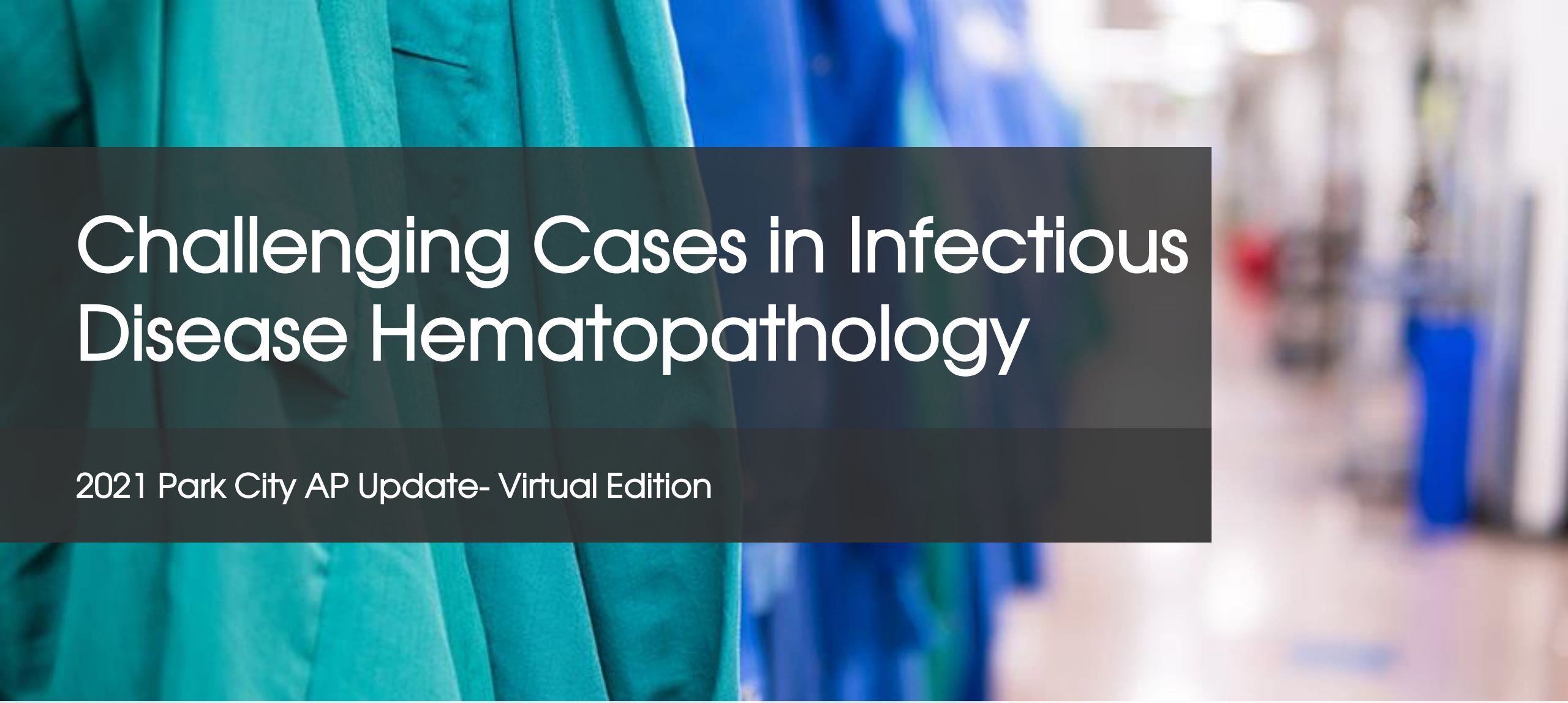

Challenging Cases in Infectious Disease Hematopathology

2021 Park City AP Update- Virtual Edition

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Agenda

- For a brief review of patterns of reactive lymphadenopathy- see Dr. Rets' presentation (not repeated here)
- Case 1
- Case 2
- Case 3
- Case 4
- Bonus Mini-Case!
- Conclusion and Take Home Points

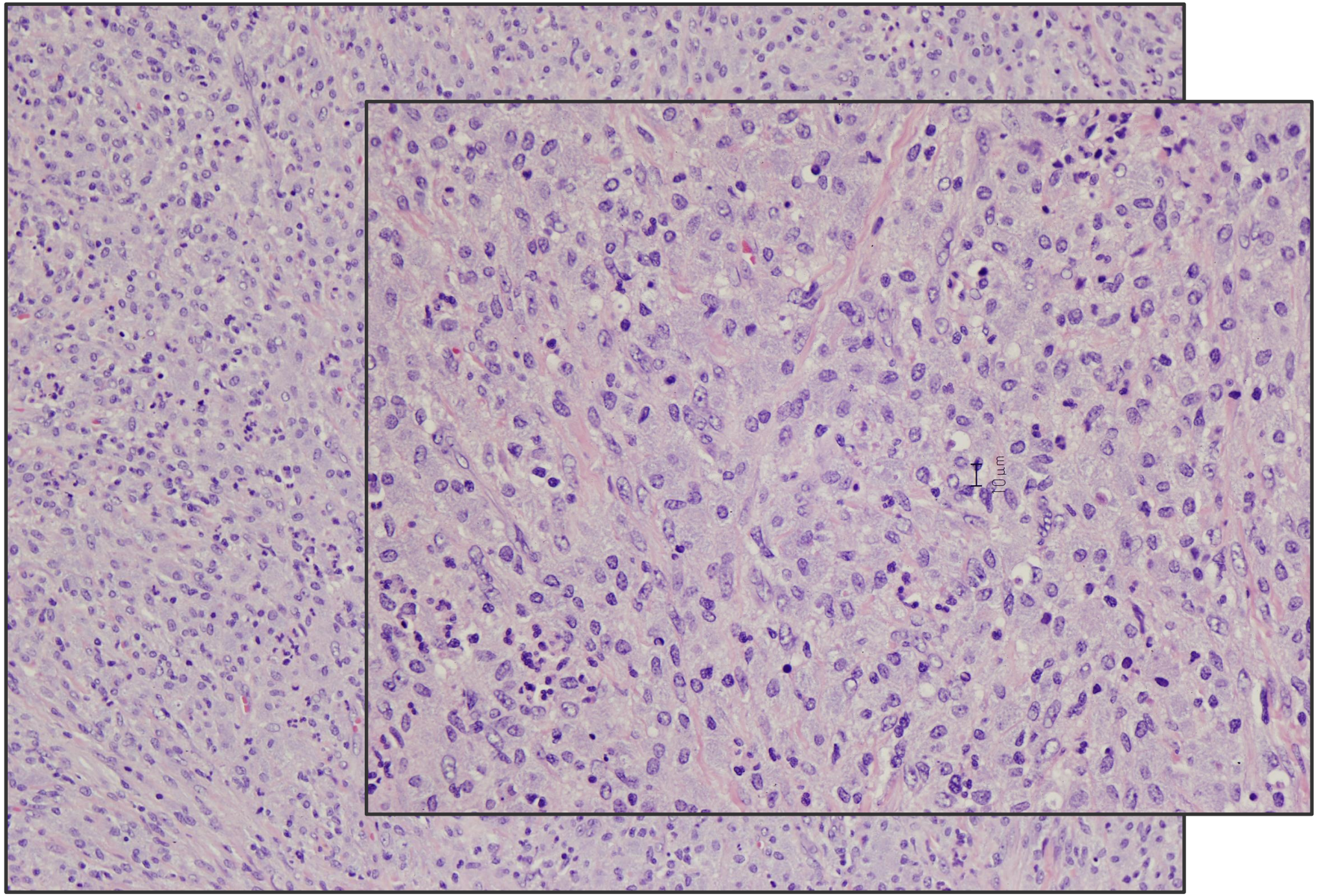
Case 1

The case of the unexplained neck lump

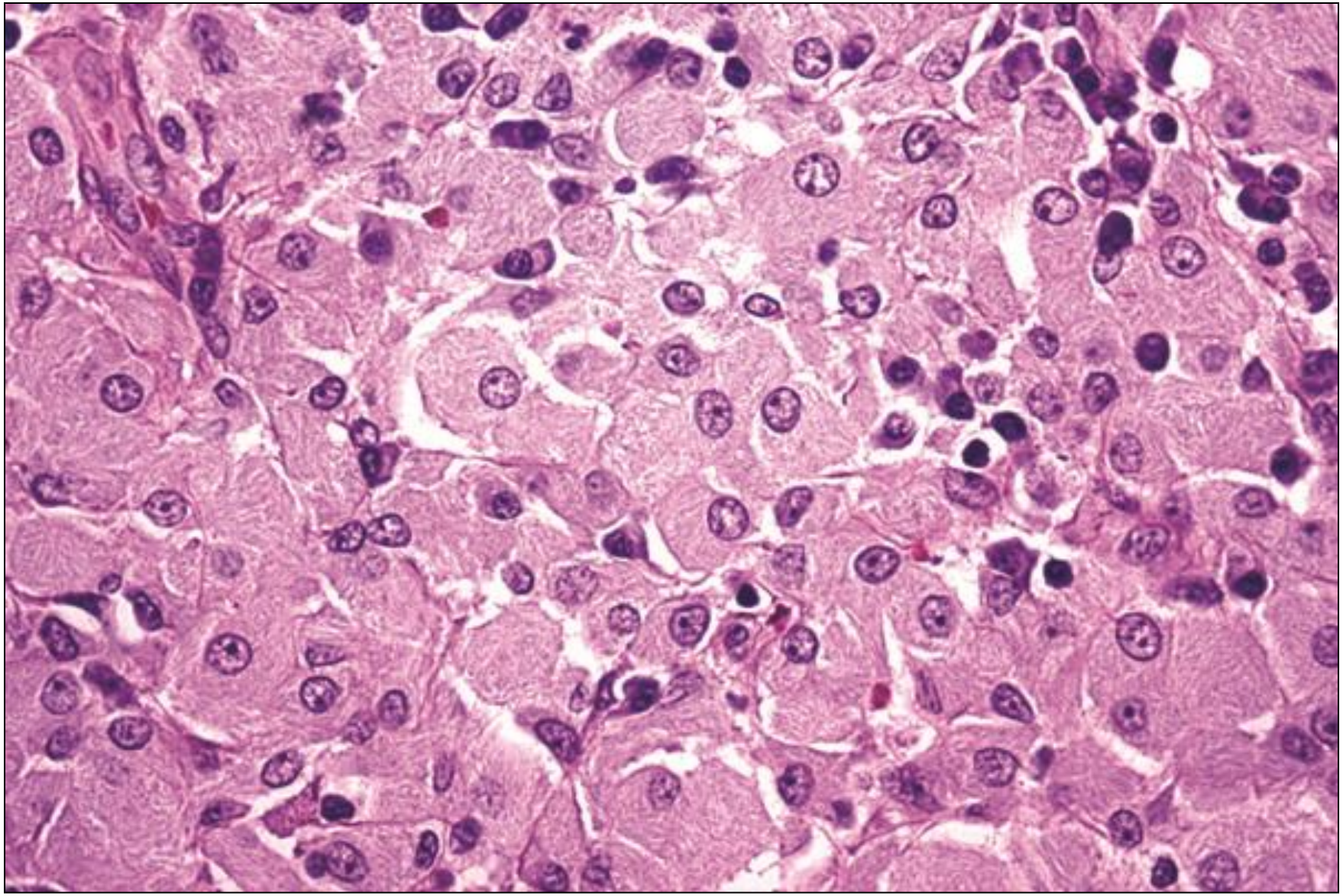
Clinical History

- 5 year old girl with isolated right cervical lymphadenopathy
- No history of acute illness; nobody else in home is ill
- No B symptoms
- Excisional biopsy of right cervical lymph node

H+E, lymph node



Images courtesy Dr. David Brink



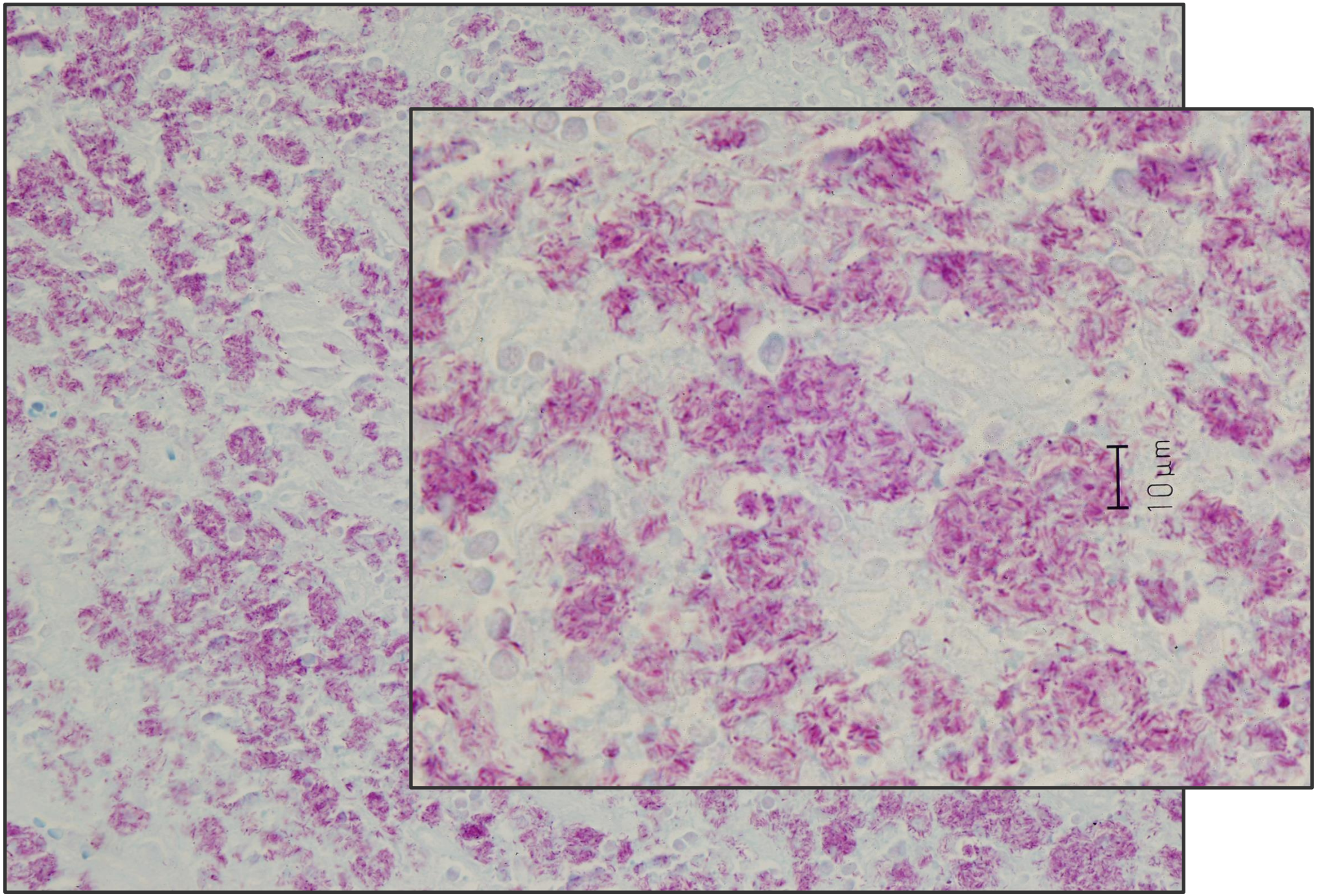
Higher power view from a different case with the same diagnosis

