Proper Utilization of Selected Markers in Gynecologic Pathology

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Capital Health

DALHOUSIE UNIVERSITY
Inspiring Minds

Disclosure

- I have no financial relationships to disclose

- and -

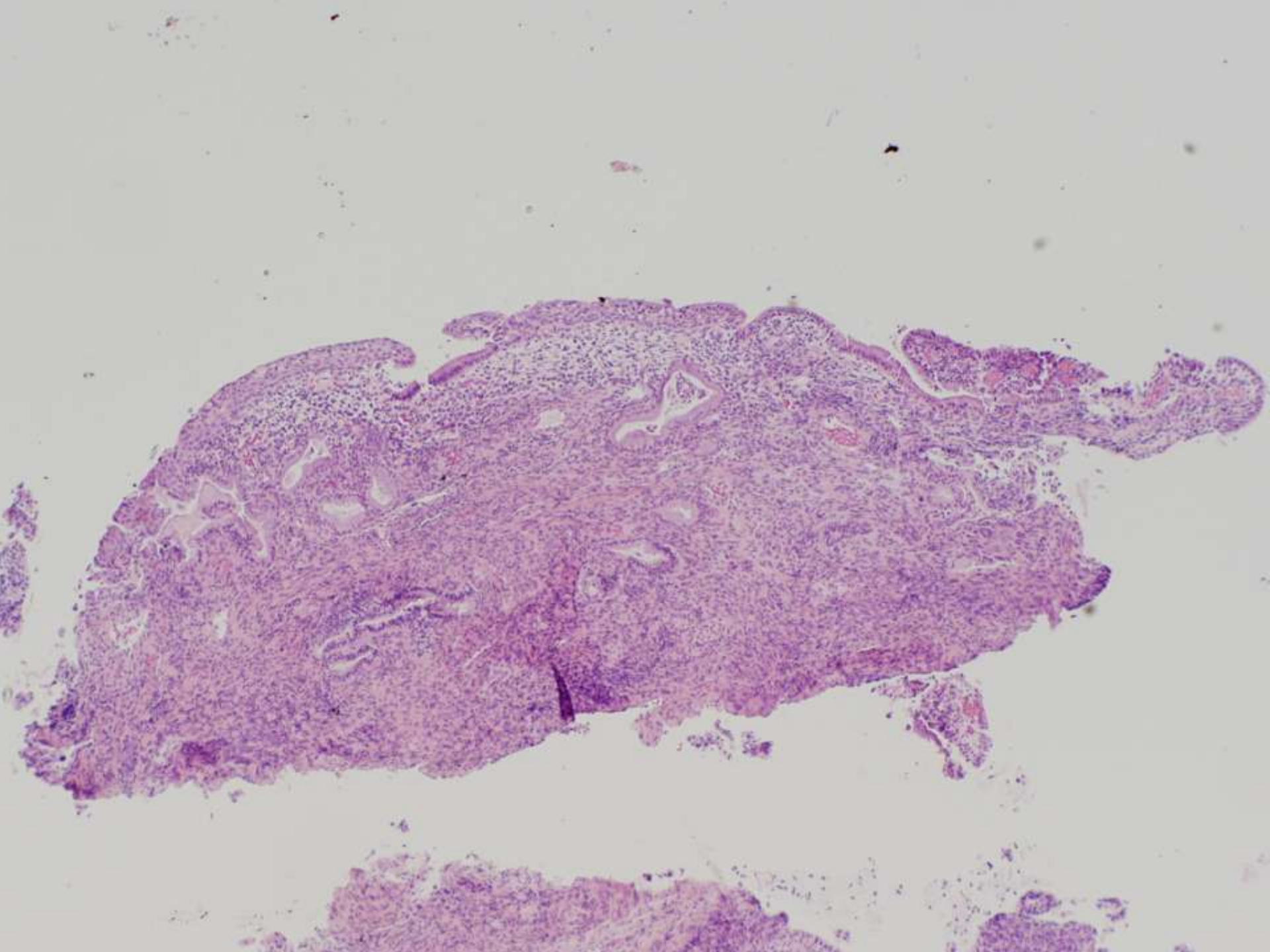
- I will not discuss off label use and/or investigational use in my presentation

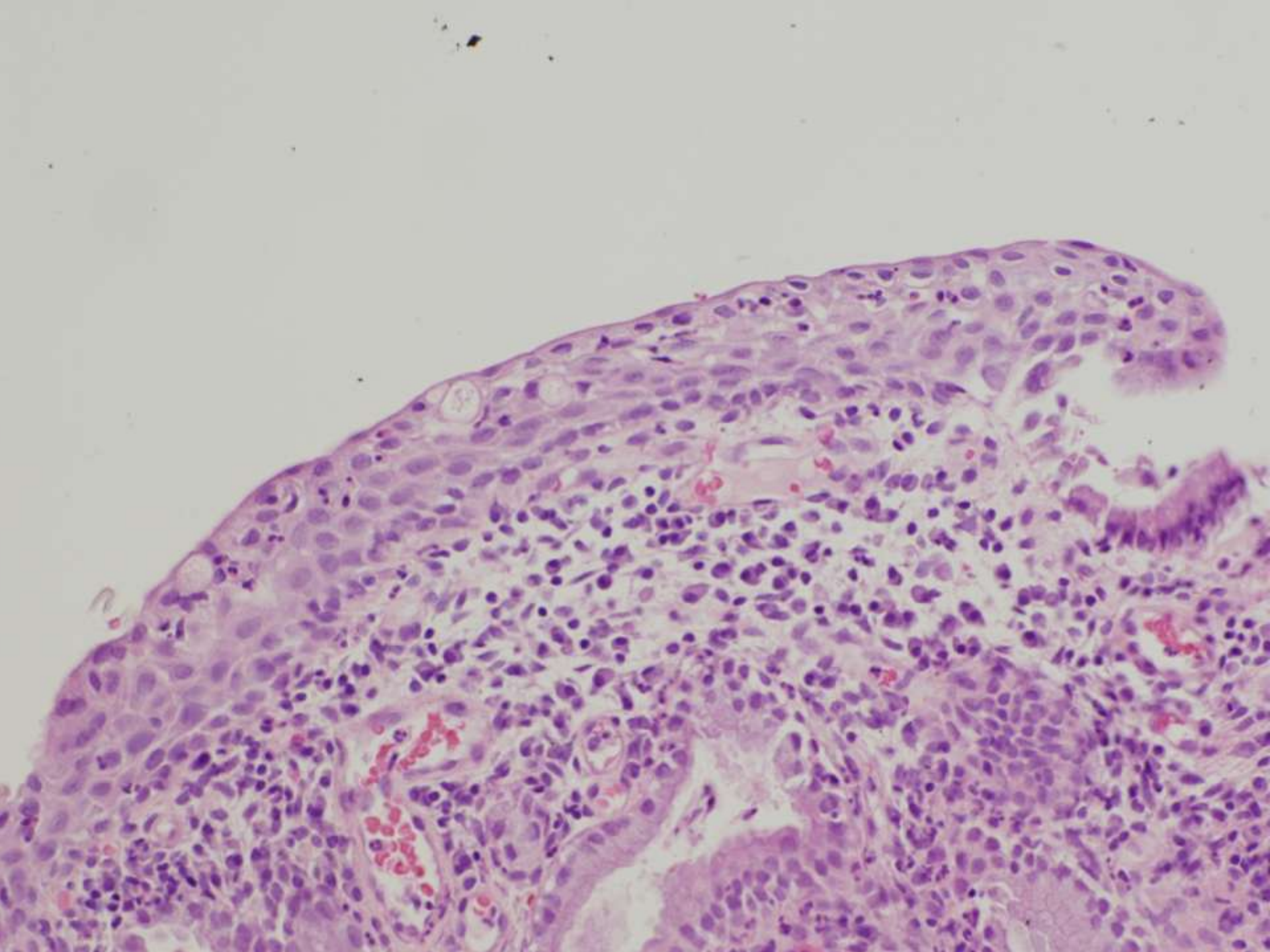
Outline

- Case based presentation of IHC stains & panels used in GYN pathology:
  - HPV related cervical lesions
  - Cervical vs. endometrial carcinomas
  - Endometrial carcinoma subtypes
  - Ovarian surface epithelial carcinomas
- Proper interpretation of stains commonly used (e.g. p53, p16) as well as potential pitfalls and limitations
- Utilization of PAX-8 and WT-1, two IHC markers to be soon added at CDHA
- Summarize utility and limitations of each stain

Case 1 *(CE-14-15)*

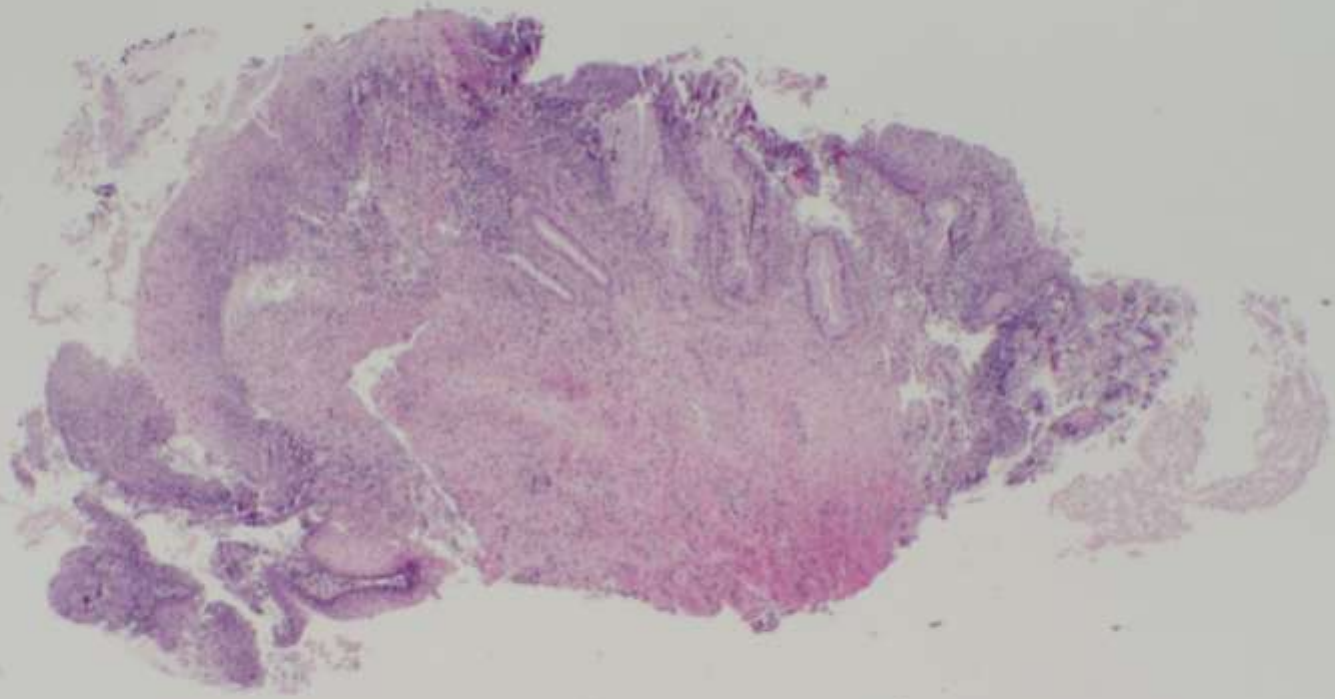
31 year old female with previous abnormal Pap (ASC-H) (cervical biopsy)

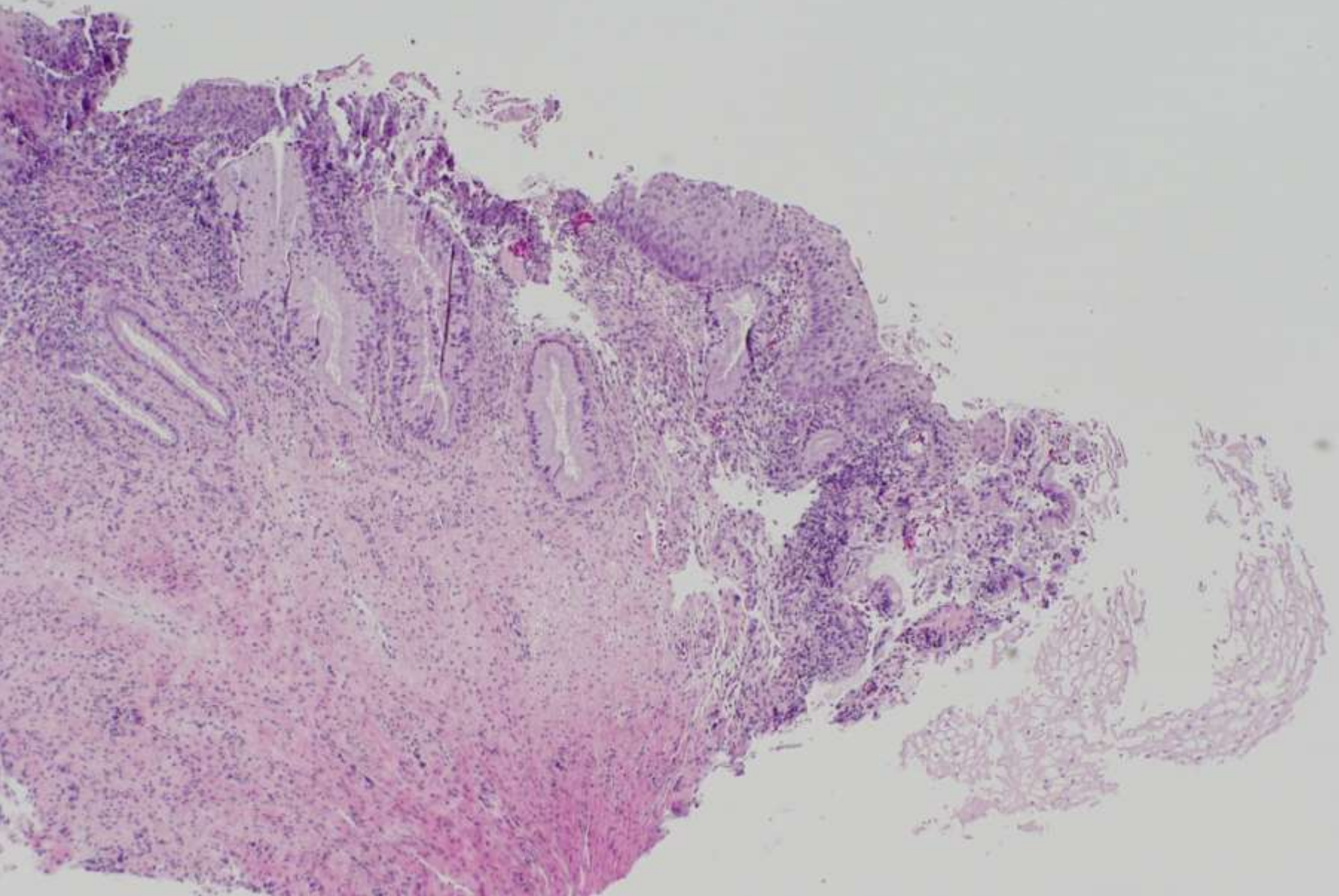


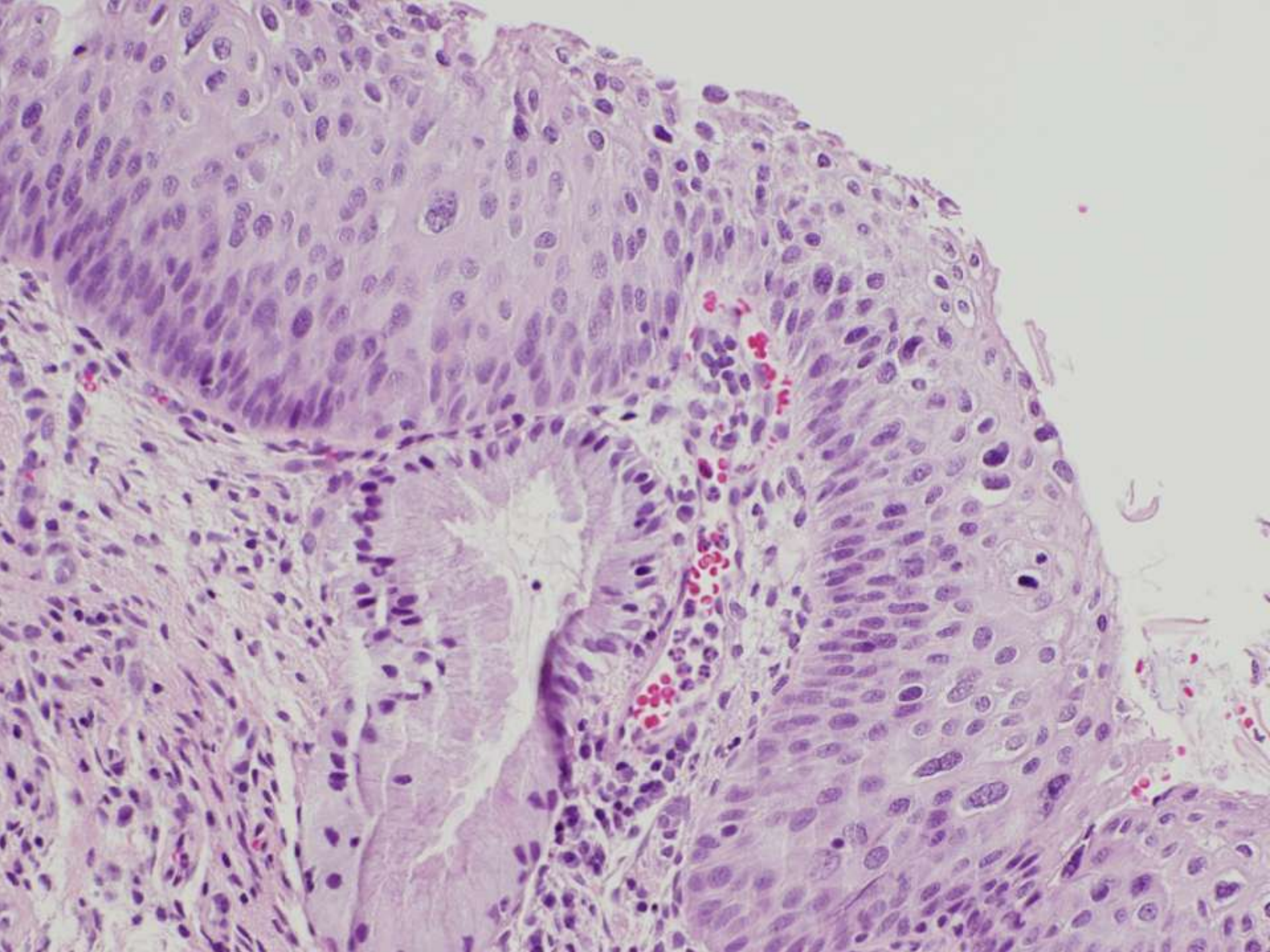


Case 2 *(SP-13-43566)*

24 year old female with previous abnormal Paps (ASC-H → ASCUS) (cervical biopsy)

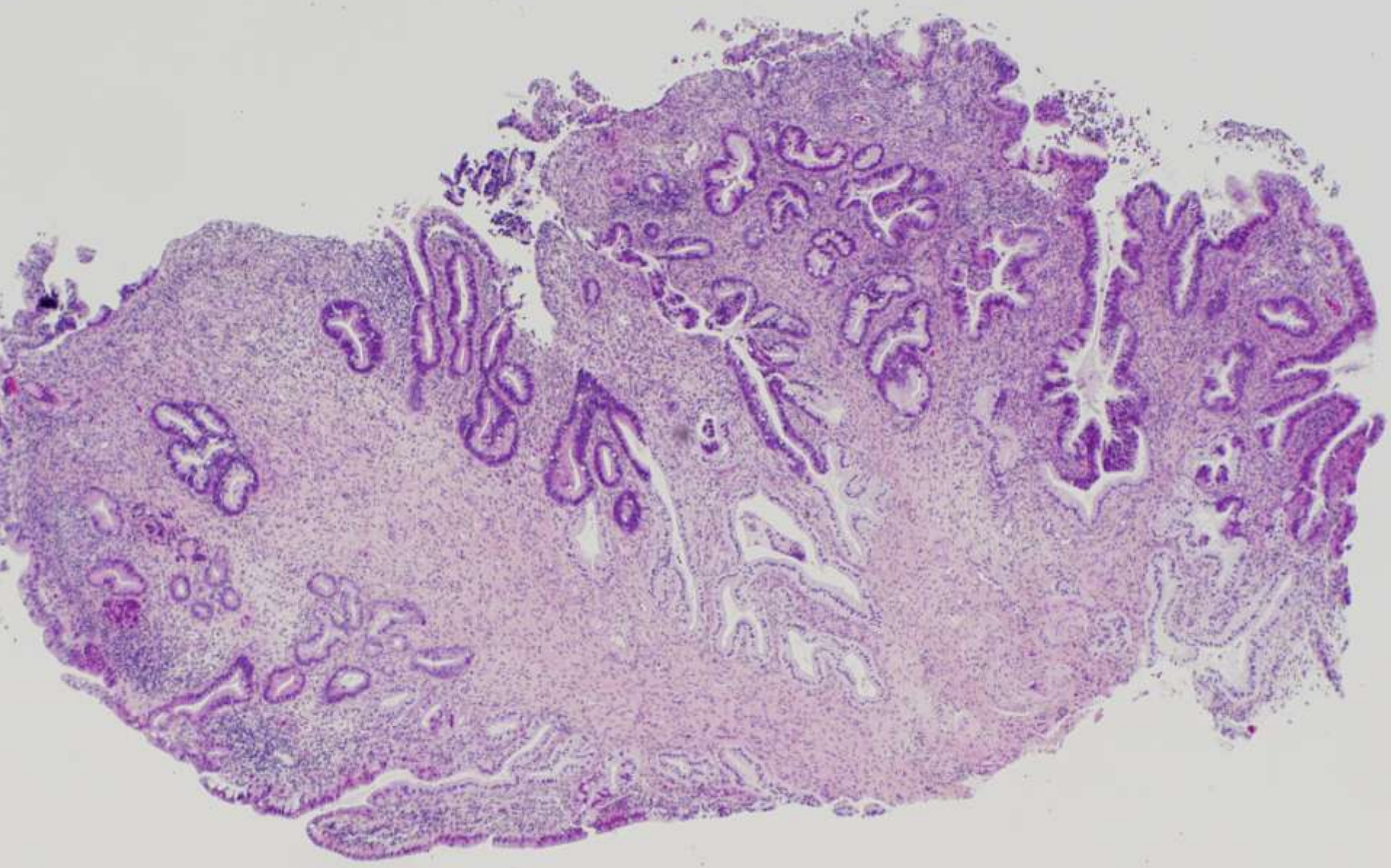


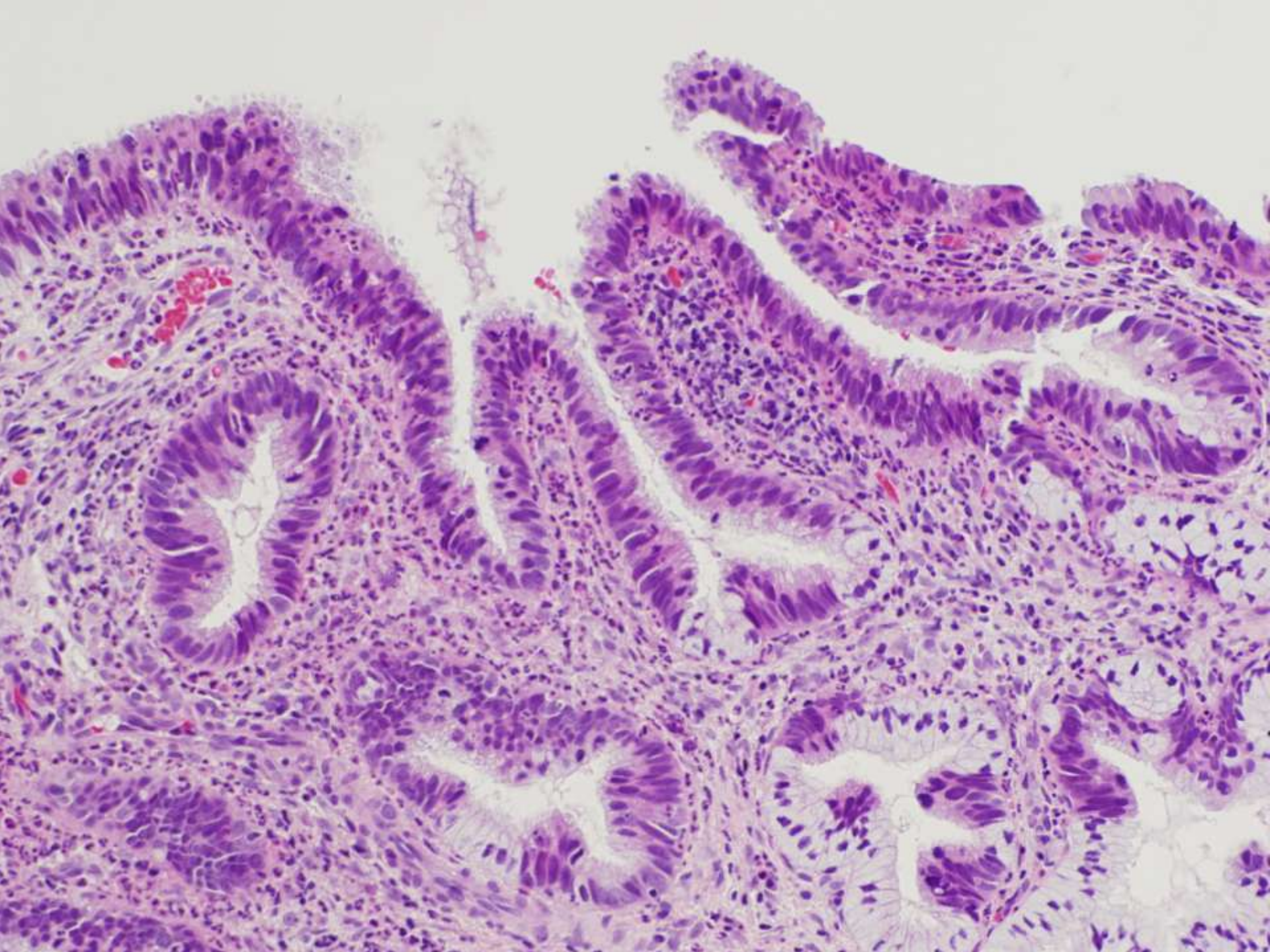


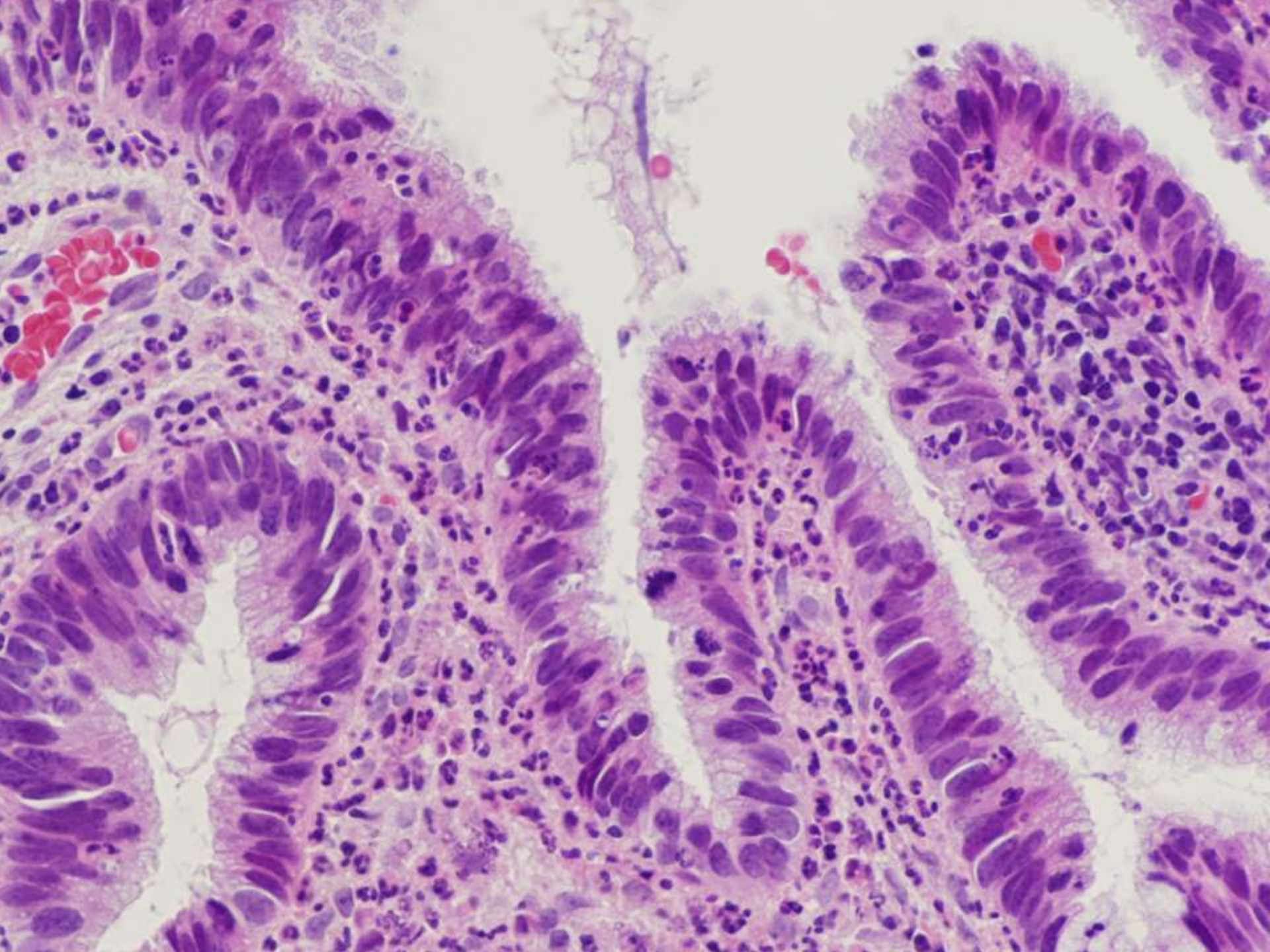


Case 3 *(SP-13-17887)*

29 year old female with previous abnormal Paps (ASCUS → Negative), colposcopic impression CIN 1-2 (cervical biopsy)







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32:76–115, Lippincott Williams & Wilkins, Baltimore

Original Article

The Lower Anogenital Squamous Terminology Standardization Project for HPV-associated Lesions: Background and Consensus Recommendations From the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology

Teresa M. Darragh, M.D., Terence J. Colgan, M.D., J. Thomas Cox, M.D., Debra S. Heller, M.D., Michael R. Henry, M.D., Ronald D. Luff, M.D., Timothy McCalmont, M.D., Ritu Nayar, M.D., Joel M. Palefsky, M.D., Mark H. Stoler, M.D., Edward J. Wilkinson, M.D., Richard J. Zaino, M.D., David C. Wilbur, M.D., and For Members of the LAST Project Work Groups

LAST Project Recommendations

TABLE 3. *Summary of recommendations*

Recommendation	Comment
Squamous Intraepithelial Lesions, WG2	
1. A unified histopathological nomenclature with a single set of diagnostic terms is recommended for all HPV-associated preinvasive squamous lesions of the lower anogenital tract.	
2. A 2-tiered nomenclature is recommended for non-invasive HPV-associated squamous proliferations of the lower anogenital tract which may be further qualified with the appropriate –IN terminology.	-IN refers to the generic intraepithelial neoplasia terminology, without specifying the location. For a specific location the appropriate complete term should be used. Thus for an –IN3 lesion: cervix = CIN3, vagina = VaIN3, vulva = VIN3, anus = AIN3, perianus = PAIN3, and penis = PeIN3
3. The recommended terminology for HPV-associated squamous lesions of the lower anogenital tract is Low Grade Squamous Intraepithelial Lesion (LSIL) and High Grade Squamous Intraepithelial Lesion (HSIL), which may be further classified by the applicable –IN subcategorization.	

2 tiered system – LSIL and HSIL +/- (-IN)

LAST Project Recommendations

TABLE 3. (*continued*)

Recommendation	Comment
Biomarkers in HPV-associated Lower Anogenital Squamous Lesions, WG4	
1. p16 IHC is recommended when the H&E morphologic differential diagnosis is between precancer (–IN 2 or – IN 3) and a mimic of precancer (e.g. processes known to be not related to neoplastic risk such as immature squamous metaplasia, atrophy, reparative epithelial changes, tangential cutting, etc.).	Strong and diffuse block positive p16 results support a categorization of precancerous disease.
2. If the pathologist is entertaining an H&E morphologic interpretation of –IN 2 [under the old terminology; which is a biologically equivocal lesion falling between the morphologic changes of HPV infection (low grade lesion) and precancer], p16 IHC is recommended to help clarify the situation. Strong and diffuse block positive p16 results support a categorization of precancer. Negative or non-block positive staining strongly favors an interpretation of low grade disease or a non-HPV associated pathology.	
3. p16 is recommended for use as an adjudication tool for cases in which there is a professional disagreement in histologic specimen interpretation, with the caveat that the differential diagnosis includes a precancerous lesion (–IN2 or –IN3).	
4. WG4 recommends against the use of p16 IHC as a routine adjunct to histologic assessment of biopsy specimens with morphologic interpretations of negative, -IN1, and –IN3.	
a. SPECIAL CIRCUMSTANCE p16 IHC is recommended as an adjunct to morphologic assessment for biopsy specimens interpreted as ≤–IN1 that are at high risk for missed high-grade disease, which is defined as a prior cytologic interpretation of HSIL, ASC-H, ASC-US/HPV16 +, or AGC (NOS).	Any identified p16 positive area must meet H&E morphologic criteria for a high grade lesion to be reinterpreted as such.

