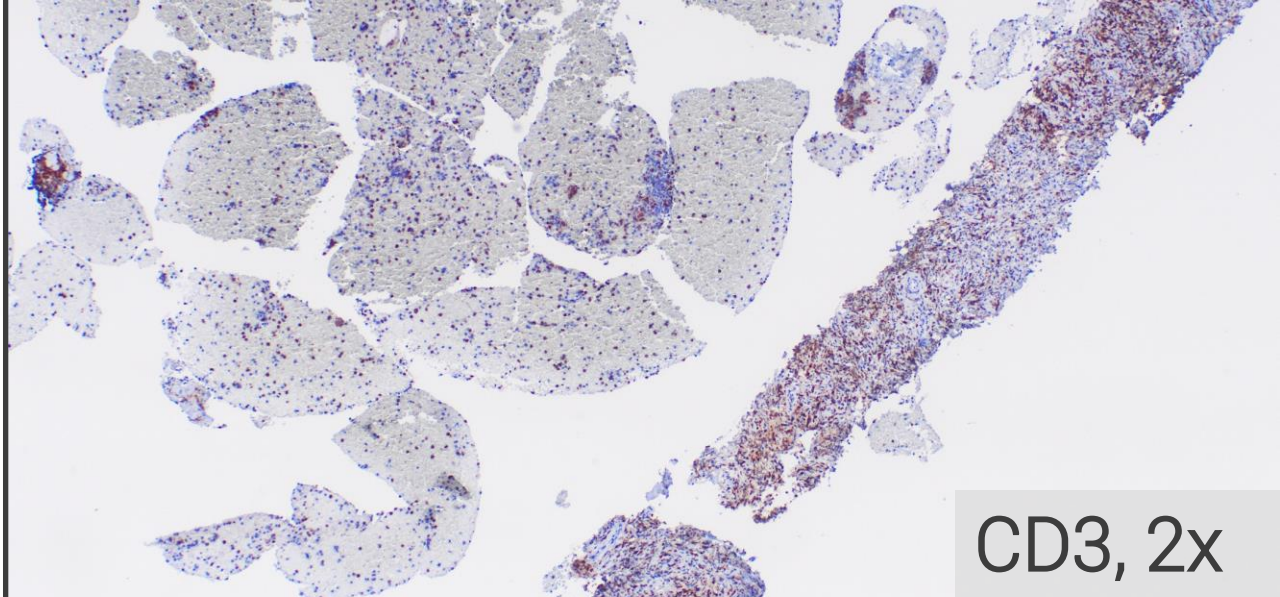
20x



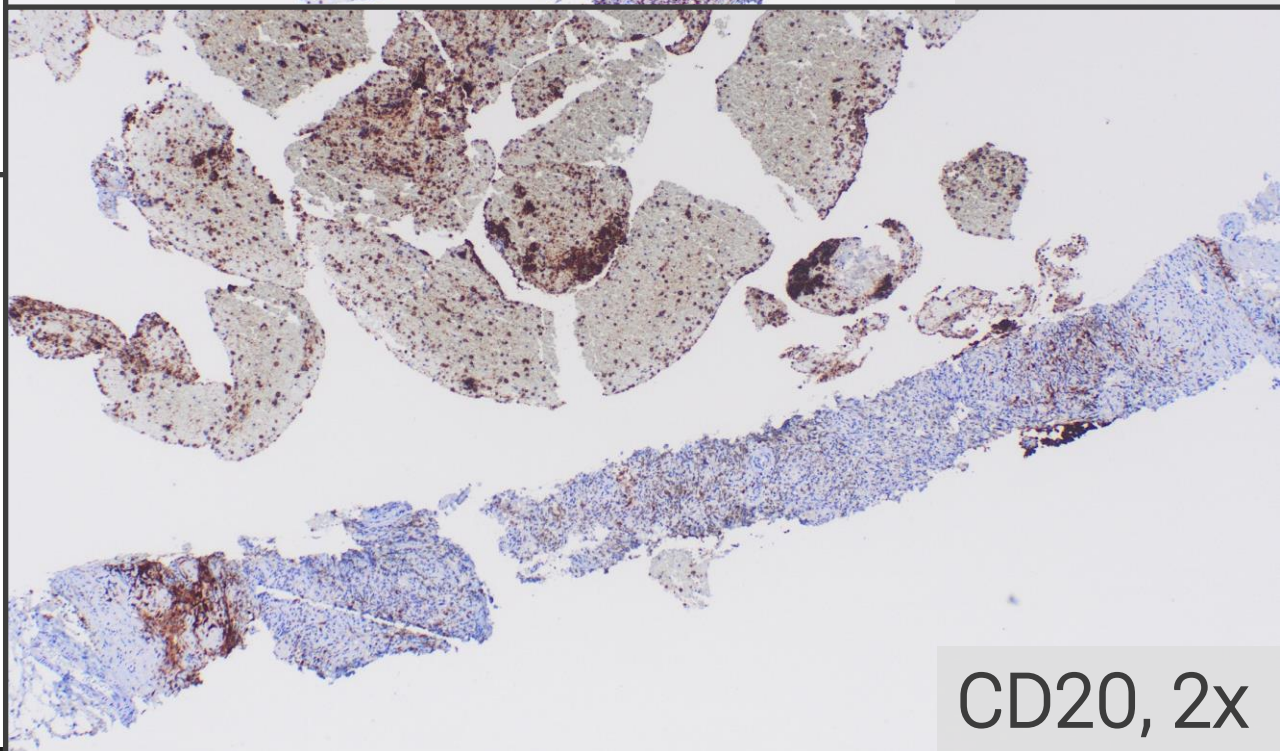
Case 3, H+E, 2x

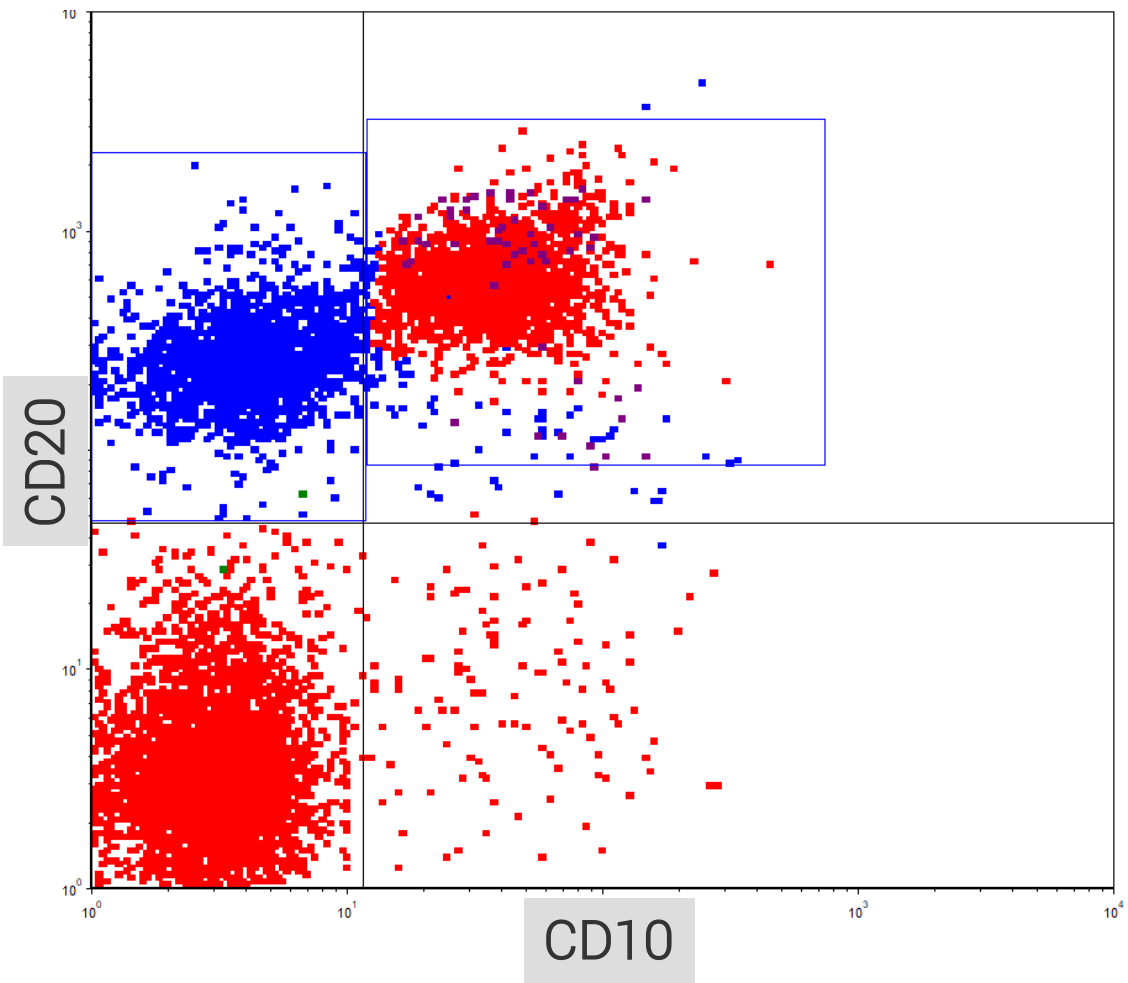


CD3, 2x

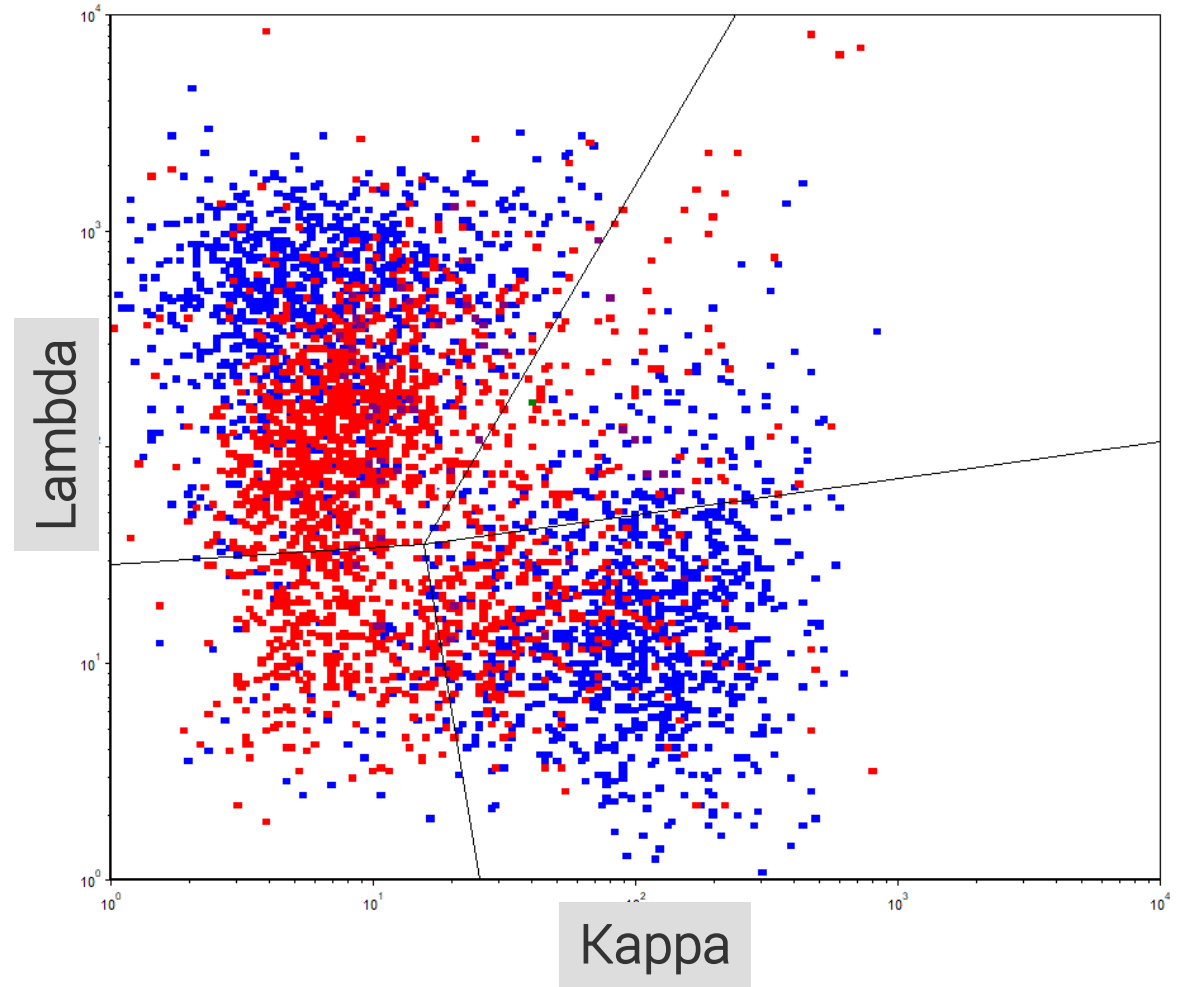


CD20, 2x