Differential Diagnosis

- Lysosomal storage disease
  - » E.g. Niemann-Pick disease, Gaucher disease
- Whipple disease
- Rosai-Dorfman disease
- Mycobacterial infection
  - » *Mycobacterium tuberculosis*
  - » Non-tubercular mycobacteria
- Fungal infection
  - » *Histoplasma capsulatum*, *Cryptococcus neoformans*
- Cat scratch disease (*Bartonella henselae*)

Fite stain, lymph node

PAS and GMS stains negative



Images courtesy Dr. David Brink

Case 1 Diagnosis

Mycobacterium avium complex (MAC) lymphadenitis

Mycobacterium avium complex (MAC)

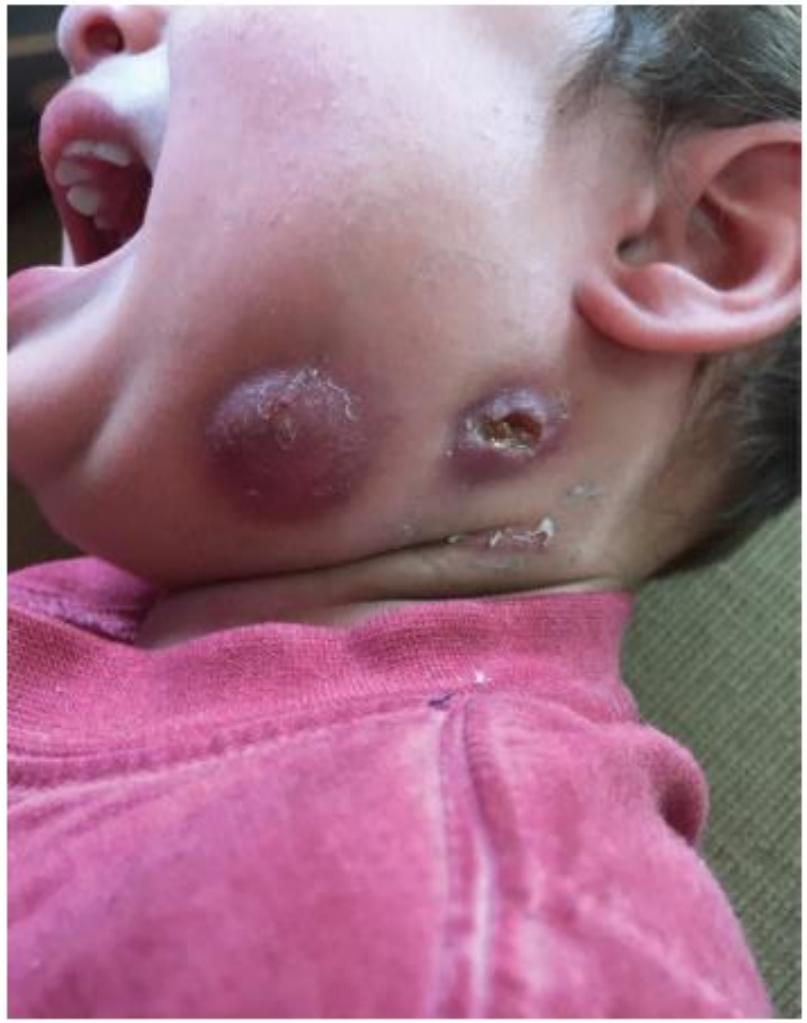
- Nontuberculous mycobacterial infections are rare (1-1.8 cases per 100,000 persons)[1]
- Associated with HIV infection or with other causes of immunocompromise[2]
  - » May involve bone marrow, lymph nodes, spleen in severely immunocompromised patients
- MAC may also cause isolated cervical adenopathy in immunocompetent children[1]

1. Gallois Y, Cogo H, Debuisson C, et al. Int J Pediatr Otorhinolaryngol. 2019; 122:196-202.
2. O'Malley DP, George TI, Orazi A, Abbondanzo SL. Atlas of Nontumor Pathology Fascicle 7: Benign and Reactive Conditions of Lymph Node and Spleen. Washington, DC; American Registry of Pathology; 2009.

Isolated MAC lymphadenitis in children

- Children between 2-6 years
- Most common sites affected: submandibular, preauricular, or parotid lymph nodes; may also affect lateral cervical lymph nodes
- Non-tender node enlarges over 3-6 weeks
- In ~10% of cases, sinus draining to skin may develop
- Infections other than lymphadenitis or skin/soft tissue infections rare in kids
- Possible seasonal increase in late winter/early spring
- Treatment- excision is considered curative
  - » I+D contraindicated because may lead to sinus tract formation

King SI. J Pediatr Child Health. 2017; 53:1091-95.
Evans MJ, Smith NM, Thorton CM, et al. J Clin Pathol. 1998; 51:925-27.
Nunes Rosado FG, Stratton CW, Mosse CA. Arch Pathol Lab Med. 2011; 135:1490-93.
Tebrugge M, Pantazidou A, MacGregor D, et al. PLOS One. 2016; 11(1):e0147513.



MAC infection with extension to the skin. Successfully treated with complete excision.

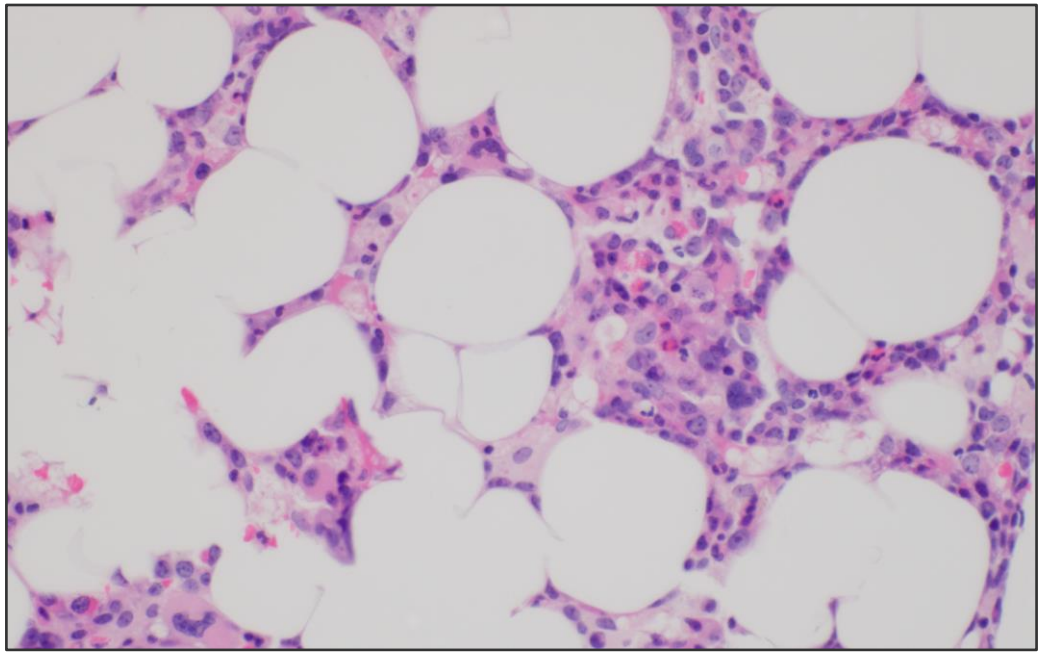
Image from: King SI. J Pediatr Child Health. 2017; 53:1091-95.

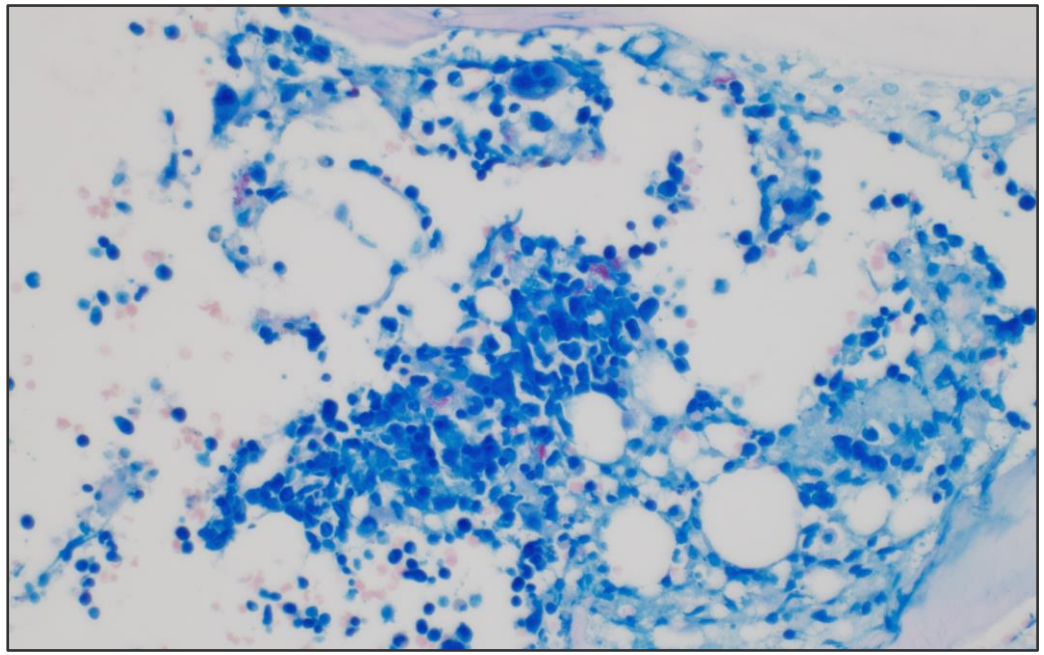
MAC Histologic Features

- Increased macrophages with abundant granular or foamy cytoplasm
  - » Organisms may be visible in cytoplasm on H+E staining
- Macrophages may expand sinuses or may diffusely replace the lymph node architecture
- Lymphocyte depletion is common
- Well-formed granulomas typically not seen

1. O'Malley DP, George TI, Orazi A, Abbondanzo SL. Atlas of Nontumor Pathology Fascicle 7: Benign and Reactive Conditions of Lymph Node and Spleen. Washington, DC; American Registry of Pathology; 2009.

MAC in Bone Marrow





37 year old woman with history of RA treated with prednisone and multiple previous infections (including MAC one year prior to this biopsy). Also has history of treated CML. She presented acutely with fevers, dry cough, pancytopenia, and pulmonary opacifications.

