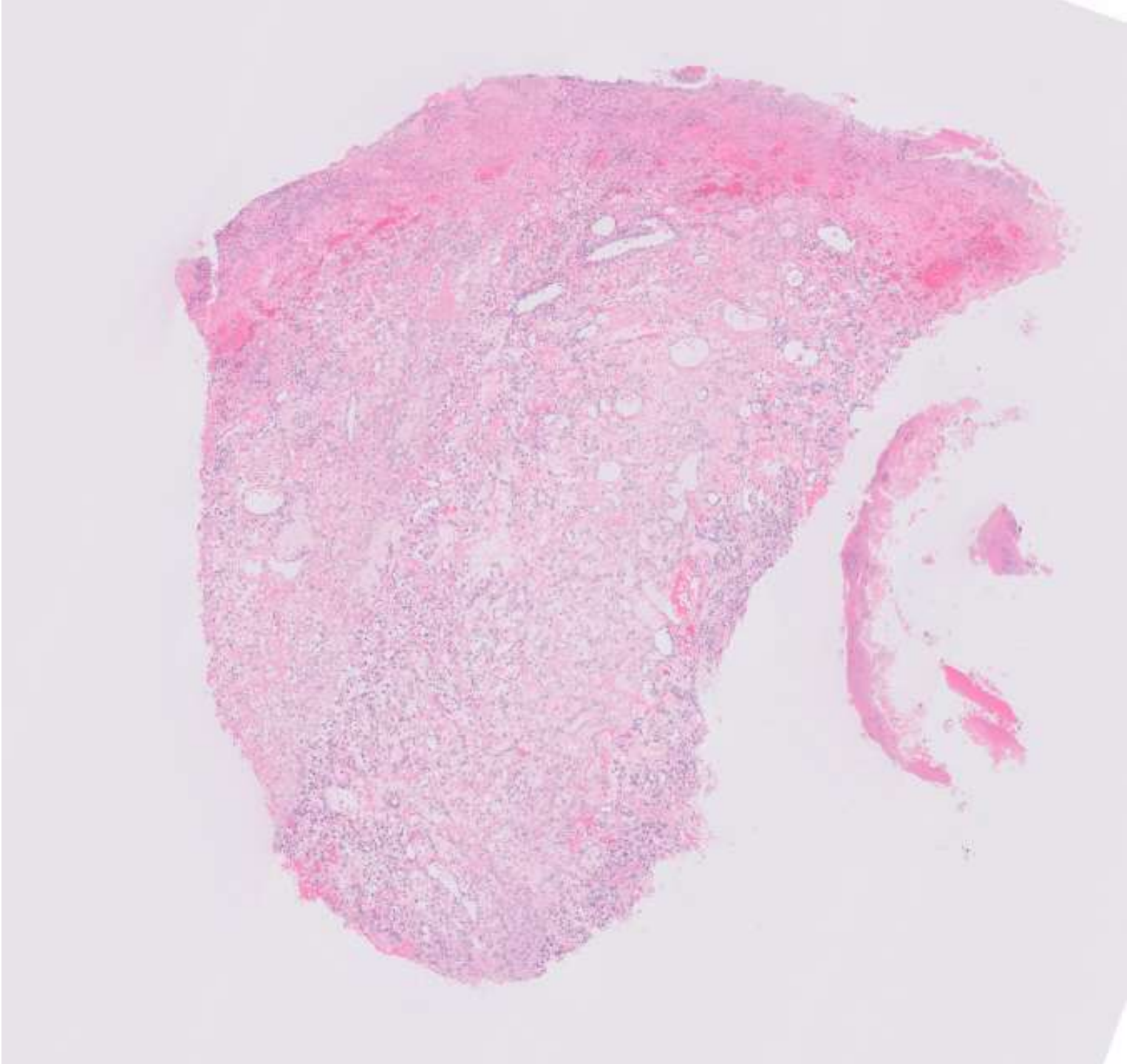
# SEPT 2021 DIAGNOSIS LIST

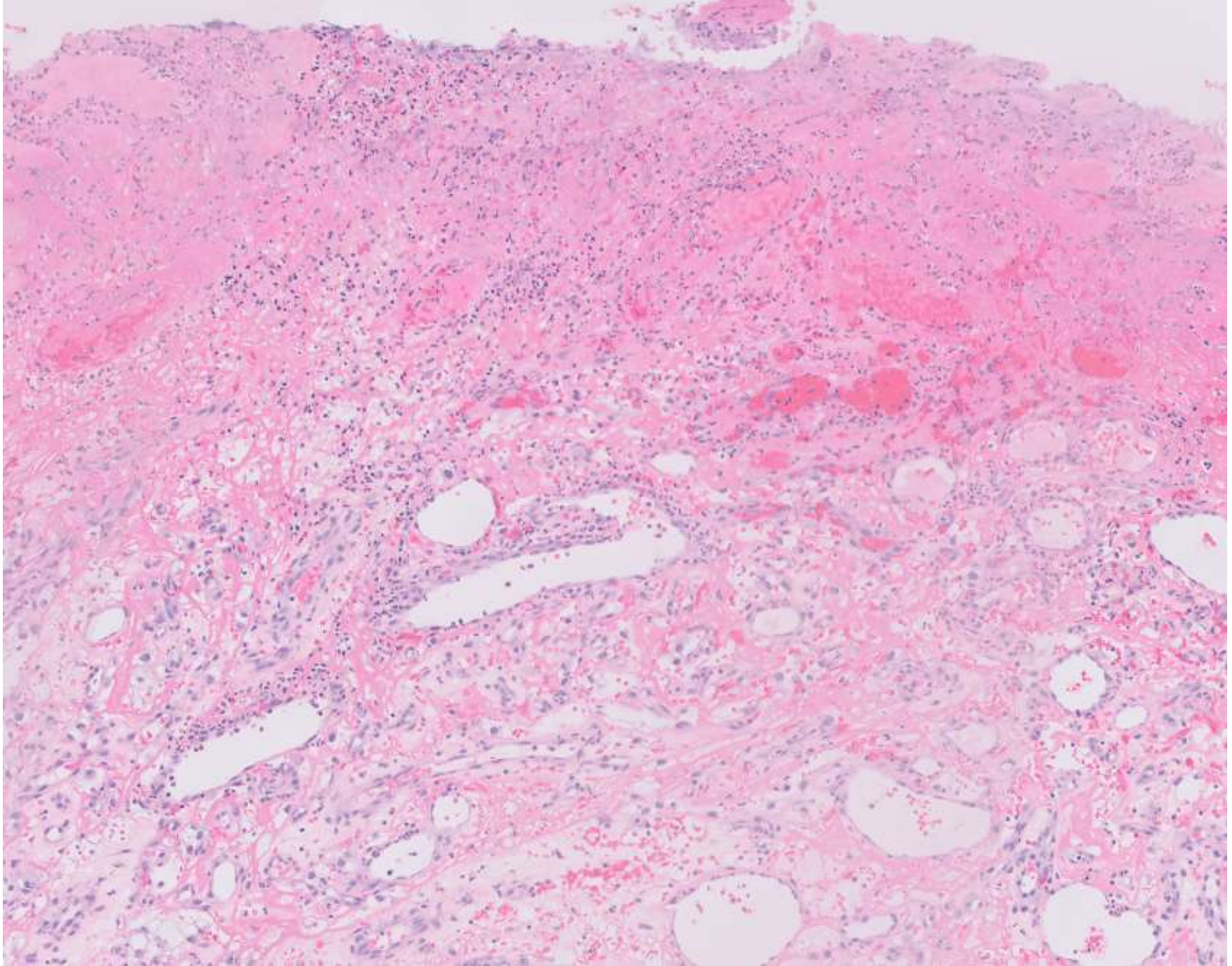
21-0901: metastatic clear cell renal cell carcinoma [ear; GUpath]
21-0902: invasive secretory carcinoma [breast; breast path]
21-0903: adenovirus [liver;non-neoplastic GI path]
21-0904: AML with mutated NPM1 and FLT3 [peripheral blood; hemepath]
21-0905: gelatinous transformation/serous atrophy [bone marrow; hemepath]
21-0906: Balamuthia infection [brain; neuropath+Idpath]
21-0907: myxopapillary ependymoma [spinal cord; neuropath]

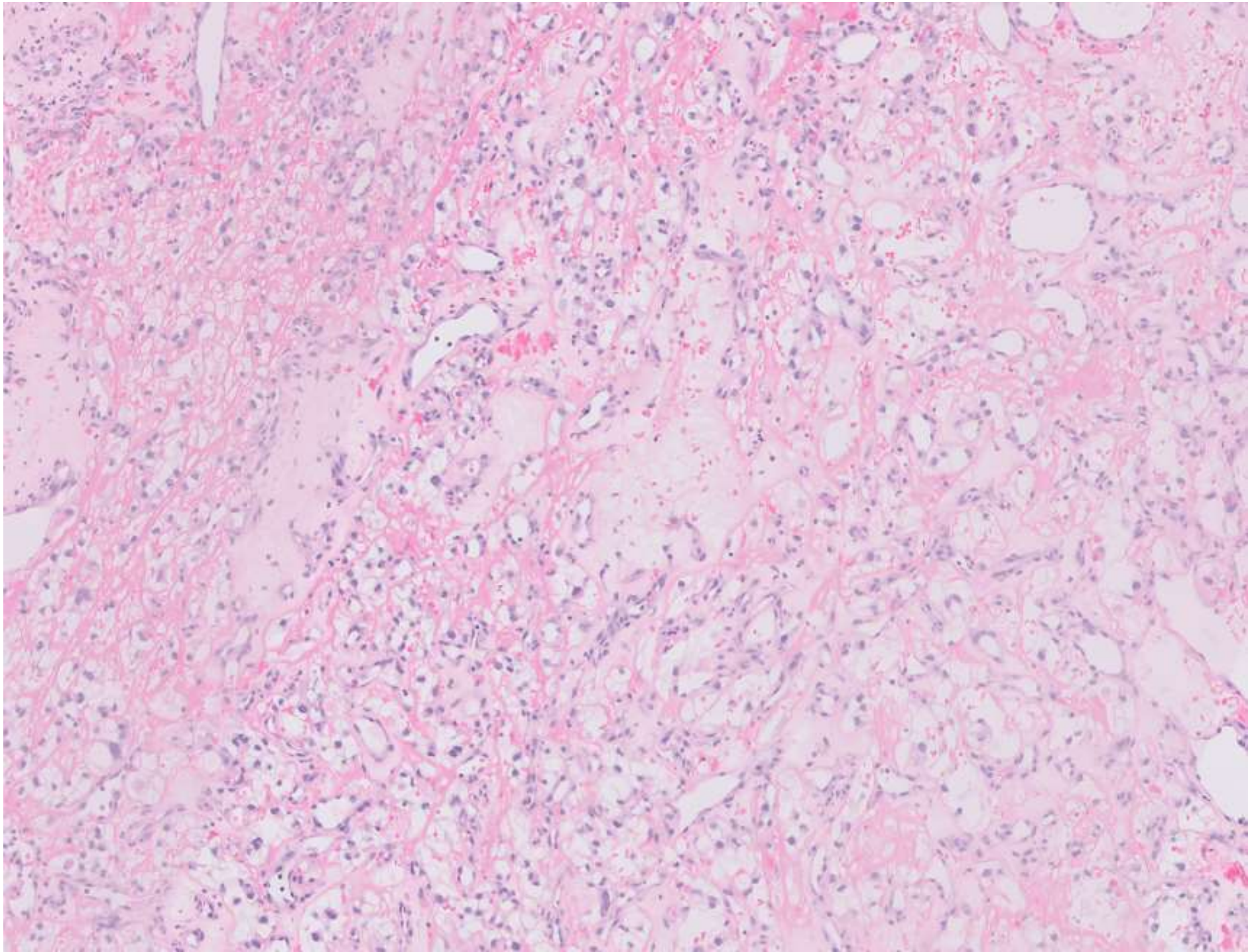
# 21-0901

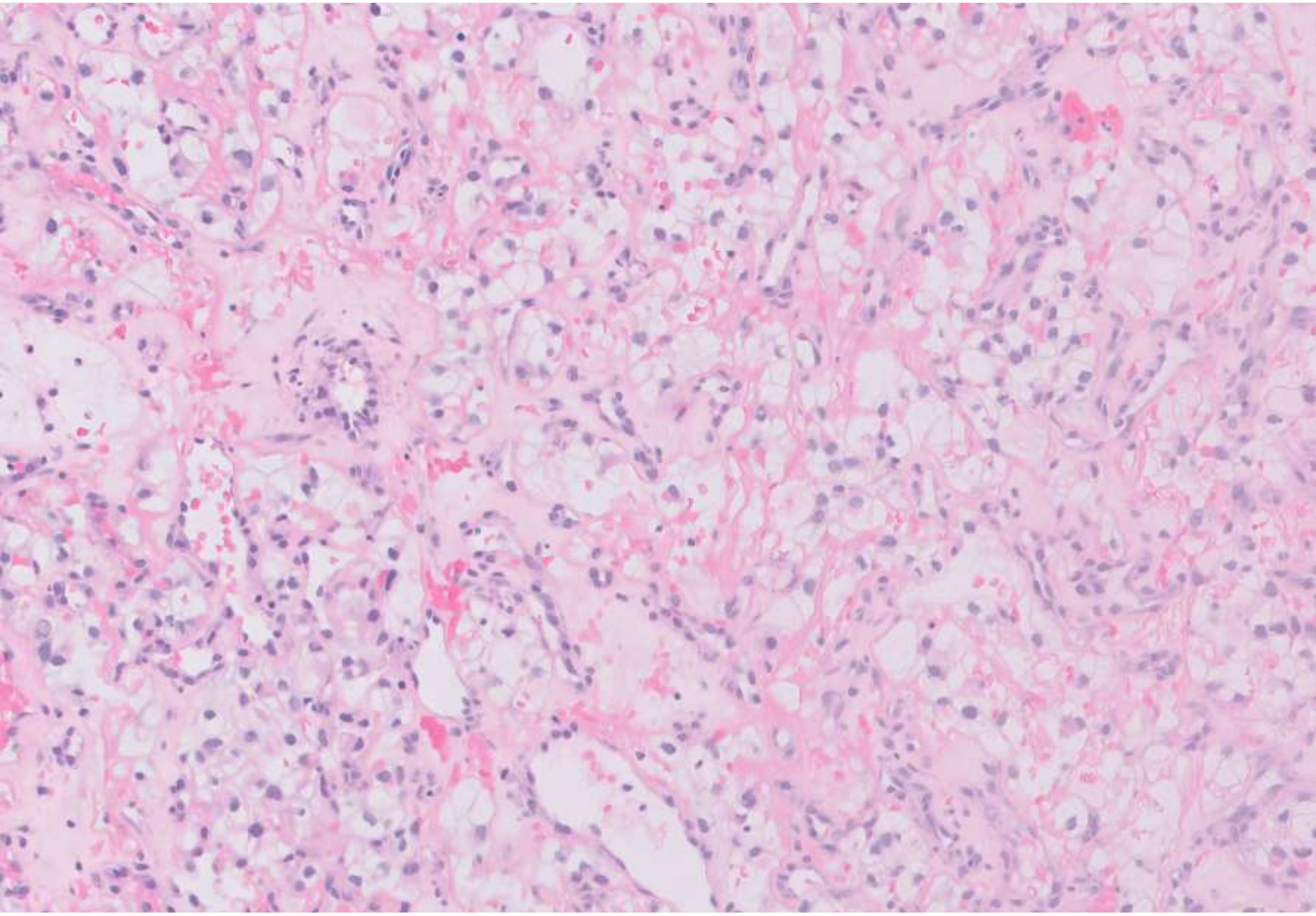
**Emily Chan; USCF**

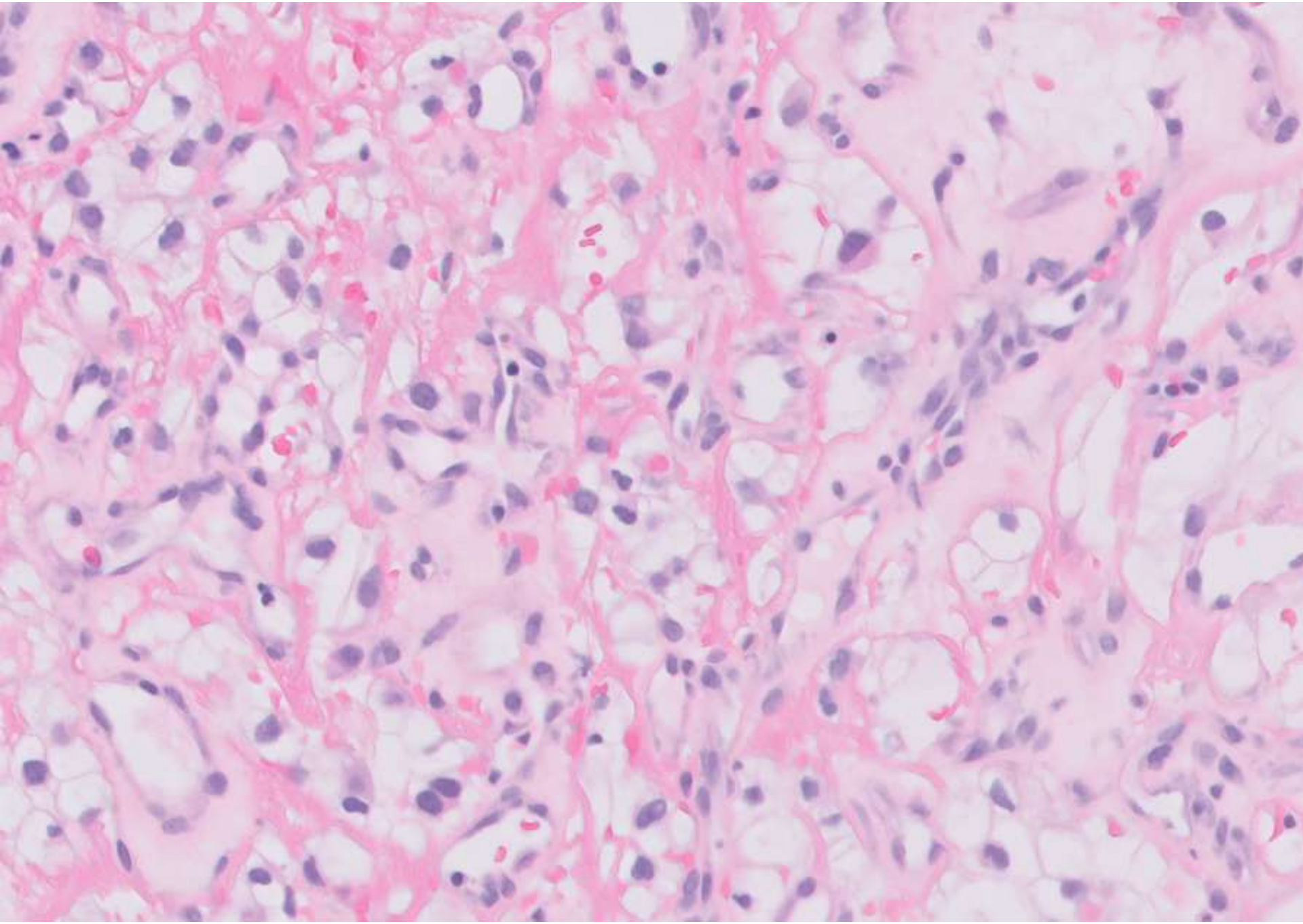
75-year-old man with 2.5 cm right epididymal mass











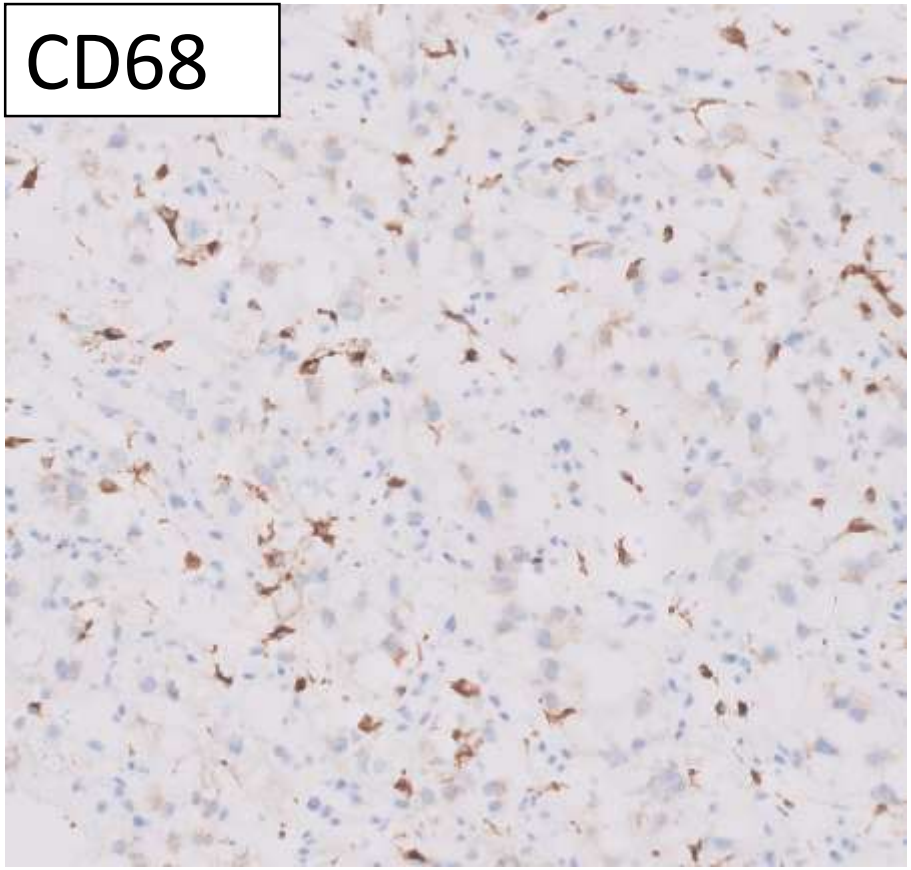
# Differential diagnosis

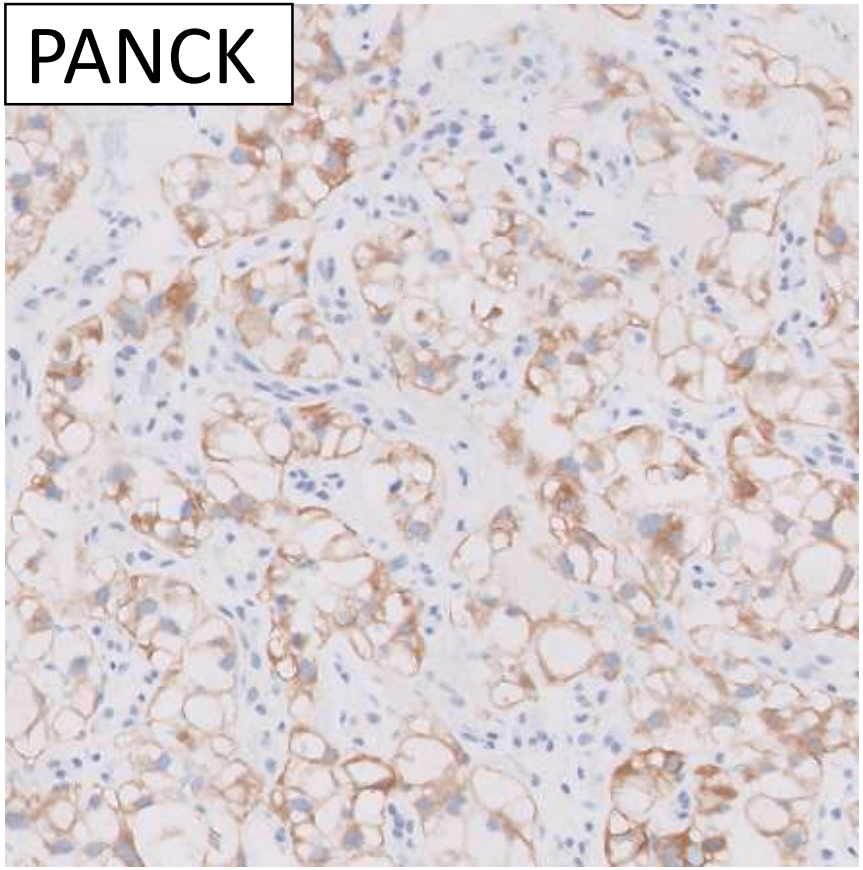
- Granulation tissue
- Capillary hemangioma/pyogenic granuloma
- Paraganglioma
- Adnexal/sebaceous gland tumor
- Endolymphatic sac tumor
- Metastasis

# ?Metastasis: Check medical records and talk to your surgeon

- Does the patient have any cancer history, ever had full body imaging?
  - Answer: Not that they knew of…

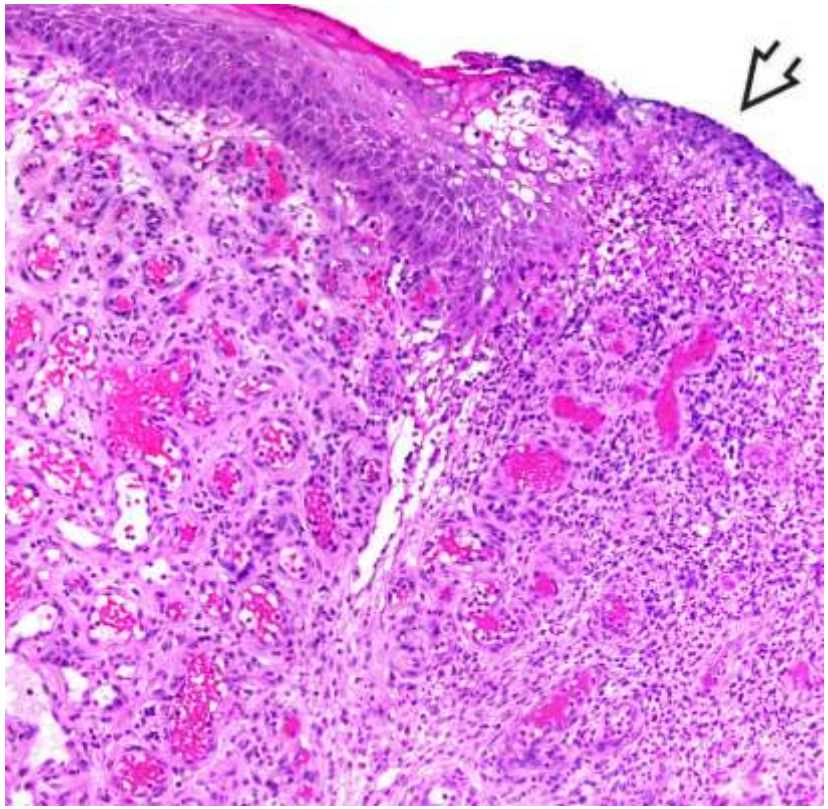
# Granulation tissue??