About half of CD20+ B-cells express CD10



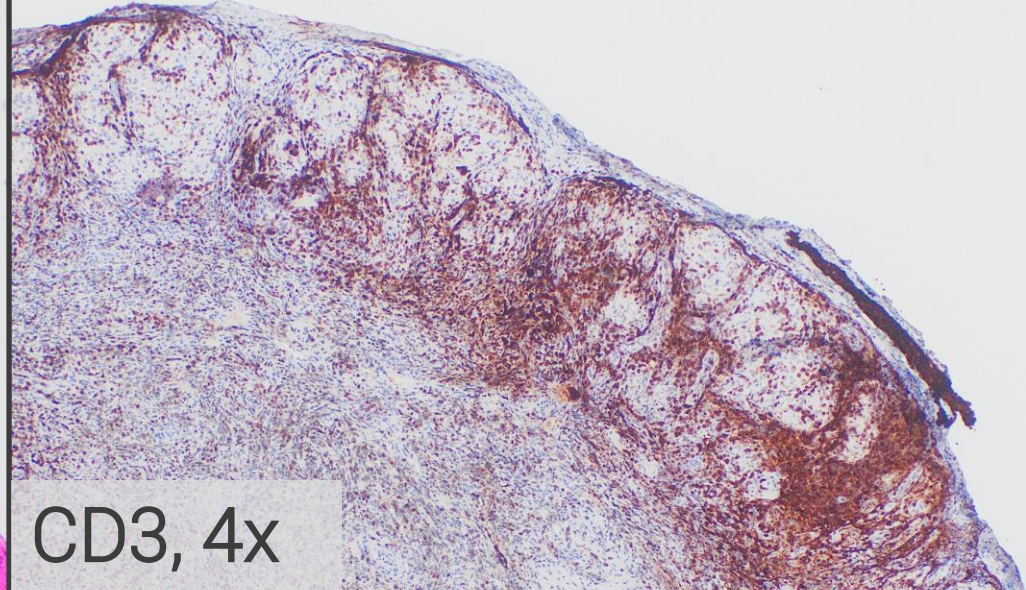
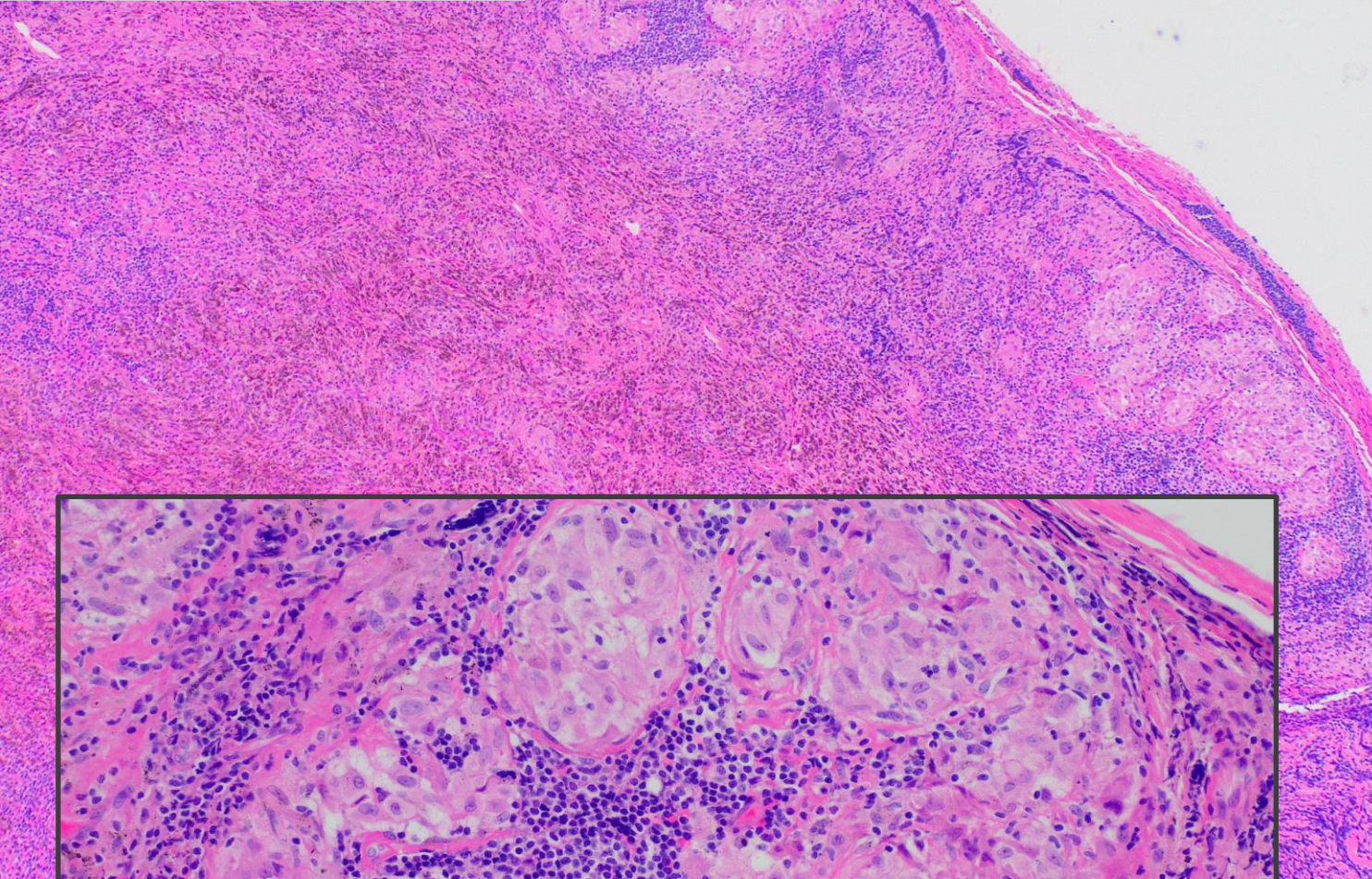
CD10+ B-cells: K/L ratio: 0.2  
 CD10- B-cells: K/L ratio: 1.1