1. HSIL vs. B9 mimic
2. Entertaining –IN 2
3. Difference of opinion
4. High risk for miss

p16 and HPV related neoplasia

- Surrogate of high risk HPV DNA integration
  - Viral oncogenes E6/E7 interact with cell-cycle proteins
  - pRB normally inhibits transcription of p16
  - E7 inactivates pRB causing ↑ p16 IHC expression
- Strong and diffuse block positive supports precancerous lesion
  - Nuclear +/- cytoplasmic staining
  - Basal cells, extending up ≥ 1/3 thickness

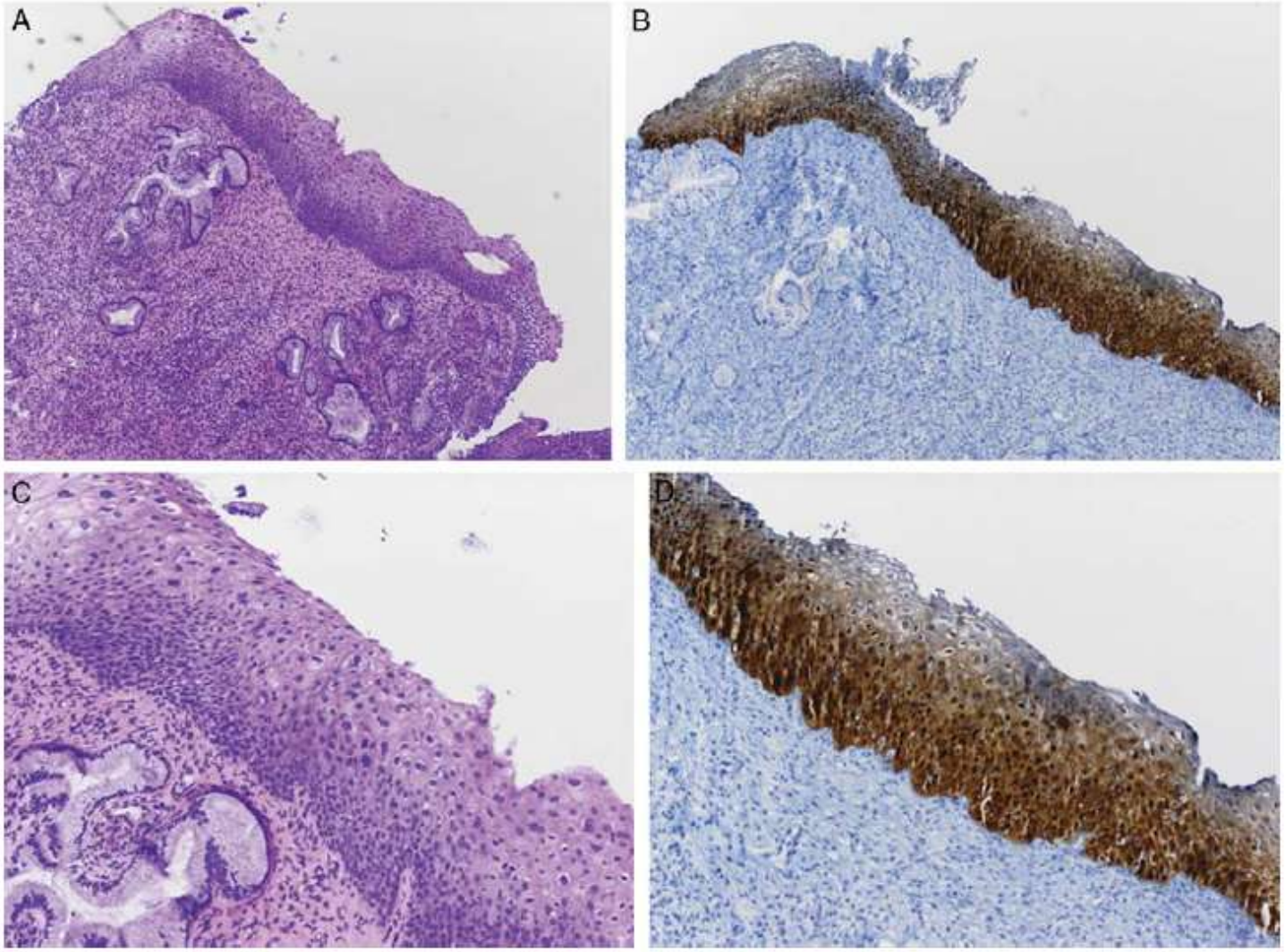
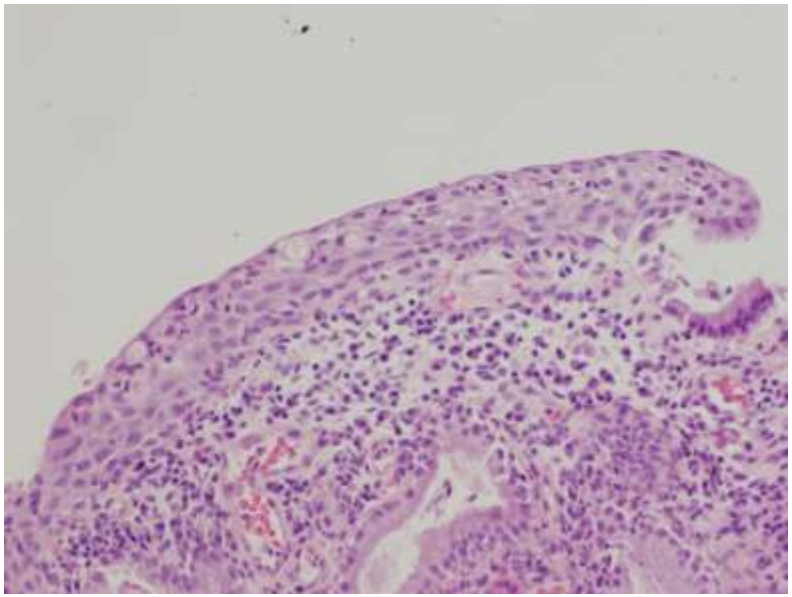


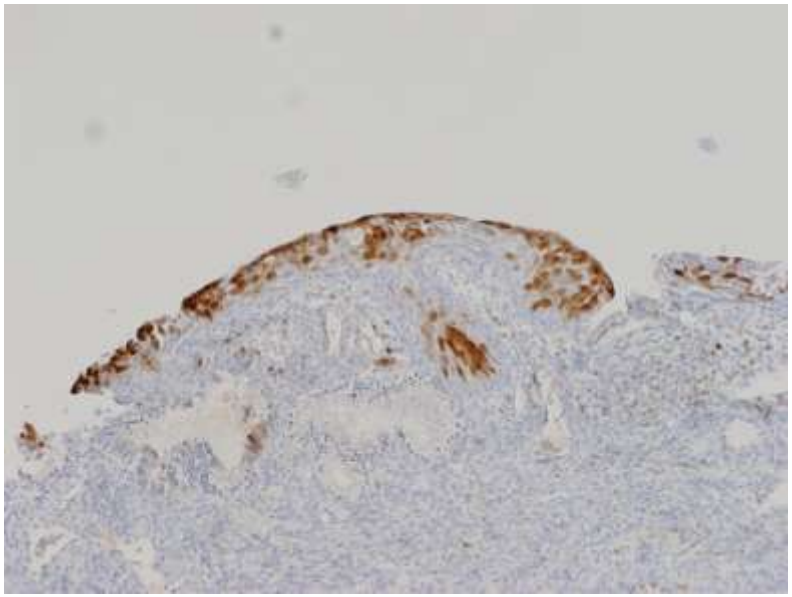
FIG. 14. A cervical biopsy with SIL showing partial maturation; some might question the lesion grade (? CIN2). Panels A & C demonstrate H&E morphology at low and medium power with atypical parabasal like cells extending into the middle third of the epithelium (C). Panels B & D are the corresponding p16 IHC stains with diffuse strong staining meeting the definition of p16 strong diffuse block positive described in the text. Therefore, this case is best interpreted as HSIL.

Case 1 *(CE-14-15)*

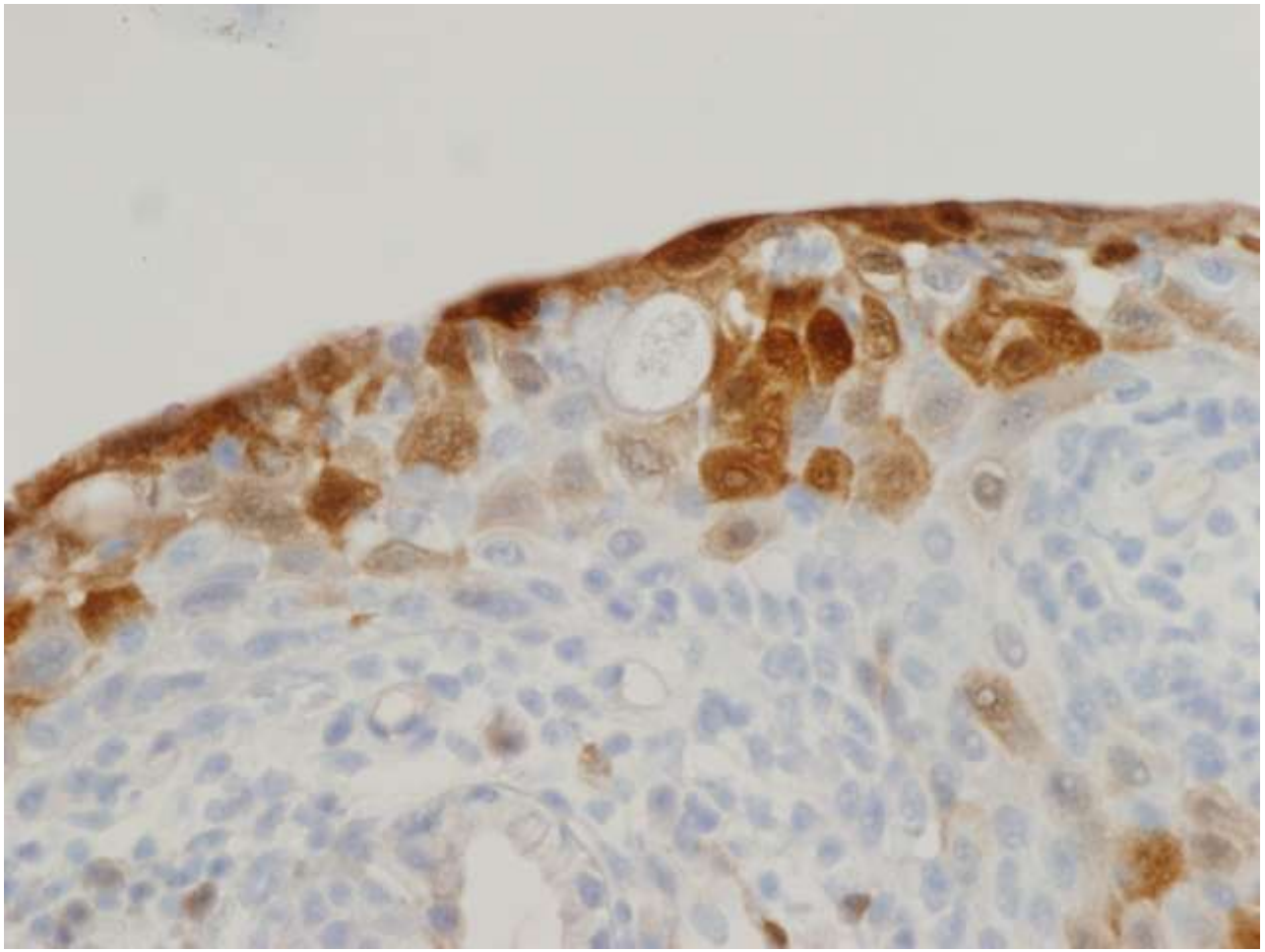
H&E



p16



Case 1 *(CE-14-15) cont.*

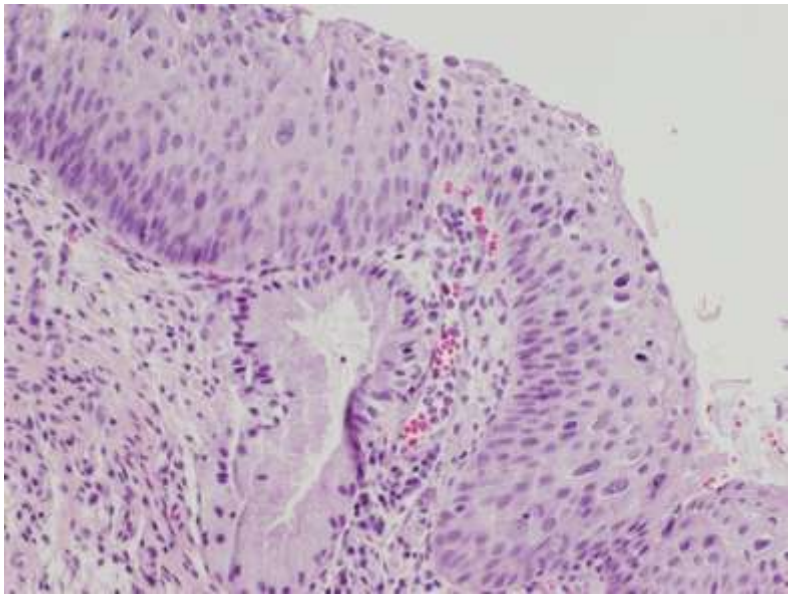


Dx: Possible Koilo, negative for HSIL

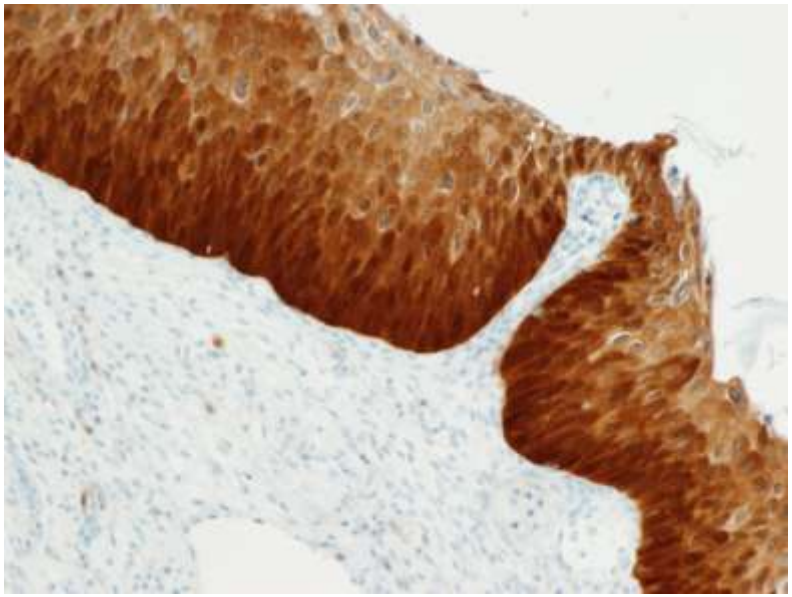
p16 “negative”

Case 2 *(SP-13-43566)*

H&E



p16

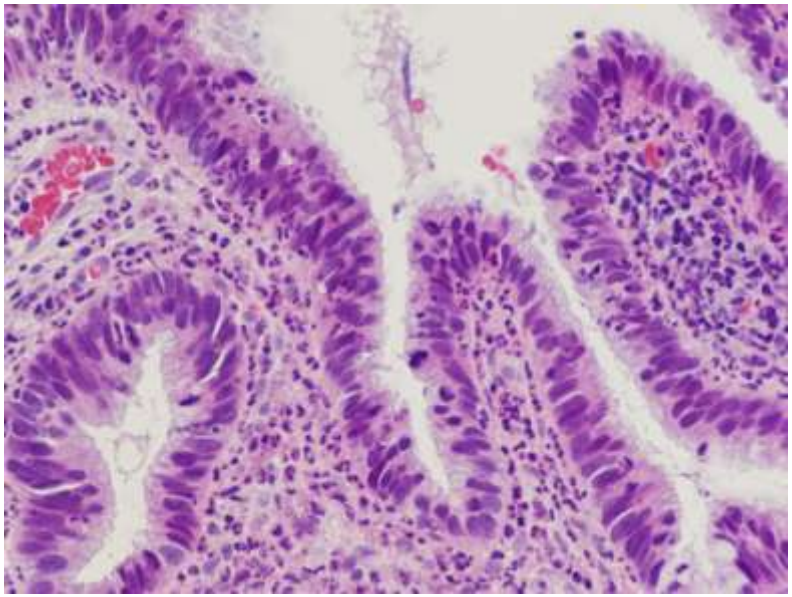


p16 “positive”

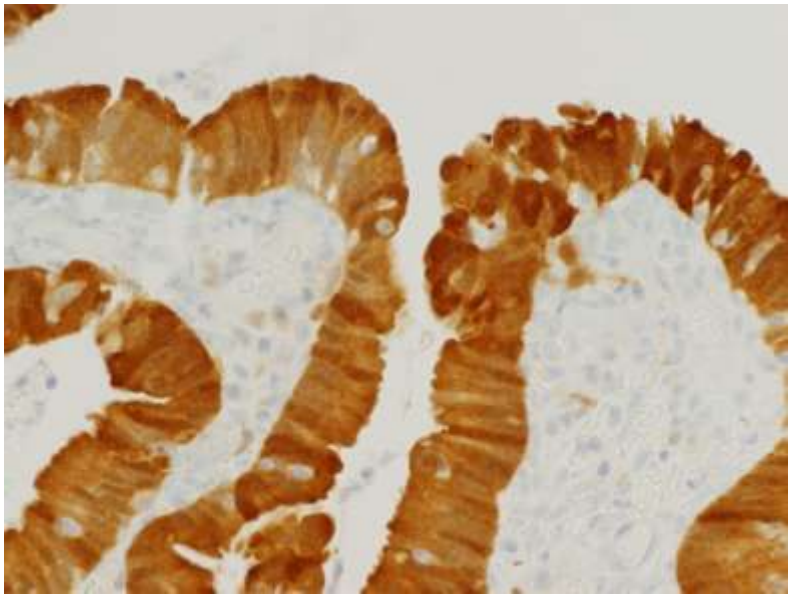
Dx: HSIL (CIN 2)

Case 3 *(SP-13-17887)*

H&E



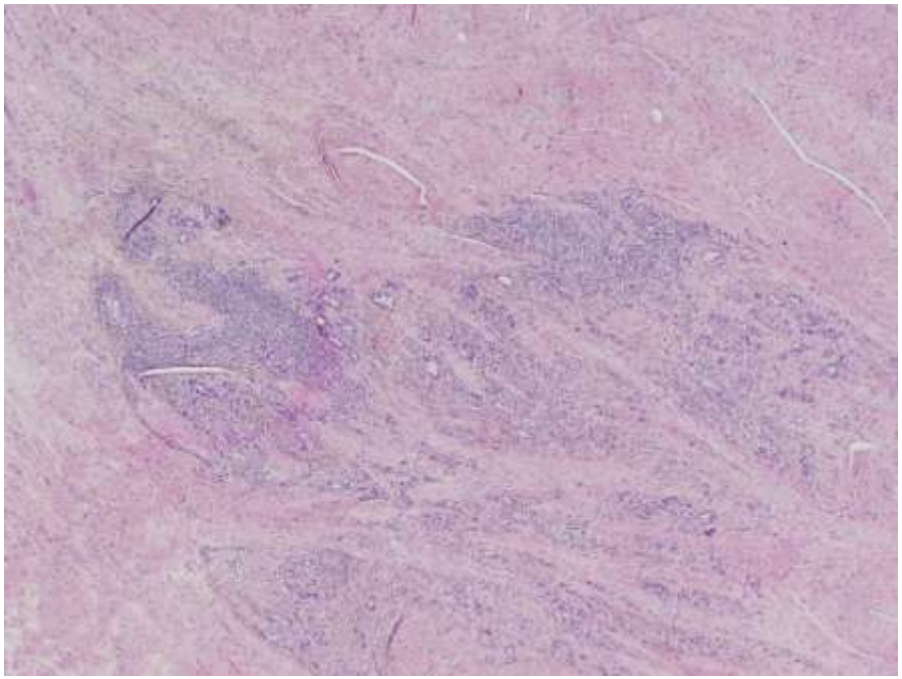
p16

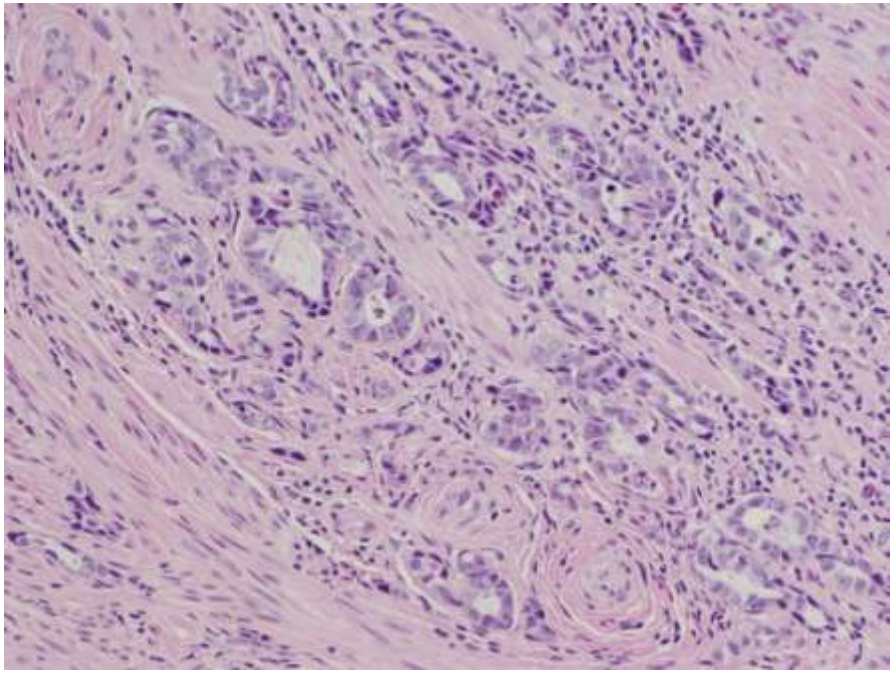


p16 “positive”

Dx: AIS

Case 4 *(SP-13-44471)* *(hysterectomy)*

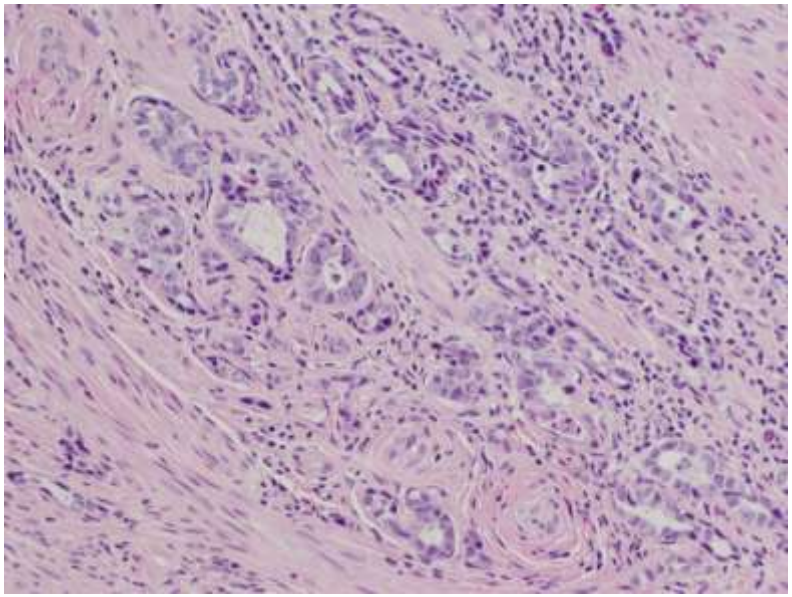




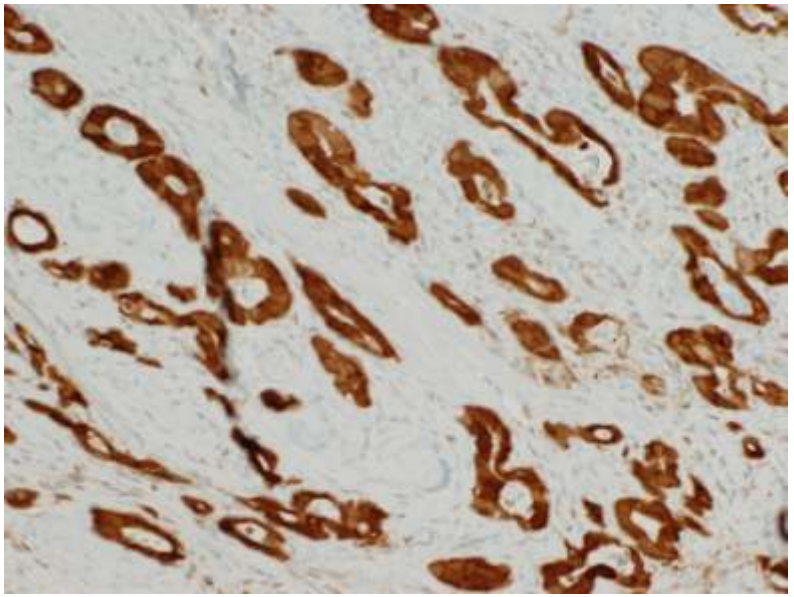
62 year old woman with deceptive pattern of endocervical adenocarcinoma

Case 4 *(SP-13-44471)*

H&E



p16

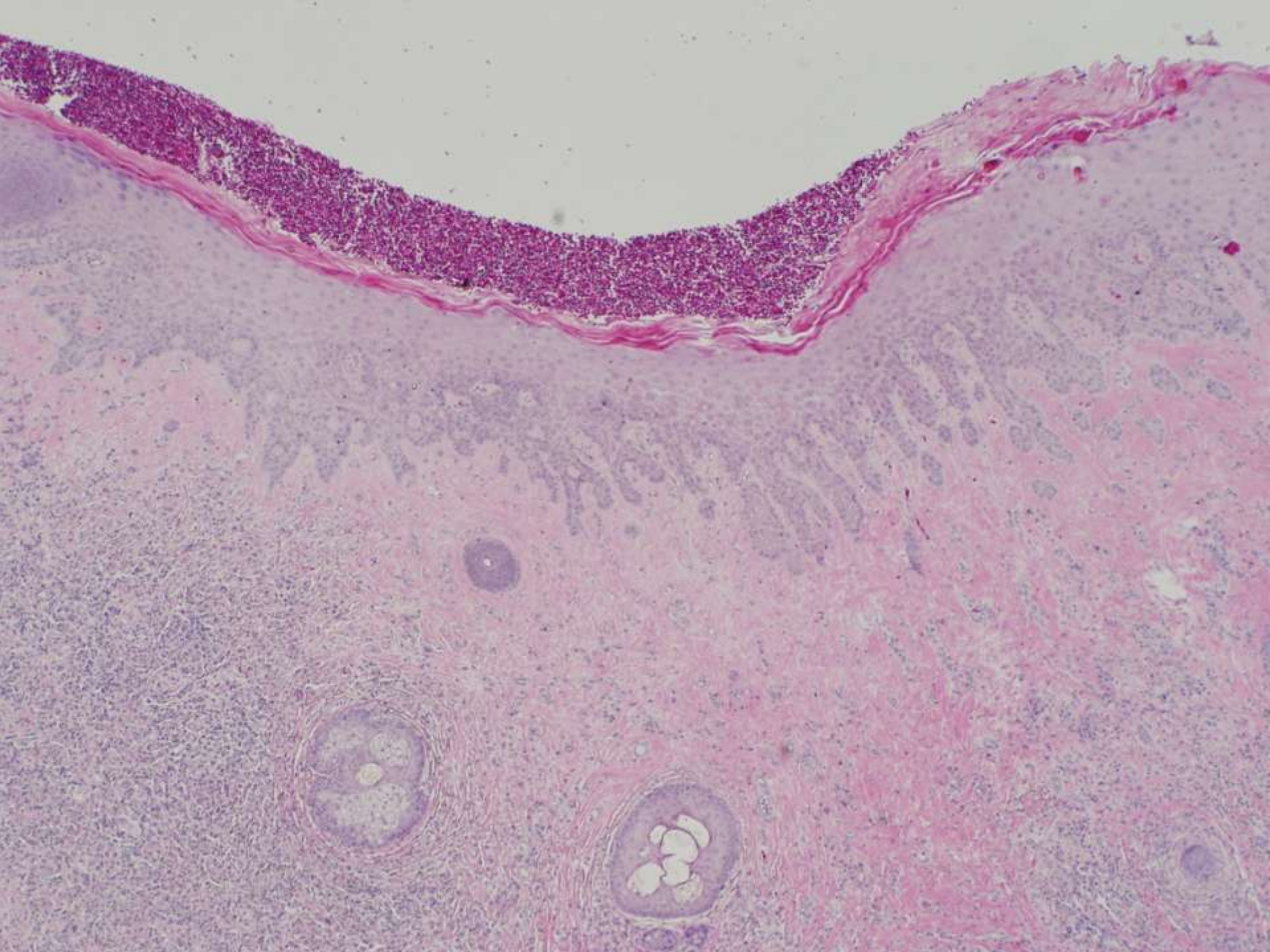


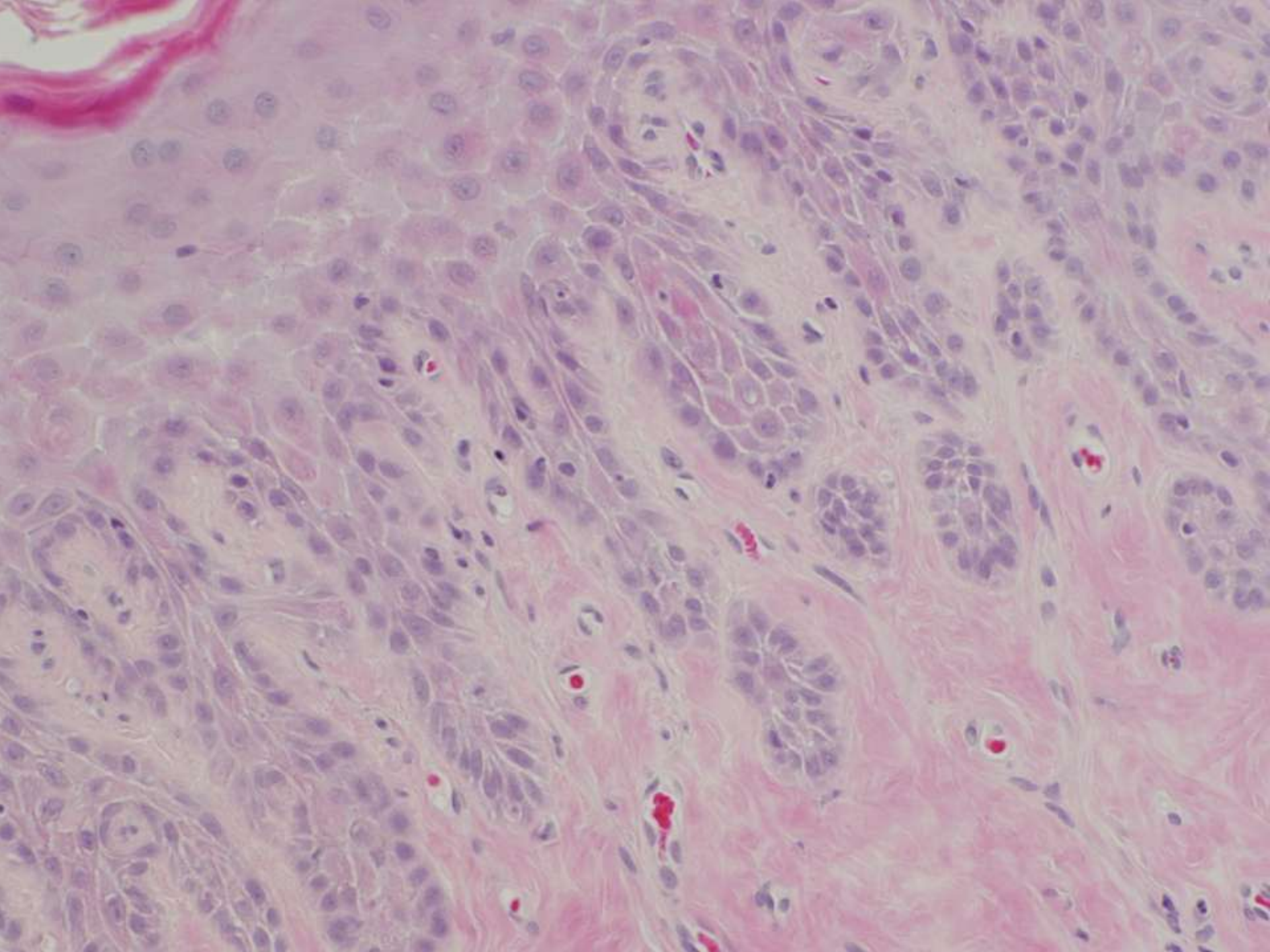
Dx: Endocervical AdenoCa

p16 “positive”

Case 5 *(SP-13-2719)*

80 year old female with history of vulvar carcinoma (vulvar biopsy)

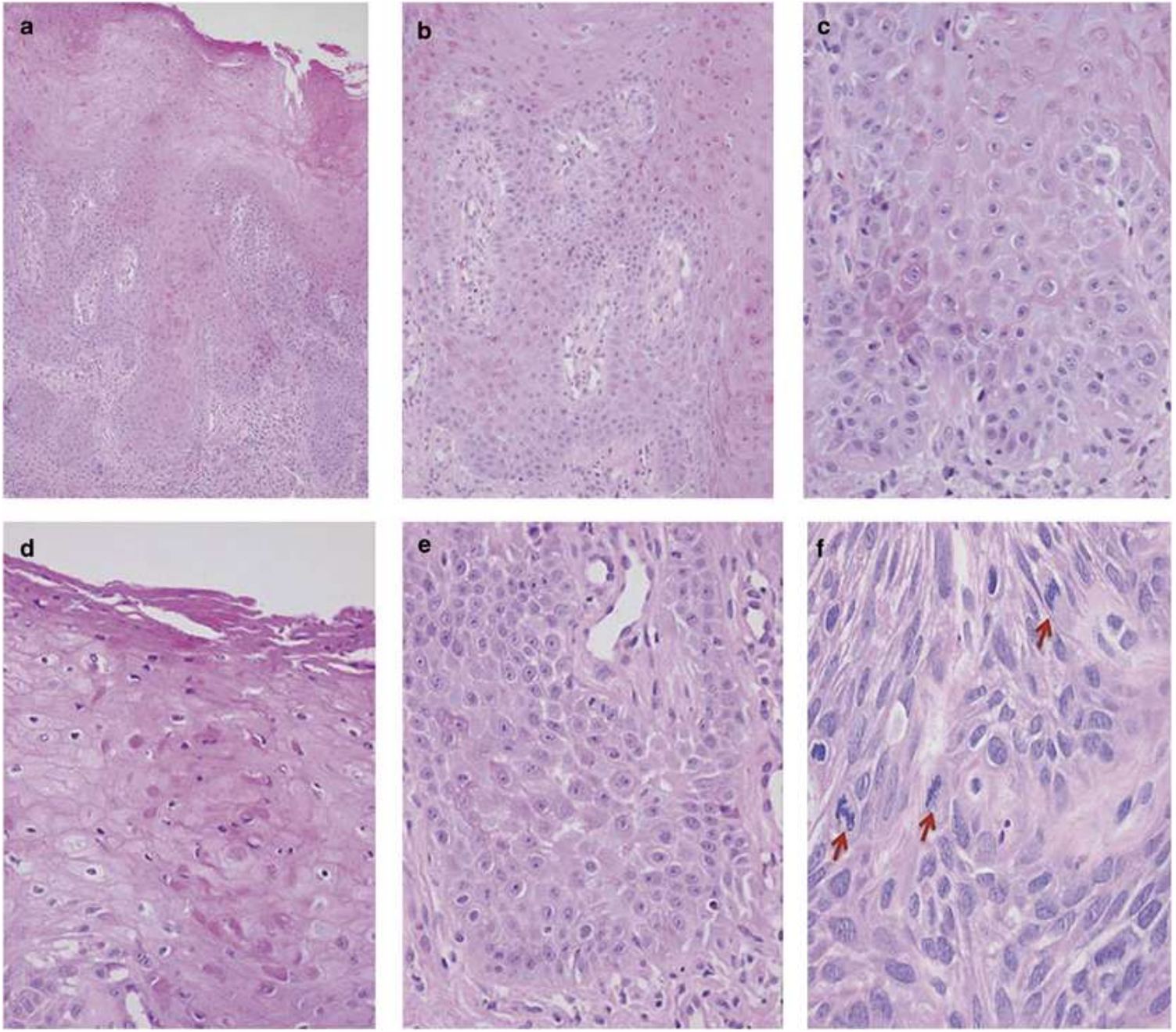




Vulvar SCC and precursors

- 2 different pathways leading to SCC
  - HPV dependent (less common)
    - VIN, usual type (HSIL – VIN 2-3)
  - HPV independent (80%)
    - Often arise in association with lichen sclerosus
    - differentiated type (d-VIN) as direct precursor
      - Seen adjacent to 80% of vulvar SCC

d-VIN

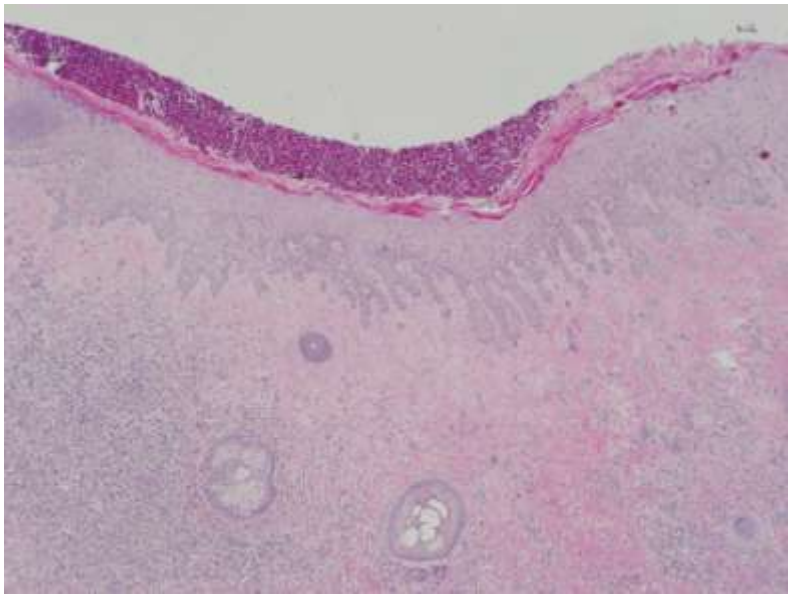


p53 IHC and d-VIN

- d-VIN is typically associated with TP53 mutations
  - Mutation often present in contiguous SCC
  - Cells typically negative for HPV and p16
- p53 IHC reactivity present in basal cells (strong and continuous) and typically with suprabasilar extension
- Ki67 typically intense but restricted to basal / parabasal cells

