Pathology of the Female Peritoneum, an Update

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THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

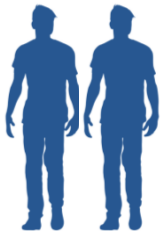
No conflicts of interest

Pathology of the Female Peritoneum, an Update

- Peritoneal inclusion cyst
- Well Differentiated Papillary ~~Mesothelioma~~ Mesothelial Tumor
- ~~Malignant~~ Mesothelioma

Peritoneal Inclusion Cyst
Uncommon

20’s and 30’s



Less frequent

Rare in children

Reported cases in mother/daughter, sisters

Peritoneal Inclusion Cyst

Origin

- Reactive vs Neoplastic
- Hormonal Influence:
  grows during pregnancy
- A rare case with hx of asbestos exposure

Association

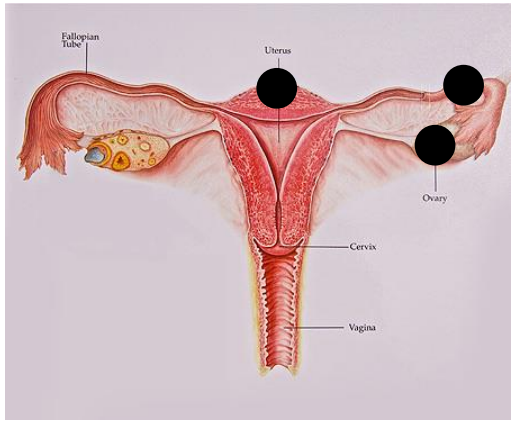
- Abdomino/pelvic surgery
- Pelvic inflammatory disease
- Endometriosis

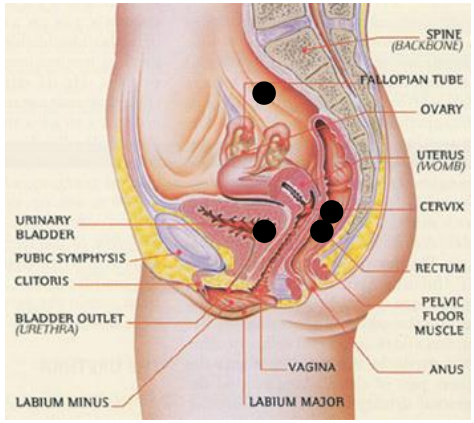
Symptoms

- Abdomino/pelvic mass or pain
- Inguinal or incisional hernia
- Non-specific symptoms
- 10% of cases are incidental
- Usually without ascites

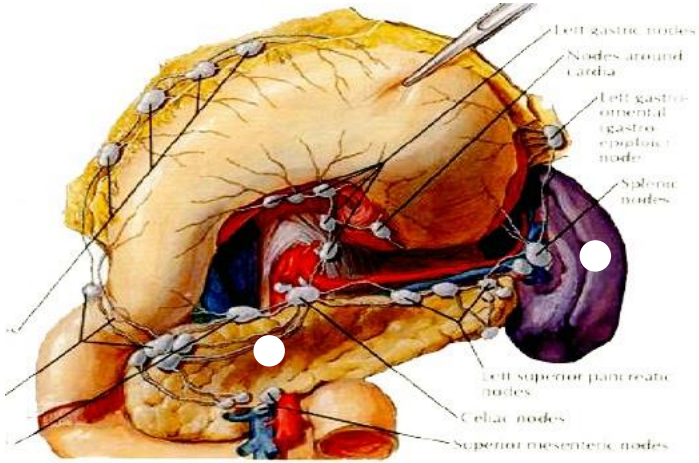
Peritoneal Inclusion Cyst

Pelvis

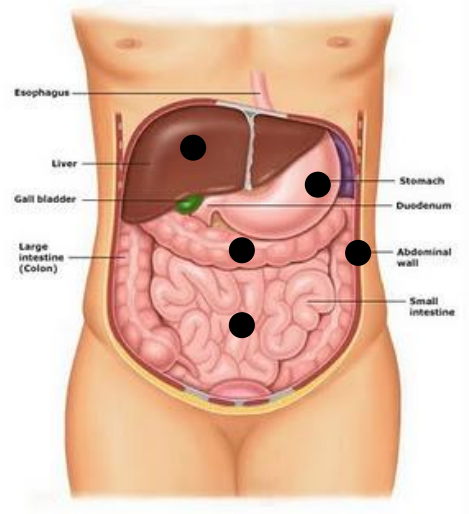




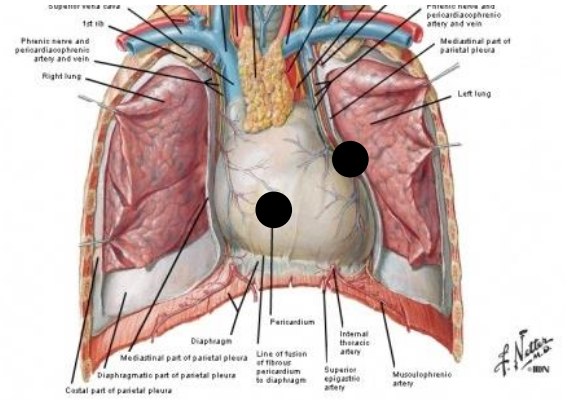
Retroperitoneum



Abdomen



Pericardium / Pleura

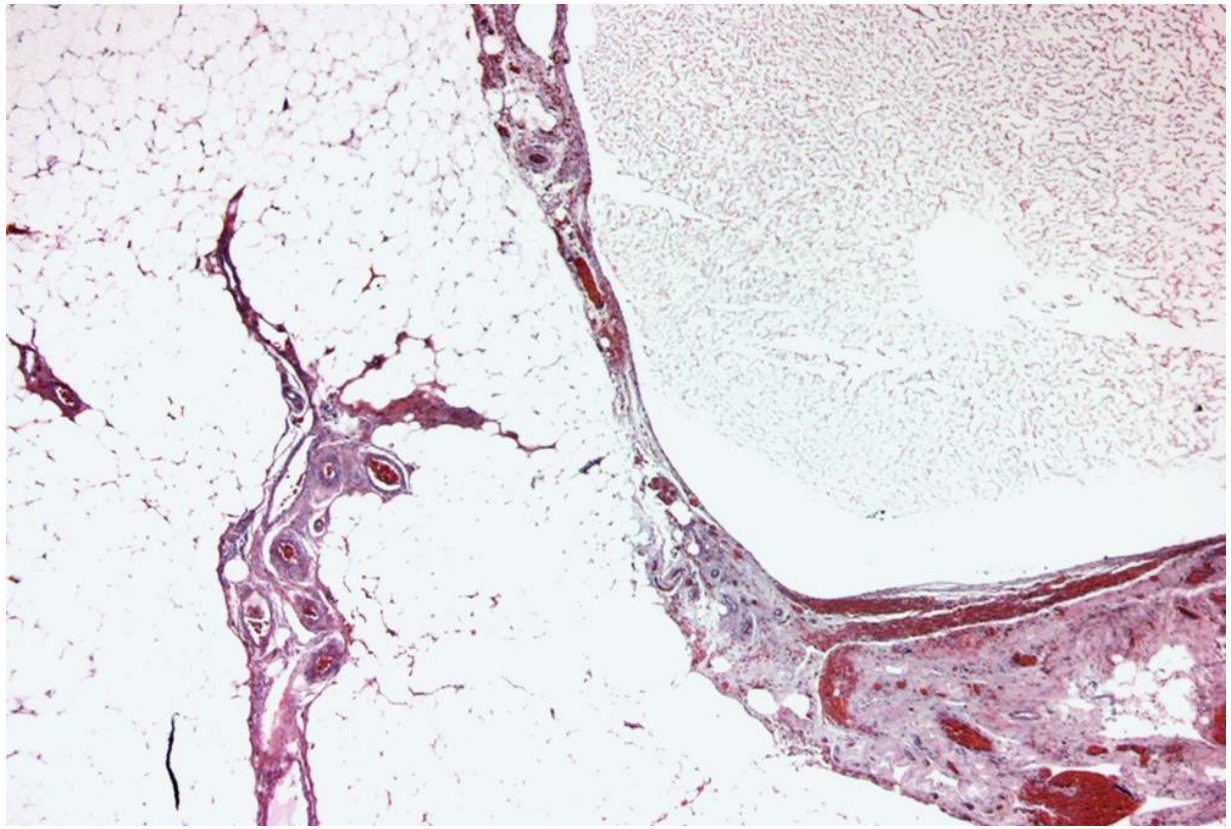


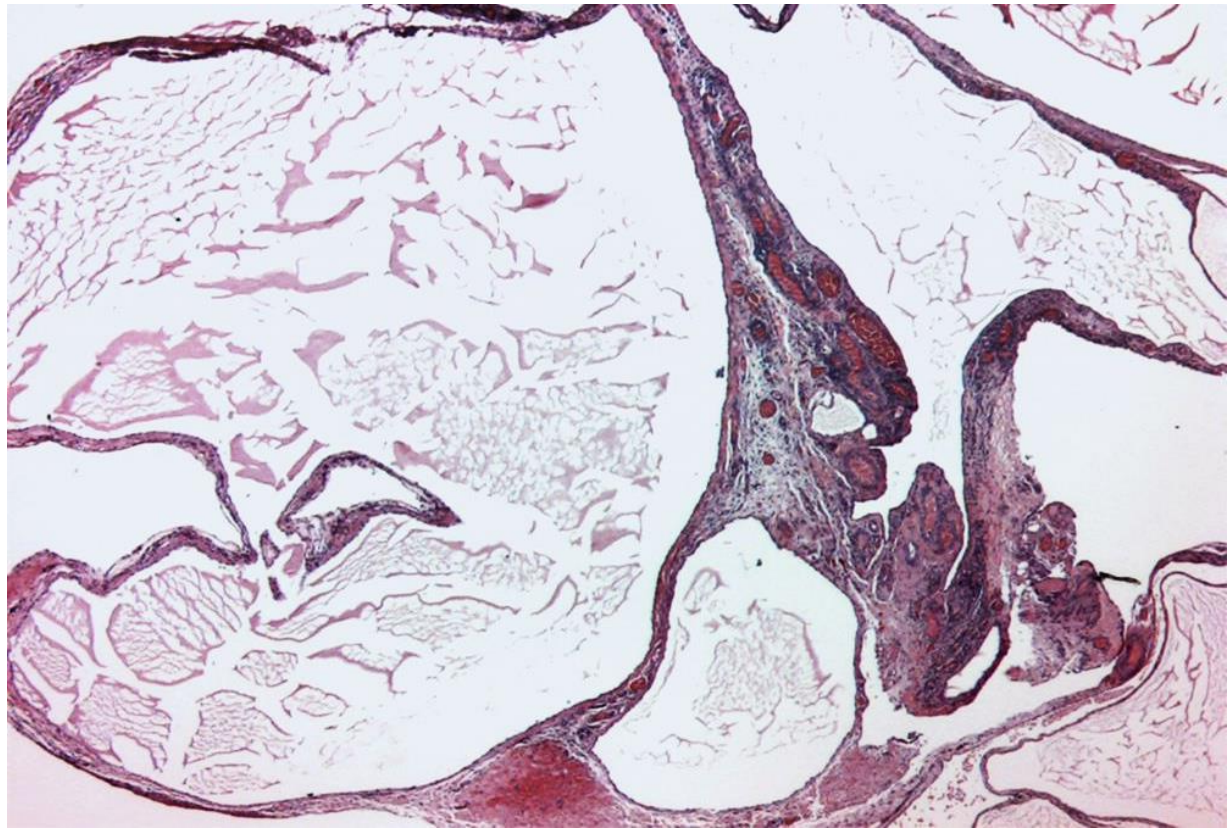
Peritoneal Inclusion Cyst

Gross

- Solitary, localized, diffuse
- Cyst (s)

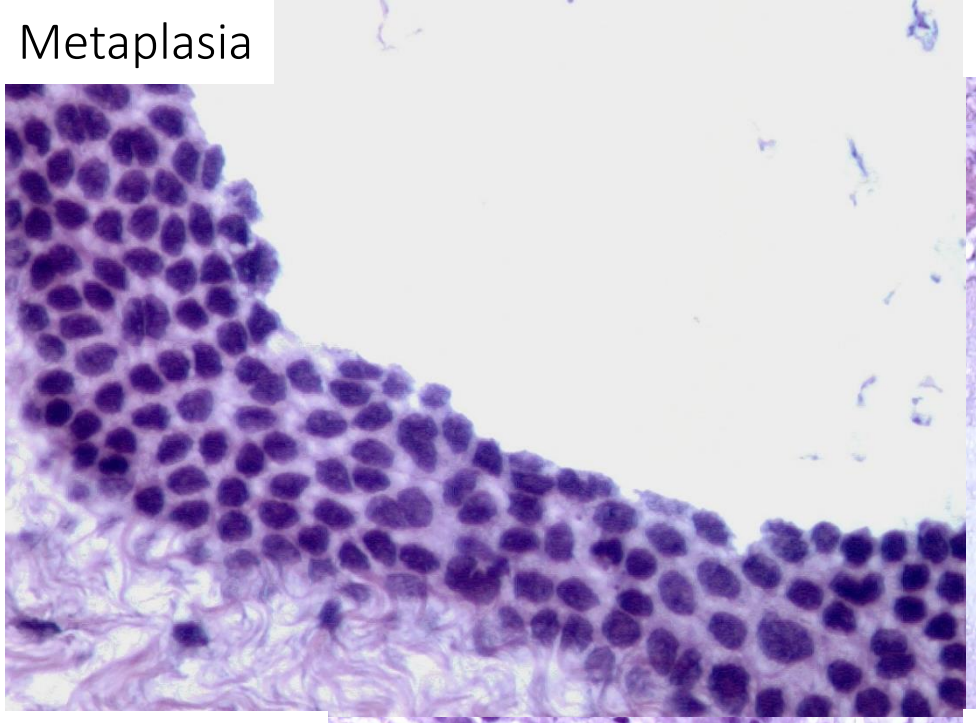
  A few mm - 20 cm



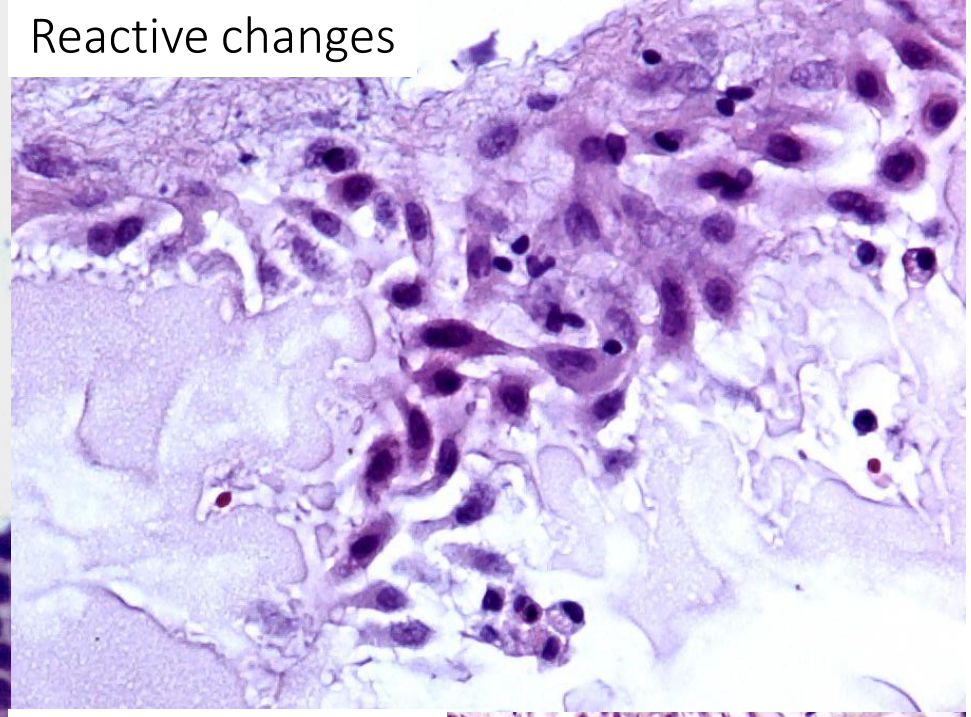


Peritoneal Inclusion Cyst

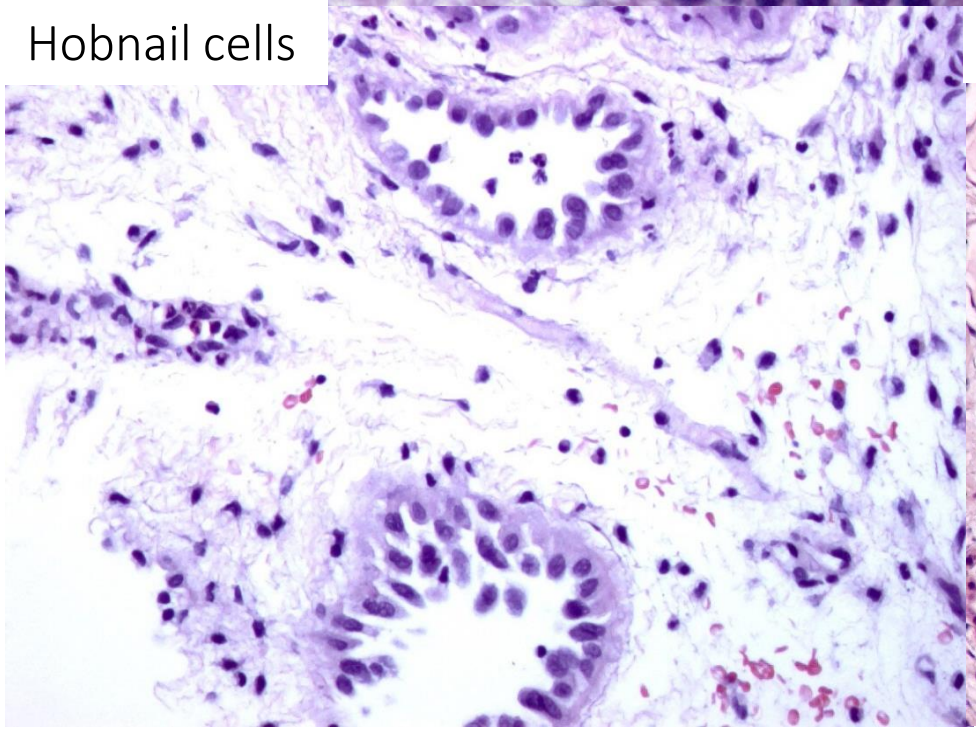
Metaplasia



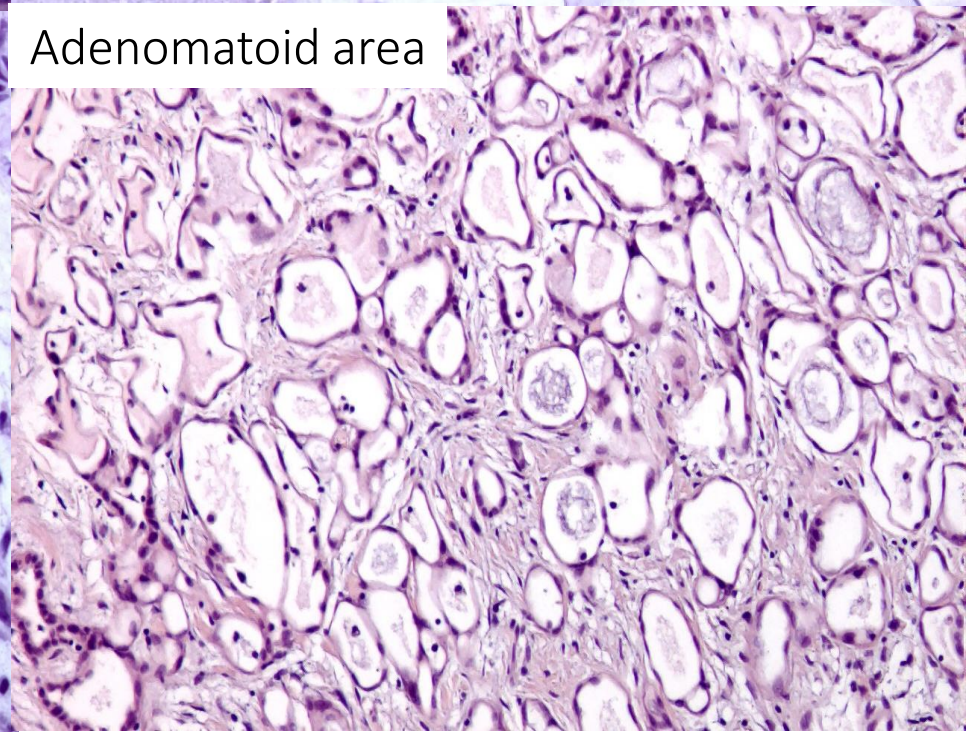
Reactive changes

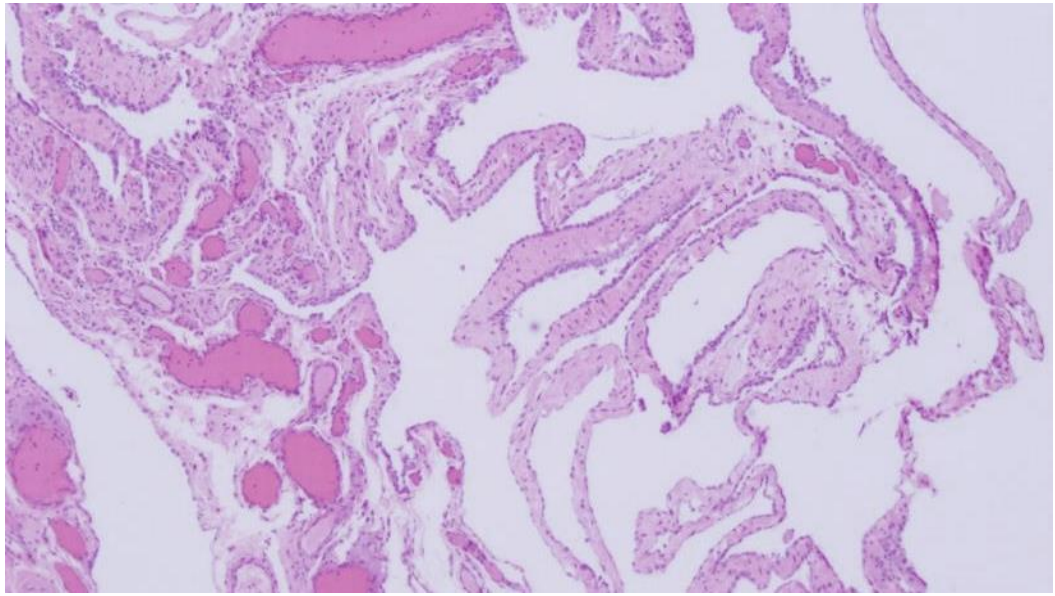
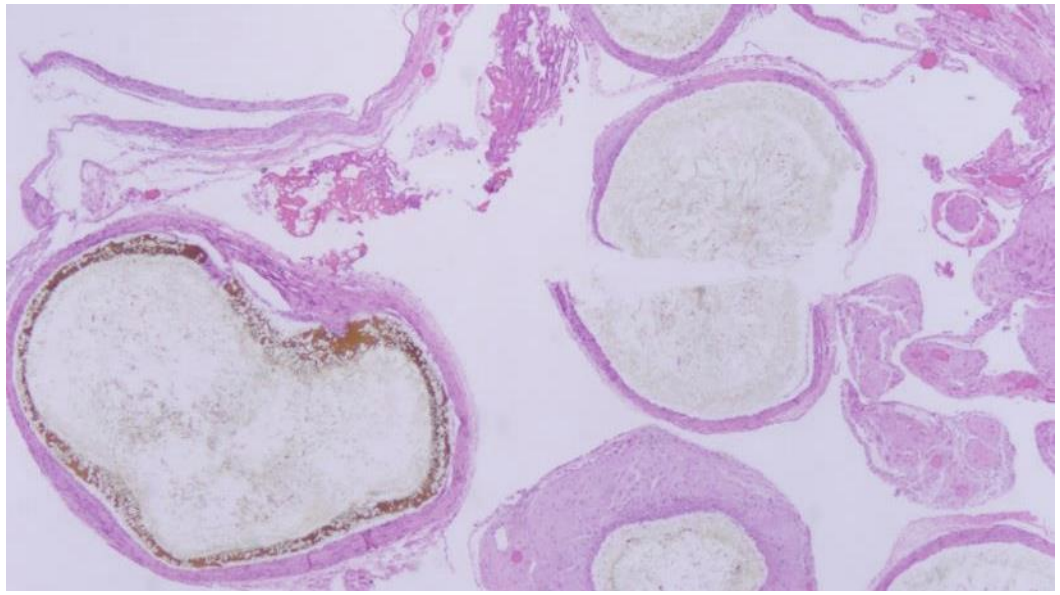
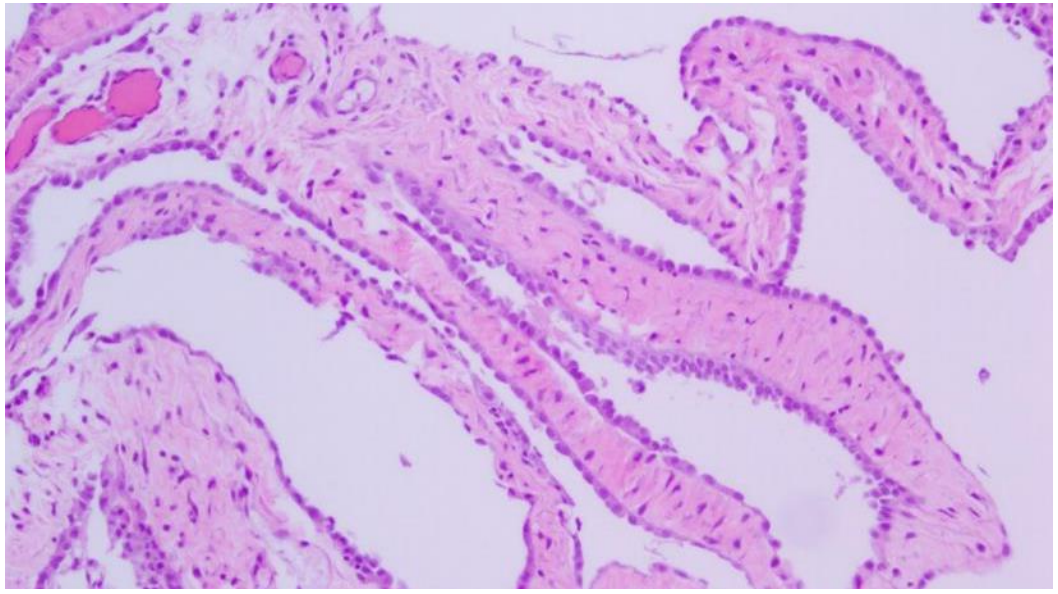
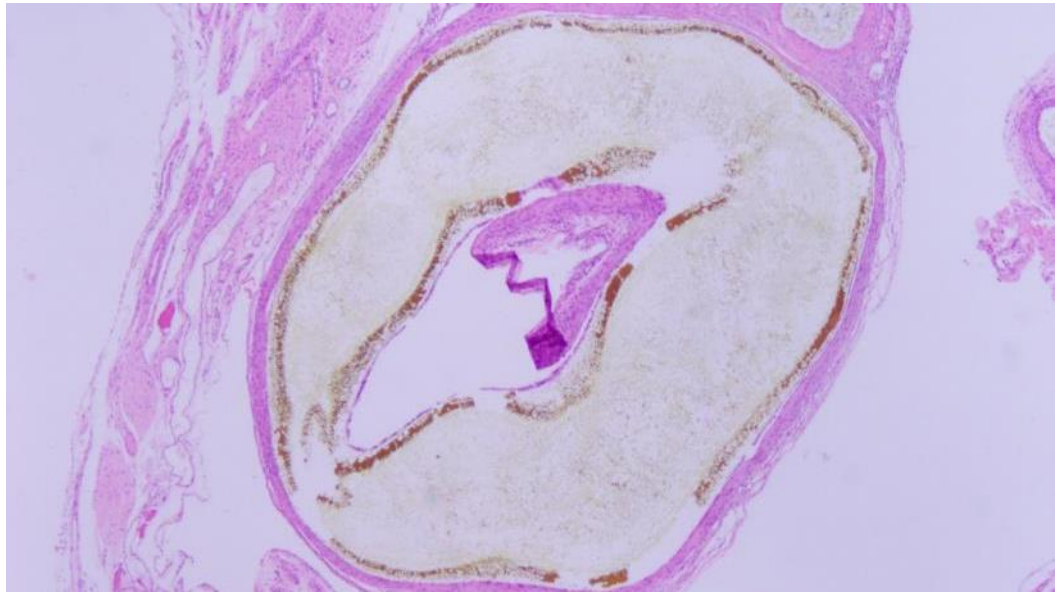


