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#GynPath

Ovarian Mucinous Tumors: Primary or Metastasis? A Practical Approach to Differential Diagnosis

MAY 21, 2020/ 1:00PM EST (UTC-5H)

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pathCast

Primary ovarian mucinous tumors

- Account for 10%–15% of all primary ovarian tumors
- 80% are benign
- Most of the remainder are mucinous borderline tumors
- Primary mucinous carcinomas are rare – only 3% – 5% of primary ovarian carcinomas are of mucinous type

(Prat et al. 2018) (Frumovitz et al. 2010)

Metastatic ovarian mucinous tumors

- Most mucinous carcinomas involving the ovary are metastases as opposed to ovarian primary carcinomas
- In a study of consecutive cases from a single institution only 23% of mucinous carcinomas in the ovary were primary ovarian
 - 45% gastrointestinal tract, including appendix
 - 20% pancreatobiliary
 - 10% of ovarian metastases are from unknown primary tumors

(Seidman et al. 2003) (Frumovitz, Schmeler et al. 2010)

Ovarian Mucinous Tumors

Primary ovarian

- **Mullerian mucinous tumor**
- **Associated teratoma/Brenner tumor**
- Unilateral
- Very large
- Expansile growth pattern
- Mural anaplastic nodules
- Uniformly bland cystadenoma
- Associated cystadenofibroma

Metastatic

- **'Metastatic morphologies'**
- **Extraovarian spread/pseudomyxoma peritonei**
- Bilateral
- Not so large
- Infiltrative growth pattern
- Multinodular gross appearance
- Lymphovascular involvement
- Ovarian surface/hilar involvement
- Lack of CK7
- Positivity for SATB2

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Ovarian Mucinous Tumors

Primary ovarian

- Practically all are unilateral
- Exception:
Müllerian mucinous tumors

Metastatic

- 75% are bilateral
- Exceptions:
Colorectal
Endocervical
Appendiceal (LAMN)

(Lee and Young 2003)

Ovarian Mucinous Tumors

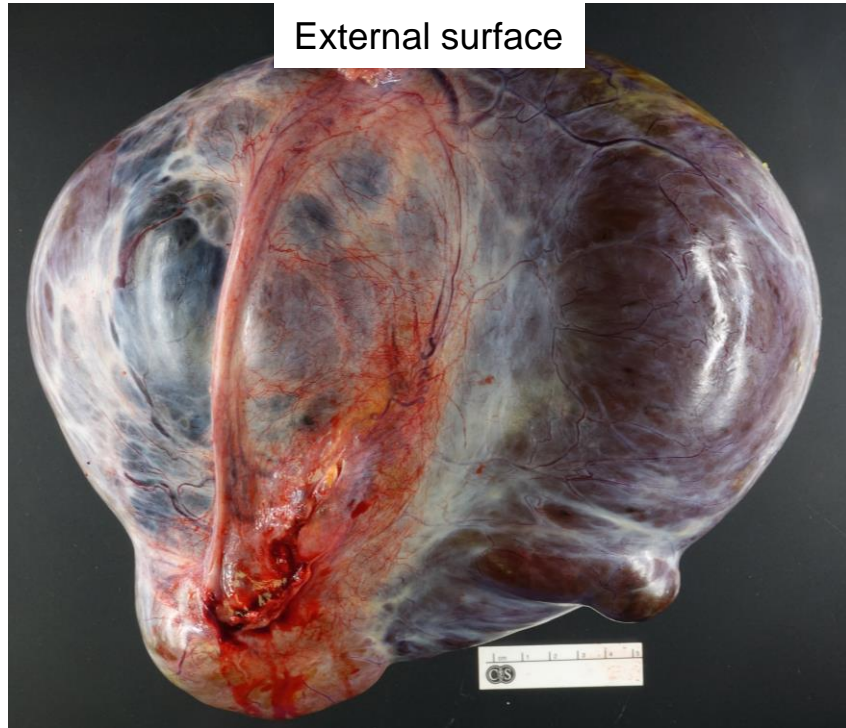
- 10 cm cut off: correctly classifies 83% of cases as primary or metastatic
- 12 cm cut off: 100% of primary tumors and 80% of metastases correctly classified (86% overall)
- 13 cm cut off: correct classification for 98% of primary tumors

(Lee and Young 2003) (Seidman, Kurman et al. 2003) (Yemelyanova, Vang et al. 2008)

Case 1

- 34 year-old female presented to the ER with abdominal pain
- CT scan revealed with a 25 cm left adnexal multiseptated cystic mass
- Operative report indicated absence of extraovarian involvement
- Salpingo-oophorectomy was performed
- Specimen was sent for intra-operative consultation

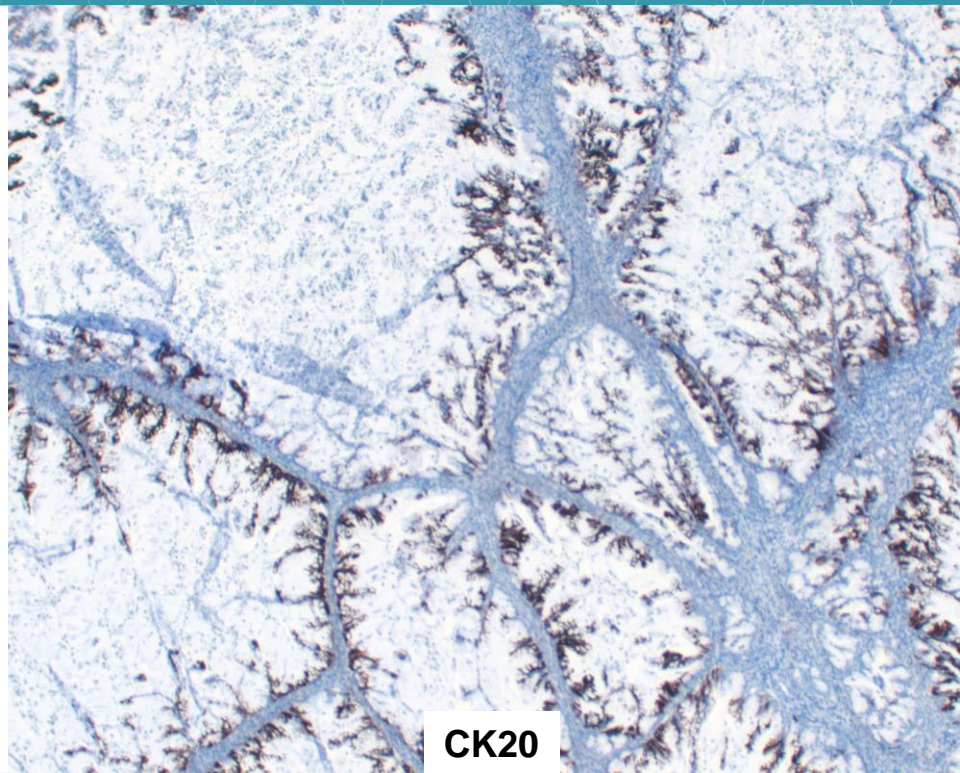
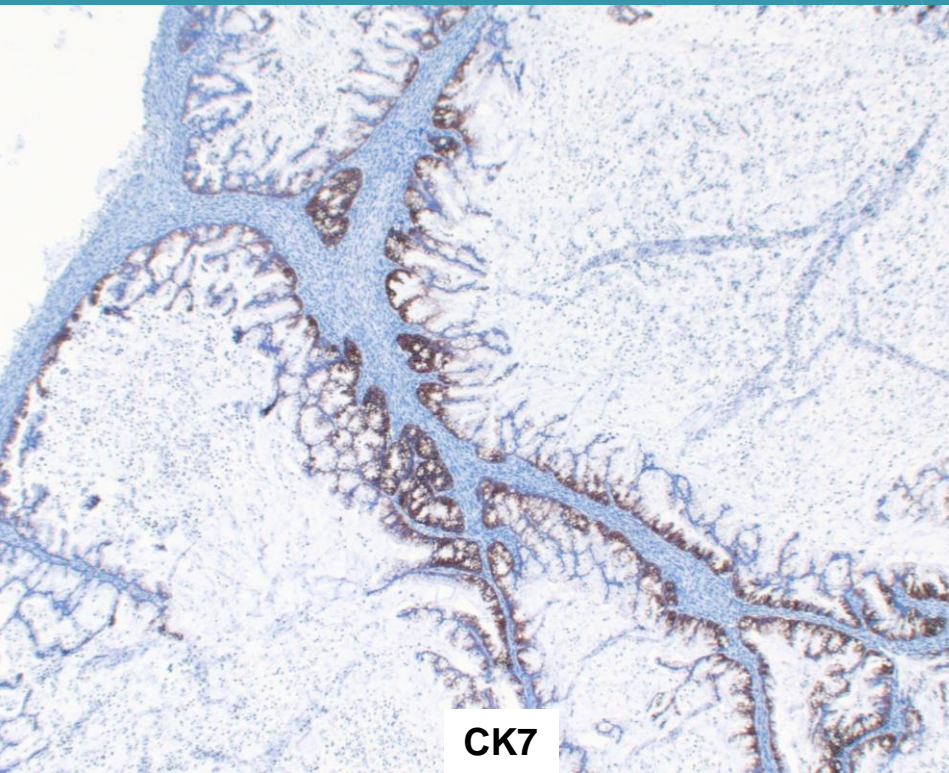
Case 1



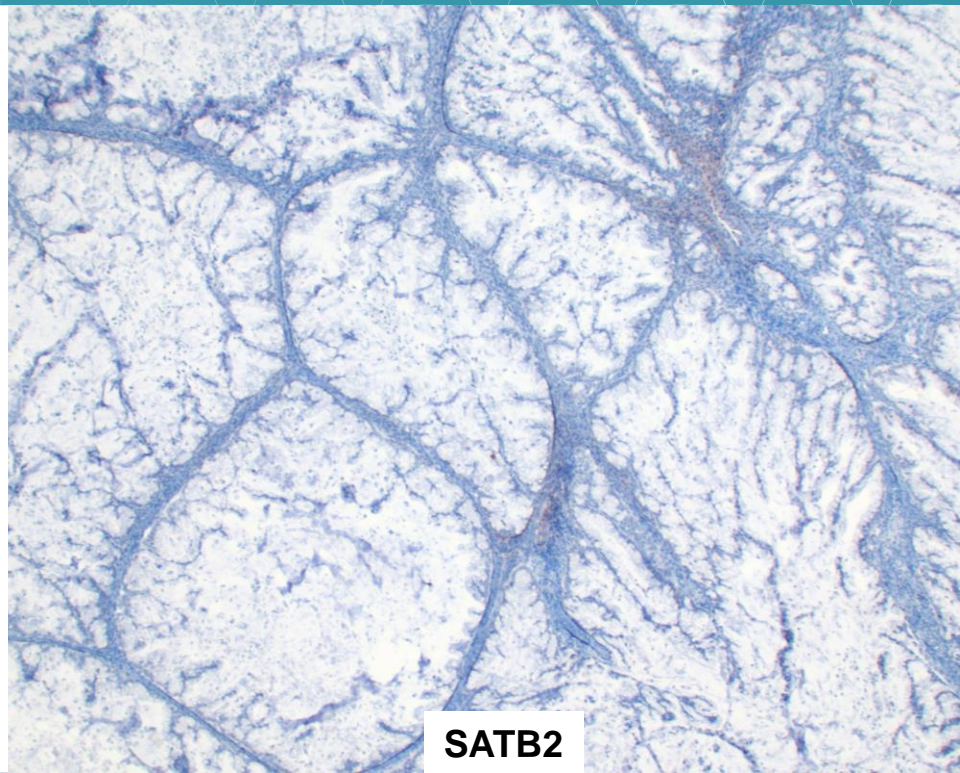
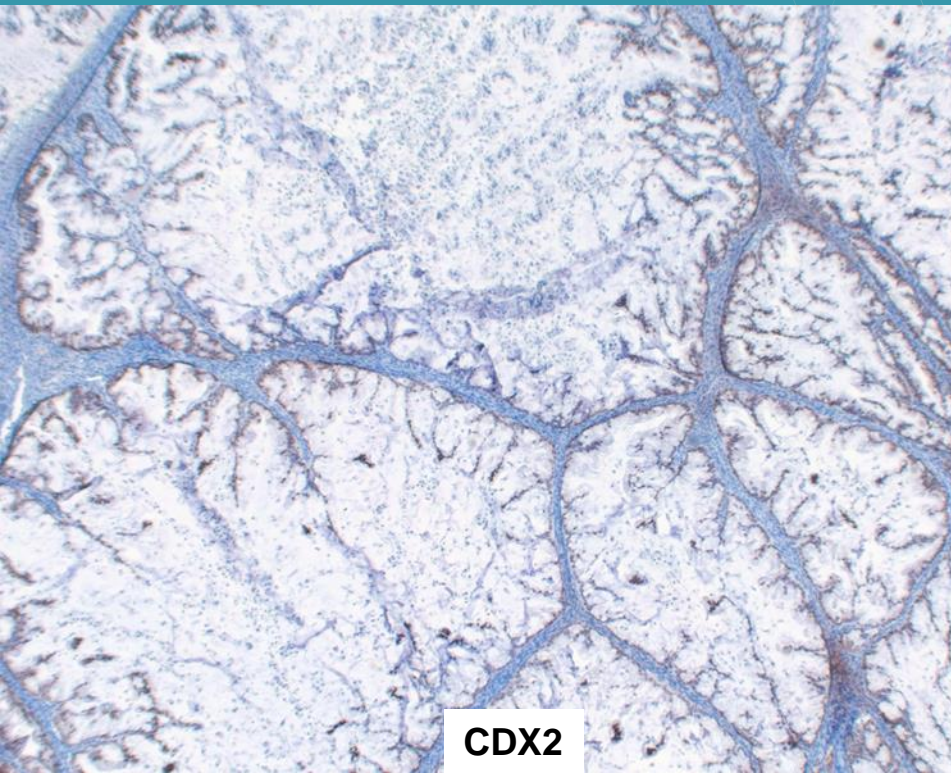
Case 1

Scanned slide – Left ovarian mass

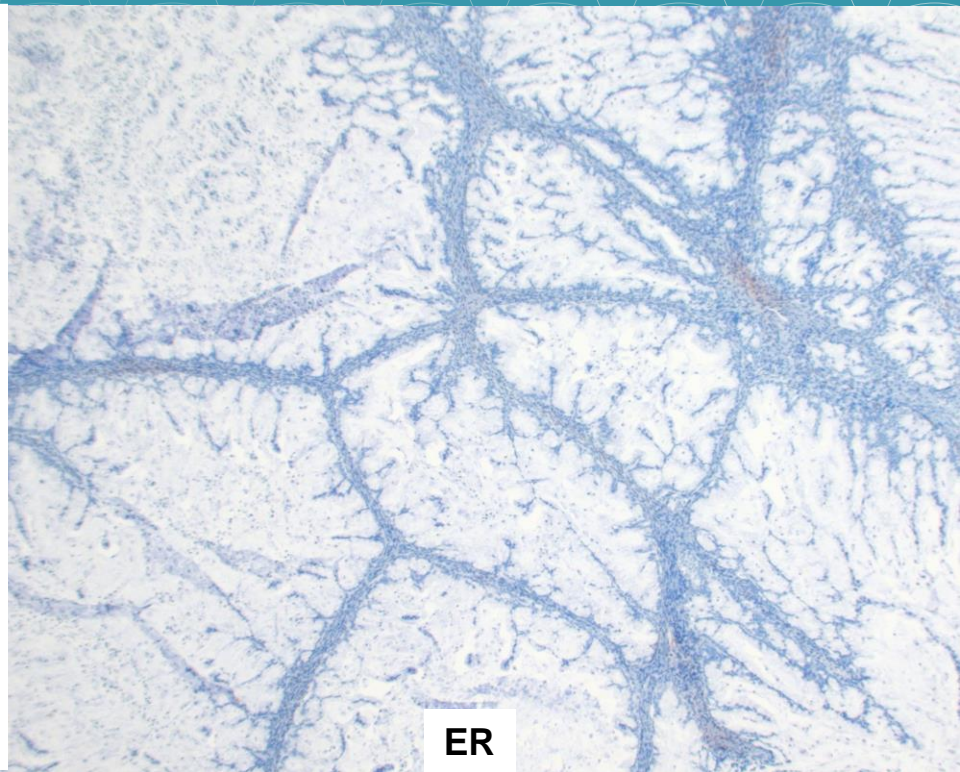
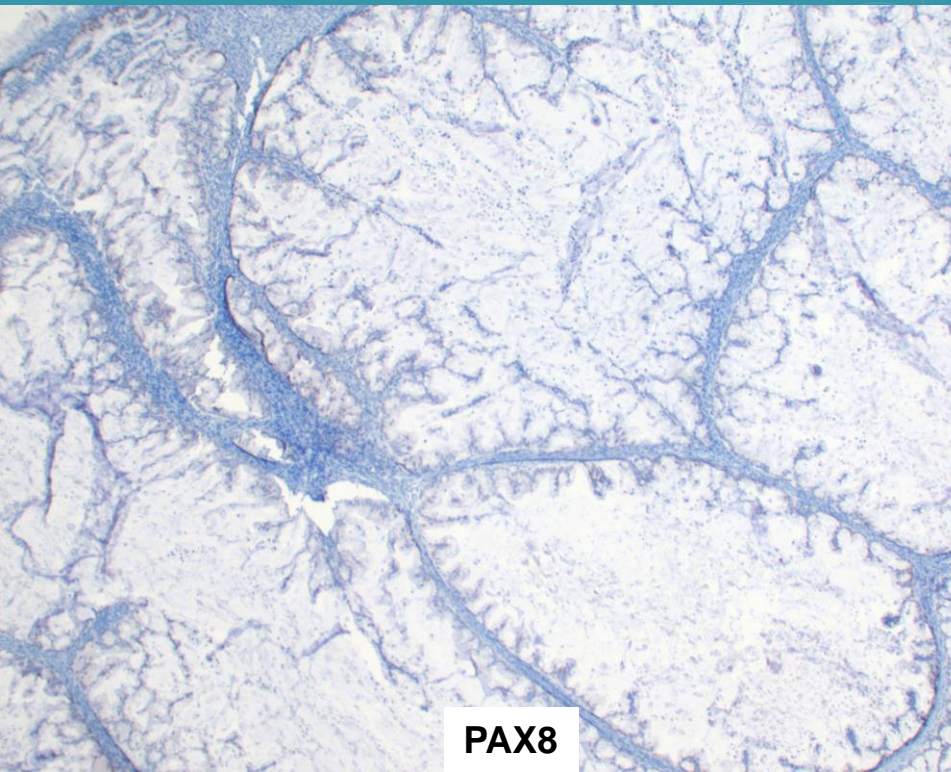
Case 1



Case 1



Case 1



Case 1

What is the most appropriate diagnosis?

