SLIDE SEMINAR

Andrew Wotherspoon

The Royal Marsden Hospital

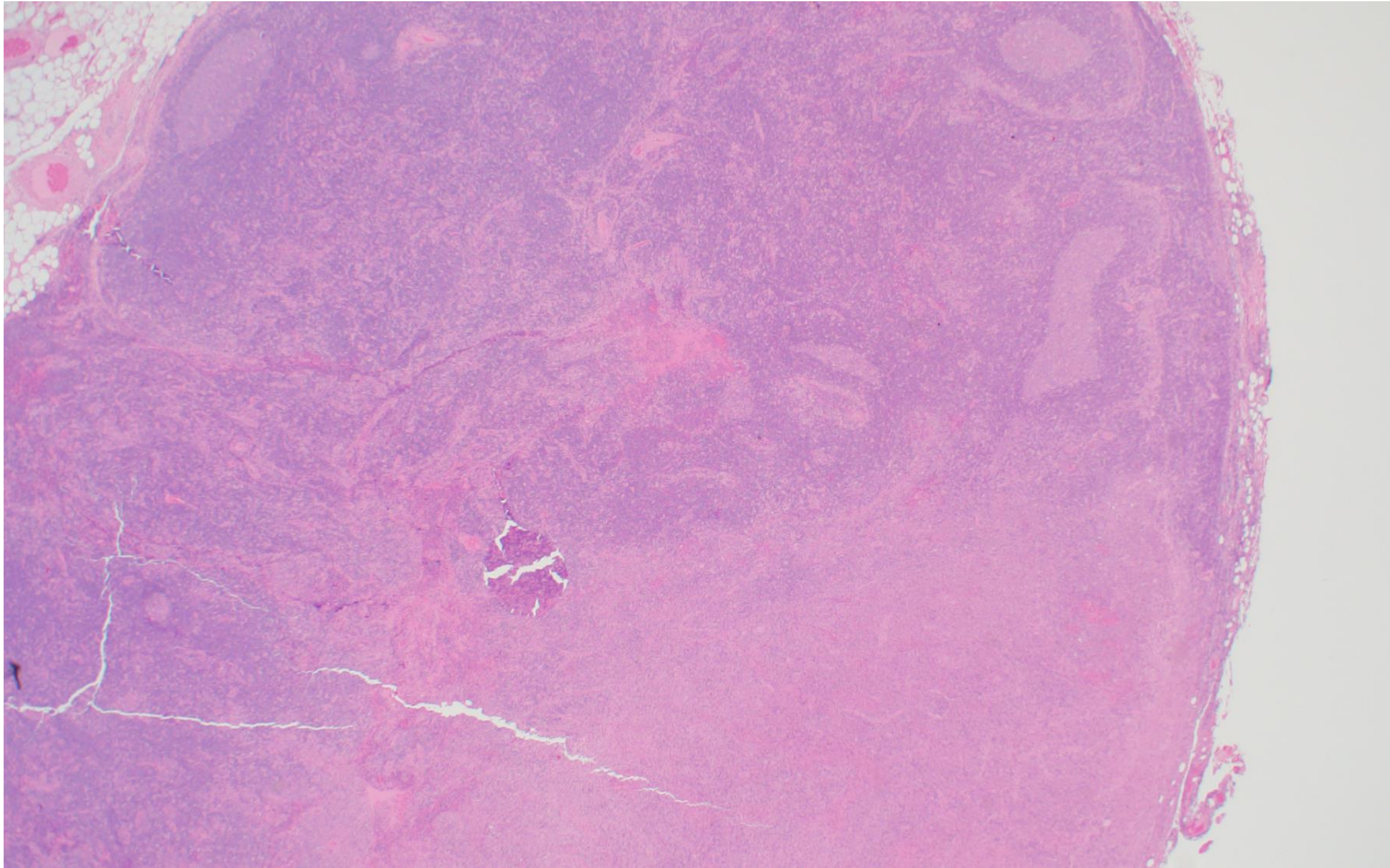
London, UK

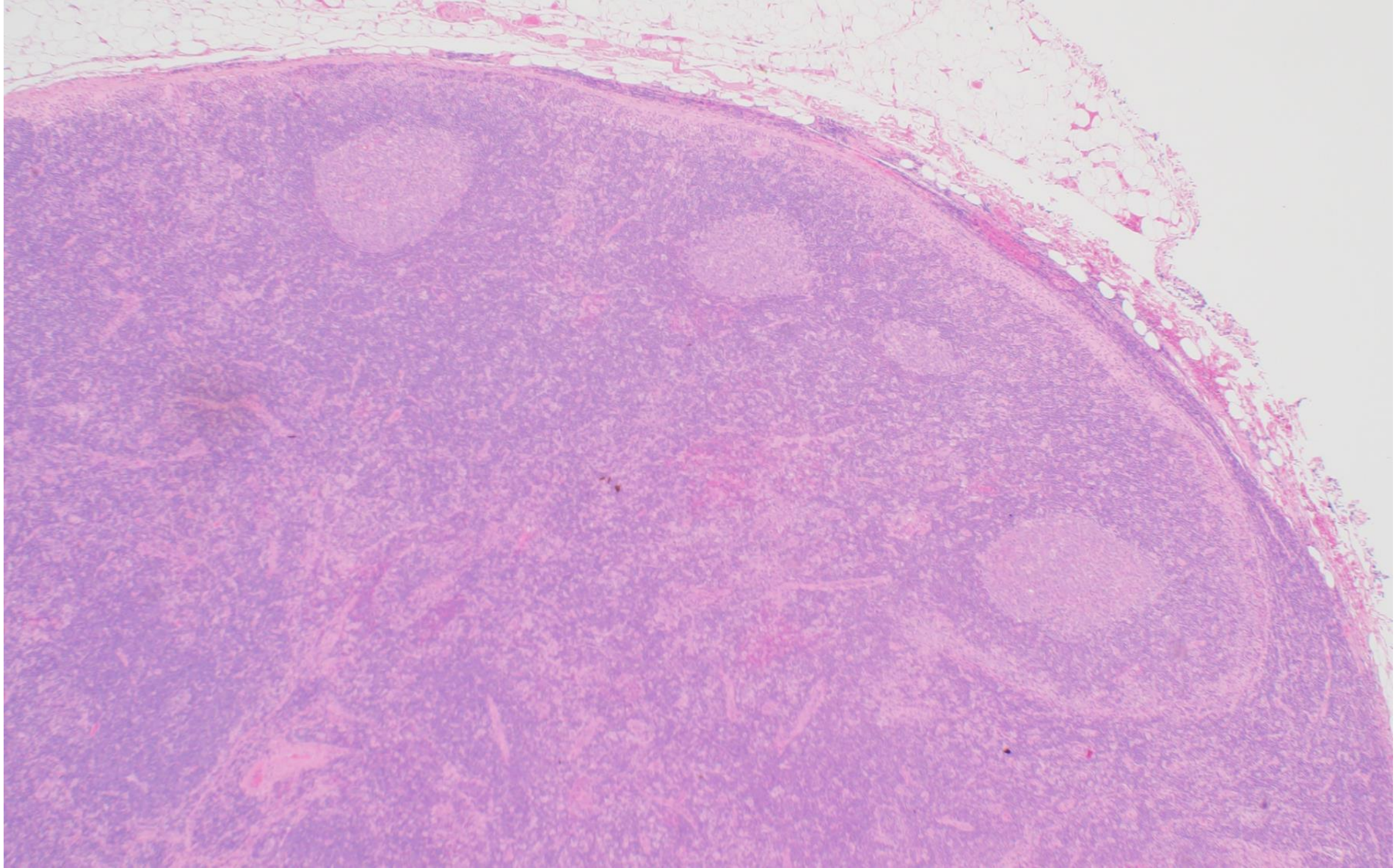
Case 1

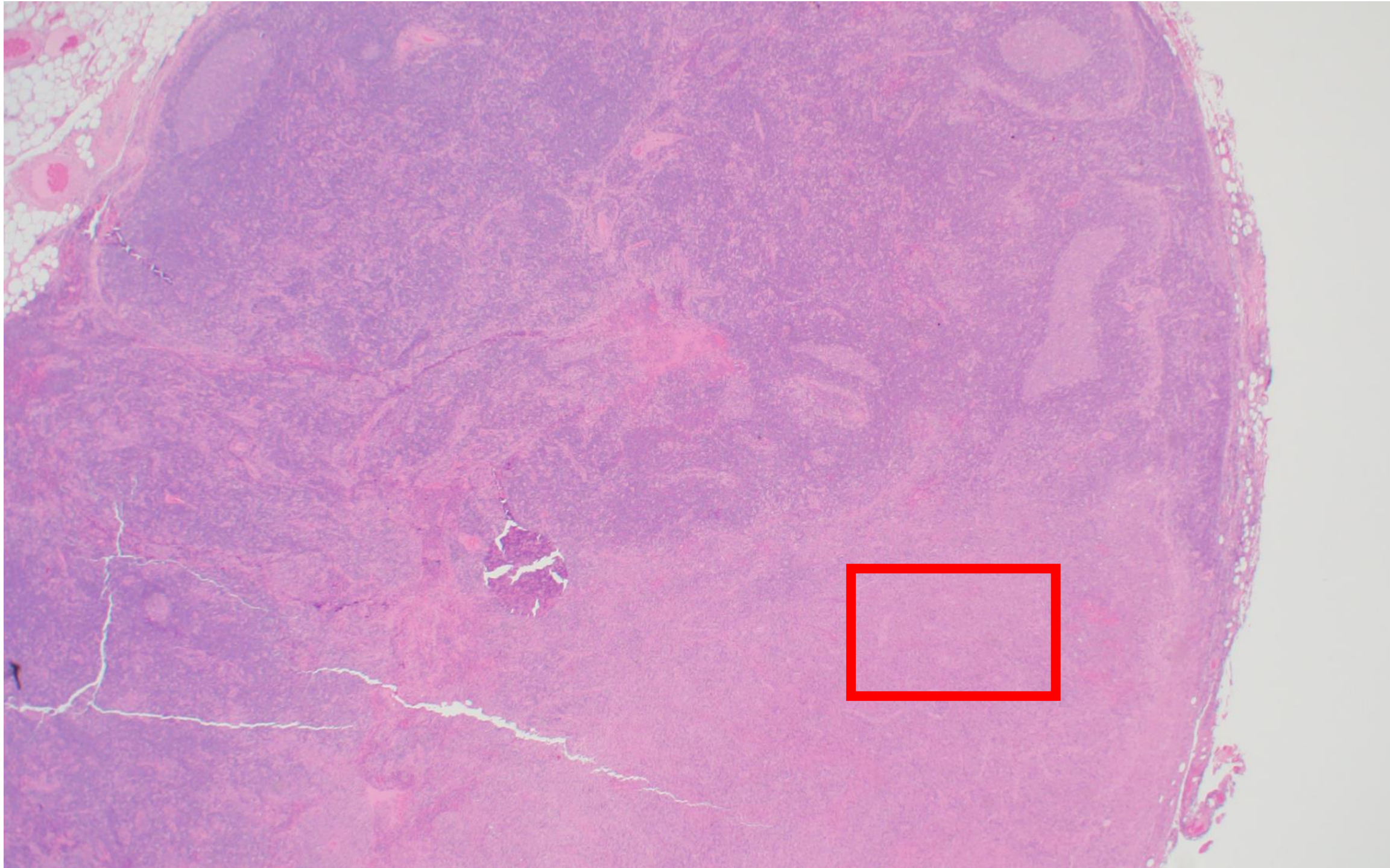
26- year old male

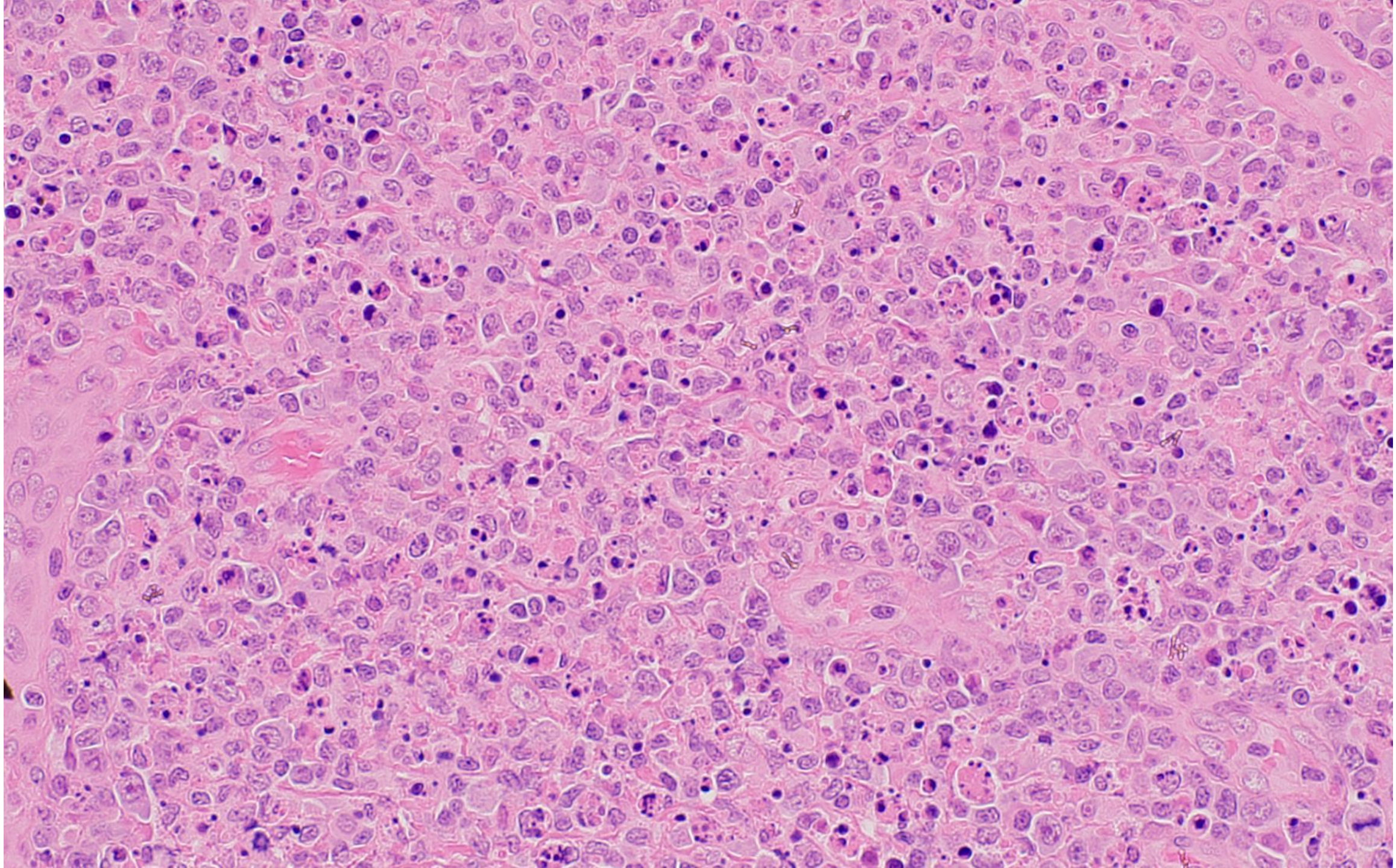
Cervical lymphadenopathy

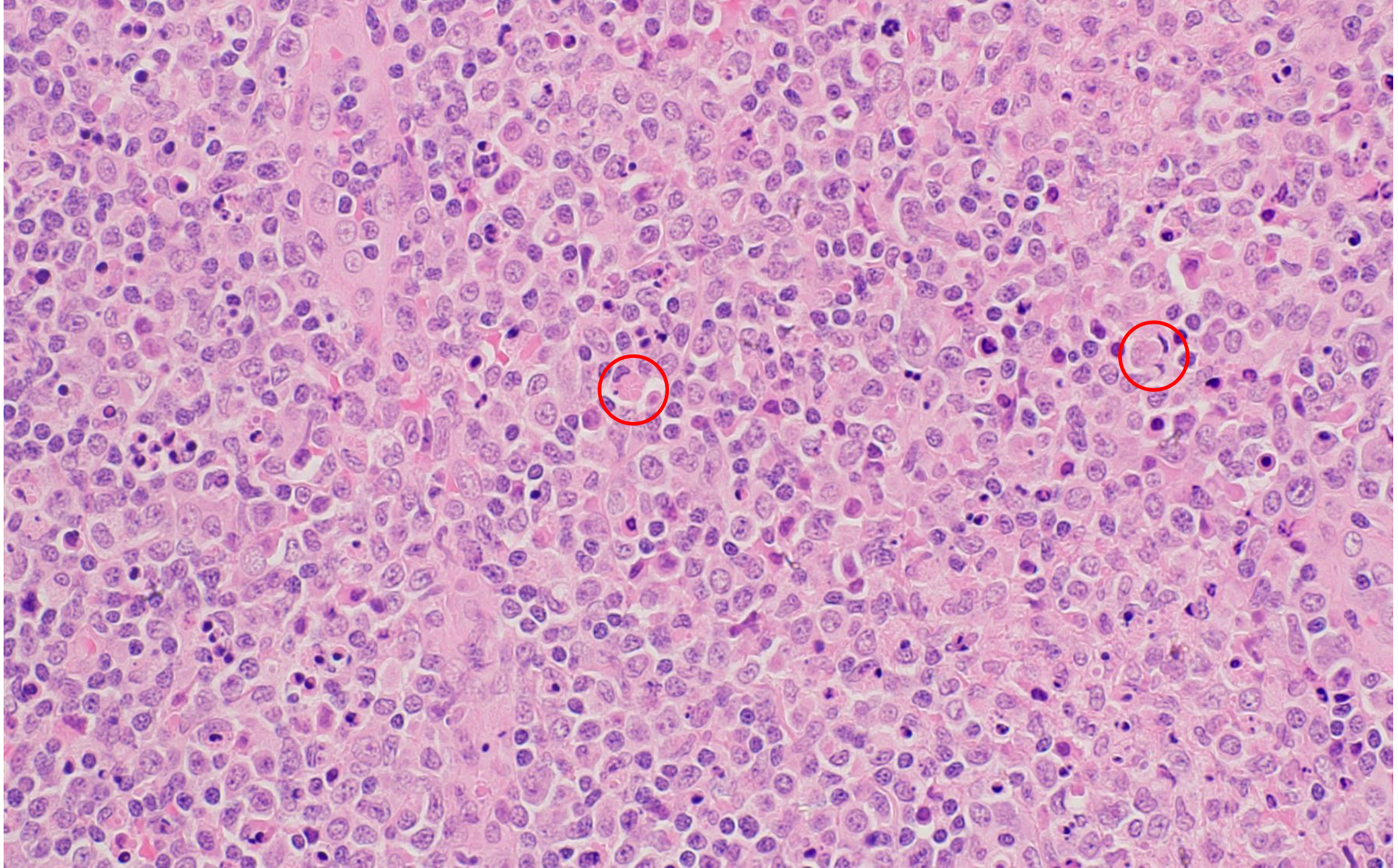
?lymphoma





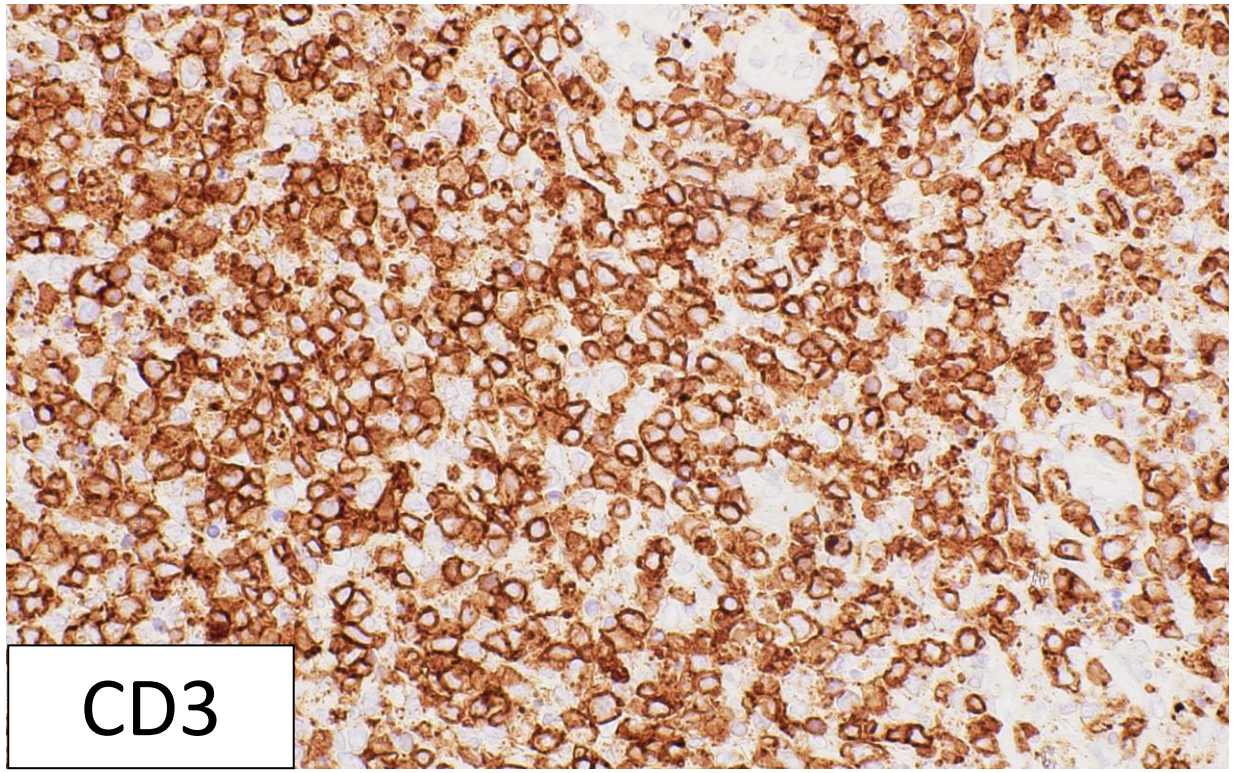


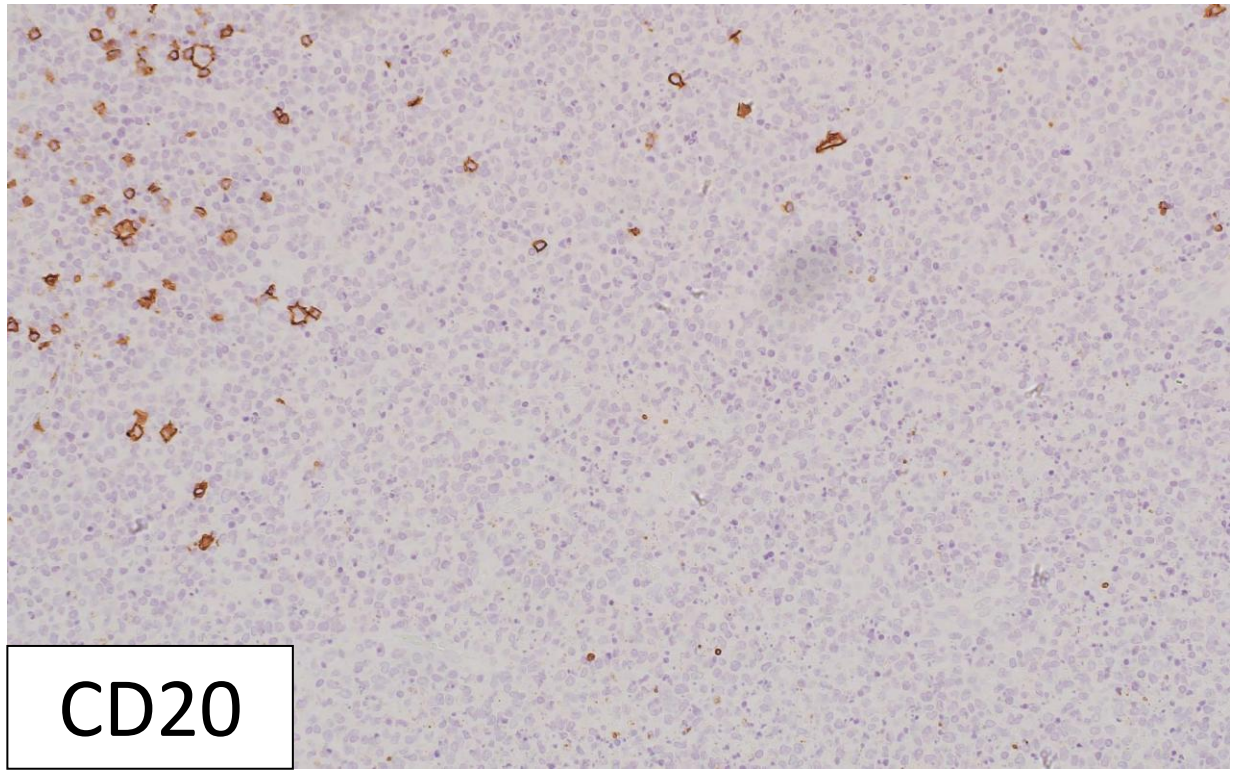


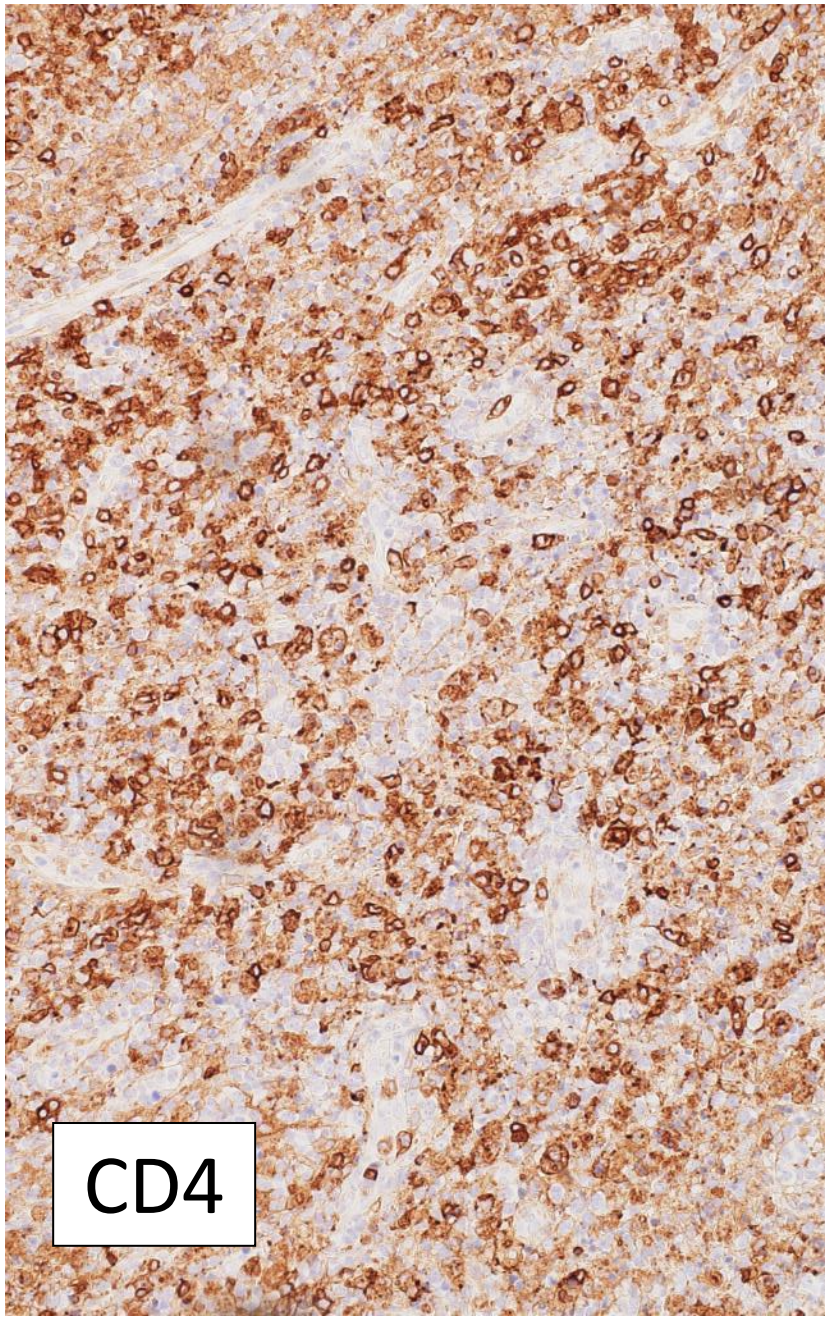


Morphology

- Partial nodal effacement by necrotic process
- Necrotic area contains abundant karyorrhectic debris, but no neutrophils
- Medium and large ?atypical cells associated with the necrosis