# Case 3

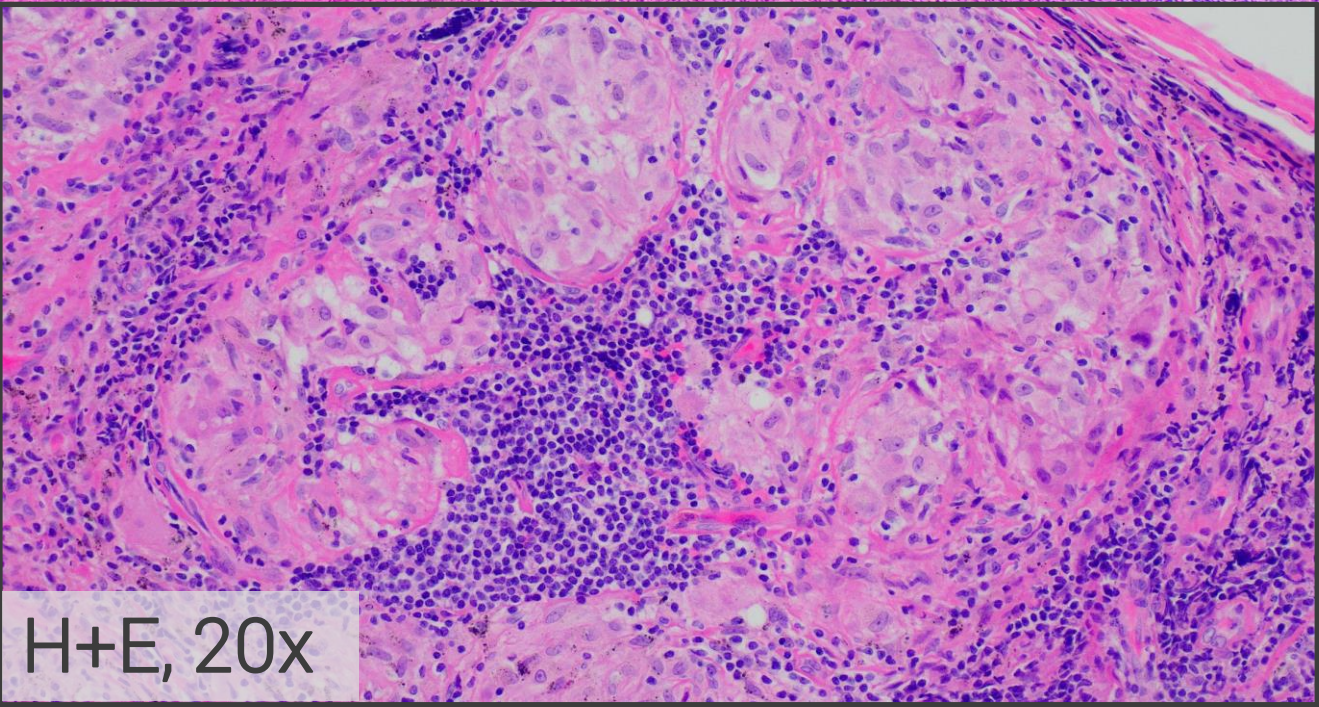
FNA and CNB Diagnosis:

- Non-necrotizing granulomatous inflammation
- Crystalline material and anthracotic pigment present
- Atypical B-cell population by flow cytometry