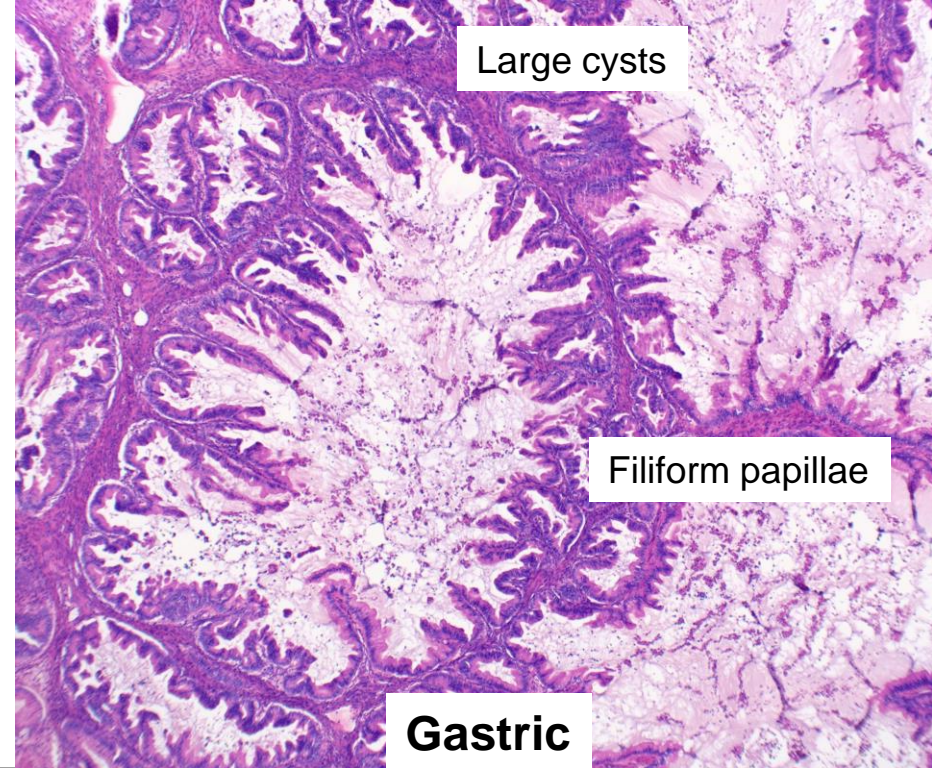
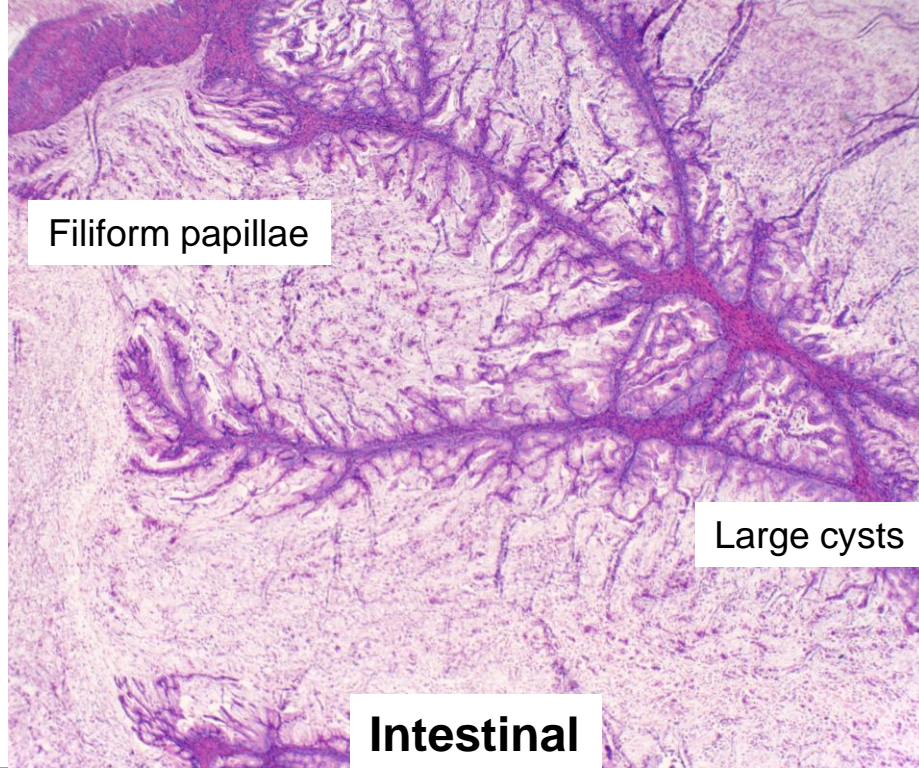
- a. Mucinous adenocarcinoma, expansile invasion, ovarian primary
- b. Mucinous adenocarcinoma, infiltrative invasion, ovarian primary
- c. Mucinous borderline tumor, gastrointestinal type, ovarian primary
- d. Mucinous borderline tumor, müllerian type, ovarian primary
- e. Mucinous tumor, the differential diagnosis includes primary ovarian and metastasis

Case 1

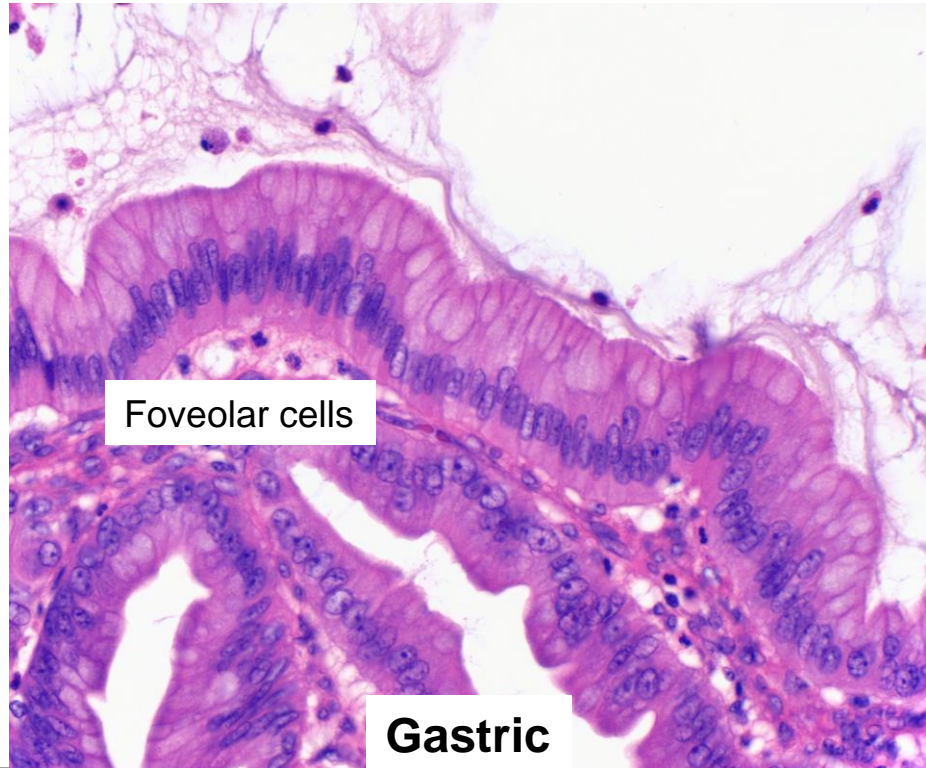
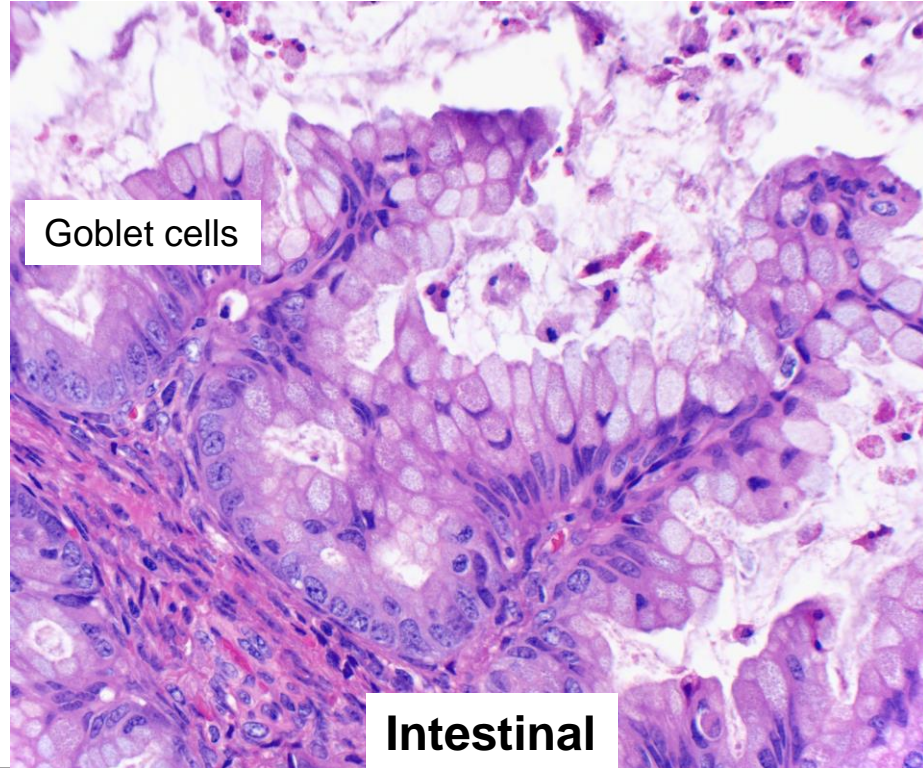
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Mucinous Borderline Tumor, gastrointestinal type



Mucinous Borderline Tumor, gastrointestinal type



Primary Ovarian Mucinous Tumors

Do you need to find goblet cells?

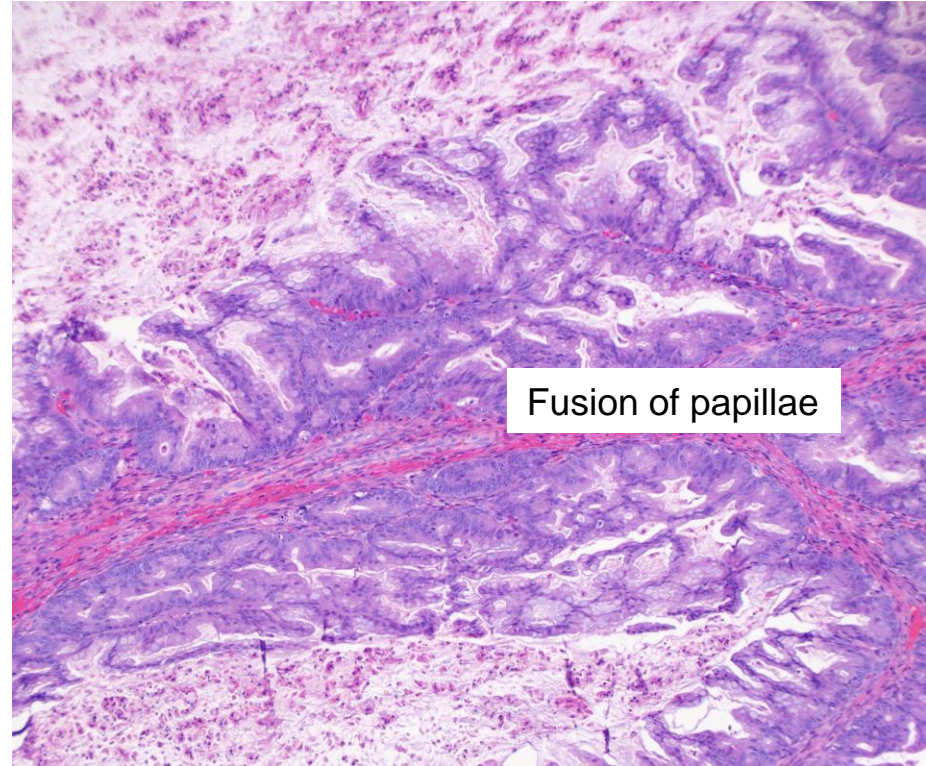
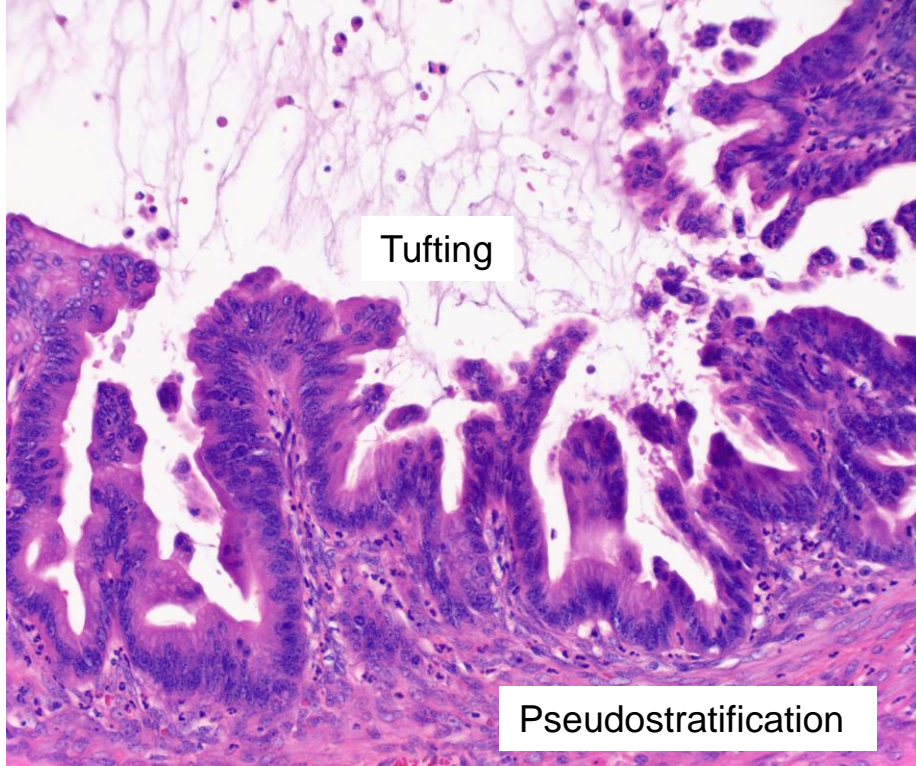
Primary Ovarian Mucinous Tumors

Do you need to find goblet cells?

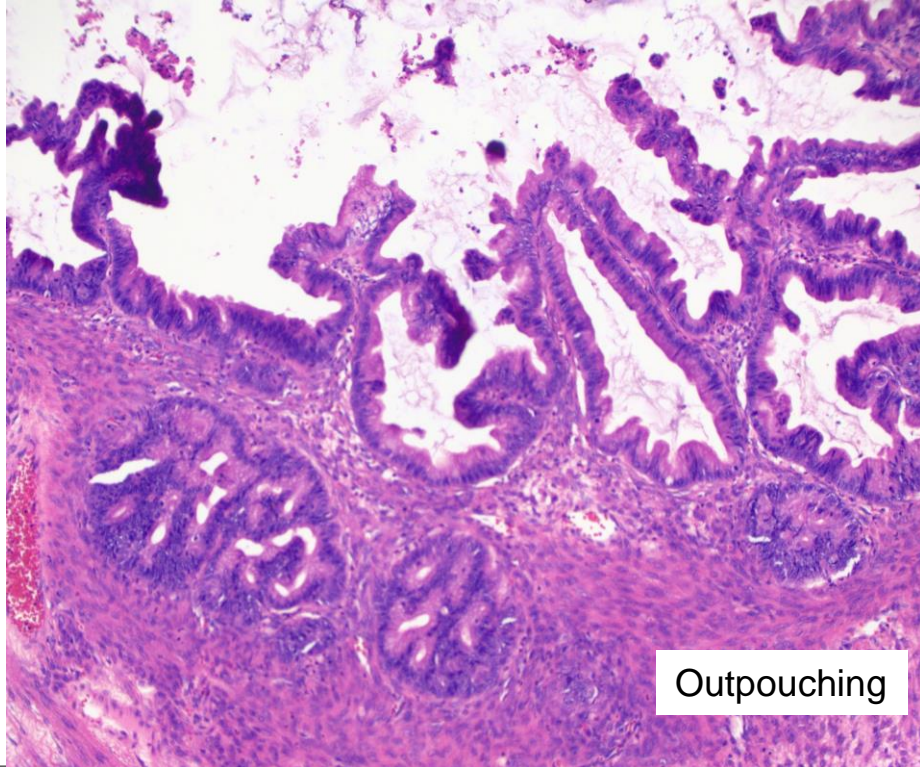
- **Goblet cells are not a prerequisite** for an intestinal type mucinous tumor
- Based on their mucin histochemical profile, **many of these exhibit gastric or pancreaticobiliary differentiation**

(McCluggage 2010)

Mucinous Borderline Tumor, gastrointestinal type



Mucinous Borderline Tumor, gastrointestinal type



Mucinous Borderline Tumor, gastrointestinal type

- **Mucinous borderline tumor:** At least 10% of the epithelial volume must demonstrate increased proliferation with papillary infoldings or pseudostratification and mild to moderate nuclear atypia
- **Mucinous cystadenoma with focal epithelial proliferation:** Increased proliferation/atypia but insufficient for a diagnosis of borderline tumor

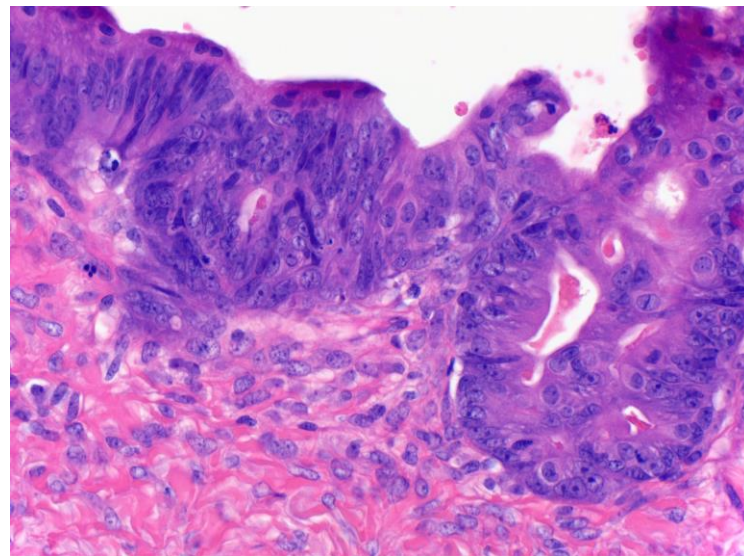
Mucinous Borderline Tumor, gastrointestinal type

Mucinous borderline tumor with intraepithelial carcinoma

- Marked cytologic atypia
- Complex architecture
 - Micropapillae
 - Cribriforming
- Does not affect prognosis

Microinvasion 5 or 10 mm =
no affect in prognosis

(Rioped, Ronnett et al. 1999, Hauptmann, Friedrich et al. 2017)



OMT - Challenge # 1

**Primary ovarian mucinous borderline tumor
versus adenocarcinoma with expansile
invasion?**

Primary ovarian mucinous carcinoma

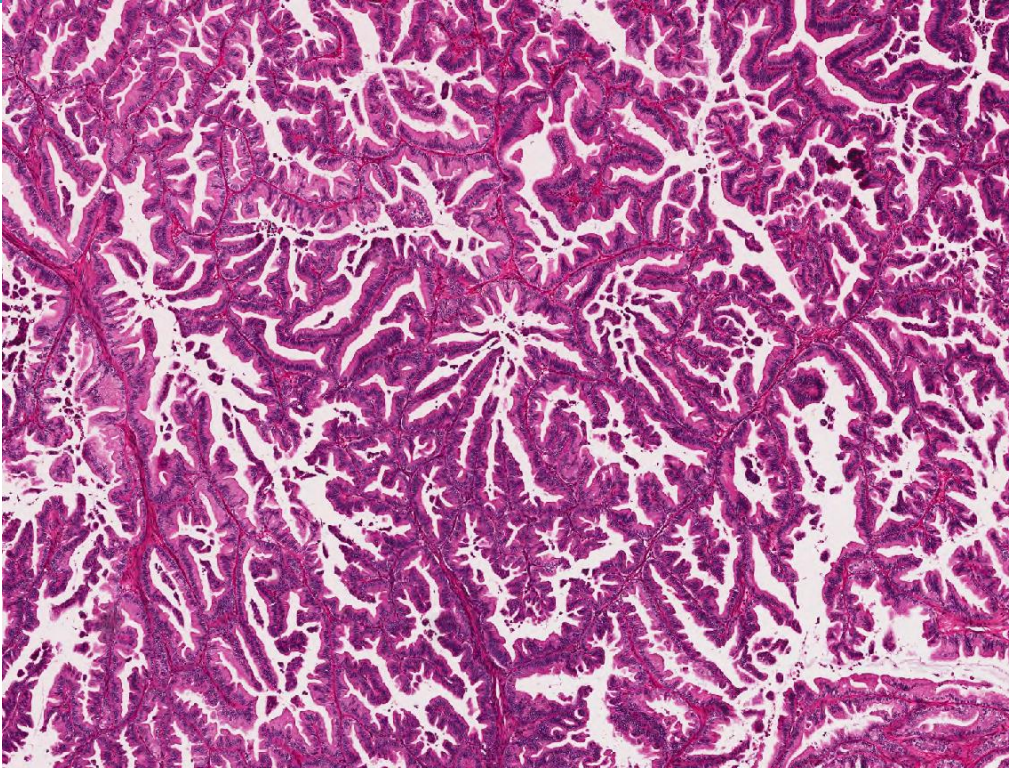


Mucinous adenocarcinoma, expansile/confluent invasion

- Closely packed glands with a confluent back to back arrangement and no or minimal intervening stroma
- Obliteration of cystic spaces

(McCluggage 2010) (Tabrizi et al. 2010)

Primary ovarian mucinous carcinoma



Mucinous adenocarcinoma, expansile/confluent invasion

- Low grade
- Display adenoma – borderline – carcinoma sequence
- Most show MBT and IEC

(McCluggage 2010) (Tabrizi et al. 2010)

Primary ovarian mucinous carcinoma

Mucinous adenocarcinoma, infiltrative/destructive invasion

- Stromal invasion in the form of glands, cell nests, or individual cells, disorderly infiltrating the stroma with desmoplastic stromal reaction
- Very rare in primary tumors!
- Metastasis until proven otherwise
- Poor prognosis

Ovarian Mucinous Tumors

Primary ovarian

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Mucinous tumors – müllerian type

- a.k.a ‘seromucinous’ tumors / mucinous tumor, endocervical type

International Journal of Gynecological Pathology
35:78–81, Lippincott Williams & Wilkins, Baltimore
© 2015 International Society of Gynecological Pathologists

Review

Seromucinous Tumors of the Ovary. What’s in a Name?