CD3


CD20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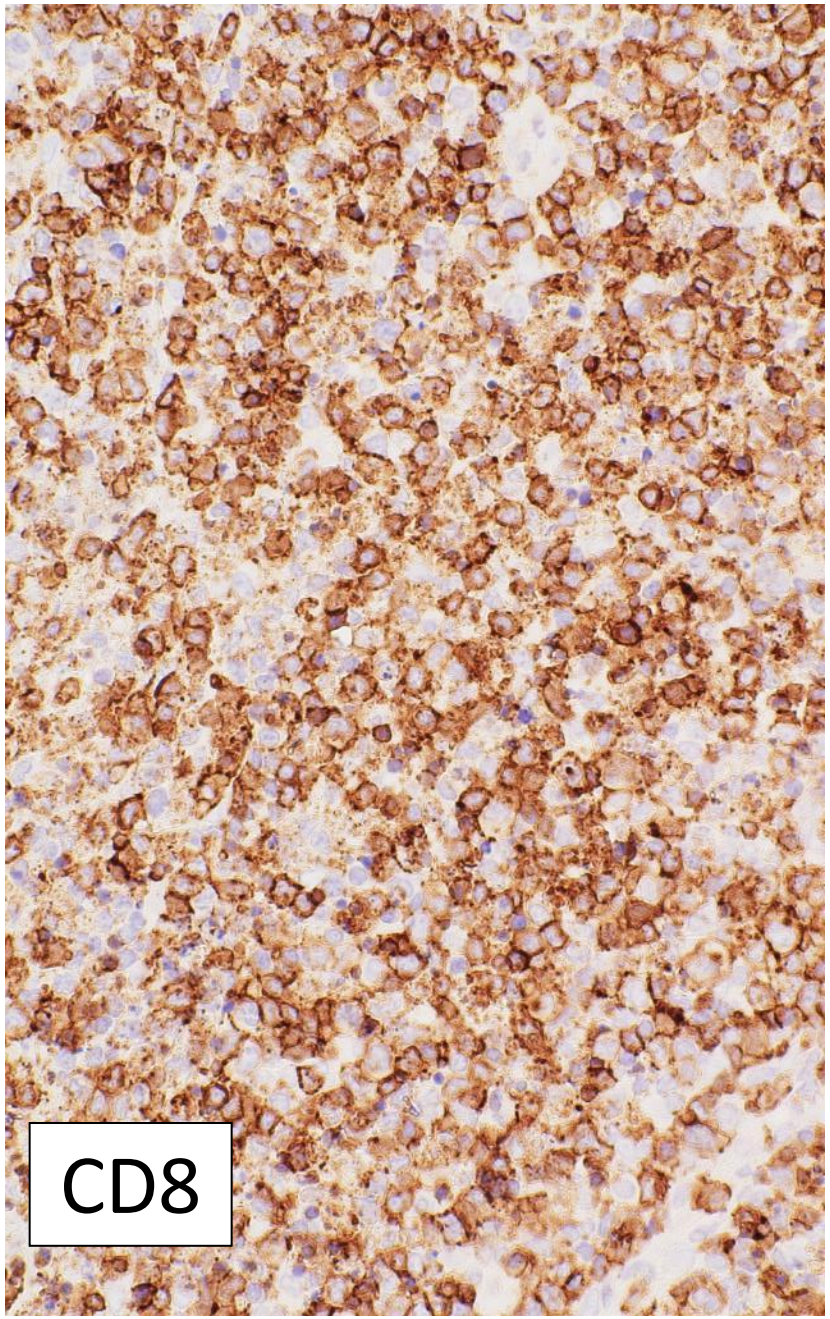
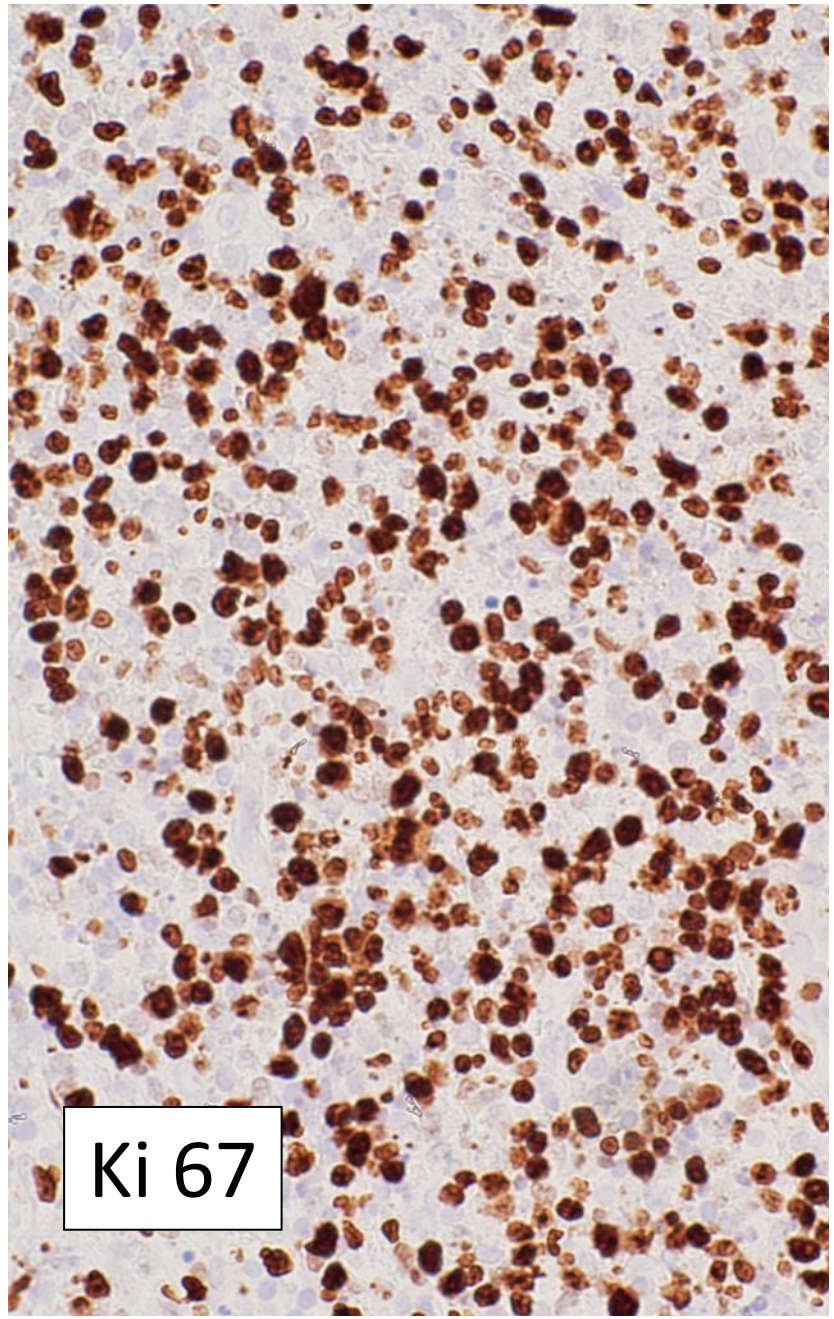

CD8


Ki 67

Immunohistochemistry

- Atypical lymphoid cells are T-cells
- Many are CD8+
- High proliferation

? Peripheral T-cell lymphoma, NOS

Features against.....

- **Clinical:**

PTCL, NOS would be a very unusual diagnosis in a 26-yr old

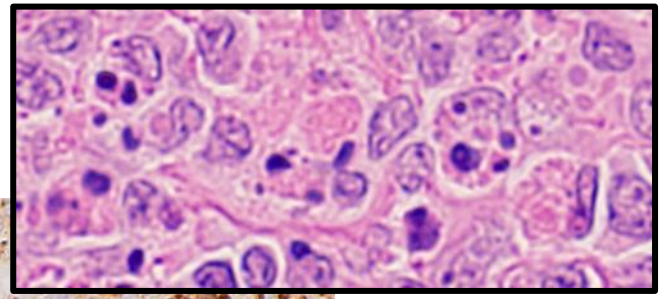
The only nodal PTCL that typically occurs in young adults is anaplastic large cell lymphoma, ALK positive. Uncommonly adult T-cell lymphoma/leukaemia (ATLL) (HTLV-1 associated) may occur in the 3rd decade

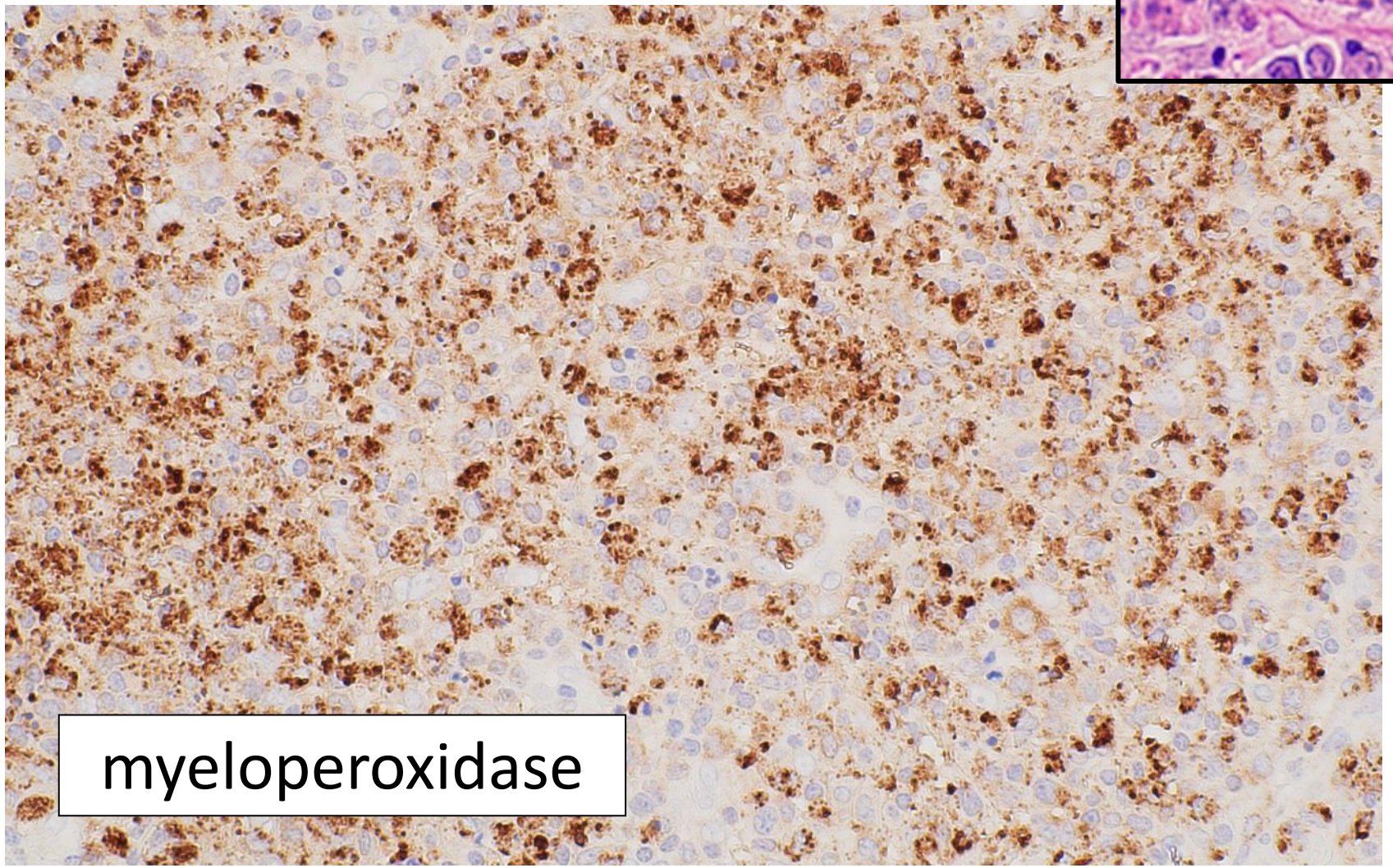
Features against.....

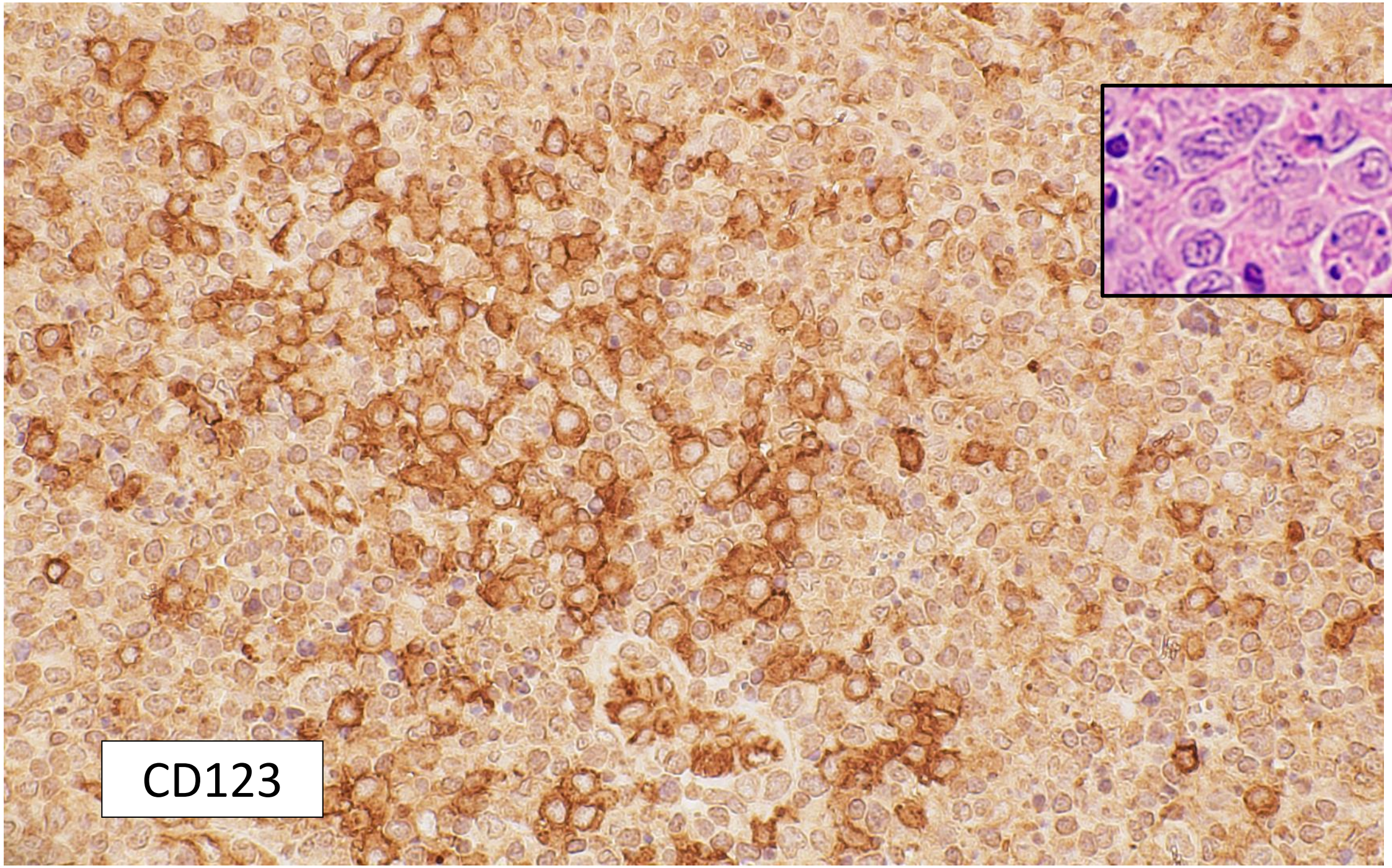
- **Morphology**

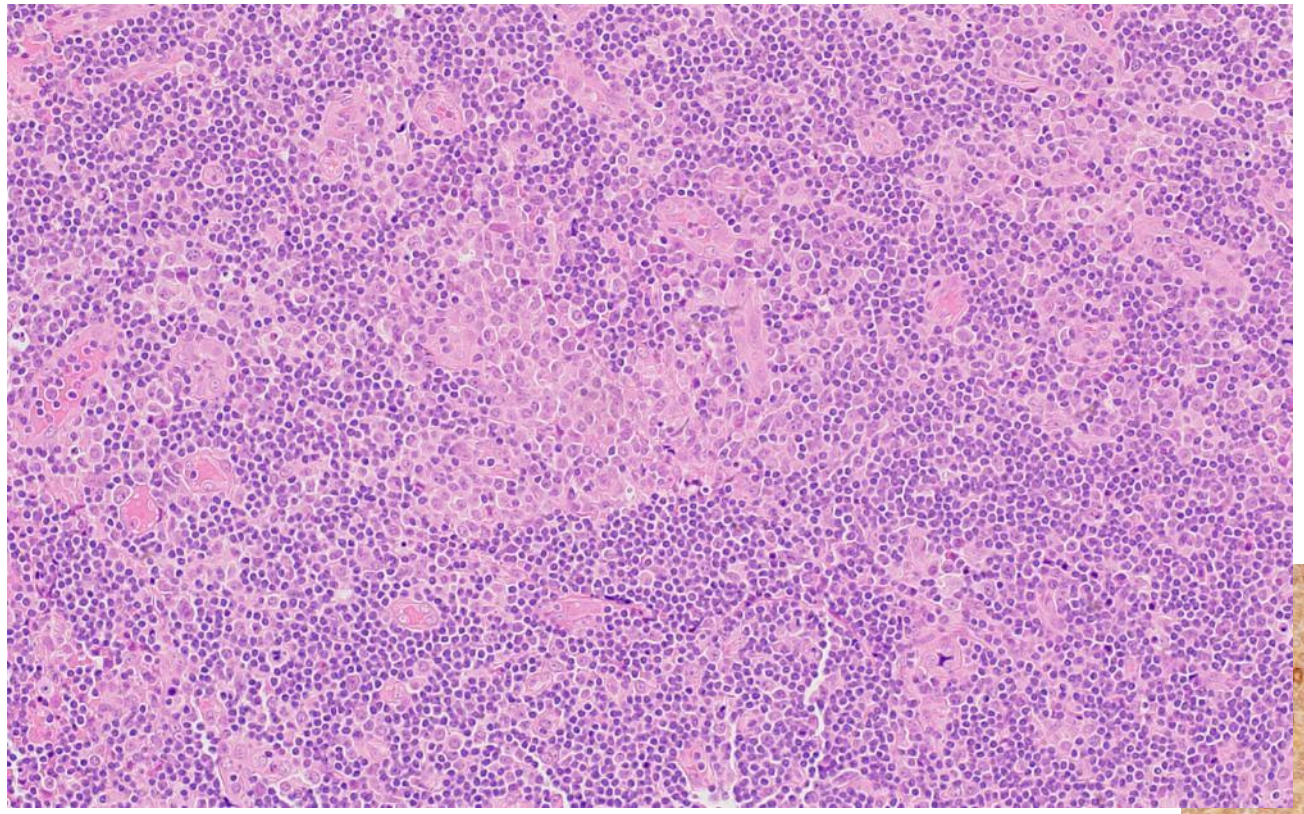
- Paracortical necrotising process devoid of neutrophils should always alert to a diagnosis of **histiocytic necrotising lymphadenitis – Kikuchi disease** (localised, self limiting and reactive) or **systemic lupus erythematosus** (SLE) which may give an identical appearance in lymph nodes.
- Necrotising process not a typical feature of PTCL, NOS.

Immunohistochemistry contd....

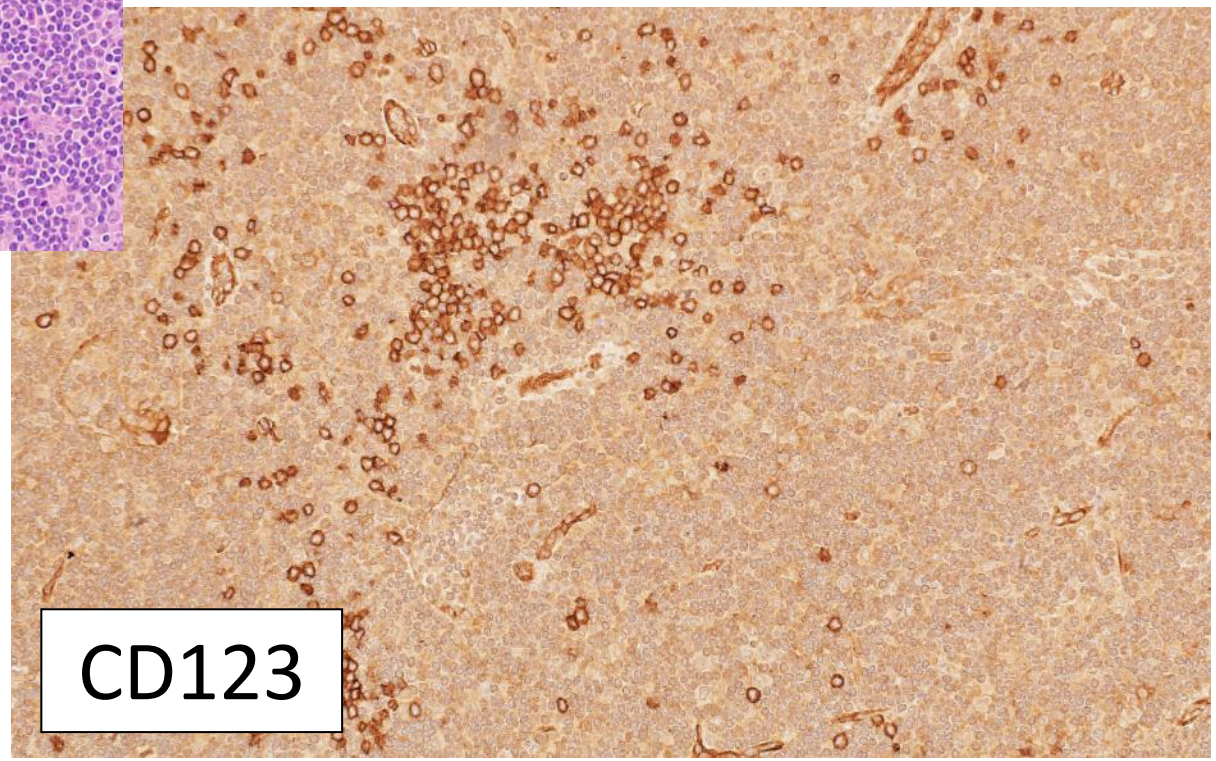





CD123



Plasmacytoid dendritic cells



Molecular genetics

- Do not send for clonality analysis
- May encounter clonal/oligoclonal patterns of T-cell receptor PCR which although reactive, may help confirm a misdiagnosis!