Case 5 *(SP-13-2719)*

H&E



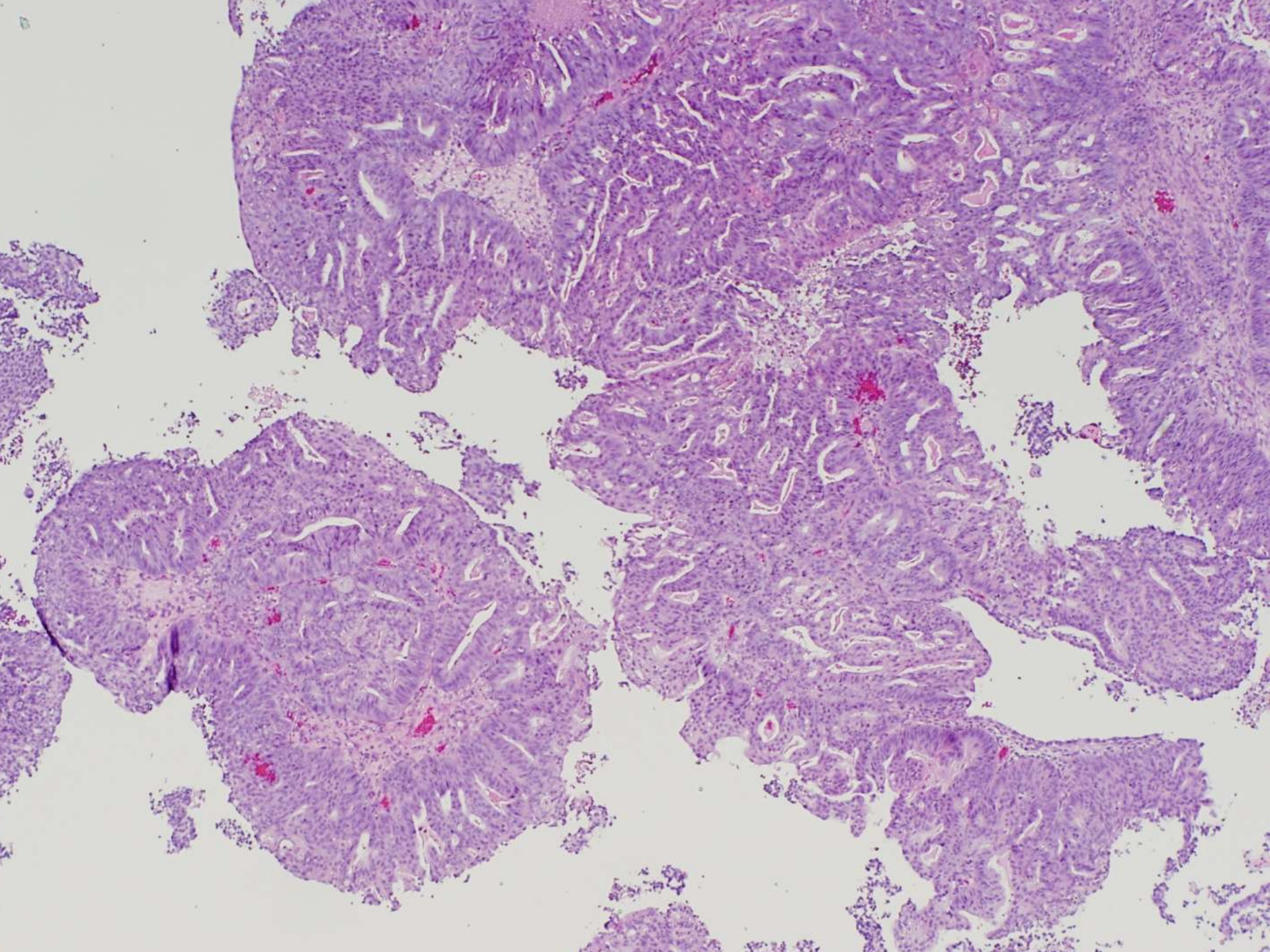
Dx: d-VIN

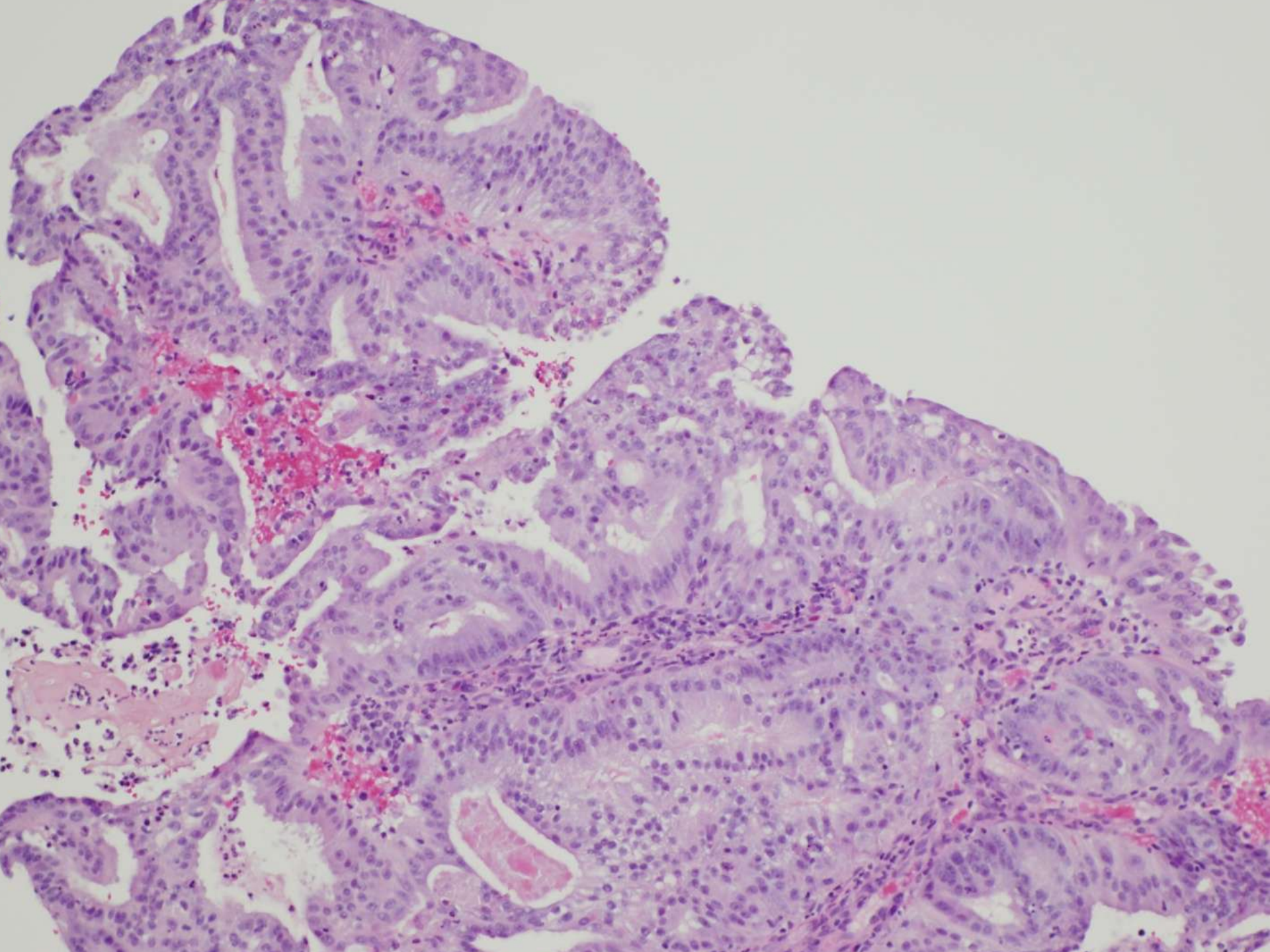
p53

p53 “positive”

Case 6a *(CE-12-2341)*

39 year old female with infiltrating mass involving LUS and cervix (differential curettage)





Endocervical (ECA) vs. Endometrioid Endometrial Carcinoma (EEC)

- Clinical factors
  - Location, age, RF, history
- Morphologic features
  - Precursor lesions, foam cells & squamous morules in EEC
- IHC Panel
  - ER, Vimentin, p16, CEA

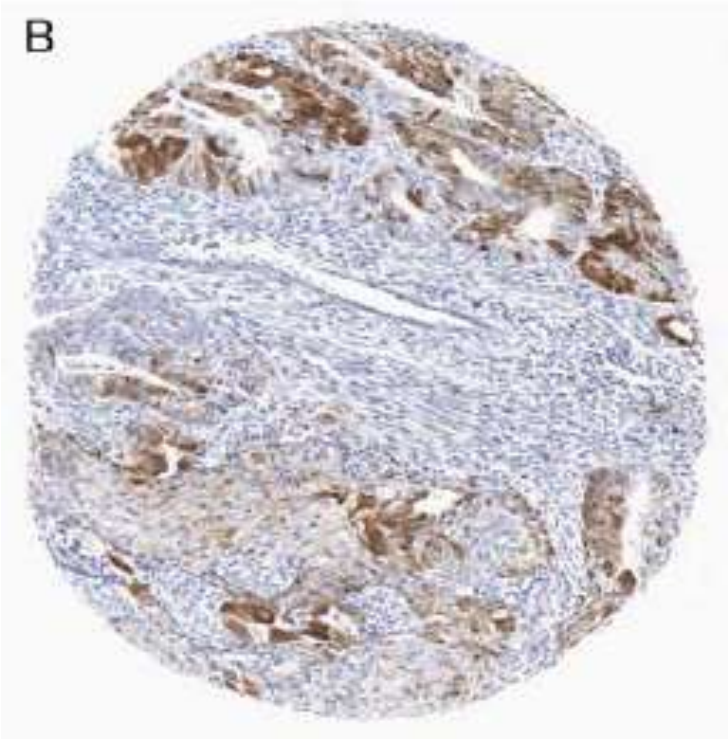
A Panel of 3 Markers Including p16, ProExC, or HPV ISH is Optimal for Distinguishing Between Primary Endometrial and Endocervical Adenocarcinomas

Christina S. Kong, MD, Andrew H. Beck, MD, and Teri A. Longacre, MD

Endometrial*	Endocervical
• ER (+)	• ER (-)
• Vimentin (+)	• Vimentin (-)
• p16 (-) / patchy	• p16 (+) (strong, diffuse)

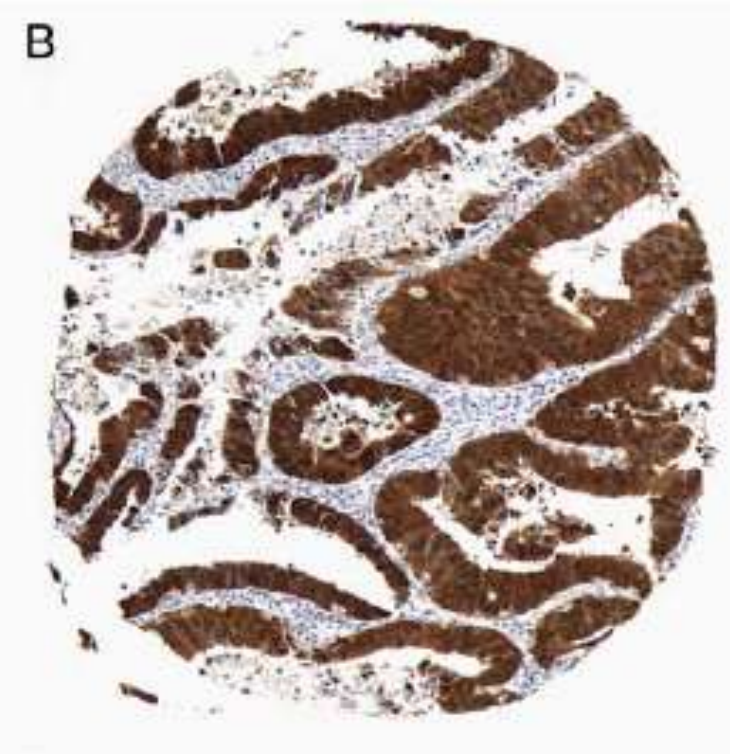
p16 in EEC vs. ECA

EEC



p16 “negative”

ECA



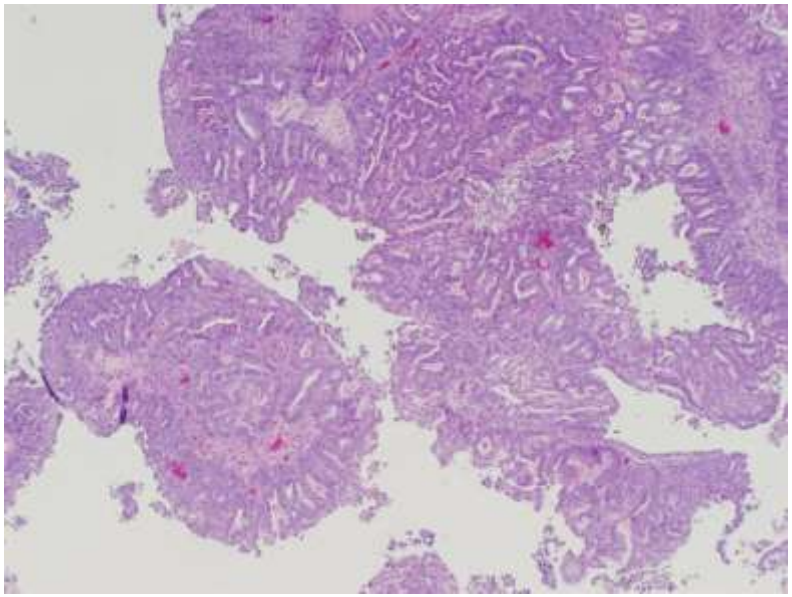
p16 “positive”

Limitations of IHC in EEC vs. ECA

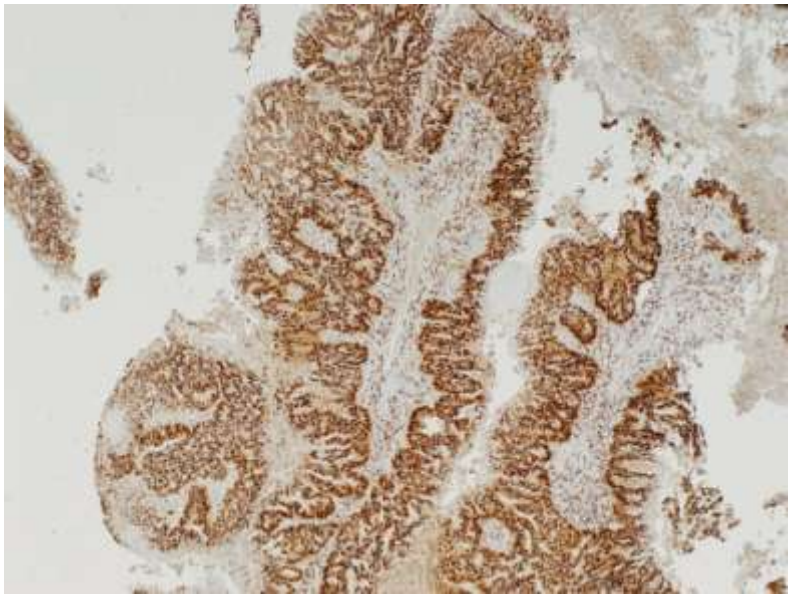
- Does not apply to “Type 2” endometrial carcinomas (CCC, USC)
  - Less frequently ER (+), more p16 (+)
- Less reliable in high grade EEC, mucinous lesions, and LUS tumors

Case 6a *(CE-12-2341)*

H&E



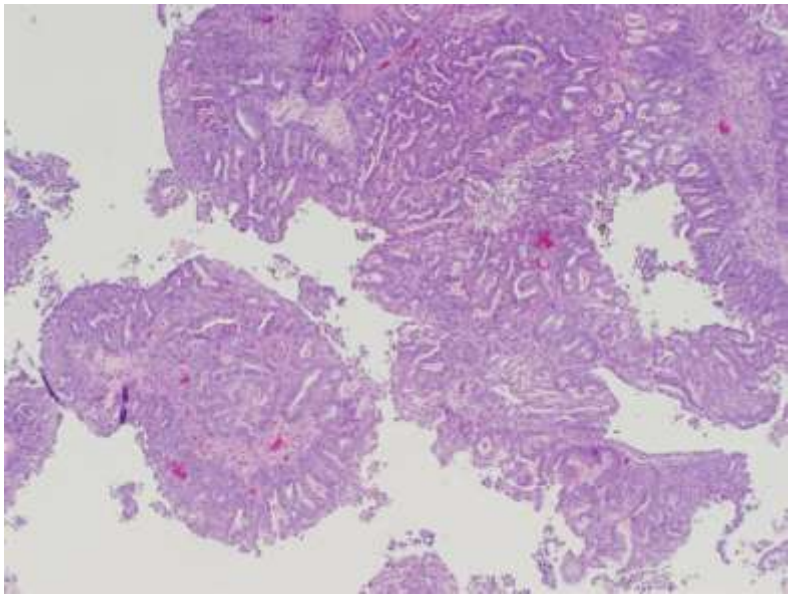
ER



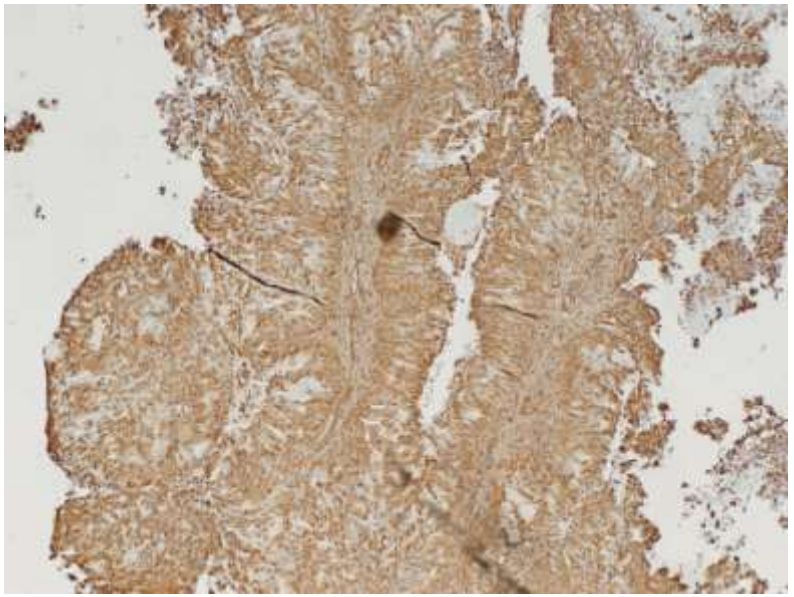
positive

Case 6a *(CE-12-2341)*

H&E



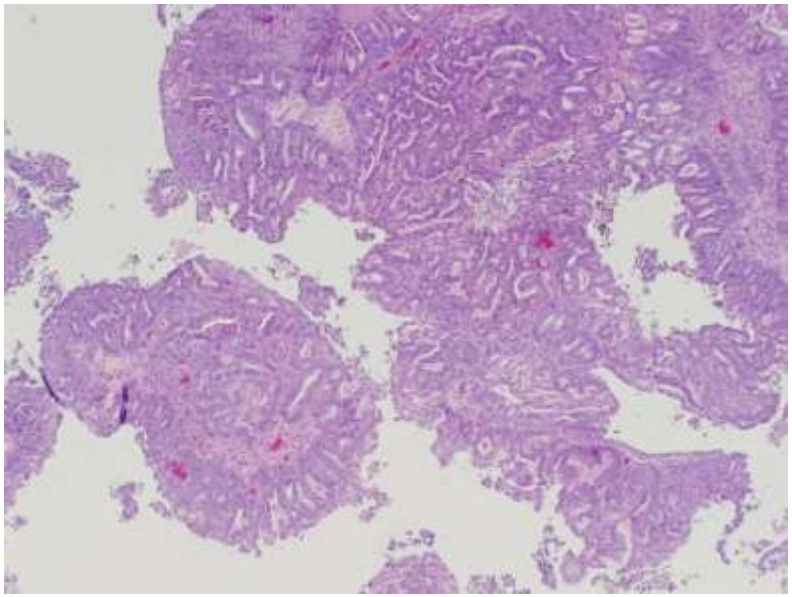
Vimentin



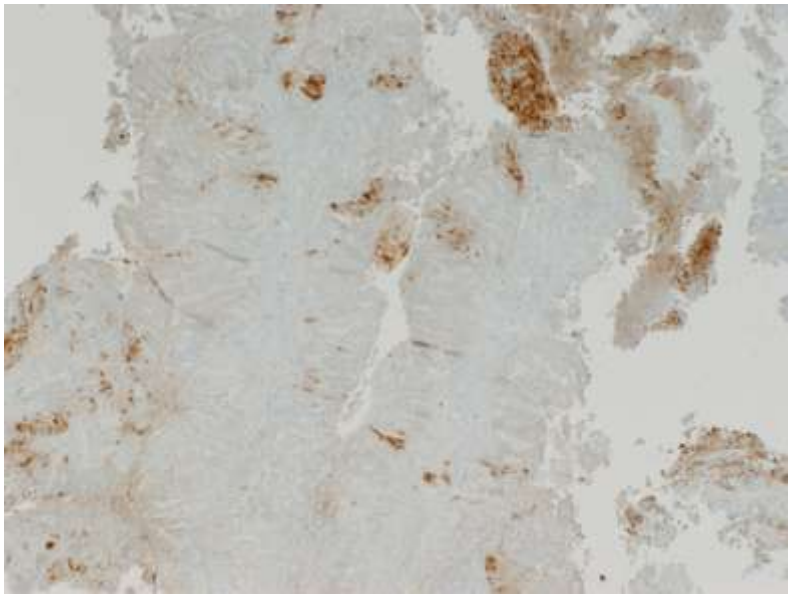
positive

Case 6a *(CE-12-2341)*

H&E



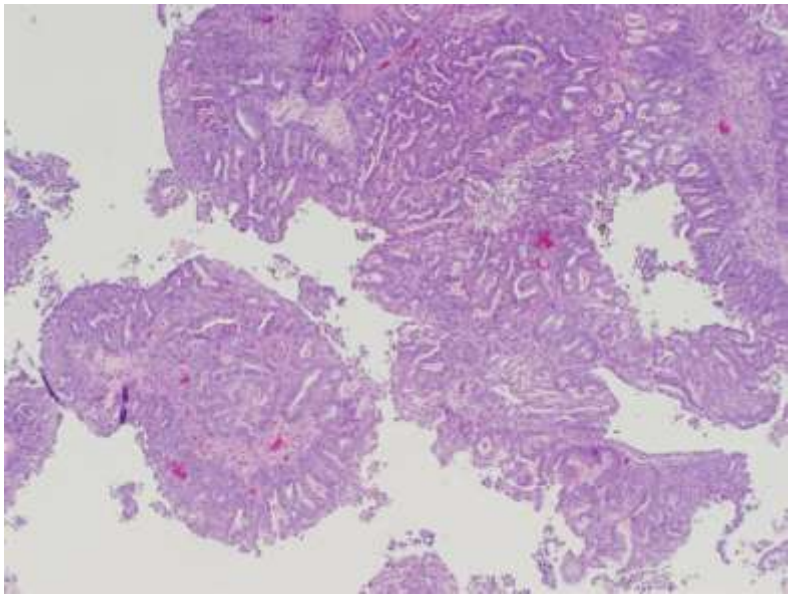
p16



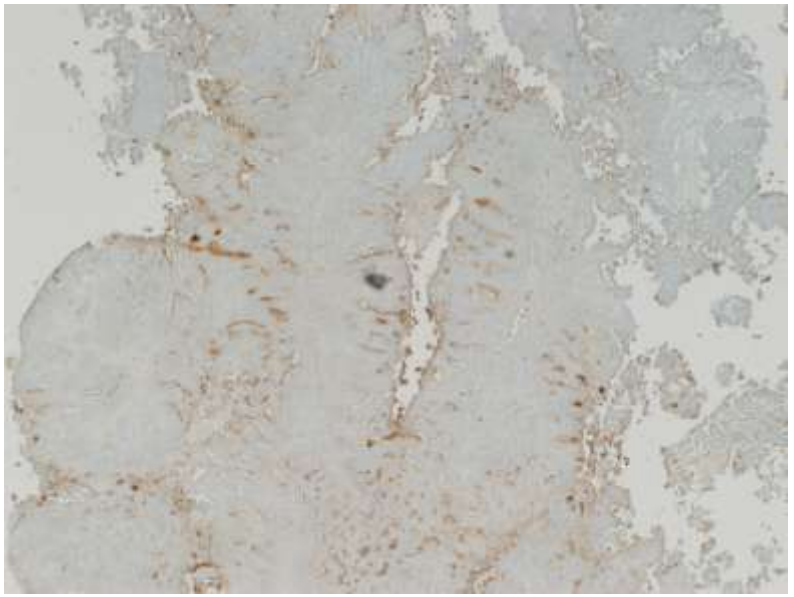
p16 “negative”

Case 6a *(CE-12-2341)*

H&E



CEA

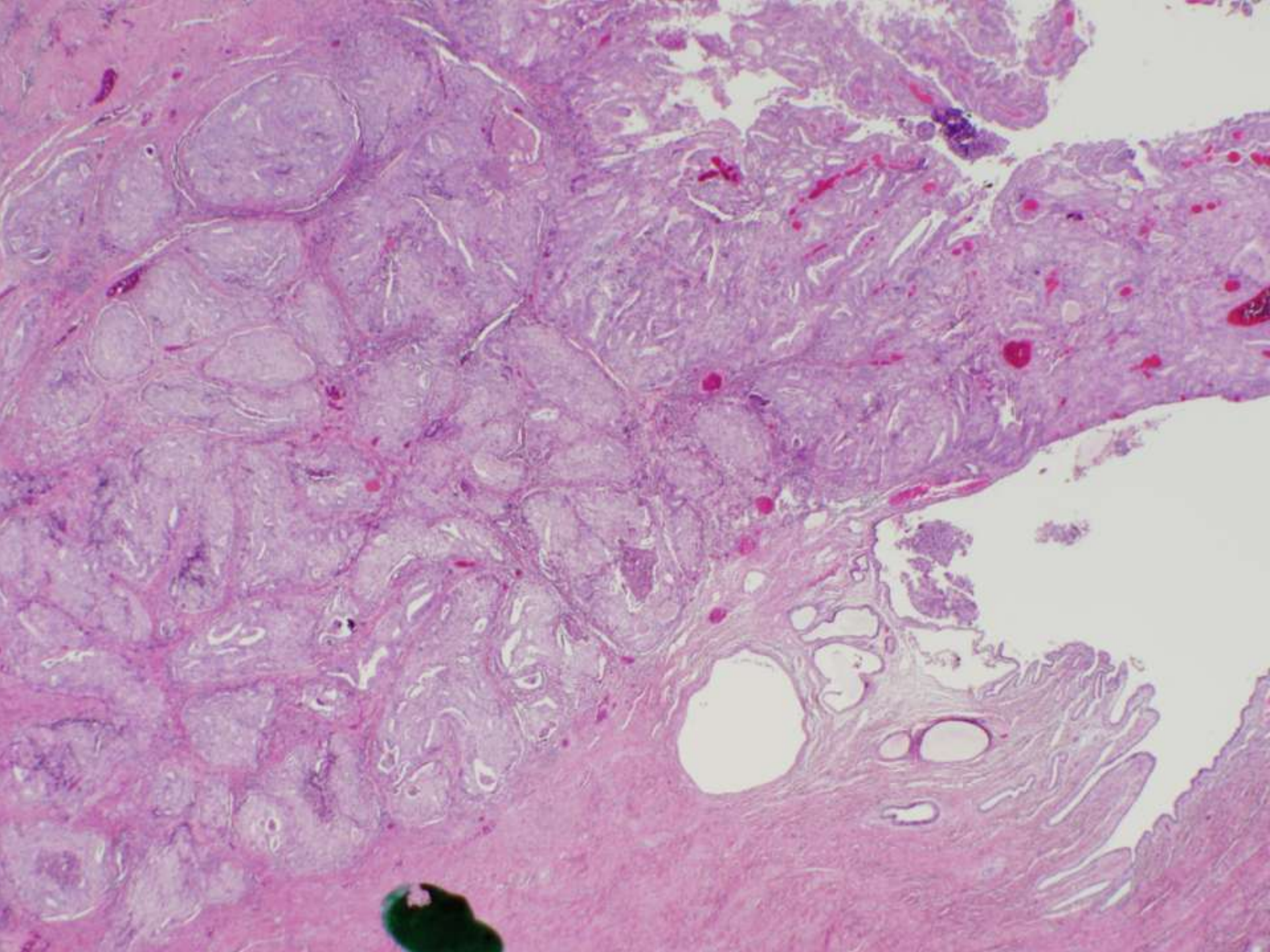


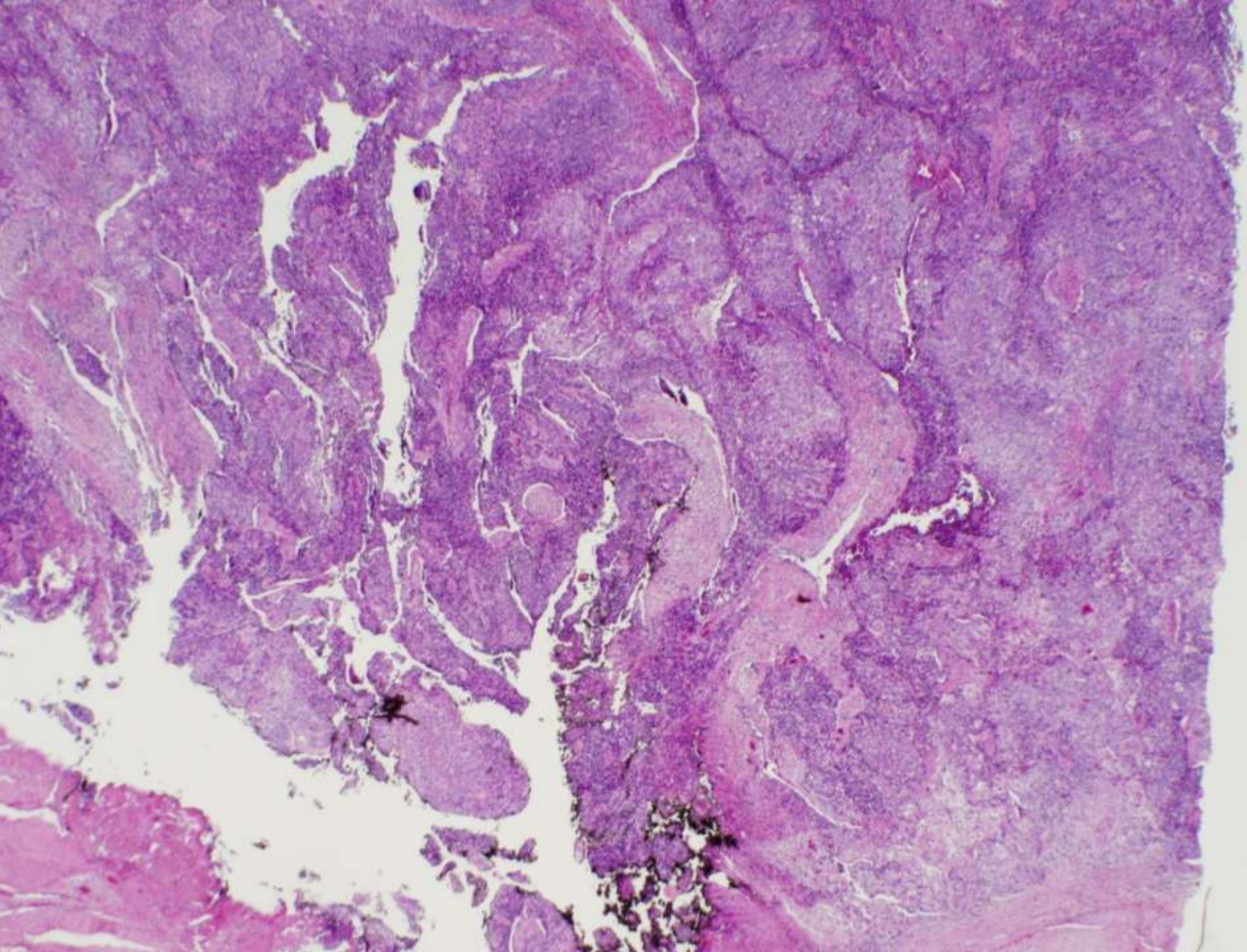
negative

Dx: c/w EEC

Case 6b (SP-12-38415)

39 year old female with infiltrating mass involving LUS and cervix (hysterectomy)