Hobnail cells

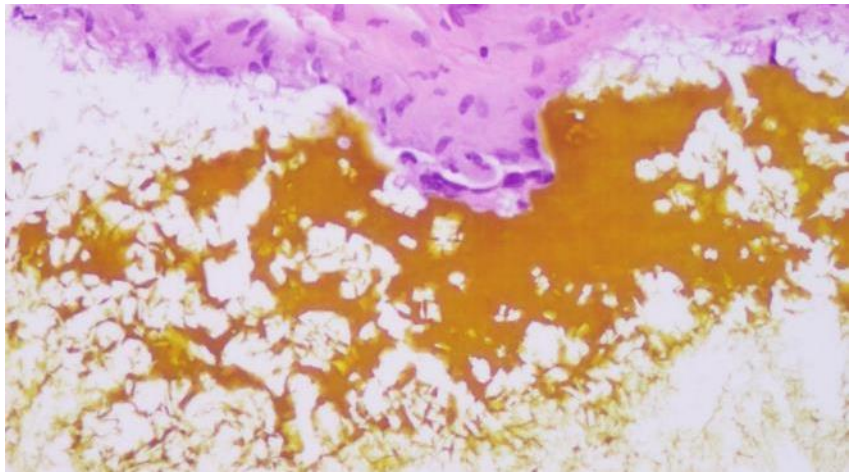


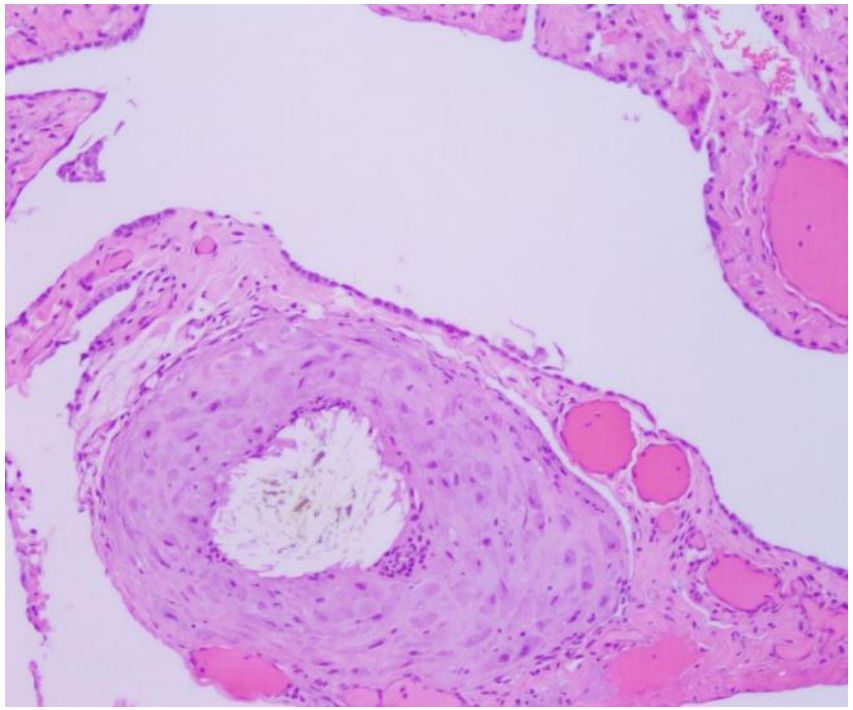
Adenomatoid area

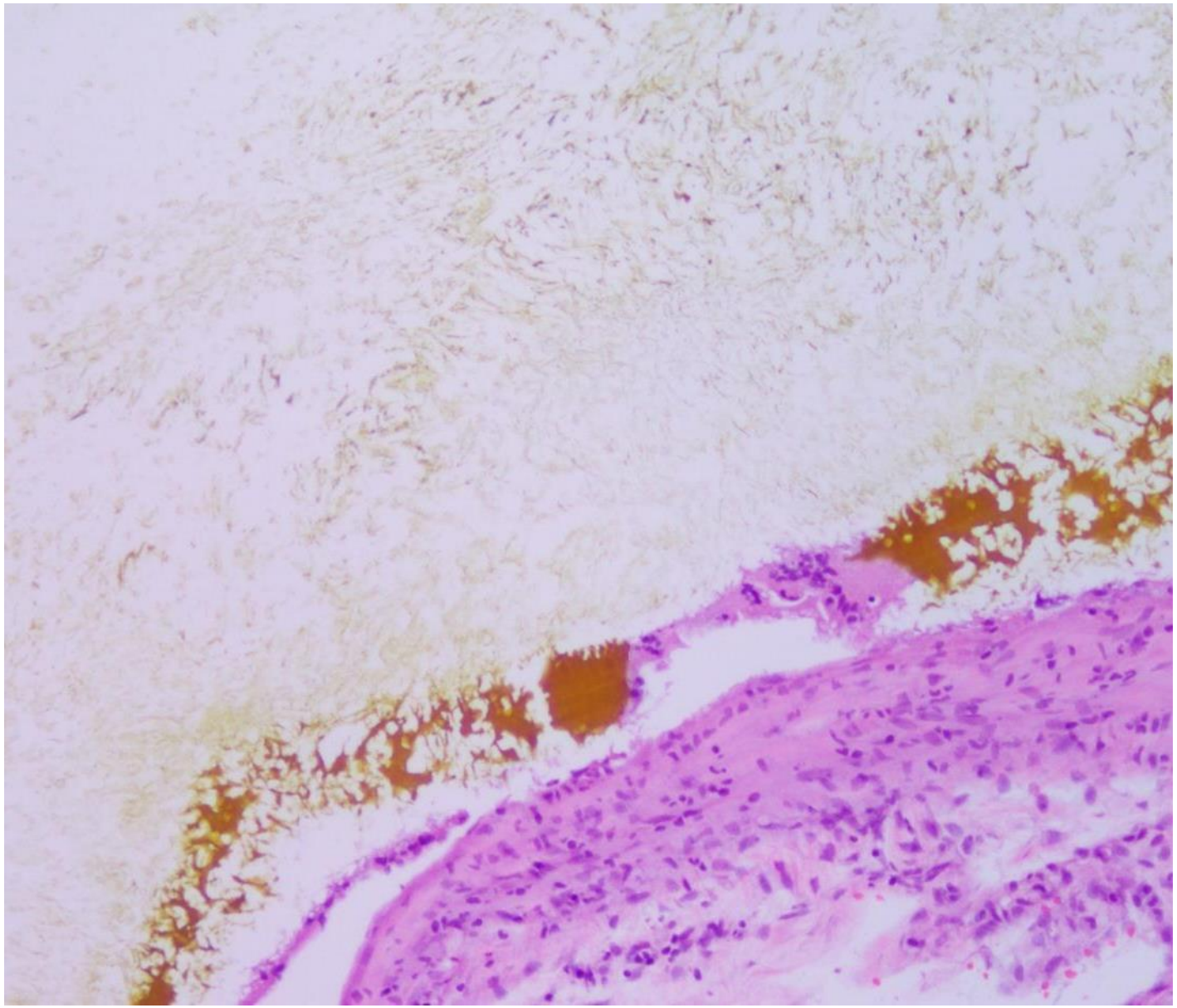


Bile deposition, s/p cholecystectomy, peritoneal inclusion cyst, removed during C-section

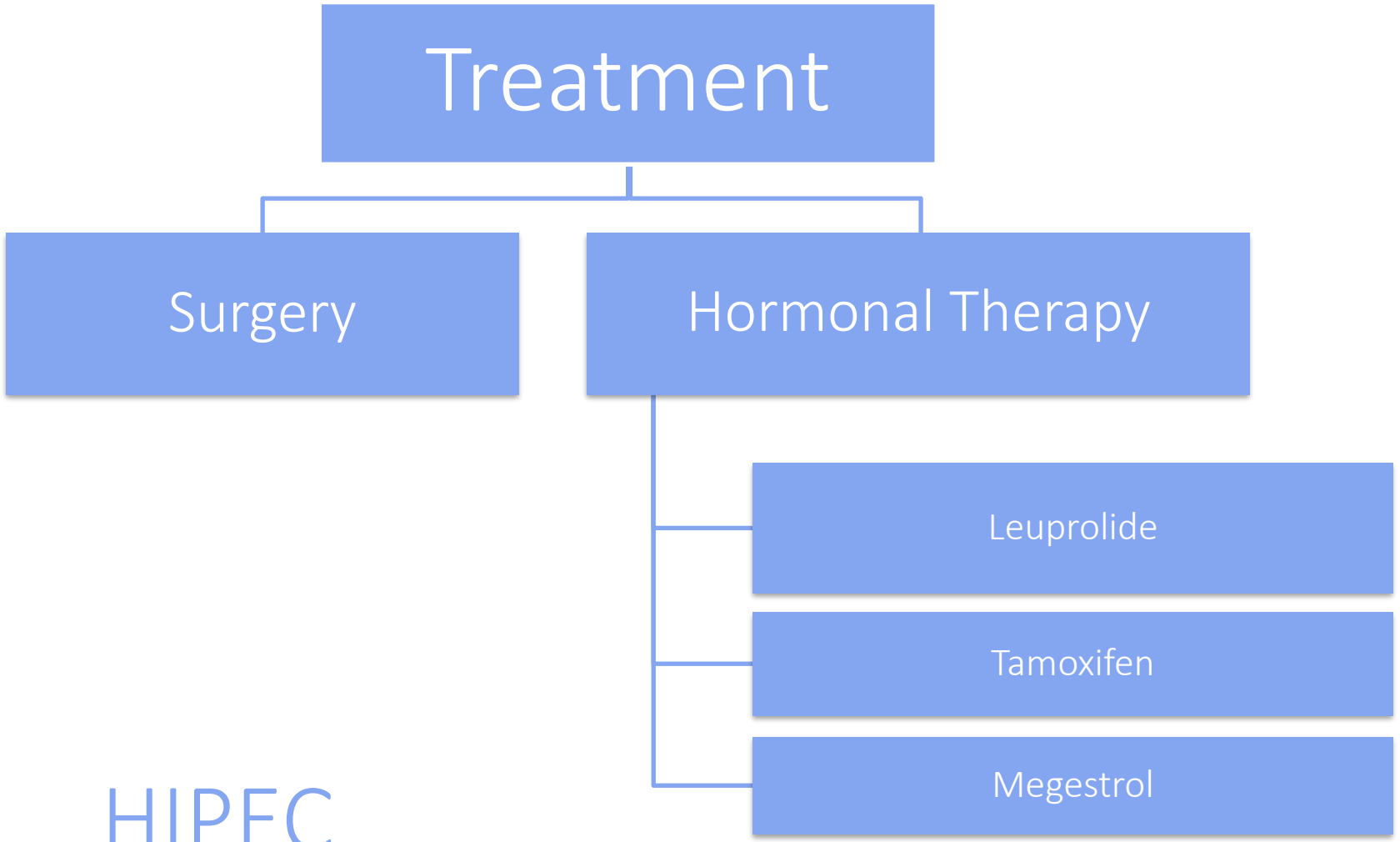






Bile deposition, s/p cholecystectomy, peritoneal inclusion cyst, removed during C-section

Peritoneal Inclusion Cyst



HIPEC

Peritoneal Inclusion Cyst – Prognosis

Benign behavior

No Tx → pts can die due to local compression effect

A rare case with malignant transformation in 10 yrs

Recurrences in up to 50% of the cases

A. OMENTUM, BIOPSY: BENIGN MULTILOCULAR PERITONEAL INCLUSION CYSTS.

B. SOFT TISSUE, "SIGMOID IMPLANT," BIOPSY:
1. BENIGN MULTILOCULAR PERITONEAL INCLUSION CYSTS.
2. ONE BENIGN LYMPH NODE.

C. SOFT TISSUE, "PELVIC MASS," BIOPSY: BENIGN MULTILOCULAR PERITONEAL INCLUSION CYSTS.

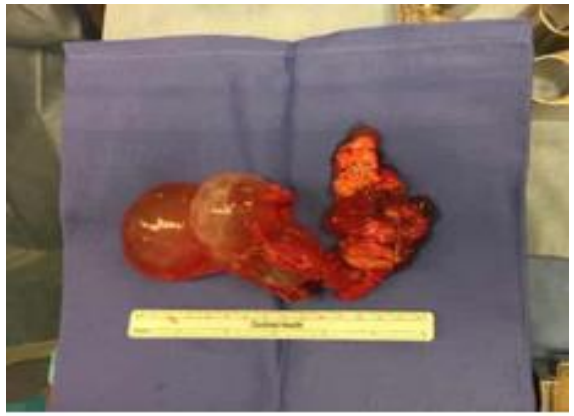
D. SOFT TISSUE, "SIGMOID IMPLANT,' BIOPSY: BENIGN MULTILOCULAR PERITONEAL INCLUSION CYSTS.

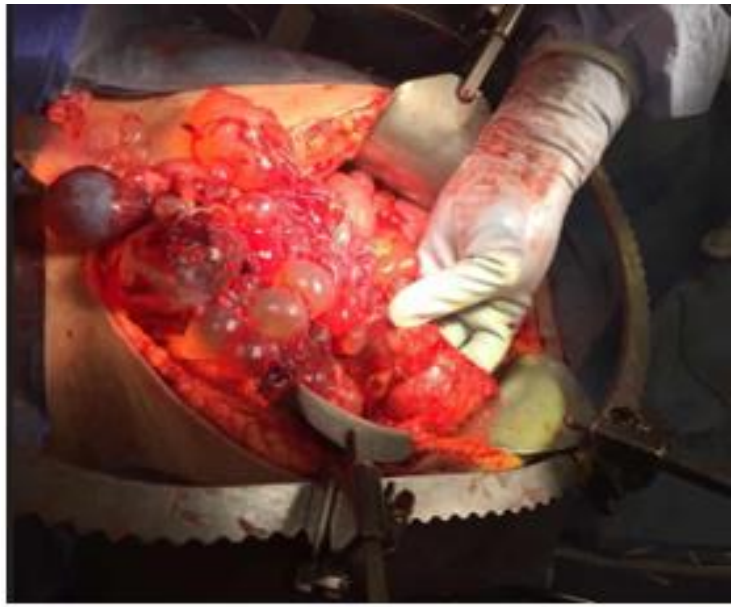
E. APPENDIX, APPENDECTOMY: NO SIGNIFICANT PATHOLOGIC ABNORMALITY.

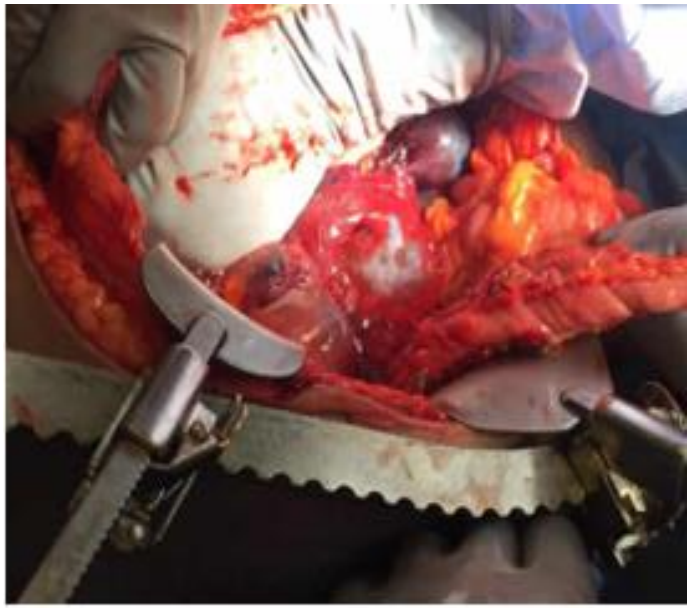
F. SOFT TISSUE, "BLADDER IMPLANT," BIOPSY: BENIGN MULTILOCULAR PERITONEAL INCLUSION CYSTS.

G. SOFT TISSUE, "CUL DE SAC IMPLANT," BIOPSY: BENIGN MULTILOCULAR PERITONEAL INCLUSION CYSTS.

Matted cysts up to 30 cm







Molecular Findings

- *TNS3*::*MAP3K3* and *ZFPM2*::*ELF5* fusions

  Panagopoulos I, et al. 2015

- No genomic alterations in a cohort of 5 cases

  Devins KM, et al. 2024

Well Differentiated Papillary Mesothelial Tumor

Clinical Features

- Incidental
- Occasionally
  - Acute abdomen due to bleeding or torsion
  - Abdominal/pelvic pain
- No ascites

Gross

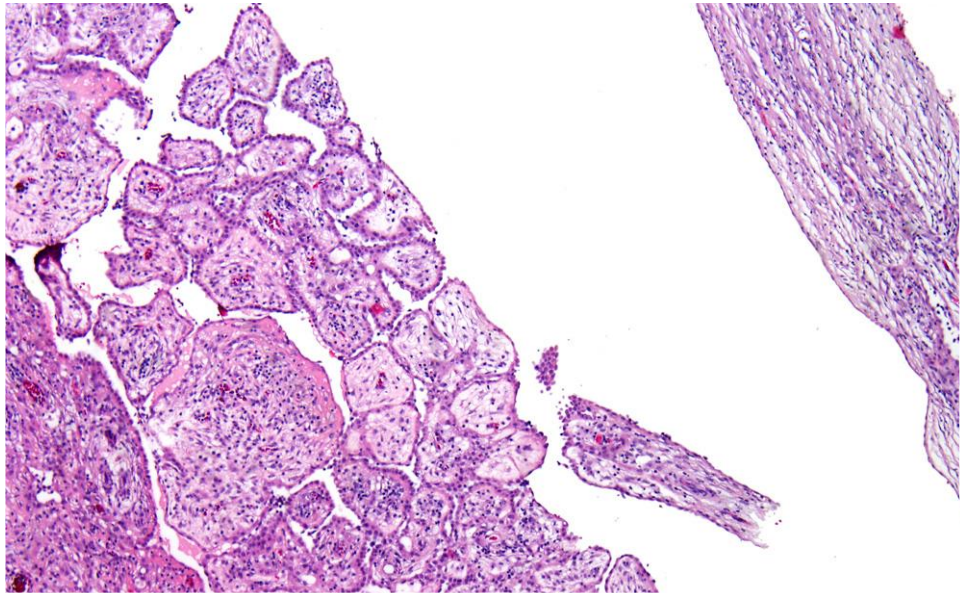
- Single or multiple lesions
- A few mm up to 2 cm

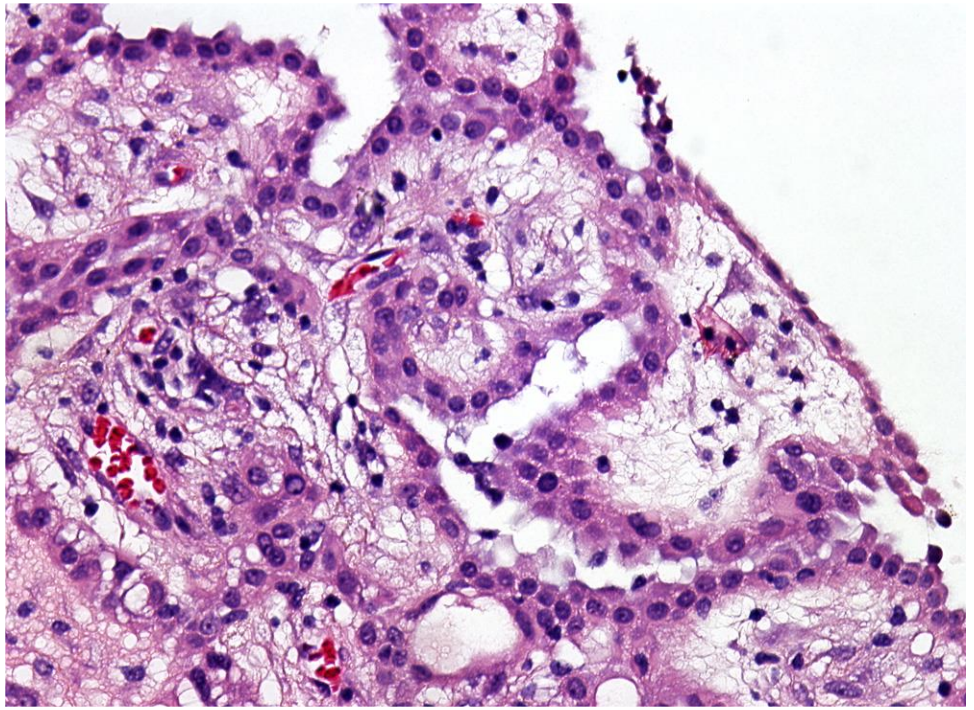
  Malpica et al, 2012
- Up to 5 cm

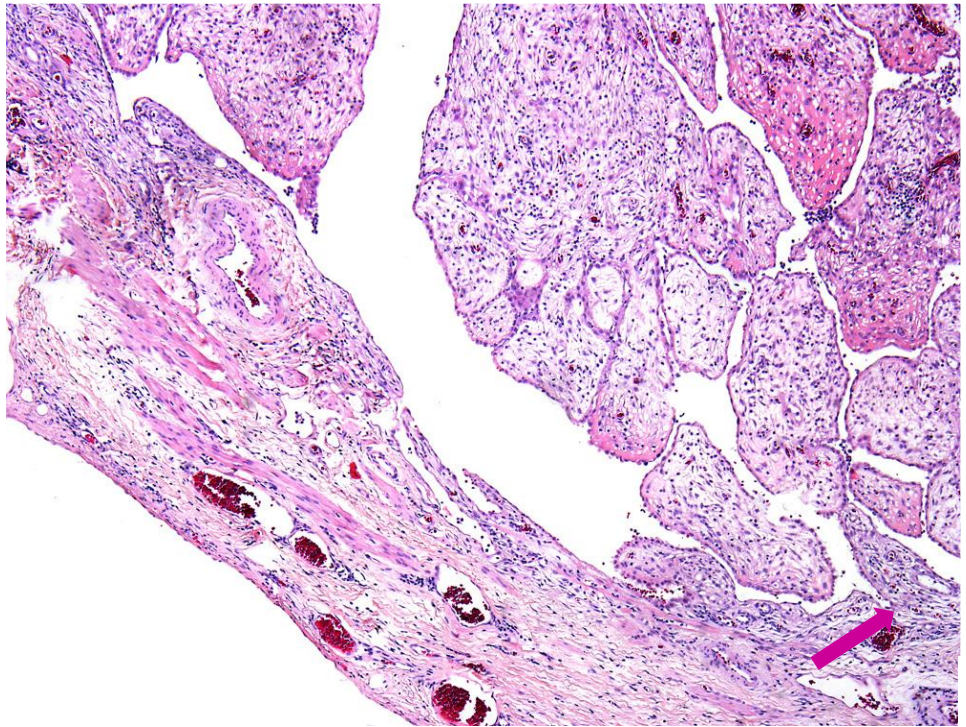
  Chen et al, 2013

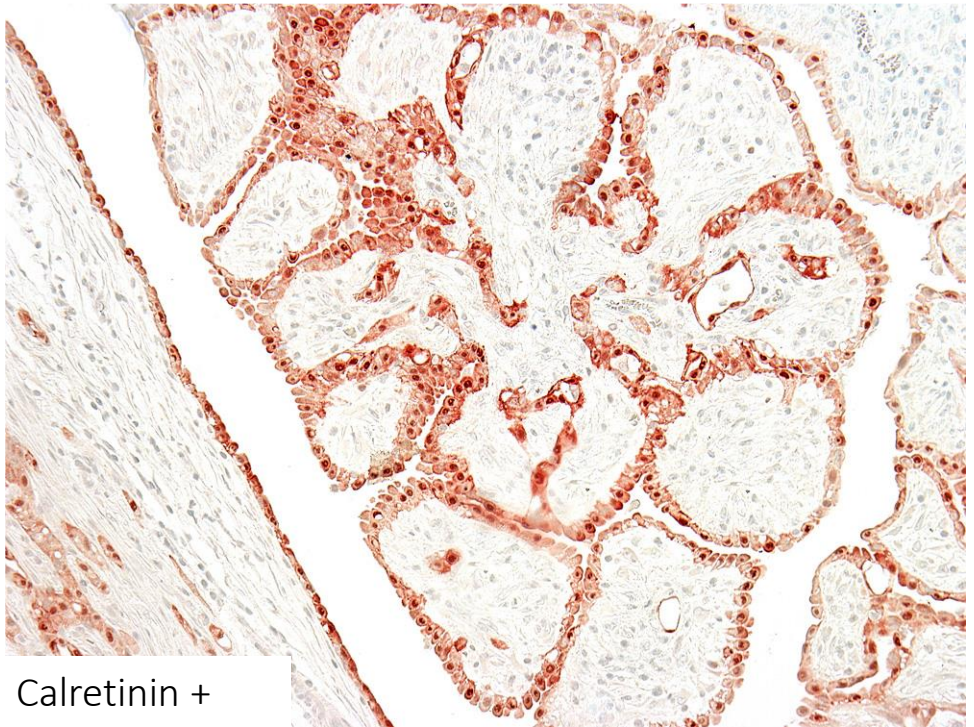
Well Differentiated Papillary Mesothelial Tumor

WDPMT in the fimbrial end of the fallopian tube -a perfect example!
1.5 cm lesion, non-coalescent papillae, no invasion into the wall, bland cytology and up to 1 mitosis per 10 HPFs



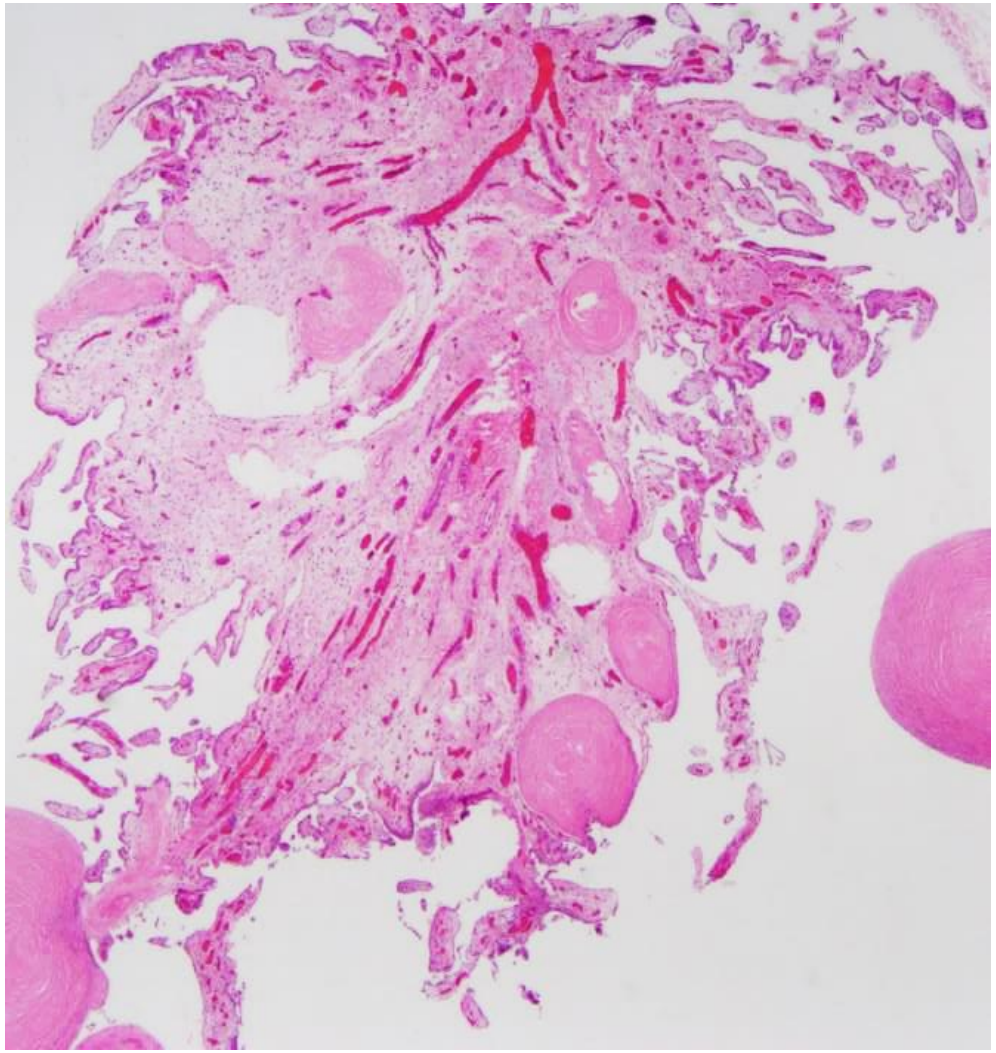




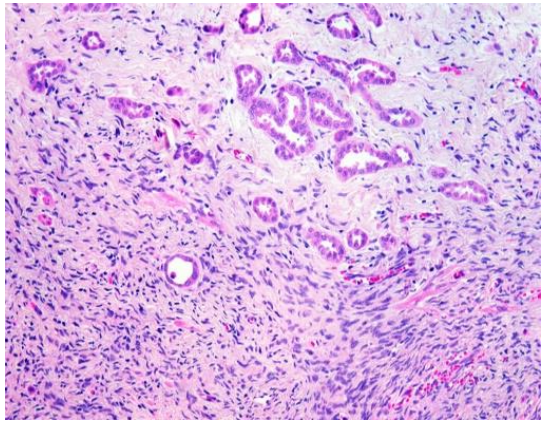


Calretinin +

Dx Challenges



- Detached fragment of tumor
- Large tumor size
- Multifocal involvement
- Papillary cores with an exuberant mesothelial component
- “Seedling” vs. true invasion

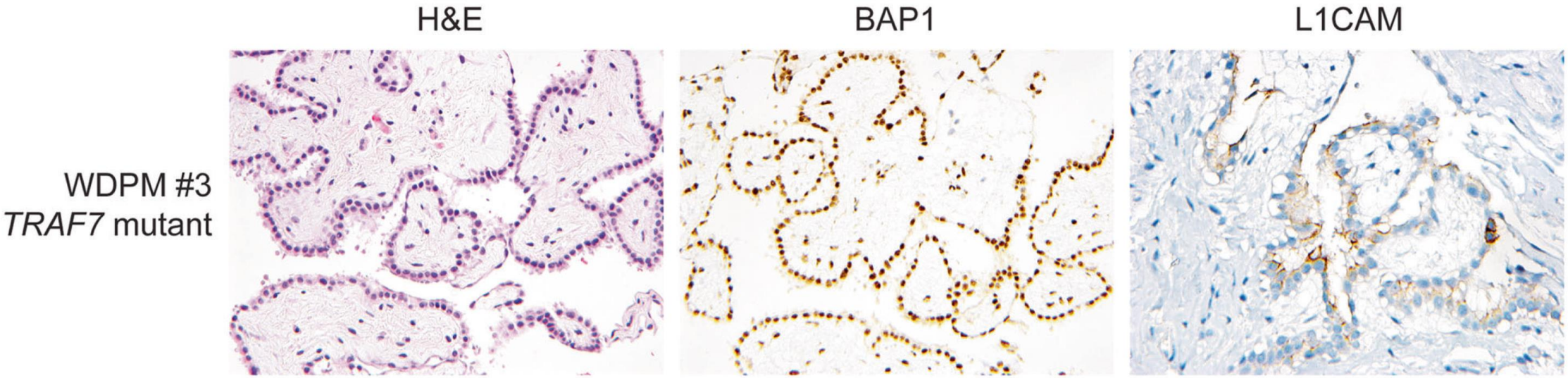


“Seedling” < 0.5 mm

Well-differentiated papillary mesothelioma of the peritoneum is genetically defined by mutually exclusive mutations in TRAF7 and CDC42