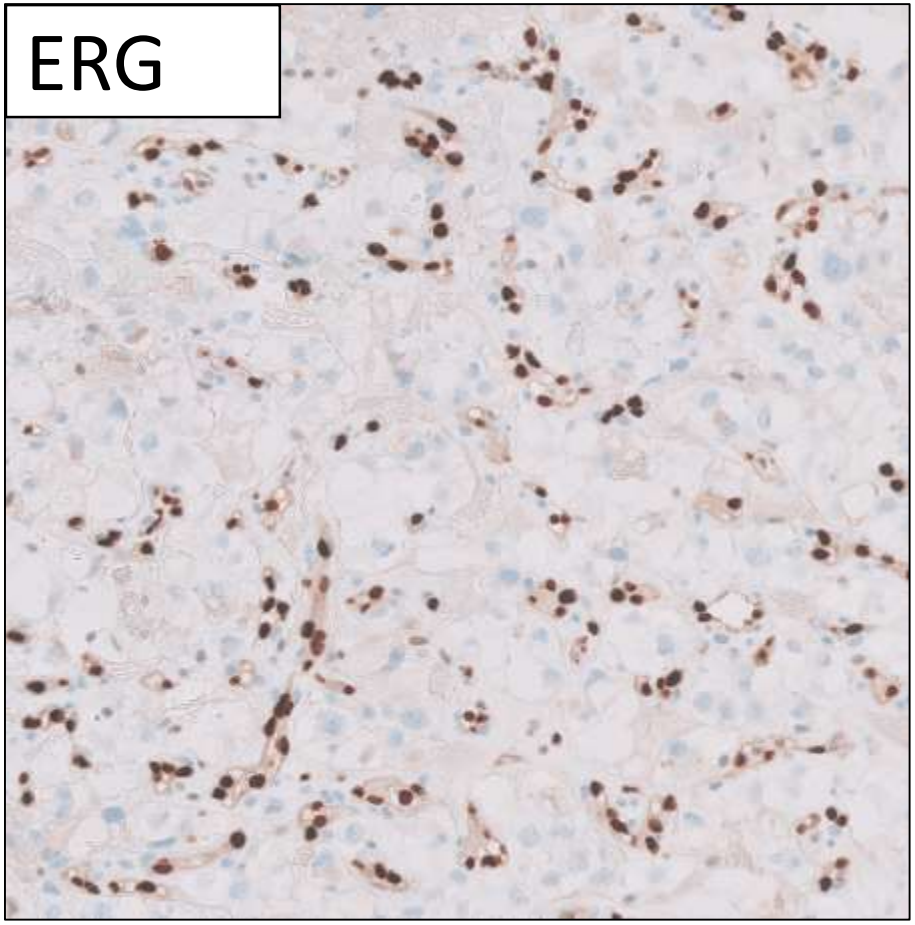
# Capillary hemangioma/pyogenic granuloma

- Etiology: local irritants/trauma
- Lobulated/polypoid mass
- Ulcerated surface
- Can have epithelioid endothelial cells
- IHC:
  - Negative for epithelial marker
  - Positive for vascular markers



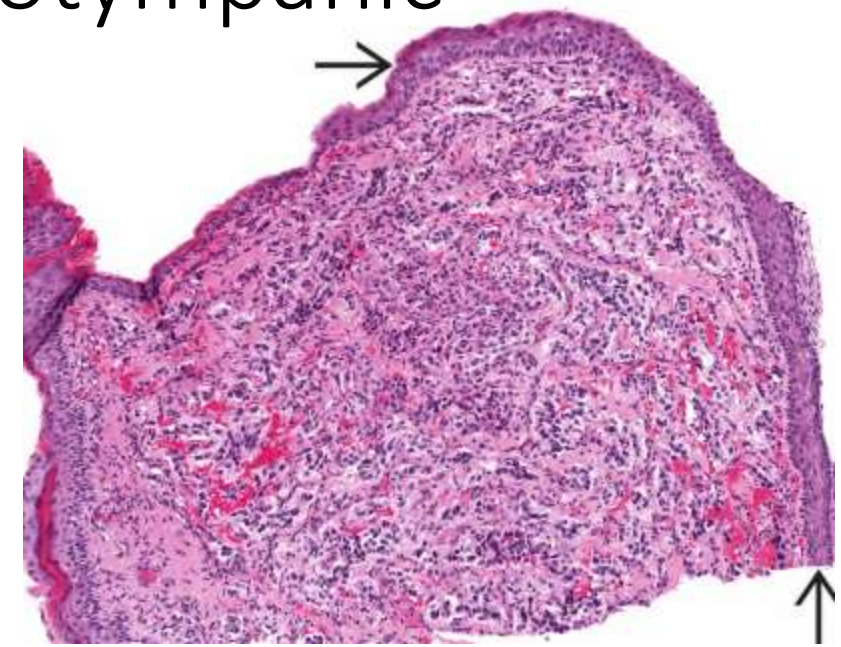
https://app.expertpath.com/document/pyogenic-granuloma

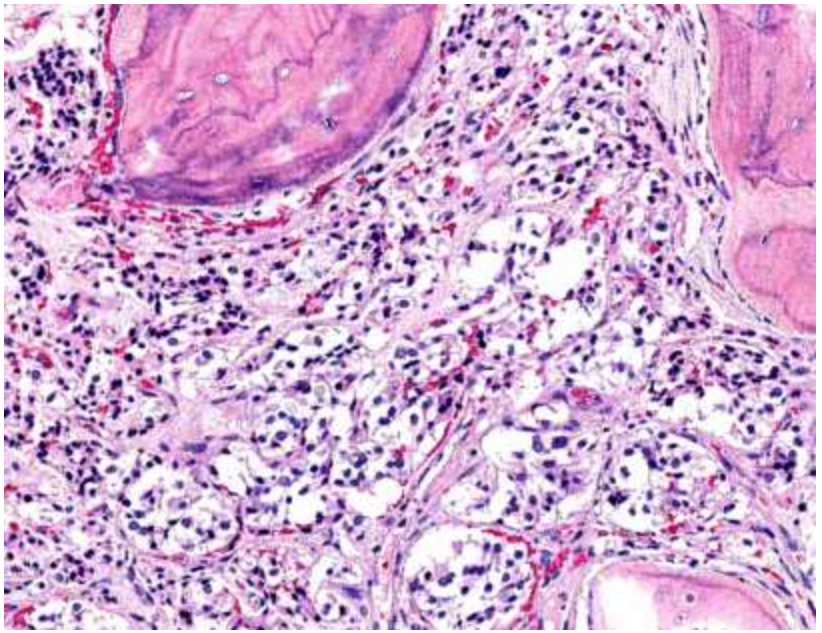
# Our tumor:



# Paraganglioma, jugulotympanic

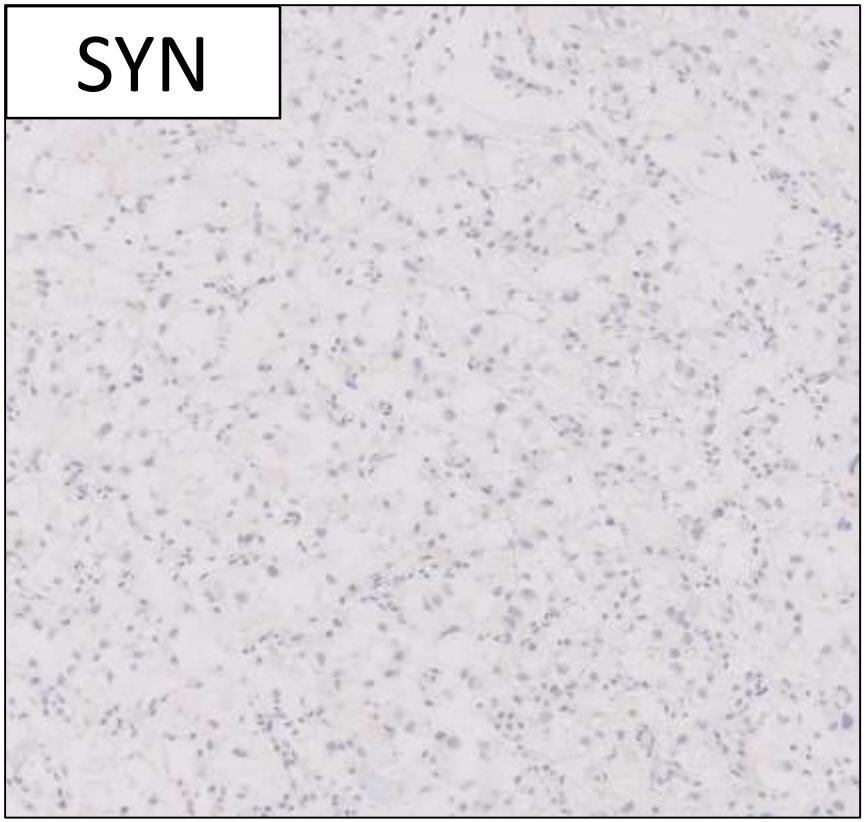
- Most common middle ear tumor
- Presentation: pulsatile tinnitus, hearing loss
- Arises from paraganglia along inferior tympanic nerve
- ~50% familial, screen for SDH mutation
- 8-10% can be aggressive
- Histo: nested arrangement of tumor cells with surrounding vascular network
- IHC:
  - Negative for epithelial markers
  - Positive for neuroendocrine markers. S100 highlights sustentacular cells

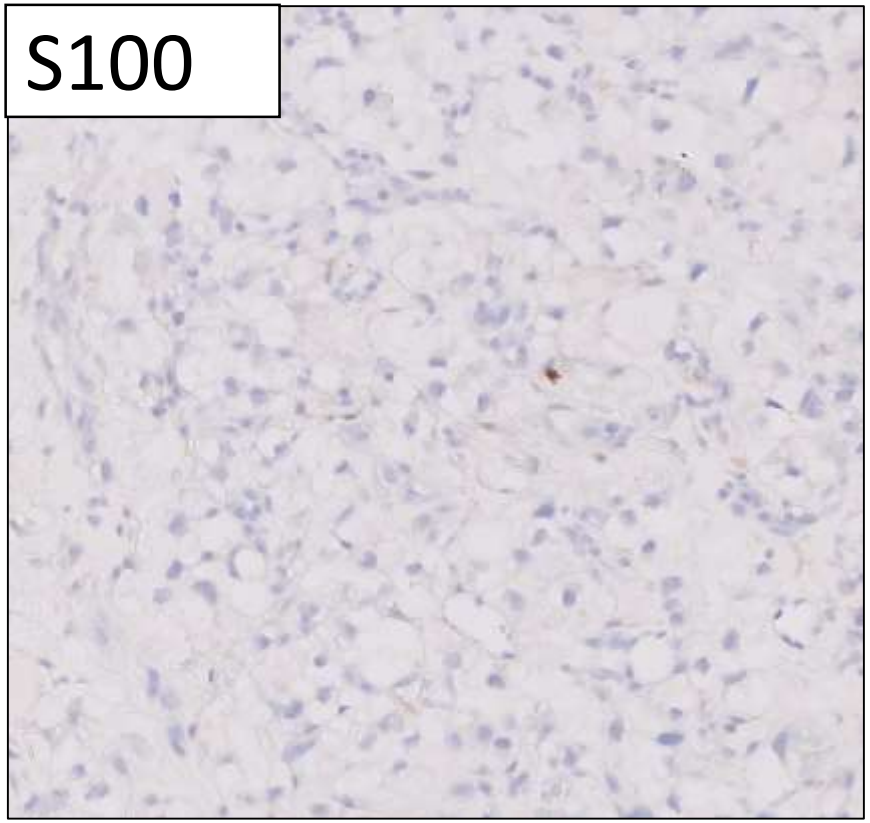




Source: https://app.expertpath.com/document/jugulotympanic-paraganglioma

# Our tumor:

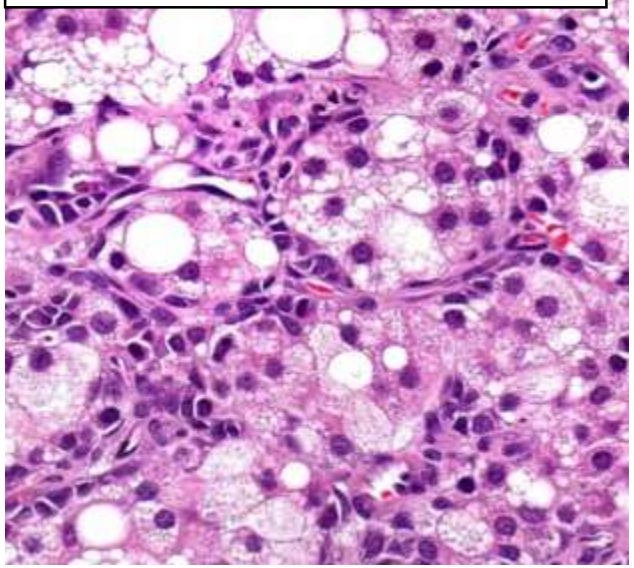


# Sebaceous gland tumor

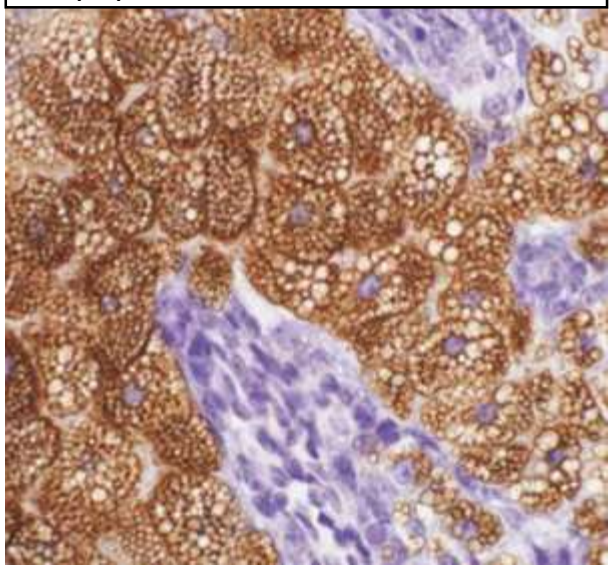
- Histology: numerous lipid vacuoles in cytoplasm, associated basaloid/squamous cells
- IHC Pitfall:
  - Androgen receptor can be positive in ccRCC
  - Adipophilin shows granular cell staining in ccRCC but should be strong membrane in sebaceous tumors

A sebaceous carcinoma



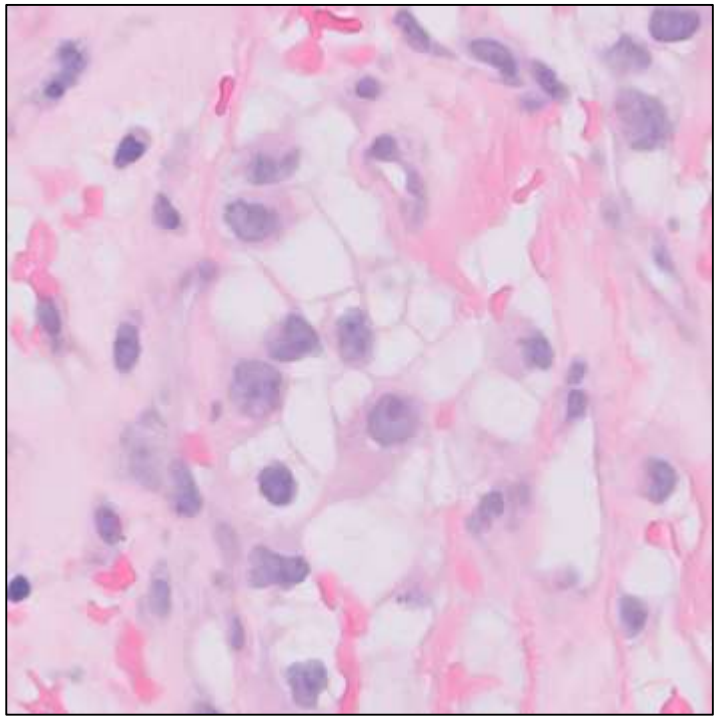
https://app.expertpath.com/document/sebaceous-carcinoma-and-sebaceous

Adipophilin in a sebaceous adenoma

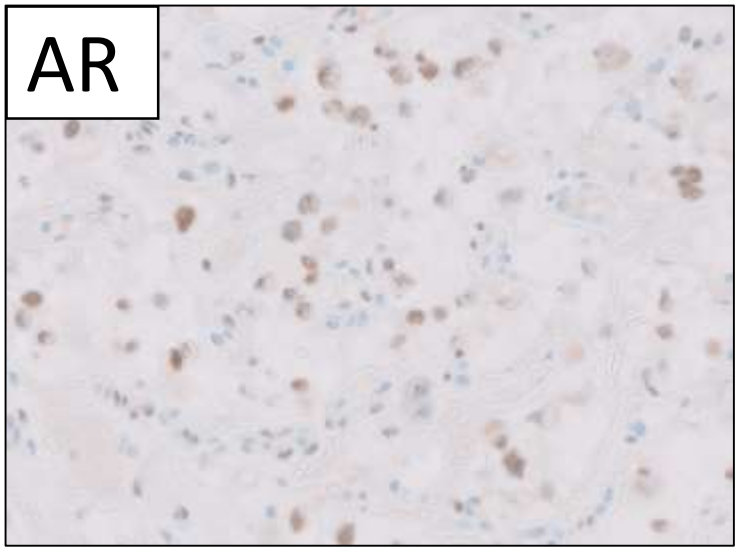


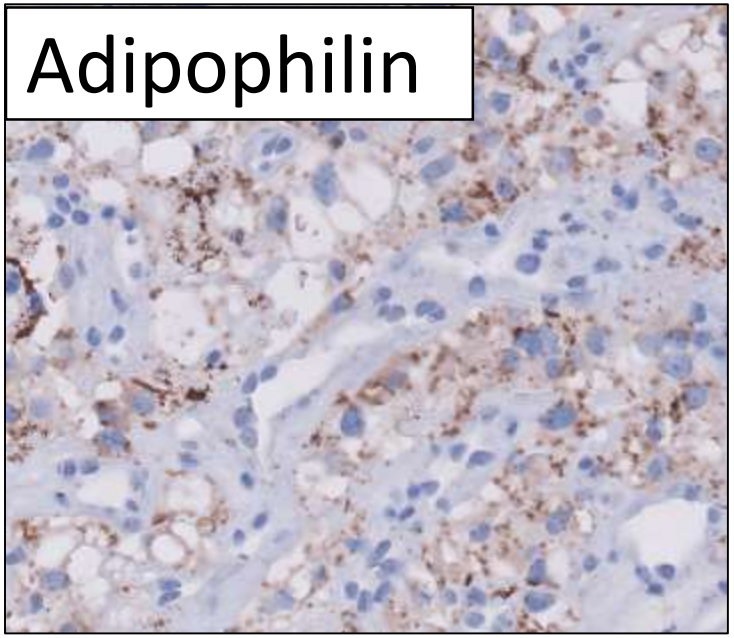
Ostler DA, Prieto VG, Reed JA, Deavers MT, Lazar AJ, Ivan D. Adipophilin expression in sebaceous tumors and other cutaneous lesions with clear cell histology: an immunohistochemical study of 117 cases. Mod Pathol. 2010 Apr;23(4):567-73.

# Our tumor:



Cells too optically clear!

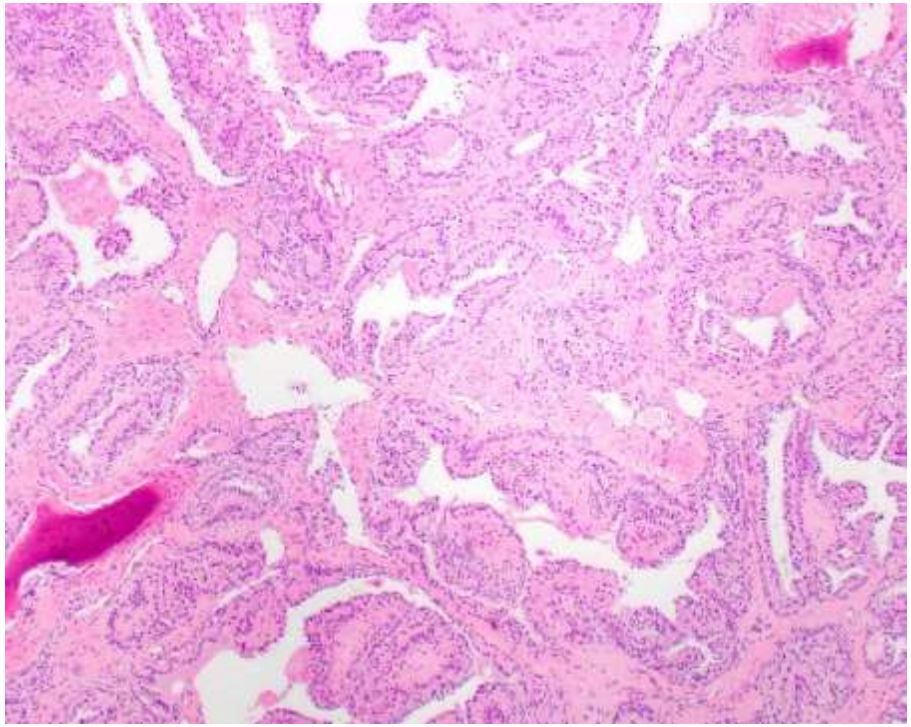


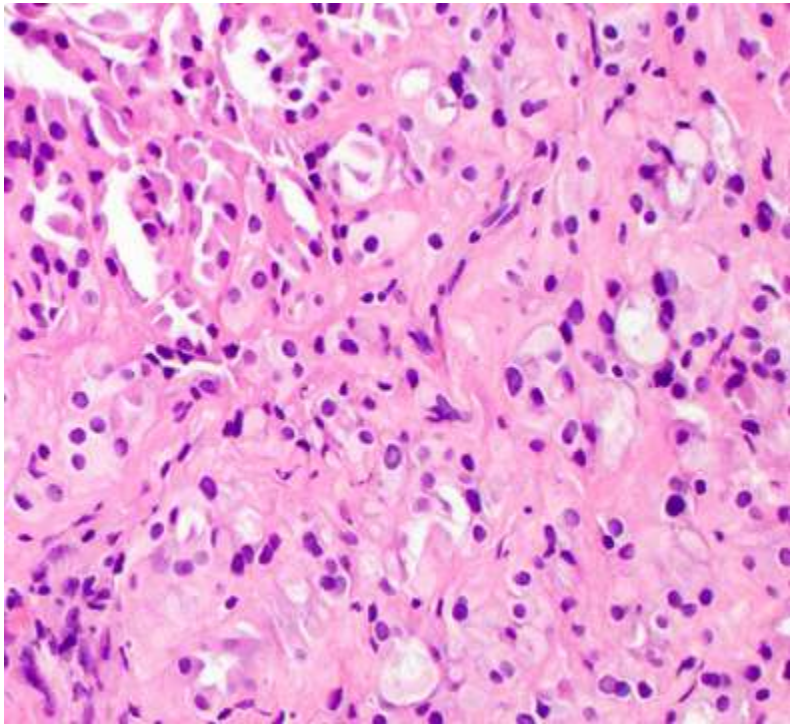



# Endolymphatic sac tumor

- Very rare low-grade tumor
- Has many names
- Average age in 5$^{th}$ decade, F>M
- Can be locally aggressive
- Associated with von Hippel-Lindau syndrome (3.6%)
- Pitfall: Overlapping IHC profile with metastatic ccRCC and PTC
  - PAX8, CAIX and CK7 positive

# Endolymphatic sac tumor vs ccRCC





**CAIX and pax-8 Commonly Immunoreactive in Endolymphatic Sac Tumors: A Clinicopathologic Study of 26 Cases with Differential Considerations for Metastatic Renal Cell Carcinoma in von Hippel-Lindau Patients**

Lester D. R. Thompson[1,9] · Kelly R. Magliocca[2] · Simon Andreasen[3] · Katlin Kiss[4] · Lisa Rooper[5] · Edward Stelow[6] · Bruce M. Wenig[7] · Justin A. Bishop[8]

Head and Neck Pathology (2019) 13:355–363
https://doi.org/10.1007/s12105-018-0973-8

# Endolymphatic sac tumor vs ccRCC

| Antigen | Source | Result | %/# of cases |
|---|---|---|---|
| Cytokeratin (AE1/AE3) | Dako | P, S, D, C | 100% (16/16) |
| Epithelial membrane antigen (EMA) (E29) | Ventana | P, S, D, C | 100% (12/12) |
| CK7 (OV-TL-12/30) | Dako | P, S, D, C | 100% (20/20) |
| CAIX (CA9) | Cell Marque | P, S, D, M | 100% (25/25) |
| pax-8 | LifeSpan BioSciences | P, S, D, N | 85% (22/26) |
| CD10 (SP67) | Ventana | Non-reactive | 0% (0/16) |
| RCC | Vector Laboratories | Non-reactive | 0% (0/15) |

*P* positive, *S* strong, *D* diffuse, *C* cytoplasmic, *M* membrane, *N* nuclear

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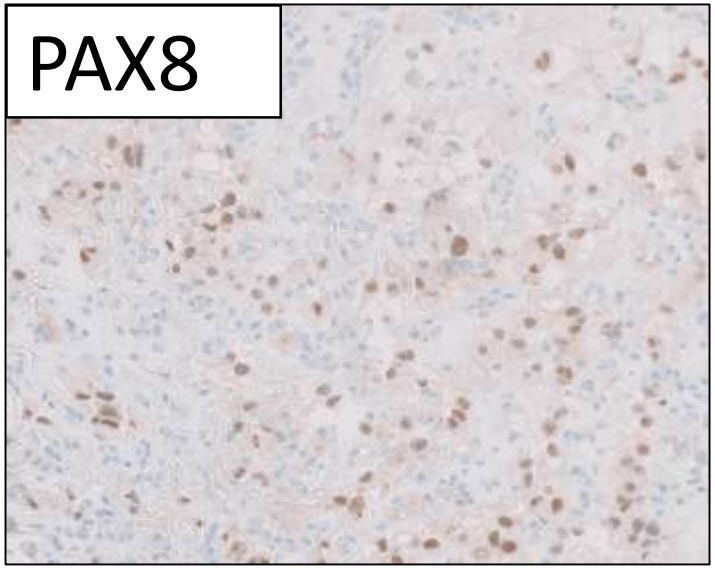
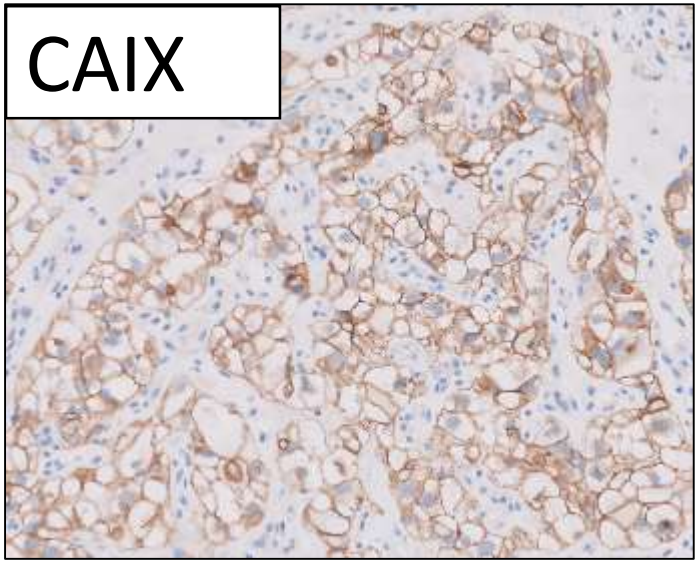
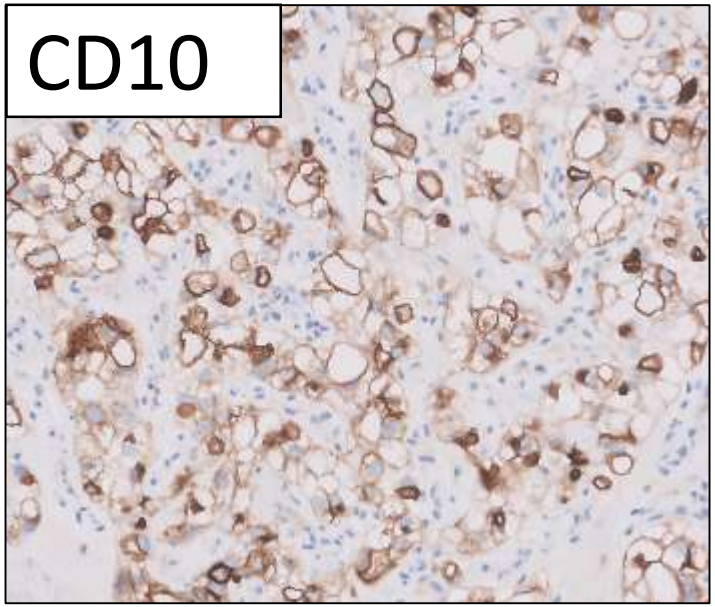
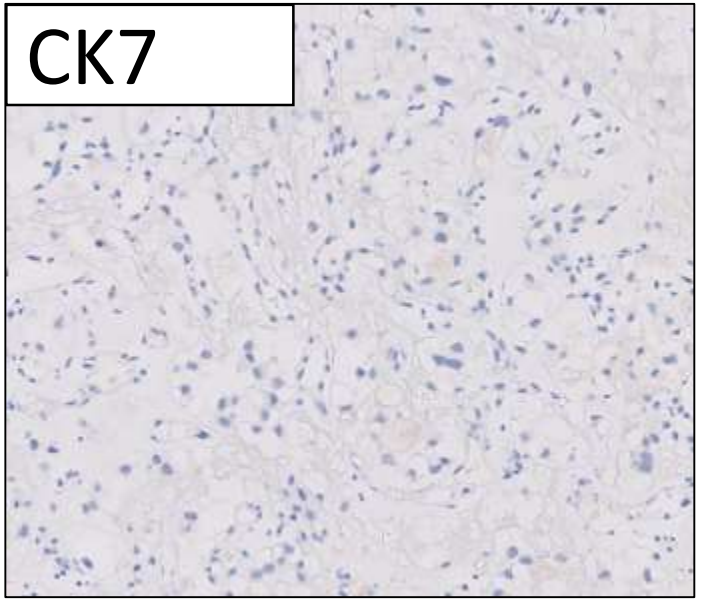
# Our tumor:



# Final diagnosis:

- Clear cell neoplasm most compatible with metastatic clear cell renal cell carcinoma
    - Comment: Please check for renal mass!
    - Only case reports in the literature of ccRCC presenting as an ear mass

# Follow-up

- Whole body imaging showed a 6.7 cm left kidney mass, 2.4 cm left adrenal mass, right paraspinal/intramuscular mass and thorax masses
- Shortly after, presented to the ER with a pathologic fracture to right tibia, curettage also showed ccRCC
- Patient started on immunotherapy/TKI