Case 3
Diagnosis:

Histiocytic necrotising lymphadenitis Kikuchi lymphadenitis (Kikuchi-Fujimoto lymphadenitis) or lupus lymphadenitis (SLE)

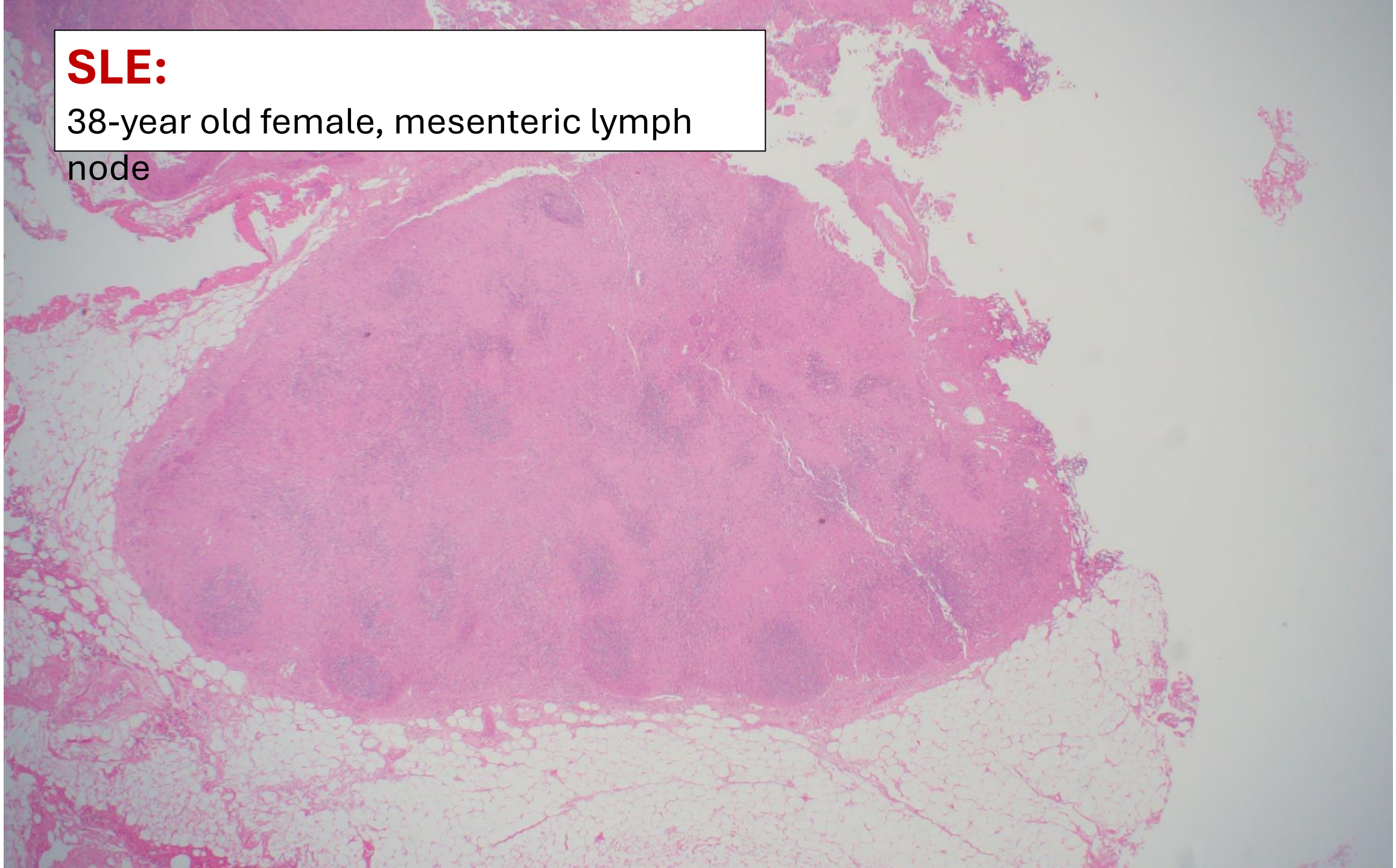
Kikuchi disease/Kikuchi lymphadenitis (Kikuchi-Fujimoto lymphadenitis)

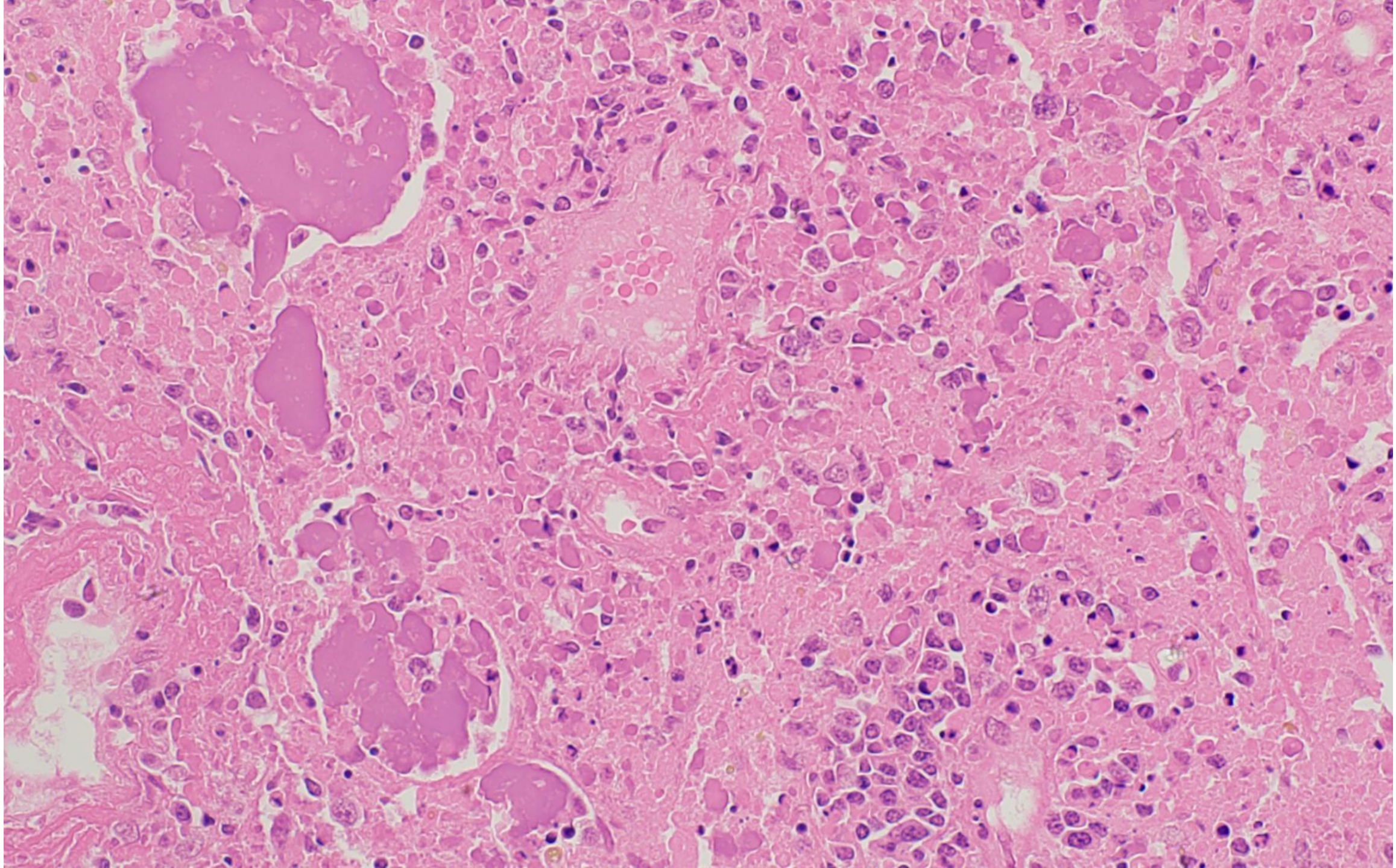
- Predominantly young adults, esp women of Asian descent
- Cervical lymphadenopathy +/-fever and leucopaenia
- Most cases resolve spontaneously
- 3 stages:
  - proliferative
  - necrotising
  - xanthomatous

Kikuchi disease (Kikuchi-Fujimoto lymphadenitis)

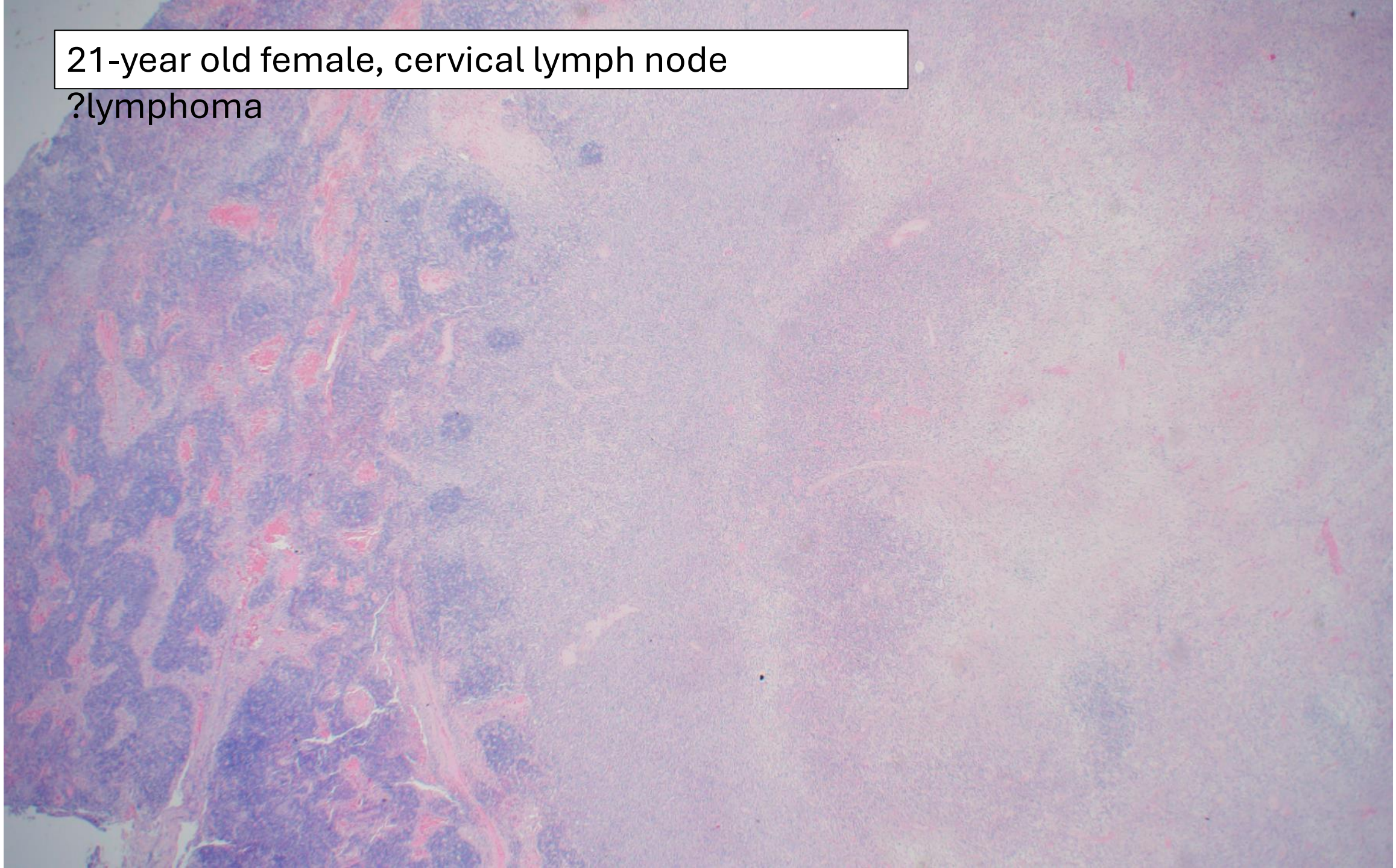
HISTOLOGY

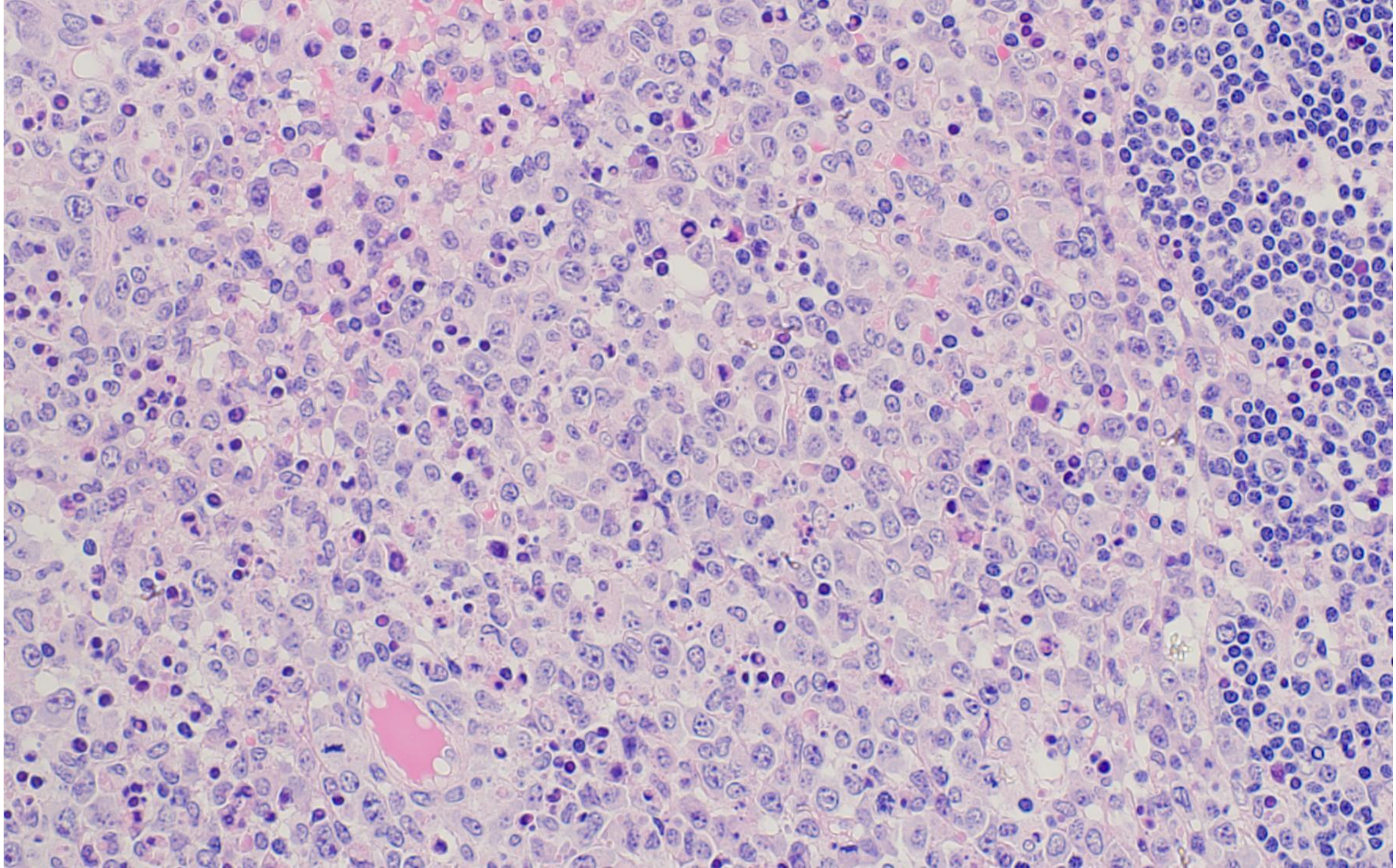
- Paracortical clusters of plasmacytoid dendritic cells, crescentic histiocytes, karyorrhectic bodies – no neutrophils.
- Histologically indistinguishable from lupus lymphadenitis
- All cases should also undergo serological testing to exclude SLE
- Features that favour SLE: extensive necrosis, haematoxylin bodies, plasma cells, occ neutrophils.

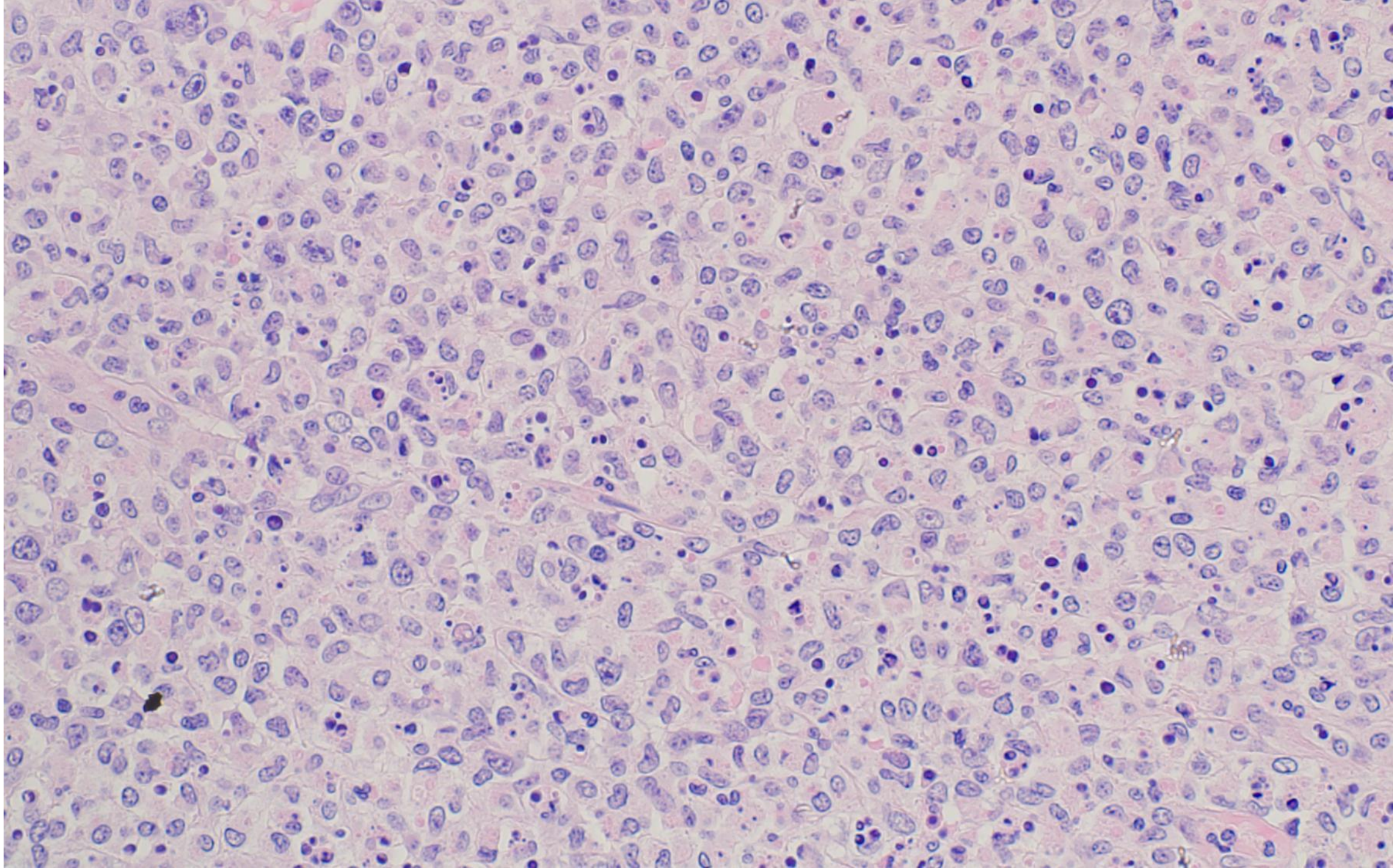

SLE:
38-year old female, mesenteric lymph node

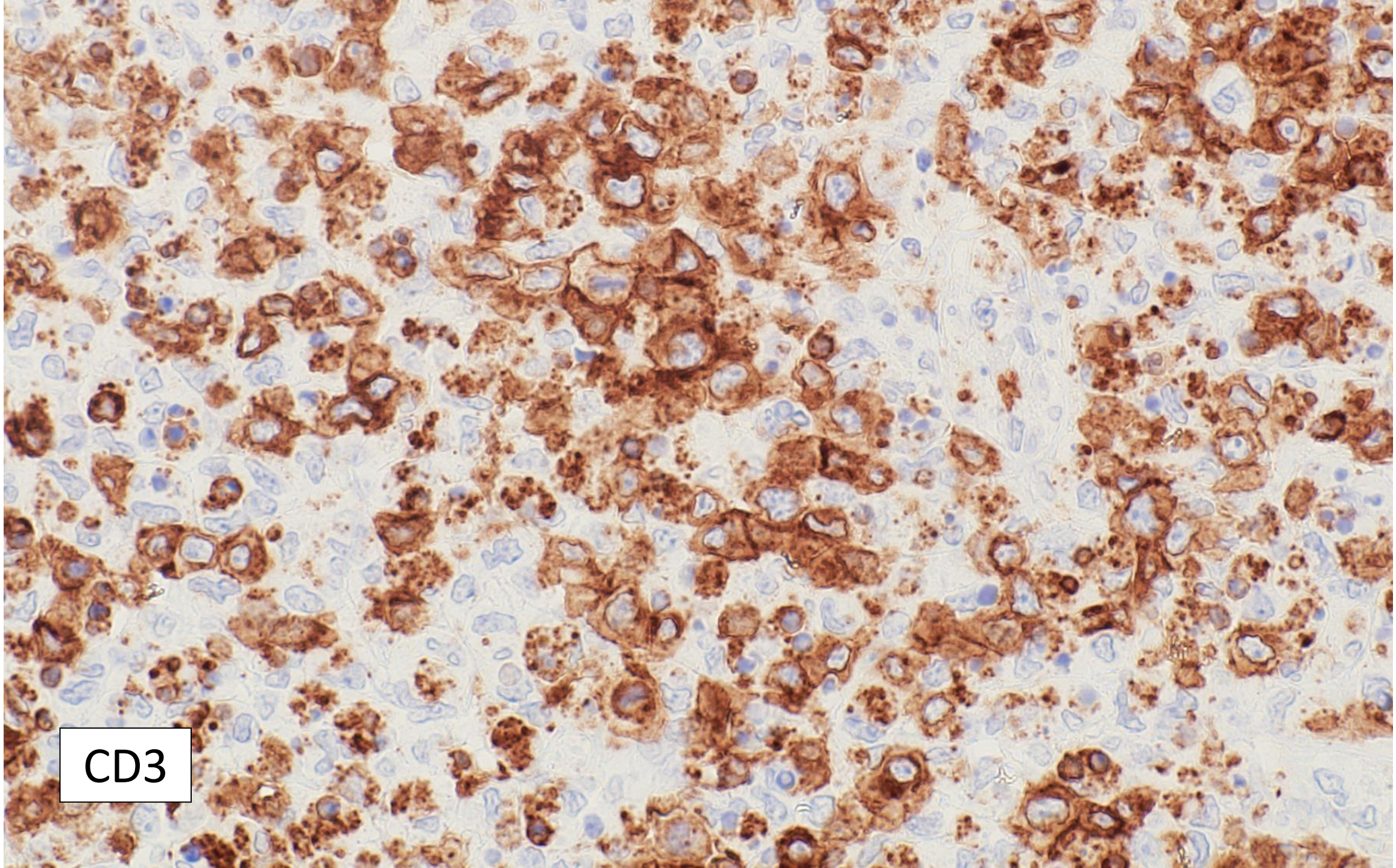


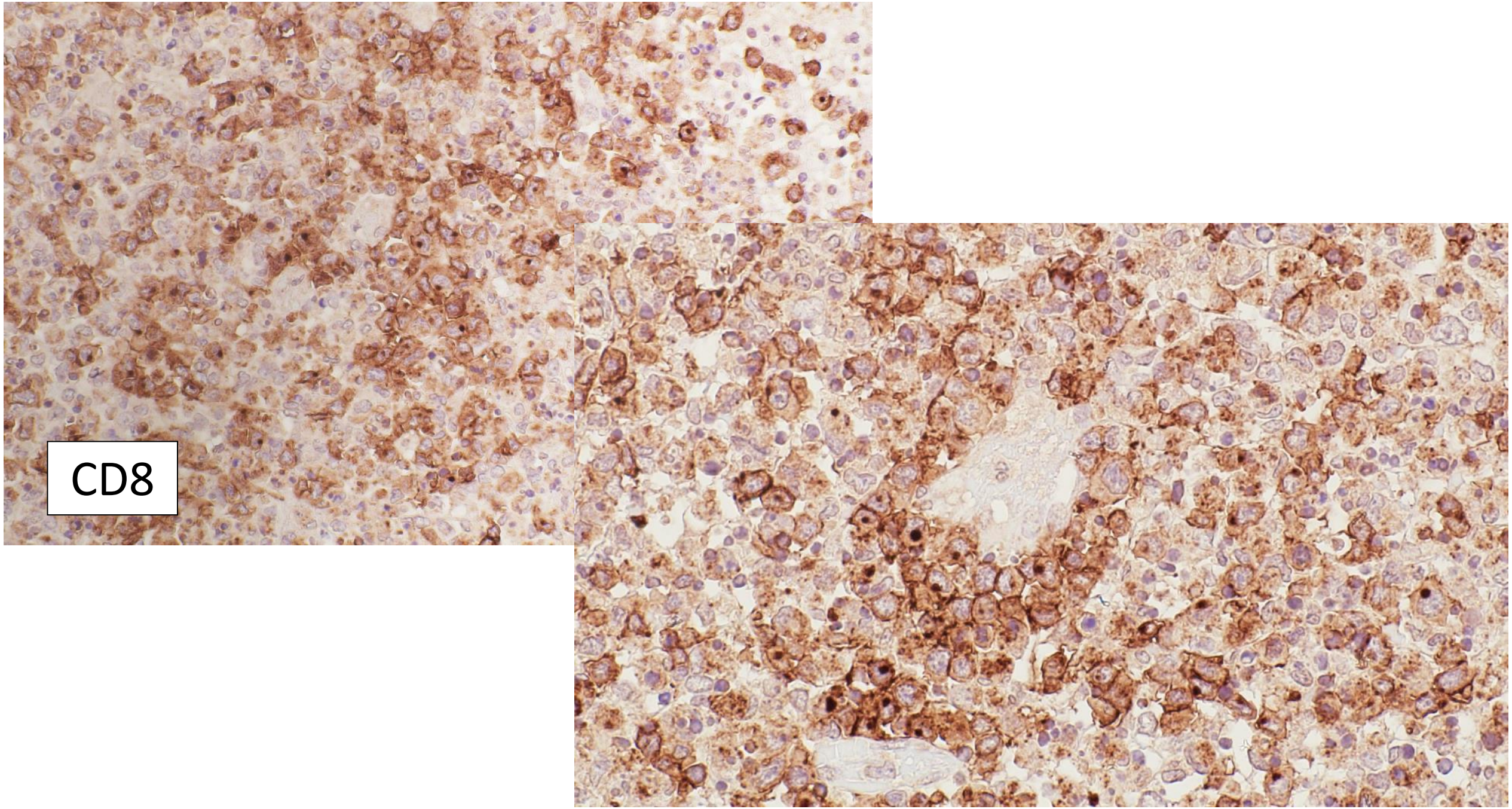
Pitfall:
Sometimes the T-cells are markedly atypical!