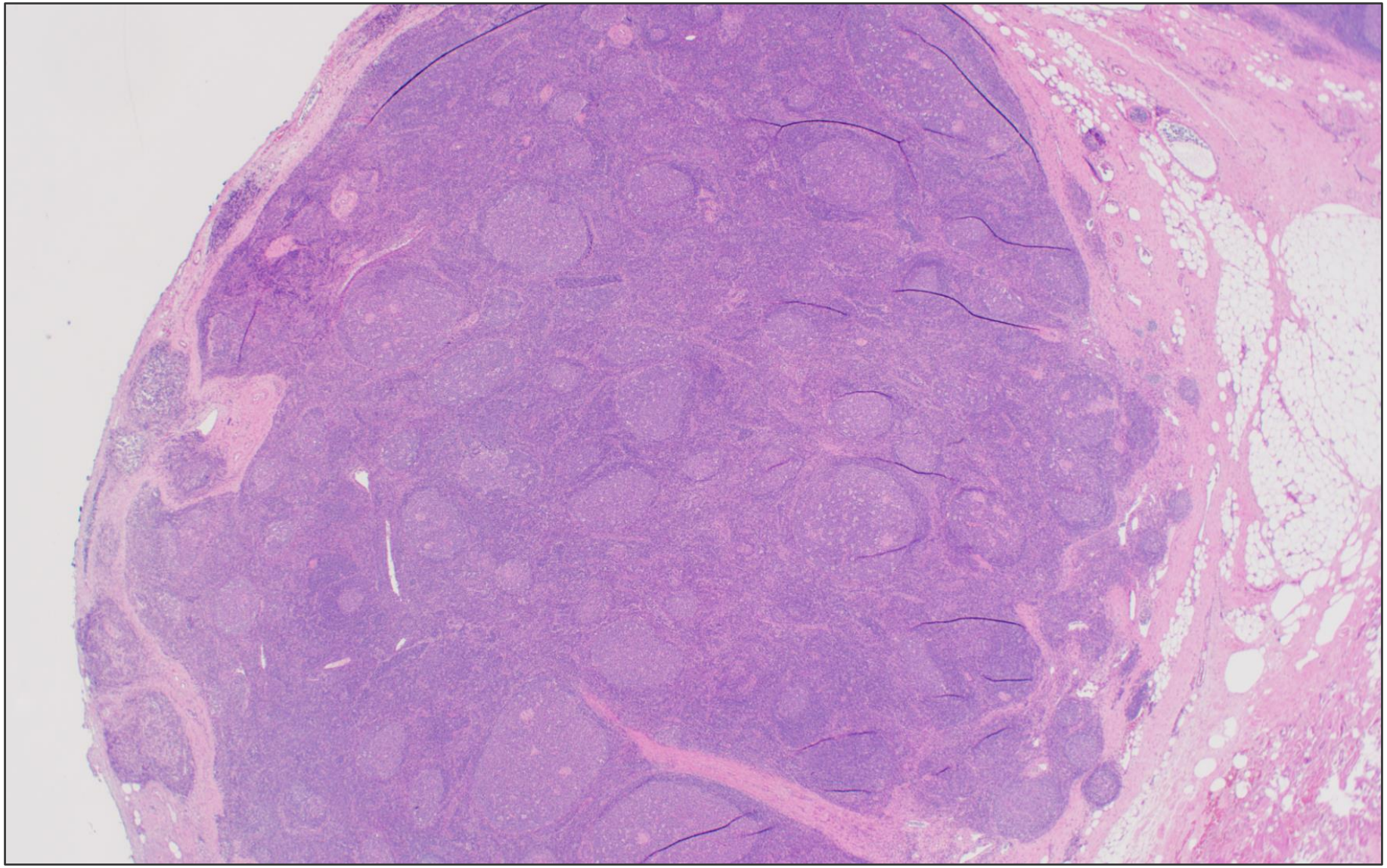
Pathologic Feature	*M. tuberculosis*	*M. leprae*	*M. avium intracellulare*
Caseous necrosis (gross or microscopic)	√	√ (tuberculoid)	
Enlarged, firm nodes (gross)		√	
Well formed granulomas	√	√	
Multinucleated giant cells	√	√ (“leprae cells” in lepromatous)	
Diffuse infiltrate of macrophages		√	√
Follicular hyperplasia		√	
Lymphocyte depletion			√
Thickened capsule		√	
Ziehl-Neelsen (Z-N) or Fite stain patterns	Rare organisms at periphery of necrosis or within macrophages	Z-N may be negative; many organisms in macrophages with Fite	Many organisms in macrophages with Z-N or Fite

Case 2

Doctor, there's a funny bump under my chin!

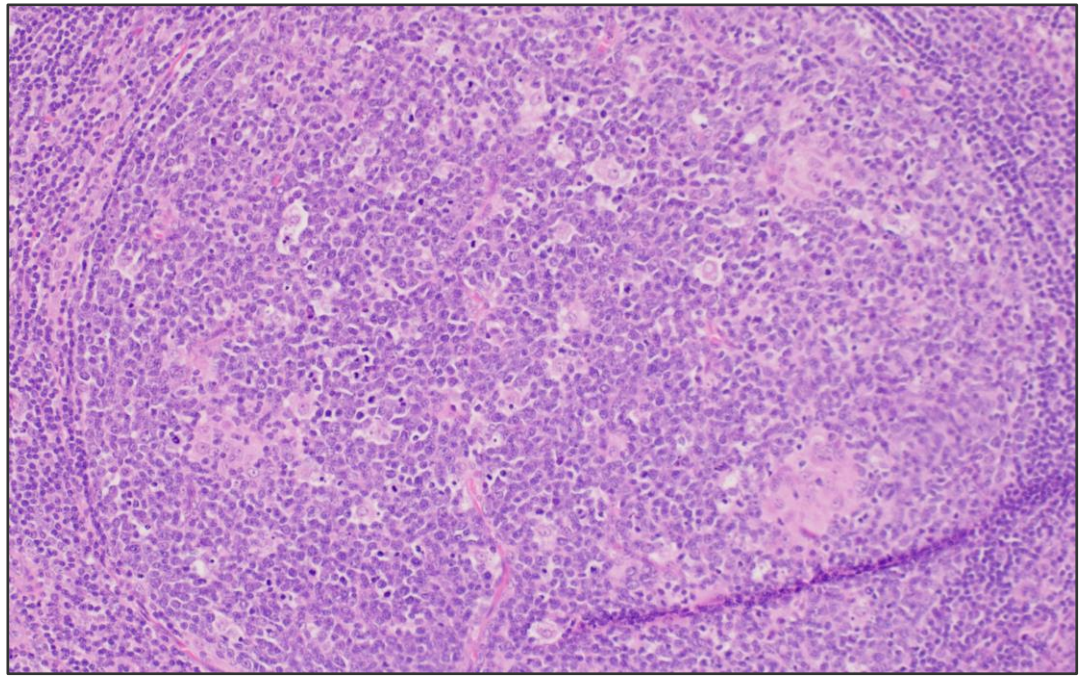
Clinical History

- 23 year old woman with enlarged submental lymph node, sent for Hematopathology consultation
- No previous medical history
- No other sites of lymphadenopathy, no hepatosplenomegaly



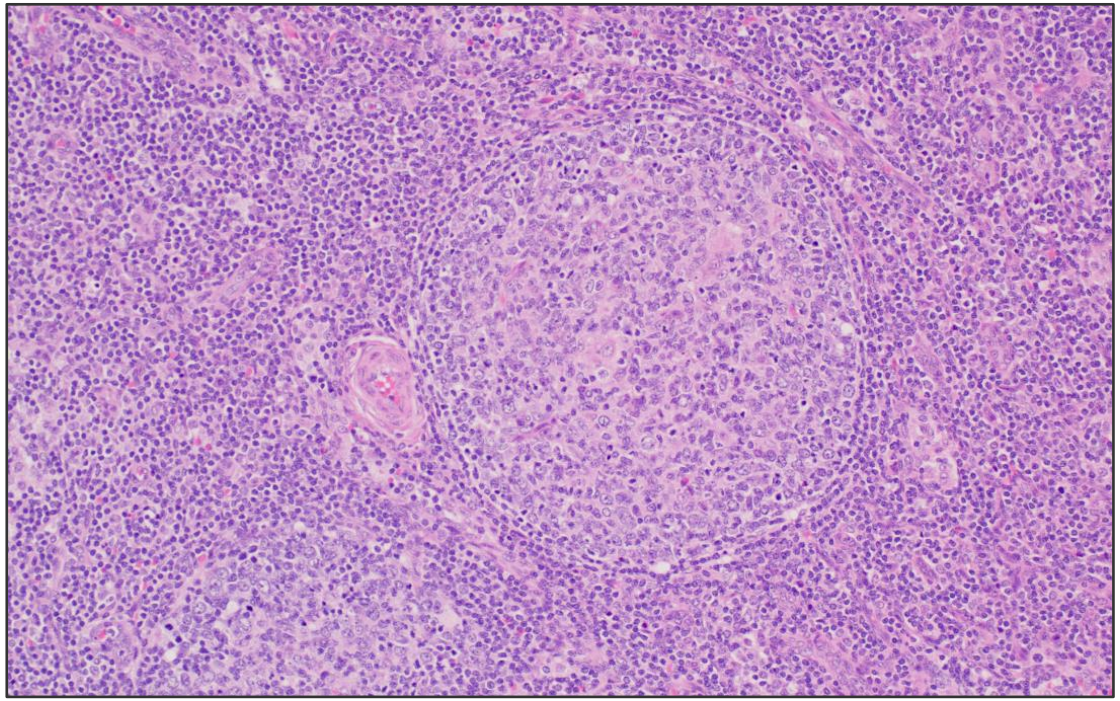
H+E, 2X

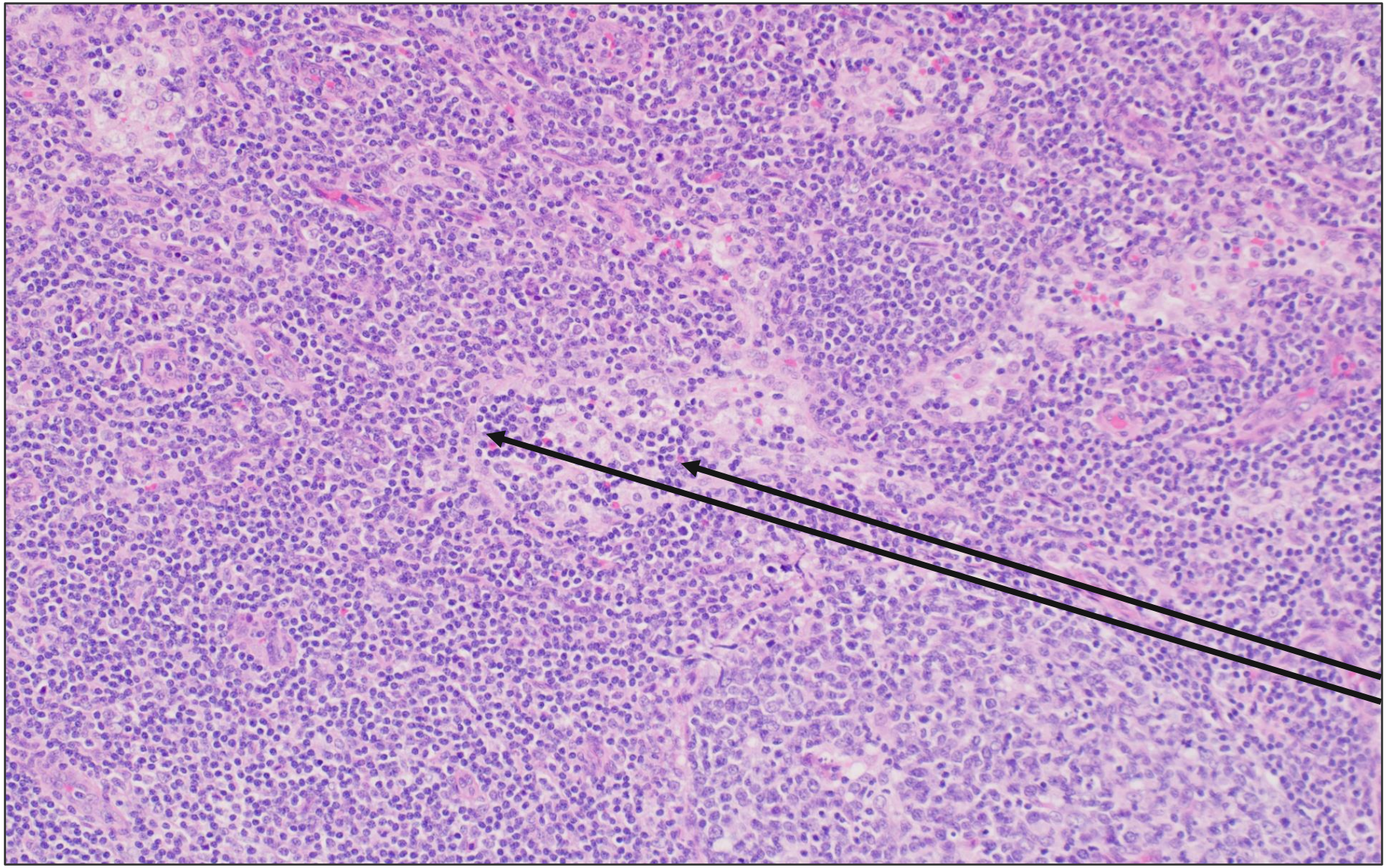
Florid follicular hyperplasia



H+E, 20X

Epithelioid histocytes in germinal centers (single and clustered)





H+E, 20X

Monocytoid lymphocytes in sinuses; CD20 staining showed these to be B-cells

Case 2 Diagnosis

Toxoplasma lymphadenitis

Toxoplasma gondii diagnosis

- Histologic triad- follicular hyperplasia, epithelioid histiocytes in germinal centers, monocytoid B-cells in sinuses
  - » True granulomas and multinucleated giant cells are absent
  - » Cysts are rarely found in lymph nodes
- Most commonly involves cervical lymph nodes
- May be asymptomatic or have mononucleosis-like symptoms
- Other tests that can be helpful
  - » Serology is key diagnostic test
    - Look for IgG and IgM antibodies
    - Paired acute and convalescent samples 3 weeks apart
  - » Immunohistochemistry for *T. gondii*

McCabe RE, Brooks RG, Dorfman RF, Remington JS. Rev Infect Dis. 1987; 9(4):754-74.
arupconsult.com