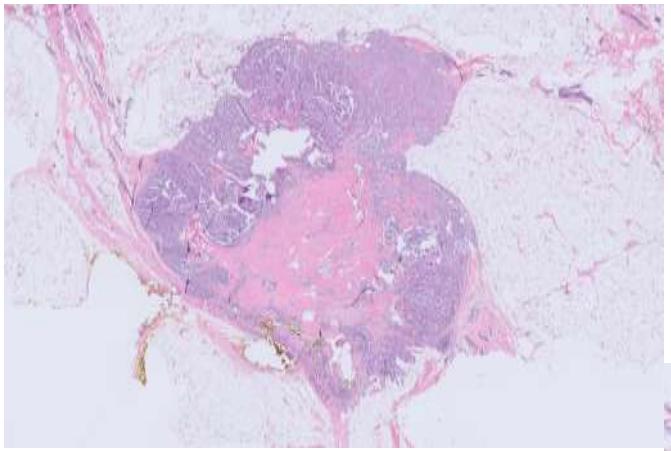
# Take home points

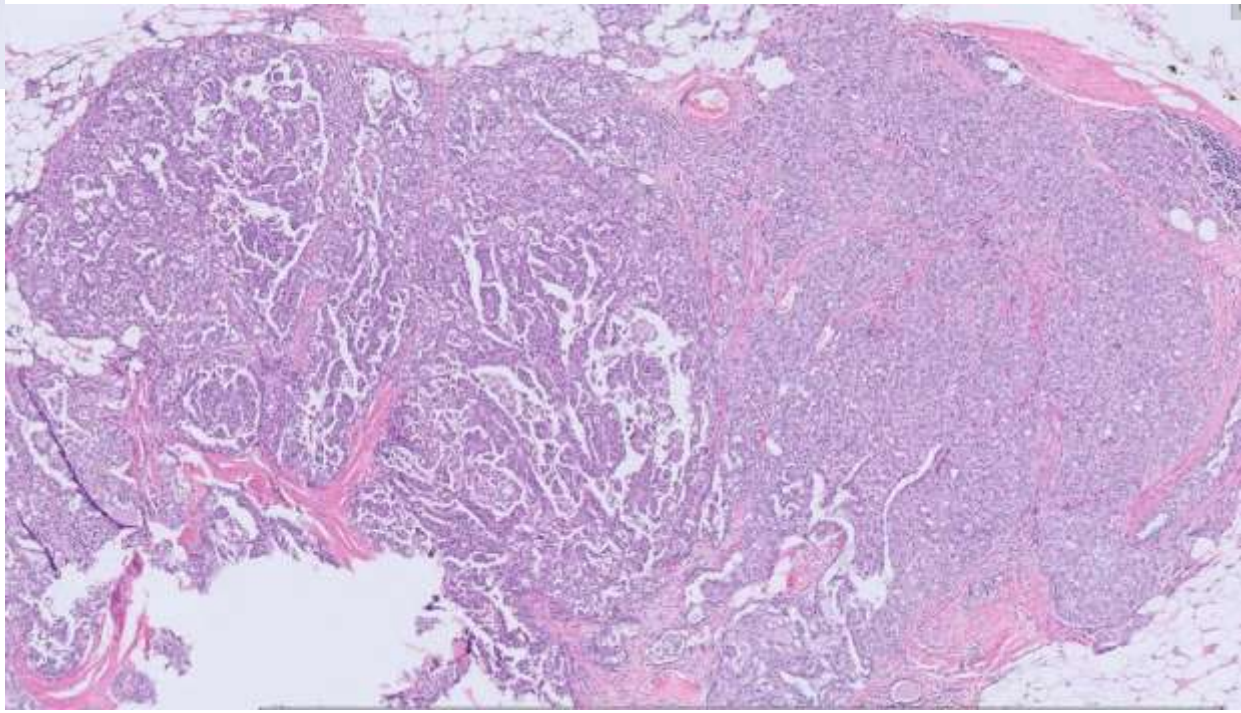
- Review differential diagnosis of a vascular lesion in the middle ear/ear canal
- ccRCC can rarely present itself as an ear mass
- Some morphologic mimics of ccRCC in the ear can also stain like ccRCC and also occur in patients prone to getting ccRCC
  - e.g. Endolymphatic sac tumor in VHL patients

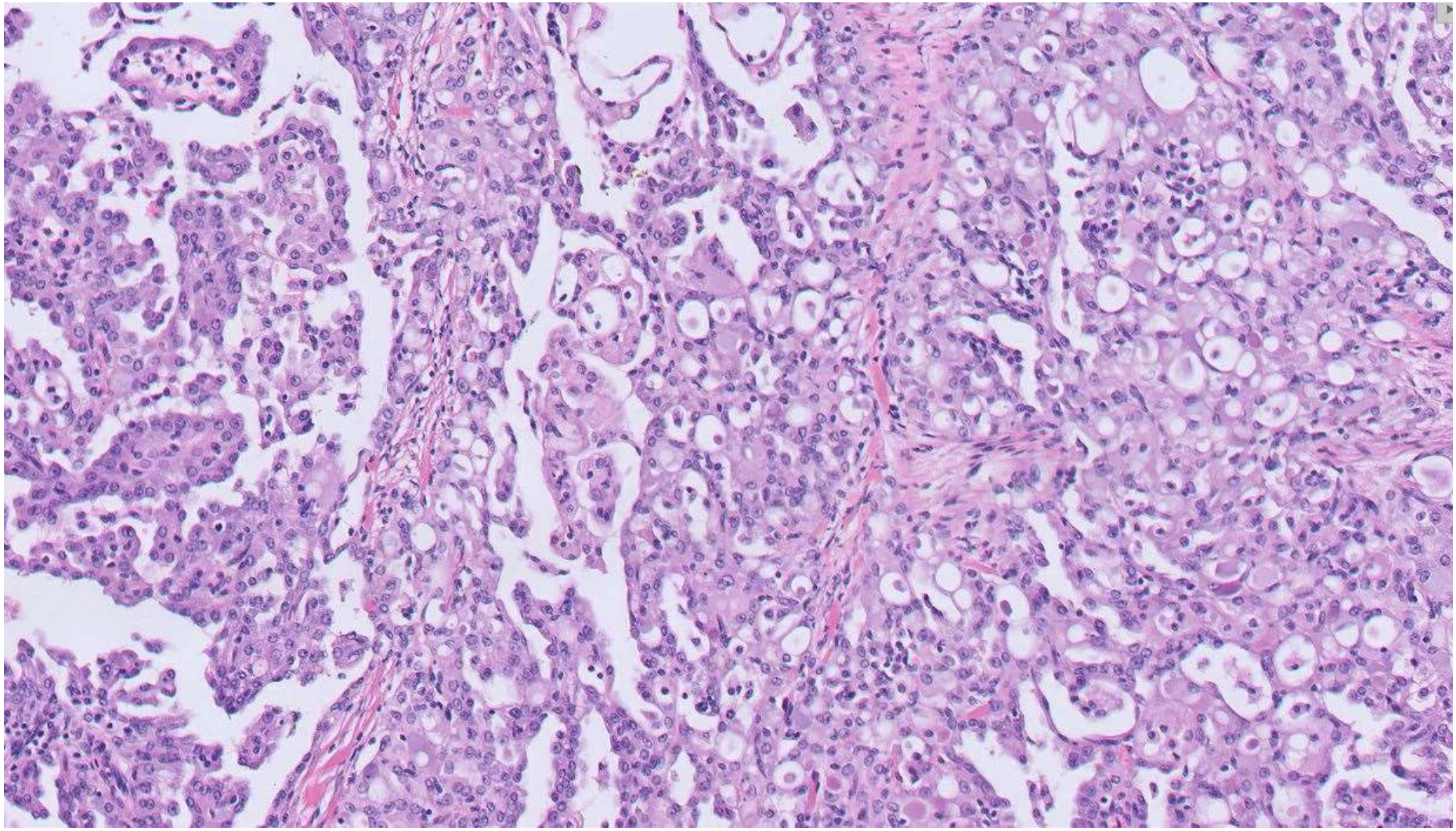
# 21-0902

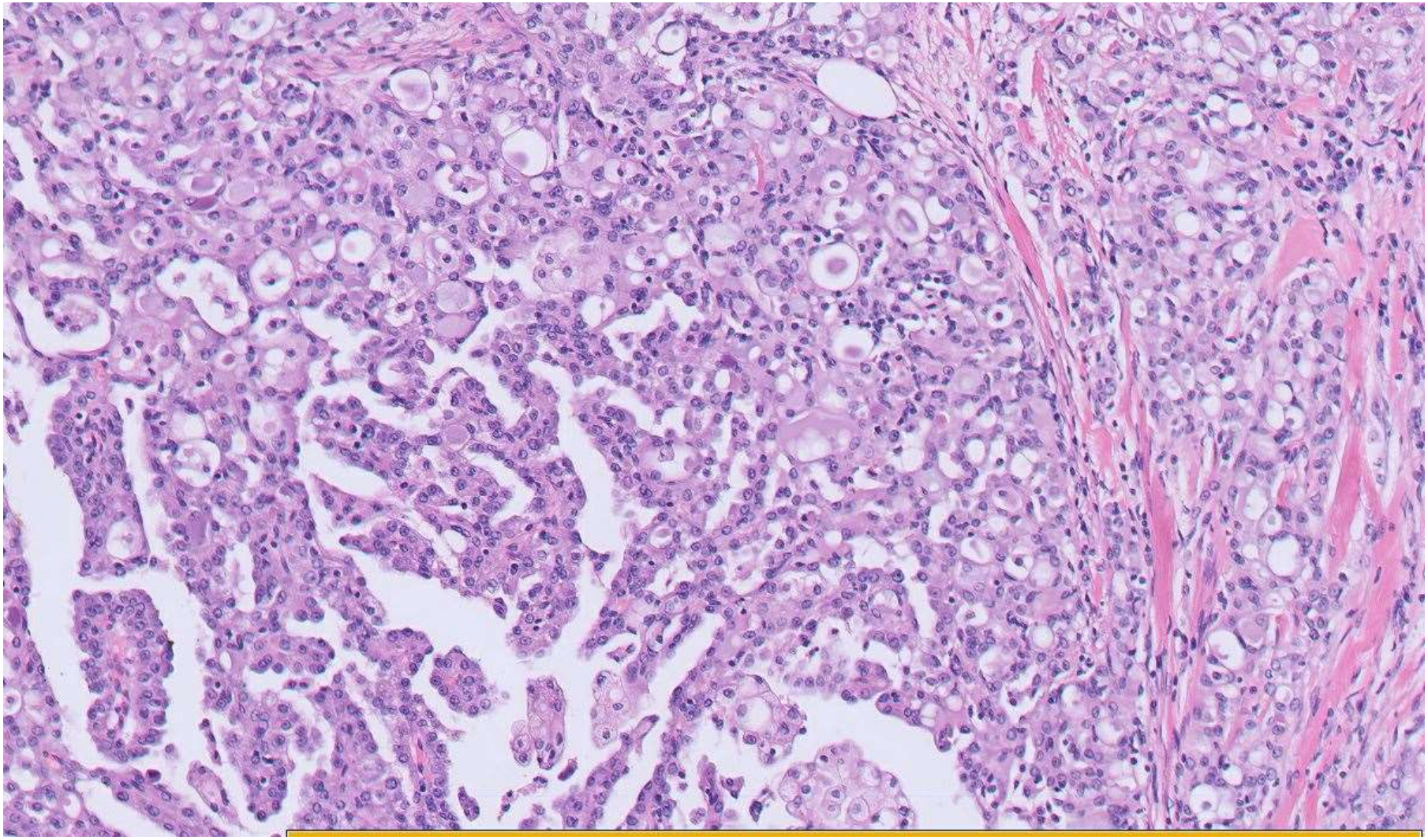
**Roshanak Derakhshandeh/Megan Troxell; Stanford**

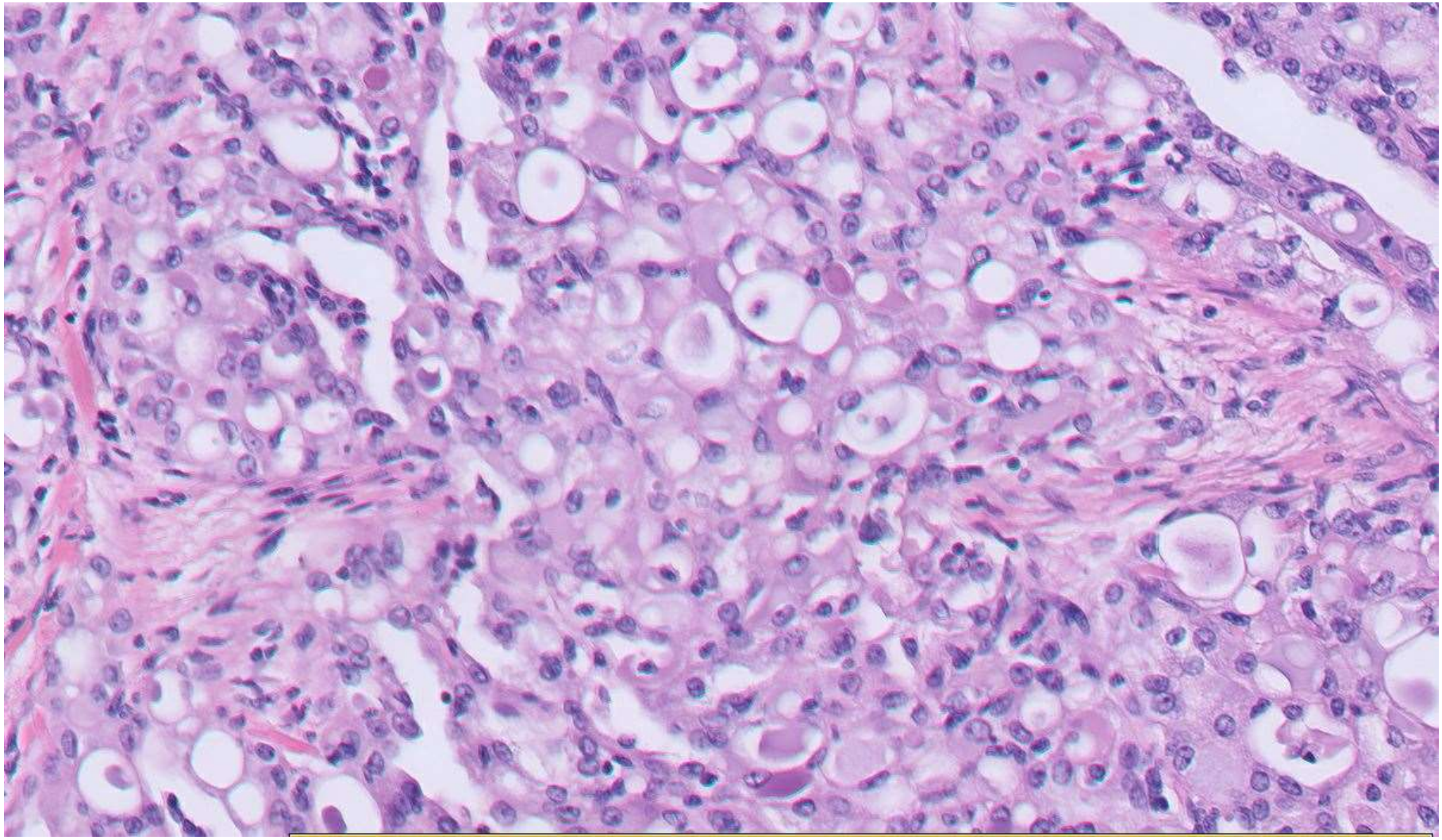
68-year-old F with left breast lesion.



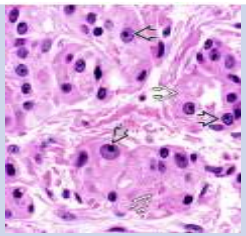
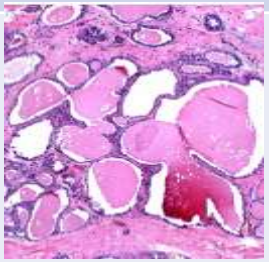
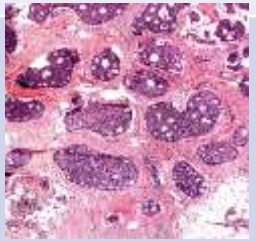
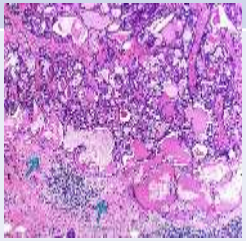


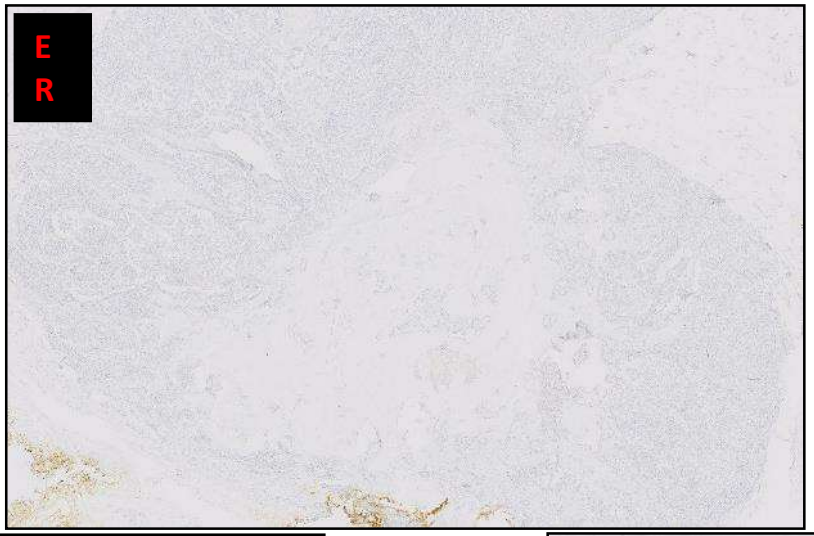






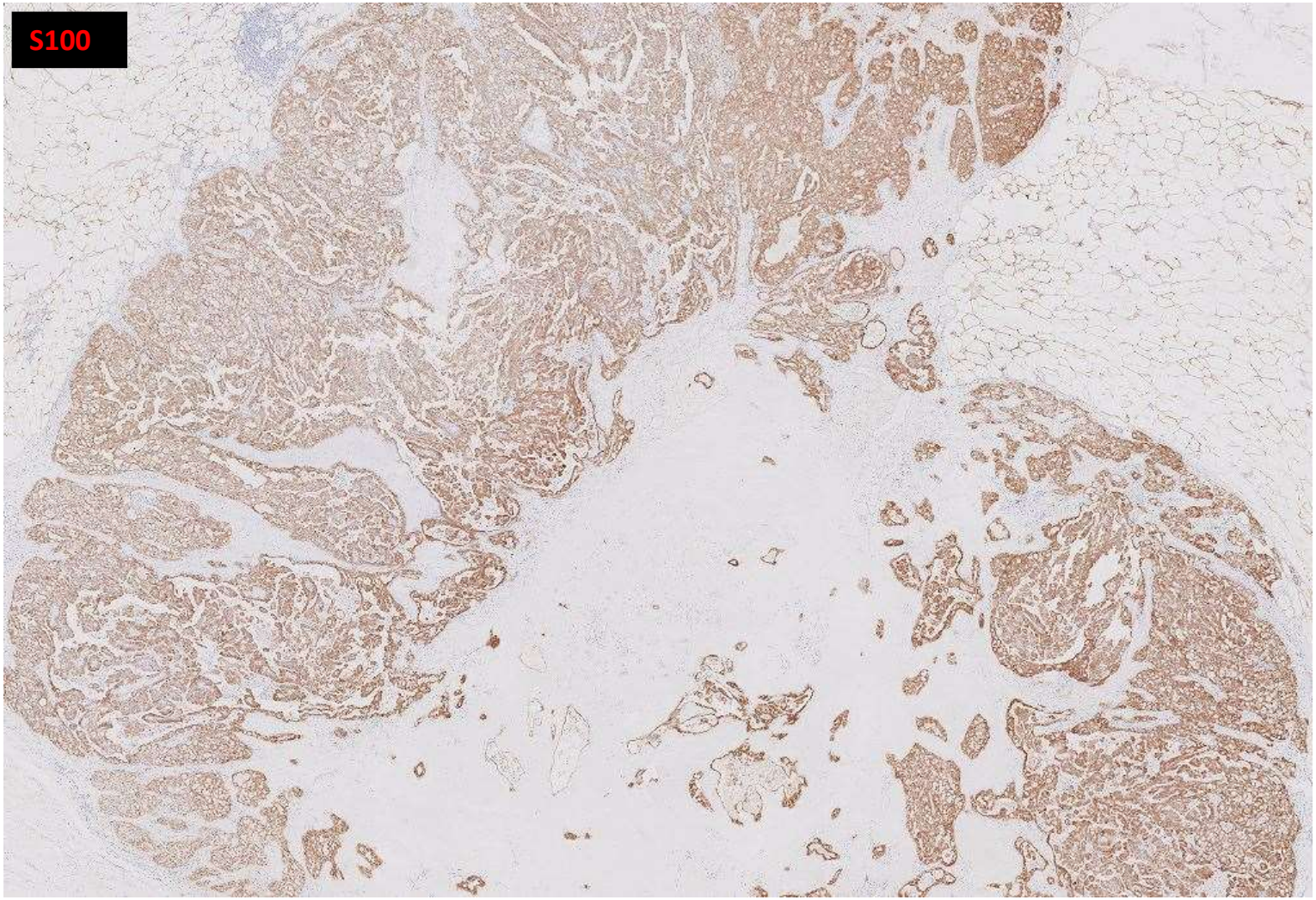
**Differential Diagnosis**

| | Morphology | IHC | |
|---|---|---|---|
| **Carcinoma with Apocrine Differentiation** | Usually has solid pattern rather than glandular with secretions<br>Mostly grade 2 or 3 due to nuclear pleomorphism and mitotic activity | Hormone receptor positivity (~ 50%)<br>HER2 positivity (~ 50%) |  |
| **Cystic Hypersecretory Carcinoma** | Evident cystic spaces filled with densely eosinophilic secretory material<br>Cells have pleomorphic hyperchromatic nuclei and cytoplasm is generally scant<br>Majority of cases are in situ carcinoma | Triple negative (ER, PR, Her-2 negative)<br>Positive for S100 |  |
| **Invasive Cribriform Carcinoma** | Cytoplasm is usually not abundant and lacks foamy eosinophilic quality<br>Secretions often present but are not darkly eosinophilic | Strongly positive: ER (> 95%) and PR (> 75%) expression<br>HER2: Negative in vast majority of cases |  |
| **Secretory Carcinoma** | Intracellular and extracellular eosinophilic bubbly secretory material is characteristic<br>Cells have low to moderate nuclear grade and low proliferative rate | Majority: negative for ER, PR, and HER2<br>Positive for S100 |  |


E
R


P
R


Her-2


S100

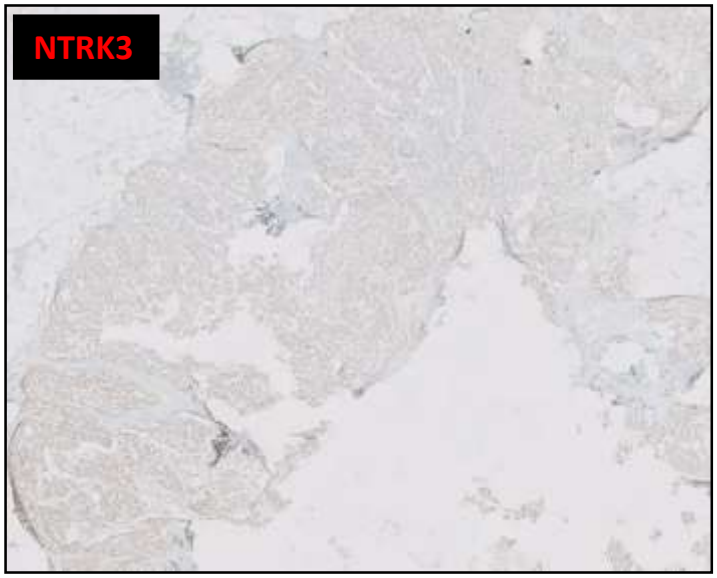
# Secretory Carcinoma (Low-grade translocation-driven carcinoma)

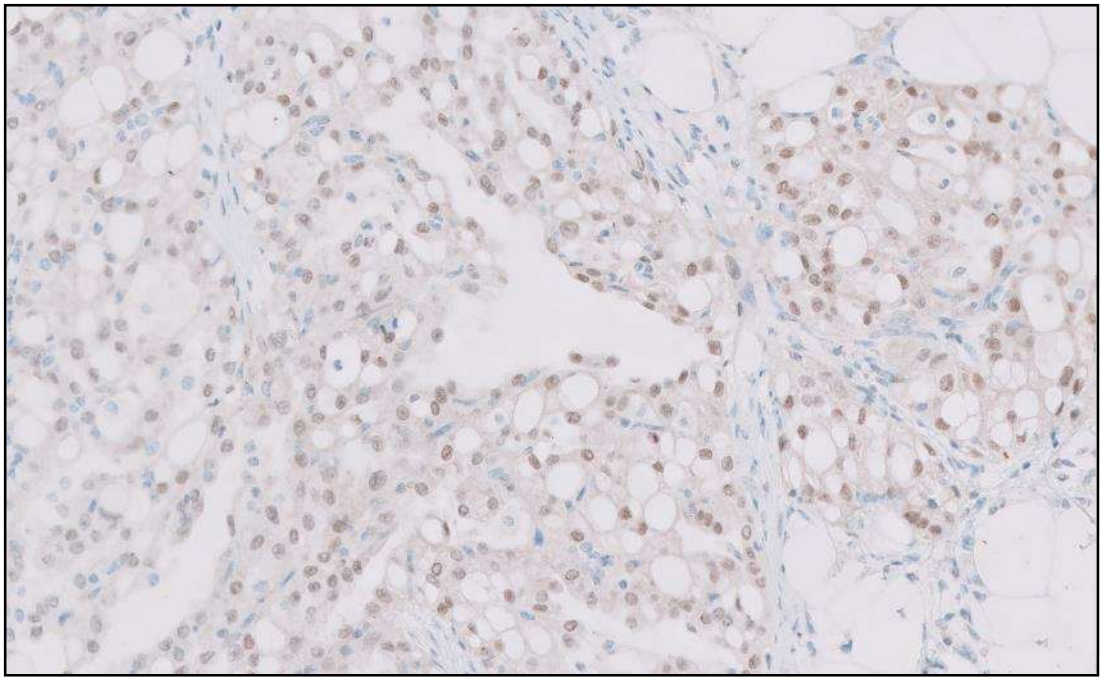
- Rare, < 0.02% of all breast cancers
- Initially described in children, most common childhood breast cancer
- Recent studies show mainly affects older patients, but with significantly younger median age (53 - 56 years) compared with invasive ductal carcinoma

- **Morphology:**
  - Polygonal tumor cells with eosinophilic granular or vacuolated cytoplasm, arranged in microcytic, solid, tubular or papillary growth pattern.
  - The intra and extracellular secretions are positive for PAS, mucicarmine, and Alcian blue.
  - Vast majority are grade 1-2 (Nottingham)
- **IHCs:**
  - Express: CEA, S100, mammaglobin, SOX10, MUC4; mostly express CK5/6
  - Most cases: triple negative for ER, PR and Her-2
- **Molecular:**
  - t(12;15)(p13;q25) *ETV6-NTRK3* fusion

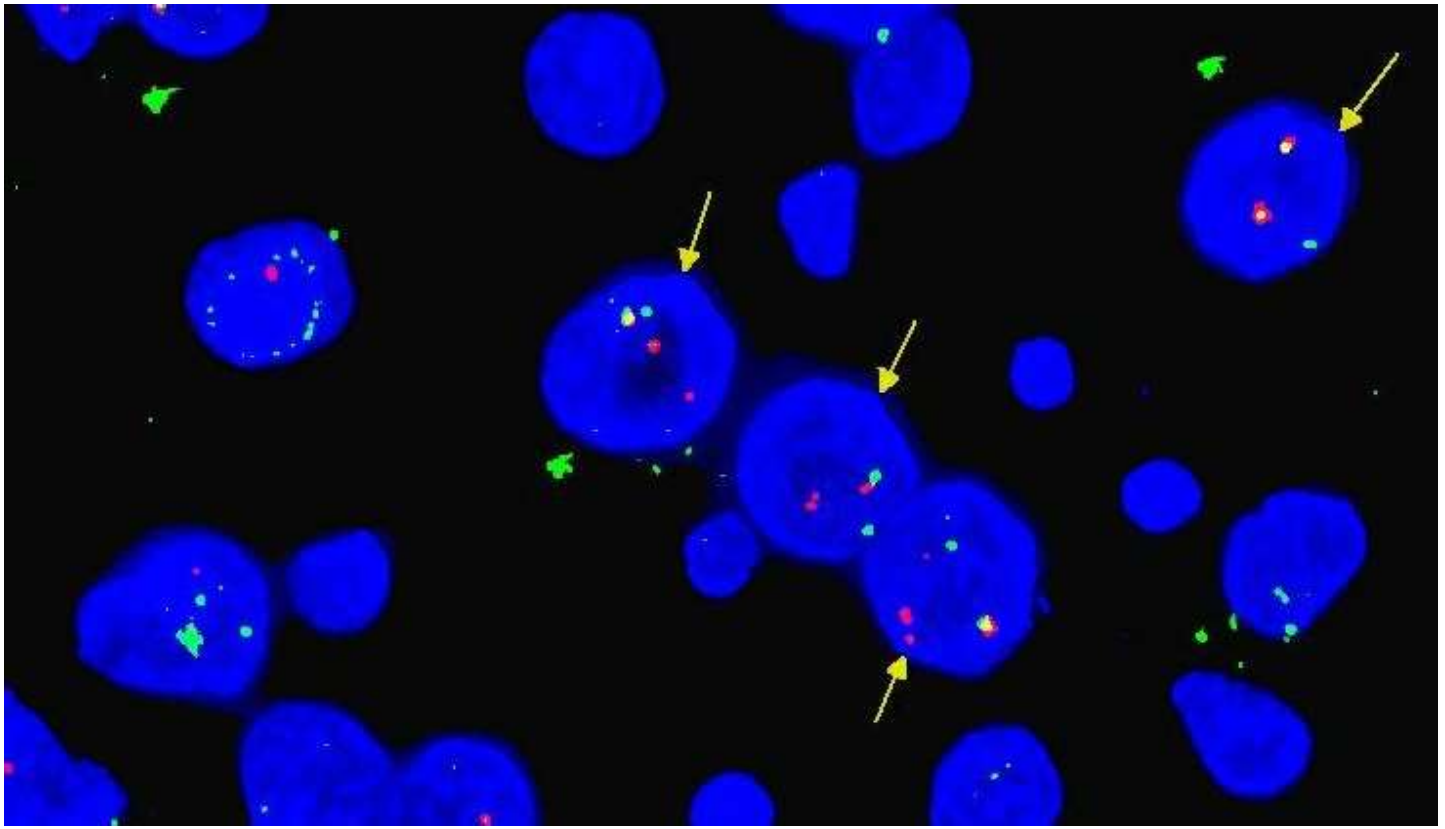
# Ancillary Study

- Rapid/reliable molecular confirmation of *ETV6-NTRK3*:
  - FISH either ETV6 break apart or ETV6 and NTRK convergence probes
  - PCR by using ETV6 and NTRK3 primers
- IHC: panTRK antibodies used as screening or as part of diagnostic panel
  - more reliable TRK antibodies will be necessary for IHC as a biomarker
- Small molecules inhibitors that target *NTRK* have recently been developed and have shown promising efficacy
  - Secretory carcinoma may not require systemic therapy (surgery/XRT)