21-year old female, cervical lymph node
?lymphoma






CD3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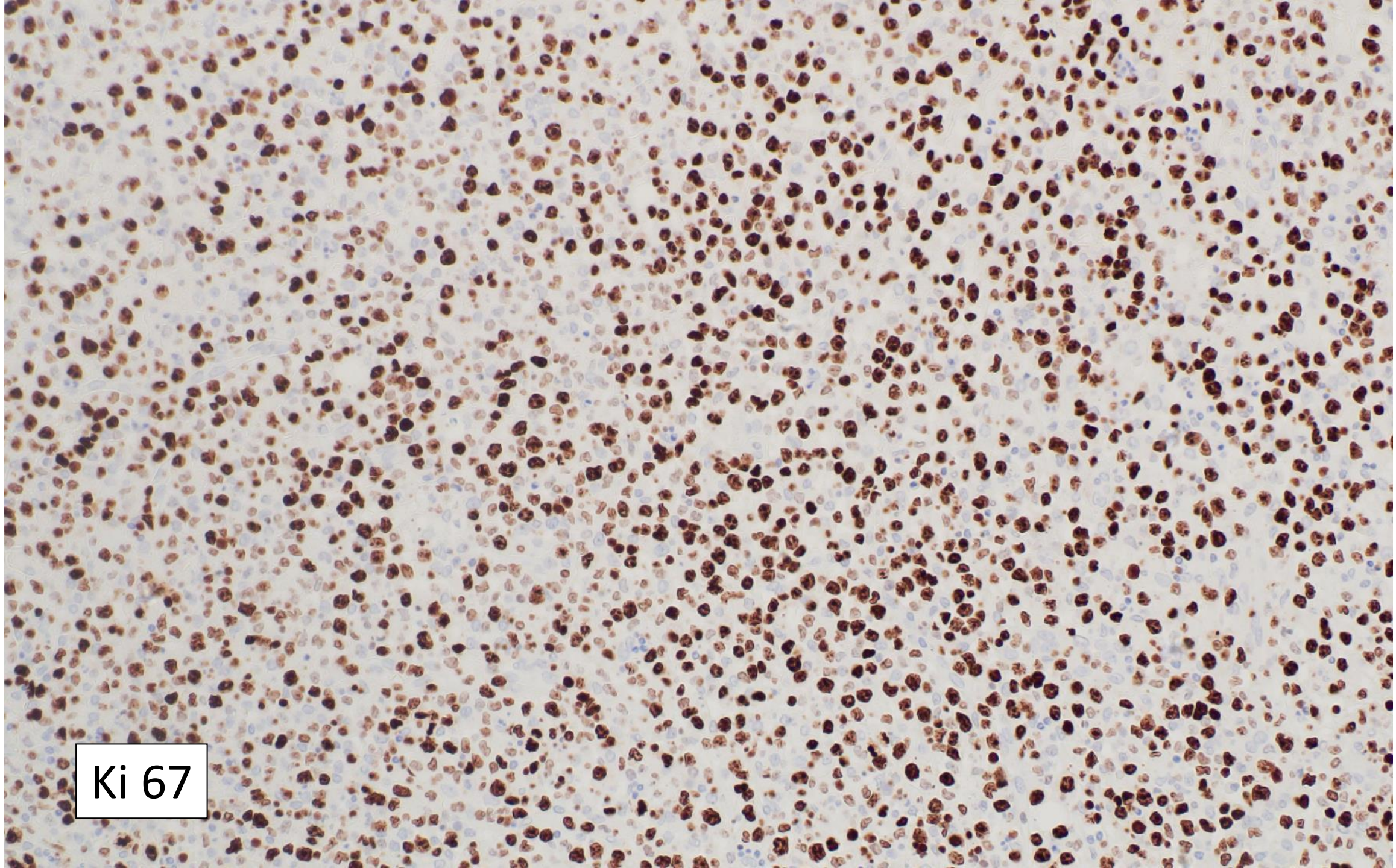
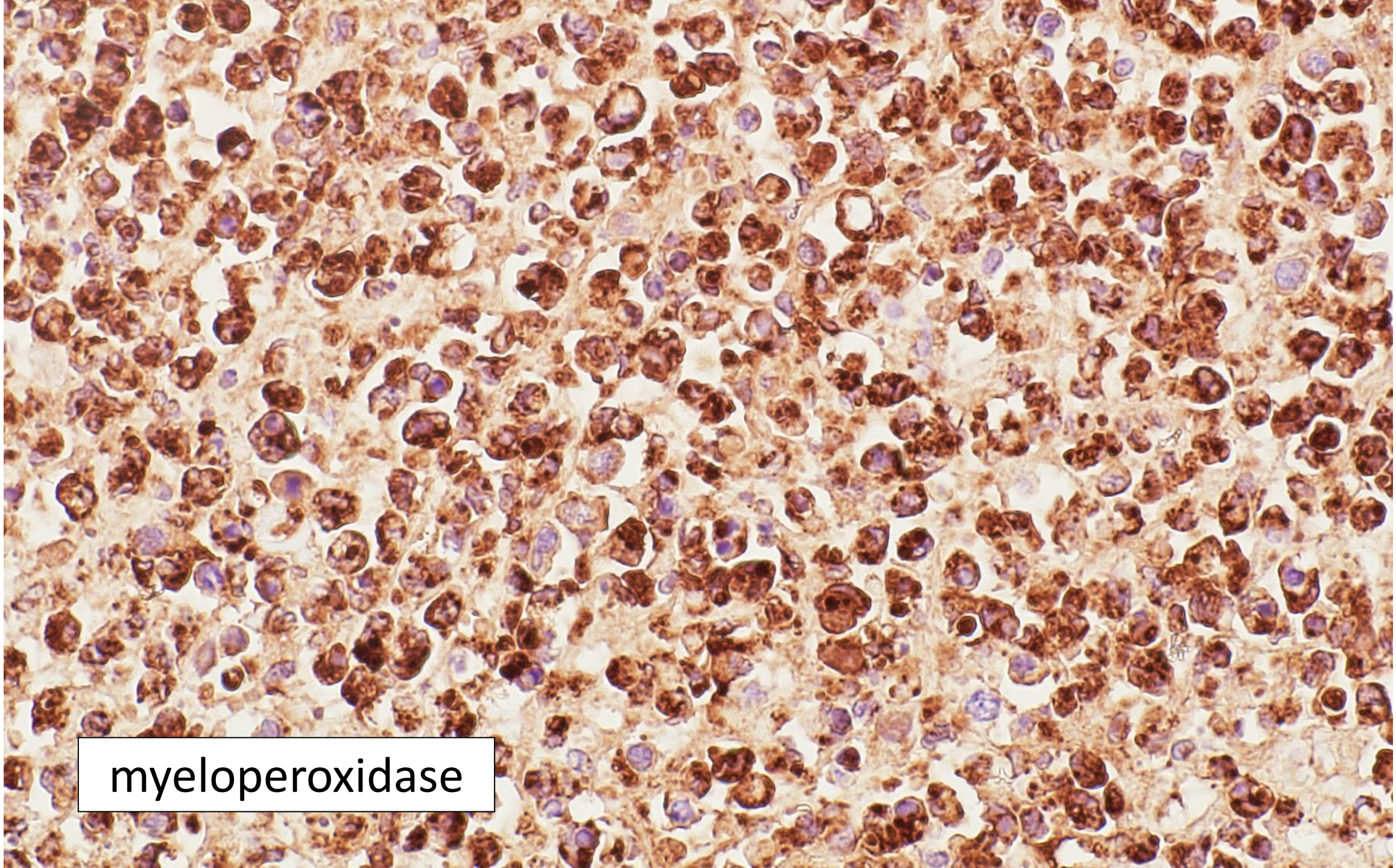

Ki 67


myeloperoxidase

Immunohistochemical panel for histiocytic necrotising lymphadenitis

CD3, CD20, CD4(highlights histiocytes and small T-cells), CD8 (cytotoxic T-cells, which may look ‘atypical’), myeloperoxidase (MPO) (MPO+ histiocytes), CD123 (plasmacytoid dendritic cells),

You may perform EBER-ISH which will be negative

D/D
Necrosis in lymph nodes

Reactive

- Herpes simplex lymphadenitis: neutrophils, viral inclusions
- Infectious mononucleosis: geographic necrosis, polymorphous infiltrate, EBER positive large B-cells, EBV serology.

Lymphoma

NK/T-cell lymphoma (if nodal, classified as PTCL, NOS) – necrosis (c.f extranodal NK/T-cell lymphoma, nasal type) is only occasionally a feature; EBER positive

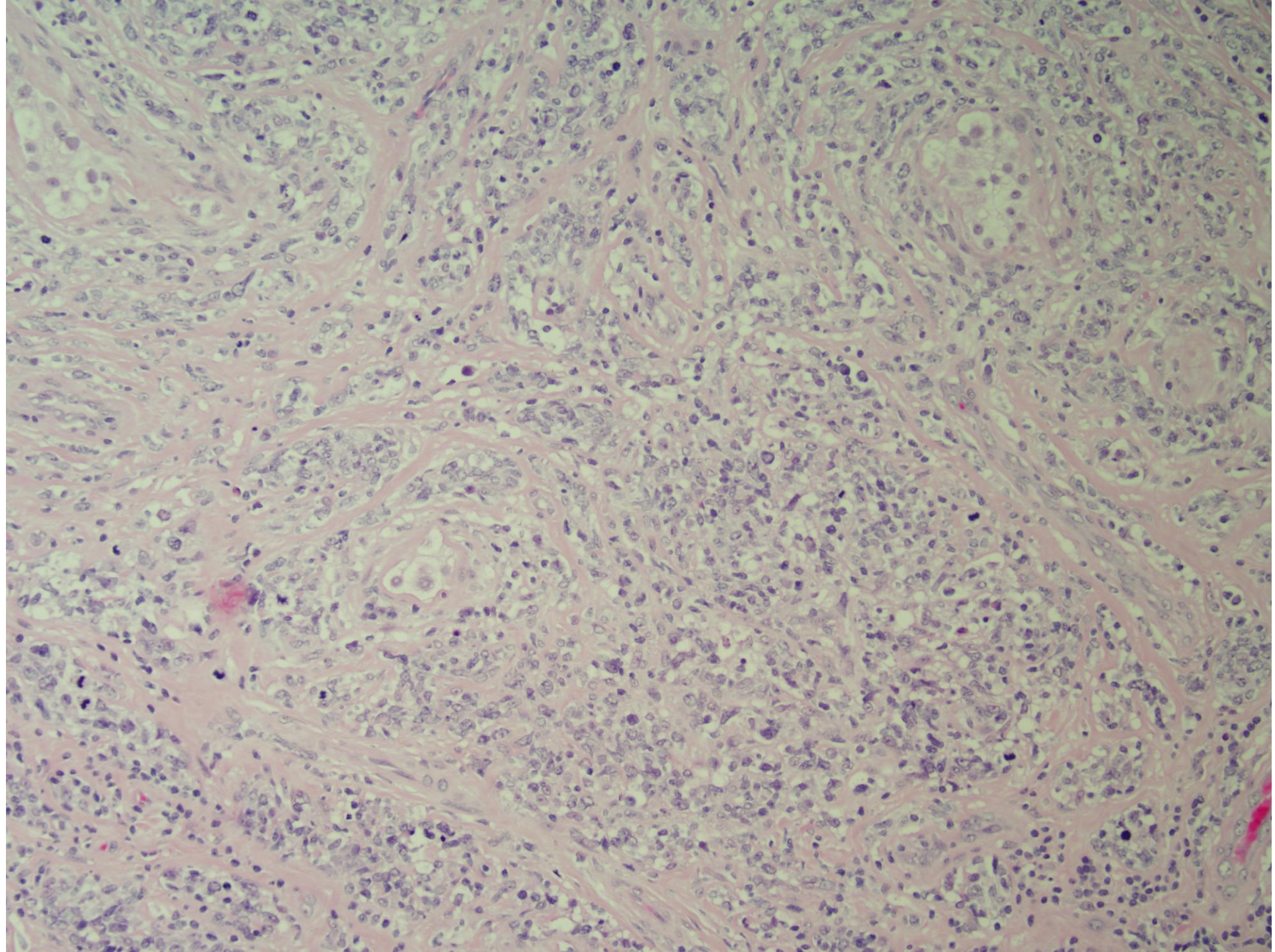
Large B-cell lymphomas – positive for B-cell markers.

Case 2

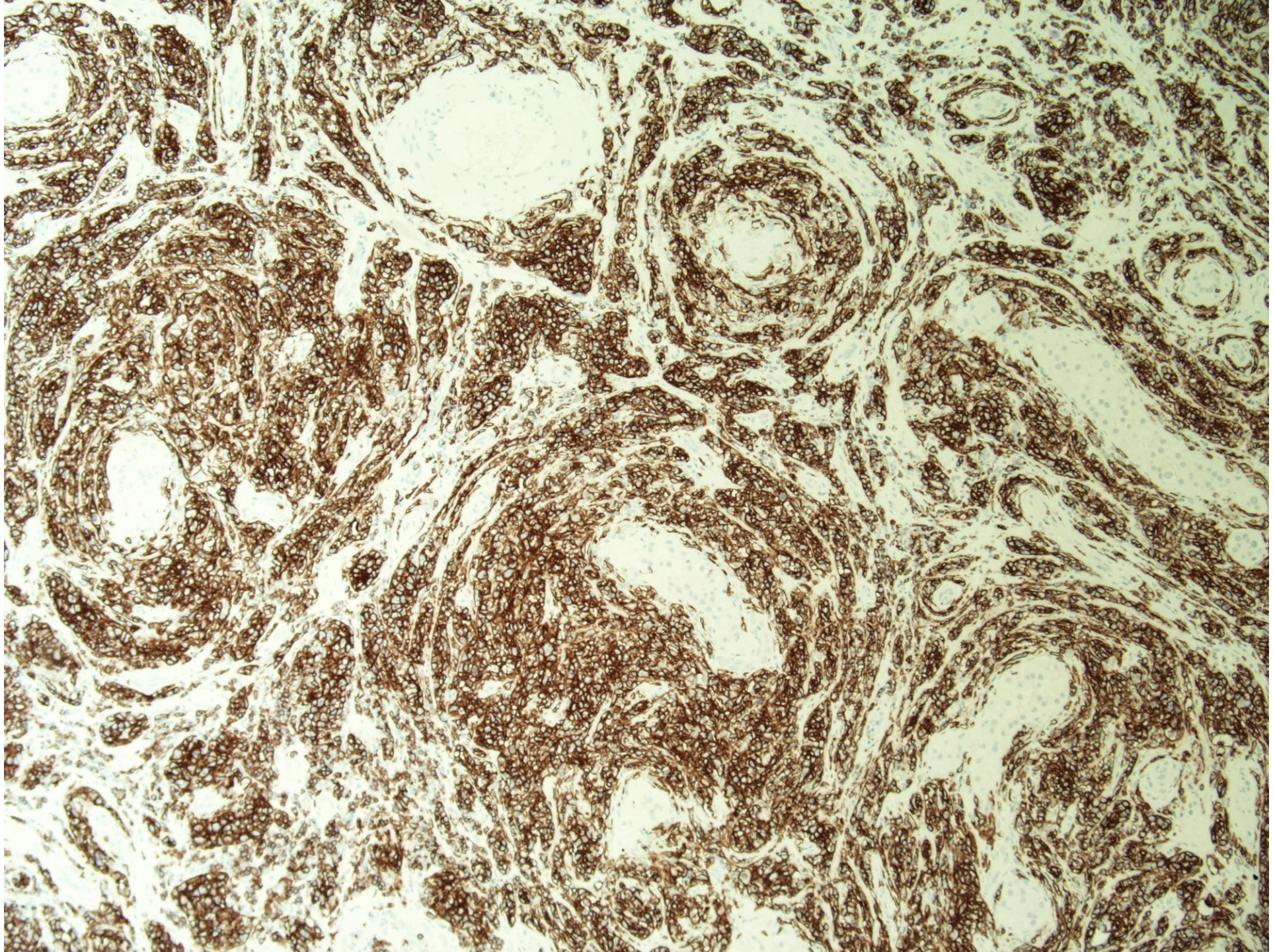
30 year old male

Right testis

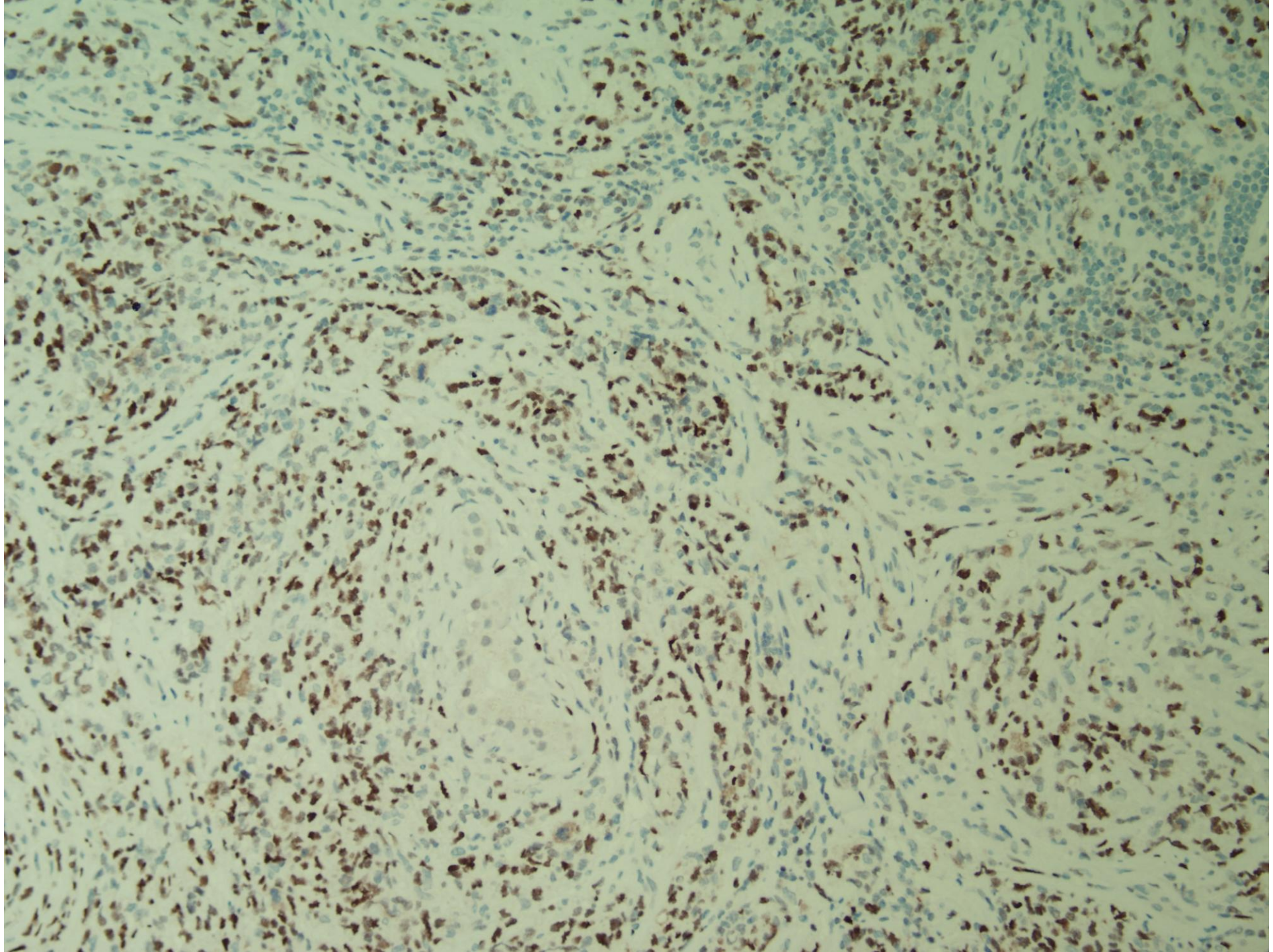
Testicular swelling



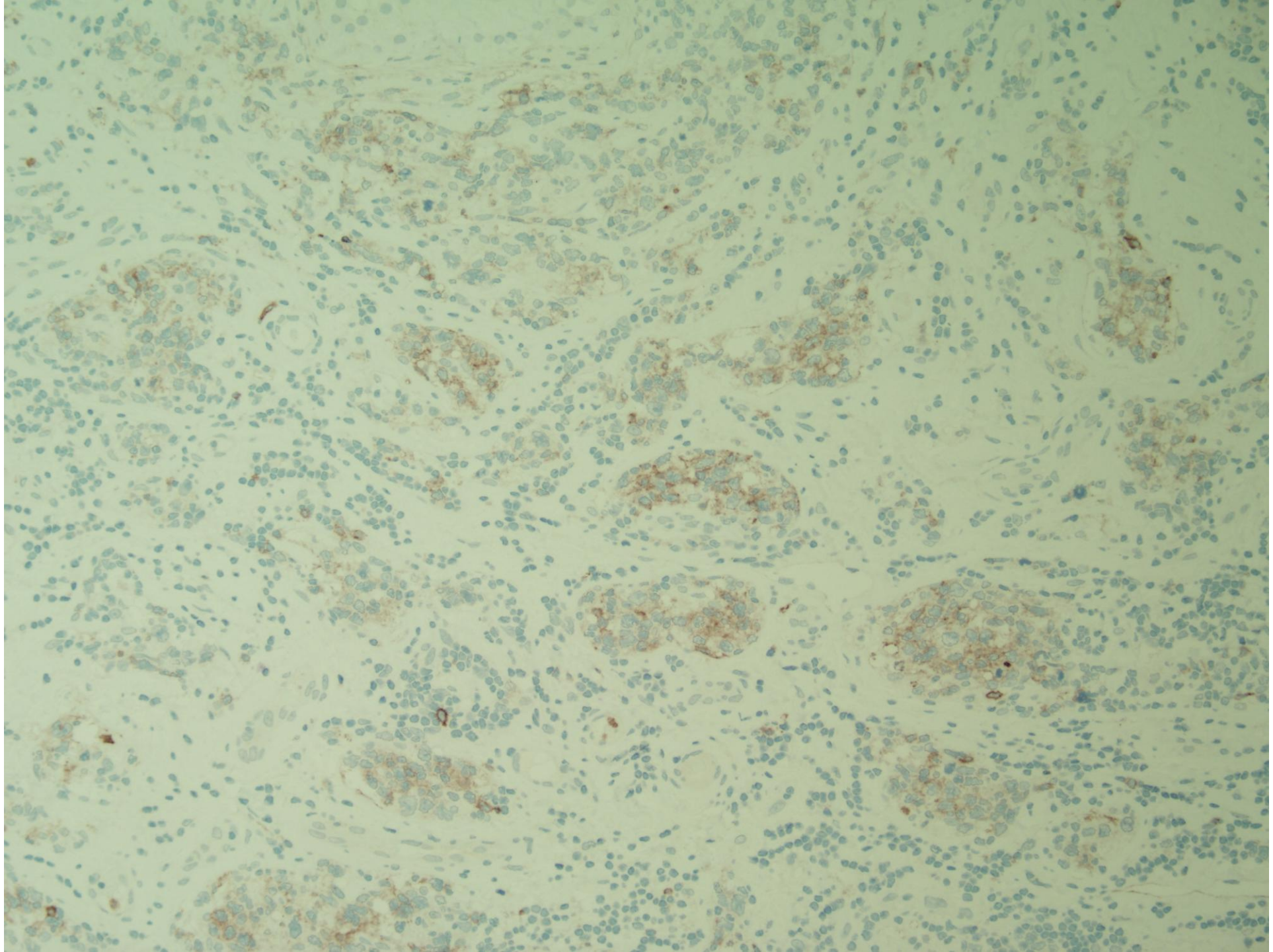
CD20



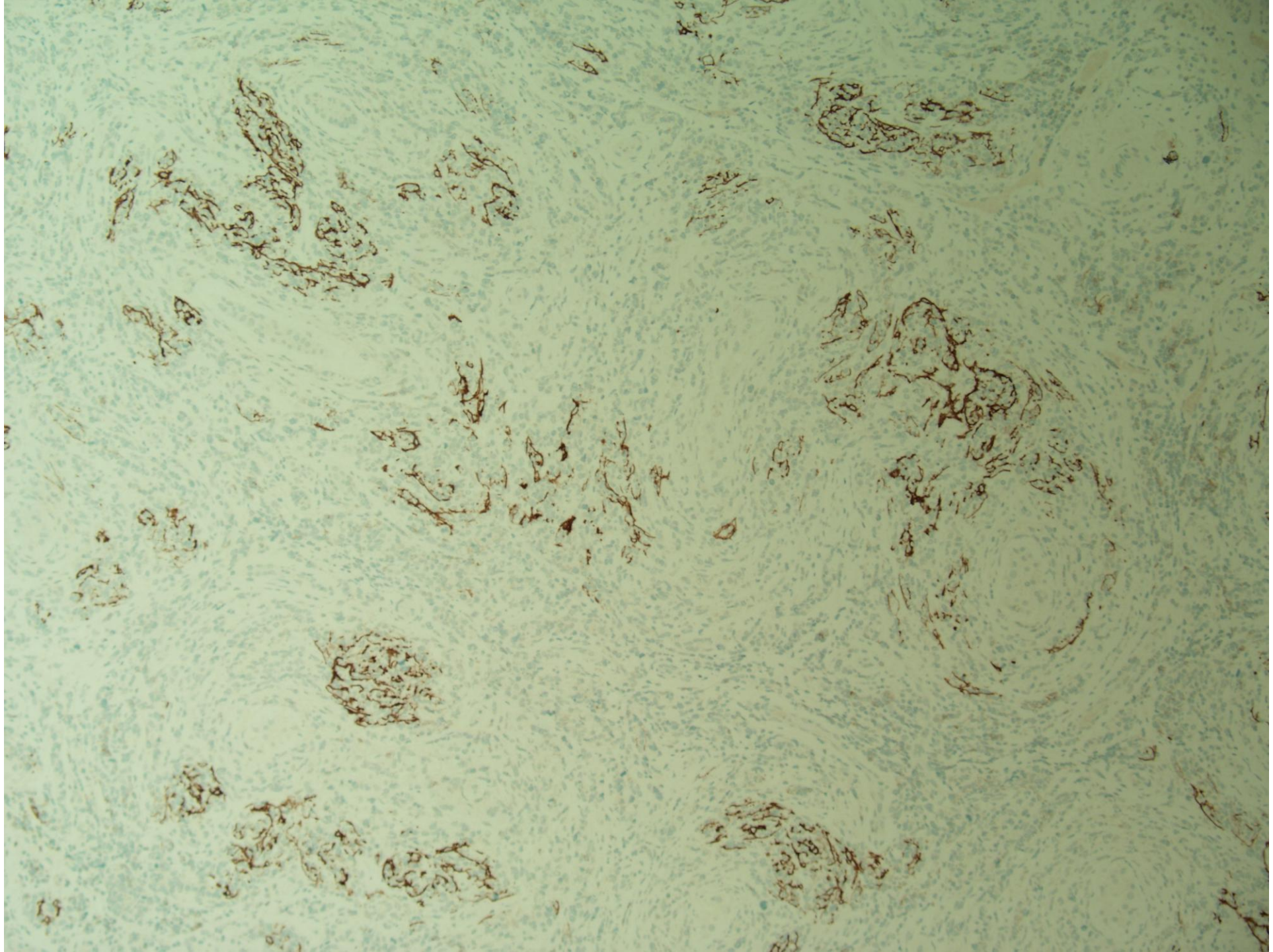
bcl-6



CD10



CD21



Case 2

Immunophenotype

- **Positive**
- CD20, CD19, PAX5, CD10 (patchy, weak), bcl-6, bcl-2 (weak)
- CD30 positive in many of the large cells

- **Negative**
- MUM1, TdT, CD5, CD23, cyclinD1, MYC protein

Case 2

- FISH studies
  - No evidence of a translocation involving
    - BCL2 (18q21)
    - BCL6 (3q27)
    - MYC (8q24)
- Targeted NGS
  - Likely pathogenic EZH2 missense variant c.1936T>A (tyr646Asn) – 16.1% VAF
  - No pathogenic variants detected in ATM, ARID1A, BCL2, BRAF, BTK, CARD11, CCND3, CD79B, CREBBP, CXCR4, EP300, FOXO1, KLF2, MAPSK1, MYD88, NOTCH1, NOTCH2, PLCG2, NRAS, KRAS, HRAS or TP53

Diagnosis?

