Pitfalls in Hematopathology

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Agenda

- Examples of “great mimickers”
- Discuss differential diagnoses and use of ancillary studies

Causes of diagnostic error in hematopathology

Major causes of diagnostic errors:

- Inadequate material;
- Inadequate workup;
- Inadequate clinical correlation;
- Over or under interpretation;
- Challenges in hematopathology.

Human factor:

- It is all about the differential diagnosis
- Rare entities, or entities outside of the routine can be overlooked

PMID: 18830390

Is it just a field of leaves? No….

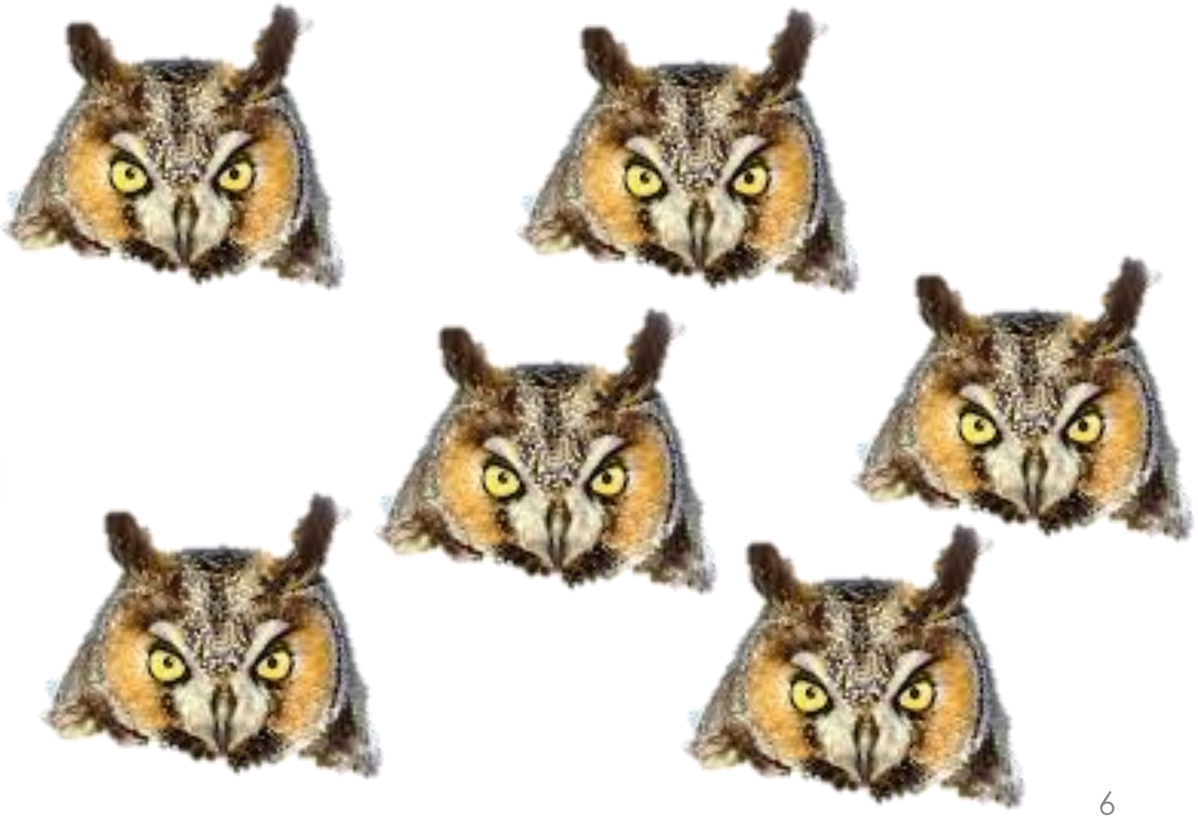
How hard is it to notice a gecko?

It is obviously a gecko!

Butterflies disguised as owls?
Lymphoma disguised as sarcoma/carcinoma?

Night moth

Long-eared owl

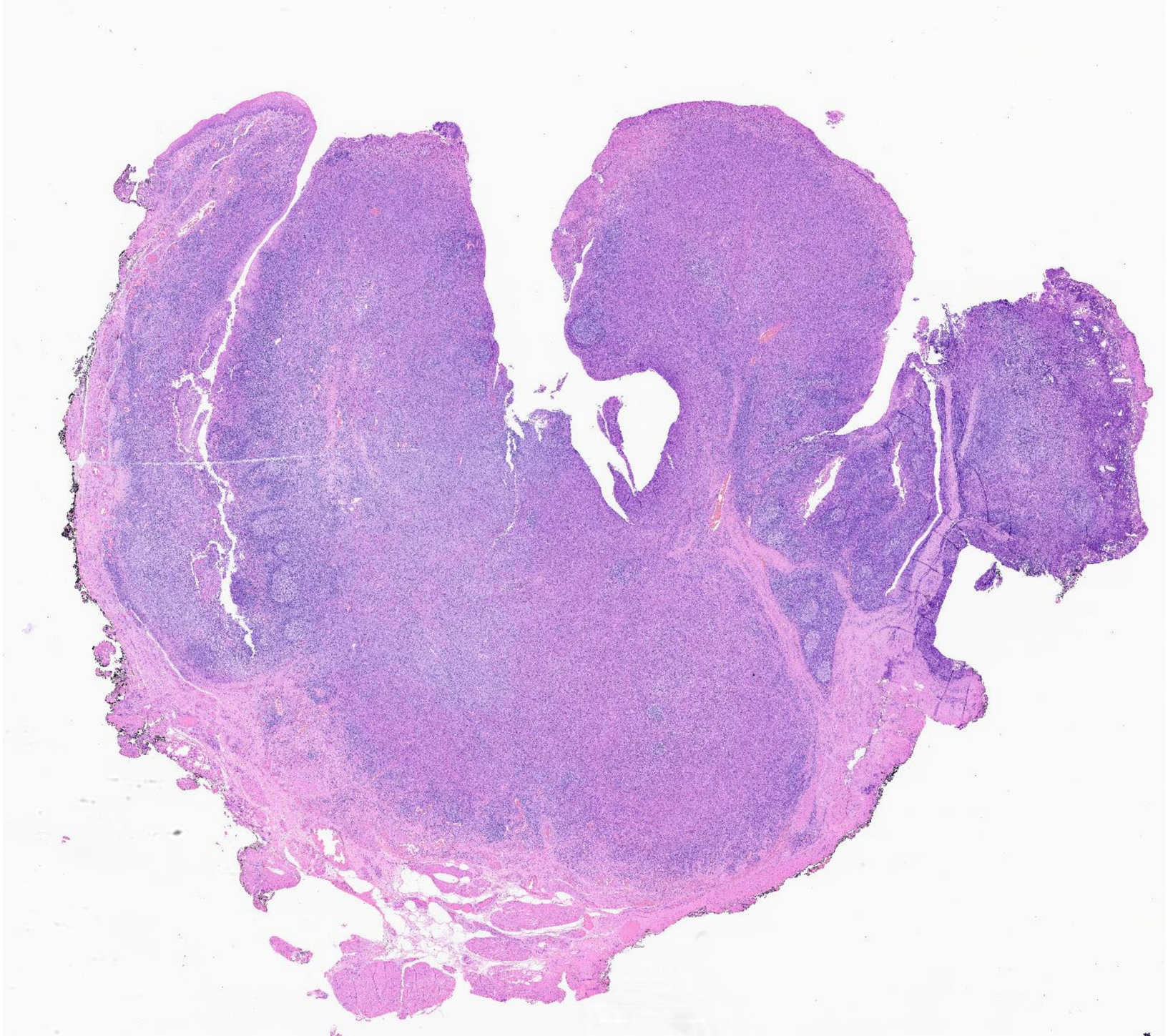


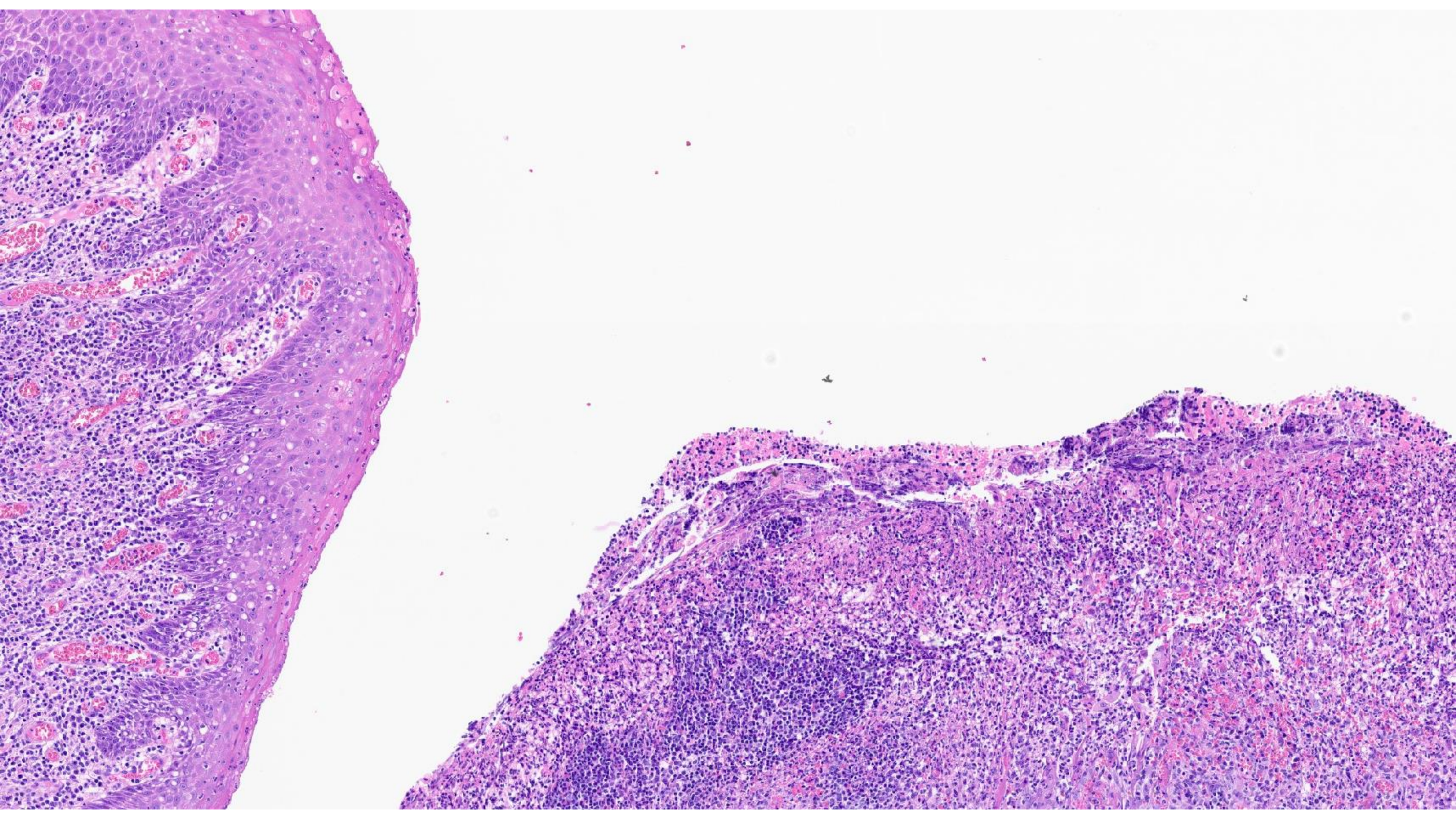
The “Great Mimicker”

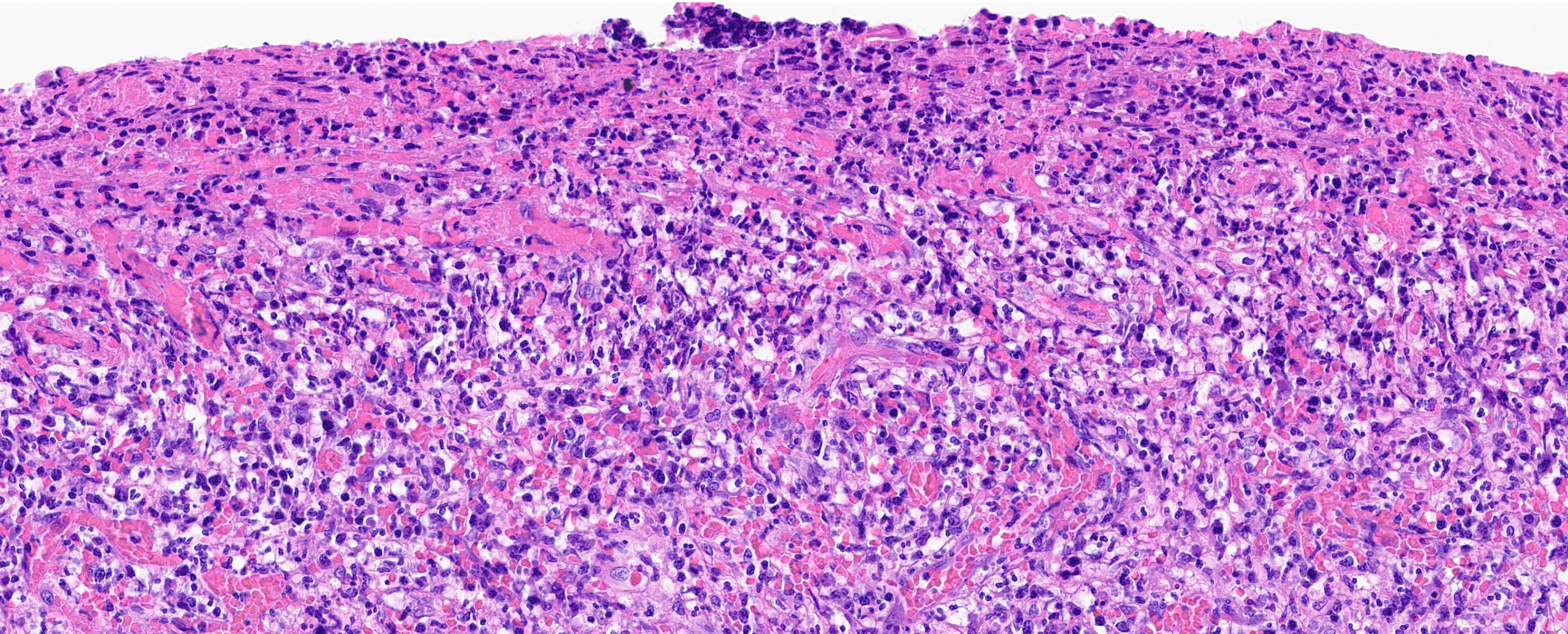
Some images are a courtesy of Dr. Anamarija Perry, Hematopathologist, University of Michigan

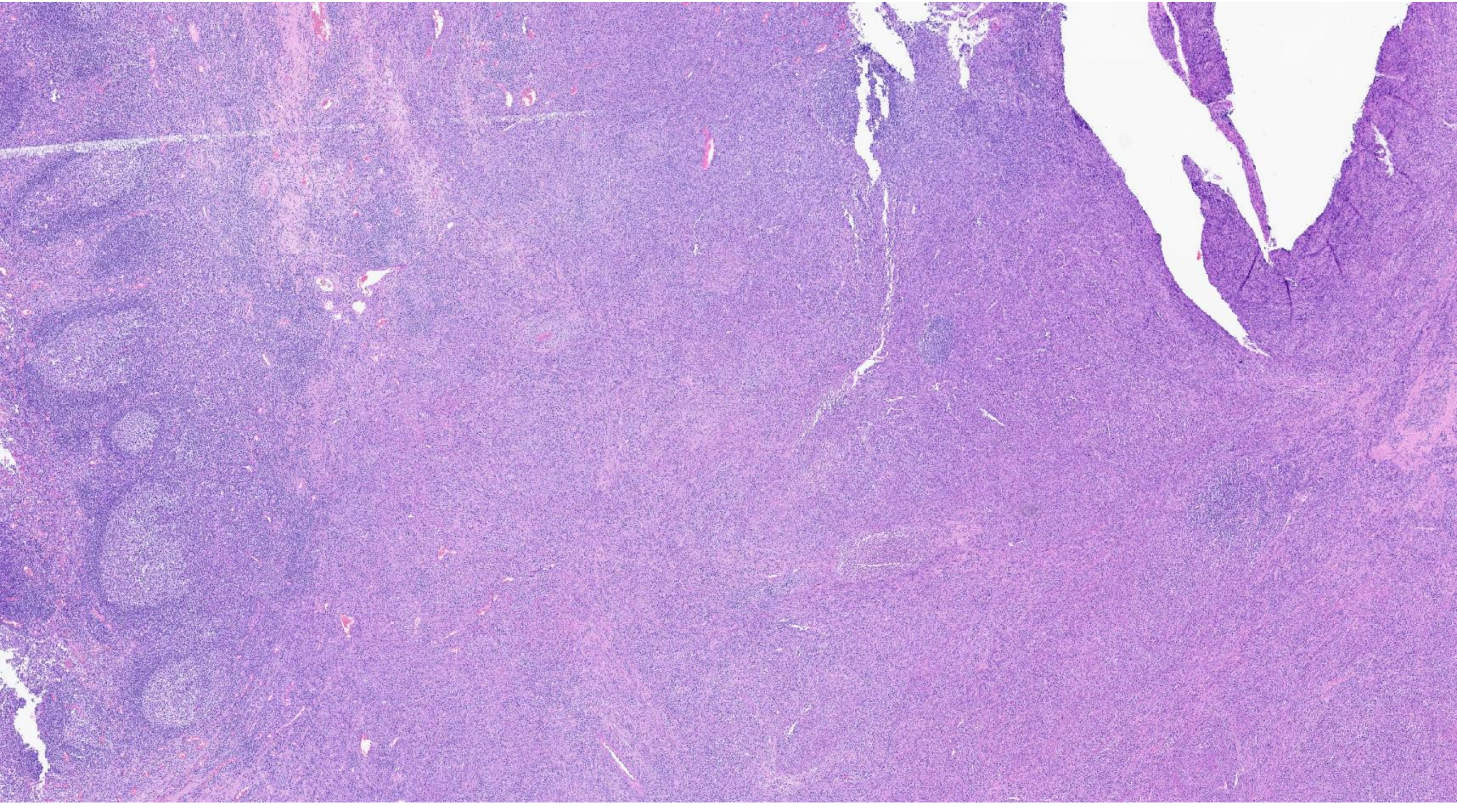
Case #1

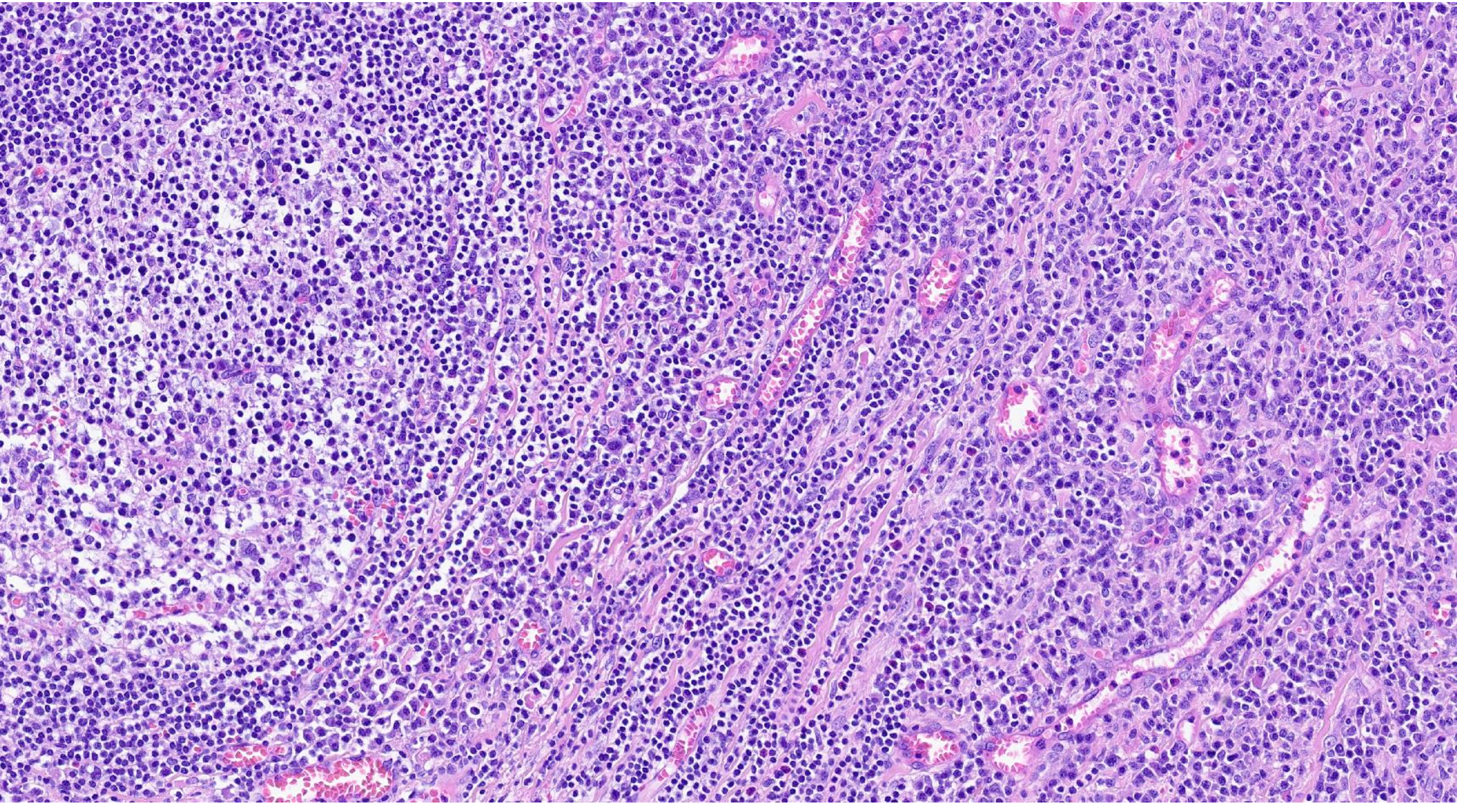
- 42-year-old male with “fungating ulcerated tonsillar tumor”
- Per surgical note “appears malignant”
- Excisional biopsy was performed
- Rule out carcinoma/lymphoma

