

# Selected Cases in Non-Gynecologic Cytopathology: Inflammatory and Infectious Disease

Park City Anatomic Pathology Update  
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# Disclosures

- I have no conflicts of interest to disclose.

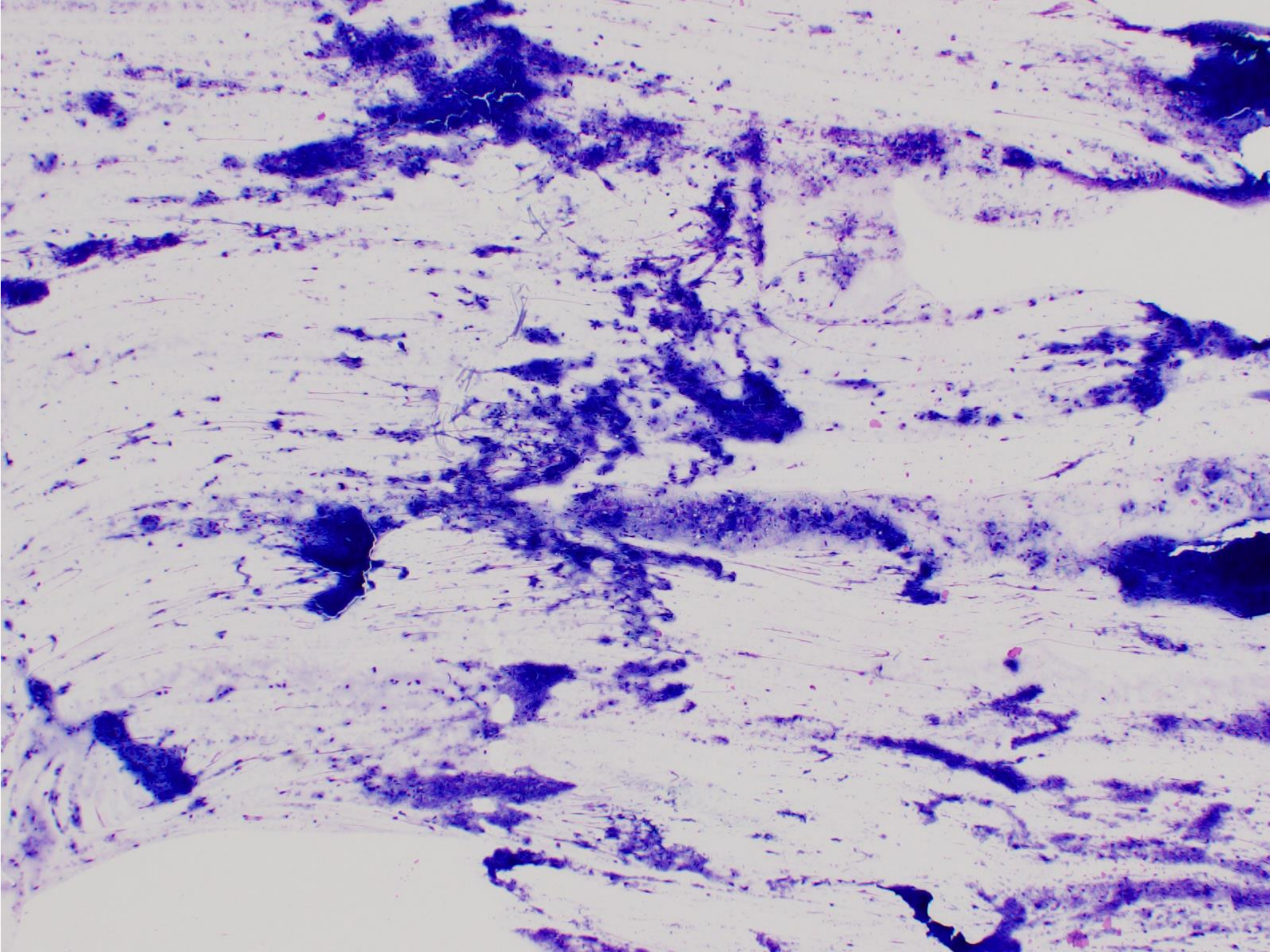
# Learning Objectives

- Using a case-based approach, to review selected infectious and inflammatory/non-neoplastic conditions that may mimic malignant lesions radiologically
- To discuss some of the diagnostic challenges to rapid on-site assessment via aspiration or touch imprint cytology for these lesions
- To review traditional ancillary techniques that may assist in the diagnosis of these entities in cytologic and small biopsy samples

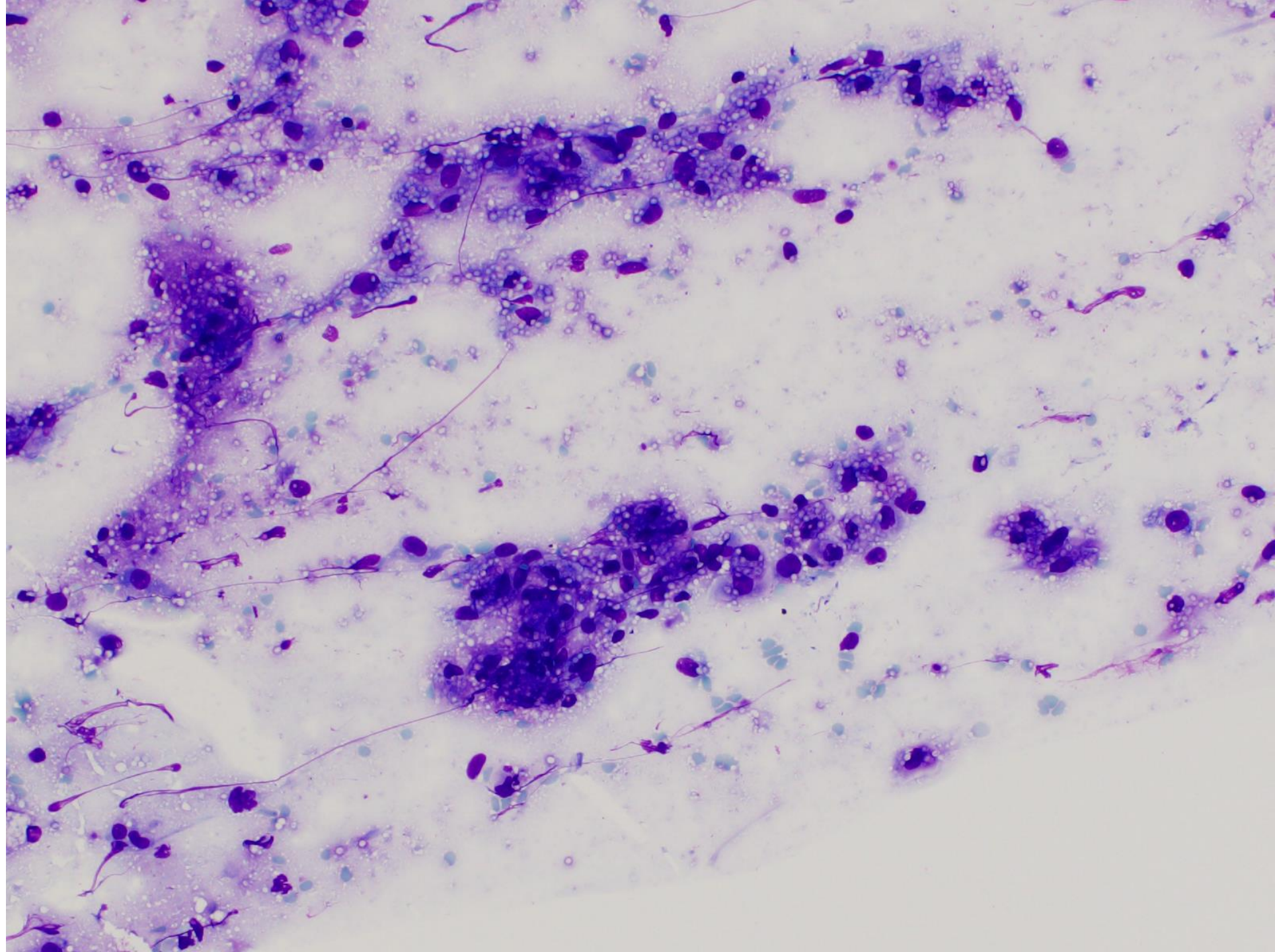
# Case 1

- 51-year-old male with a history of papillary renal cell carcinoma (pT2 pN1, negative margins) s/p radical nephrectomy 2 years prior
- Declined adjuvant systemic treatment
- Recent interval development of new multiple right lower lobe lung nodules suspicious for metastasis

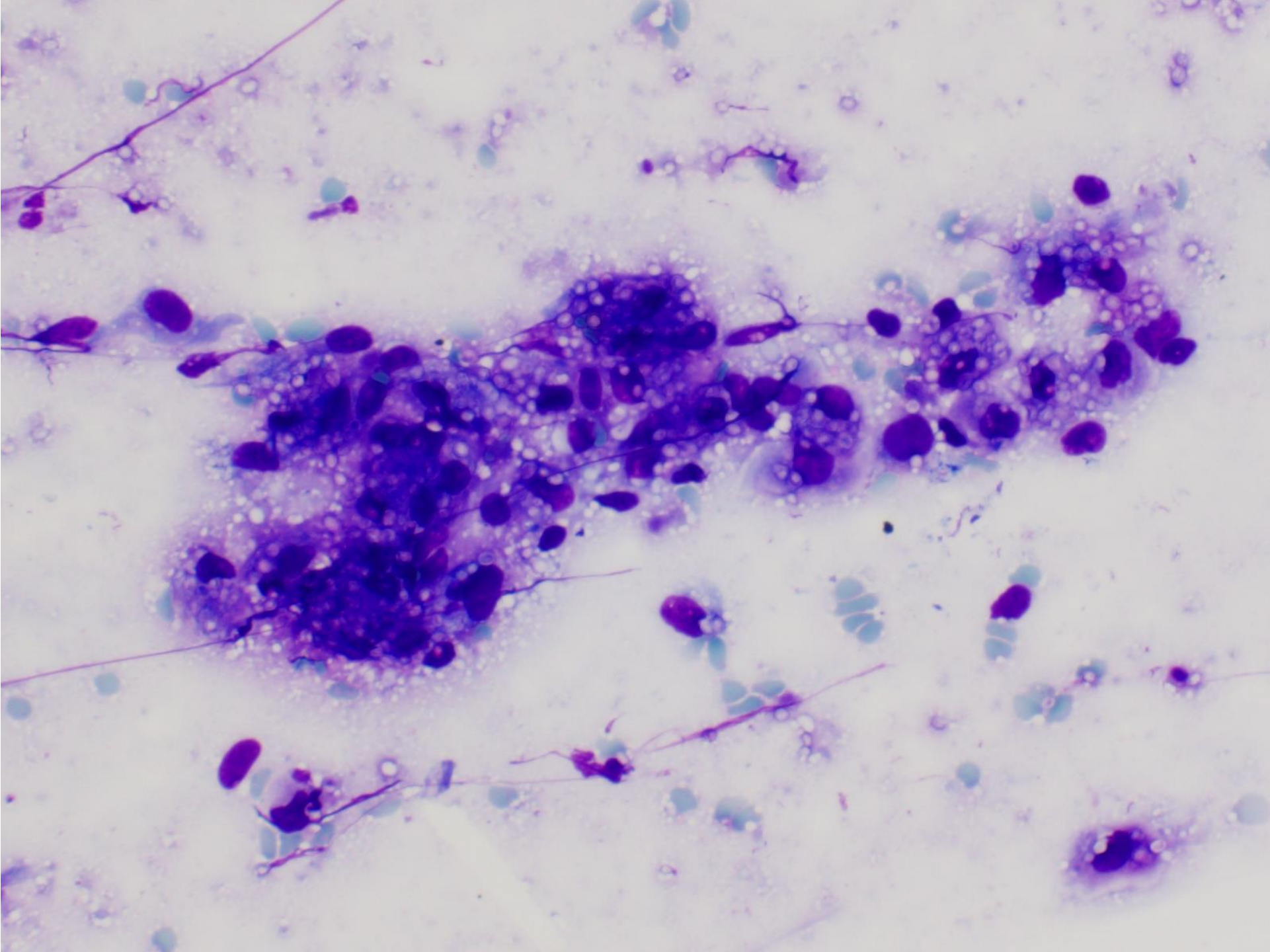
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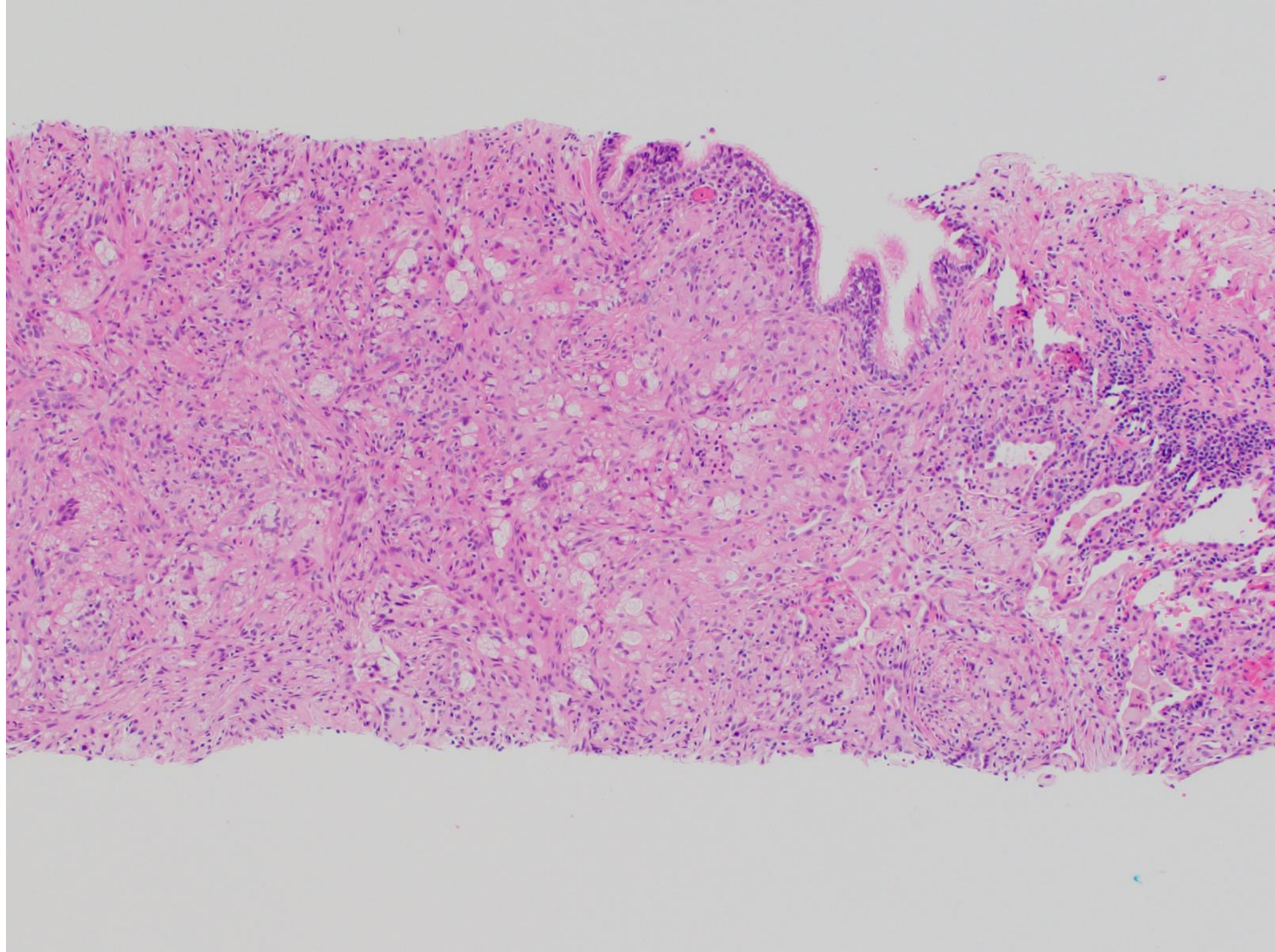


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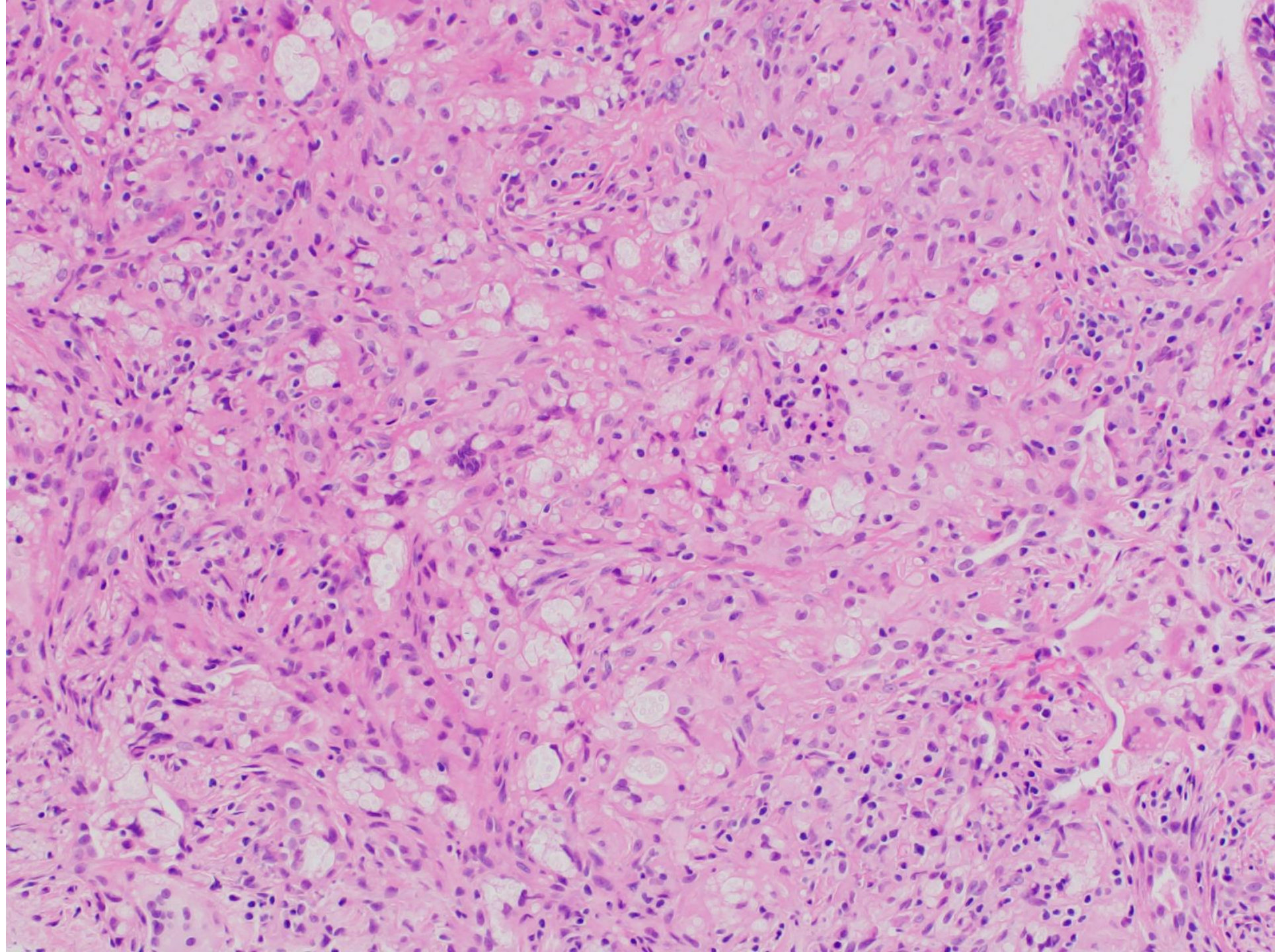
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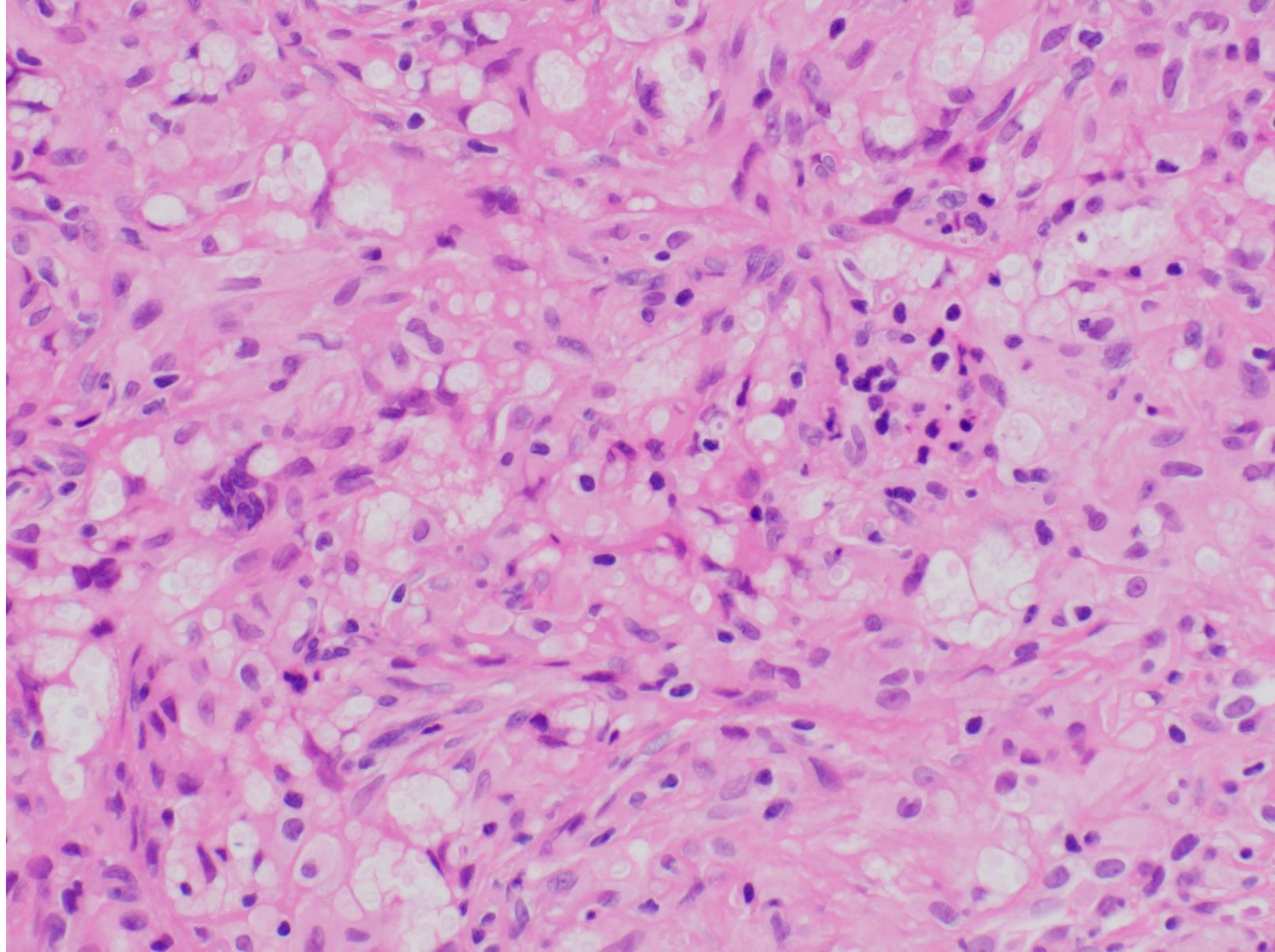