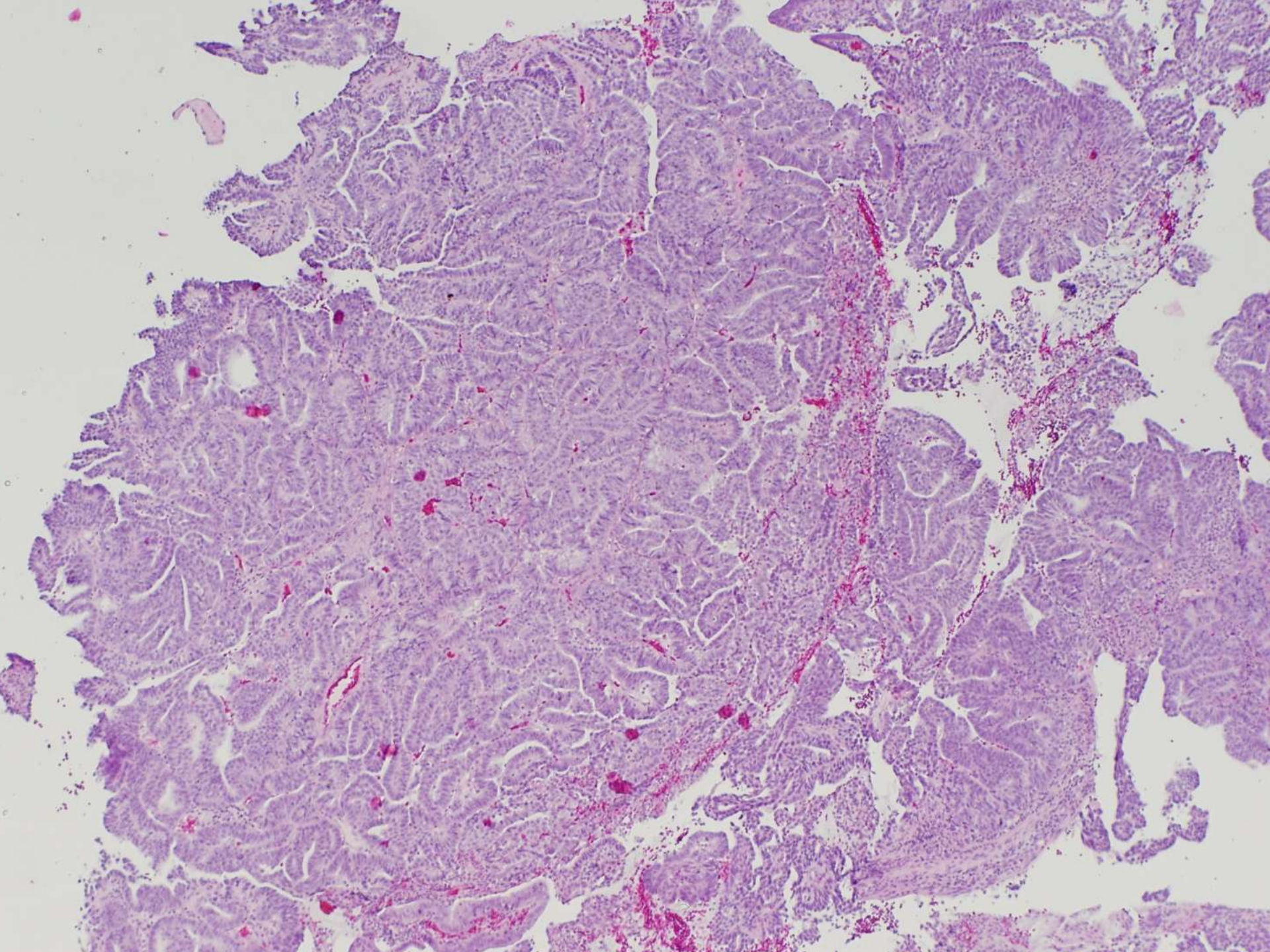


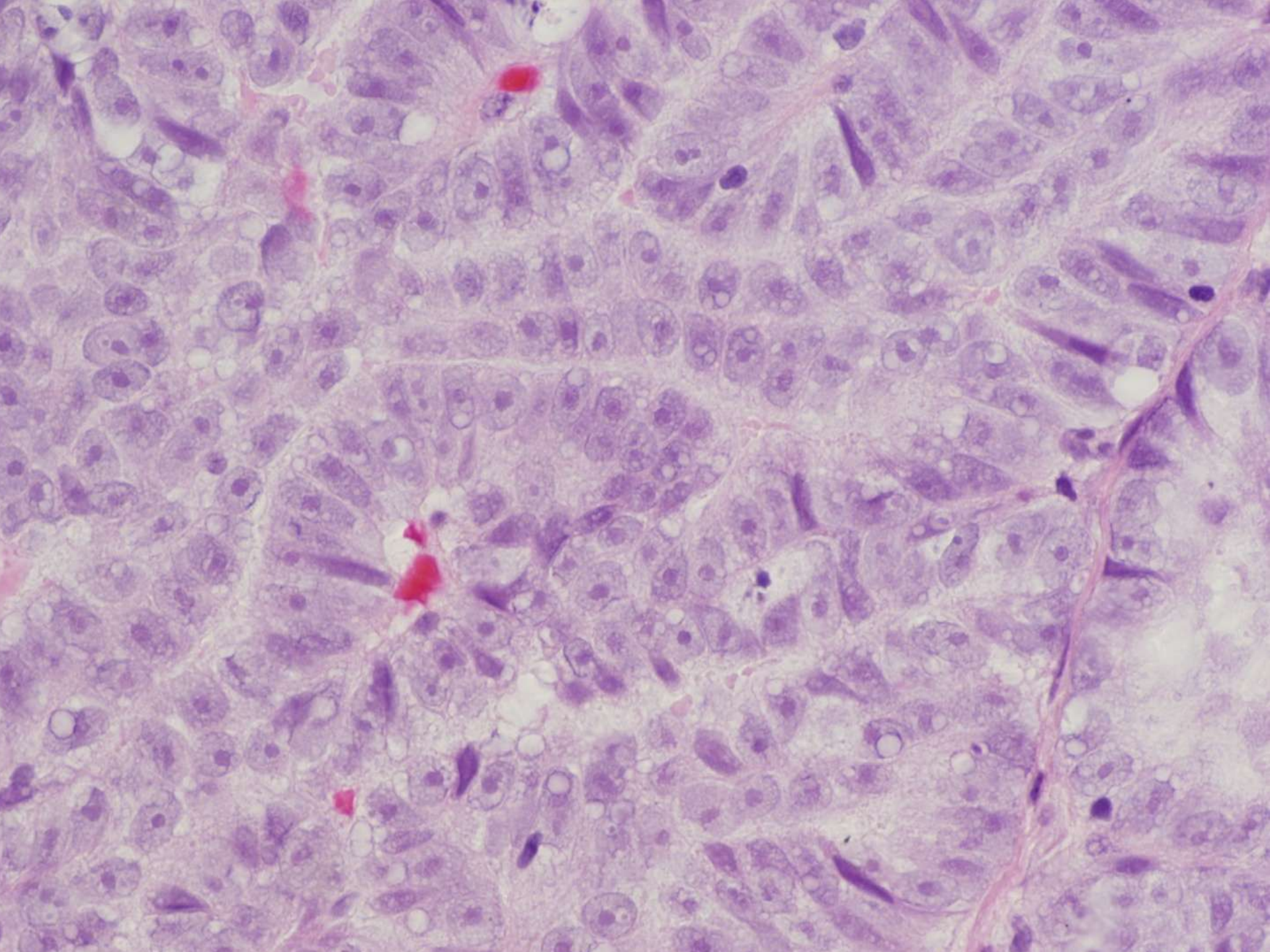


Case 7a *(CE-12-2966)*

61 year old female with PV bleeding, thickened uterine lining on U/S, and tubo-ovarian mass

(endometrial biopsy)





Subtyping Endometrial Ca

- Clinical factors (e.g. age, RF, history)
- Morphologic features (architecture, cytology, other)
  - Problematic morphologies
    - Papillary endometrioid carcinoma
    - Tubular serous carcinoma
- IHC Panel
  - ER, p16, p53, (PTEN, IMP-3)

Characteristic IHC Profiles

- Endometrioid
  - ER (+), p16 (-) / patchy, p53 (-)
- Uterine serous carcinoma
  - ER (-), p16 (+), p53 (+)
- Clear cell carcinoma
  - ER (-), p16 (+/-), p53 (+/-)

Limitations of IHC in typing EC

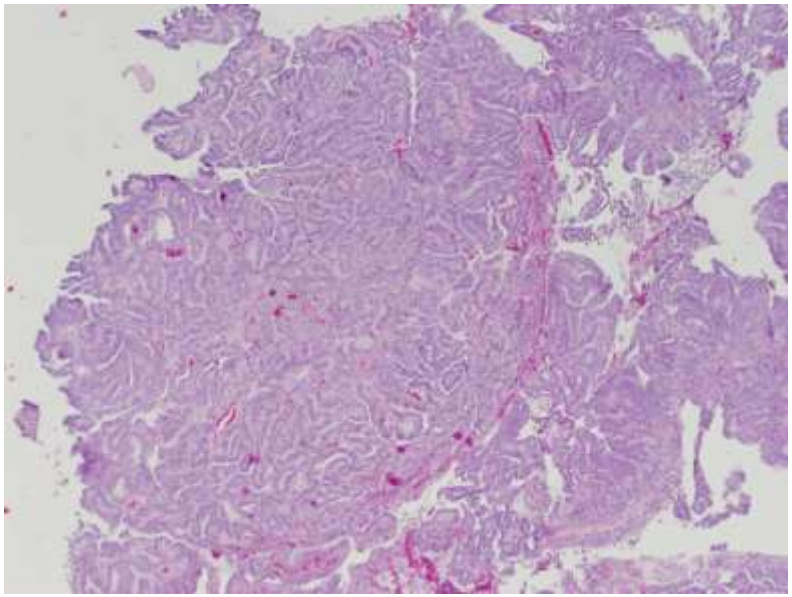
- Overlap in general
- High grade tumors
- Mixed tumors

Be careful with p53

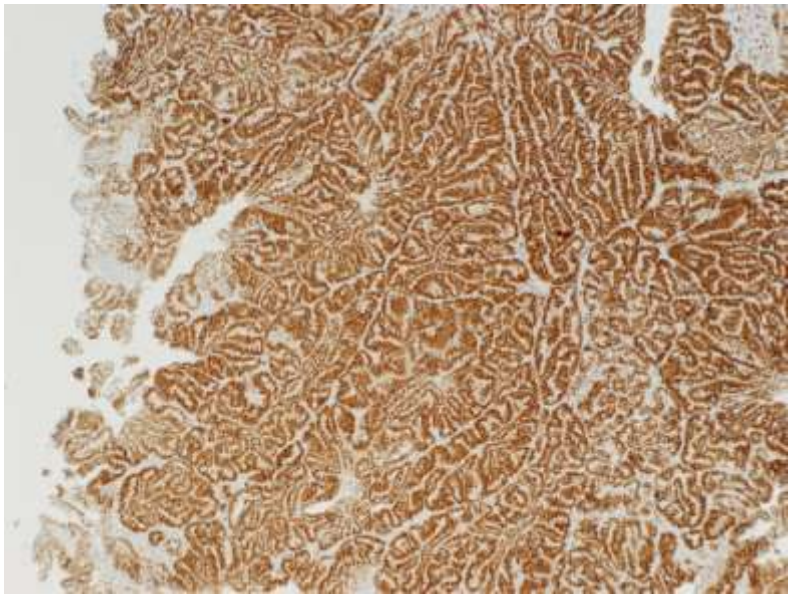
- negative, null, non-specific, positive

Case 7a *(CE-12-2966)*

H&E



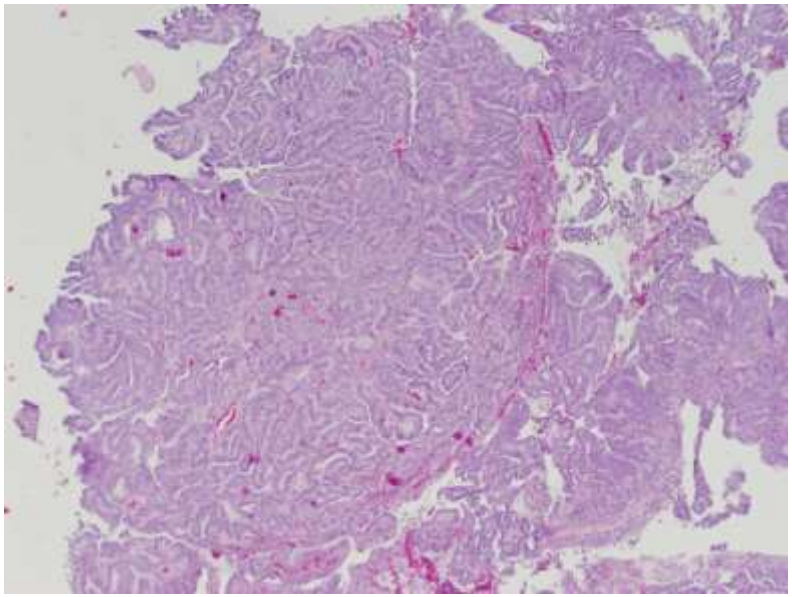
ER



positive

Case 7a *(CE-12-2966)*

H&E



p53

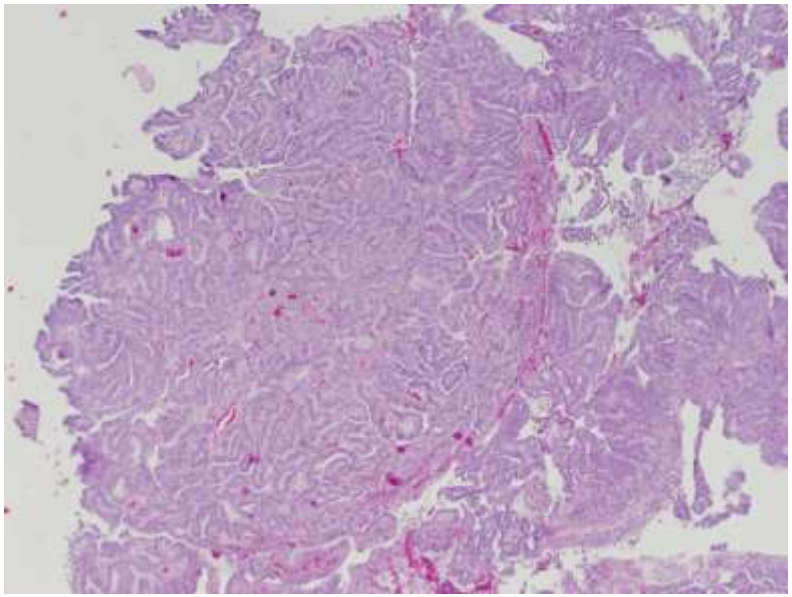
negative

Case 7a *(CE-12-2966)*

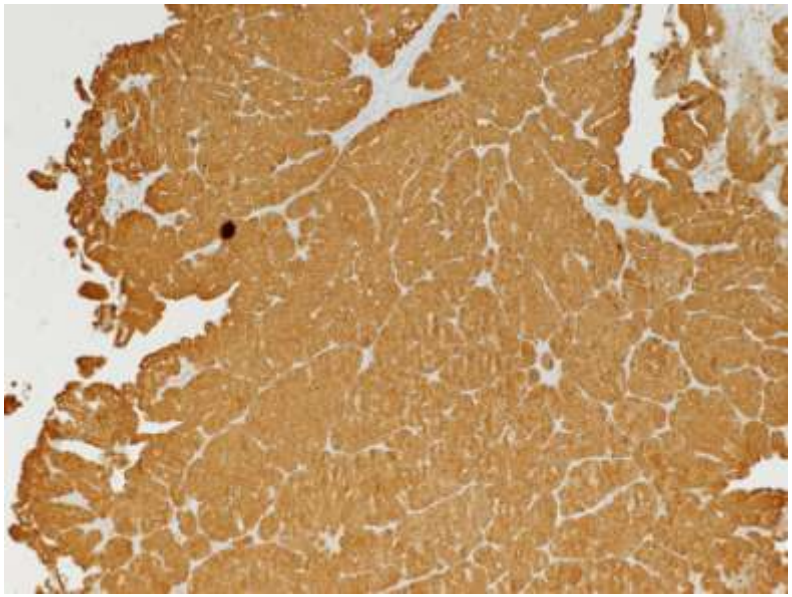
p53 “negative” (*null pattern*)

Case 7a *(CE-12-2966)*

H&E



p16



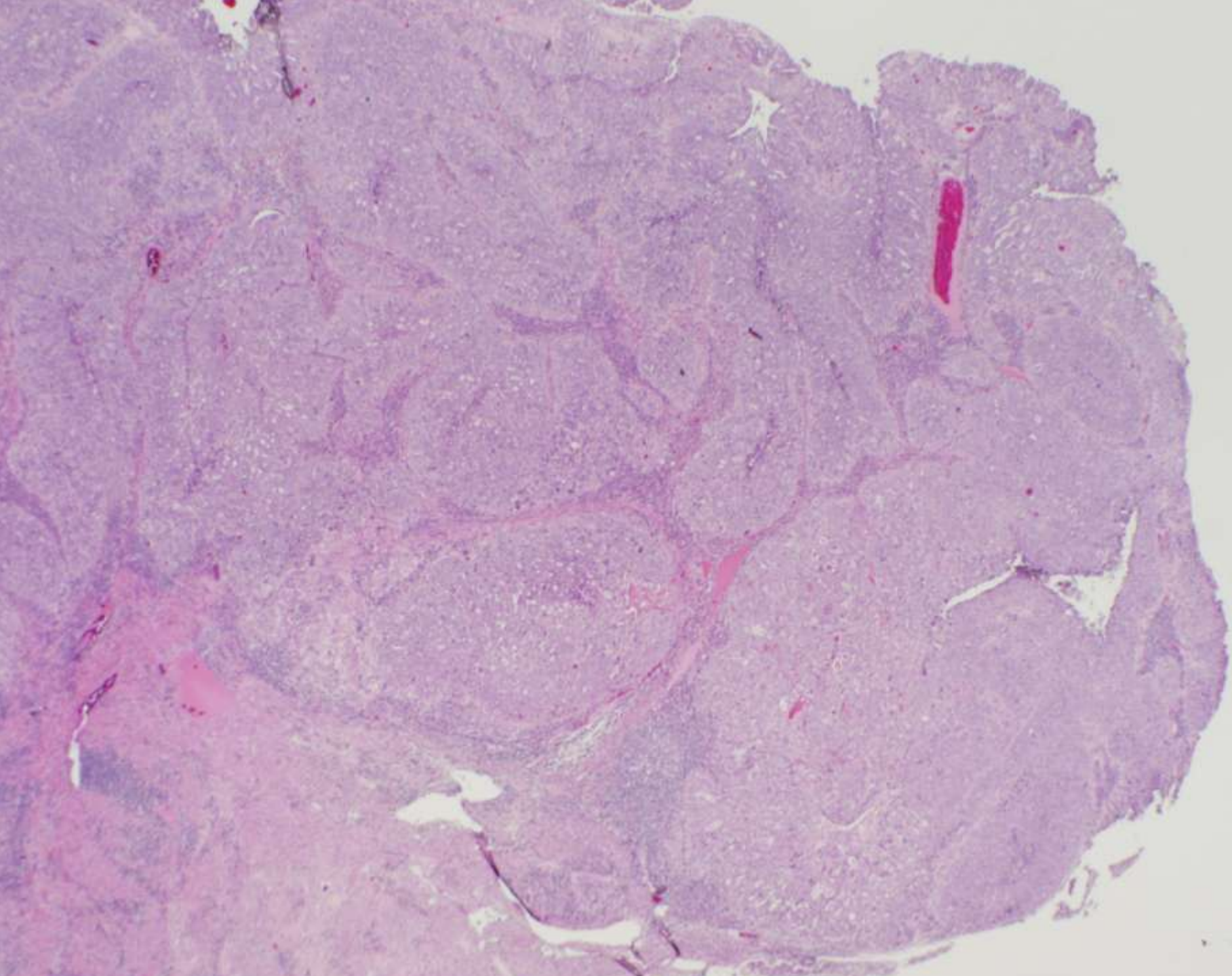
positive

Dx: Favor USC

Case 7b *(SP-13-7612)*

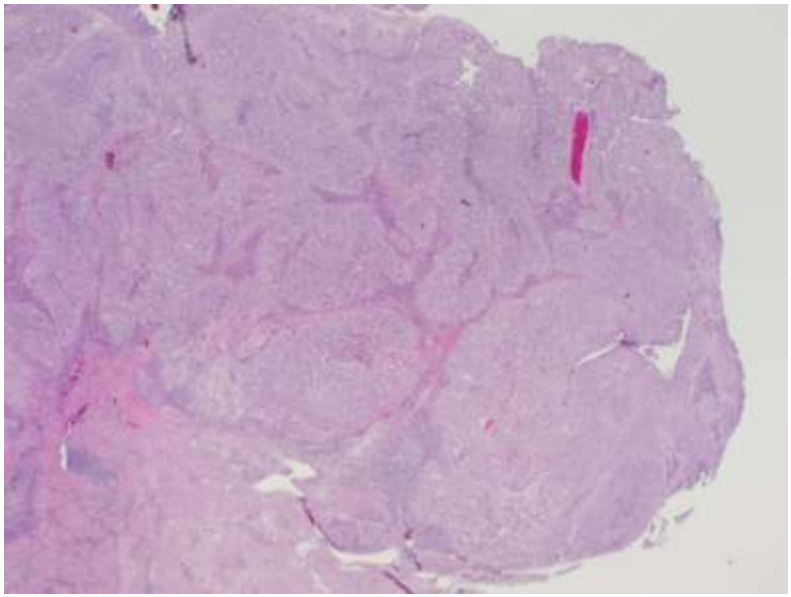
61 year old female with PV bleeding, thickened uterine lining on U/S, and tubo-ovarian mass

(hysterectomy / BSO)



Case 7b *(SP-13-7612)*

H&E



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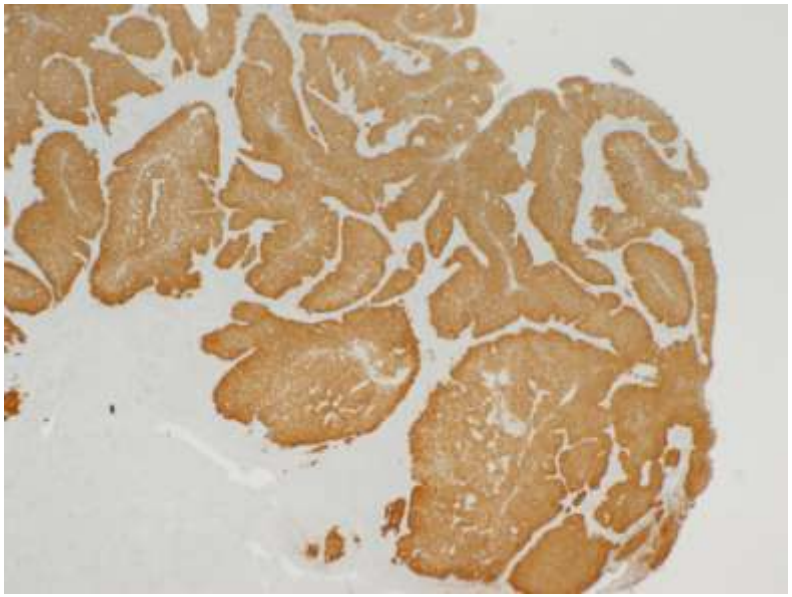
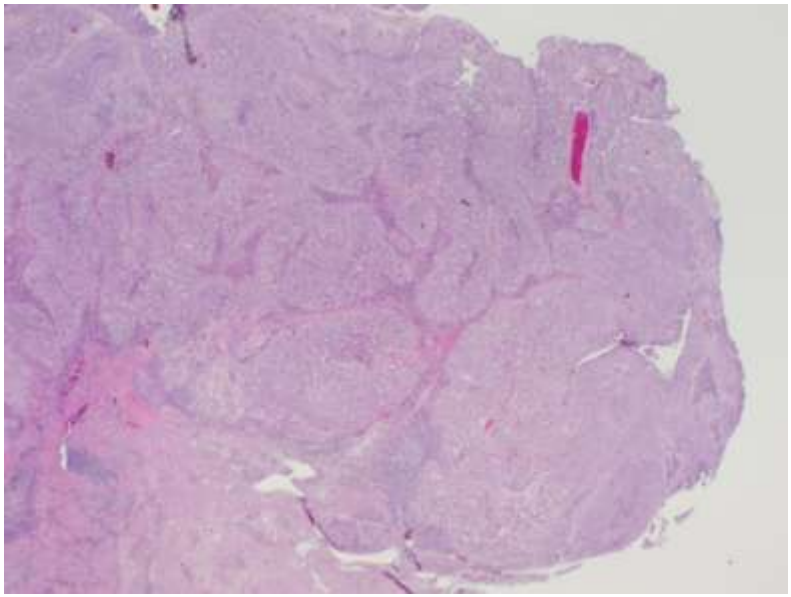


positive

Case 7b *(SP-13-7612)*

H&E



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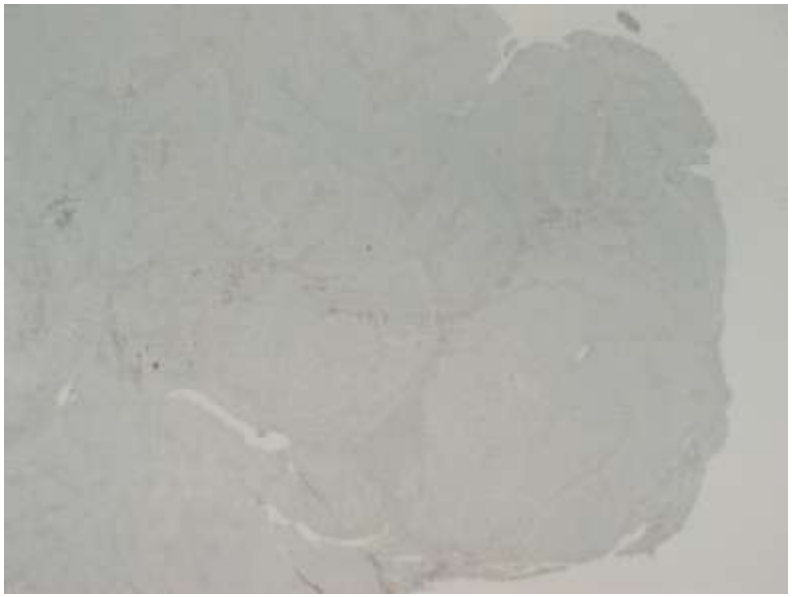
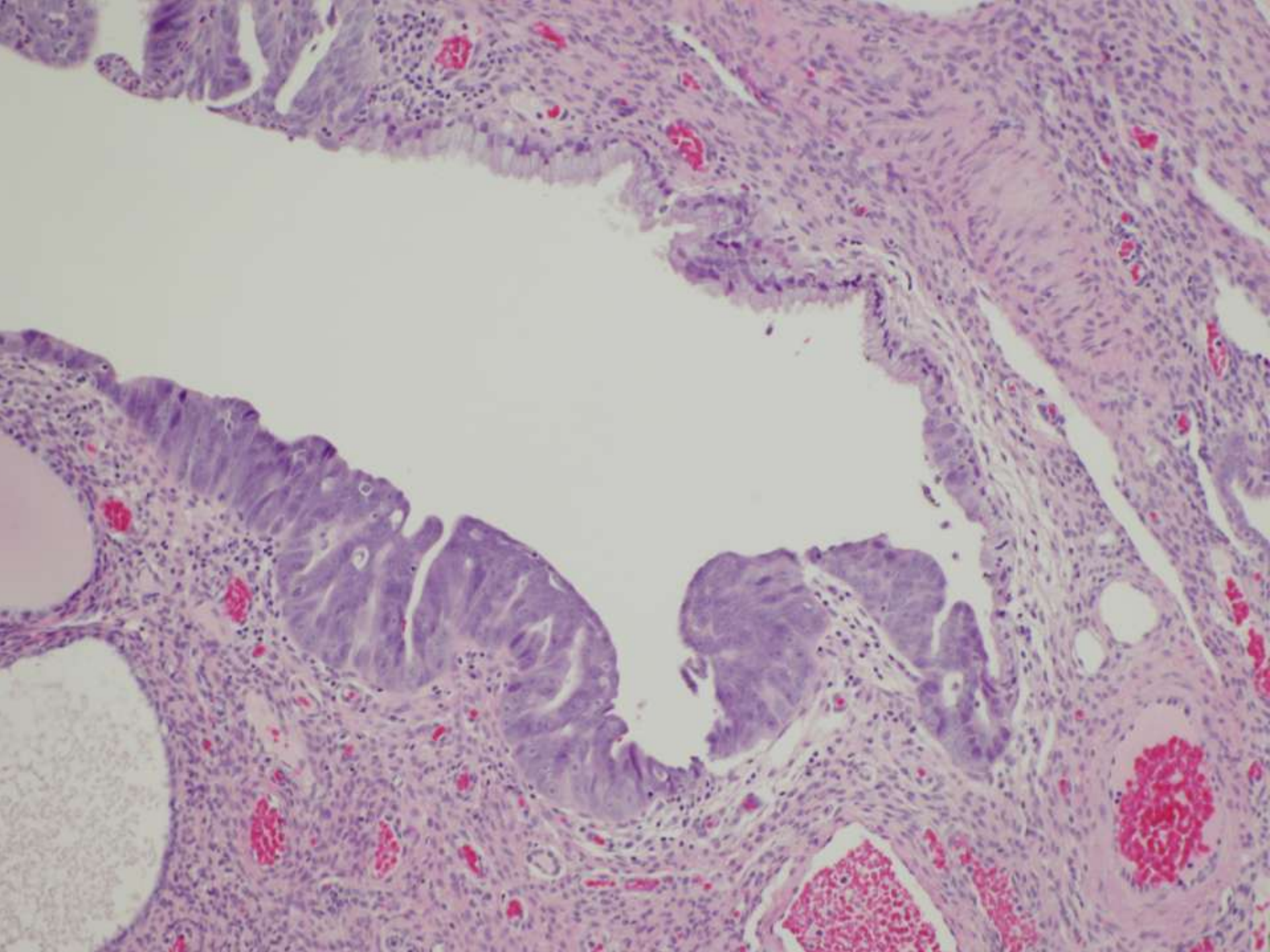
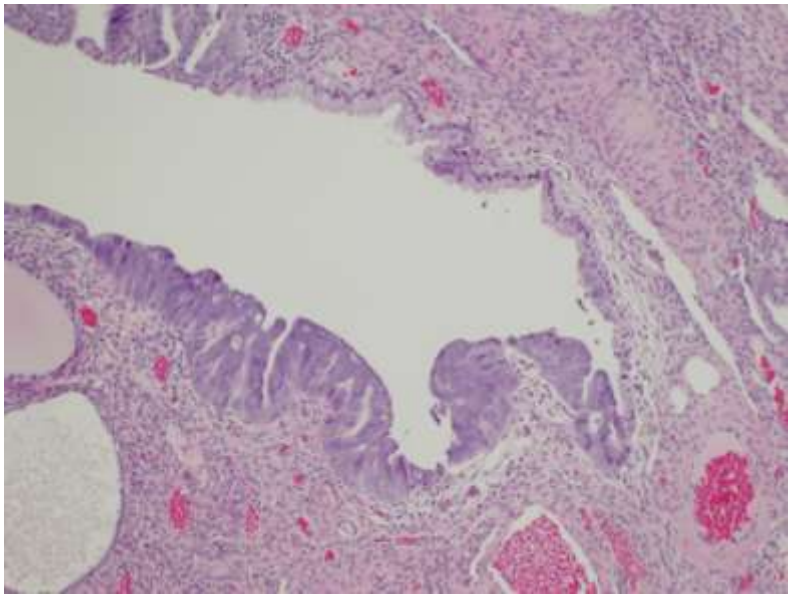


“null pattern”



Case 7b *(SP-13-7612)*

H&E



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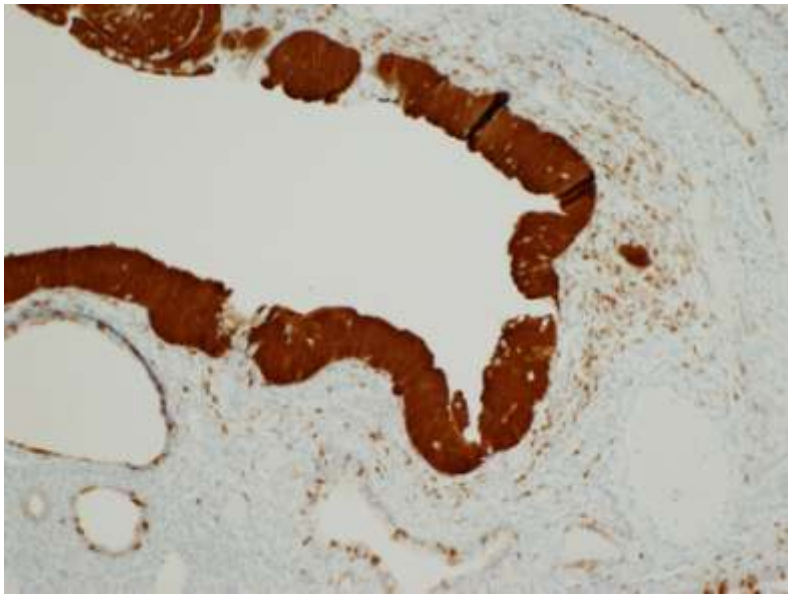
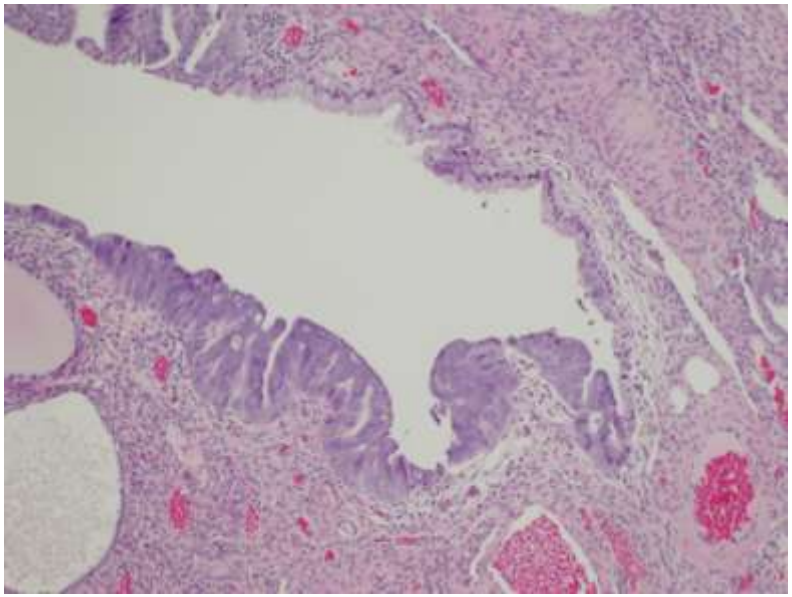