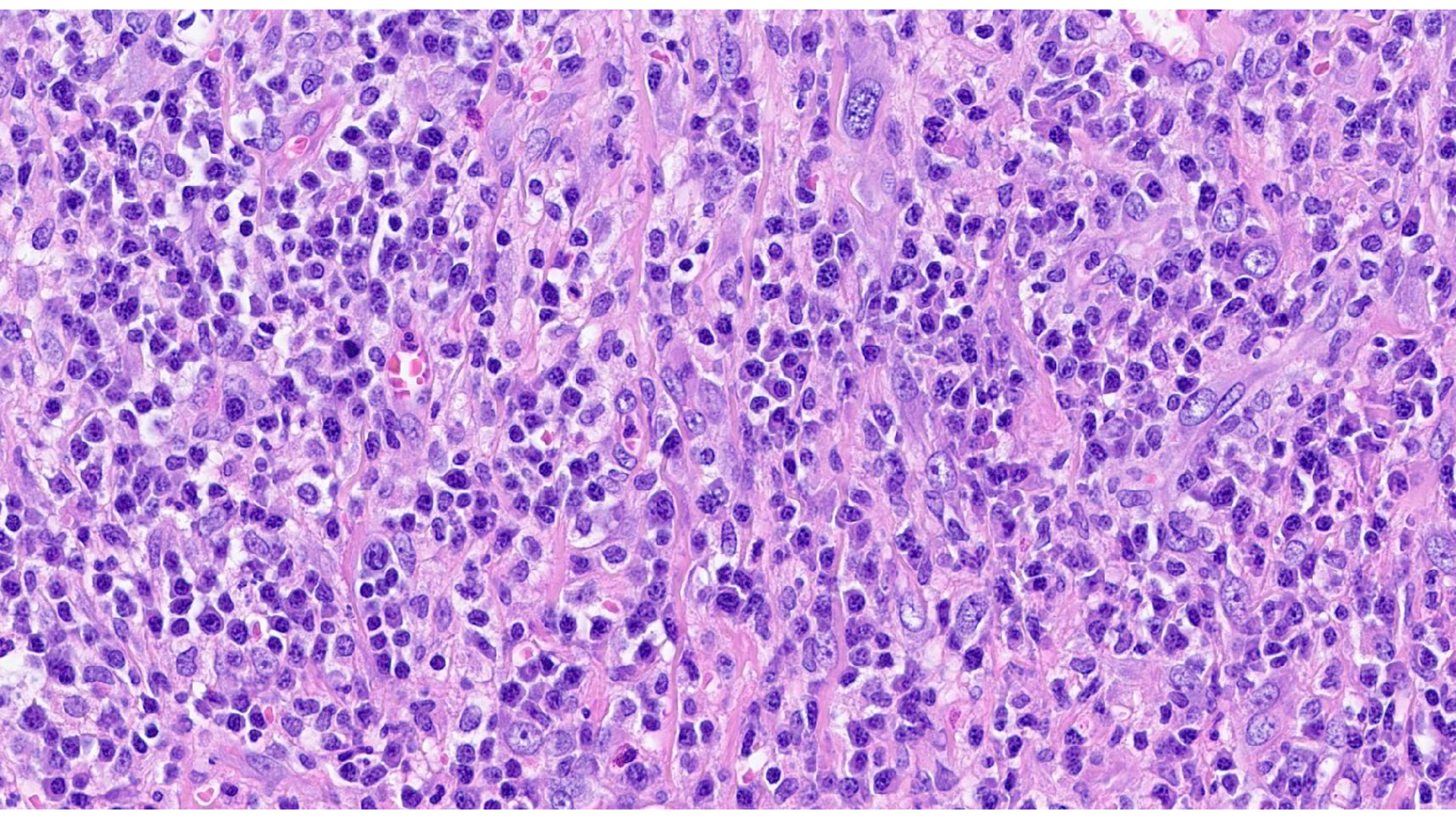


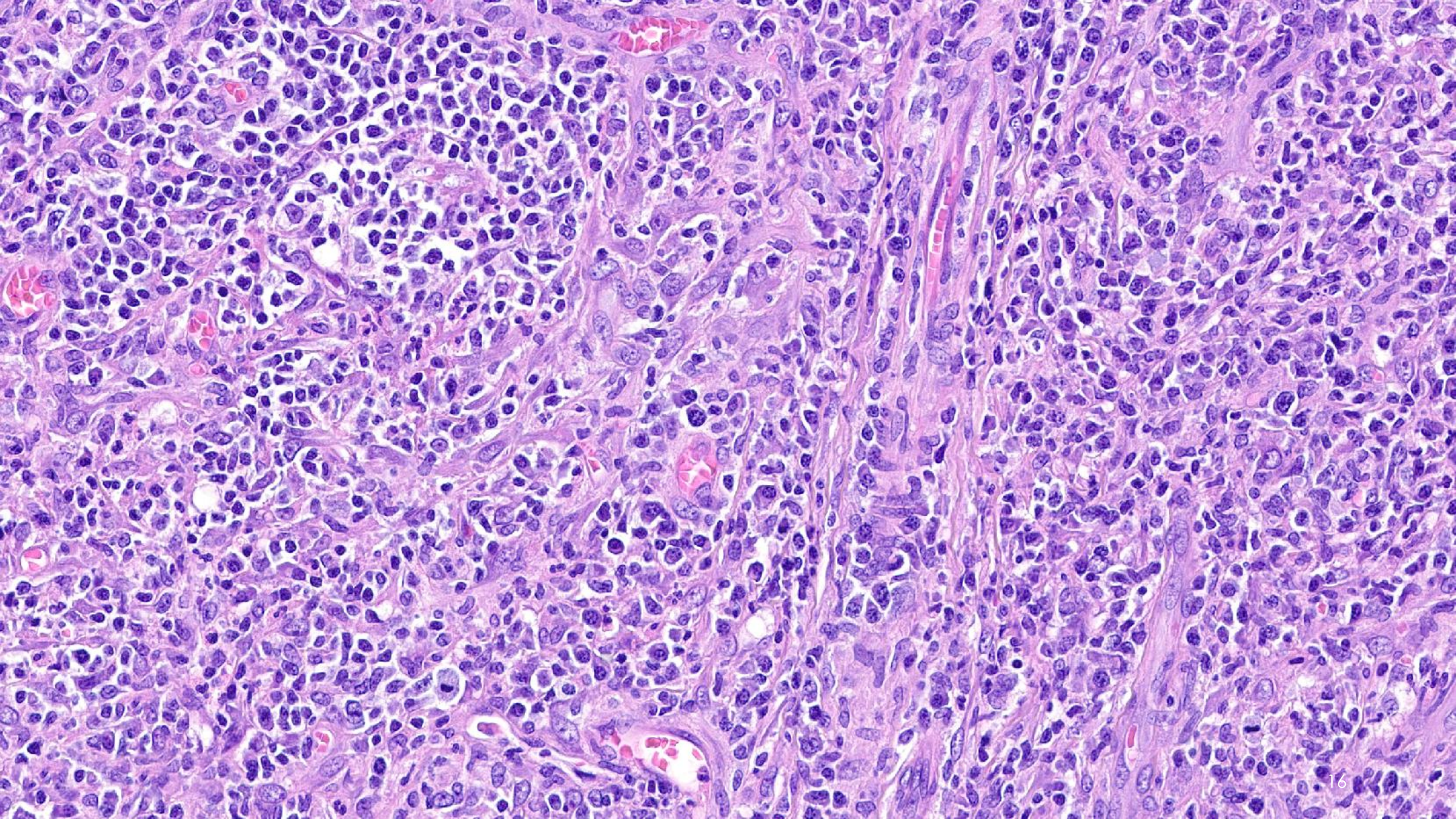


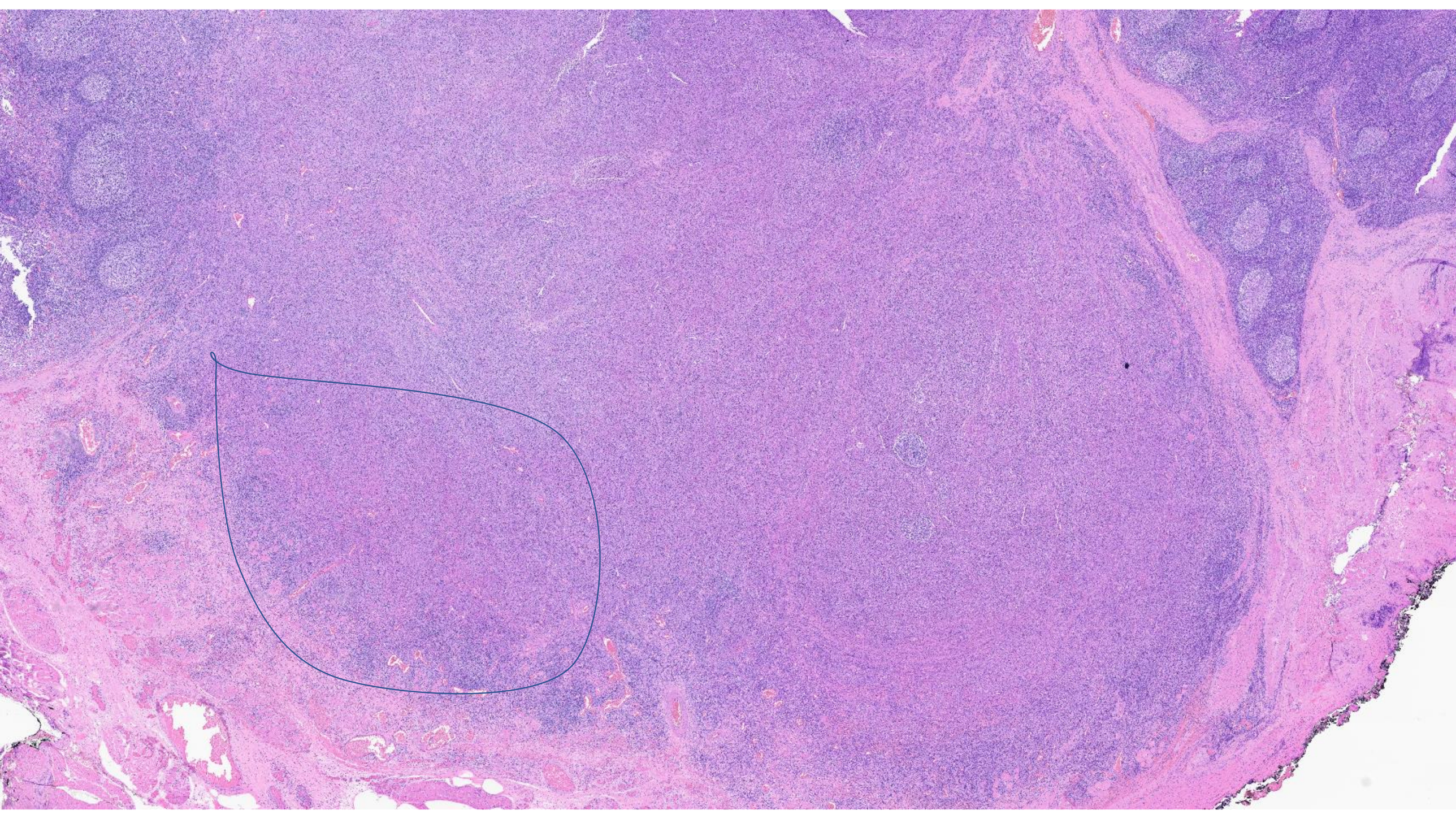


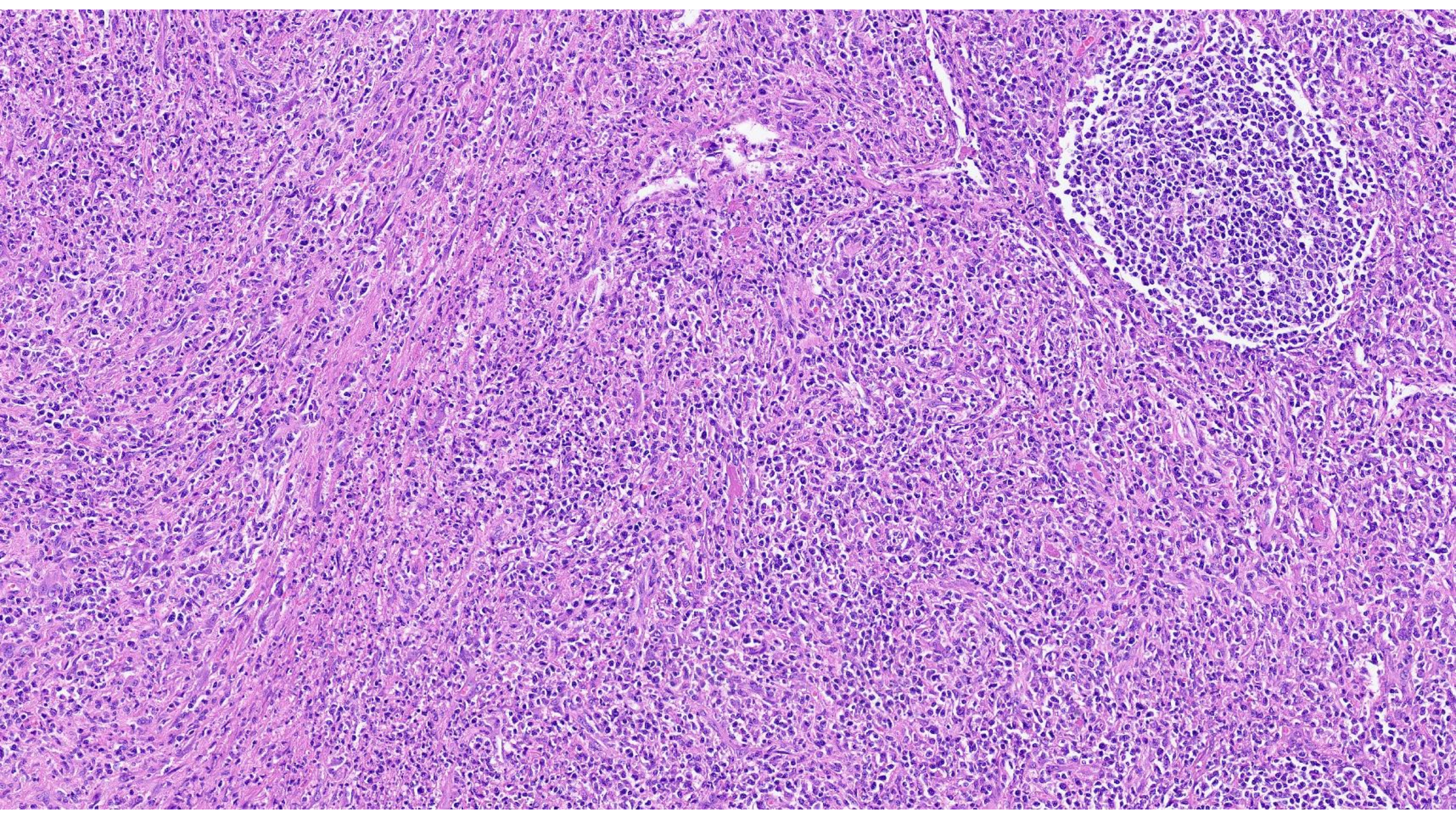


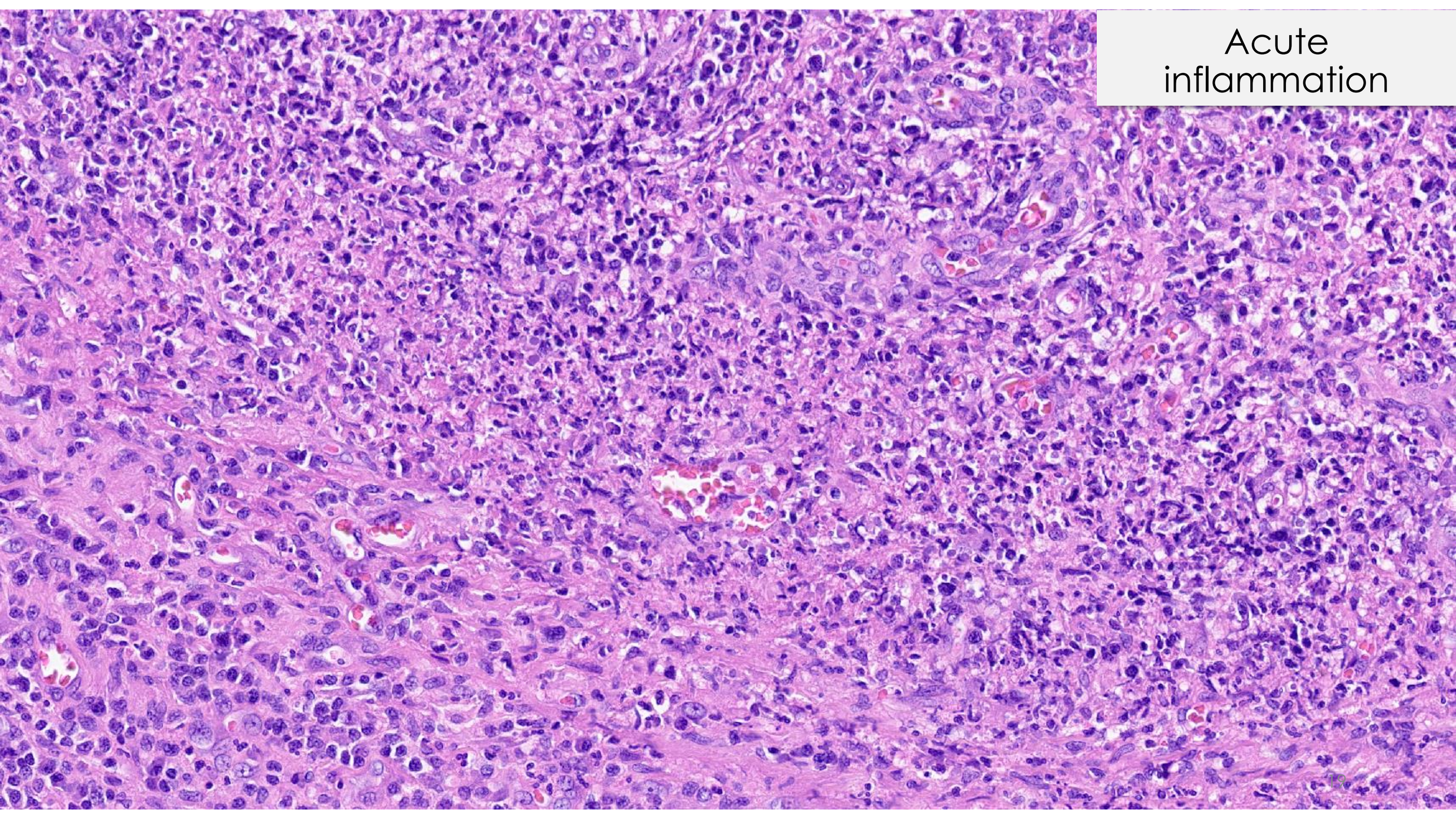




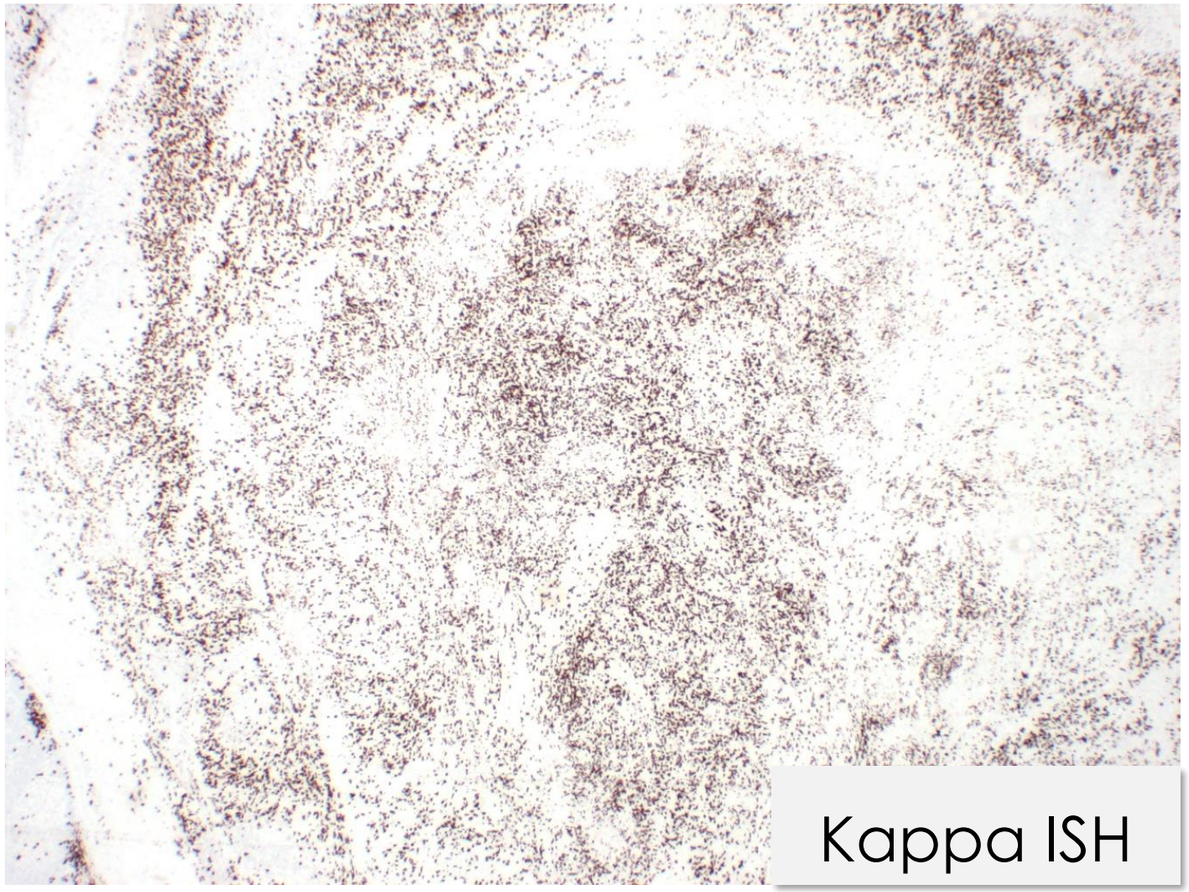




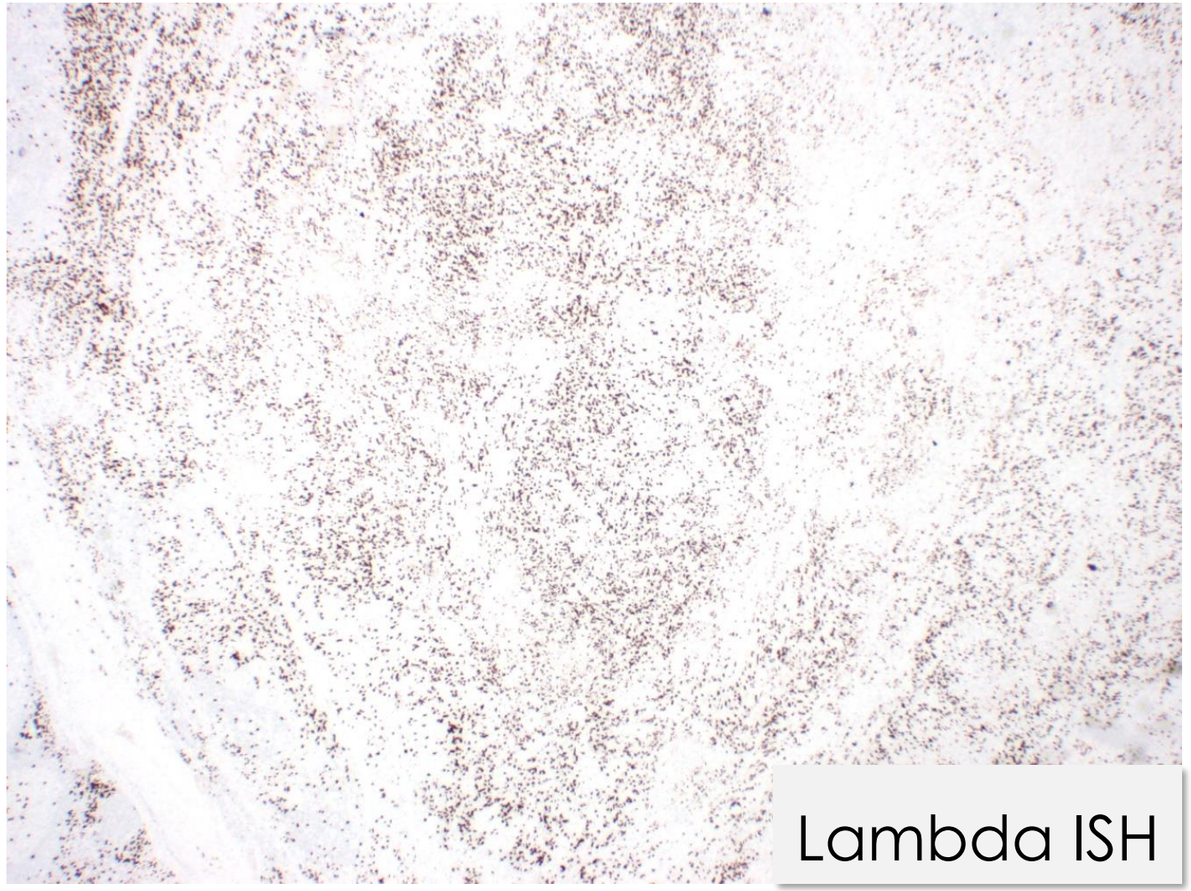



Acute
inflammation

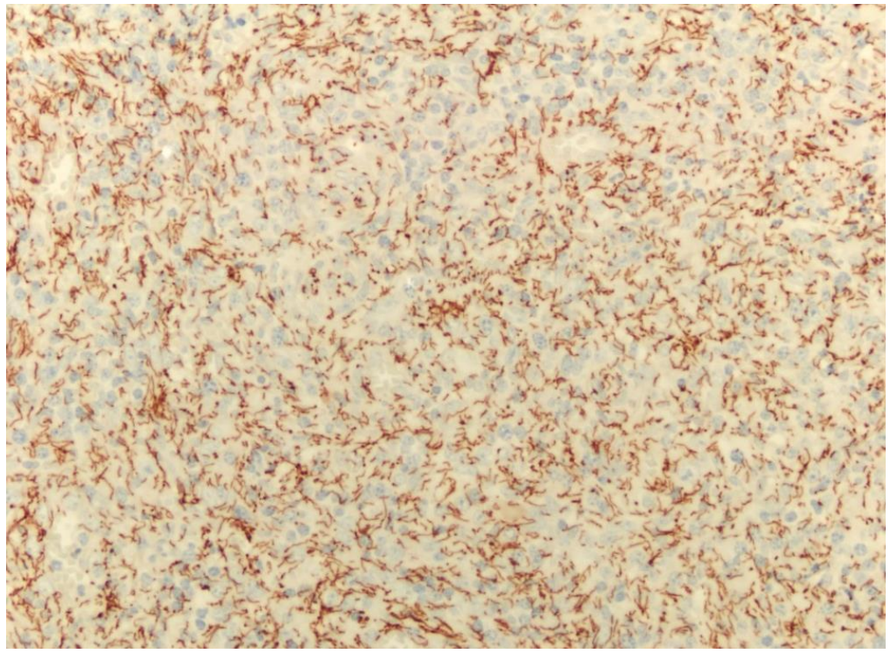
Polytypic plasmacytosis

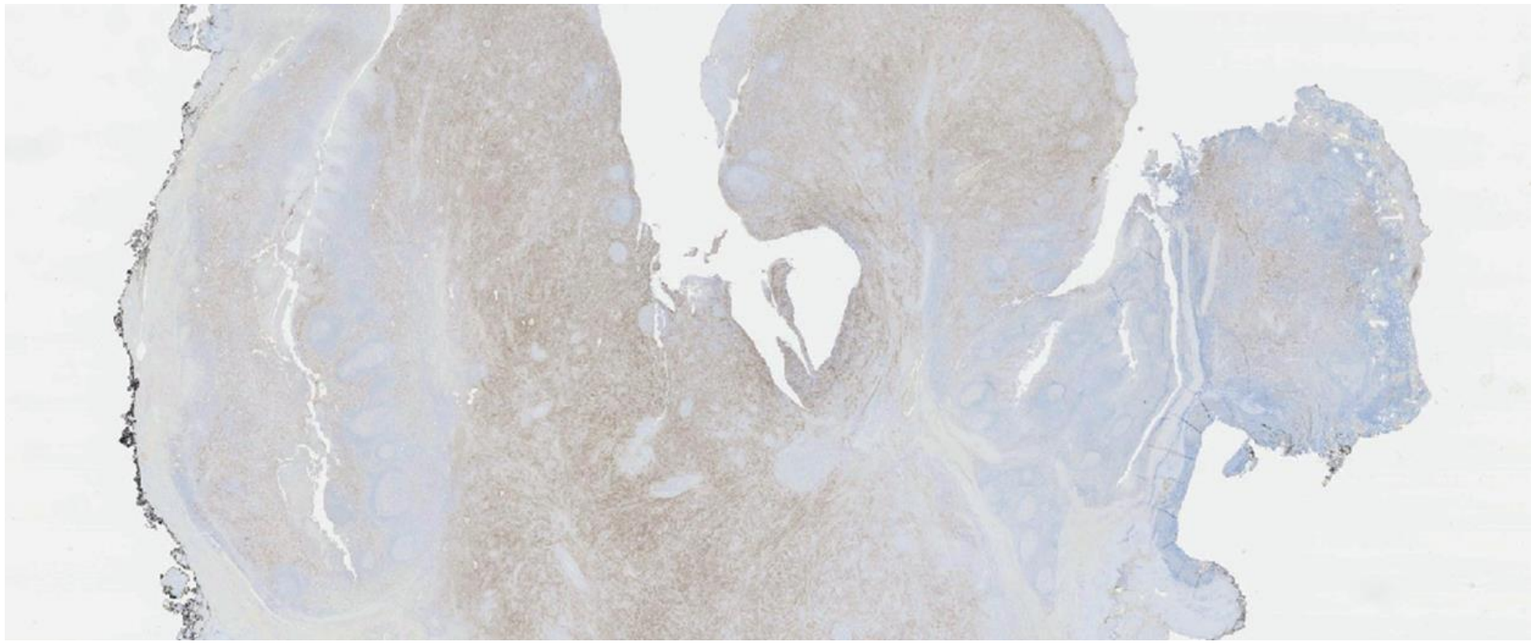


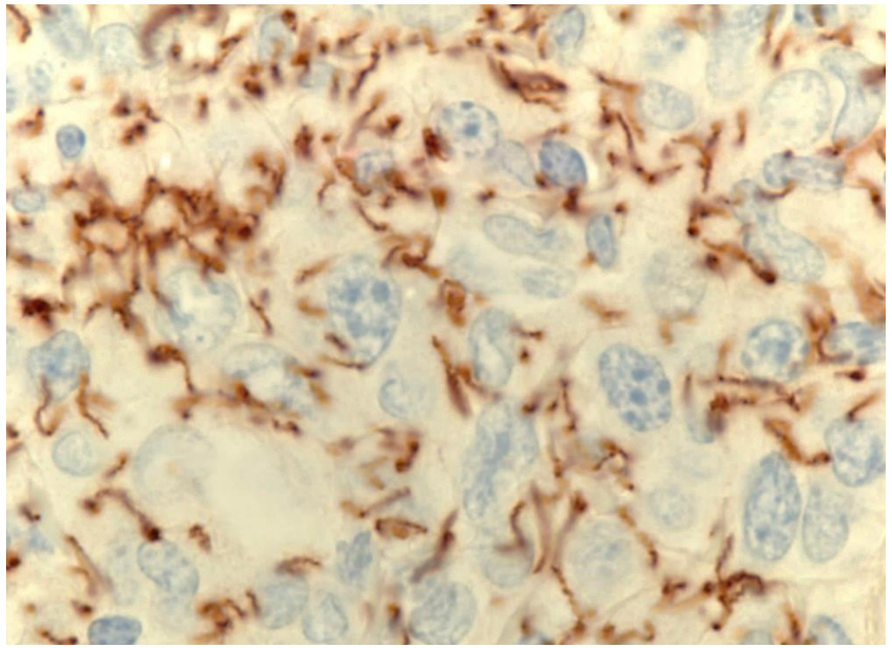
Kappa ISH



Lambda ISH







Spirochete immunostain

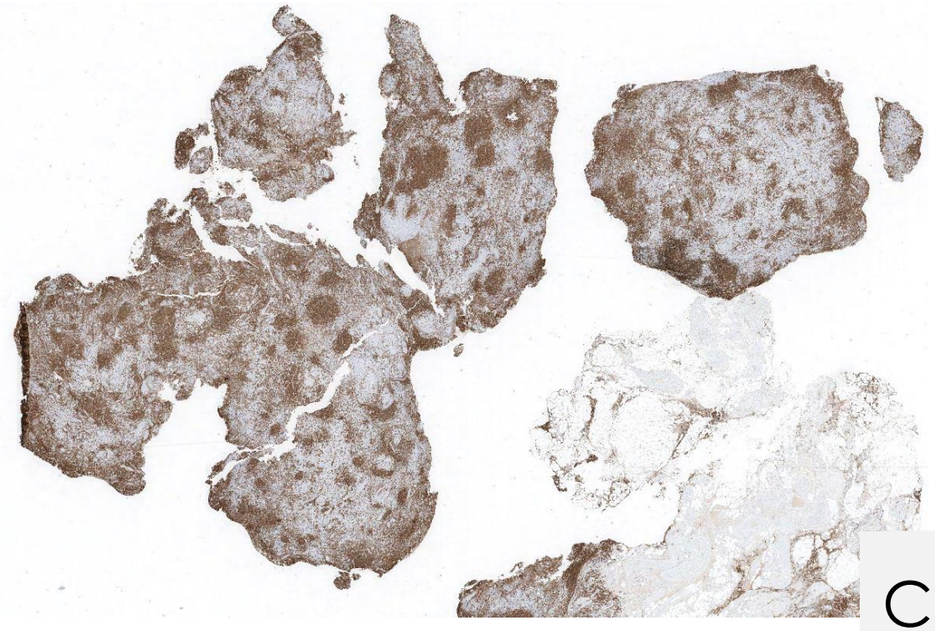
(*Treponema pallidum*)

Final diagnosis

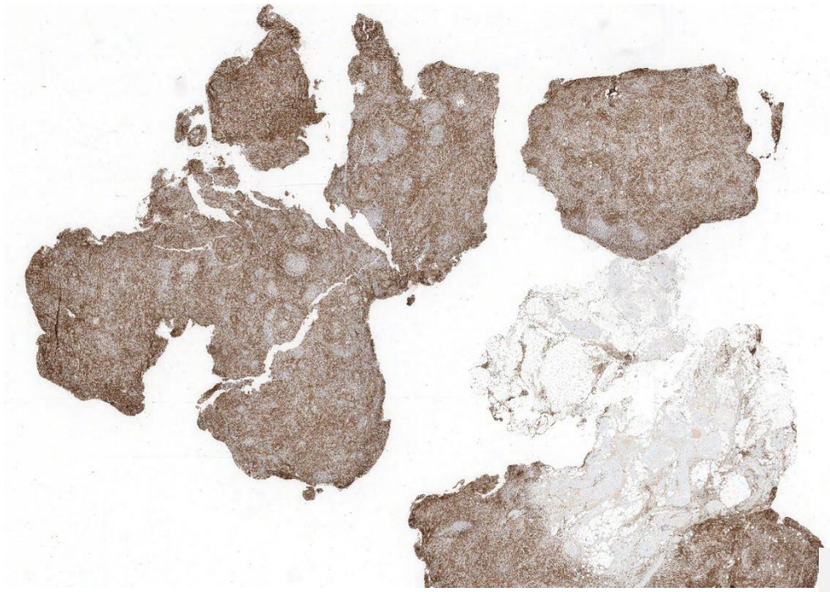
- Tonsil with numerous spirochetes, consistent with syphilis, favor primary lesion (chancre)

Case #2

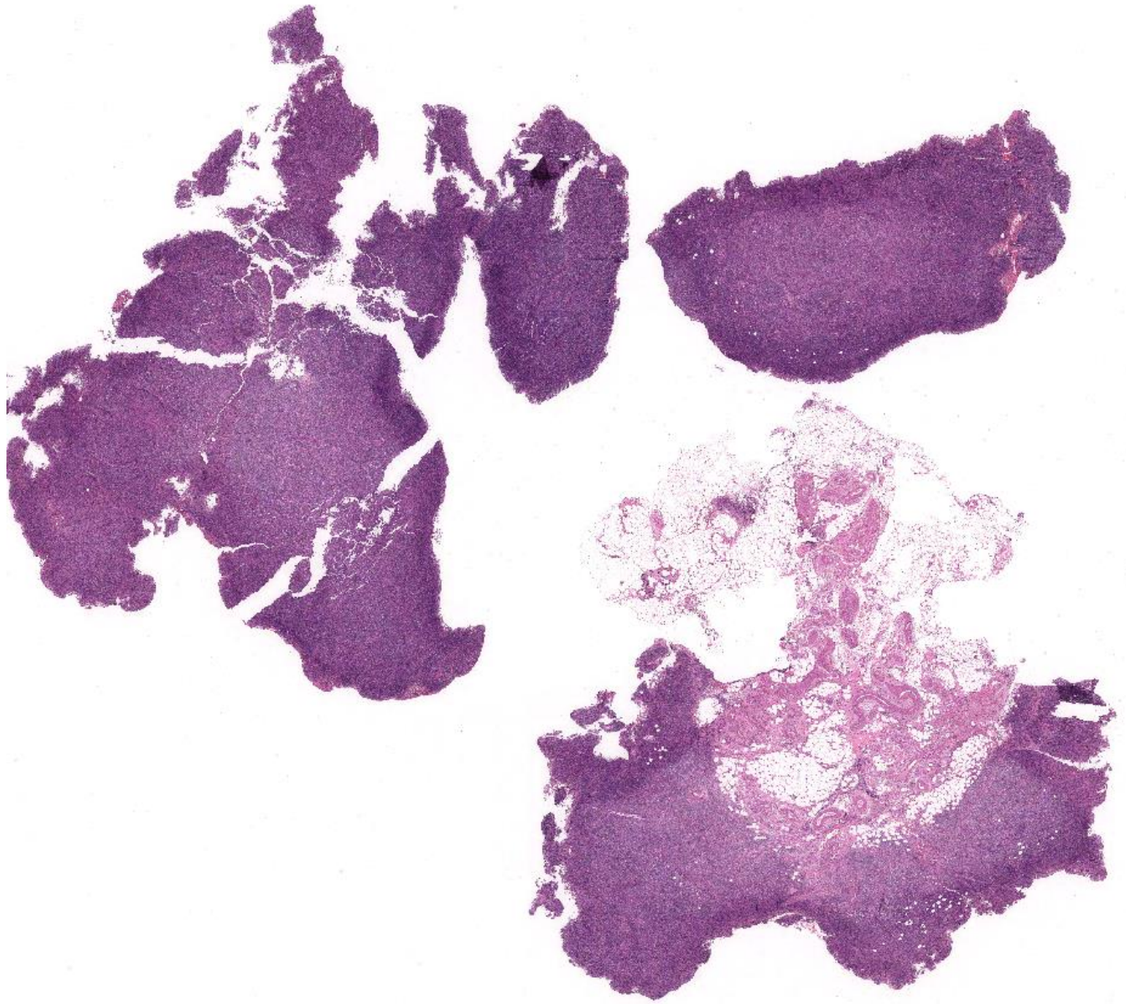
- 57-year-old female with diffuse lymphadenopathy, malaise and night sweats
- History of autoimmune disease
- R/O lymphoma
- Inguinal lymph node biopsy was performed