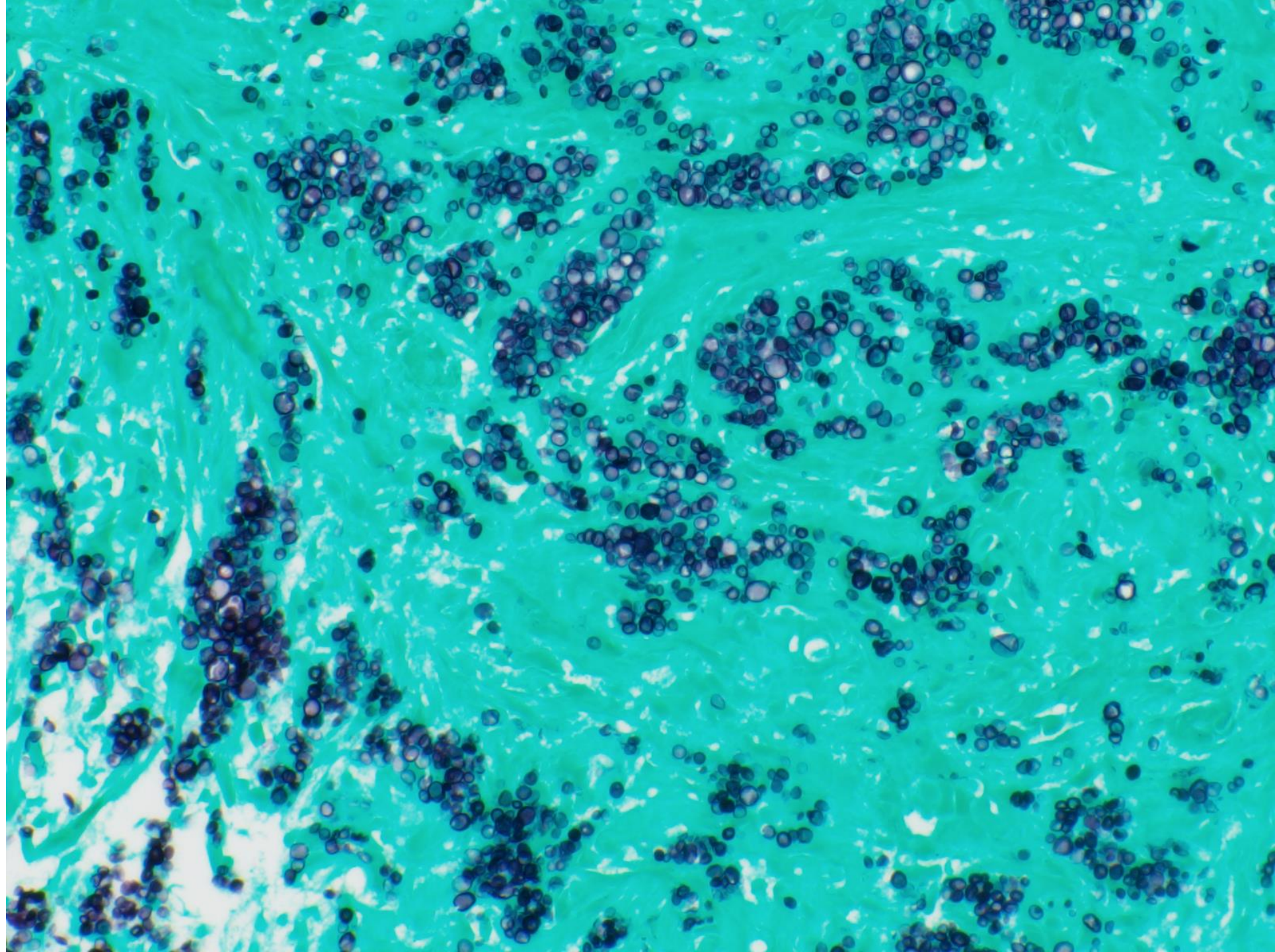
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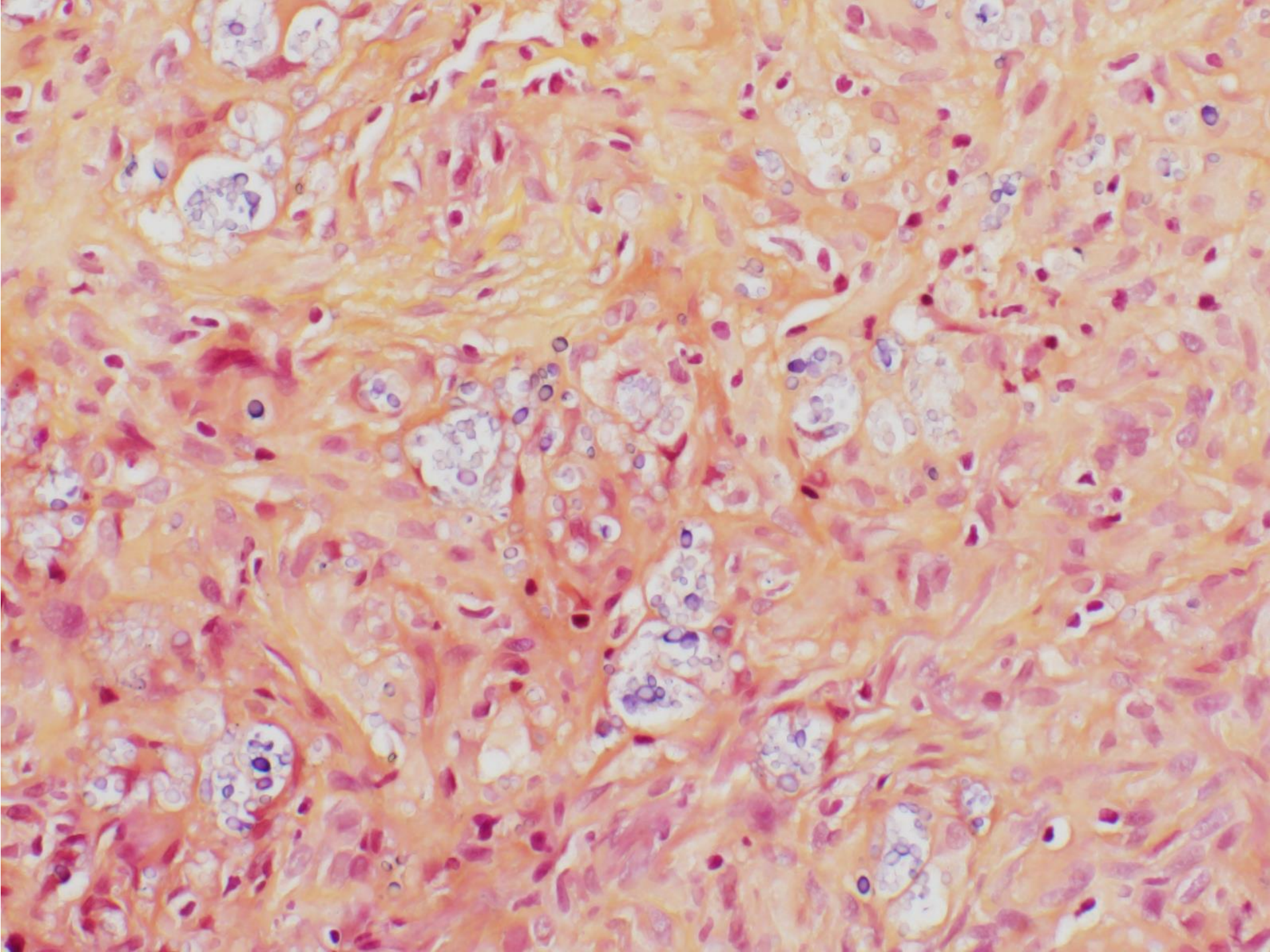
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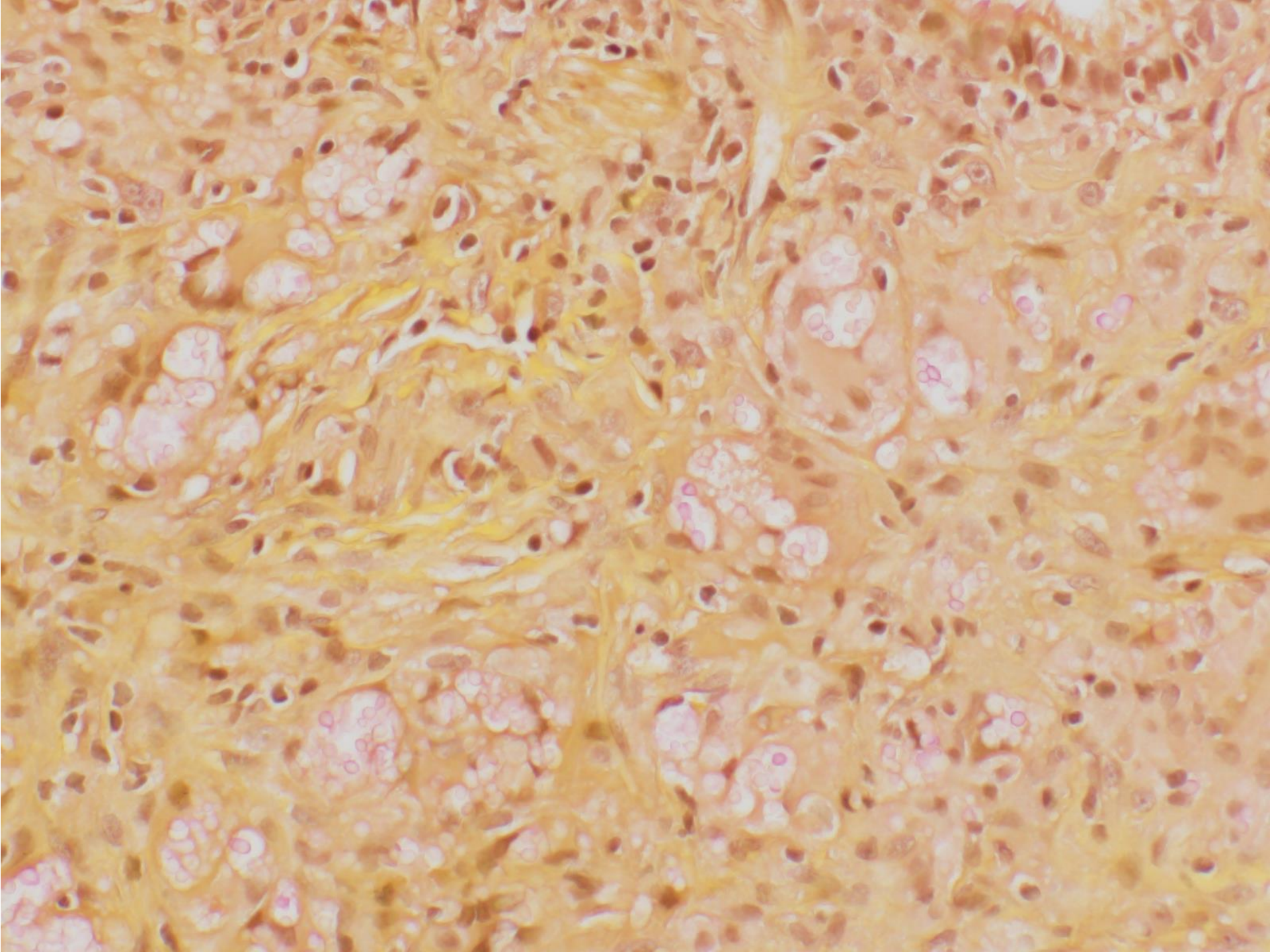
GMS



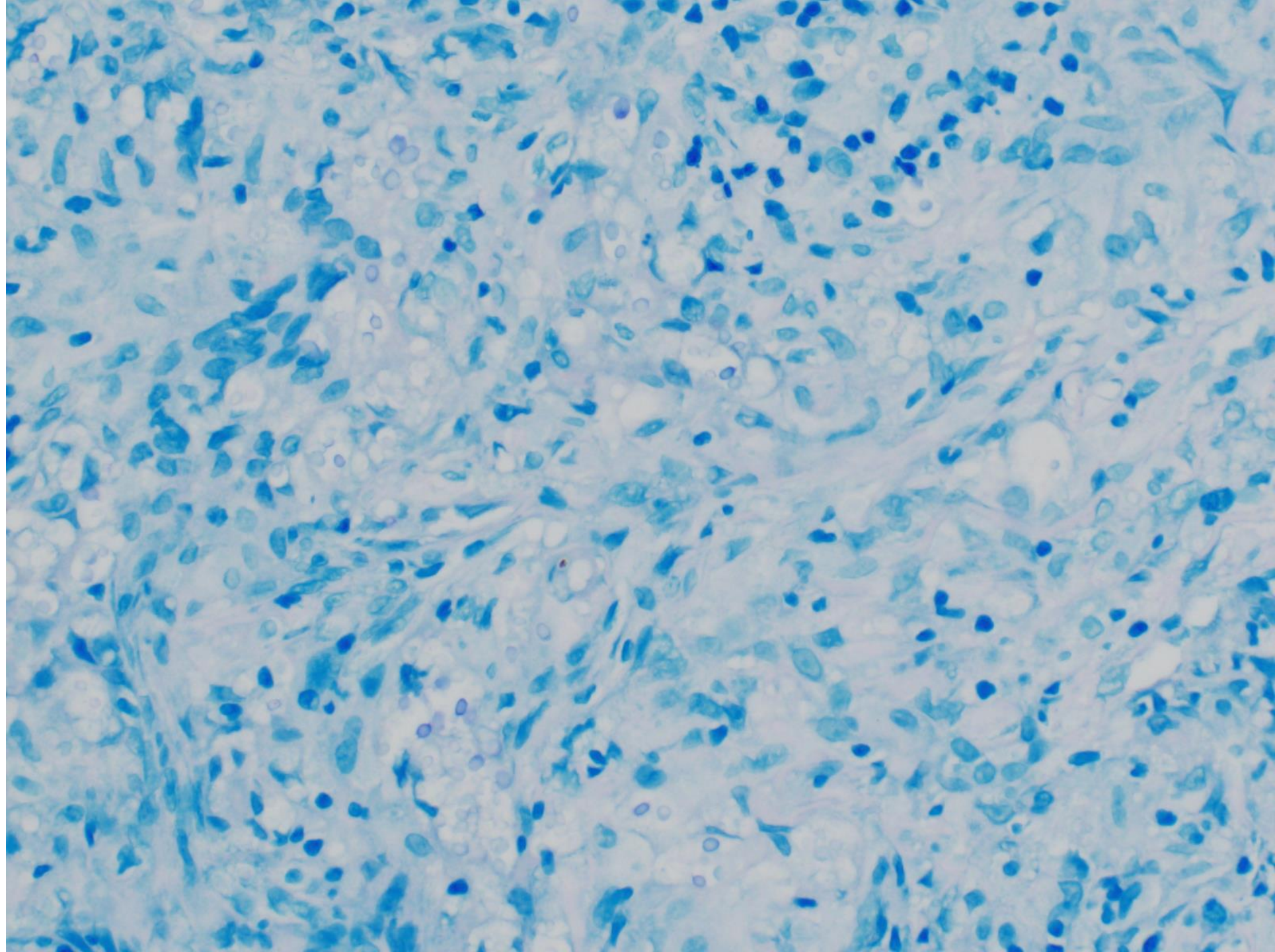
Gram stain



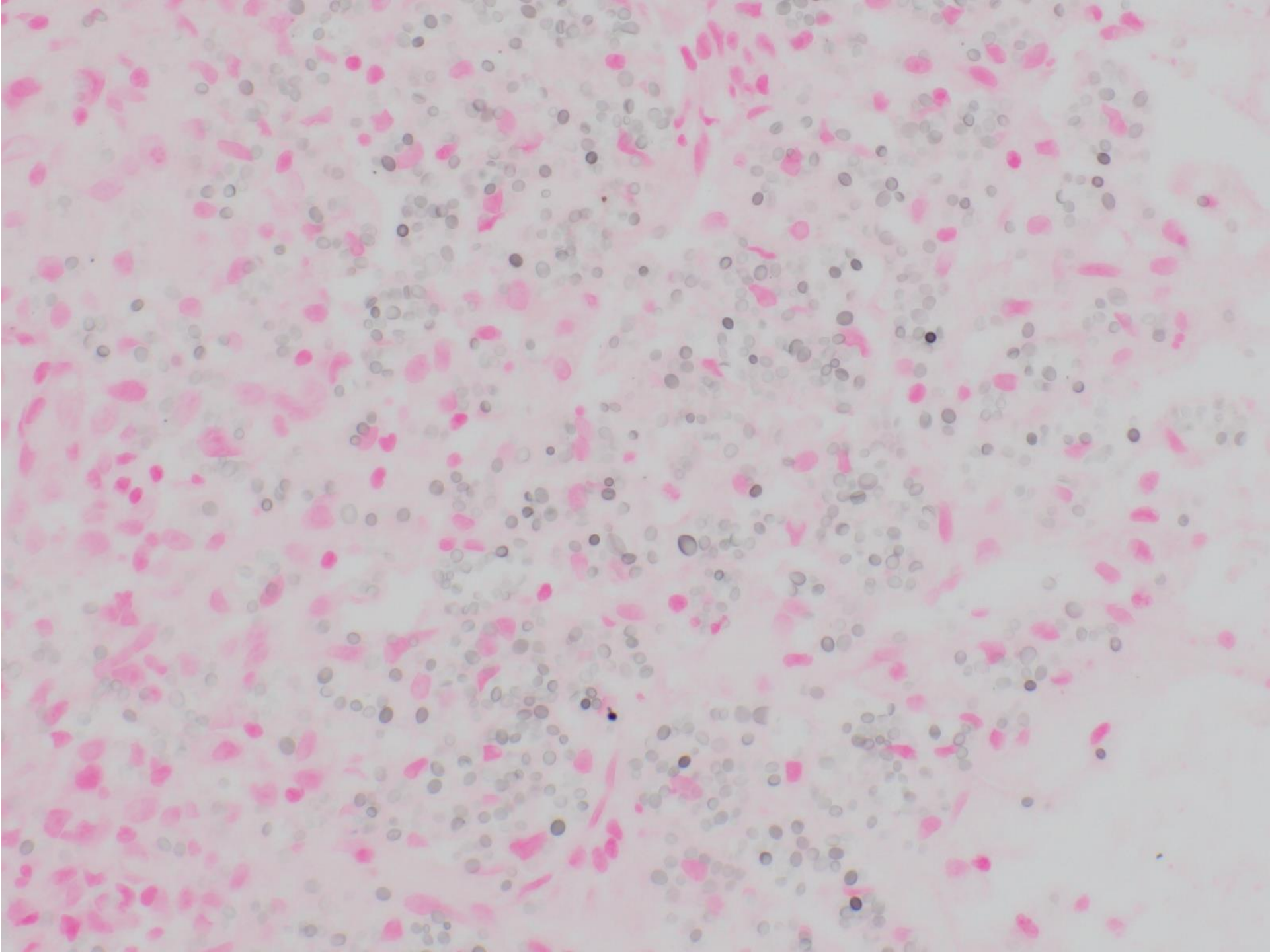
Mucicarmine



AFB



Fontana-  
Masson



# Fungal infection

- No tissue sent for culture
- Intracellular forms which are GMS positive, focally Fontana-Masson positive, negative for Gram stain, mucicarmine and AFB
- Morphologic differential diagnosis includes *Histoplasma* spp, *Candida* spp, (less likely due to Gram negativity), capsule-deficient *Cryptococcus* spp (less likely owing to faint positivity for Fontana-Masson), and small form of *Blastomyces*
- Molecular testing attempted but non-diagnostic
  