Primary testicular follicular lymphoma

Testicular follicular lymphoma

- Provisional entity in ICC
- Subtype of classical FL in WHO5

- Usually seen in young boys
- Rarely seen in adults (Bacon et al, AJSP; 2007)
- Most grade 3
- Most lack expression of bcl-2 protein
- Lack IHG::BCL2
- Lack TP53 abnormalities
- Mostly localised
- Excellent prognosis

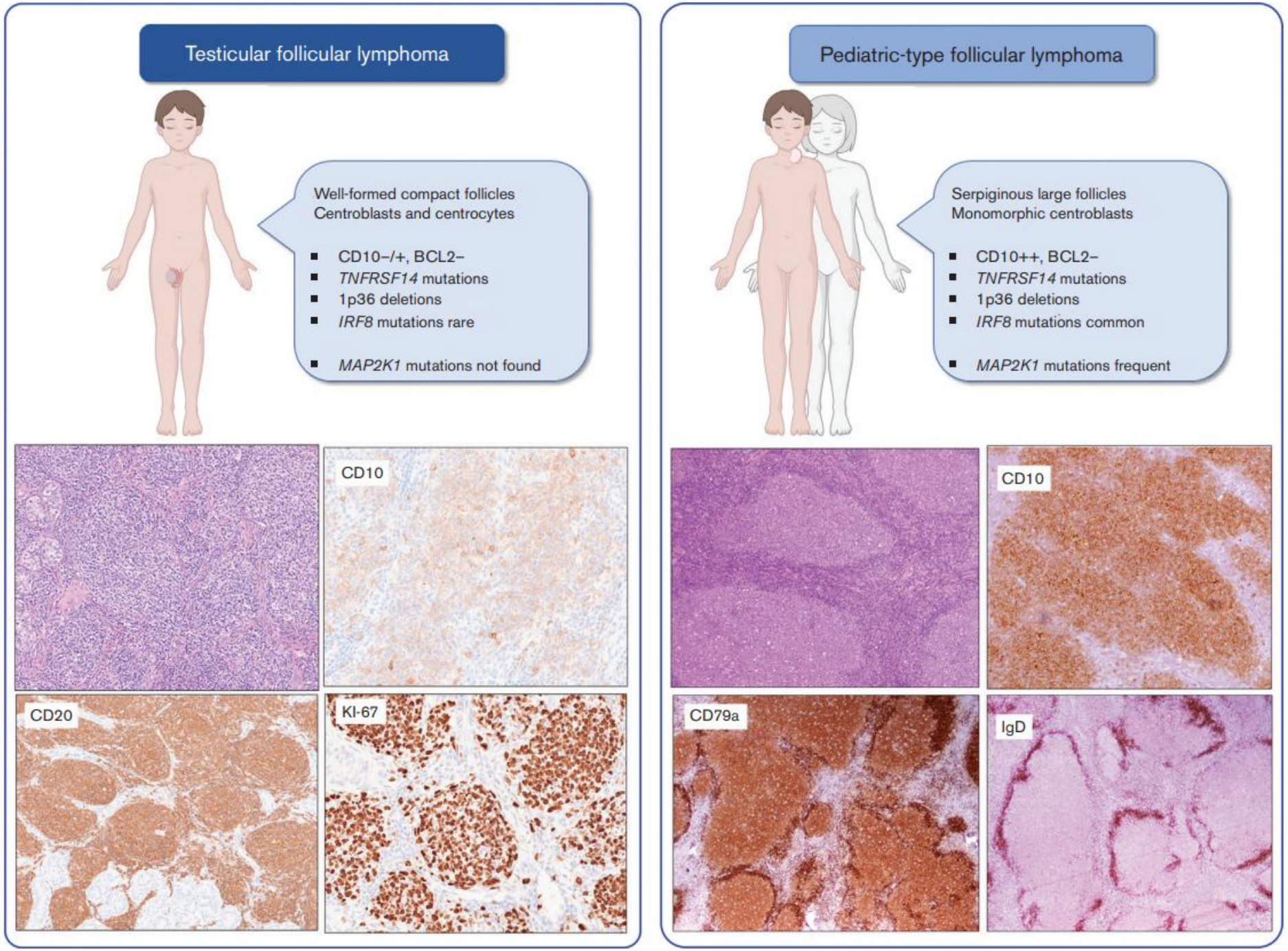
Testicular follicular lymphoma

- Associated with mutation/deletion in TNFRSF14 – 57%
  (Zhang et al, Blood Adv 2025)

- Mutations in EZH2, KMT2D less common

TNFRSF14

- Critical regulator
  - Germinal centre B cell activation
  - Immune recognition and modulation
- Inactivation of TNFRSF14
  - Re-education of tumour microenvironment
  - Increase in CD4+ T follicular helper (TFH) cells supporting lymphoma cell survival and promotion of immune evasion through exclusion of cytotoxic T cells



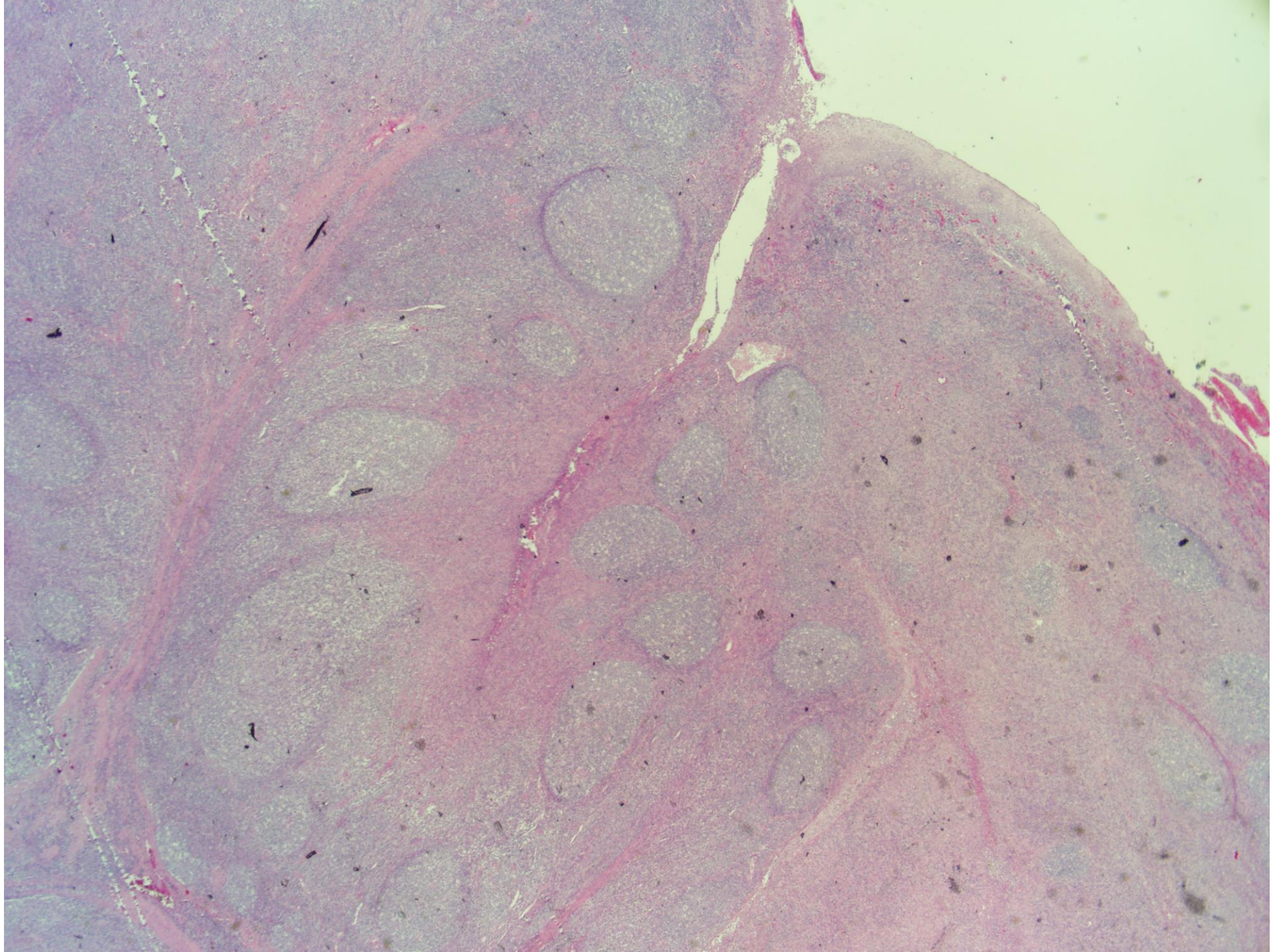
Jaffe and Quintanilla-Martinez
Blood Adv 2025