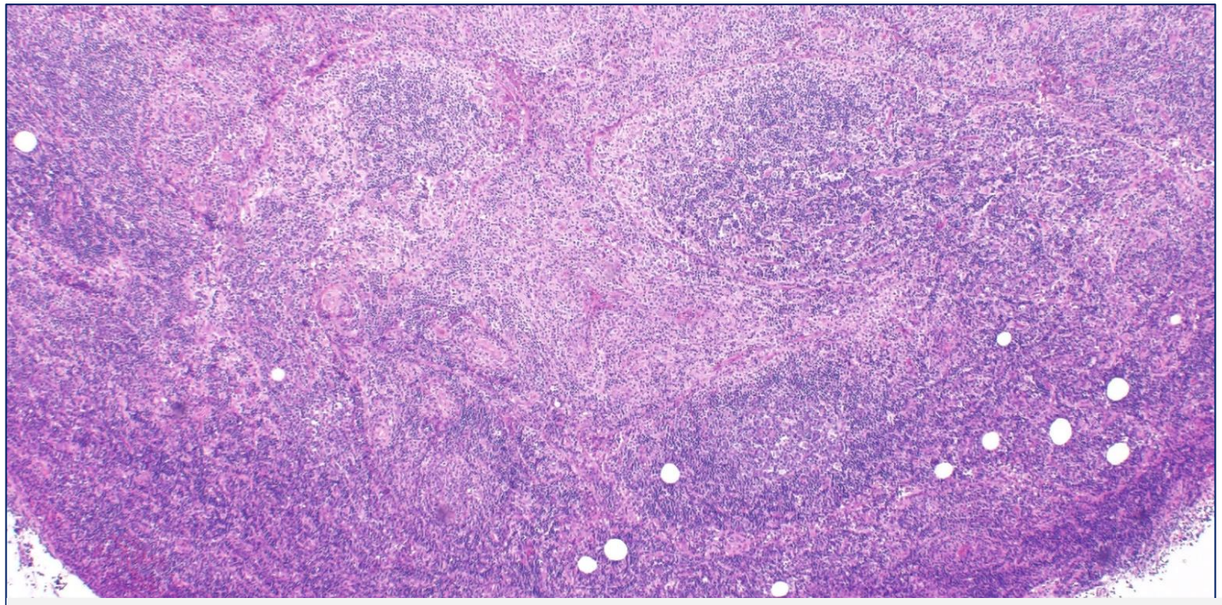


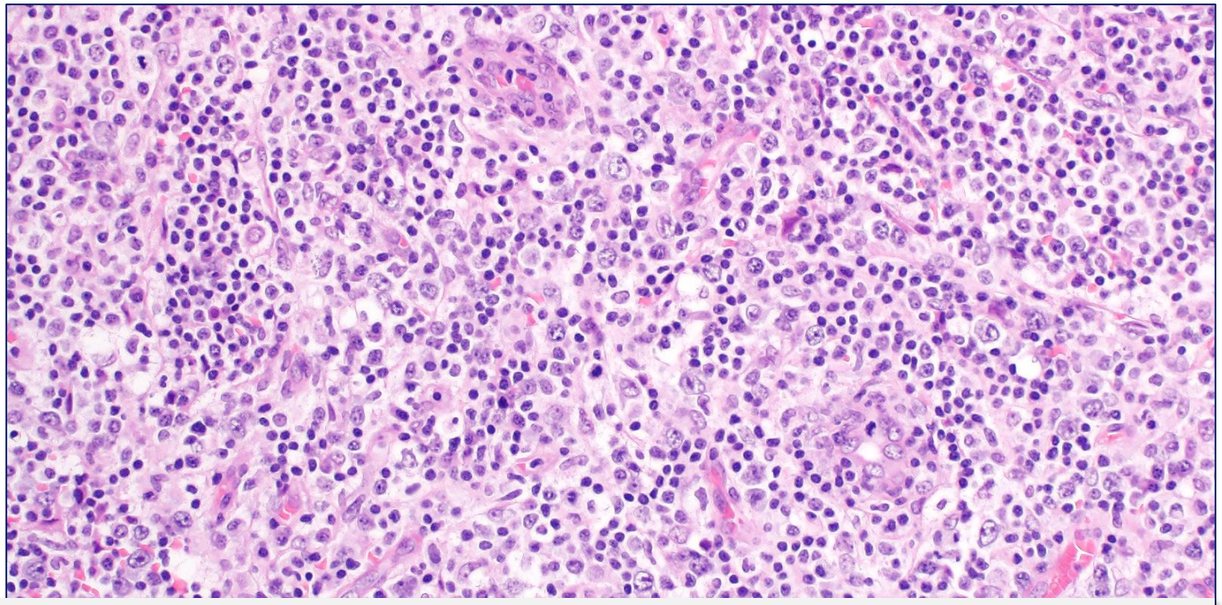
CD20



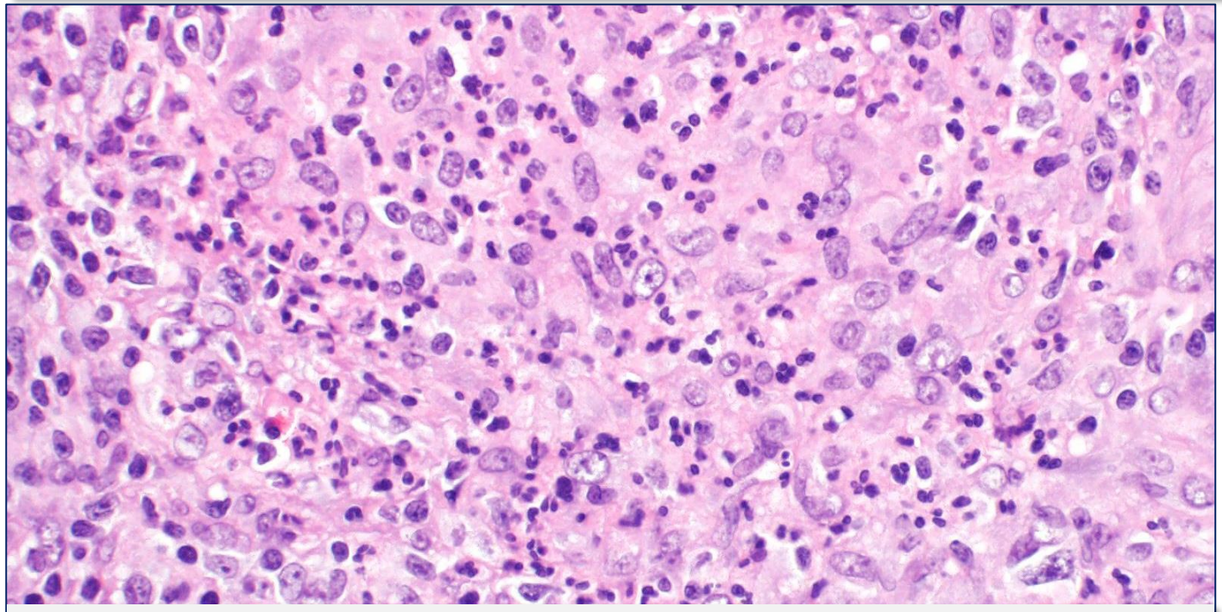
CD3



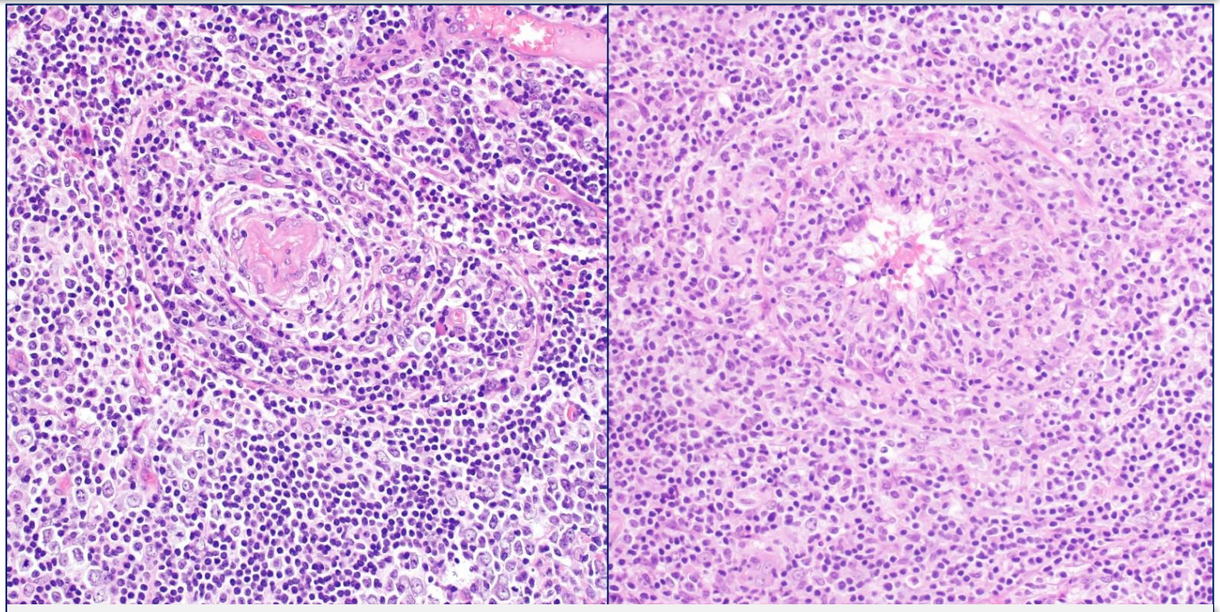




Plasmacytosis, mixed lymphohistiocytic inflammation



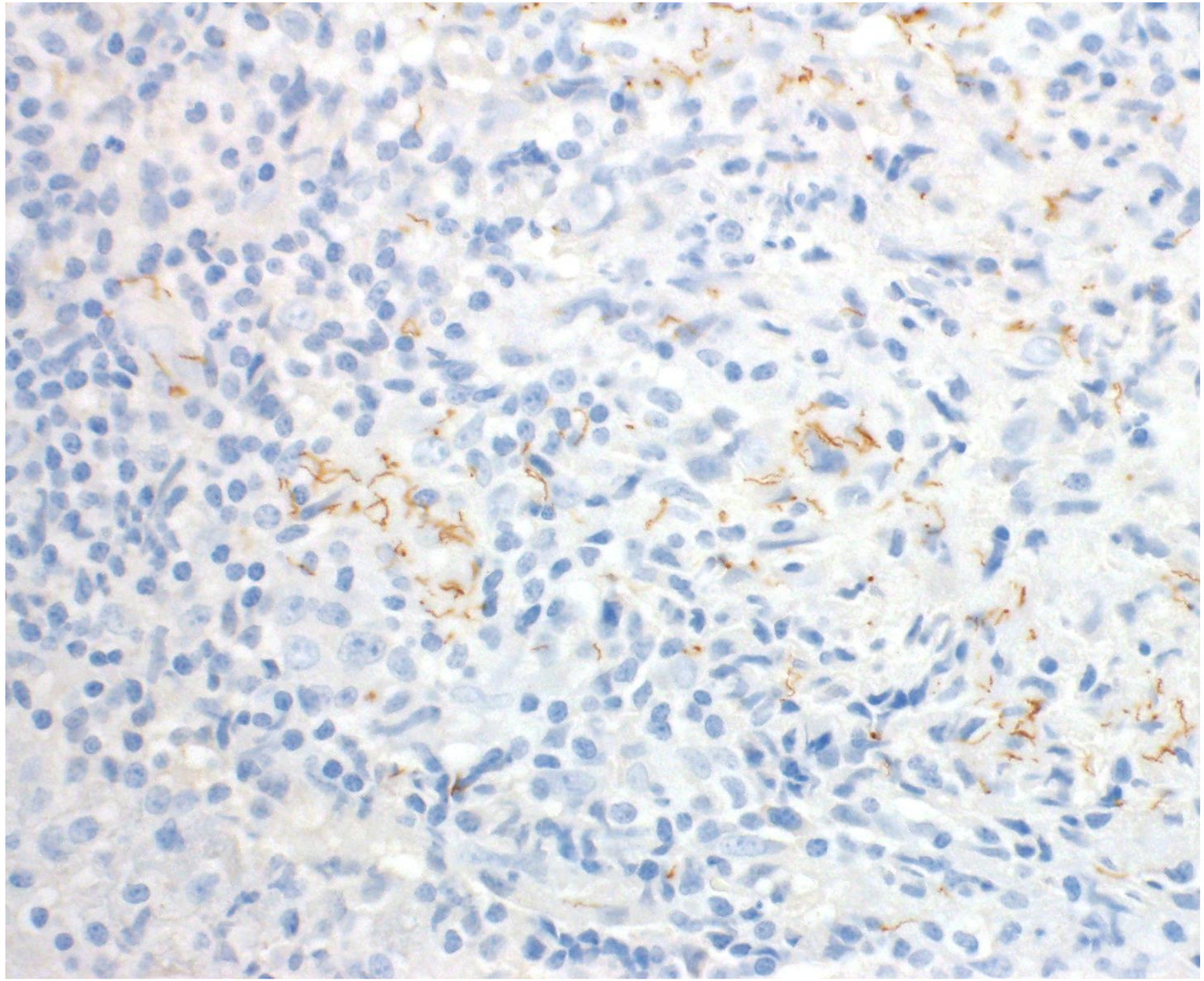
Neutrophils



Vasculitis

Spirochete immunostain

(*Treponema pallidum*)



Final diagnosis

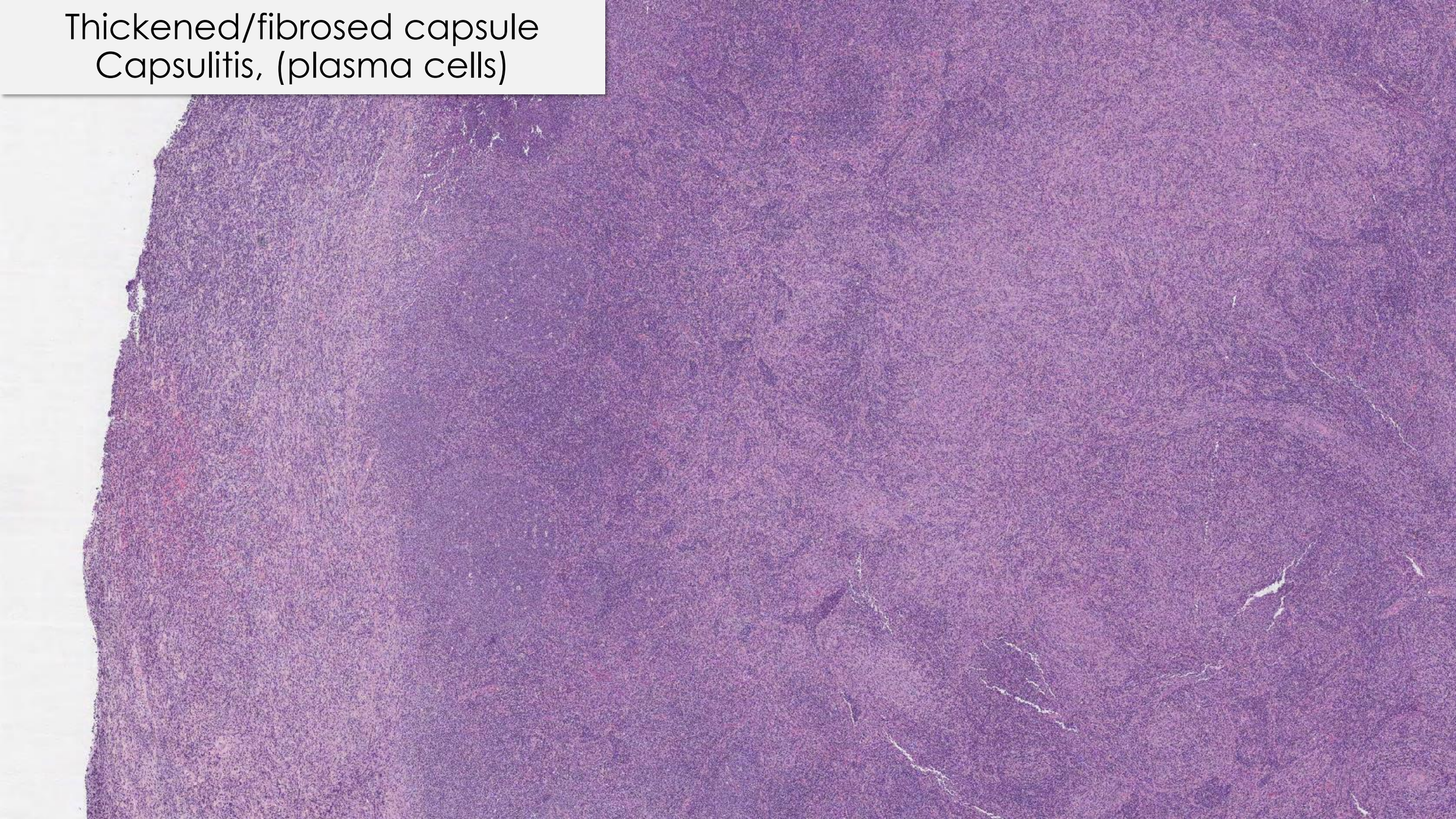
- Syphilitic (luetic) lymphadenitis

Histology of syphilis – lymph nodes

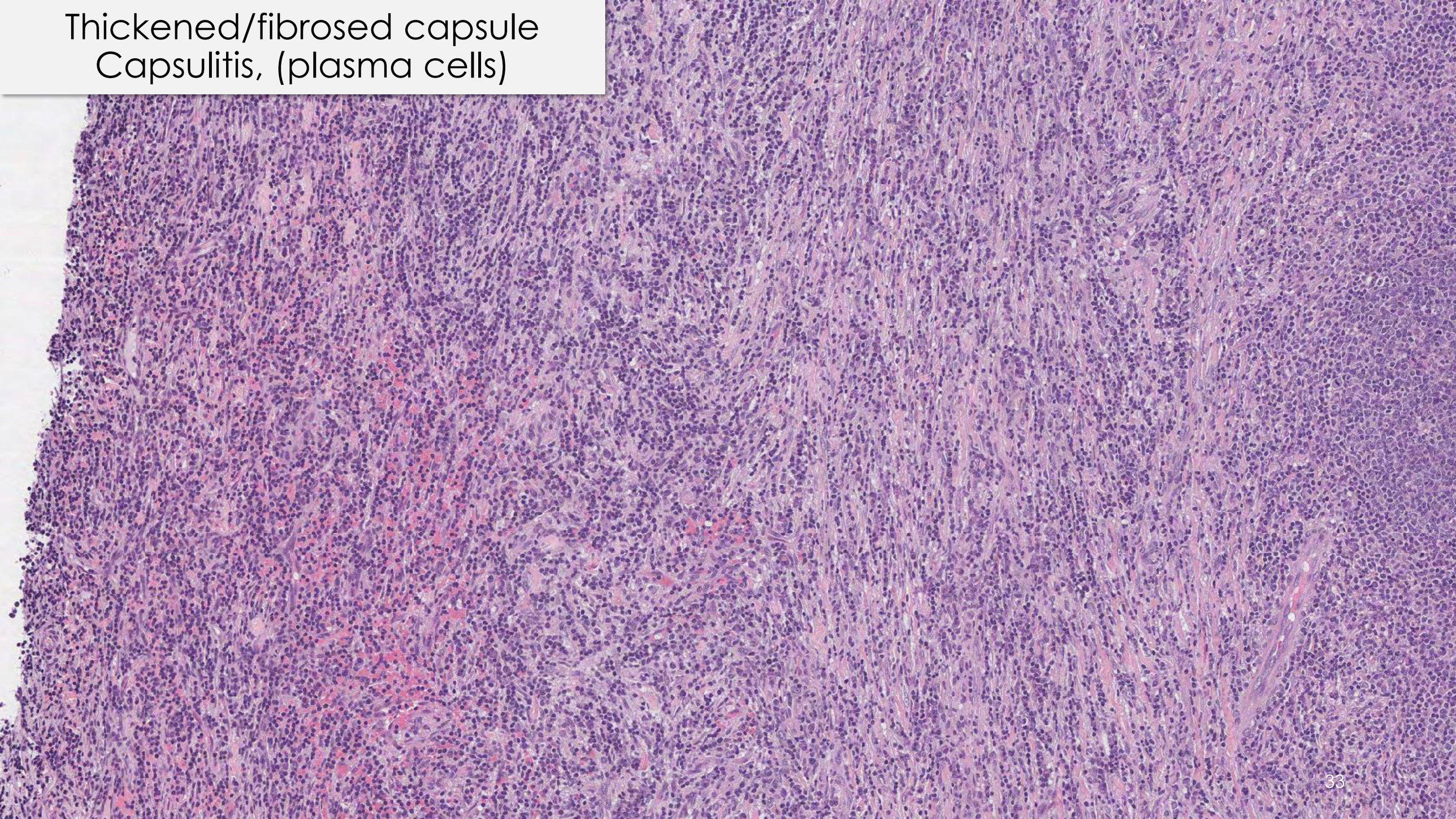
- Thickened/fibrosed capsule
- Capsulitis, vasculitis (plasma cells)
- Follicular hyperplasia
- Interfollicular plasmacytosis (particularly in medulla)
- Stromal/vascular hyperplasia
- Non-caseating loose epithelioid granulomas
- Multinucleated giant cells not associated with granulomas
- Gummatous lymphadenitis - lymph node replaced by necrotic material

Thickened/fibrosed capsule
Capsulitis, (plasma cells)

Thickened/fibrosed capsule
Capsulitis, (plasma cells)



Thickened/fibrosed capsule
Capsulitis, (plasma cells)



Thickened/fibrosed capsule
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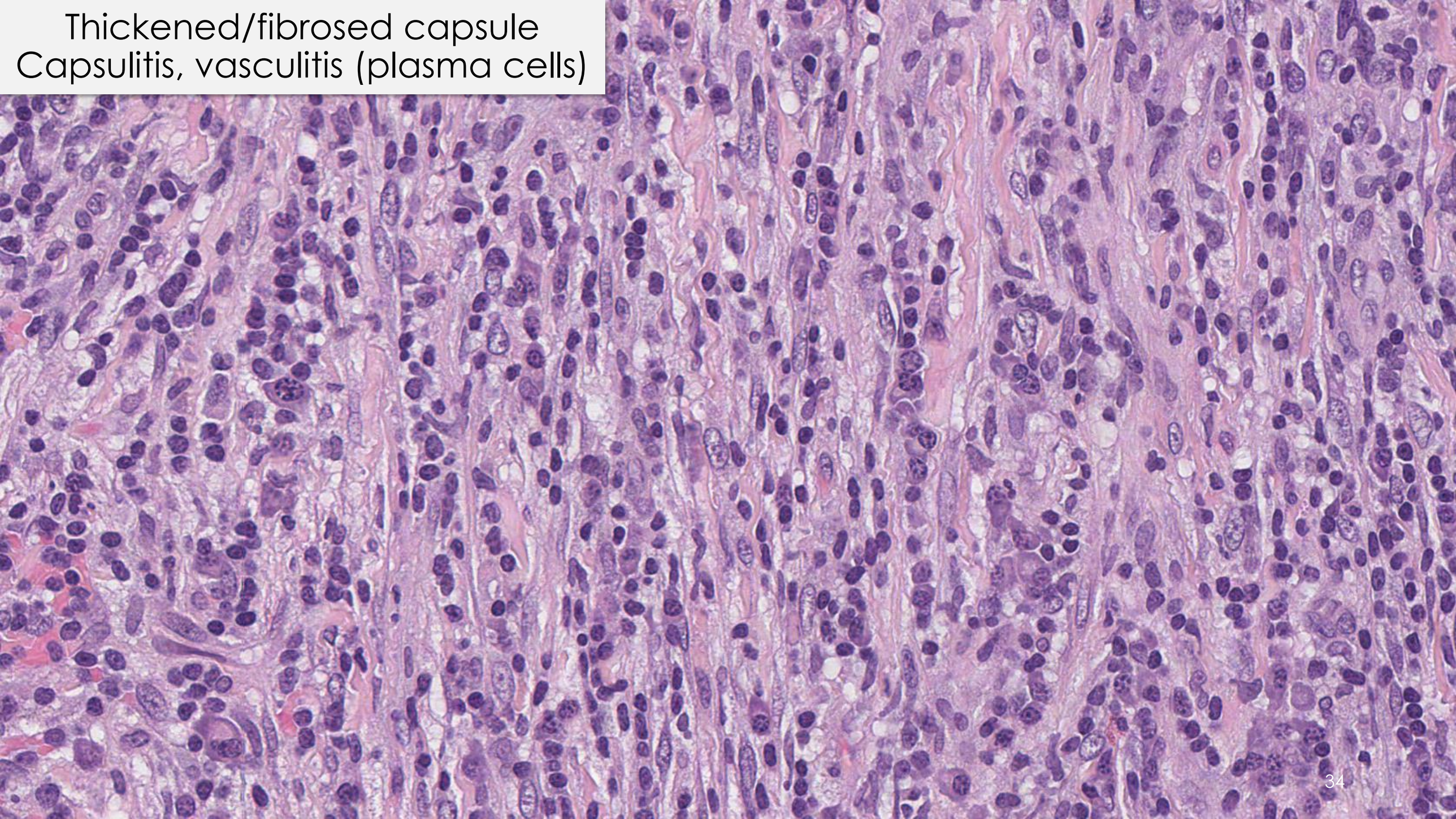
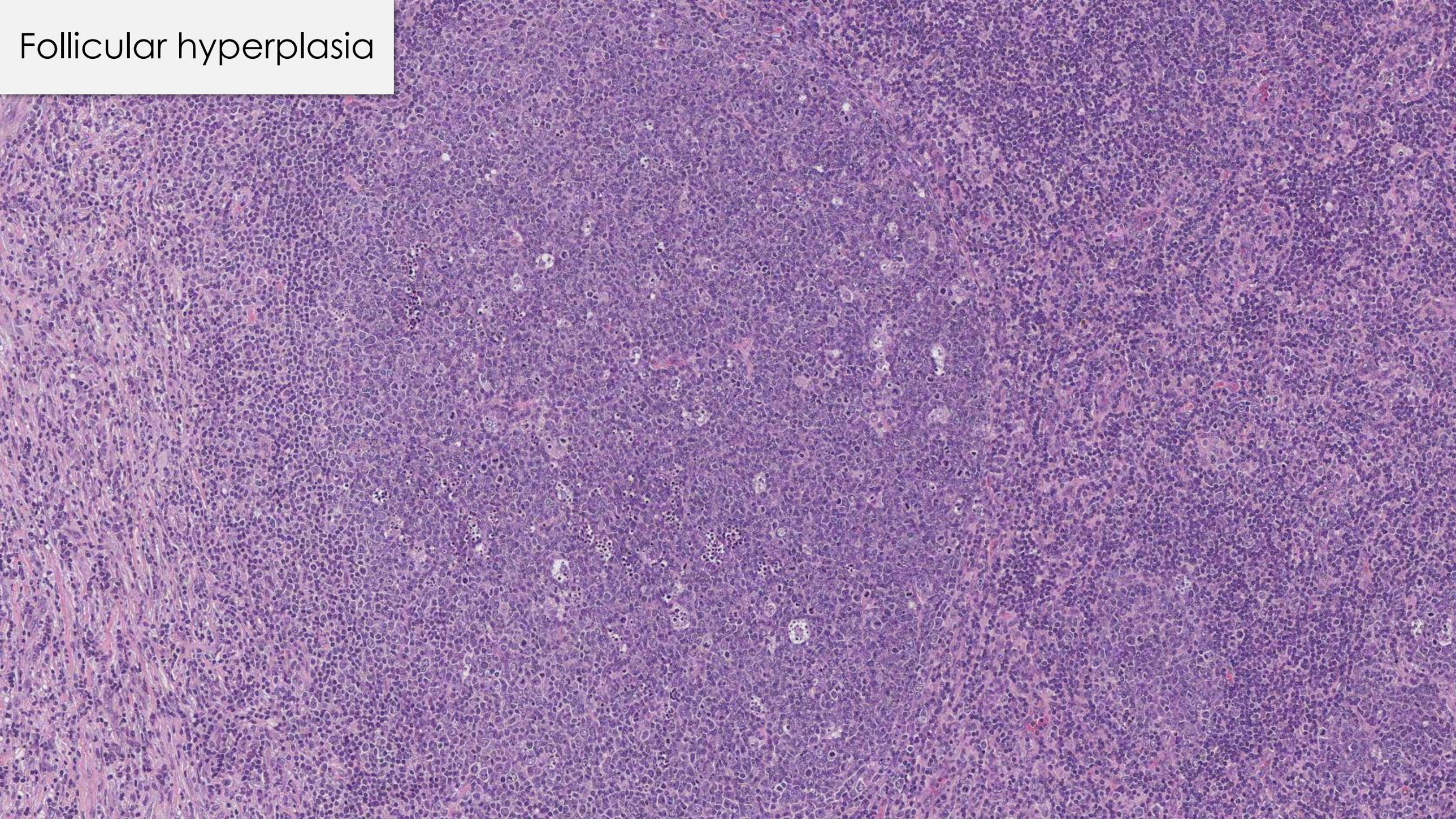
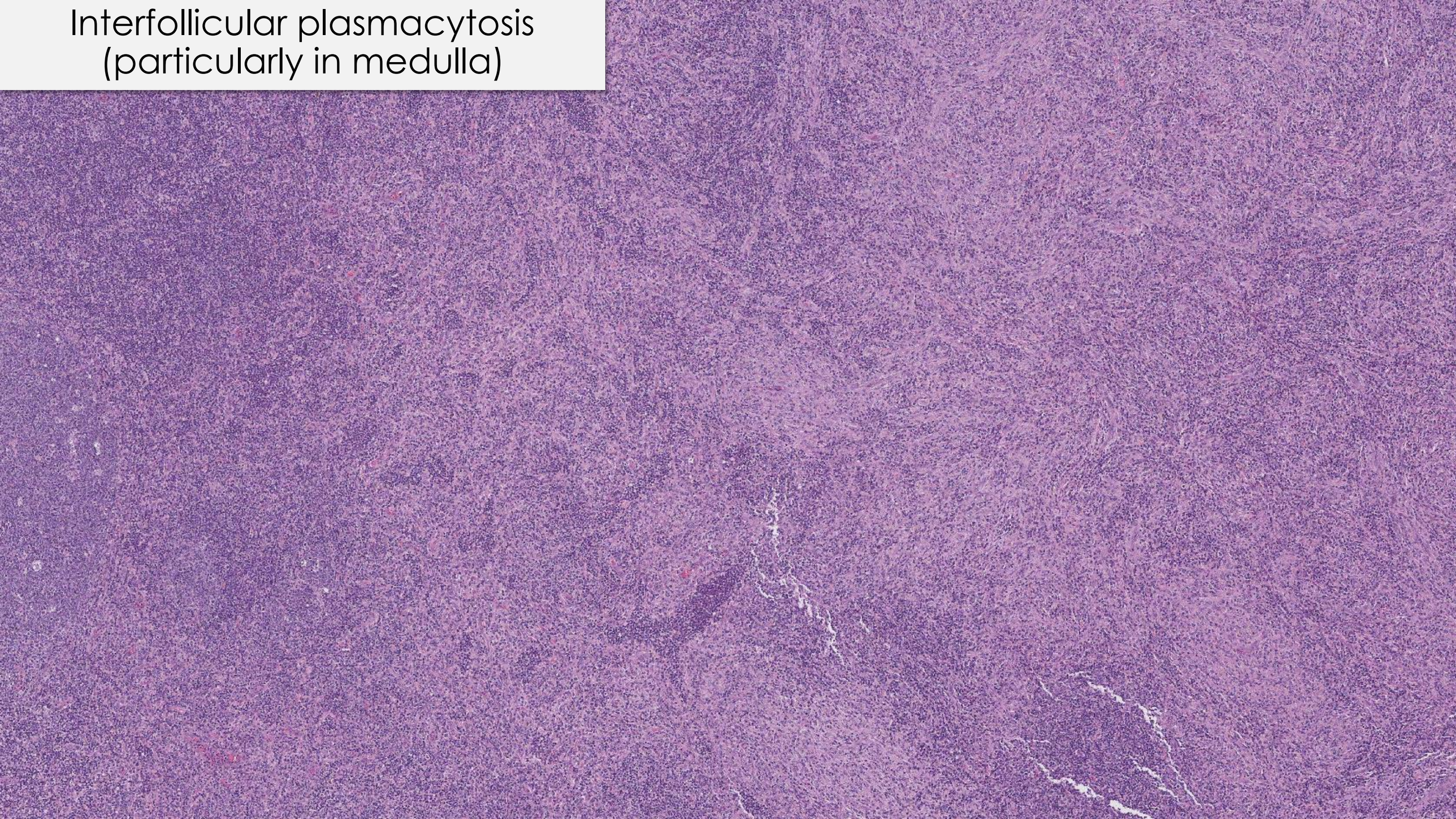


Follicular hyperplasia



Interfollicular plasmacytosis
(particularly in medulla)