Differential Diagnostic Considerations

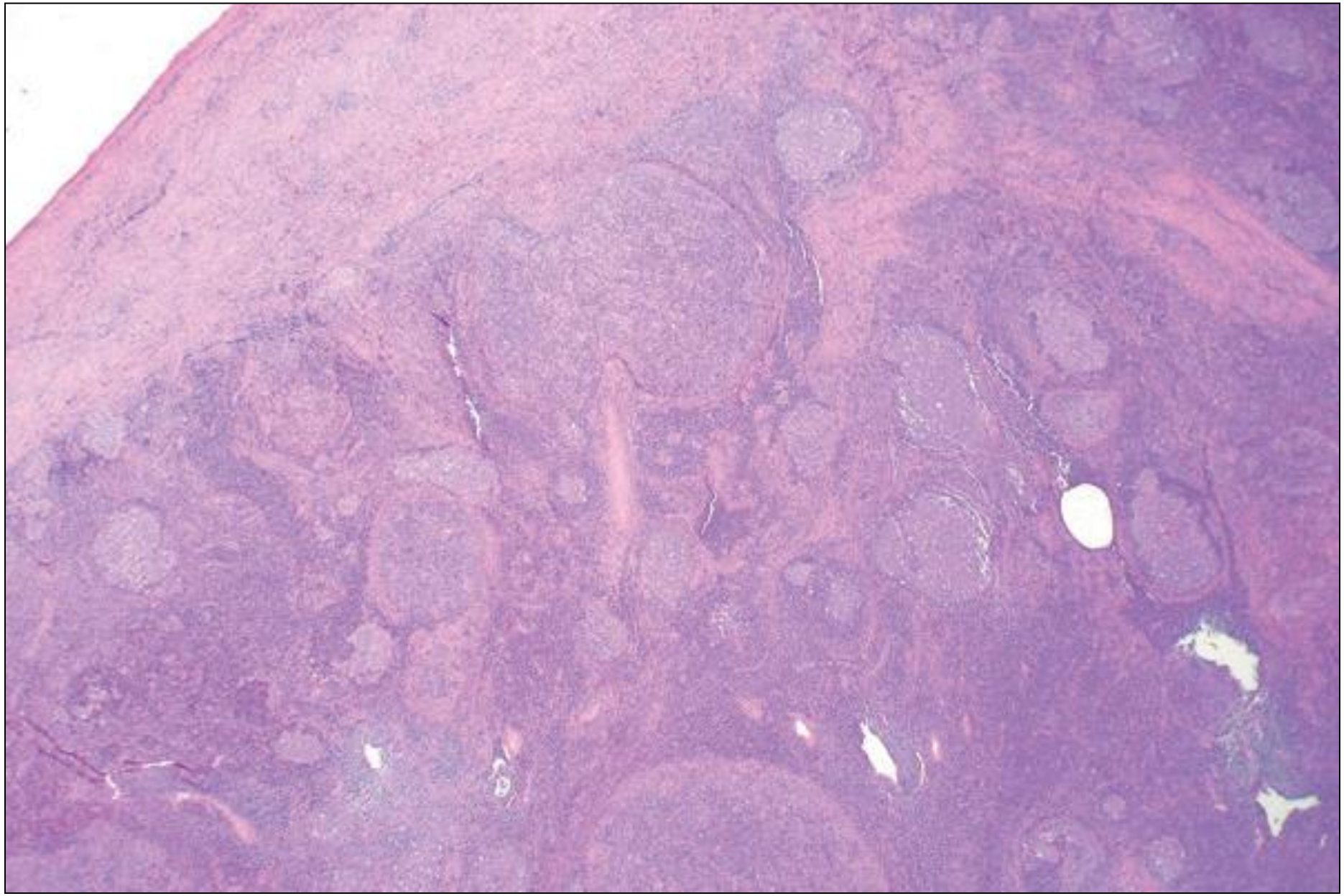
- Leishmanial lymphadenitis
  - » Organisms may be visible in histiocytes/granulomas
- Early stages of these diseases may have some histologic overlap
  - » Cat scratch disease (*B. henselae*)
  - » Infectious mononucleosis
  - » CMV lymphadenitis

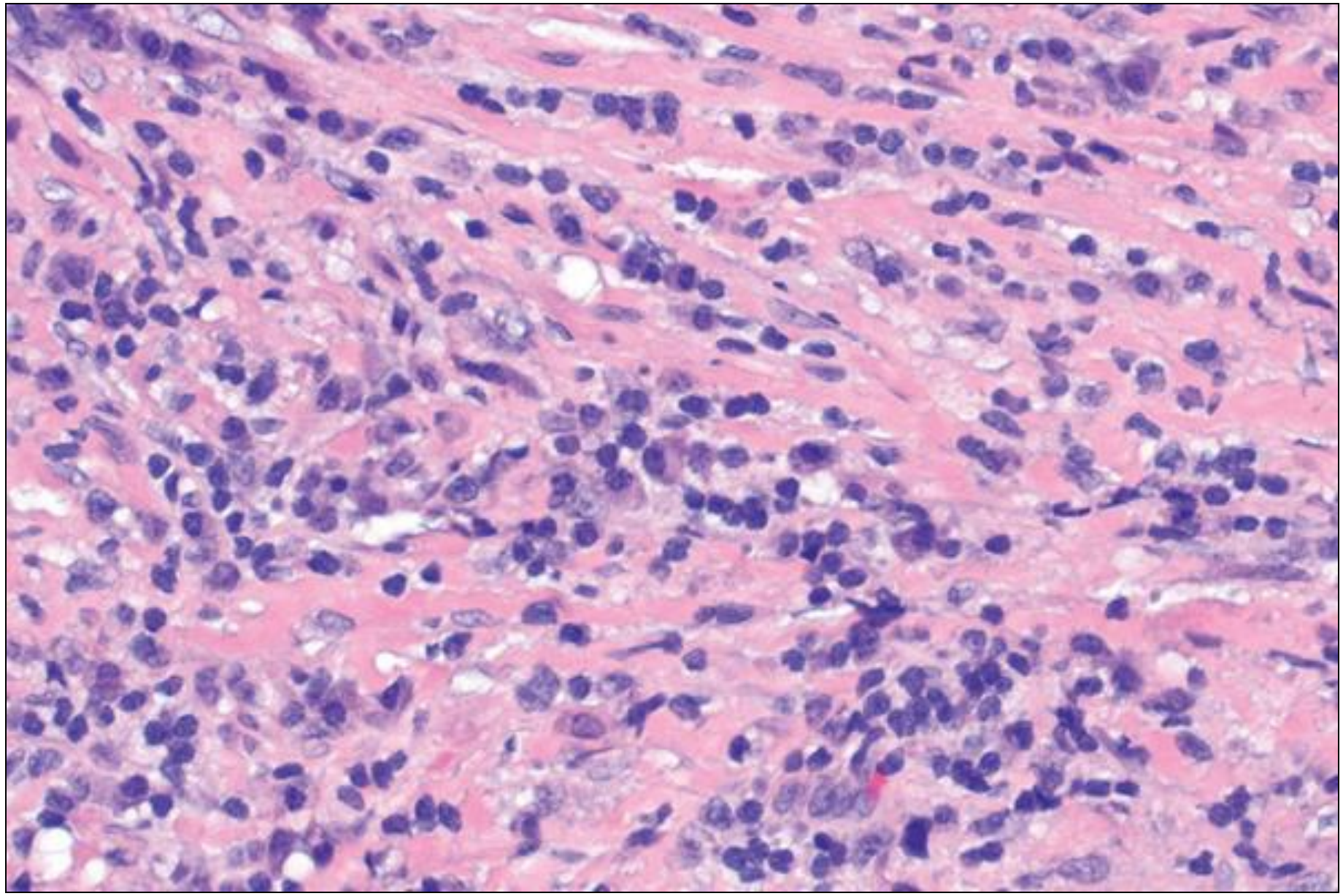
Case 3

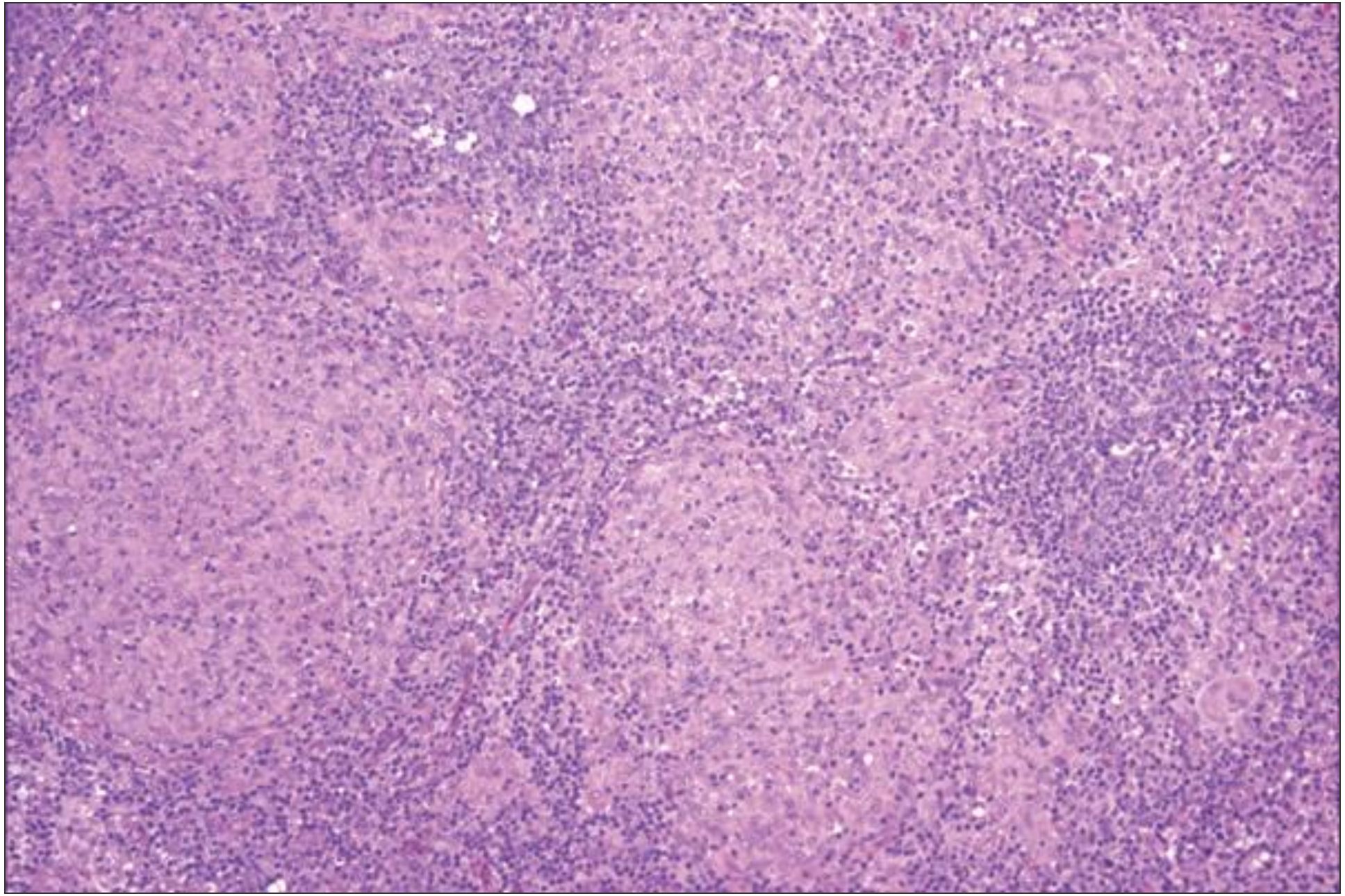
The case of the prominent plasma cells

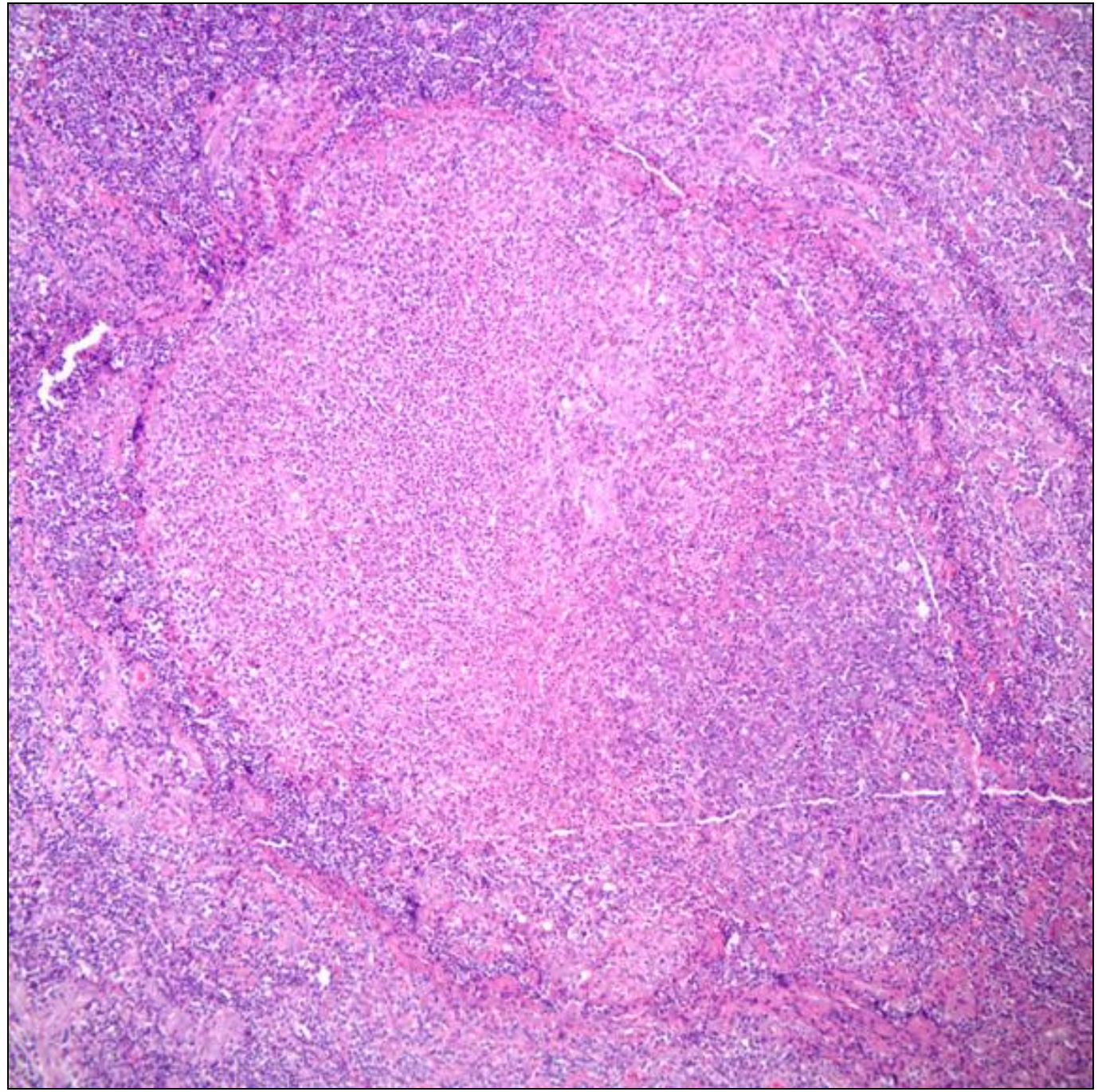
Images in this case courtesy Dr. Tracy George