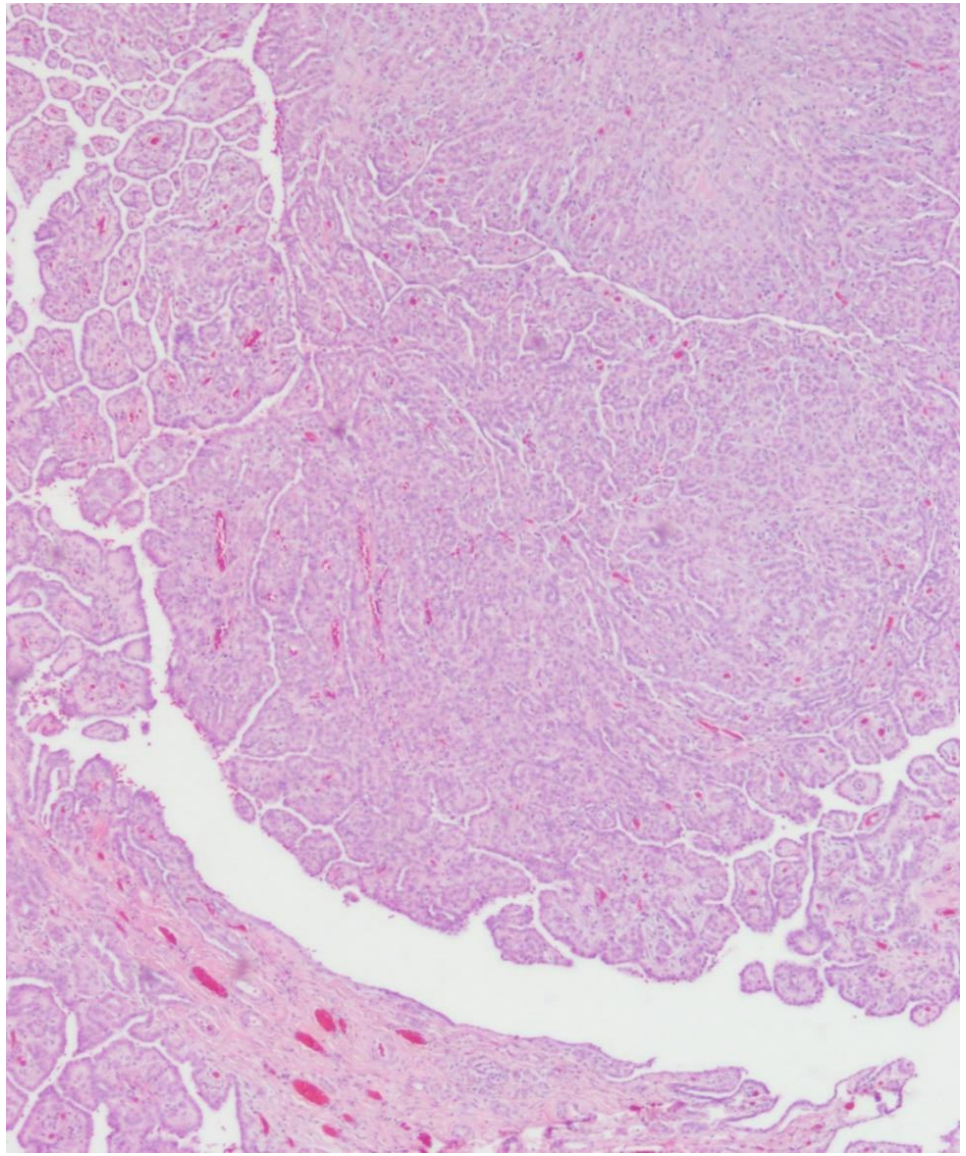
Meredith Stevers[1] · Joseph T. Rabban[1] · Karuna Garg[1] · Jessica Van Ziffle[1,2] · Courtney Onodera[2] · James P. Grenert[1,2] · Iwei Yeh[1,2] · Boris C. Bastian[1,2] · Charles Zaloudek[1] · David A. Solomon[1,2]

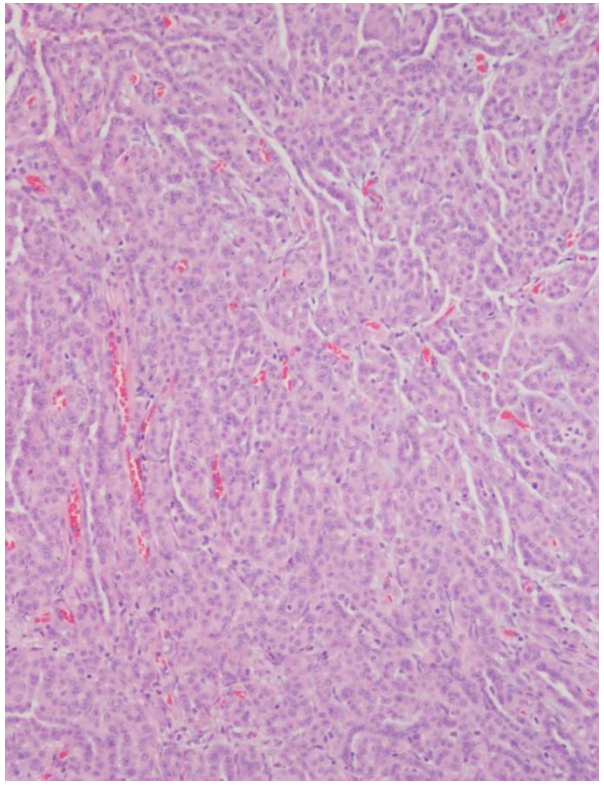
Received: 15 June 2018 / Revised: 28 July 2018 / Accepted: 28 July 2018 / Published online: 31 August 2018

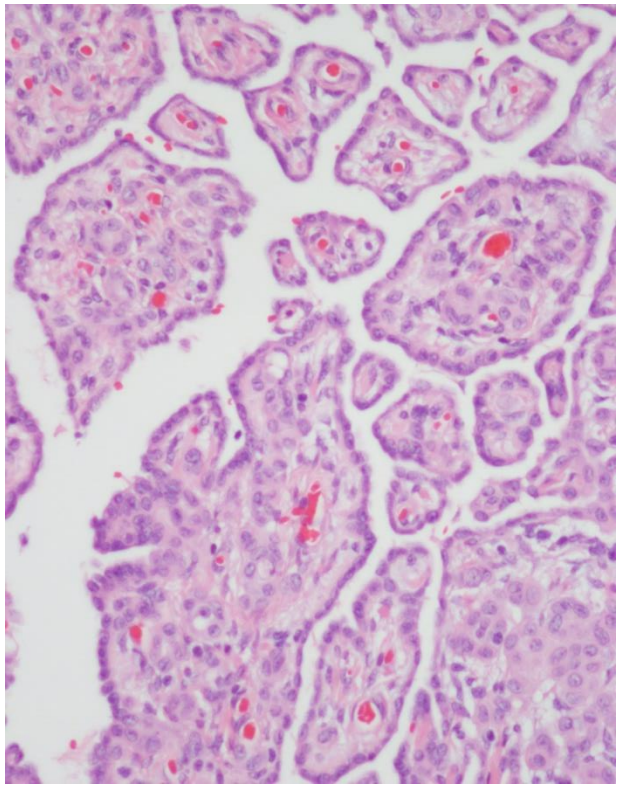


Other WDPMT specific mutations are *EHD1, ATM*, FBX, FBXO10, SH2D2A, CDH5, MAGED1*, and *TP73*
Shrestha R, et al. 2020

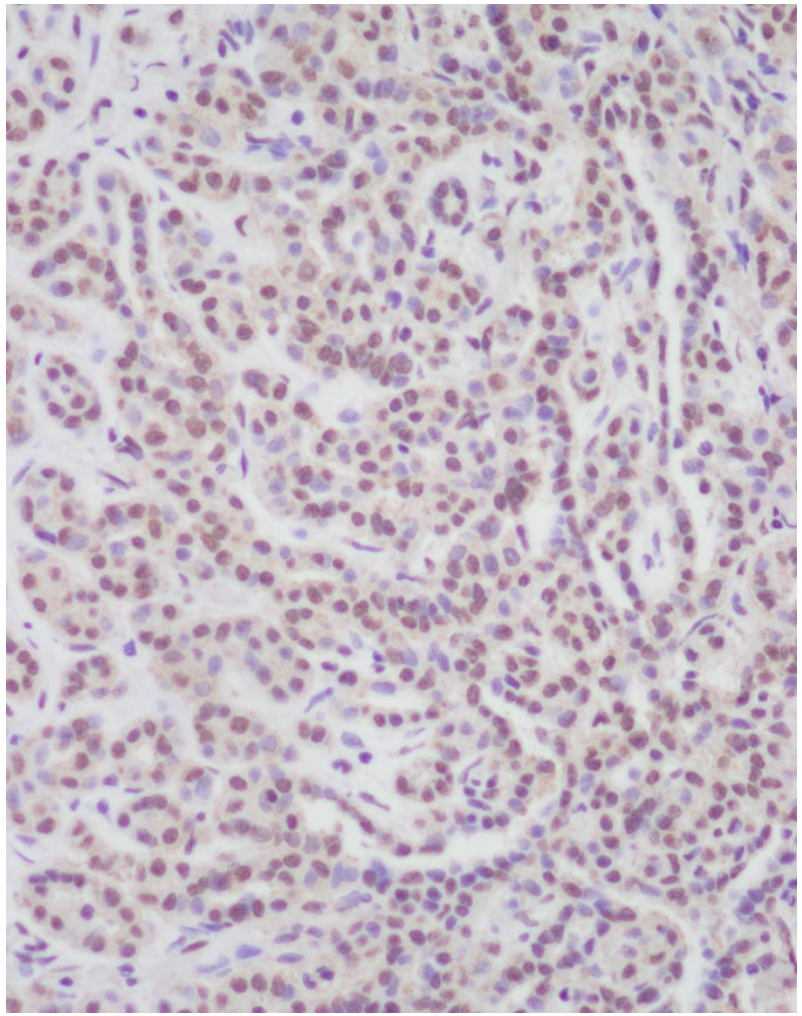
* Malignant peritoneal mesothelioma in a male infant with *ATM* mutation
Mijalovski A, et al. 2018







48 y.o. female with an incidentally found, 0.5 cm nodule in the left fallopian tube



BAP-1 retained

No *CDKN2A* homozygous deletion by FISH

Targeted next generation sequencing

↓

CDC42 somatic mutation

Well Differentiated Papillary Mesothelial Tumor

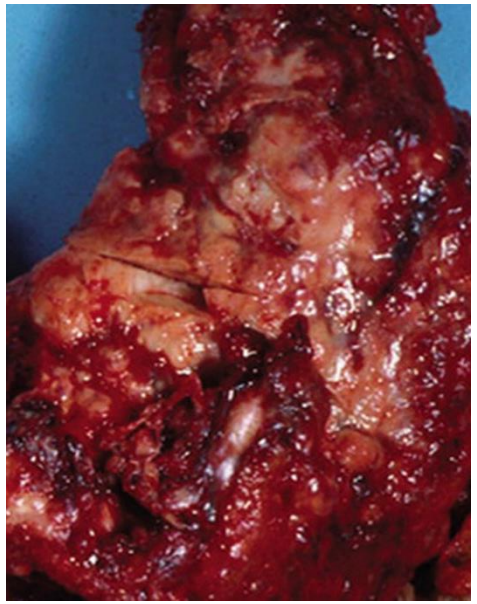
- Treatment
  - Excision
- Behavior
  - A rare case has recurred
    - In our study, 1/26 cases recurred
    - In Chen's study, no recurrences
    - In Daya's study, 1 patient alive with disease 4 years after diagnosis
  - Follow-up required

Mesothelioma of the Peritoneum in Women, Confounding Clinical Features

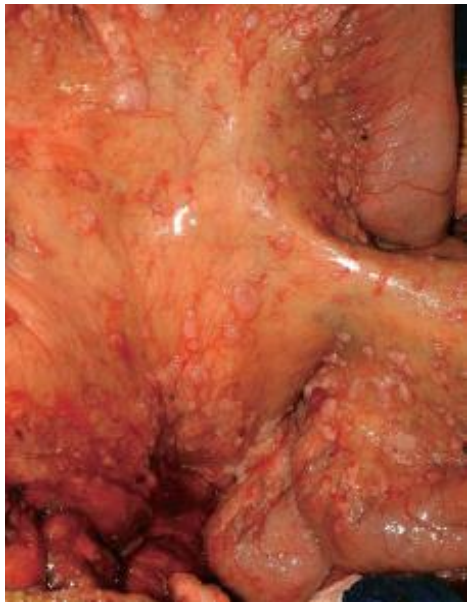
- Young pt 
- Elevated CA125
- Incidental finding
- No ascites
- Unusual symptoms:
  - Myasthenia gravis
  - Lymphadenopathy
  - Pain due to thrombosis