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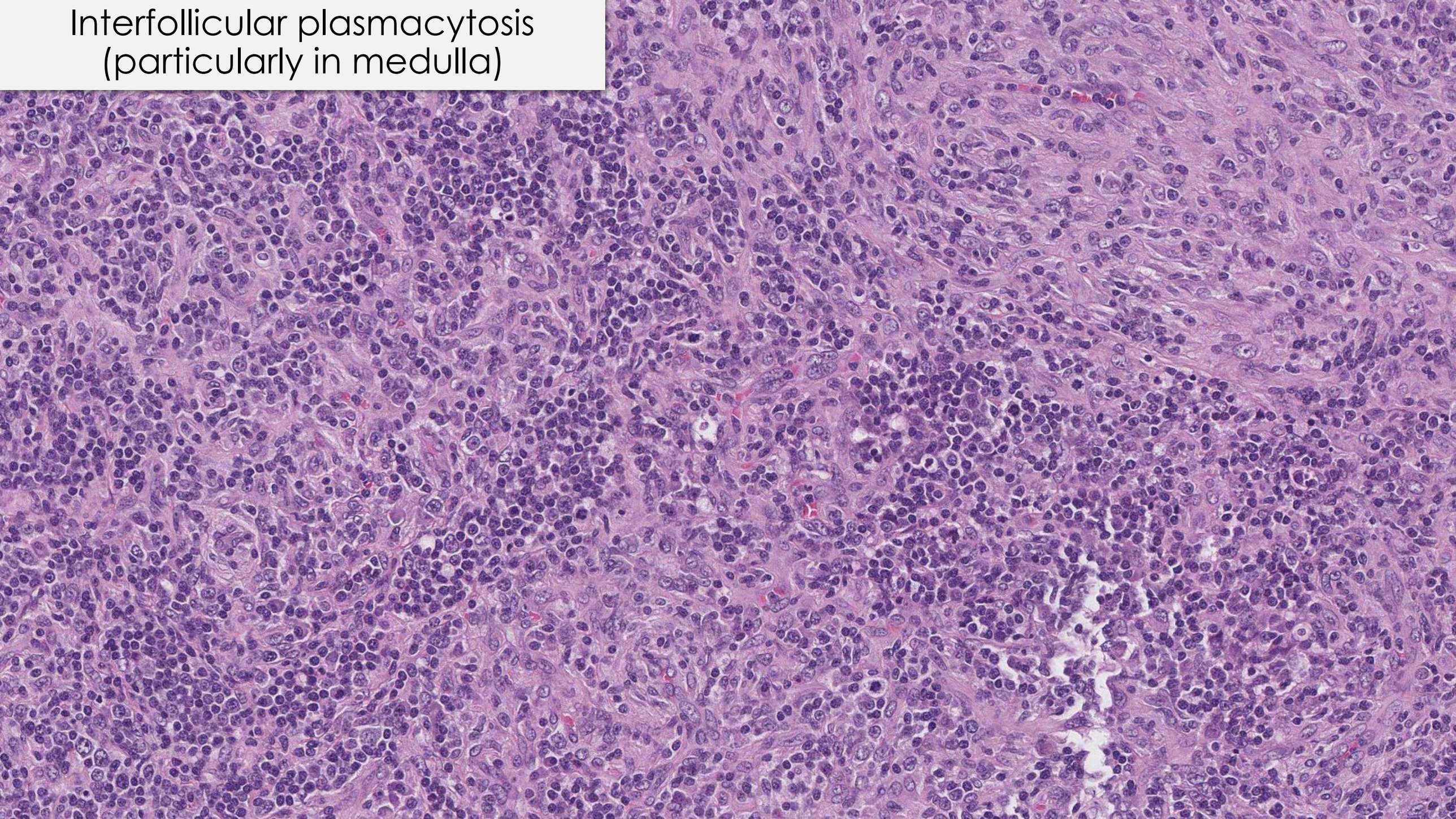

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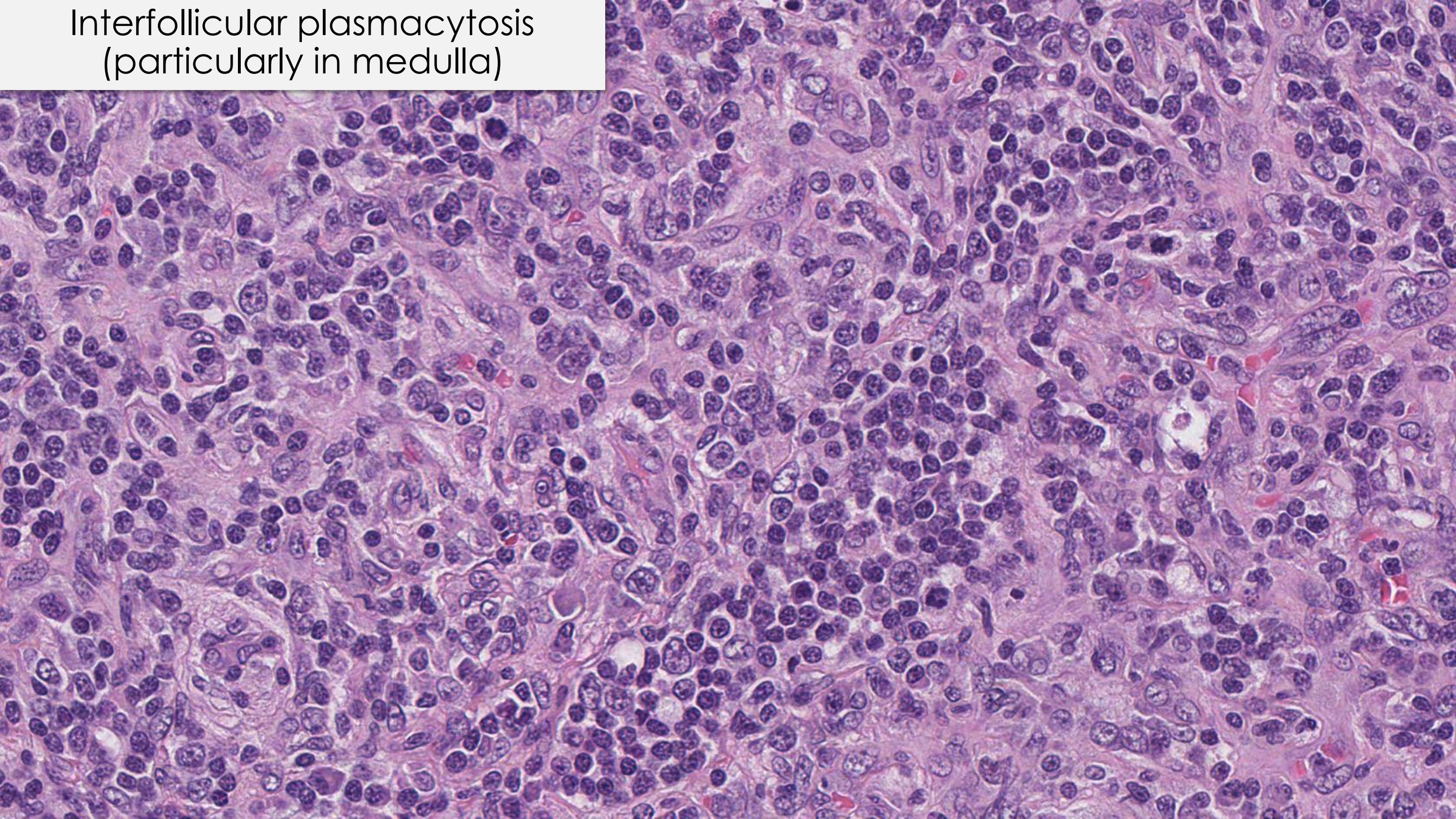
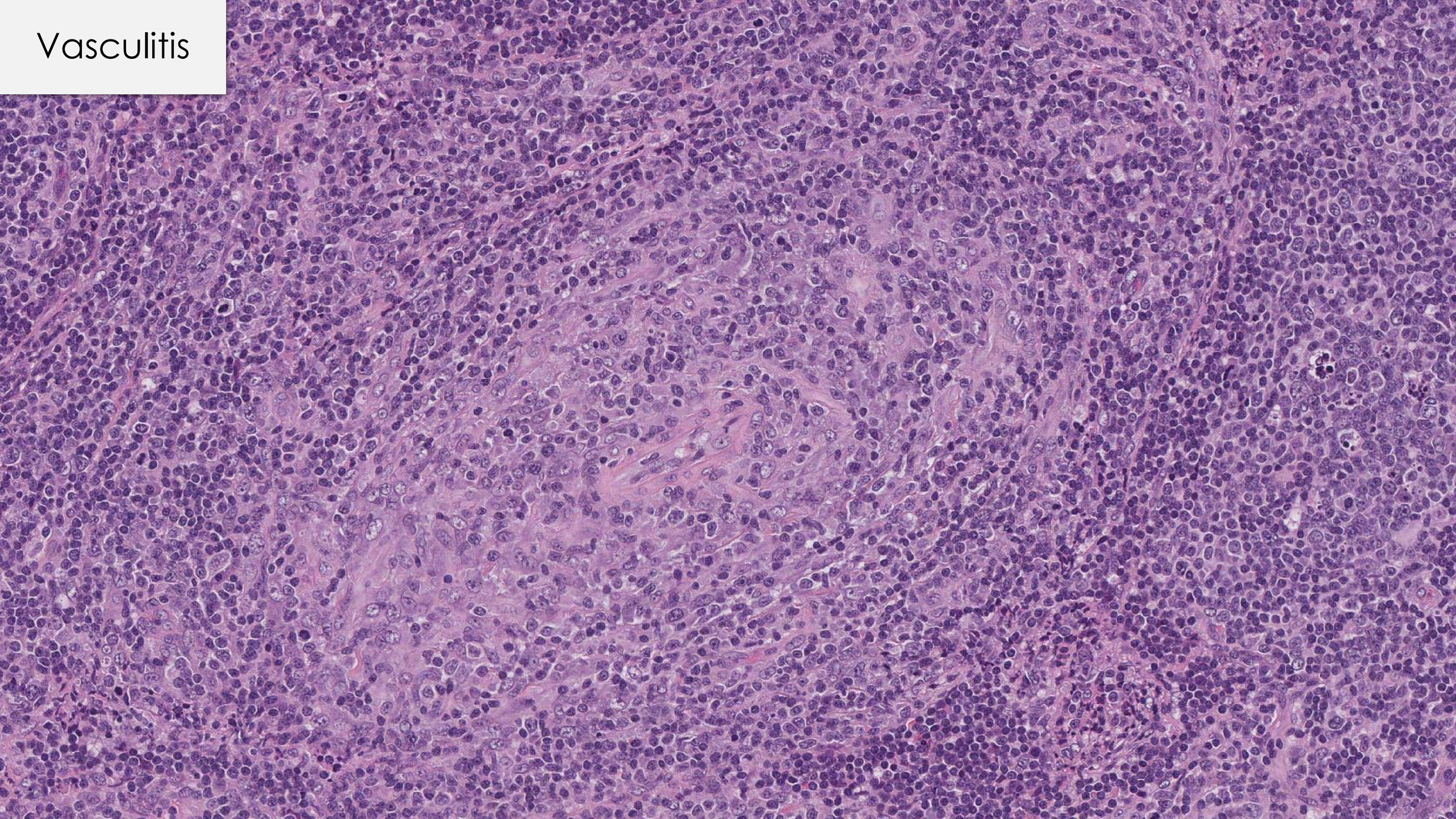


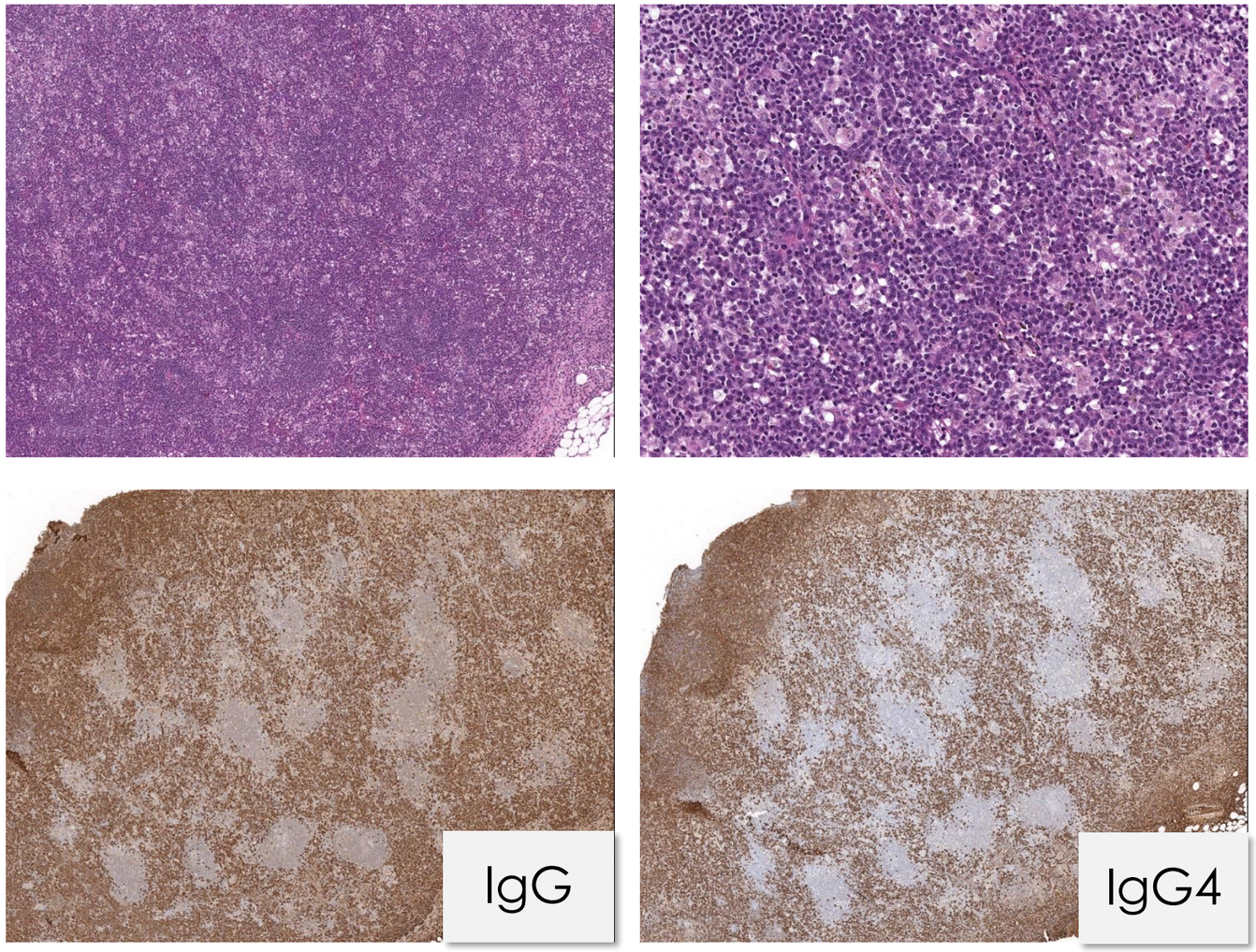
Vasculitis



Differential diagnosis

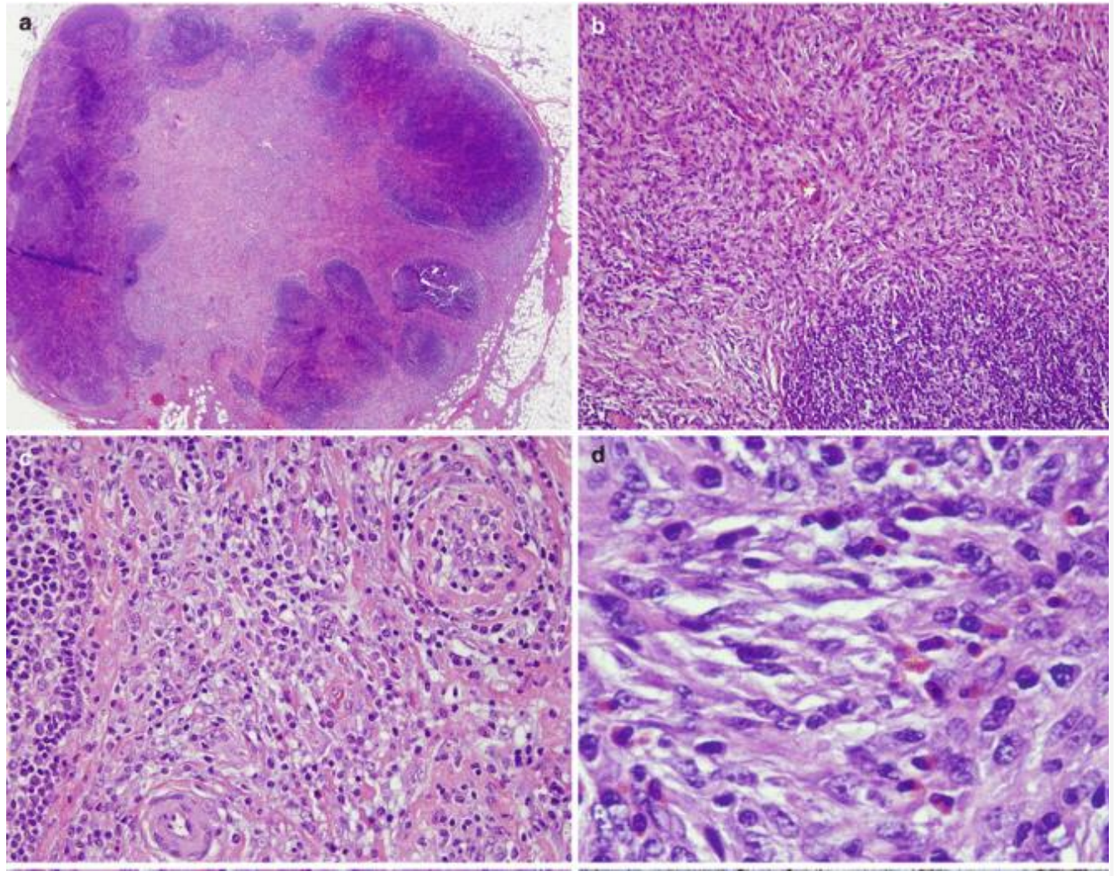
- Syphilitic (luetic) lymphadenitis
- Nonspecific reactive changes
- Autoimmune lymphadenopathy (due to plasmacytosis)
- IgG4-related disease
  - Plasmacytosis, fibrosis, phlebitis
  - Increased IgG4/IgG ratio; no spirochetes
- Inflammatory pseudotumor of lymph nodes
  - Fibrosis, plasmacytosis, vascular proliferation
  - Spirochete stain recommended
- Lymphogranuloma venereum (Chlamydia trachomatis)
  - Stellate microabscesses
  - No spirochetes; Giemsa or WS for Chlamydia

IgG4-related disease

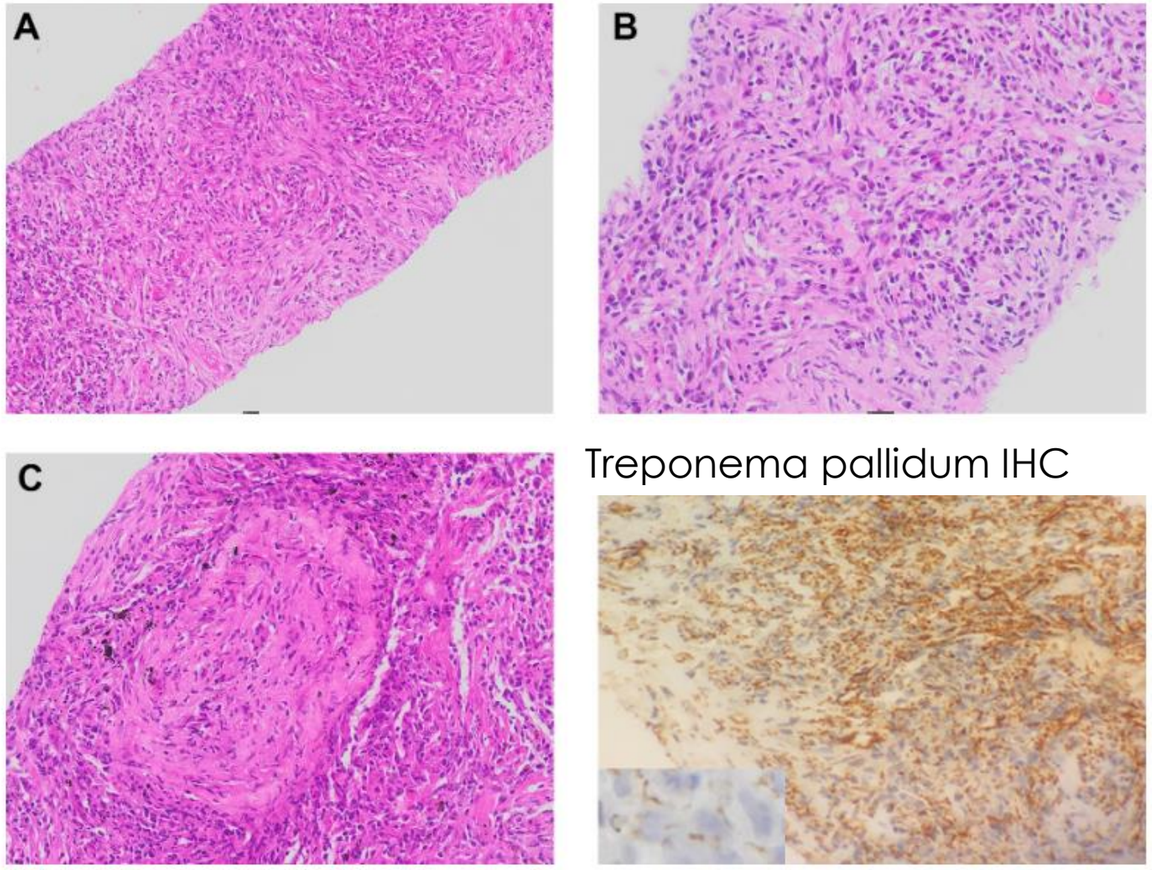


Syphilitic Pulmonary Inflammatory Pseudotumor

Inflammatory pseudotumor of lymph nodes



Syphilitic Pulmonary Inflammatory Pseudotumor



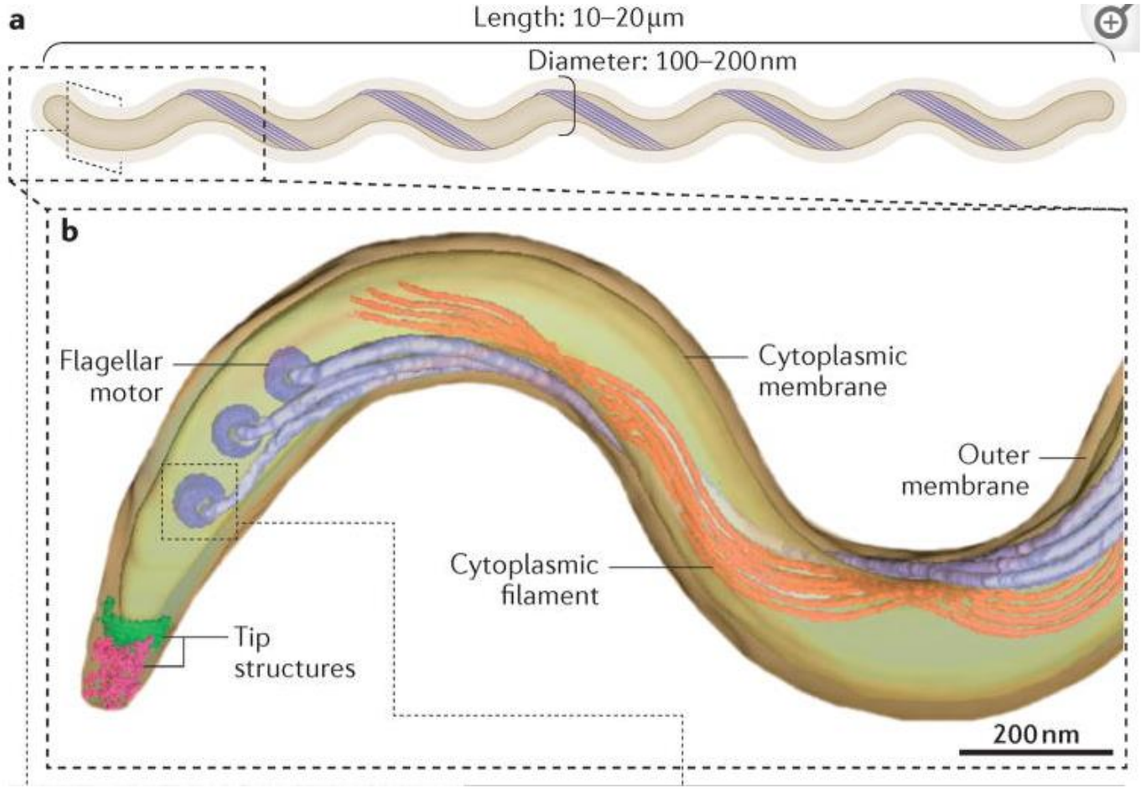
Treponema pallidum IHC

Miranda et al. (eds). Atlas of lymph node pathology. Springer

PMID: 32486870

Syphilis – facts

- Transmitted sexually or vertically from mother to fetus
- Caused by bacterial spirochete *Treponema pallidum* *(slender, spiral organism)*
- Transmitted- by <u>close contact</u> penetrates mucous membranes or skin
- Symptoms – due to <u>host response</u> to *T. pallidum*
- Treatment - penicillin



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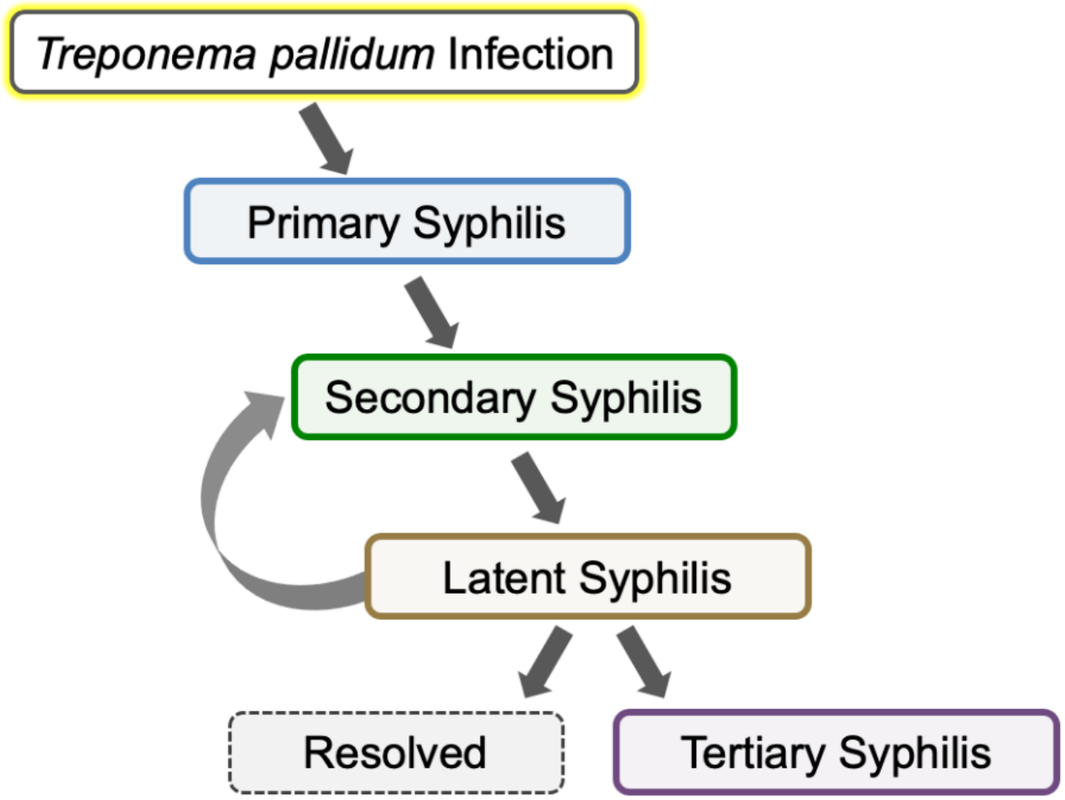
Syphilis – clinical presentation



Neurosyphilis
Ocular syphilis
Otosyphilis

Primary infection

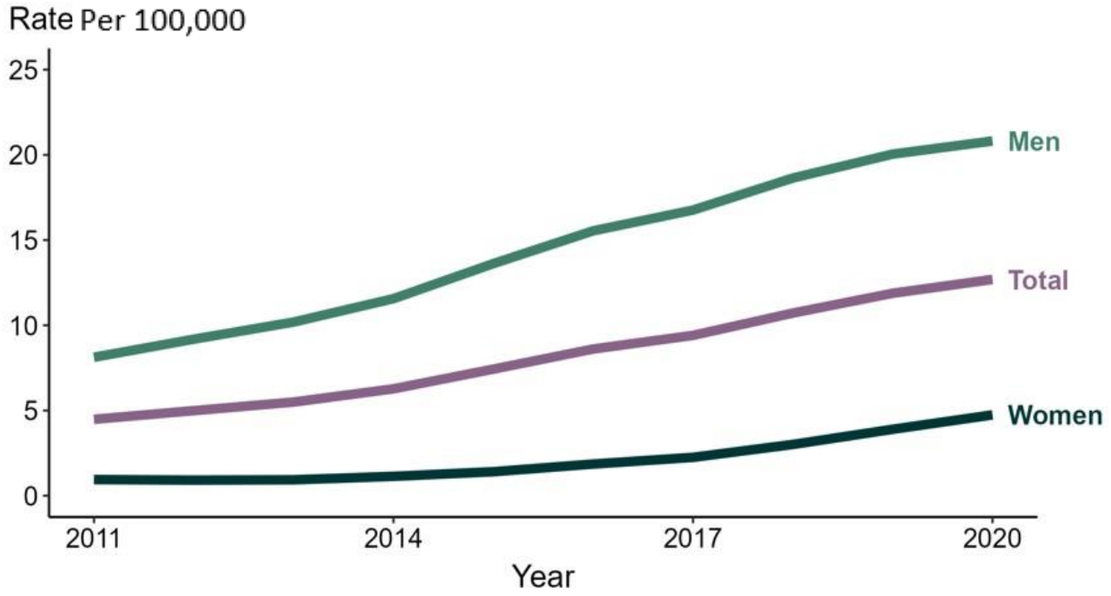
- Sore (chancre)
- Regional lymphadenopathy