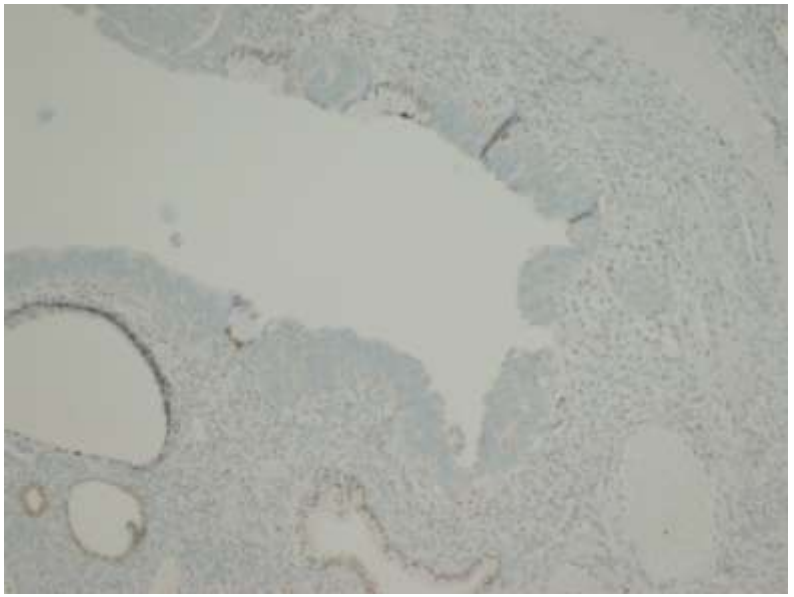
positive

Case 7b *(SP-13-7612)*

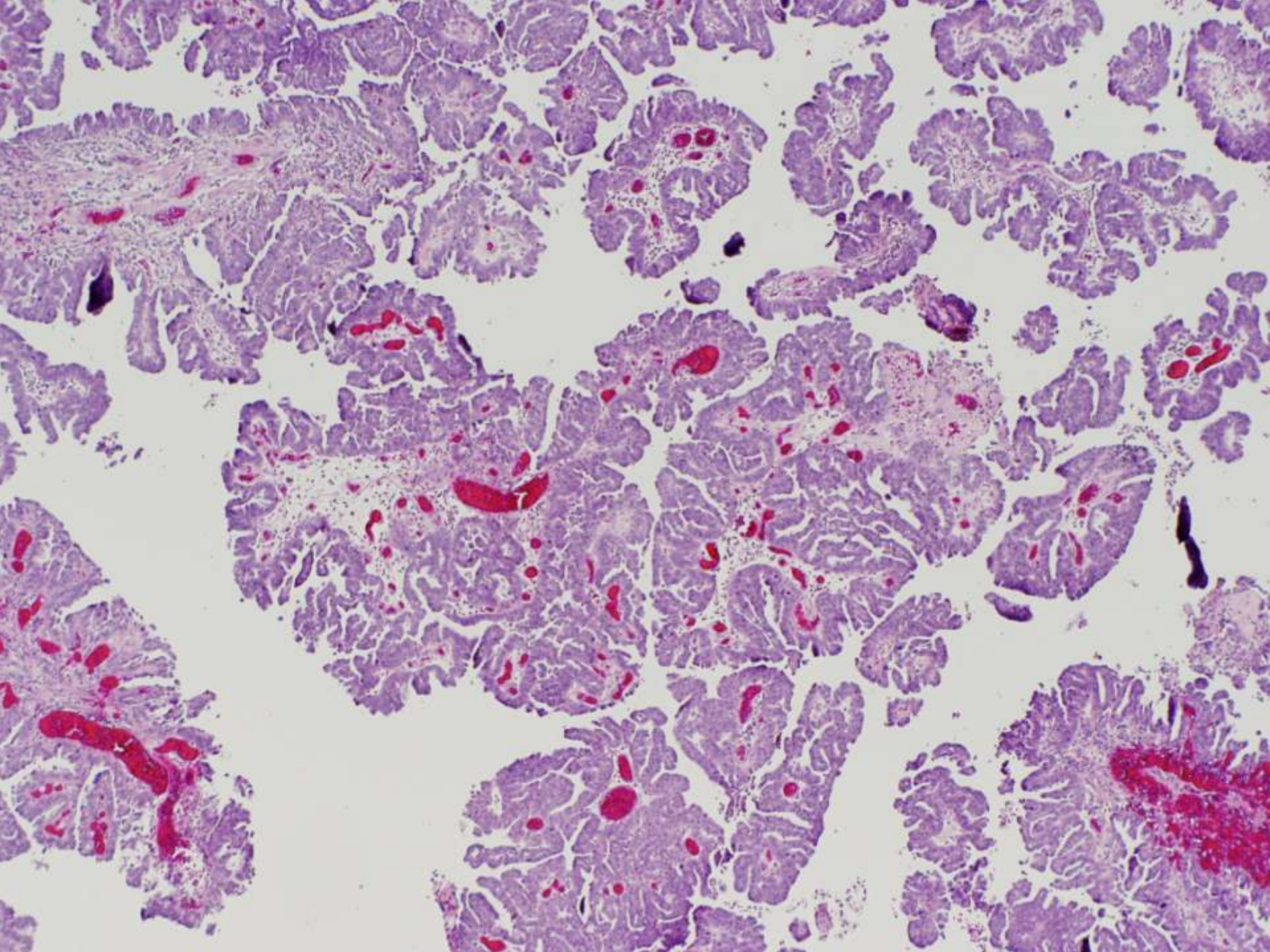
H&E



p53

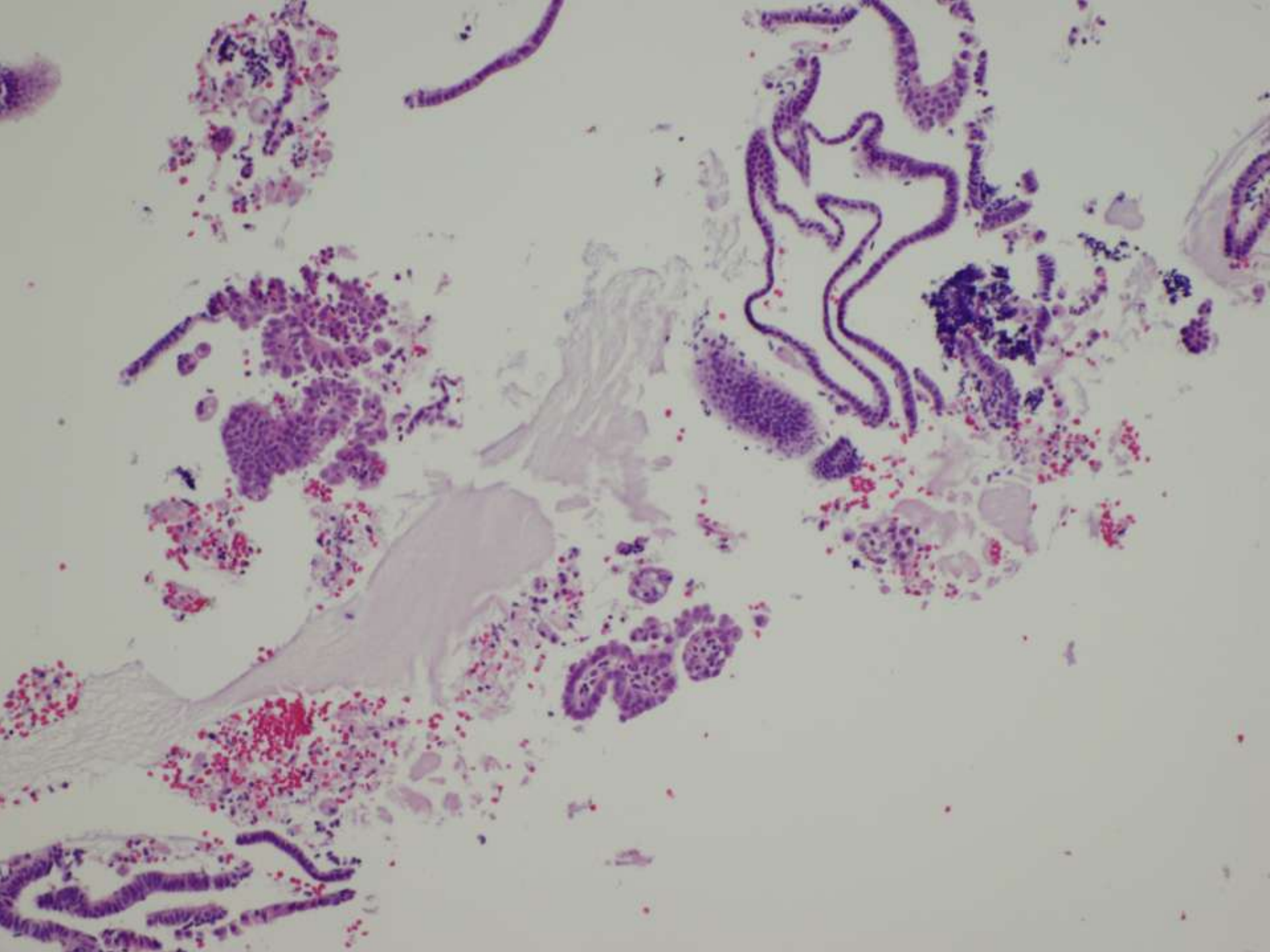


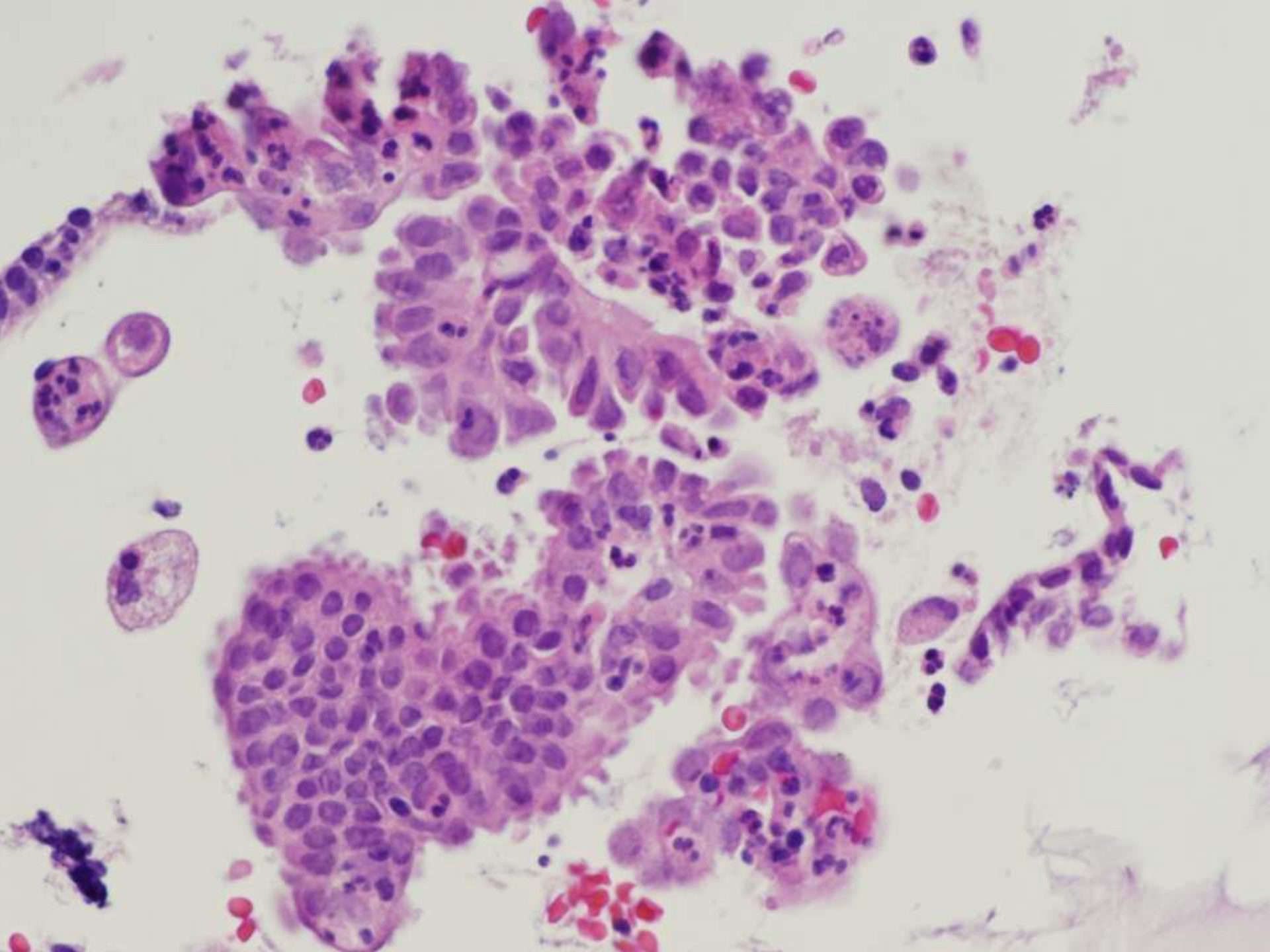
“null pattern”



Case 8 *(CE-14-70)*

54 year old female with endometrial cells on Pap, thickened endometrium on U/S (endometrial biopsy)





International Journal of Gynecological Pathology
31:206–210, Lippincott Williams & Wilkins, Baltimore

Original Article

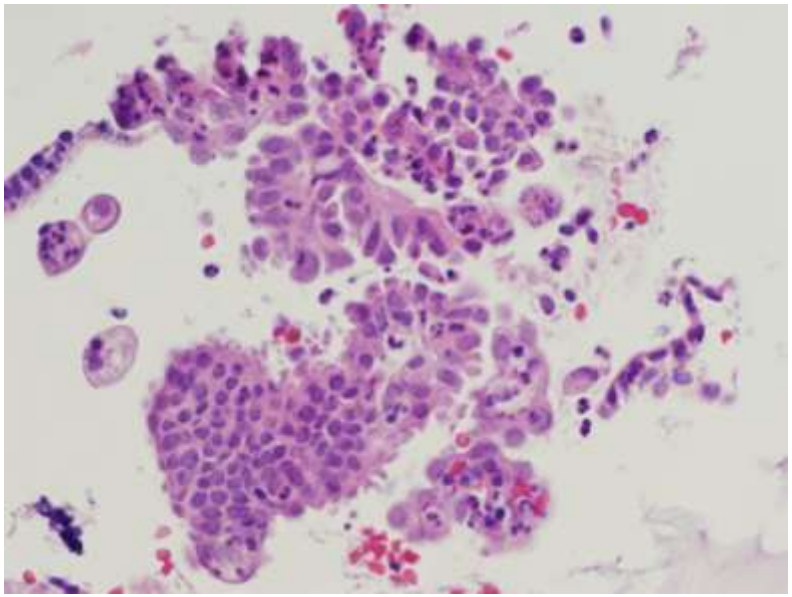
Papillary Syncytial Metaplasia Associated With Endometrial Breakdown Exhibits an Immunophenotype That Overlaps With Uterine Serous Carcinoma

W. Glenn McCluggage, F.R.C.Path, and Hilary A. McBride, F.I.B.M.S.

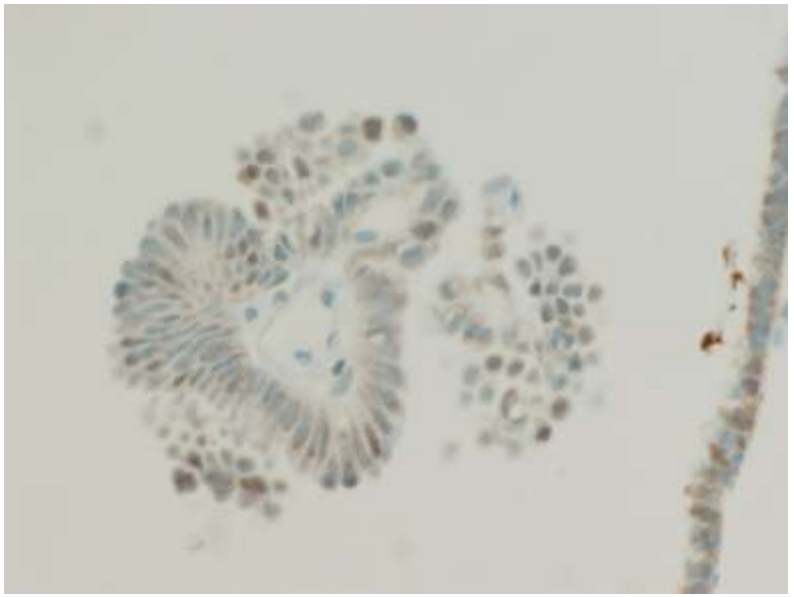
- PSM unexpectedly shows diminished ER and strong and diffuse expression of p16*
- p53 may be positive but with ‘wild-type’ pattern
- Ki67 index low
- HMGA2 negative

Case 8 *(CE-14-70)*

H&E



p53

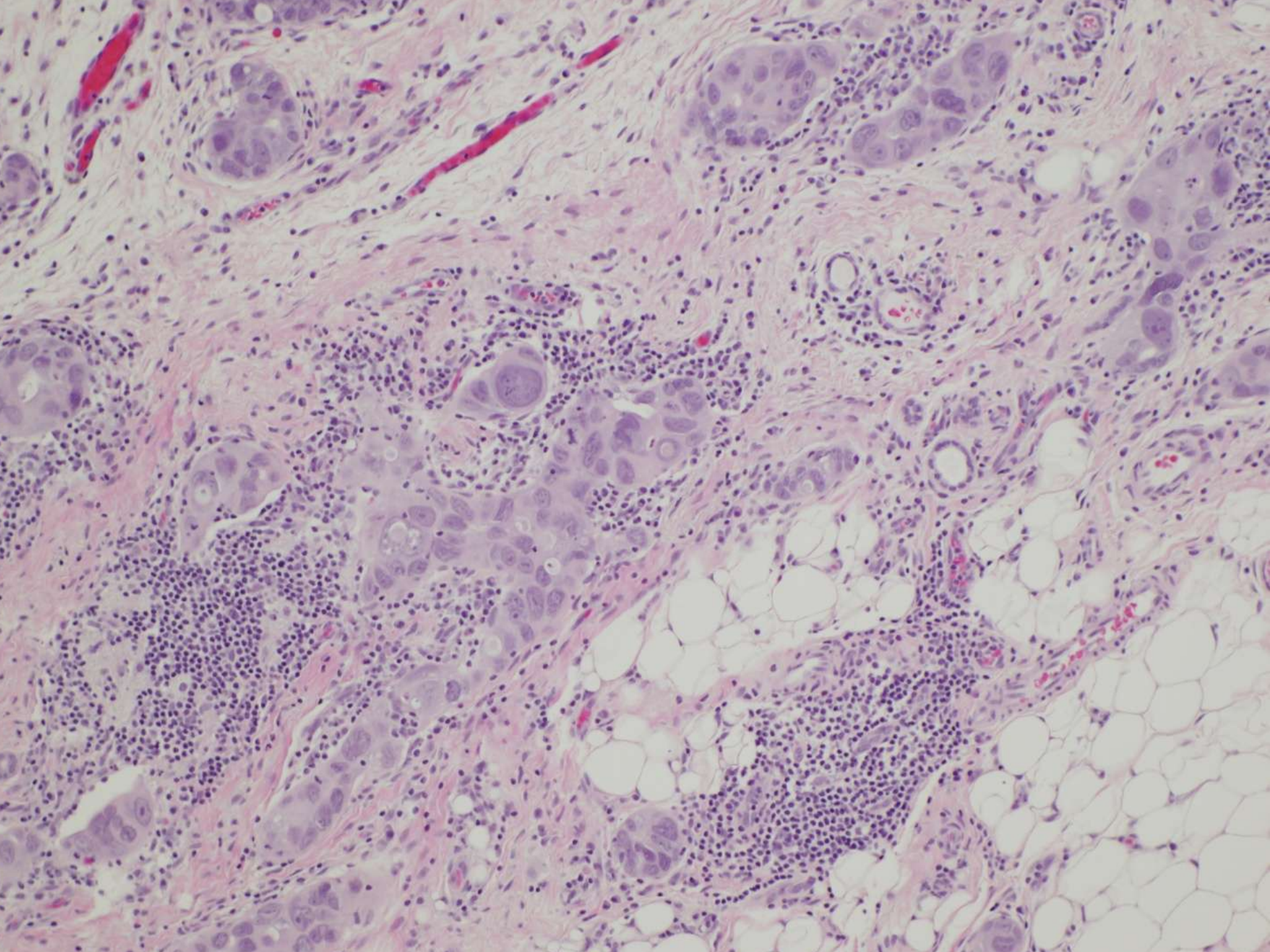


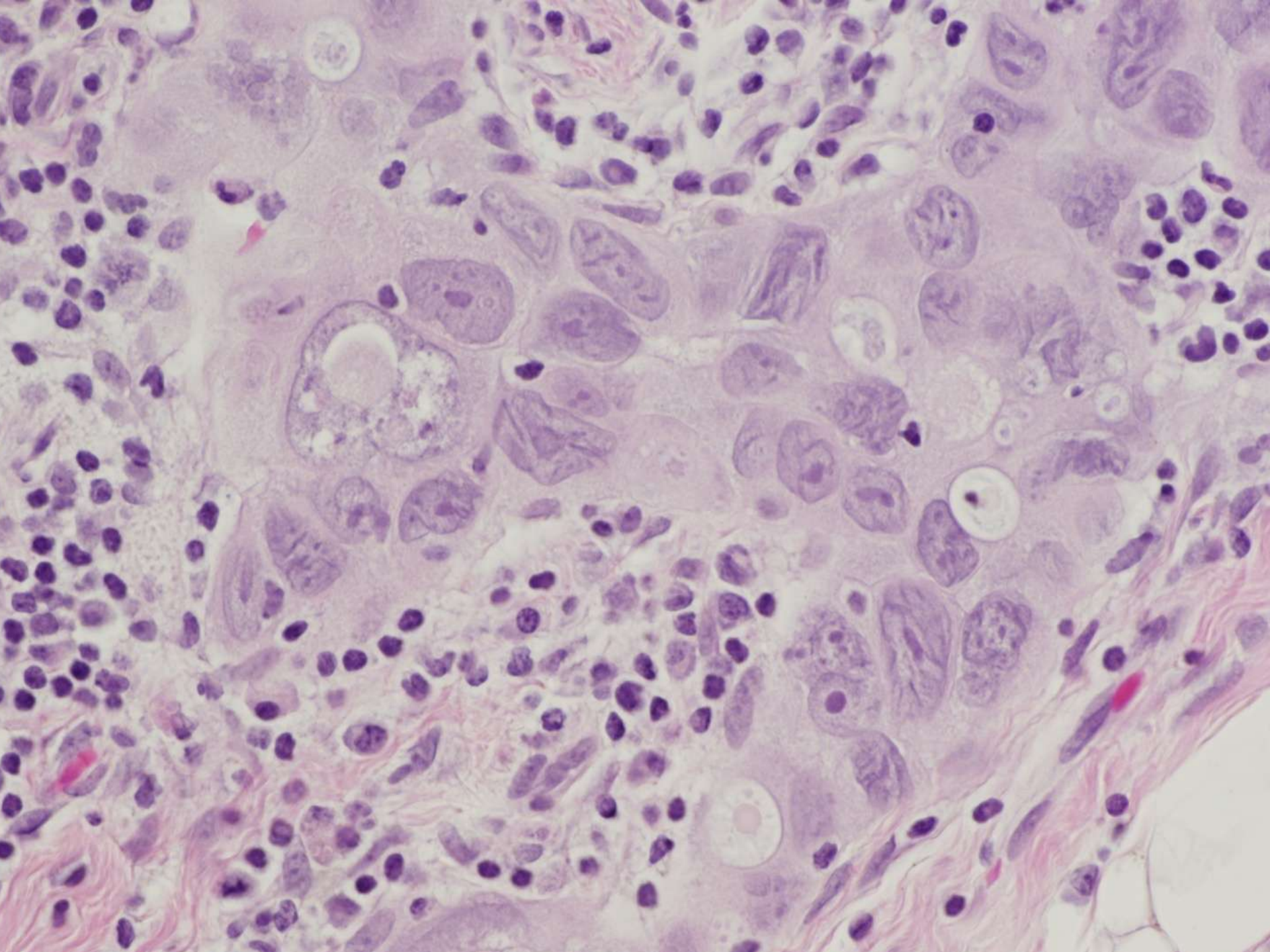
Negative (wild-type)

Dx: Surface metaplastic / reparative changes

Case 9 *(SP-13-42263)*

72 year old female treated with neo-adjuvant chemotherapy for presumed ovarian cancer – no gross residual at surgical debulking (omentectomy)





IHC Markers in Ddx of Ovarian SEC

- ER
  - Negative in CCC, Positive in others
- p53 and p16
  - Positive in HGSC, Negative in others
- WT-1
  - Positive in HGSC, Negative in others
- HNF-1β
  - Positive in CCC, Negative in others

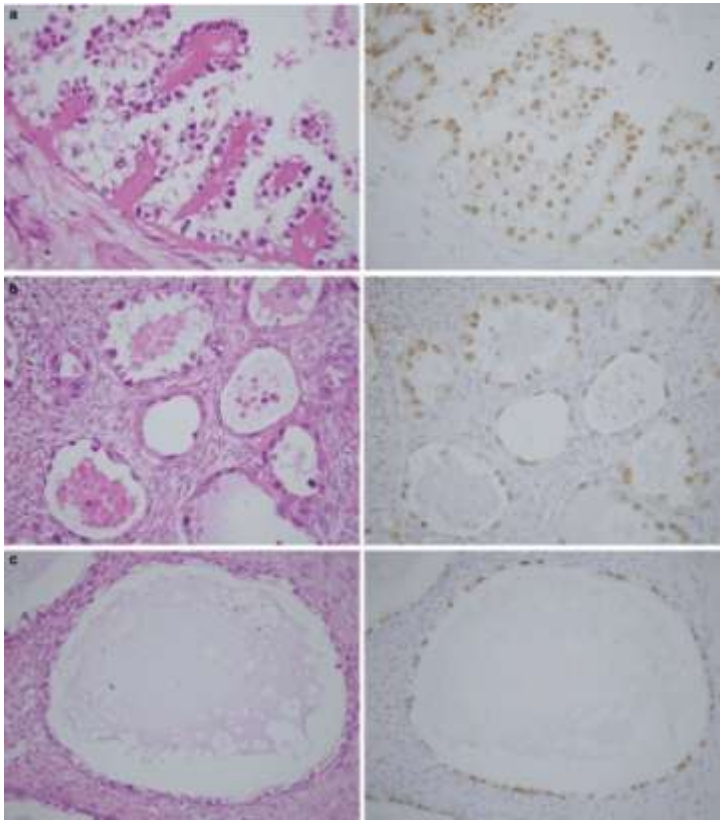
WT-1

- Marker of upper tract HGSC (> 90% positive)
- Less commonly positive in lower tract serous carcinomas (EIC, USC) (7-20%)
- Also positive in mesothelioma, Wilms tumor, DSRCT, others

Int J Gynecol Pathol. 2013 Sep;32(5):433-43

HNF-1β

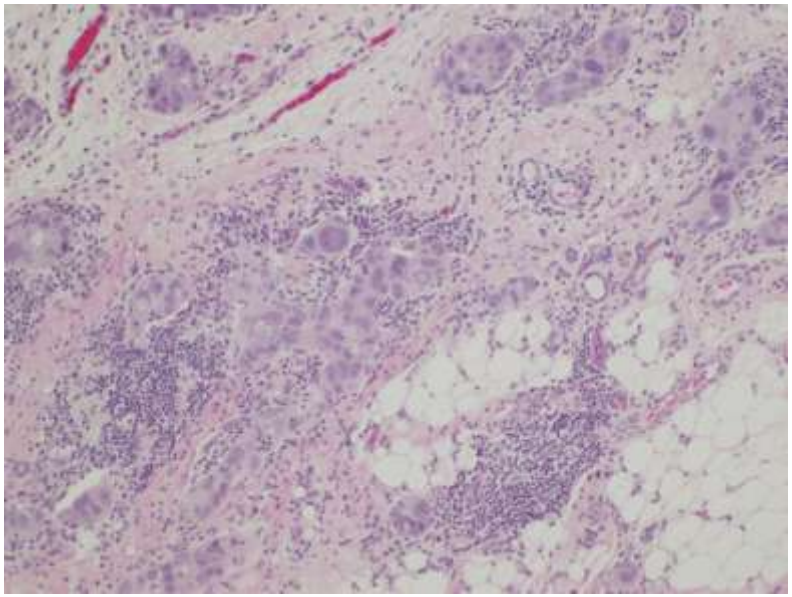
- Positive in the majority of CCC
- Positive in adjacent endometriosis
- Negative in other SEC



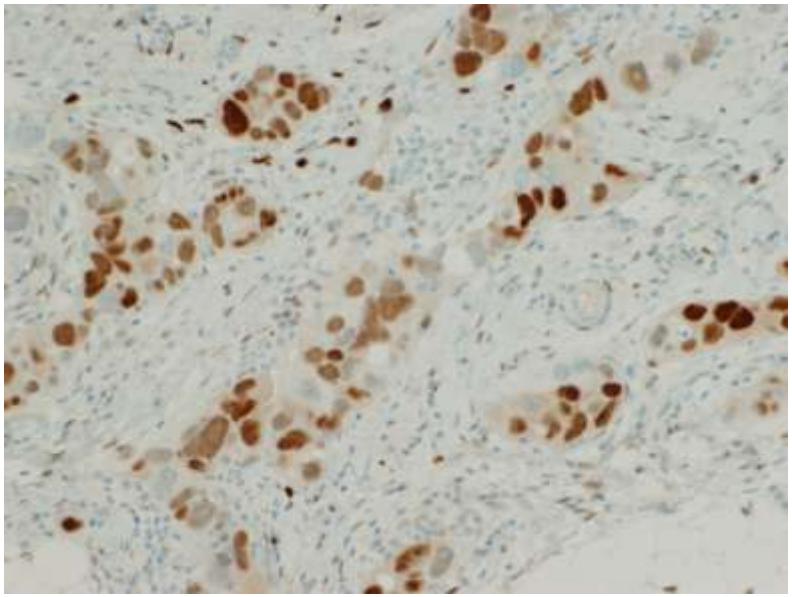
Kato et al. *Modern Pathology* (2006) 19, 83–89.