- Patient is asymptomatic
- No significant social or travel history
- Infectious disease consultation in progress



# Point of the Spear: Tissue Procurement and the Utility of Rapid On-site Assessment (ROSE)

- The “frozen section” of minimally invasive tissue procurement procedures
- Role of ROSE:
  - ❖ Ensure adequacy of tissue via real-time feedback to proceduralist (minimize non-diagnostic rate, number of sites biopsied)
  - ❖ Provide preliminary diagnosis/differential diagnosis
  - ❖ Ensure appropriate disposition of tissue for
    - Diagnostics
    - Prognostics
    - Theranostics
    - Clinical trials/research studies
- Use of fine needle aspiration vs. touch imprint cytology will vary with proceduralist and intended target

# Selected Diagnostic Considerations in Lung Pathology

Clinicoradiologic Presentation	Benign	Malignant
Cavitary/cystic lesion	Bacterial (aspiration)	Squamous cell carcinoma
	Fungal	
	Parasitic (echinococcosis)	
Diffuse ground glass opacities	Viral	Adenocarcinoma, lepidic pattern
	Pneumocystis jirovecii	
Tissue Reaction		
Granulomatous	Fungal	Metastatic seminoma
	Mycobacterial	Lymphoma
	Sarcoidosis	
	Granulomatosis with polyangiitis	
Amorphous extracellular material	Pneumocystis jirovecii	N/A
	Pulmonary alveolar proteinosis	
	Pulmonary amyloidosis	

# Infectious Disease Dx in Anatomic Pathology

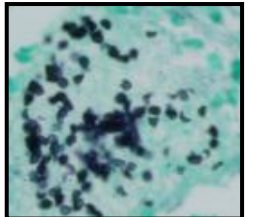
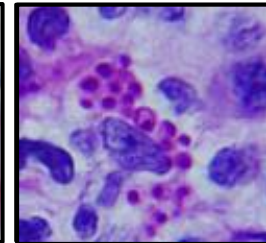
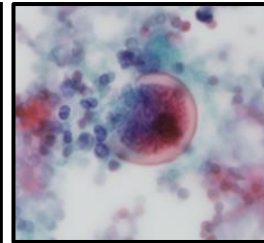
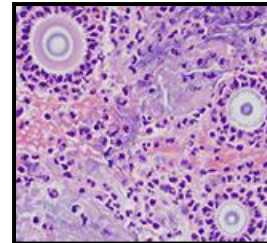
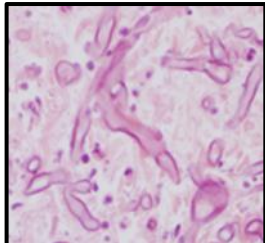
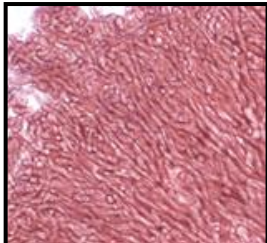
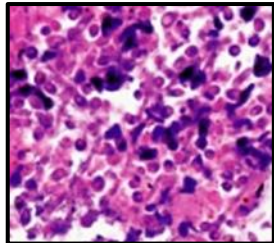
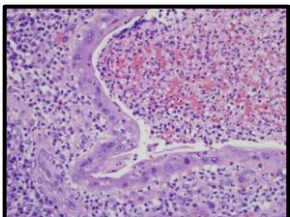
## Patient Populations

- Immunocompetent: community acquired, regional considerations
- Immunocompromised:
  - HIV
  - Autoimmune diseases treated with steroids
  - Transplant patients
  - Oncologic patients – chemotherapy
  - Oncologic patients – immunotherapy

## Ancillary Testing

- Microbiologic studies
- Histochemical stains
- Molecular assays
  - FFPE (tissue or cell blocks): PCR/sequencing
  - Limitations:
    - ✓ May not be widely available
    - ✓ PCR inhibitors in the specimen
    - ✓ Low levels of fungal DNA
    - ✓ Mixtures of different fungal sequences

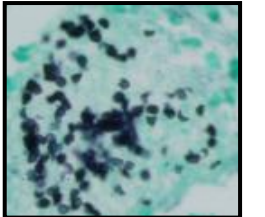
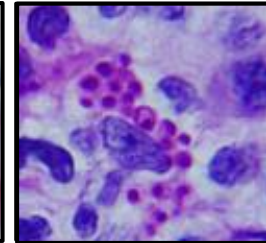
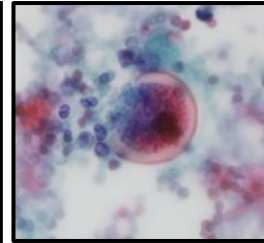
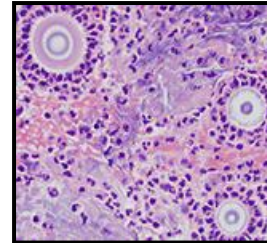
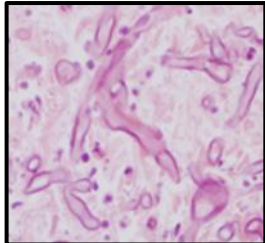
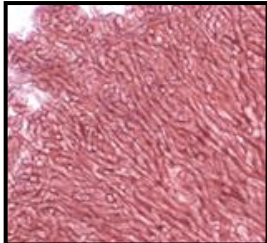
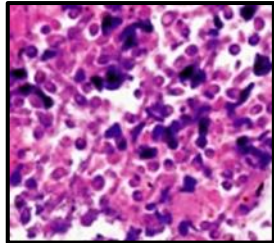
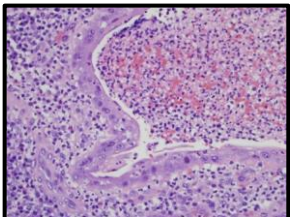
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<b>Demographics</b>	Worldwide	Worldwide	Worldwide	Worldwide	North American deserts	Americas, (Ohio, Mississippi River Valleys)	North America	Worldwide
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<b>Shape</b>	Tear drop-shaped	45 degree acute angle branching	Broad, ribbon-like contour, irregular, right angle branching	Round-oval, clear capsule	Spherical, refractile	Oval, intracellular or extracellular due to cellular rupture	Spherical, double-contoured wall	Cup-shaped cysts
<b>Budding</b>	Pseudohyphae	Septated hyphae	Broad, non-septated hyphae	Narrow based with thick capsule	Endospores	Single, narrow	Broad-based	N/A
<b>Associated tissue response</b>	Respiratory space colonization; tissue invasion	Tissue/vascular invasion, "fungus ball"	Tissue/vascular invasion	Granulomatous	Necrotizing granulomatous inflammation	Granulomatous	Neutrophilic, granulomatous inflammation	Minimal; intraalveolar material
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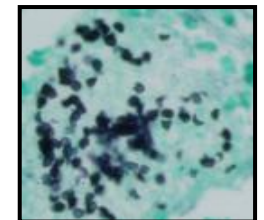
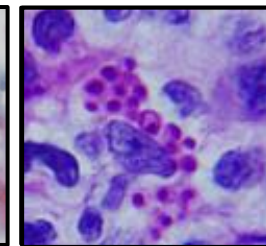
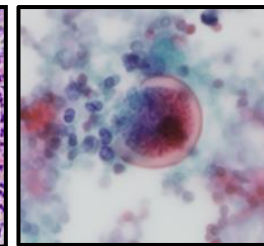
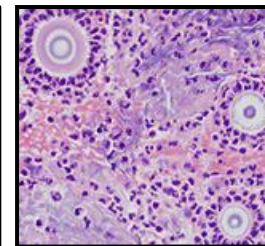
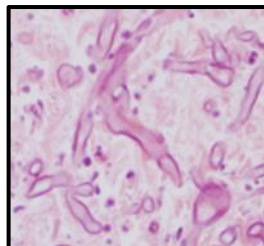
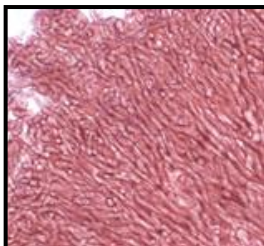
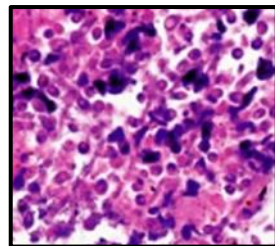
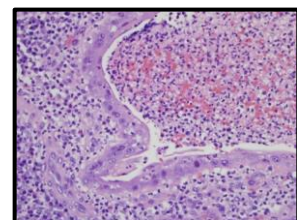
Squamous metaplasia adjacent to fungus ball

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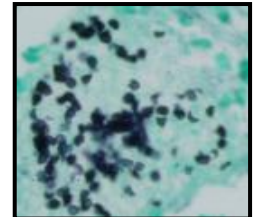
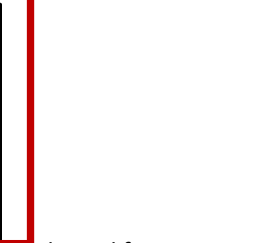
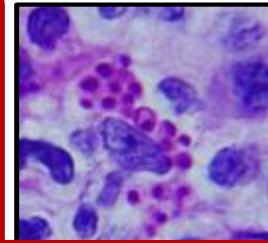
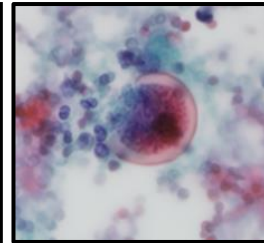
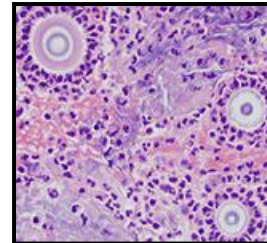
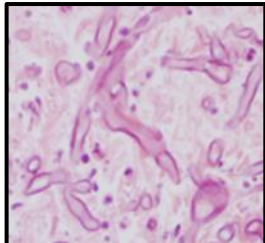
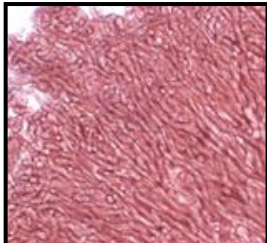
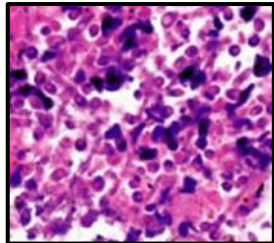
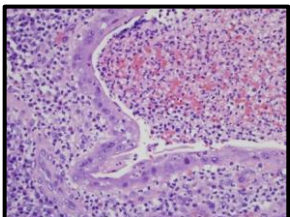
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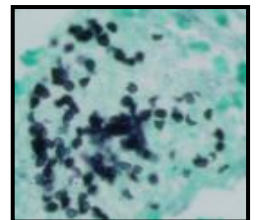
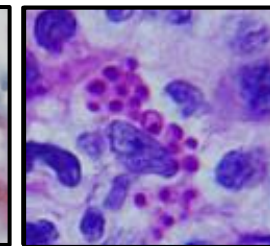
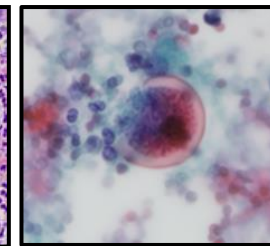
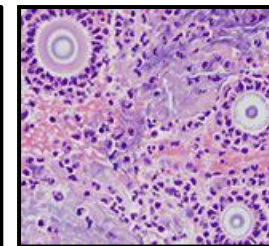
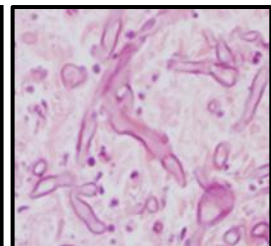
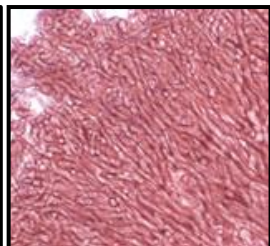
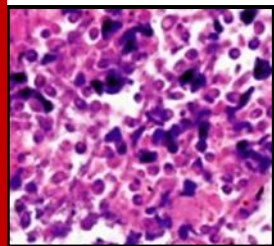
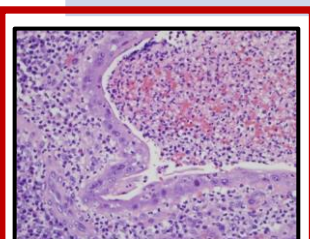
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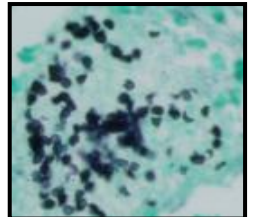
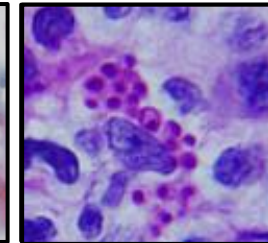
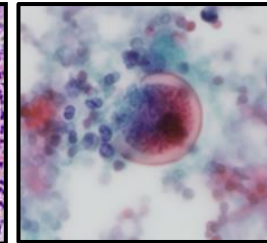
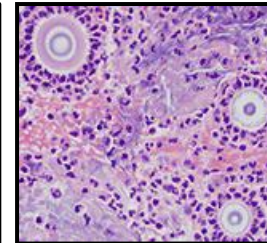
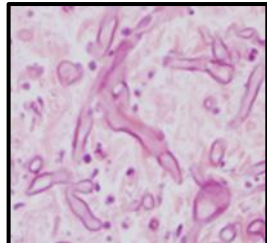
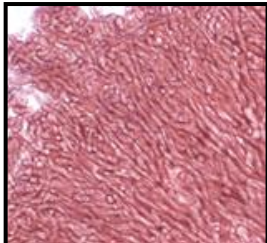
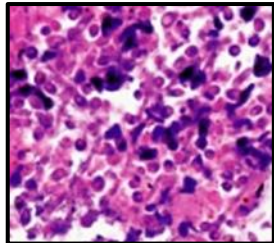
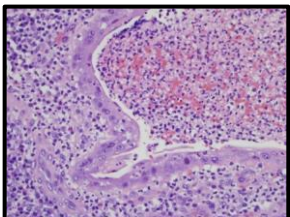
Squamous metaplasia adjacent to fungus ball

Criterion	Candida spp.	Aspergillus spp	Mucorales (Phycomycosis, zygomycosis)	Cryptococcus spp.	Coccidioides spp.	Histoplasma spp.	Blastomyces spp.	Pneumocystis jirovecii
<b>Demographics</b>	Worldwide	Worldwide	Worldwide	Worldwide	North American deserts	Americas, (Ohio, Mississippi River Valleys)	North America	Worldwide
<b>Size (microns)</b>	2-10	10-30	10-30	4-15	Spherule (15-60), endospores (1-2)	1-5	8-20	4-8
<b>Shape</b>	Tear drop-shaped	45 degree acute angle branching	Broad, ribbon-like contour, irregular, right angle branching	Round-oval, clear capsule	Spherical, refractile	Oval, intracellular or extracellular due to cellular rupture	Spherical, double-contoured wall	Cup-shaped cysts
<b>Budding</b>	Pseudohyphae	Septated hyphae	Broad, non-septated hyphae	Narrow based with thick capsule	Endospores	Single, narrow	Broad-based	N/A
<b>Associated tissue response</b>	Respiratory space colonization; tissue invasion	Tissue/vascular invasion, "fungus ball"	Tissue/vascular invasion	Granulomatous	Necrotizing granulomatous inflammation	Granulomatous	Neutrophilic, granulomatous inflammation	Minimal; intraalveolar material
<b>Pap Stain</b>	Cyanophilic	Cyanophilic	Cyanophilic	Pale, cyanophilic	Orangeophilic	Dark outline	Blue-green	Not visible (in proteinaceous material)
<b>DQ stain</b>	Dark blue to purple	Variable	Poor	Blue to purple	Colorless or light blue	Dark blue	Pale blue	Negative images
<b>Selected special stains</b>	GMS+, PAS-	GMS+, PAS+	GMS +/-, PAS poorly +	GMS, mucicarmine	PAS, GMS	GMS, PAS	GMS, PAS	GMS+, PAS-
<b>Molecular studies</b>	PCR & sequencing on FFPE	PCR on FFPE	PCR on FFPE	PCR & sequencing on FFPE	PCR & sequencing on FFPE	PCR & sequencing on FFPE	PCR +/- sequencing on FFPE	PCR on FFPE



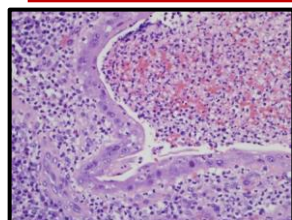


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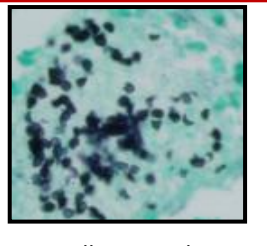
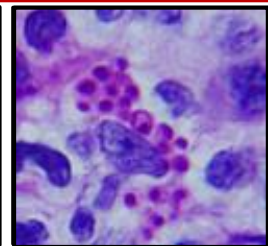
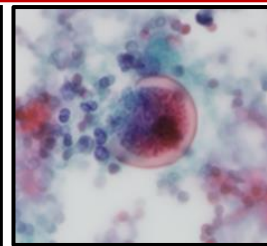
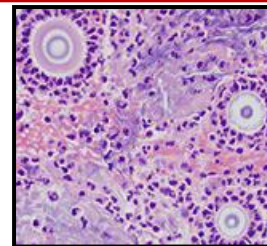
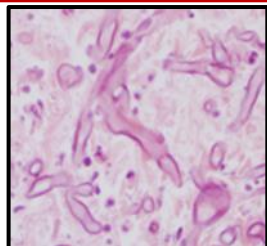
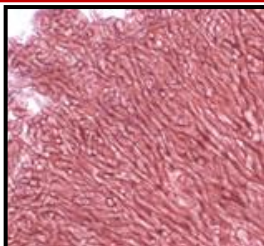
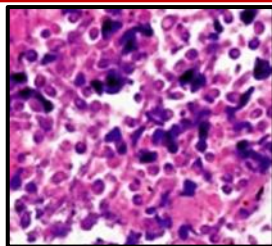


Squamous metaplasia adjacent to fungus ball

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Squamous metaplasia adjacent to fungus ball



# Fungal Infection - Special Stains

Stain	Interpretation	Benefits	Limitations
GMS	Organisms: black Background: green	Highlights all fungi, including <i>Pneumocystis</i>	Dirty background staining can obscure organisms
PAS	Organisms: red/pink Nuclei: blue	Positive in most fungi	Suboptimal for <i>Mucorales</i>
Fontana Masson	Pigment: black Nuclei: red	Positive in pigmented filamentous fungi, <i>Cryptococcus</i> spp.;	Variability in staining; can stain hyaline fungi non- specifically
Mucicarmine	Mucin: red; nuclei: black; Background: yellow	Positive in <i>Cryptococcus</i> spp. Capsule	Dirty background and light staining can hamper interpretation