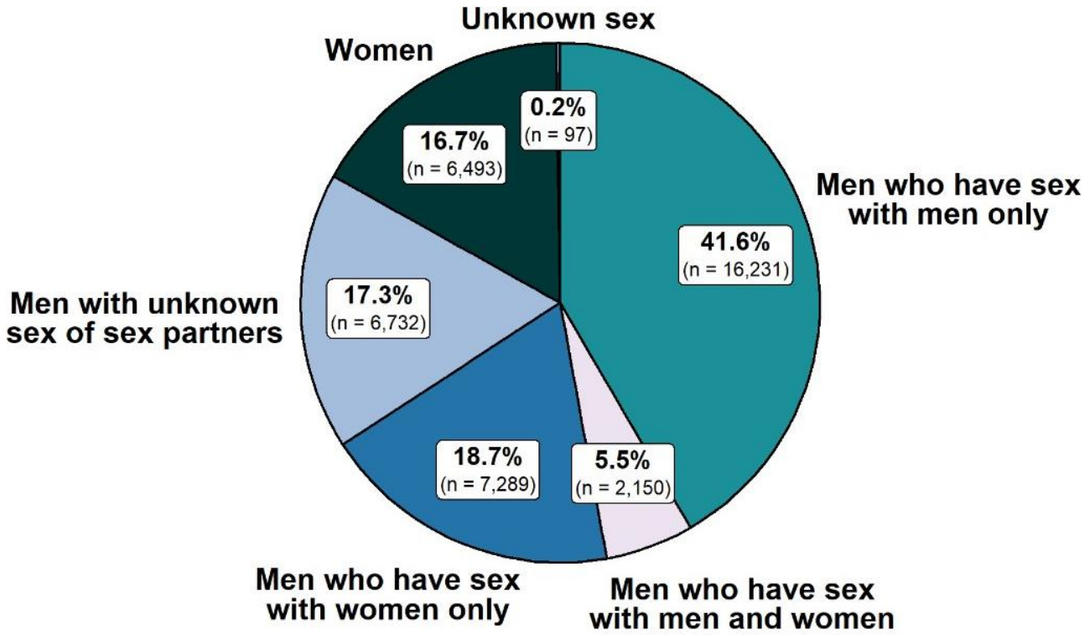
Secondary syphilis

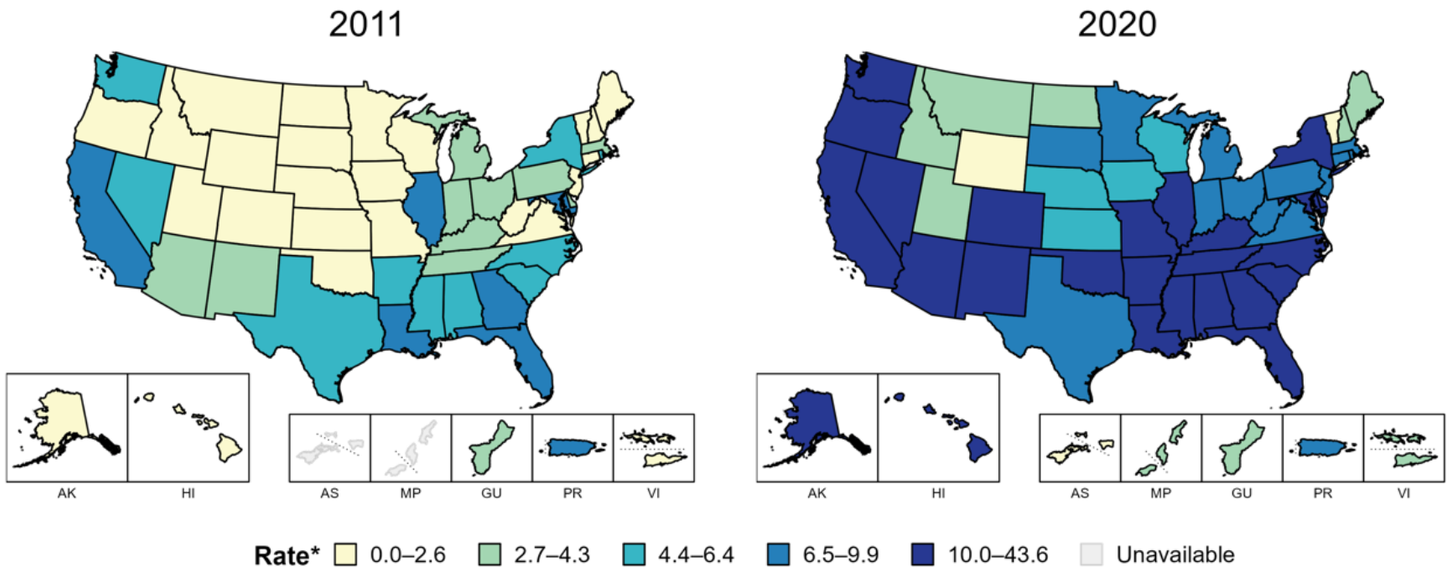
- Rash/sores, localized or generalized (palms, soles)
- Condylomata lata
- Fever, headache
- Lymphadenopathy

https://www.std.uw.edu/go/comprehensive-study/syphilis/core-concept/all;
https://www.cdc.gov/std/syphilis/images.htm

Primary and secondary syphilis recently increased



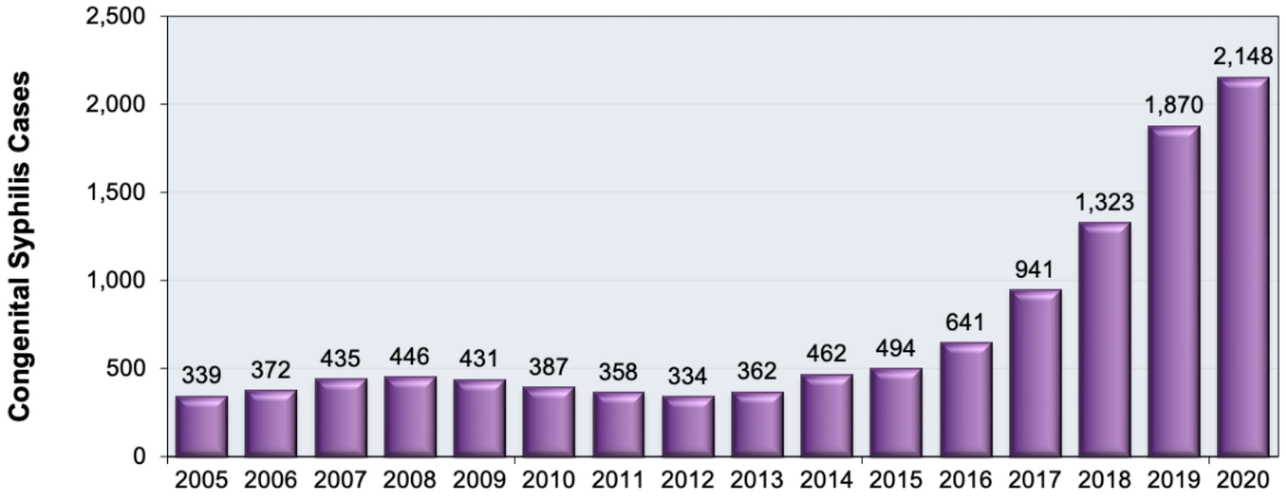




* Per 100,000

https://www.cdc.gov/std/statistics/2020/default.htm

Congenital syphilis – reported cases by year of birth, United States, 2005-2020



Early congenital syphilis:

- Glaucoma, cataracts
- Cortical demineralization of bones
- Hepatosplenomegaly
- Anemia and thrombocytopenia

Late congenital syphilis:

- Saddle nose due to destruction of cartilage
- Frontal bossing due to periostitis
- Tibial thickening (saber shins)
- Joint swelling (clutton joints)
- Perforation of hard palate
- Abnormal tooth development (Hutchinson's teeth, mulberry molars), Neurologic deafness and optic atrophy

https://www.cdc.gov/std/syphilis/images.htm

Diagnosis – clinical laboratory and tissue-based tests

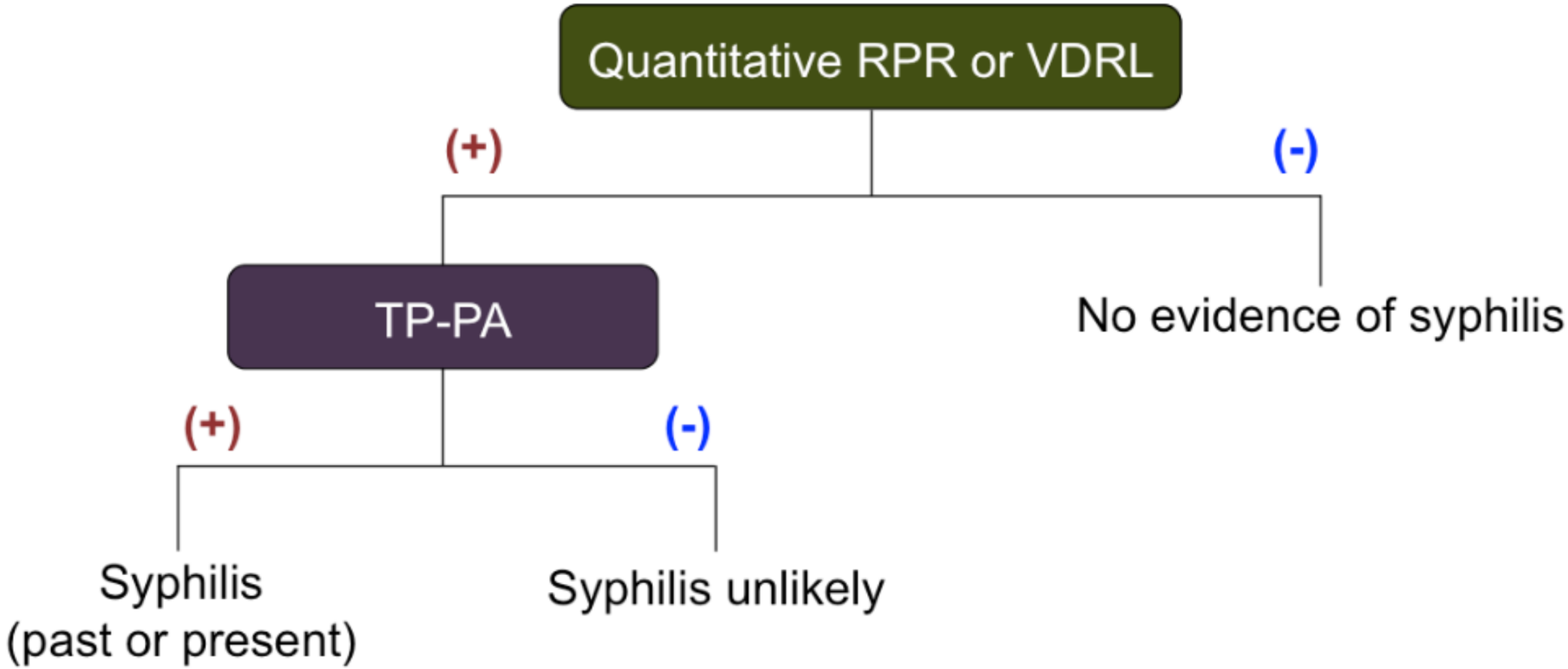
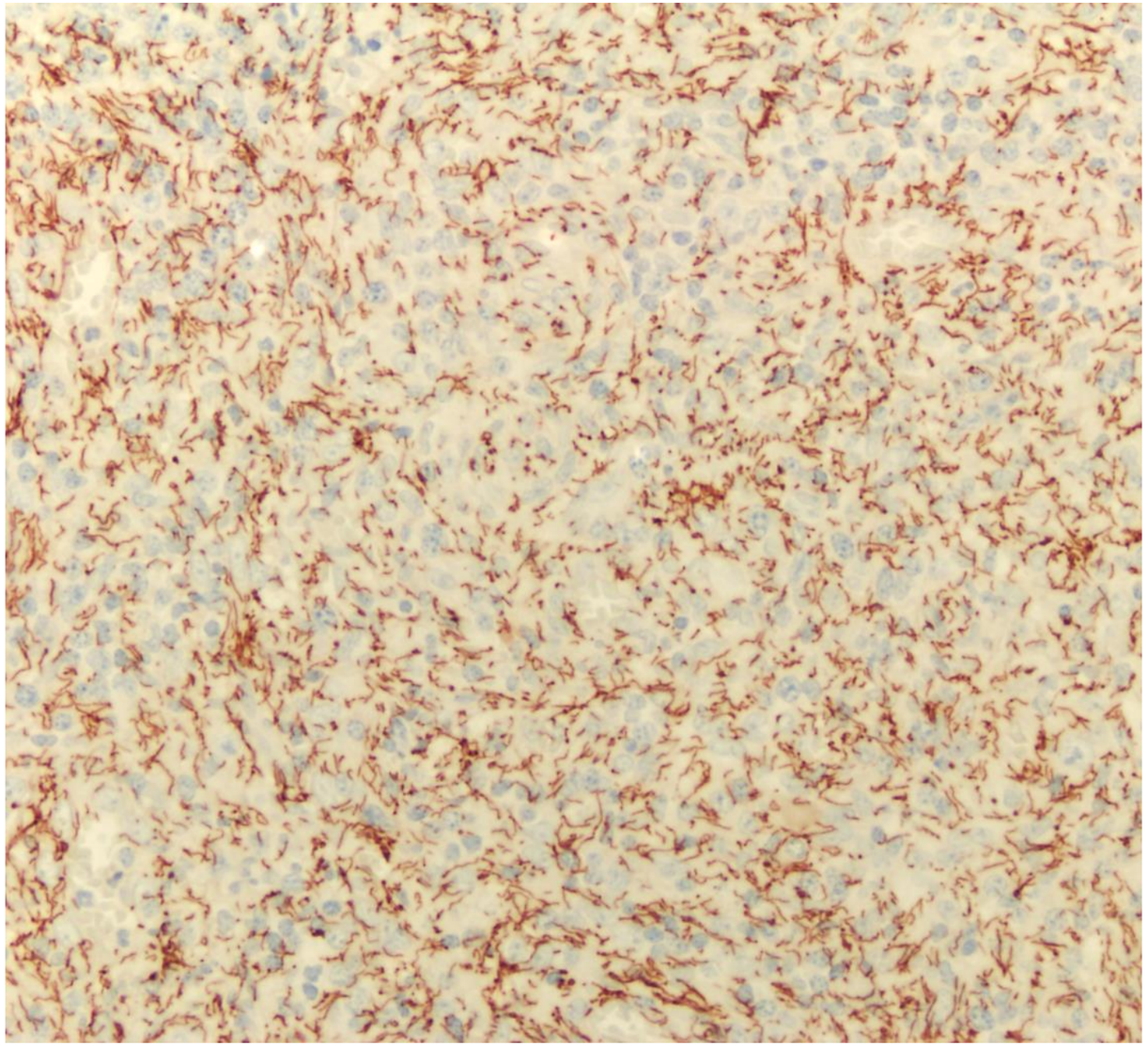


Figure 23 - Syphilis Serologic Screening—Traditional Sequence Algorithm
The traditional (standard) serologic screening sequence algorithm uses a quantitative nontreponemal test (RPR or VDRL) for screening followed by a treponemal test for confirmation of positive screening tests.
Abbreviations: RPR = rapid plasma reagin; VDRL = Venereal Disease Research Laboratory; TP-PA = *Treponema pallidum* particle agglutination.

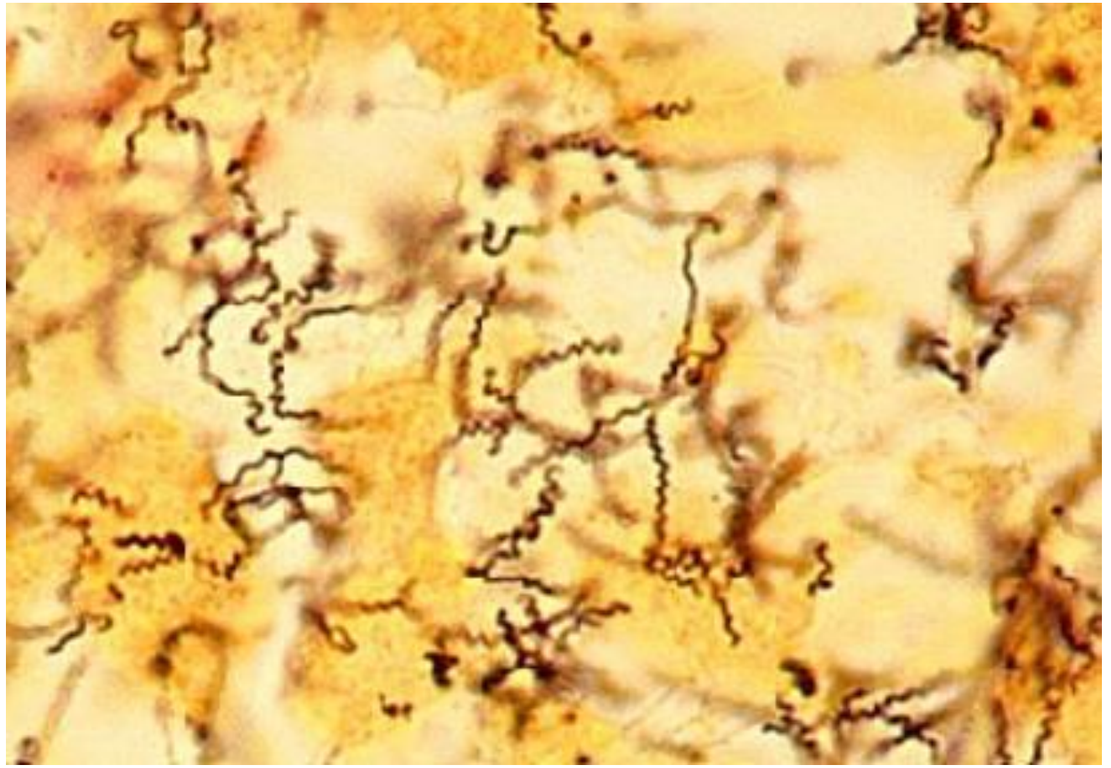
https://stacks.cdc.gov/view/cdc/48172

T. Pallidum immunohistochemistry is a preferred method

T. Pallidum immunohistochemistry



Warthin Starry silver stain



Other methods:

- Immunofluorescence
- Dark-field microscopy
- *In situ* hybridization
- Molecular studies

When to do spirochete stain?

- Reactive appearing nodes with plasmacytosis
- Capsular thickening
- Vasculitis!!!
- Loose granulomas/epithelioid histiocytes
- Be more liberal in inguinal lymph nodes
- Clinical history
  - In patients with history of HIV, particularly new diagnosis and if inguinal node is biopsied
  - History of rash with lymphadenopathy

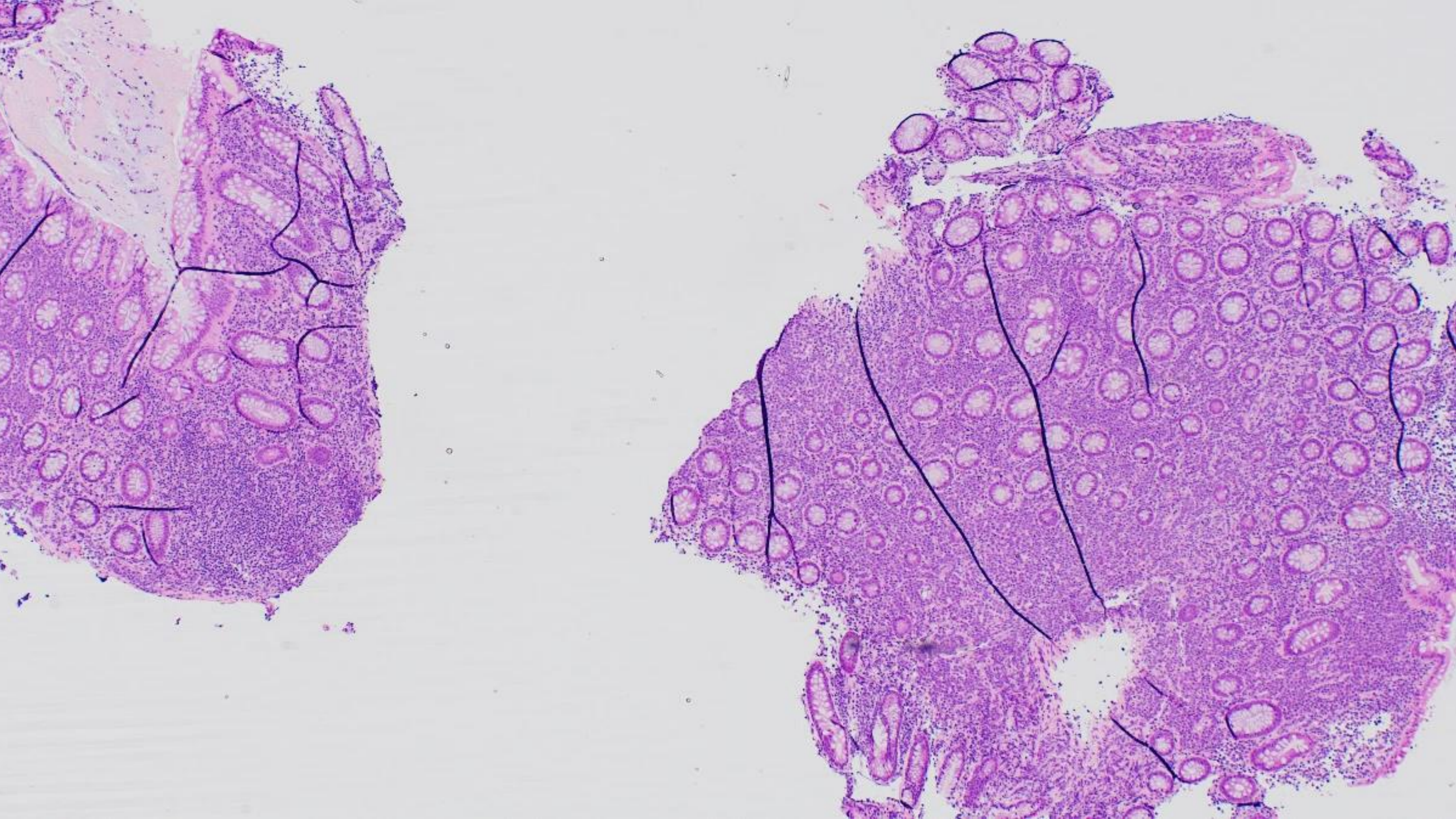
Conclusions

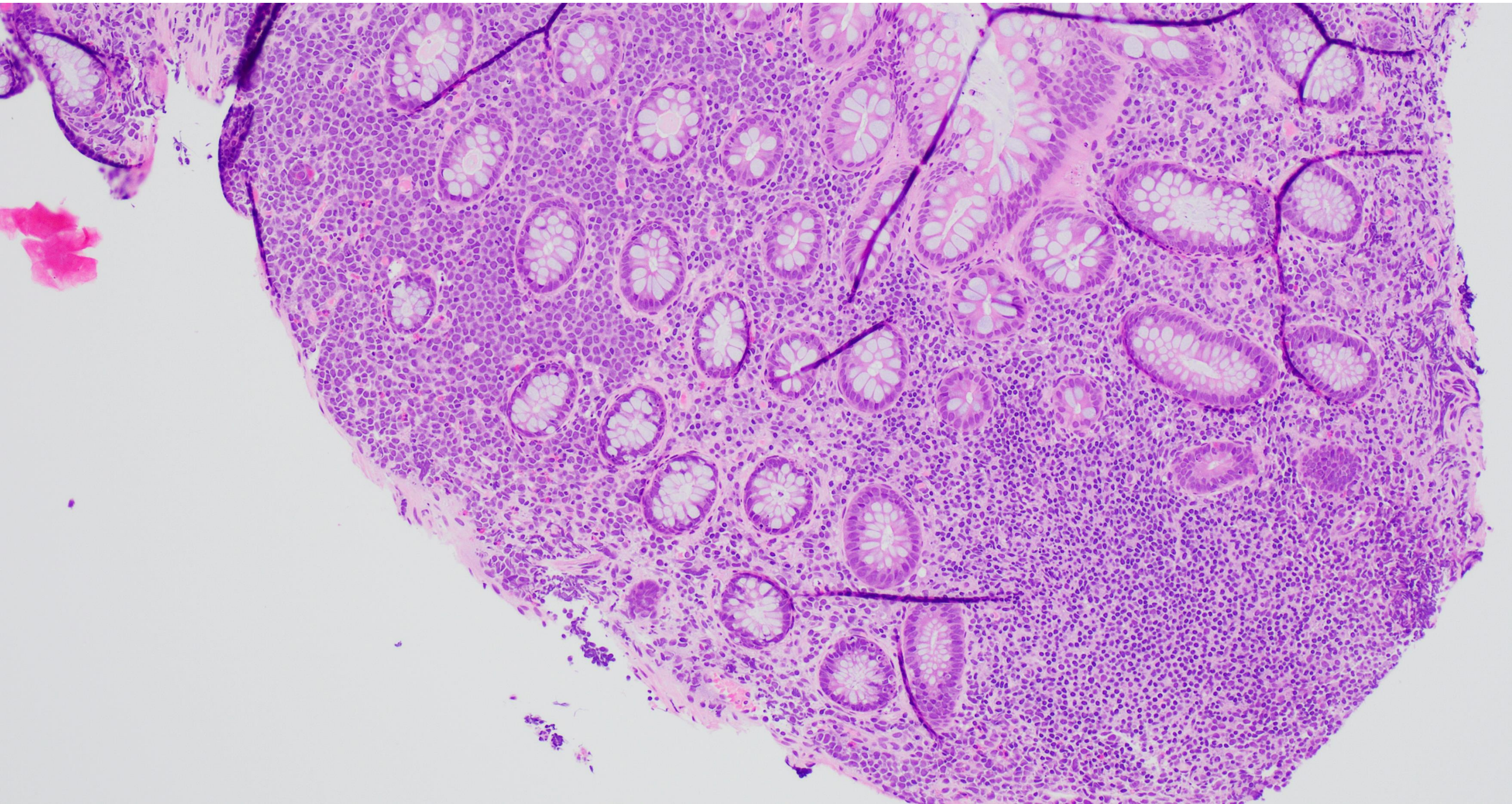
- Syphilis is a challenging disease to diagnose
- Keep it in mind when looking at reactive lymph nodes
- If lymph node biopsy is done, syphilis is not suspected

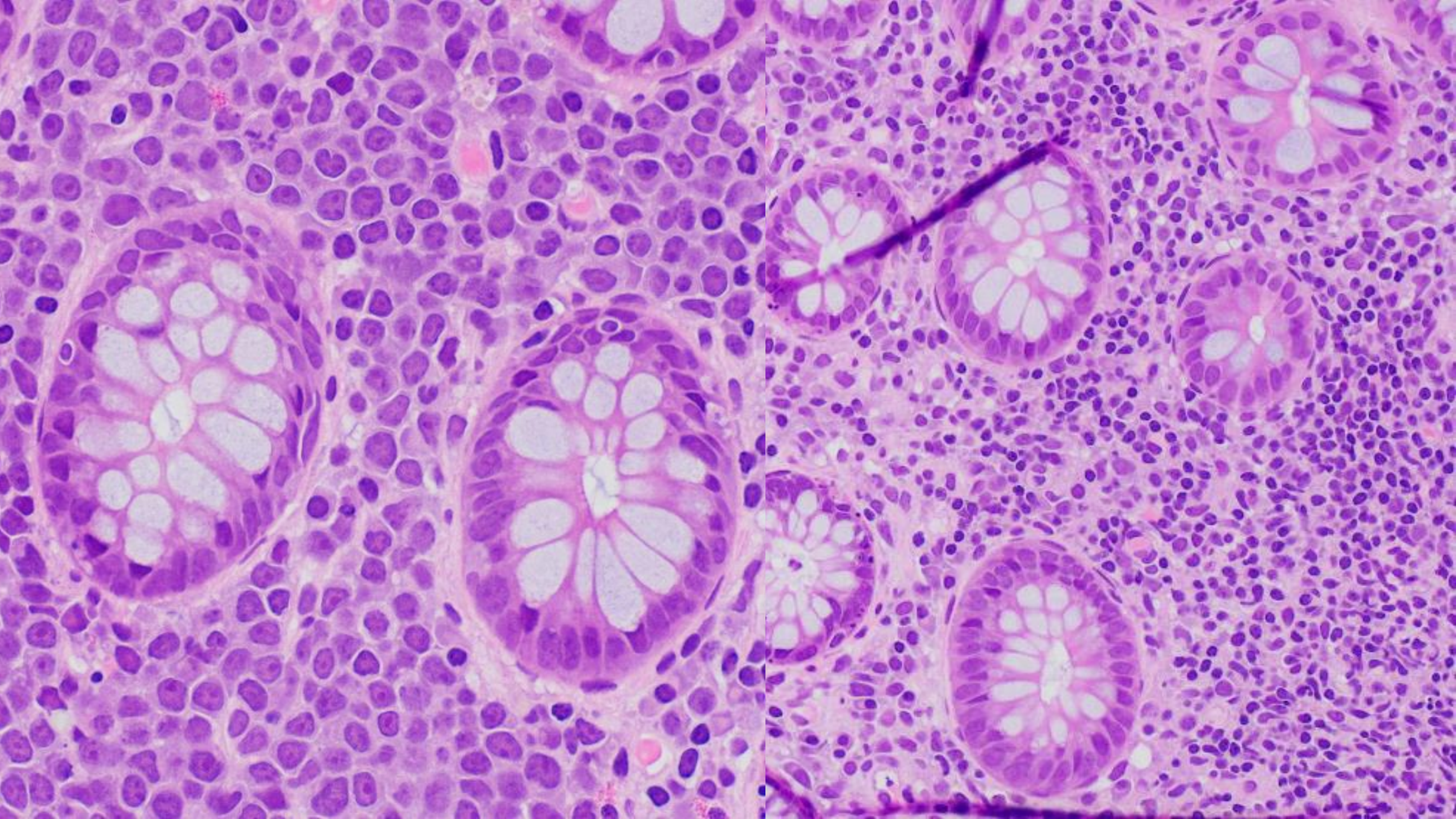
Routine colon biopsy with a twist

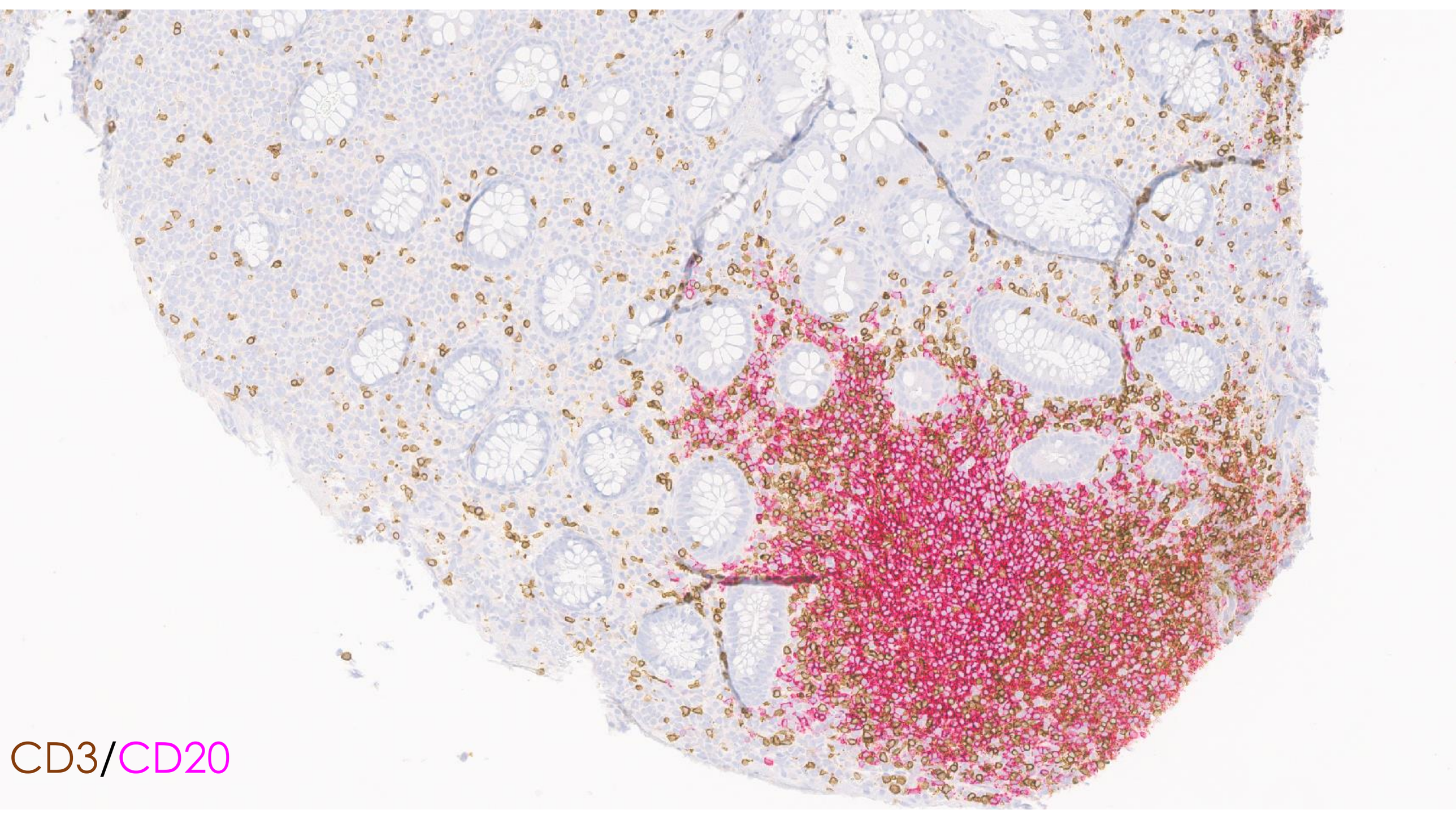
Case #3

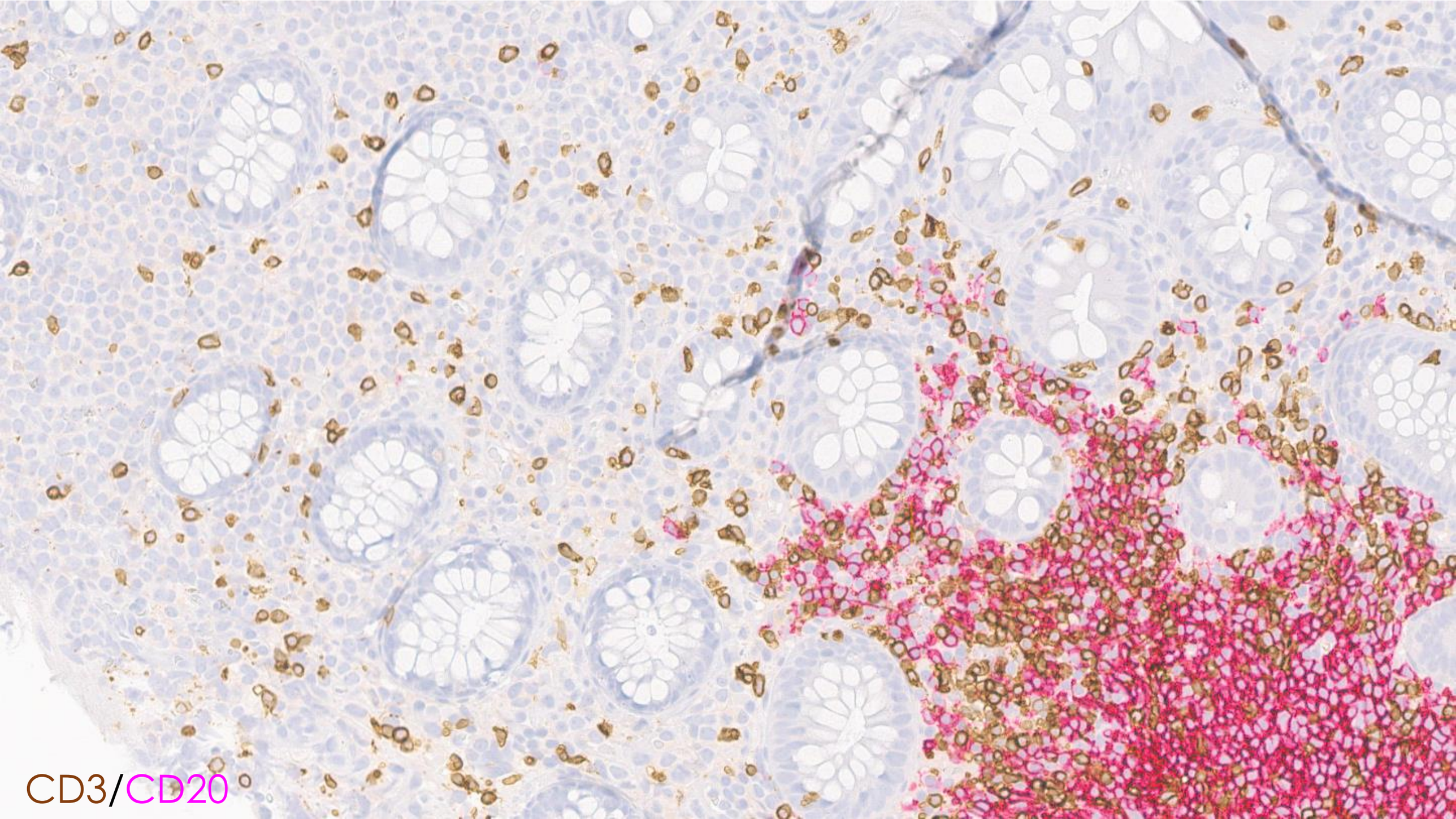
- 47-year-old male with a history of lymphocytic colitis
- Remote history of AML
- Routine colonoscopy
- Endoscopic evaluation is normal

