# Scotland and Northern Ireland EQA Scheme

## Circulation 46

Special Educational Cases E1 and E2

*Presented by Dr K Robertson*

# Case E1

- Female
  - 42 year old with heavy menstrual and intermenstrual bleeding.  IUS in situ for 3 years. Bloods normal (including CA125)
  - Posterior uterine leiomyoma on ultrasound scan
  - Treated with Norethisterone and tranexamic acid then switched to Ulipristal
  - Persistent debilitating menorrhagia and abdominal discomfort.  Underwent subtotal hysterectomy

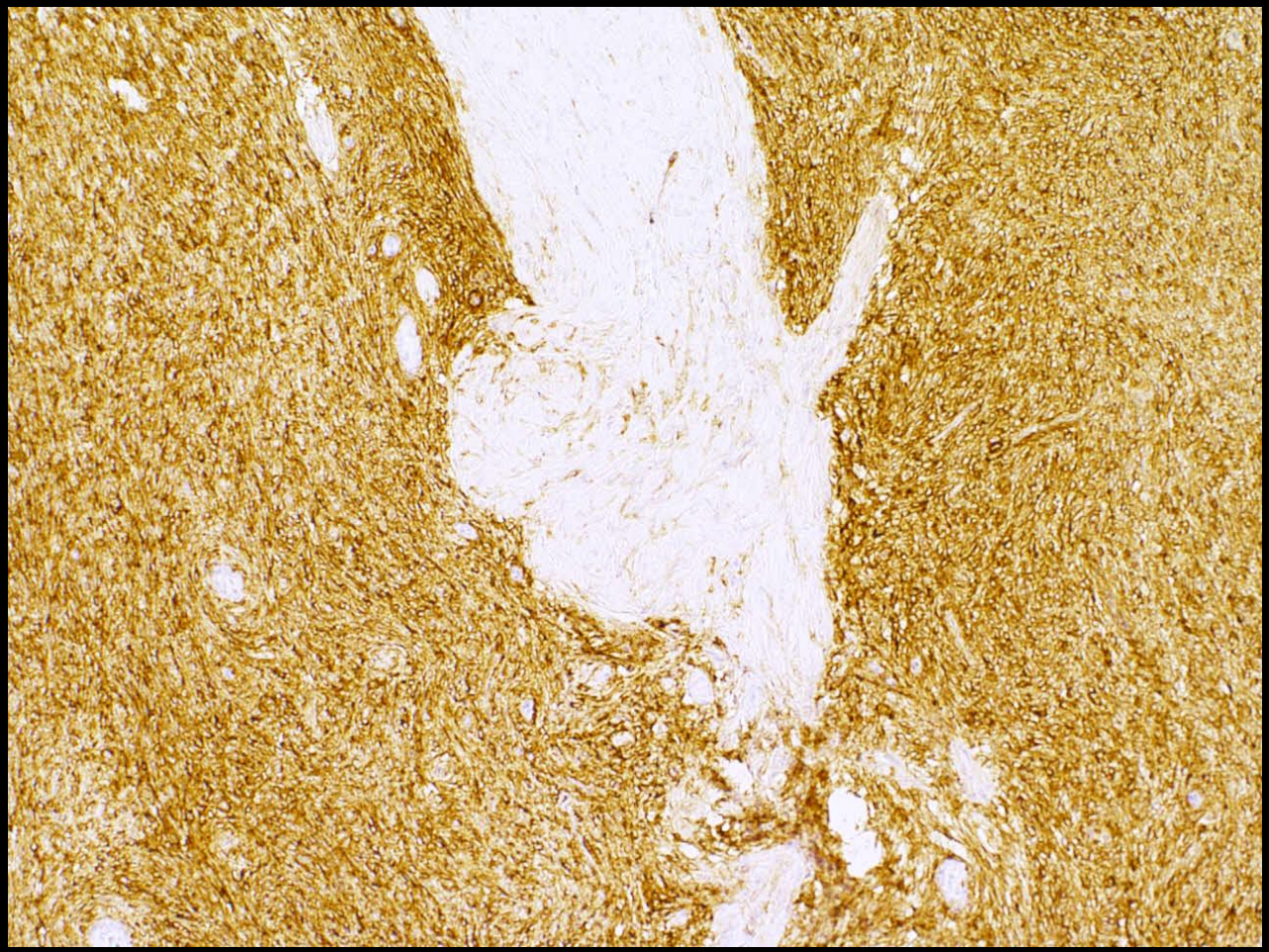
# Case E1

- Macroscopy
  - Distorted uterus measuring 120mm (SI) x 90mm (left-right) x 85mm (anterior-posterior)
  - Clotted blood in endometrial cavity
  - Large lobulated pale fleshy lesion projecting into endometrial cavity, involving the posterior wall of the uterus. Invades outer half of myometrium.