Robert J. Kurman, M.D. and Ie-Ming Shih, M.D., Ph.D.

Mucinous tumors – müllerian type

- Proposed nomenclature: **Mixed müllerian tumors**
- Contain a mixture of ciliated cells, mucinous cells, hobnail cells, endometrioid cells, squamous cells (10% rule)
- Positive for CK7, PAX8 and ER; Negative for CK20, CDX2 and SATB2
- Negative for WT-1 (? serous)
- *ARID1A* mutations (characteristic of endometrioid and clear cell tumors)

(Kurman and Shih 2016)

Mucinous tumors – müllerian type

- Majority are borderline. Adenoma and carcinoma are rare
- Correspond to only ~5% of ovarian borderline tumors
- Bilateral (40%)
- Associated with endometriosis (30-50%)
- 20% extraovarian spread. Follows a pattern similar to SBT, no pseudomyxoma peritonei

(Hauptmann et al. 2017) (Nagamine and Mikami 2020)

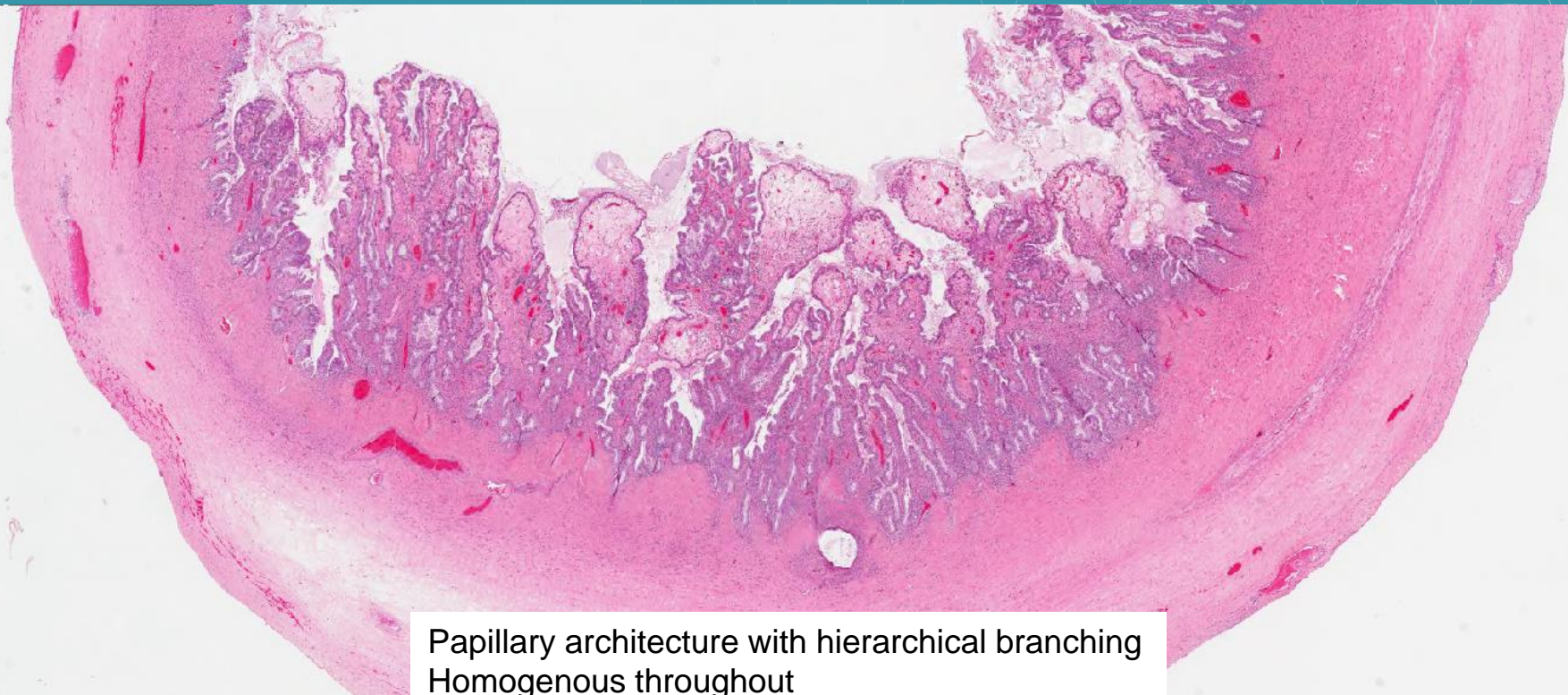
Mucinous tumors – müllerian type

- Mean size 8-10 cm
- Unilocular or oligolocular
- Papillary projections seen grossly

(Hauptmann et al. 2017) (Nagamine and Mikami 2020)

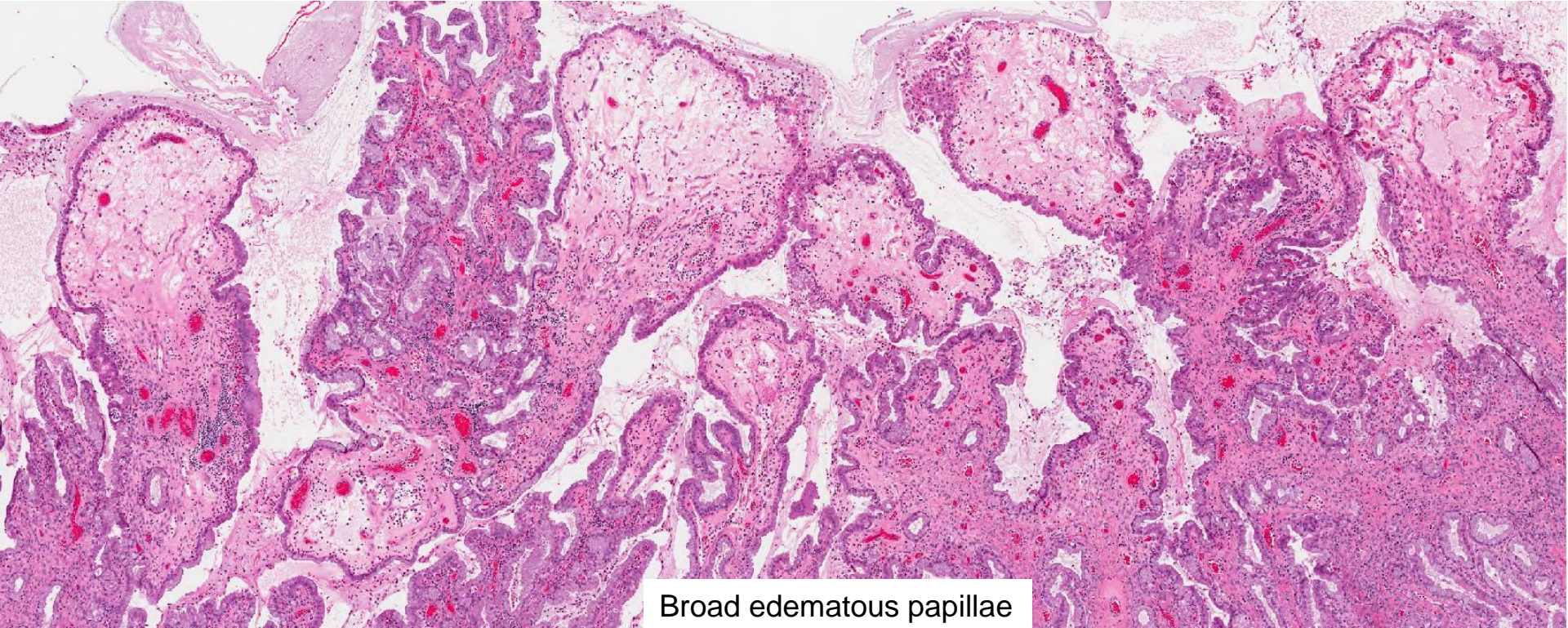


Mucinous tumors – müllerian type



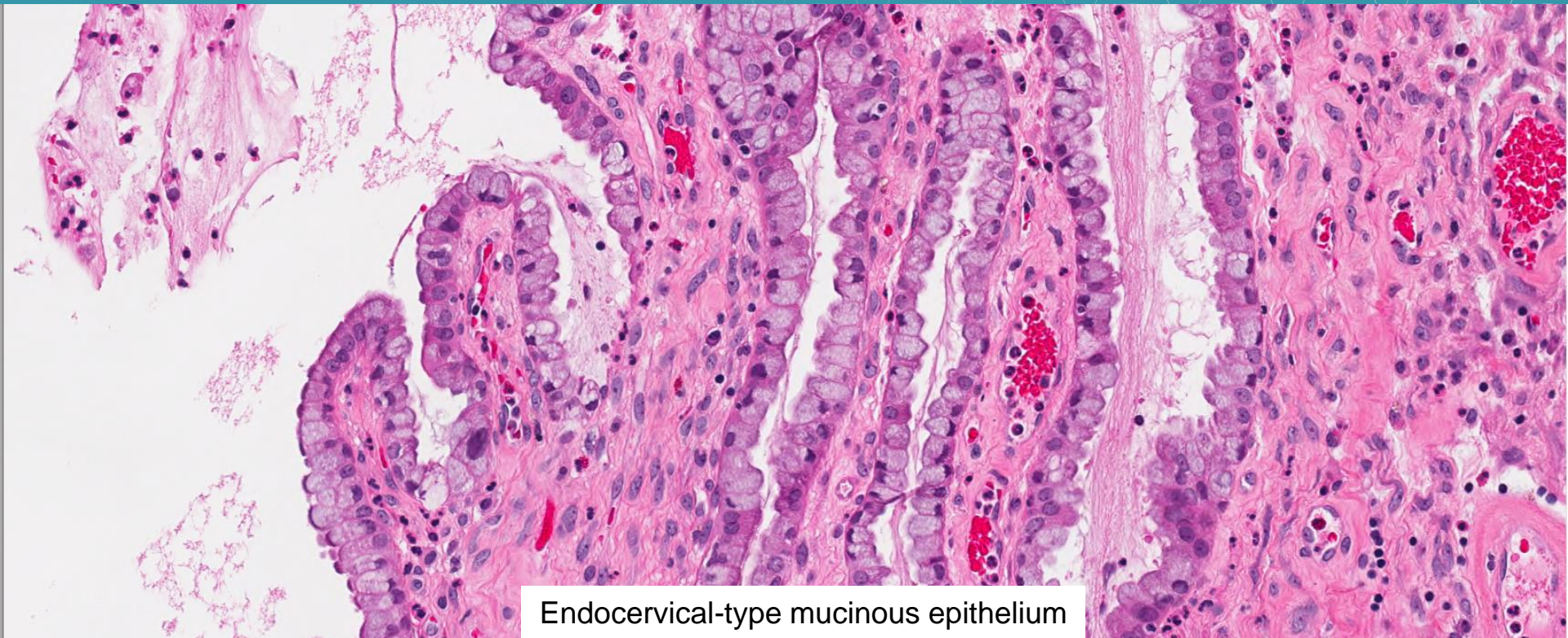
Papillary architecture with hierarchical branching
Homogenous throughout

Mucinous tumors – müllerian type



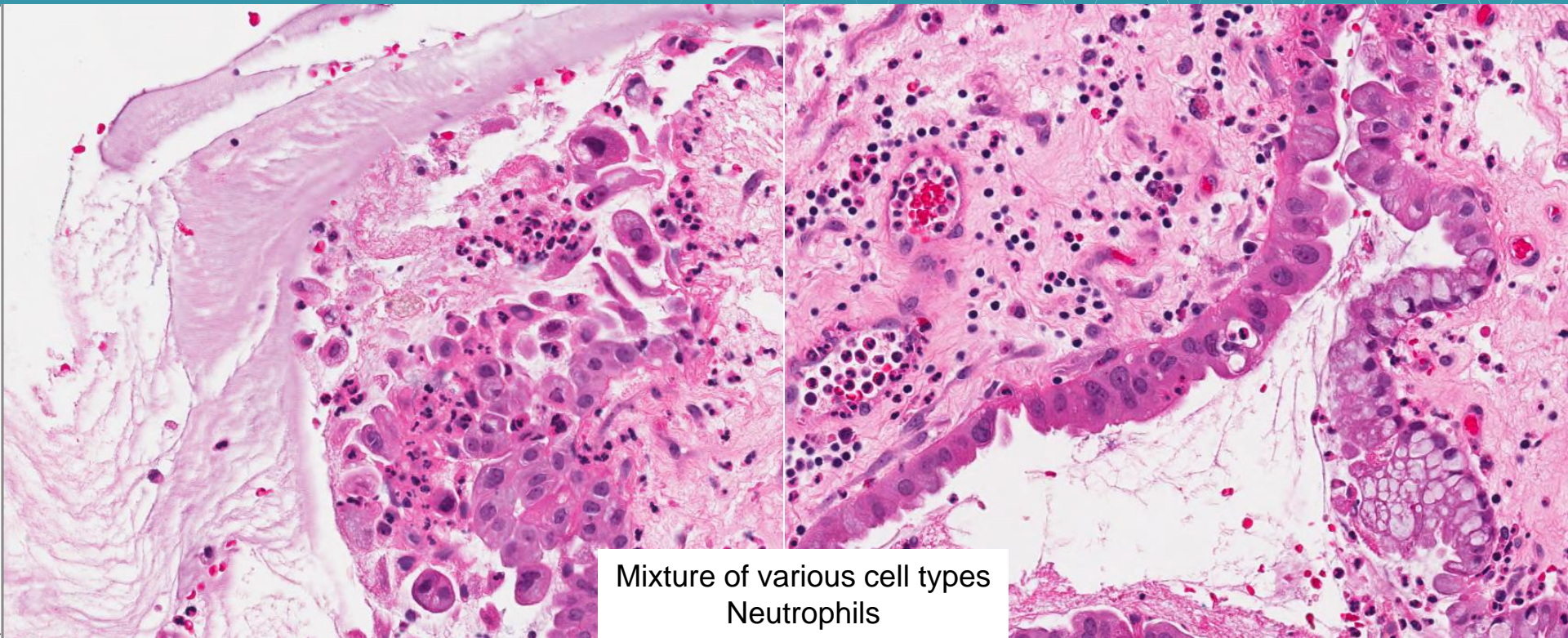
Broad edematous papillae

Mucinous tumors – müllerian type



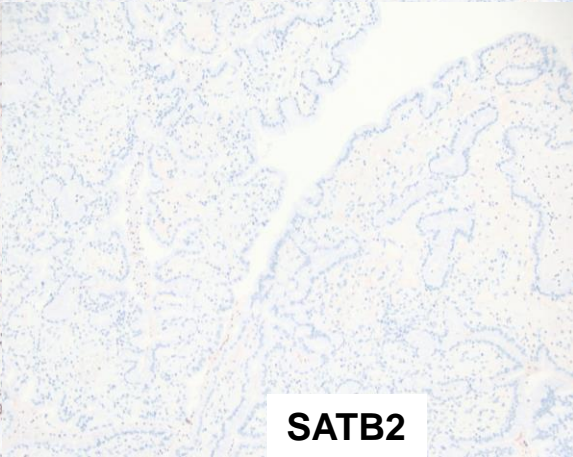
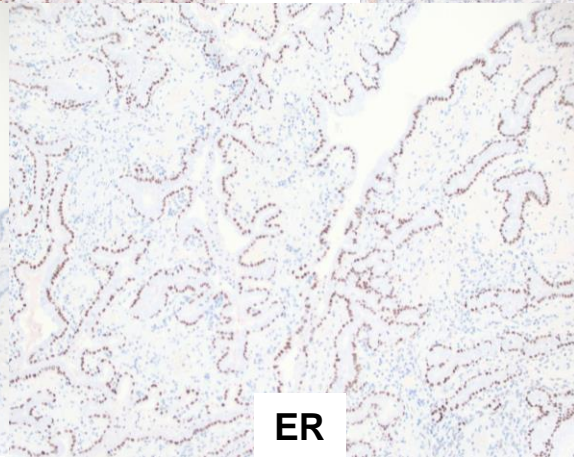
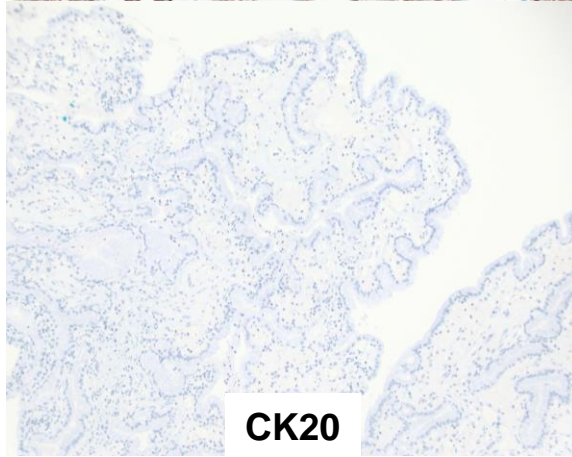
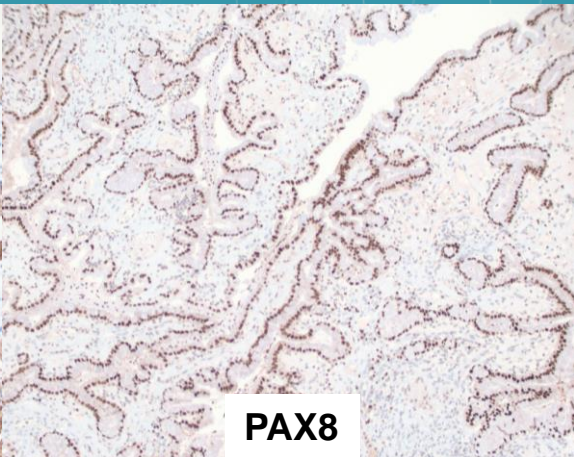
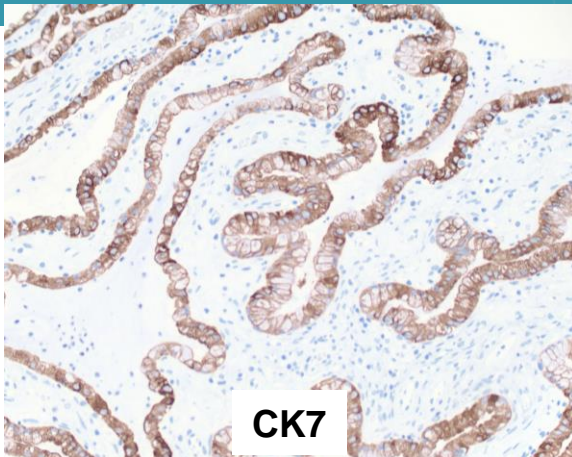
Endocervical-type mucinous epithelium

Mucinous tumors – müllerian type



Mixture of various cell types
Neutrophils

Mucinous tumors – müllerian type



Mucinous tumors – müllerian type

How do you recognize müllerian mucinous tumors?