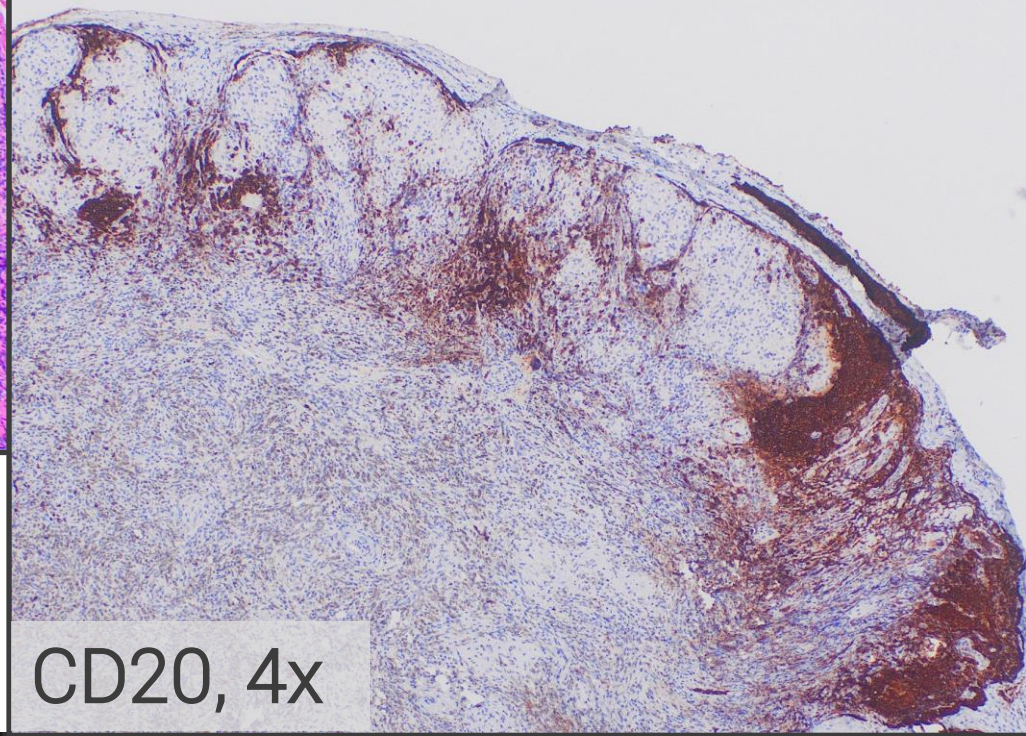
Case 3, H+E, 4x



CD3, 4x



H+E, 20x



CD20, 4x



# Case 3

## Final Diagnosis:

- » Non-necrotizing granulomatous lymphadenitis with anthracosis.
- » No evidence of lymphoma.
- » No organisms by special stains.

Previously identified monoclonal population likely represented a small reactive clone.

# Case 3: Reactive Clone

## Core Needle Biopsy in Lymphoma Diagnosis

### *The Diagnostic Performance and the Role of the Multidisciplinary Approach in the Optimization of Results*

*Marianne de C. Gonçalves, MD, PhD,\* Claudia Regina G.C.M. de Oliveira, MD, PhD,\*  
Alex F. Sandes, MD, PhD,† Celso A. Rodrigues, MD, PhD,‡ Yana Novis, MD,§  
Públio C.C. Viana, MD,|| Márcia M.P. Serra, PhD,¶ and Maria Claudia N. Zerbini, MD, PhD#*

- Immunohistochemistry considered essential to diagnosis in every case it was performed
- Performed slightly more frequently on CNB (96.3%) compared to excision (91.5%)

PMID: 36395467

# Case 3: Reactive Clone

## Core Needle Biopsy in Lymphoma Diagnosis

### *The Diagnostic Performance and the Role of the Multidisciplinary Approach in the Optimization of Results*

*Marianne de C. Gonçalves, MD, PhD,\* Claudia Regina G.C.M. de Oliveira, MD, PhD,\*  
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- Flow cytometry was considered essential in 66.7% of cases where it was performed
- Essential in 12% of CNB compared to 6.8% of excisions
  - » Multiple neoplastic populations better separated by flow cytometry
  - » Specific phenotype for T-cell lymphomas (Adult T-cell lymphoma/leukemia)