NTRK3



FISH study: *ETV6*



# Take Home Point: WHO criteria

- **Essential:**
  - Morphology (intracytoplasmic and extracellular secretions) plus IHC (triple negative, S100, mammaglobin)
- **Desirable:**
  - Can be confirmed by FISH showing ETV6 rearrangement or identification of ETV6-NTRK3 by PCR or sequencing

- Staged according to the guidelines for invasive carcinoma of the breast

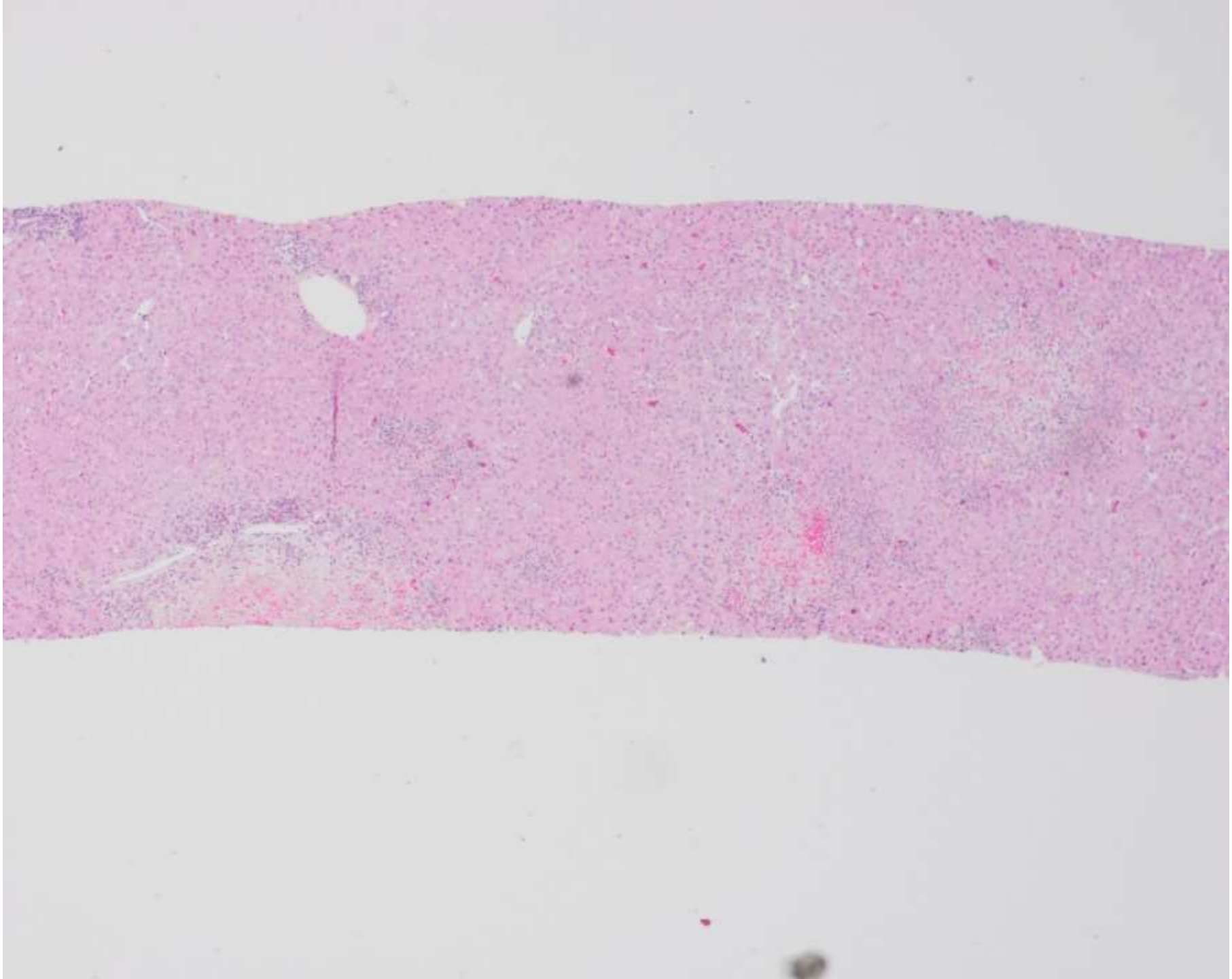
# References:

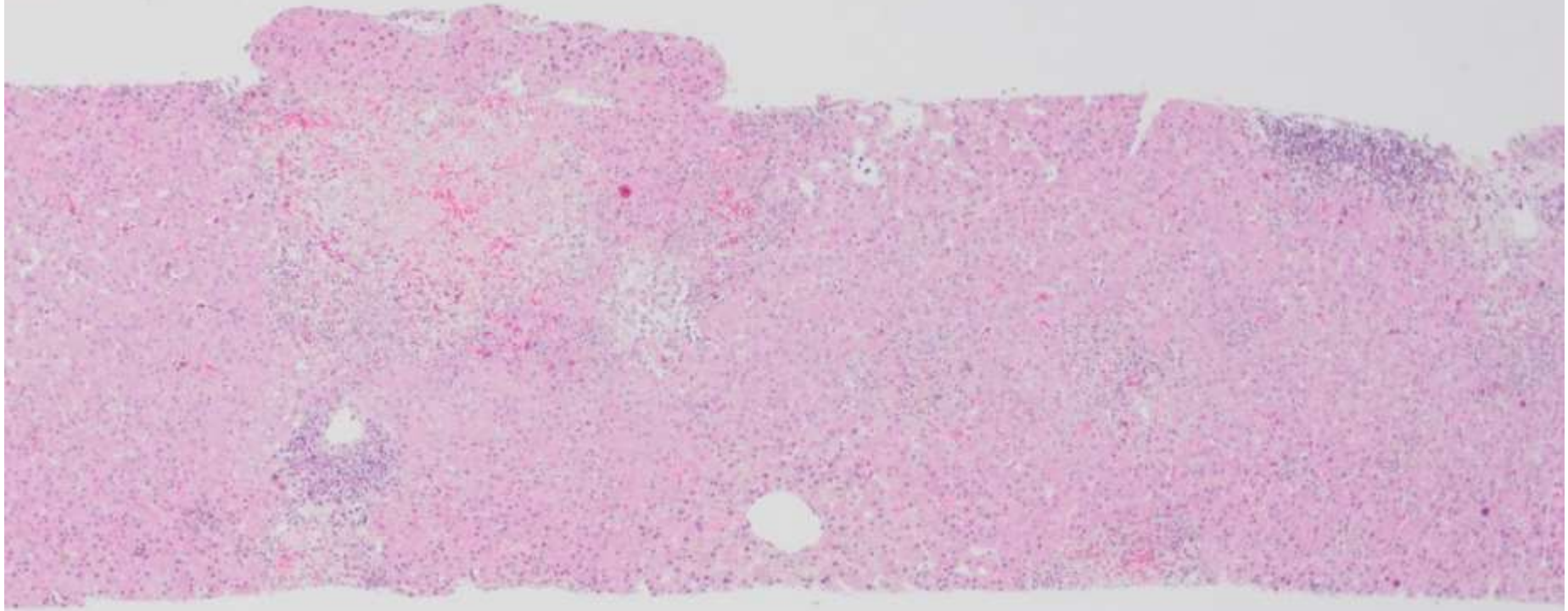

1. Tognon C, Knezevich SR, Huntsman D, et al. Expression of the ETV6-NTRK3 gene fusion as a primary event in human secretory breast carcinoma. Cancer Cell. 2002;2(5):367-376. doi:10.1016/s1535-6108(02)00180-0
2. Breast Tumours, WHO Classification of Tumours, 5th Edition, Volume 2
3. Krings, G., *et al.* Genomic profiling of breast secretory carcinomas reveals distinct genetics from other breast cancers and similarity to mammary analog secretory carcinomas. *Mod Pathol* **30,** 1086–1099 (2017).
4. McDivitt RW, Stewart FW. Breast carcinoma in children. *JAMA*. 1966;195(5):388-390.
5. Horowitz DP, et al. Secretory carcinoma of the breast: results from the survival, epidemiology and end results database. *Breast*. 2012;21(3):350-353.

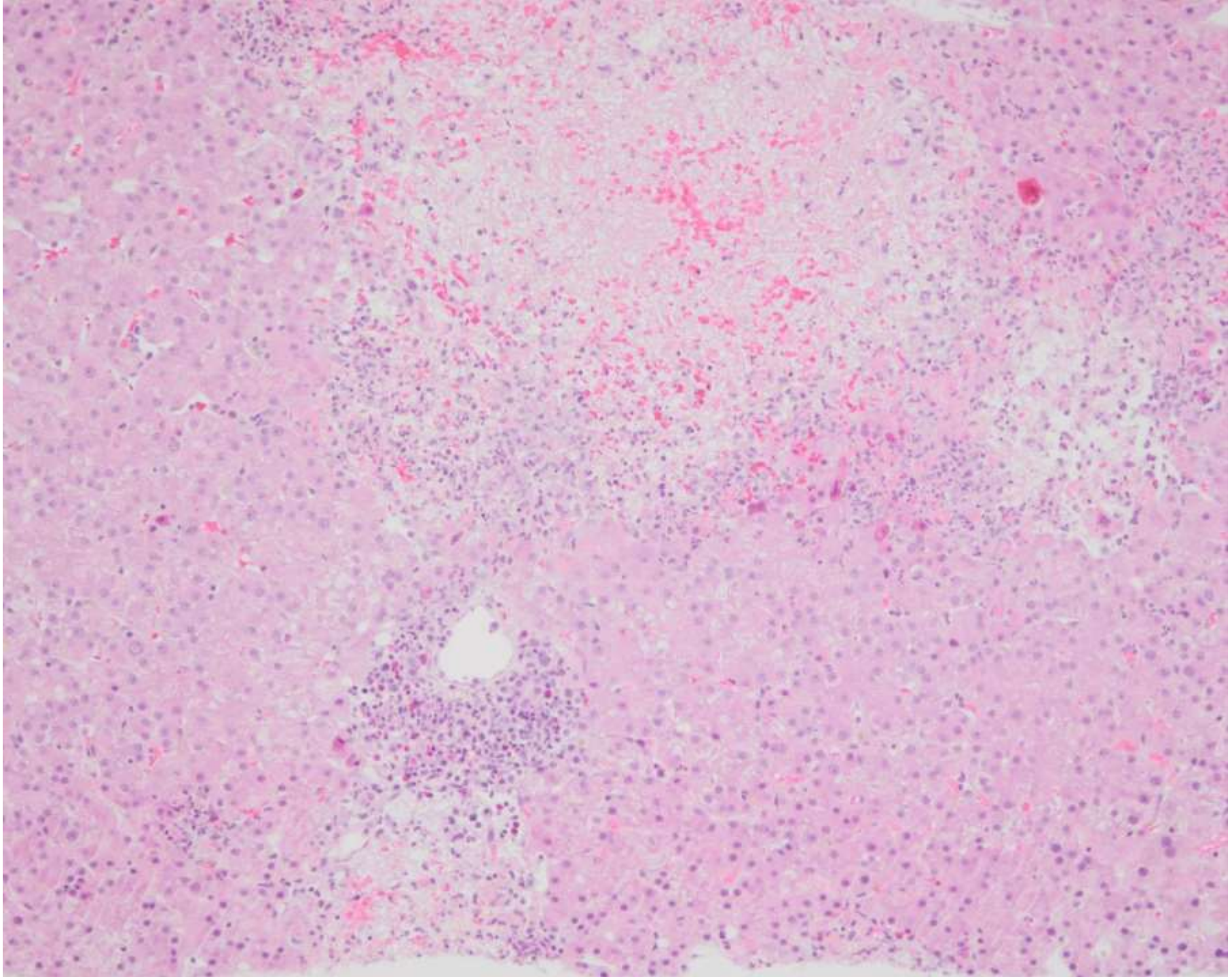
# 21-0903

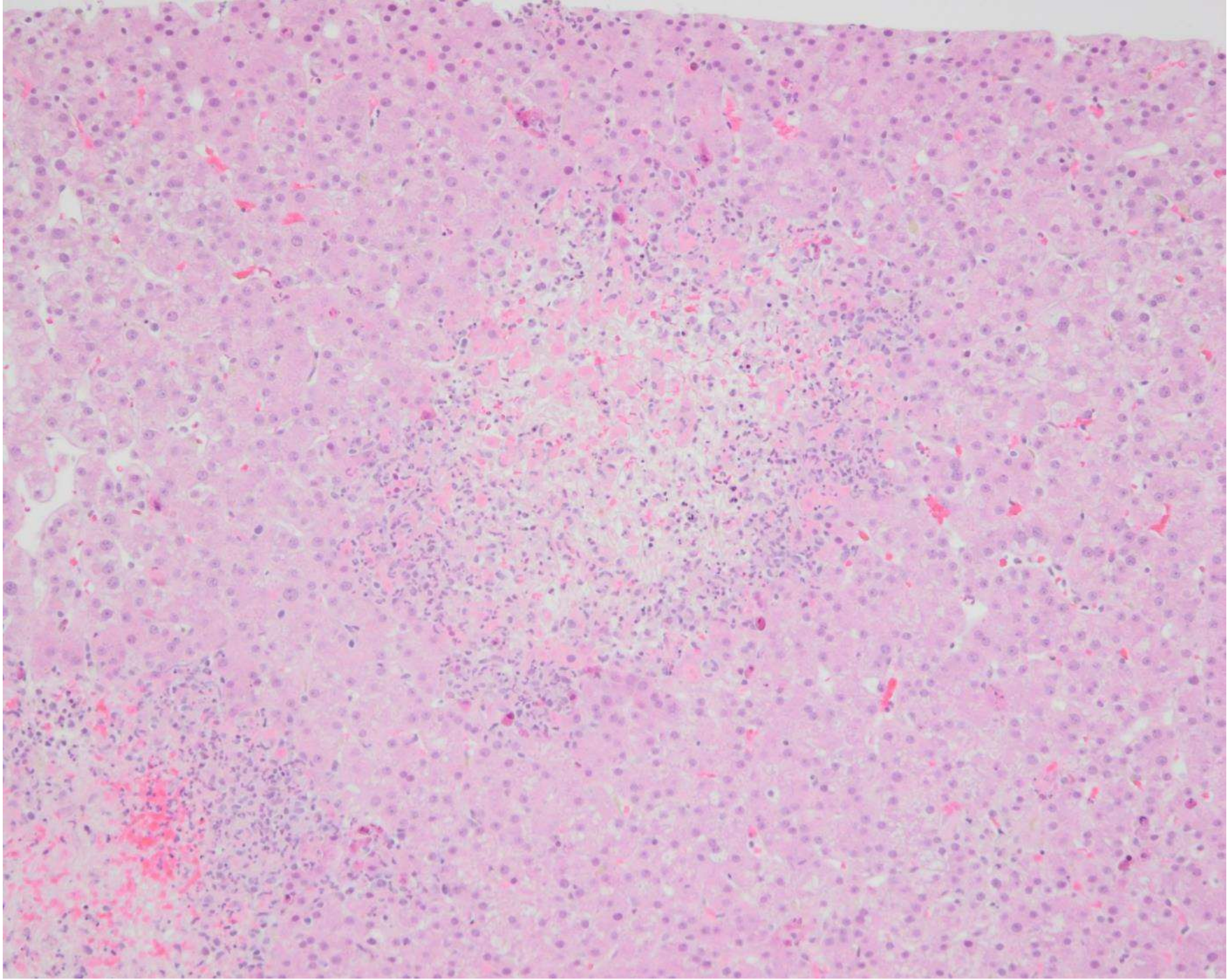
**Richard Garcia-Kennedy; CPMC**

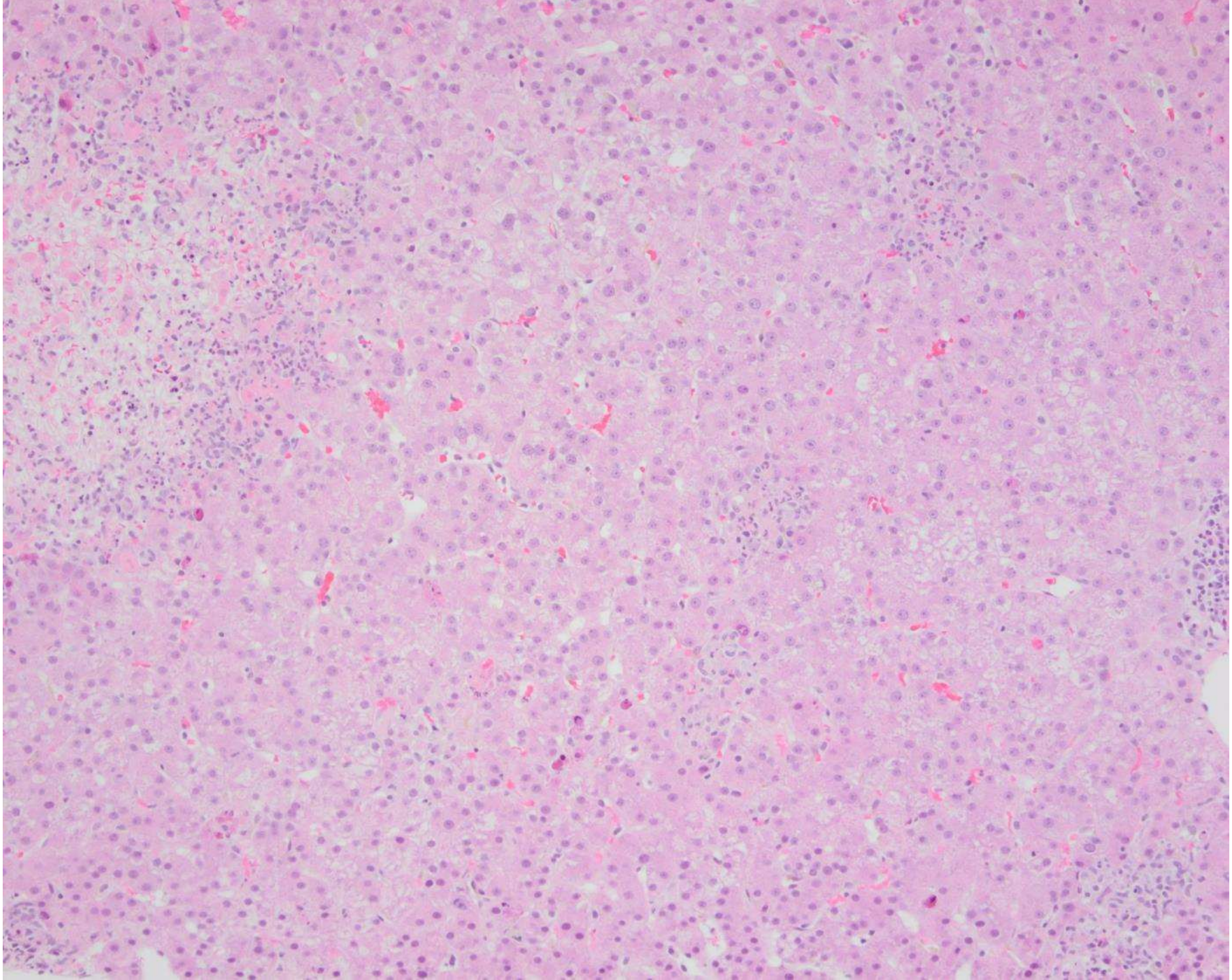
68-year-old F s/p liver transplant for HCV/HCC day 16 – elevated LFTs.

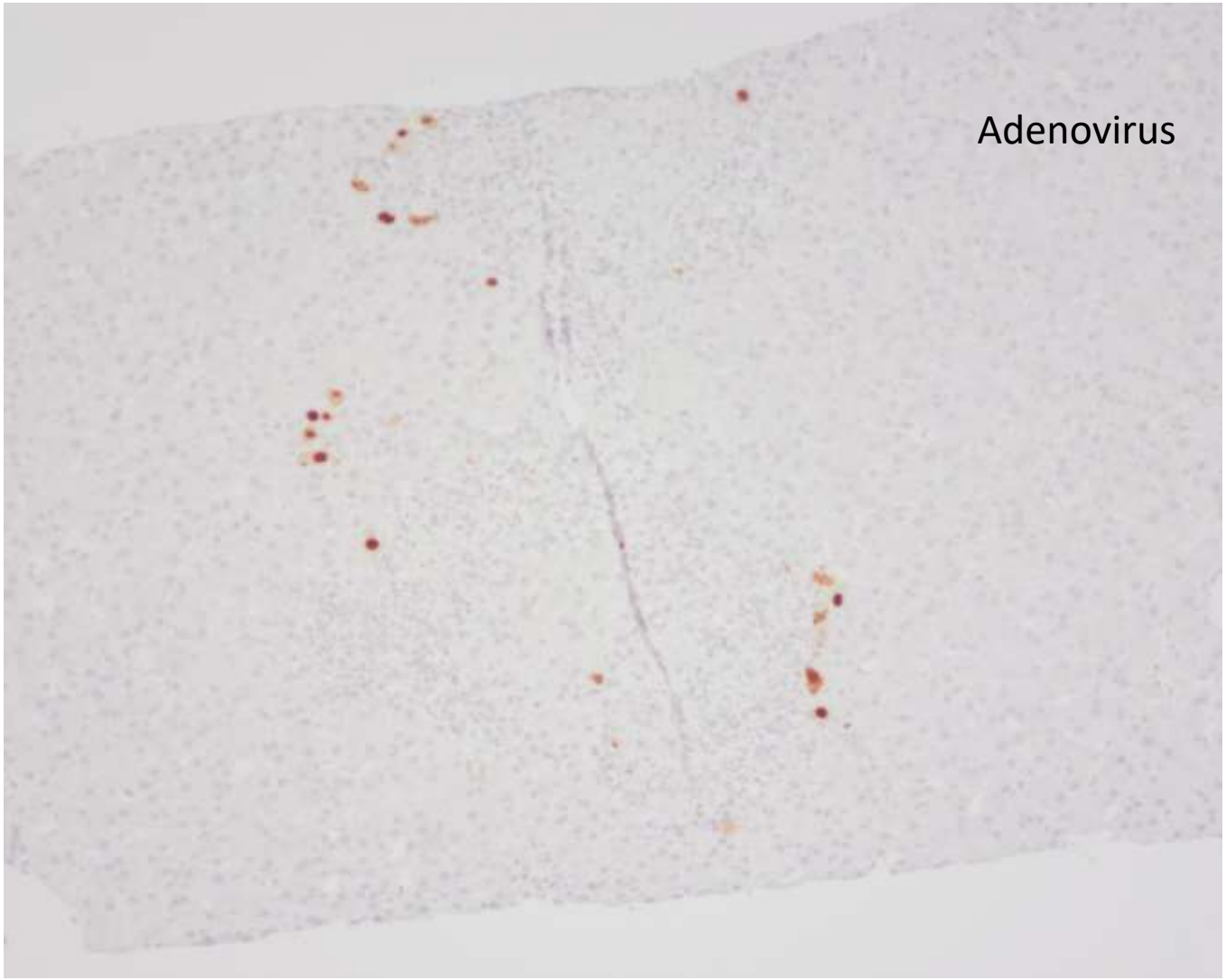


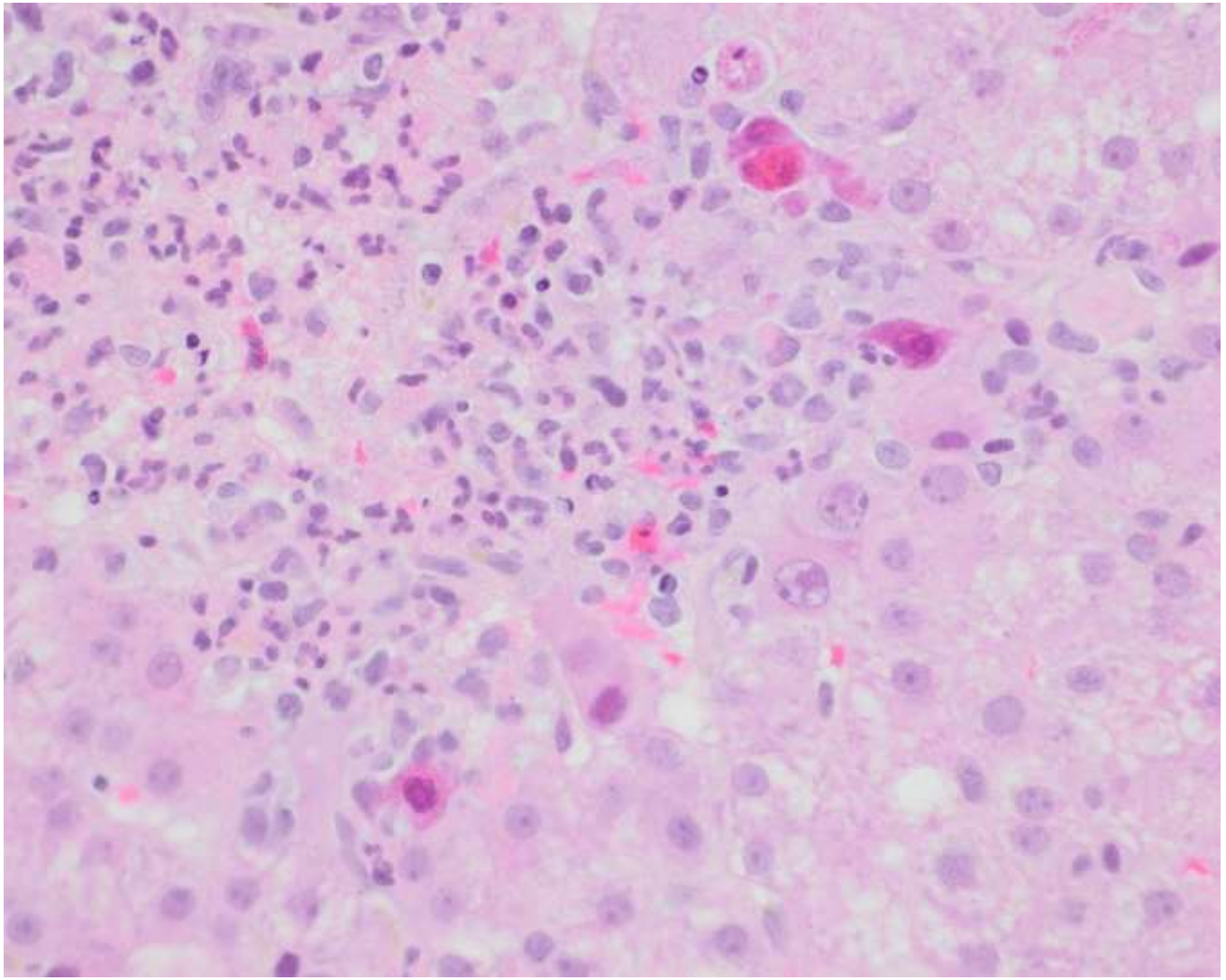


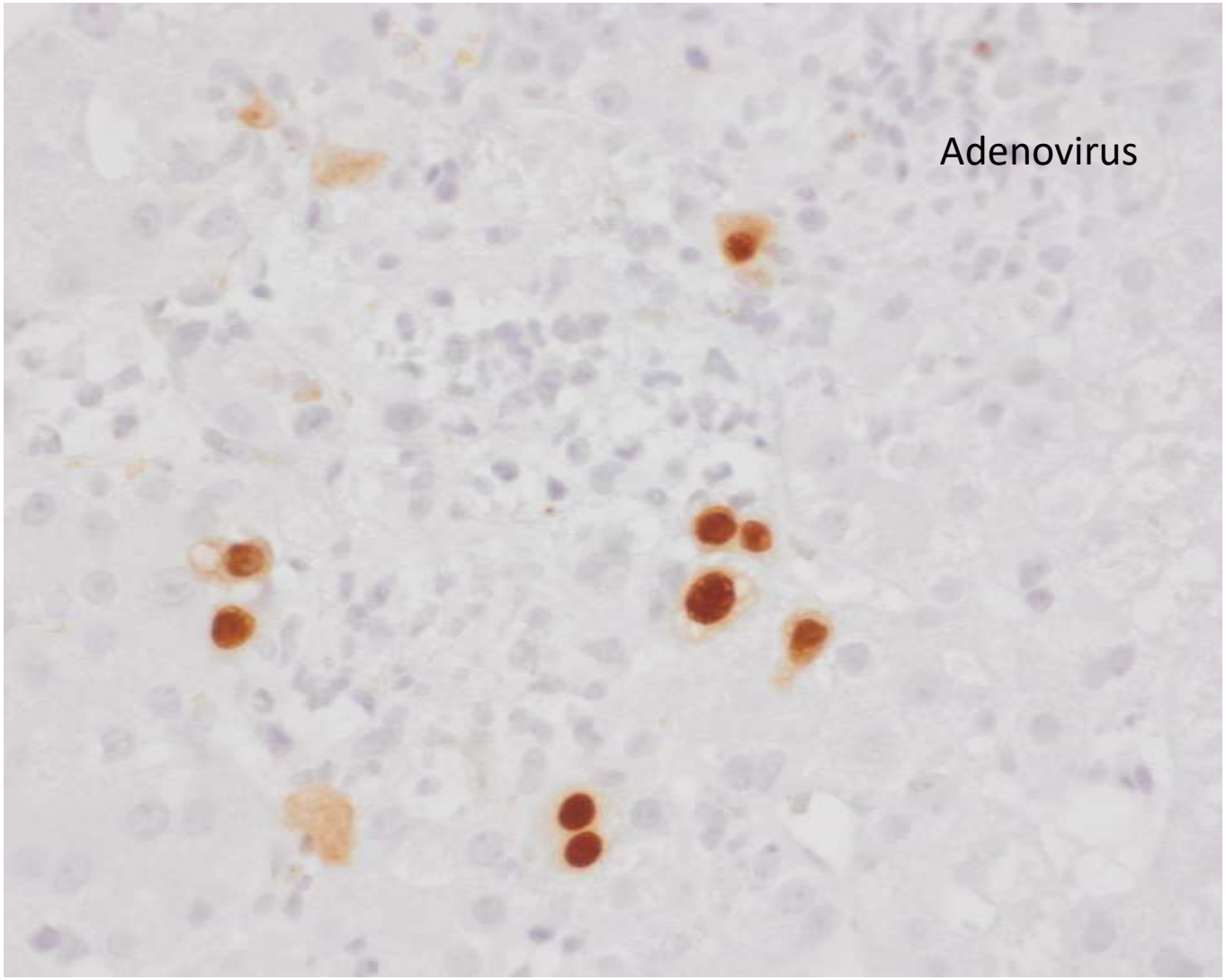







Adenovirus




Adenovirus

- **Adenovirus Hepatitis: Clinicopathologic Analysis of 12 Consecutive Cases From a Single Institution**
- Am J Surg Pathol.. 2017 Jun;41(6):810-819.
- Kurt B Schaberg [1], Neeraja Kambham, Richard K Sibley, John P T Higgins
- **Abstract**
- Adenoviruses are common pathogens that usually cause self-limited infections. However, in the immunocompromised host they can cause severe infections involving multiple organs including the liver. A search of the pathology database at Stanford University Medical Center (1995 to 2016) identified 12 cases of adenovirus hepatitis including biopsy and autopsy specimens. There were 8 pediatric patients, 7 of which had received orthotropic liver transplants and 1 of which was receiving chemotherapy for lymphoblastic leukemia. There were 4 adult patients, of which 1 was actively

# -Non-zonal coagulative necrosis or -Random/miliary necrotizing abscesses

- HSV HSV HSV
- (CMV)
- VZV
- (AdV)
- Embolic anything
  - Mycotic atypicals
  - Pyelephlebitis
- Sepsis / cholangitis
- Fungals ala coccidioides, cryptococcus
- Entamoeba
- AFB
- (Preservation injury)

# 68 yo F s/p OLT 2nd HCV/HCC d16 – elevated LFTs

- Real story: acute hepatitic liver failure with ALT/AST rising through thousands, PT rising, cholesterol dropping.
- 12 yo mentally delayed donor who had aspirated around a feeding tube.