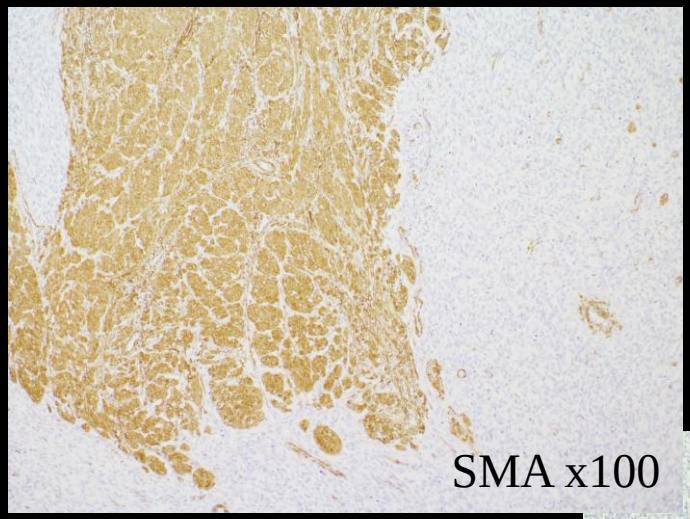
# Case E1

- Additional information -
  - Tumour is strongly positive for CD10

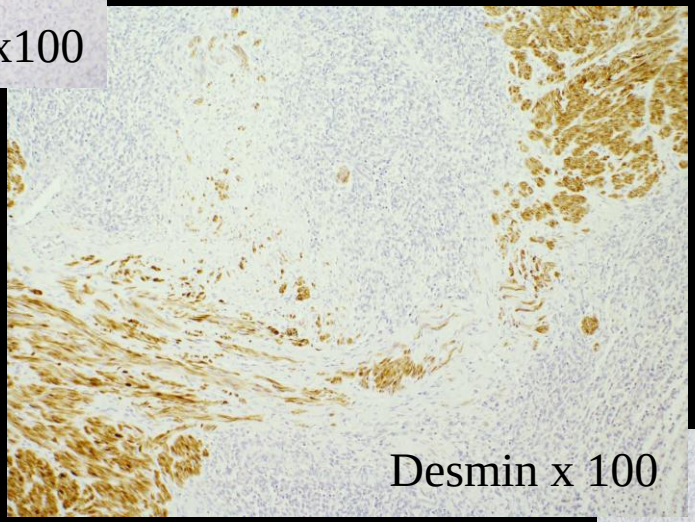
# CD10



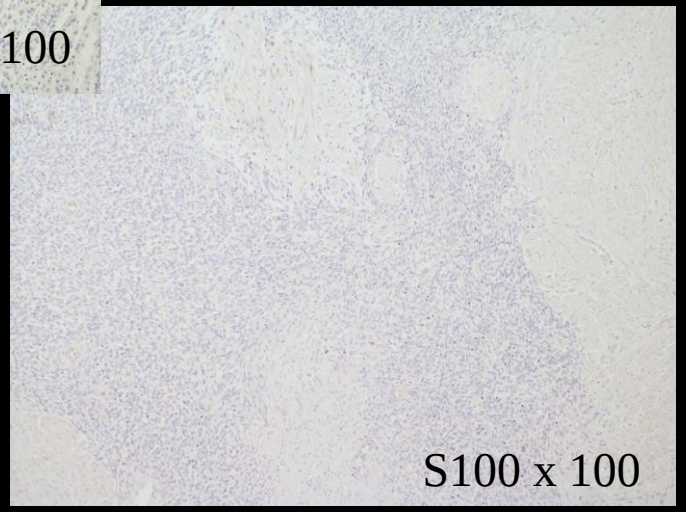
- Additional information -
  - Tumour is negative for SMA, Desmin



SMA x100



Desmin x 100



S100 x 100

# Case E1

- Also negative for
  - Calretinin
  - Inhibin
  - EMA
  - MelanA
  - PanCK

# Case E1

- Diagnosis:
  - Low Grade Endometrial Stromal Sarcoma
  - FIGO 1b (> 5cm in size)

# Case E1

- Responses: 92 responses in total
  - 50 – Endometrial Stromal Sarcoma/Endometrial Stromal Tumour/Stromal Sarcoma/Uterine Stromal Sarcoma
  - 40 – Low Grade Endometrial Stromal Sarcoma
  - 1 – Endometrial Stromal Sarcoma – would do molecular testing to distinguish Low Grade from High Grade
  - 1 – Endometrial Stromal Nodule

# Case E1

- Differential diagnosis
  - Endometrial stromal sarcoma low grade
  - Endometrial stromal sarcoma high grade
  - Endometrial stromal nodule

  - Other mesenchymal lesions
    - E.g. cellular leiomyoma

# Case E1

- Endometrial stromal nodule
  - Benign
  - Well circumscribed margin
    - Can have limited infiltration (adjacent nests of tumour cells measuring <3mm in greatest dimension from the main tumour mass and < 3 in number are acceptable)
  - Cells resemble proliferative-phase endometrial stroma
  - Most tumours harbour a t(7;17p21;q15) which results in a fusion between *JAZF1* and *SUZ12*
  - Immunoprofile identical to that of endometrial stromal sarcoma

# Case E1

- Low Grade Endometrial Stromal Sarcoma