PMID: 36395467

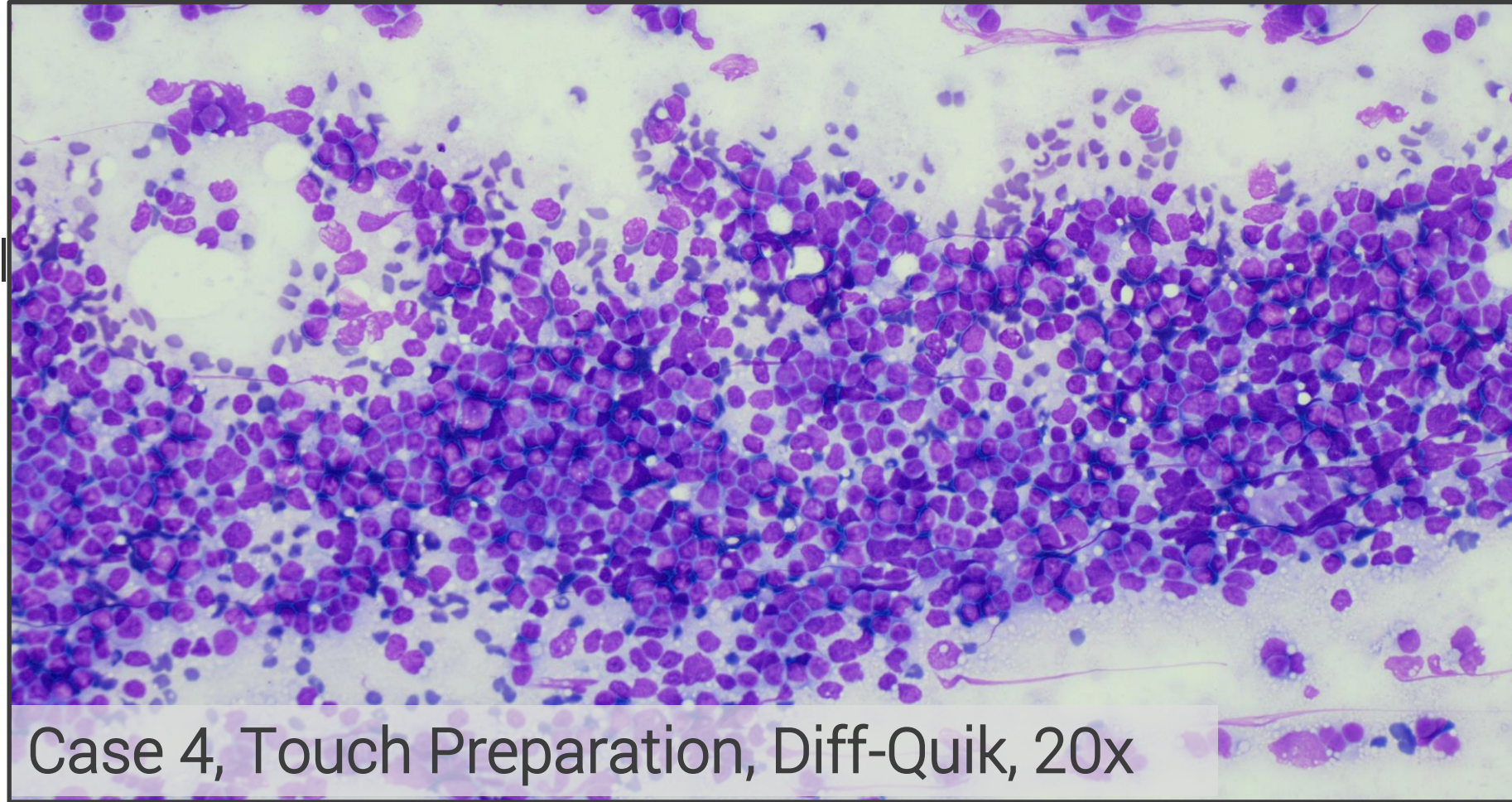
# Case 3: Reactive Clone

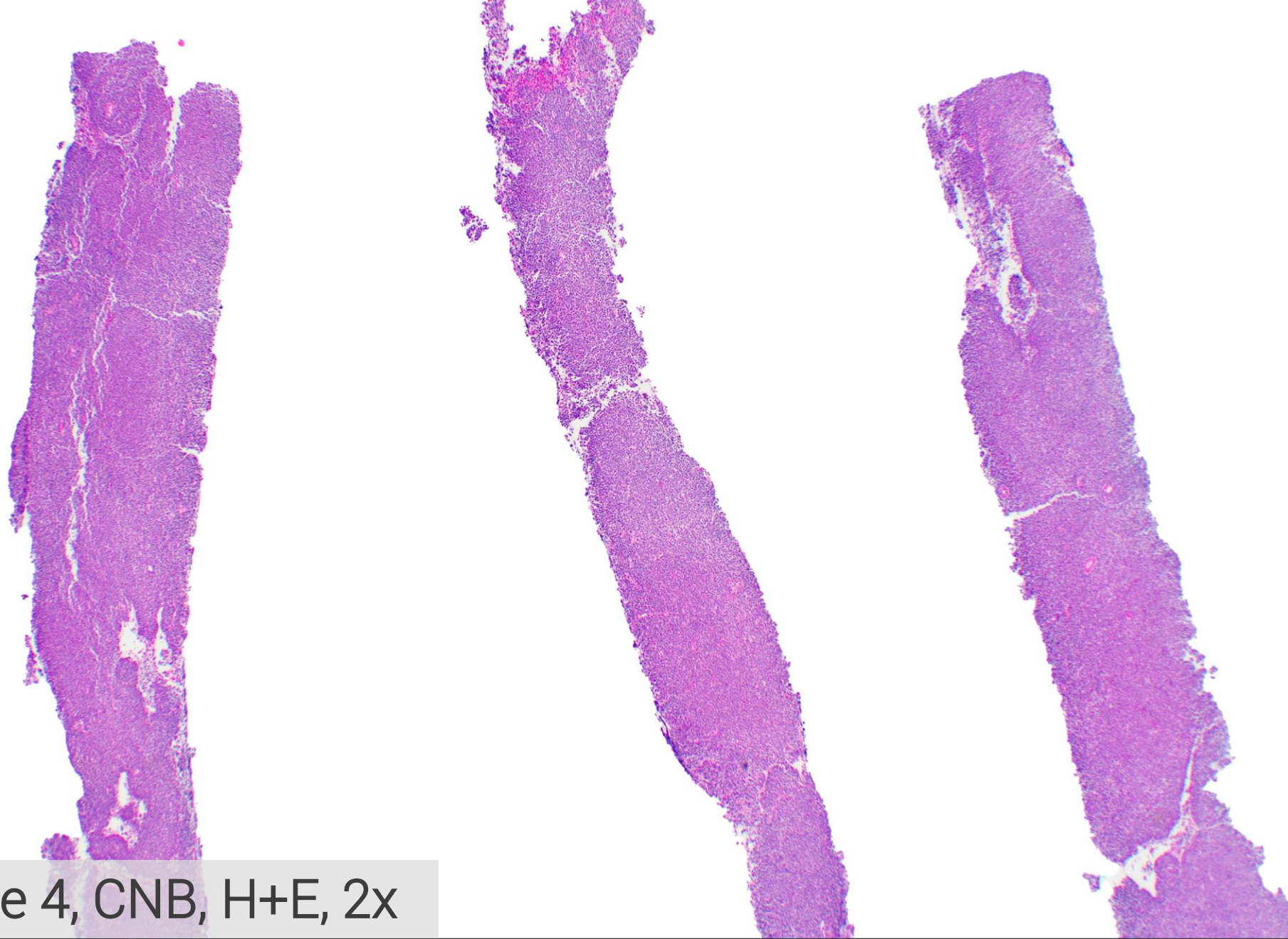
- Flow cytometry can raise concern, but morphologic correlate is