•

Donor issues Rejection Viral infections (CMV) Biliary strictures Recurrent ds

Surgical (wound, wind, water) Atypical infections (fungus, AFB) Chronic rejection

Drugs….. PTLD

---

0 1 yr 10 yr

- Hepatologist Ray Merriman really gets credit for figuring this out and getting her treated
- Knew a Peds hepatologist who had heard UCSF BMT was trialing an AdV drug that was working
- Got an FDA I&D through hoops overnight
- Got drug from company in Atlanta overnight
- Got research institute pharmacist to come in on a weekend to dispense
- Brincidofovir – lipidized prodrug of cidofovir
- w/in 24 hrs was turning around
- Got Brincidofovir x 2 wks and has done well x 4 years
- Got several donor specimens tested and found AdV (12 yo donor)

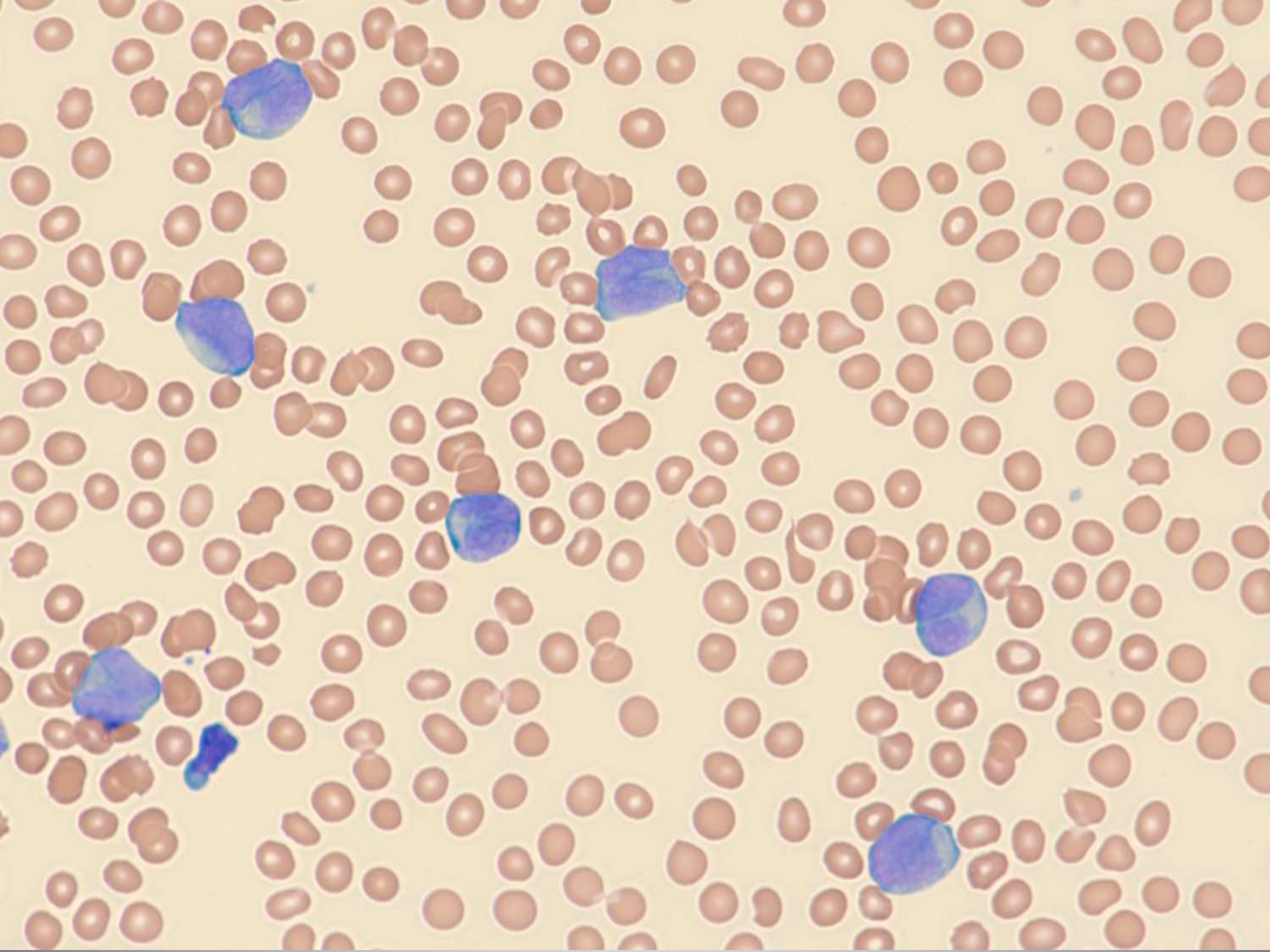
# 21-0904

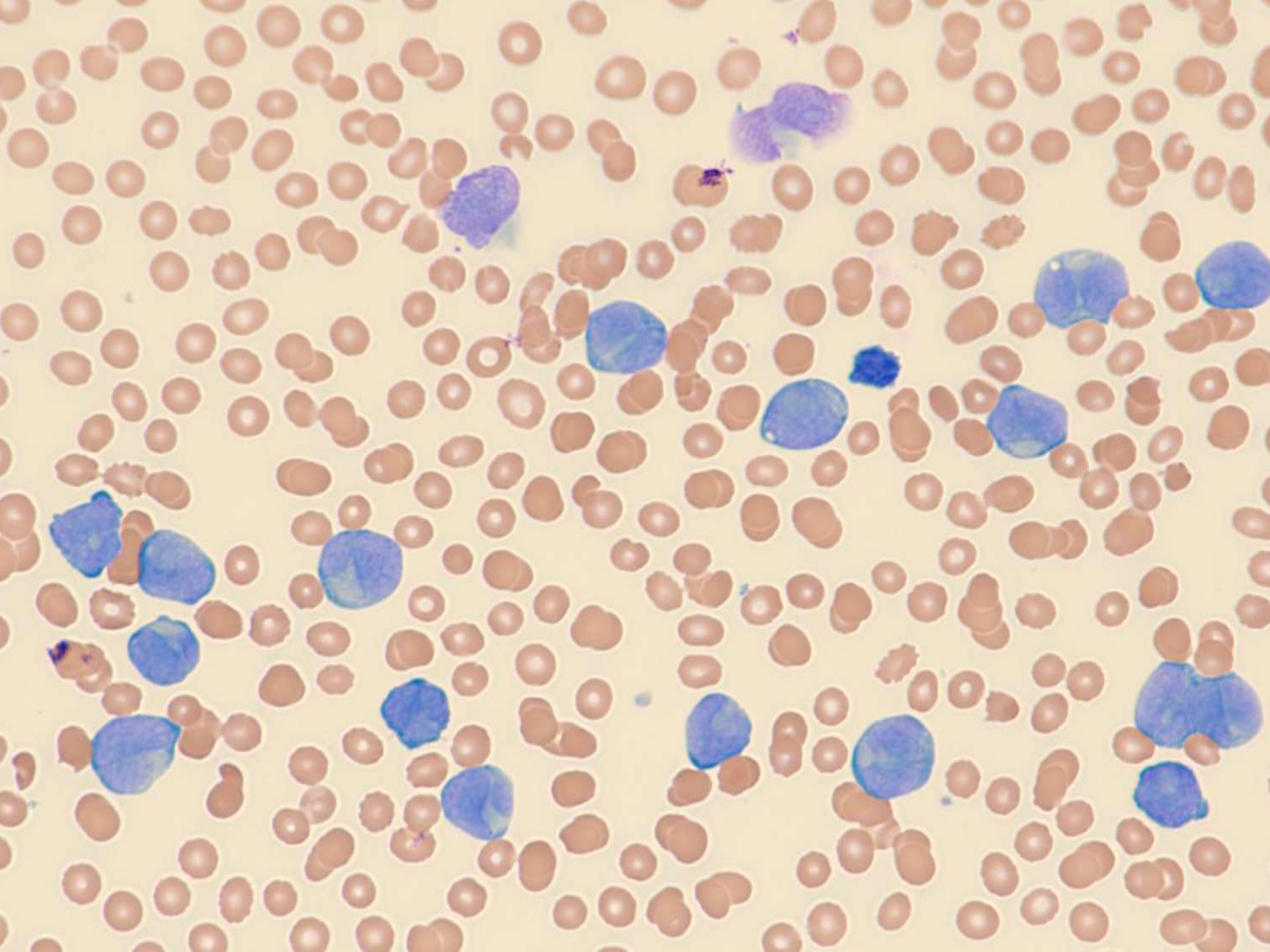
**Brent Tan; Stanford**

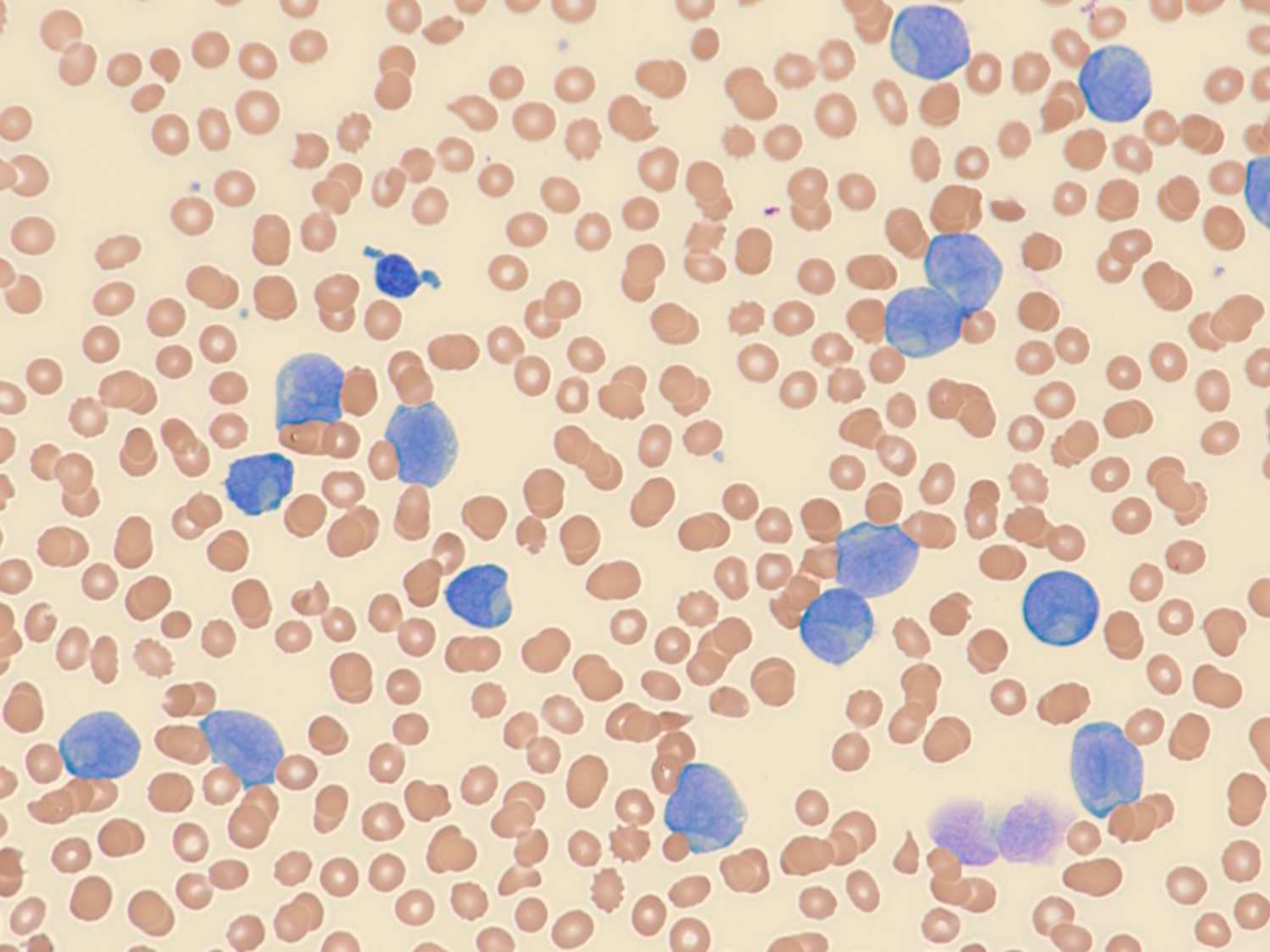
58-year-old M with leukocytosis. Peripheral blood smear.

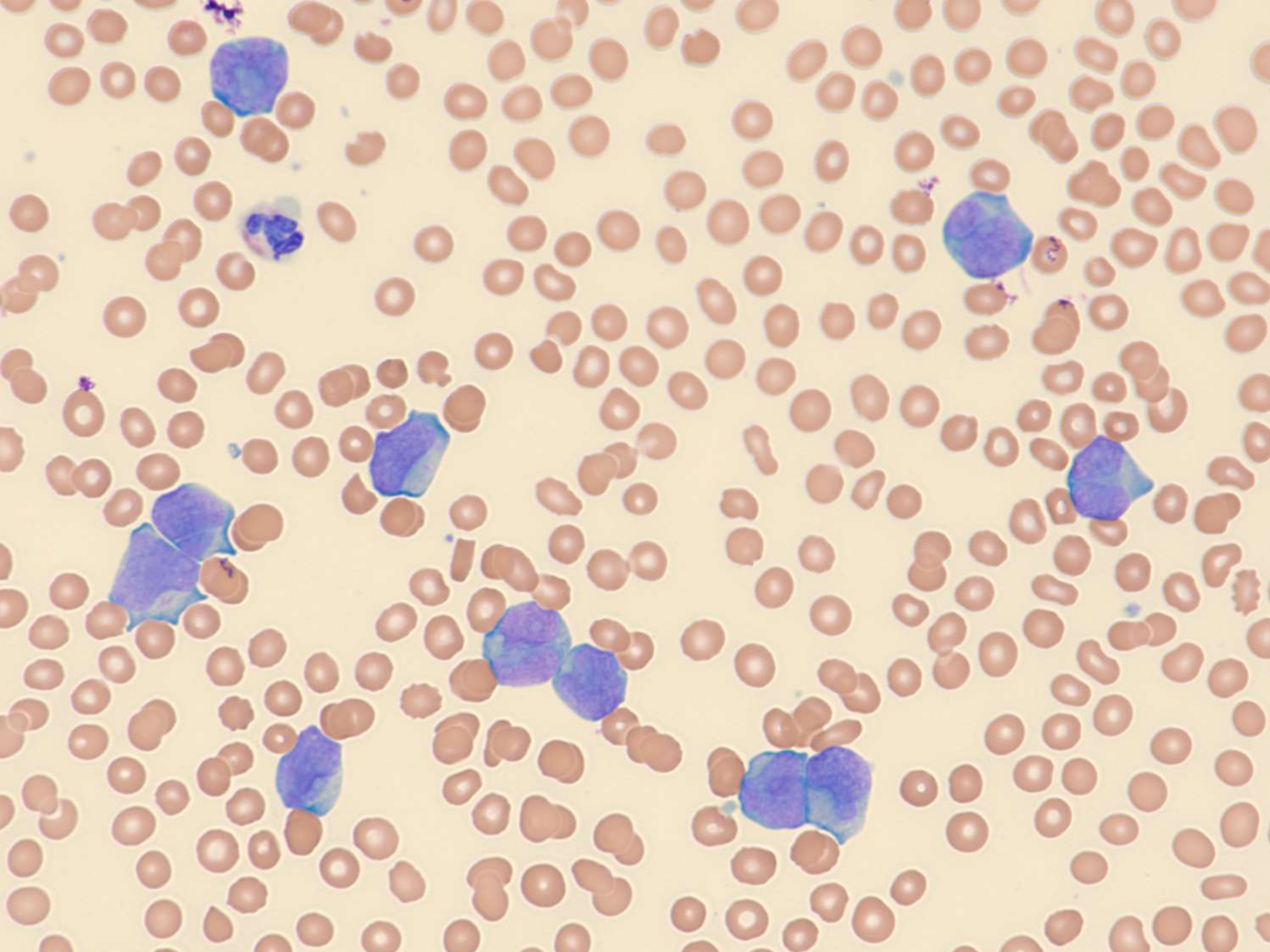
58-year-old man with no past medical history

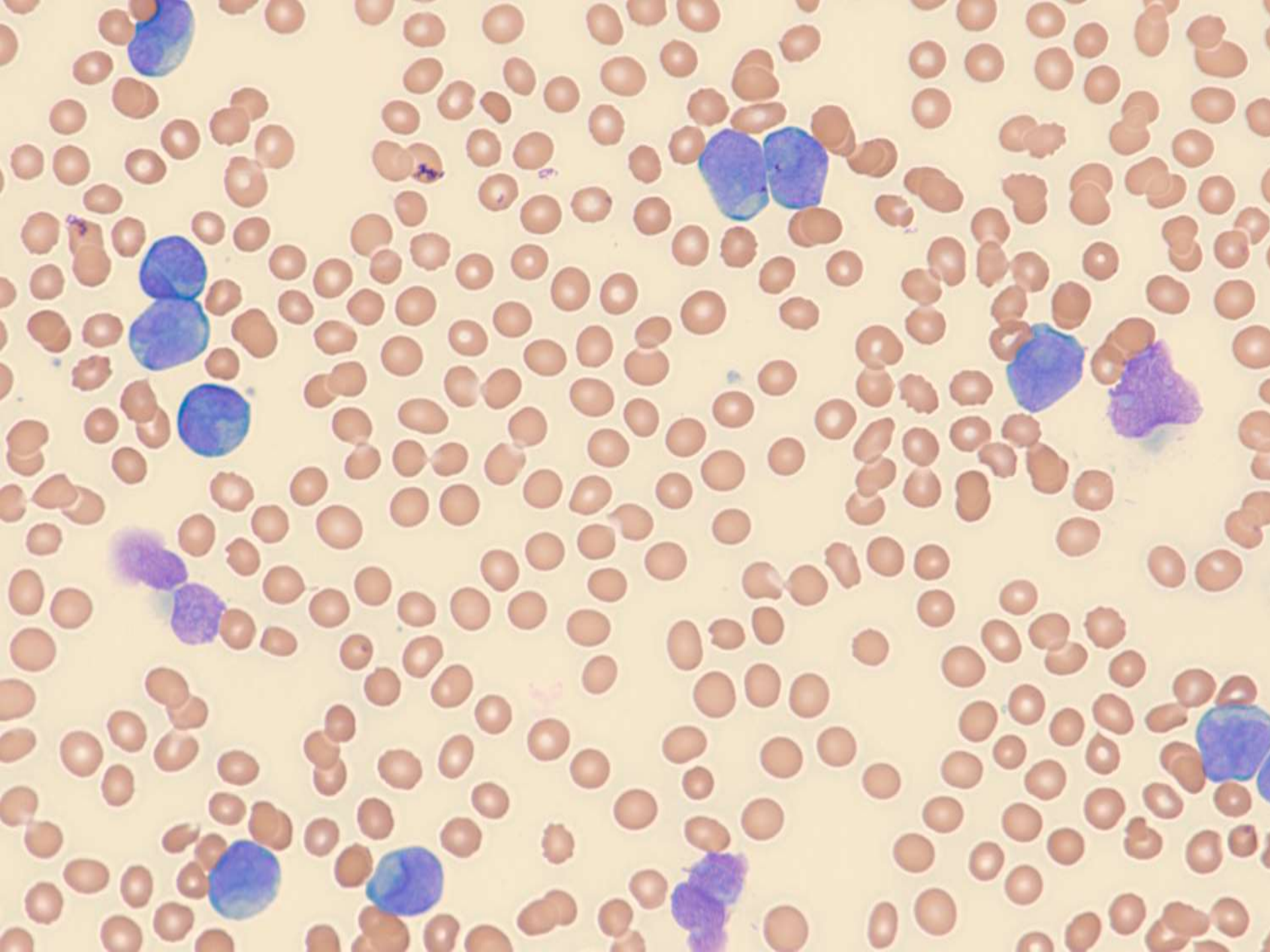
| | | |
|---|---|---|
| WBC: | 126 K/mL | (L) |
| HGB: | 10.7 g/dL | (L) |
| PLT: | 45 K/mL | (L) |
| D-dimer | 12,000 ng/μL FEU | (HH) |

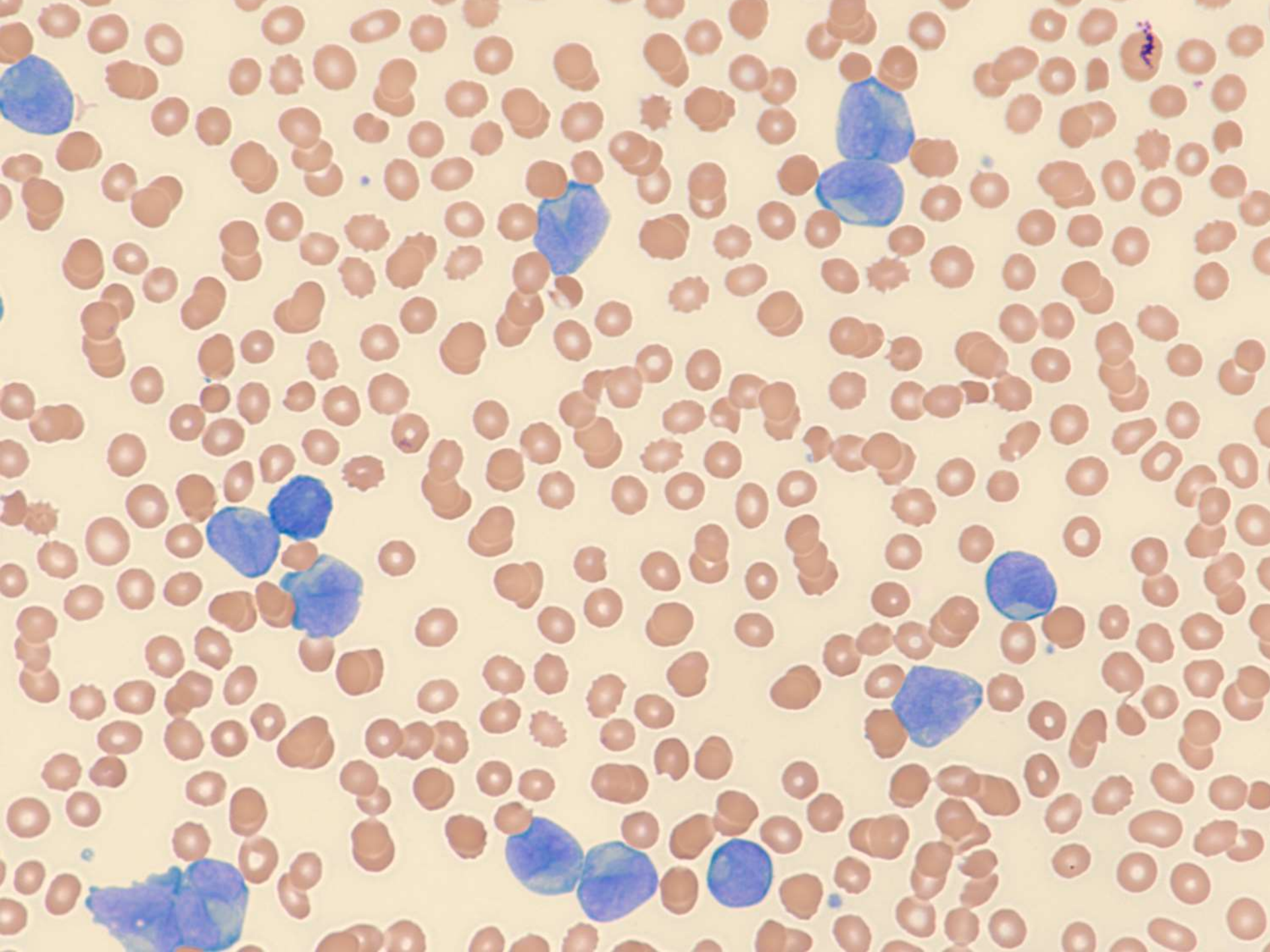












# Additional studies

- Flow cytometry revealed abnormal myeloid blasts expressing MPO, CD13, CD33, CD117, CD38, CD64, and CD4, and lacking CD34, CD11B, and HLA-DR.

- FISH for *PML-RARA* was negative

Diagnosis:

a) APL with cryptic *PML-RARA*

b) APL with *PML-RARA* and *FLT3*

c) APL with *NPM1-RARA*

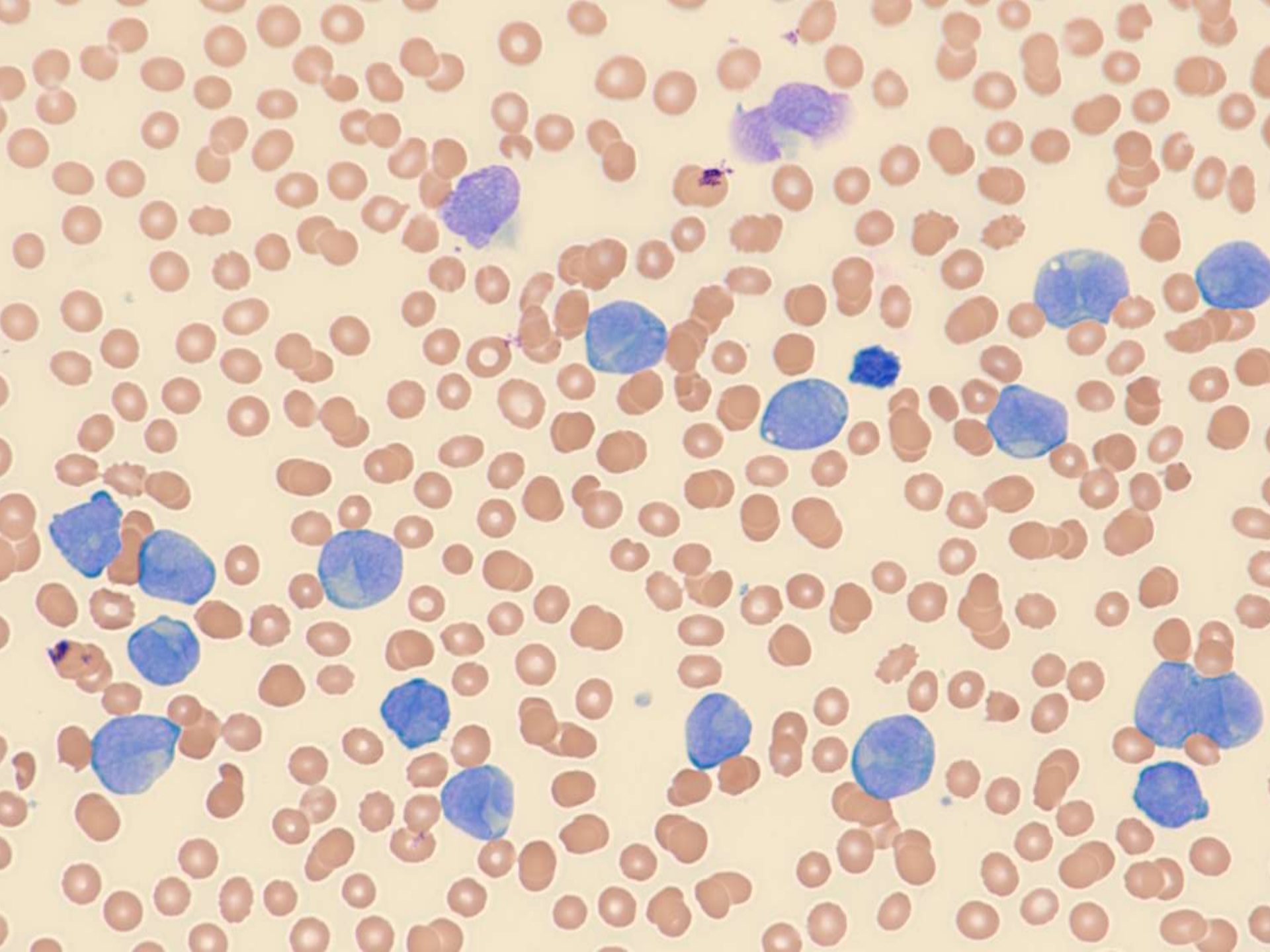
d) AML, NOS with *FLT3*

e) AML with mutated *NPM1* and *FLT3*

# APL with *PML-RARA* morphology:

- Hypergranular variant
  - Numerous azurophilic granules
  - Auer rods and Faggot cells (with multiple Auer rods)
  - Occasional clefted nuclei
  - Various degrees of differentiation with non-blast, hypergranular granulocytes

- Hypogranular variant
  - Rare cells with azurophilic granules or Auer rods
  - >50% of cells with clefted nuclei
  - APL with *FLT3* is often the hypogranular variant



# Flow immunophenotype

- CD34- (hypogranular often partial CD34+)
- HLA-DR- (hypogranular often partial HLA-DR+)
- Bright MPO (RARELY diminished or even negative by flow because of antibody binding to soluble MPO)
- CD11b-
- Homogeneous CD33 with variable CD13
- CD56 -/+
- CD2 -/+ (often + in hypogranular variant)
- Dim CD45 with variable SSC (hypogranular variant may be low SSC)

# Clinical features

- Disseminated intravascular coagulation
  - Fibrinolysis
  - Coagulopathy
  - Pulmonary or CNS hemorrhage
- High D-dimer (this case 12,000 ng/μL)

**Table 3.** Sensitivity, specificity, positive predictive value, and negative predictive value of D-dimer concentrations ≥19 000 ng/μL FEU for the diagnosis of acute promyelocytic leukemia, and schistocytes ≥10/1000 RBC for the diagnosis of disseminated intravascular coagulation

| | Sensitivity (95% CI) | Specificity (95% CI) | Positive predictive value (95% CI) | Negative predictive value (95% CI) |
|---|---|---|---|---|
| Threshold for diagnosis of APL<br>D-dimer concentration ≥19 000 ng/μL FEU | 96 (79–100) | 92 (84–96) | 74 (55–88) | 99 (94–100) |
| Threshold for diagnosis of DIC<br>Schistocytes ≥10/1000 RBC | 36 (18–58) | 89 (82–94) | 39 (24–57) | 87 (83–90) |

APL, acute promyelocytic leukemia; DIC, disseminated intravascular coagulation; CI, confidence interval; RBC, red blood cell.