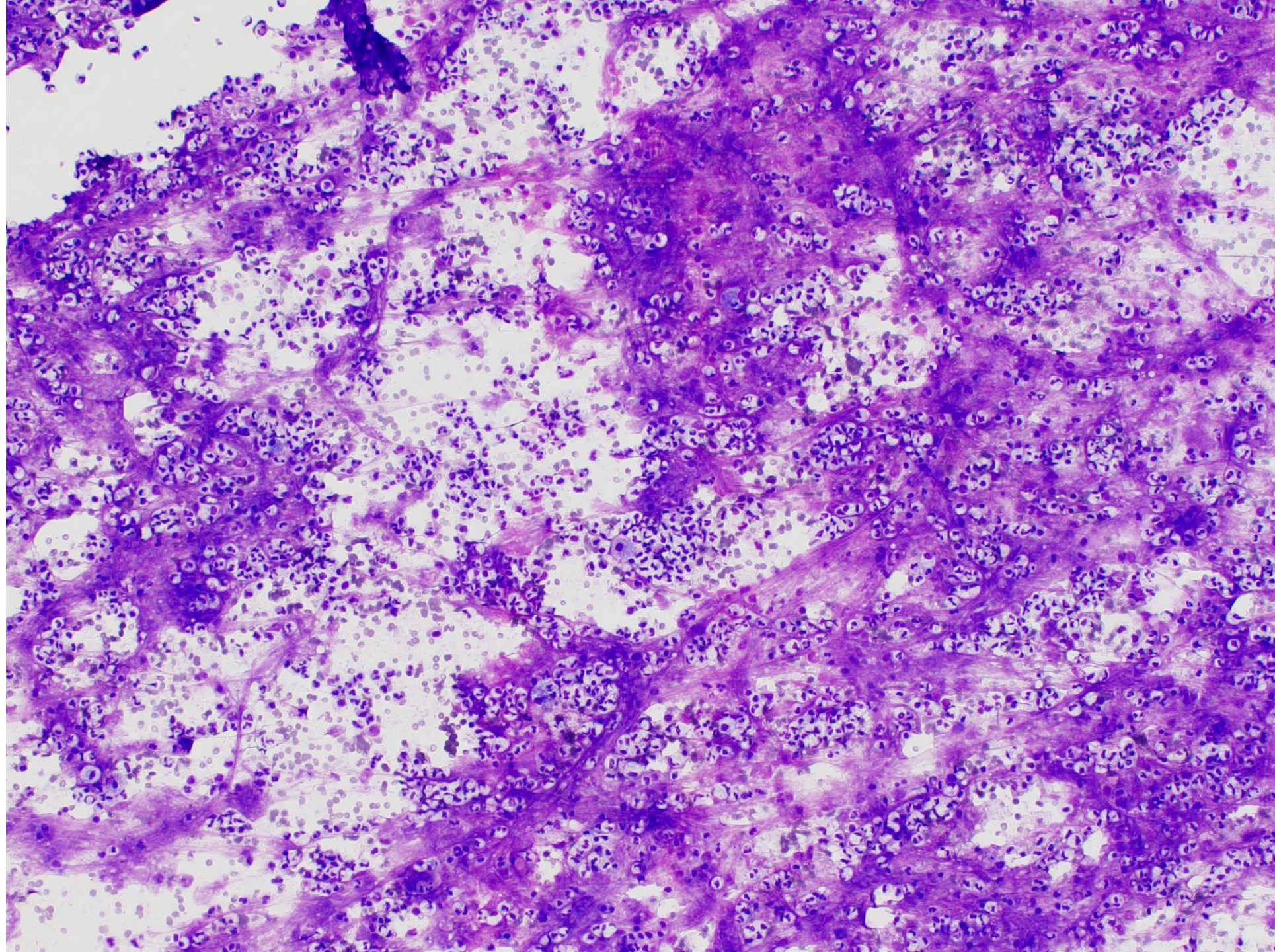
# Case 1: Take Home Points – Fungal Infection

- Knowledge of patient background including immune status, systemic treatment with steroids or anticancer agents and basic radiologic characteristics of the targeted lesion is critical
- Employing ROSE and having a low threshold to consider tissue allocation for microbiologic studies are major assets in the diagnosis of infectious disease in small biopsies
- Traditional morphologic analysis and histochemical stains remain foundational tools in morphologic detection of infectious disease
- Molecular testing offers promise in rapid analysis from FFPE but bears limitations

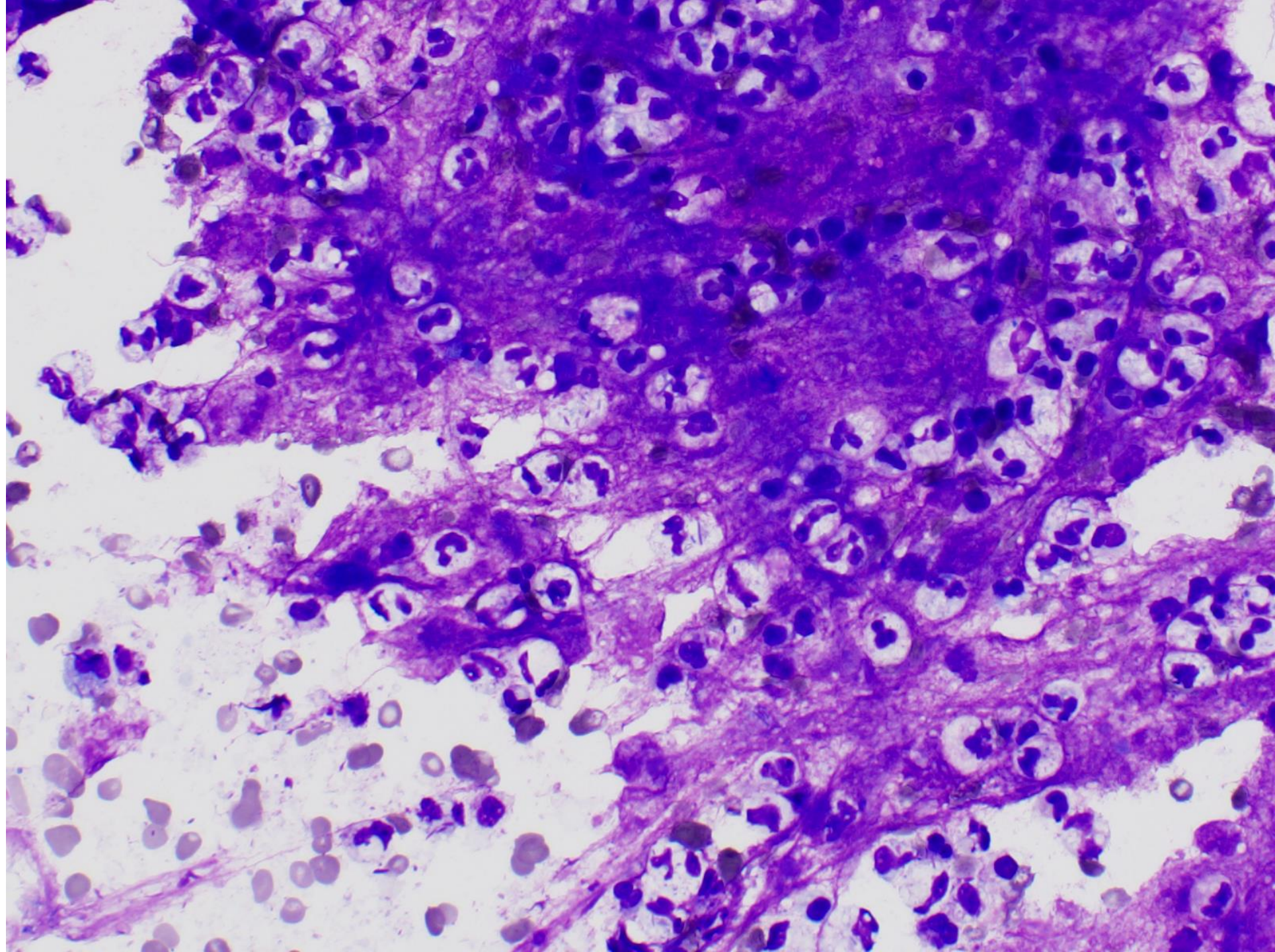
## Case 2

- 43-year-old female initially presented with persistent abdominal pain
- Imaging studies revealed ascites and findings concerning for peritoneal carcinomatosis and associated pelvic mass
- Given the strong concern for malignancy, omental and peritoneal biopsies with intraoperative frozen section assessment was requested with no malignancy identified

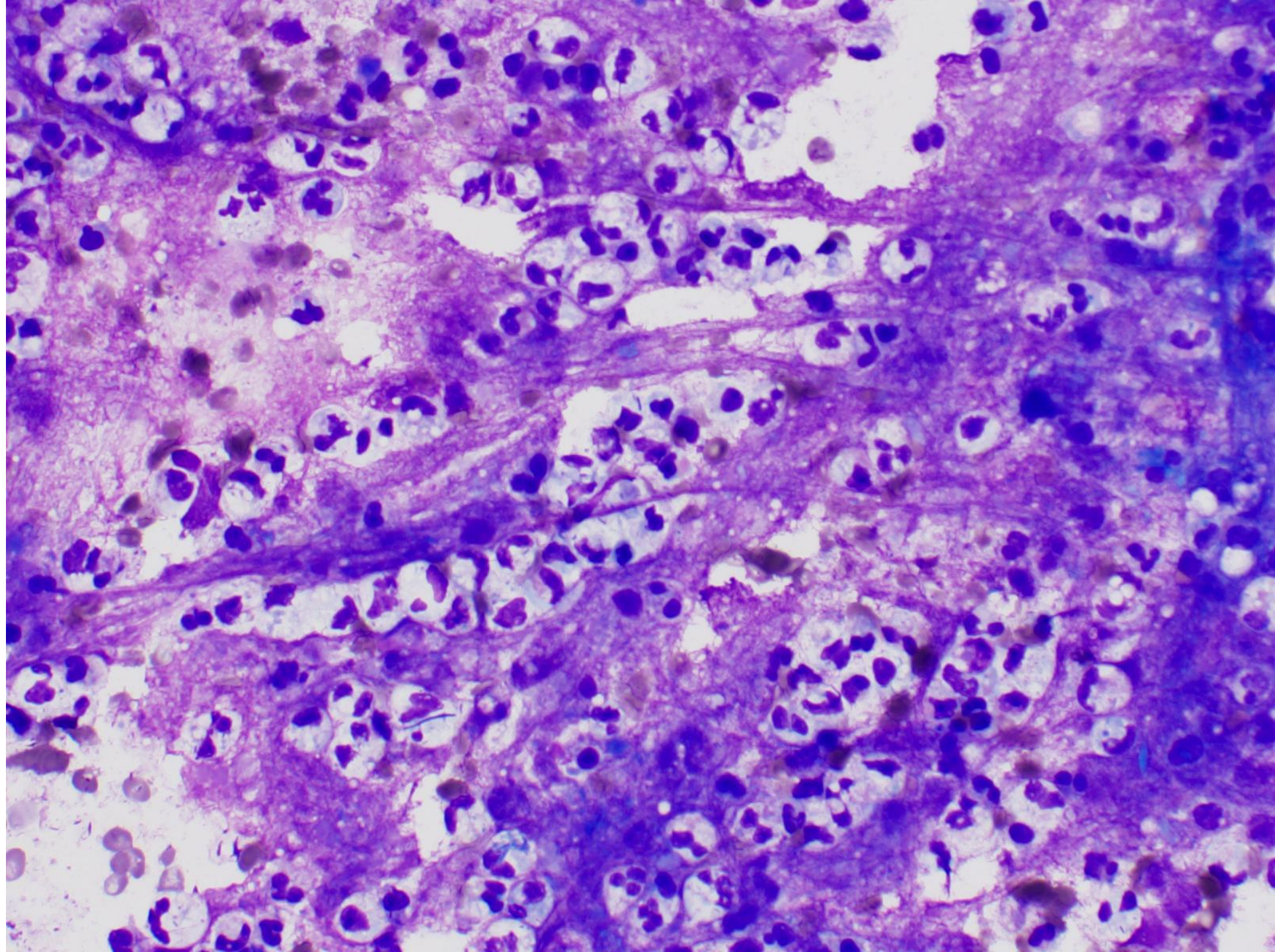
FNA pelvic  
mass



FNA pelvic  
mass

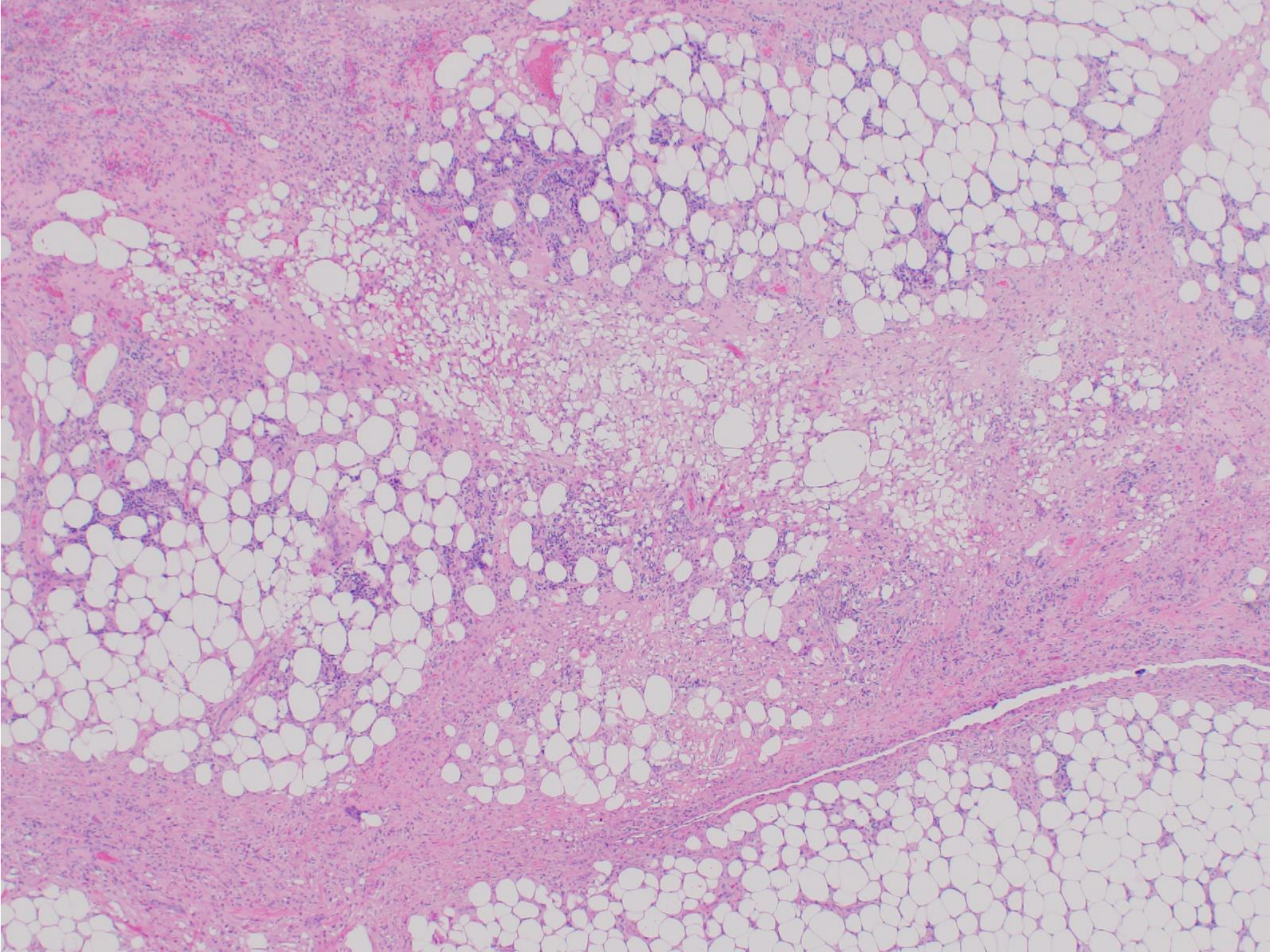


FNA pelvic  
mass; clinical  
concern for  
infection  
directed  
submission of  
material for  
cultures

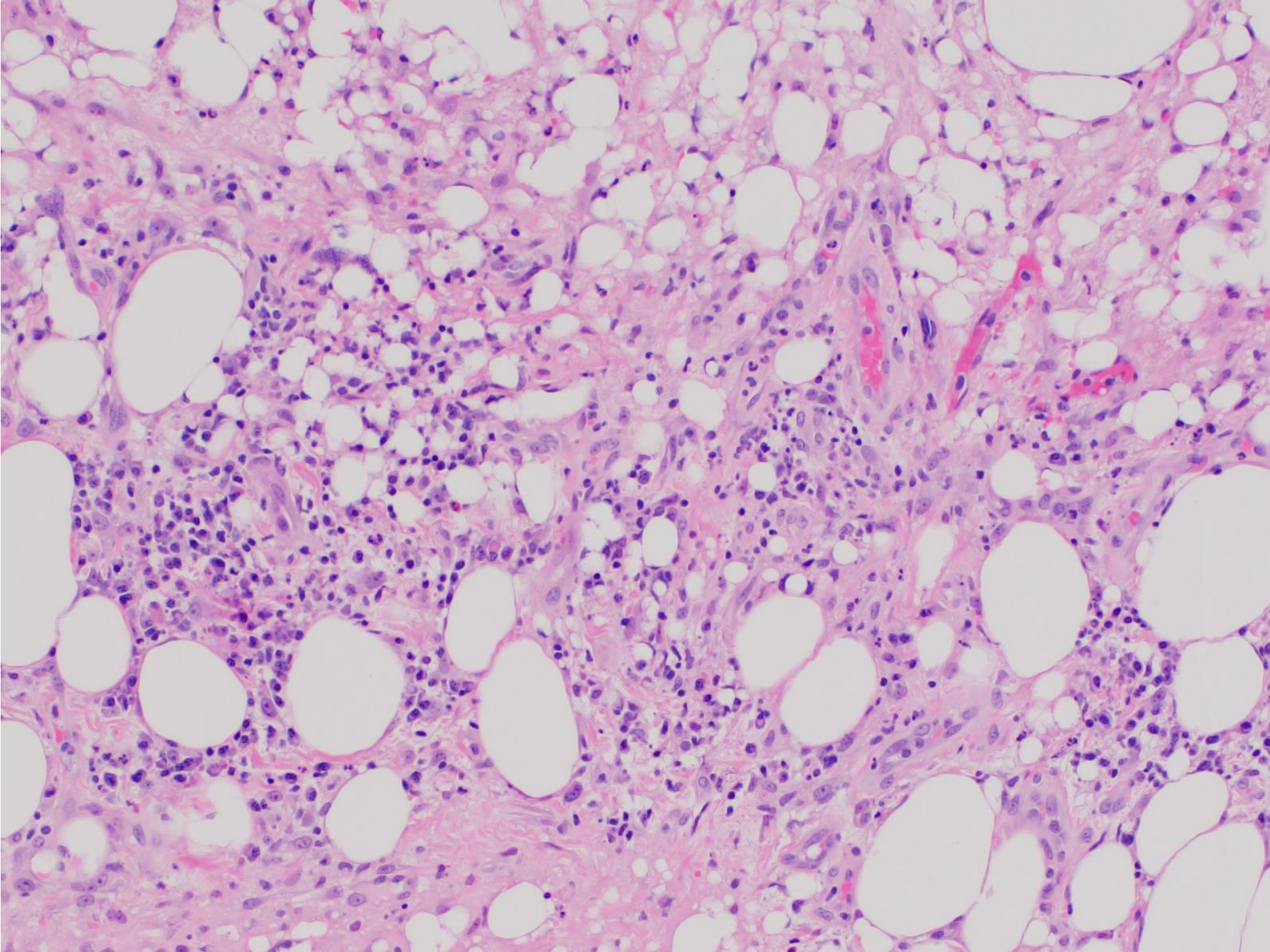




Biopsy omental  
mass

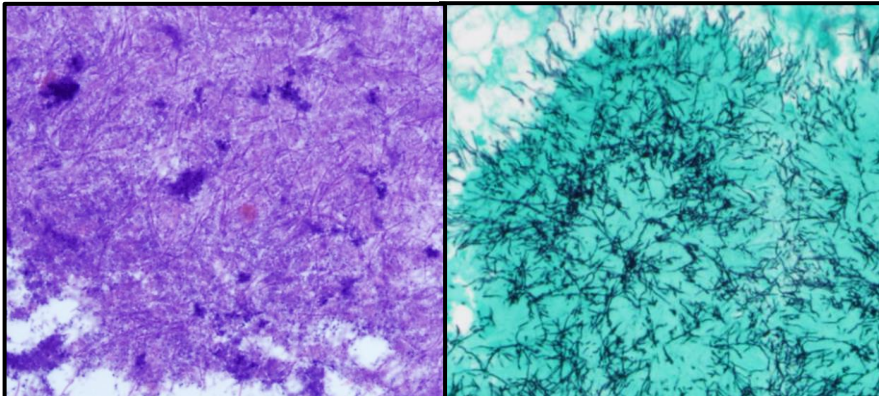


Biopsy omental  
mass



## Case 2: Peritoneal Infections Mimicking Carcinomatosis

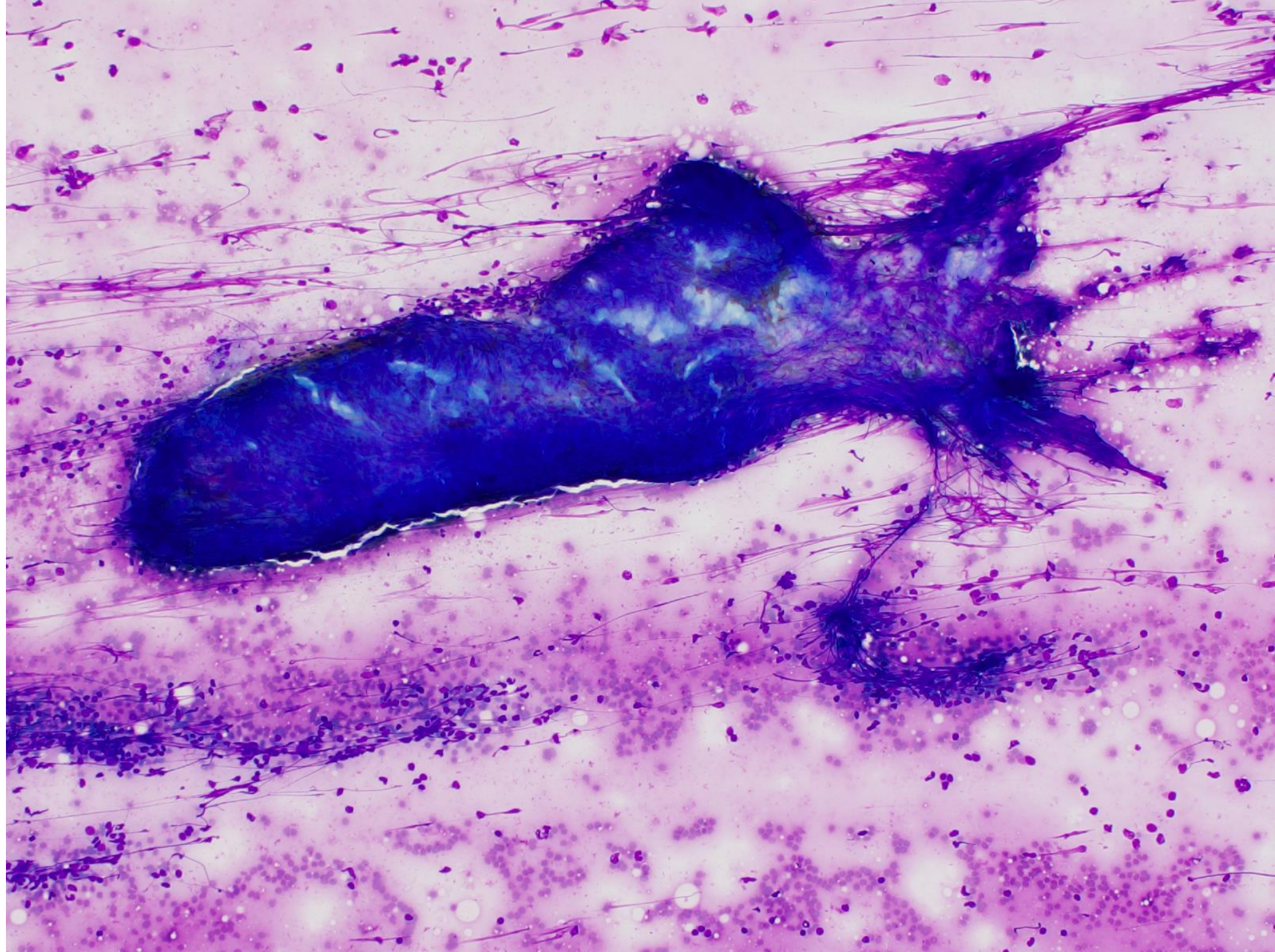
- Pelvic inflammatory disease (less than 15% of acute cases are not sexually transmitted)
- Pelvic/peritoneal actinomyces
- Peritoneal tuberculosis