Architecture + Cell types + Immunohistochemistry

Why is it so important to recognize müllerian mucinous tumors?

Metastasis are not in the differential!

Mucinous tumors – müllerian type

Müllerian mucinous tumor

=

Primary ovarian

No exception!

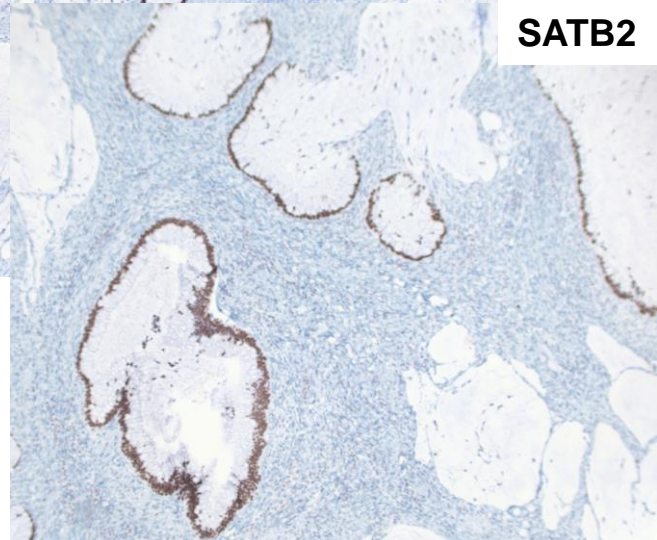
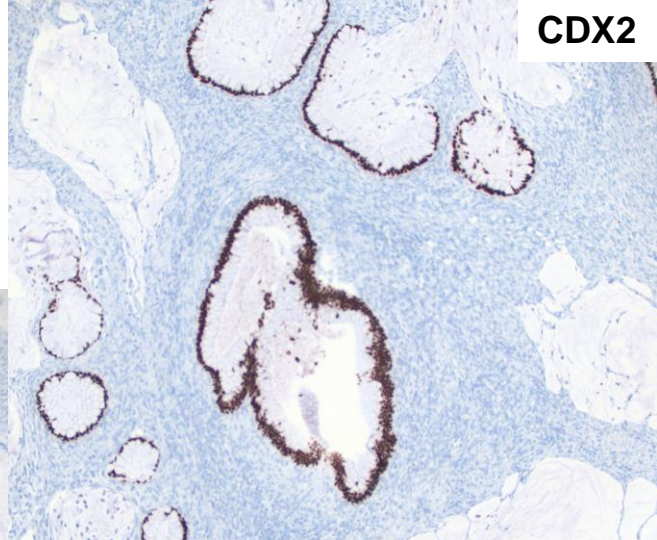
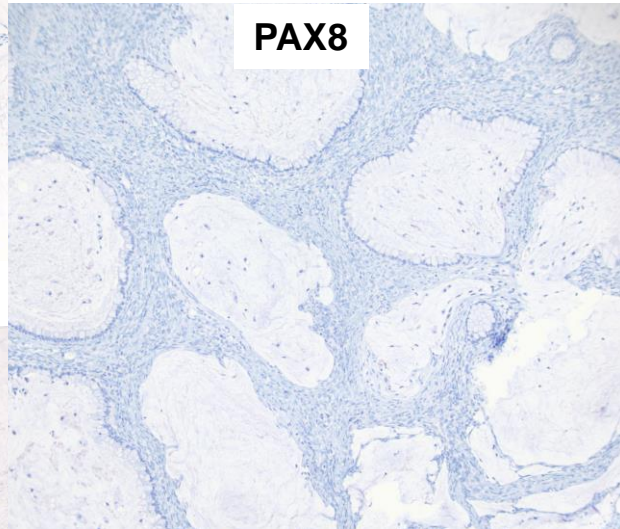
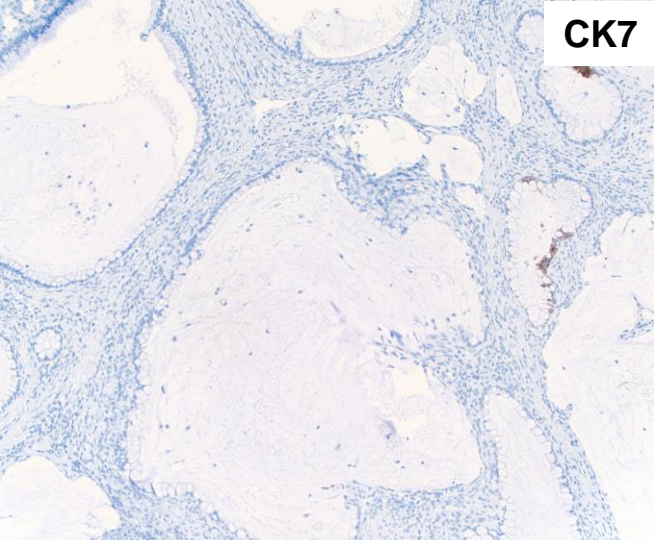
Case 2

- 20 year-old female presented with abdominal discomfort
- Pelvic ultrasound revealed with a 9 cm complex adnexal cyst with internal echos and a 5 cm hyperechoic structure
- A cystectomy was performed and sent to permanents



Case 2

Scanned slide – left ovarian cyst, block A8



Case 2

What is the most appropriate diagnosis?

- a. Mucinous neoplasm, suspicious for appendiceal primary
- b. Mucinous neoplasm, suspicious for colorectal primary
- c. Mucinous neoplasm, suspicious for pancreatobiliary primary
- d. Mucinous neoplasm, consistent with ovarian primary
- e. Mucinous neoplasm, differential includes appendiceal primary and ovarian primary

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What is the most appropriate diagnosis?

- a. Mucinous neoplasm, suspicious for appendiceal primary
- b. Mucinous neoplasm, suspicious for colorectal primary
- c. Mucinous neoplasm, suspicious for pancreatobiliary primary
- d. Mucinous neoplasm, consistent with ovarian primary
- e. **Mucinous neoplasm, differential includes appendiceal primary and ovarian primary**

Case 2

Scanned slide – left ovarian cyst, block A2

Case 2

What is the most appropriate diagnosis?

Primary ovarian mucinous neoplasm with intestinal differentiation and pseudomyxoma ovarii arising in association with a mature cystic teratoma

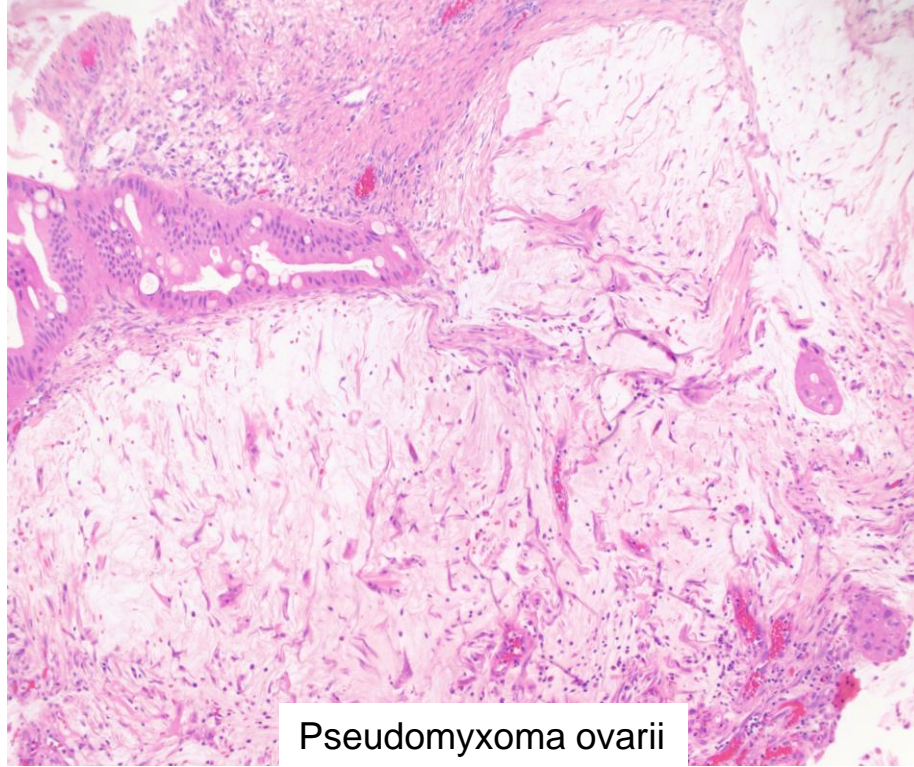
Ovarian Mucinous Tumors

Primary mucinous neoplasms, teratoma associated

- Mature teratomatous component often represents a small proportion of tumor volume (sample well!)
- Extensive pseudomyxoma ovarii in 55%
- Pseudomyxoma peritonei in 25% +/- epithelial component
- Display adenoma, borderline and/or carcinoma morphology
- May have aggressive behavior if peritoneal carcinomatosis

(Simons, Simmer et al. 2020) (McKenney et al. 2008)

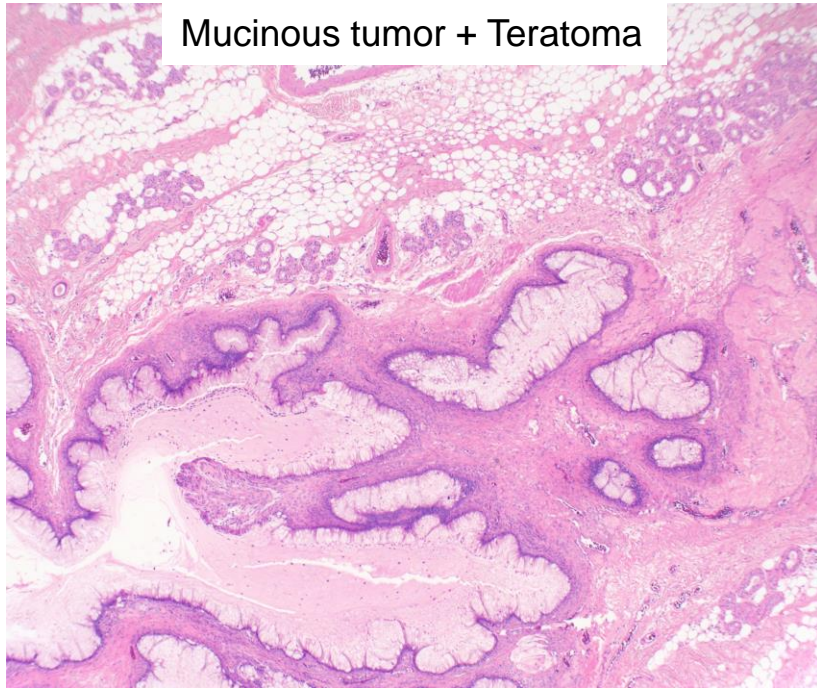
Ovarian Mucinous Tumors



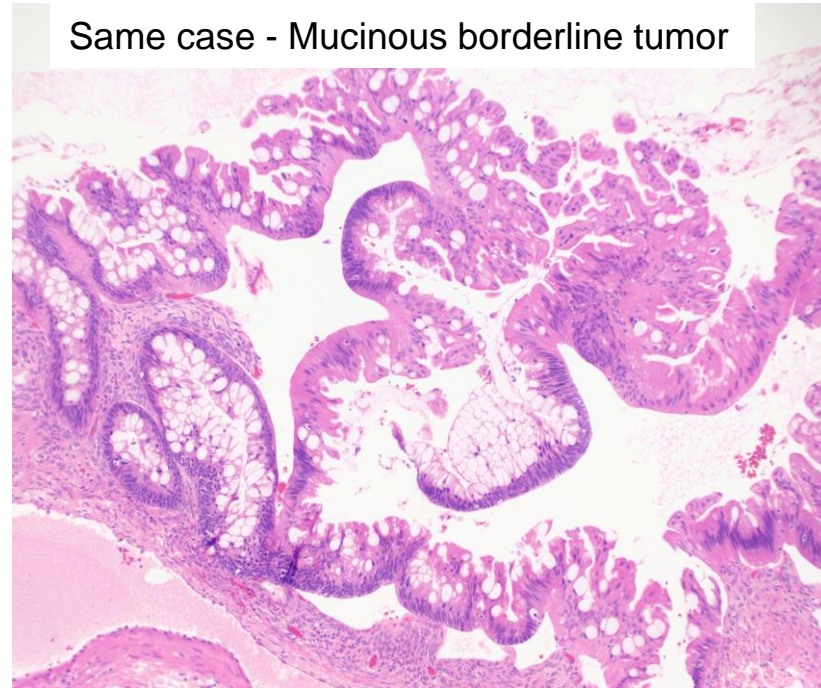
Pseudomyxoma ovarii

Ovarian Mucinous Tumors

Mucinous tumor + Teratoma

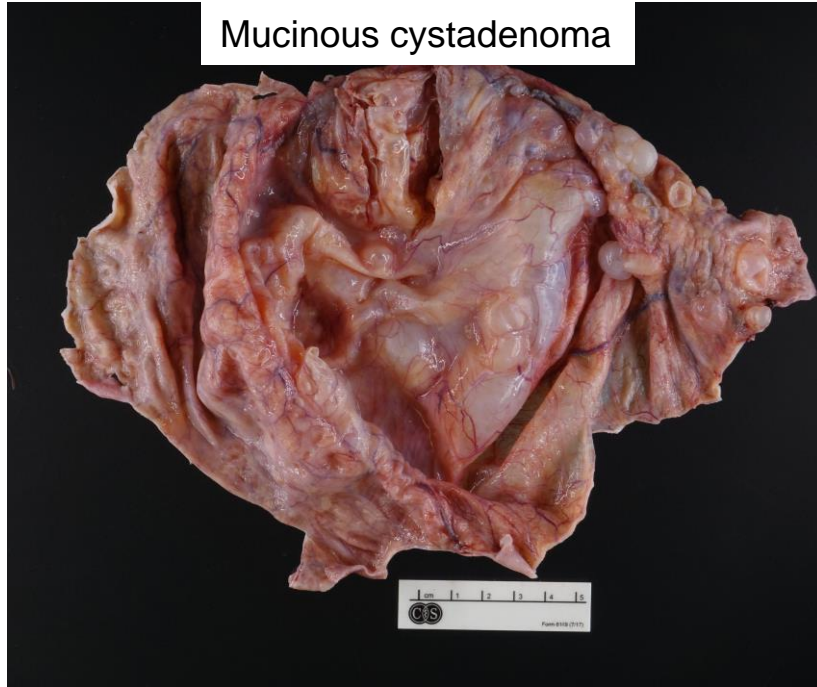


Same case - Mucinous borderline tumor

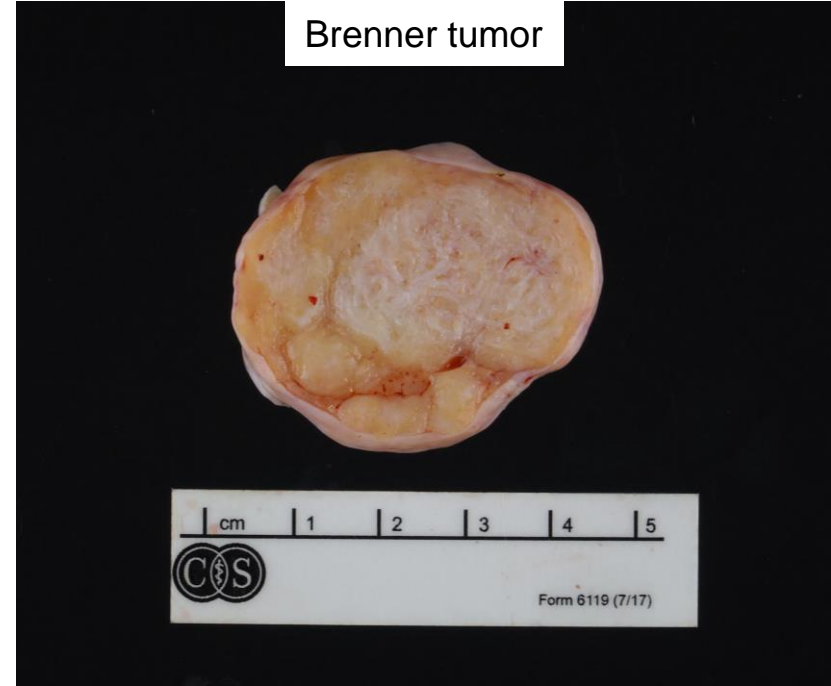


Ovarian Mucinous Tumors

Mucinous cystadenoma

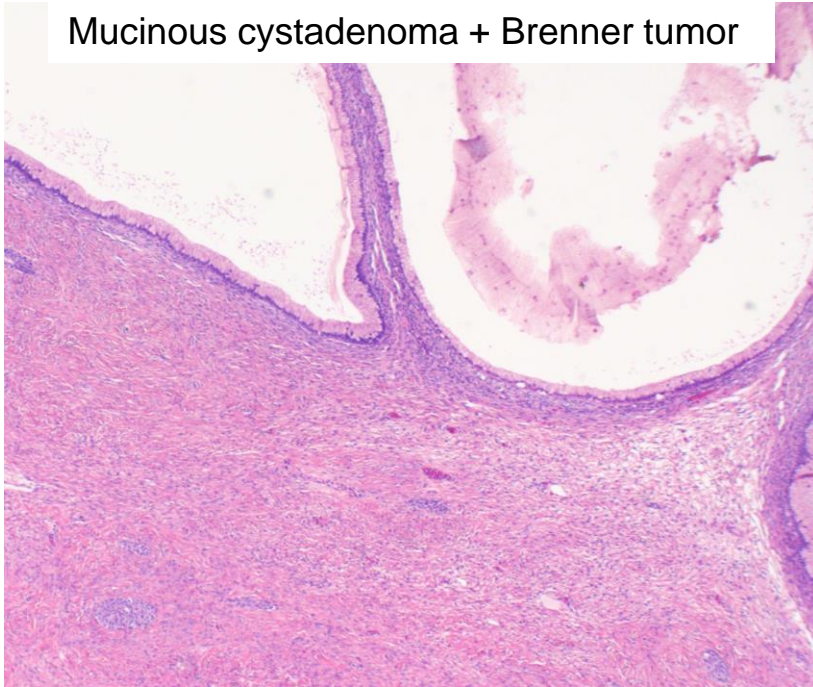


Brenner tumor

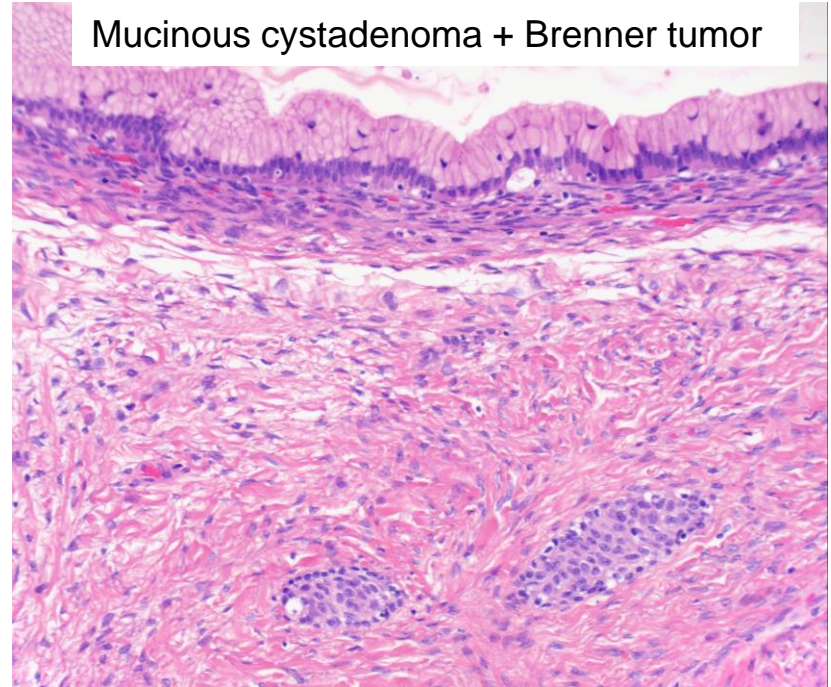


Ovarian Mucinous Tumors

Mucinous cystadenoma + Brenner tumor



Mucinous cystadenoma + Brenner tumor



Ovarian Mucinous Tumors

Teratoma related

- Younger (mean 43 years-old)
- Pseudomyxoma ovarii
- SATB2 +
- **Ovarian primary!**