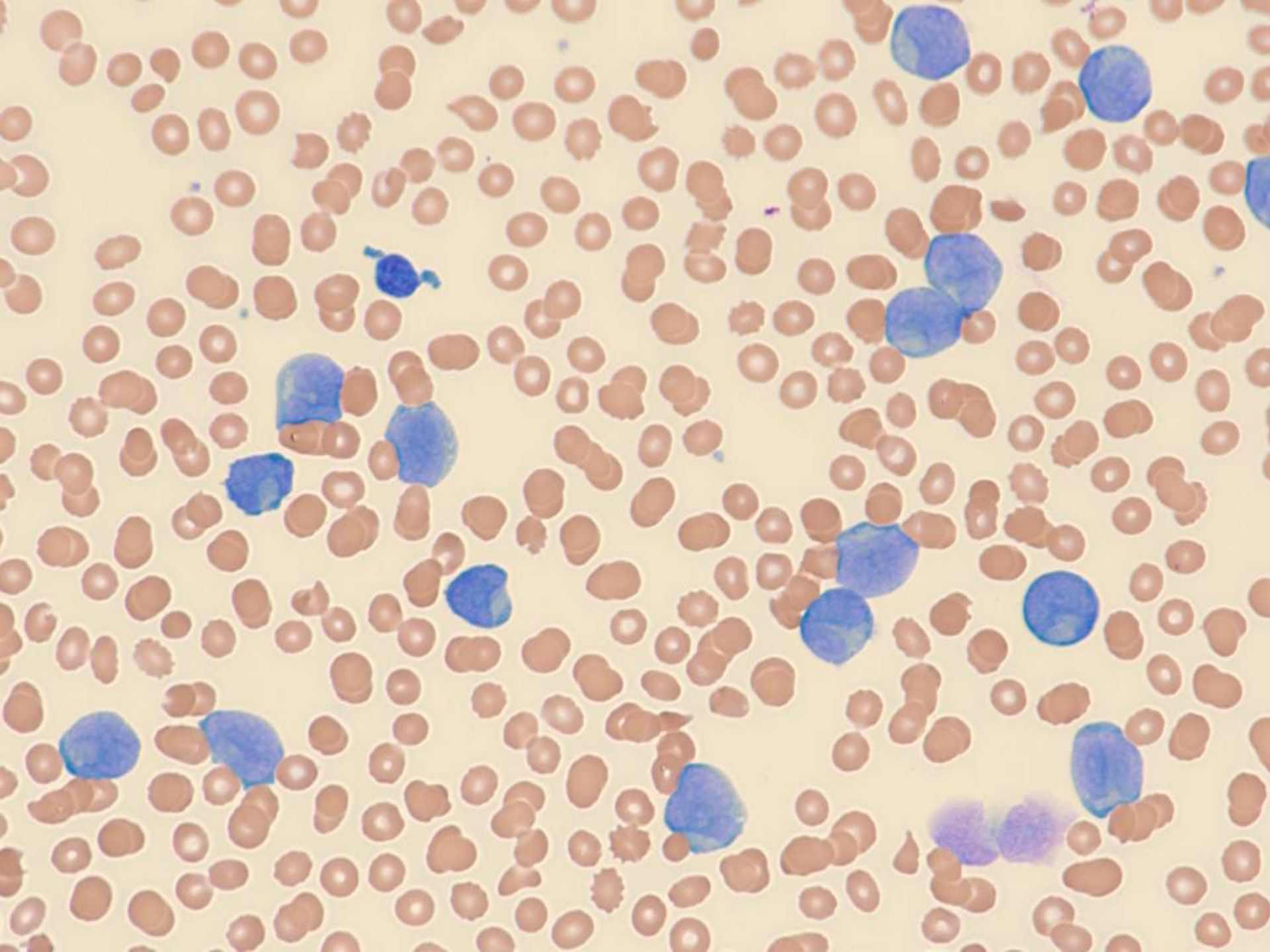
Shahmarvand, N. *et al*. *Int. Jnl. Lab. Hem.* 2017, 39:375–383

# APL with variant *NPM1-RARA*

- APL with *NPM1-RARA*
  - Predominance of hypergranular promyelocytes
  - Few hypogranular promyelocytes
  - No Auer rods
  - ATRA responsive
- APL with *ZBTB16-RARA*
  - Regular nuclei, numerous granules,
  - No Auer rods
  - Pelgeroid neutrophils
  - ATRA resistant
- APL with *STAT5b-RARA*
  - ATRA resistant

# AML with *FLT3*

- AML, NOS with *FLT3* is not recognized in the WHO as an AML with recurrent genetic abnormality
- *FLT3* is the most common mutation in AML
- *FLT3* can occur in nearly any AML with recurrent genetic abnormality or defined entity
  - AML with mutated *NPM1*
  - AML with *inv(16)*
  - AML with biallelic mutation of *CEBPA*
  - AML with MRC with complex karyotype
  - Therapy-related AML



# AML with *NPM1* and *FLT3*

- AML with mutated *NPM1* was new in the 2016 WHO
- Prognosis
  - *NPM1* without *FLT3 ITD* — Good
  - *NPM1* with *FLT3 ITD* with low VAF — Good
  - *NPM1* with *FLT3 ITD* with high VAF — Intermediate
  - *NPM1* with *FLT3 ITD* and *DNMT3a* — Poor
  - *NPM1* at high VAF — Poor

Patel, S. S. *et al. Blood* **131**, 2816–2825 (2018).
Papaemmanuil, E. *et al. New England Journal of Medicine* **374**, 2209–2221 (2016).

# Flow immunophenotype

AML with *NPM1*

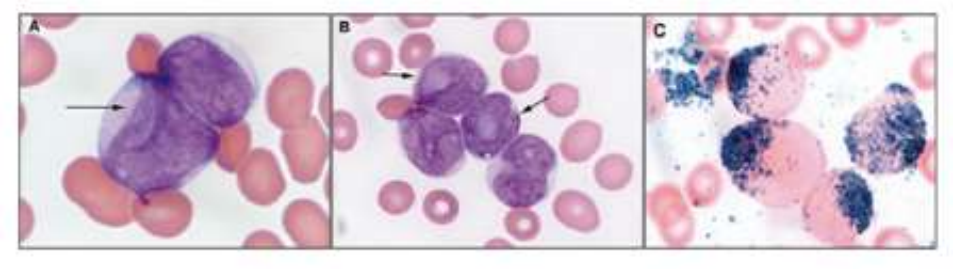
- CD34 -/+
- HLA-DR -/+
- Neg or moderate MPO
- CD11b-
- Bright CD33
- Variable CD13
- CD56 +/-
- CD2 -/+
- Monocytic differentiation to moderate CD45 and higher SSC)

APL with *PML-RARA*

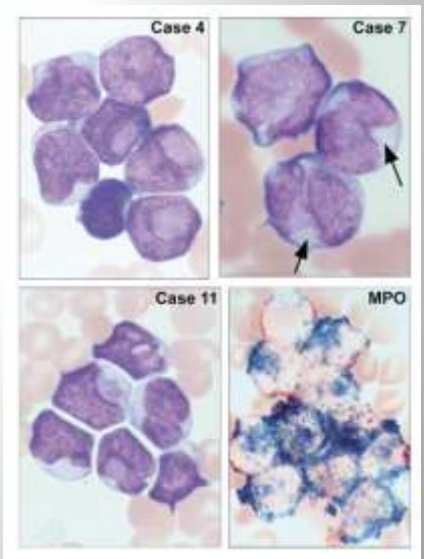
- CD34 -/+
- HLA-DR -/+
- Bright MPO
- CD11b-
- Homogeneous CD33
- Variable CD13
- CD56 +/-
- CD2 -/+
- Dim CD45 with variable SSC (hypogranular variant may be low SSC)

# AML with mutated *NPM1* morphology:

- Monocytic morphology
- "Cuplike" nuclei
  - In AML, associated with *NPM1* and/or *FLT3*
  - Associated with lack of *CD34* and *HLA-DR*
  - Associated with MPO positivity
  - Higher D-dimer levels (>5000 ng/μL)
  - Occurs rarely in ALL




Chen, W. *et al. Cancer* 2009: **115**, 5481–5489




Kussick, S. J. *et al. Leukemia* 2004; **18**, 1591–1598

# Summary

- AML with mutated *NPM1* with or without *FLT3* has cup-like nucleoli and may mimic APL with *PML-RARA*
  - Nuclear cups may take the form of clefts
  - Similar immunophenotype
- APL with *PML-RARA*
  - Rarely FISH negative
  - PCR or sequencing may detect a cryptic *PML-RARA*
  - Nearly always has high D-dimer
- APL with variant *PML-RARA* includes a variety of different morphologies
  - APL with *NPM1-RARA:* ATRA responsive
  - APL with *ZBTB16-RARA:* ATRA resistant
  - APL with *STAT5b-RARA:* ATRA resistant
- Consider AML with *NPM1* in your differential diagnosis for APL before investigating for a cryptic *PML-RARA*

# 21-0905

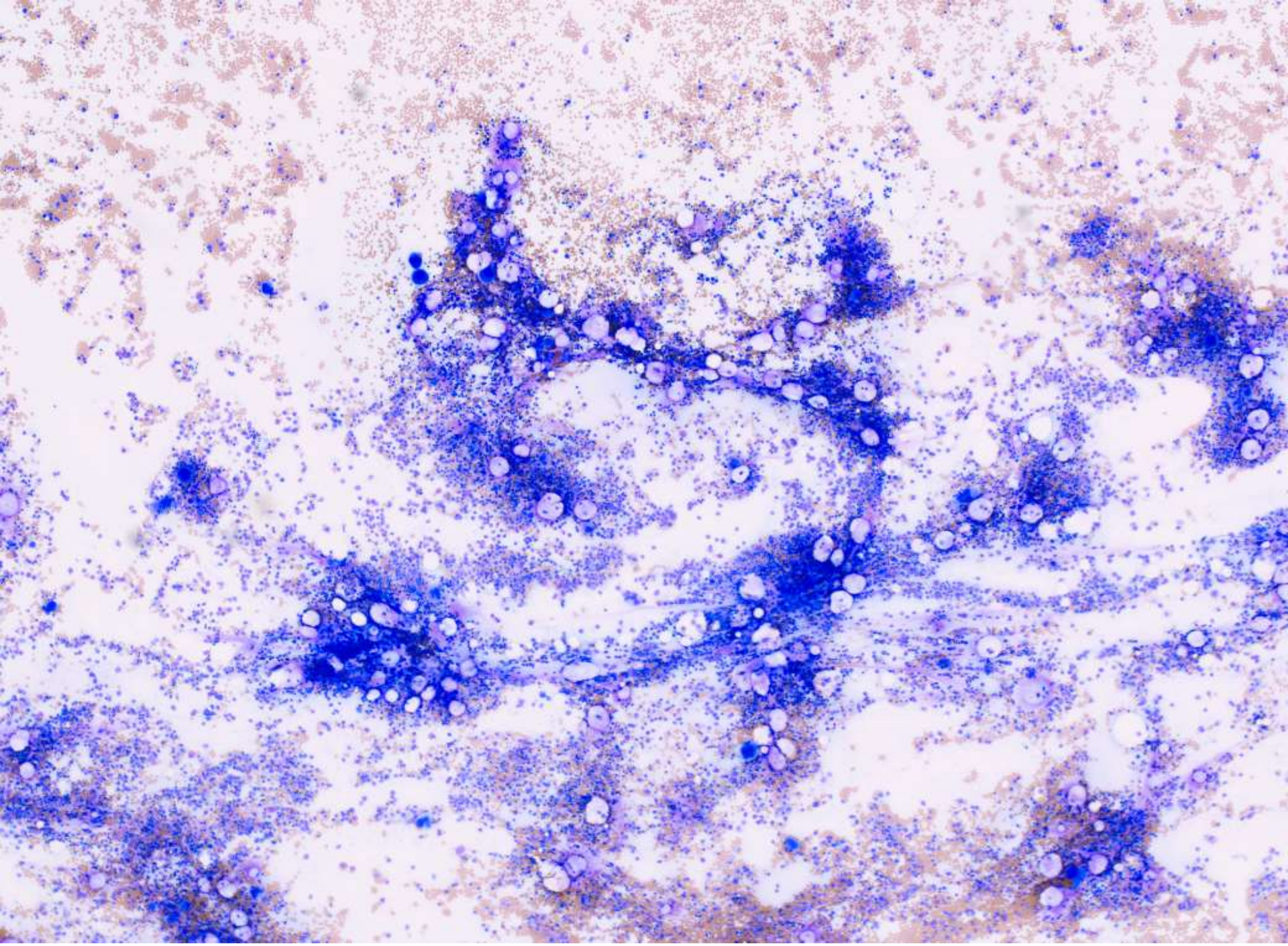
**Jing Zhang/Brent Tan; Stanford**

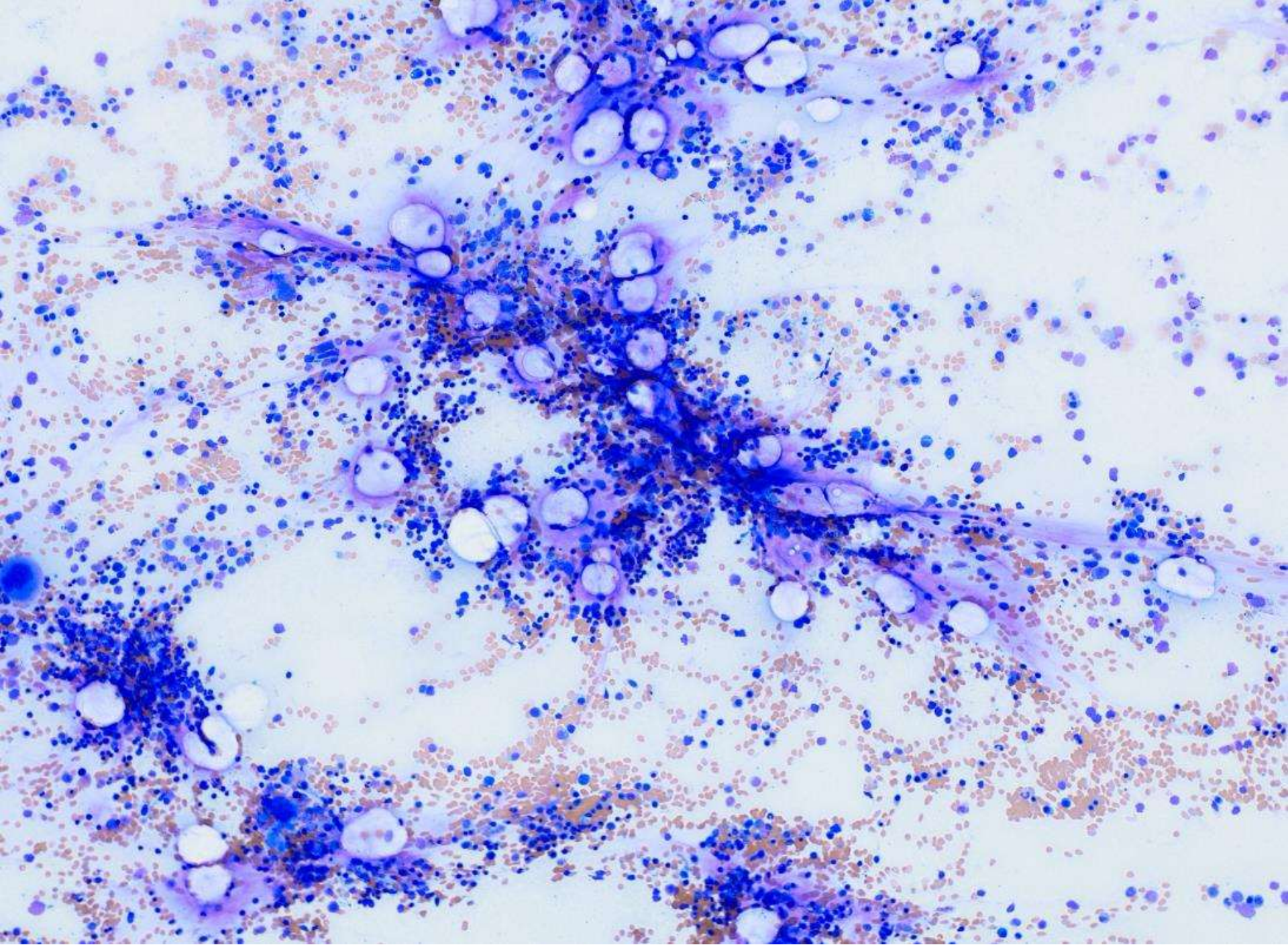
30-year-old M with no prior medical history presenting for pancytopenia and weight loss (20 pound weight loss). Recent dietary change to pescatarian/plant based diet.

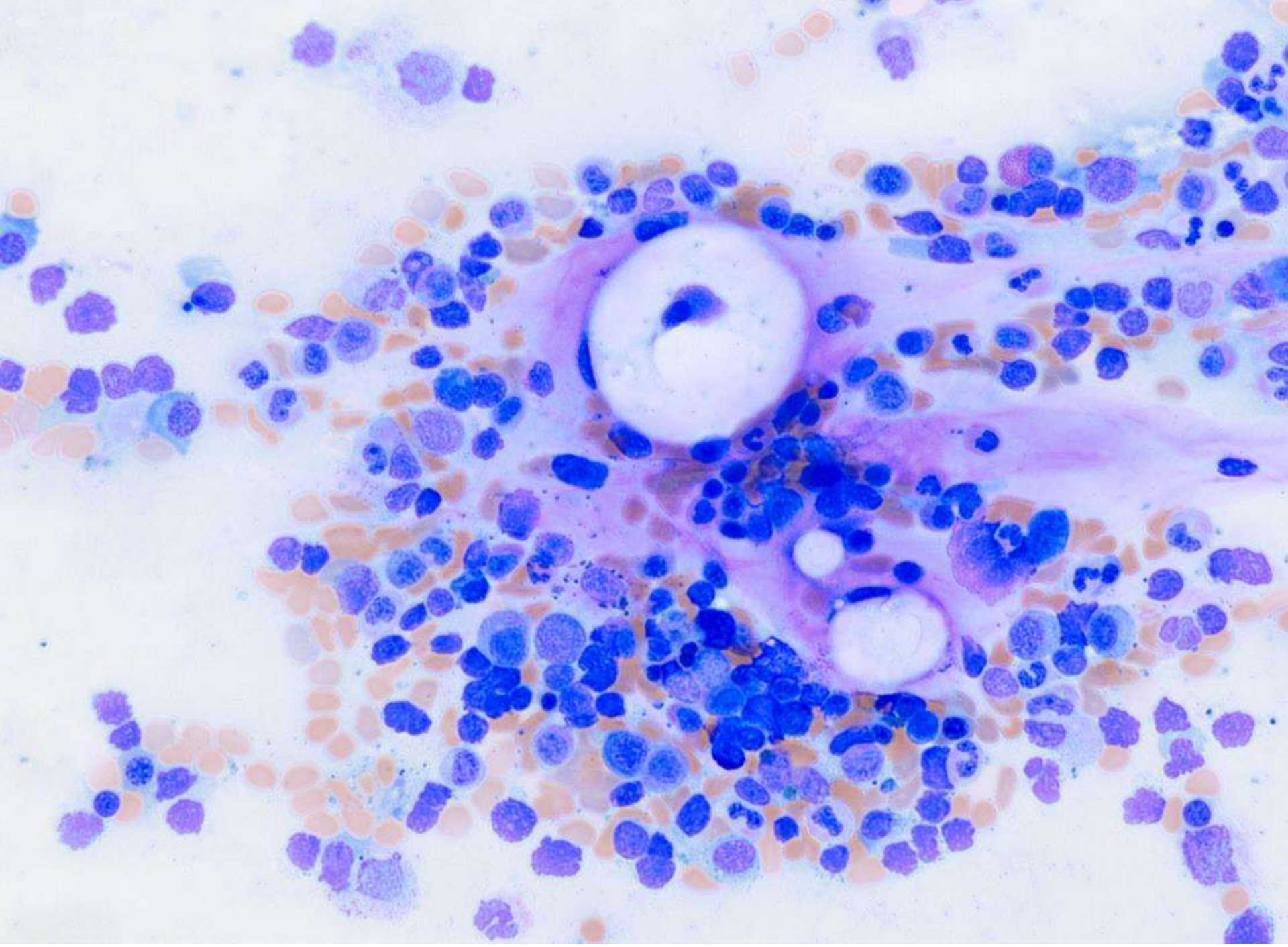
# Lab values

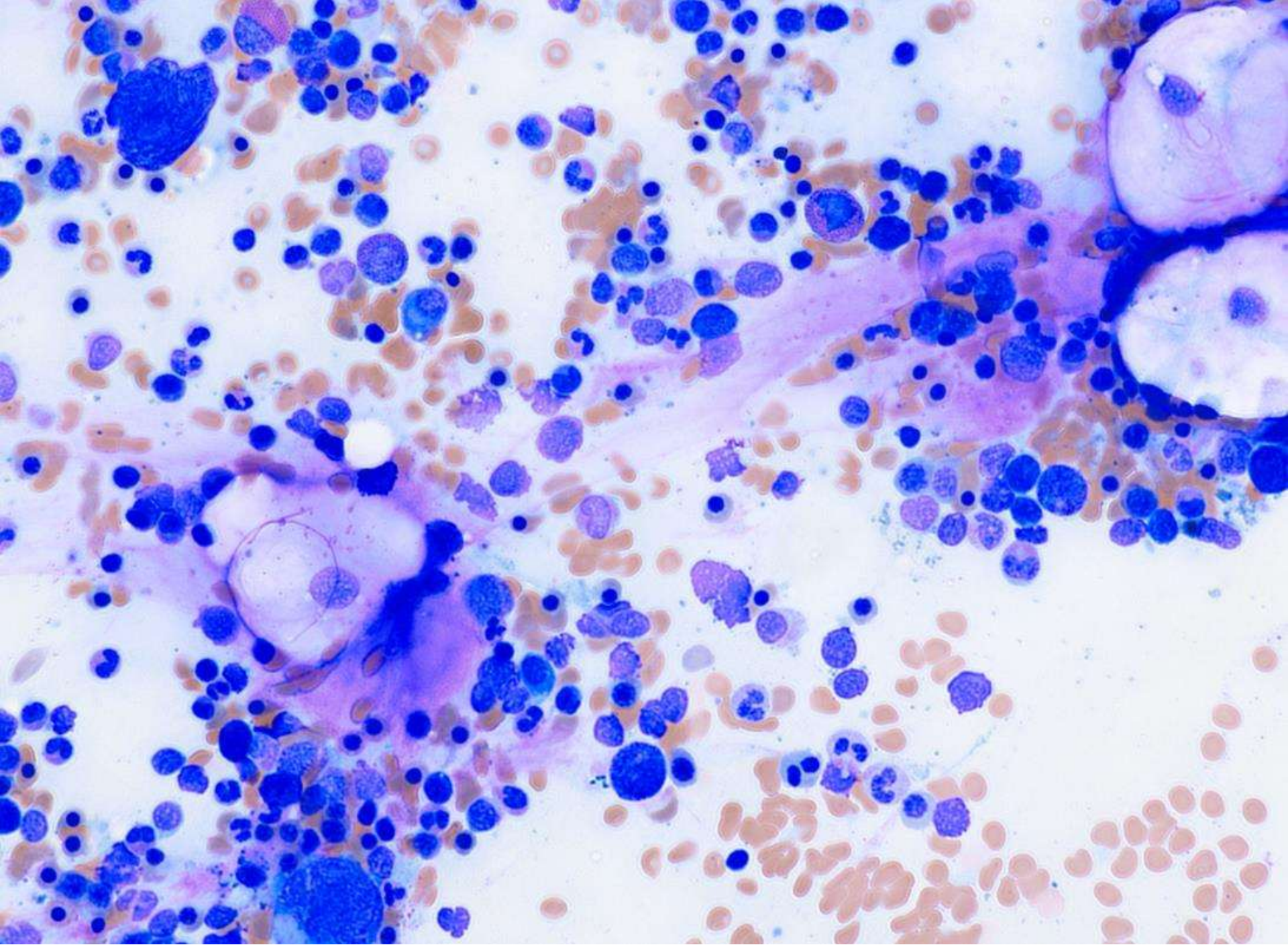
| | |
|---|---|
| WBC | 2.2 (L) |
| Hemoglobin | 11.0 (L) |
| Hematocrit | 31.7 (L) |
| Platelet count | 93 (L) |
| MCV | 106.0 (H) |
| RDW | 11.8 |
| RBC | 2.99 (L) |
| MCH | 36.8 (H) |
| MCHC | 34.7 |