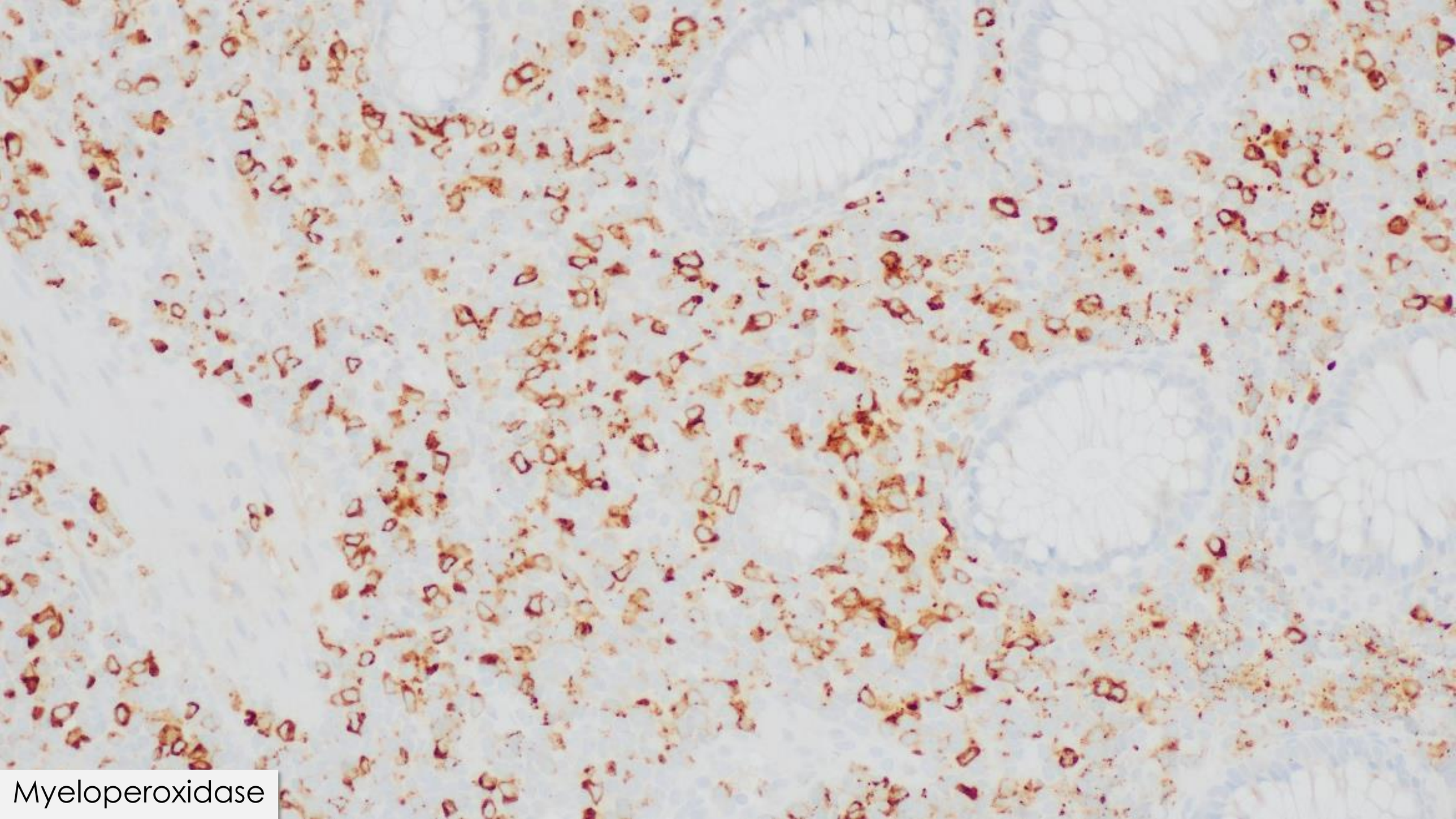







CD3/CD20


CD3/CD20


Myeloperoxidase

Final diagnosis

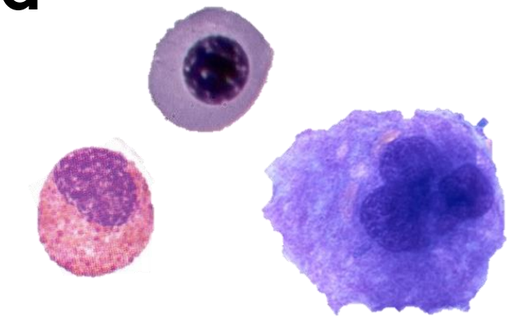
- Myeloid sarcoma

Myeloid sarcoma: differential diagnosis

Myeloid sarcoma: DDX

- **Lymphoma**:
  - DLBCL
  - Lymphoblastic
  - Blastic mantle cell lymphoma
  - Burkitt lymphoma
- **Carcinoma** (neuroendocrine)
- **Sparse immature myeloid cell infiltrate** (preserved underlying architecture) in patients with AML or receiving growth factors

Clues for myeloid sarcoma



- Admixed erythroid cells, megakaryocytes and eosinophilic myelocytes
- Immunophenotype:
  - Negative: B- and T-cell markers
  - Positive: CD43 (sensitive), CD13, CD33, CD34, CD117, MPO (granulocyte lineage specific), CD68 and lysozyme (monocytic markers)
- Immunophenotypic aberrancies:
  - +: T-cell markers - CD4 (monocytic); CD3, CD5, CD7 (T/Myeloid MPAL)
  - + B-cell marker (CD19 in t(8;21)/*RUNX1-RUNX1T1*) or in B/myeloid MPAL)

Myeloid sarcoma - extramedullary mass-lesion

Facts:

- 2-9% patient with AML
- Prognosis similar to AML
- Most frequently involves skin, soft tissue, lymph nodes, and gastrointestinal tract.

Diagnosis:

- Extramedullary mass lesion composed of myeloid blasts.
- Effacement of tissue architecture
- Positive immunophenotyping for granulocytic and/or monocytic markers

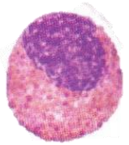
Myeloid sarcoma = diagnosis of AML

- *IDH1* and *IDH2* (prognosis and therapeutic targets)
- *FLT3*-internal tandem duplication (*FLT3*-ITD) (prognosis and therapeutic targets)
- *NPM1* (prognostic stratification and therapy)
- *KMT2A* rearrangement (prognostic stratification and emerging therapy with Menin inhibitors)

WHO 5th edition

Conclusions: Myeloid sarcoma can be challenging

- Keep myeloid sarcoma in mind when suspecting "lymphoma" - negative for B- and T-cell markers and positive for CD43
- Eosinophilic myelocytes

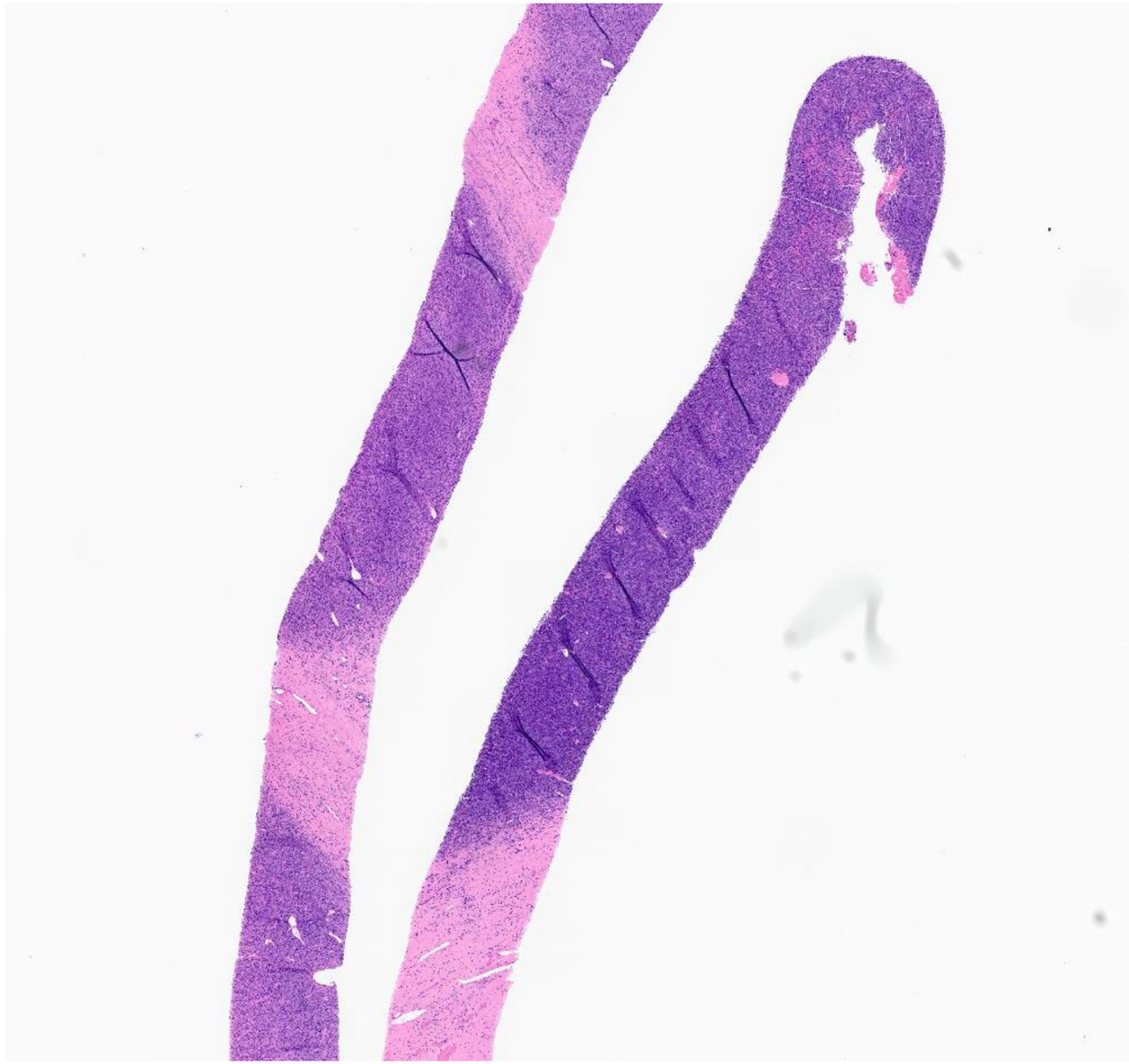


When soft-tissue sarcoma crosses into hematopathology

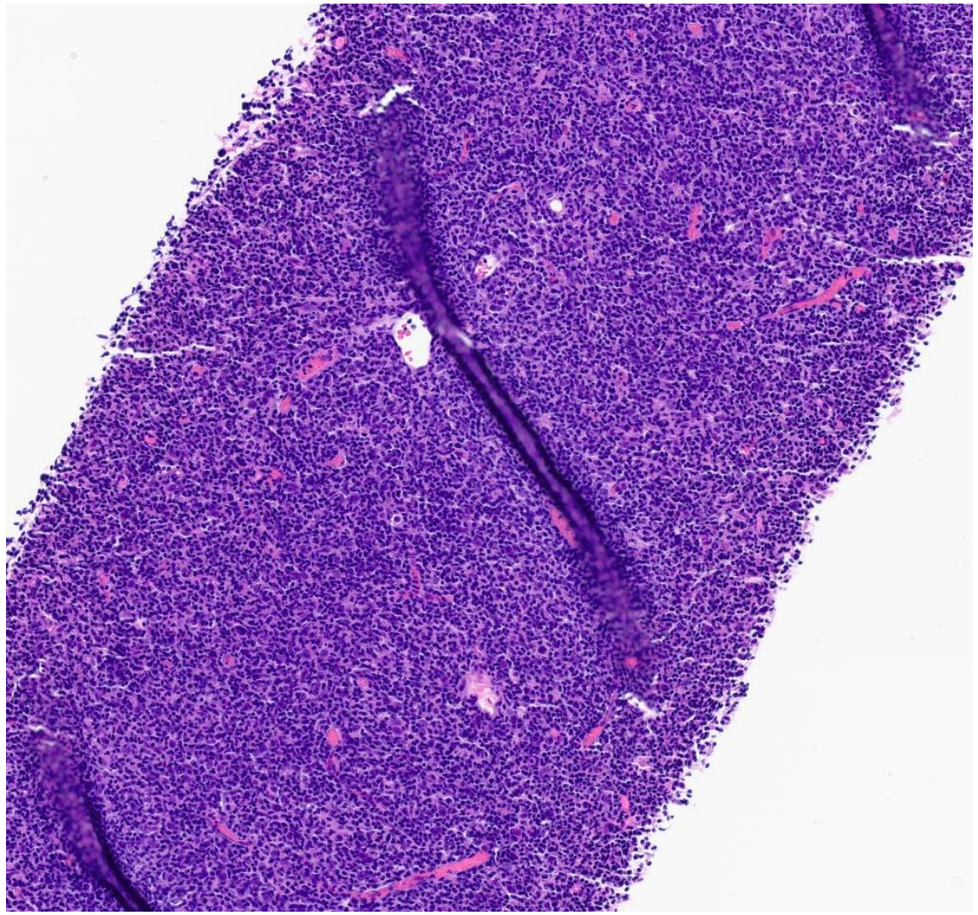
Case #4

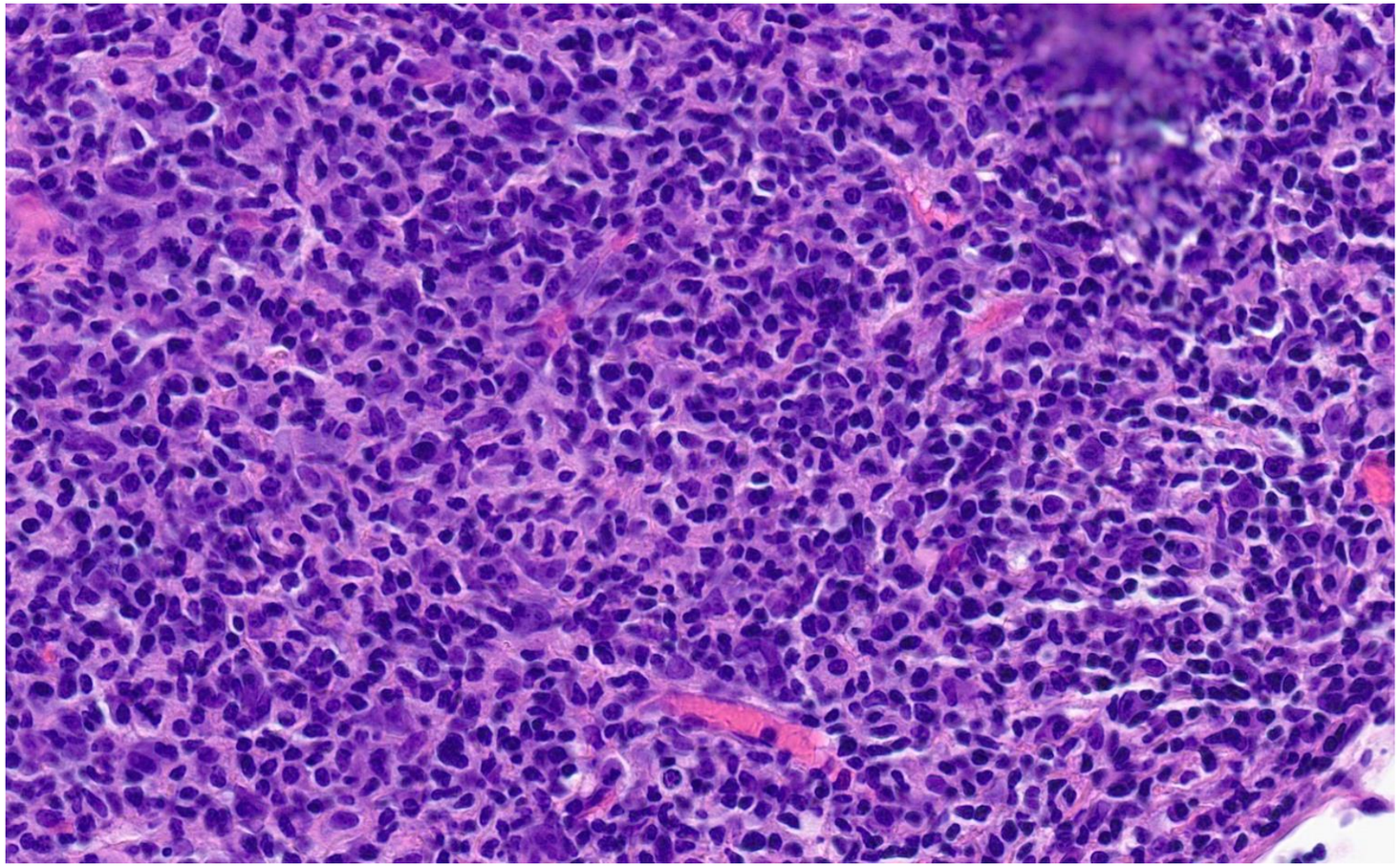
- 85-year-old male with a history of recent weight loss presents with retroperitoneal mass and diffuse peritoneal lymphadenopathy
- Radiology is suspicious for lymphoma
- Flow cytometry – small population of CD10-positive kappa-restricted B-cells
- Question to hematopathology consult service - ”What is the best classification of this high-grade B-cell lymphoma?”

Retroperitoneal mass, needle core biopsy



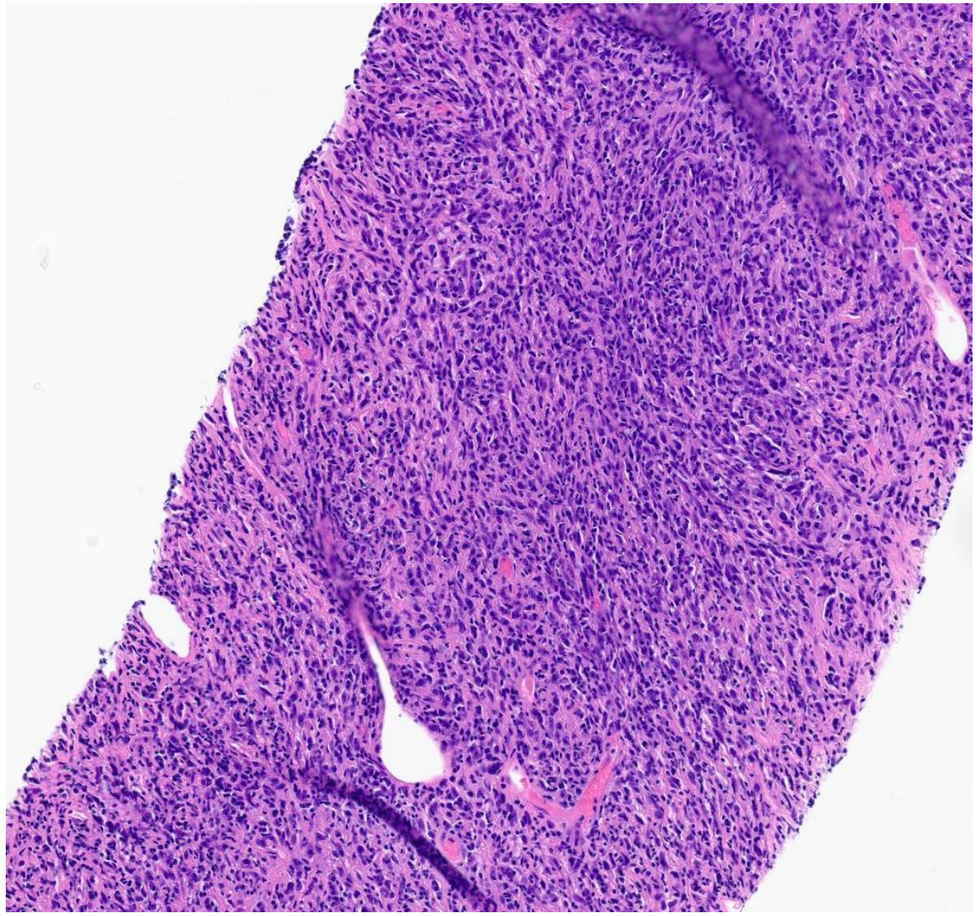
Retroperitoneal mass, needle core biopsy

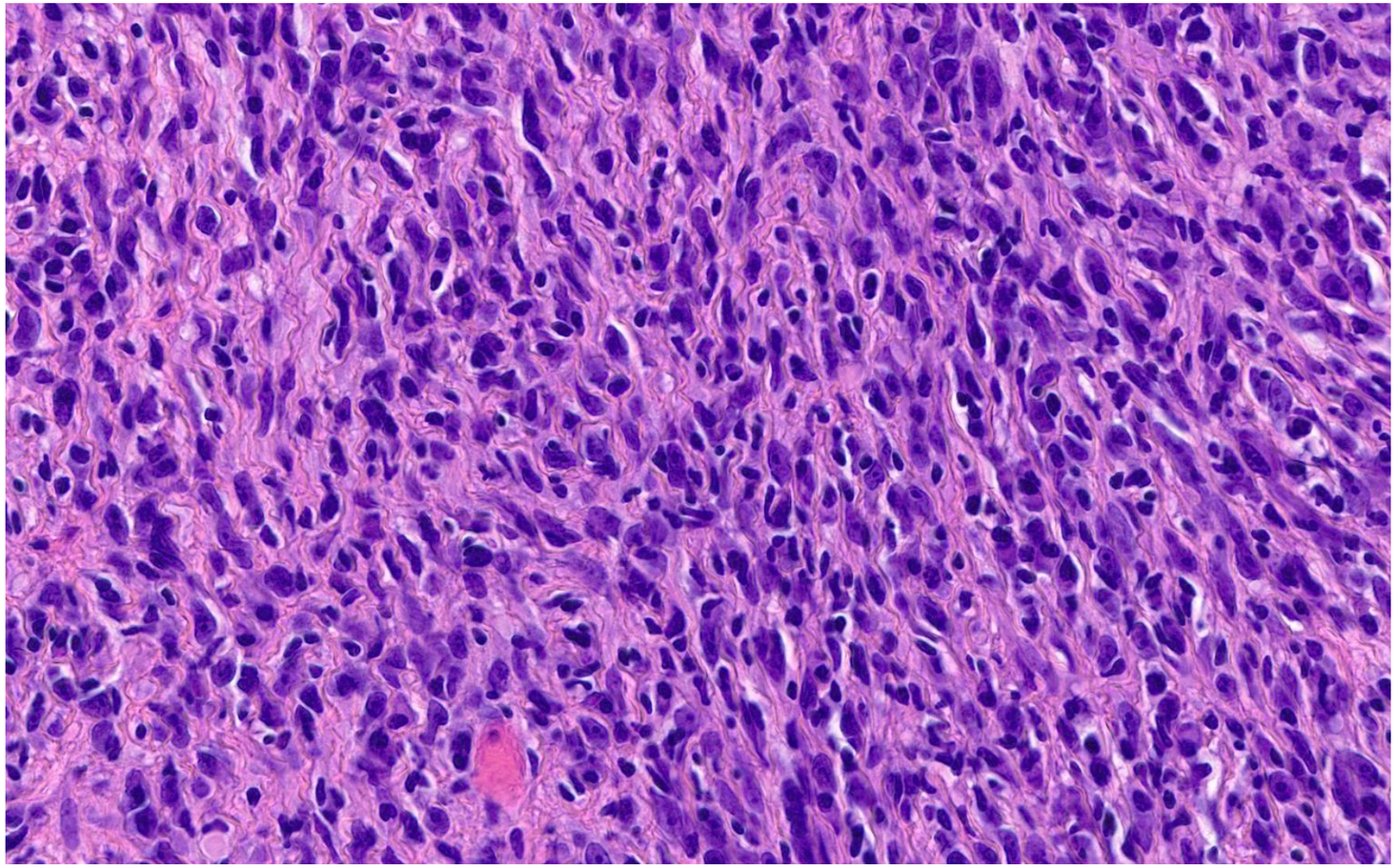




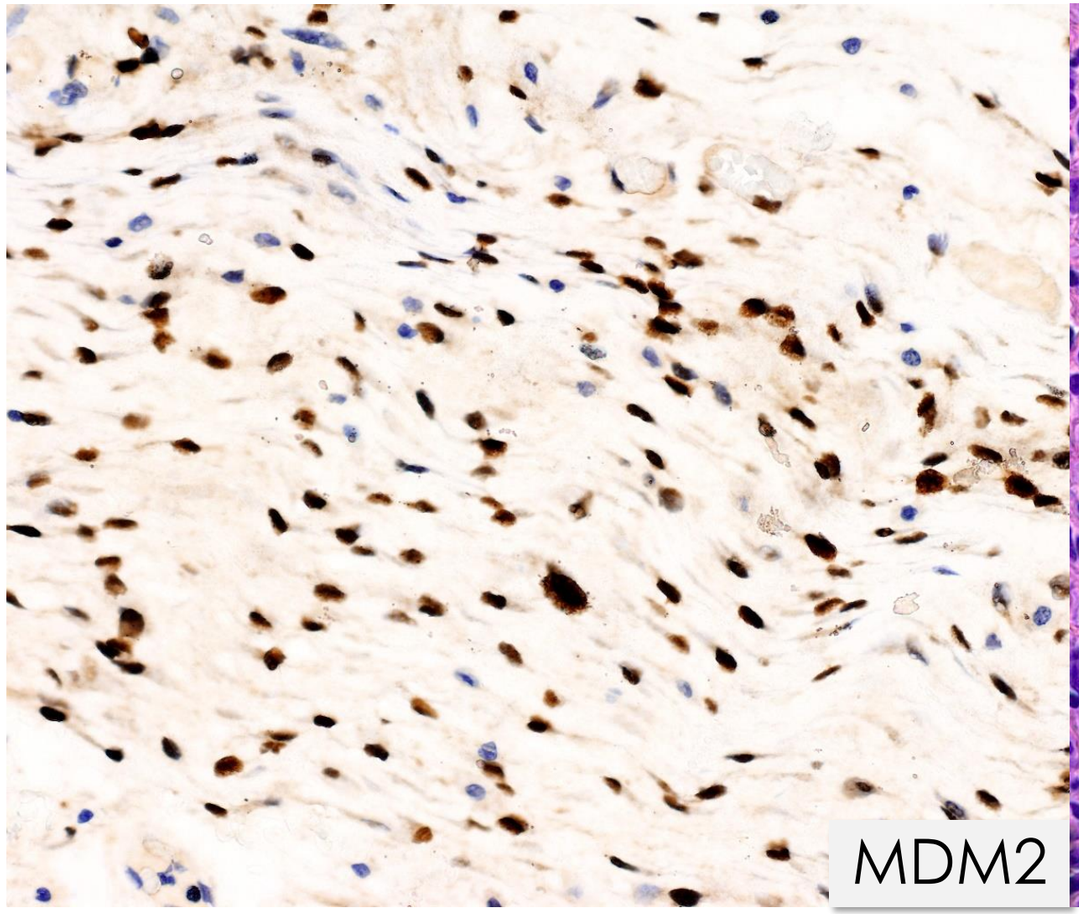
Retroperitoneal mass, needle core biopsy