Brenner tumor related

- Older (mean 61 years-old)
- Calcifications
- SATB2 -
- **Ovarian primary!**

Ovarian Mucinous Tumors

Associated teratoma or Brenner tumor

=

Primary ovarian

Practically no exception

Ovarian Mucinous Tumors

Primary ovarian

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- **Associated teratoma/Brenner tumor**
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Ovarian Mucinous Tumors

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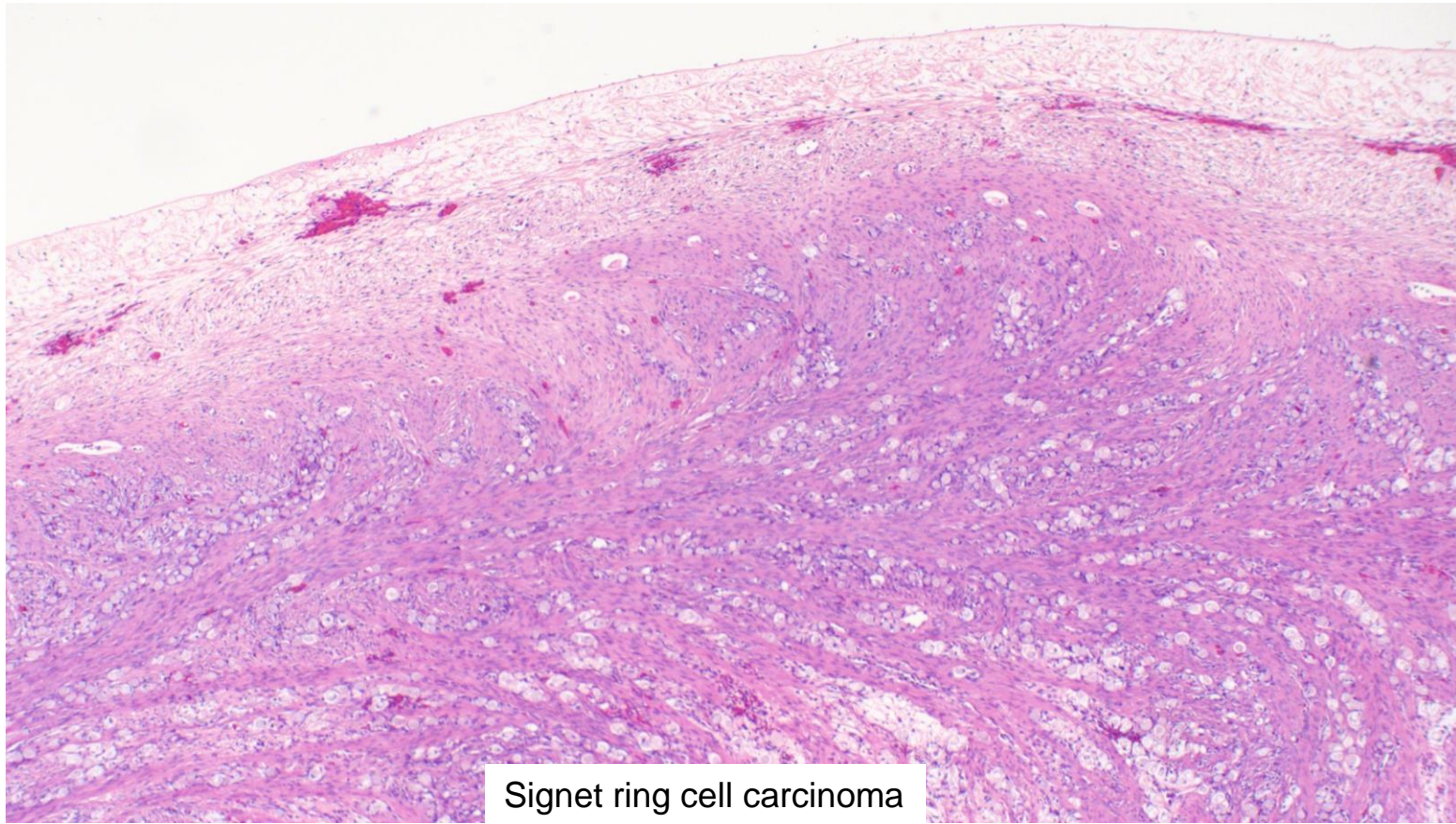
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Metastatic morphologies



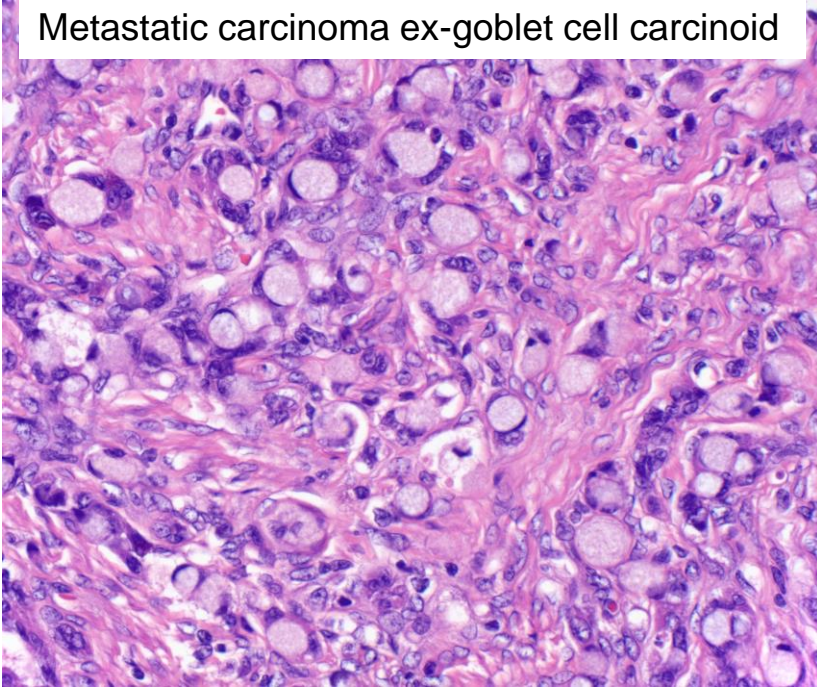
Metastatic morphologies



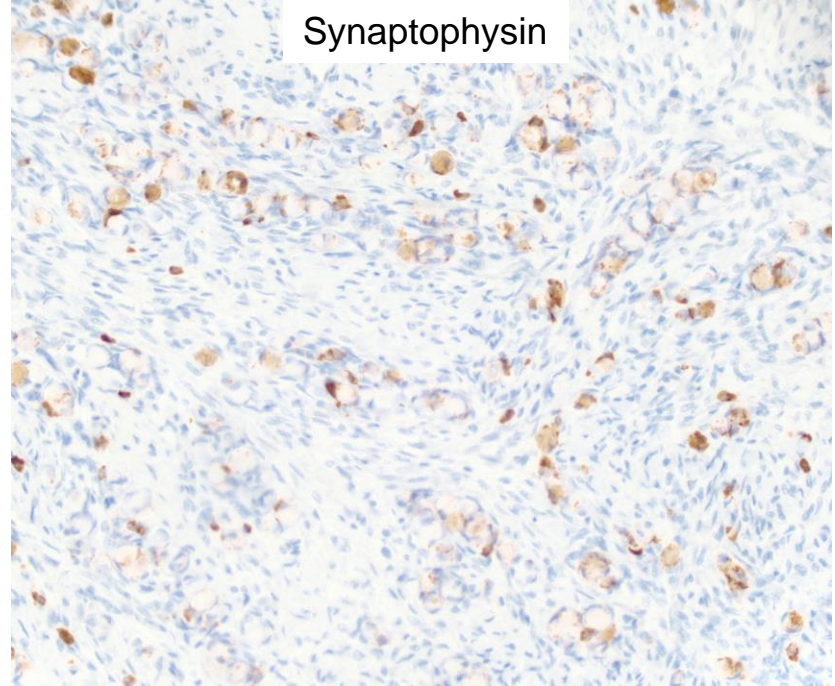
Signet ring cell carcinoma

Metastatic morphologies

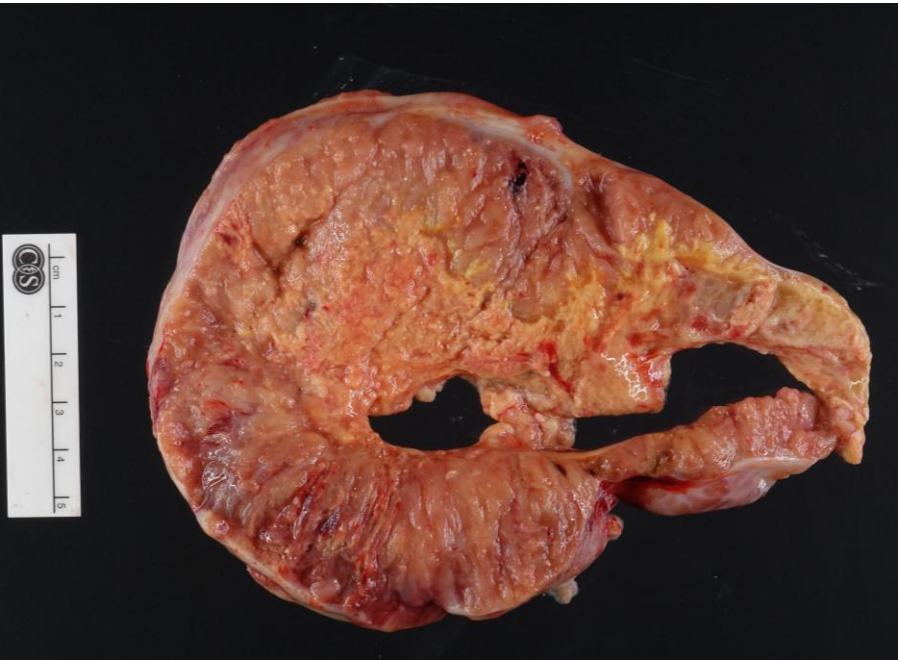
Metastatic carcinoma ex-goblet cell carcinoid



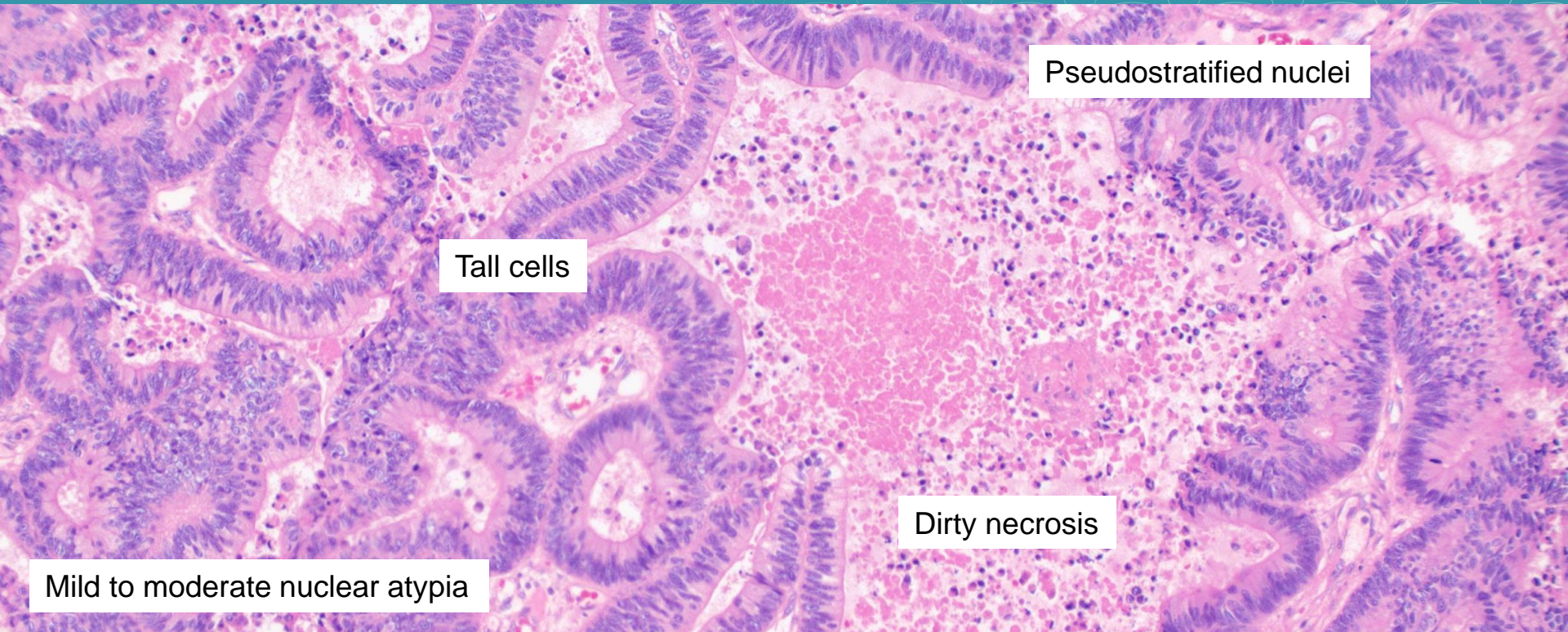
Synaptophysin



Metastatic morphologies



Metastatic morphologies – Colorectal carcinoma



Mild to moderate nuclear atypia

Tall cells

Pseudostratified nuclei

Dirty necrosis

Metastatic morphologies – Colorectal carcinoma



Segmental dirty necrosis

Metastatic morphologies

Predominant signet ring carcinoma

=

Metastatic

No exception!

Metastatic ovarian mucinous tumors

‘Ovarian morphologies’

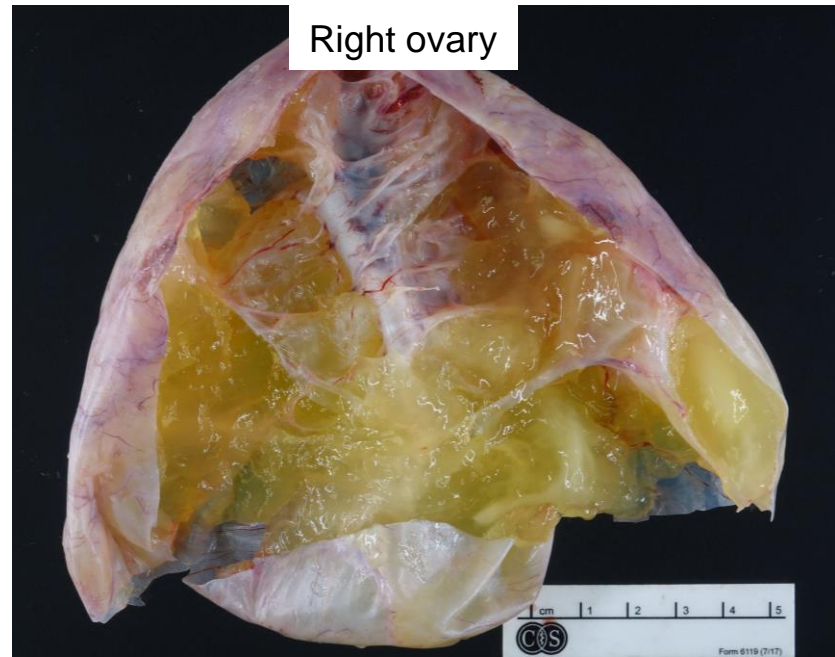
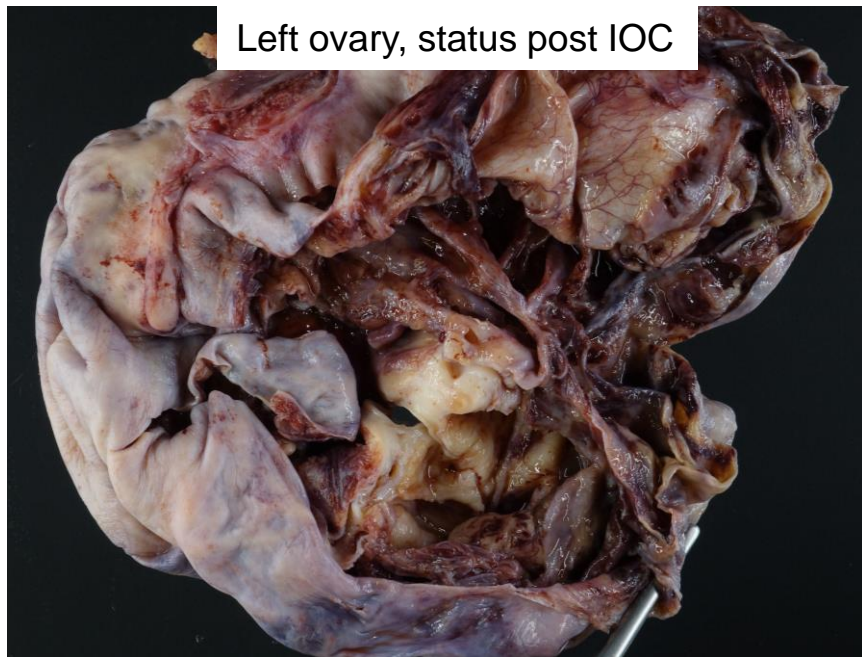
OMT Challenge # 2

**Ovarian mucinous tumor:
Primary or metastatic?**

Case 3

- 46 year-old female presented with abdominal distention, constipation, inability to tolerate food and liquids
- Abdominal CT revealed a 25 cm cystic abdominal mass involving the left ovary
- Laparotomy revealed a mucinous neoplasm in bilateral ovaries and appendix with peritoneal and omental deposits