needed for not just for specific diagnostic classification but for diagnosis of lymphoma

# ■ Case 4

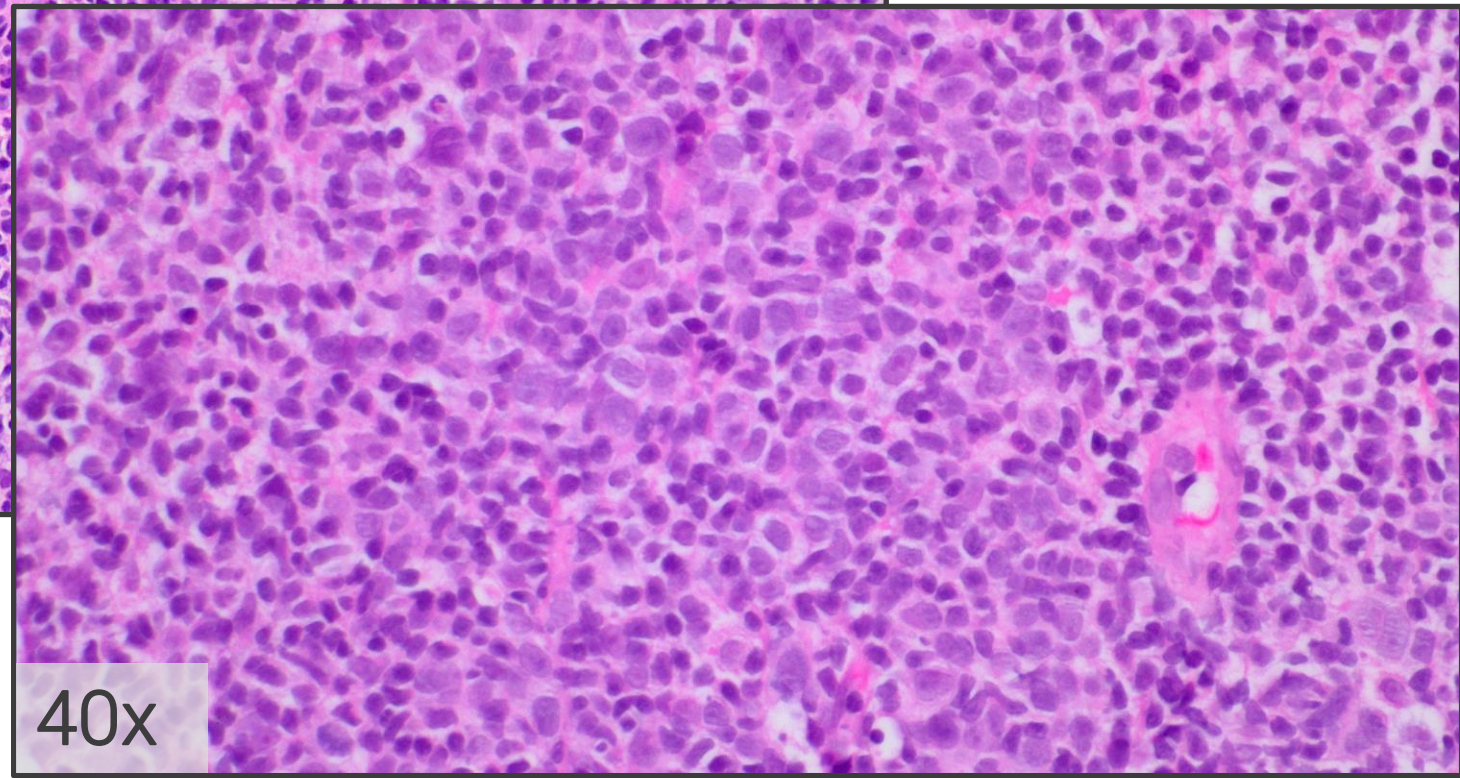
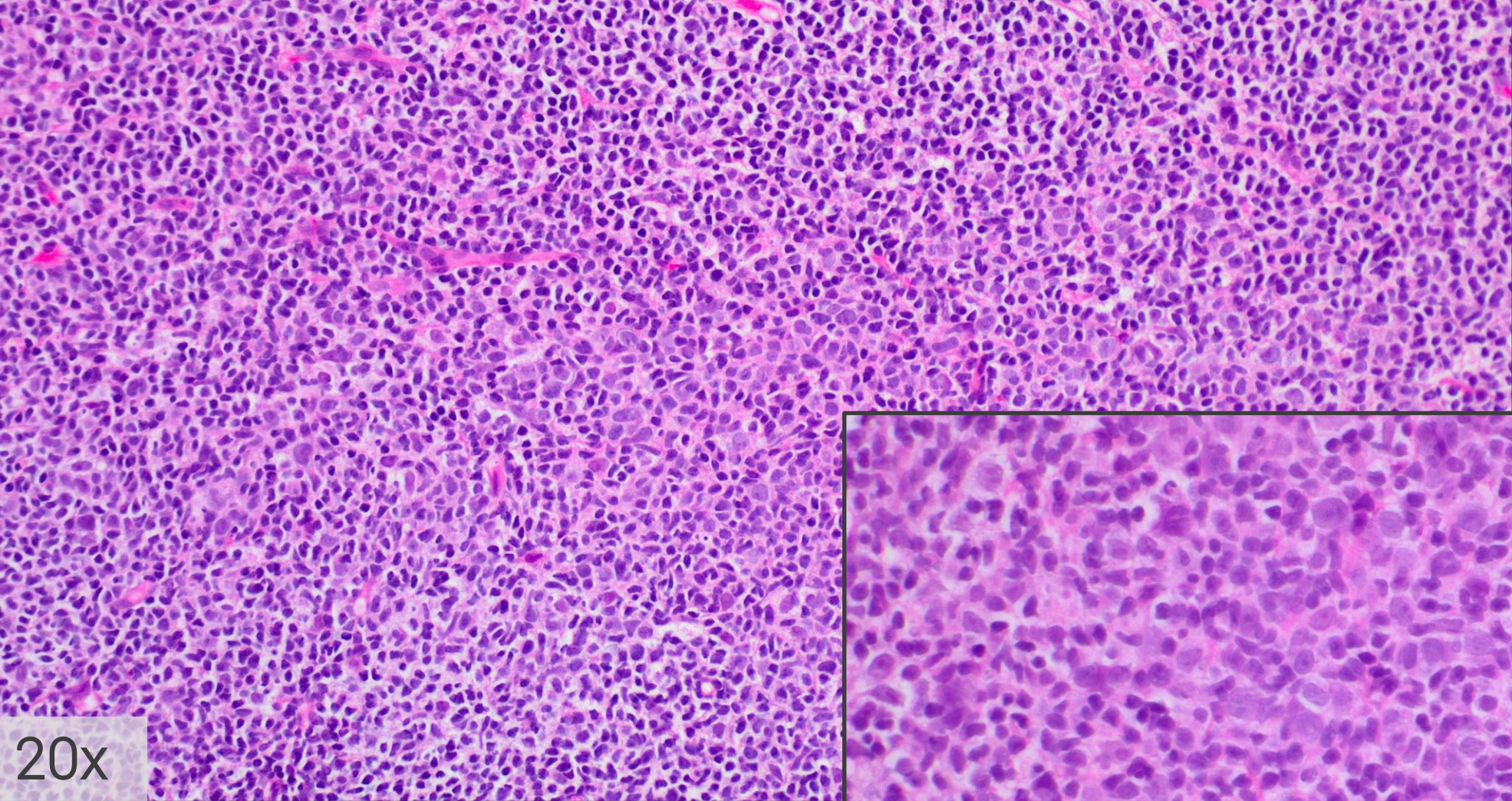
# Case 4