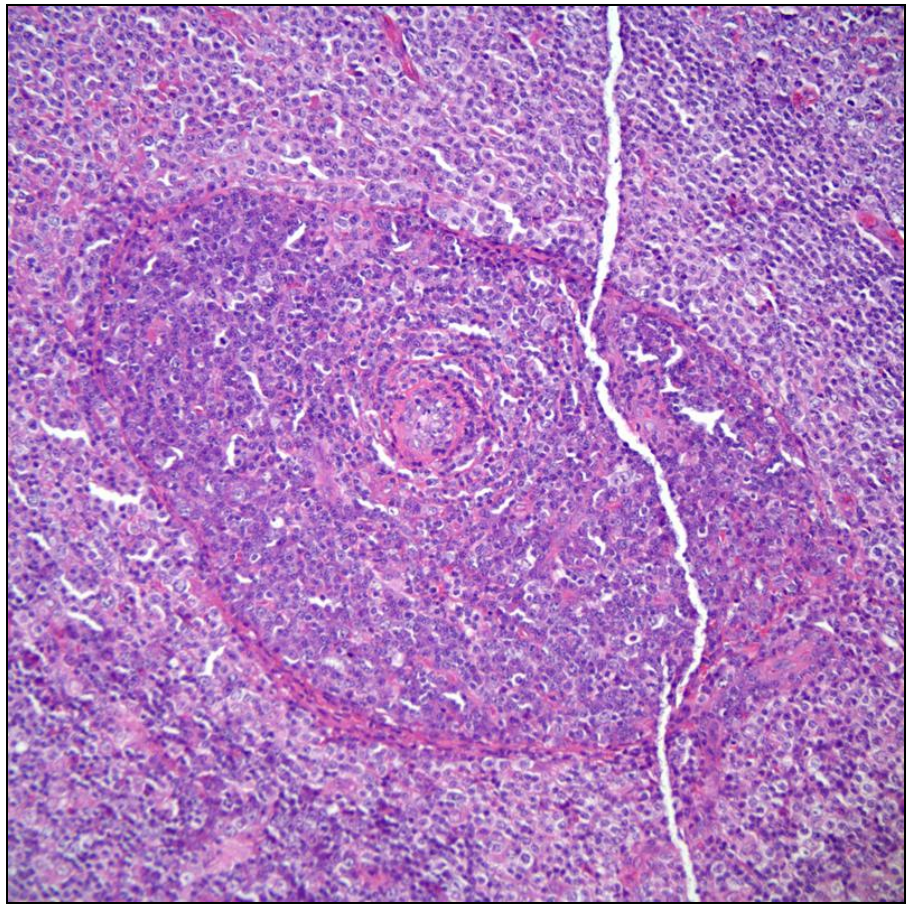
29 year old male with unintentional weight loss and an enlarged inguinal lymph node

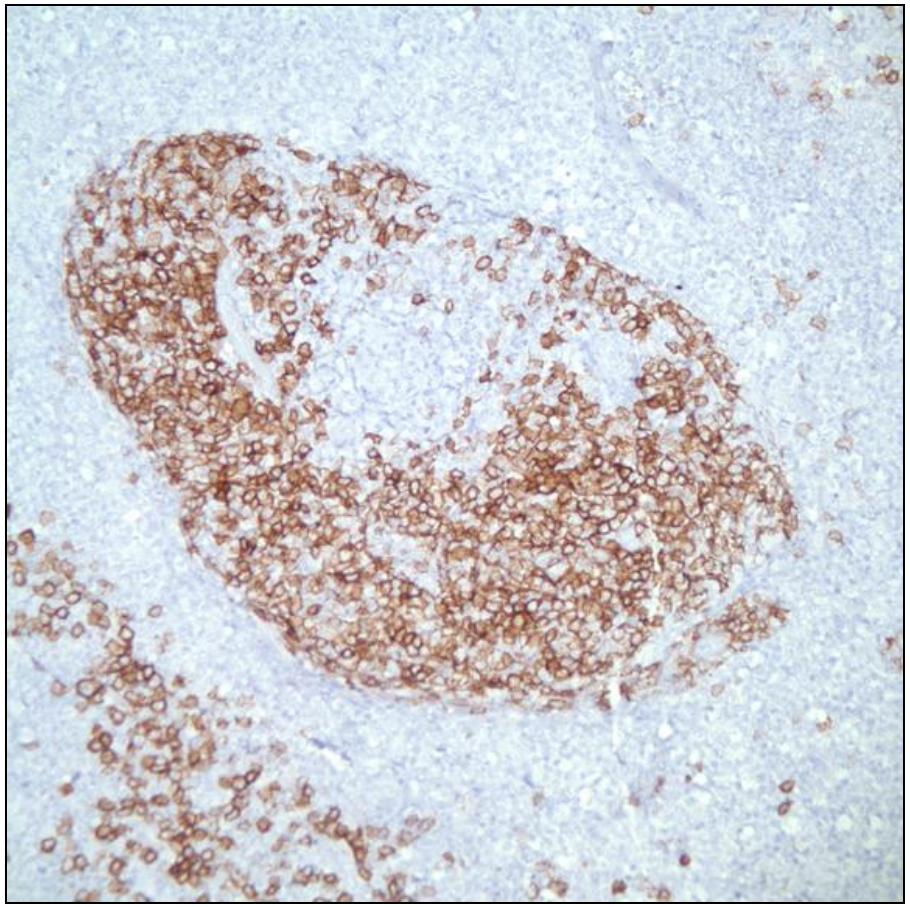












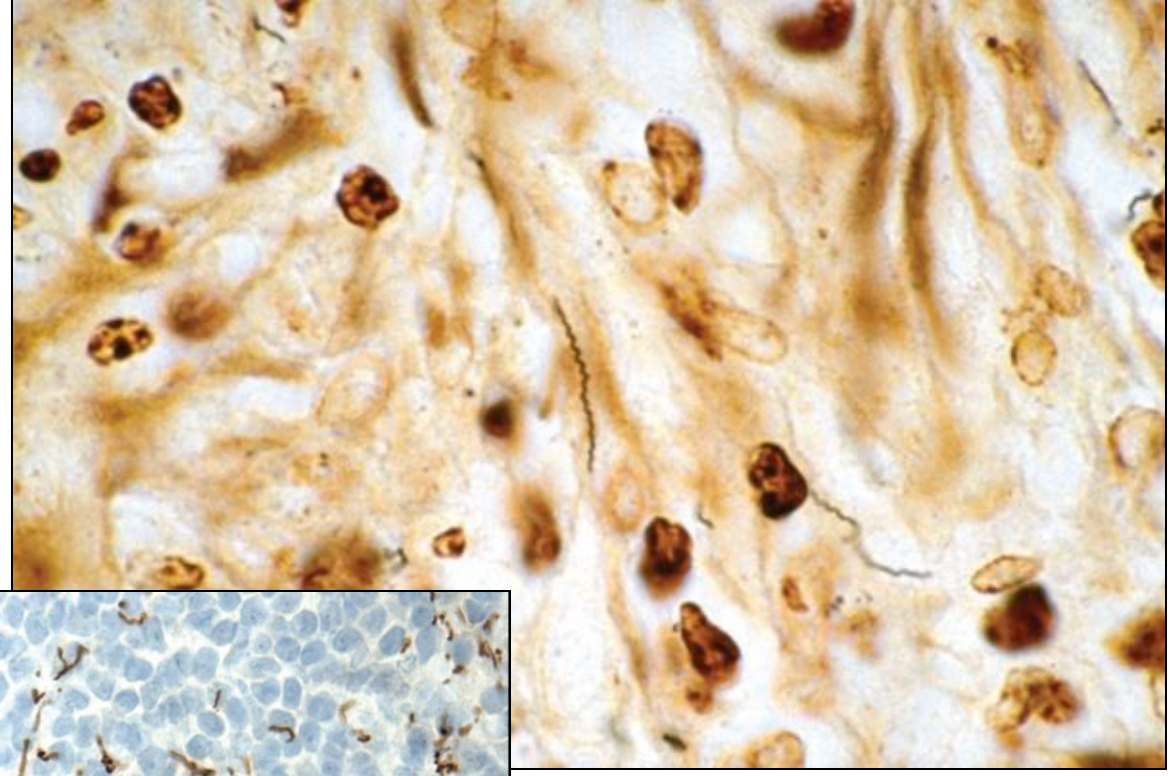
CD138

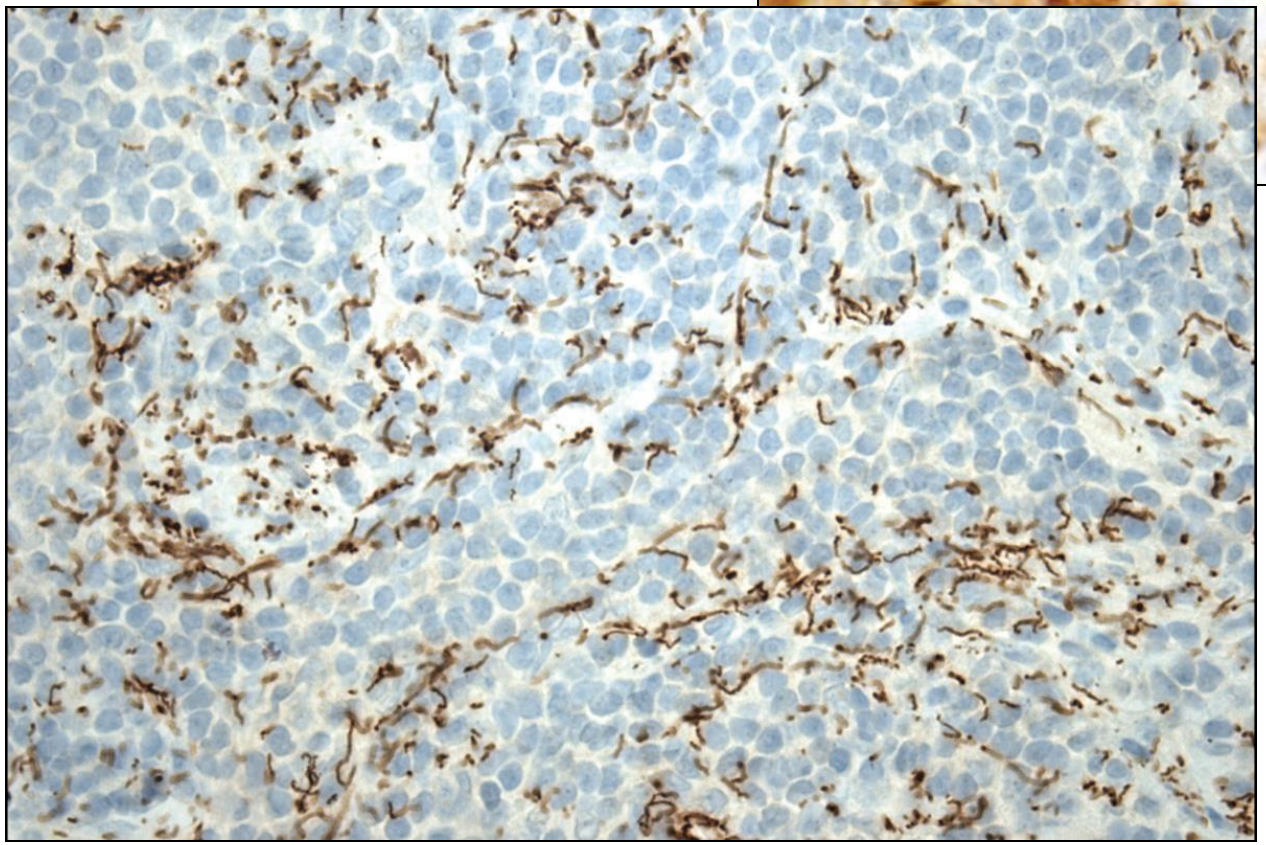
Differential Diagnosis

- Lymphadenopathy with prominent plasma cells
  - » Rheumatoid arthritis and other autoimmune disorders
  - » Luetic lymphadenitis (syphilis)
  - » Plasma cell variant Castleman disease (multifocal Castleman)
  - » IgG4-related disease
  - » Rosai-Dorfman disease
- Plasma cell neoplasm involving lymph node

Disorders with lymph node plasmacytosis	Key Morphologic Observations	Key Stains/Ancillary Tests
Rheumatoid arthritis	Follicular hyperplasia Increased paracortical polytypic PC	Meet RA clinicopathologic criteria (including ↑ RF, anti-CCP, CRP, ESR)
Luetic lymphadenitis (syphilis)	Capsular fibrosis with PC Sarcoidosis-type granulomas Vasculitis	Warthin Starry positive T. pallidum IHC positive Syphilis serology positive
Plasma cell Castleman disease	Increased PC in paracortex (may be poly- or monotypic) Other features of HV CD (variable)	HHV-8 positive (~50%) Severe systemic inflammatory sx
IgG4-related disease	Varied morphologic patterns; all include increased polytypic PC	IgG and IgG4 IHC • >10 IgG4 positive PC per HPF and/or IgG4:IgG ratio in PC ≥ 40% Elevated serum IgG4
Rosai-Dorfman disease	Histiocyte aggregates in sinuses Emperipolesis May have plasma cell clusters with Russell bodies	Histiocytes are positive for CD68, CD163, and S100; negative for CD1a and langerin
Plasma cell neoplasm	Increased monotypic plasma cells	May have other sx and lab findings supporting plasma cell myeloma

Warthin Starry





IHC for *Treponemal organisms*

Case 3 Diagnosis

Luetic (syphilitic) lymphadenitis

Syphilis (*Treponema pallidum*)

- 115,045 new diagnoses of syphilis in 2018
- Multistage disease
  - » Primary- chancre; heals in 3-6 weeks even without treatment
  - » Secondary- characteristic non-pruritic mucocutaneous lesions; multiple other systemic symptoms including **lymphadenopathy**
  - » Latent- asymptomatic period that can last for years
  - » Tertiary- rare, happens with untreated disease, may occur late, affects multiple organ systems, fatal
- Treatment- penicillin

U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. Syphilis - CDC fact sheet (detailed).