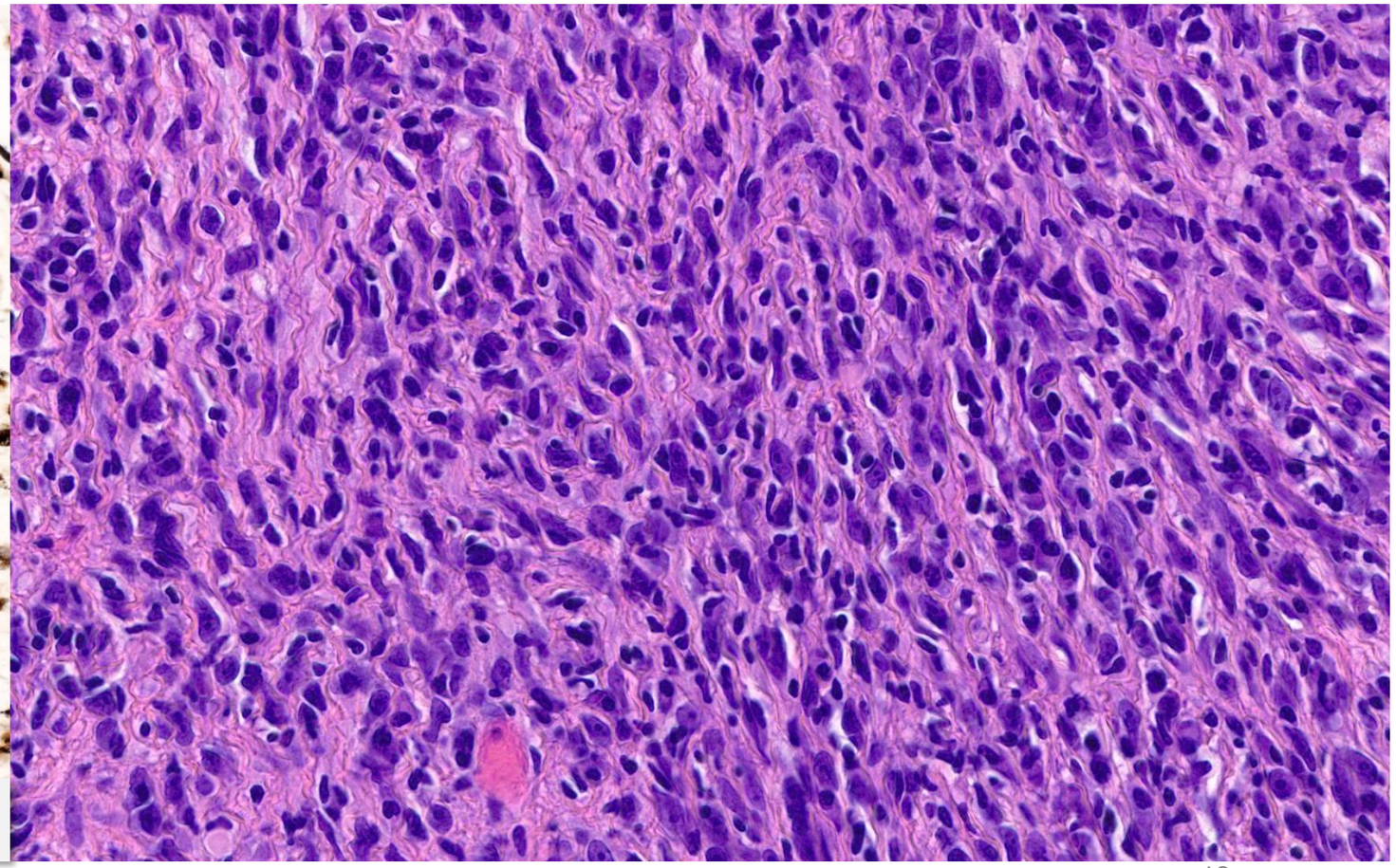
- **CD3** – highlights scattered abundant small T-cells
- **CD20** and numerous other B-cell markers CD19, CD79a, PAX5) – highlight numerous B-cells, variable in size





MDM2 immunostain – positive nuclear stain



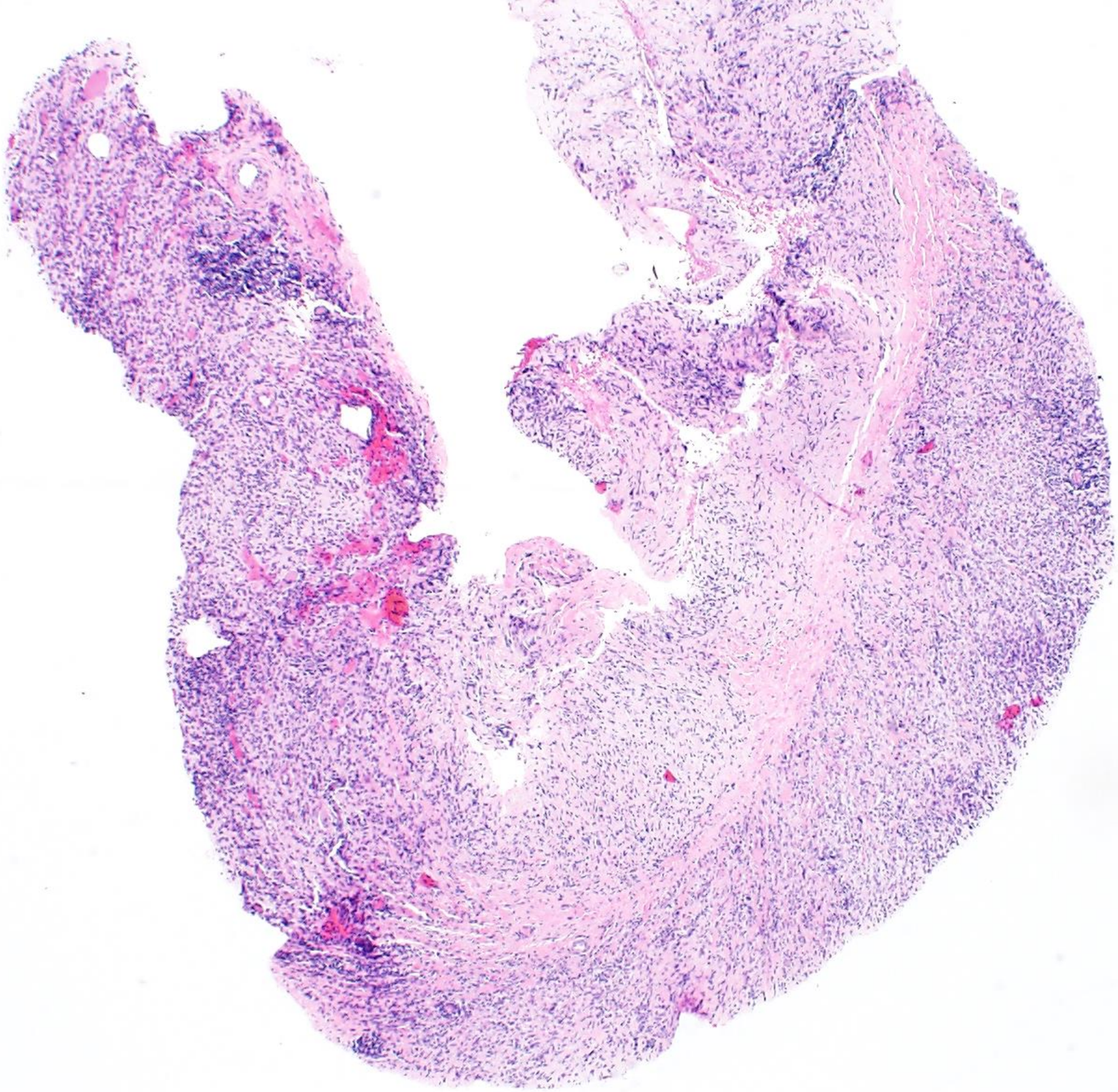


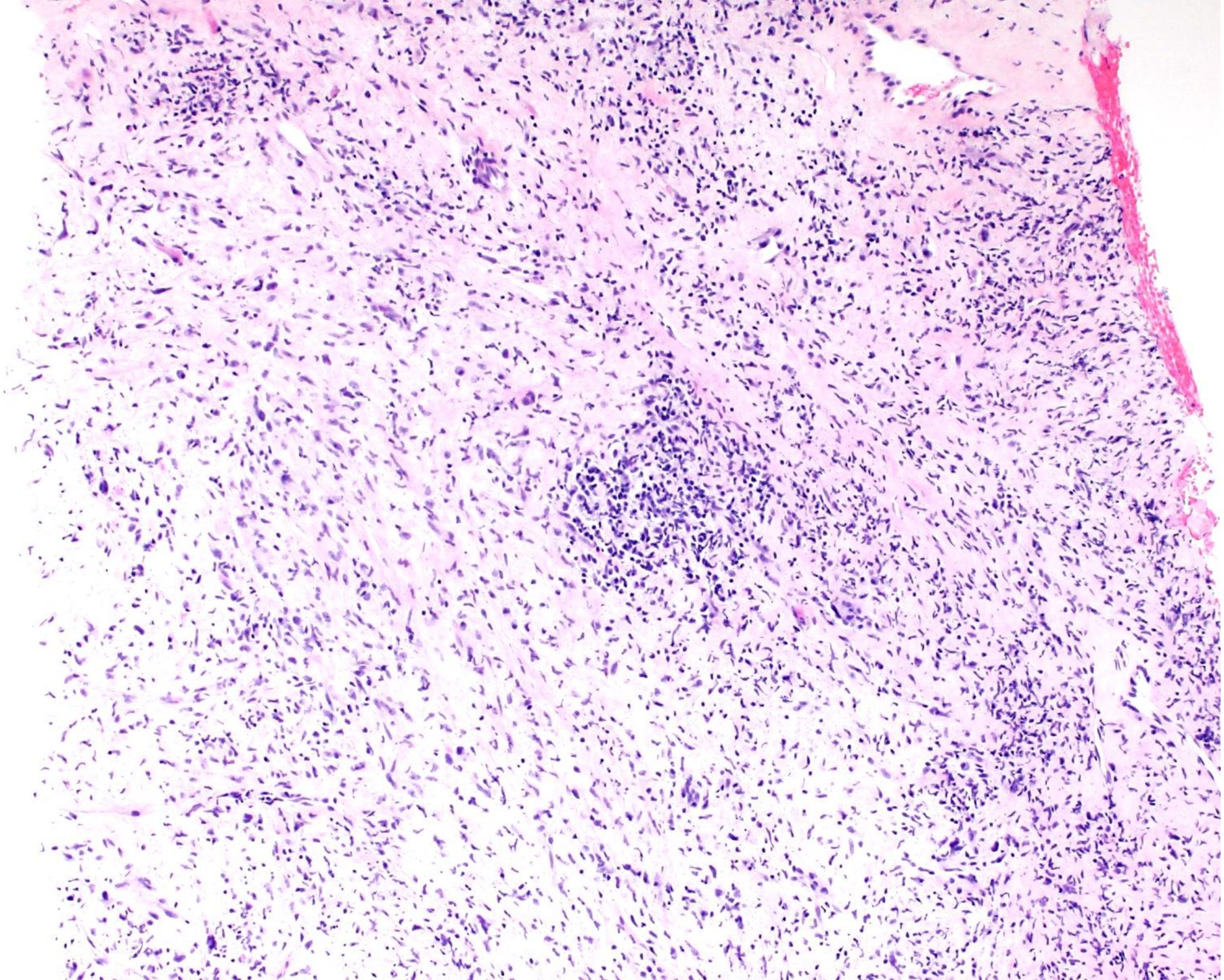
Final diagnosis

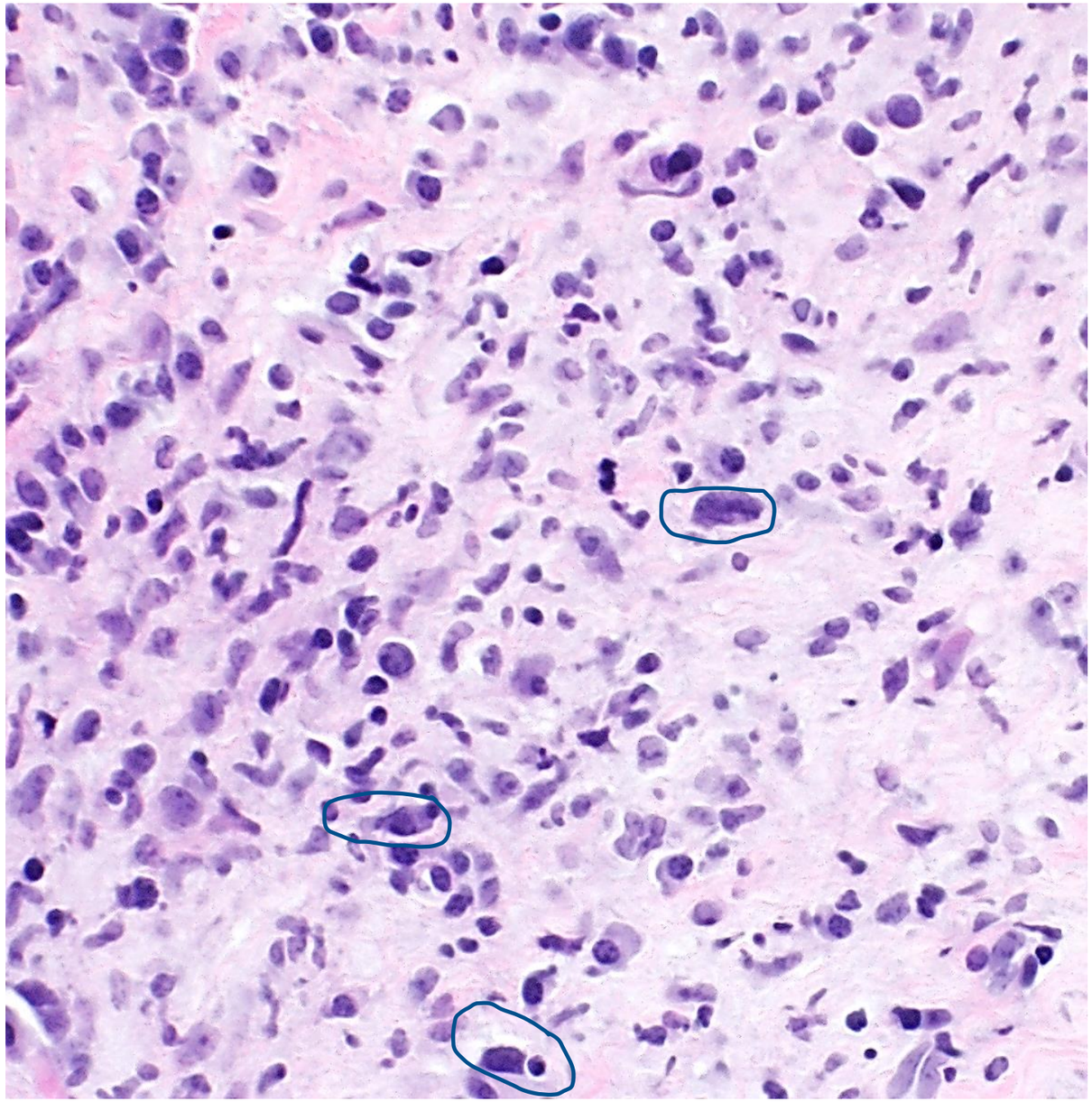
- Dedifferentiated liposarcoma, MDM2-FISH amplified

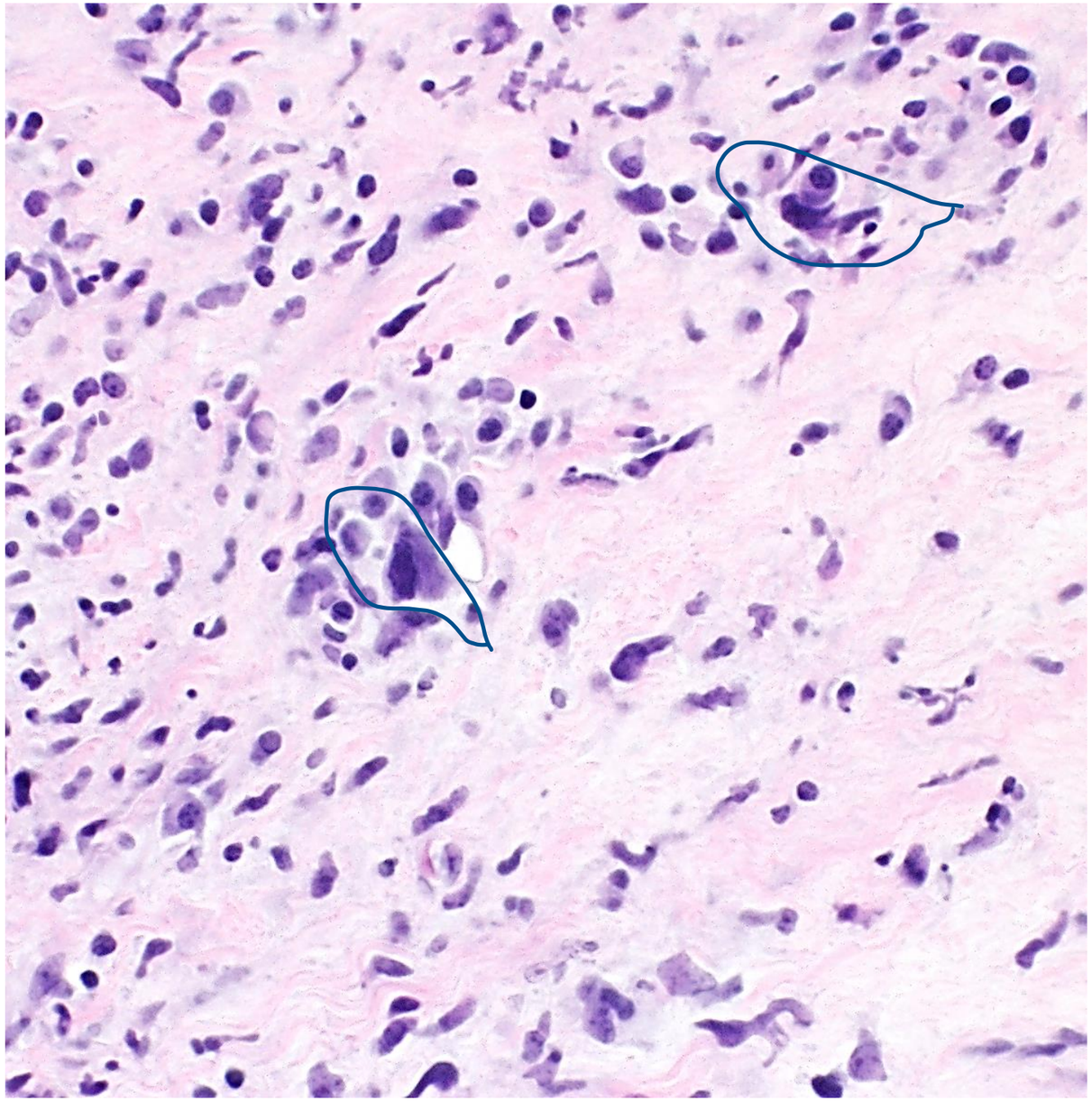
Case #5

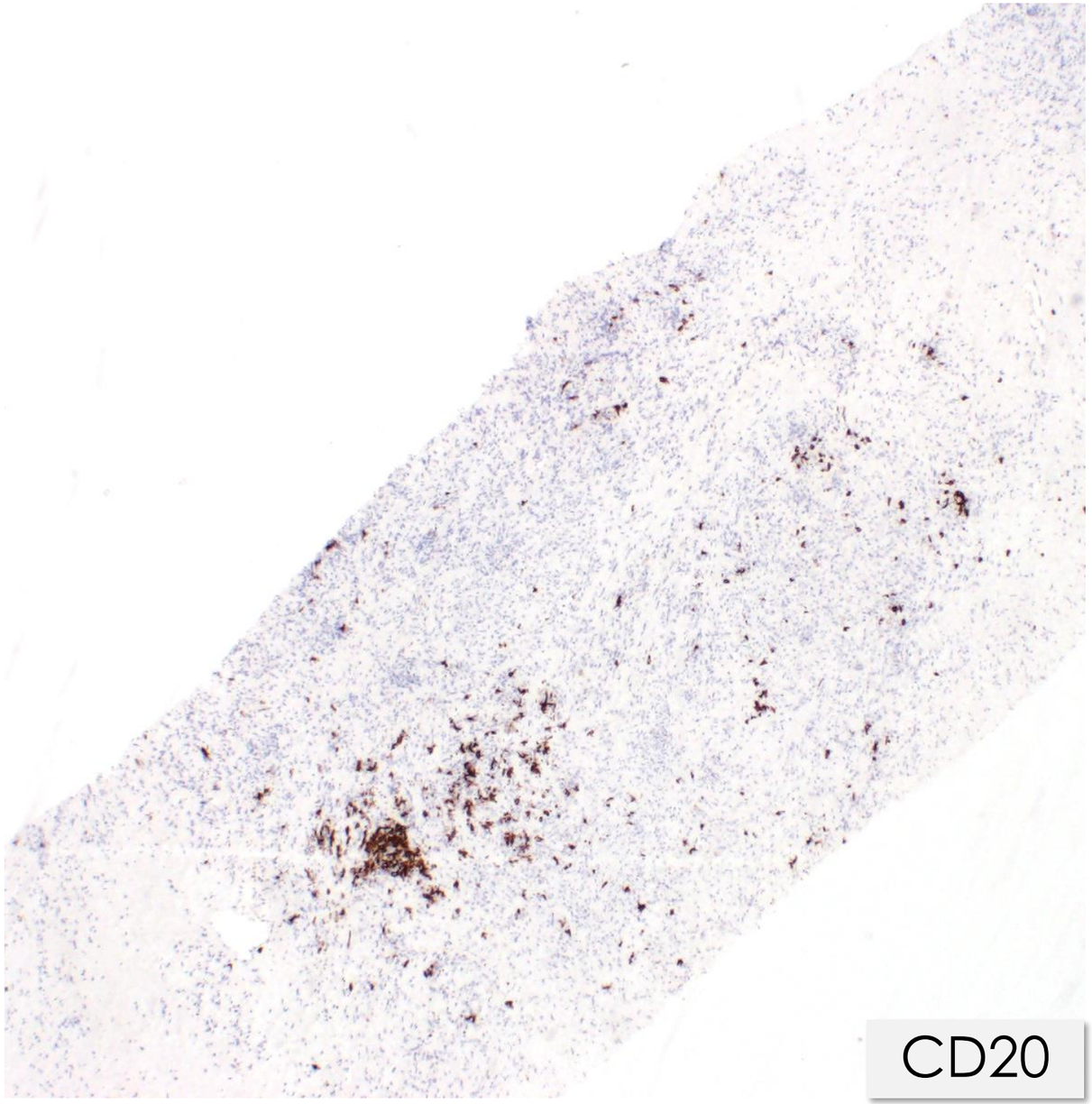
- 75-year-old male with an enlarged inguinal lymph node