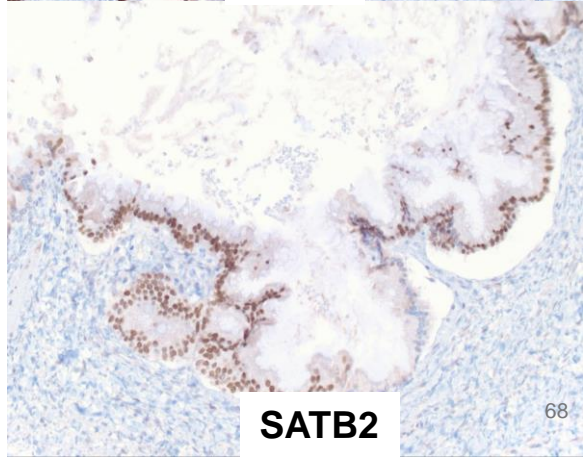
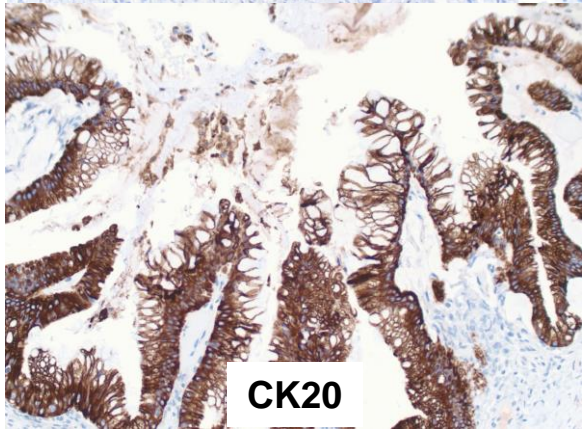
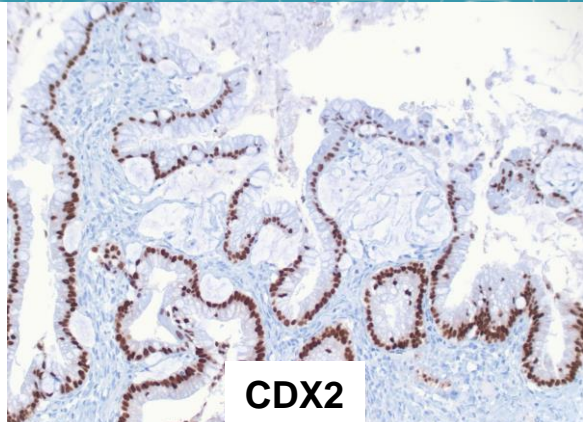
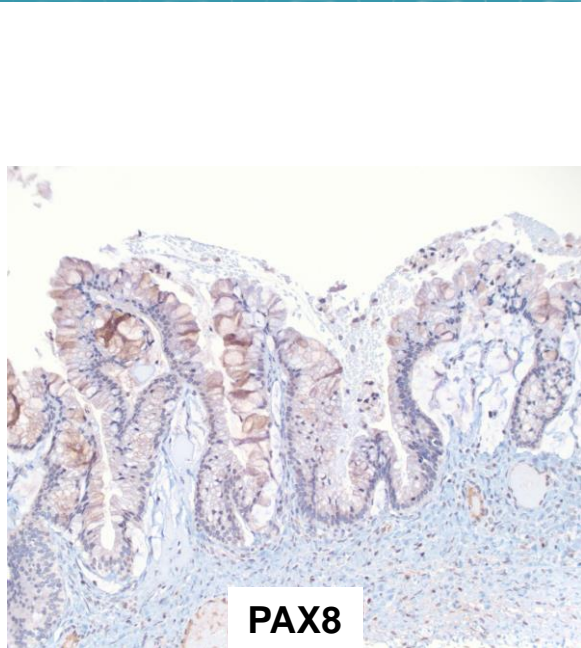
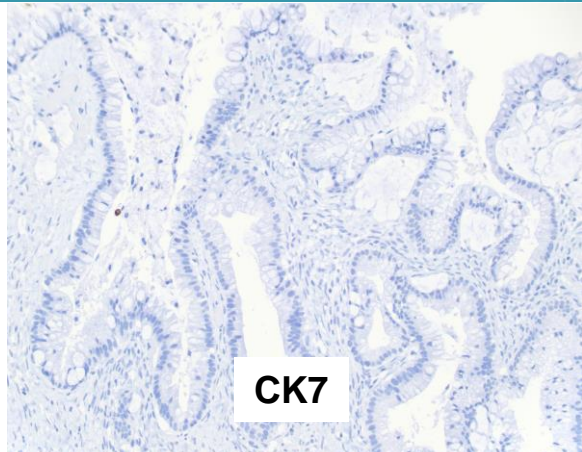
Case 3



Case 3

Scanned slide – Right ovary, block A6

Case 3



Case 3

Appendix



Case 3

Scanned slide – Appendix, block D2

Case 3

What is the most appropriate diagnosis?

- a. Mucinous adenocarcinoma, ovarian primary, metastatic to the appendix
- b. Mucinous adenocarcinoma, appendiceal primary, metastatic to the ovaries
- c. Mucinous borderline tumor, appendiceal primary, metastatic to the ovaries
- d. Low grade appendiceal mucinous neoplasm, metastatic to the ovaries

Case 3

What is the most appropriate diagnosis?

- a. Mucinous adenocarcinoma, ovarian primary, metastatic to the appendix
- b. Mucinous adenocarcinoma, appendiceal primary, metastatic to the ovaries
- c. Mucinous borderline tumor, appendiceal primary, metastatic to the ovaries
- d. **Low grade appendiceal mucinous neoplasm, metastatic to the ovaries**

Appendiceal metastases

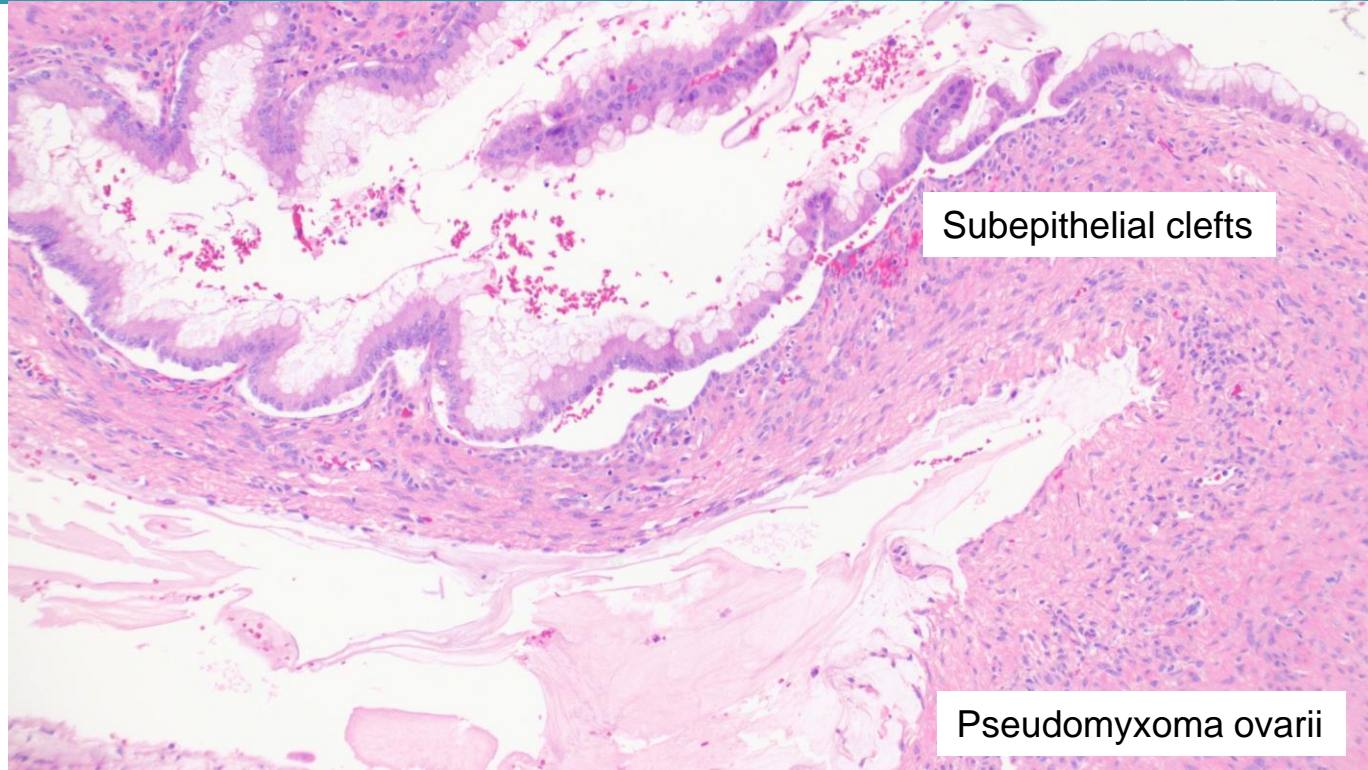
Ovarian metastases with mucinous differentiation arise most frequently from appendiceal primary tumors

LAMN is deceptively bland, mimicking an ovarian mucinous cystadenoma or mucinous borderline tumor

Others:

- Goblet cell carcinoid
- Adenocarcinoma

Appendiceal metastases - LAMN

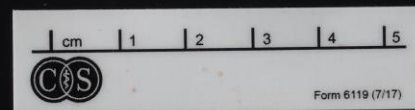
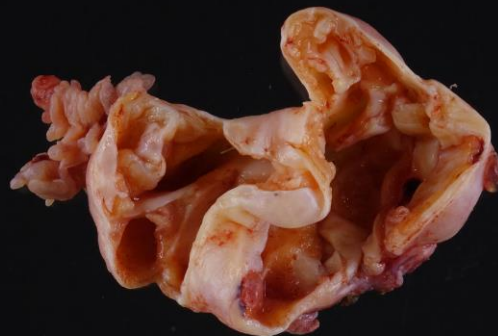
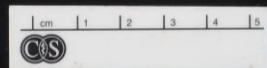


Appendiceal metastases - LAMN



Metastatic ovarian mucinous tumors

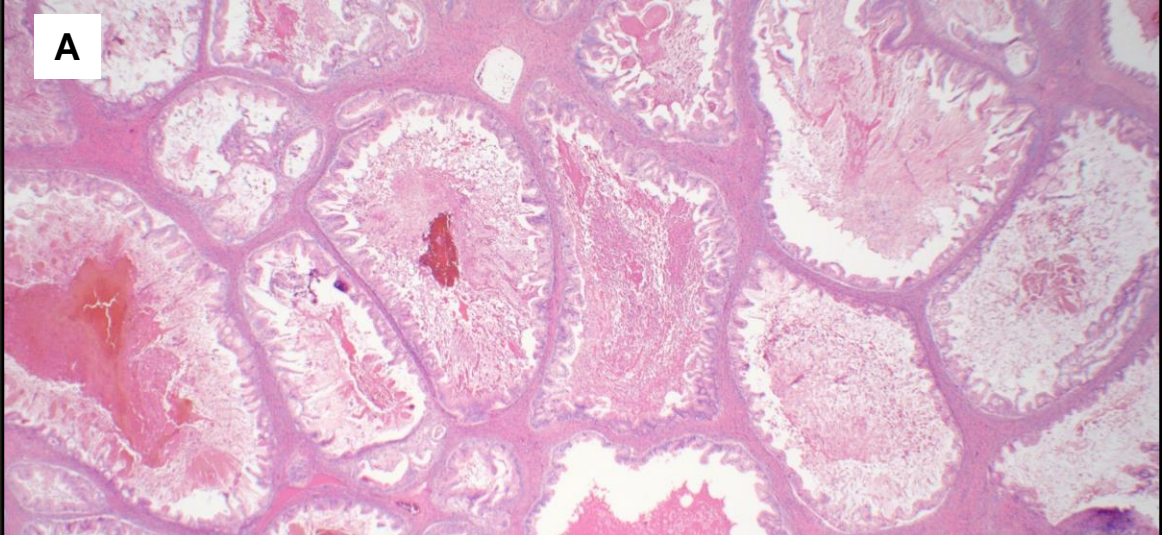
‘Ovarian morphologies’

A**B****C**

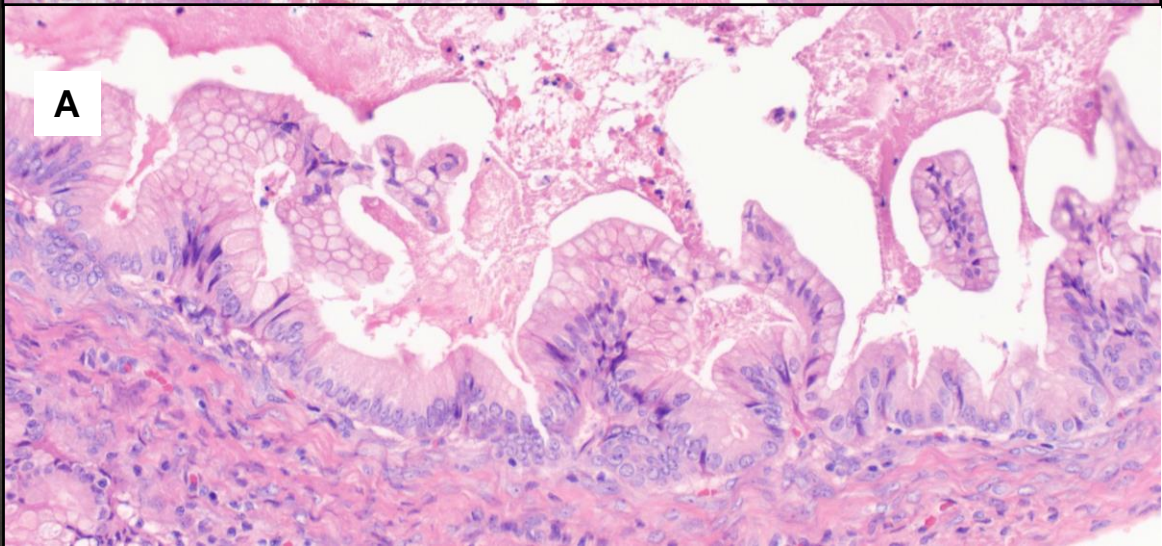
A

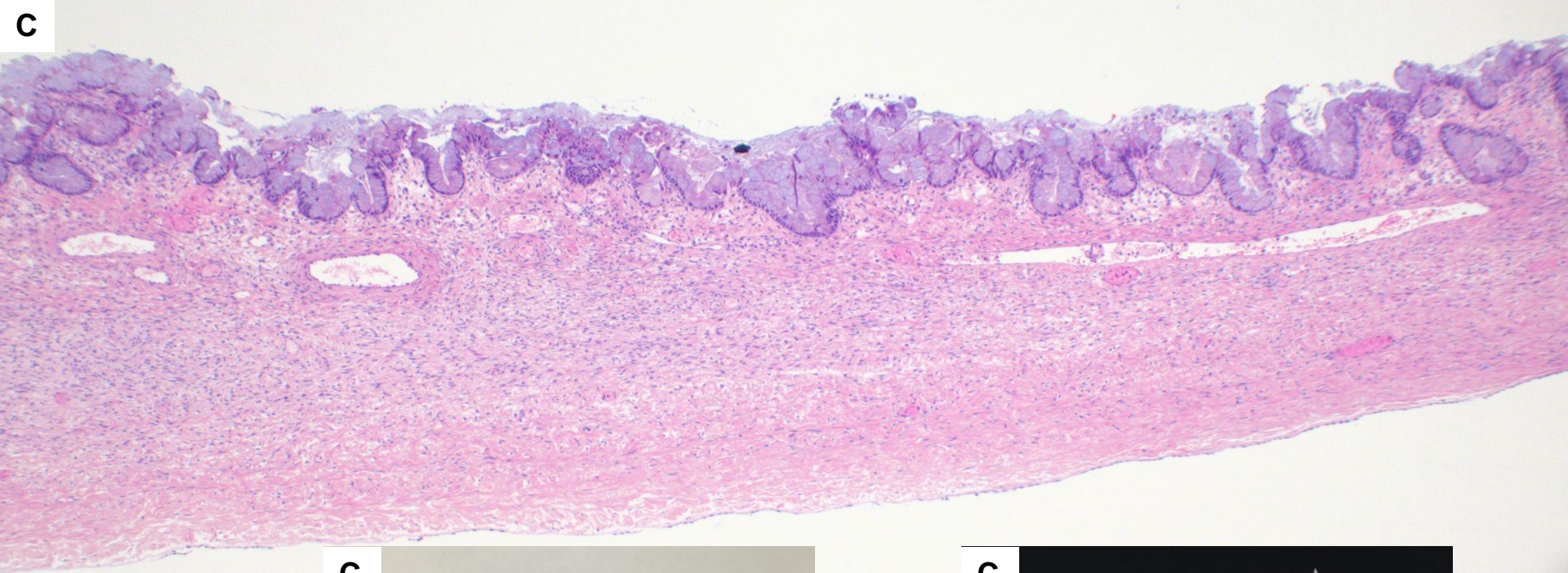


A



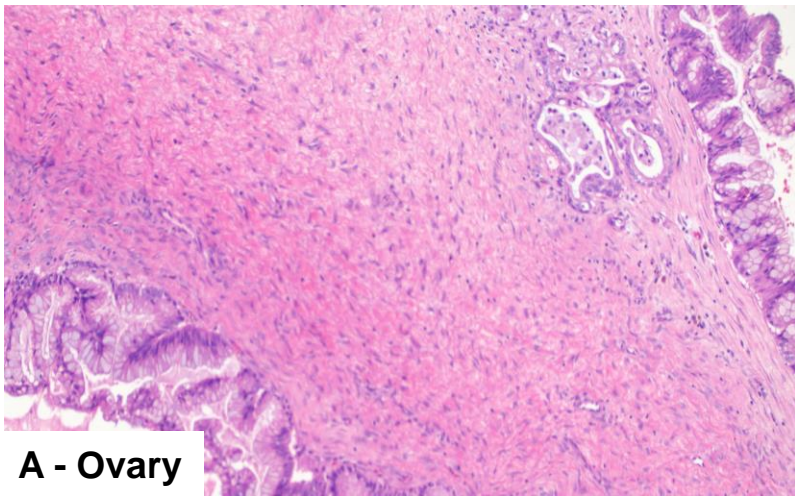
A



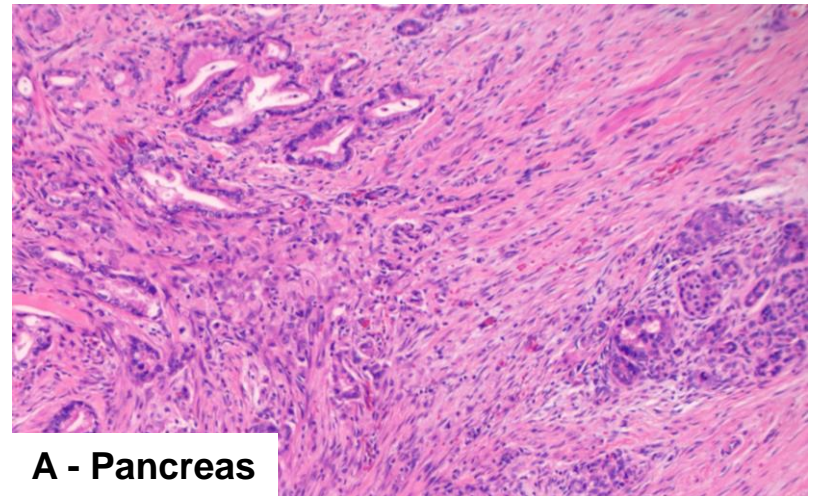


Pancreatobiliary metastases

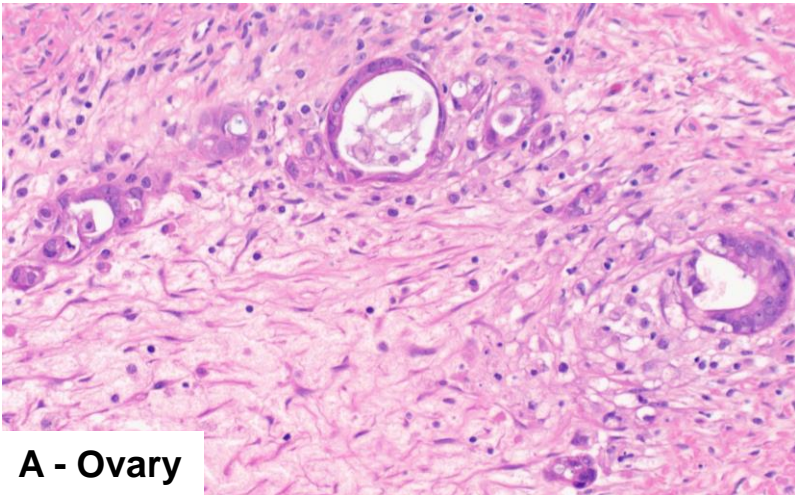
- Large cystic structures with deceptively bland cytologic features
- **Maturation phenomenon:** Small invasive single cells or glands with marked atypia next to the cystic structures
- Focal atypia or infiltration usually present
- Needs adequate sampling