- Tumor detected in :
  - Endometrial biopsy
  - Pap smear

Gross



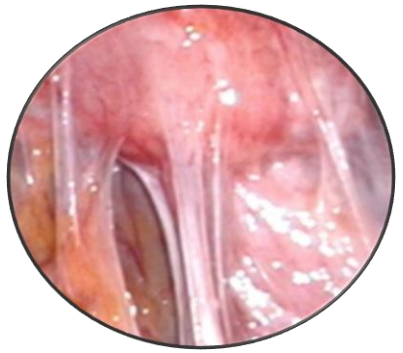
Plaques



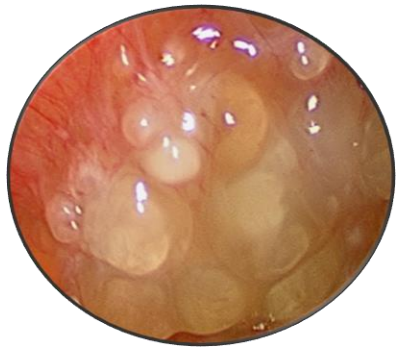
Nodules

Confounding Features

Adhesions



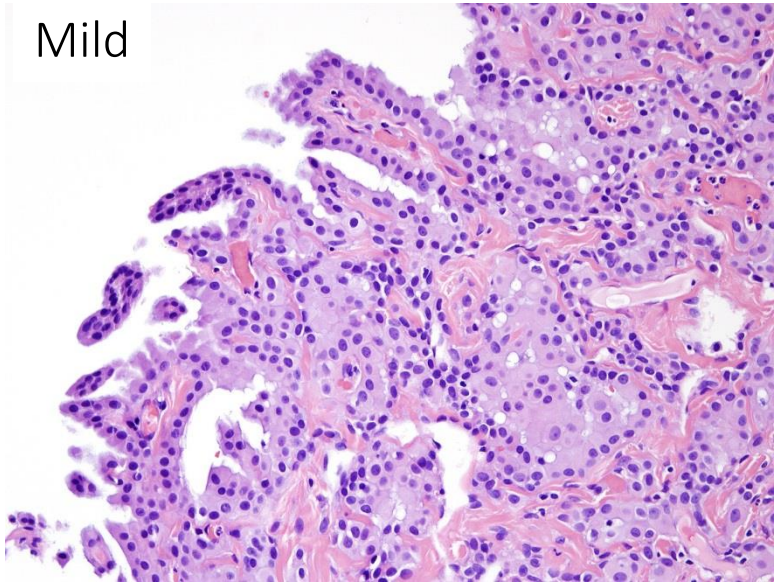
Gelatinous nodules

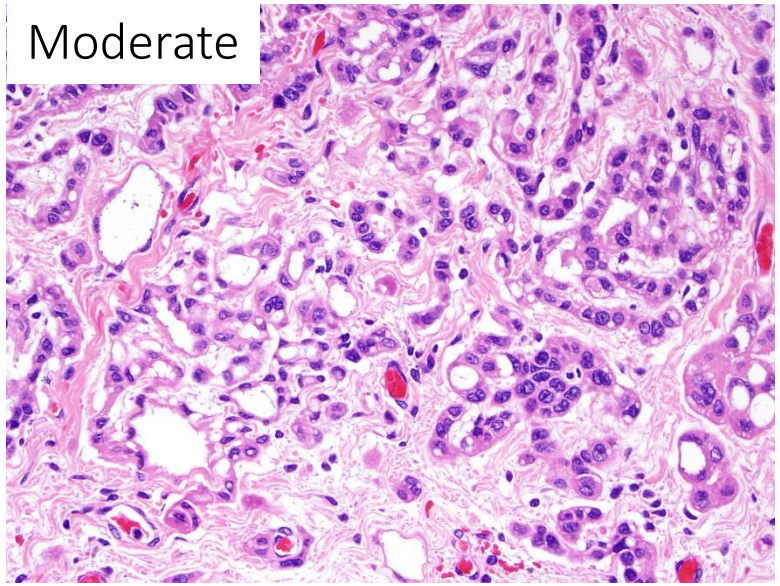


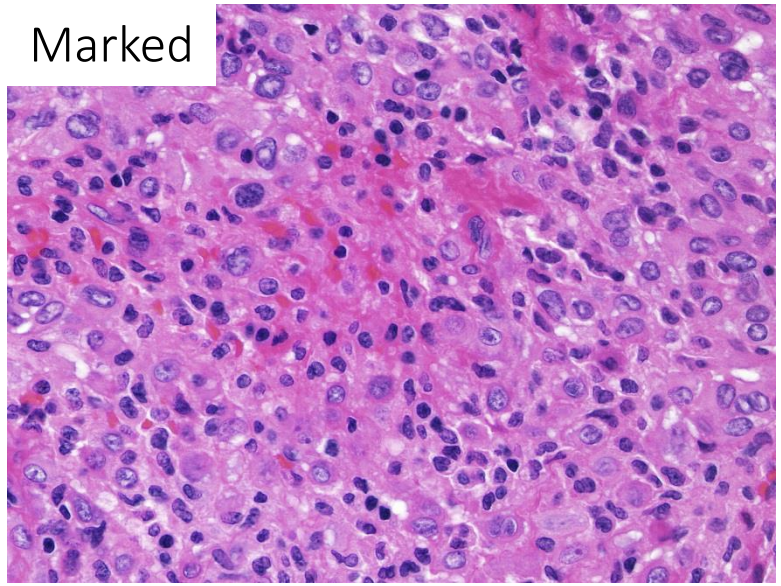
Mucinous Ascites

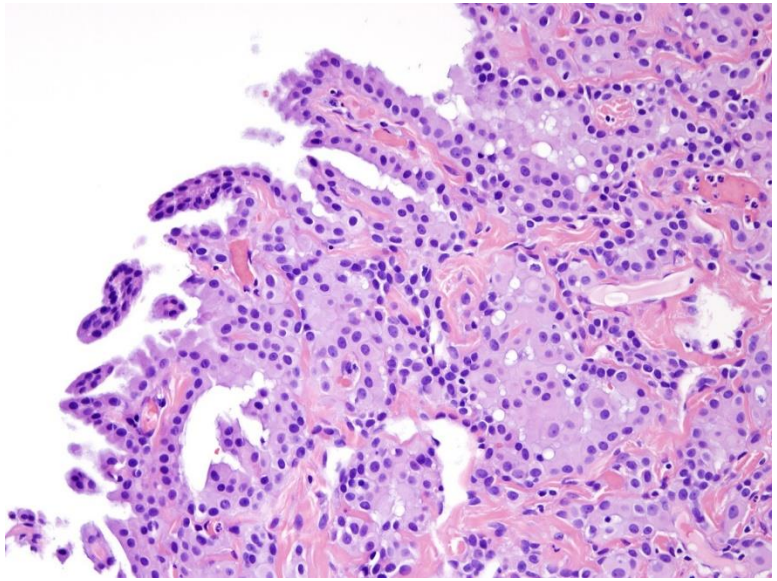
Histology

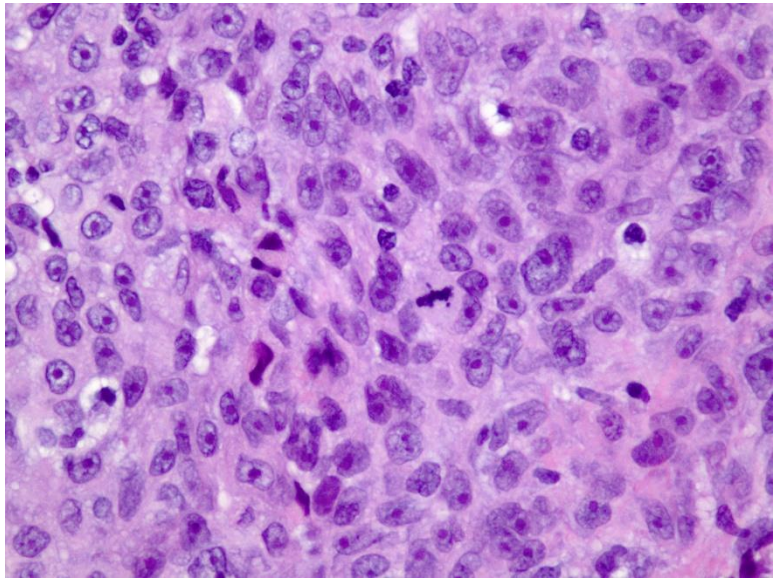
Atypia





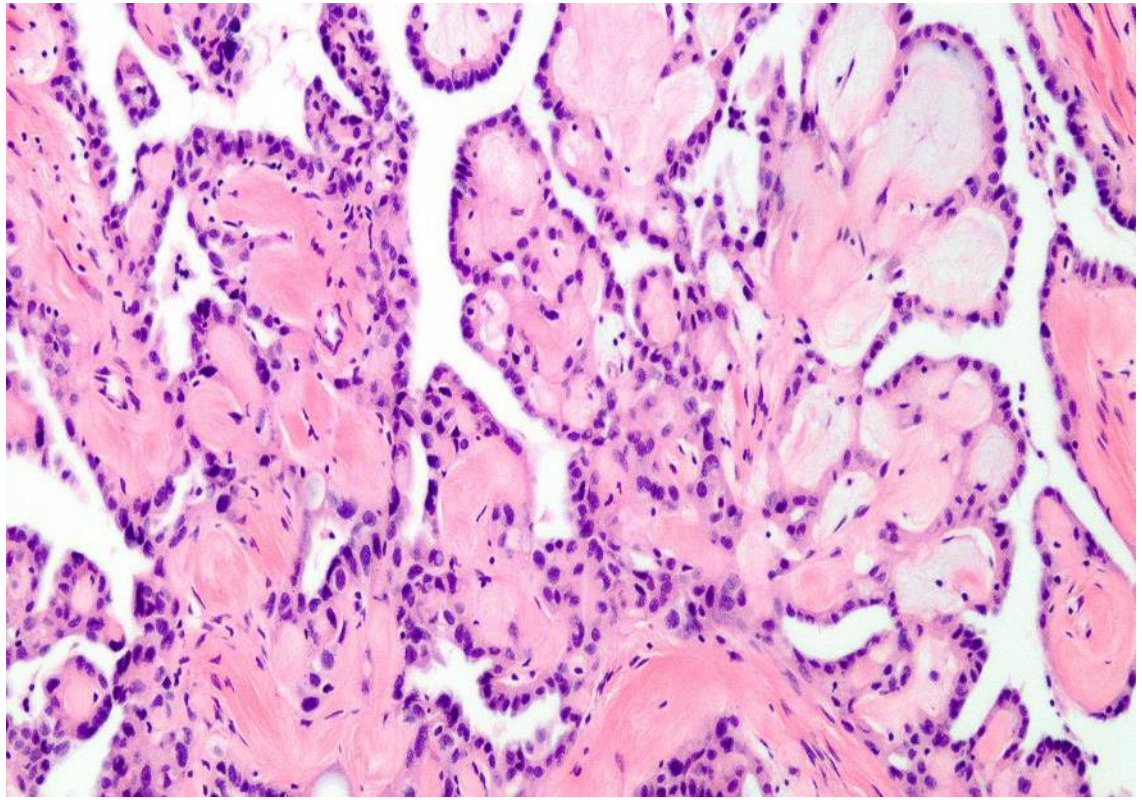


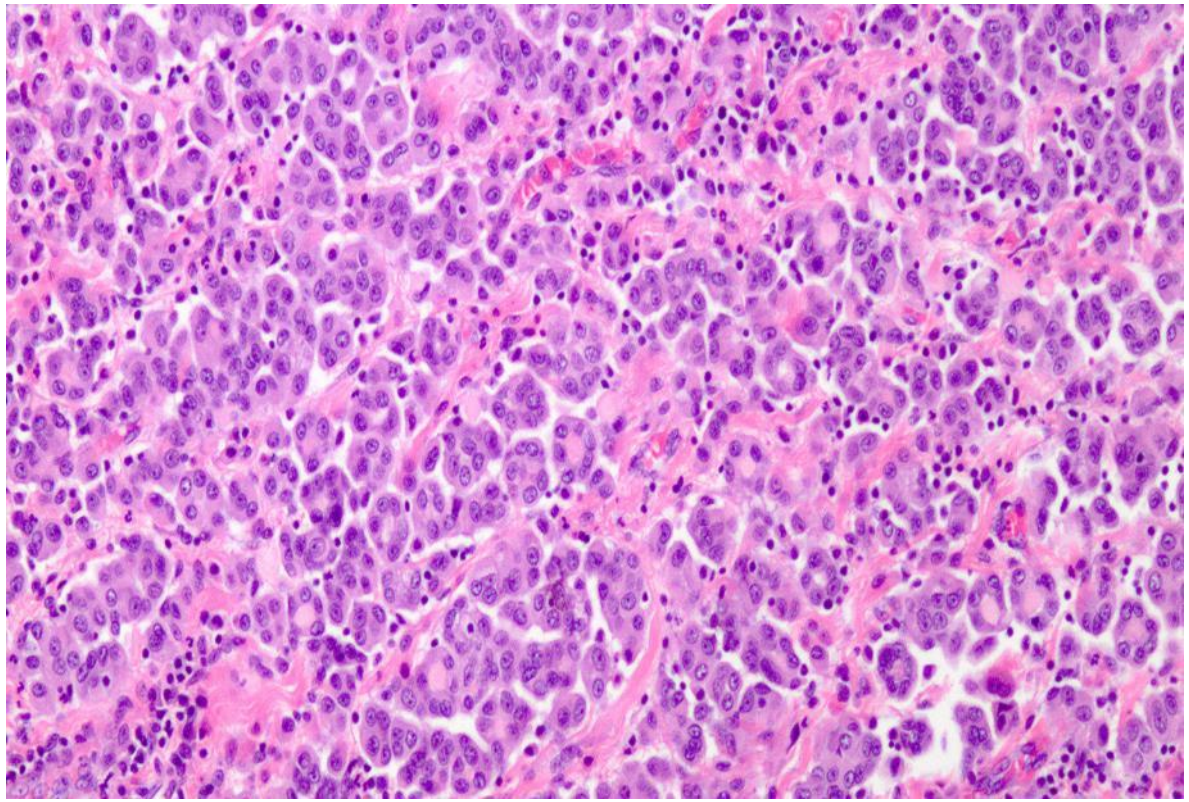




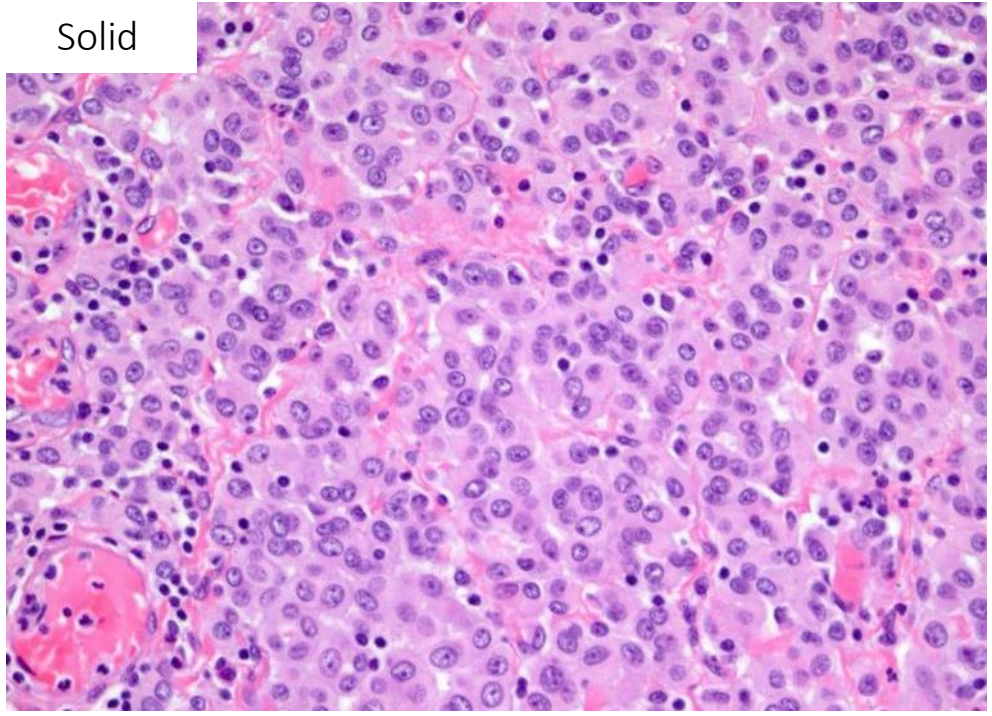
Variable mitotic index, usually low

Papillary Pattern

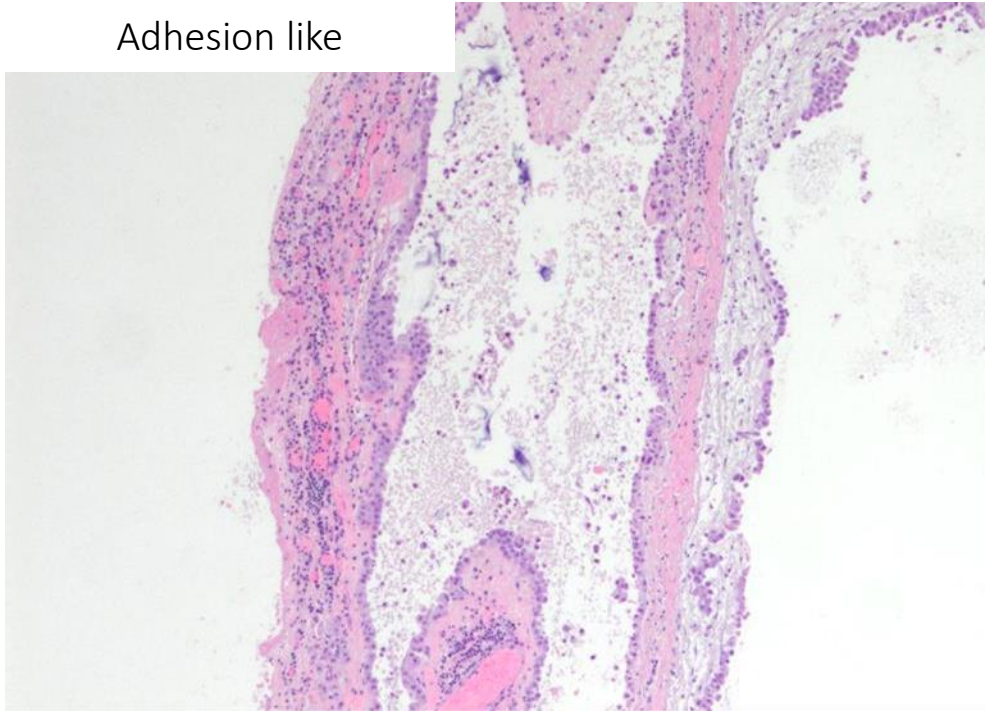




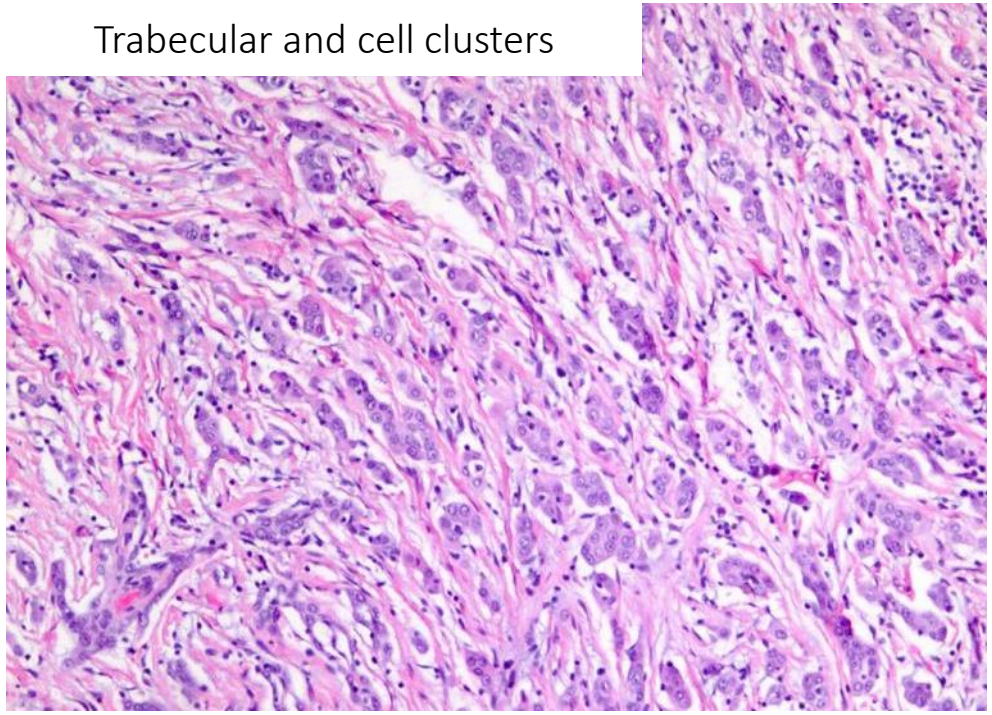
Solid



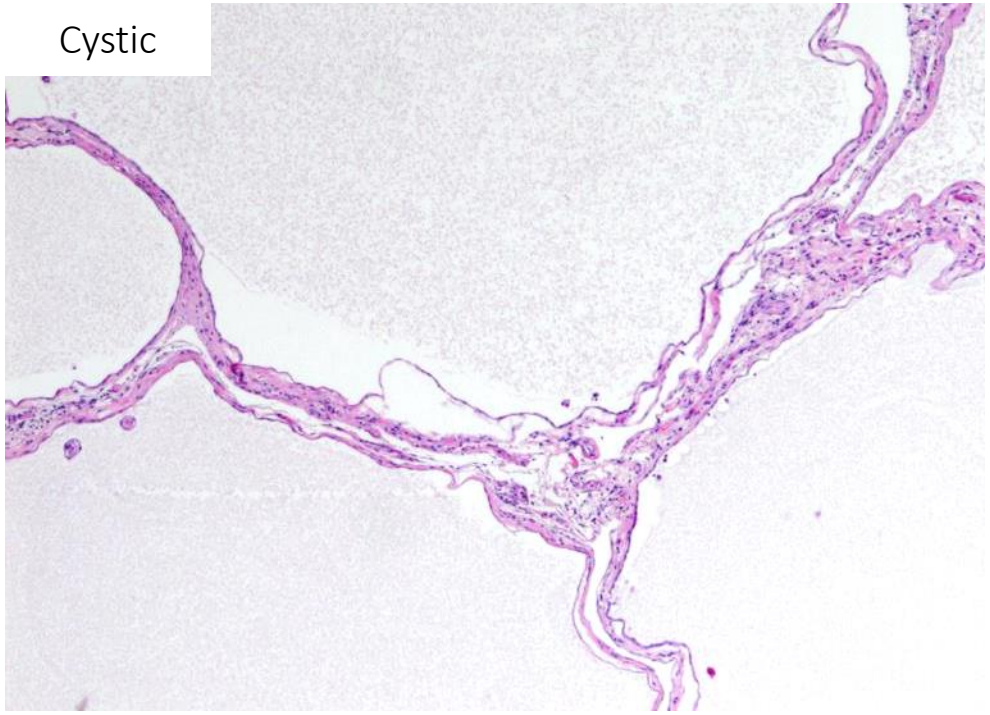
Adhesion like



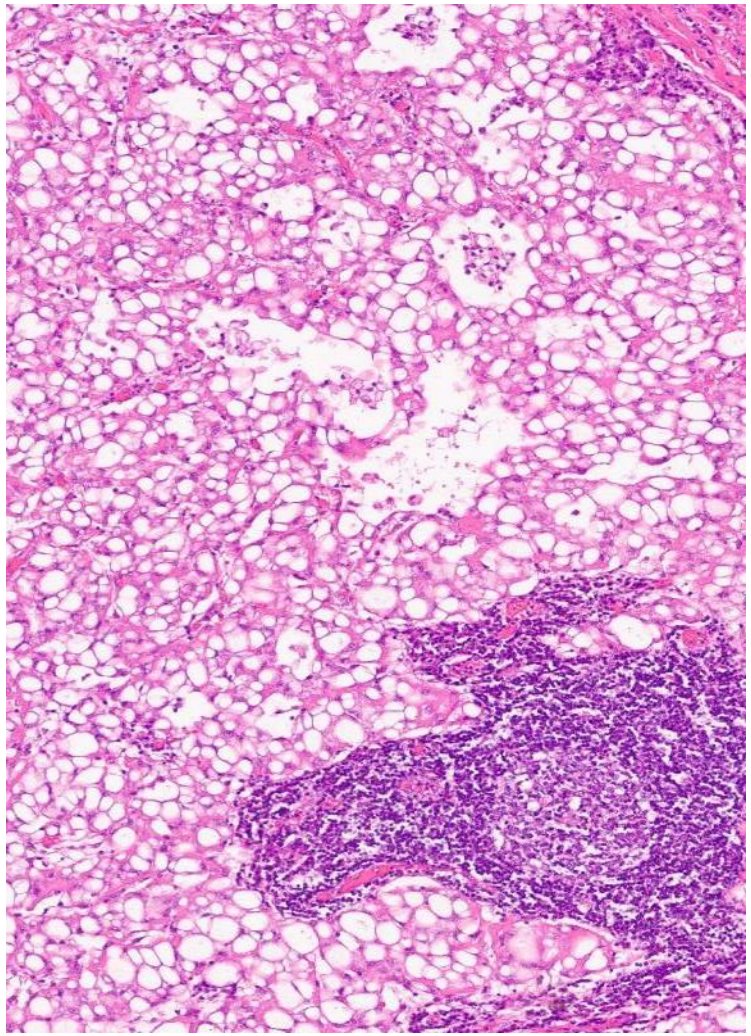
Trabecular and cell clusters



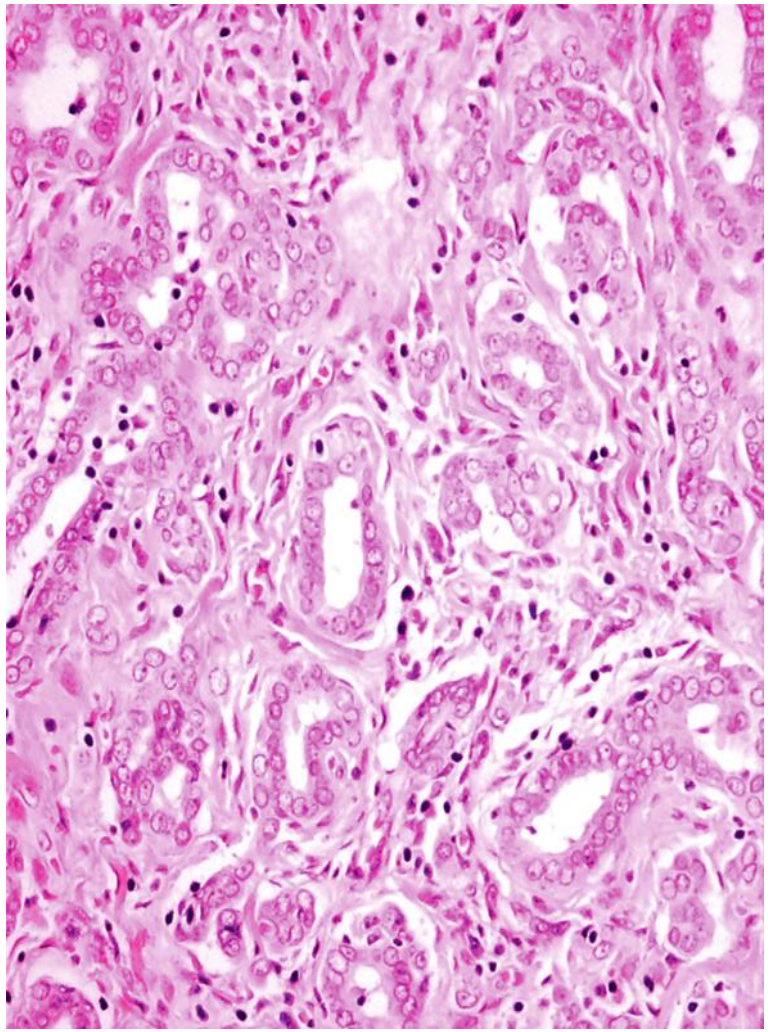
Cystic



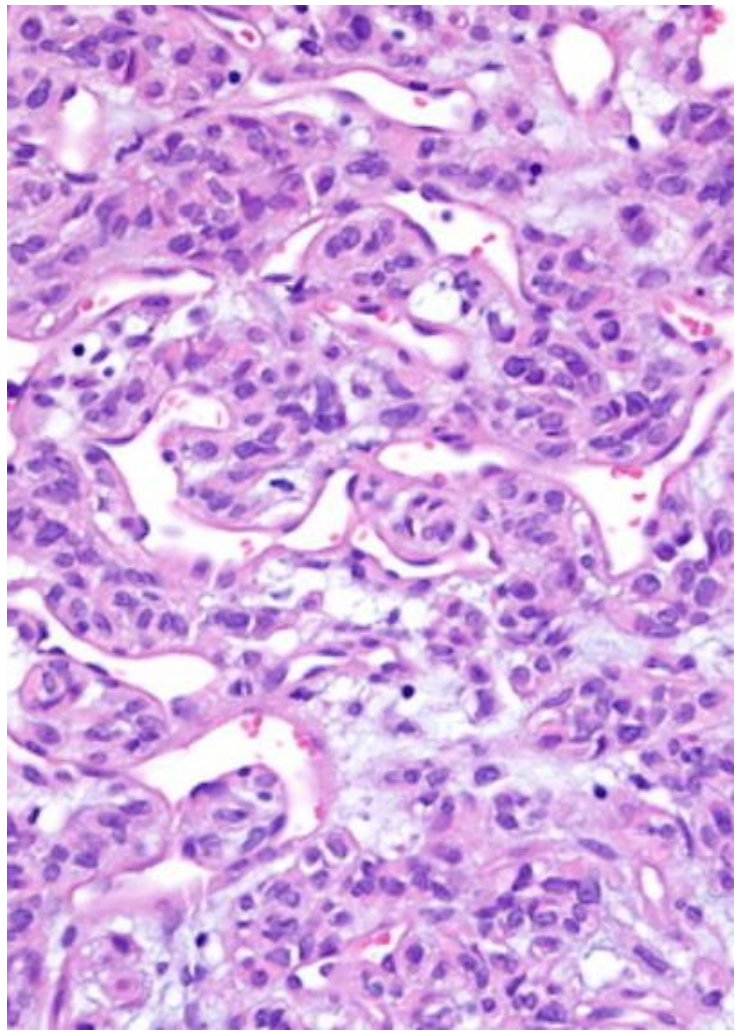
Adenomatoideo



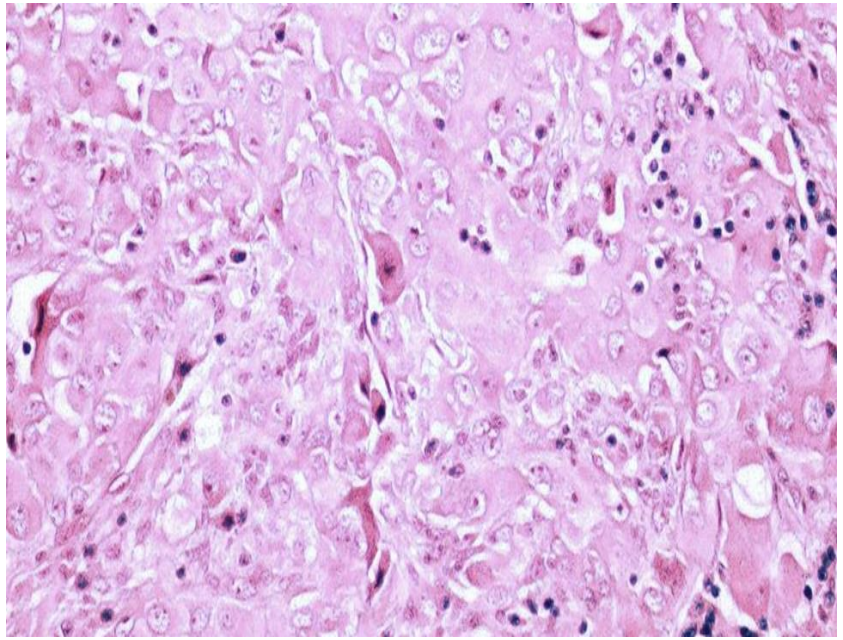
Tubular



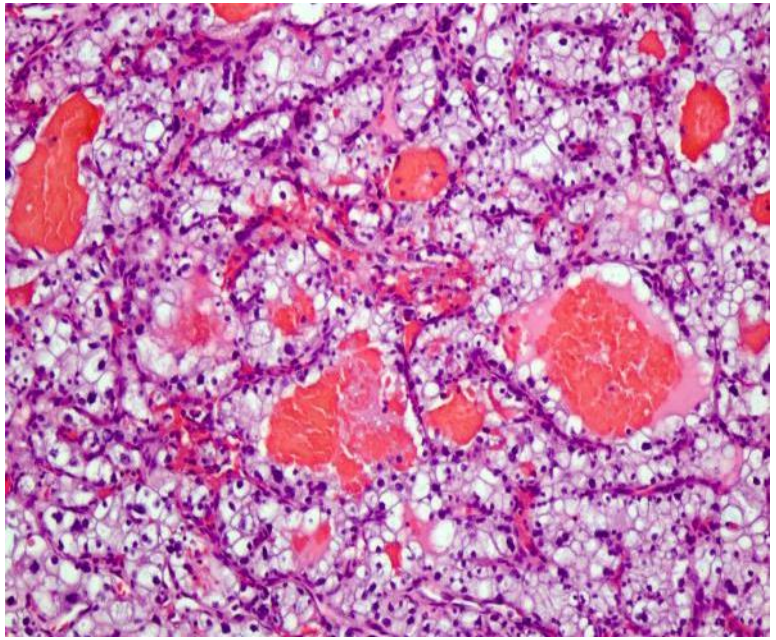
Hemangiopericitico



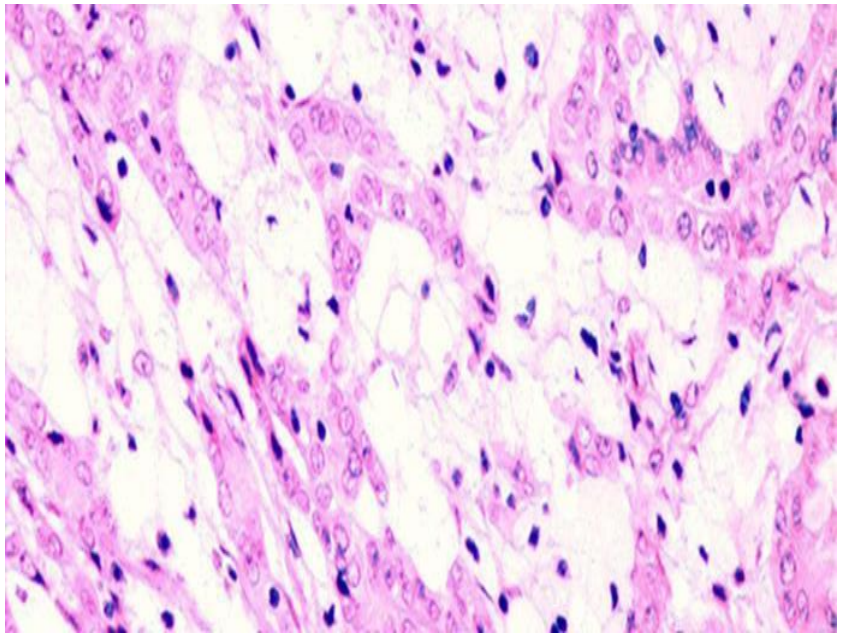
Deciduoid

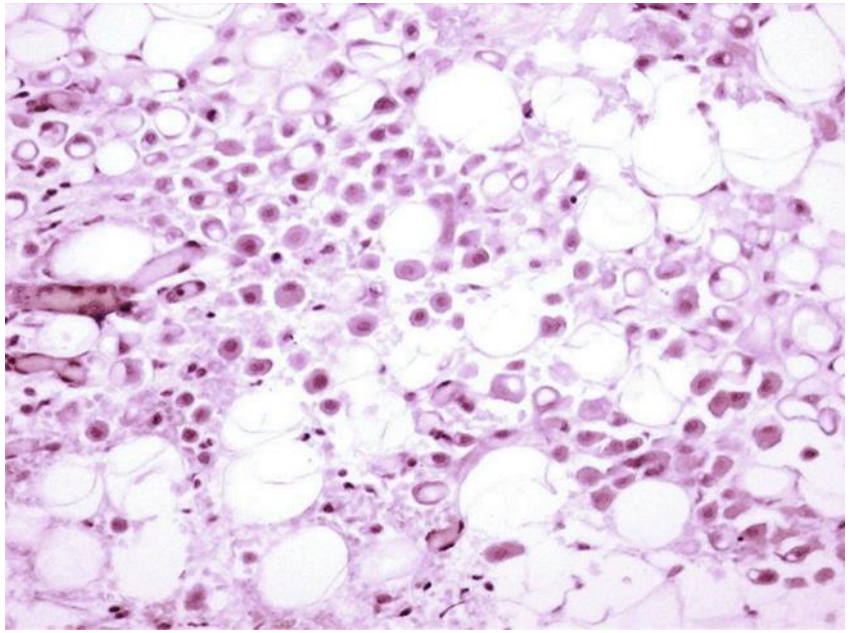