Case 9 *(SP-13-42263)*

H&E



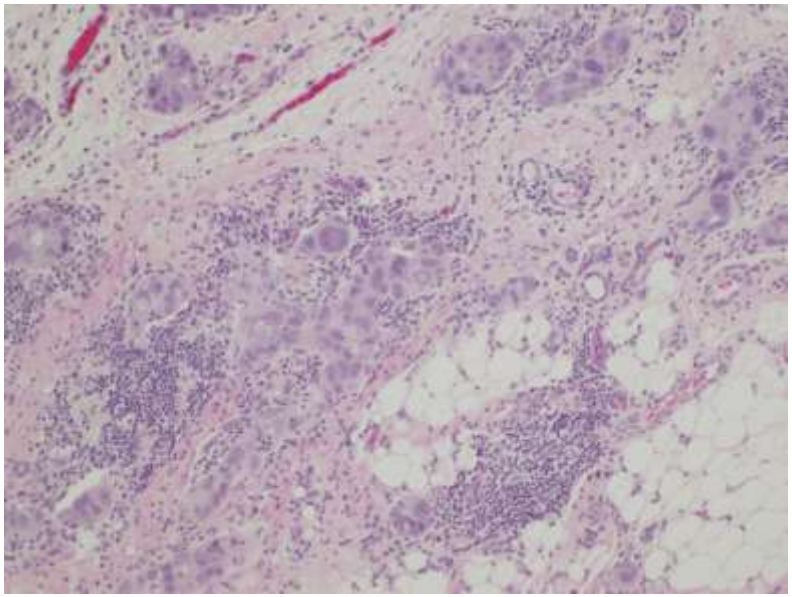
ER



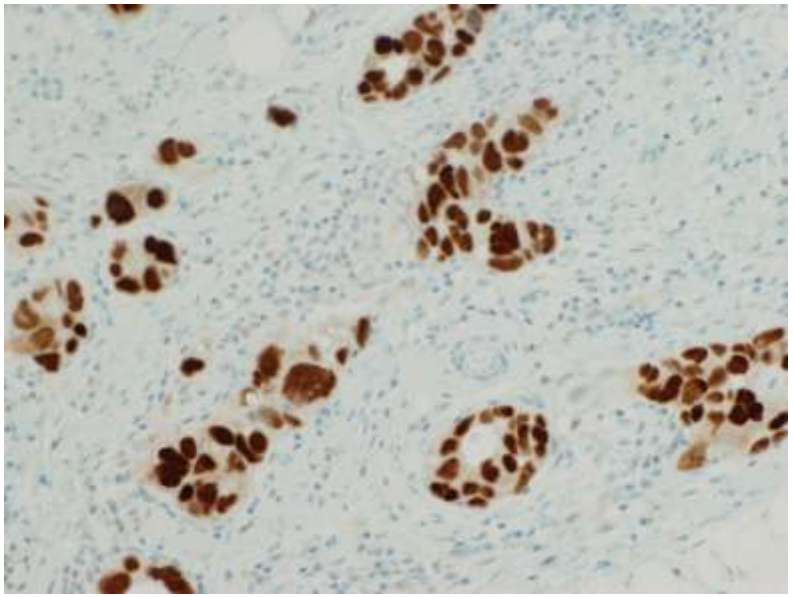
Positive

Case 9 *(SP-13-42263)*

H&E



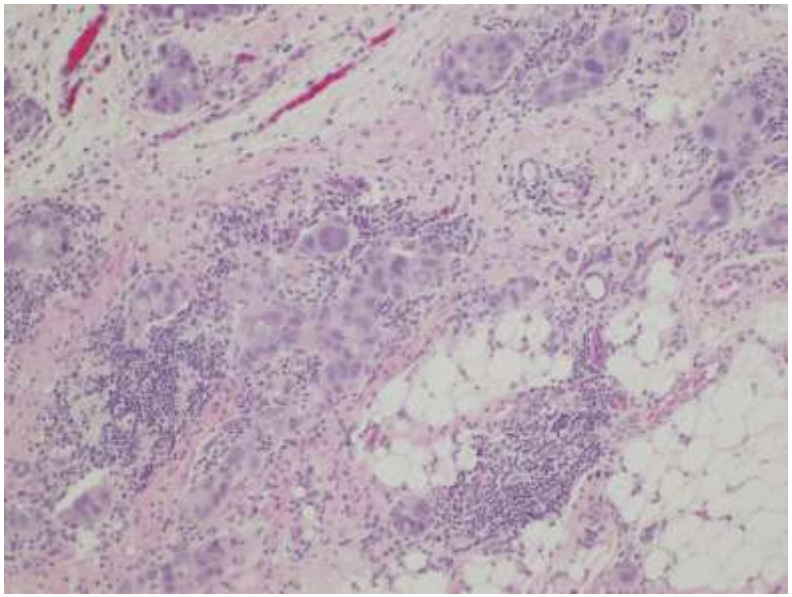
p53



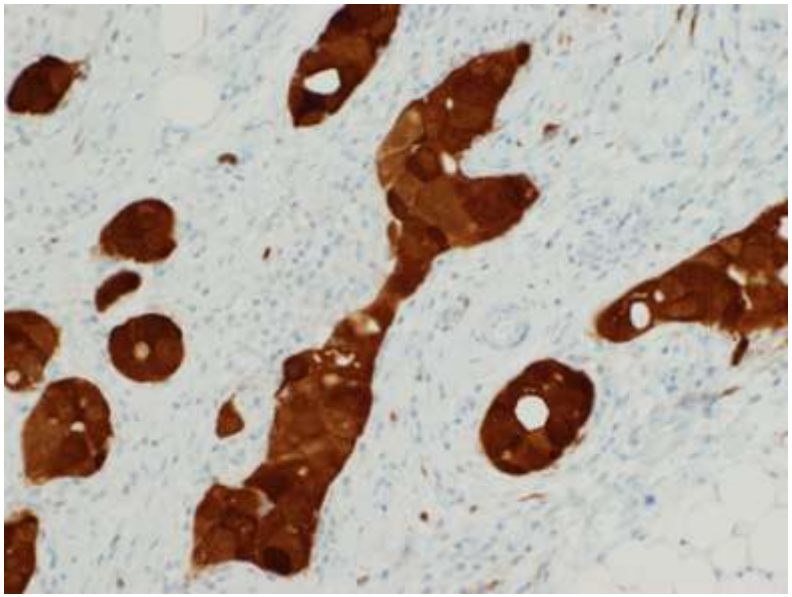
Positive

Case 9 *(SP-13-42263)*

H&E



p16

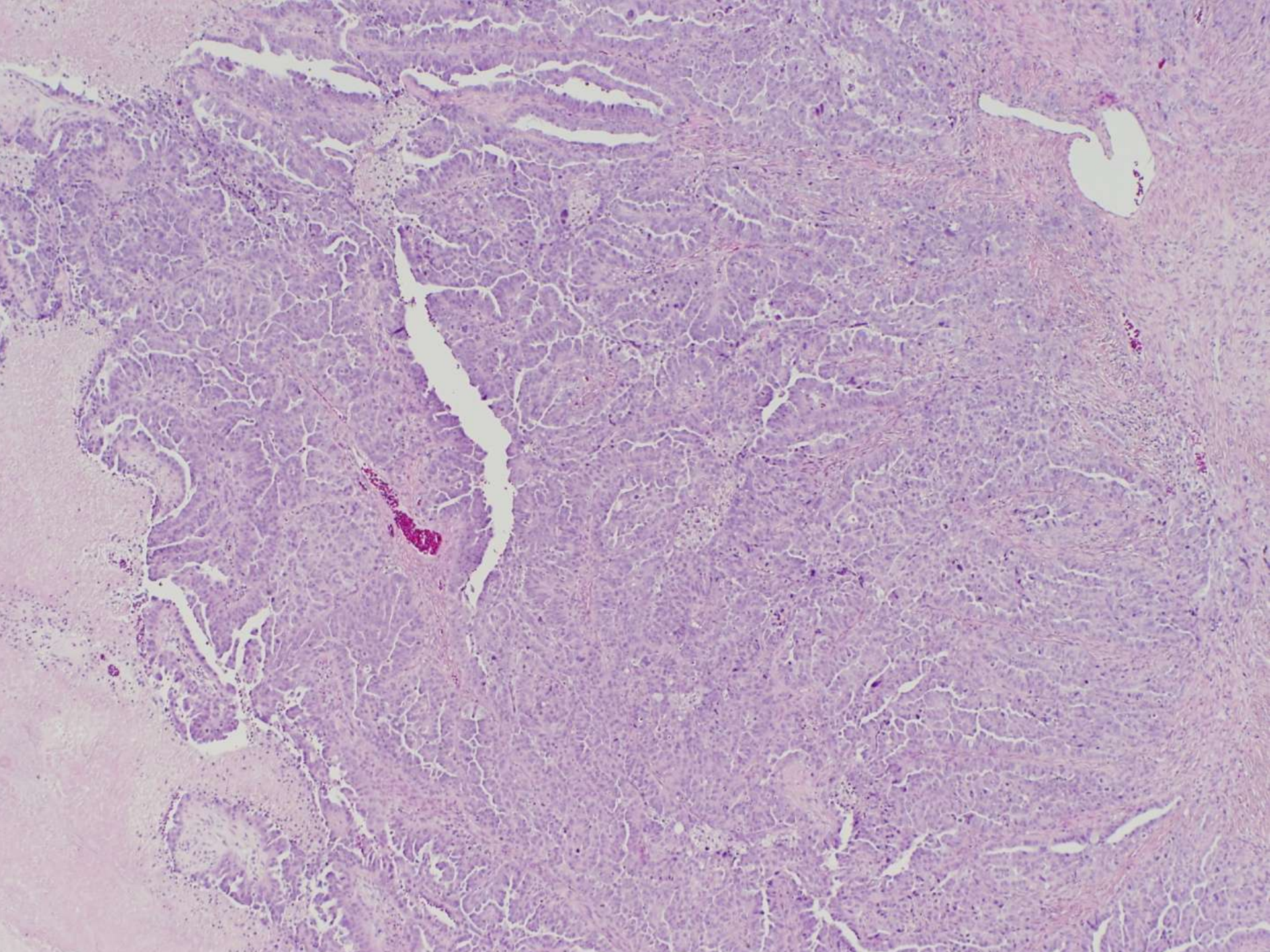


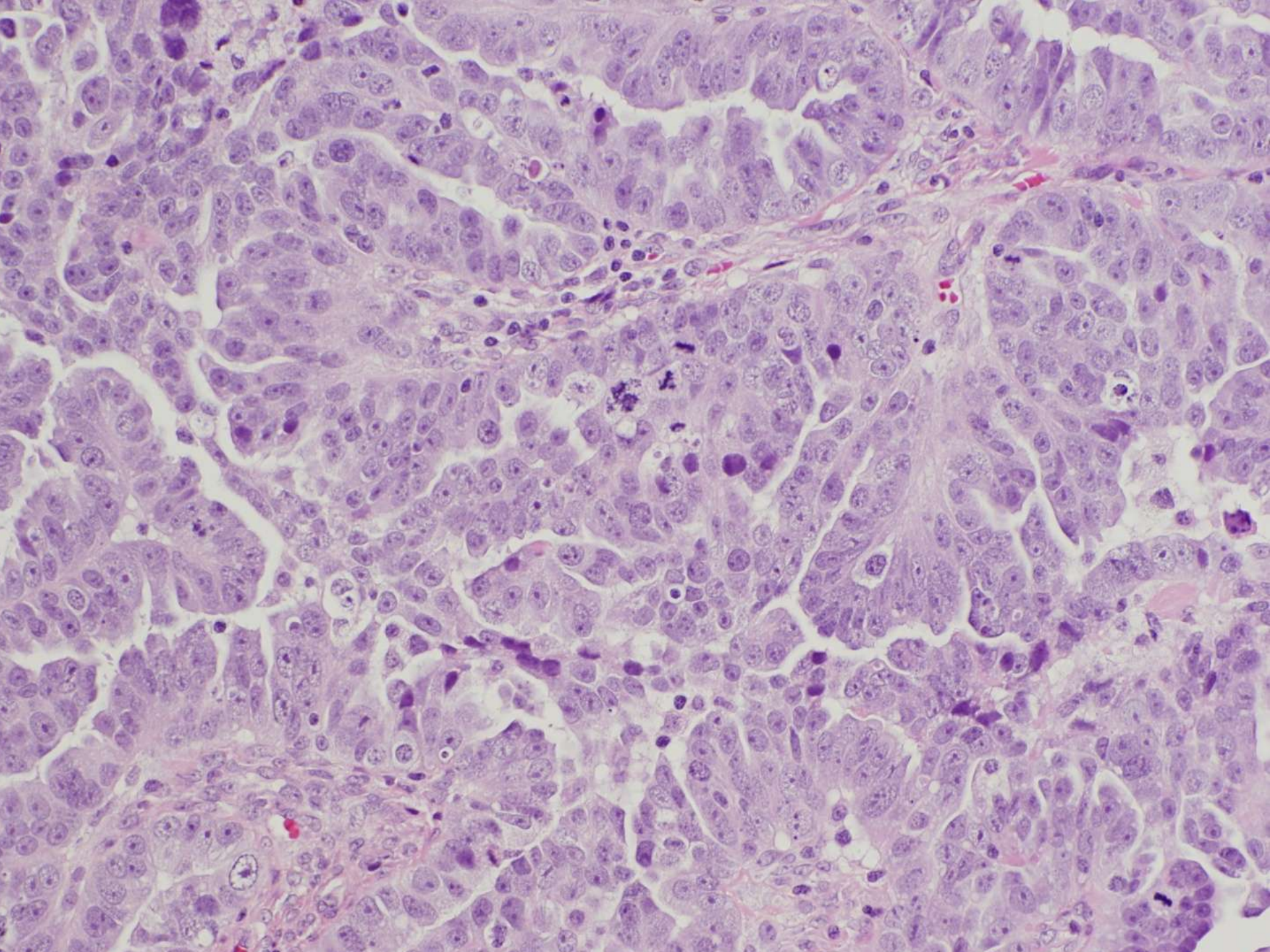
Positive

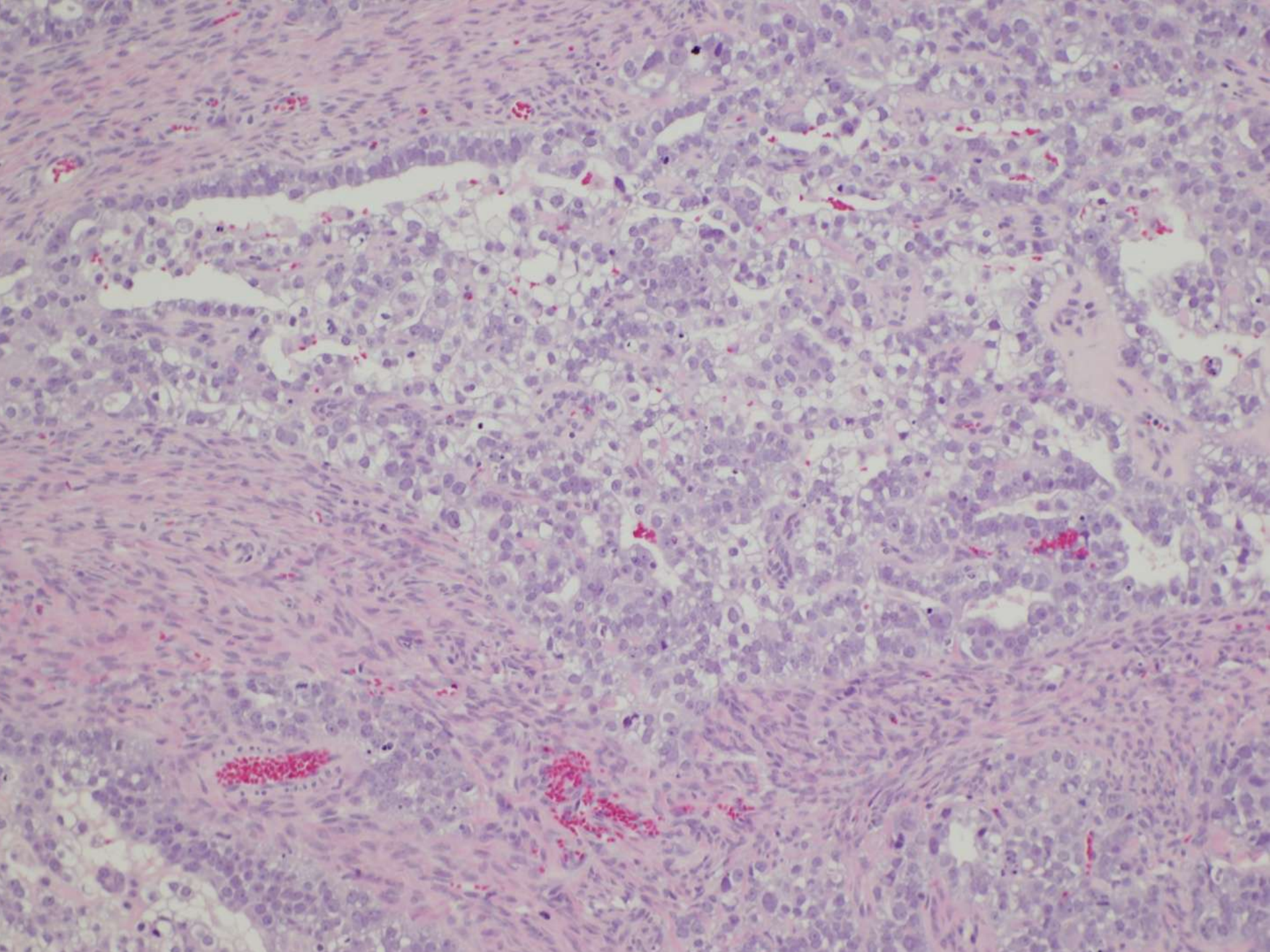
Dx: c/w HGSC of tubo-ovarian origin

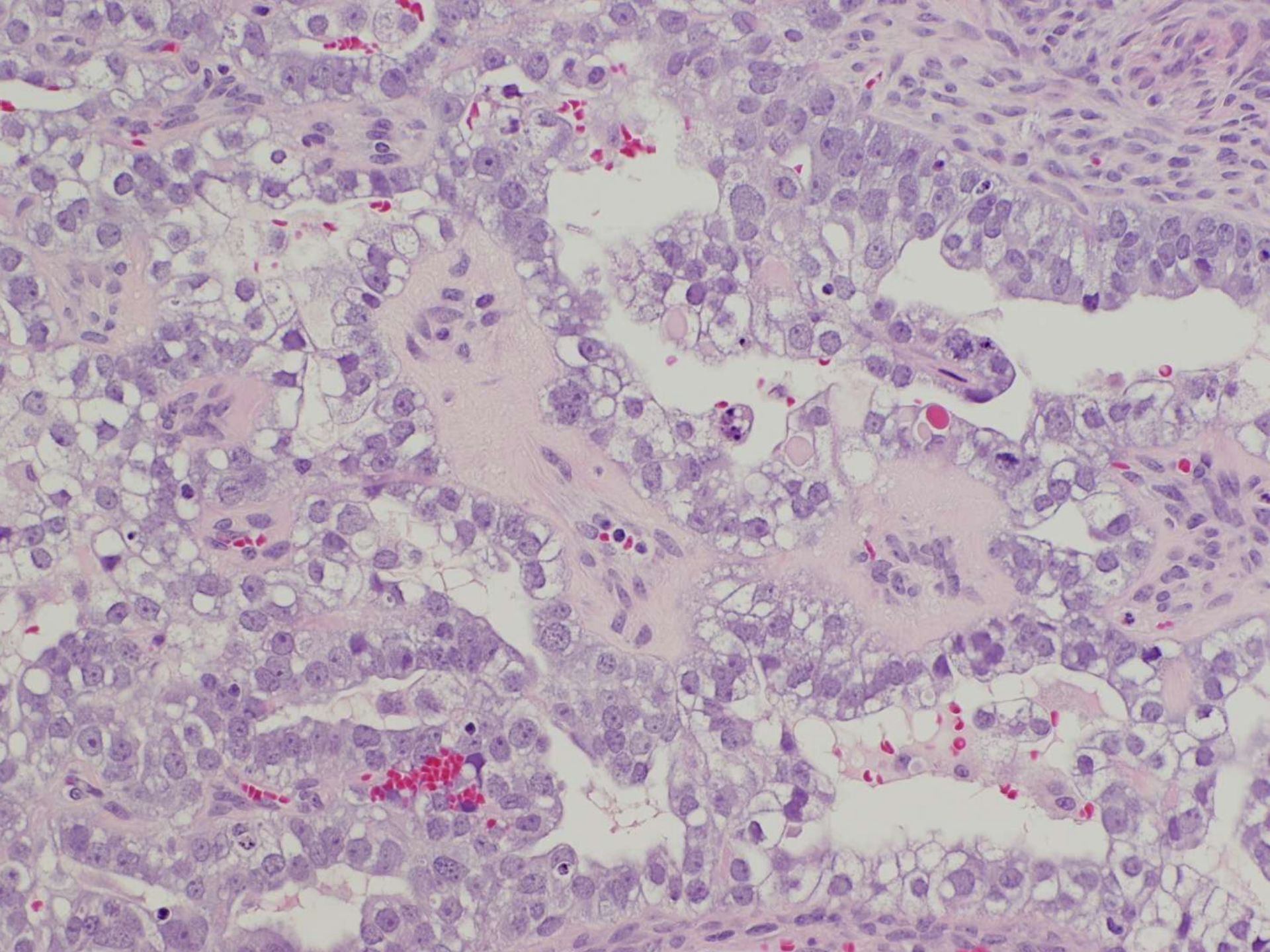
Case 10 *(SP-13-44483)*

64 year old female with Stage III “Ovarian Cancer” (BSO and omentectomy)









Mixed Ovarian Epithelial Carcinomas With Clear Cell and Serous Components are Variants of High-grade Serous Carcinoma

An Interobserver Correlative and Immunohistochemical Study of 32 Cases

Guangming Han, MD, C. Blake Gilks, MD,* Samuel Leung, MSc,* Carol A. Ewanowich, MD,† Julie A. Irving, MD,* Teri A. Longacre, MD,‡ and Robert A. Soslow, MD§*

(*Am J Surg Pathol* 2008;32:955–964)

- Most examples diagnosed as Mixed OSEC (serous and CCC) represent HGSC with clear cell zones
- Similar presentation, behavior, cytologic atypia, mitotic activity, and IHC profiles as pure HGSC

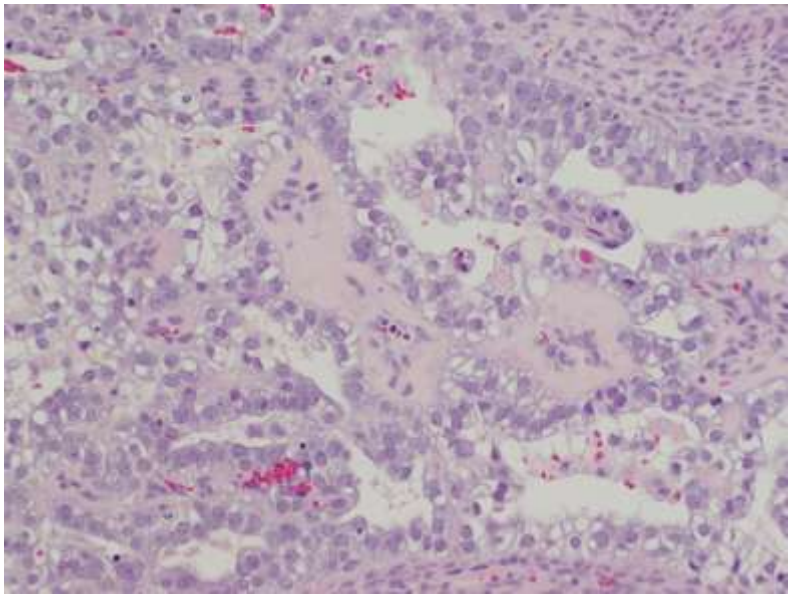
OCCC vs. HGSC

	CCC	HGSC
Clinical	Presents at younger age and low stage	Presents at older age and high stage
	Associated with endometriosis	Associated with "STIC"
	Better outcome in low stage (stage matched)	Better outcome in high stage (stage matched)
	Higher proportion in Asian populations	Higher proportion in European populations
	Higher incidence of thromboembolic complications and $\uparrow Ca^{2+}$ (vs. HGSC)	Lower incidence of thromboembolic complications and $\uparrow Ca^{2+}$ (vs. CCC)
Morphologic	Small to medium round papillae with simplified architecture	Large irregular papillae with hierarchical branching
	Micropapillae uncommon	Micropapillae common
	Papillae frequently lined by single layer of cells	Epithelial stratification and budding of tumor cells
	Variable cytologic atypia and often few mitotic figures	Diffuse cytologic atypia and numerous mitotic figures
	Tubulocystic areas, hyalinized papillae and stroma, abundance of clear or hobnail cells, hyaline globules, coexistent endometriosis	Occasional clear cells, other CCC features not typically seen. Psammoma bodies more frequent (vs. CCC)
IHC	ER^-; $HNF\text{-}1\beta^+$; $WT1^-$; $p53^-$	ER^+; $HNF\text{-}1\beta^-$; $WT1^+$; $p53^+$
Molecular	*TP53* wild	*TP53* mutant
	High frequency of *ARID1A* and *PIK3CA* mutations	Undetectable/low frequency of *ARID1A* and *PIK3CA* mutations
	BRCA dysfunction uncommon	BRCA dysfunction common

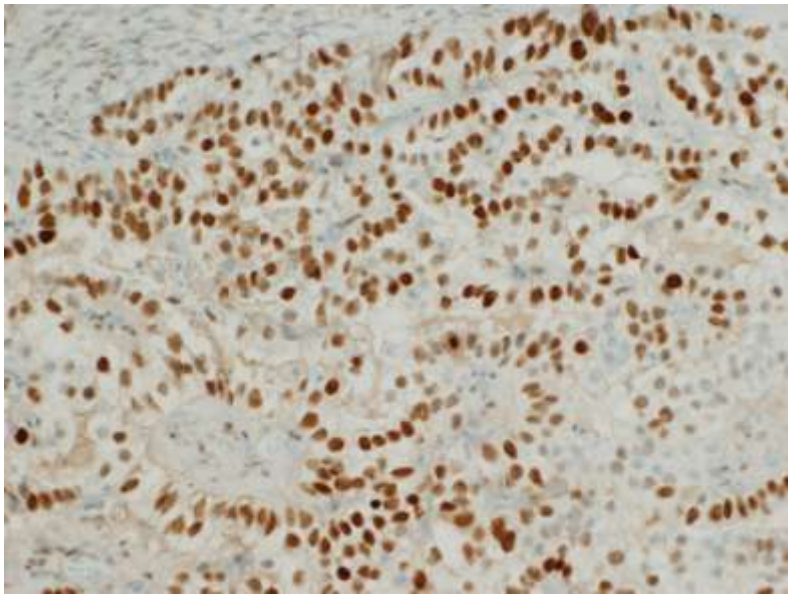
CCC indicates clear cell carcinoma; HGSC, high-grade serous carcinoma; IHC, immunohistochemistry; STIC, serous tubular intraepithelial carcinoma.