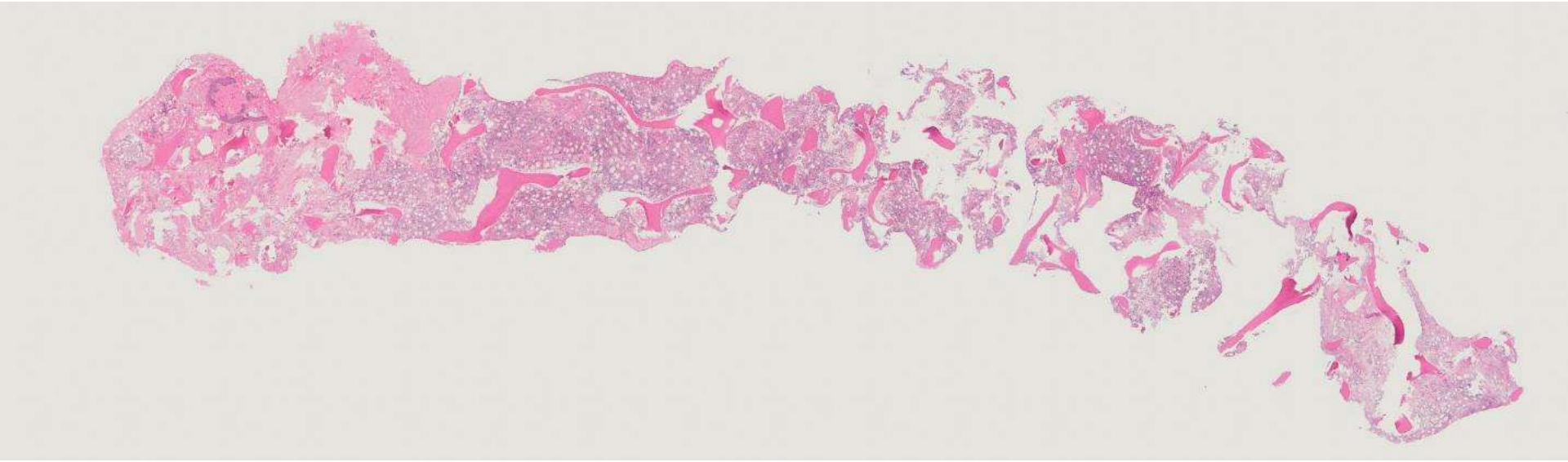
Pancytopenia with macrocytic anemia

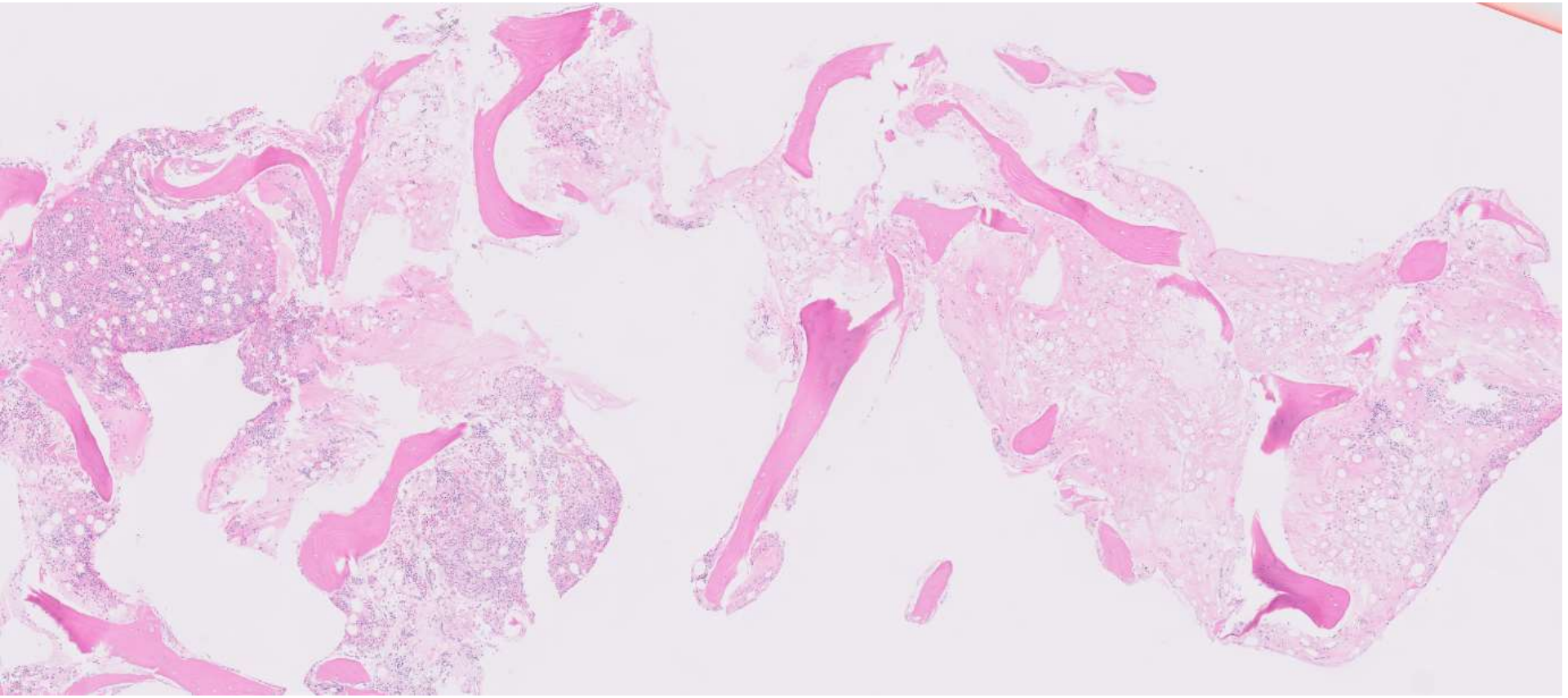


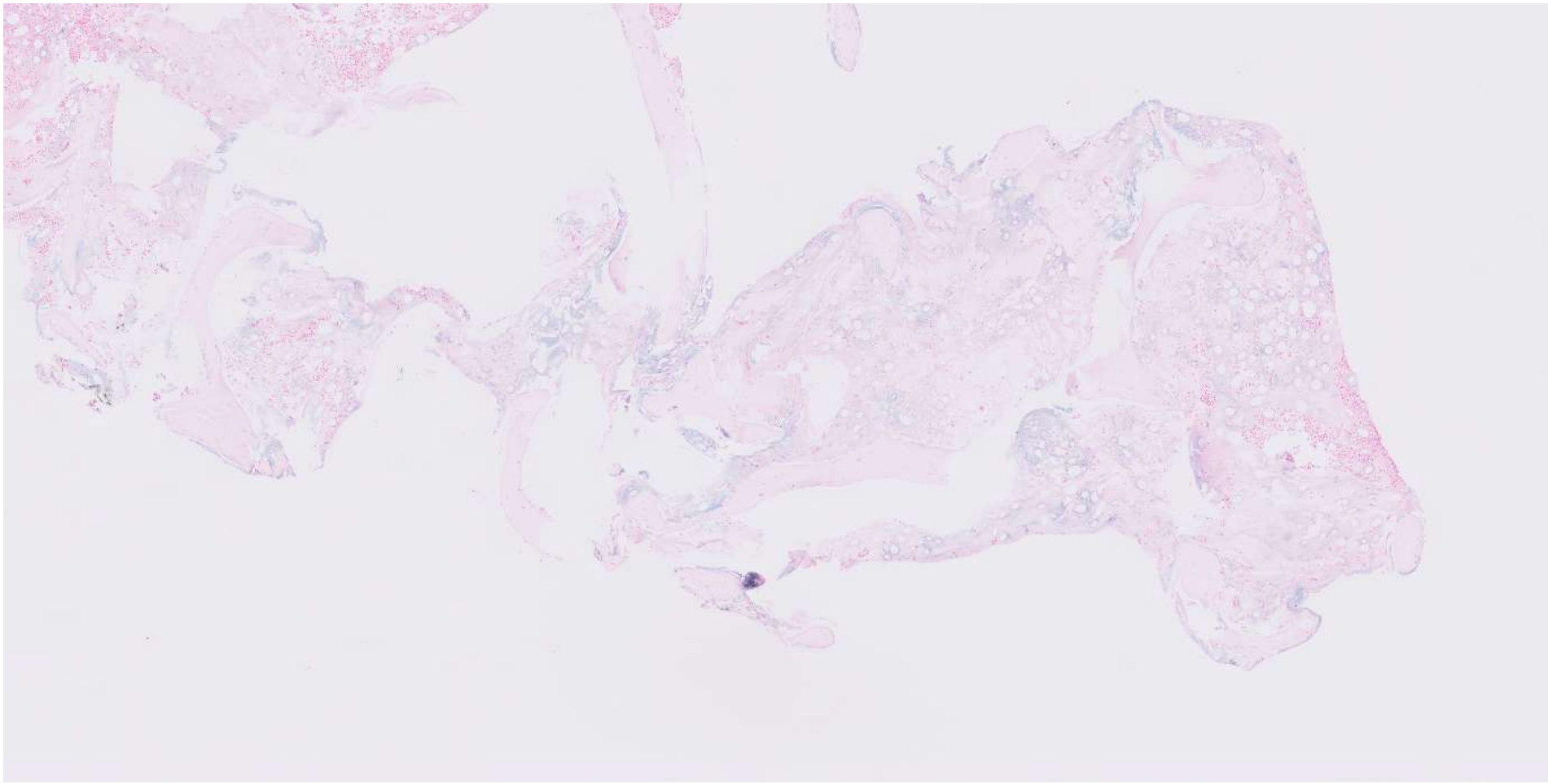


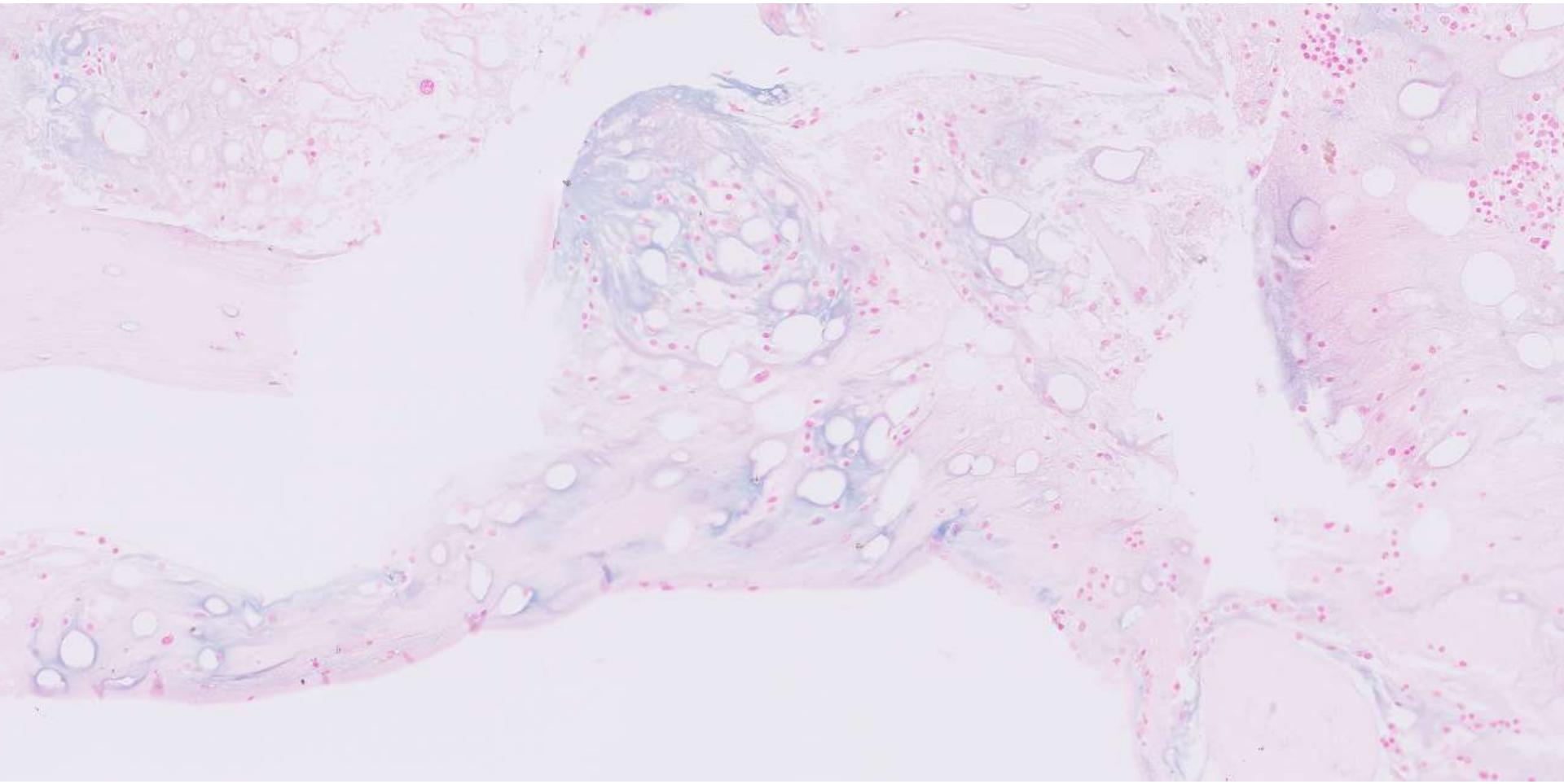


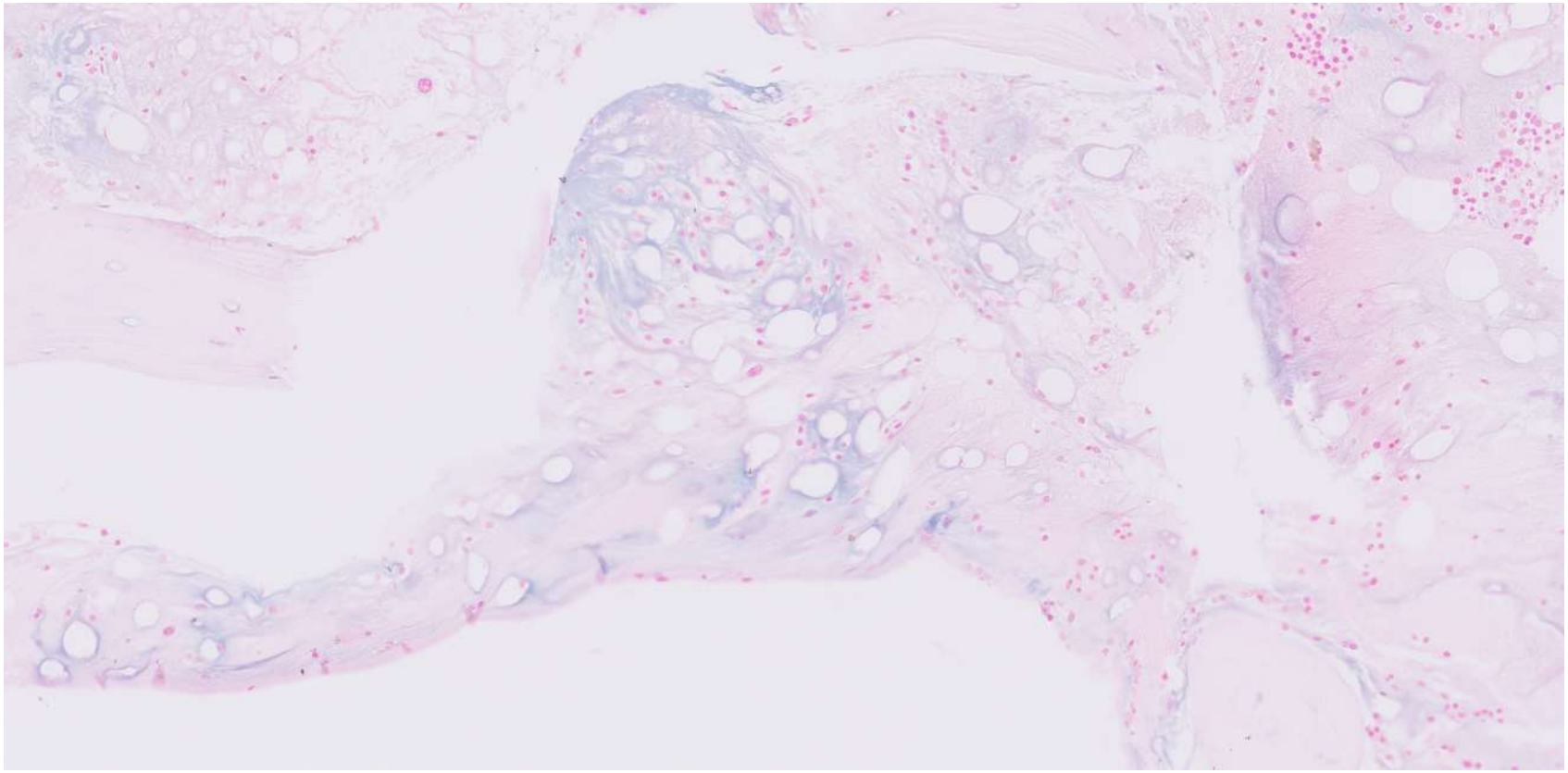












Alcian blue stain

# Differential Diagnosis

- Serous atrophy/gelatinous transformation of bone marrow
- Amyloidosis
- Marrow Necrosis

# Differential Diagnosis

- **Serous atrophy/gelatinous transformation of bone marrow**
- Amyloidosis
- Marrow Necrosis

# Background

- recognized at the turn of this century in autopsy specimens of patients suffering from prolonged starvation and cachexia and has also been termed “starvation marrow” or “serous (fat) atrophy.”
- a morphologic sign of a generalized severe illness of a patient and is associated with weight loss and cachexia in most cases

# Underlying causes

| | | |
|---|---|---|
| Tumors | 37.5% | Non-Hodgkin's lymphomas 27, carcinomas 16.8, multiple myeloma 5.5, Hodgkin's disease 4.3, others 4.5 |
| Malnutrition | 16.8% | Alcoholism 13, anorexia nervosa 8, vegetarianism 3, others 2 |
| Infections | 11.8% | AIDS 8.5, "Acute fevers" 5, bacterial endocarditis 2, pneumonia 1.8, tuberculosis 1 |
| Maldigestion | 10.1% | Stomach ulcers 3.5, post-gastrectomy states 3, pancreatic failure 2.8, Crohn's disease 2, liver cirrhosis 1, others 3.3 |
| Heart failure | 7.0% | Chronic heart failure 10.8 |
| Metabolic disorders | 5.4% | Diabetes mellitus (type I) 6.8, hypothyroidism 1.5 |
| Others | 11.4% | MDS 3.3, angiopathy 3, iron deficiency 3, renal failure 3, psychoses 2.3, rest: cases #52, #74, #99 |
| All | 100% | ~155 cases |

Impact points: 1 point per case (one definite underlying disease) in 128 patients, 2 half points (2 diseases) in 24 patients, 3 third points (3 diseases) in 3 patients.

Bohm, Joachim. Gelatinous Transformation of the Bone Marrow: The Spectrum of Underlying Diseases. Am J Surg Pathol. 2000;24(1):56

# Demographic

| GMT grade | n | M:F | % M | Mean age (yrs) | <40 yrs (%) |
|---|---|---|---|---|---|
| Maximum | 10 | 8:2 | 80 | 37.7 | 60 |
| +++ | 32 | 26:6 | 81 | 49.3 | 47 |
| ++ | 78 | 49:29 | 63 | 59.1 | 21 |
| + | 35 | 18:17 | 51 | 62.4 | 14 |
| All | 155 | 101:54 | 65 | 56.4 | 27 |

GMT, gelatinous bone marrow transformation.

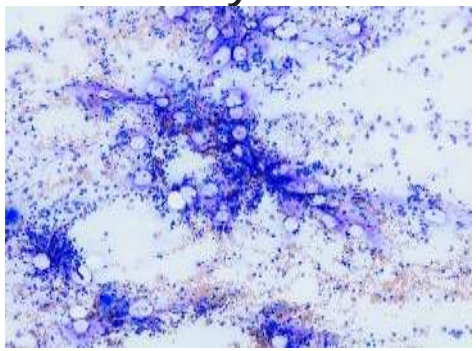
**younger adults (<40 years old): anorexia nervosa in women and AIDS in men**
**(40–60 years old): alcoholism and lymphomas**
**(>60 years old) lymphomas, carcinomas, and chronic heart failure**

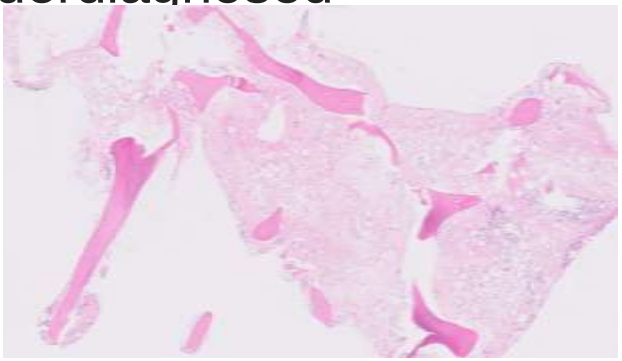
Shergill KK Gelatinous transformation of bone marrow: rare or underdiagnosed?. *Autops Case Rep*. 2017;7(4):8-17

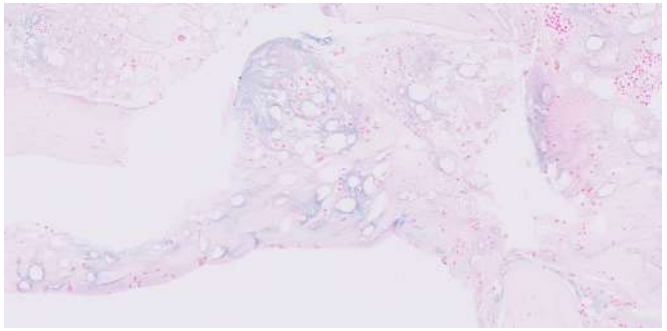
Bohm, Joachim. Gelatinous Transformation of the Bone Marrow: The Spectrum of Underlying Diseases. Am J Surg Pathol. 2000;24(1):56

# Diagnosis

- Histologic features: atrophy of fat cells and a loss of hematopoietic cells with the deposition of gelatinous substances in the marrow
- histochemical studies: gelatinous substances in GMT consist of acid mucopolysaccharides, mainly of hyaluronic acid, which strongly stain with alcian blue at pH 2.5
- Likely overall underdiagnosed







# Prognosis

35 cases that showed resolution of GTBM on follow-up on repeated biopsy/aspirate after the initiation of treatment

- -- nutritional diet (15 cases)
- -- packed red blood cell (PRBCs) transfusion (one case)
- -- (G-CSFs) (three cases)
- -- treatment of the underlying disease

# Follow-up

- Denies history of infections, fevers, or chills
- Negative HIV test taken 3 weeks after BM biopsy
- Cytogenetics/Heme-STAMP on BM aspirate was negative
- Endoscopy/GI biopsy series negative
- Medical nutritional therapy referral –
  - Patient has replaced animal-based foods with plant-based foods
  - 16:8 intermittent fasting schedule
  - Avoids gluten/overall low carb diet
  - Unclear if less liberal diet could cause reversal of current condition

# Citations


- Bohm, Joachim. Gelatinous Transformation of the Bone Marrow: The Spectrum of Underlying Diseases. Am J Surg Pathol. 2000;24(1):56.
- Shergill KK, Shergill GS, Pillai HJ. Gelatinous transformation of bone marrow: rare or underdiagnosed?. Autops Case Rep. 2017;7(4):8-17. Published 2017 Dec 8. doi:10.4322/acr.2017.039

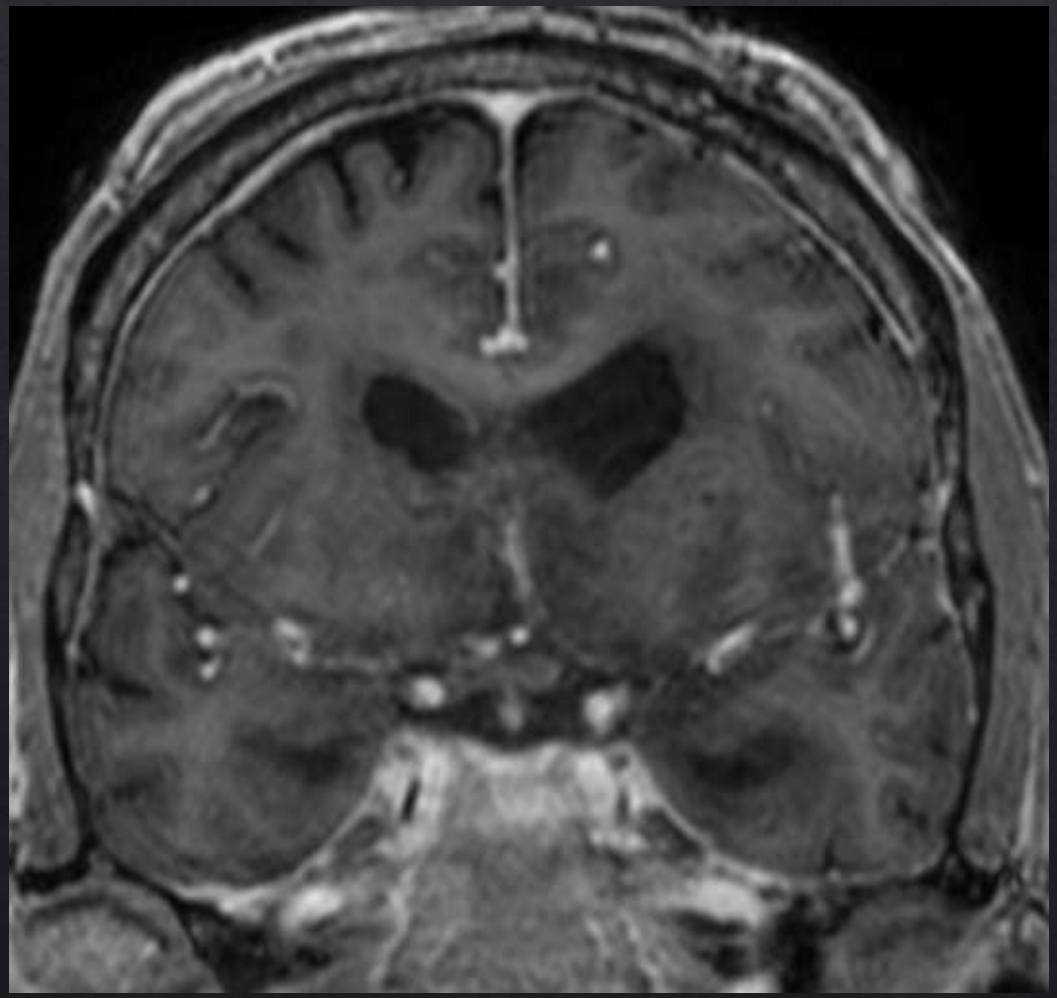
# 21-0906

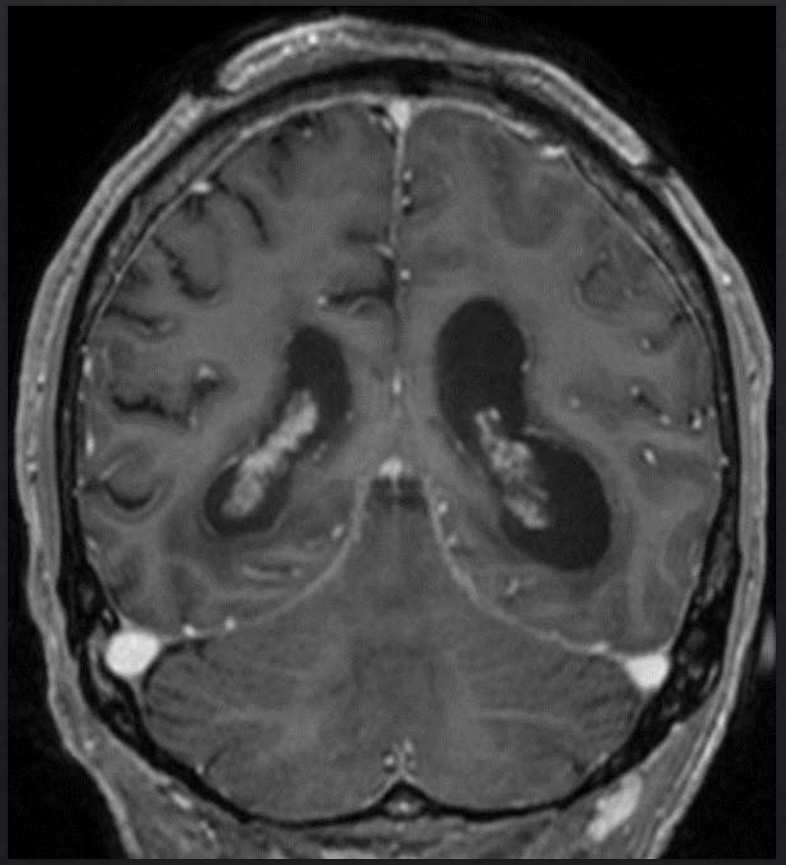
**Angus Toland/Jeff Nirschl/Hannes Vogel; Stanford**

76-year-old M with presenting with fatigue, fever, and G-tube site erythema. History of laryngeal squamous cell carcinoma s/p resection and radiation therapy 2010. Soon after developed altered mental status which progressively worsened over ~10 days. LP showed red blood cells and mixed inflammation; no organisms. MRI showed hydrocephalus with multiple acute infarctions and meningitis. No response to broad spectrum antimicrobial therapy; transitioned to comfort care given dismal prognosis. CSF and blood cultures remained negative. Section of brain shown.