# Case 3

- 24-year-old male presenting with facial and bilateral orbital edema
- MRI showed an ill-defined abnormal enhancement of the left retromaxillary fat pad, lacrimal gland

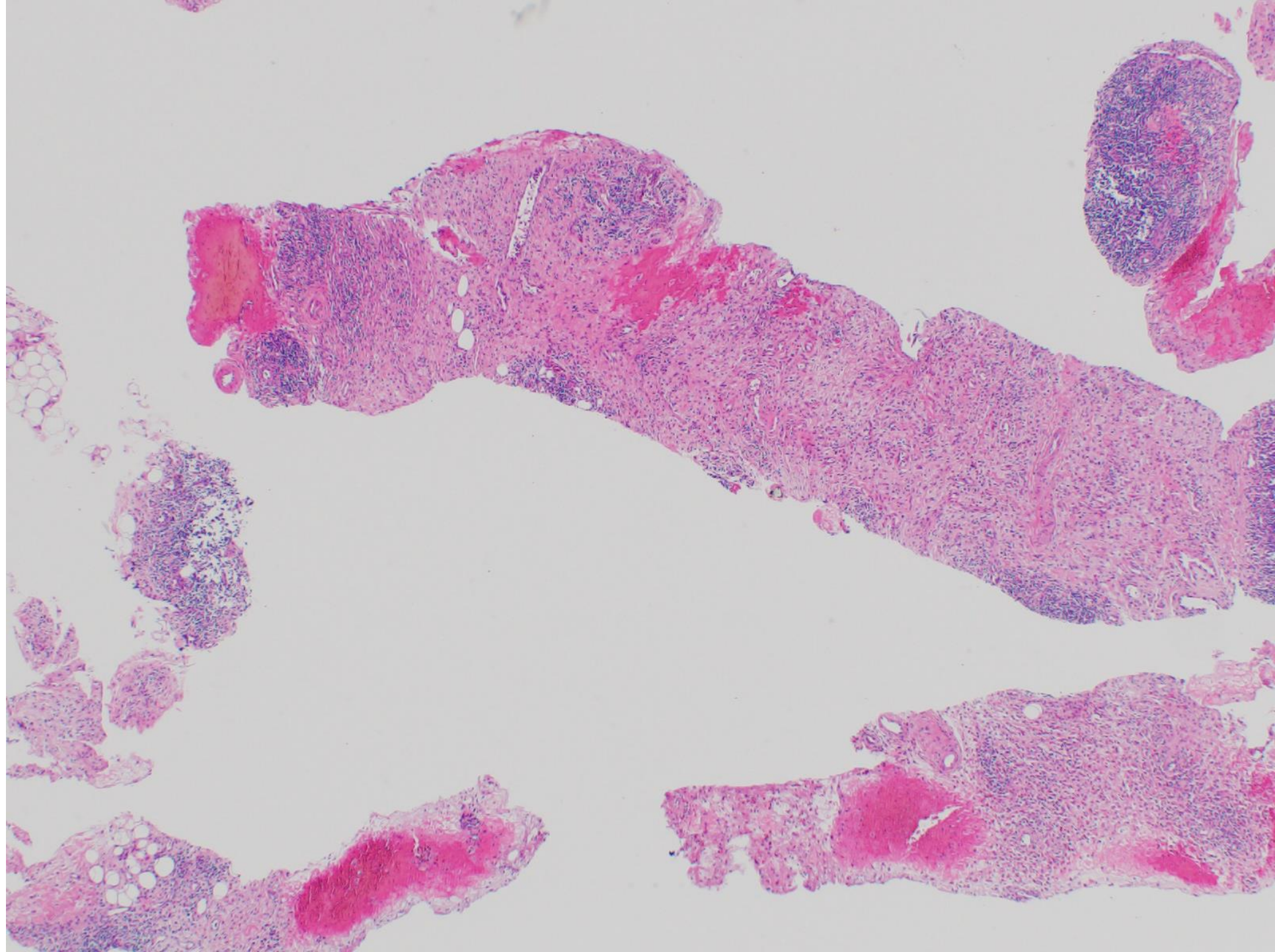
TP of CNB  
Left face



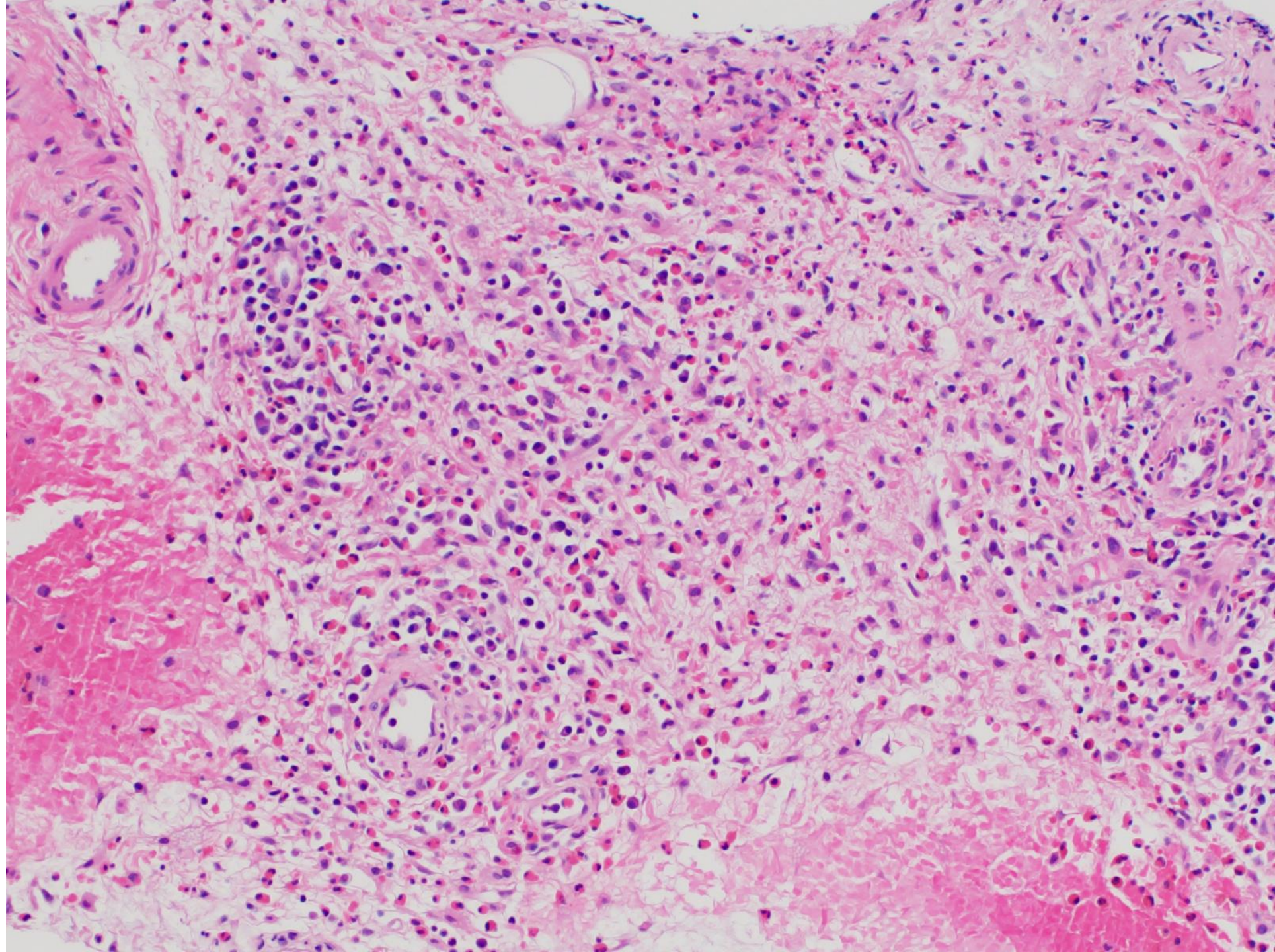


CNB

Left face



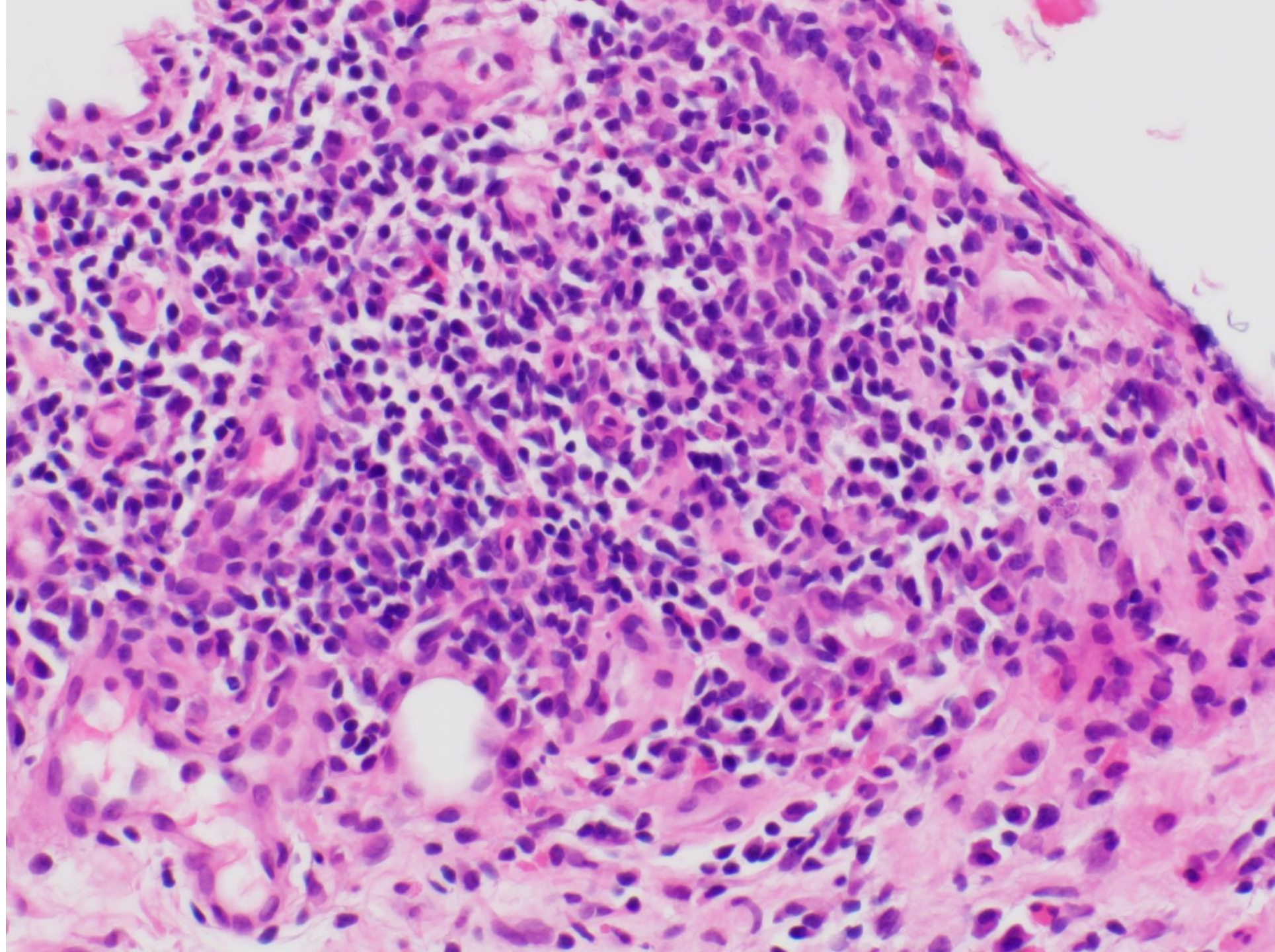
CNB  
Left face



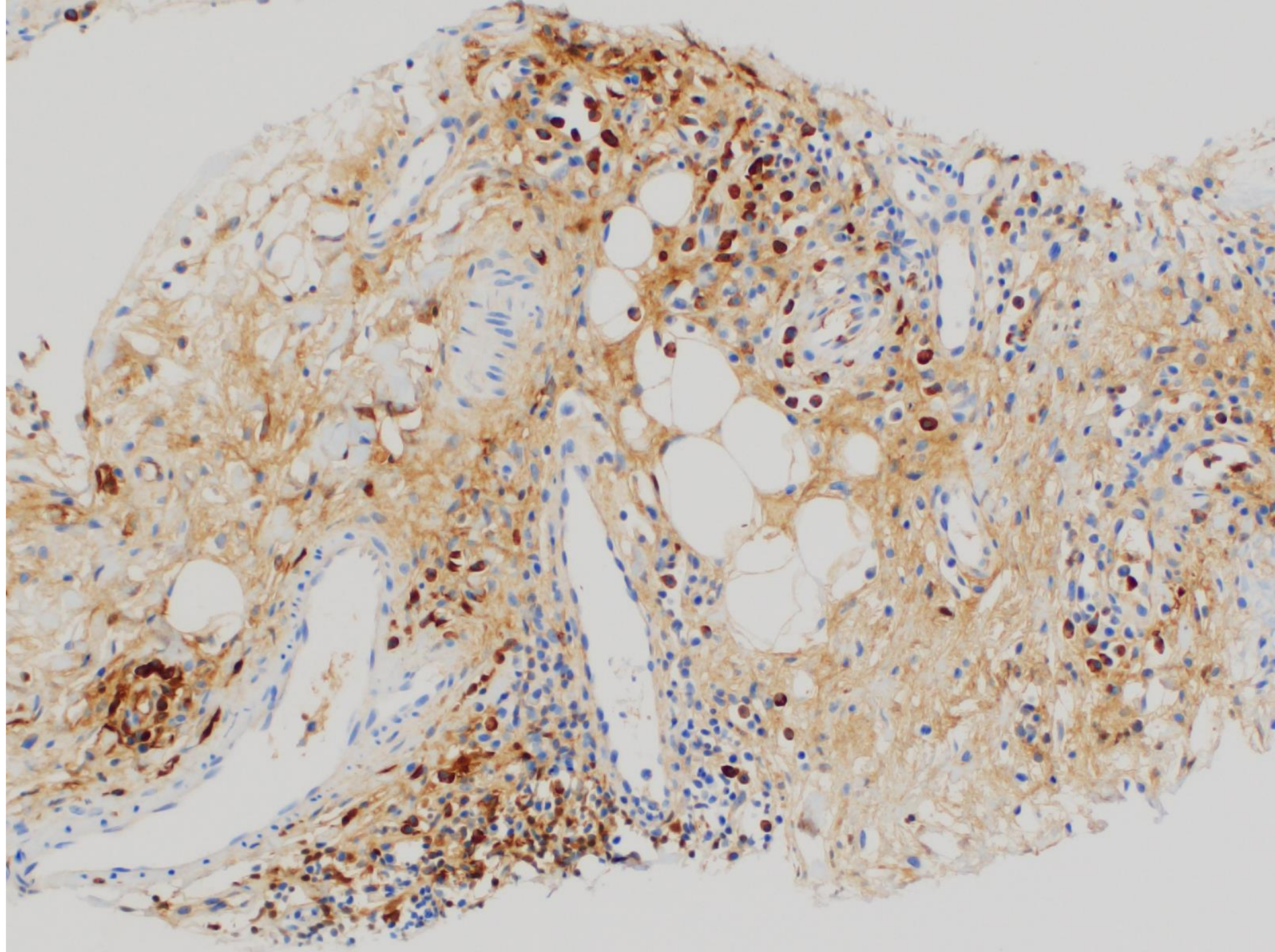


CNB

Left face



IgG4



# IgG4 Sclerosing Disease-Clinical Features

- Originally described as autoimmune pancreatitis
- Extrapancreatic tissues affected include biliary tract, lung, liver, kidneys
- Other common sites include salivary gland, orbital disease, retroperitoneum (retroperitoneal fibrosis)
- Associated with elevated IgG4 serum levels

# IgG4 Sclerosing Disease-Histologic Features

- Three major histopathologic features:
  1. Dense lymphoplasmacytic infiltrate
  2. Fibrosis, arranged at least focally in a storiform pattern
  3. Obliterative phlebitis
  
- Other associated features:
  1. Phlebitis without lumen obliteration
  2. Increased eosinophils

# Case 3 - Fibrotic lesions: Additional Selected Differential Diagnoses

- Fat necrosis
- Reactive myofibroblastic proliferations
- Low grade mesenchymal neoplasms such as desmoid fibromatosis
- Hodgkin lymphoma, classic nodular sclerosing variant

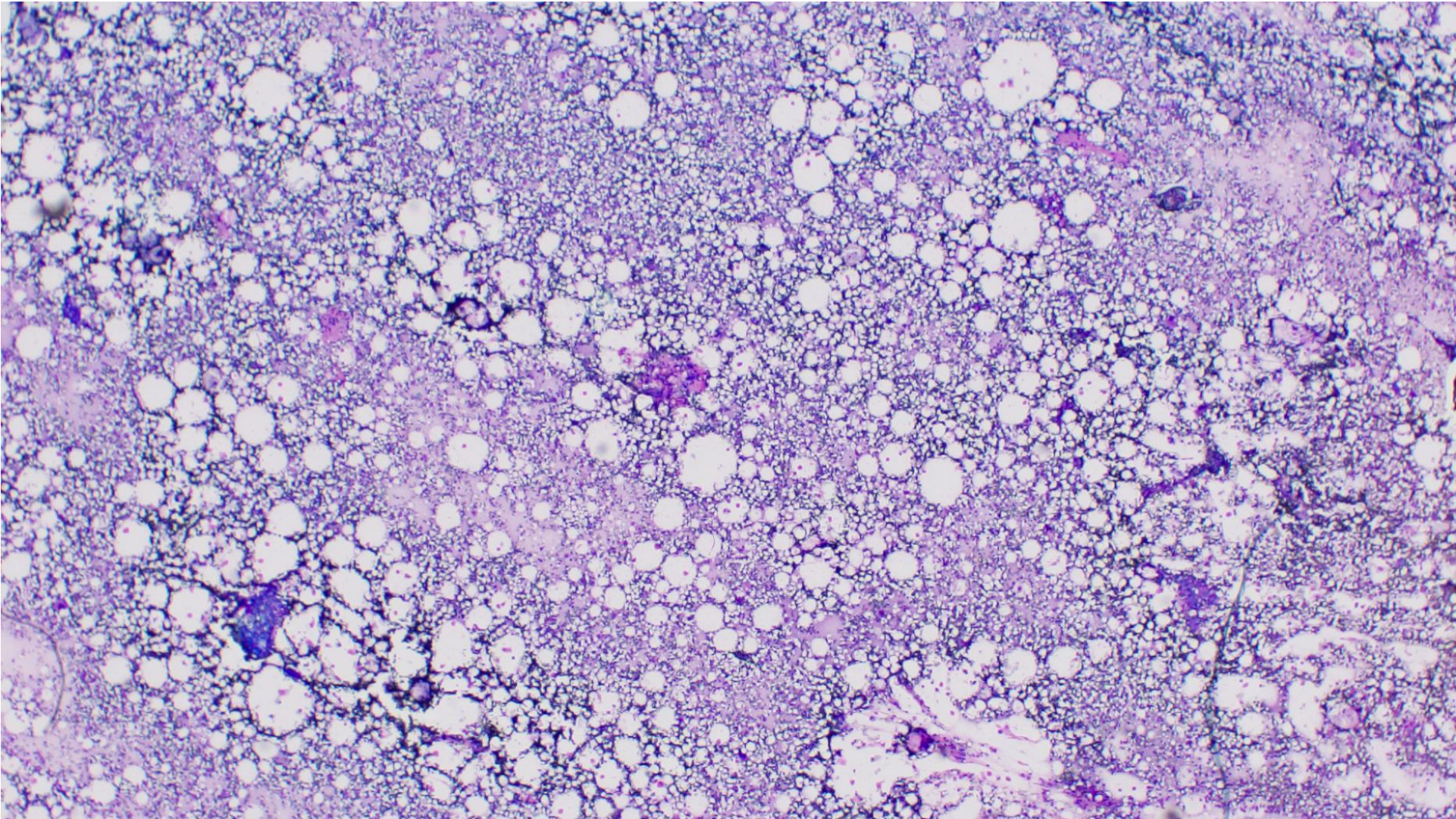
# Case 3: Take Home Points – Fibrotic Lesions Mimicking Malignancy