Case 10 *(SP-13-44483)*

H&E



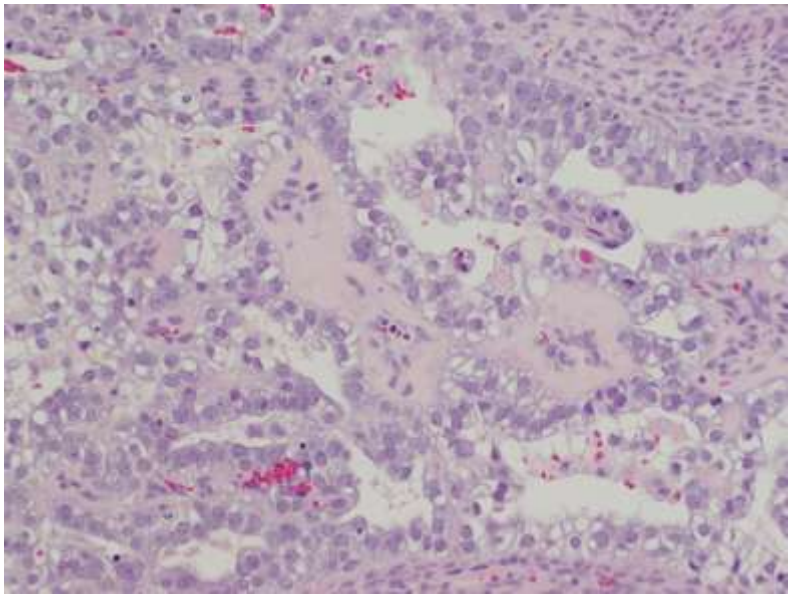
ER



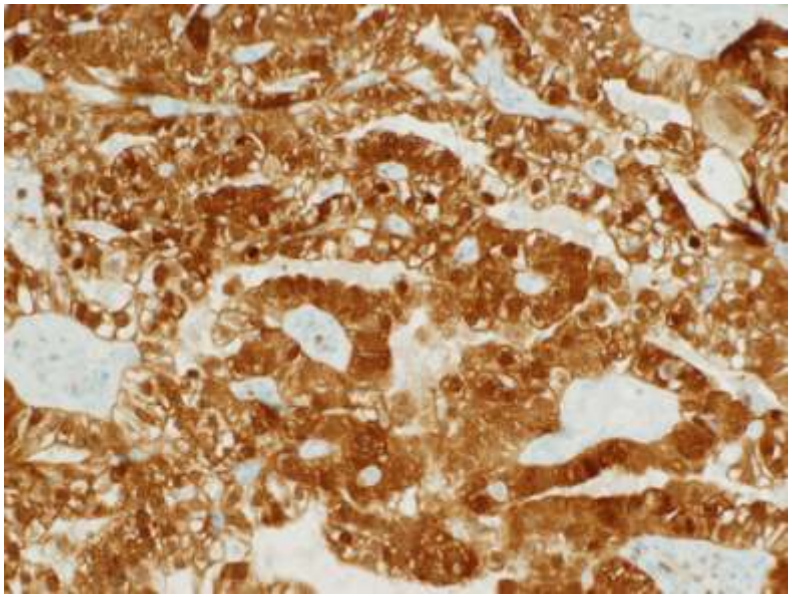
Positive

Case 10 *(SP-13-44483)*

H&E



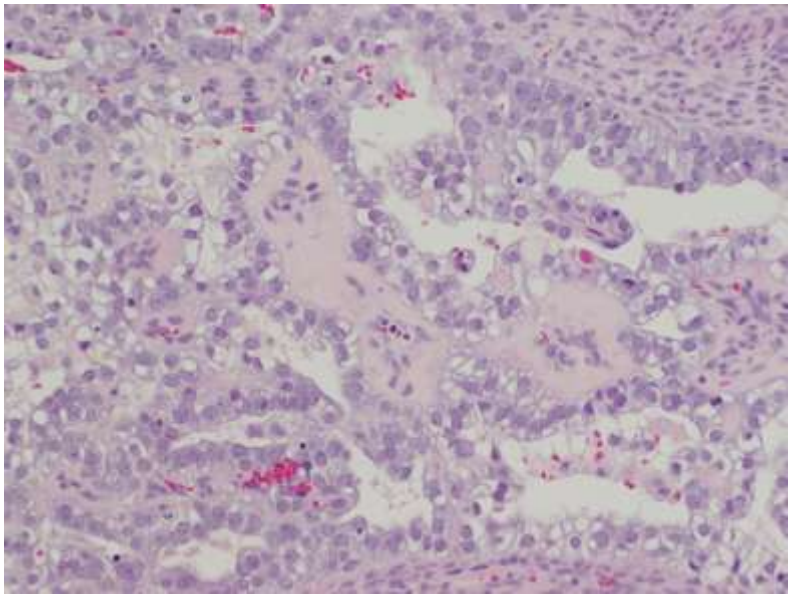
p16



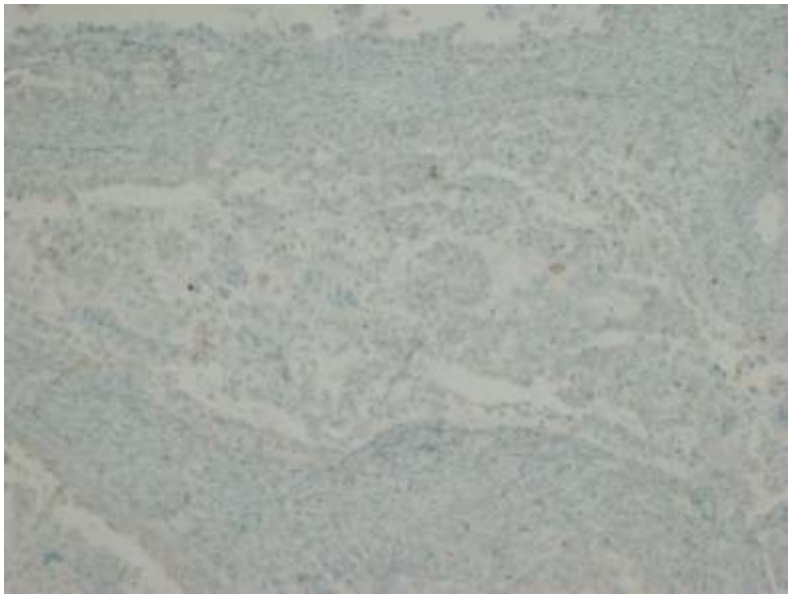
Positive

Case 10 *(SP-13-44483)*

H&E



p53

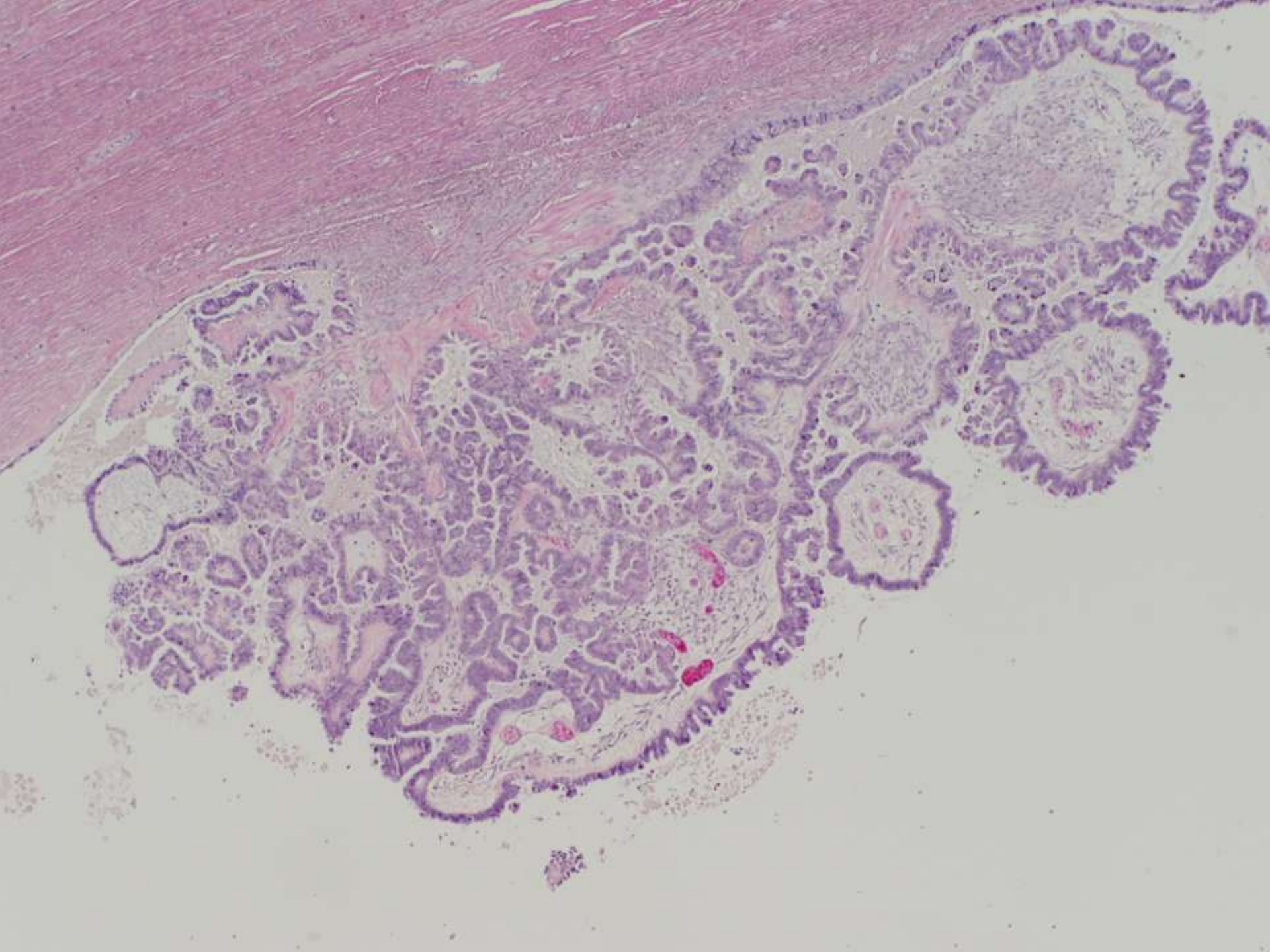


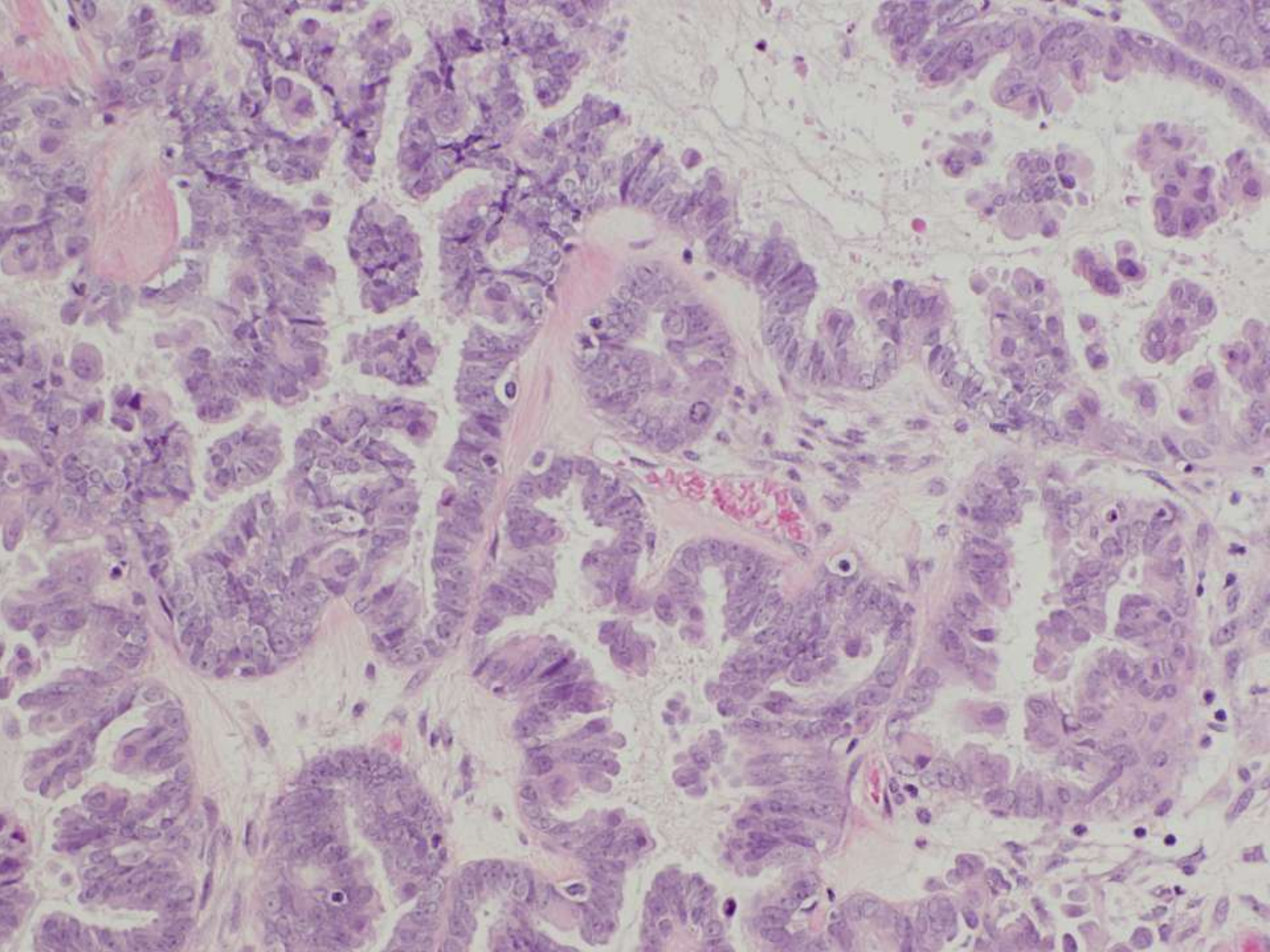
Null pattern

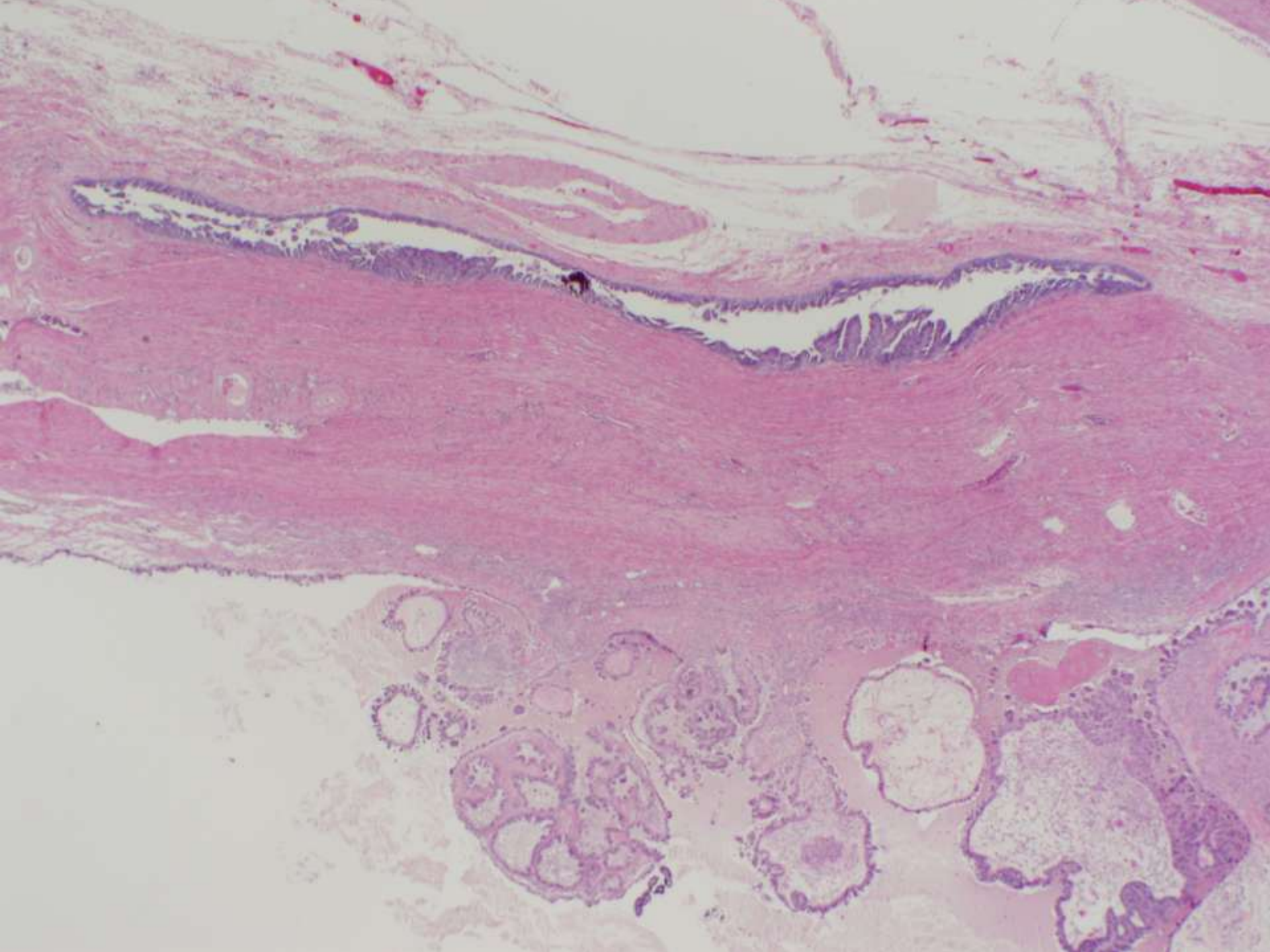
Dx: c/w HGSC with clear cell zones

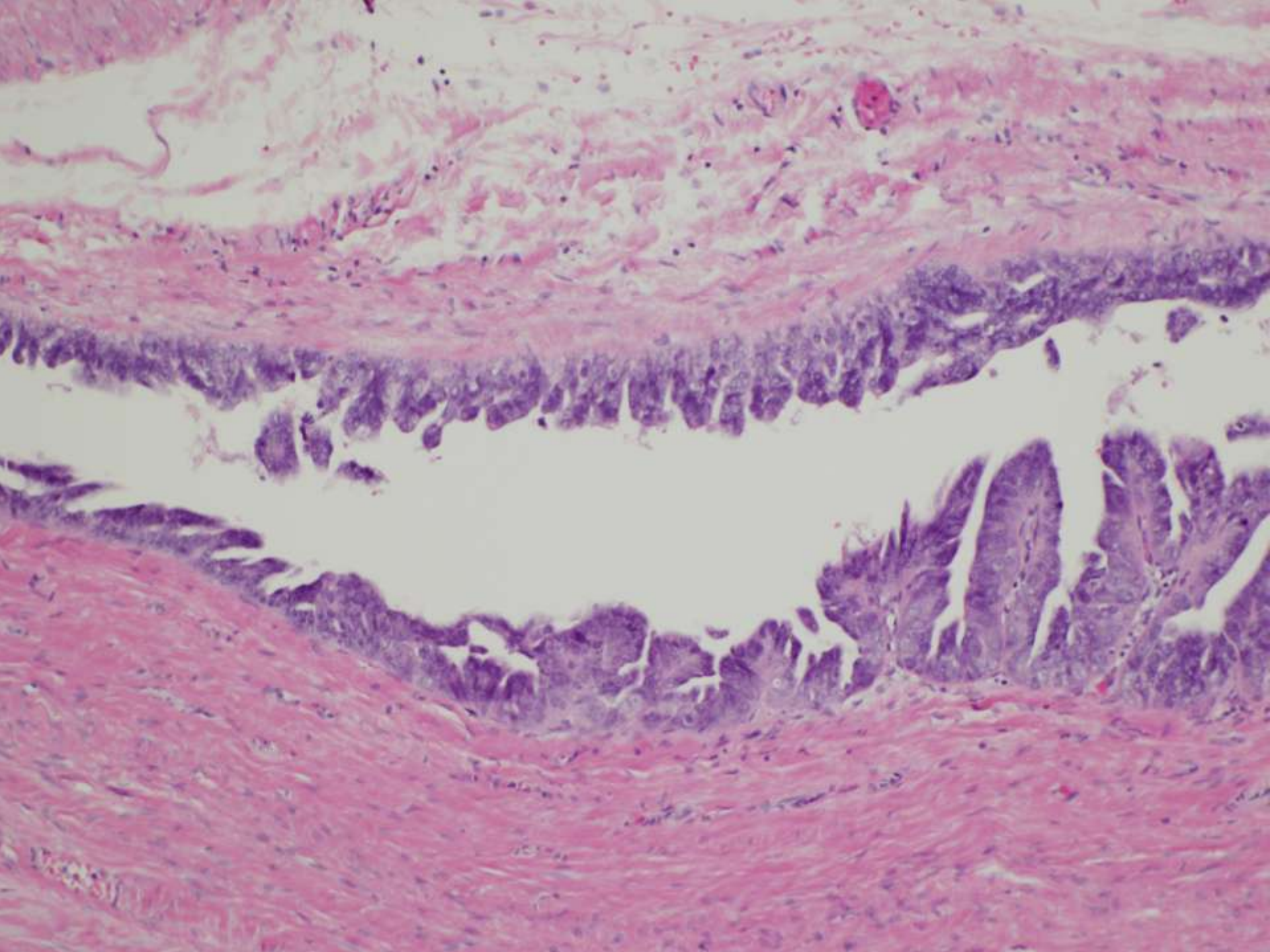
Case 11 *(CE-13-3184)*

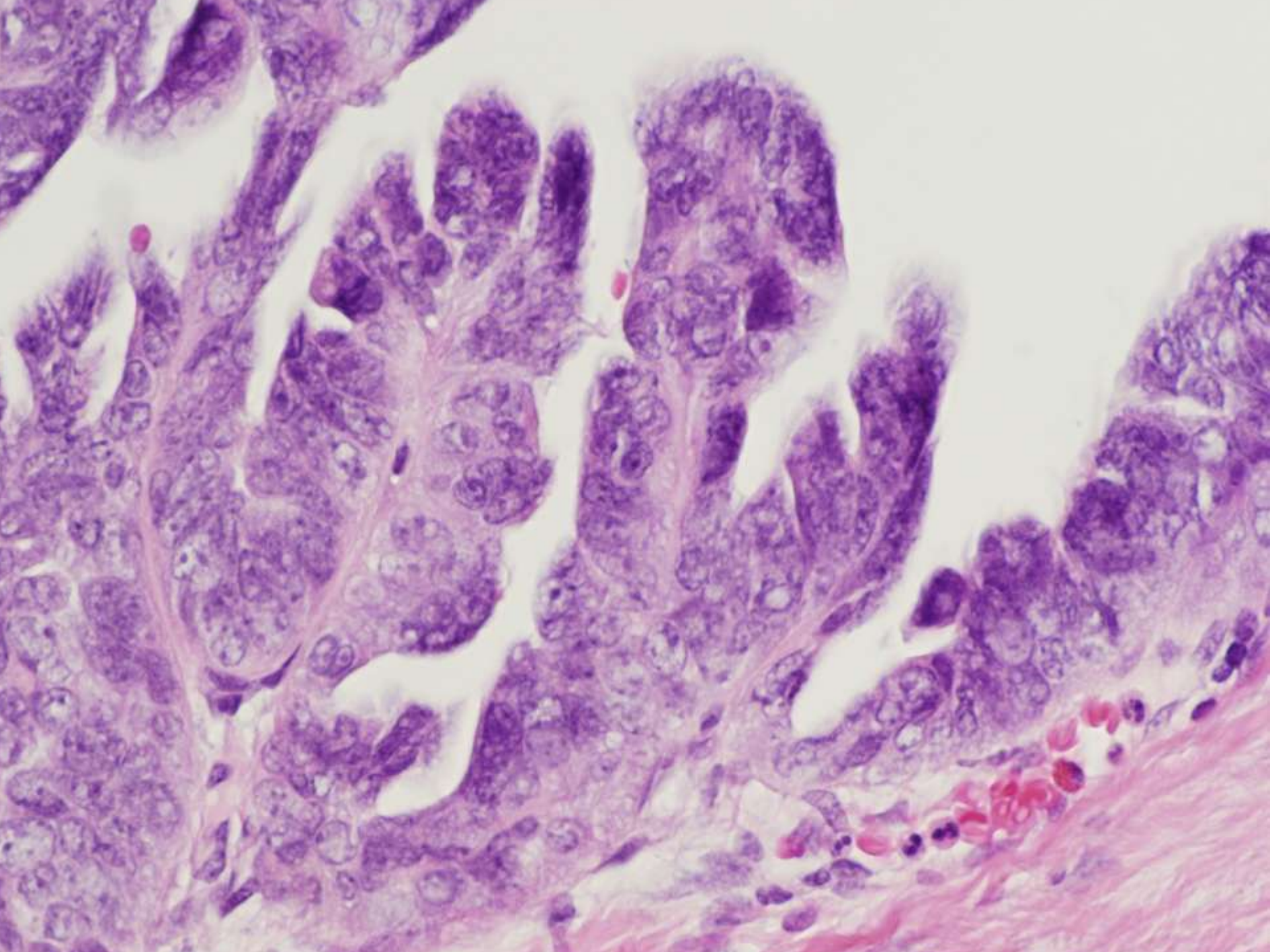
72 year old female with right ovarian mass and high stage disease – nodes, omentum etc. (BSO and omentectomy)











Low-Grade Ovarian Serous Neoplasms (Low-Grade Serous Carcinoma and Serous Borderline Tumor) Associated With High-Grade Serous Carcinoma or Undifferentiated Carcinoma: Report of a Series of Cases of an Unusual Phenomenon

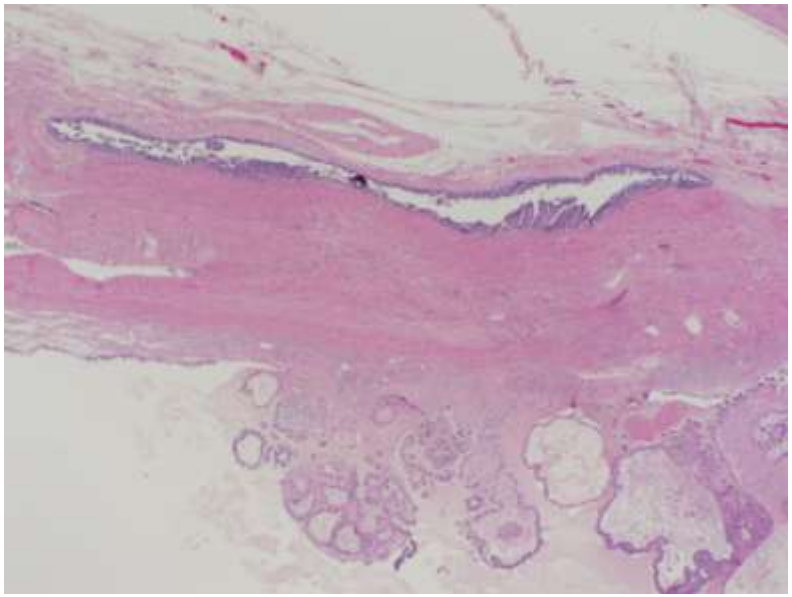
Clinton Boyd, MB and W. Glenn McCluggage, FRCPath

Am J Surg Pathol • Volume 36, Number 3, March 2012

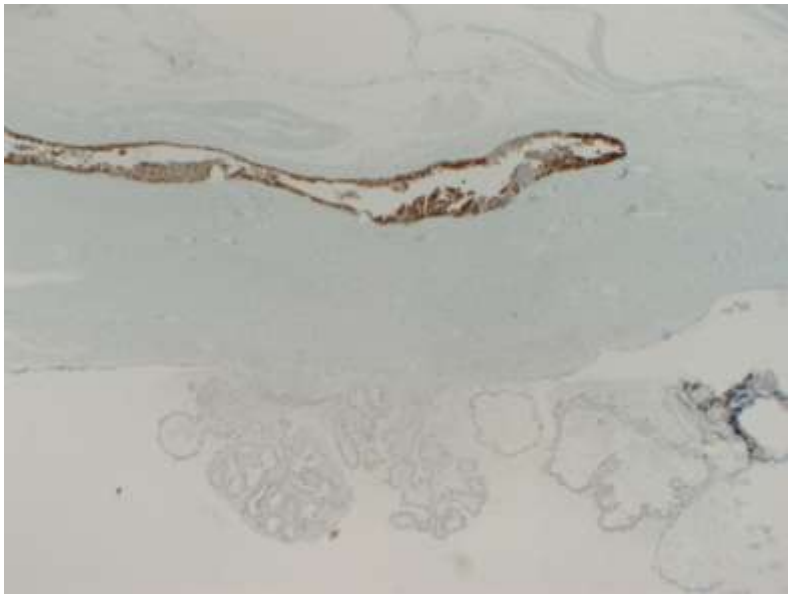
- HGSC and LG serous neoplasms (SBT, LGSC) have different molecular pathways (TP53 vs. BRAF/KRAS)
- HGSC may occasionally co-exist/arise from LGSN
- p53 may help in distinguishing them
  (p16 typically positive in SBT but not LGSC)

Case 11 *(CE-13-3184)*

H&E

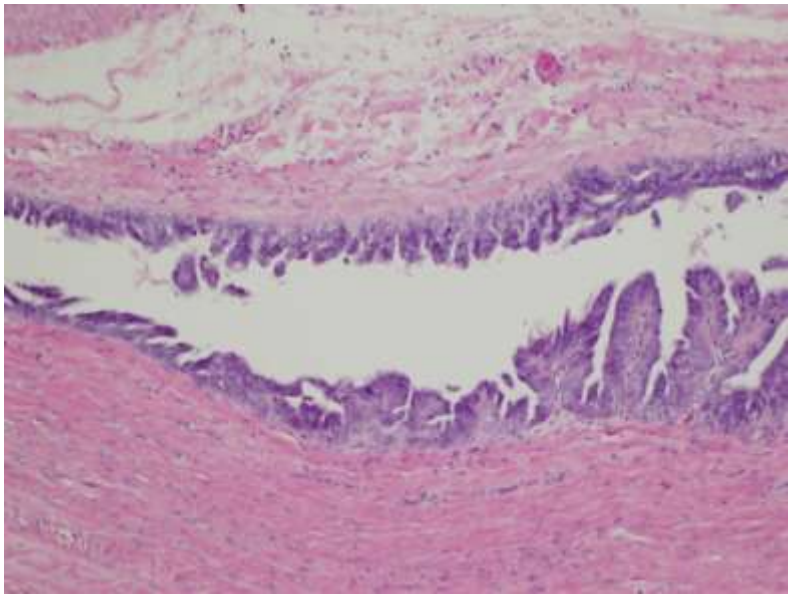


p53



Case 11 *(CE-13-3184)*

H&E



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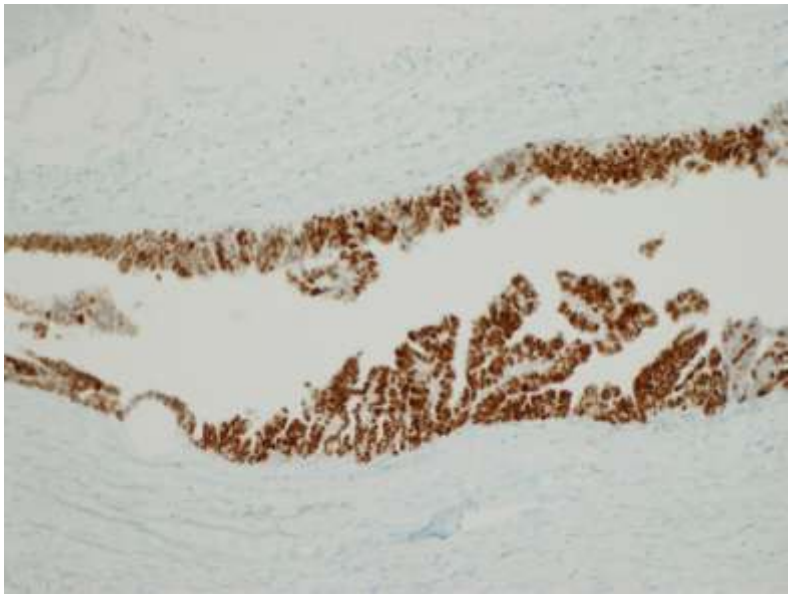
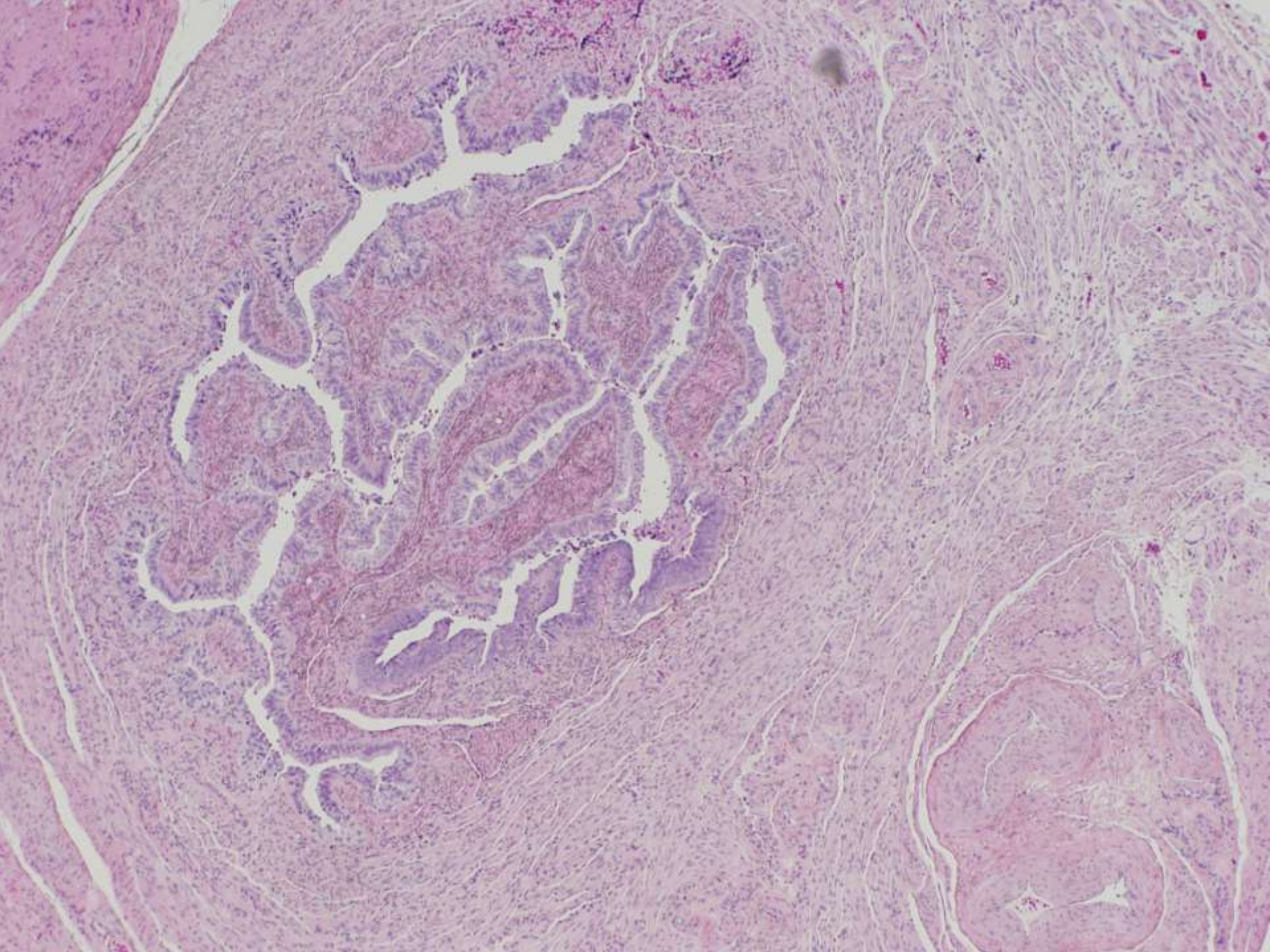


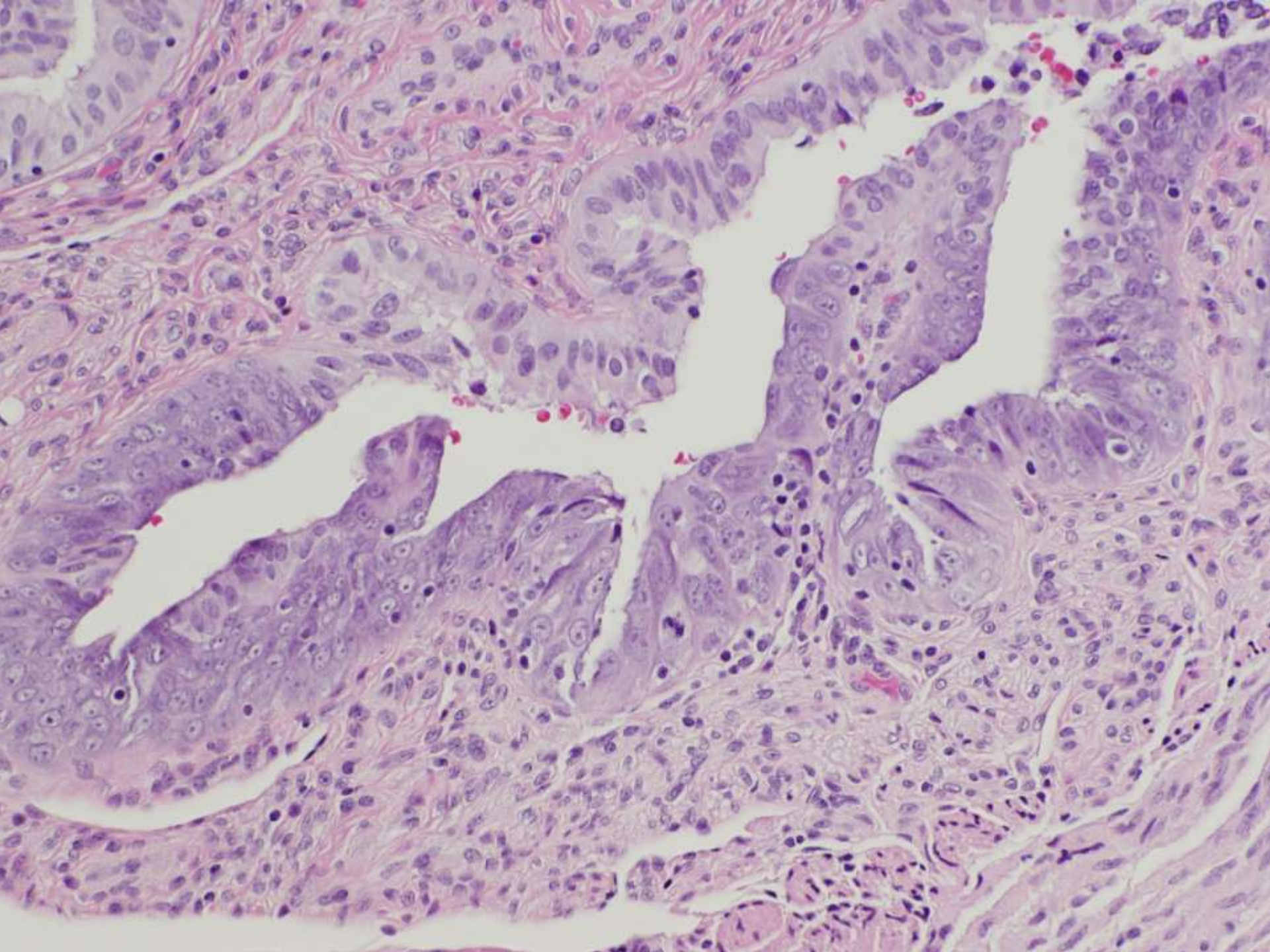
Positive

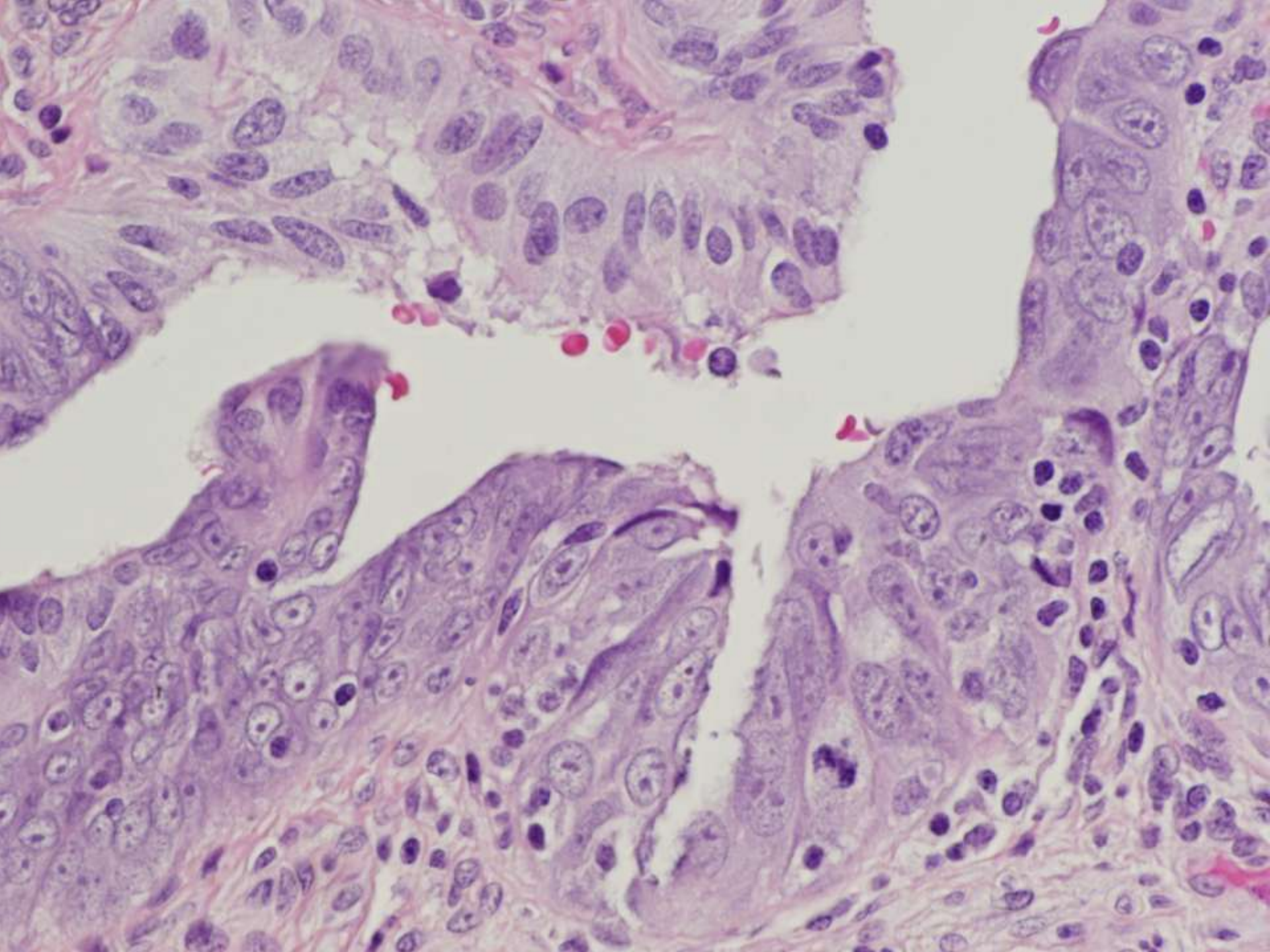
Dx: HGSC arising in association with SBT

Case 12 *(SP-13-42699)*

47 year old female with cystic right ovary (RSO)







ORIGINAL ARTICLE

Diagnosis of Serous Tubal Intraepithelial Carcinoma Based on Morphologic and Immunohistochemical Features: A Reproducibility Study

Kala Visvanathan, MBBS, FRACP, MHS,† Russell Vang, MD,‡§ Patricia Shaw, MD,¶ Amy Gross, MS,* Robert Soslow, MD,‖ Vinita Parkash, MD, Ie-Ming Shih, MD, PhD,†‡§ and Robert J. Kurman, MD†‡§*

(*Am J Surg Pathol* 2011;35:1766–1775)

TABLE 1. Diagnostic Criteria Used in Round 1

Morphologic classification used in round 1

Normal/reactive: < 2 diagnostic features* in any length of nonciliated cells

Atypical:

– 2 diagnostic features* in ≥ 10 consecutive nonciliated cells

≥ 2 diagnostic features* in < 10 consecutive nonciliated cell

STIC†: > 2 diagnostic features* in ≥ 10 consecutive nonciliated cells

*Diagnostic features

- Nuclear enlargement (> 2X nuclear area compared with nonciliated cells within the focus of interest or in adjacent normal mucosa) and/or nuclear rounding
- Marked pleomorphism
- Abnormal chromatin (hyperchromasia and/or vesicular nuclei with prominent nucleoli)
- ≥ 1 mitotic figure (either normal or abnormal)
- Epithelial stratification (> 2 cell layers)
- Nuclear molding
- Apoptotic bodies

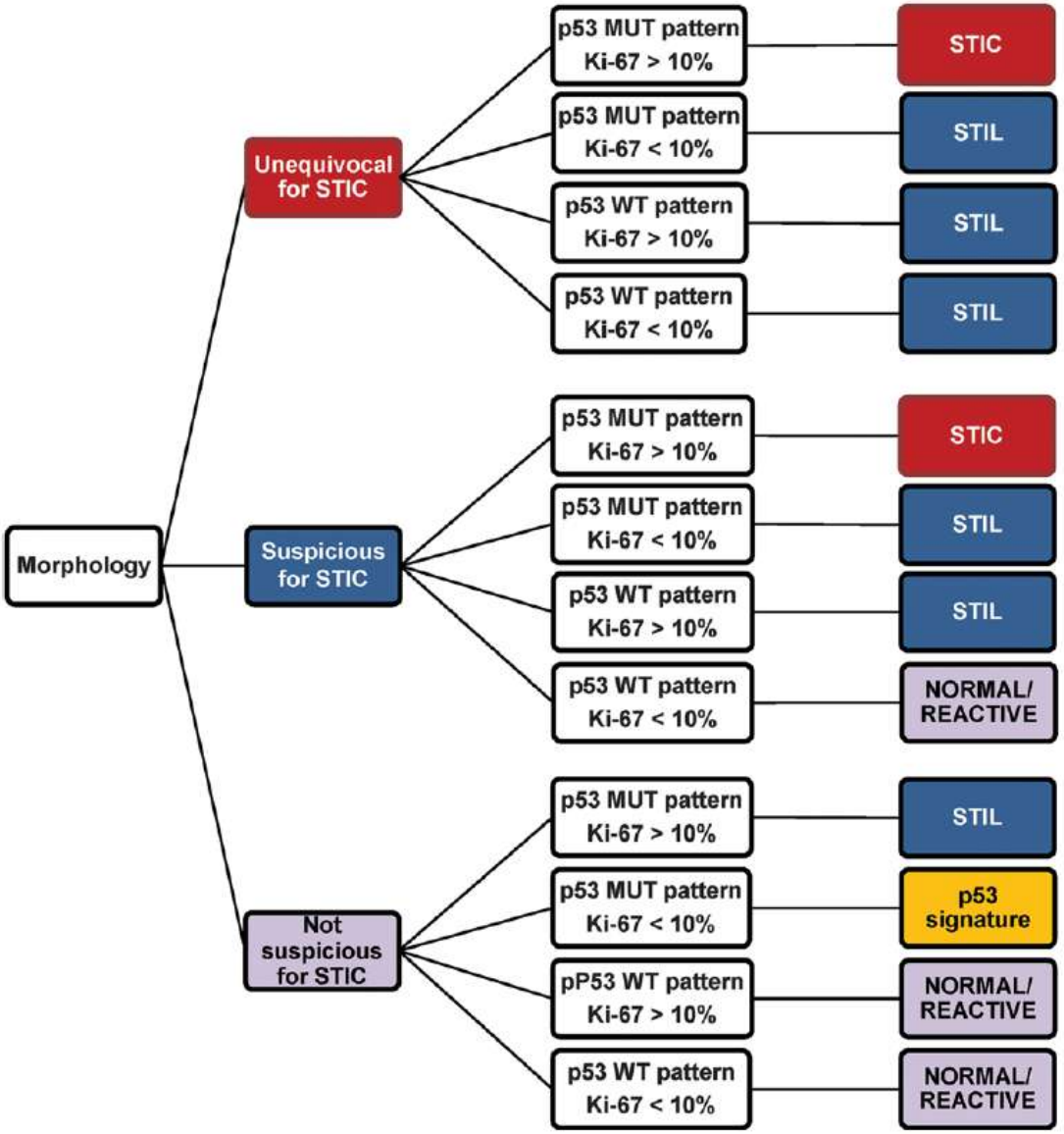
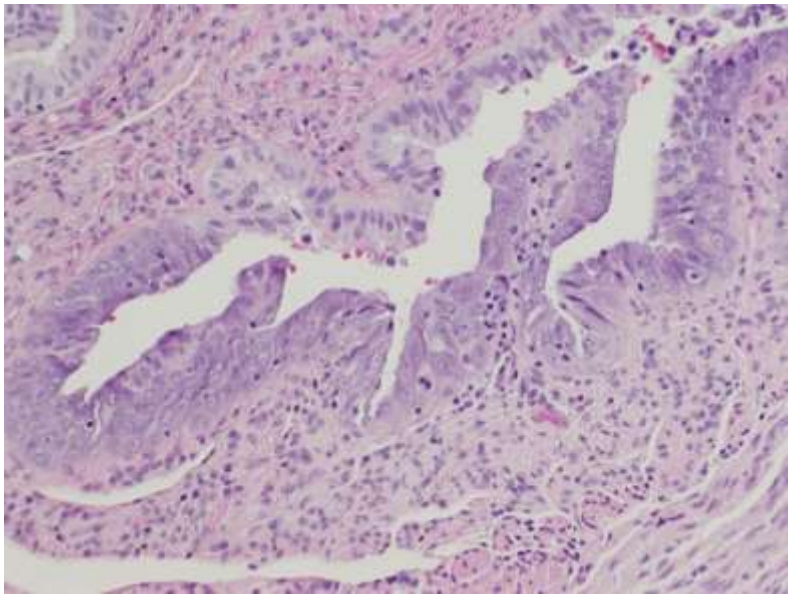


FIGURE 3. Algorithm for the diagnosis of STIC. Foci showing a Ki-67 labeling index >10% are considered Ki-67 high, whereas a Ki-67 labeling index of <10% is considered low. Diffuse moderate-to-strong expression of p53 in >75% of at least 12 epithelial cells (with or without intervening ciliated cells) or complete absence of staining has been shown to be compatible with a TP53 mutation either missense or nonsense (p53 MUT versus p53WT pattern in algorithm).