36-year-old female patient with abdominal pain and imaging showing a mesenteric mass, hepatosplenomegaly, splenic infarcts, and lymphadenopathy

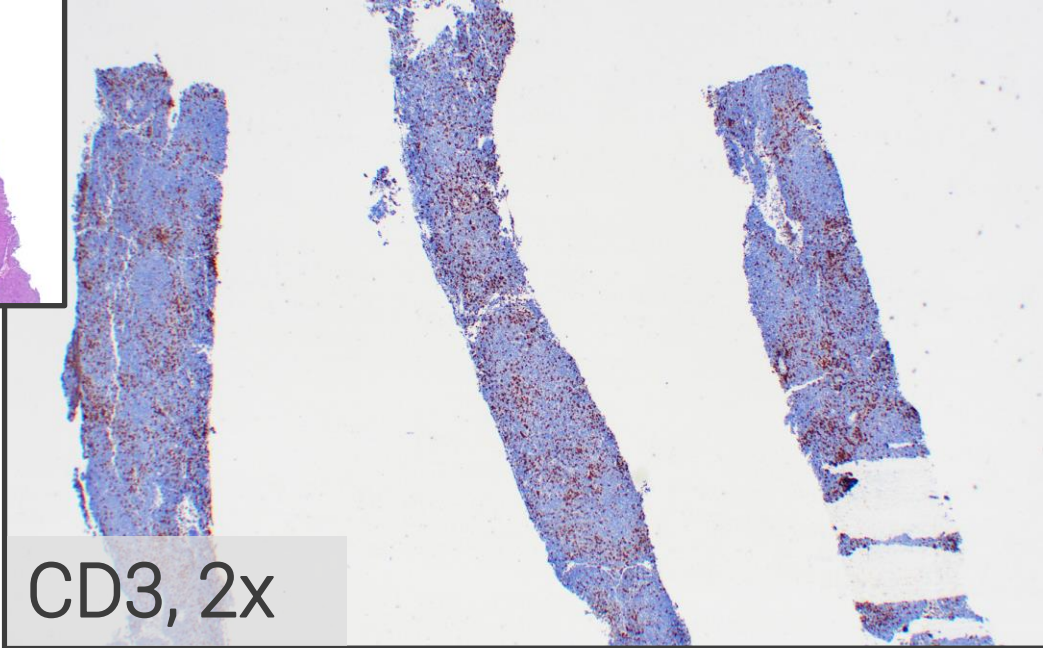




Case 4, CNB, H+E, 2x



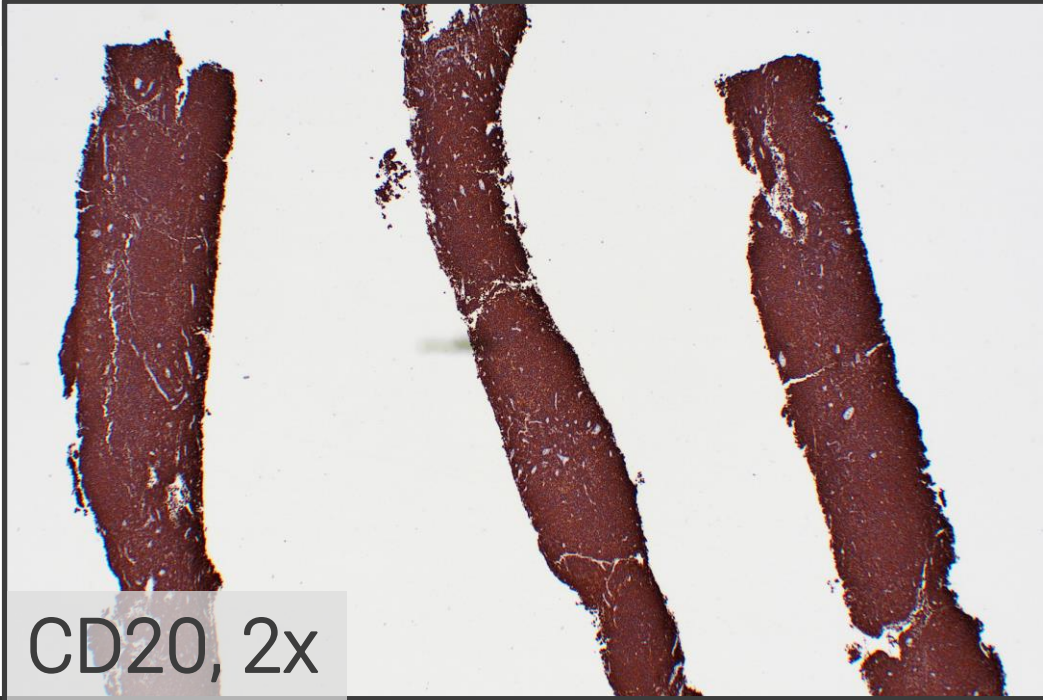




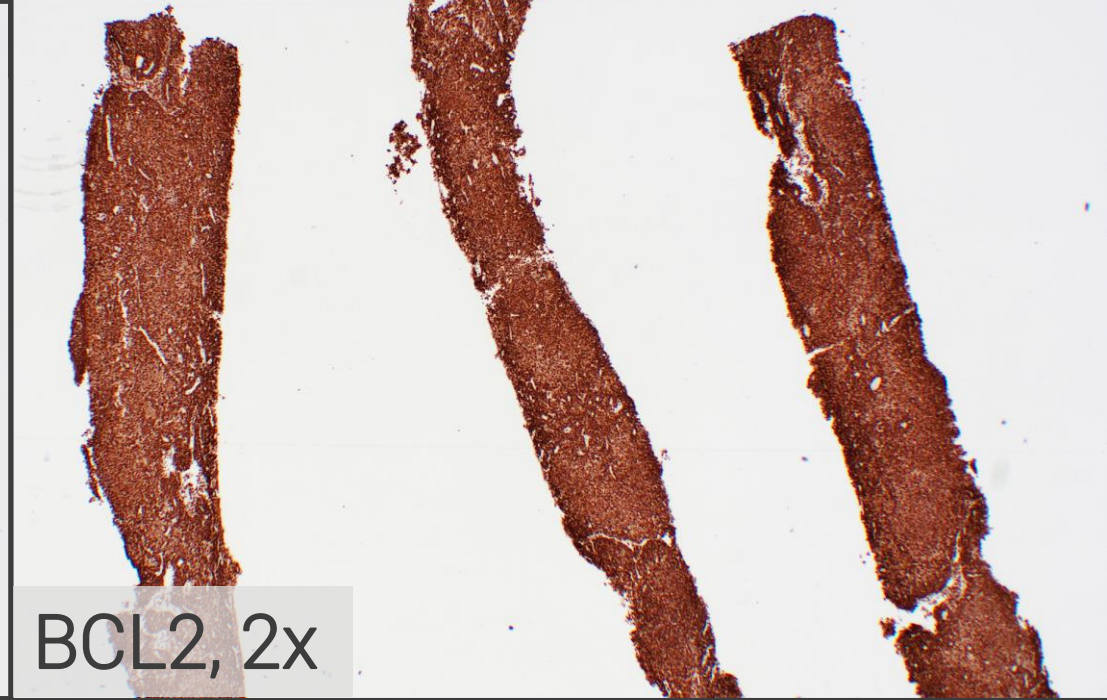
CD3, 2x



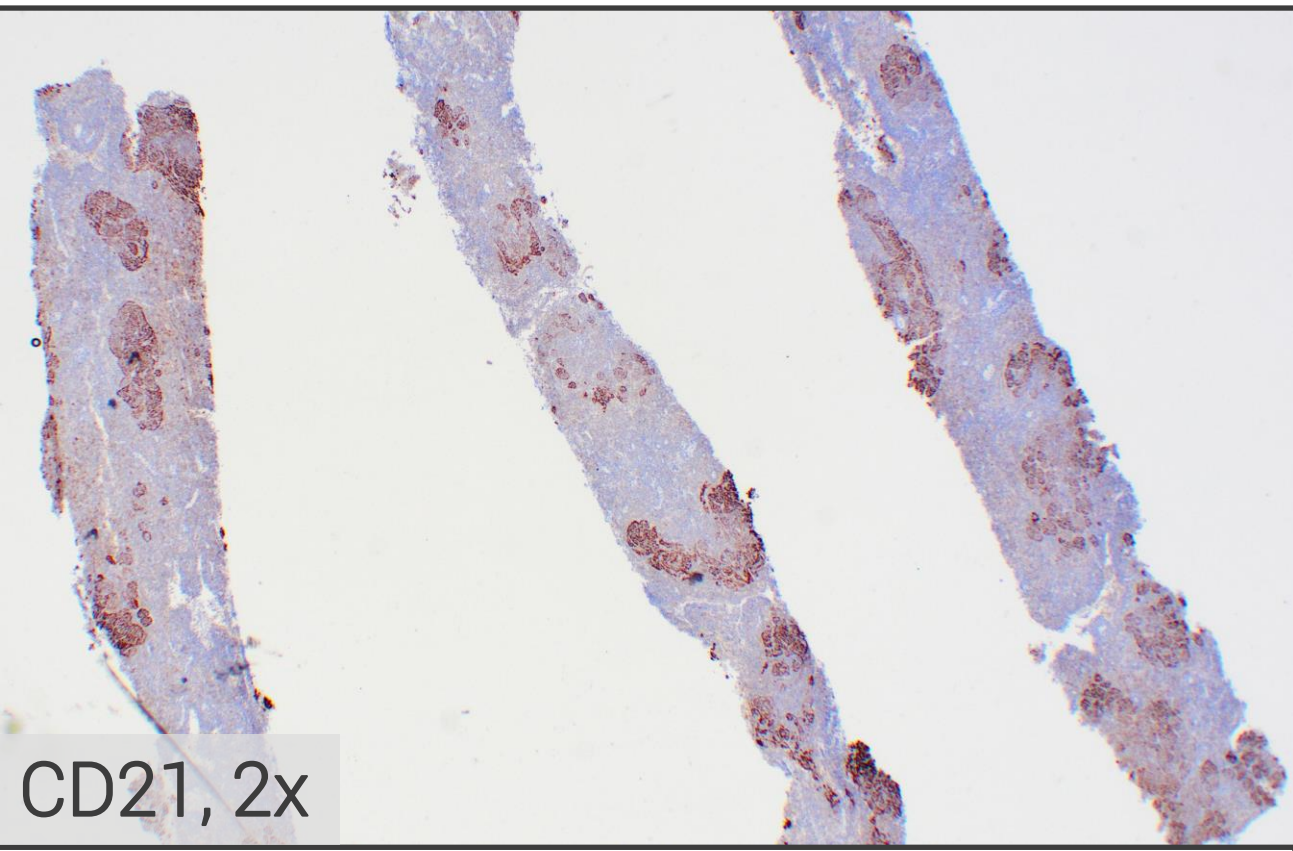
CD10, 2x



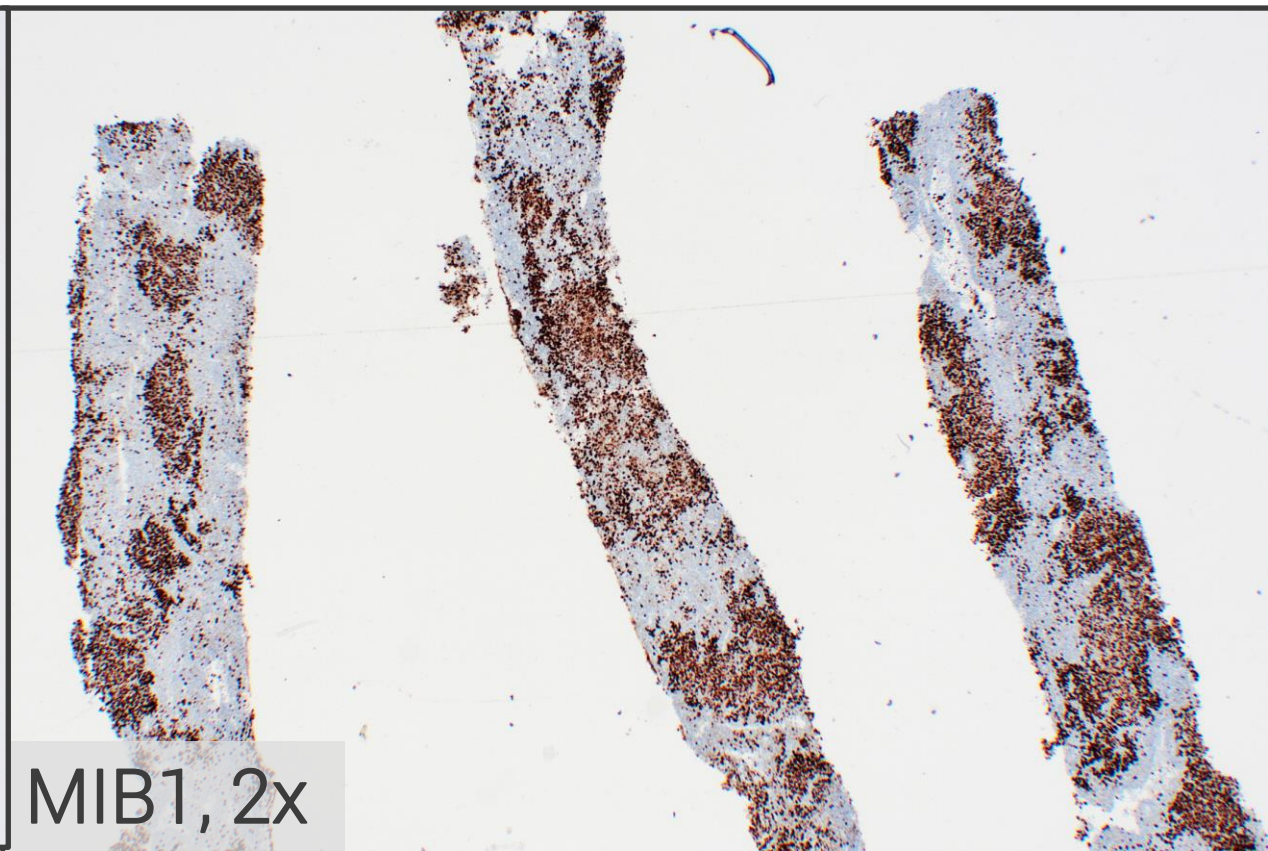
CD20, 2x



BCL2, 2x



CD21, 2x



MIB1, 2x

# Case 4

## Final Diagnosis:



- Follicular Lymphoma with high proliferative rate, worrisome for high grade on a limited specimen.
- “There are patchy areas where there are >15 centroblasts in high power fields, but no significant sheeting is observed, which is consistent with grade 3A follicular lymphoma. The lesion has a high proliferative rate (up to 75%) and given the limited sample and clinical presentation of splenomegaly and adenopathy elsewhere, a higher grade lesion (e.g. 3B or diffuse large B cell lymphoma) cannot be excluded. An excisional biopsy is recommended for accurate grading. Please correlate clinically.”

# Case 4: Follicular Lymphoma

- We generally don't grade follicular lymphoma in core needle biopsy samples, but to describe the features in the comment as consistent with low grade or concerning for high grade.
- Based on typically having insufficient high-power fields for grading and the possibility of unsampled higher grade areas.

# Case 4: Follicular Lymphoma

## Core needle biopsy is an inferior tool for diagnosing cervical lymphoma compared to lymph node excision

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- Took needle core biopsies out of 56 lymph node excisional biopsies at gross, then had 2 pathologists come to a diagnosis on each specimen and then compared them

# Case 4: Follicular Lymphoma

- 9 cases of follicular lymphoma were evaluated this way
  - » 1/9 was suspected FL by CNB but required excisional biopsy for definitive diagnosis
  - » 2/9 same grading on both specimens
  - » 5/9 showed different grading