Clear cells

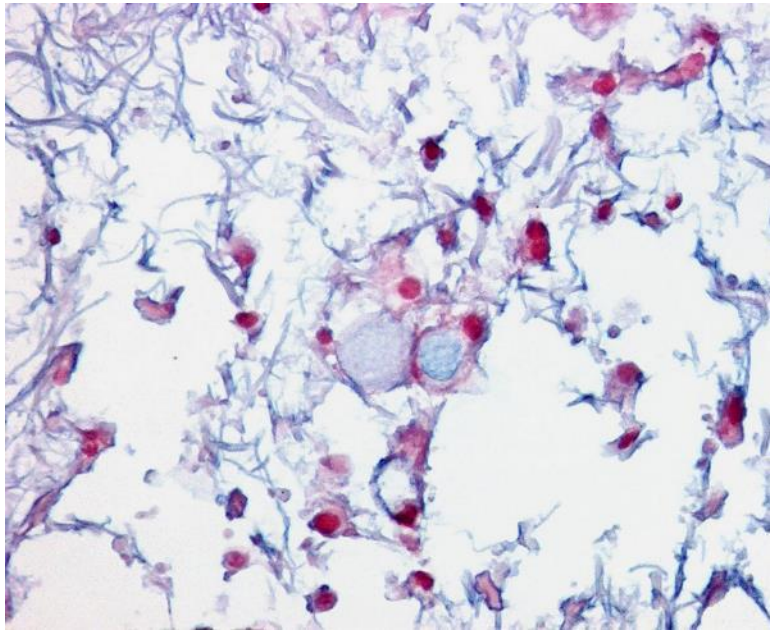


Numerous histiocytes

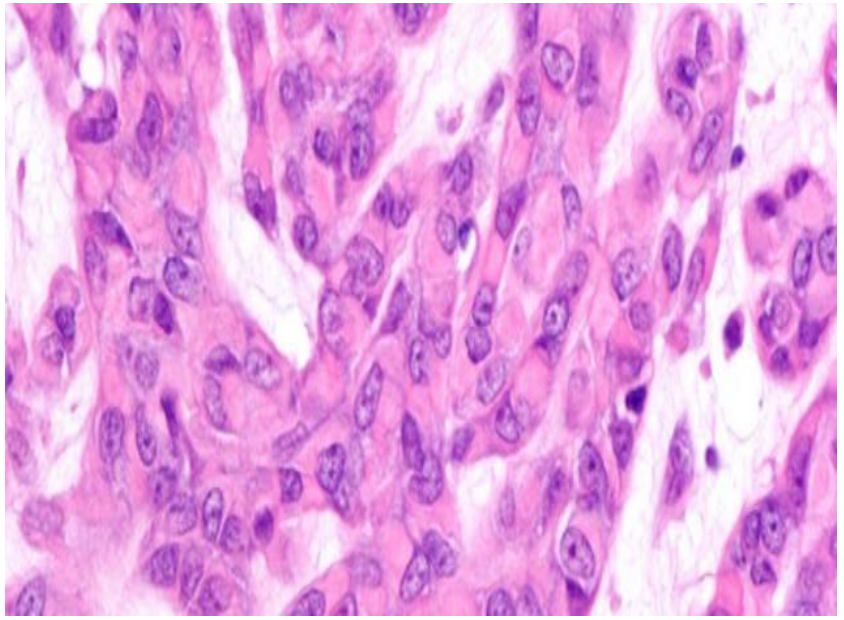




Signet ring cells

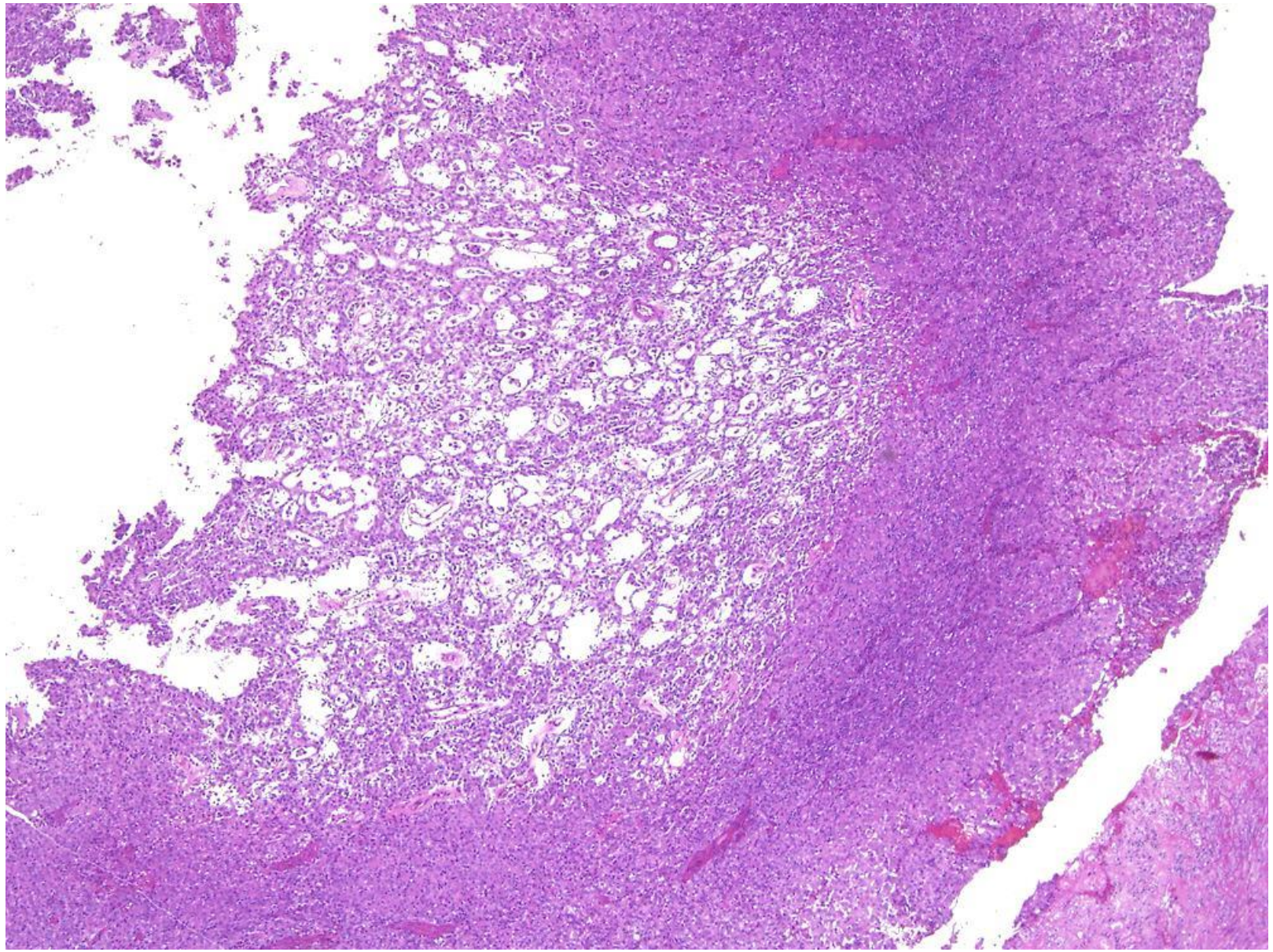


Signet ring cells, Alcian Blue, ph 2.5 +

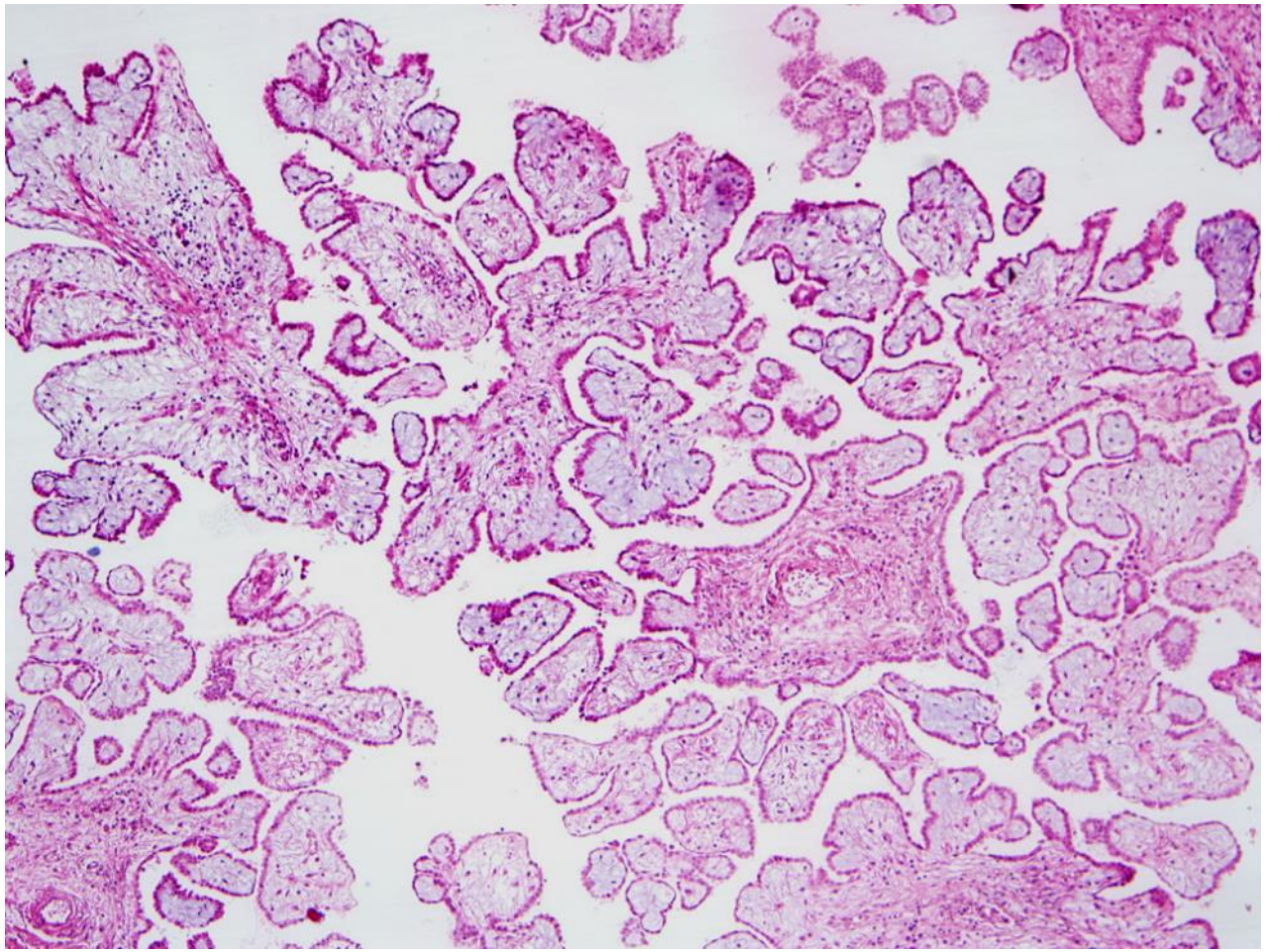


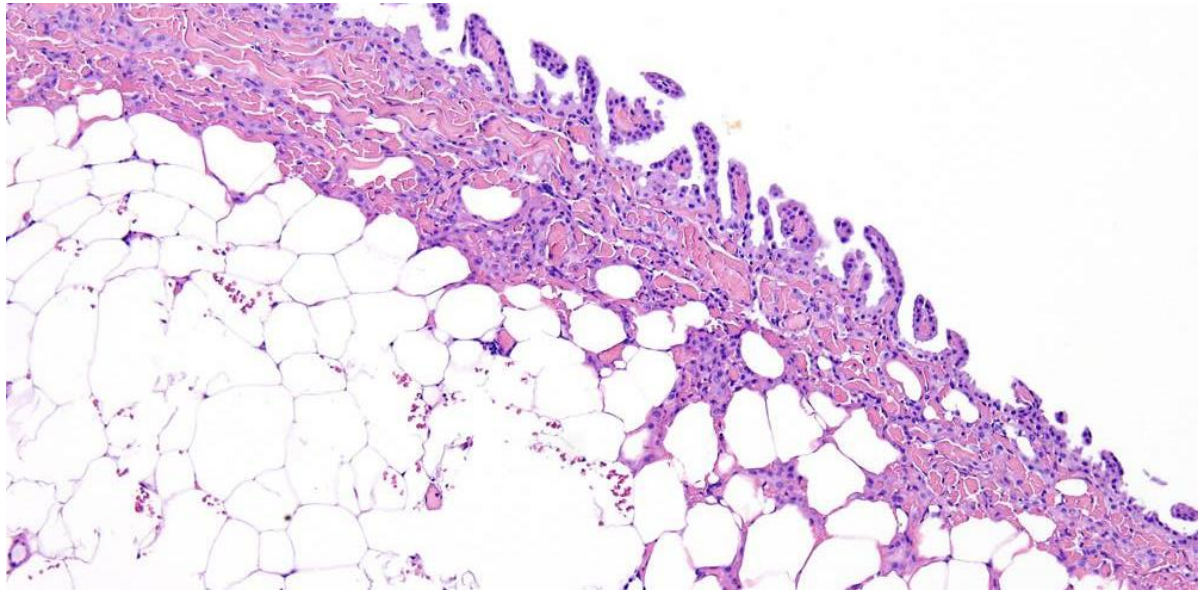
Rhabdoid cells

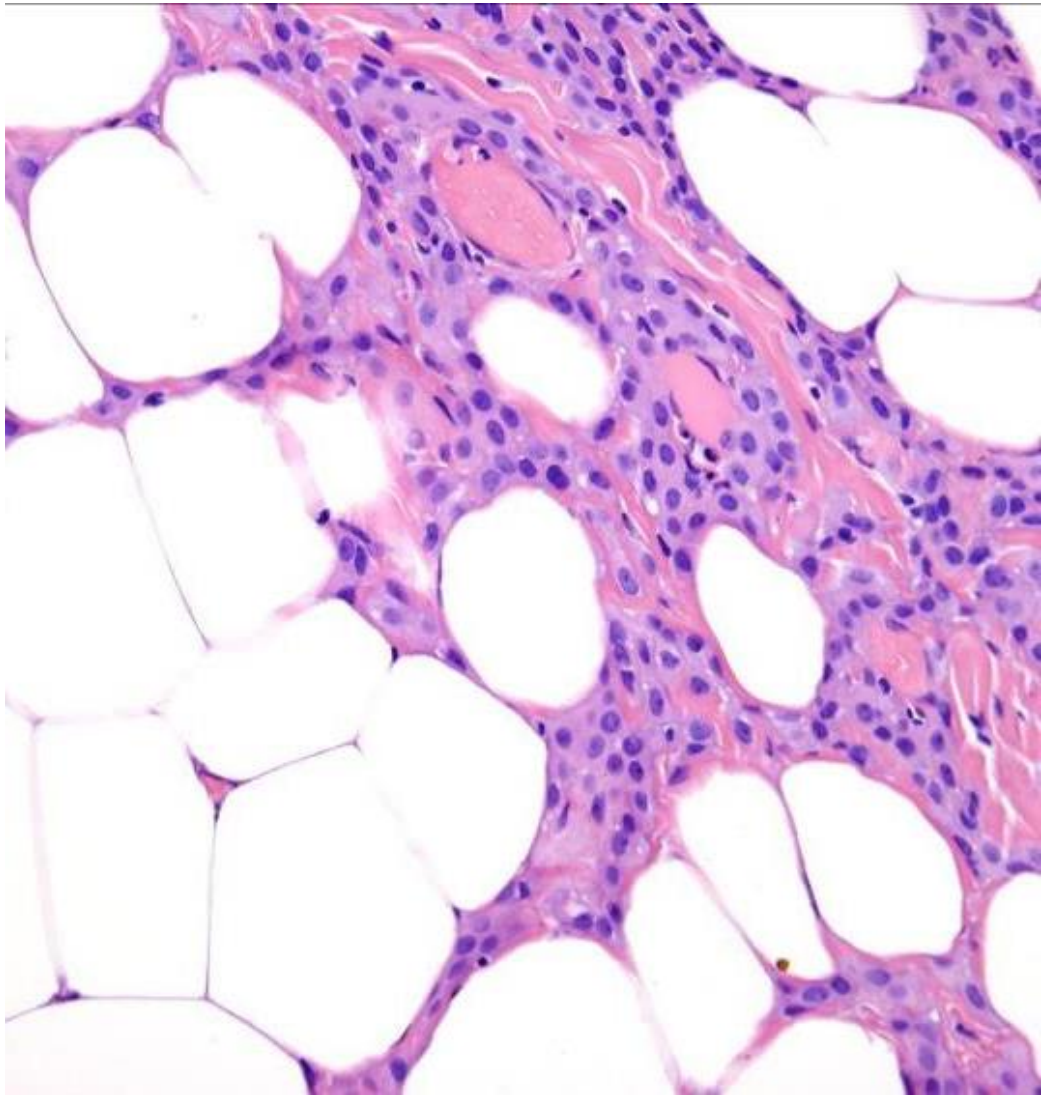
Forming a discrete and large mass –no invasion in the sections examined, this tumor measured 9 cm and was located in the cul de sac

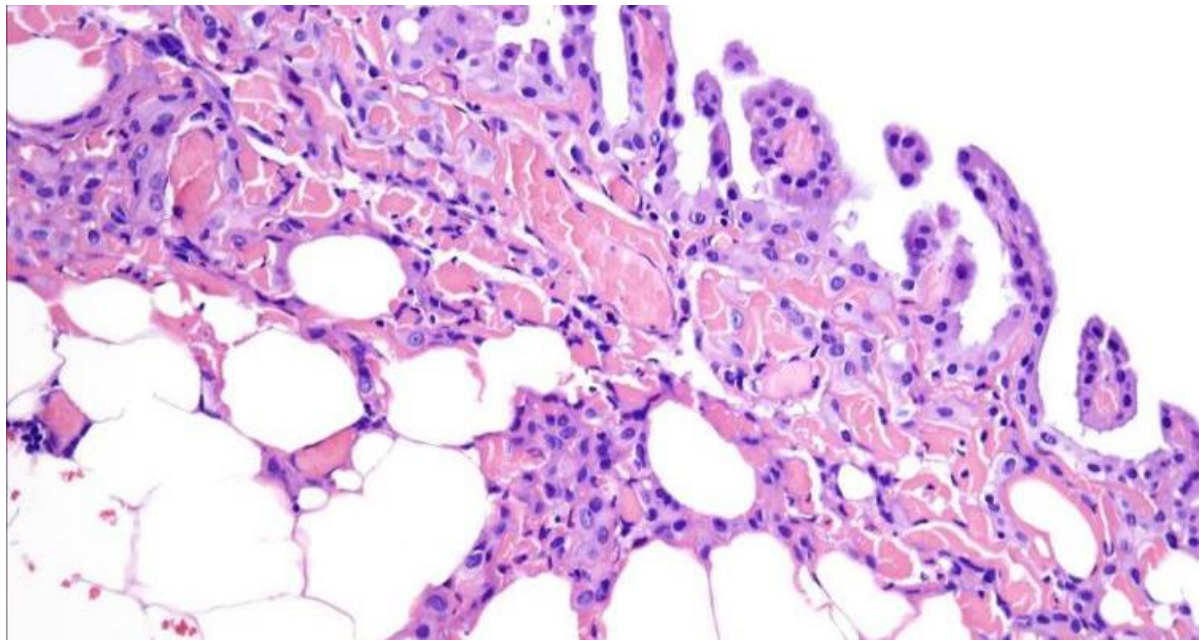


Mesothelioma mimicking a well differentiated papillary mesothelial tumor, but with diffuse involvement of the peritoneum



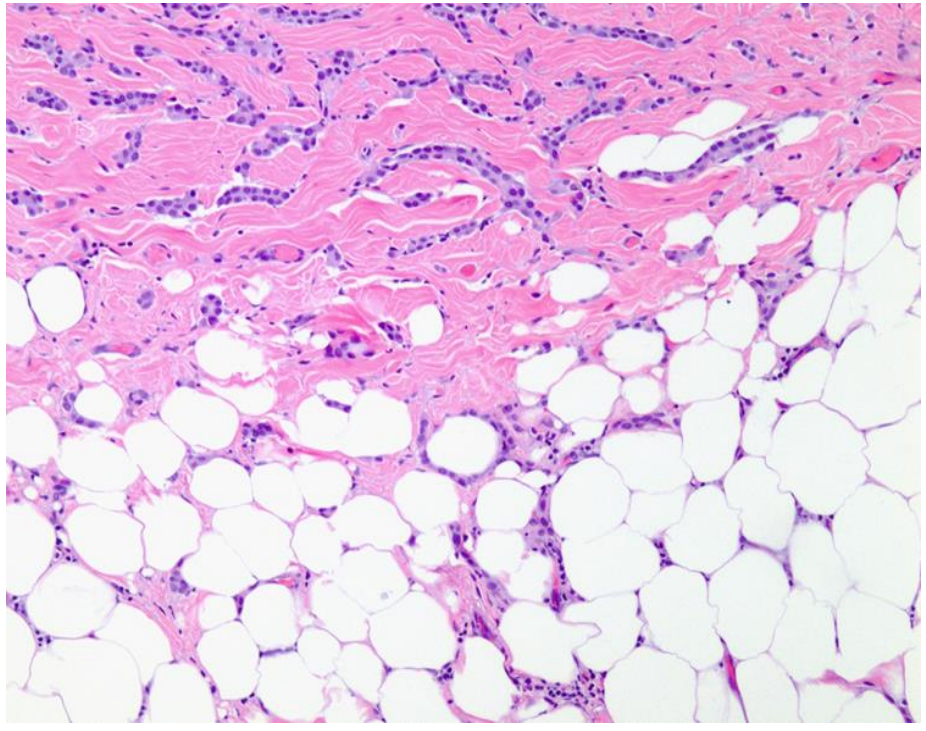


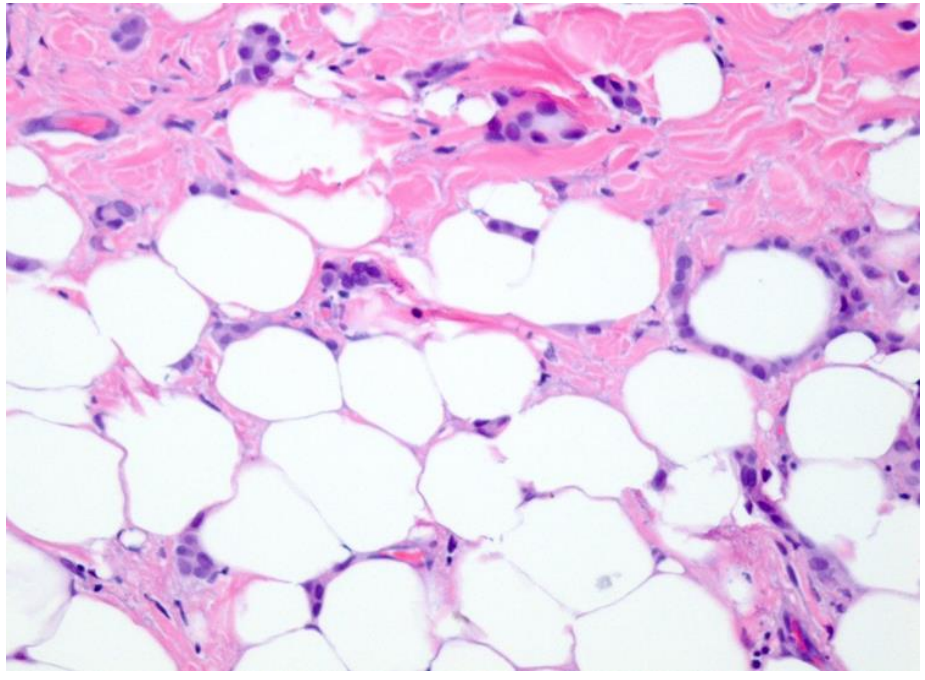


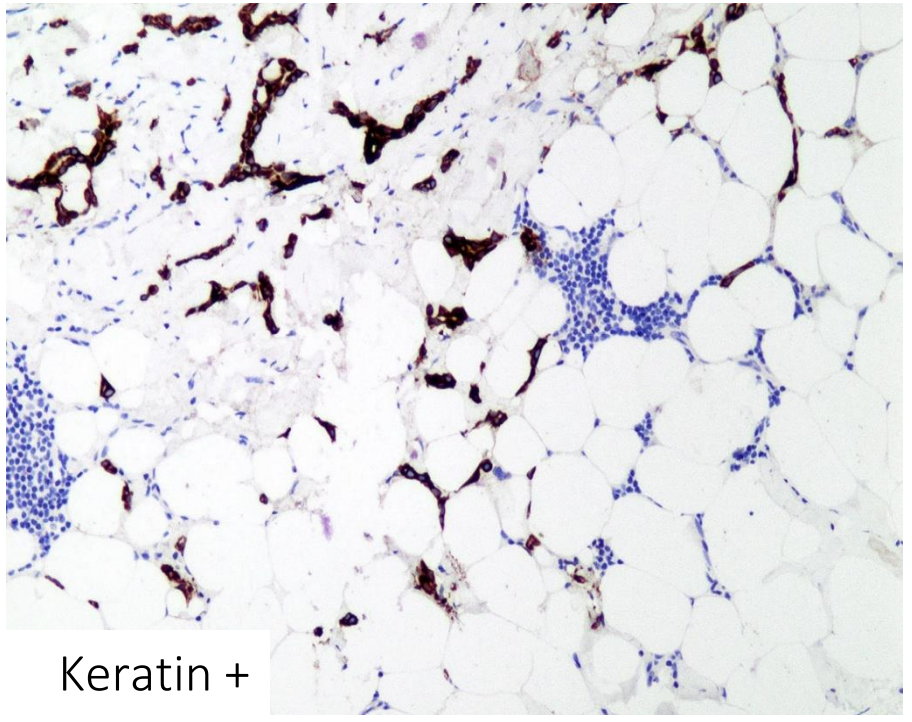


Focal Invasion

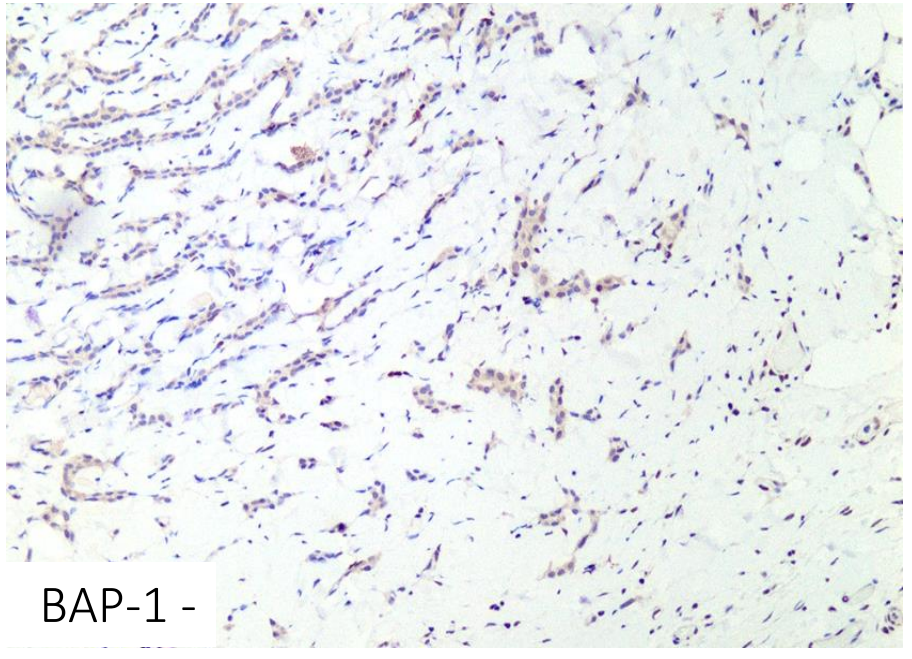
Mesothelioma as an Incidental Finding



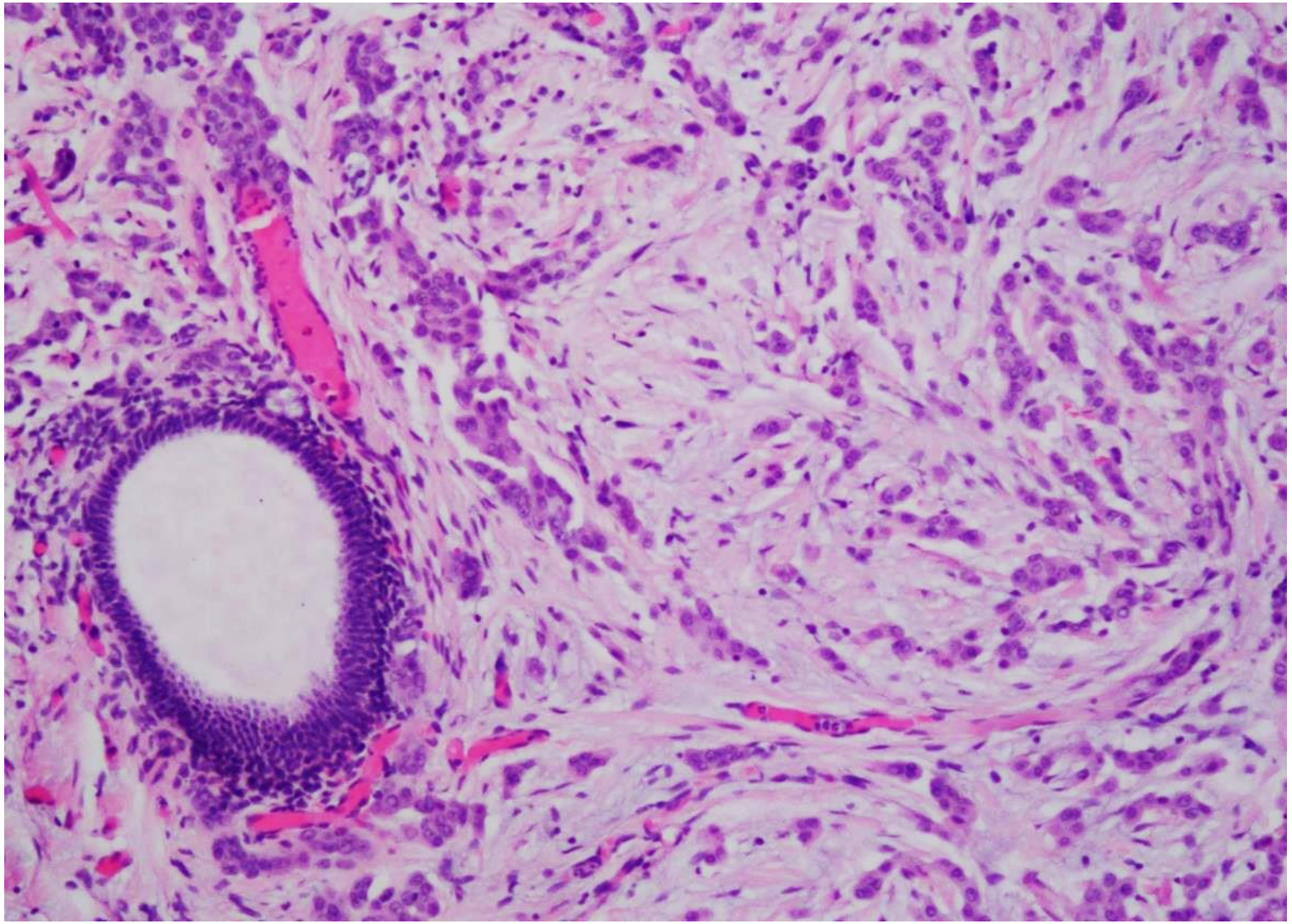




Keratin +

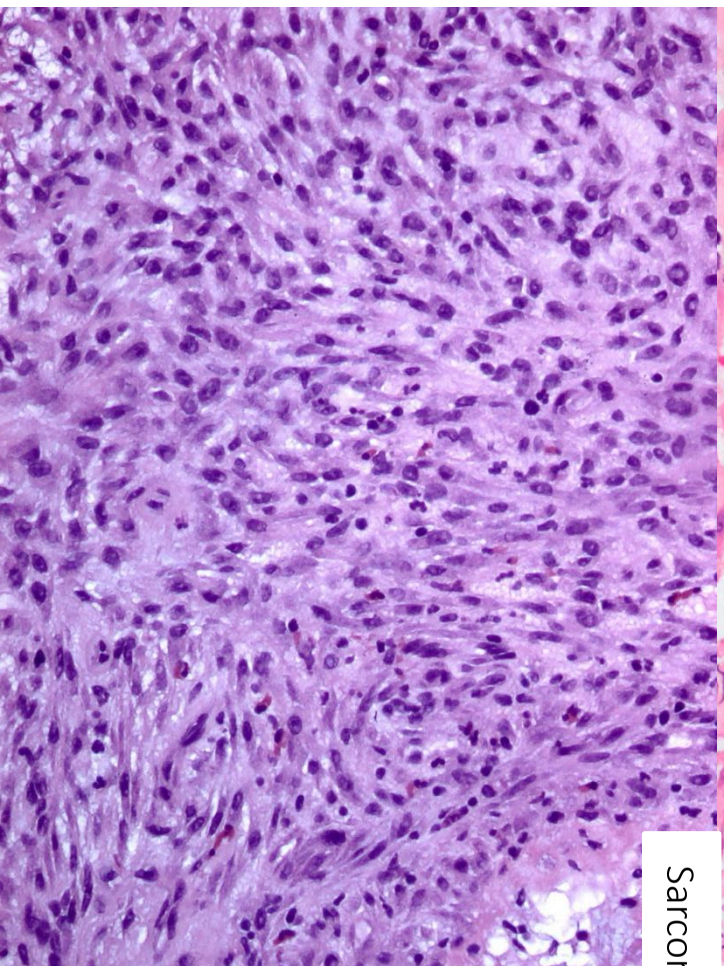


BAP-1 -

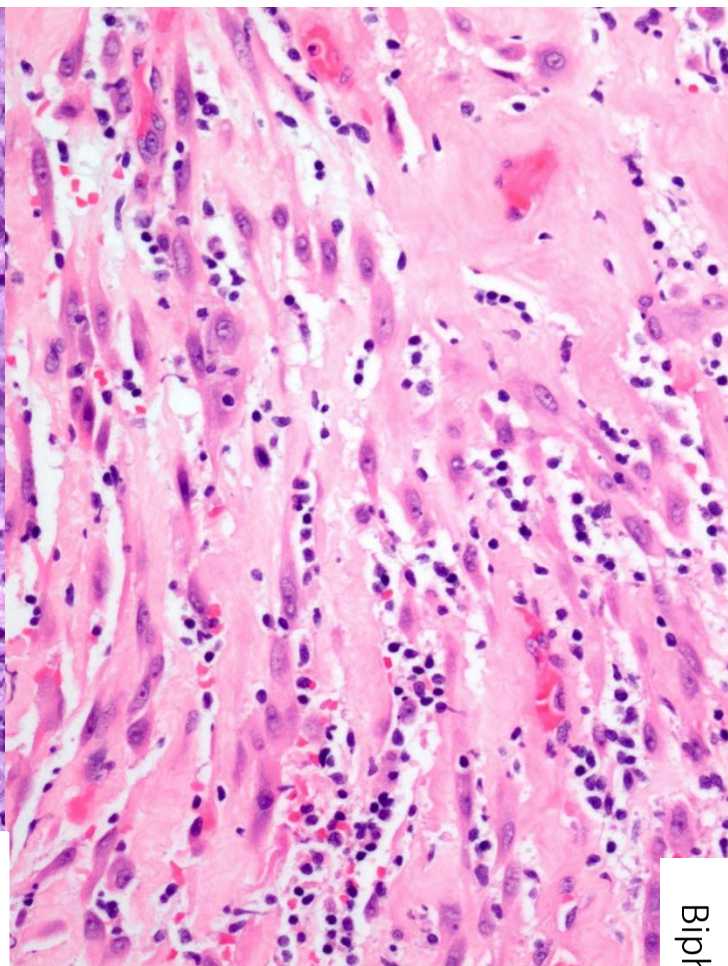


Mesothelioma and endometriosis

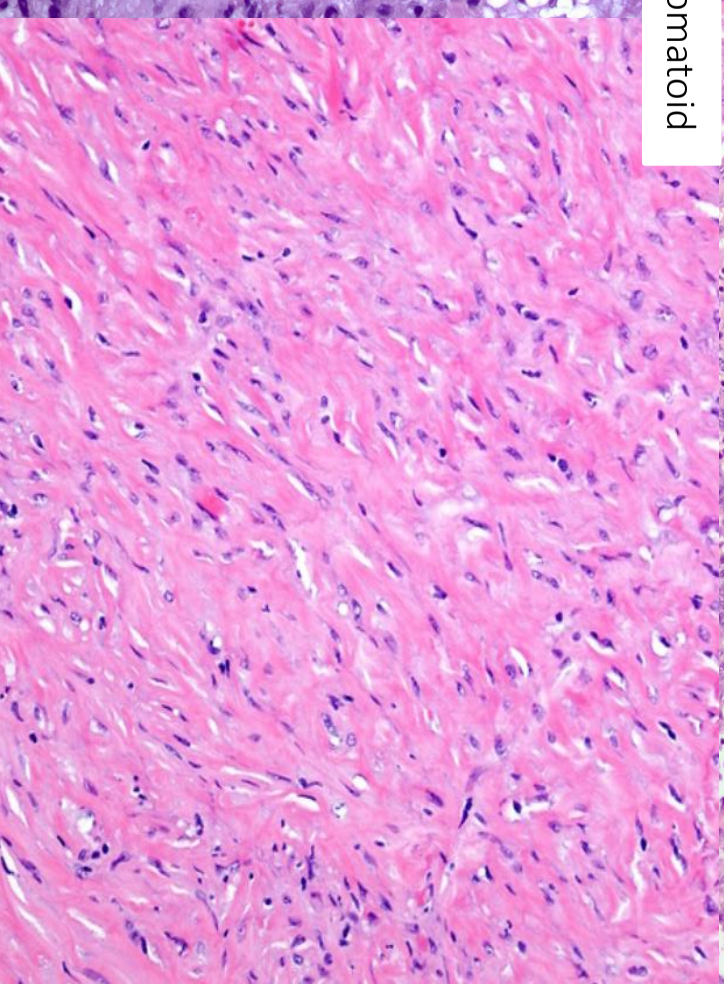
Calretinin and D2-40, best markers for spindle cell morphology