# Toland/Nirschl/Vogel

- 76-year-old man presenting with fatigue, fever, and G-tube site erythema
- History of laryngeal squamous cell carcinoma s/p resection and radiation therapy 2010
  - Tracheostomy tube in place
  - G-tube dependent due to esophageal stenosis since 02/2020
  - Chest CT concerning for pneumonia
    - AFB culture positive for Mycobacterium avium complex
  - Soon after developed altered mental status which progressively worsened over ~10 days
    - LP showed red blood cells and mixed inflammation; no organisms
    - MRI showed hydrocephalus with multiple acute infarctions  and meningitis
    - No response to broad spectrum antimicrobial therapy; transitioned to comfort care given dismal prognosis
      - CSF and blood cultures remained negative



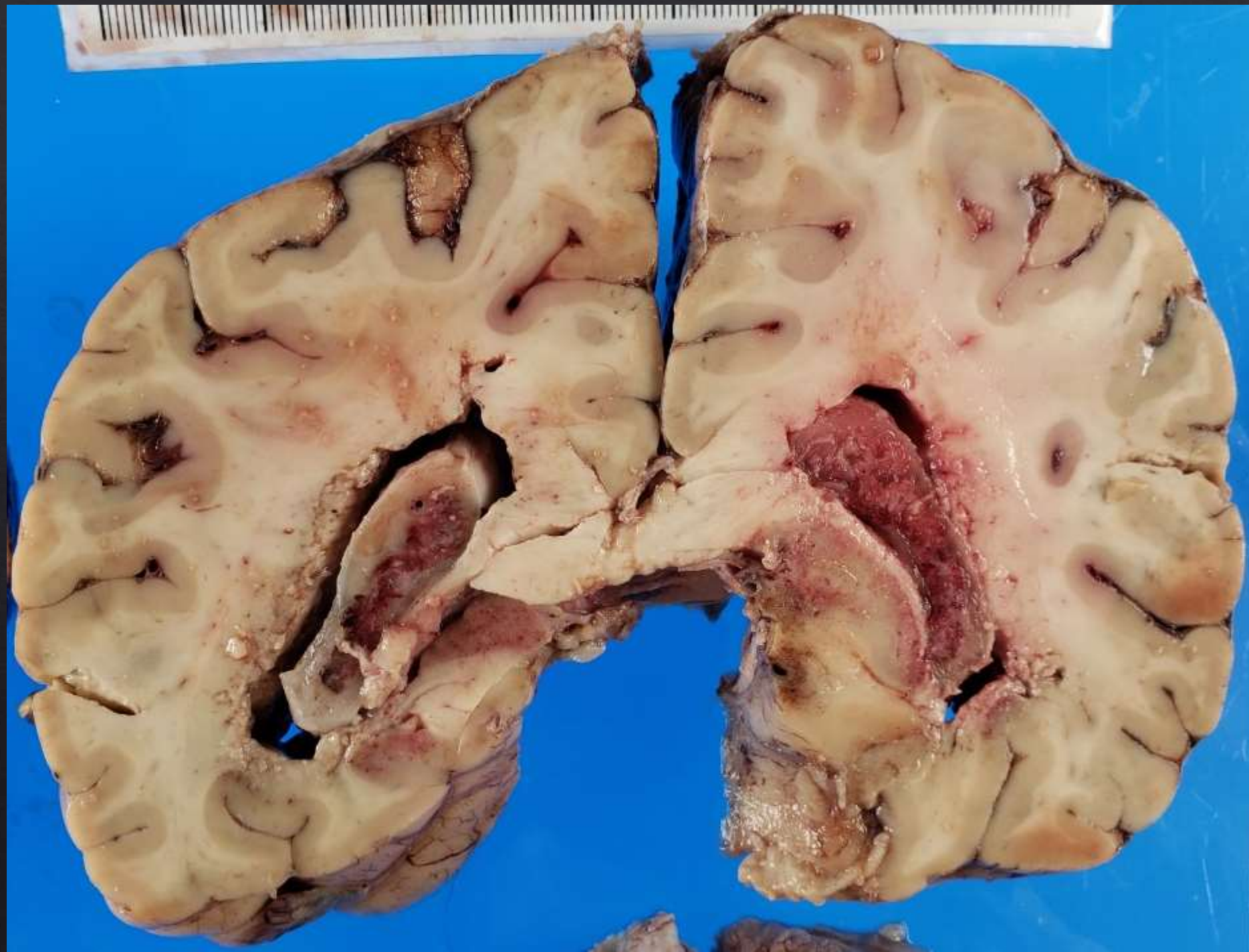


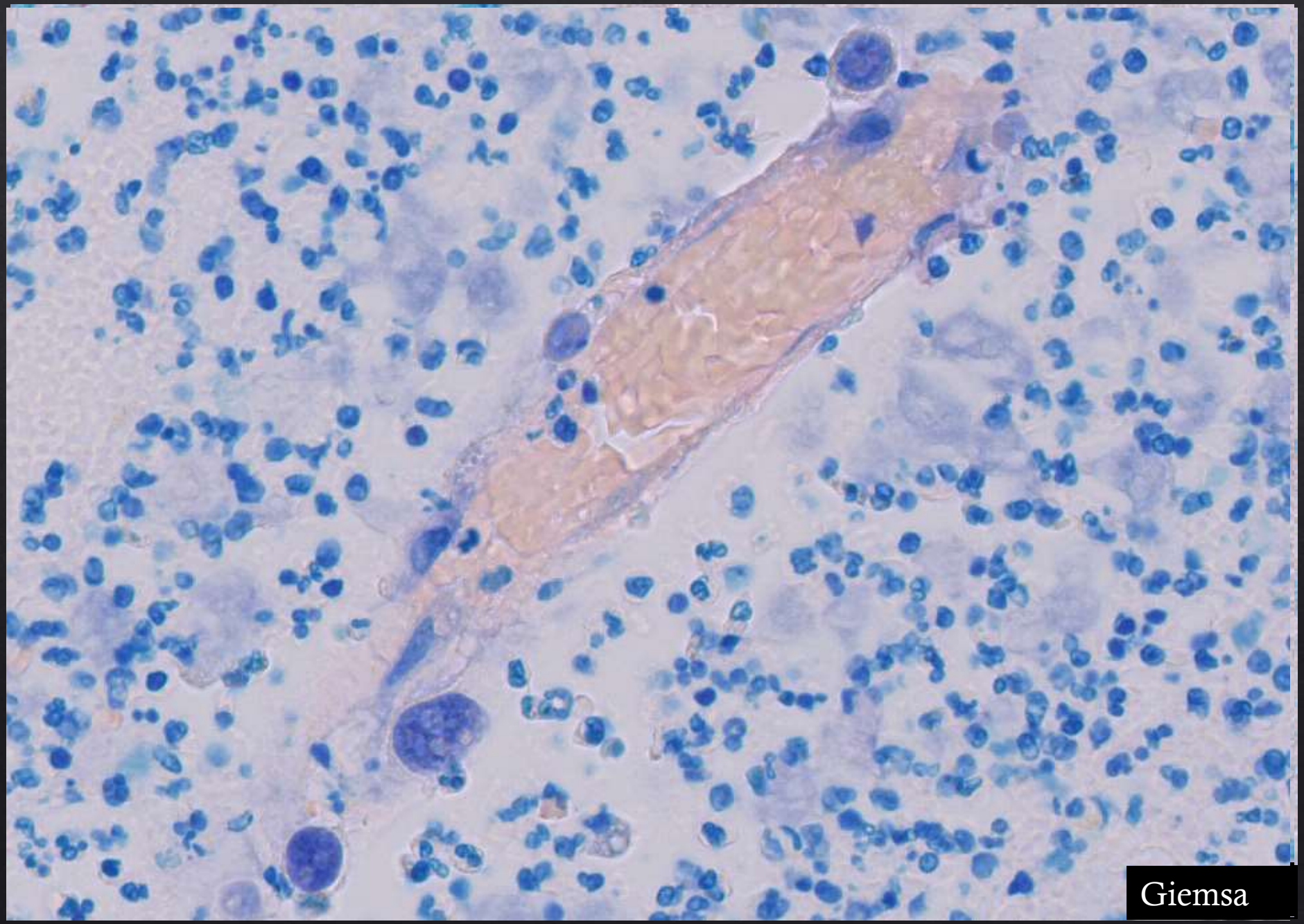
# General Autopsy

- Multifocal subacute pneumonia
  - No organisms identified; post-mortem cultures negative

# Brain Cutting

- 1500 g brain with scattered foci of hemorrhage and dusky base
  - Thickened and fibrotic choroid plexi




Giemsa

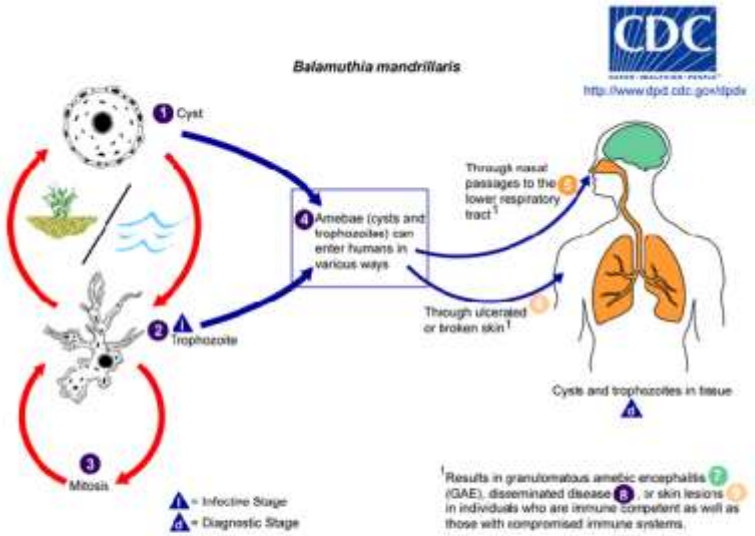
# PCR and immunofluorescence testing performed at CDC

- Positive for *Balamuthia mandrillaris*

# *Balamuthia mandrillaris*

- Free-living soil amoeba
- Rarely causes granulomatous amoebic encephalitis and cutaneous infections
  - Encephalitis results from dissemination from lungs or wounds
  - Typically presents with fever, seizures, altered mental status
  - Length from symptom onset to diagnosis widely variable; median 24 days (range 4-450 days)
  - PCR or immunofluorescence on CSF or brain biopsy often required for diagnosis

# Life Cycle




*Balamuthia mandrillaris* has only recently been isolated from the environment and has also been isolated from autopsy specimens of infected humans and animals. *B. mandrillaris* has only two stages, cysts **(1)** and trophozoites **(2)**, in its life cycle. No flagellated stage exists as part of the life cycle. The trophozoites replicate by mitosis **(3)**. The trophozoites are the infective forms, although both cysts and trophozoites gain entry into the body **(4)** through various means. Entry can occur through the nasal passages to the lower respiratory tract **(5)**, or ulcerated or broken skin **(6)**. When *B. mandrillaris* enters the respiratory system or through the skin, it can invade the central nervous system by hematogenous dissemination causing granulomatous amebic encephalitis (GAE) **(7)**, or disseminated disease **(8)**, or skin lesions **(9)** in individuals who are immune competent as well as those with compromised immune systems. *B. mandrillaris* cysts and trophozoites are found in tissue.

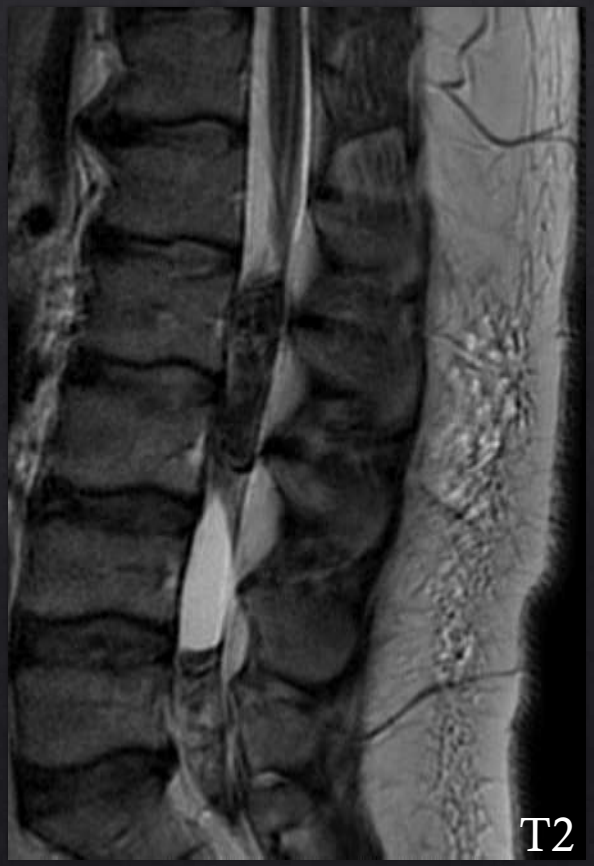
# References

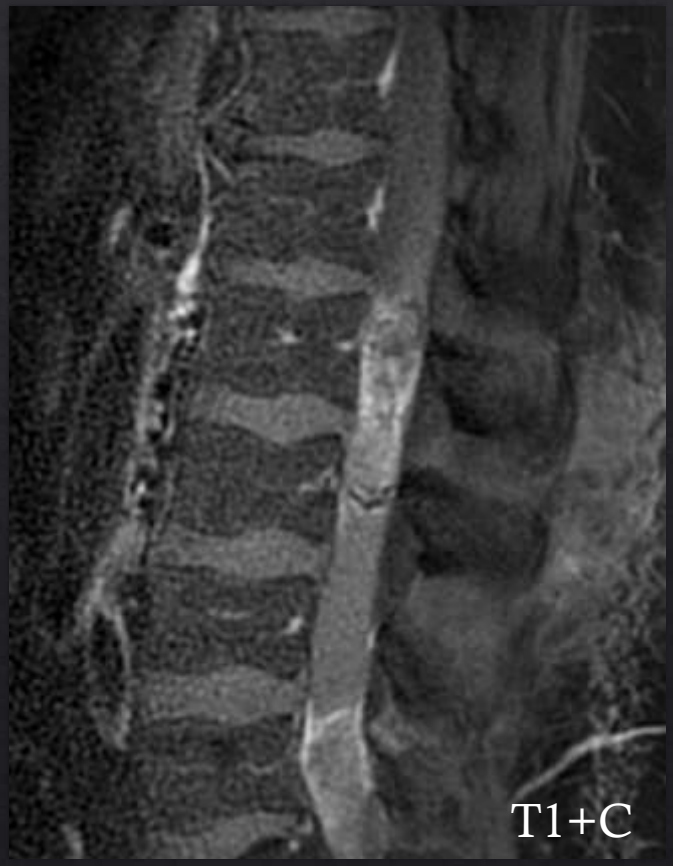

- Cope JR, Landa J, Nethercut H, Collier SA, Glaser C, Moser M, Puttagunta R, Yoder JS, Ali IK, Roy SL. The Epidemiology and Clinical Features of Balamuthia mandrillaris Disease in the United States, 1974-2016. Clin Infect Dis. 2019 May 17;68(11):1815-1822.

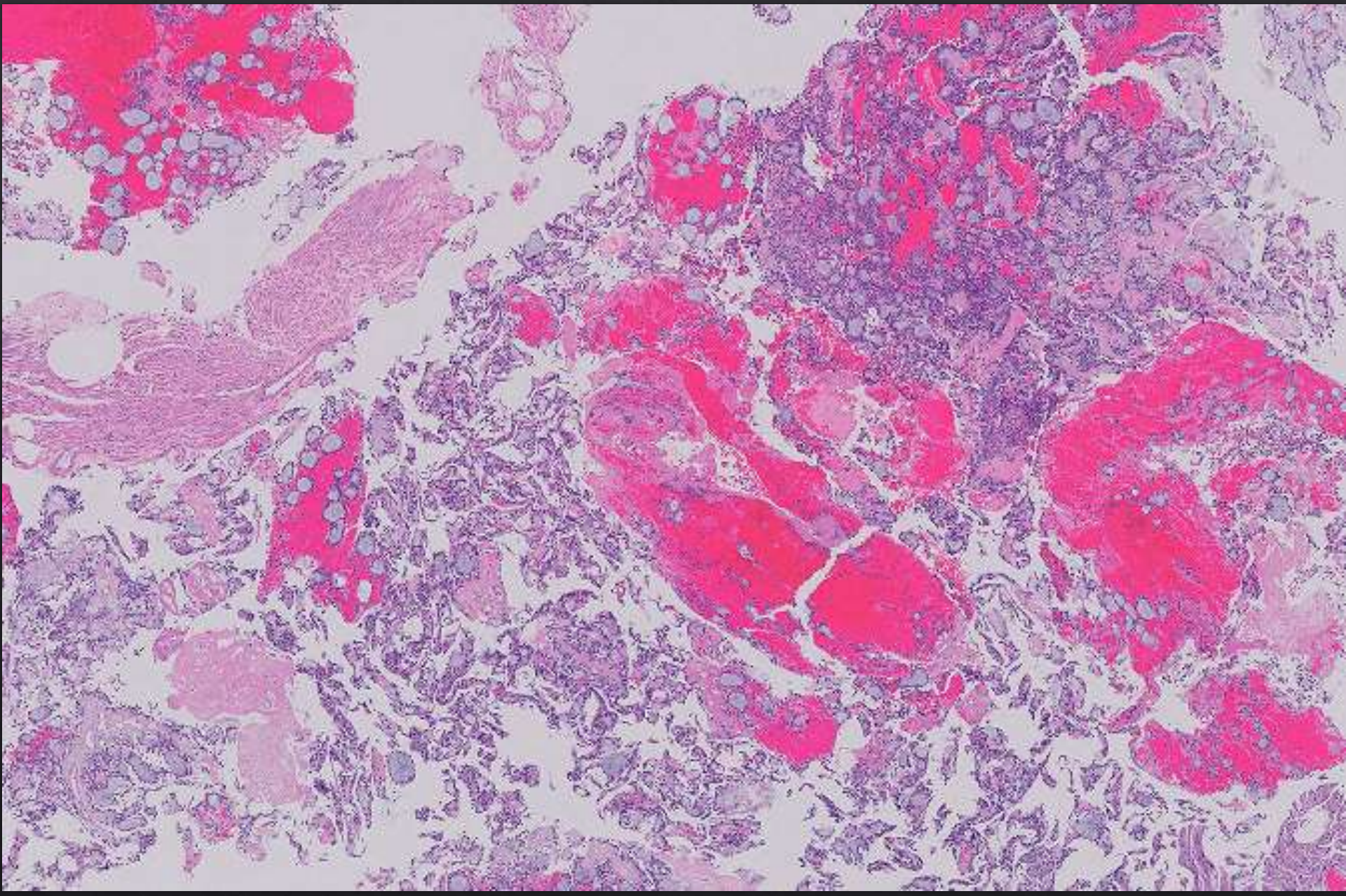
# 21-0907

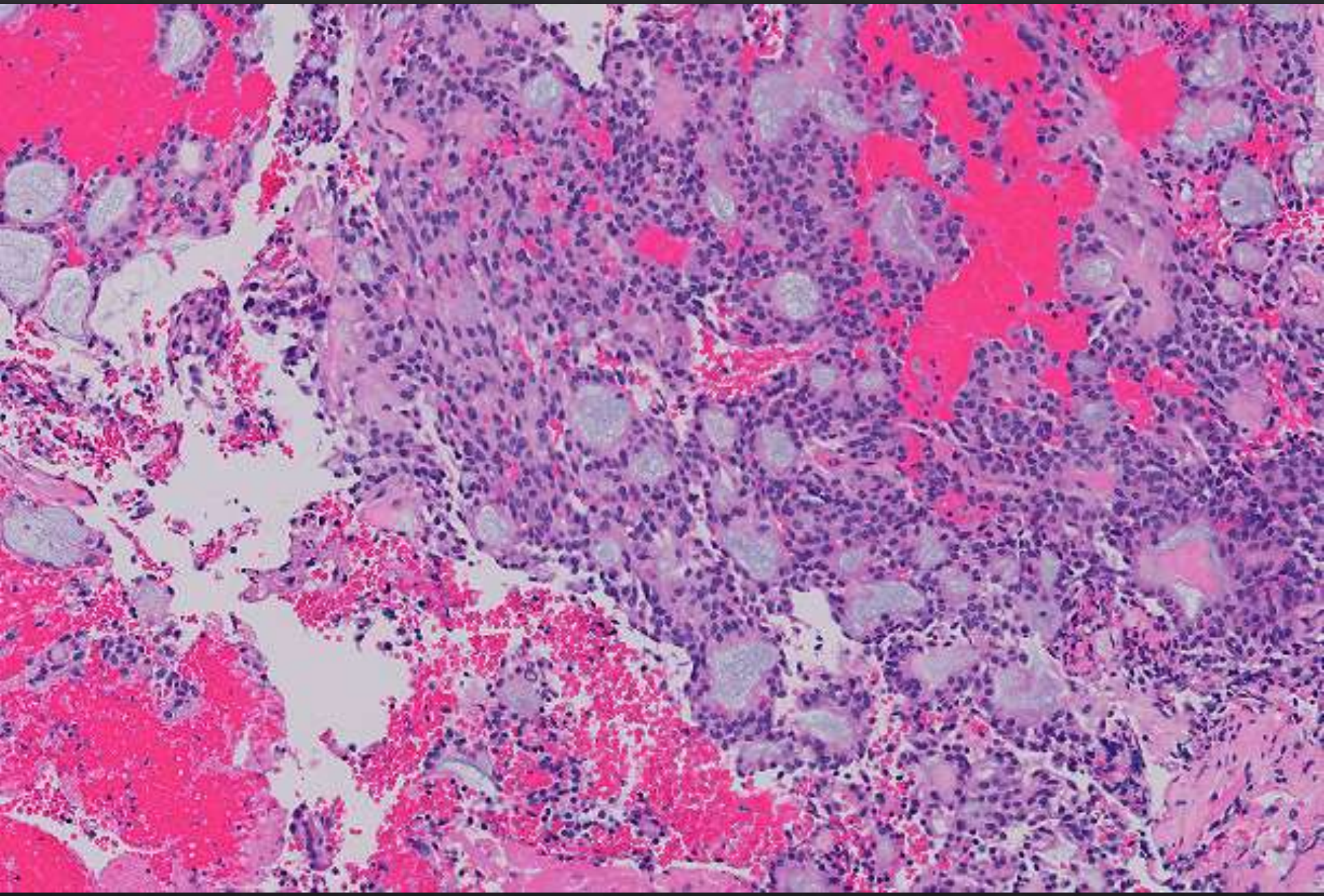
**Angus Toland/Don Born; Stanford**

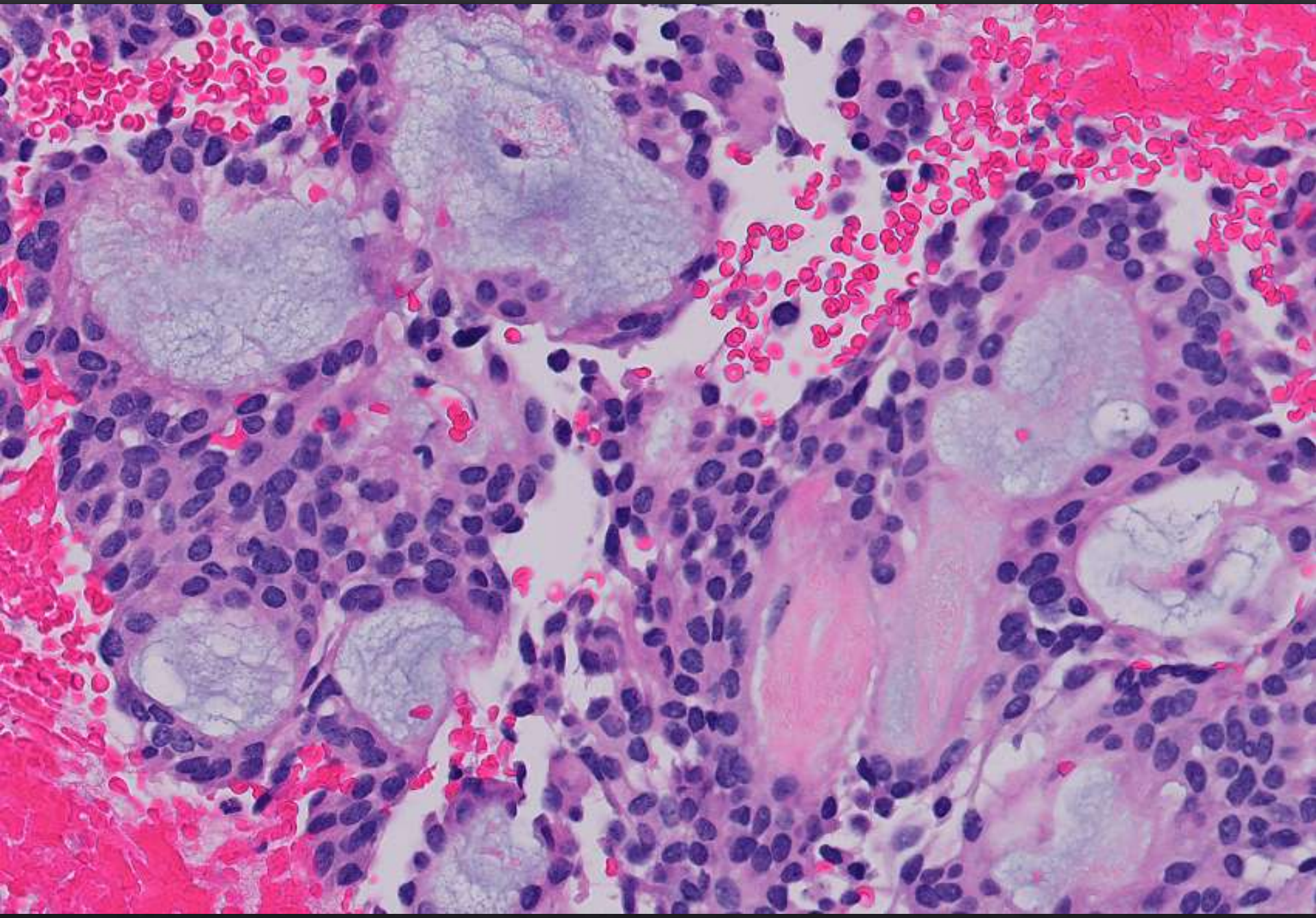
46-year-old M with several years of low back and leg pain and recent development of leg weakness. Imaging demonstrated an intradural extramedullary mass in the L3-L4 region.

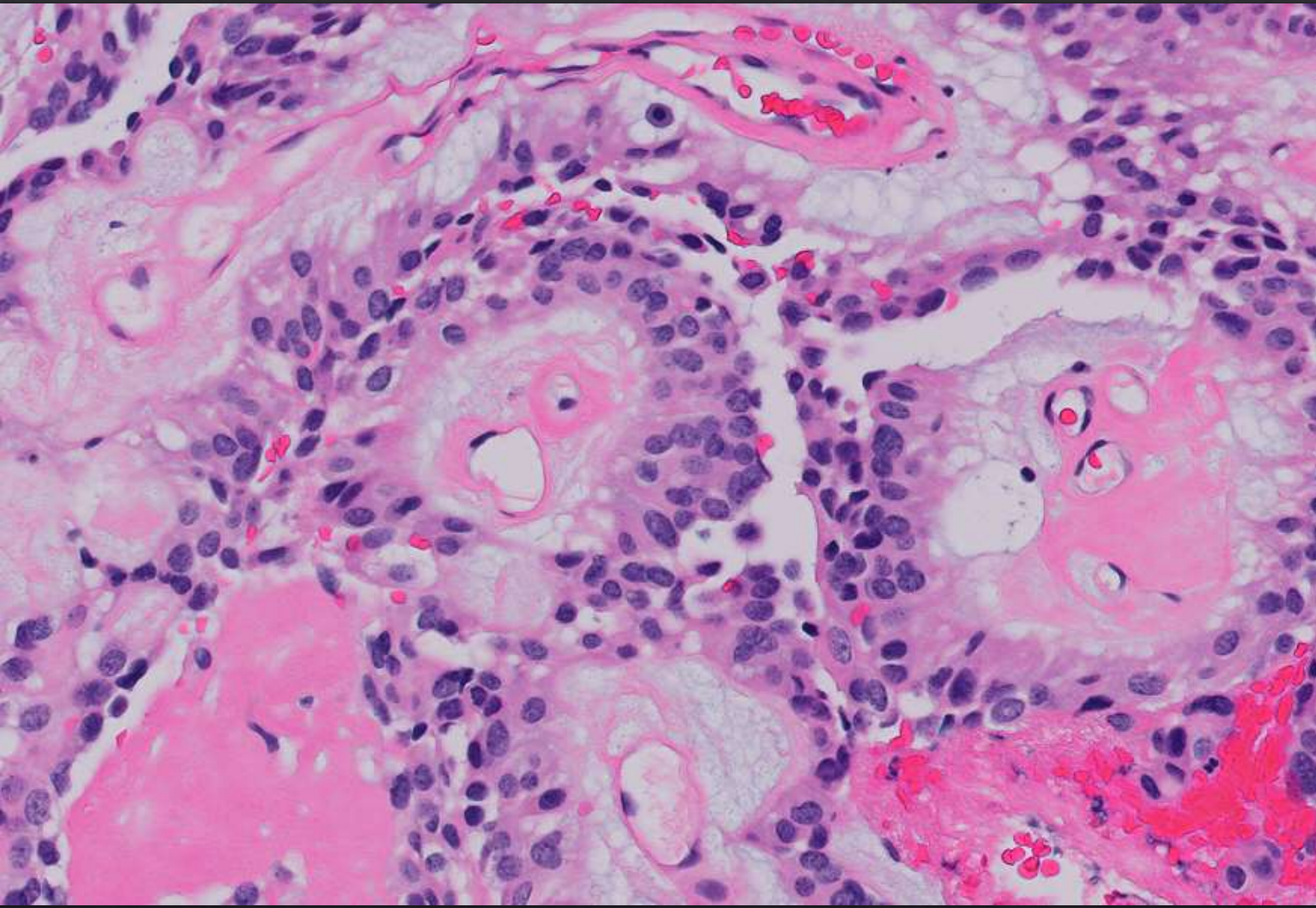

T2


T1+C









# Myxopapillary Ependymoma, WHO grade 2

- Ependymomas are a heterogeneous group of tumors occurring throughout the CNS
  - New classification scheme incorporates tumor location, histology, and molecular features
  - Recent study suggests myxopapillary ependymoma show no difference in progression free survival compared to grade 2 spinal ependymomas
  - DDx includes schwannoma, paraganglioma, and metastasis

**Table 1.** Recommended ependymal tumor types

| Tumor type | WHO grade |
|---|---|
| Supratentorial ependymoma, ~~*C11orf95*~~ fusion-positive | |
| Supratentorial ependymoma, *YAP1* fusion-positive | |
| Supratentorial ependymoma | Grade 2/ 3 |
| Posterior fossa ependymoma, Group PFA | |
| Posterior fossa ependymoma, Group PFB | |
| Posterior fossa ependymoma | Grade 2/ 3 |
| Spinal ependymoma, *MYCN*-amplified | |
| Spinal ependymoma | Grade 2/ 3 |
| Myxopapillary ependymoma | Grade 2 |
| Subependymoma | Grade 1 |

Sufficient data are currently unavailable for a WHO grade to be assigned to molecularly defined ependymomas.

*ZFTA*

Ellison DW, et. al. cIMPACT-NOW update 7: advancing the molecular classification of ependymal tumors. Brain Pathol. 2020

# Diagnosis

- Monomorphic cells with round to ovoid nuclei and eosinophilic, fibrillary cytoplasm
  - Perivascular pseudorosettes with myxoid change
  - Mitotic figures and necrosis rare if any
- GFAP+ (perivascular spoking), EMA dot-like, S100+
  - Alcian Blue can highlight myxoid areas
- Negative for cytokeratins, neuroendocrine markers (synaptophysin, chromogranin)

# References


- Vera-Bolanos E, et. al. Clinical course and progression-free survival of adult intracranial and spinal ependymoma patients. Neuro Oncol. 2015 Mar;17(3):440-7. doi: 10.1093/neuonc/nou162. Epub 2014 Aug 13. PMID: 25121770; PMCID: PMC4483095.
- Abdallah A, et. al. Long-Term Surgical Resection Outcomes of Pediatric Myxopapillary Ependymoma: Experience of Two Centers and Brief Literature Review. World Neurosurg. 2020 Apr;136:e245-e261. doi: 10.1016/j.wneu.2019.12.128. Epub 2019 Dec 30. PMID: 31899399.
- Ellison DW, Aldape KD, Capper D, Fouladi M, Gilbert MR, Gilbertson RJ, Hawkins C, Merchant TE, Pajtler K, Venneti S, Louis DN. cIMPACT-NOW update 7: advancing the molecular classification of ependymal tumors. Brain Pathol. 2020 Sep;30(5):863-866. doi: 10.1111/bpa.12866. Epub 2020 Jun 23.