  - » 1/9 was considered “semi-severe” discrepancy with therapeutic implications:
    - DLBCL and FL by CNB that was FL grade 3A by excisional biopsy

# Case 4: Follicular Lymphoma

- WHO 5<sup>th</sup> Edition Updates:
  - » Classic Follicular Lymphoma
    - Cases with at least in part follicular growth, are composed of centrocytes and centroblasts, and harbor *IGH:BCL2* fusion
    - Grading no longer mandatory based on reproducibility and questionable clinical significance, now optional
    - Clinical outcomes among patients with grades 1, 2, and 3A not significantly different
    - Cases with focal or extensive diffuse growth pattern in otherwise grade 3A were recommended to be called DLBCL with follicular lymphoma even without sheets of large cells in 4<sup>th</sup> edition
      - › Treatment decisions in these cases should be based on multidisciplinary conference and pending research
  - » Follicular Large B-cell Lymphoma
    - Corresponds to grade 3B follicular lymphoma
  - » Follicular Lymphoma with Uncommon Features

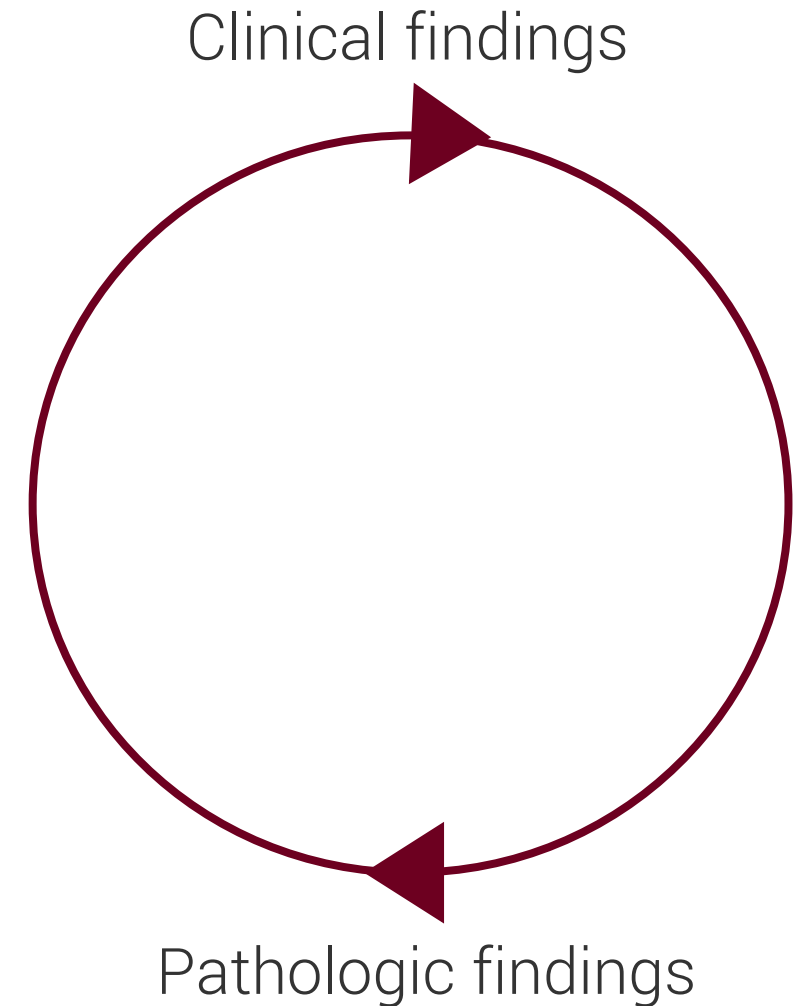
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■ Can we make any recommendations?



# Ideal Specimen Procurement

- Individualized to the patient and clinical scenario
  - » How accessible is the lymphadenopathy
  - » Patient individualized risks of undergoing surgical excision
  - » Timeliness of core needle biopsy versus surgical excision
  - » History of previously diagnosed lymphoma
  - » Clinical concern for Hodgkin Lymphoma or T-cell lymphoma?



# Ideal Specimen Procurement

- Adequacy goals for a CNB procedures:
  - » Clinical history is part of adequacy
  - » Minimum of 3 cores from different areas in the lymph node
  - » Larger gauge needles when possible
  - » Send fresh material for flow cytometry
  - » Embed the cores in multiple blocks so that one can be used for morphology and IHC while another block can be preserved for molecular studies

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Thanks!



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