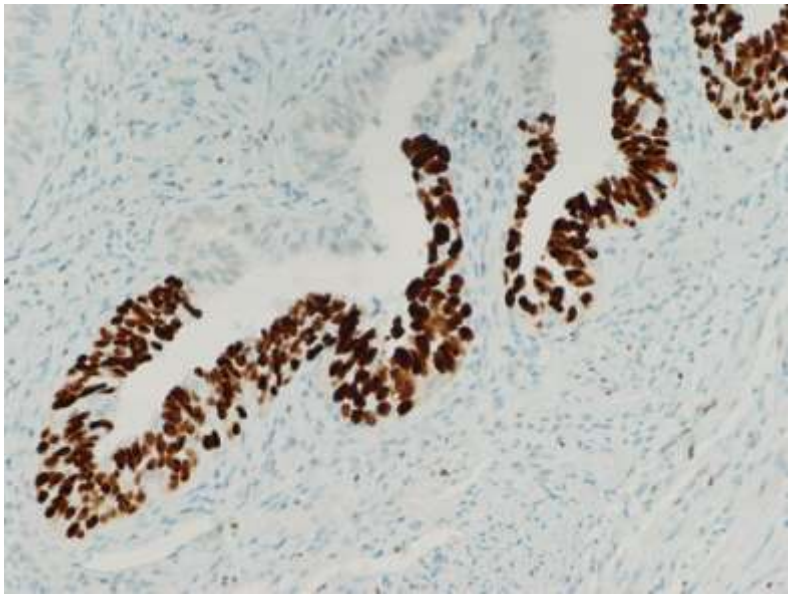
p53 (+)
- > 75% cells
- “null”

Case 12 *(SP-13-42699)*

H&E



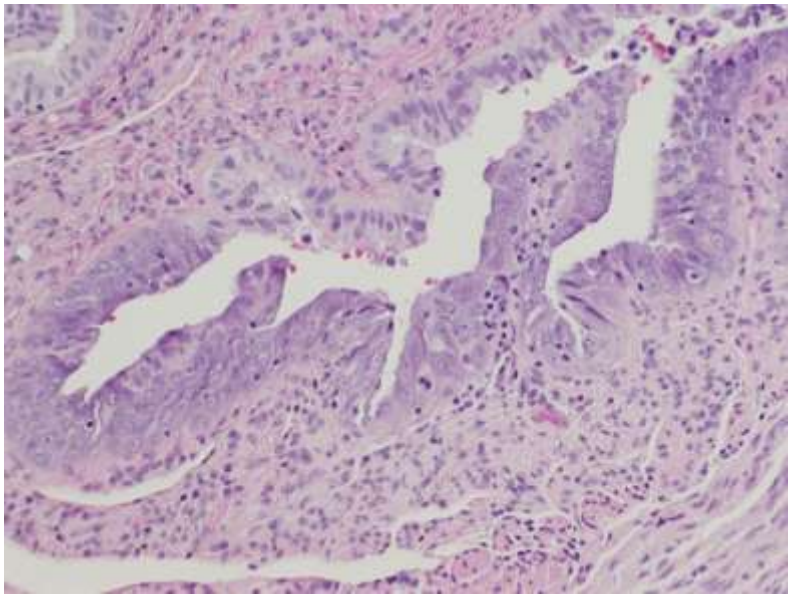
p53



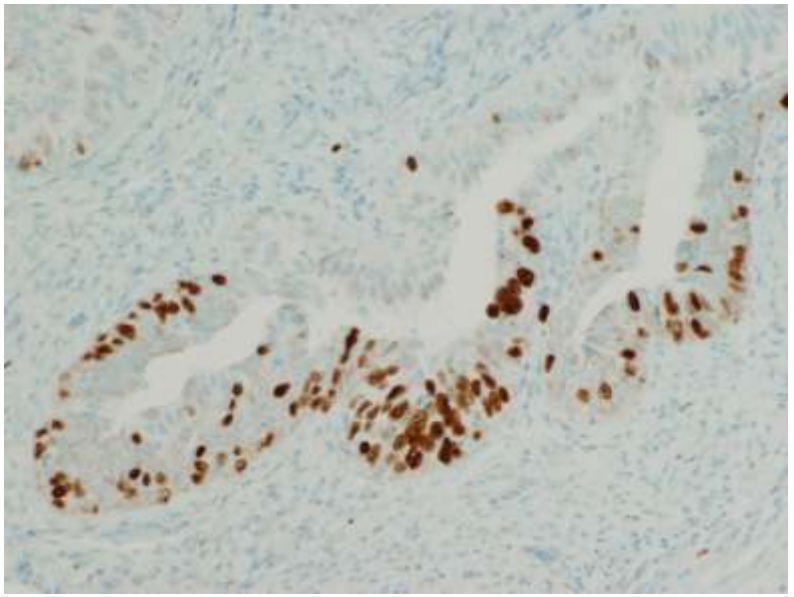
Positive

Case 12 *(SP-13-42699)*

H&E



Ki67



> 10%

Dx: STIC

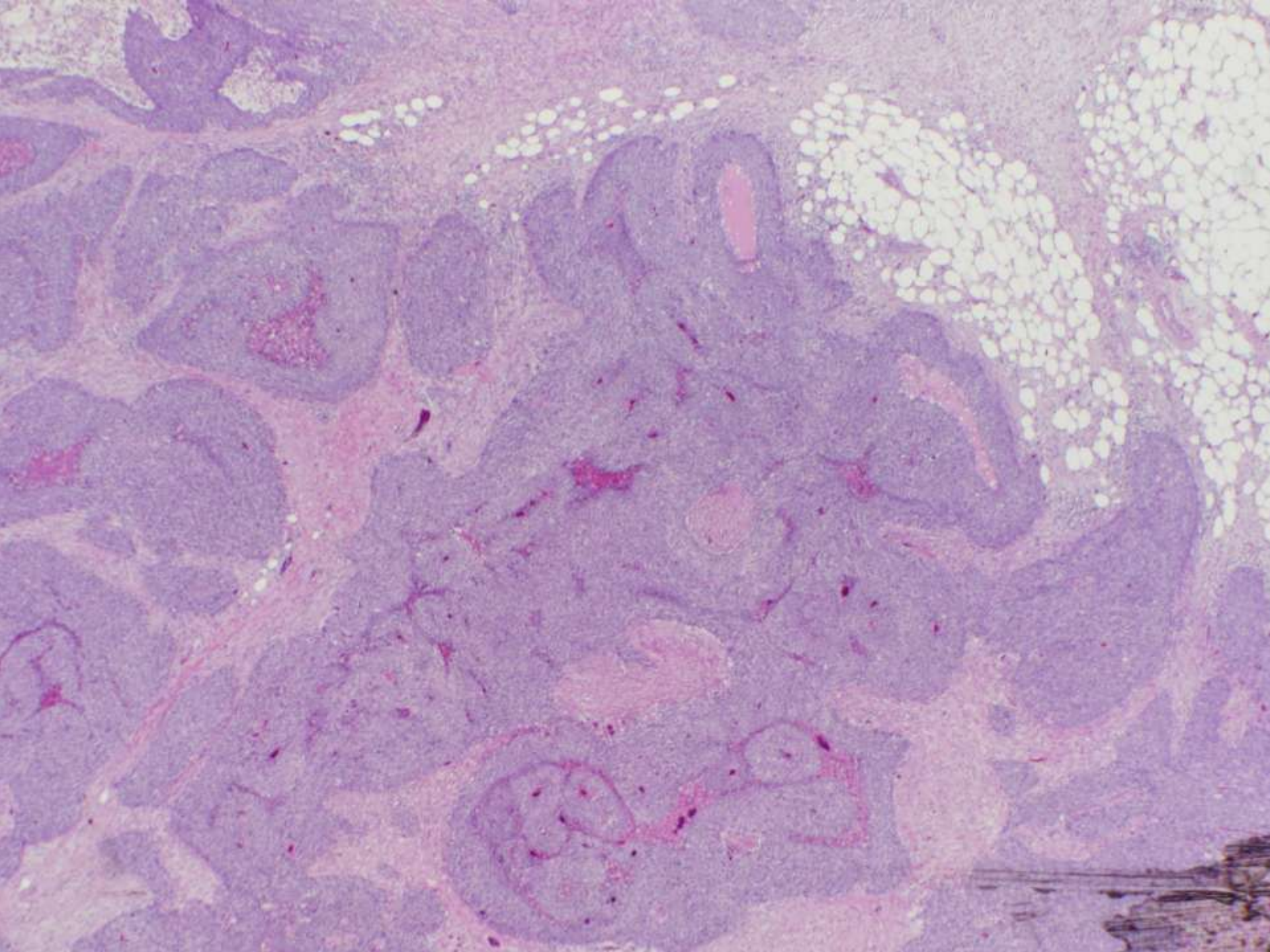
Case 13 *(SP-13-29934)*

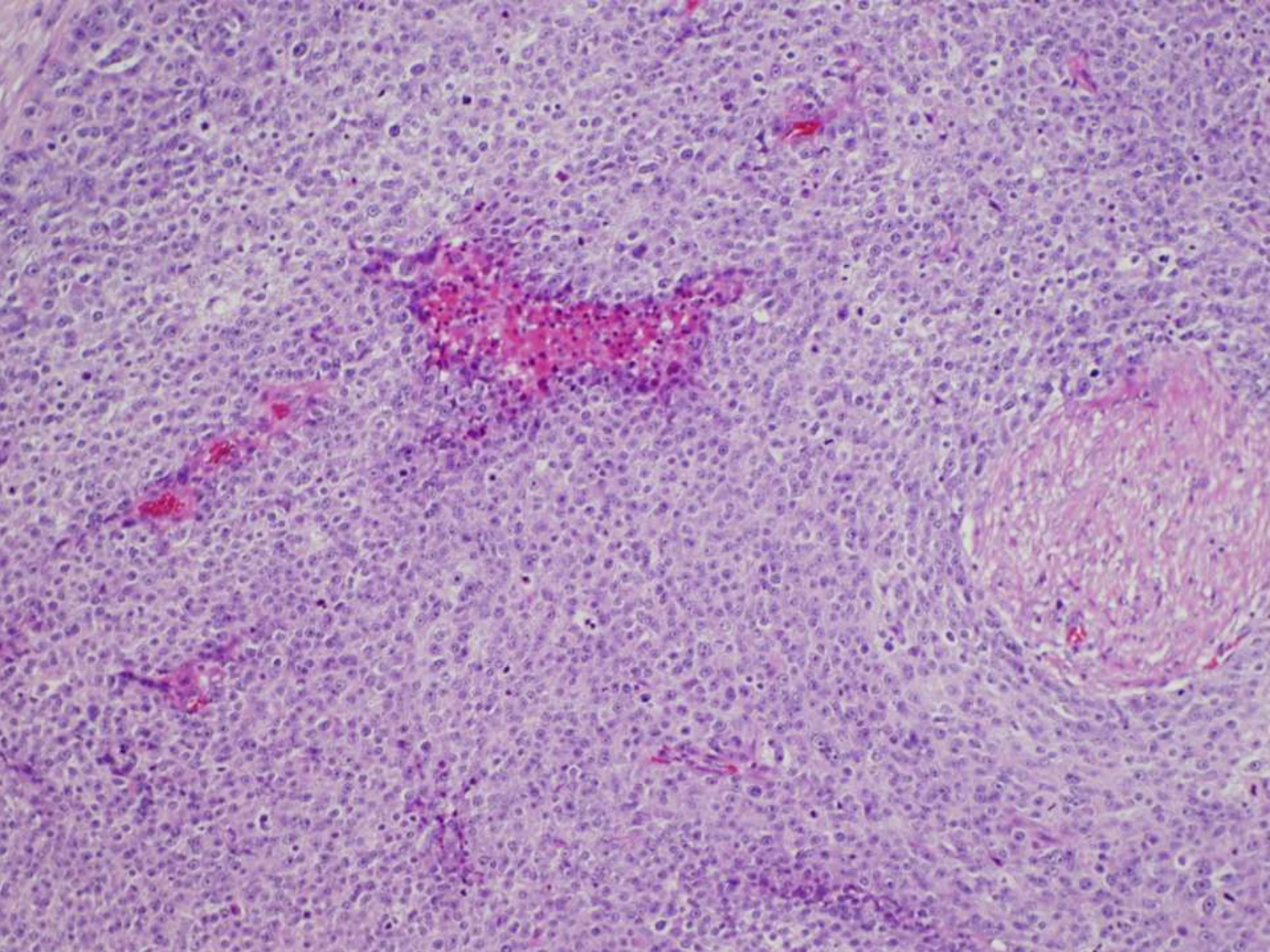
58 year old female with omental mass (omentectomy, LSO, and staging)

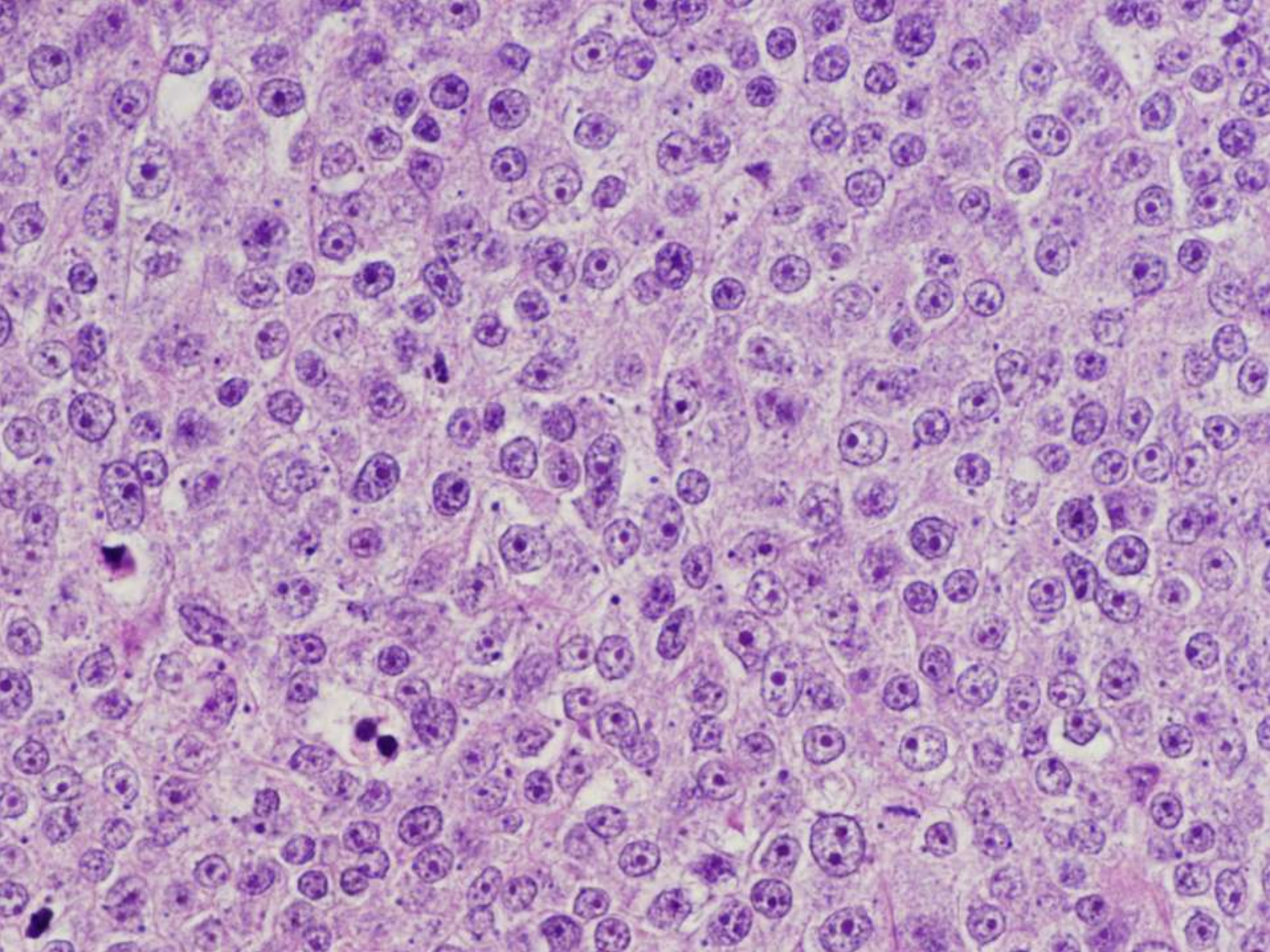
PMHx

-Hysterectomy / RSO for benign disease

-Bilateral PD breast carcinomas







IHC Panel in Breast vs. Tubo-ovarian origin

- Not helpful: CK7, ER
- Positivity for WT-1, CA-125, p53, PAX-8 all favor tubo-ovarian origin
- Positivity for GCDFP, mammoglobin favor breast carcinoma

PAX-8

- Present in renal, bladder, thyroid, thymic, and majority of ‘Mullerian’ malignancies
- When DDx includes Mullerian – negative in breast Ca, mesothelioma, and GI Ca

A Comprehensive Analysis of PAX8 Expression in Human Epithelial Tumors

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TABLE 1. (*continued*)

Tumor Type	No. Positive	Total No. Cases (%Positive)
Ovary		
Serous carcinoma, high grade	164	165 (99)
Mucinous ACA	10	25 (40)
Endometrioid ACA	11	12 (92)
Mixed carcinoma	6	7 (86)
Clear cell carcinoma	2	2 (100)
Transitional	3	3 (100)
Fibroma	0	4 (0)
Sclerosing stromal tumor	0	2 (0)
Germ cell tumor	0	2 (0)
Sertoli-Leydig tumor	1	5 (20)
Granulosa cell tumor	0	7 (0)
Sex cord stromal tumor, NOS	1	2 (50)
Small cell carcinoma	0	7 (0)
Endomyometrium		
Endometrial ACA	152	155 (98)
MMMT	3	5 (60)
Leiomyoma	0	2 (0)
Cervix		
HSIL	2	2 (100)
SCC	2	2 (100)
ACIS	5	5 (100)
Invasive ACA	1	2 (50)
Small cell carcinoma	0	5 (0)
Gestational neoplasms	0	4 (0)

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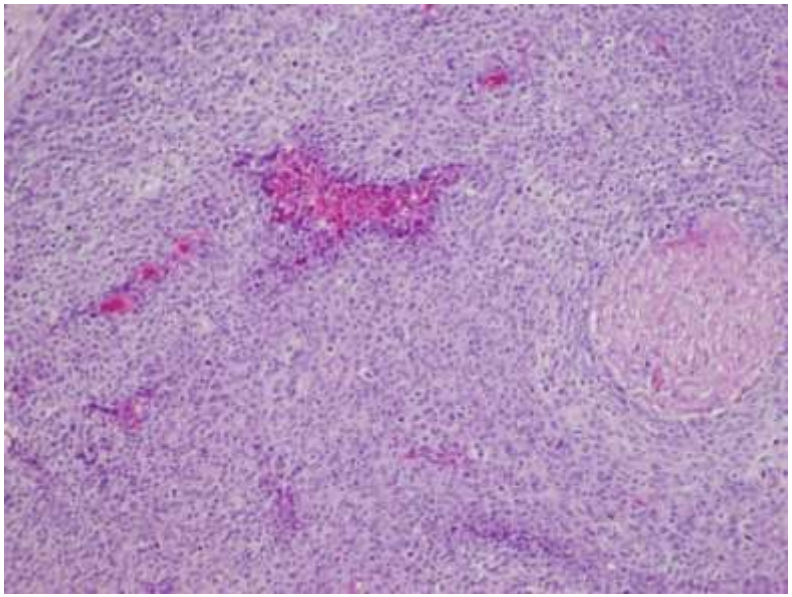
Gastrointestinal		
Gastric ACA	0	22 (0)
Gastric (M)	0	10 (0)
Colon ACA	0	41 (0)
Colon (M)	0	11 (0)
Colon (SQ)	0	2 (0)
Anal (SQ)	0	2 (0)
Appendiceal (M)	0	30 (0)
Gallbladder ACA	0	1 (0)
Cholangiocarcinoma	2	2 (100)
Esophageal ACA	2	8 (25)
Esophageal (M)	0	2 (0)
Esophageal (SQ)	0	7 (0)
Pancreatic ACA	1	12 (8)
Pancreatic (M)	0	4 (0)
Pancreatic (solid pseudopapillary)	0	1 (0)
Hepatocellular carcinoma	0	6 (0)
Breast		
Invasive ductal carcinoma	0	91 (0)
Invasive lobular carcinoma	0	19 (0)
Mixed carcinoma	0	19 (0)

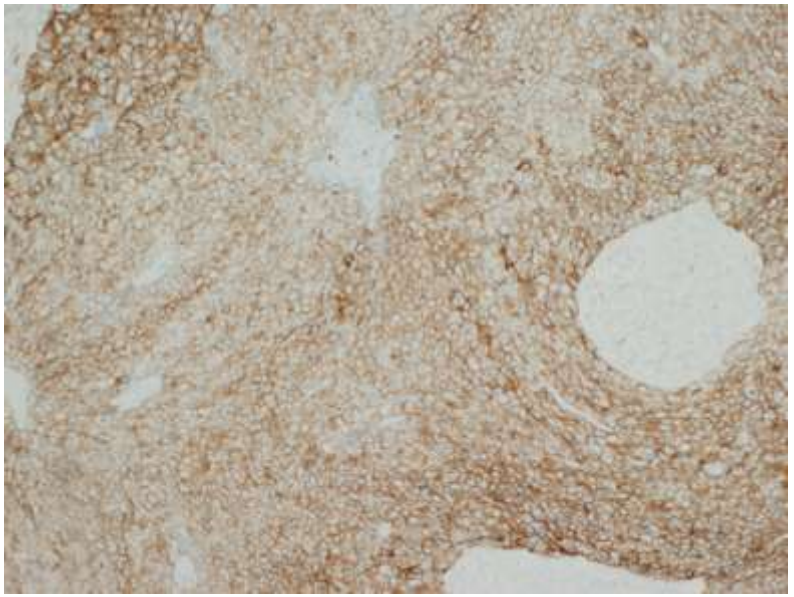
Head and neck		
Squamous cell carcinoma	0	5 (0)
Squamous dysplasia	0	6 (0)
Acinic cell carcinoma	1	3 (33)
Adenoid cystic carcinoma	0	13 (0)
Basal cell adenoma/carcinoma (salivary gland)	0	4 (0)
Mucoepidermoid carcinoma	0	8 (0)
Olfactory neuroblastoma	0	3 (0)
Polymorphous low grade ACA	0	3 (0)
Pleomorphic adenoma	0	4 (0)
Carcinoma ex pleomorphic adenoma	0	1 (0)
Sinonasal adenocarcinoma	0	2 (0)
High grade salivary gland ACA	0	4 (0)
Salivary duct carcinoma	0	5 (0)
Myoepithelial carcinoma	0	2 (0)
Salivary carcinomas/ACA, NOS	0	12 (0)
Atypical carcinoid (larynx)	0	6 (0)
Clear cell odontogenic carcinoma	0	1 (0)
PD carcinoma, NOS	0	3 (0)
Lung		
Adenocarcinoma	0	120 (0)
Squamous cell carcinoma	4	12 (33)
Adenosquamous	0	3 (0)
Carcinoid	0	2 (0)
Small cell carcinoma	0	9 (0)

Case 13 *(SP-13-29934)*

H&E



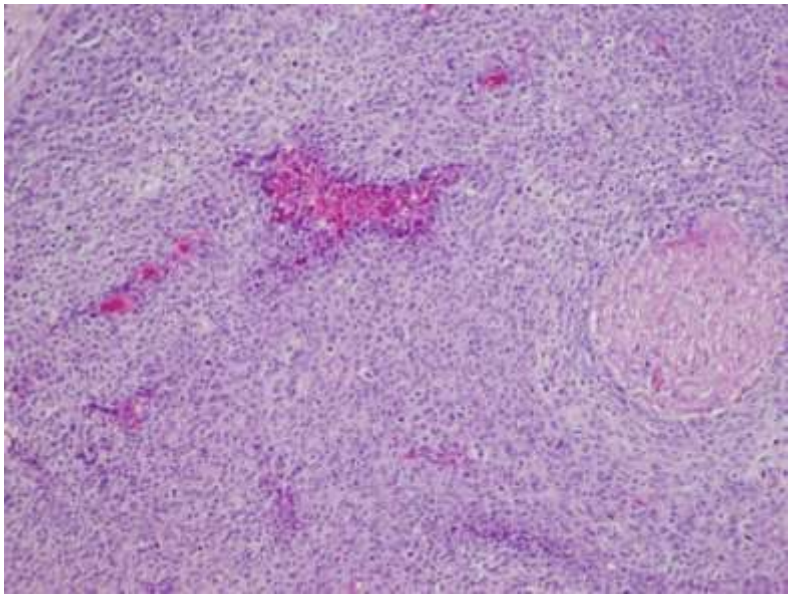
CK7



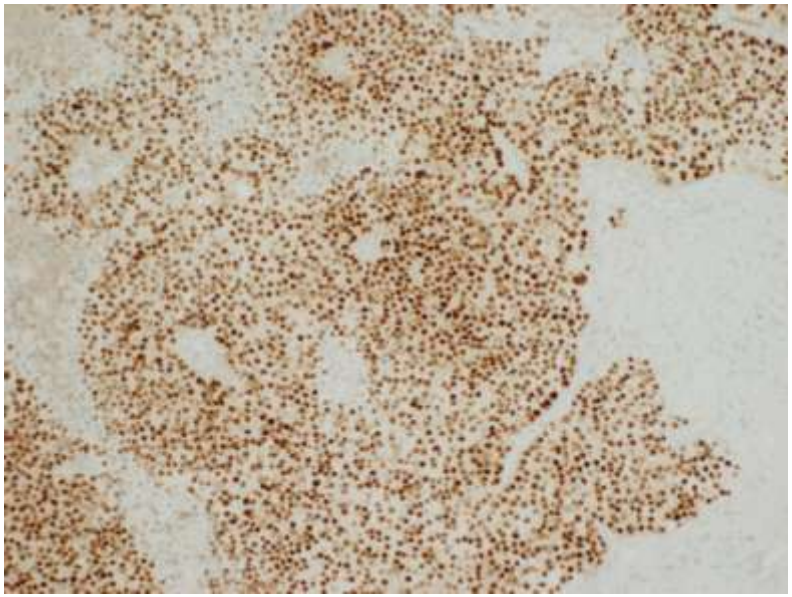
Positive

Case 13 *(SP-13-29934)*

H&E



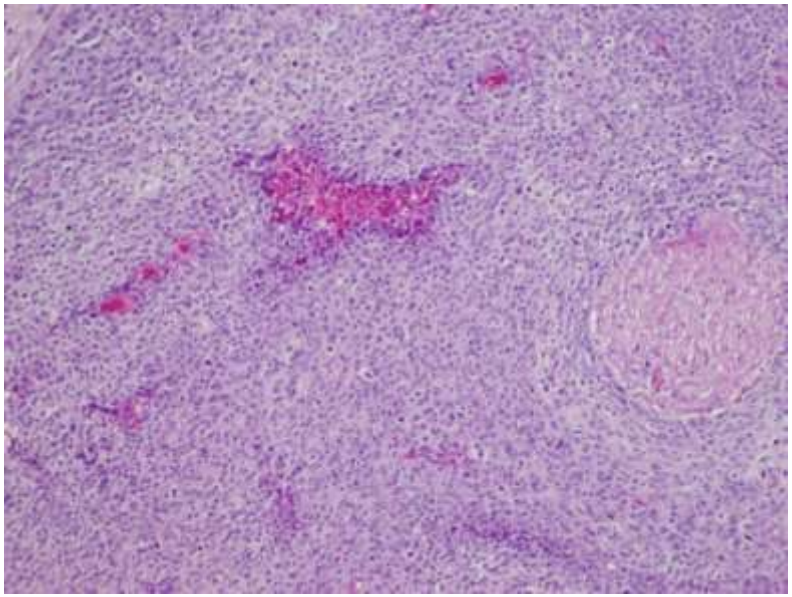
ER



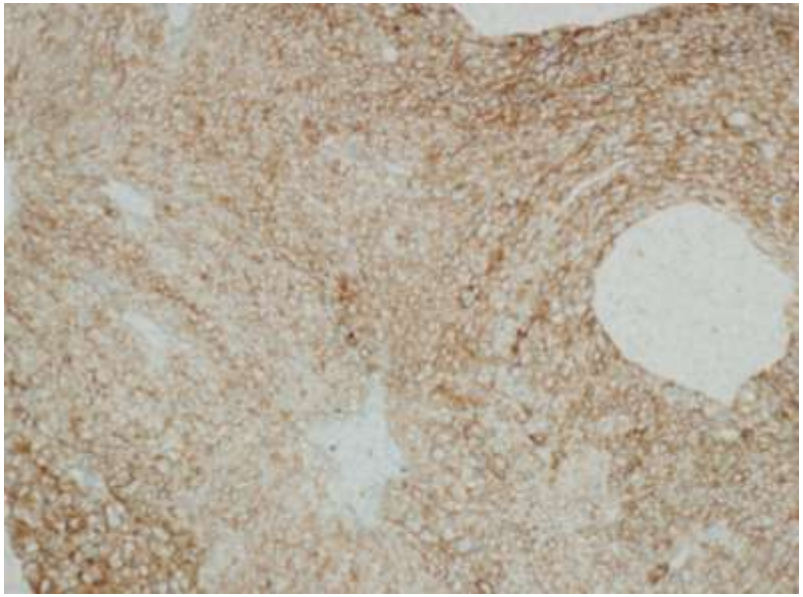
Positive

Case 13 *(SP-13-29934)*

H&E



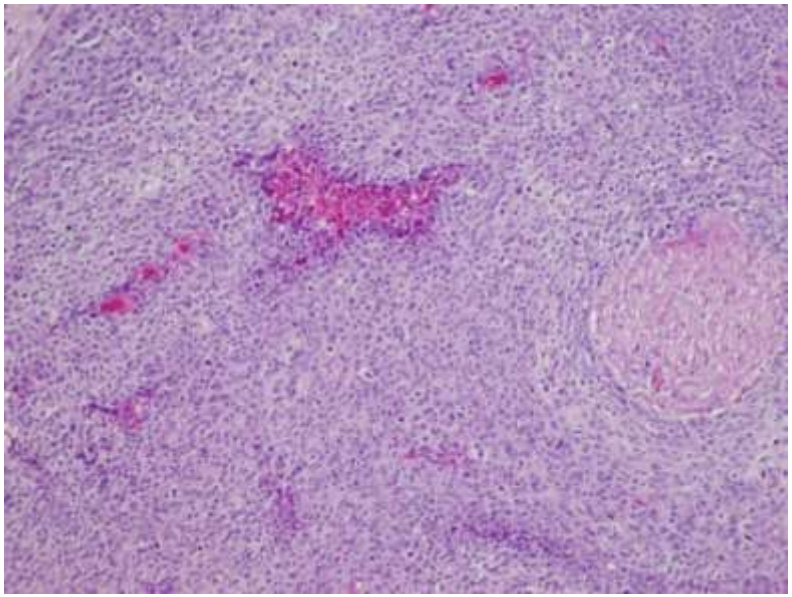
CA-125



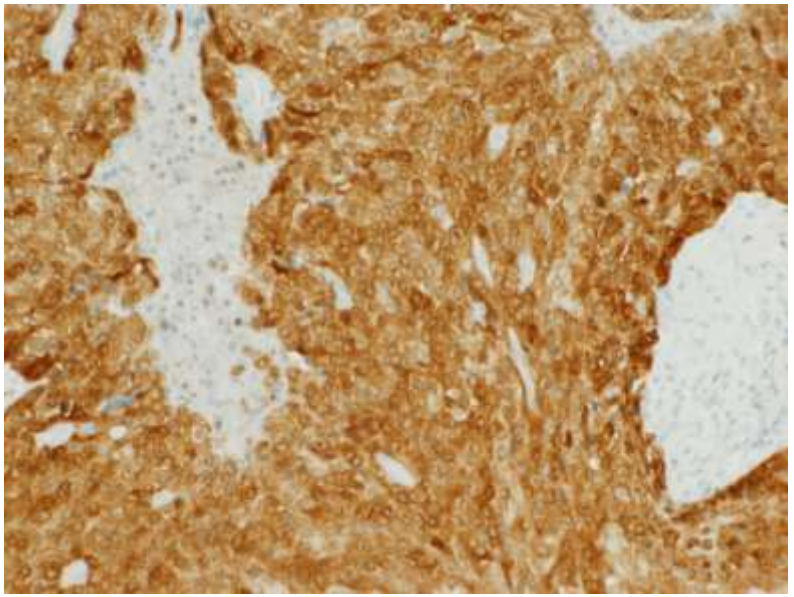
Positive

Case 13 *(SP-13-29934)*

H&E



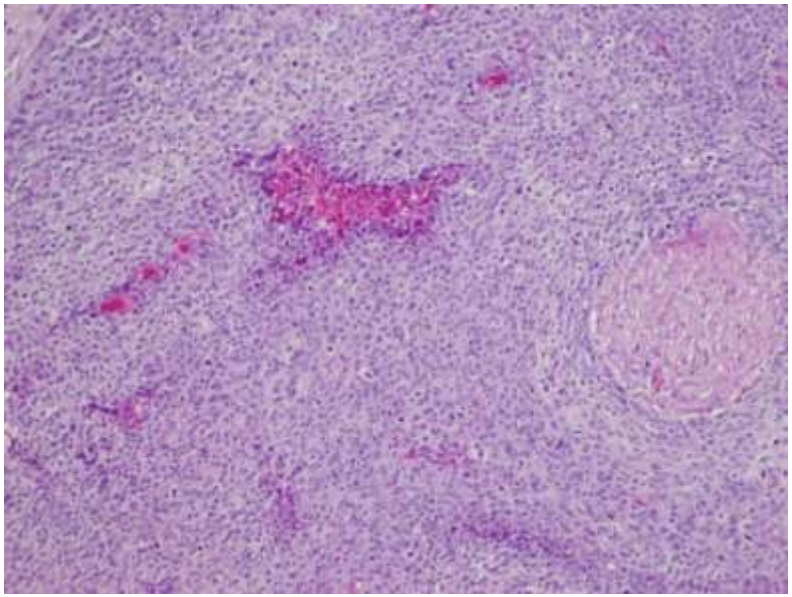
p16



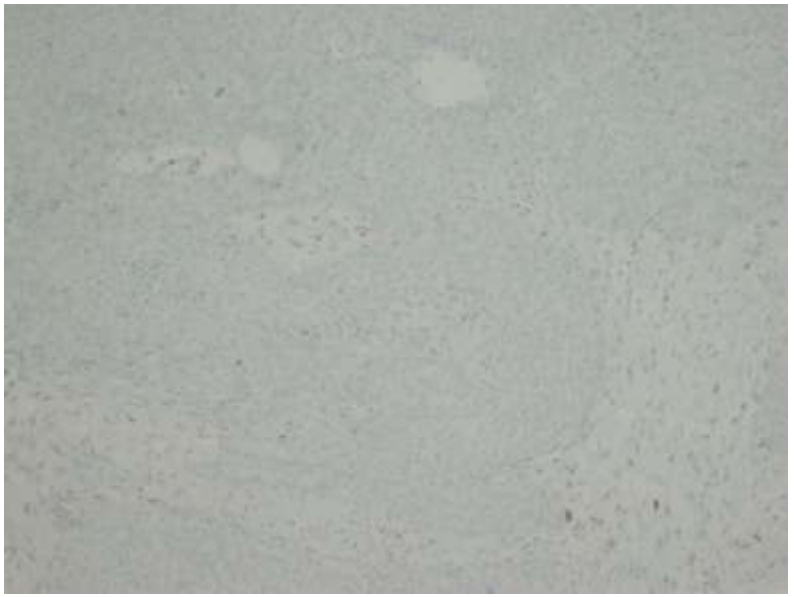
Positive

Case 13 *(SP-13-29934)*

H&E



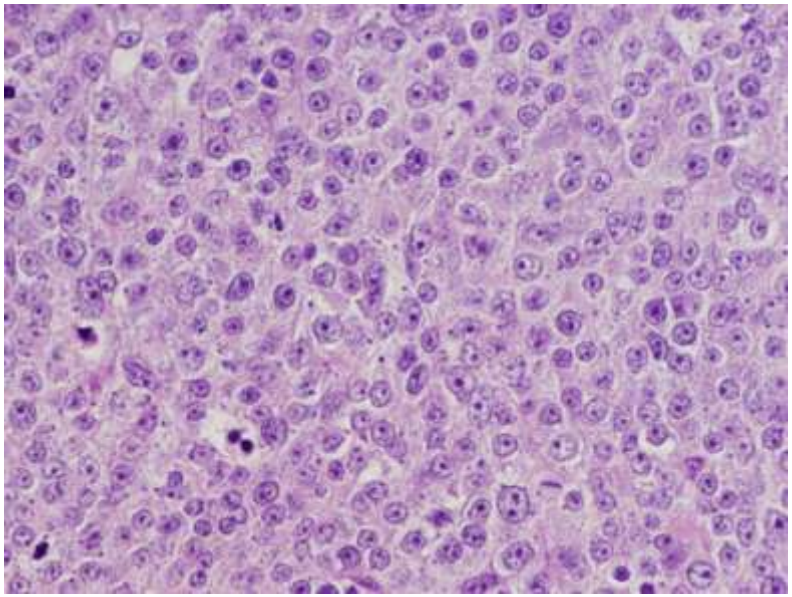
p53



Null

Case 13 *(SP-13-29934)*

H&E



Additional IHC (MSH, Toronto)

- PAX-8 (+)
- WT-1 (+)

Dx: HG carcinoma, m/c/w HGSC of upper tract

Summary of IHC Markers

p16

- Surrogate of high risk HPV integration / related tumors
  - Strong and diffuse required
- Cervical adenoCa vs. EEC
- Diagnosing / subtyping u-VIN
- Marker of USC/HGSC (vs. EEC, other OSEC, LGSC/SBT)
- Pitfall in PSM

p53

- Diagnosing / subtyping d-VIN
- Marker of USC/HGSC
  - Overexpression and null immunophenotype
  - Differentiate from increased “wild-type” pattern
- DDx with PSM
- HGSC vs. LGSC / SBT
- STIC

WT-1

- Marker of HGSC
  - Less common in other OSEC
    - Useful post chemo setting
  - Uncommon in other epithelial neoplasms
    - Mesothelioma, WT, DSRCT, etc.
  - Less common in USC

PAX-8

- Sensitive marker of mullerian origin
  - (~ 100% in most types)
- Extremely helpful in certain contexts
  - vs. breast, colorectal, lung (~ 0%)
- Also (+) in GU, thyroid, thymus

Notable Panels

- ECA vs. EEC
  - ER, vimentin, p16 (+/- CEA)
- Uterine Ca
  - ER, p16, p53, (PTEN, IMP-3)
- OSEC
  - ER, p16, p53, WT-1, HNF-1β
- STIC algorithm
  - Morphology + p53 and Ki67
- Breast vs. ovarian
  - GCDFP, mammoglobin, CA-125, p53, WT-1, PAX-8

THANK YOU !