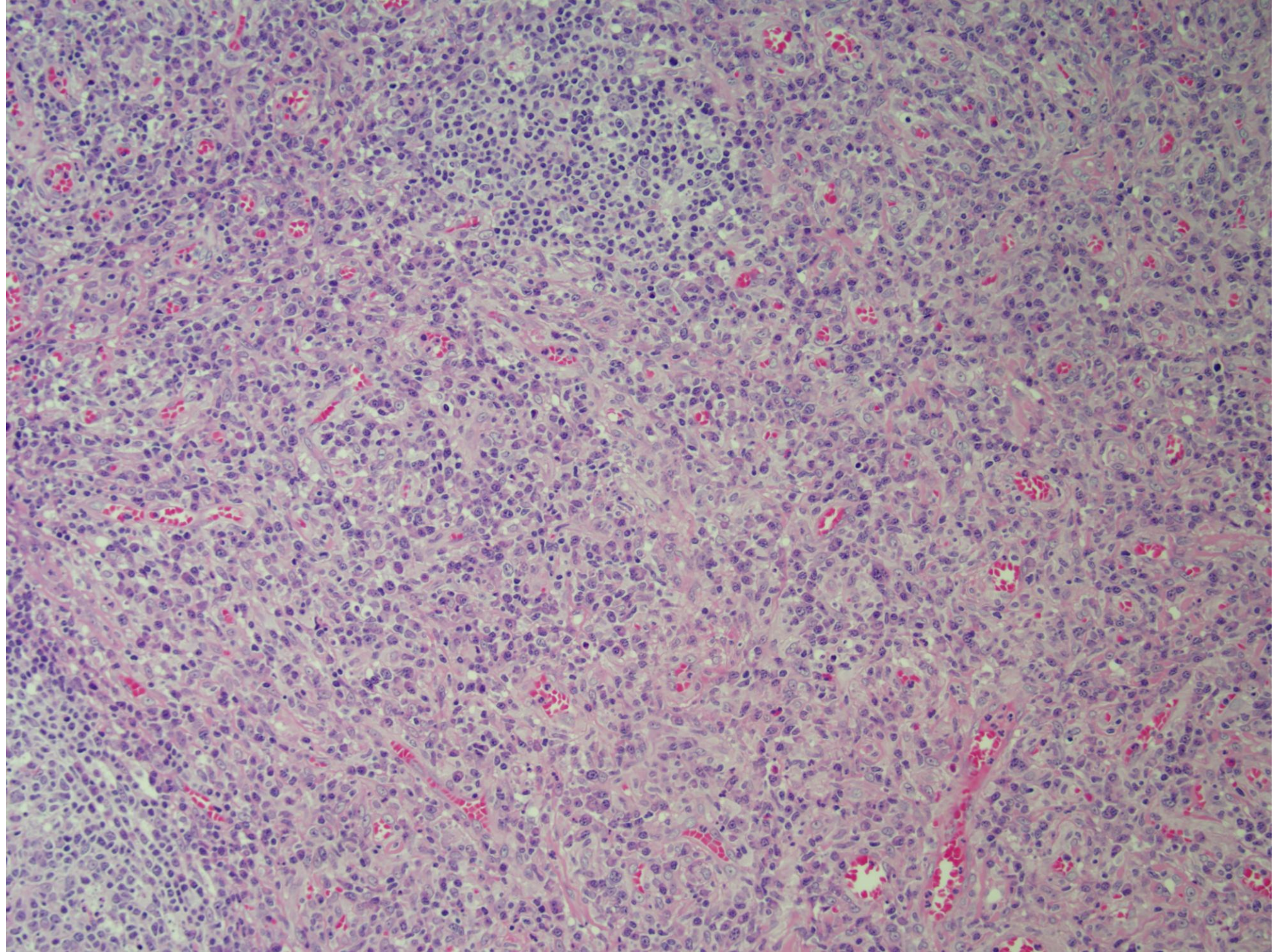
Case 3

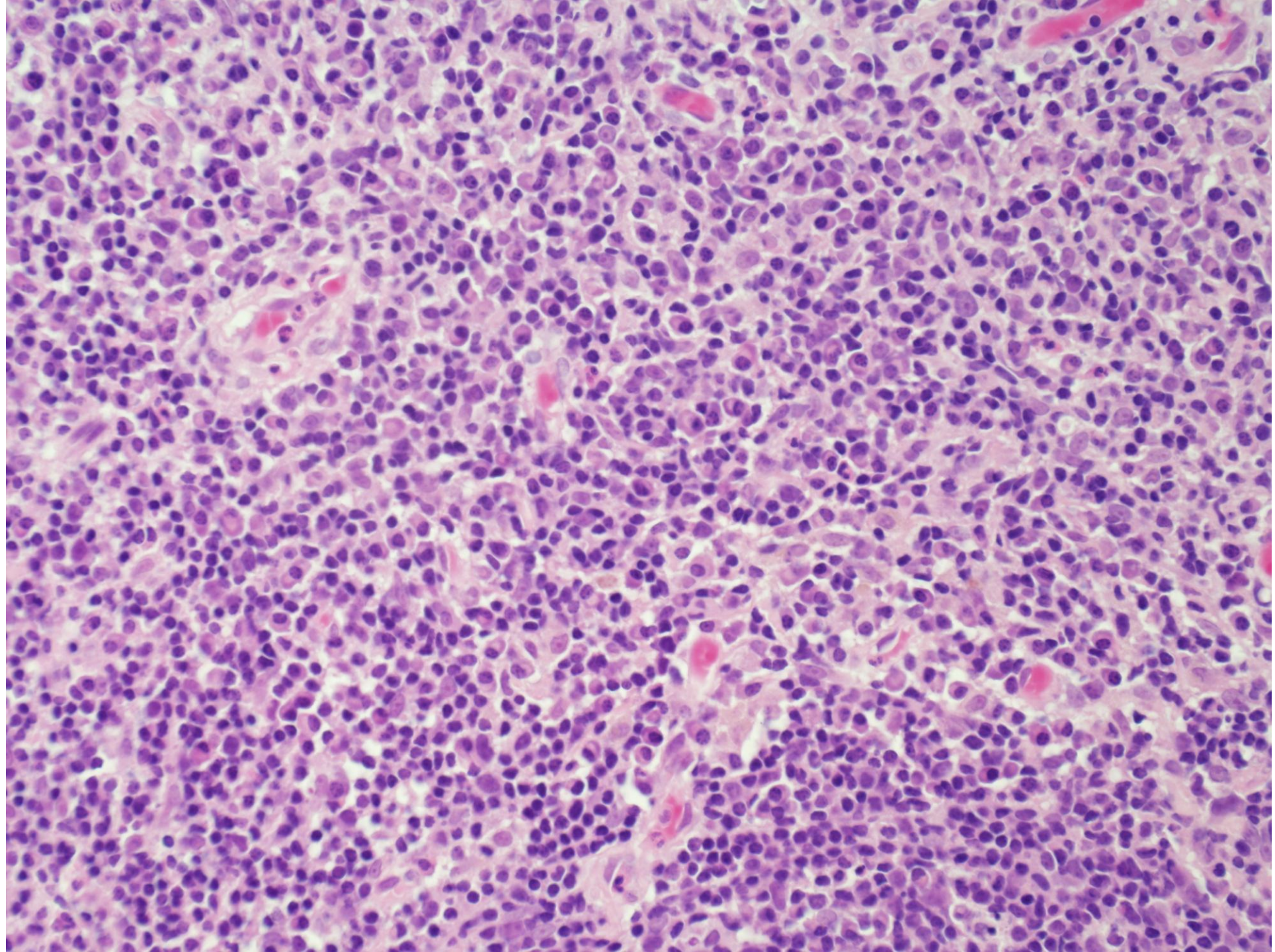
64 year old male

Tonsil

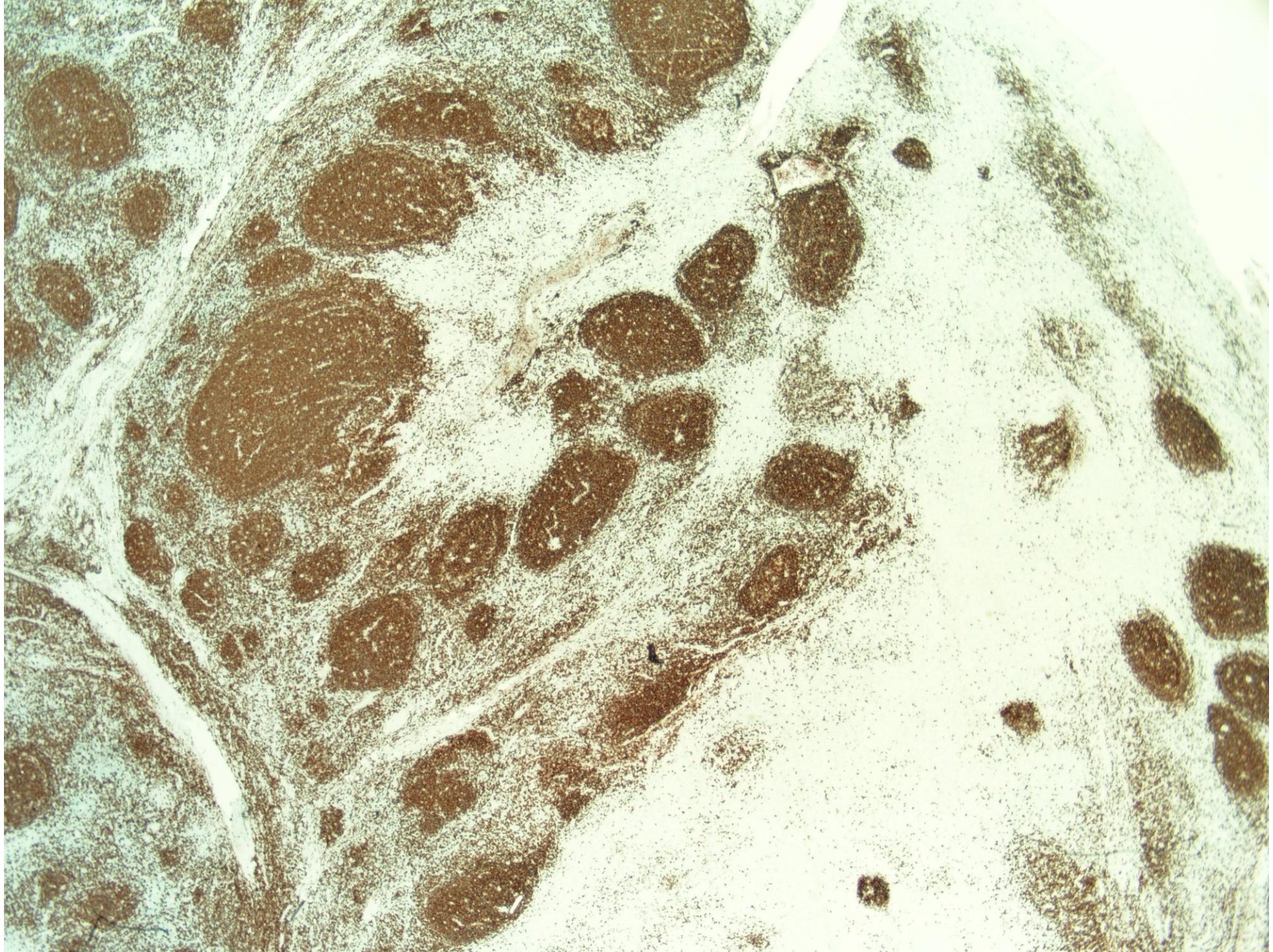
Tonsil swelling and lump in neck



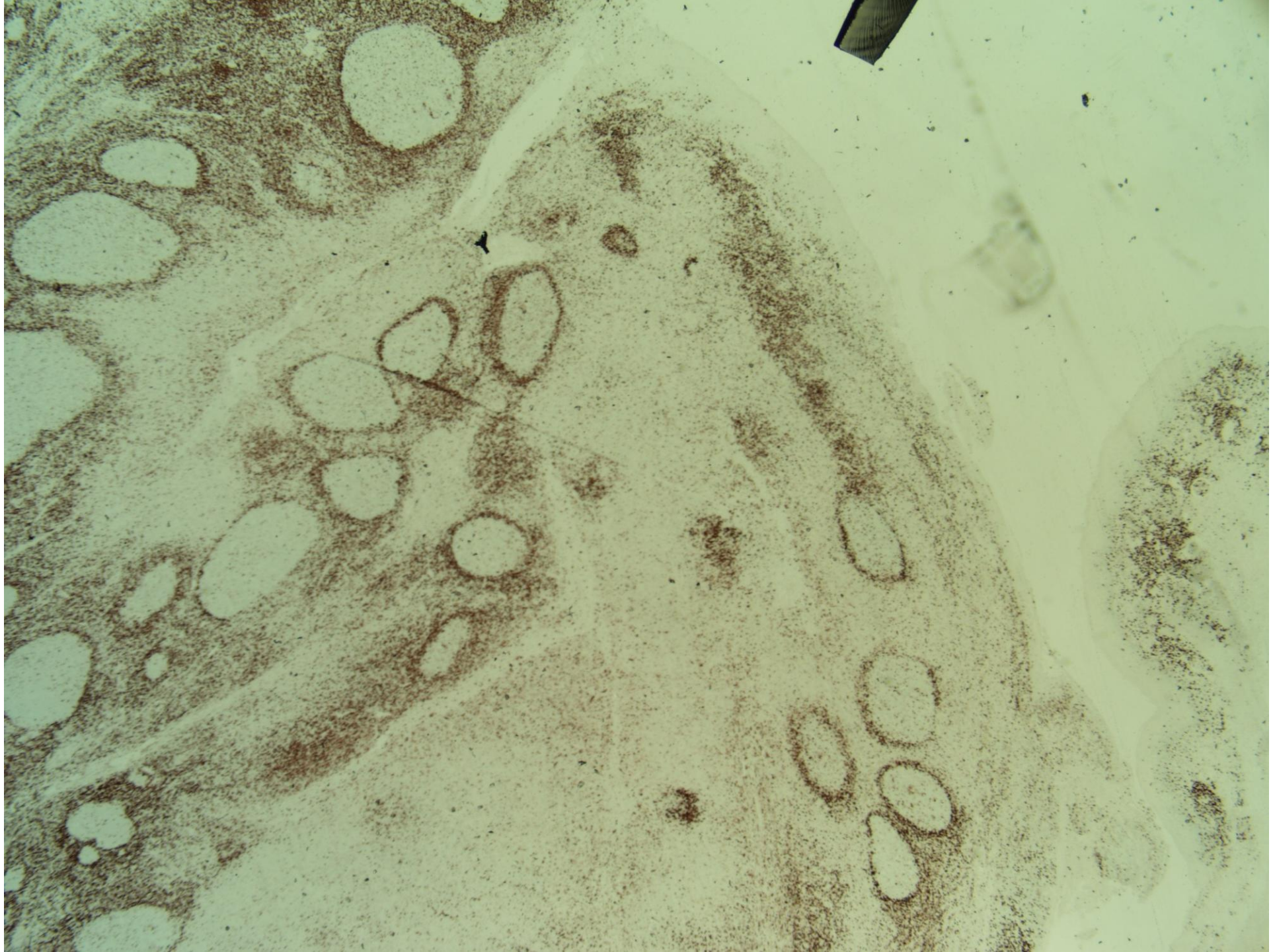




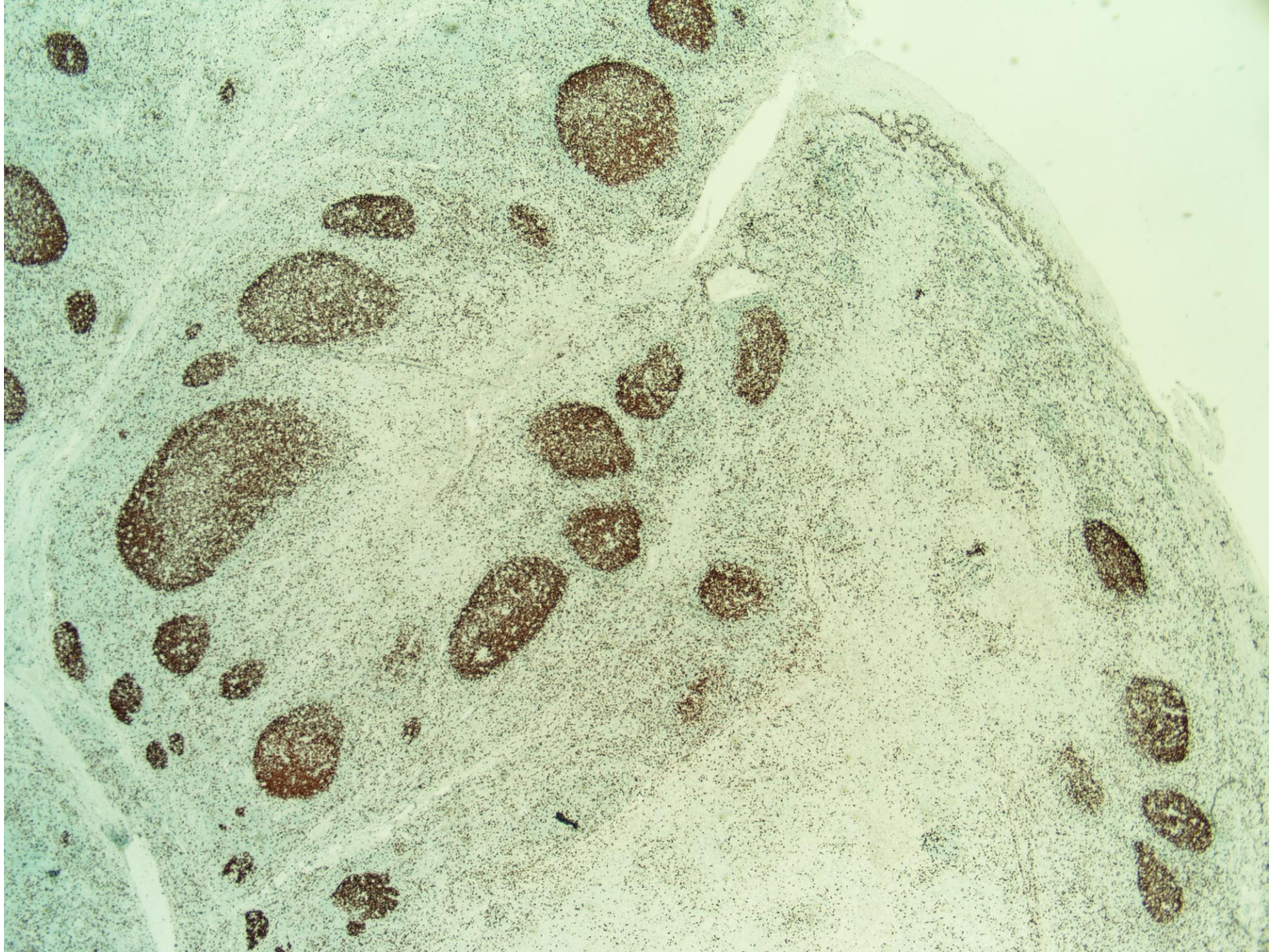
CD20



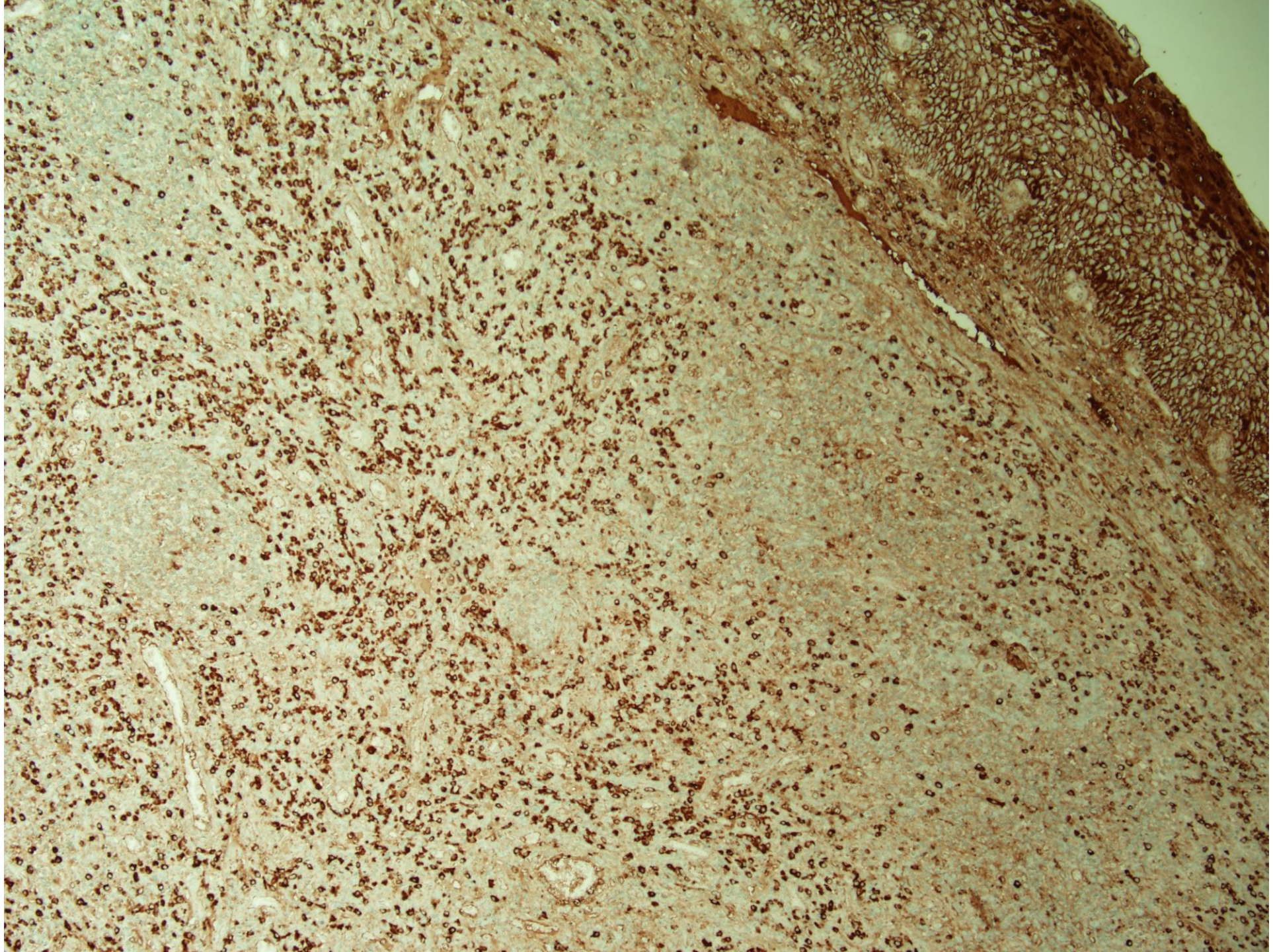
bcl-2



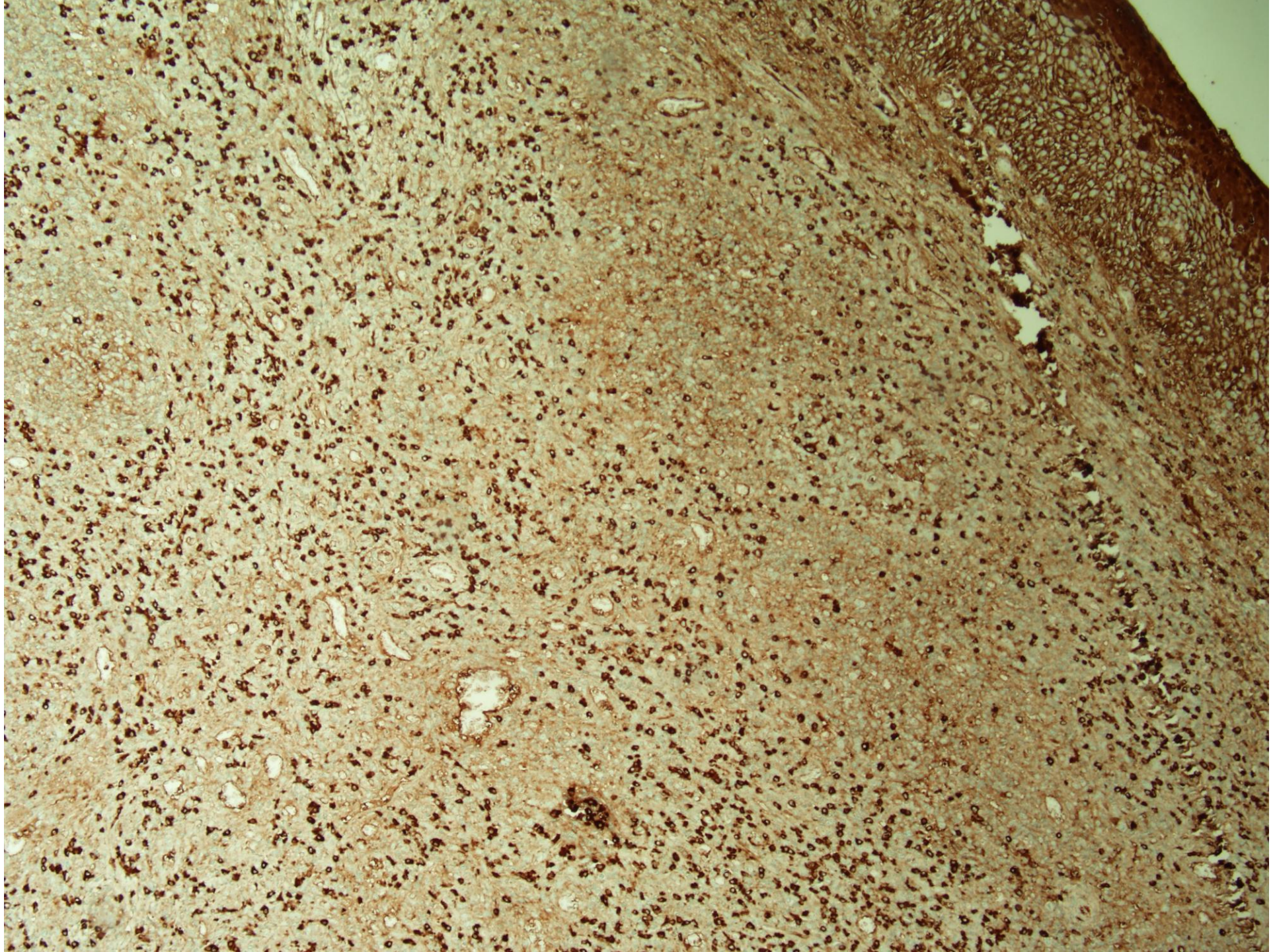
MIB1



kappa



lambda

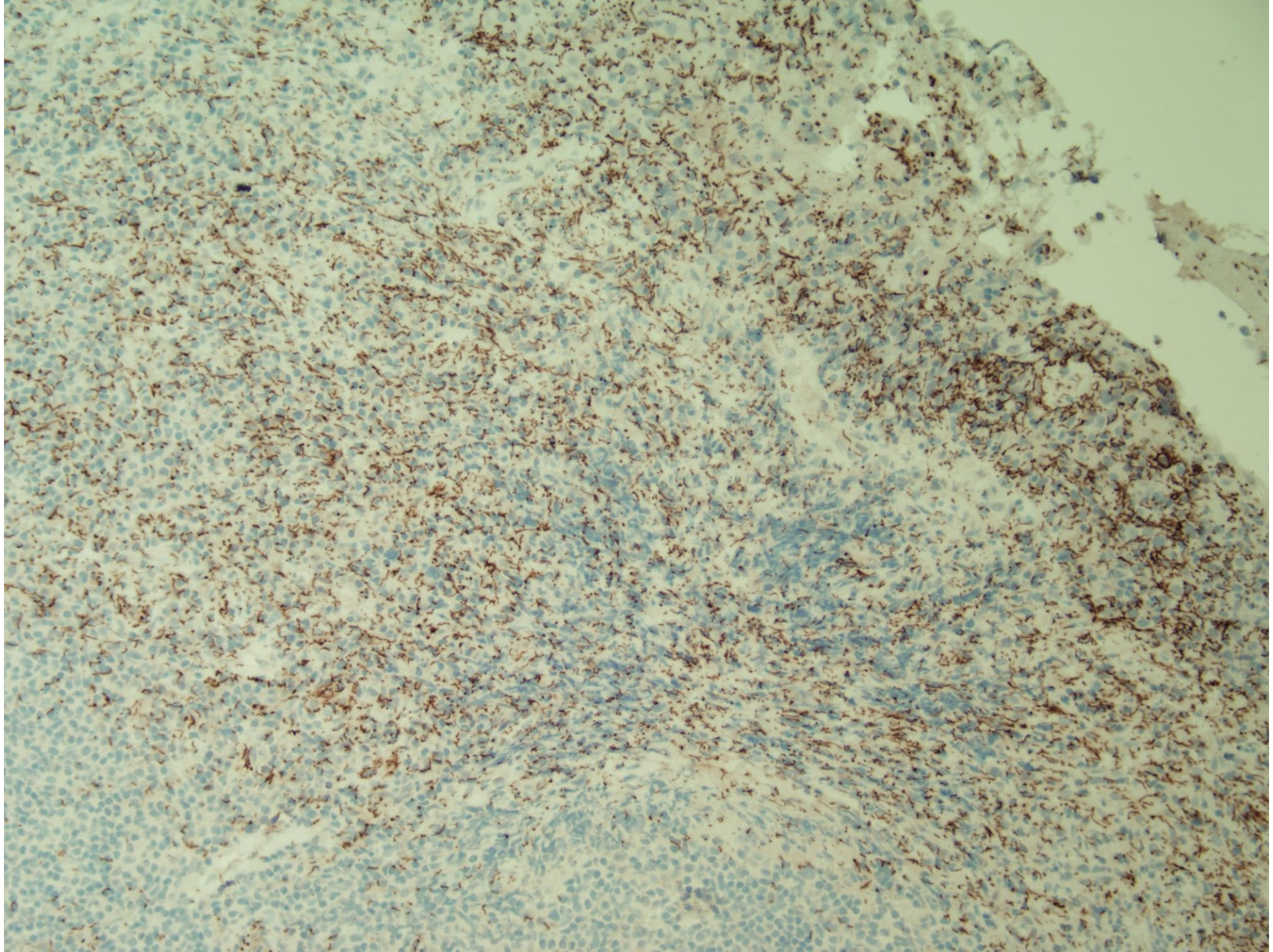


Plasma cells

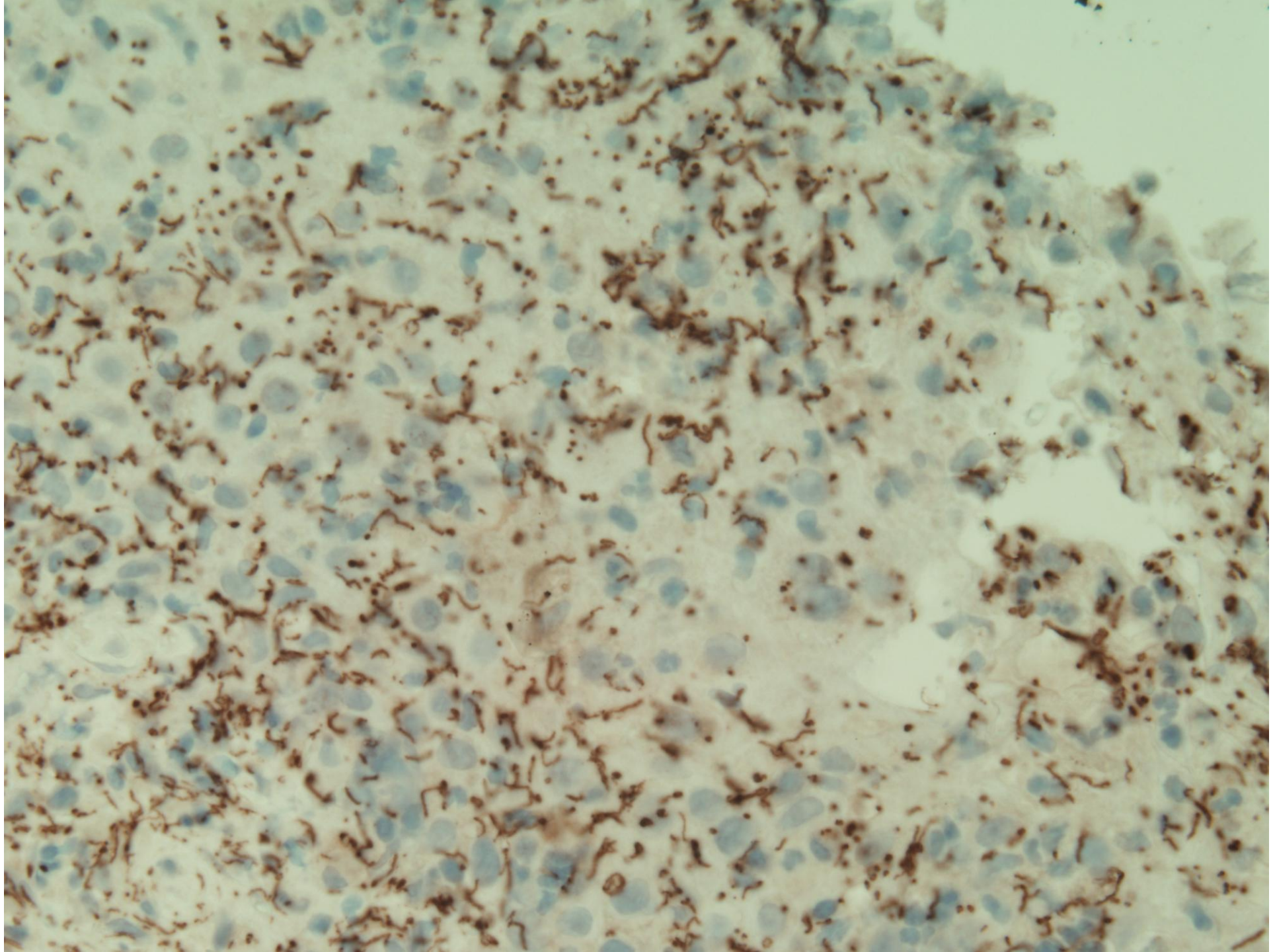
- Mature plasma cells (normal morphology)
- CD138+, CD19+, CD56-, cyclinD1- (normal immunoprofile) and **polytypic for light chains**

Diagnosis?

Treponema



Treponema



Syphilis

Sexually transmitted diseases

- 23.8% increase in STI diagnoses in 2022 compared to 2021 in UK
  - Chlamydia 24.3%
  - Gonorrhoea 50.3%
  - Syphilis 15.2%
- Most of the syphilis infections occurred in men who had sex with men
- Similar trends have emerged in US and Canada (figures for 2020-2021)
  - US rise of 28.6%
  - Canada rise of 20%
- The increases exceed the 13.4% rise in STI testing in 2022 compared to 2021

Syphilis

- Caused by spirochaete *Treponema pallidum*
- Obligate human pathogen (no known animal reservoir)
- Renowned for
  - Invasiveness
  - Immunoevasiveness
- Transmission occurs during sexual contact with an actively infected partner
  - Exudate containing as few as 10 organisms can cause disease
- Long generation time (30-33 hours)
  - Treatment requires long-acting penicillin

Syphilis

- Primary syphilis
  - Single ulcer (chancre) or multiple lesions on genitals or other body sites involved in sexual contact and regional lymphadenopathy
    - Develops about 3 weeks post infection
  - Spontaneous resolution

Syphilis

- Secondary syphilis
  - Develops 6-8 weeks later
  - Fever
  - Headache
  - Maculopapular rash
    - Flank
    - Shoulders
    - Arms
    - Chest
    - Back
    - Often involves palms of hands & soles of feet

Syphilis

- Latent phase
  - Develops as signs of secondary phase subside
    - May last many years
  - A patient in the first 1-2 years of latent phase is considered infectious due to a 25% risk of secondary syphilis-like relapses

Syphilis

- Tertiary syphilis
  - Develops in 15-40% of untreated individuals
  - Destructive cardiac or neurological conditions
  - Severe skin or visceral lesions (gummas)
  - Bony involvement

  - Possibly less common than is historically due to widespread use of antibiotics

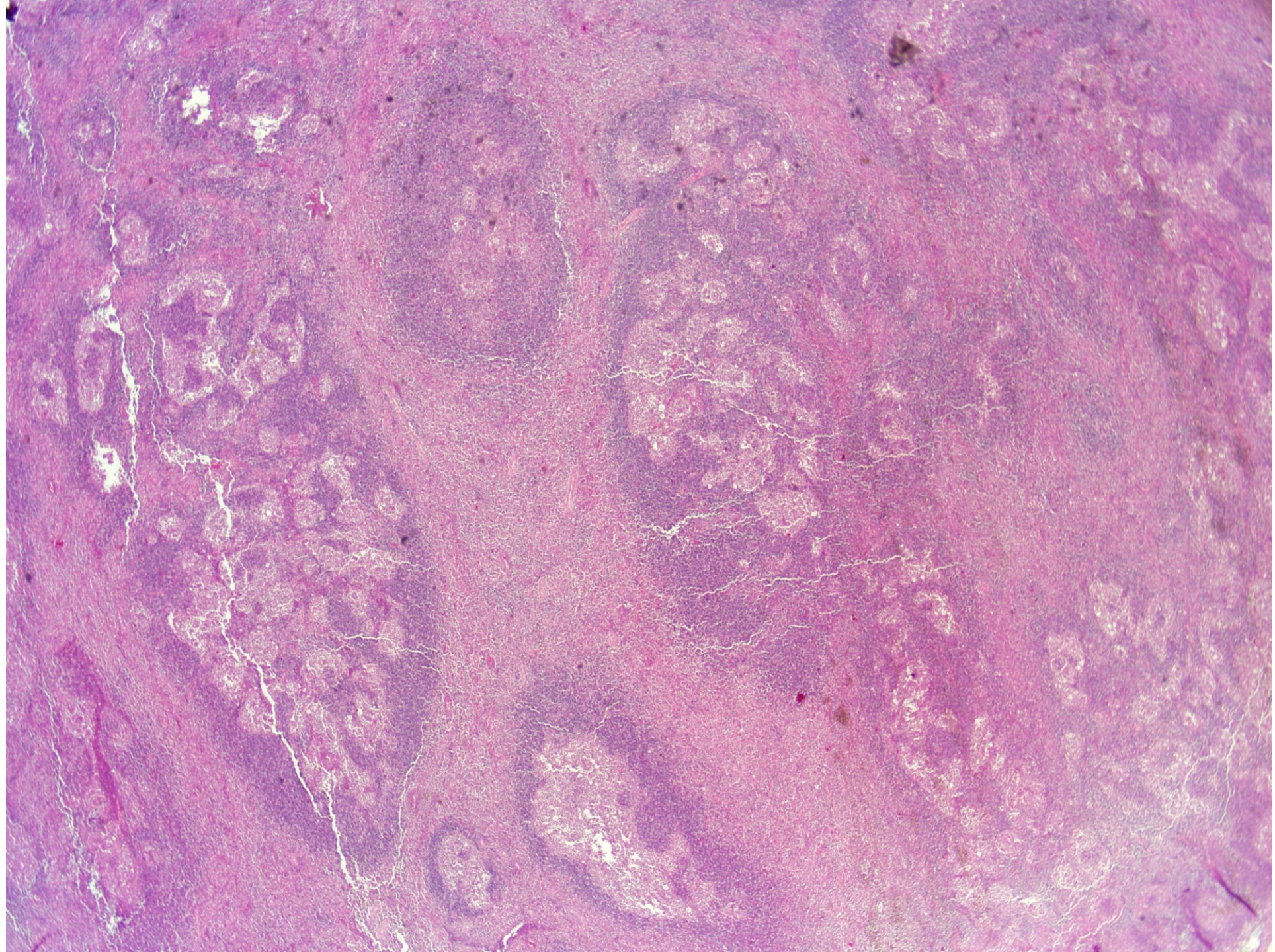
  - HIV infection predisposes to neuro-ophthalmological complications