  - Malignant; <1% of all uterine malignancies but second most common uterine mesenchymal malignancy
  - Cells resemble proliferative-phase endometrial stroma
    - Minimal cytological atypia
    - Usually low mitotic activity although high mitotic rate does not preclude diagnosis
    - Infiltrative growth pattern and/or lymphovascular invasion

# Case E1

- Can show smooth muscle differentiation, fibromyxoid change,  sex cord-like differentiation, and/or endometrioid-type glands

- 10% involve the adnexae
- 30% have lymph node involvement

# Case E1

- Immunoprofile:
  - Diffuse and strong positivity for CD10 (not always!)
  - SMA and Desmin may be positive
  - Negative for h-caldesom (positive in areas showing smooth muscle or sex cord-like differentiation)
  - ER, PR and WT-1 typically positive
  - Inhibin, calretinin, MelanA, CD99 in areas of sex cord-like differentiation

# Case E1

- Molecular
  - Most tumours harbour a t(7;17p21;q15) which results in a fusion between *JAZF1* and *SUZ12*.
  - Other rearrangements also seen; t(6;7)(p21;p15), t(6;10;10)(p21;q22;p11) and t(1;6)(p34;p21)

- Prognosis
  - Stage is most important predictive factor
  - Five-year disease specific survival for Stage 1 and Stage II is 90% compared to 50% for stages III and IV

# Case E1

- High Grade Endometrial Stromal Sarcoma
  - Malignant
  - May coexist with low-grade ESS
  - Round-cell morphology rather than spindle cell as in low-grade ESS
  - Commonly shows confluent permeative and destructive growth with invasion into outer half of myometrium
  - May have pseudo-papillary/glandular areas
  - Mitotic activity typically > 10 per 10 hpfs