Syphilis- Laboratory Diagnosis

- Lymph node biopsy not required, but sometimes happens if reason for lymphadenopathy is unclear
- 2 types of assays
  - » Treponemal- EIA, CIA, TP-PA, FTA-ABS
  - » Non-treponemal- RPR, VDRL
- 2 major current strategies
  - » Traditional algorithm
    - Screen with treponemal test, confirm with non-treponemal
    - Can detect active infection
  - » Reverse algorithm
    - Screen with non-treponemal test, confirm with treponemal test

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IgG4-related disease

- Lymph node histologic diagnosis is tricky
  - » Significant overlap with multiple other disorders; focal involvement
  - » Requires correlation with serum IgG4 and clinical features
- 5 major patterns of IgG4 lymphadenopathy
  - » All have polytypic plasmacytosis, excess of IgG4+ PC, increased tissue eosinophils
    - Multicentric Castleman-disease like (HHV-8 negative)
    - Follicular hyperplasia **most common pattern**
    - Paracortical expansion
    - Progressive transformation of germinal centers
    - Inflammatory pseudotumor-like
  - » Rosai-Dorfman disease may have increased IgG4-positive PC also!

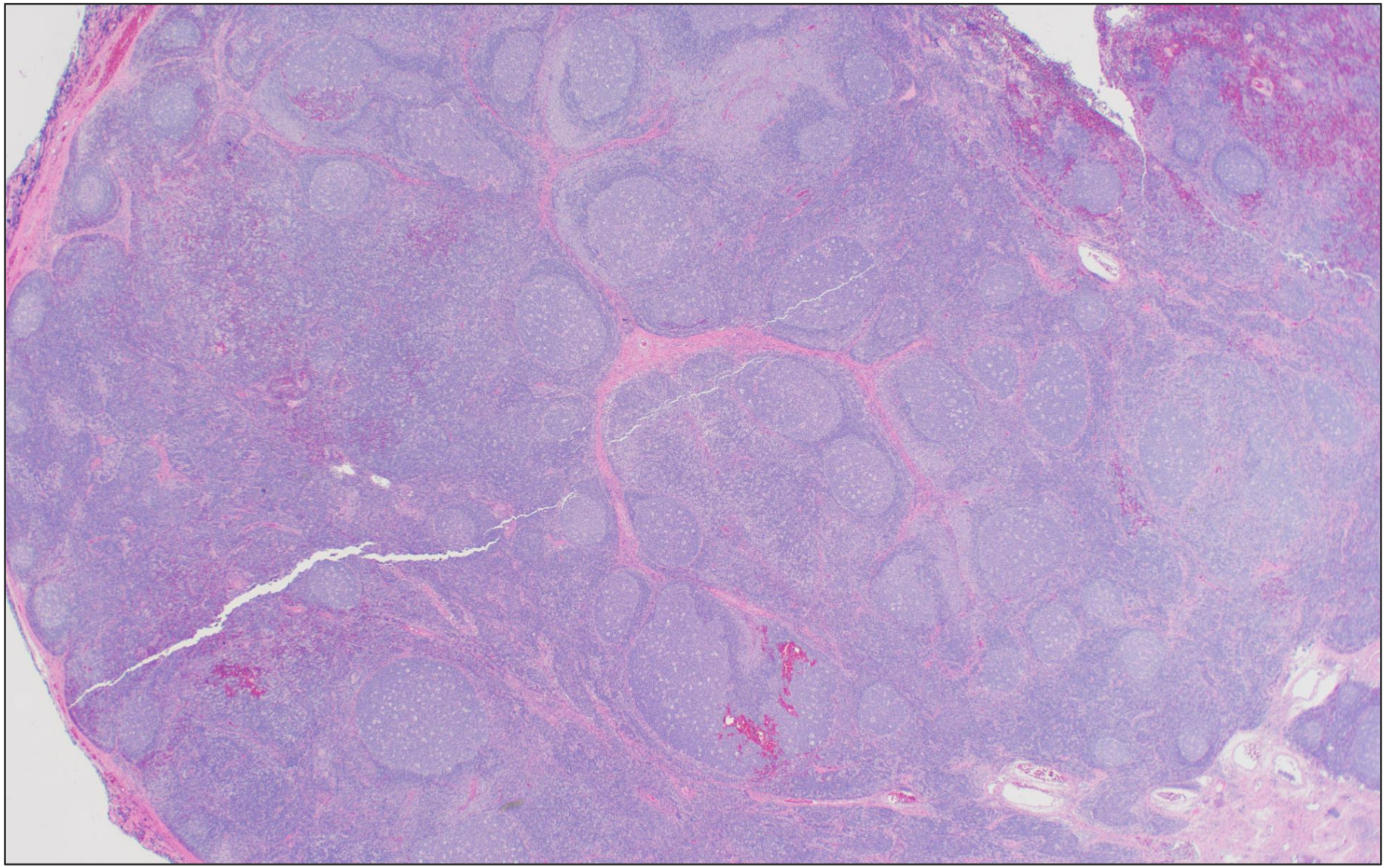
Wick MR, O'Malley D. Semin Diagn Pathol. 2018; 35:61-66.

Case 4

Return to the realm of the unexplained neck lump (different patient this time, though!)

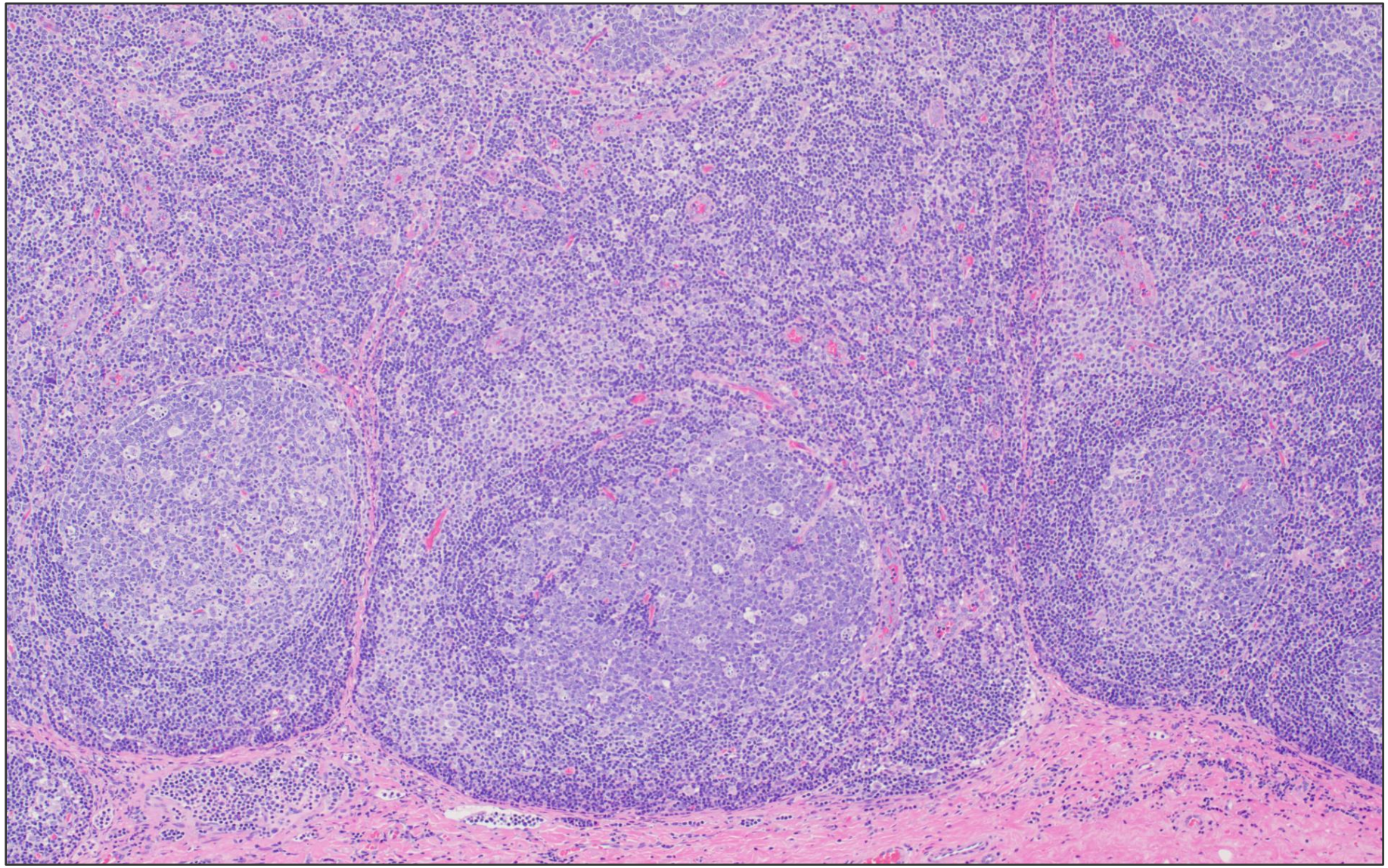
Clinical History

- 9 year old previously healthy girl with 6 week history of non-tender cervical and mediastinal lymphadenopathy
  - » No B-symptoms, no rash, no cough
- Paternal grand-uncle with Hodgkin lymphoma in childhood
- Family pets include cat (for past 6 months), turtle, and fish
  - » No major animal-caused injuries to patient
- Recent travel to Maui before parents noticed her neck node enlargement
- Excisional biopsy, right cervical lymph node