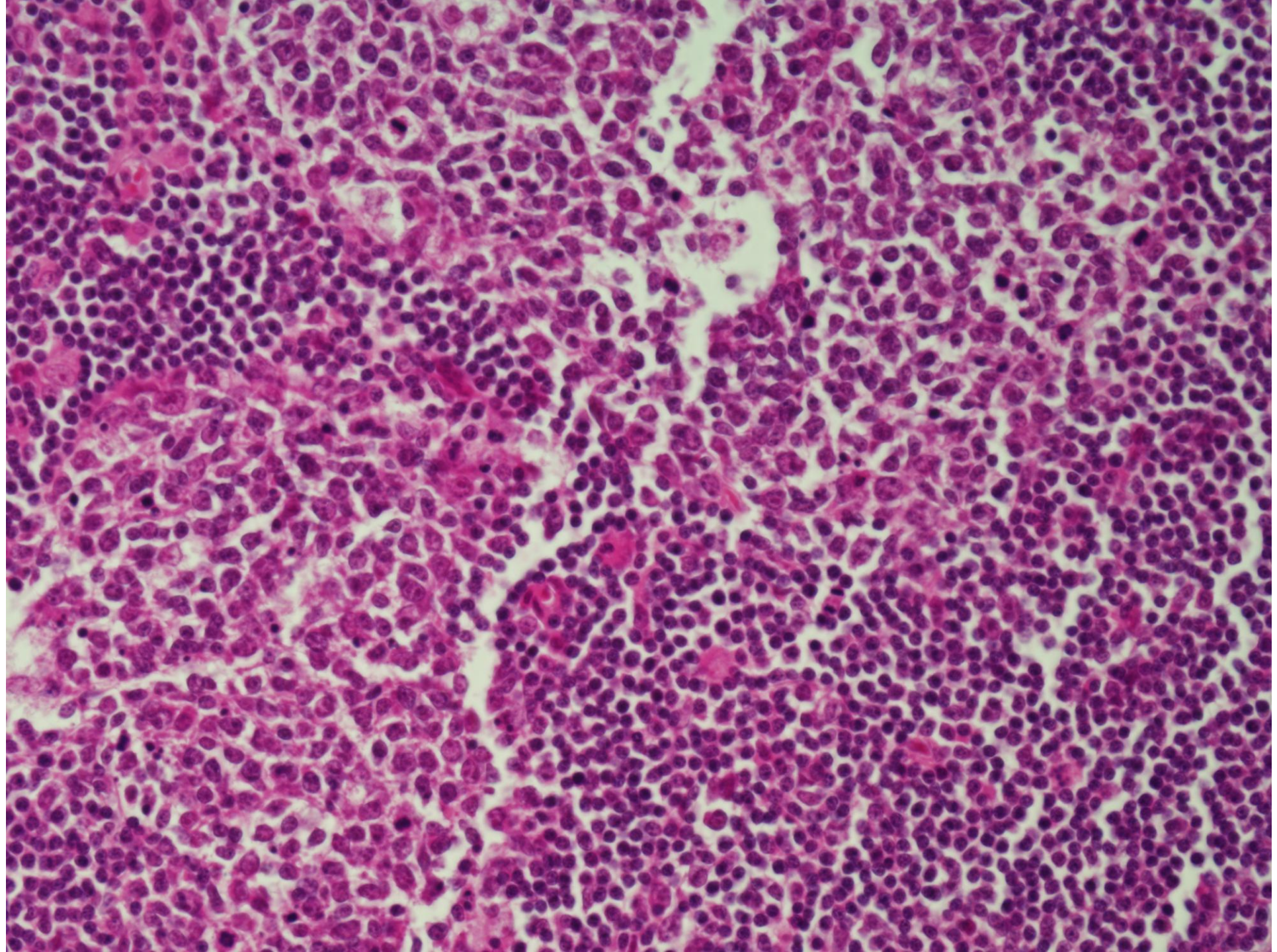
Case 4

18 year old male

Left level II lymph node

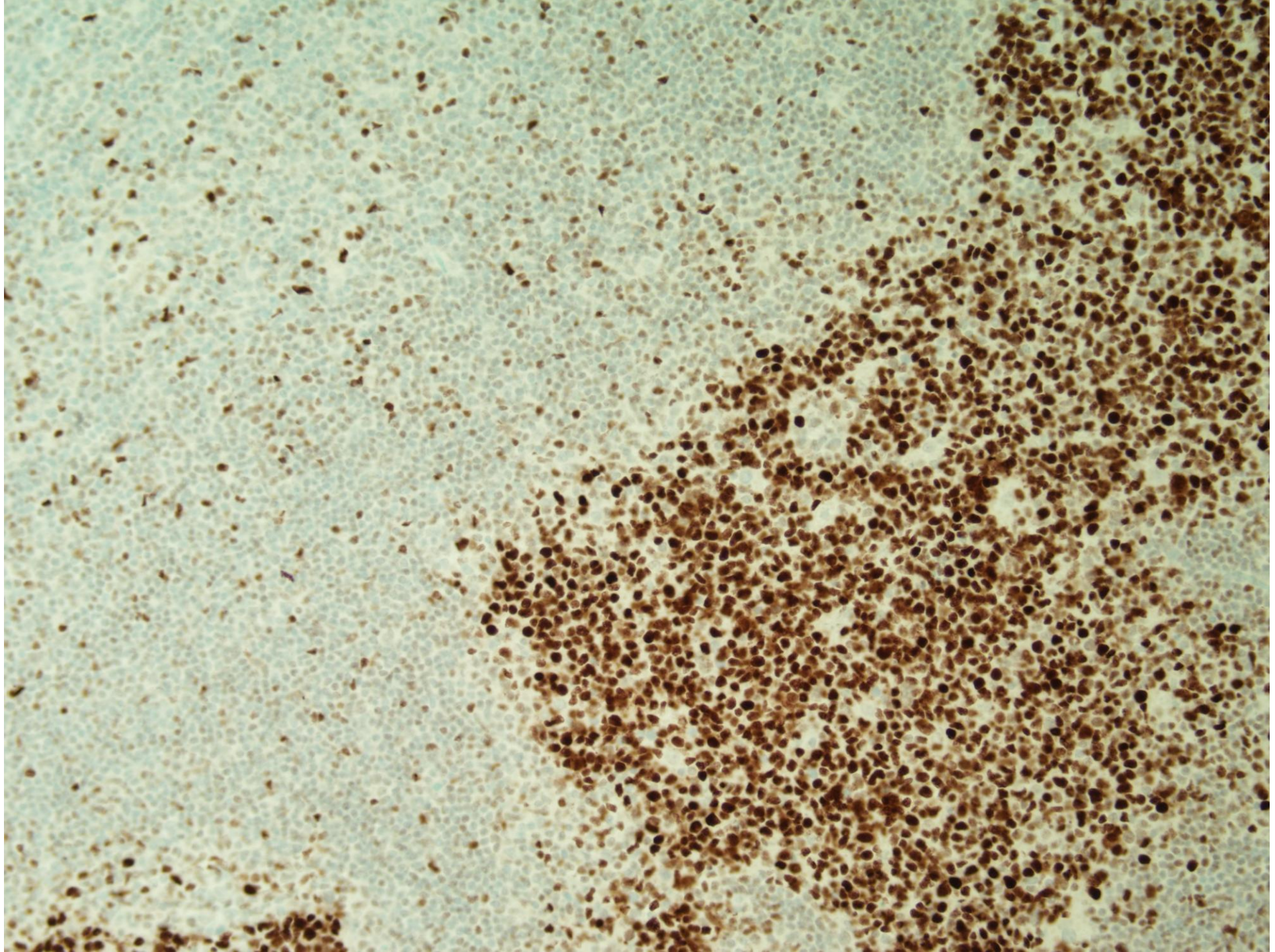
Cervical lymphadenopathy



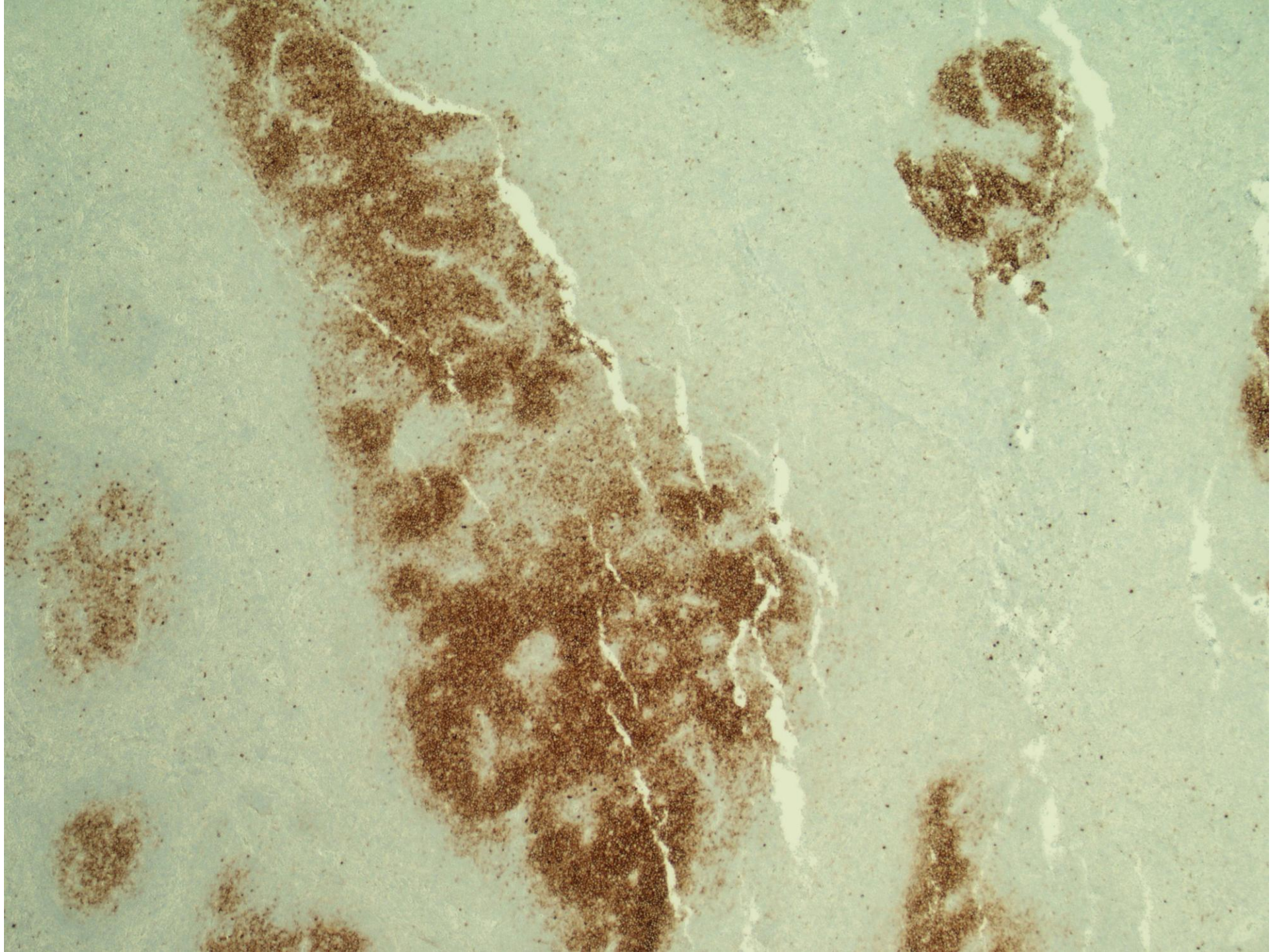


CD20

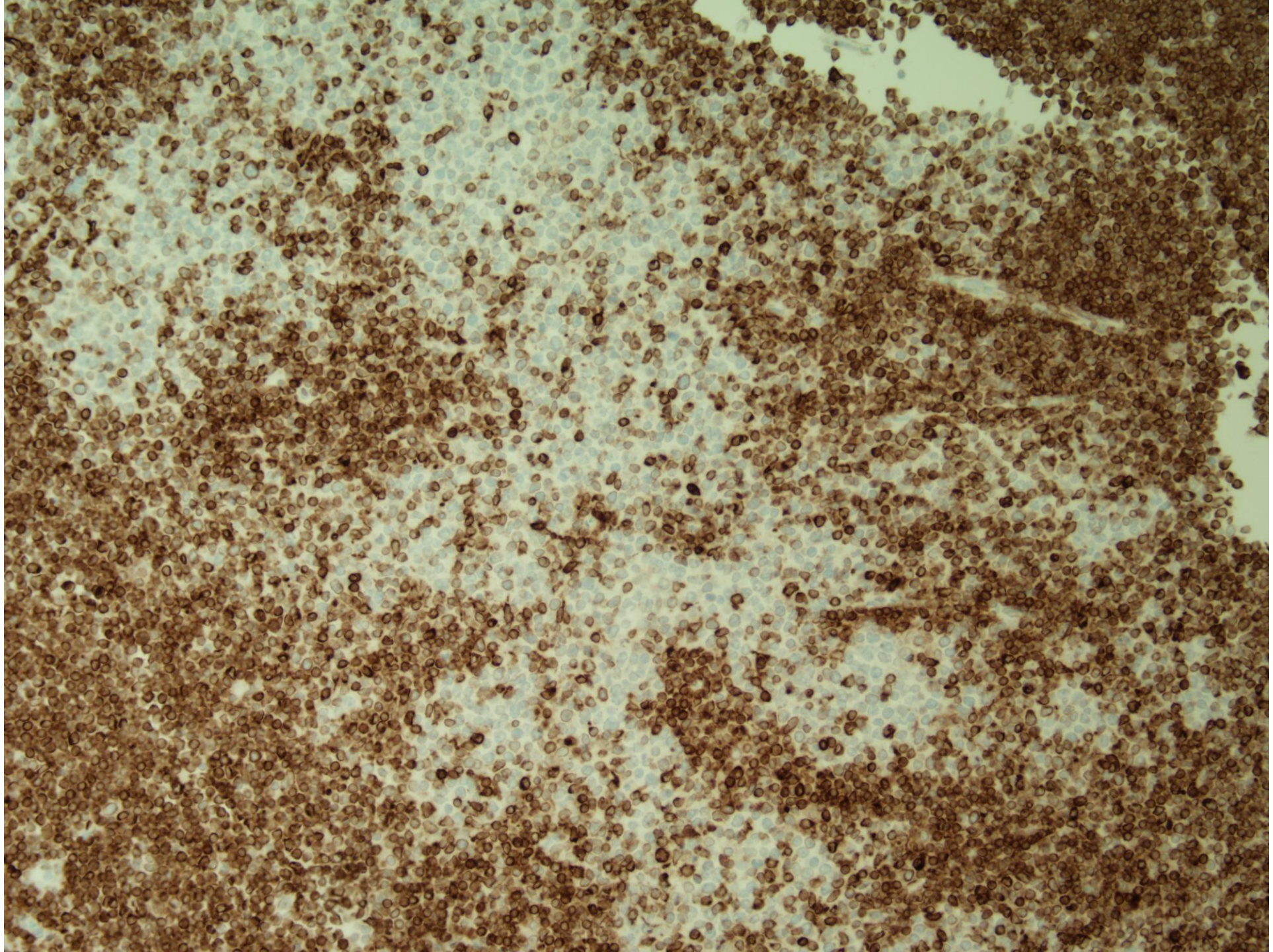
bcl-6



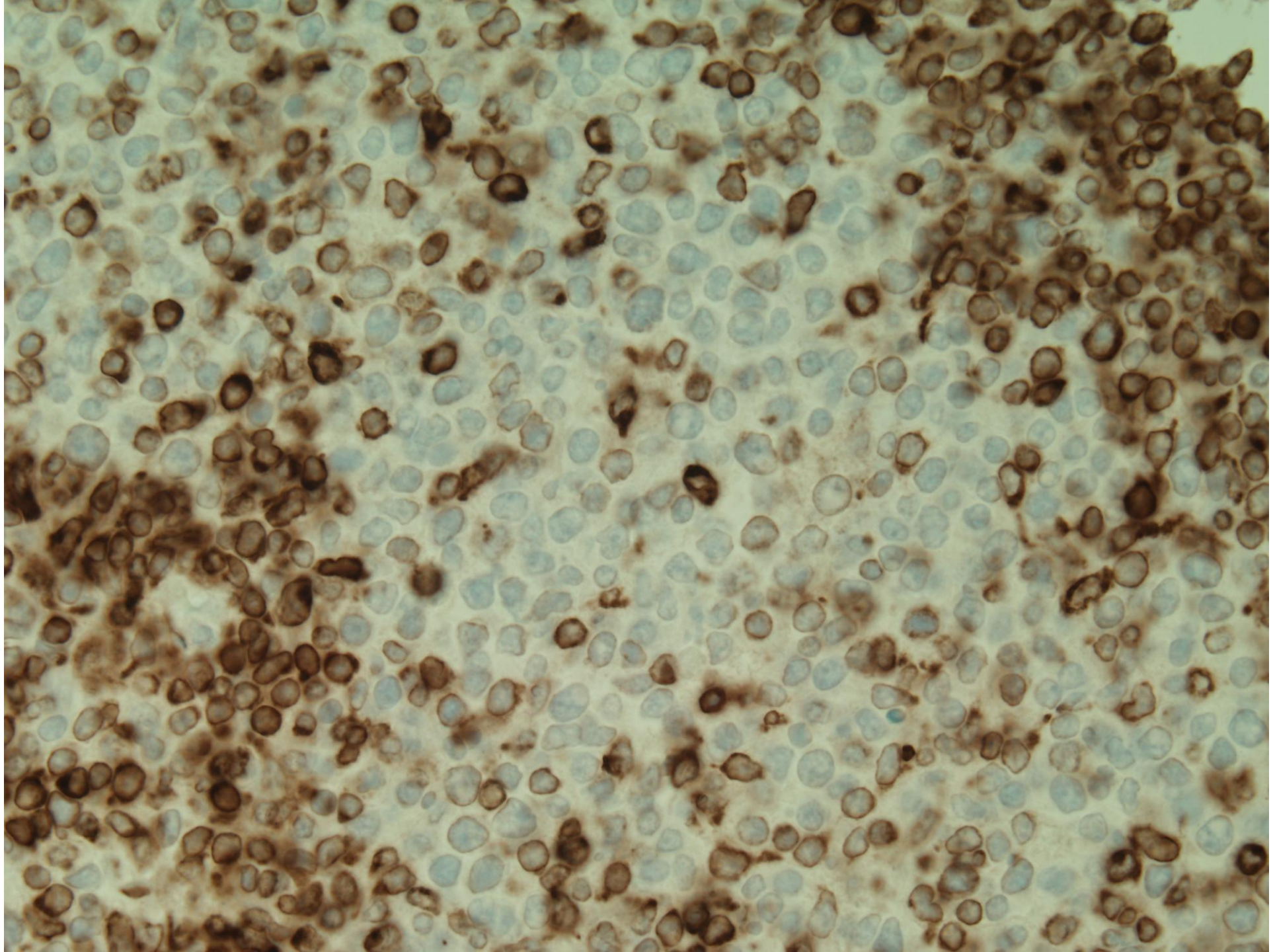
CD10



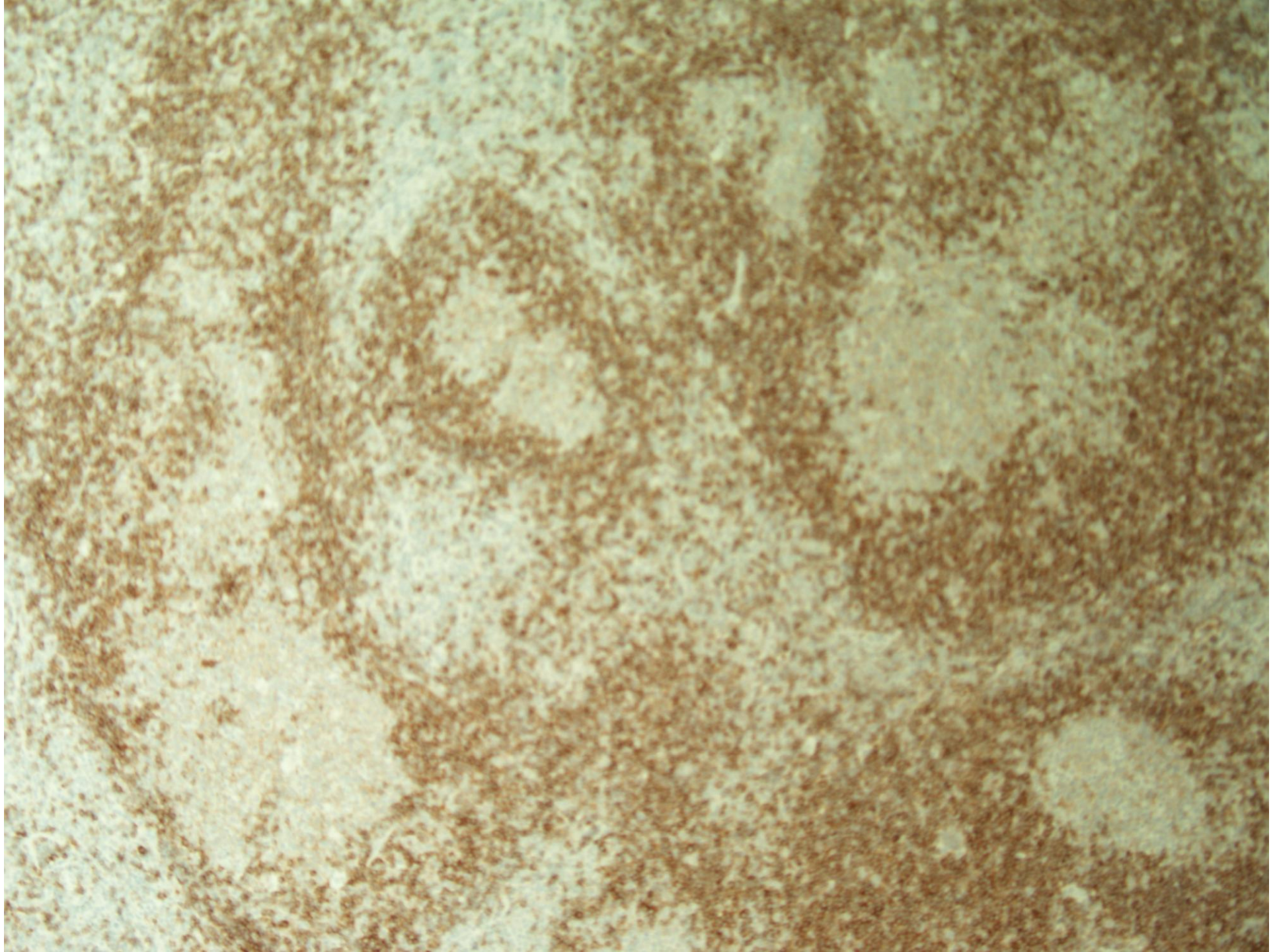
bcl-2



bcl-2



IgD



Diagnosis?

Paediatric-type follicular lymphoma

Paediatric-type follicular lymphoma

- 1-2% childhood lymphoma
- Predominantly paediatric/young adult (median age 15-18yrs)
- Marked male predominance (M:F > 10:1)
- Mostly single painless enlarged lymph node
  - Mostly head & neck region
  - Less commonly inguinal, femoral, axillary
  - Para-aortic and mesenteric involvement not reported
- No B symptoms

Paediatric-type follicular lymphoma

- Purely follicular growth pattern
- May be marginal zone differentiation
- Often residual normal lymph node architecture at the periphery (node within node)
- Follicles often consist of monotonous population of intermediate-sized blastoid cells
- Tingible body macrophages absent

Paediatric-type follicular lymphoma

- Immunophenotype:
  - B cell markers positive (CD20, CD79a, PAX5)
  - Germinal centre markers (bcl-6, CD10 [strong])
  - FDC meshworks (relative absence of cells in interfollicular areas)
  - Negative (or very weak) expression of bcl-2 protein
  - MUM1 negative
  - Proliferation intermediate to high (>30%). No polarity

Paediatric-type follicular lymphoma

- Low genetic complexity
- Absence of BCL2, BCL6, IRF4 rearrangements
- Mutations in epigenetic modifiers (EP300, CREBBP, EZH2, KMT2D, ARID1A) rare
- Deletion 1p34
- TNFSF14
  - Deletion in 25-40%
  - Mutation in 44-54%
- MAP2K1 mutation in 43-49%

Paediatric-type follicular lymphoma

Differential diagnosis

- Paediatric nodal marginal zone lymphoma
  - Absence of germinal centres with features similar to those seen in progressive transformation of germinal centres in PNMZL
  - Absent interfollicular proliferation
  - Diminished number of PD1+ cells in germinal centres
- Florid follicular hyperplasia
- Classic follicular lymphoma

Paediatric nodal marginal zone lymphoma

- Rare - <2% childhood lymphomas
- Mostly head & neck region
- Often low stage
- Predominance in young males

Paediatric nodal marginal zone lymphoma

- Inter-follicular proliferation of cells with marginal zone morphology
- Follicles enlarged with disrupted FDC meshworks and follicle centres resembling PTGC
- Plasmacytoid differentiation may be observed

- Immunophenotype
  - May be positive for CD43
  - Typically negative for CD10 and bcl-6

A unifying hypothesis for PNMZL and PTFL: morphological variants with a common molecular profile

Julia Salmeron-Villalobos,[1,2,*] Caoimhe Egan,[3,*] Vanessa Borgmann,[4,*] Inga Müller,[4] Blanca Gonzalez-Farre,[1,2] Joan Enric Ramis-Zaldivar,[1,2] Dominik Nann,[4] Olga Balagué,[1,2] Mónica López-Guerra,[1,2] Dolors Colomer,[1,2] Ilske Oschlies,[5] Wolfram Klapper,[5] Selina Glaser,[6] Young Hyeh Ko,[7] Irina Bonzheim,[4] Reiner Siebert,[6] Falko Fend,[4] Stefania Pittaluga,[3] Elias Campo,[1,2] Itziar Salaverria,[1,2,†] Elaine S. Jaffe,[3,†] and Leticia Quintanilla-Martinez[4,8,†]

45 cases of PNMZL

- 14 (31%) classified as PNMZL
- 31 (69%) had overlapping features between PNMZL and PTFL
  - Minor component of residual serpiginous germinal centres – PTFL
  - Dominant inter-follicular component - PNMZL

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45 cases of PNMZL

- All had low genetic complexity
- Recurrent 1p36/TNFRSF14 copy number-neutral loss of heterozygosity alterations and copy number loss (11%)
- Mutations similar to PTFL
  - MAP2K1 (42%)
  - TNFRSF14 (36%)
  - IRF8 (34%)
- No major differences in DNA methylation

A unifying hypothesis for PNMZL and PTFL: morphological variants with a common molecular profile

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Suggested term

Paediatric type follicular lymphoma with or without marginal zone differentiation

Follicular Lymphomas in children and young adults: A comparison of the pediatric variant with usual follicular lymphoma

Qingyan Liu, MD[1], Itziar Salaverria, PhD[#,2], Stefania Pittaluga, MD, PhD[1], Armin G. Jegalian, MD, PhD[*,1], Liqiang Xi, MD[1], Reiner Siebert, MD[2], Mark Raffeld, MD[1], Stephen M. Hewitt, MD, PhD[1], and Elaine S. Jaffe, MD[1]

- PFL
  - Blastoid morphology
  - High proliferation
  - Lack of bcl-2 protein expression
  - Lack t(14;18)
- UFL
  - Most grade 1-2
  - Most express bcl-2 protein (83%)
  - Lack t(14;18)

Paediatric-type follicular lymphoma

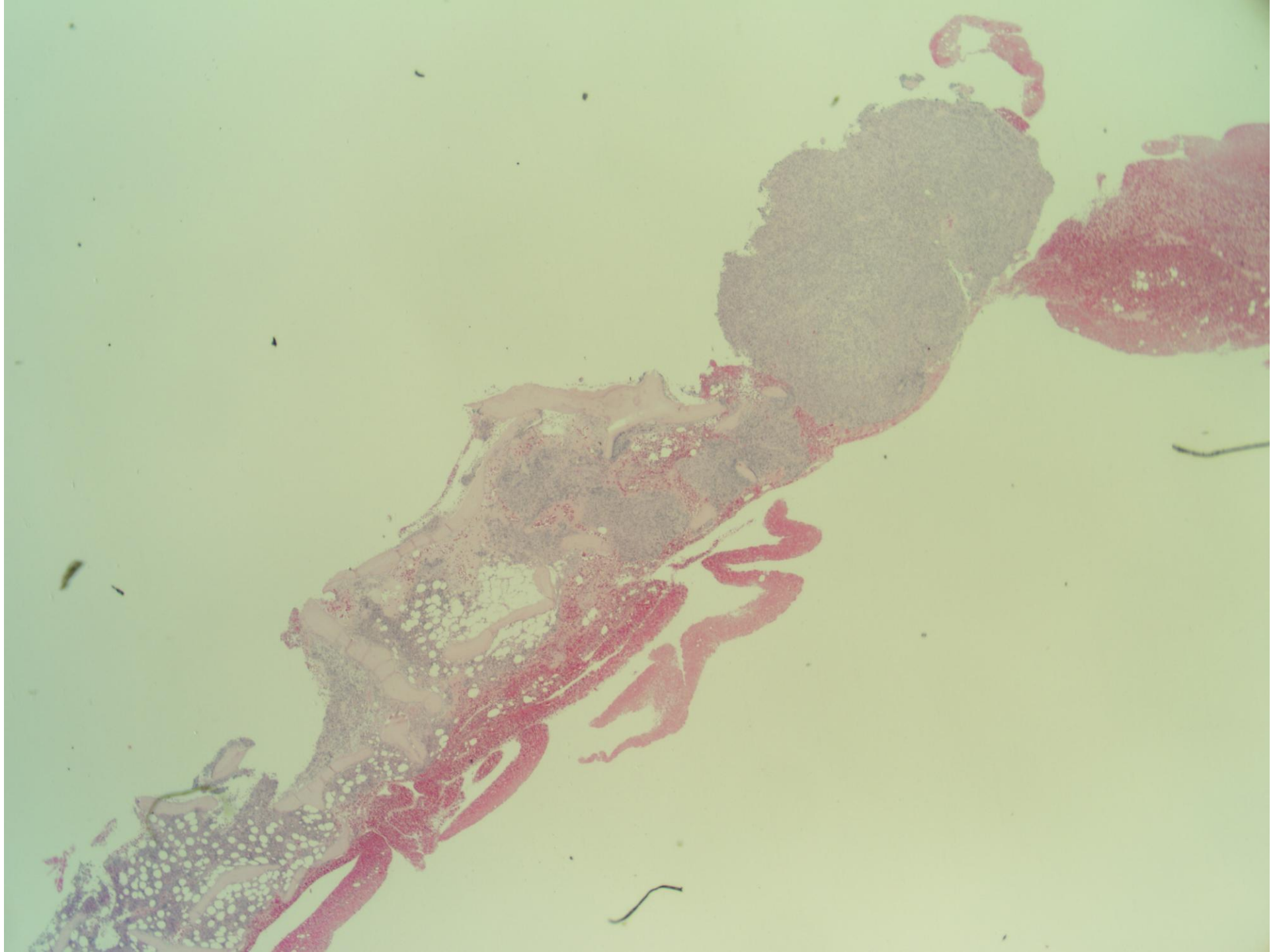
- 1-2% childhood lymphoma
- Predominantly paediatric/young adult (median age 15-18yrs)
- Marked male predominance (M:F > 10:1)
- Mostly single painless enlarged lymph node
  - Mostly head % neck region
  - Less commonly inguinal, femoral, axillary
  - Para-aortic and mesenteric involvement not reported
- No B symptoms
- Excellent prognosis
  - Survival rates 95%
  - Watch & wait after complete excision considered adequate