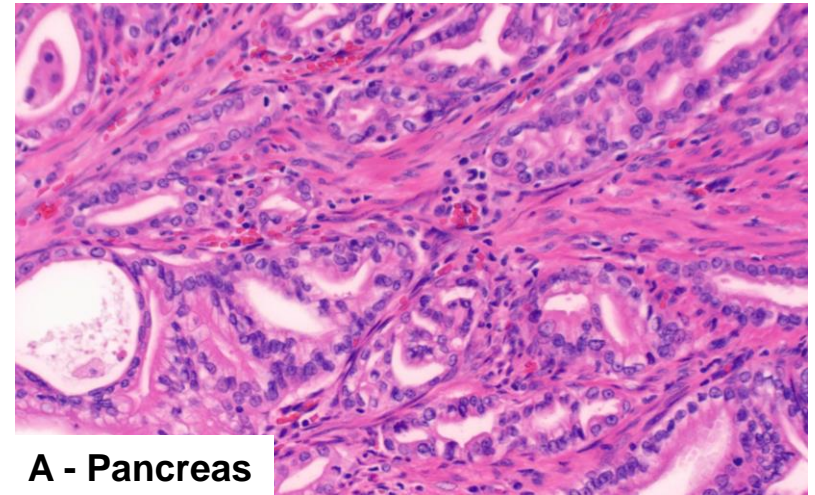
A - Ovary



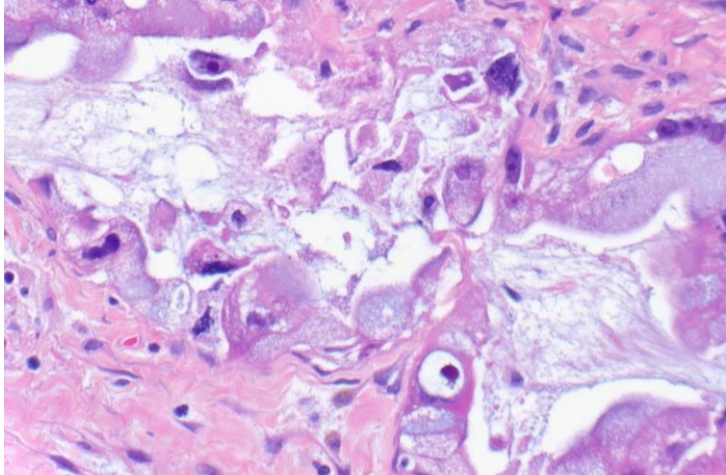
A - Pancreas



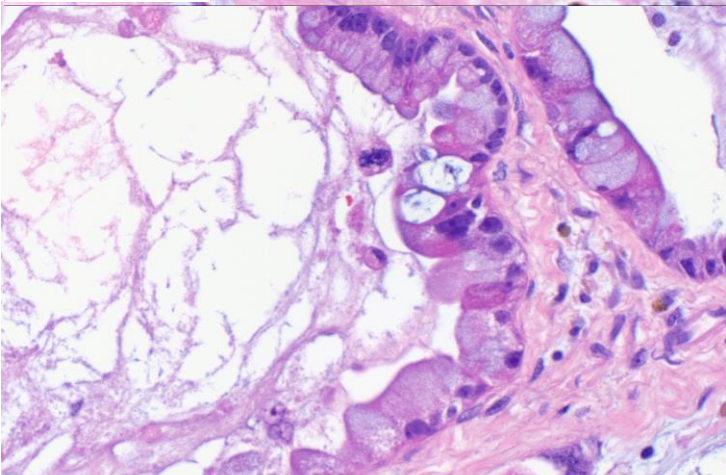
A - Ovary



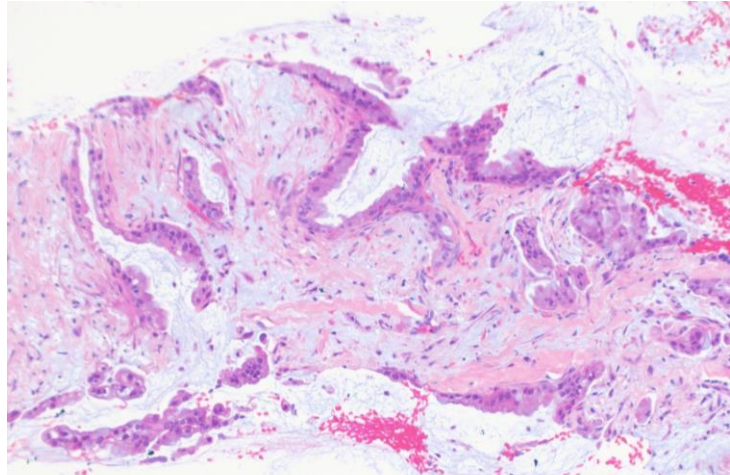
A - Pancreas



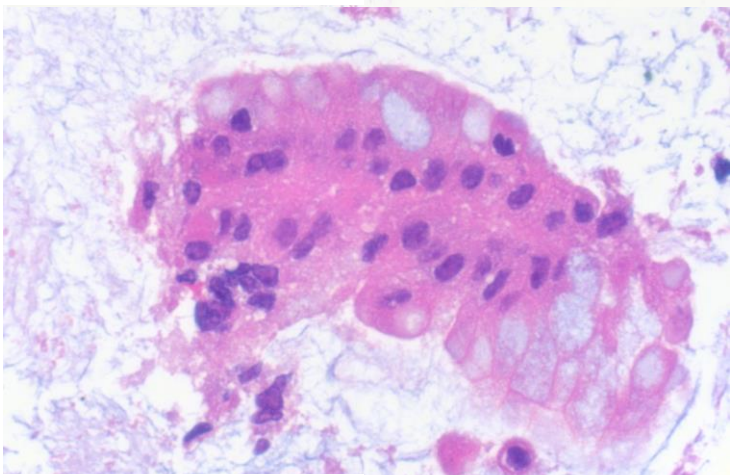
C - Ovary



C - Ovary



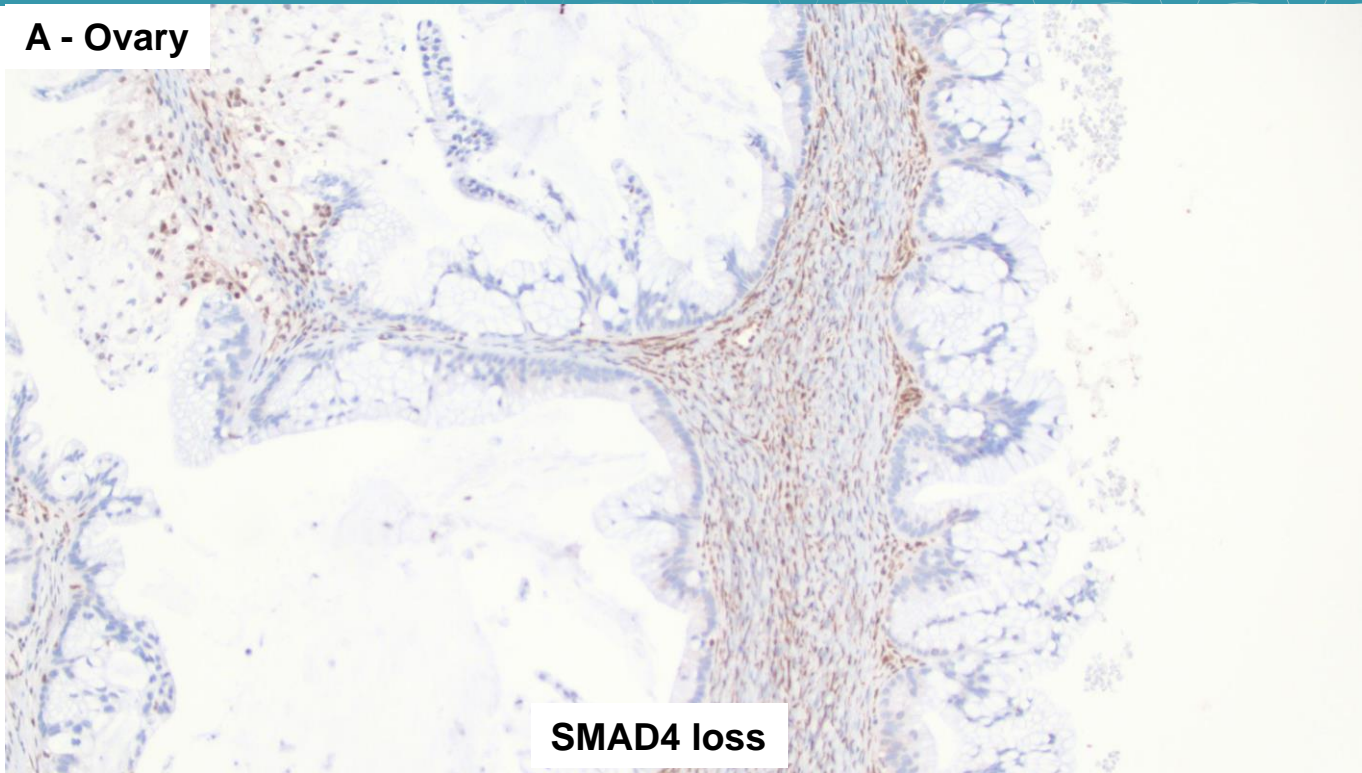
C - Pancreas core



C - Pancreas core

Pancreatobiliary metastases

A - Ovary



SMAD4 loss

Metastatic ovarian mucinous tumors

‘Ovarian morphologies’

Metastatic ovarian tumors

- 45% Gastrointestinal, most common appendix
- 20% Pancreatobiliary
- **13% Uterine cervix**
- 8% Breast
- 5% Uterus
- 10% ovarian metastases from unknown primary tumors

(Frumovitz, Schmeler et al. 2010)

Metastatic endocervical carcinoma

- Uncommon
- In many cases the cervical primary is unknown before presentation of ovarian metastasis
- Can be minimally invasive and lead to ovarian metastasis
- Often simulates primary ovarian mucinous tumors (borderline and carcinoma)
 - Commonly unilateral (65%) and <10 cm
 - Histologically

(Ronnett et al. 2008)

Metastatic endocervical carcinoma HPV positive

Ronnett et al

Am J Surg Pathol • Volume 32, Number 12, December 2008

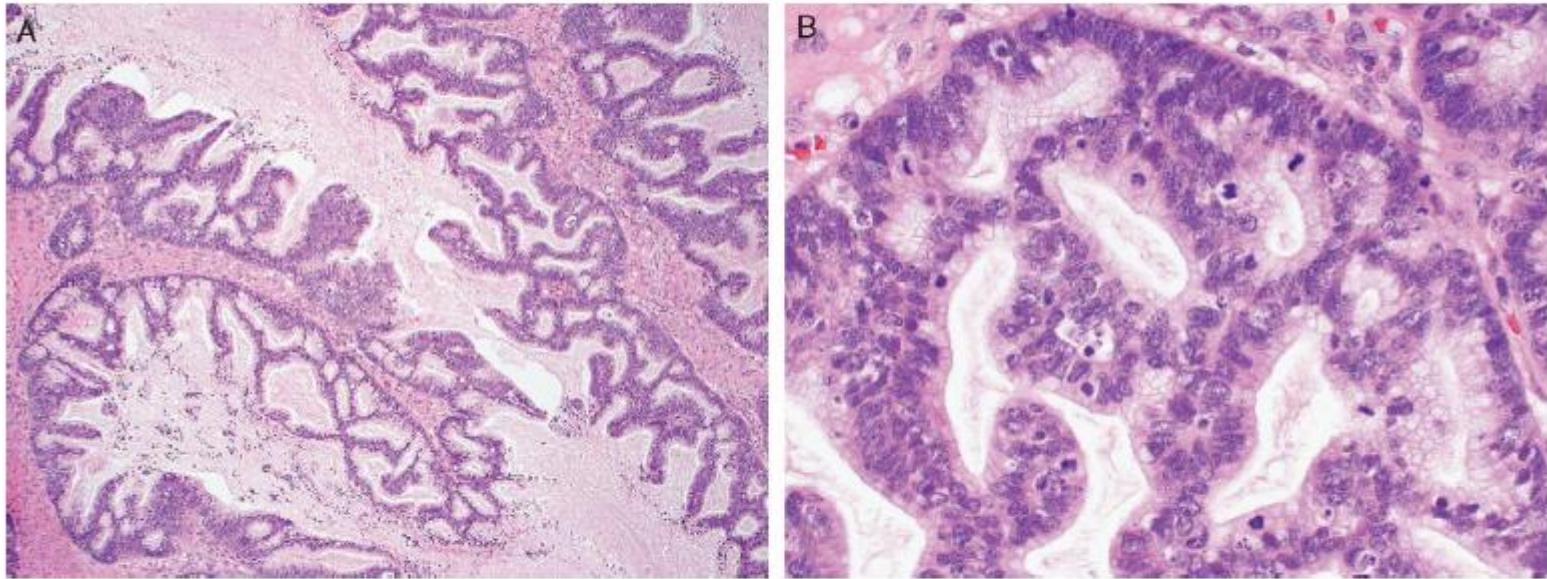


FIGURE 7. Occult invasive cervical adenocarcinoma identified subsequent to diagnosis of ovarian metastasis (case 10). A and B, Ovarian metastasis is composed of cystic glands lined by proliferative mucinous epithelium having intraluminal papillary epithelial tufts, and nuclear atypia with mitotic figures and apoptotic bodies, without evidence of stromal invasion, simulating a primary ovarian atypical proliferative (borderline) mucinous tumor with intraepithelial carcinoma.

Metastatic endocervical carcinoma HPV positive

- Confluent glandular, cribriform, or villoglandular patterns
- Cytologic features and IHC are variable
 - Usual-type: Columnar epithelium with nuclear crowding, stratification, basal apoptotic bodies, and apical mitotic figures. CK7+, CK20-, CDX2-.
Differential includes endometrioid carcinoma
 - Intestinal type: as above but with goblet cells. CK7+, CK20+/-, CDX2+/-
- **Positive for p16 and HPV ISH**

Metastatic endocervical HPV negative

- Ovarian metastases are very rare
- Most are expected to be gastric type
- Difficult differential with primary ovarian mucinous tumors both histologically and by immunohistochemistry
- Rely on the identification of the cervical primary

Ovarian Mucinous Tumors

Primary ovarian

- **Mullerian mucinous tumor**
- **Associated teratoma/Brenner tumor**
- Unilateral
- Very large
- Expansile growth pattern
- Mural anaplastic nodules
- Uniformly bland cystadenoma
- Associated cystadenofibroma

Metastatic

- **'Metastatic morphologies'**
- **Extraovarian spread/pseudomyxoma peritonei**
- Bilateral
- Not so large
- Infiltrative growth pattern
- Multinodular gross appearance
- Lymphovascular involvement
- Ovarian surface/hilar involvement
- Lack of CK7
- Positivity for SATB2

Case 4

- 58 year-old female presented to PCP with anemia, fatigue and abdominal pain
- CT scan revealed with 12 cm mass in the pelvis with multiple septations and nodular masses suggestive of a malignant ovarian neoplasm
- Exploratory laparotomy revealed Stage IIIC ovarian cancer with extensive peritoneal involvement

Case 4

Slide scan – Right ovary

Case 4

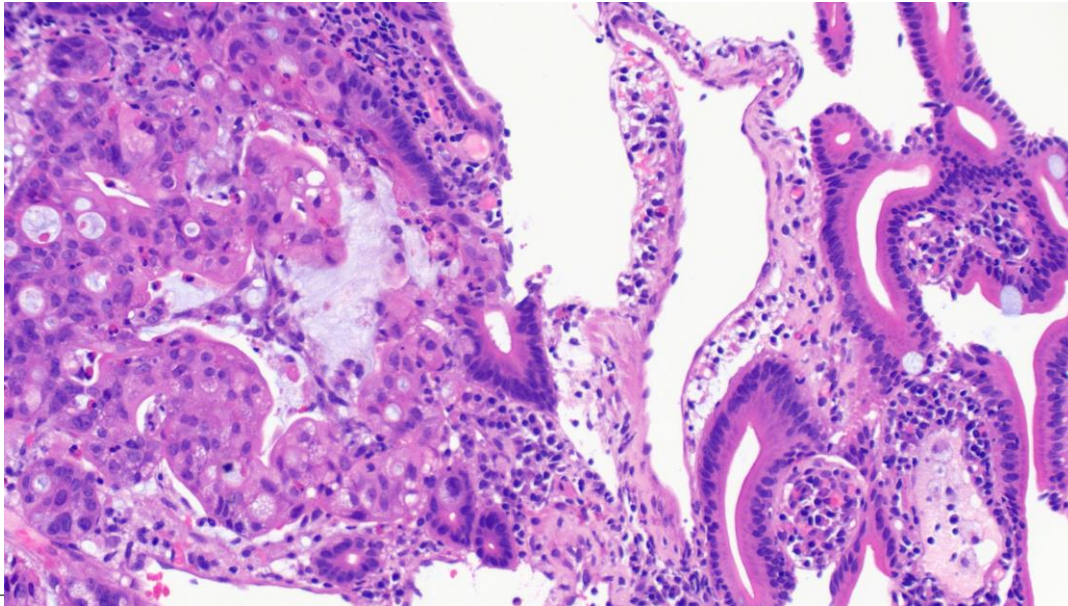
Original Diagnosis:

Mucinous adenocarcinoma, intestinal type

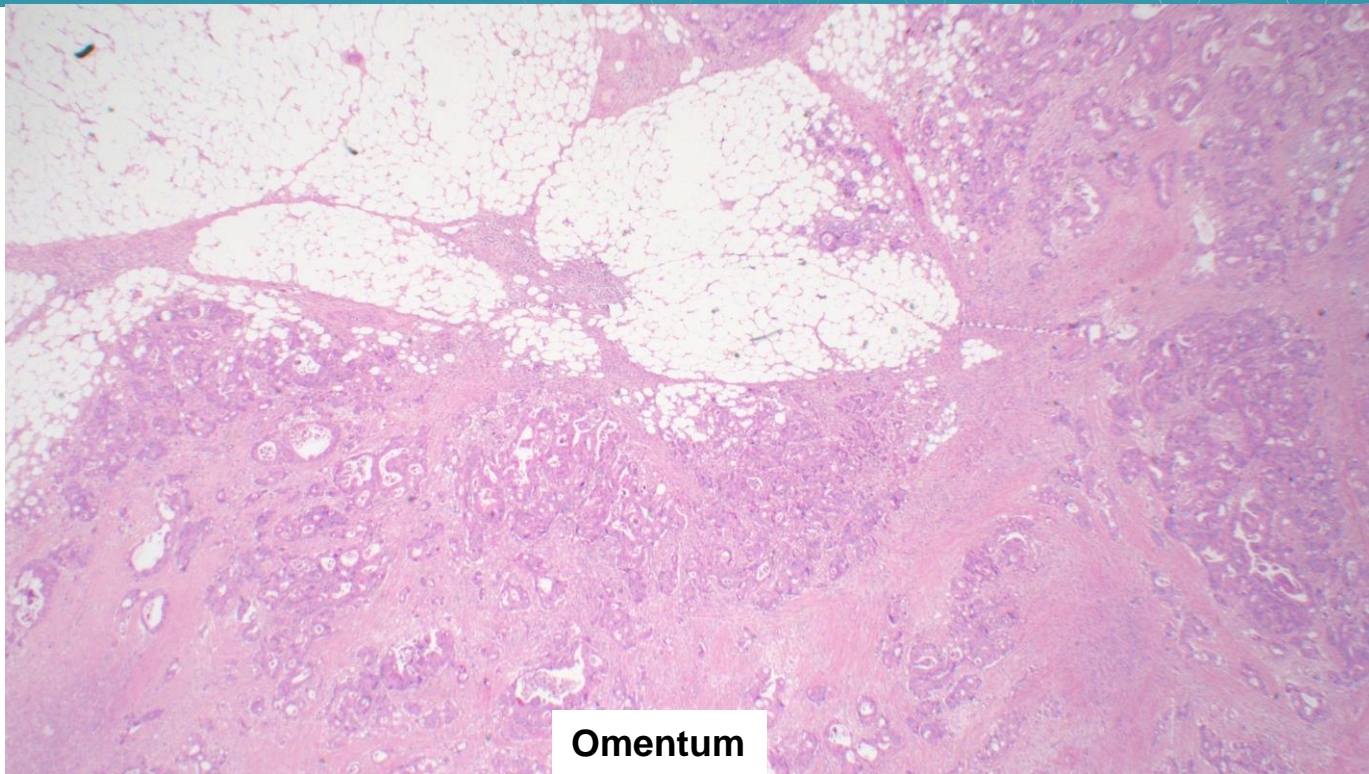
Differential includes primary ovarian versus metastasis from GI tract

Case 4

Months later - The EGD revealed a circumferential mass in the 2nd part of the duodenum **Duodenal biopsy**



Case 4



Extraovarian spread

Extraovarian spread/pseudomyxoma peritonei

=

Metastasis

Exception: OMTs arising in association with teratoma

Ovarian Mucinous Tumors

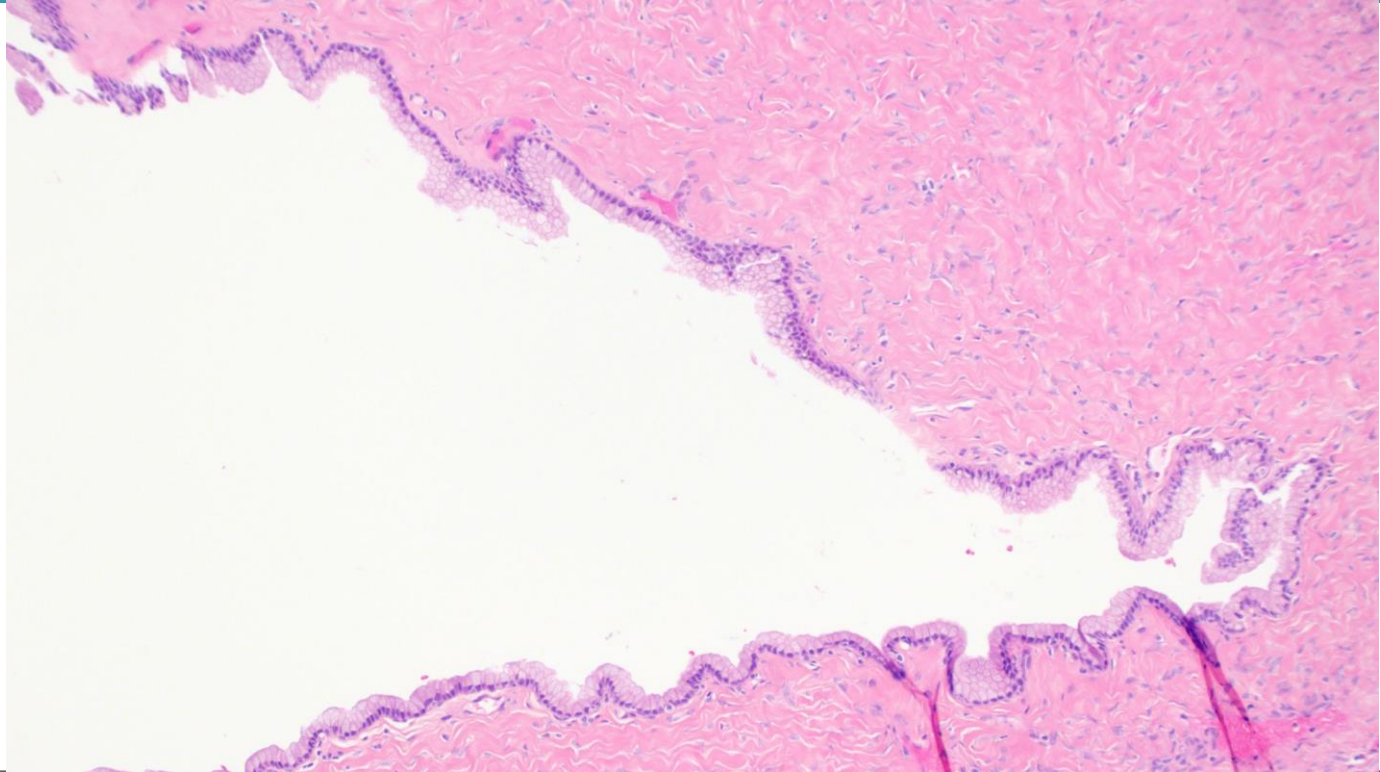
Primary ovarian

- **Mullerian mucinous tumor**
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- Unilateral
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Metastatic

- **'Metastatic morphologies'**
- **Extraovarian spread/pseudomyxoma peritonei**
- Bilateral
- Not so large
- Infiltrative growth pattern
- Multinodular gross appearance
- Lymphovascular involvement
- Ovarian surface/hilar involvement
- Lack of CK7
- Positivity for SATB2

Mucinous cystadenoma



Mucinous cystadenoma

- Can be müllerian or gastrointestinal – no need to differentiate in path report
- Single layer of cells
- Uniformly bland cytology with minimal/no atypia
- Epithelial lining may be undulating or form small, filiform papillae
- Lacks significant epithelial proliferation, complexity, and nuclear atypia
- Crypts are not considered complex architecture

Mucinous cystadenoma

- Main differential: Low grade appendiceal mucinous neoplasm (LAMN)
- Normal appendix: Rest assured this is an ovarian primary
- IHC helpful: SATB2 +
- Permanents: Do NOT include metastasis in the differential if appendiceal primary has been excluded
- Frozen section: Metastasis cannot be excluded

Mucinous cystadenoma

- Second differential: Pancreatobiliary metastasis
- Not uniformly bland cytology
- IHC often not helpful except for SMAD4 loss
- Frozen section: Metastasis cannot be excluded

Ovarian Mucinous Tumors

Primary ovarian mucinous cystadenoma

- Thin walled ovarian cyst(s)
- Bland mucinous epithelium
- Uniformly bland
- Mucin extravasation
- SATB2 negative

Low grade appendiceal mucinous neoplasm

- Thin walled ovarian cyst(s)
- Bland mucinous epithelium
- Very tall epithelium
- Pseudomyxoma ovarii
- **SATB2 positive**
- Subepithelial clefts

WD pancreatic adenocarcinoma

- Thin walled ovarian cyst(s)
- Bland mucinous epithelium
- **At least focal atypia/ infiltrative growth**
- Pseudomyxoma ovarii
- Loss of SMAD4 (50%)

OMT Challenge # 3

Interpreting immunohistochemistry

Ovarian Mucinous Tumors (OMT) Immunohistochemistry

	CK7	CK20	CDX2	SATB2	PAX8	Other
Primary OMT müllerian	+	-	-	-	+	ER+
Primary OMT gastrointestinal type NOS	+/-	-/+	-/+	-/+	+/-	ER-
Primary OMT with teratoma	-	+	+	+	-	ER-
Primary OMT with Brenner	+/-	+/-	-/+	-	-	ER-, GATA-3 +
Appendiceal metastasis	+/-	+/-	+	+/-	-	
Pancreatobiliary metastasis	+/-	+/-	+/-	-	-/+	Loss of SMAD4 in 50%
Gastroesophageal metastasis	+/-	+/-	+/-	-	-	
Colorectal metastasis	-/+	+	+	+	-	Nuclear B-catenin
Endocervical metastasis	+	-/+	-/+	-	+/-	Most p16+ and HPV ISH+

Ovarian Mucinous Tumors (OMT)

Immunohistochemistry

CK7	Positive: All primary müllerian OMTs Majority of primary OMTs gastrointestinal type NOS Majority of pancreatobiliary and gastroesophageal metastases
SATB2	Positive: Appendiceal and colorectal metastases Primary OMTs with teratoma Negative: Majority of primary OMTs gastrointestinal type NOS Primary OMTs with Brenner tumor Pancreatobiliary and gastroesophageal metastases
PAX8	Positive: All primary müllerian OMTs Some primary OMTs gastrointestinal type NOS Few pancreatobiliary metastases Negative: Primary OMTs with teratoma Appendiceal and colorectal metastases Some pancreatobiliary and gastroesophageal metastases
CK20 and CDX2	Positive: Majority of primary OMTs gastrointestinal type NOS (patchy/weak to moderate) Primary OMTs with teratoma Appendiceal and colorectal metastases Some pancreatobiliary and gastroesophageal metastases

Ovarian Mucinous Tumors (OMT) Immunohistochemistry

Extent and intensity of staining are important

Primary ovarian

- CK7 +++ (majority)
- PAX8 +/- (~40%)
- CK20 +/- (patchy)
- CDX2 +/- (patchy)
- SATB2 -

Metastatic Appendix/Low GI

- SATB2 +++
- CDX2 +++
- CK20 +++
- CK7 -/+
- PAX8 -

Metastatic Pancreatobiliary

- CK7 +
- CK20 +/-
- CDX2 +/-
- PAX8 -
- SATB2 -

(Vang et al. 2006, Chu et al. 2011, McCluggage 2012, Perez Montie et al. 2015, Moh et al. 2016, Strickland and Parra-Herran 2016, Strickland et al. 2016, Li et al. 2017, Aldaoud et al. 2019, Meagher et al. 2019)

Ovarian Mucinous Tumors (OMT) Immunohistochemistry

**Most primary ovarian mucinous tumors are CK7 positive and
SATB2 negative***

**If an ovarian tumor is CK7 negative / shows significant SATB2
positivity – suspect metastasis**

SMAD4 loss = pancreatobiliary

ER positive = müllerian type

***Exception: OMTs arising in association with teratoma**

OMT Challenge # 4

Reporting

Reporting ovarian mucinous tumors

Is it necessary to differentiate between **intestinal-type** versus **müllerian-type** in all ovarian tumors?

Yes – For adenocarcinoma

Yes – For borderline tumor

Yes – No for adenoma

Why?

Reporting ovarian mucinous tumors

Is it necessary to differentiate between **intestinal-type** versus **müllerian-type** in all ovarian tumors?

Yes – For adenocarcinoma

Yes – For borderline tumor

Why?

Directs the need to search for metastatic source

Prognosis

Reporting ovarian mucinous tumors

Recommended

Mucinous adenocarcinoma, intestinal type, consistent with ovarian primary

- Size of invasive component: 5 cm
- Pattern of invasion: Expansile
- Background mucinous borderline tumor, intestinal type, 30 cm

[when 85% of the tumor volume was borderline]

Avoid!

Mucinous adenocarcinoma, well differentiated (30 cm)

[when 85% of the tumor volume was borderline]

Reporting ovarian mucinous tumors

- Address primary site
- Include all components and provide/estimate greatest dimension for each
- Specify if intestinal type or müllerian type
- Specify if expansile or infiltrative invasion

Reporting ovarian mucinous tumors

- If you are not sure the tumor is primary in the ovary DO NOT assign the ovary as the primary site in the Synoptic Report
- Options:
 - Omit the Synoptic Report and explain why in a Comment'
 - Choose 'Cannot be determined' for primary site in Synoptic

OMT Challenge # 5

Intraoperative Consultation

Reporting ovarian mucinous tumors in frozen section

Examples:

- 'Bland mucinous neoplasm in two section examined. Defer to permanents for additional sampling'
- 'Mucinous neoplasm, at least borderline if primary. Metastases cannot be excluded. Defer to permanent for additional sampling and immunostains'
- 'Mucinous adenocarcinoma. The differential diagnosis includes ovarian primary and metastases. Defer to permanent for additional sampling and immunostains'

Prognosis

			MOC	MOC	
Metastasis	MBT intestinal	MBT Mullerian	intestinal expansile	intestinal infiltrative	MOC Mullerian
Bad!!	Excellent Recurrence may occur after cystectomy	Excellent Even for advanced stages	Excellent Poor for advanced stages	Reserved Poor for advanced stages	? Limited data

(Nagamine and Mikami 2020) (Chiesa et al. 2010) (Frumovitz et al. 2010)

Take Home Messages

When is it **safe** to assign an ovarian mucinous tumor as **primary ovarian?**

Mullerian type borderline tumor

Associated **teratoma** (including contralateral)

Associated **Brenner** tumor

Uniformly bland mucinous **cystadenoma**

Take Home Messages

When can you favor an ovarian mucinous tumor as primary ovarian?

Large and unilateral mucinous borderline tumor, gastrointestinal type

No previous history!

Negative appendix

No extraovarian spread

Compatible histology

Supportive immunohistochemistry

Take Home Messages

When is an ovarian mucinous tumor **metastatic**?

For sure!

Known extra-ovarian primary site

Almost for sure!

Extra-ovarian spread, even if primary site unknown

‘Metastatic morphologies’

Probably

Bilateral ovarian involvement

Take Home Messages

When is it reasonable to suggest that a primary site cannot be determined?

Mucinous gastrointestinal type, < 10 cm
Worrisome histologic features for metastasis
Equivocal immunohistochemistry

Take Home Messages

In the great majority of cases the distinction between primary and metastatic mucinous carcinoma of the ovary can be made

(McCluggage 2012) (Prat, D'Angelo et al. 2018)

Take Home Messages

**Integrate clinical features, gross findings,
histopathologic features and immunohistochemistry**

References

1. Aldaoud, et al. (2019). "The utility of PAX8 and SATB2 immunohistochemical stains in distinguishing ovarian mucinous neoplasms from colonic and appendiceal mucinous neoplasm." [BMC Res Notes](#) **12**(1): 770.
2. Buza (2019). "Frozen Section Diagnosis of Ovarian Epithelial Tumors: Diagnostic Pearls and Pitfalls." [Arch Pathol Lab Med](#) **143**(1): 47-64.
3. Chiesa, et al. (2010). "Ovarian intestinal type mucinous borderline tumors: are we ready for a nomenclature change?" [Int J Gynecol Pathol](#) **29**(2): 108-112.
4. Chu, et al (2011). "Determining the site of origin of mucinous adenocarcinoma: an immunohistochemical study of 175 cases." [Am J Surg Pathol](#) **35**(12): 1830-1836.
5. Frumovitz, et al. (2010). "Unmasking the complexities of mucinous ovarian carcinoma." [Gynecol Oncol](#) **117**(3): 491-496.
6. Hauptmann, et al. (2017). "Ovarian borderline tumors in the 2014 WHO classification: evolving concepts and diagnostic criteria." [Virchows Arch](#) **470**(2): 125-142.
7. Kurman, and Shih Ie (2016). "Seromucinous Tumors of the Ovary. What's in a Name?" [Int J Gynecol Pathol](#) **35**(1): 78-81.
8. Lee, and Young (2003). "The distinction between primary and metastatic mucinous carcinomas of the ovary: gross and histologic findings in 50 cases." [Am J Surg Pathol](#) **27**(3): 281-292.
9. Li, et al. (2017). "Dual Immunostain With SATB2 and CK20 Differentiates Appendiceal Mucinous Neoplasms From Ovarian Mucinous Neoplasms." [Am J Clin Pathol](#) **147**(5): 484-491.
10. McCluggage (2010). "The pathology of and controversial aspects of ovarian borderline tumours." [Curr Opin Oncol](#) **22**(5): 462-472.
11. McCluggage (2012). "Immunohistochemistry in the distinction between primary and metastatic ovarian mucinous neoplasms." [J Clin Pathol](#) **65**(7): 596-600.
12. McKenney, et al. (2008). "Ovarian mature teratomas with mucinous epithelial neoplasms: morphologic heterogeneity and association with pseudomyxoma peritonei." [Am J Surg Pathol](#) **32**(5): 645-655.
13. Meagher, et al. (2019). "A combination of the immunohistochemical markers CK7 and SATB2 is highly sensitive and specific for distinguishing primary ovarian mucinous tumors from colorectal and appendiceal metastases." [Mod Pathol](#) **32**(12): 1834-1846.
14. Moh, et al. (2016). "SATB2 Expression Distinguishes Ovarian Metastases of Colorectal and Appendiceal Origin From Primary Ovarian Tumors of Mucinous or Endometrioid Type." [Am J Surg Pathol](#) **40**(3): 419-432.

References

15. Nagamine and Mikami (2020). "Ovarian Seromucinous Tumors: Pathogenesis, Morphologic Spectrum, and Clinical Issues." Diagnosics (Basel) **10**(2).
16. Perez Montiel, et al (2015). "The value of SATB2 in the differential diagnosis of intestinal-type mucinous tumors of the ovary: primary vs metastatic." Ann Diagn Pathol **19**(4): 249-252.
17. Prat, et al. (2018). "Ovarian carcinomas: at least five different diseases with distinct histological features and molecular genetics." Hum Pathol **80**: 11-27.
18. Provenza, et al. (2008). "Anaplastic carcinoma in mucinous ovarian tumors: a clinicopathologic study of 34 cases emphasizing the crucial impact of stage on prognosis, their histologic spectrum, and overlap with sarcomalike mural nodules." Am J Surg Pathol **32**(3): 383-389.
19. Ronnett, et al. (2008). "Endocervical adenocarcinomas with ovarian metastases: analysis of 29 cases with emphasis on minimally invasive cervical tumors and the ability of the metastases to simulate primary ovarian neoplasms." Am J Surg Pathol **32**(12): 1835-1853.
20. Seidman, et al. (2003). "Primary and metastatic mucinous adenocarcinomas in the ovaries: incidence in routine practice with a new approach to improve intraoperative diagnosis." Am J Surg Pathol **27**(7): 985-993.
21. Simons, et al. (2020). "Two types of primary mucinous ovarian tumors can be distinguished based on their origin." Mod Pathol **33**(4): 722-733.
22. Strickland and Parra-Herran (2016). "Immunohistochemical characterization of appendiceal mucinous neoplasms and the value of special AT-rich sequence-binding protein 2 in their distinction from primary ovarian mucinous tumours." Histopathology **68**(7): 977-987.
23. Strickland, et al. (2016). "Immunohistochemistry in the Diagnosis of Mucinous Neoplasms Involving the Ovary: The Added Value of SATB2 and Biomarker Discovery Through Protein Expression Database Mining." Int J Gynecol Pathol **35**(3): 191-208.
24. Tabrizi, et al. (2010). "Primary ovarian mucinous carcinoma of intestinal type: significance of pattern of invasion and immunohistochemical expression profile in a series of 31 cases." Int J Gynecol Pathol **29**(2): 99-107.
25. Vang, et al. (2006). "Immunohistochemistry for estrogen and progesterone receptors in the distinction of primary and metastatic mucinous tumors in the ovary: an analysis of 124 cases." Mod Pathol **19**(1): 97-105.
26. Yemelyanova, et al. (2008). "Distinction of primary and metastatic mucinous tumors involving the ovary: analysis of size and laterality data by primary site with reevaluation of an algorithm for tumor classification." Am J Surg Pathol **32**(1): 128-138.

Thank you!

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