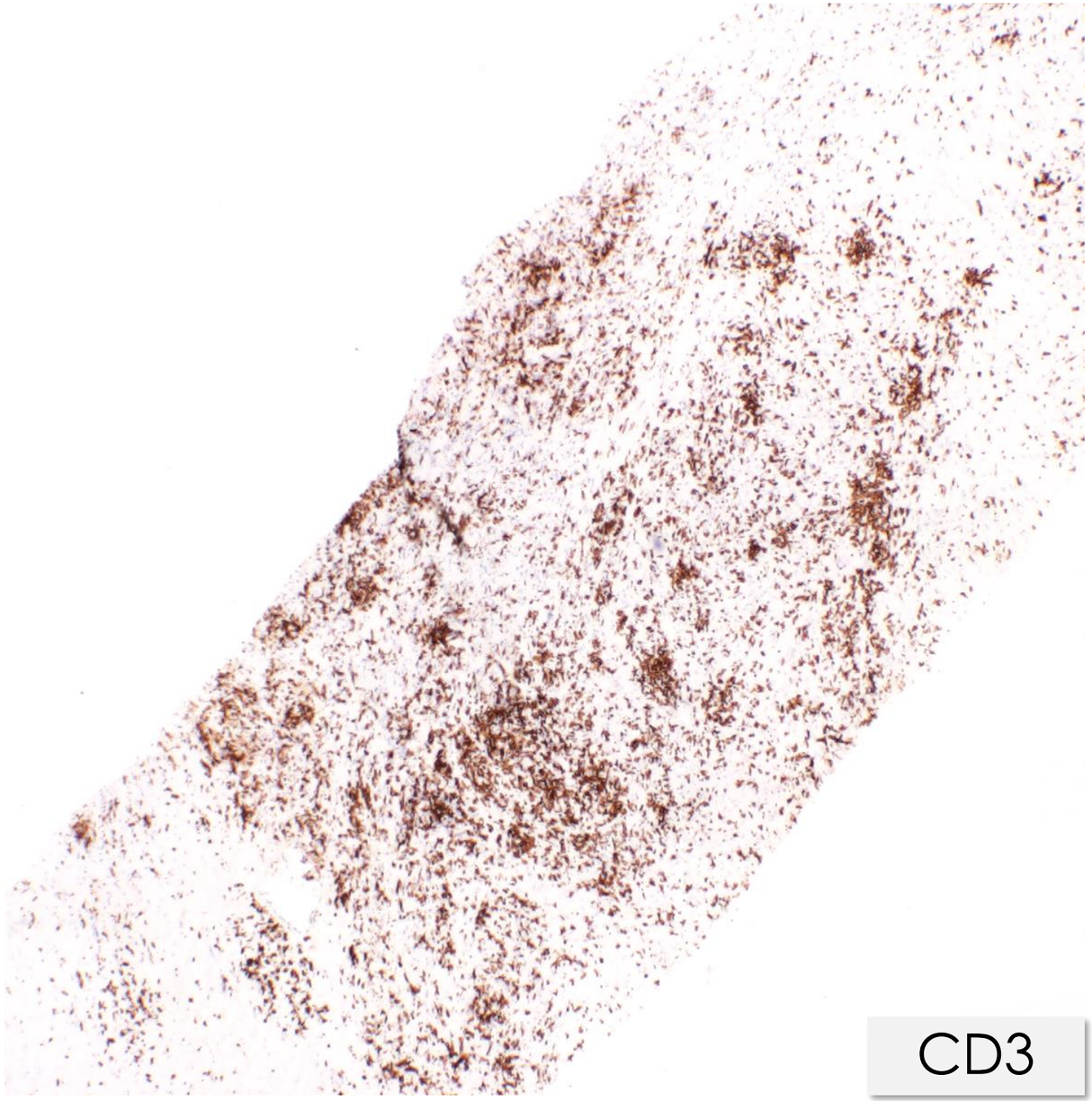




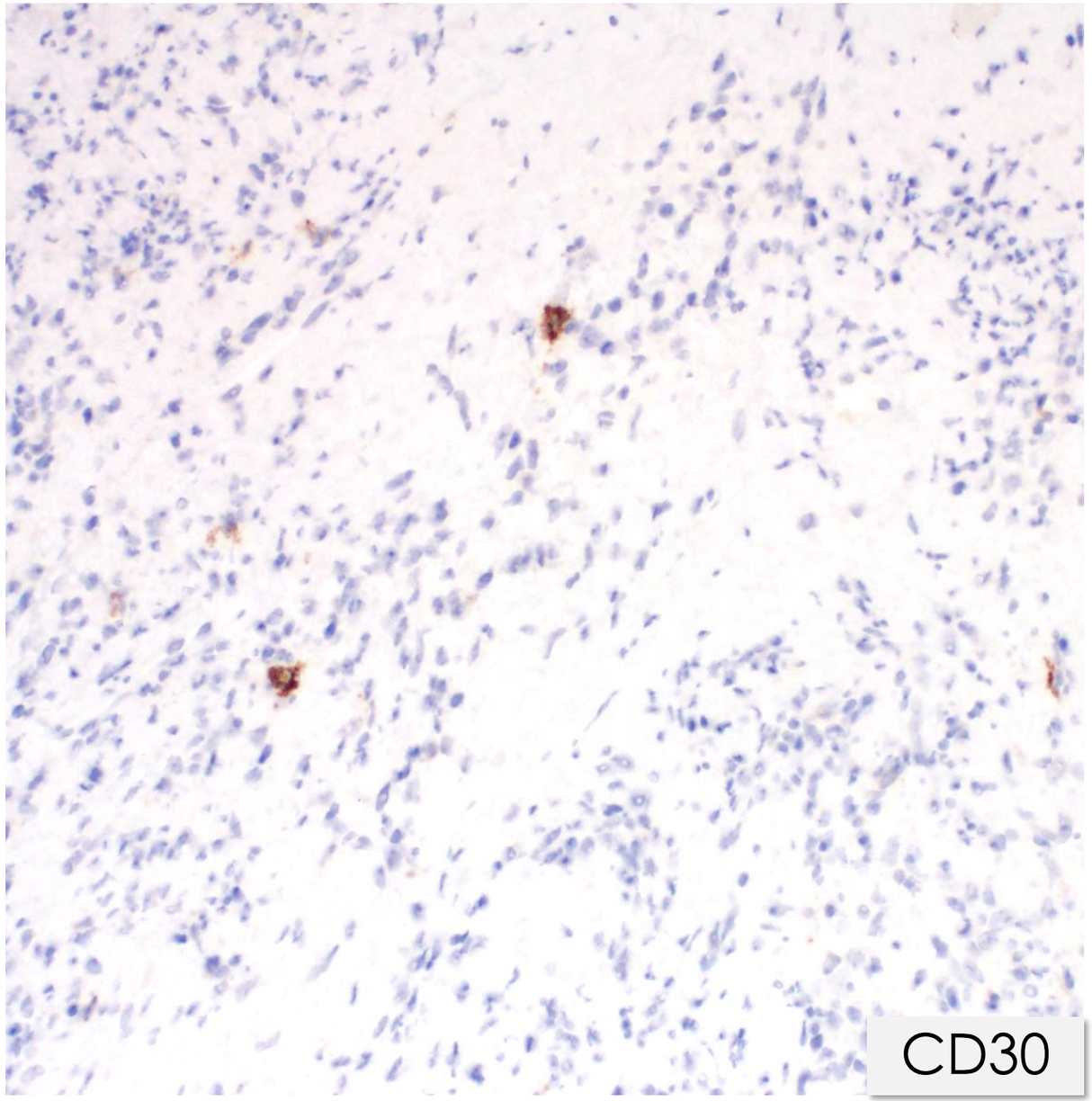


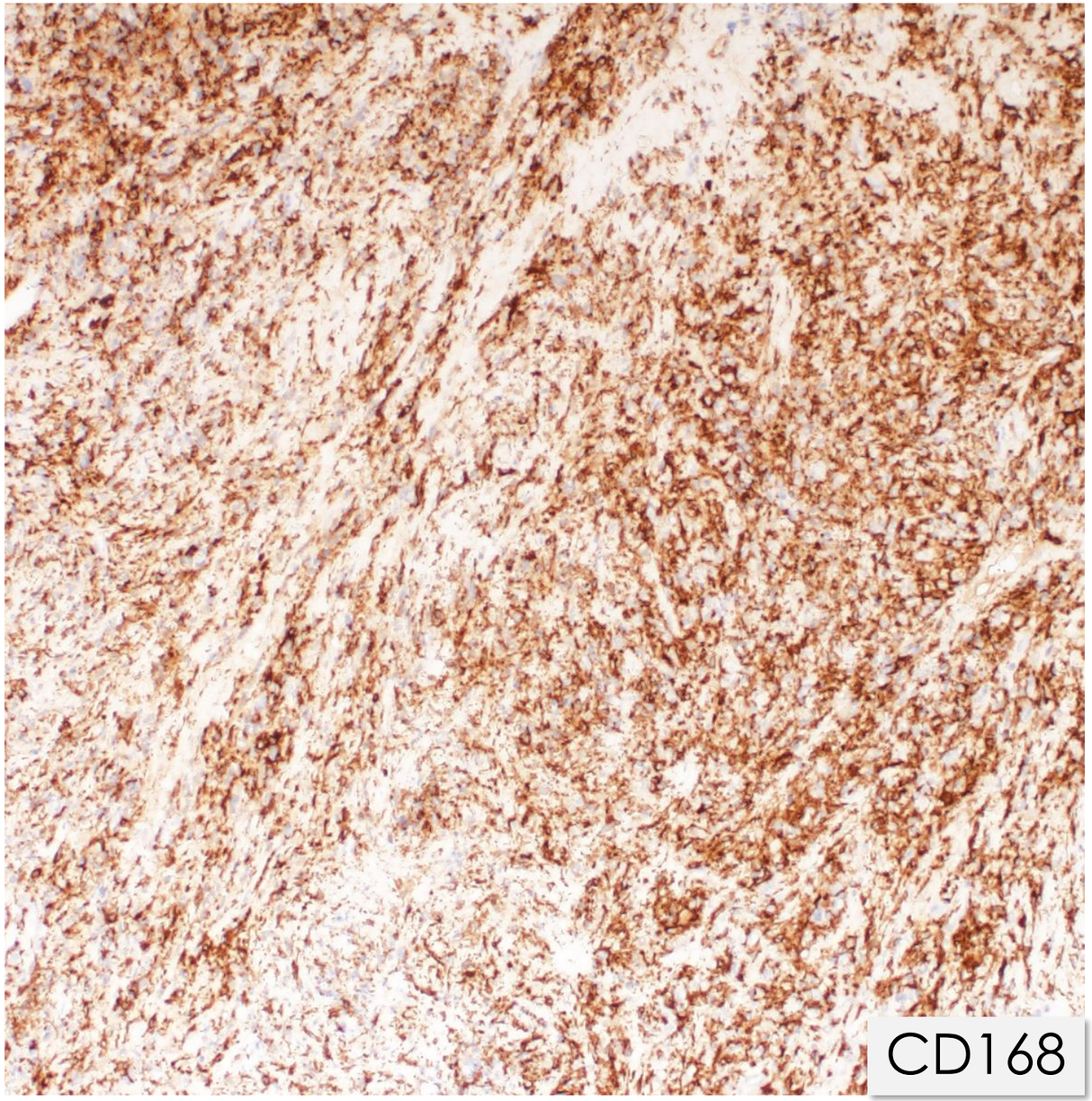


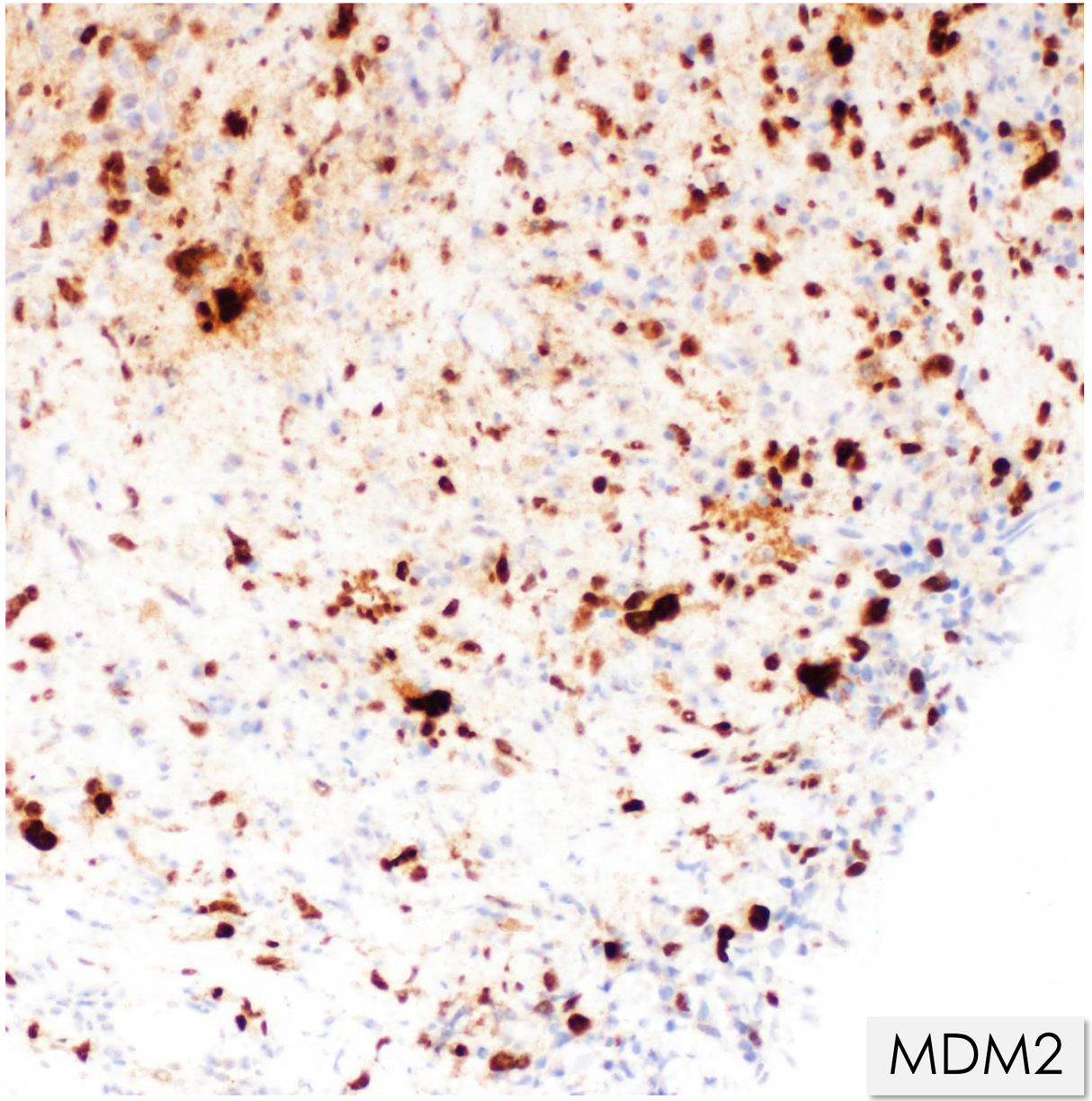
CD20



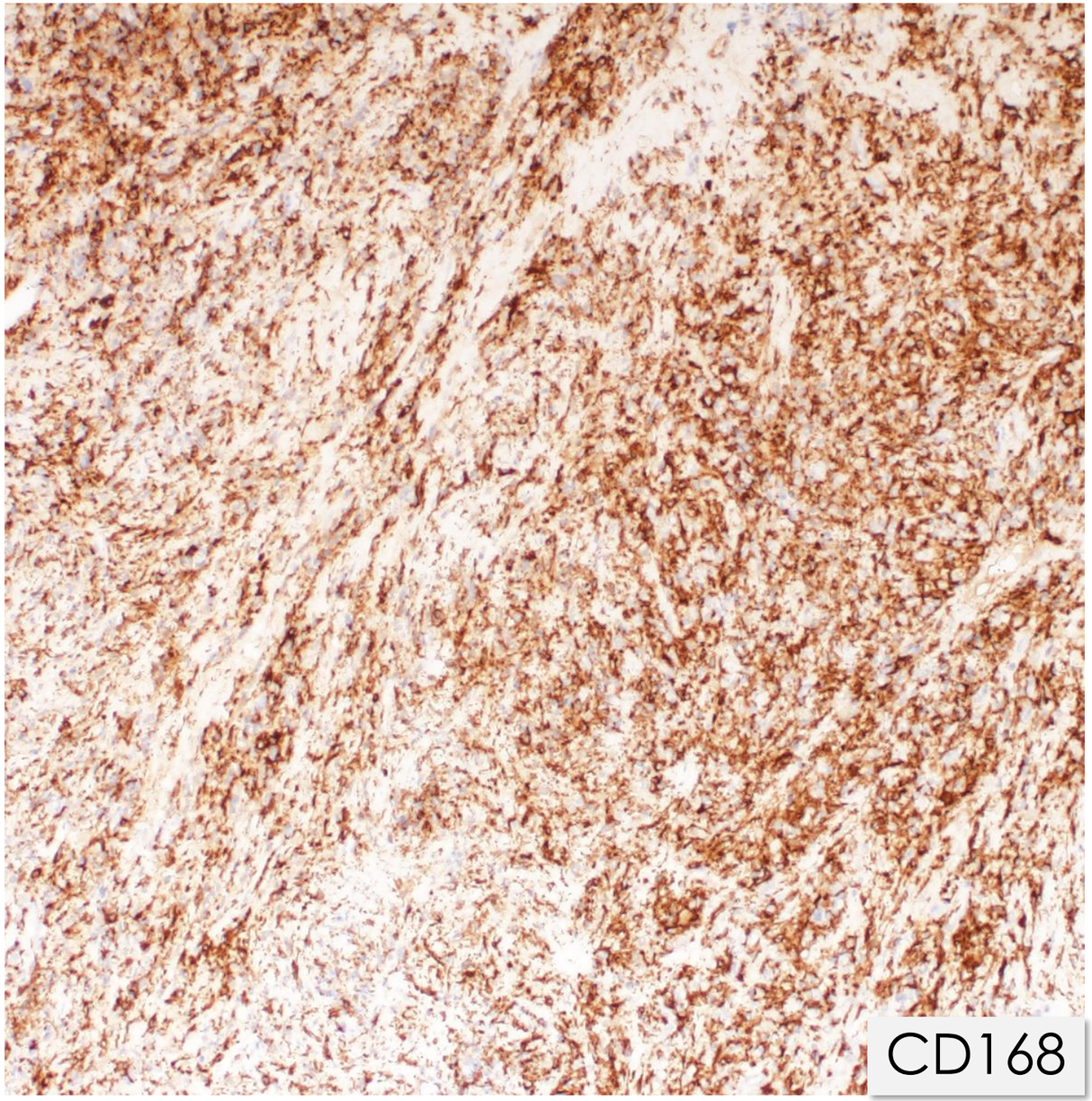
CD3


CD30


CD168



MDM2



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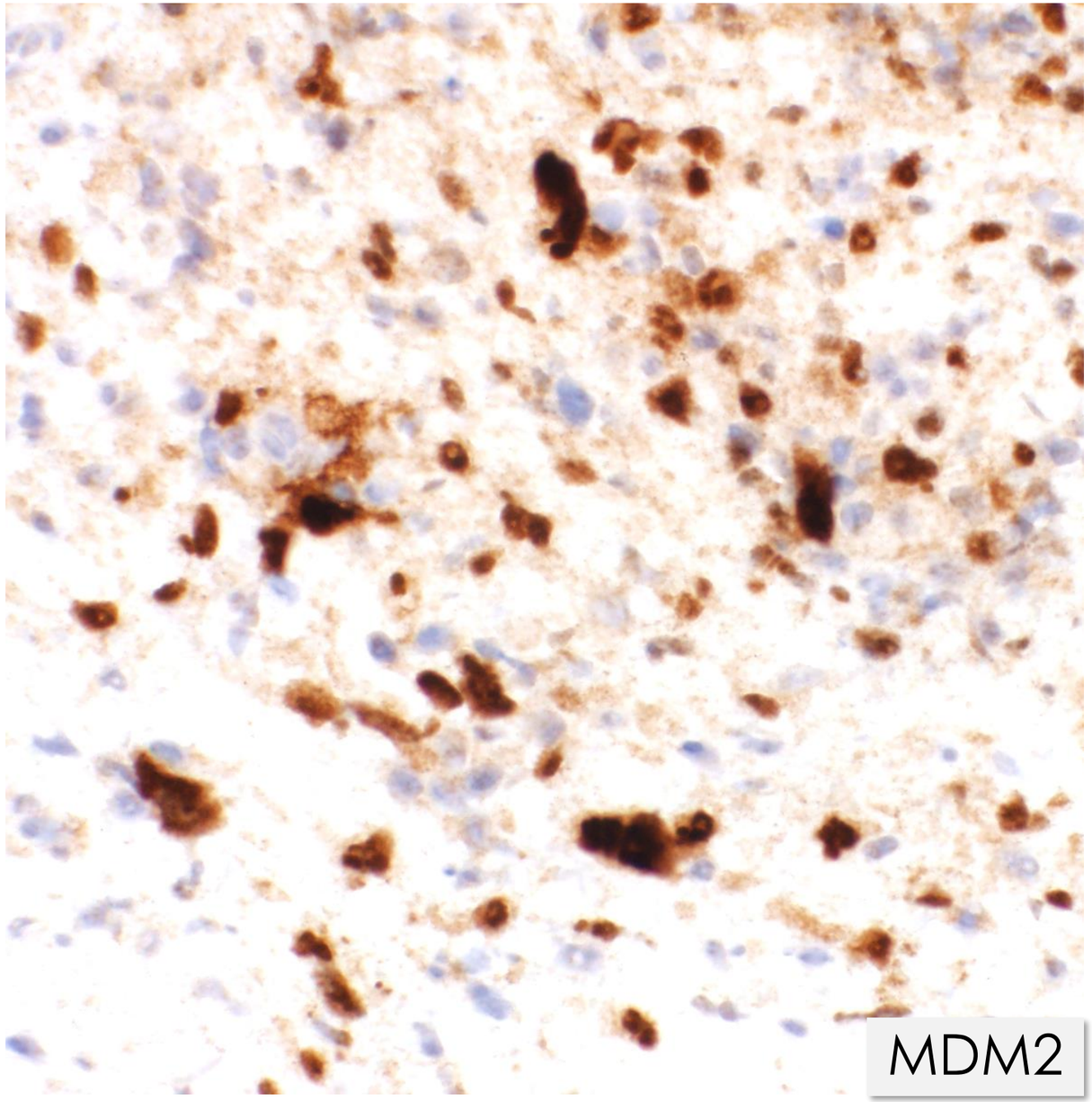
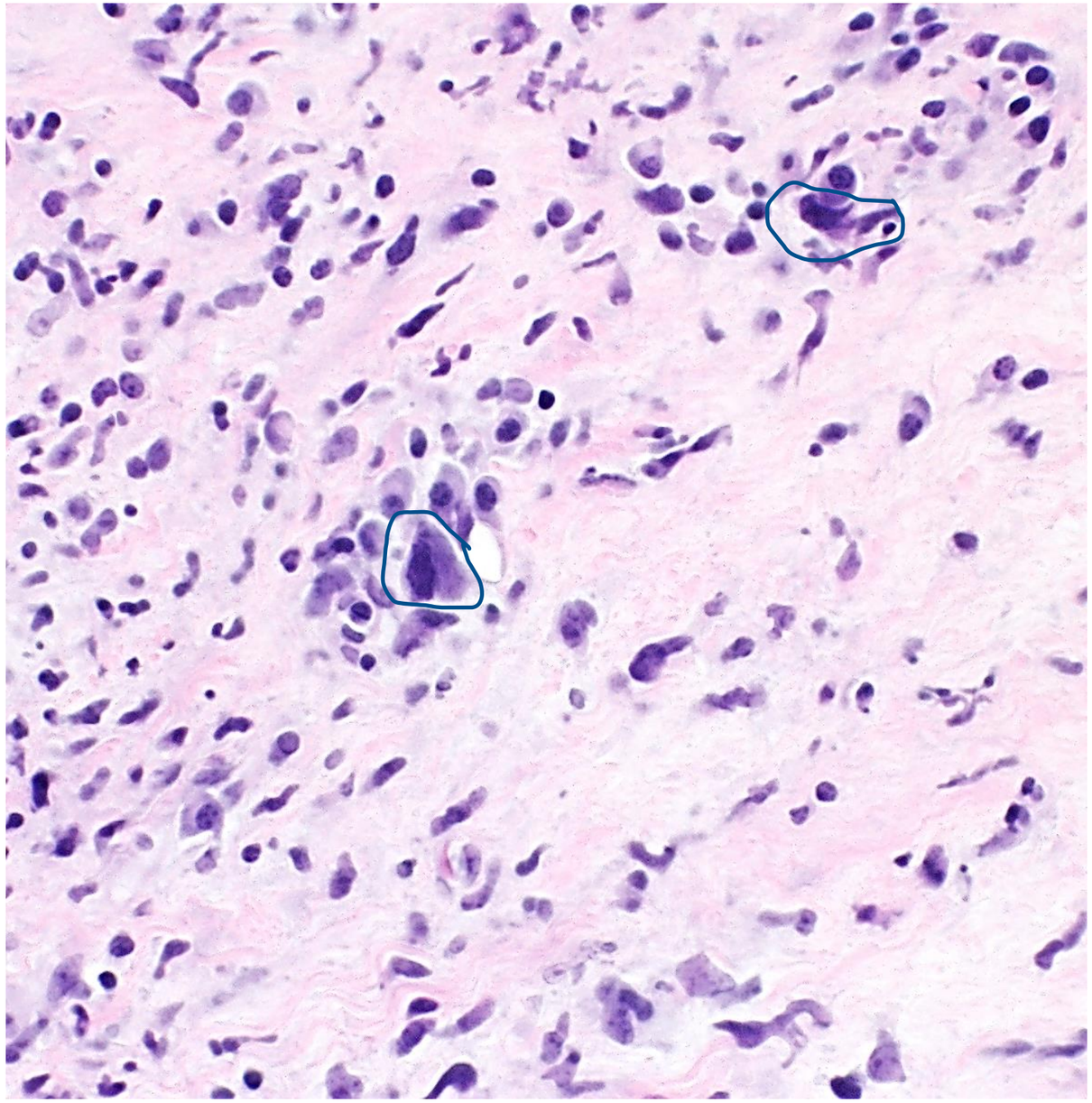
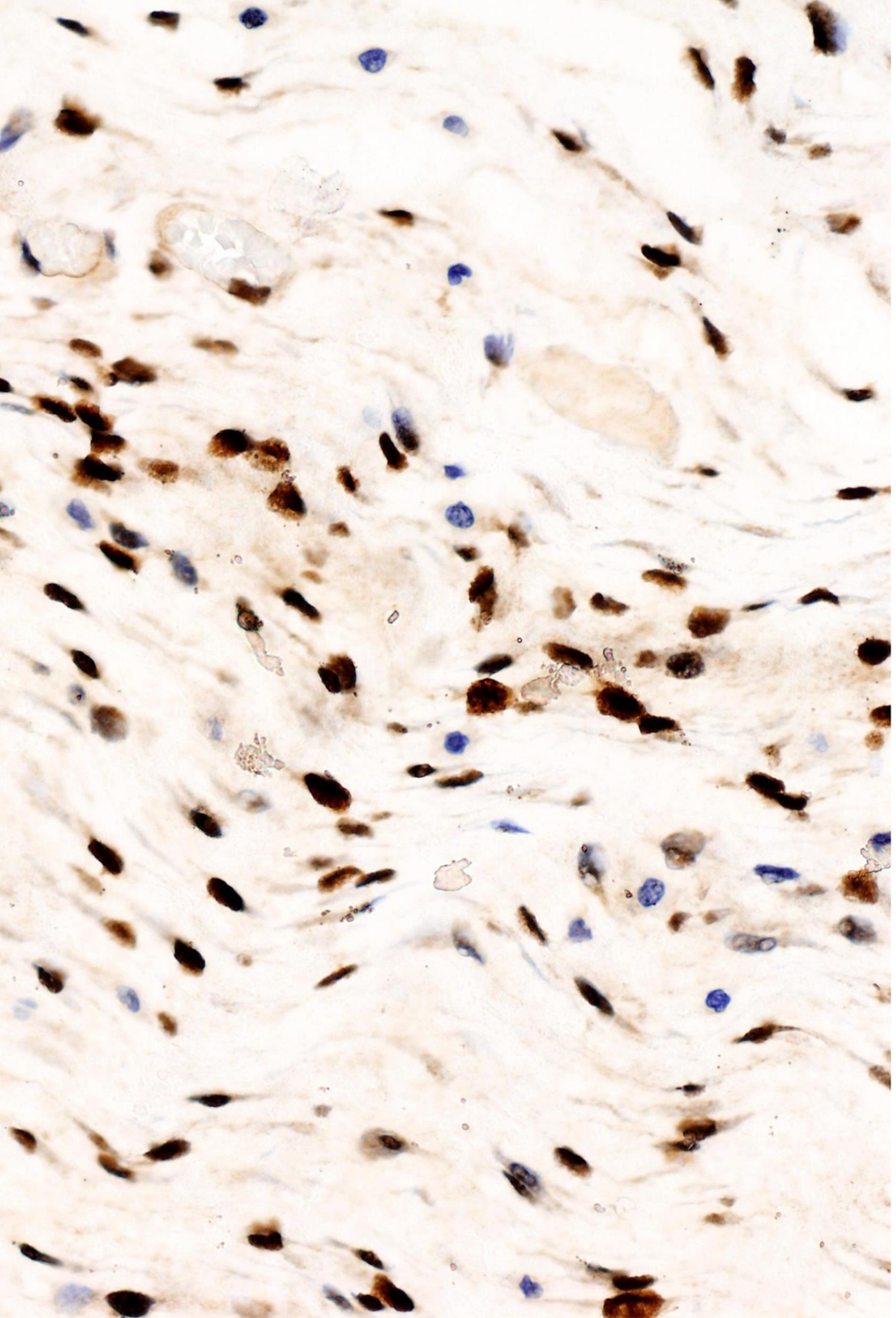

MDM2



Final diagnosis

- Inflammatory liposarcoma
- MDM2 amplified by FISH



MDM2 immunostain – nuclear positivity

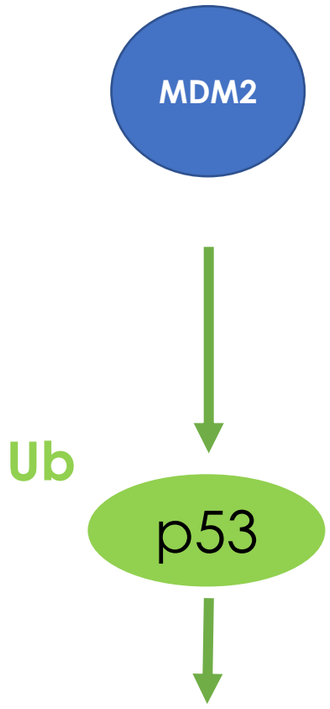
MDM2 protein:

- Ubiquitin ligase
- Useful in diagnosing well differentiated and dedifferentiated liposarcoma

- Major pitfall: positive in histiocytes

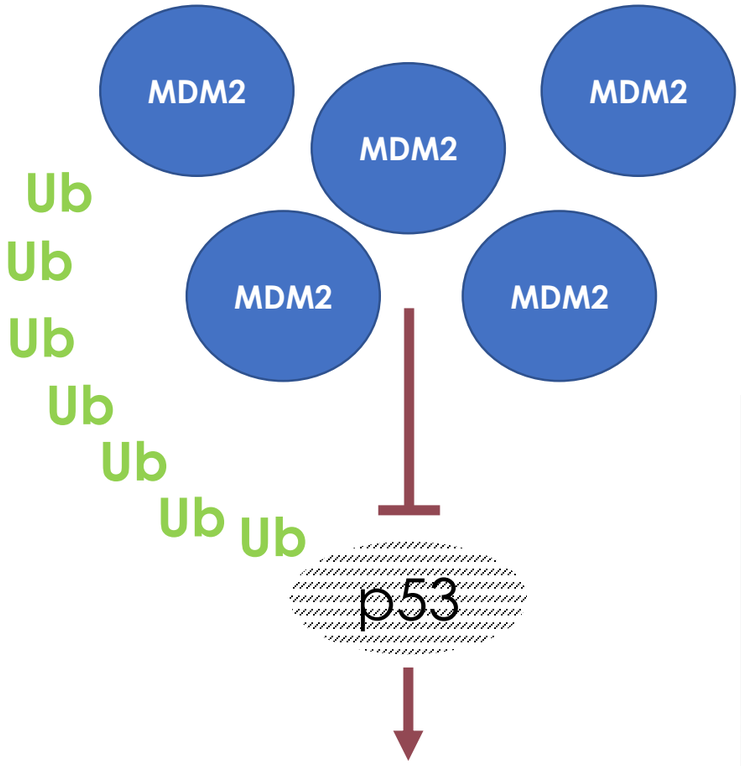
MDM2 – Ubiquitin ligase inhibits p53 and promotes carcinogenesis

Normal



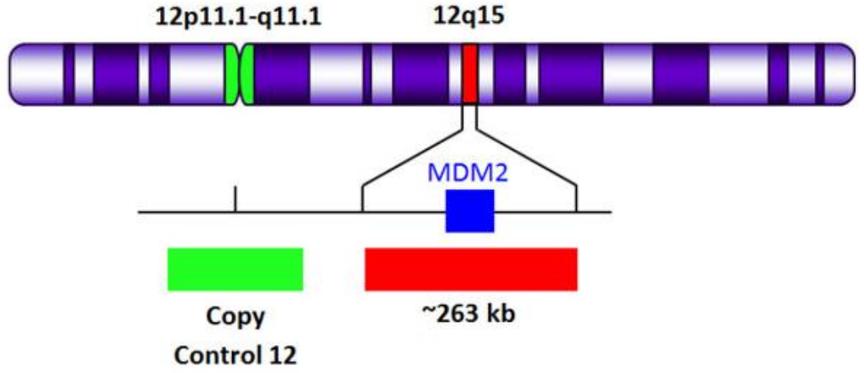
Tumor suppression

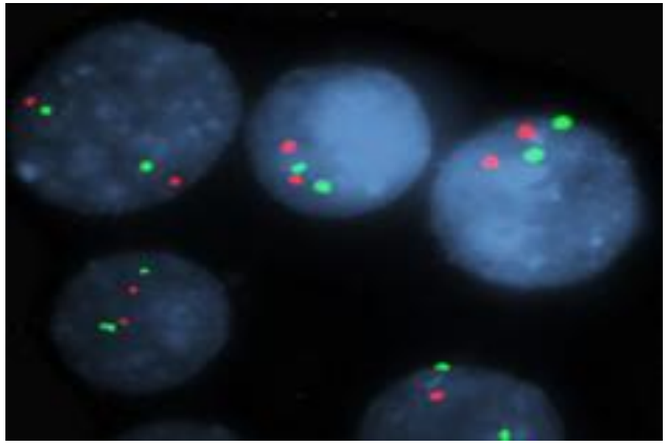
Increased



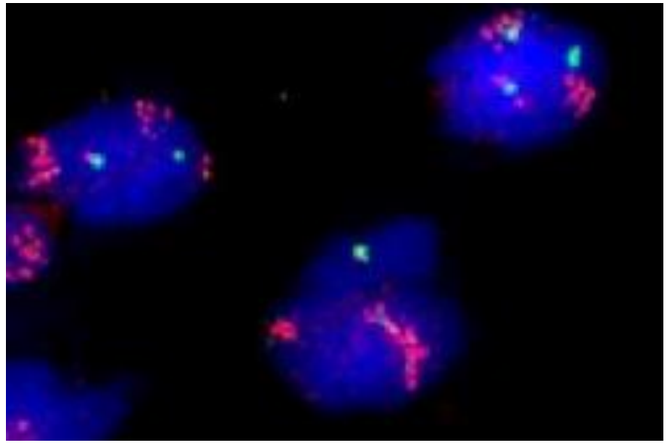
Carcinogenesis

MDM2 AMPLIFICATION BY FISH





Normal (2 green/2 red)



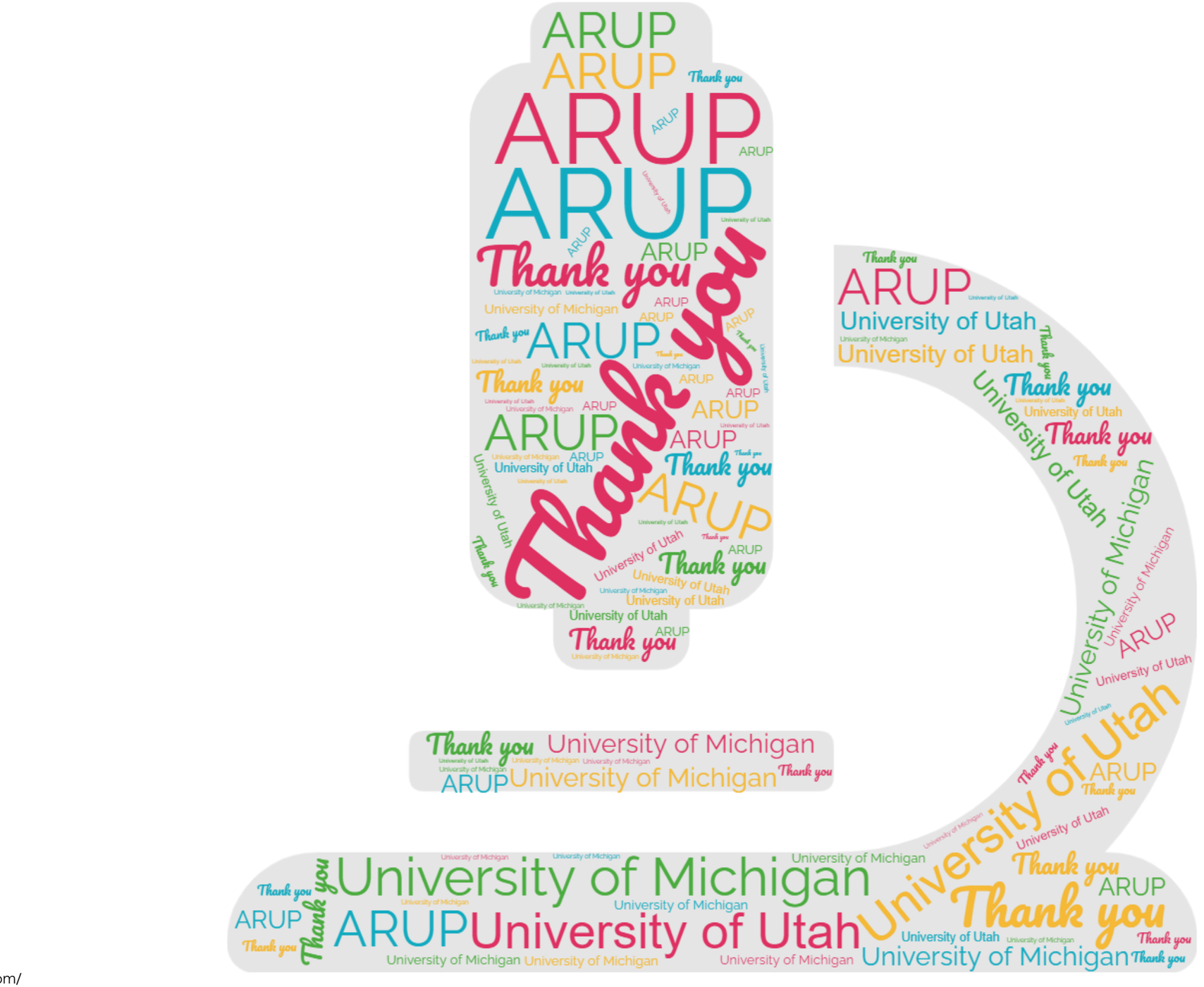
Amplified (2 green/many red)

Liposarcoma: facts

- Dedifferentiated liposarcoma = liposarcoma that progressed to non-lipogenic sarcoma.
- A well-differentiated component may not be identifiable.
- Most common site is retroperitoneum
- Consistent amplification of *MDM2* and *CDK4*.
  - Negative in pleomorphic liposarcoma
- Strong diffuse nuclear positivity MDM2 and CDK4.
- Potential therapy: oral MDM2 inhibitor Milademetan, Phase III Study

Conclusions

- Liposarcoma with marked chronic inflammation can mimic lymphoma.
- Positive nuclear MDM2 immunostain and MDM2 gene amplification by FISH confirm diagnosis of liposarcoma (dedifferentiated and inflammatory).



https://www.wordclouds.com/