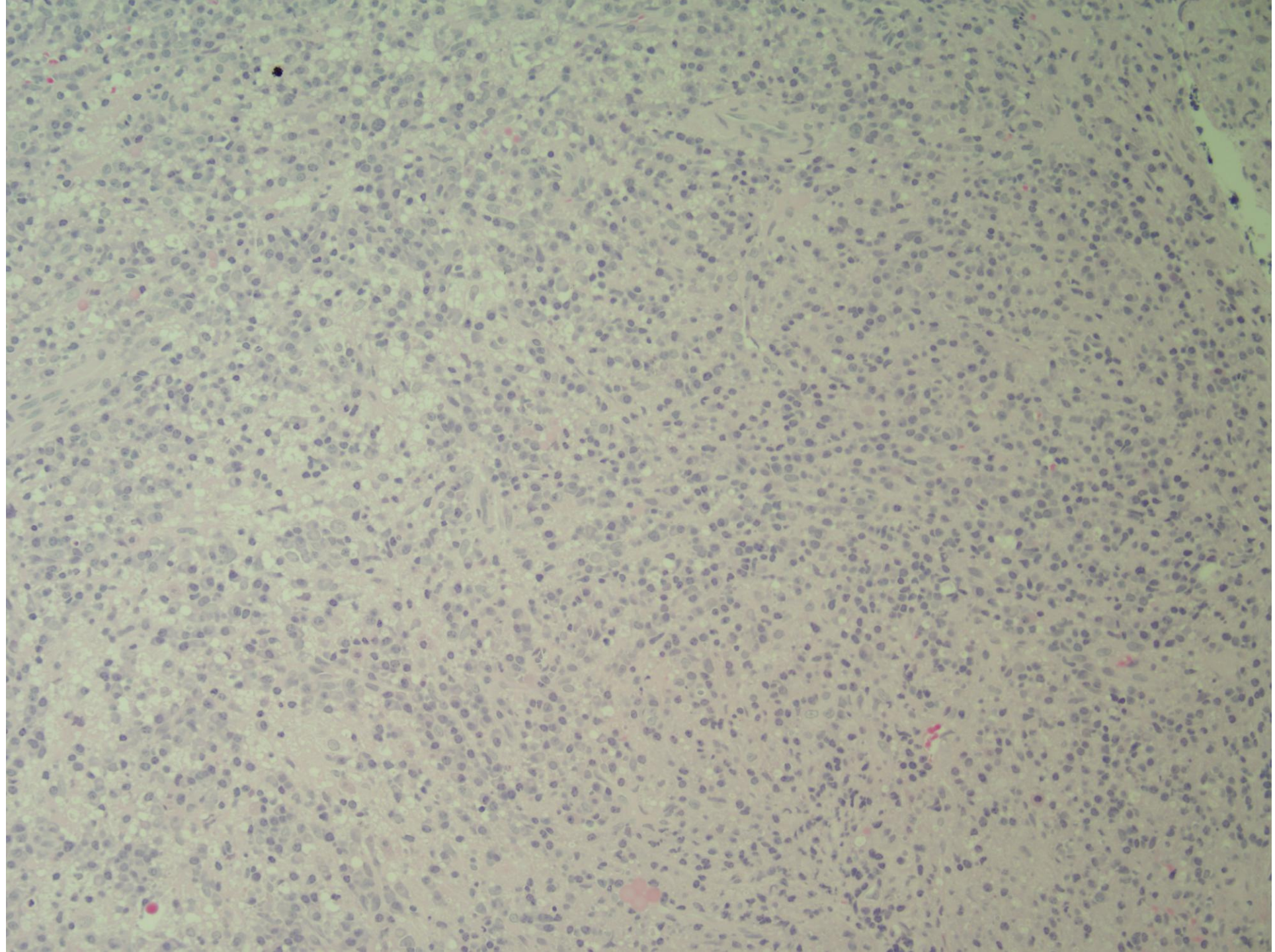
Case 5

69 year old male

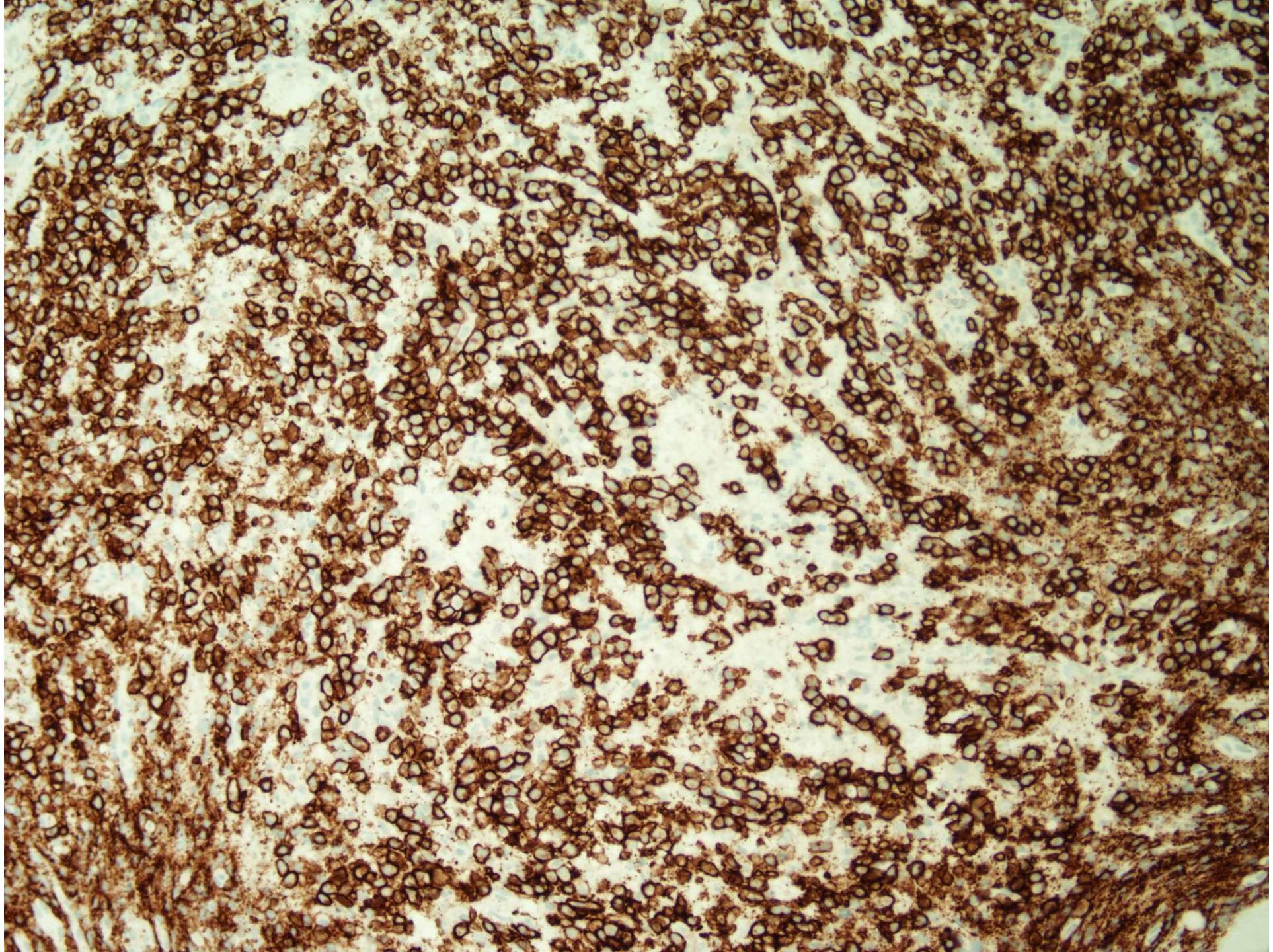
Bone marrow

Anaemia and weight loss

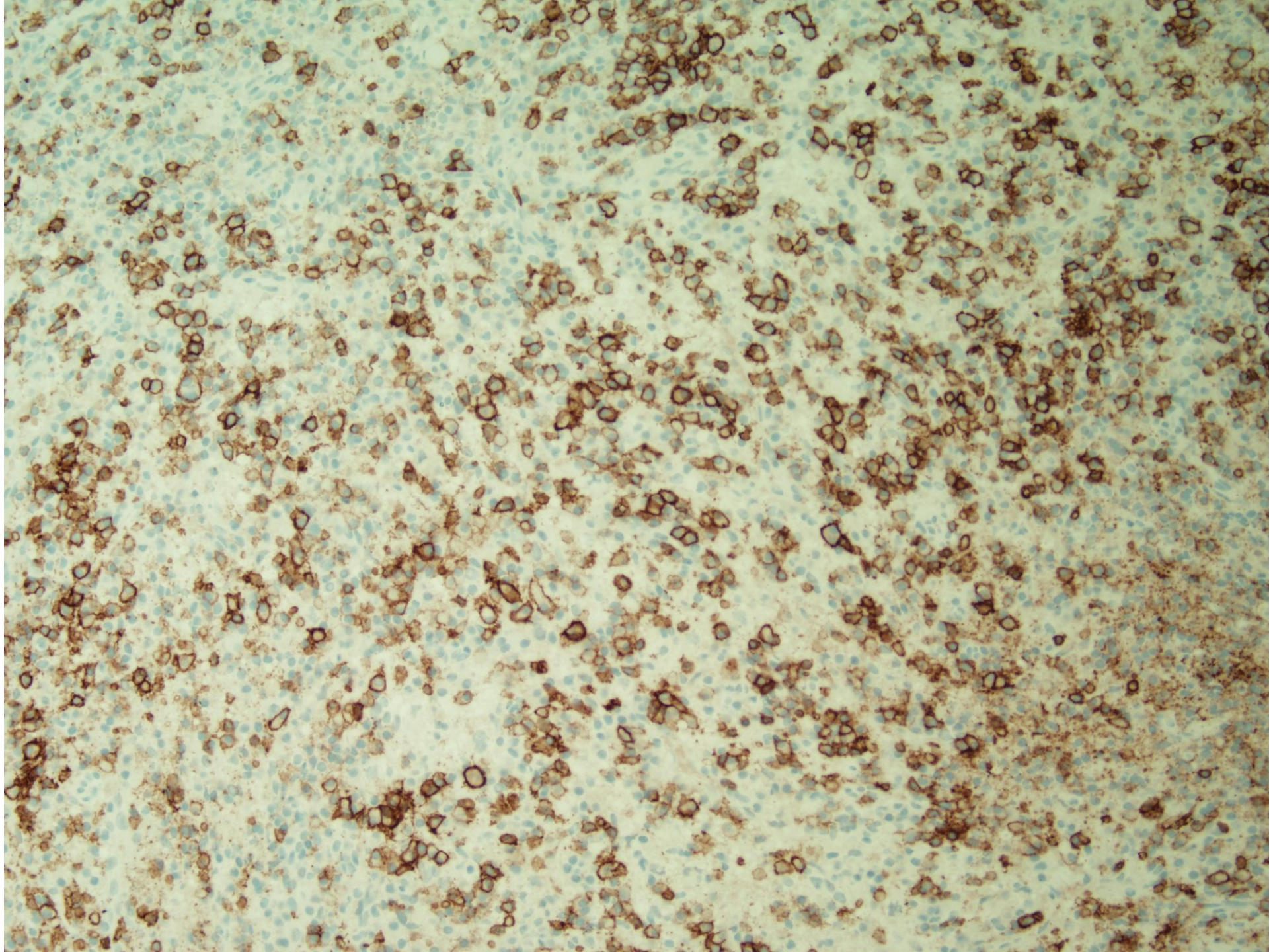




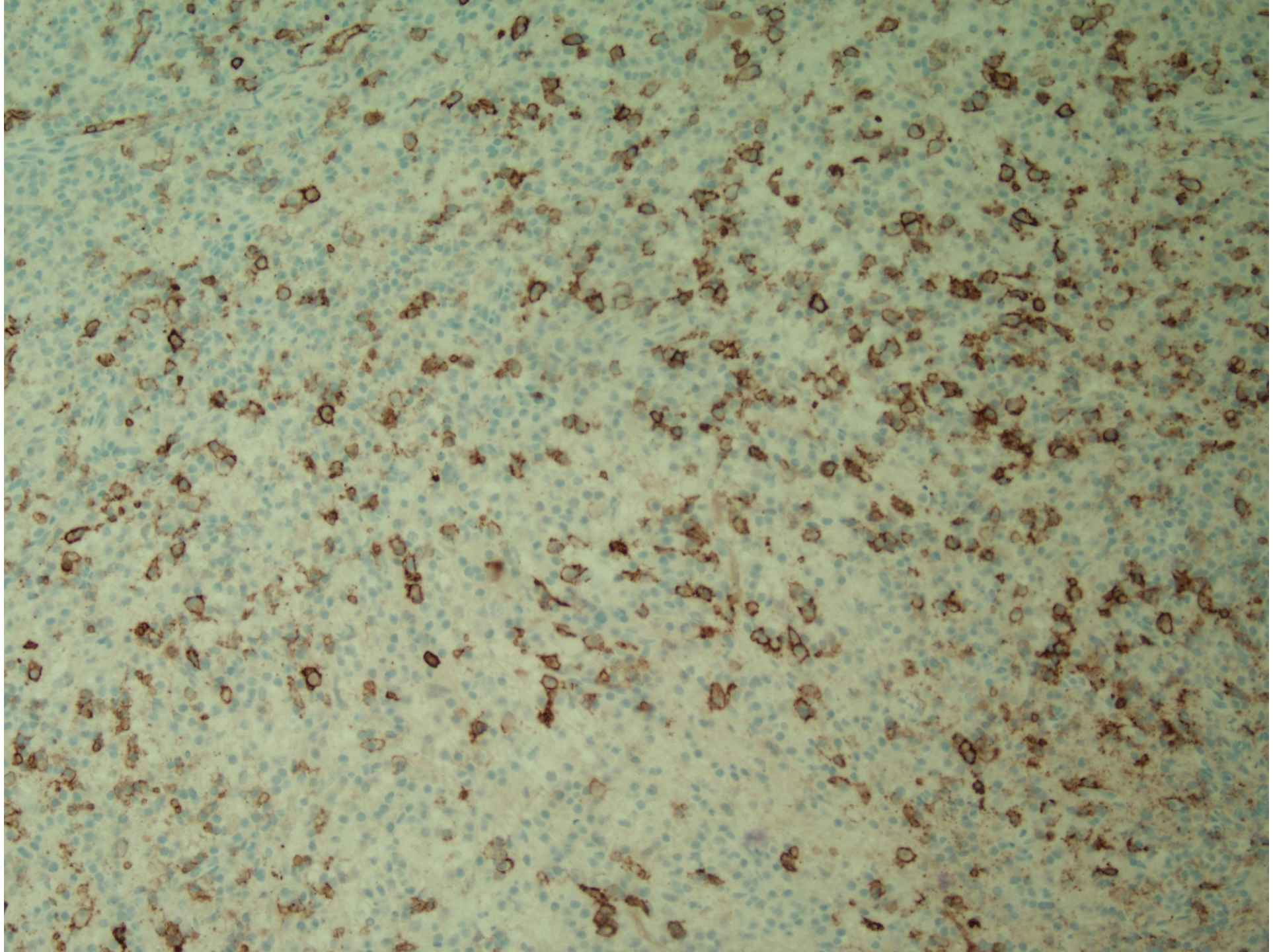
CD138



CD19



CD56



CyclinD1

Light chain staining polytypic

Molecular studies showed no clonal B cell population

No mutations detected by NGS

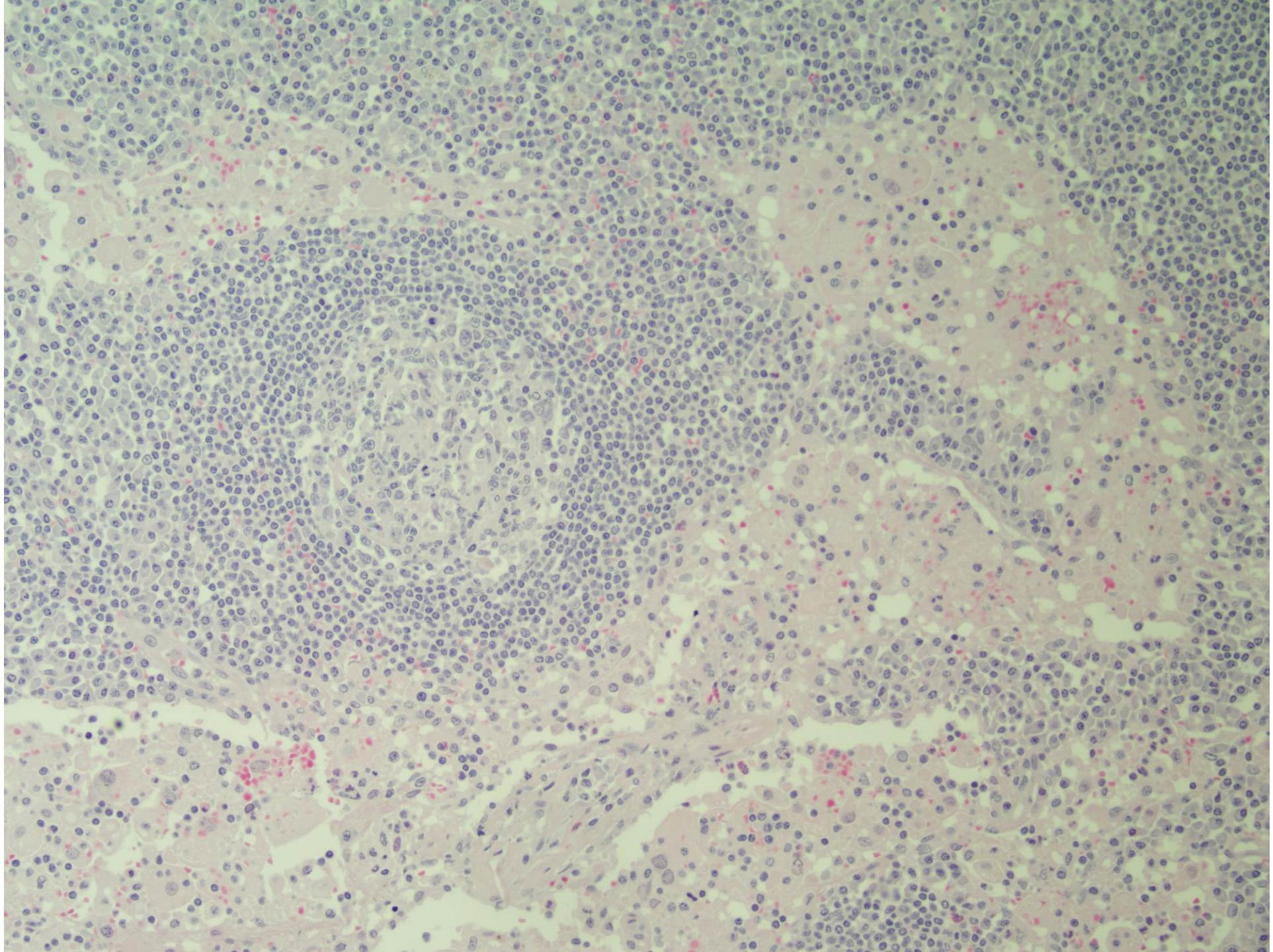
Diagnosis?

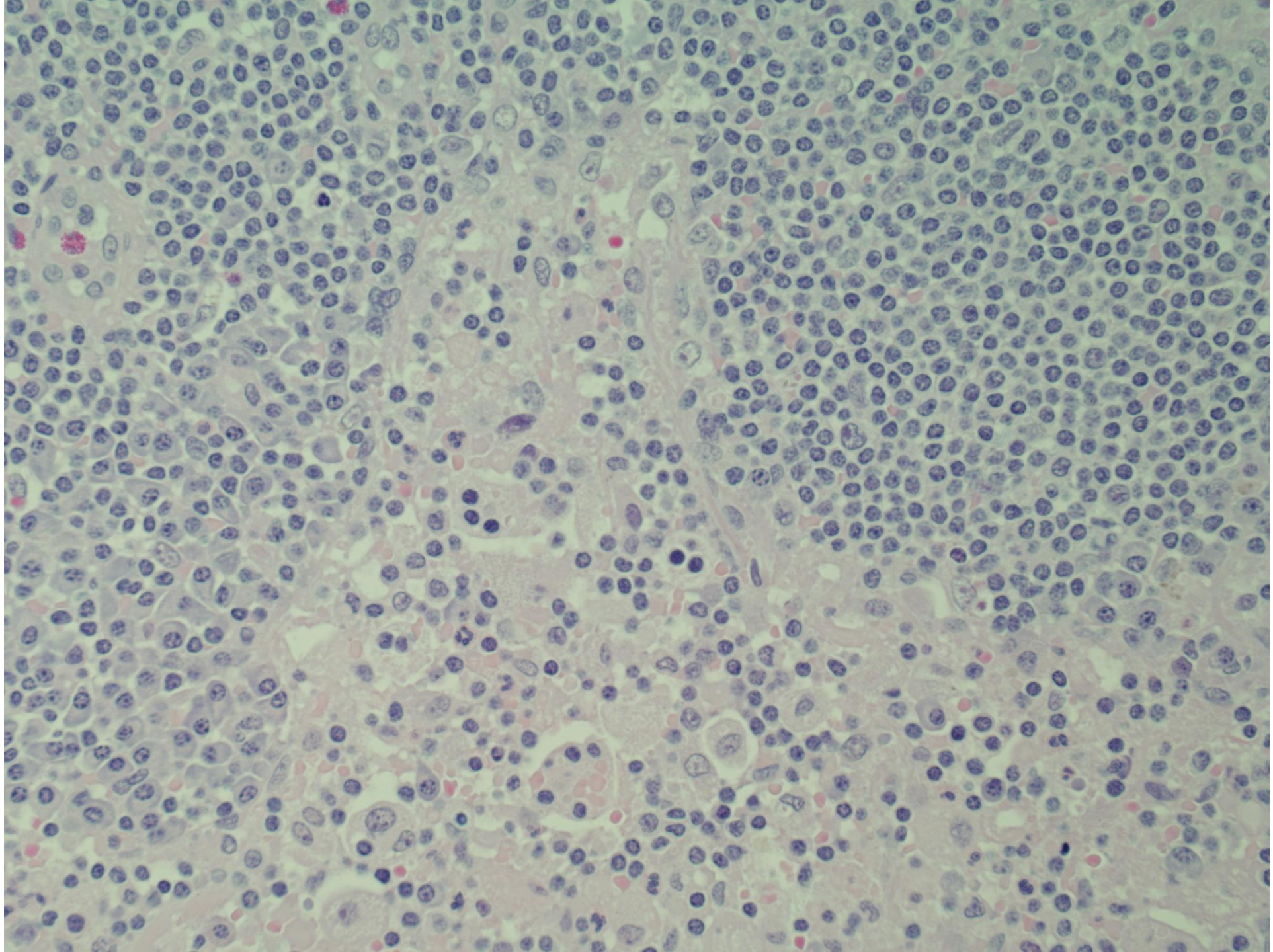
No idea!

69 year old

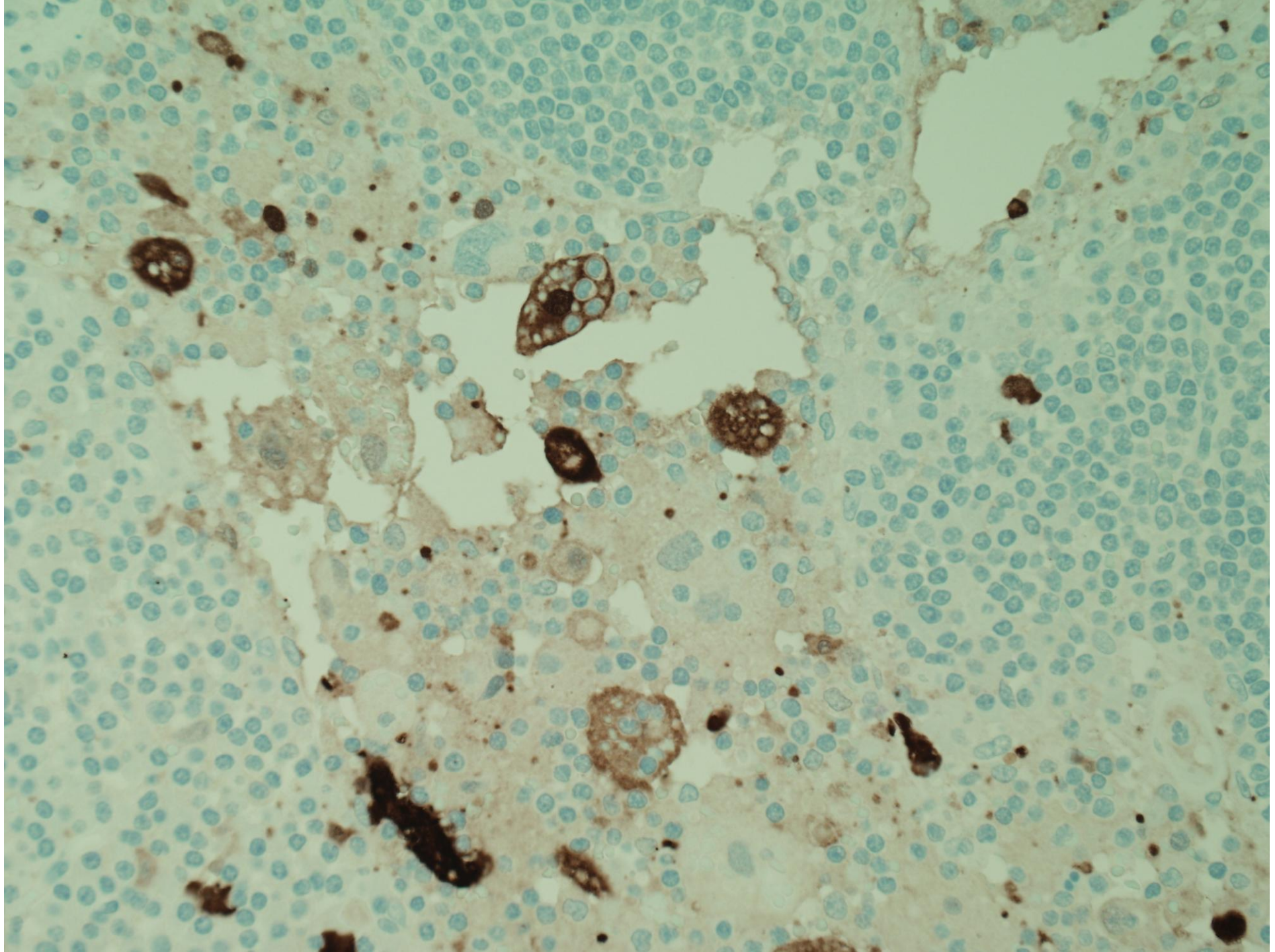
Male

- Bone marrow
- Anaemia and weight loss
- Axillary lymphadenopathy

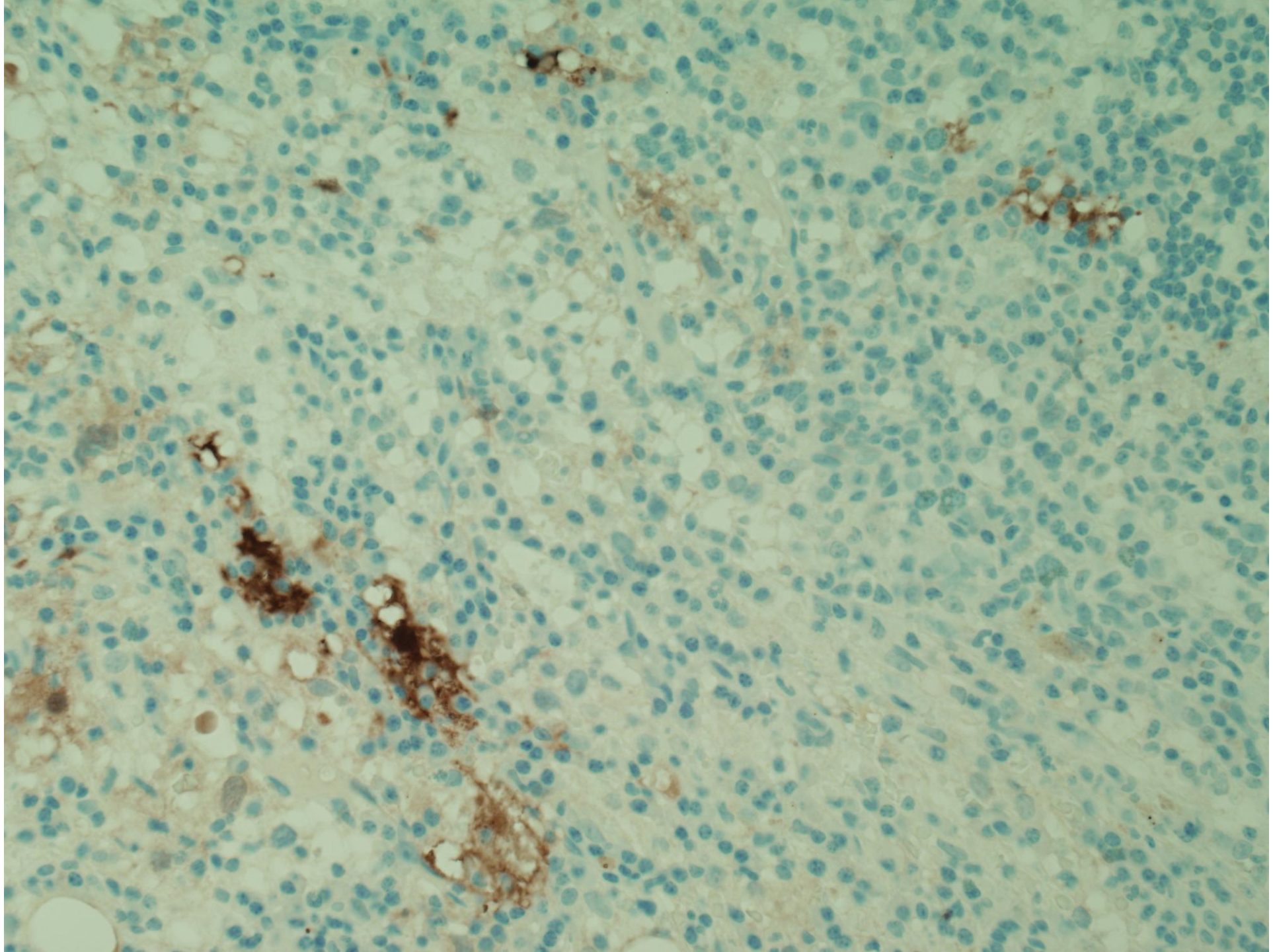




S100



S100



Rosai-Dorfman disease

Rosai-Dorfman Disease

- First described in by Destombes (1965) and later by Rosai and Dorfman (1969) as sinus histiocytosis with massive lymphadenopathy.
- Non-Langerhans cell histiocytosis
- Forms part of the ‘R group’ of histiocytoses
- Cutaneous RDD classified separately as part of the ‘C group’ of histiocytoses

Working Group of the Histiocyte Society

Rosai-Dorfman Disease

- Usually presents with massive bilateral cervical lymphadenopathy
  - Fever
  - Weight loss
  - Night sweats
- Predominantly children/young adults
- More often in African patients
- Slight male predominance

Rosai-Dorfman Disease

- Sporadic (non-cutaneous)
  - Classic nodal
  - Extranodal (bone, single organ, disseminated)
  - Neoplasia associated (Leukaemia, lymphoma, malignant histiocytosis, LCH, Erdheim-Chester disease)
  - Autoimmune disease associated (SLE, idiopathic juvenile arthritis, autoimmune haemolytic anaemia, HIV)
- Familial
  - H syndrome
  - Autoimmune lymphoproliferative syndrome (ALPS)
- Cutaneous

Working Group of the Histiocyte Society

Rosai-Dorfman Disease

- Extranodal disease in 40% (rare in absence of nodal disease)
  - Skin
  - Nasal cavity
  - Bone
  - Orbital region
  - CNS
- Extranodal disease in absence of nodal disease more common in elderly and with a different demographic

Rosai-Dorfman Disease

- Lesional cells have characteristic immunophenotype
  - S100, CD68, fascin - positive
  - CD163, CD14 - variable
  - CD1a - negative
- Mutations seen in
  - ARAF
  - MAP2K1
  - NRAS
  - KRAS
- Mutations in BRAF (V600E) generally absent although occasional cases reported

CD71 expression in Rosai–Dorfman disease: a useful adjunct marker in the differential diagnosis of histiocytic proliferations

Nurfiza N Ladak,[1,2] Kseniya Petrova-Drus,[1] Meera R Hameed,[1] Ahmet Dogan,[1] Eli L Diamond[3] & Mariko Yabe[1]

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Thank you