- Aspirates or touch preparations of fibrotic lesions may be quite hypocellular
- If admixed inflammation is identified consider IgG4 sclerosing disease vs. Hodgkin lymphoma, especially if eosinophils are present

# Case 4

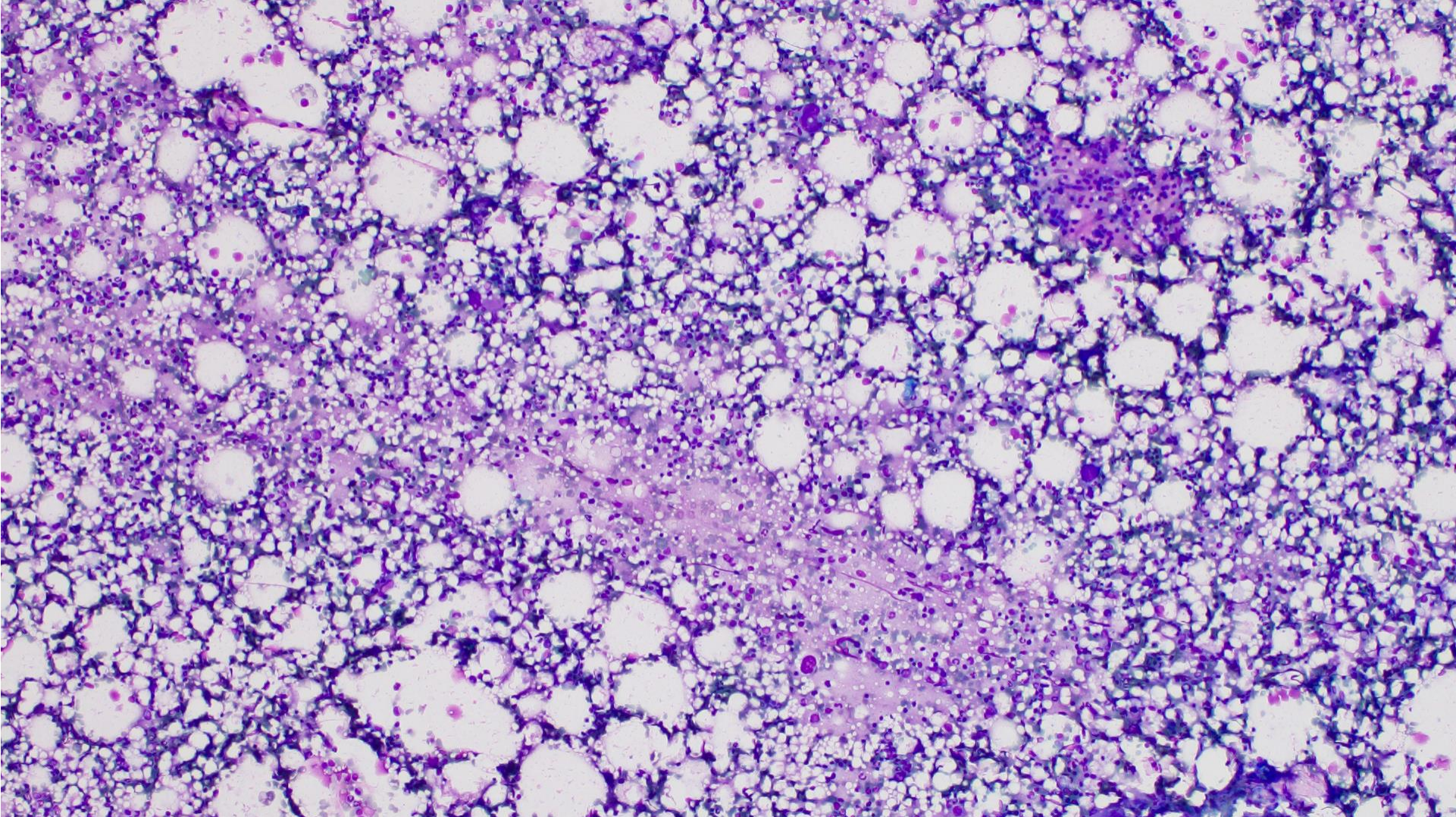
- 62-year-old male with lung carcinoid tumor s/p lobectomy 3 months prior
- Subsequent PET CT disclosed an enhancing pelvic bony lesion radiologically c/w metastasis
- For pathologic confirmation, the interventional radiologist opted to perform CT-guided fine needle aspiration followed by needle core biopsy

# FNA

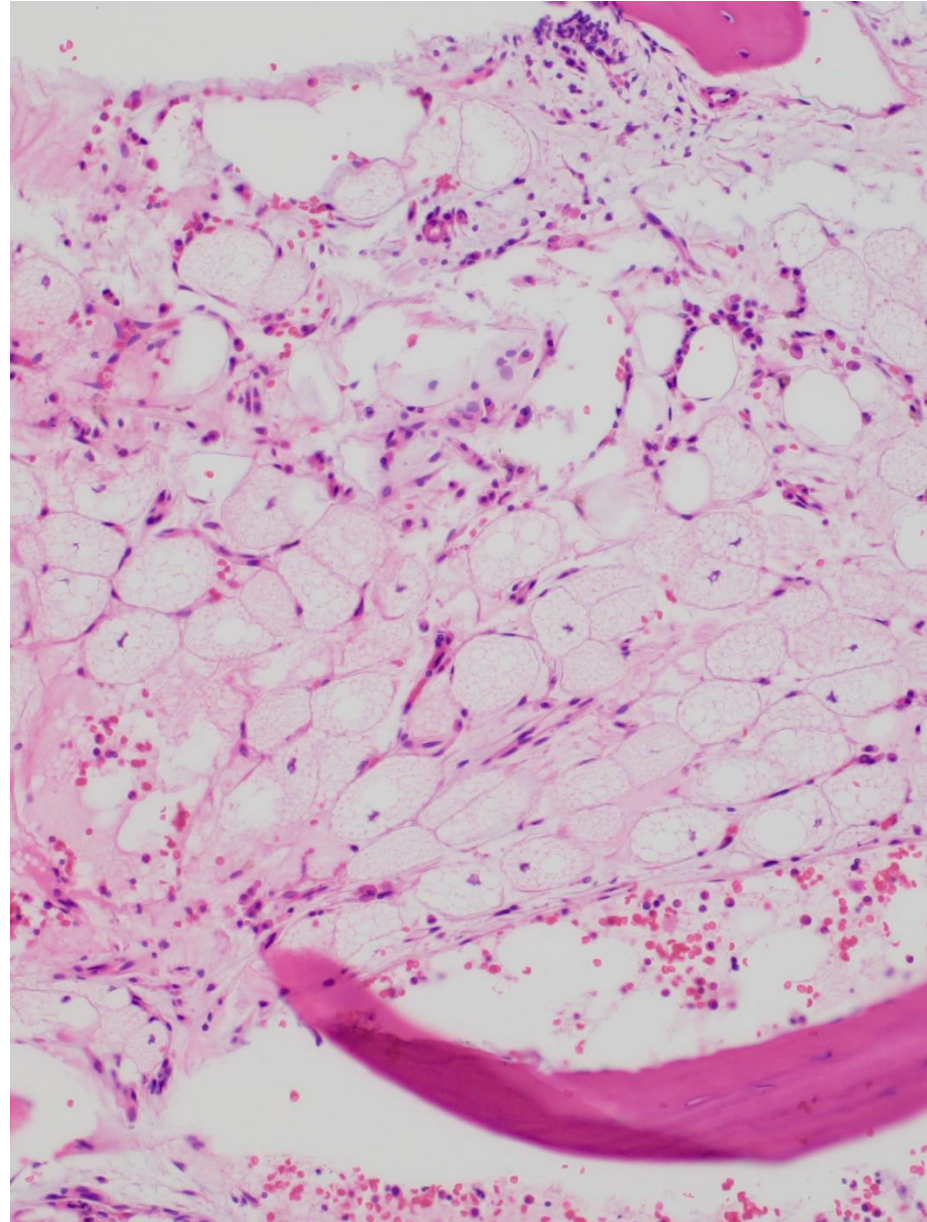
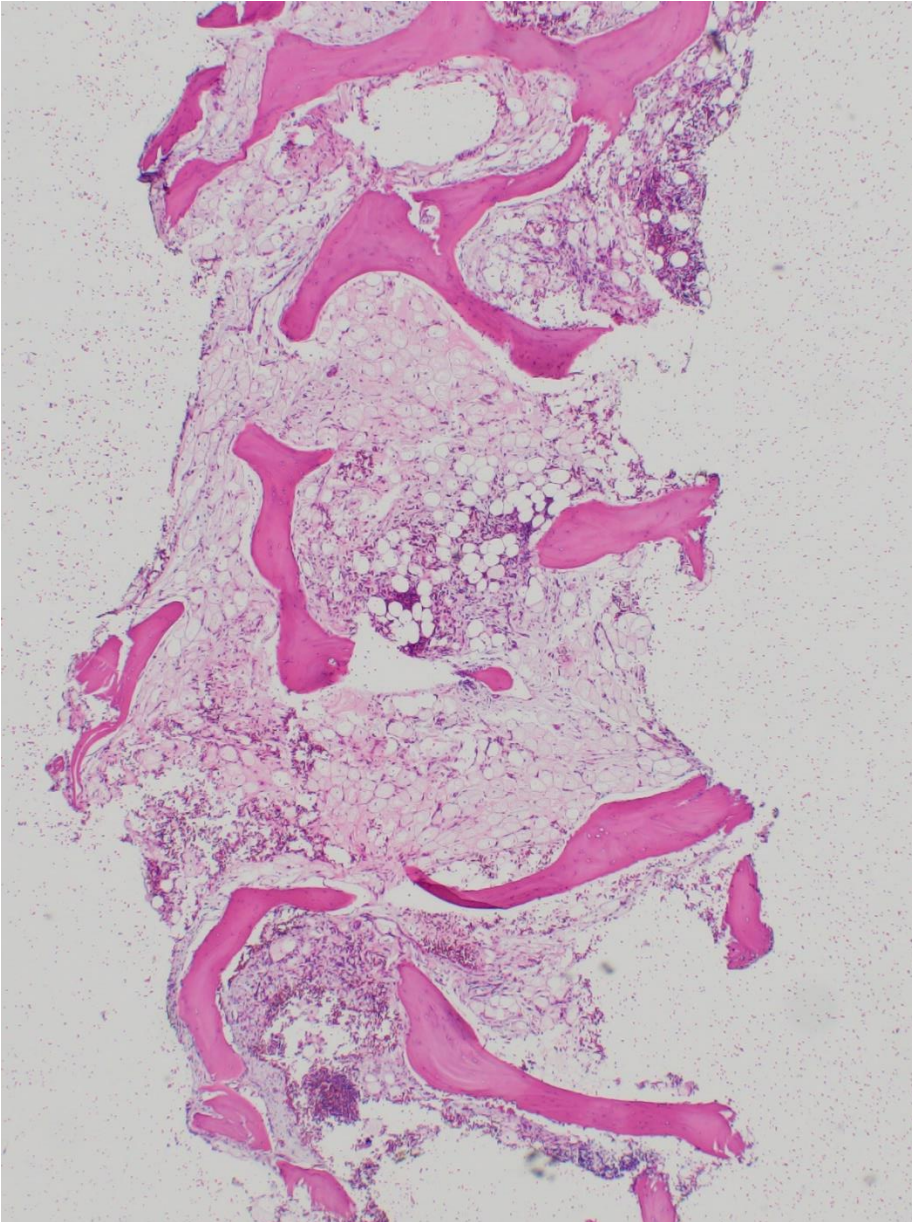




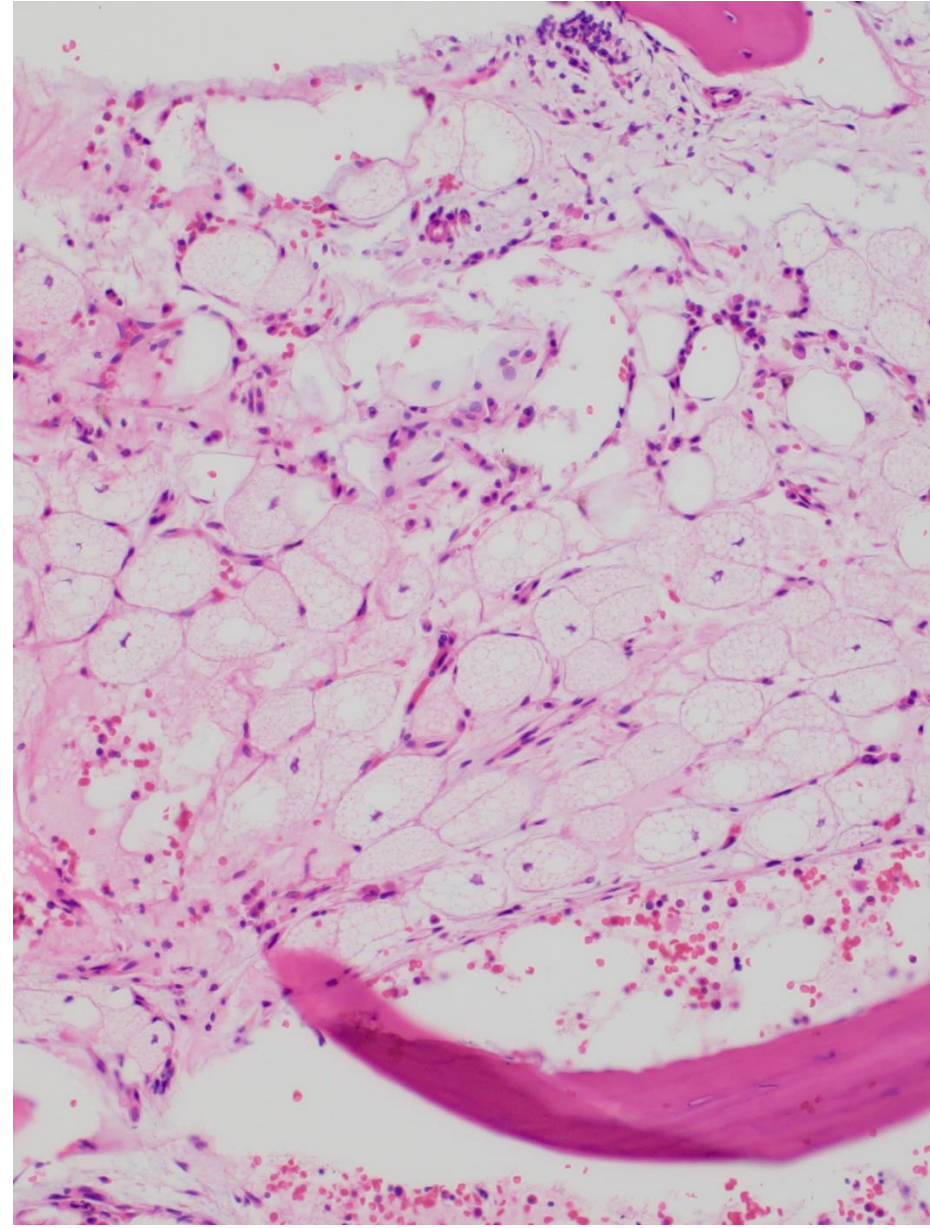
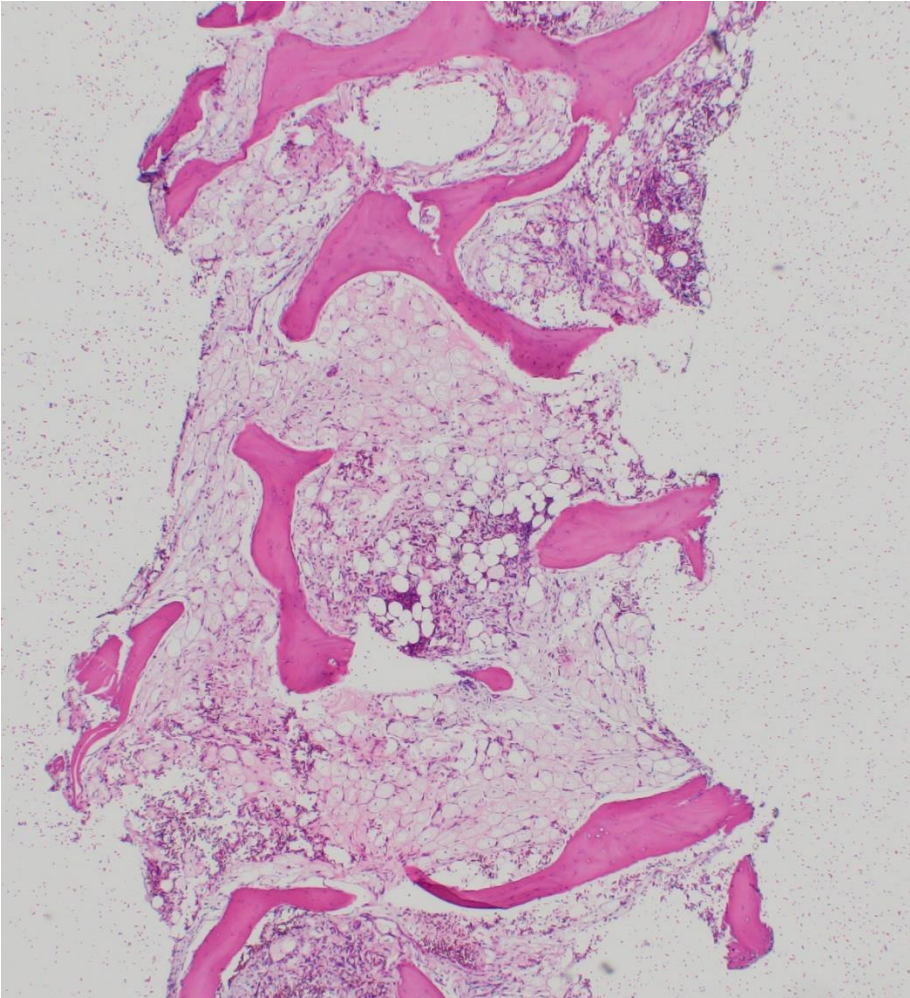
# Touch preparation of core biopsy