H+E, 2X

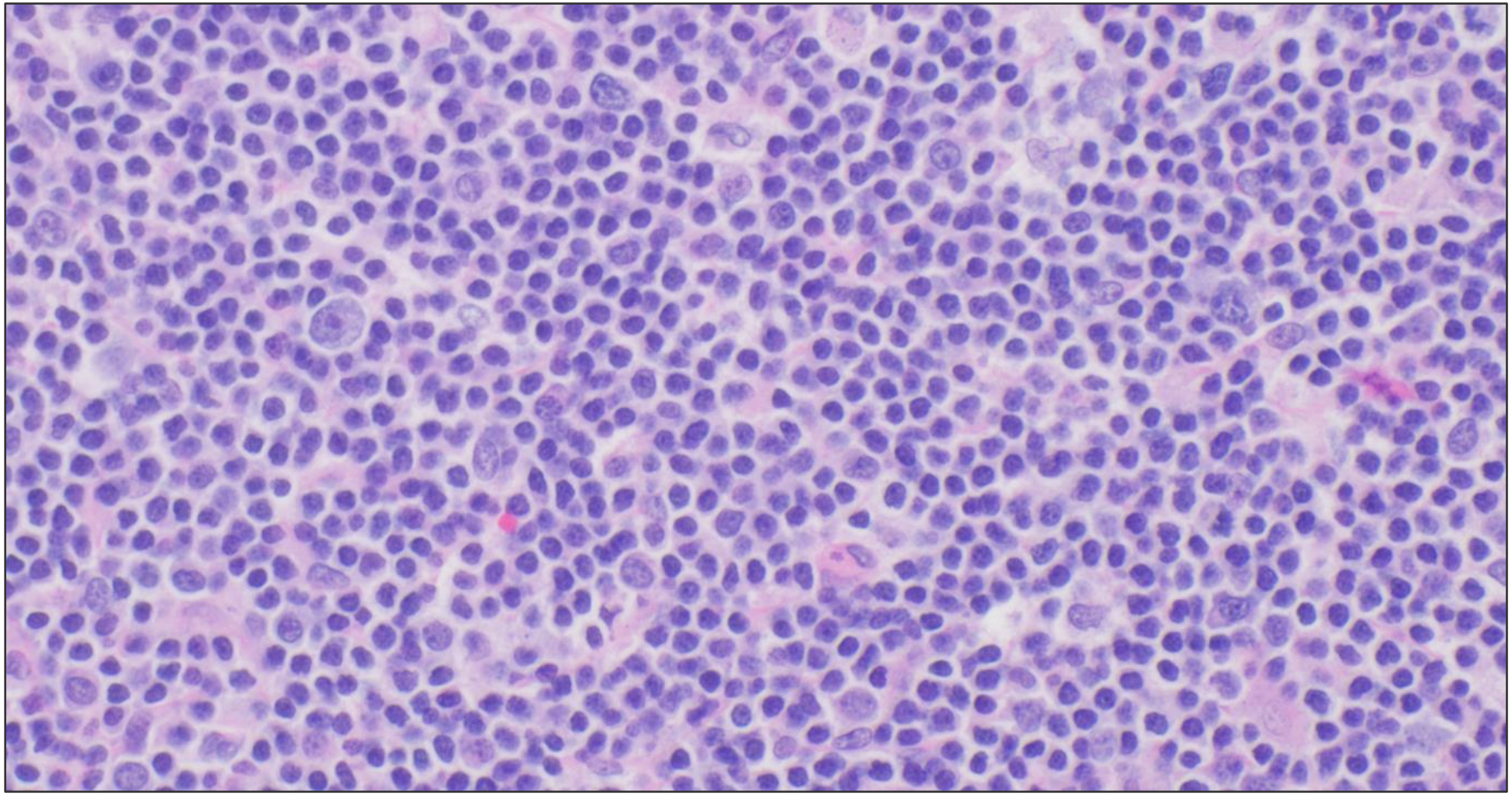
Follicular and paracortical hyperplasia



H+E, 20X

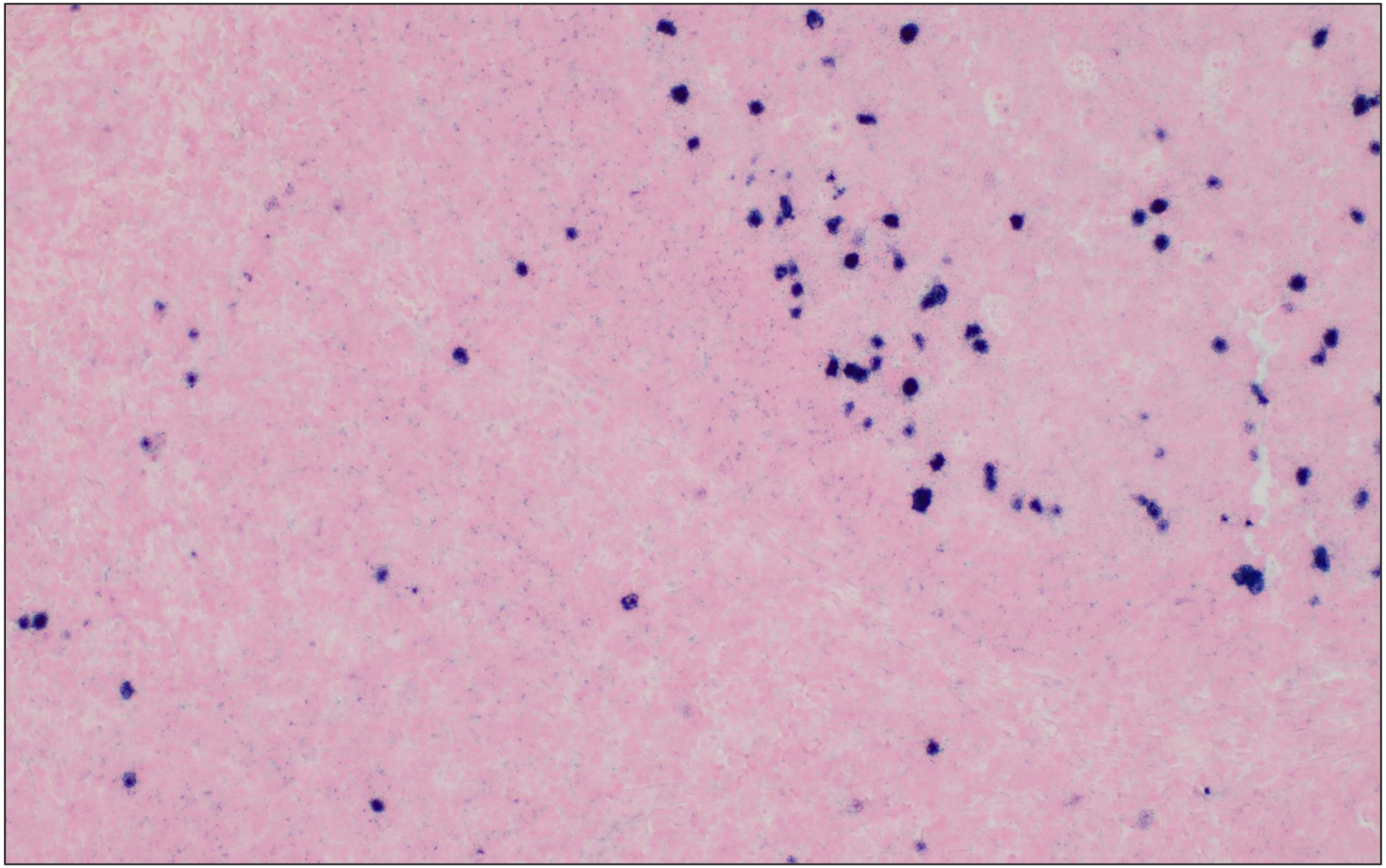
Polarized follicles with tingible body macrophages, intact mantle zones

Flow cytometry showed no abnormal B-cell or T-cell populations.



H+E, 40X

Large cells in paracortex, some with prominent nucleoli



H+E, 40X

Positive EBER ISH

Concurrent serology results

Test	Result	Reference Interval
EBV ab to viral capsid antigen (IgG)	92.7 U/mL	<21.9 U/mL
EBV ab to viral capsid antigen (IgM)	44.6 U/mL	<43.9 U/mL
EBV ab to nuclear antigen (IgG)	12.5 U/mL	<21.9 U/mL
EBV ab to early antigen (IgG)	27.6 U/mL	<10.9 U/mL
Bartonella henselae (IgM)	<1:16	<1:16
Bartonella henselae (IgG)	<1:64	<1:64

EBV serology patterns- review

Interpretation of EBV-Specific Serologic Results				
Infection	**VCA IgM**	**VCA IgG**	**EA**	**EBNA**
No previous	Negative	Negative	Negative	Negative
Acute/primary	Positive	Positive	Positive/negative	Negative
Recent	Positive/negative	Positive	Positive/negative	Positive/negative
Past	Negative	Positive	Negative	Positive
Reactivation[a]	Positive/negative	Positive	Positive	Positive

Table from ARUPconsult.com

Case 4 Diagnosis

Acute EBV lymphadenitis

Acute EBV infection

- Primary infection usually occurs in children or adolescents/young adults
  - » In kids, usually benign and self-limited
    - Common sites of involvement: Waldeyer ring, cervical lymph nodes
  - » Infectious mononucleosis (IM) more common with infection in adolescence or later (but can occur at any age)
    - Fever, malaise, pharyngyitis, lymphadenopathy
- Rare EBV positive cells can be found in reactive lymph nodes (typically <10 EBER positive cells/0.5 mm^2)

Aguilera N, Auerbach A. Semin Diagn Pathol. 2018; 35:54-60.
Pittaluga S. Semin Diagn Pathol. 2013; 30(2):130-136.
Weiss LM. O'Malley D. Mod Pathol. 2013; 26:S88-S96.

Staining for EBV in tissue

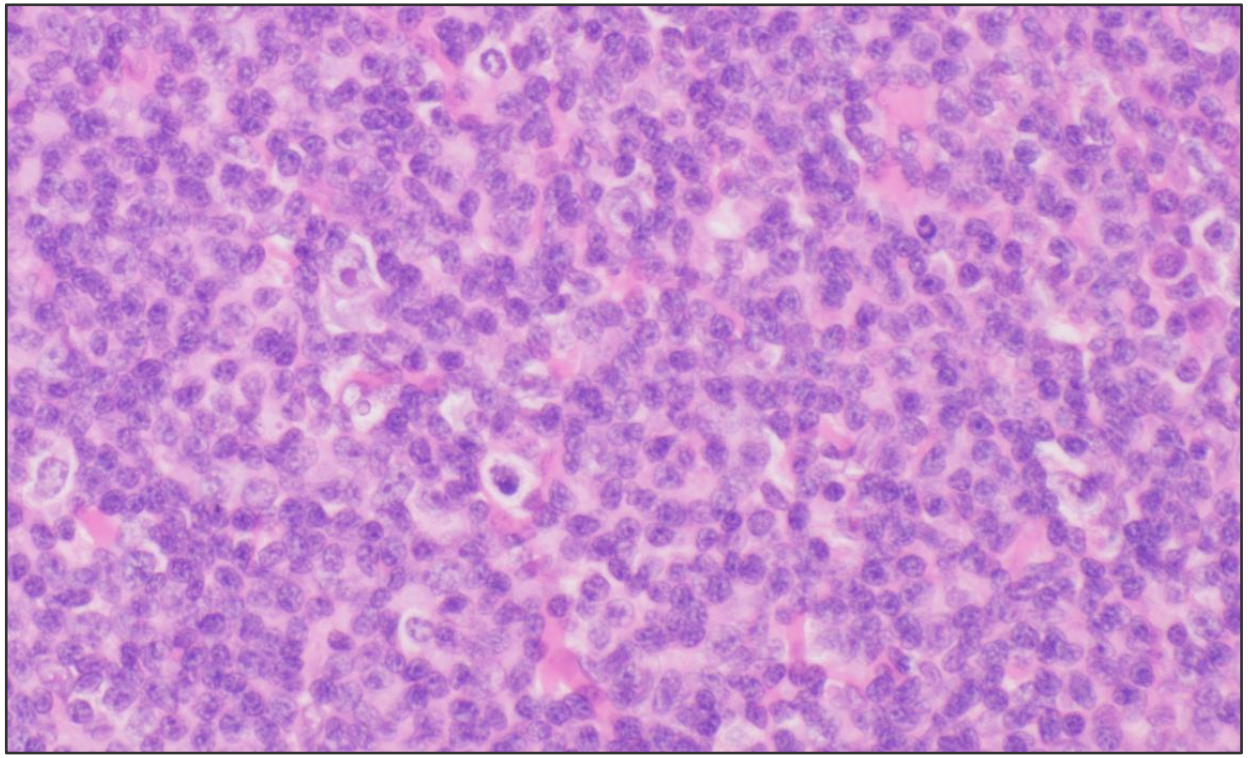
- EBER mRNA by ISH
  - » Typically diffusely positive in acute infection

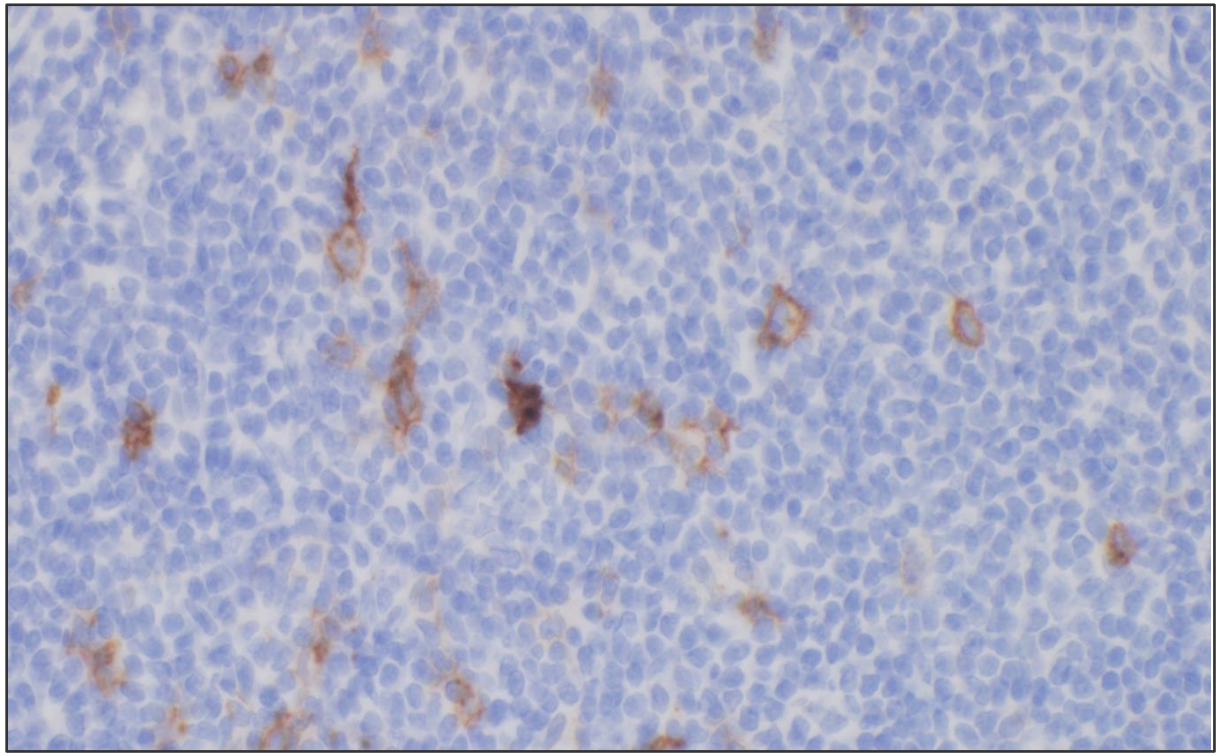
- LMP-1 by IHC
  - » Positive in smaller number of cells than EBER in acute EBV
  - » Less sensitive than EBER

EBER may be more useful in setting of acute EBV infection.

Aguilera N, Auerbach A. Semin Diagn Pathol. 2018; 35:54-60.
Pittaluga S. Semin Diagn Pathol. 2013; 30(2):130-136.
Weiss LM. O'Malley D. Mod Pathol. 2013; 26:S88-S96.

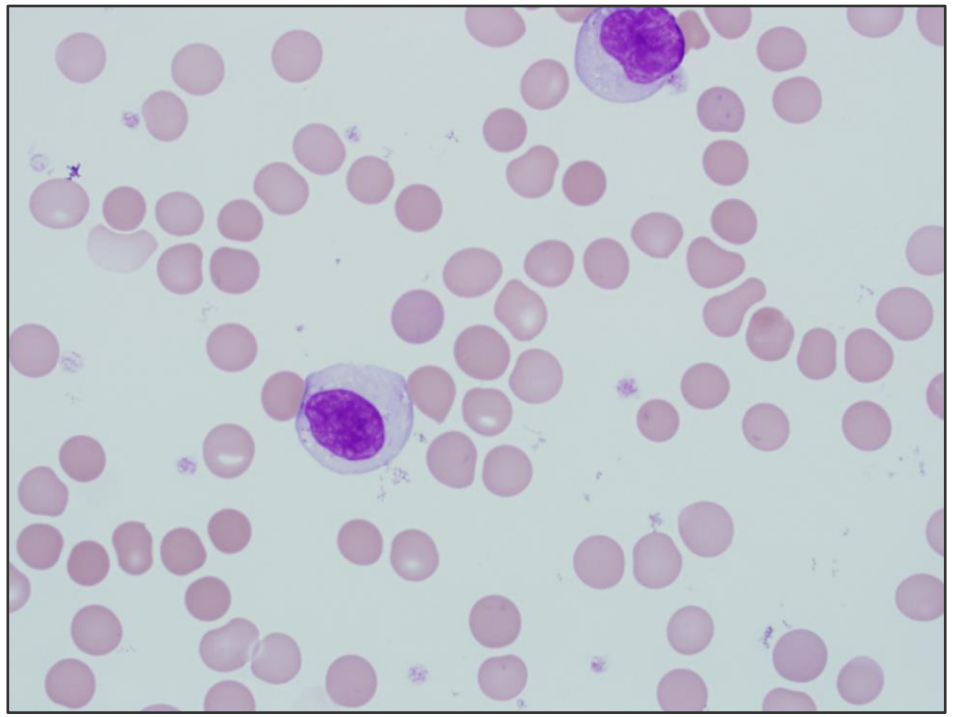
Immunoblasts can be scary and confused with Hodgkin/Reed-Sternberg cells!