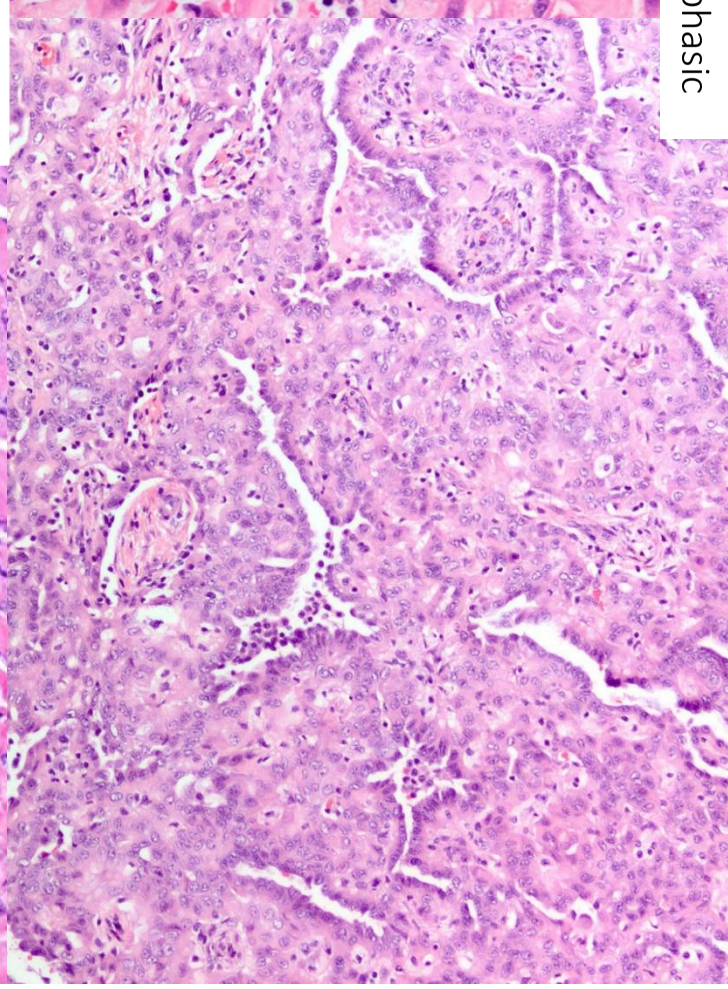


Sarcomatoid

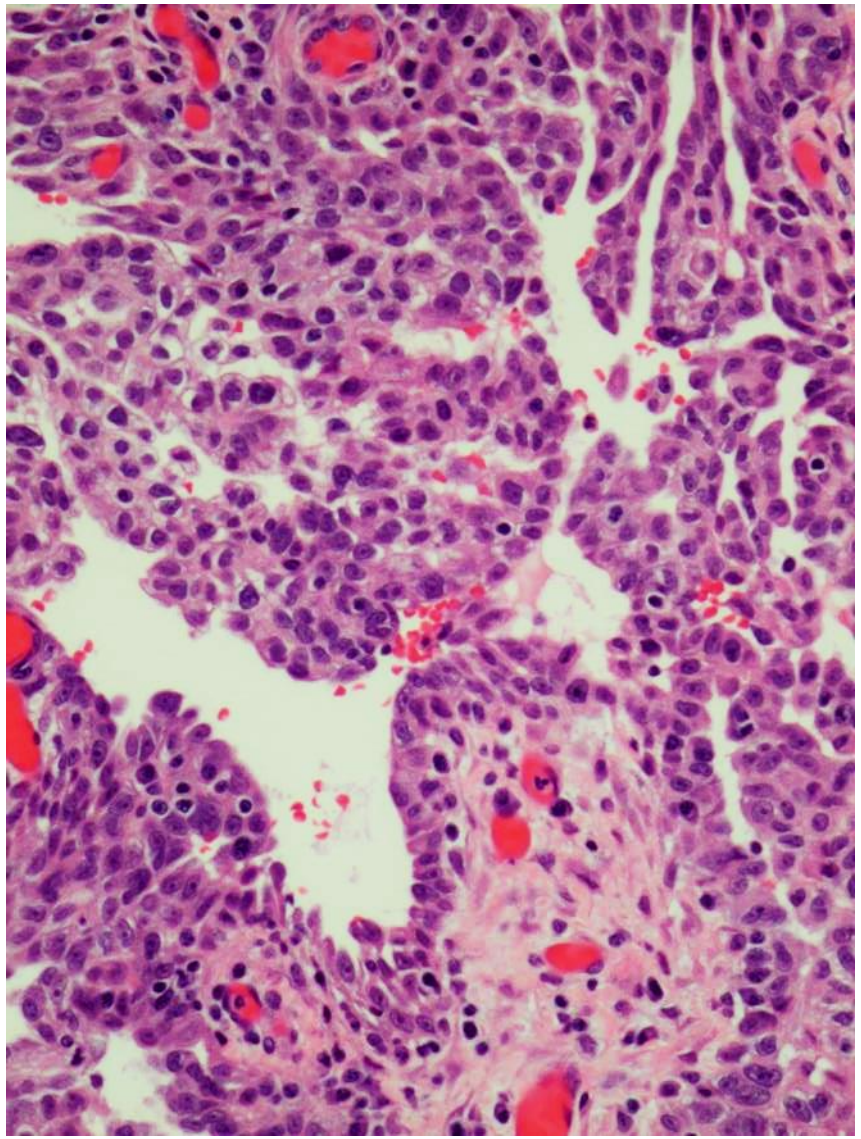


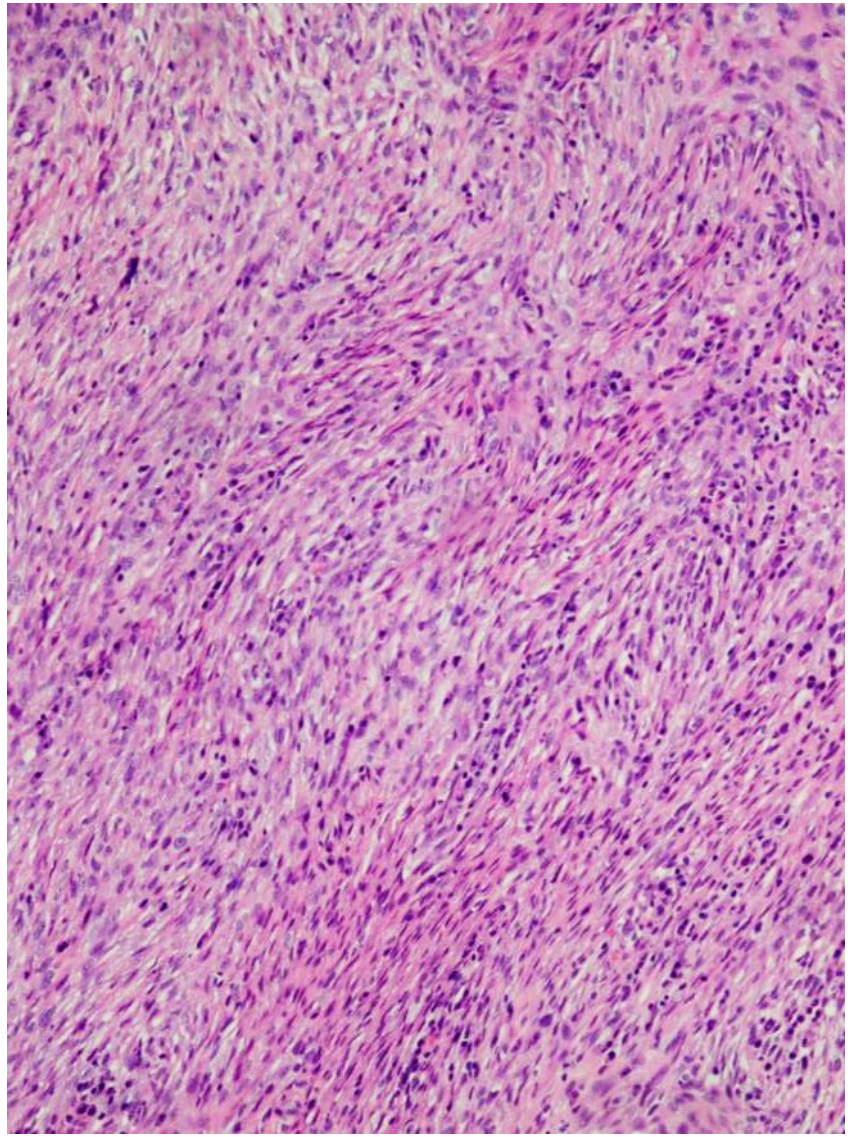
Biphasic

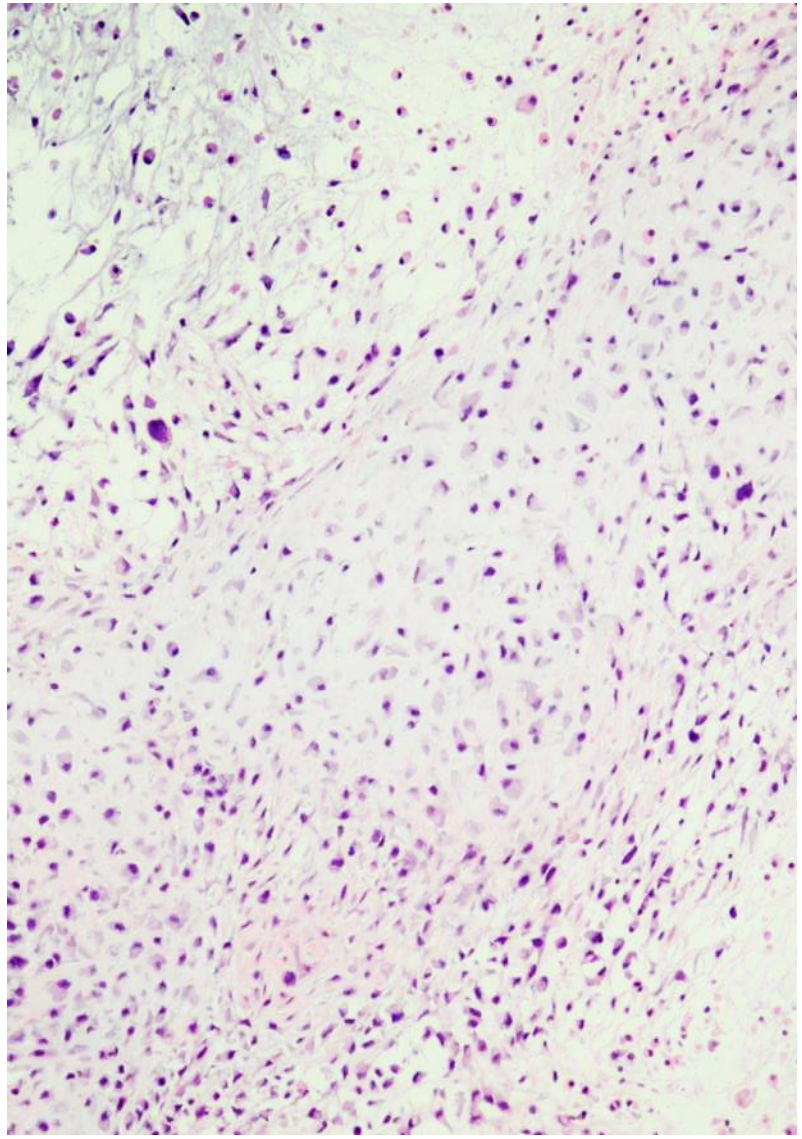




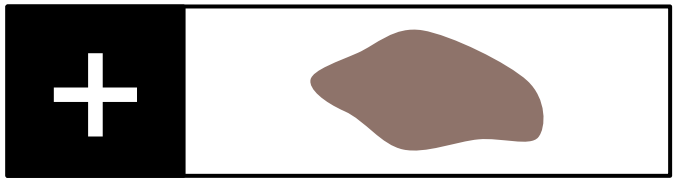
Mesothelioma, Biphasic, with Cartilage



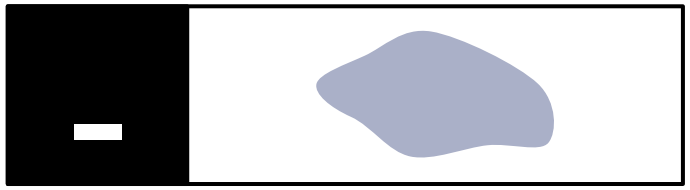




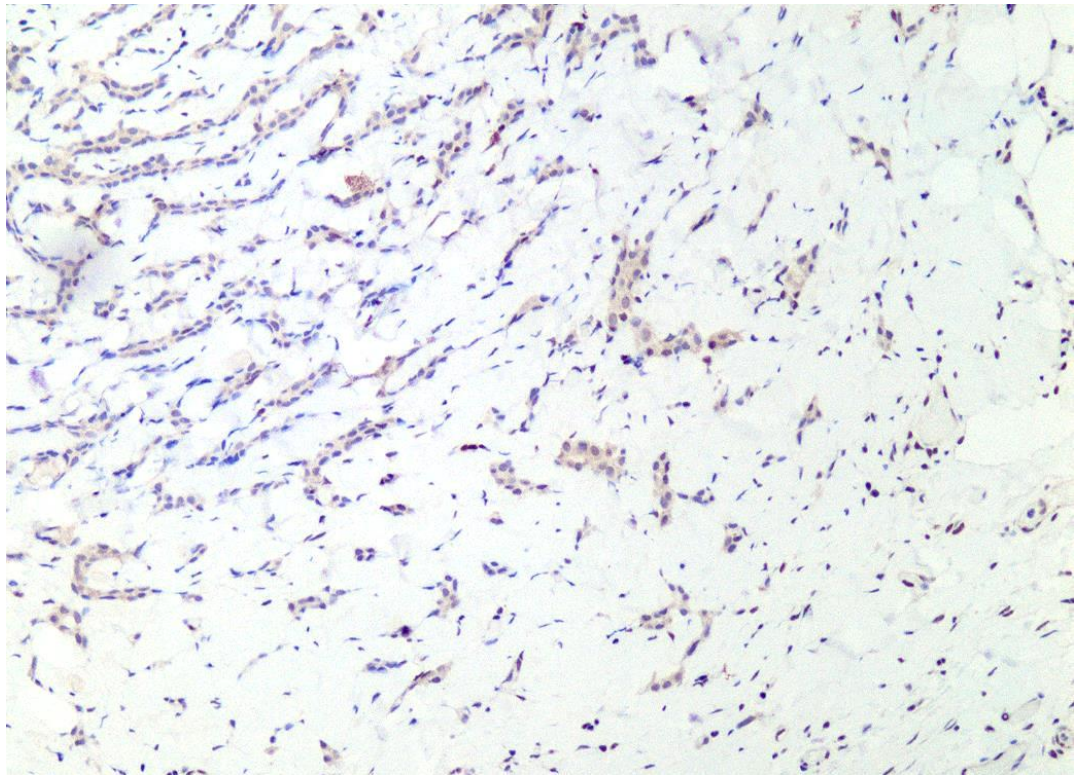
Mesothelioma of the Peritoneum – IHC Features



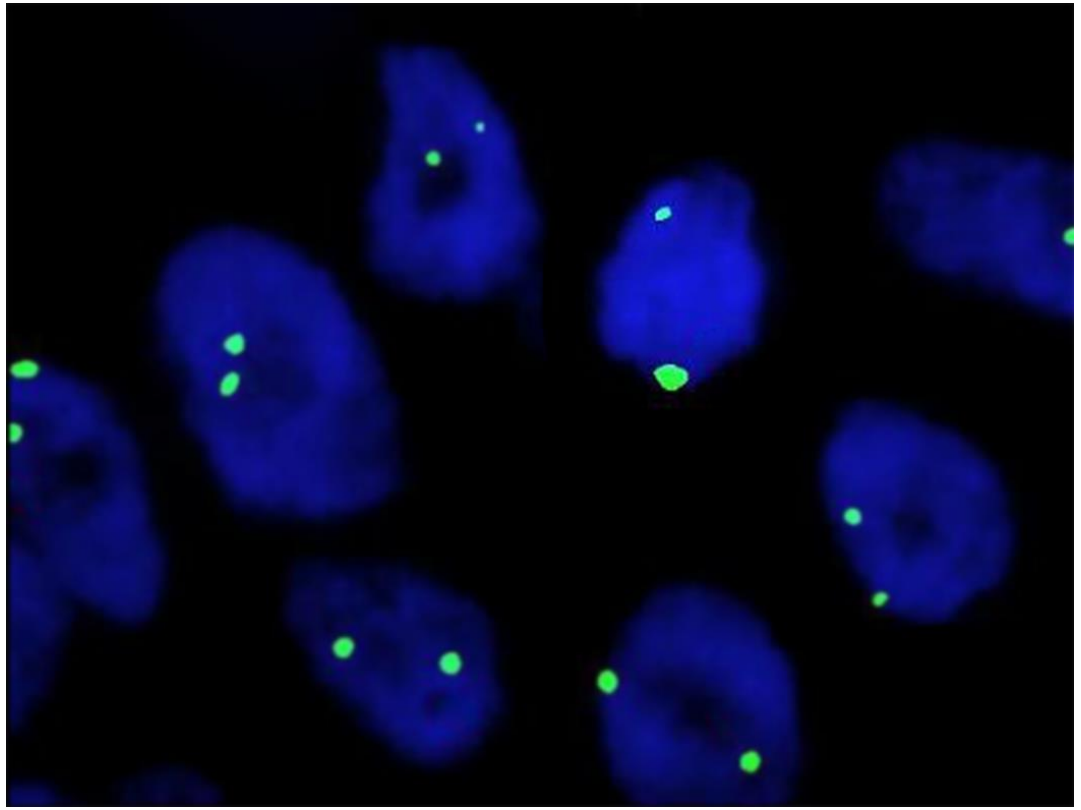
- Keratin cocktail
- Keratin 7
- WT-1
- Calretinin
- Keratin 5/6
- D2-40
- Thrombomodulin
- Mesothelin
- GATA-3



- PAX-8
- Claudin 4
- Ber-EP4
- MOC-31
- B72.3
- ER/PR



IHC: BAP1 loss
40 to 60% of cases

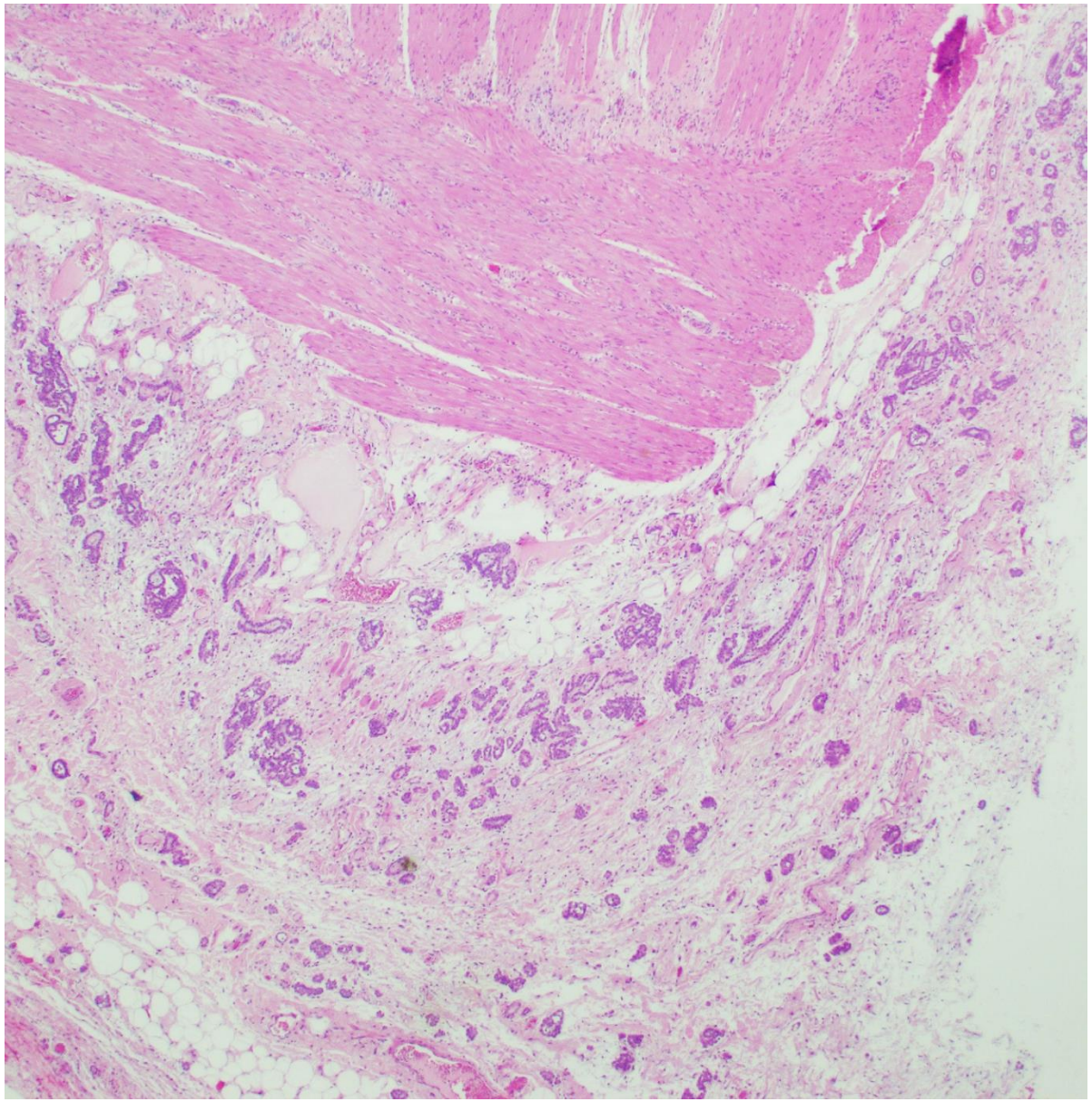


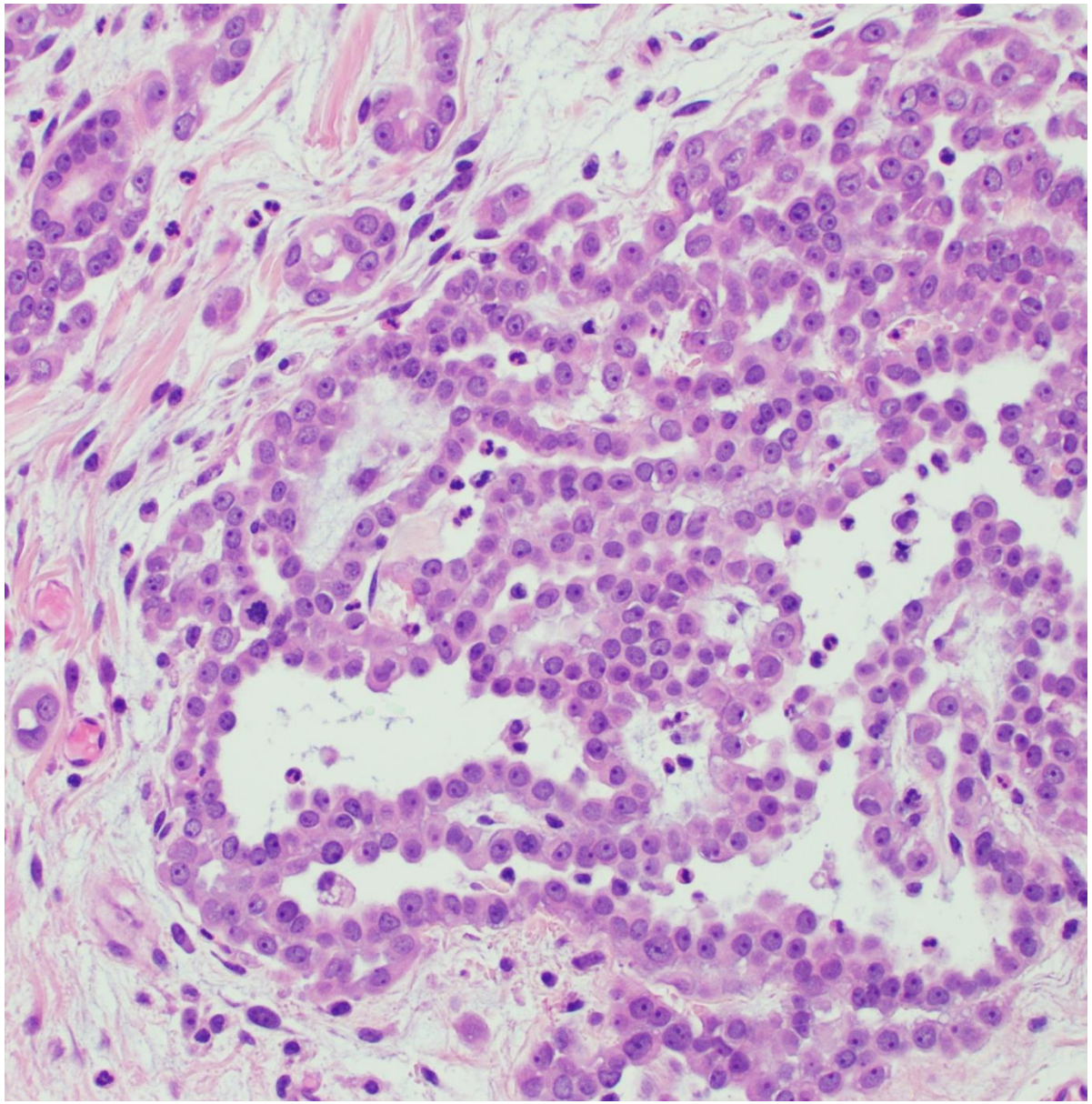
FISH: Homozygous deletion *CDKN2A (*p16)
30-50% of cases
This finding can be seen in other tumors
Mesothelial lineage has to be confirmed first

Molecular Features

- Alterations in:
  - *BAP1, SETD2, NF2, CDKN2A/B, LASTS1/2, PBRM1, TP53, PTEN,* DDX3X, *TRAF7, VHL,* and *SMARCC1*

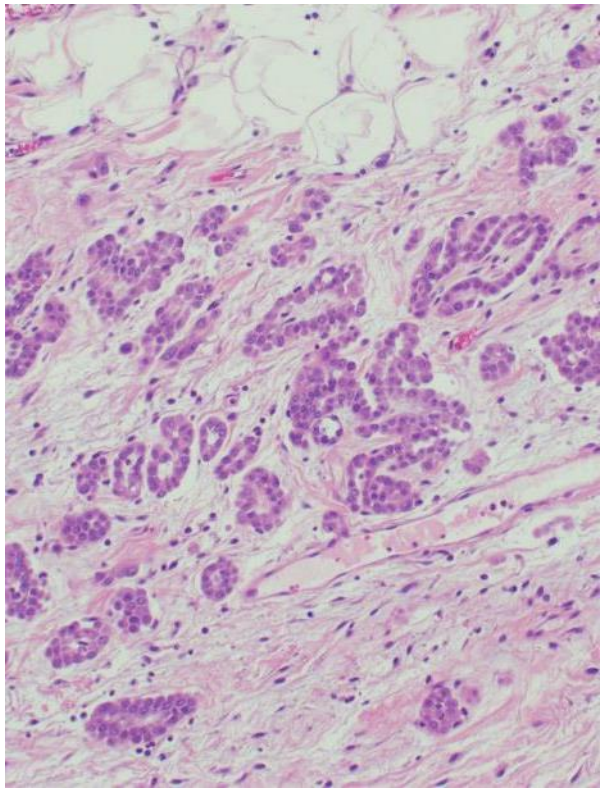
- In children and young adults
  - *ALK* rearrangements
  - *EWSR1/FUS-ATF1* gene fusions

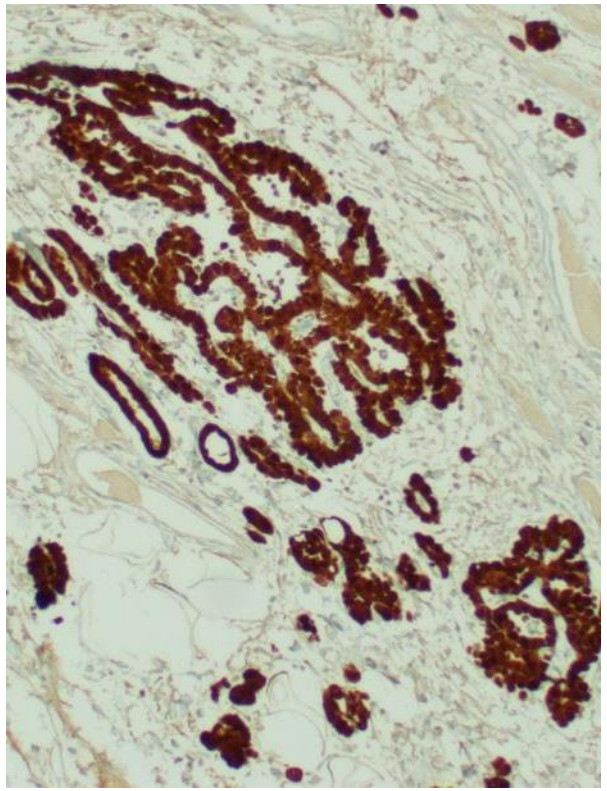




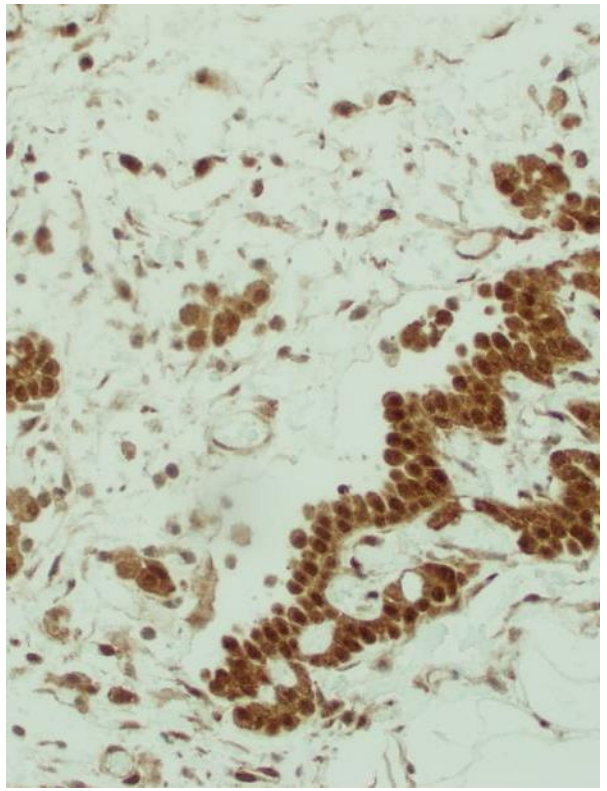
Mesothelioma coating the bowel, no discrete mass