# Core biopsy



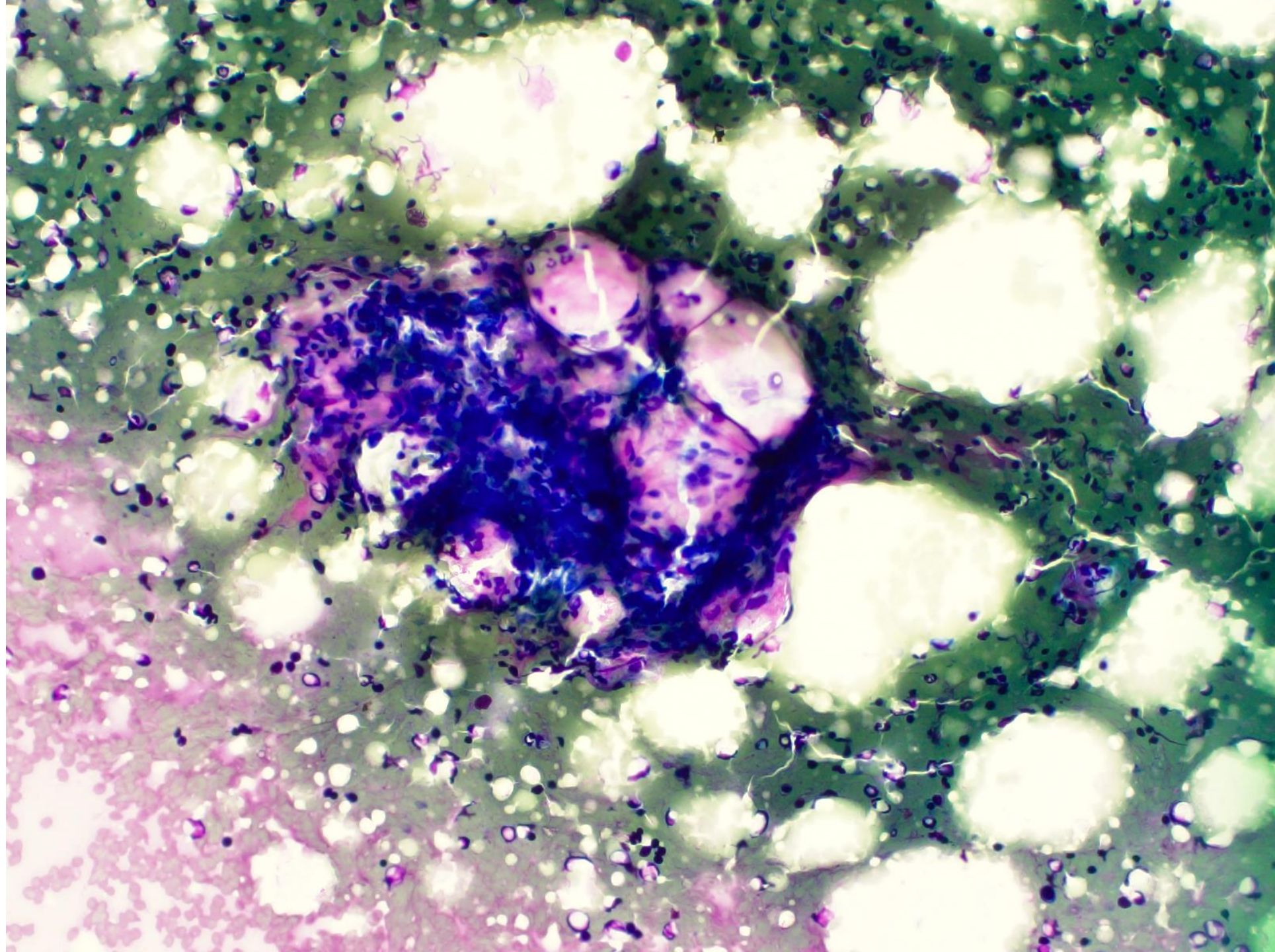
# Intraosseous Hibernoma

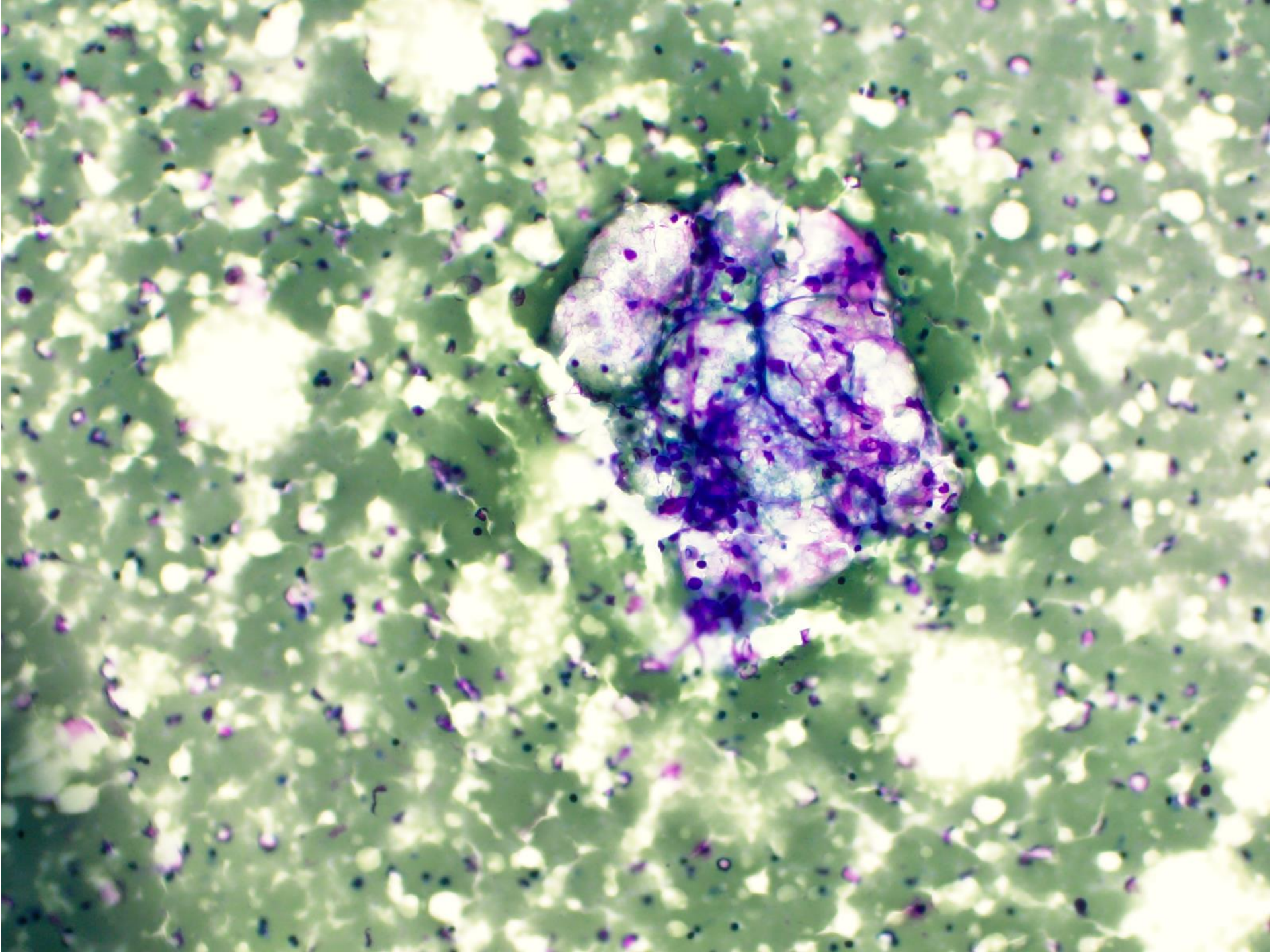


- Positive for S100
- Negative: CD68, AE1/3

# Differential Diagnoses-Histiocytic-Like Lesions

- Infections (AFB, fungal)
- Malignancy (metastatic RCC, melanoma)
- Mastocytosis: diverse clinical manifestations; cutaneous (predominantly presents in children) and systemic (adults, typically > age 50) forms; mast cell tryptase, c-kit, CD68, also CD45 and CD33 positive
- Erdheim Chester disease: preferential involvement of bone (osteosclerotic lesions), heart, vessels, lung, retroperitoneum, skin; *BRAF* V600 E mutations in about 50%, CD68+, S100/CD1a-
- Langerhans cell histiocytosis: (asymptomatic to severe constitutional symptoms); S100, CD1a, langerin +





# Intraosseous hibernoma: a potential mimic of metastatic carcinoma

Shuting Bai, MD, PhD <sup>a,\*</sup>, Carolyn Mies, MD <sup>a</sup>, Jason Stephenson, MD <sup>b</sup>, Paul J. Zhang, MD <sup>a</sup>

<sup>a</sup> *Department of Pathology and Laboratory Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA 19104*

<sup>b</sup> *Department of Radiology, Hospital of the University of Pennsylvania, Philadelphia, PA 19104*

- Hibernomas are rare benign tumors
- Intraosseous location even more uncommon
- Case reports document primarily pelvic or lower extremity bony locations
- Can be radiologically suspicious

# Conclusions

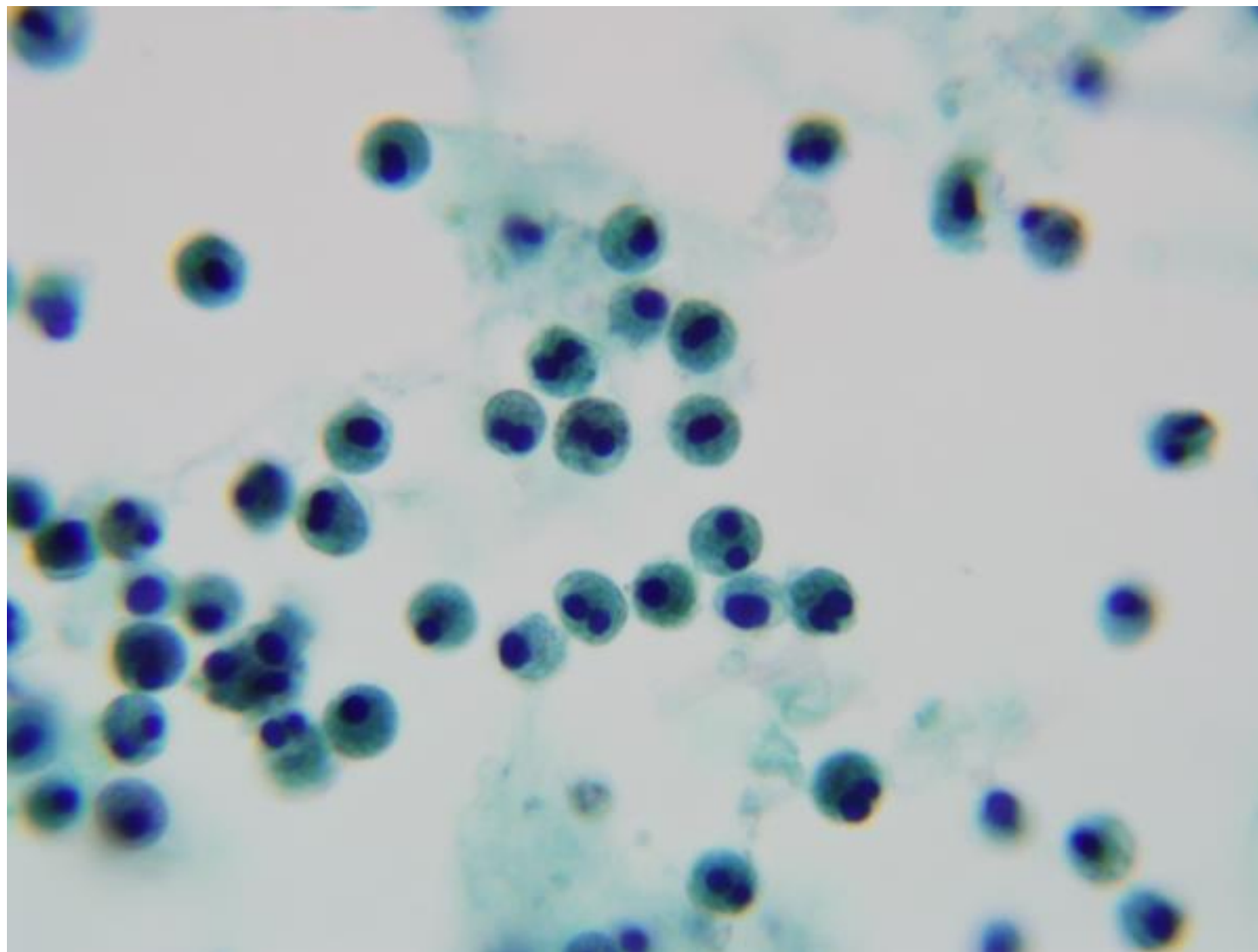
- Examples of benign lesions that can resemble malignant tumors include
  - ❖ Infections:
    - Fungal – mass forming
    - Bacterial, mycobacterial, actinomycotic – ill defined mimic of gynecologic peritoneal cancer
  - ❖ Fibrotic lesions:
    - IgG4 sclerosing disease
  - ❖ Histiocytic lesions:
    - Intraosseous hibernoma

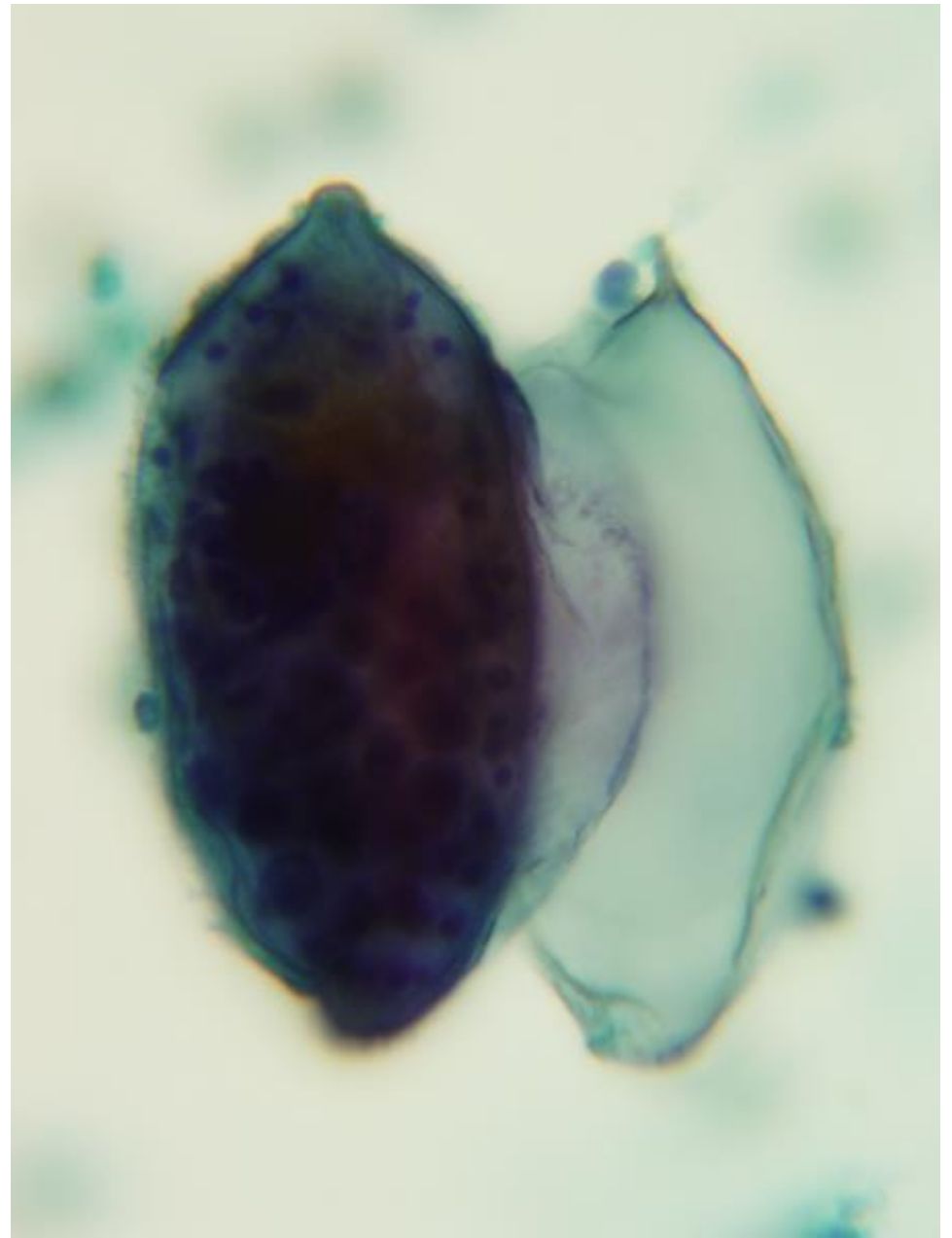
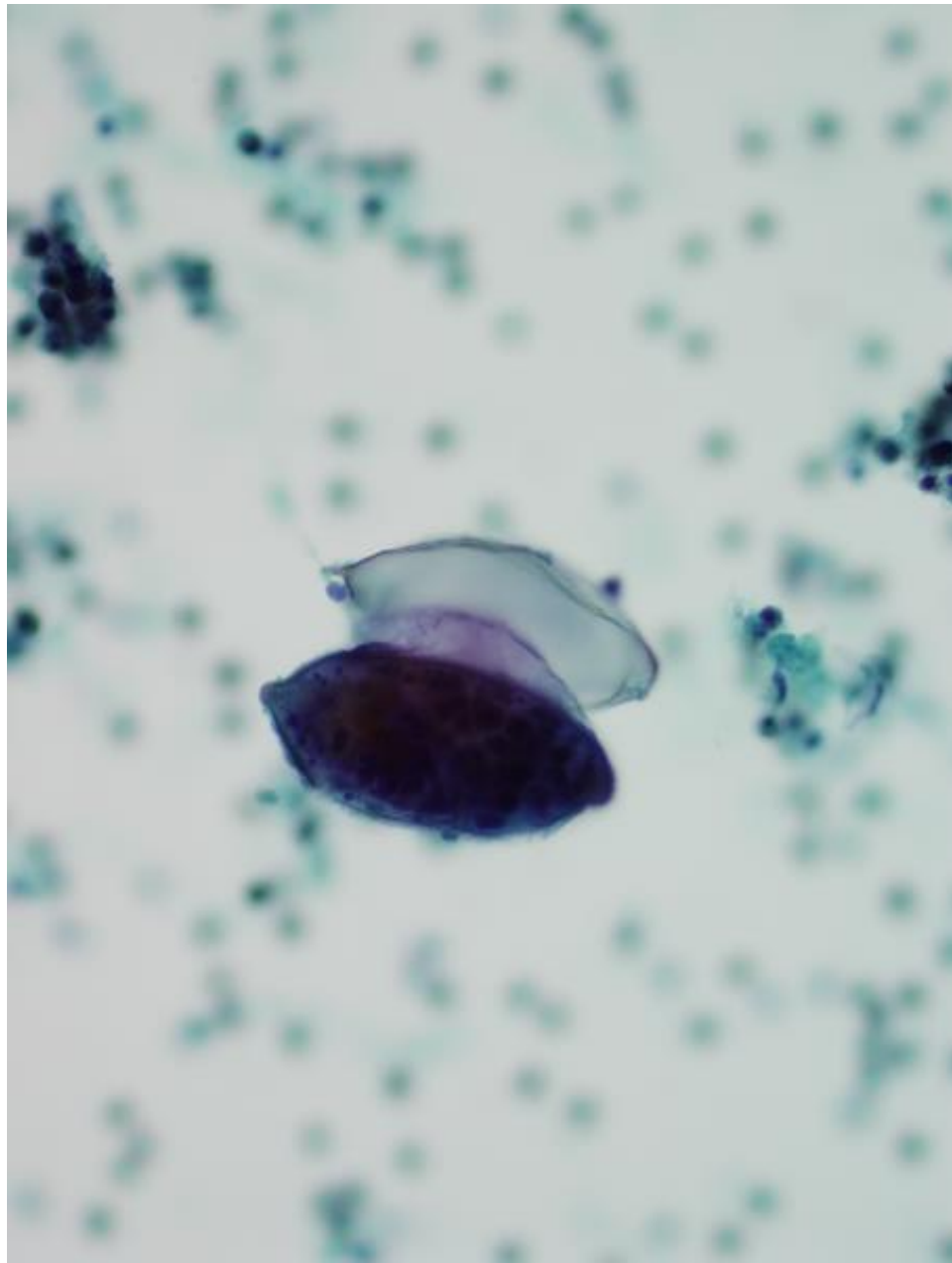


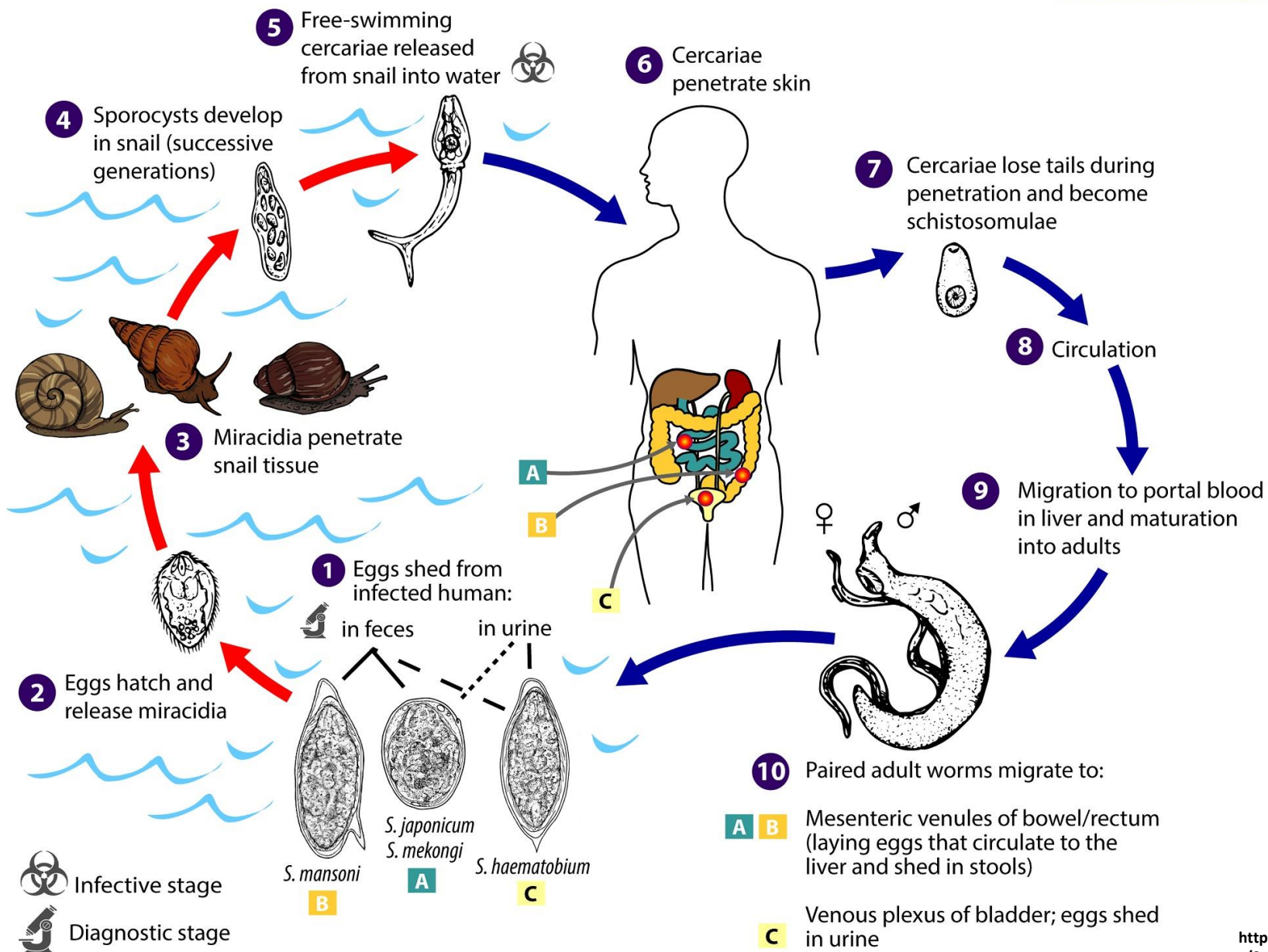
# Bonus Non-gynecologic Cytology Cases – Exfoliative Cytology