CD30

Other pathologic findings in acute EBV



Downey cells
Atypical T-lymphocytes in peripheral blood in patients with acute EBV

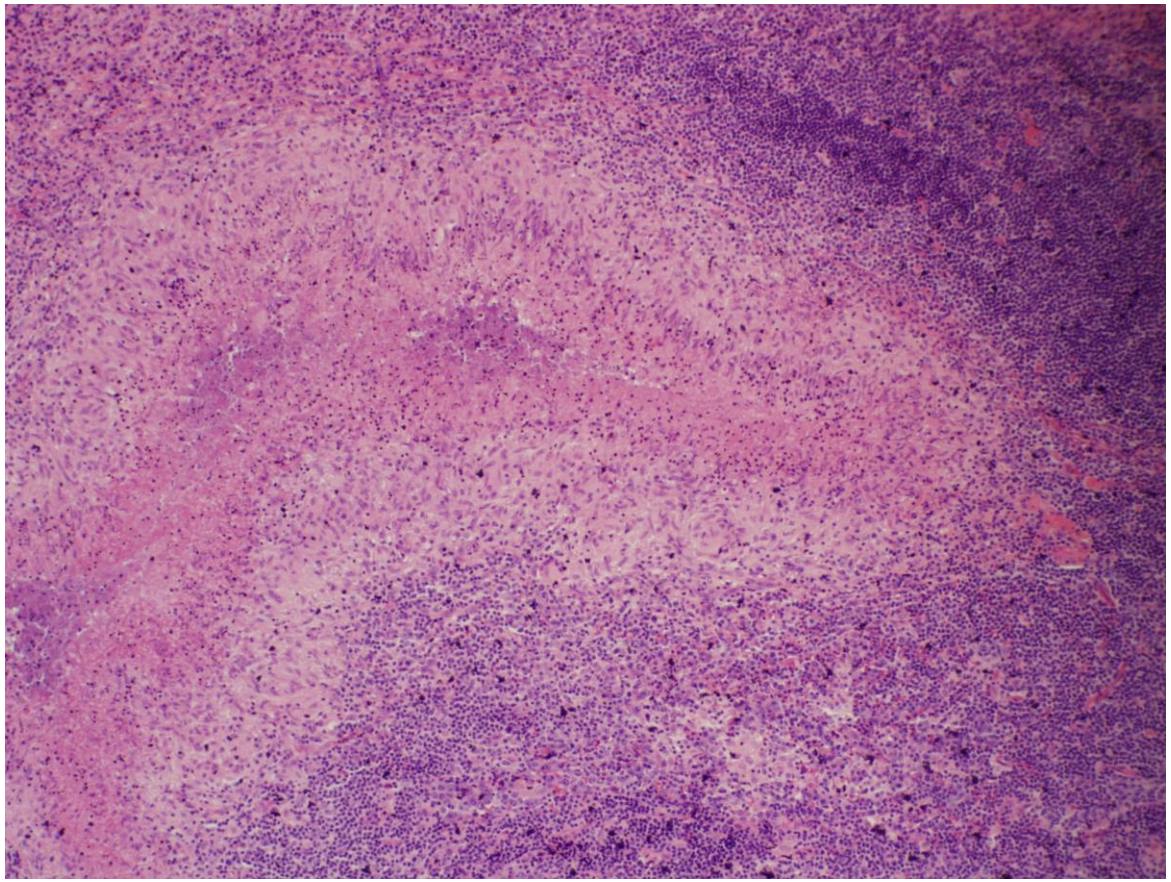
Early in infection, CD3+, CD8+ T-cells predominate in lymph nodes (responding to the EBV-infected B-cells).

CD4:CD8 ratio may be decreased by flow cytometry.

TCR gene rearrangement studies can show oligoclonal pattern.

Aguilera N, Auerbach A. Semin Diagn Pathol. 2018; 35:54-60.

What would Bartonella henselae lymphadenitis look like?

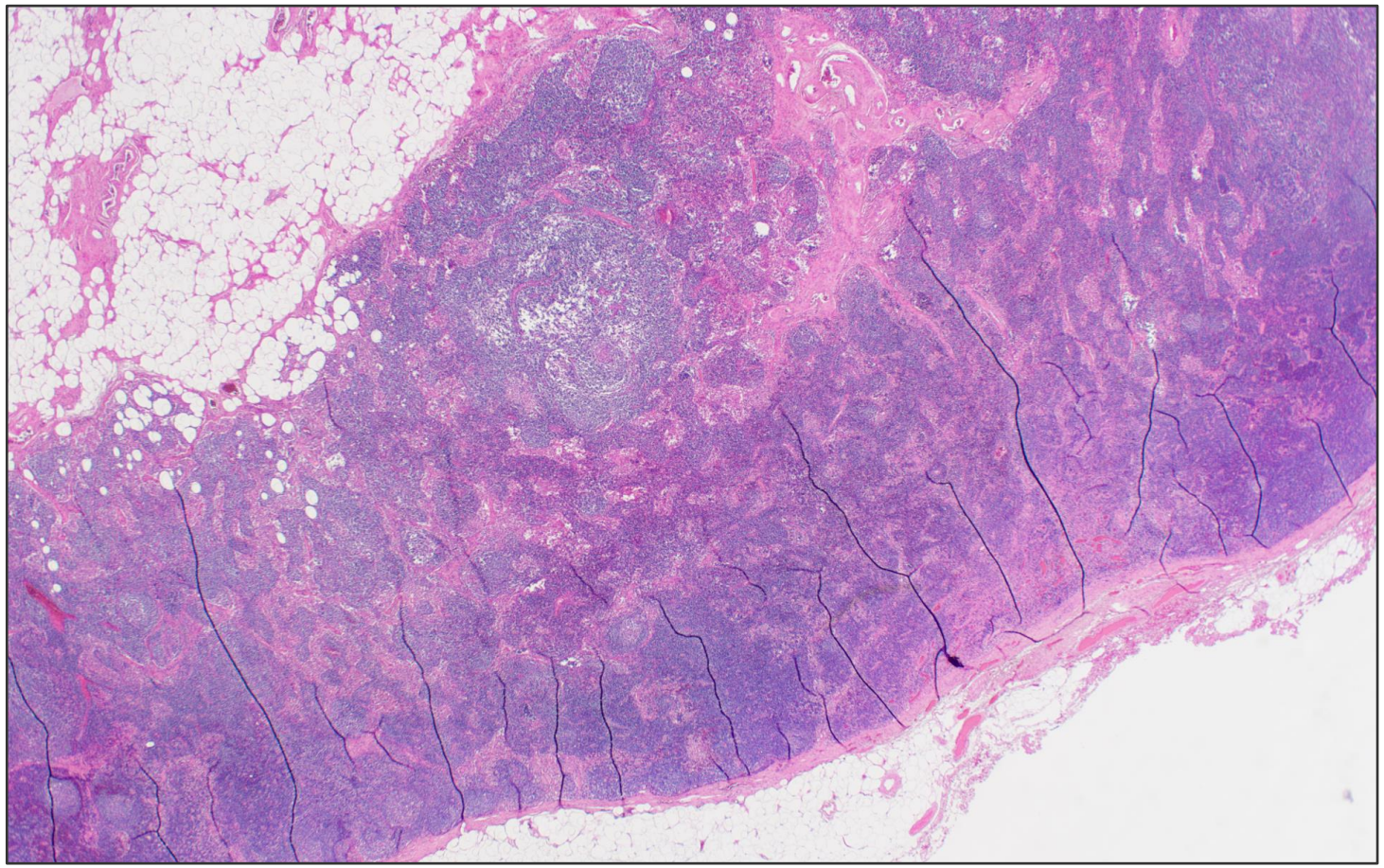


Large necrotizing suppurative (neutrophils present) granulomas with surrounding palisaded histiocytes

Positive for single or clumped curved rods with Warthin Starry stain

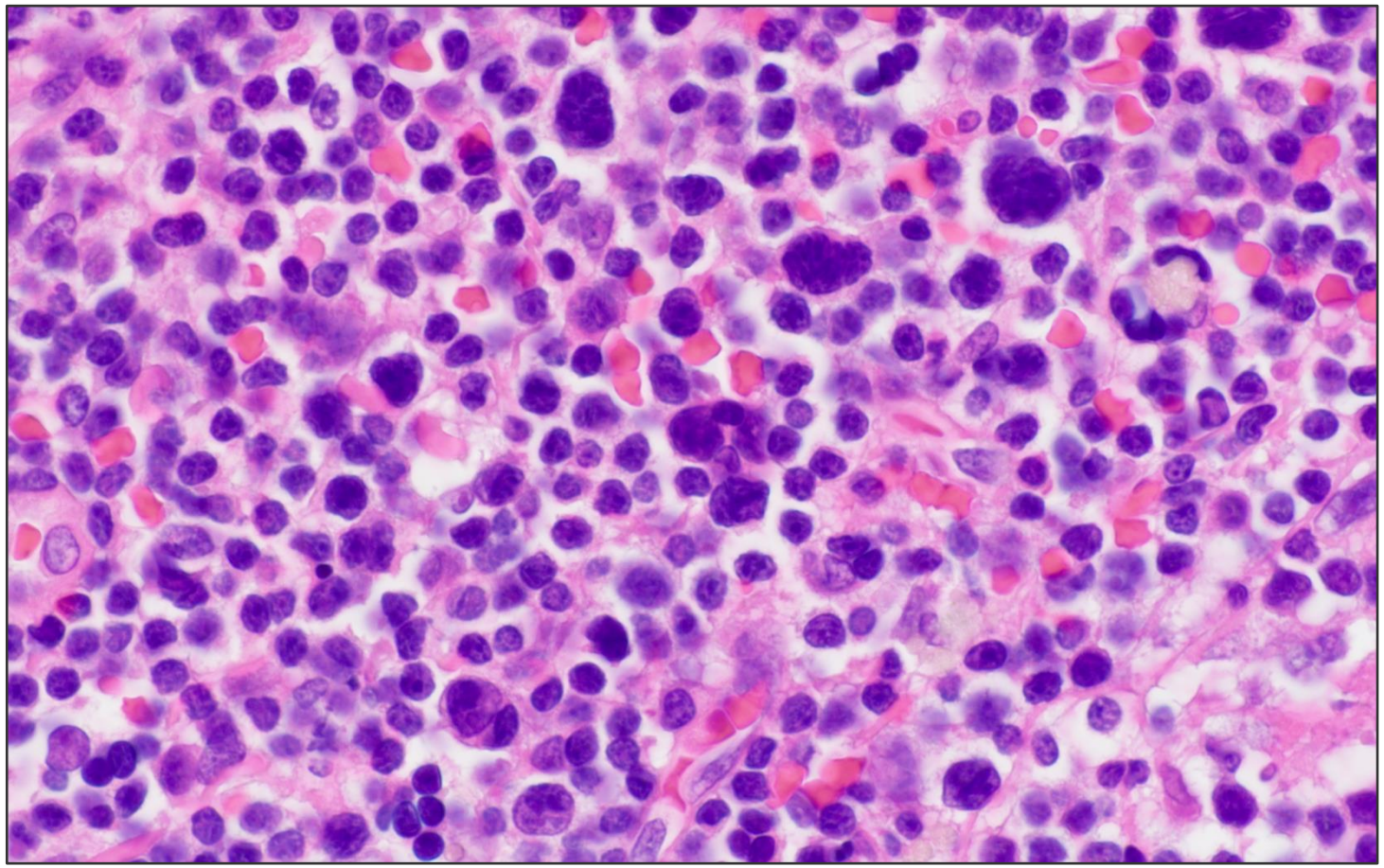
Bartonella IHC and/or PCR may also be performed

Bonus Mini-Case!



71 year old man with incidentally removed lymph node during carotid endarterectomy

H+E, 2x
Few small follicles, sinus histiocytosis, thin intact capsule



What in the world are these large cells?

They are isolated to a single focus in the lymph node.

Some look multinucleate and others have large, smudgy nuclei.

By IHC, they are CD3 positive, CD20 negative, CD30 negative, CD15 negative.

Warthin-Finkeldey like giant cells

- Multinucleated giant cells initially described independently by Warthin and Finkeldey in 1931 in tonsils and adenoids during measles prodrome
  - » AKA mulberry cells
- Subsequently described in association with other reactive processes and some lymphomas
- Positive for CD43 and CD3; appear to be formed from T-cells

Delsol G, Pradere M, Voigt JJ, Nespoulous M, et al. Histopathology. 1982; 6(4):451-65.
Kjeldsberg CR, Kim H. Hum Pathol. 1981; 12(3):267-72.
Kamel OW, LeBrun DP, Berry GJ, Dorfman RF, Warnke RF. Am J Clin Pathol. 1992; 97(2):179-83.

Take Home Points

- Don’t forget to include infectious diseases on your differential diagnosis for Hematopathology cases!
- MAC lymphadenitis is one possible cause of isolated lymphadenopathy in young children, even if they are immunocompetent
- Follicular hyperplasia, epithelioid histiocytes in germinal centers, and monocytoid cells in sinuses constitute the histologic triad of toxoplasma lymphadenitis
- Luetic lymphadenitis is associated with an increase in polytypic plasma cells, and shows morphologic overlap with IgG4-related disease, rheumatoid arthritis, and plasma cell variant of Castleman disease
- Immunoblasts in EBV lymphadenitis may be prominent and can be CD30 (weak, variable) positive- don’t confuse them with H/R-S cells

Thank you for participating.

Questions?

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