Mesothelioma
NGS, no molecular alteration

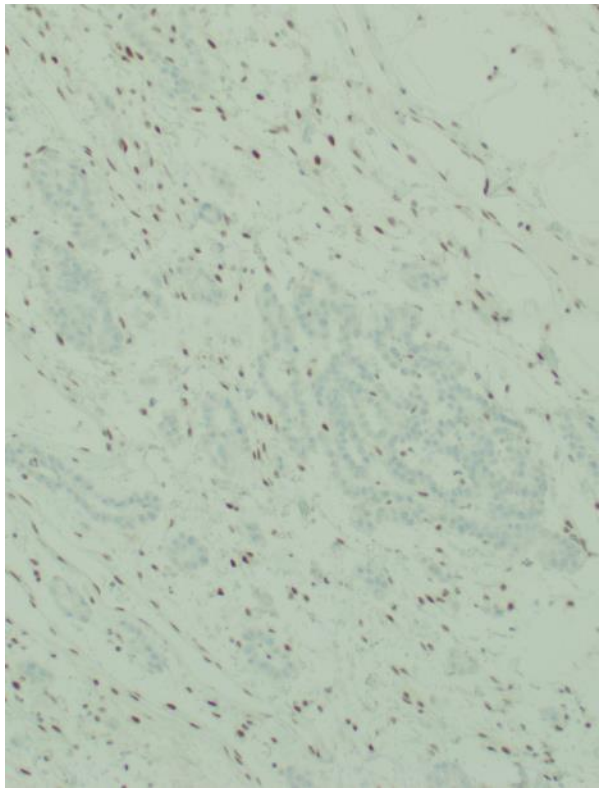




Calretinin



MTAP



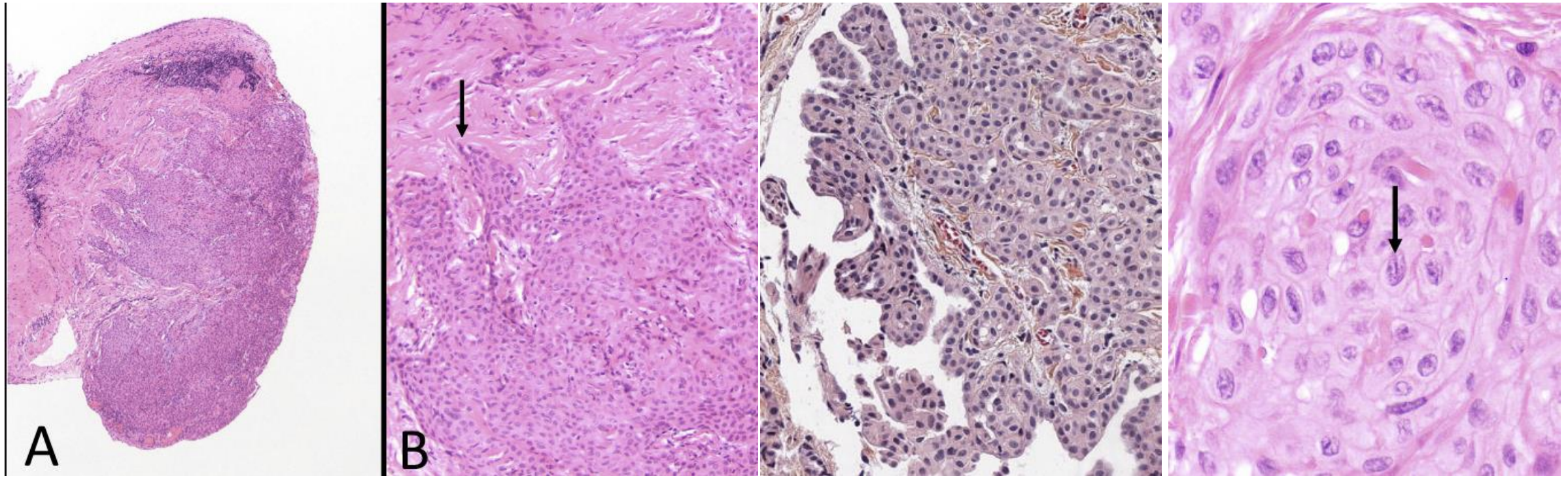
BAP-1 loss

Treatment

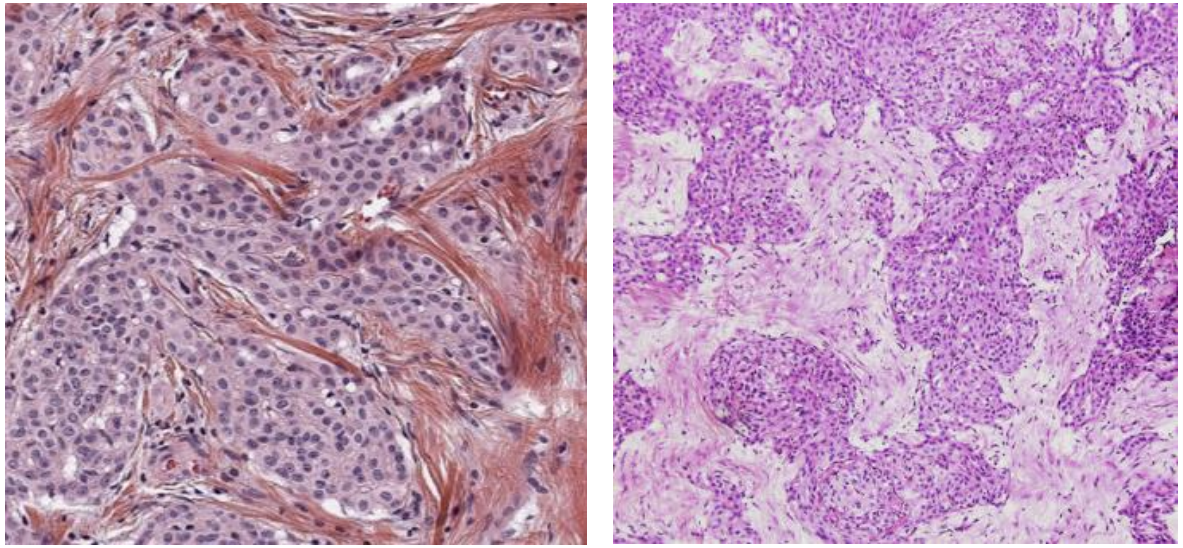
- Cytoreductive surgery
- HIPEC
  - Adjuvant systemic chemotherapy may be added

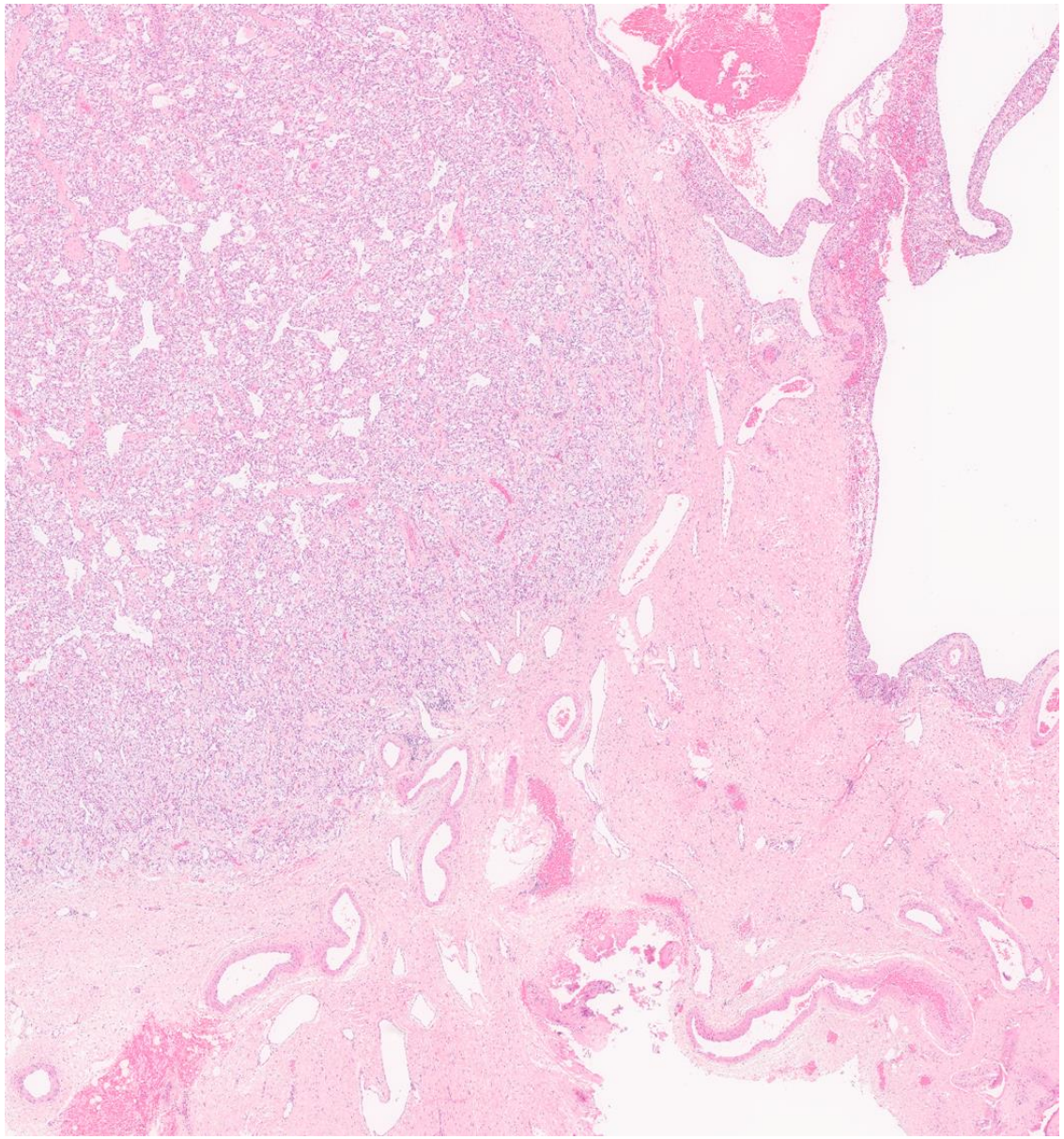
Solid and papillary mesothelial tumor

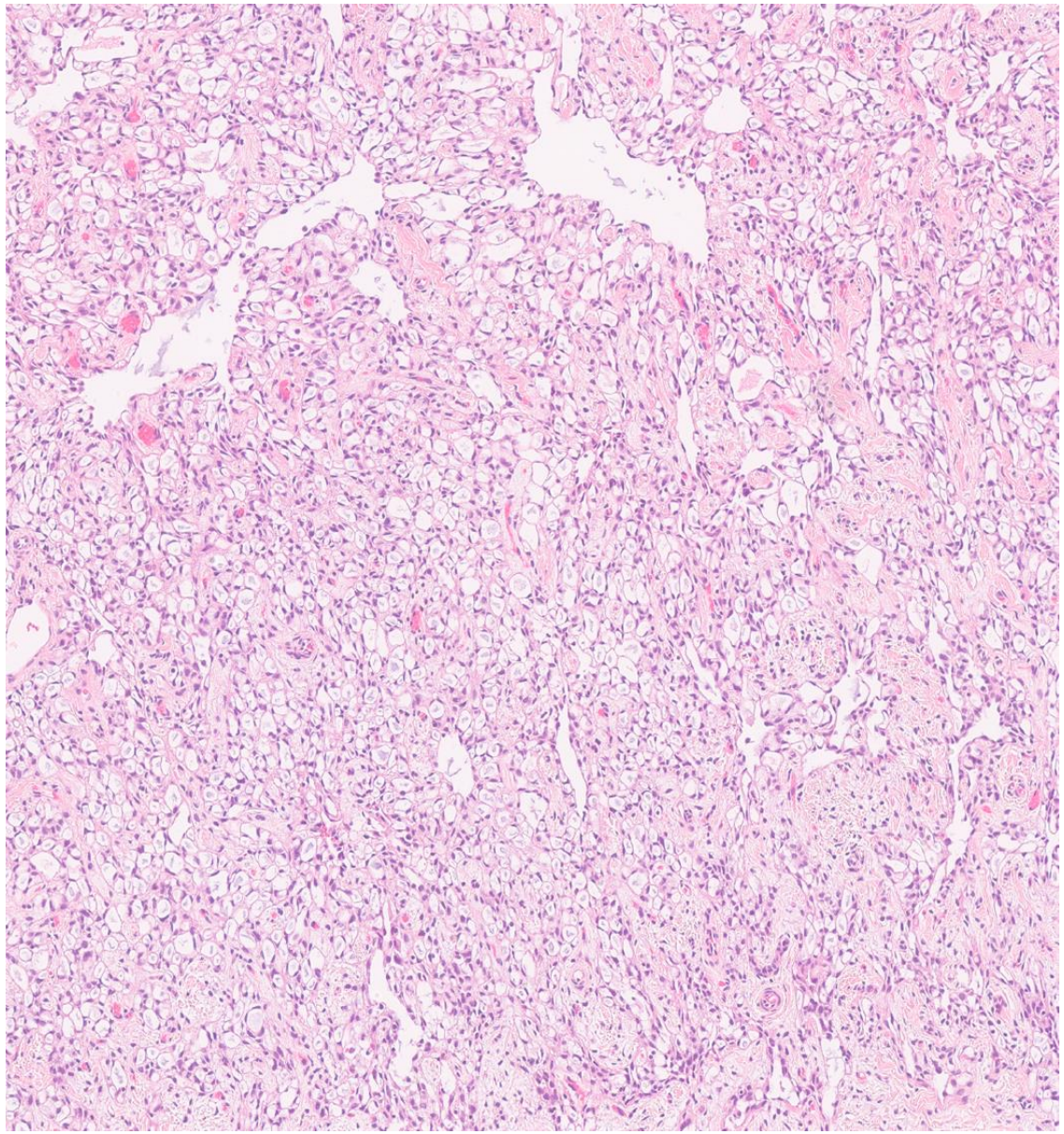
Churg A, et al. 2021

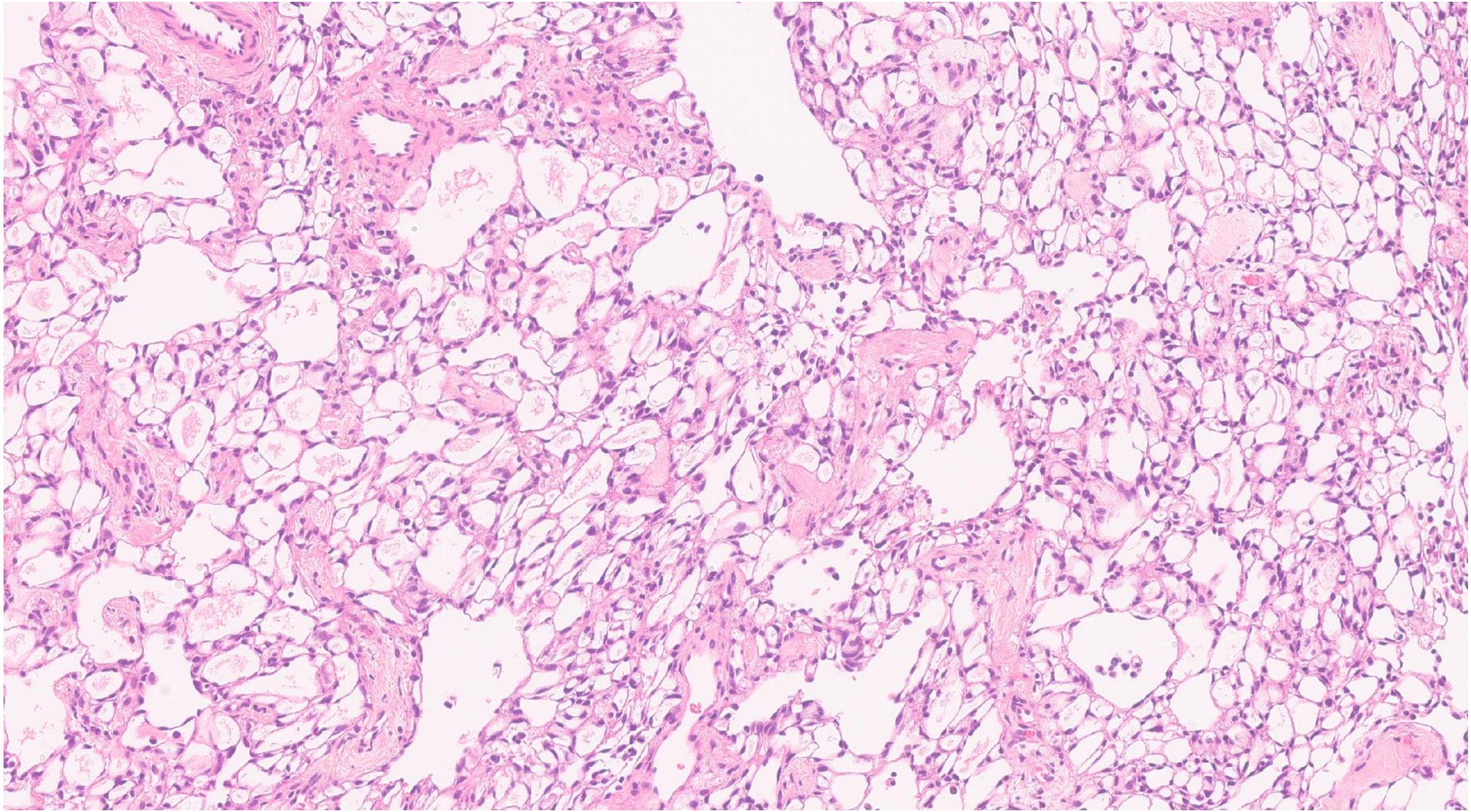


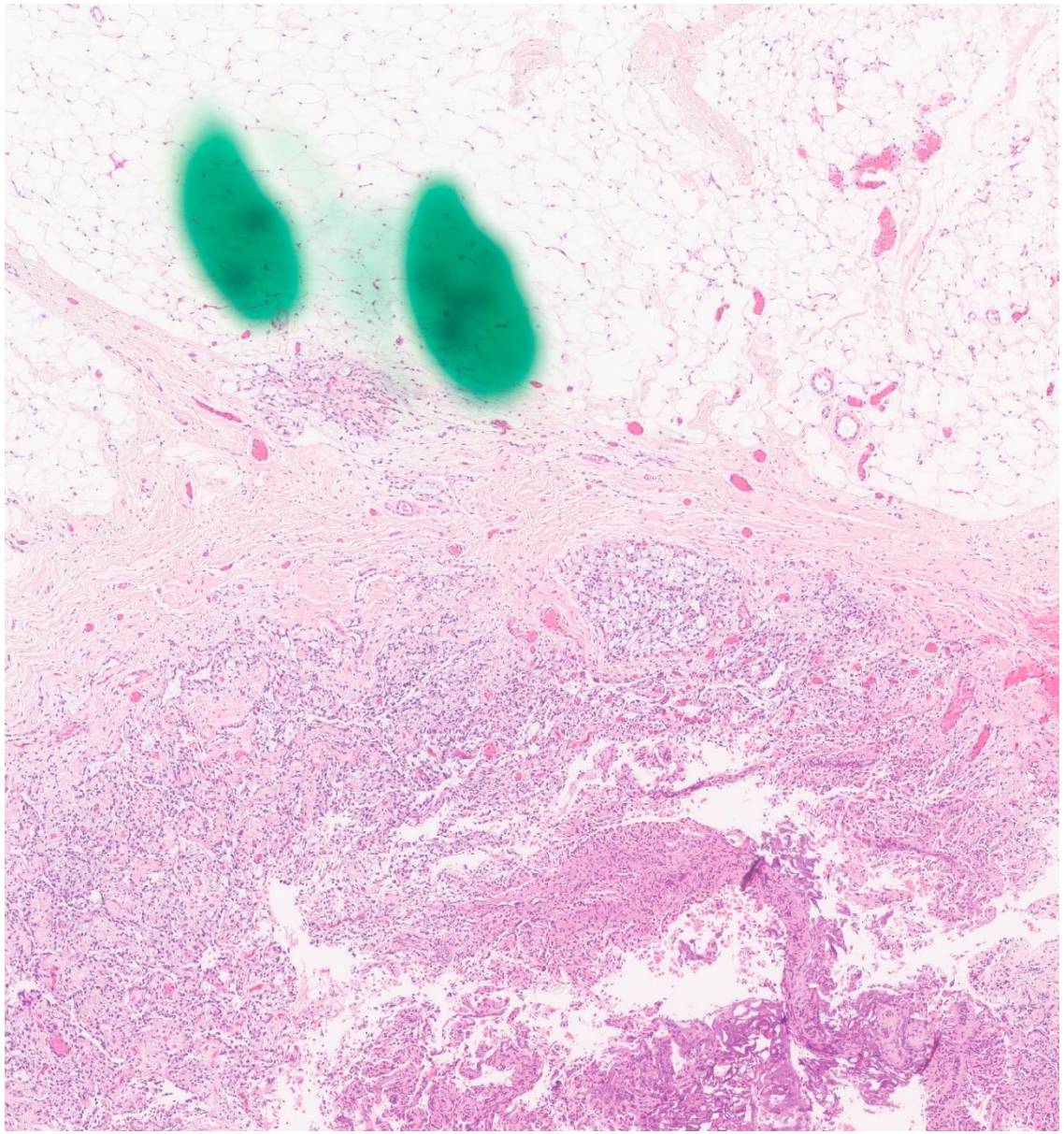
Retained BAP-1
No *CDKN2A* homozygous deletion
Potential pathogenic variants:
TSC2, MAP3K8, CTNNA1, and *ATM*