21-year-old male with  
hematuria x 3 months

## Voided urine cytology

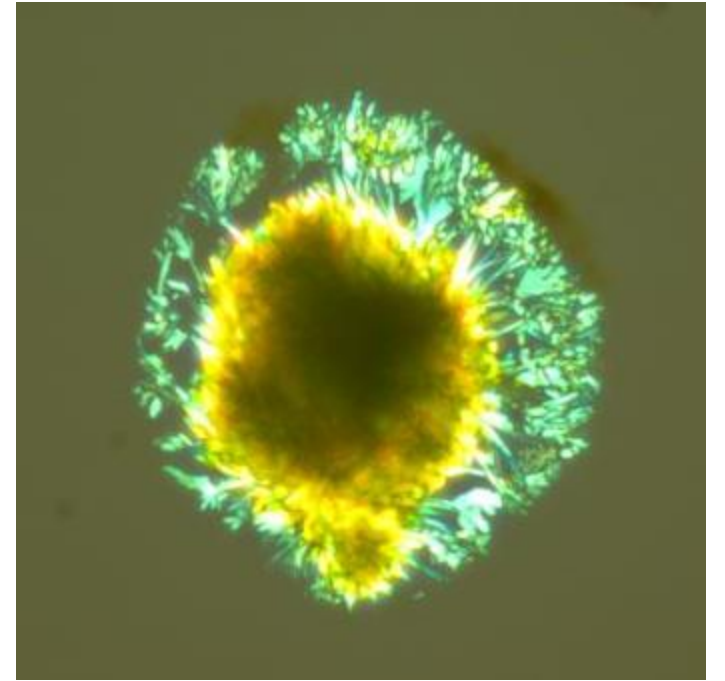
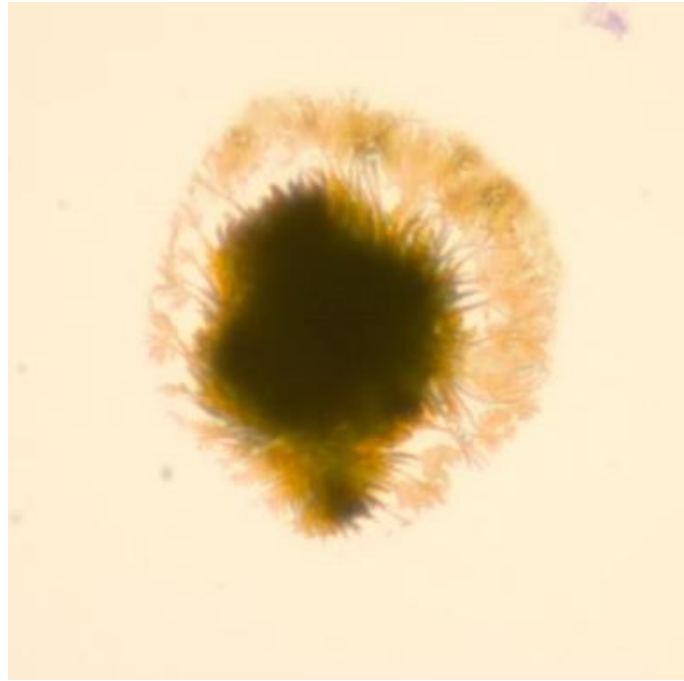
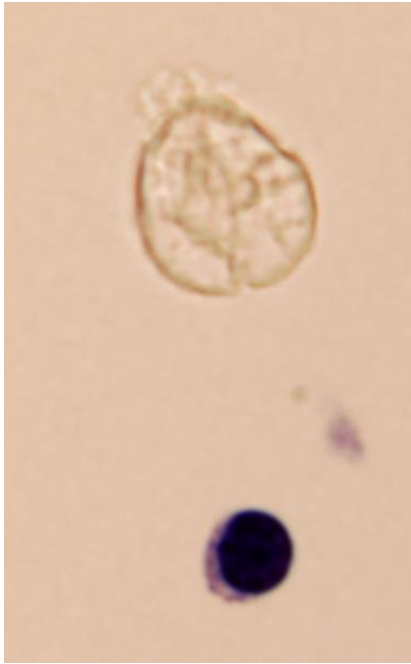




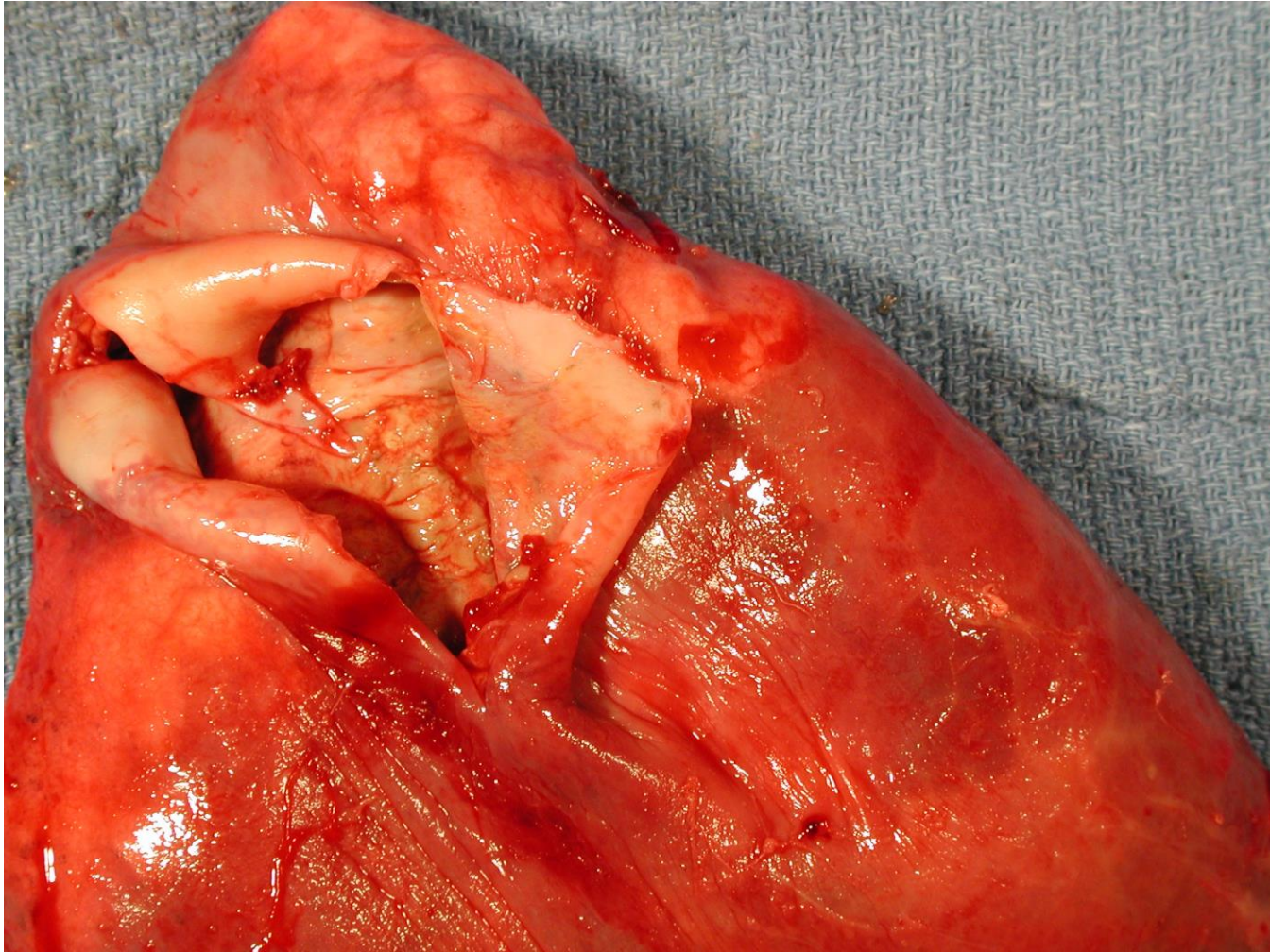


40-year-old female with a  
pleural effusion and cystic lung  
lesions

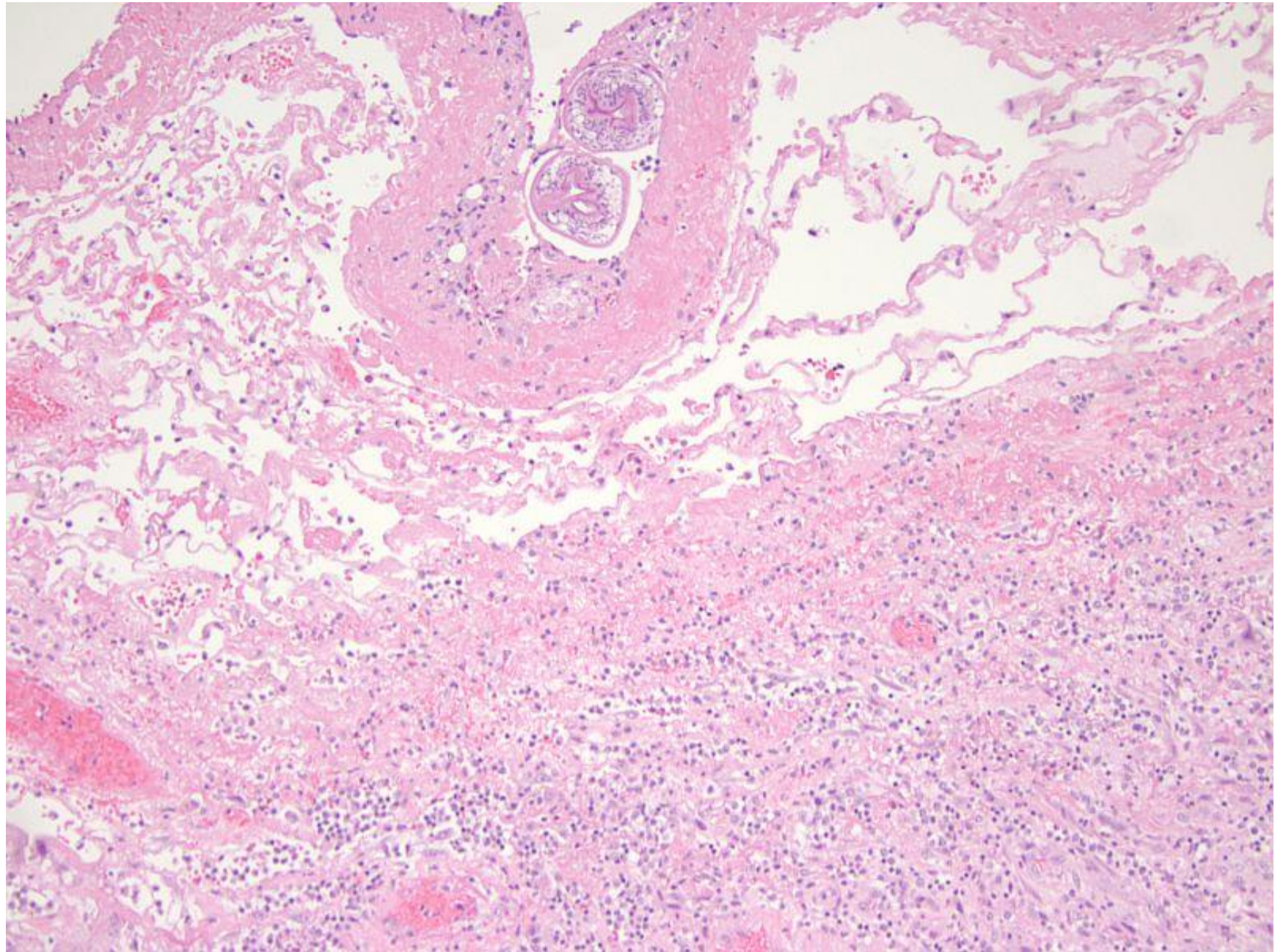
# Pleural fluid

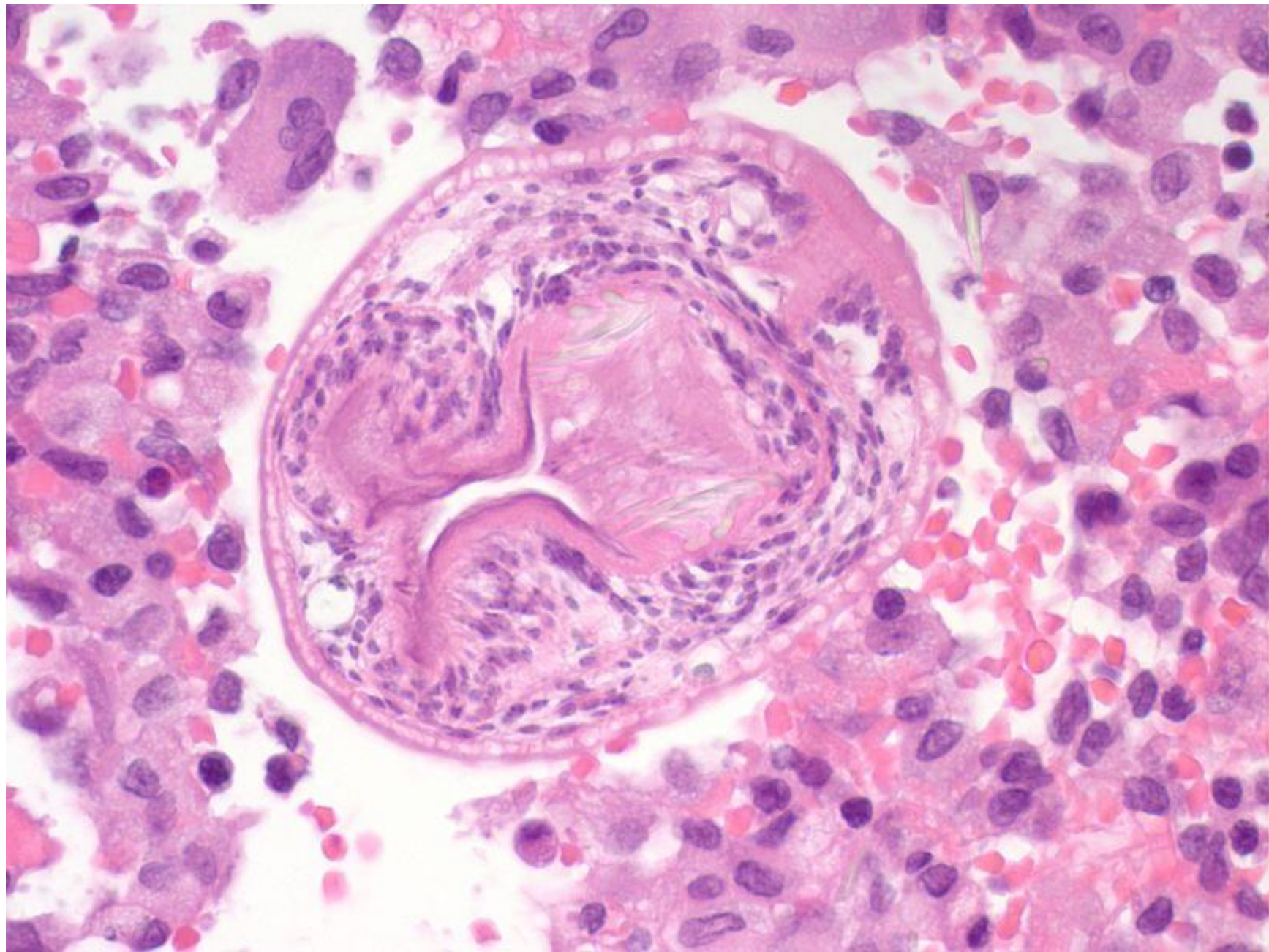


# Lobectomy





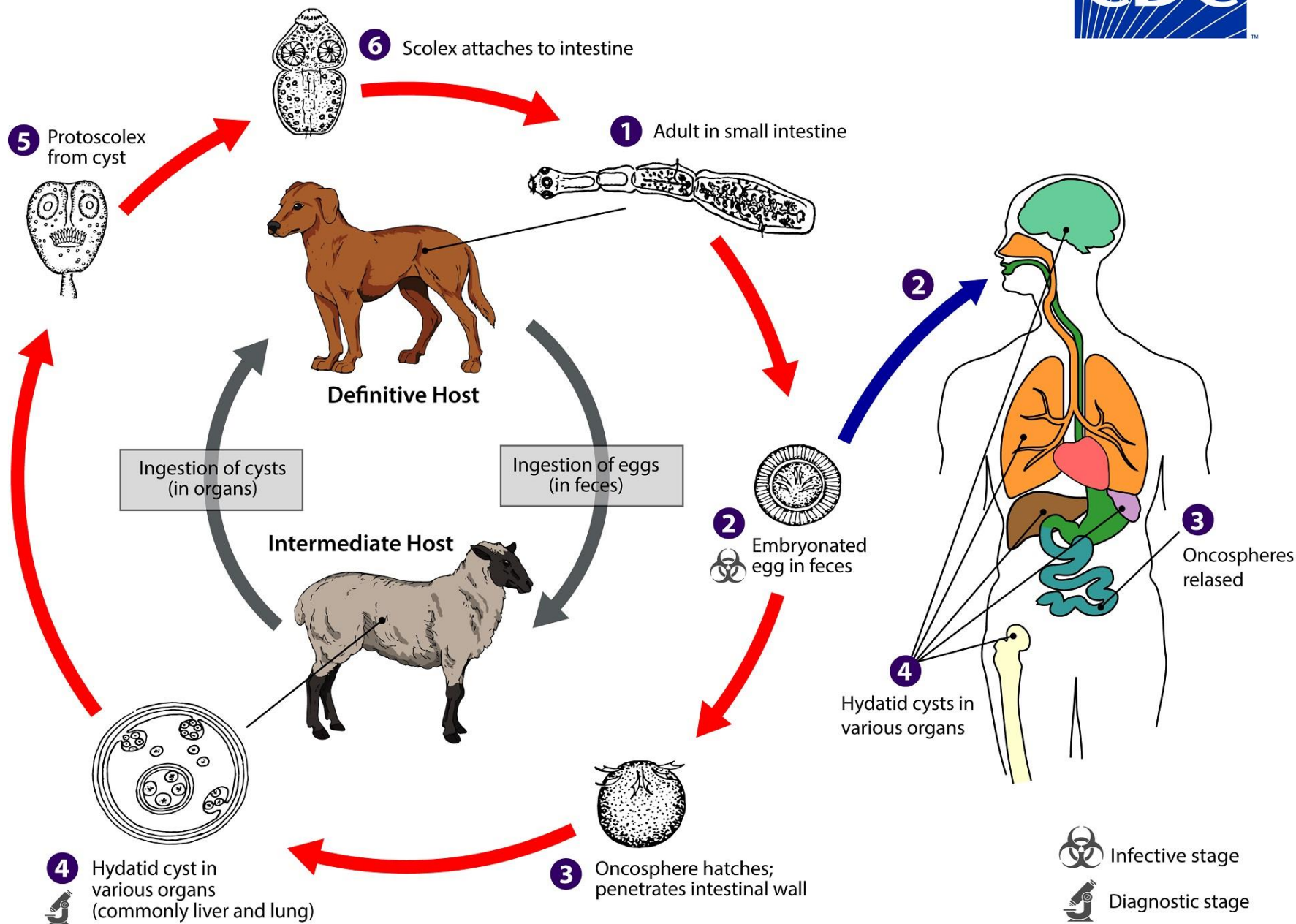




# Cystic Echinococcosis

*Echinococcus granulosus sensu lato*

Infection by larval stage of cestode *Echinococcus granulosus*



Thank you!