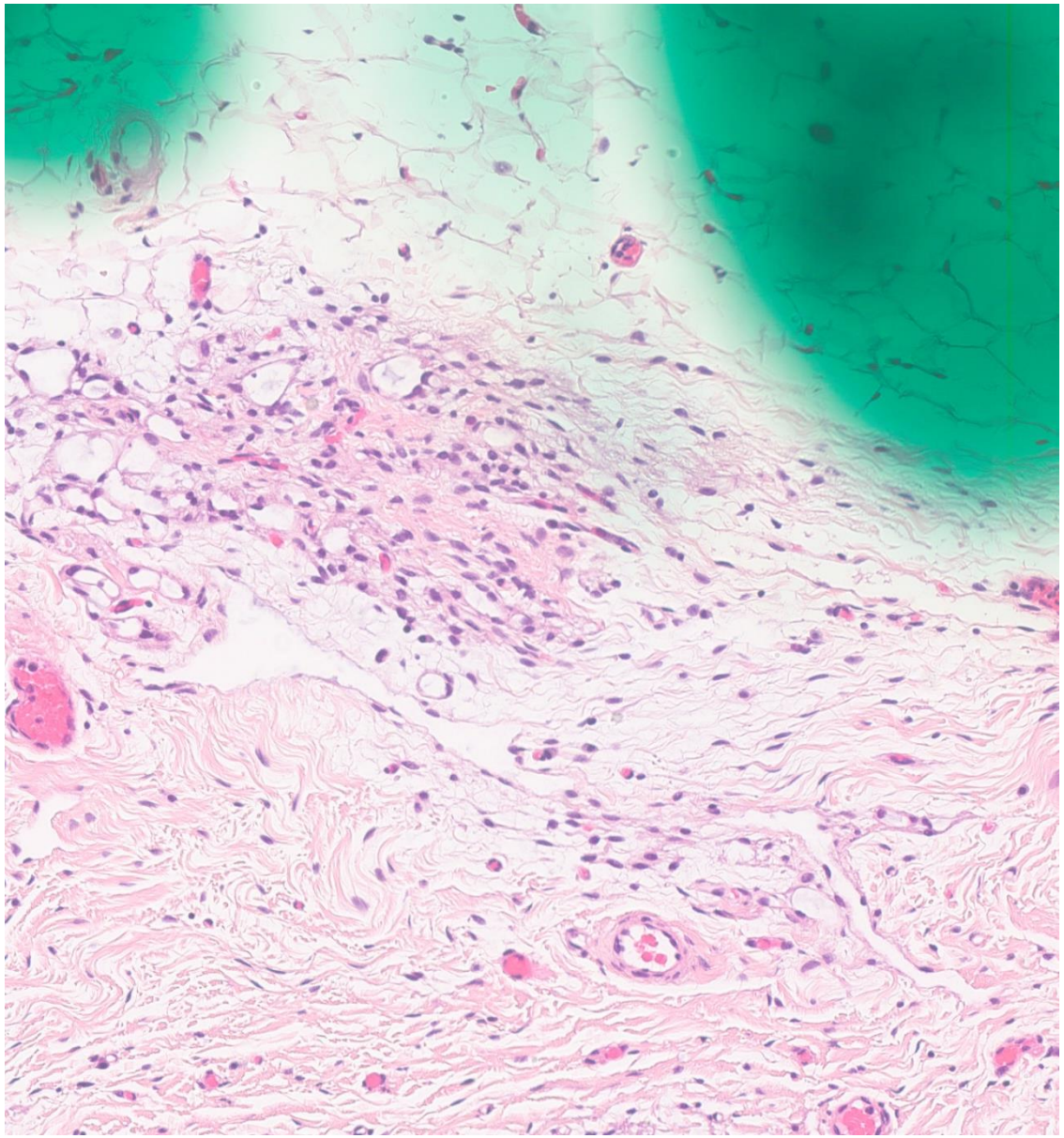




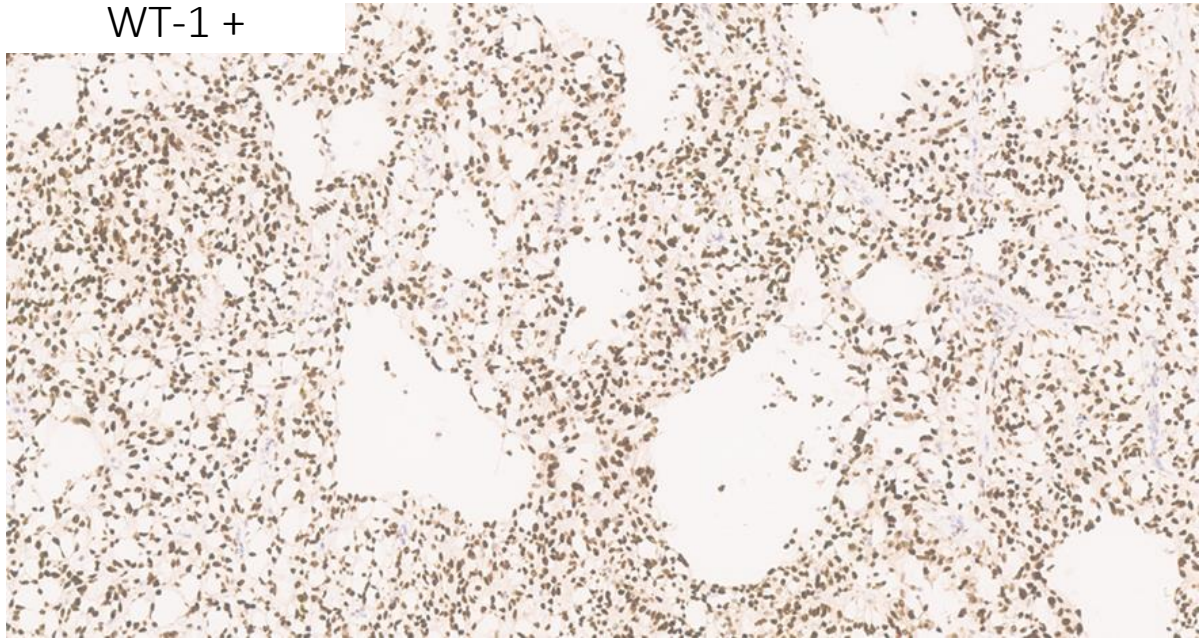




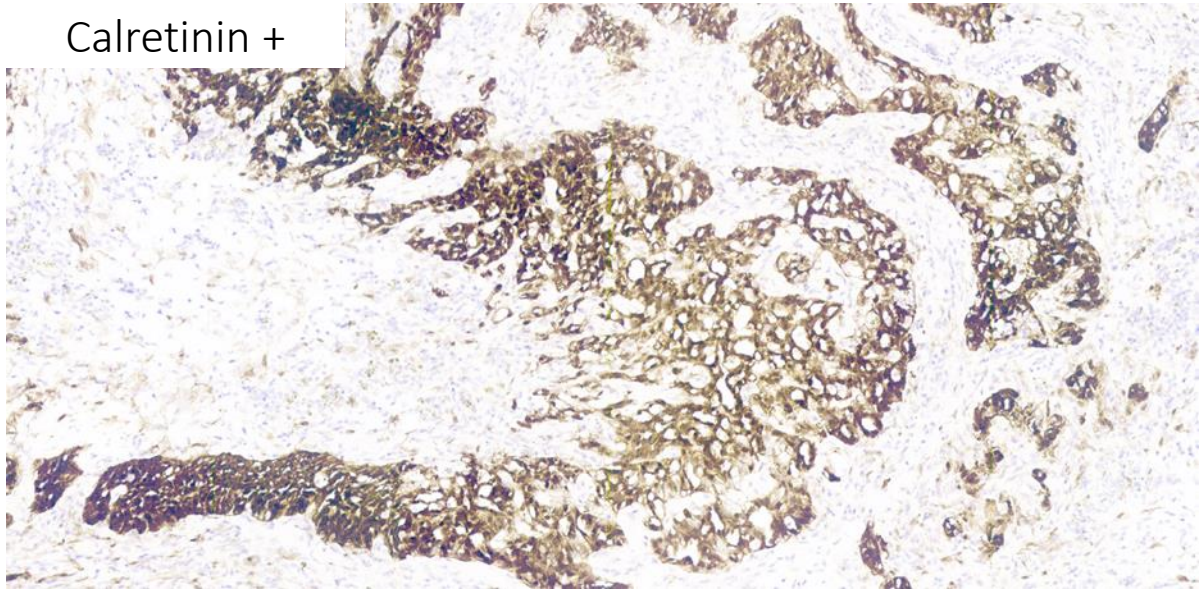




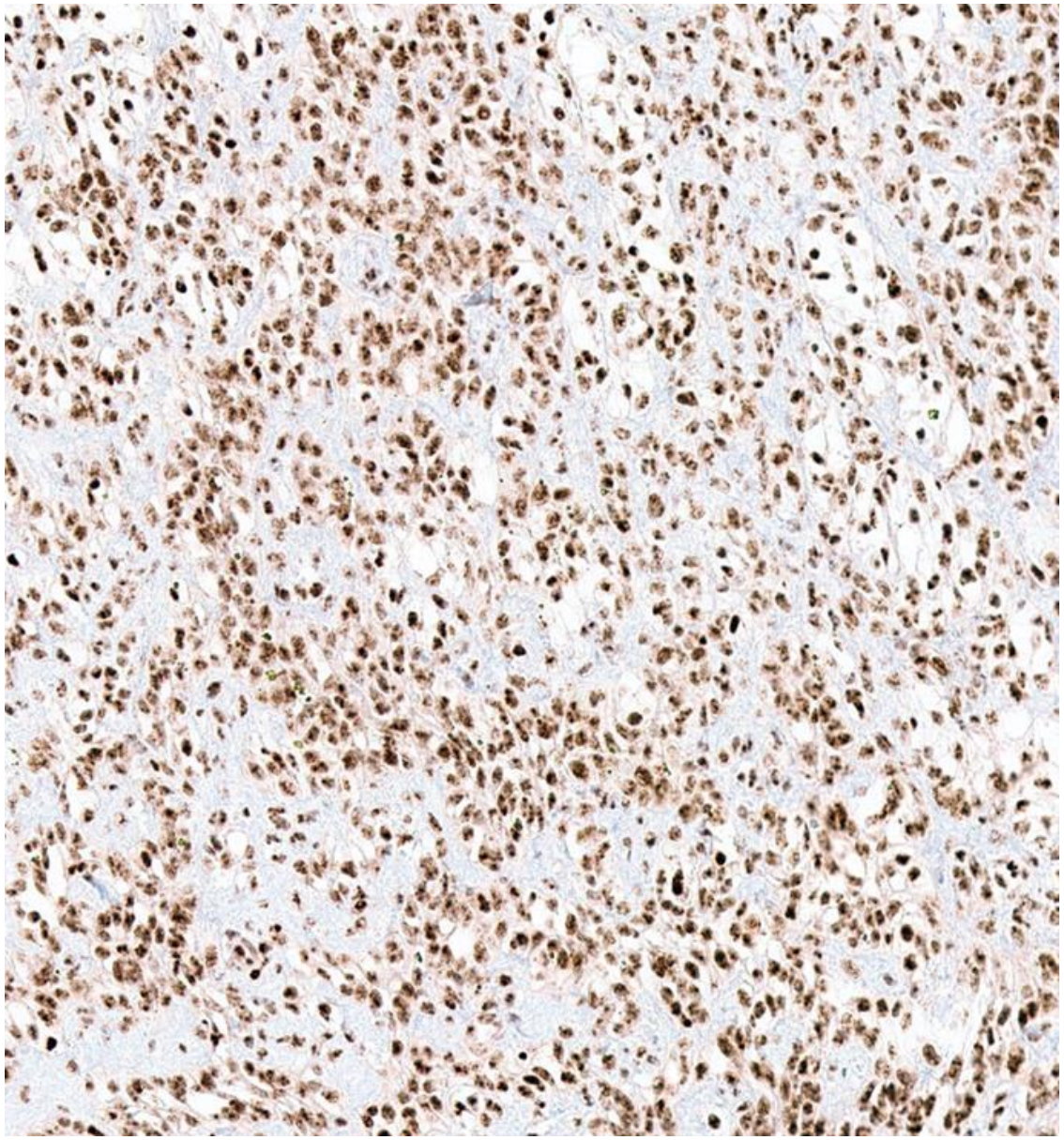
WT-1 +



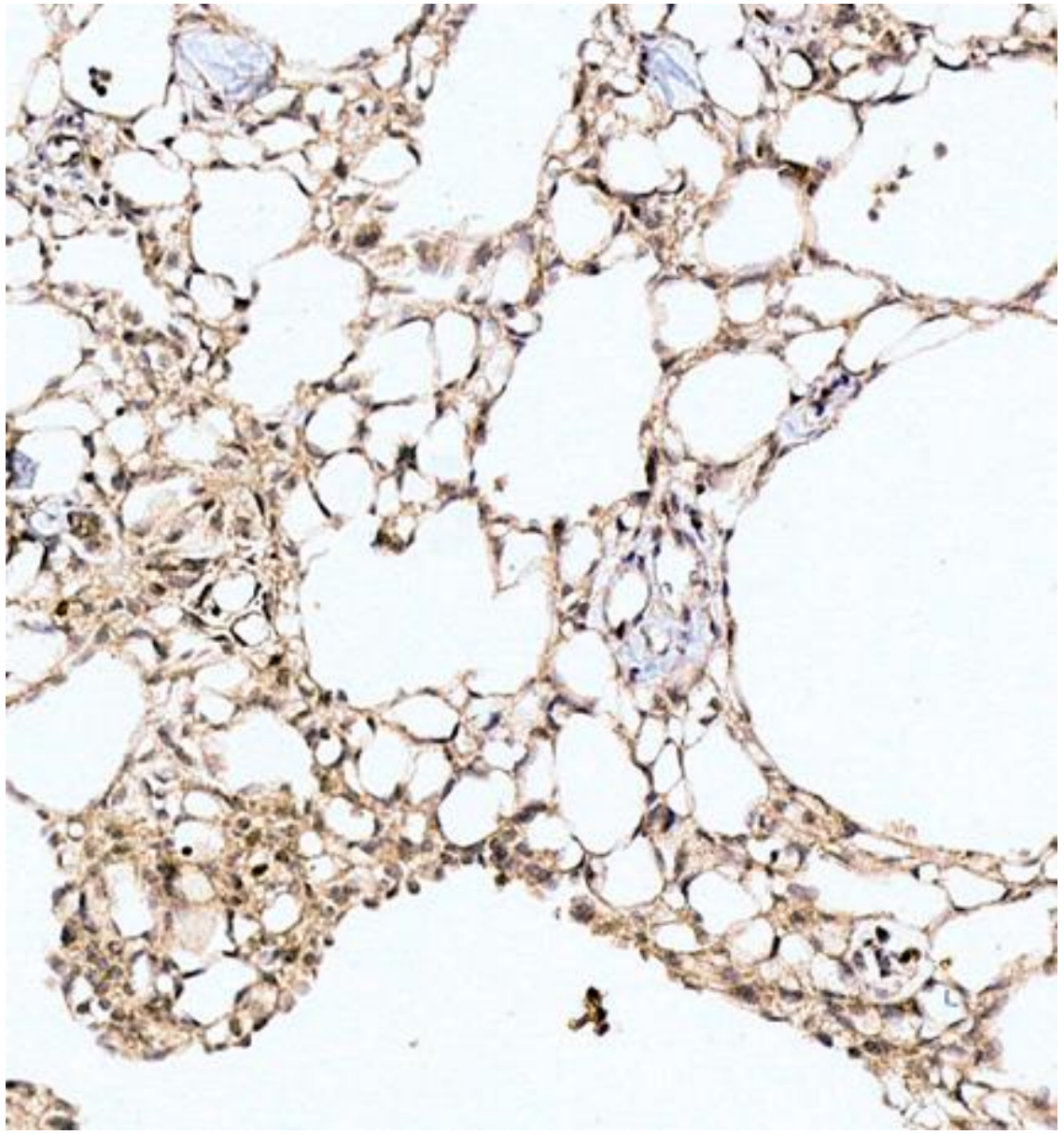
Calretinin +



D2-40 and CK 5/6, -



BAP-1, retained



MTAP +

NR4A3 Rearranged Mesothelioma

NR4A3 fusions in mesothelial neoplasms were initially described by Abbas Agaimy in 2022

- Cohort size: 7 pts (4 males, 3 females)
- Age range: 31-70 yrs (median, 40 yrs)
- Multiple or single lesions
- Size: 1.5 to 8 cm
- Well-circumscribed
- No cytologic atypia, mitosis or necrosis
- IHC: WT-1 +,
  - Limited expression of D2-40 and calretinin
  - BAP-1 intact

- Molecular Findings
  - 4 cases with *NR4A3* fusions
    - Partners (*EWSR1, NIPBL, CITED2*)
  - 2 cases with no fusions
- Tx
  - Surgery alone (3) pts
    - 1 lesion or limited number of lesions (3)
  - Surgery and chemo (1)
  - Surgery and hyperthermic chemo (2)
    - Neoadjuvant chemo (1)
    - Adjuvant chemo (1)
- Follow-up
  - 5 pts, NED (6 mos to 14 mos)
  - 1 pt with suspicion of recurrence at 7 mos (no fusion detected)

Agaimy had proposed the name mesothelial neoplasm of uncertain malignant potential for these cases

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Contents lists available at ScienceDirect

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journal homepage: www.pathologyjournal.rcpa.edu.au

CORRESPONDENCE

NR4A3 rearranged mesothelial tumour with evidence of infiltration after a 2-year follow up period: best regarded as *NR4A3* rearranged low grade mesothelioma

Francis H.X. Yap [1,*], Chow Chun Yuen [1], Tony Kiat Hon Lim [1], Jen-Hwei Sng [1], Jacqueline Hwang [1], Jolene Wong [2], Angela Takano [1]

[1] Department of Anatomical Pathology, Singapore General Hospital, Singapore
[2] Department of Sarcoma, Peritoneal and Rare Tumours (SPRinT), Singapore General Hospital, Singapore

Infiltration in the ovary at presentation
NED at 2 yrs
Tx: TRS and HIPEC

ESMO OPEN

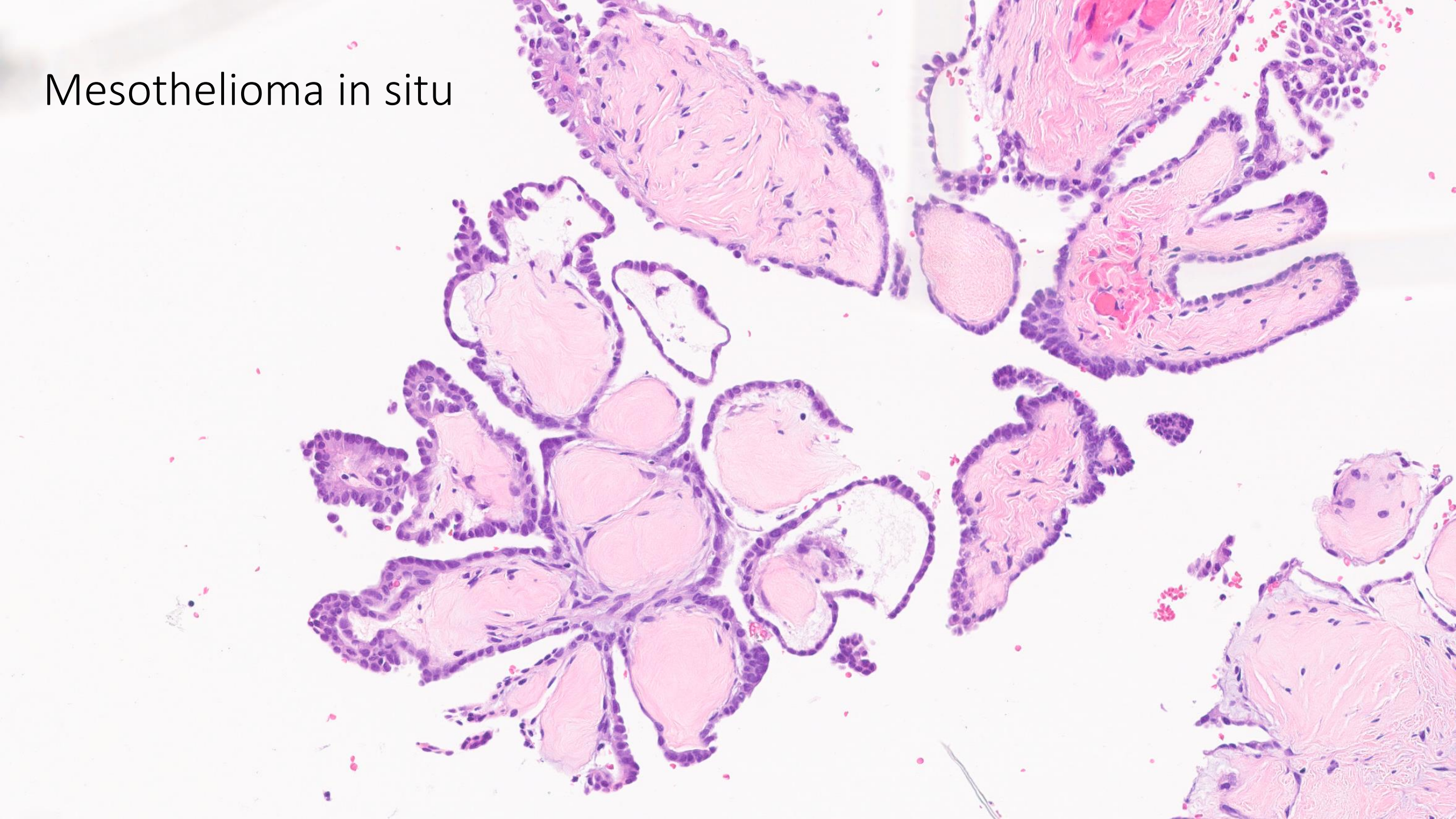
ORIGINAL RESEARCH

Update on gene fusions and the emerging clinicopathological landscape of peritoneal and pleural mesotheliomas and other neoplasms

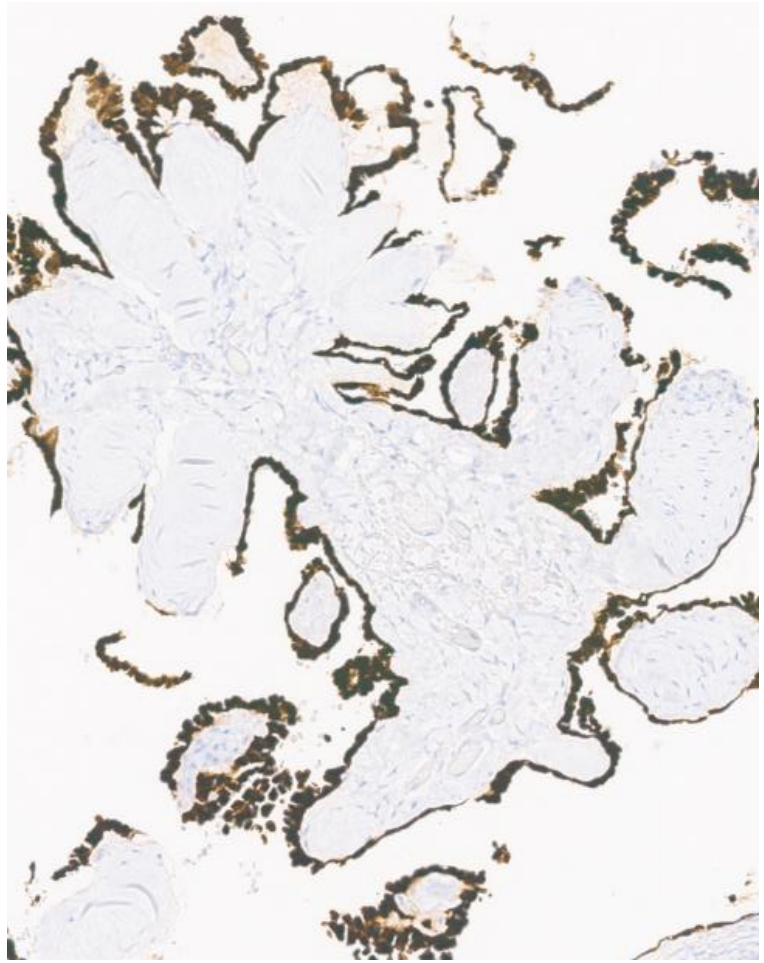
N. Benzerdjeb[1,2*], P. Dartigues[3], V. Kepenekian[2,4], F. Damiola[5,6], R. Sequeiros[6], F. Galateau-Salle[5], H. Begueret[7], E. Mery[8], D. Damotte[9,10], V. Verriele[11], J. Fontaine[1,2], S. Isaac[1,2], S. Valmary-Degano[12], L. Villeneuve[2,13], O. Glehen[2,4], A. Scherpereel[14], F. Forest[15], A. De la Fourchardiere[5], S. Paindavoine[5], A. Hourlier[5], D. Pissaloux[5], F. Tirode[5] & S. Lantuejoul[5,6,16], on behalf of the RENAPE and the NETMESO/MESOPATH Networks

4 cases (3 males, 1 female, mean age: 63.8 yrs)
Tx: Surgery (4), plus HIPEC (2, 1 also chemo due to high PCI)
F/U (14-140 mos), no death or recurrence

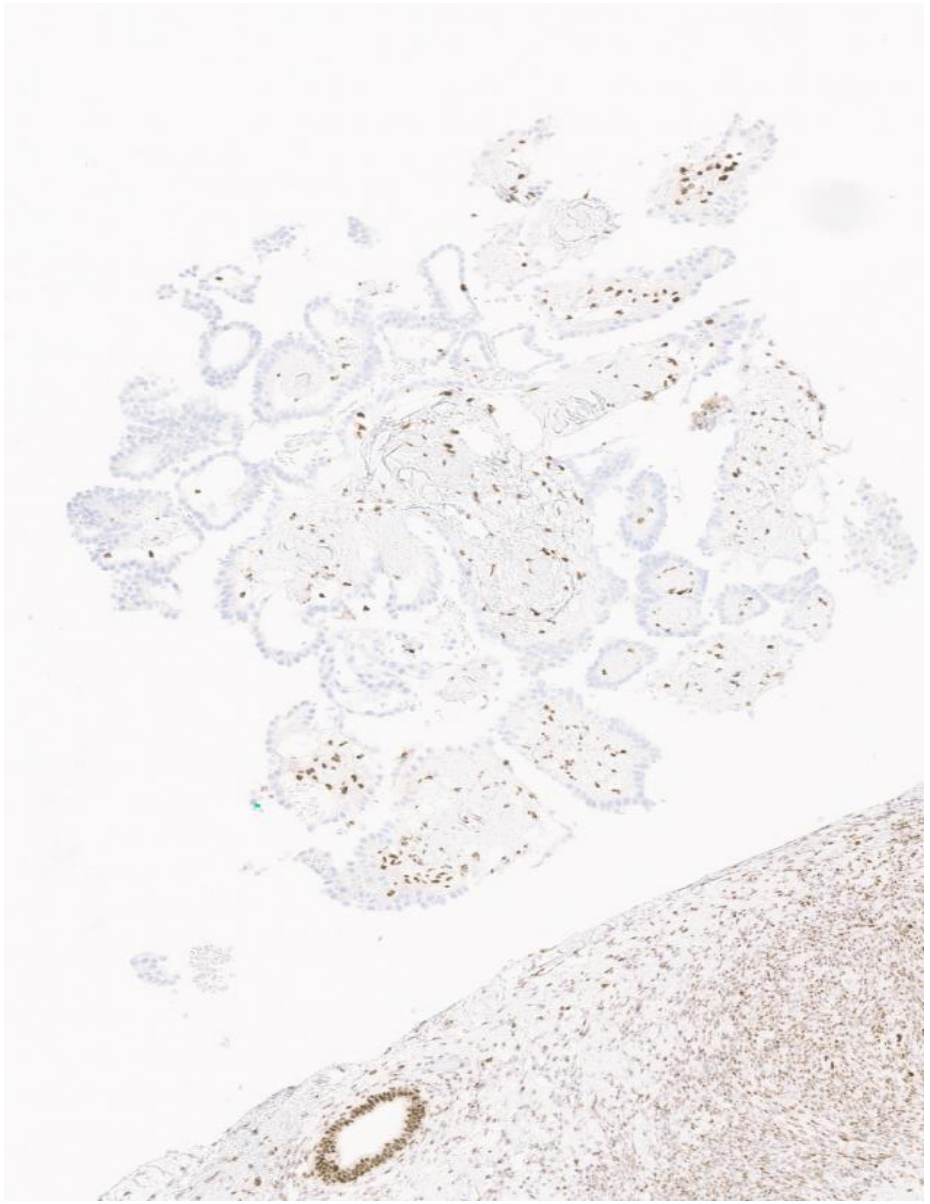
Mesothelioma in situ



Mesothelioma in situ



Calretinin +



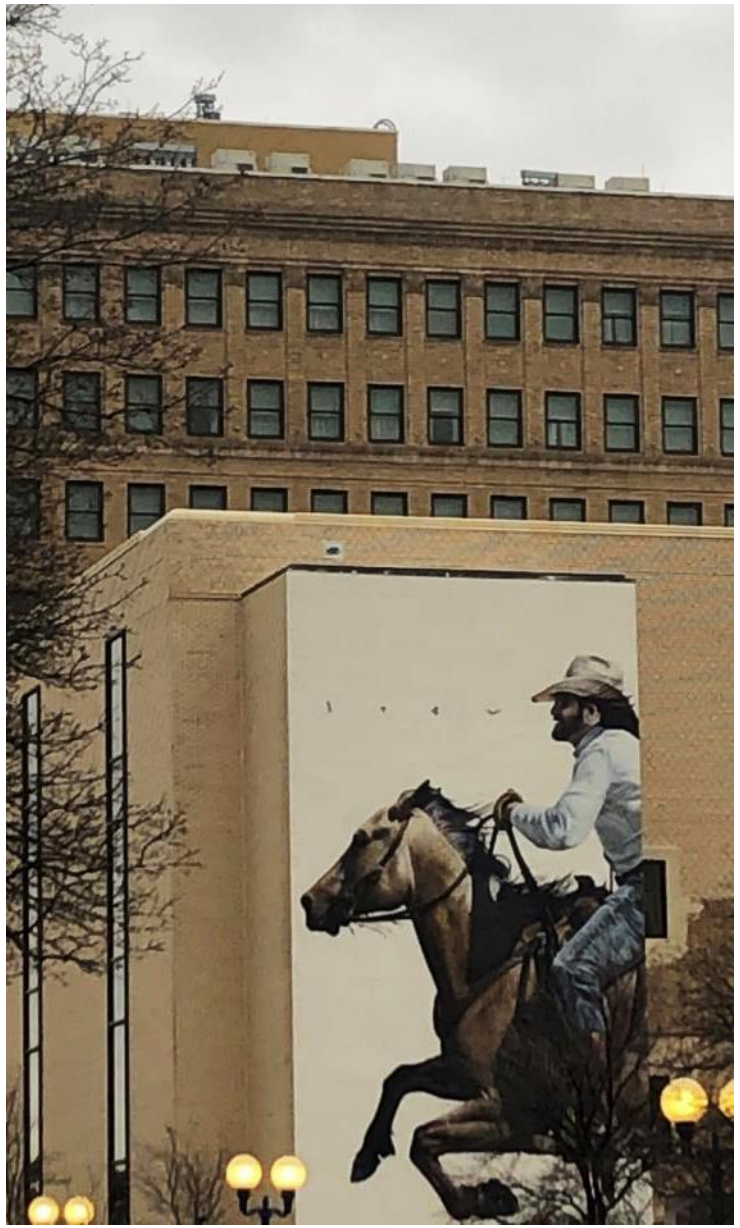
BAP-1 loss

Table 5. Summary of the Salient Molecular and Immunohistochemical Features in the Diagnosis of Mesothelioma and Other Mesothelial Lesions

Mesothelial Lesion	Salient Molecular/Immunohistochemical Features
Diffuse mesothelioma: common alterations	*BAP1* Altered in ~40%–60% of cases Enriched in epithelioid type, rare in sarcomatoid type *CDKN2A* Homozygous loss in ~30%–50% of cases Rare in epithelioid type, enriched in sarcomatoid type *MTAP* Altered in ~30%–40% of cases *NF2* Altered in ~20%–30% of cases
Diffuse mesothelioma: rare alterations	
Genomic near-haploidization	Detected by karyotype, SNP array, and/or NGS Uncommon (~3%)
ALK rearrangement	Detected by IHC, FISH, and/or NGS (orthogonal methods recommended) Rare (<1%) Considered in young patients and/or those without asbestos exposure
ATF1 rearrangement	Detected by FISH and/or NGS Rare (<1%) Considered in young patients and/or those without asbestos exposure
EWSR1::*YY1* fusion	Detected by FISH and/or NGS Rare (<1%)
Germline mutations	Detected by NGS Uncommon (~12% of patients) Germline variants reported: *BAP1*, *BRCA2*, *CHEK2*, *CDKN2A*, *ATM*, *ATR*, *RECQL4*, *BRCA1*, *TP53*, *PTEN*, *NF2*, *MLH1*, and *MSH6*, among others Enriched in young patients, those with peritoneal (versus pleural) mesothelioma, concomitant second cancer, without asbestos exposure
Mesothelioma in situ	Aberrant BAP1 IHC, *CDKN2A* FISH, and/or MTAP IHC
Adenomatoid tumor	Recurrent *TRAF7* mutations
Well-differentiated papillary mesothelial tumor	Intact BAP1 IHC, normal *CDKN2A* FISH
Peritoneal inclusion cyst	Rare gene fusions
Solid papillary mesothelial tumor	Intact BAP1 IHC, normal *CDKN2A* FISH
NR4A3-rearranged peritoneal mesothelial tumor	Identified by FISH and/or NGS

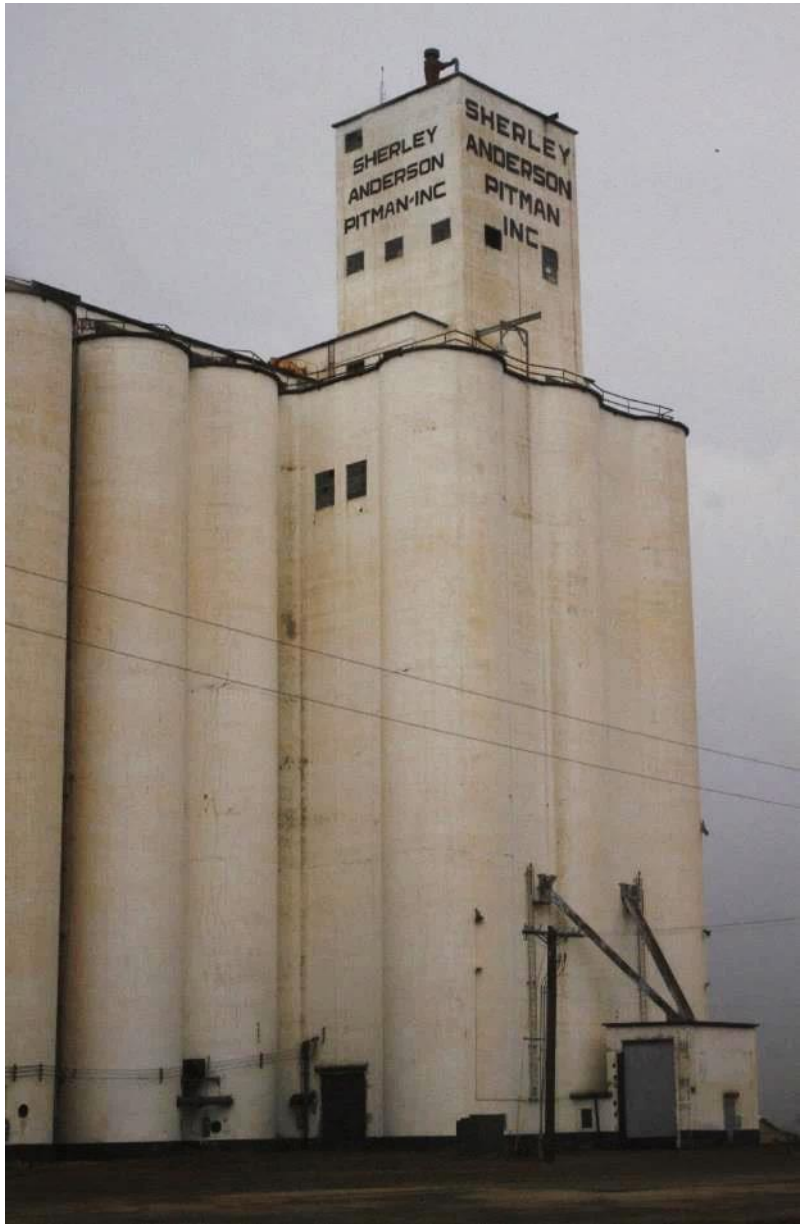
Abbreviations: FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NGS, next-generation sequencing; SNP, single-nucleotide polymorphism.

Hung YP, Chirieac LR, 2024



Downtown, Amarillo

Steel House, Robert Bruno, Lubbock



Silos, Farwell