# Case E1

- Molecular
  - Typically harbours the *YWHAE-FAM22* genetic fusion as a result of t(10;17) (q22;p13)

- Prognosis
  - Earlier and more frequent recurrences compared to low-grade ESS
  - Better prognosis compared to undifferentiated stromal sarcoma

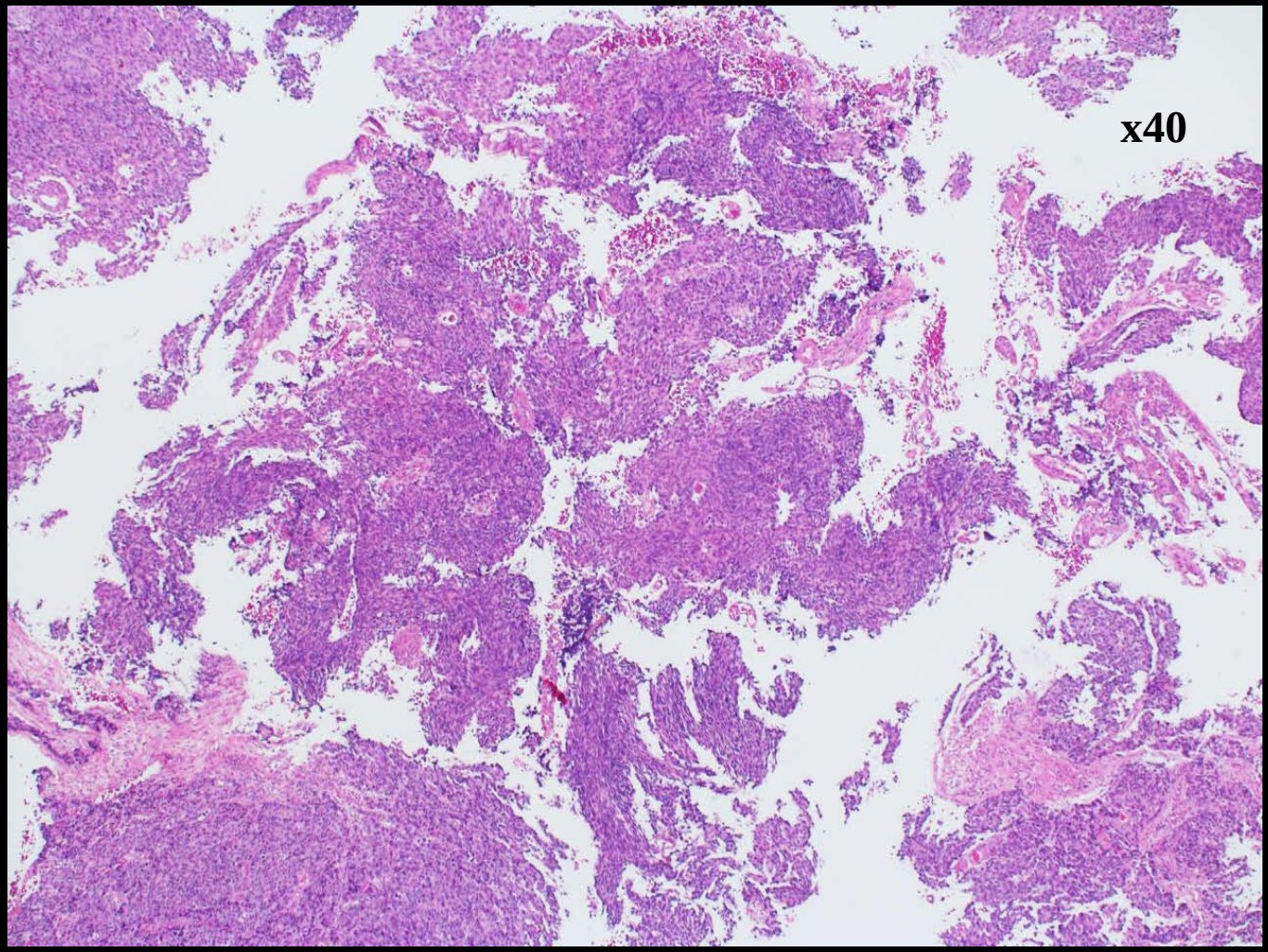
# Case E1

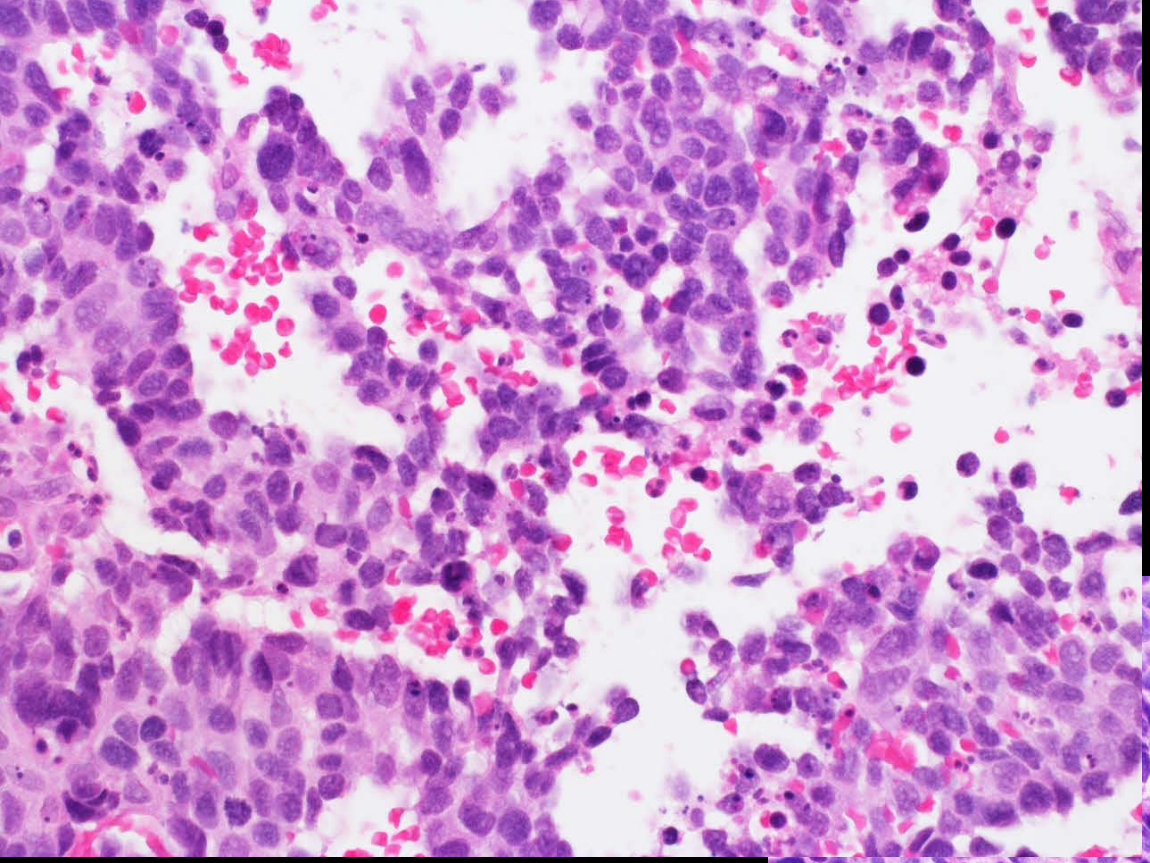
- Learning points
  - Not everything that looks like a leiomyoma radiologically is a leiomyoma
  - Good example of a rare tumour

# Case E2

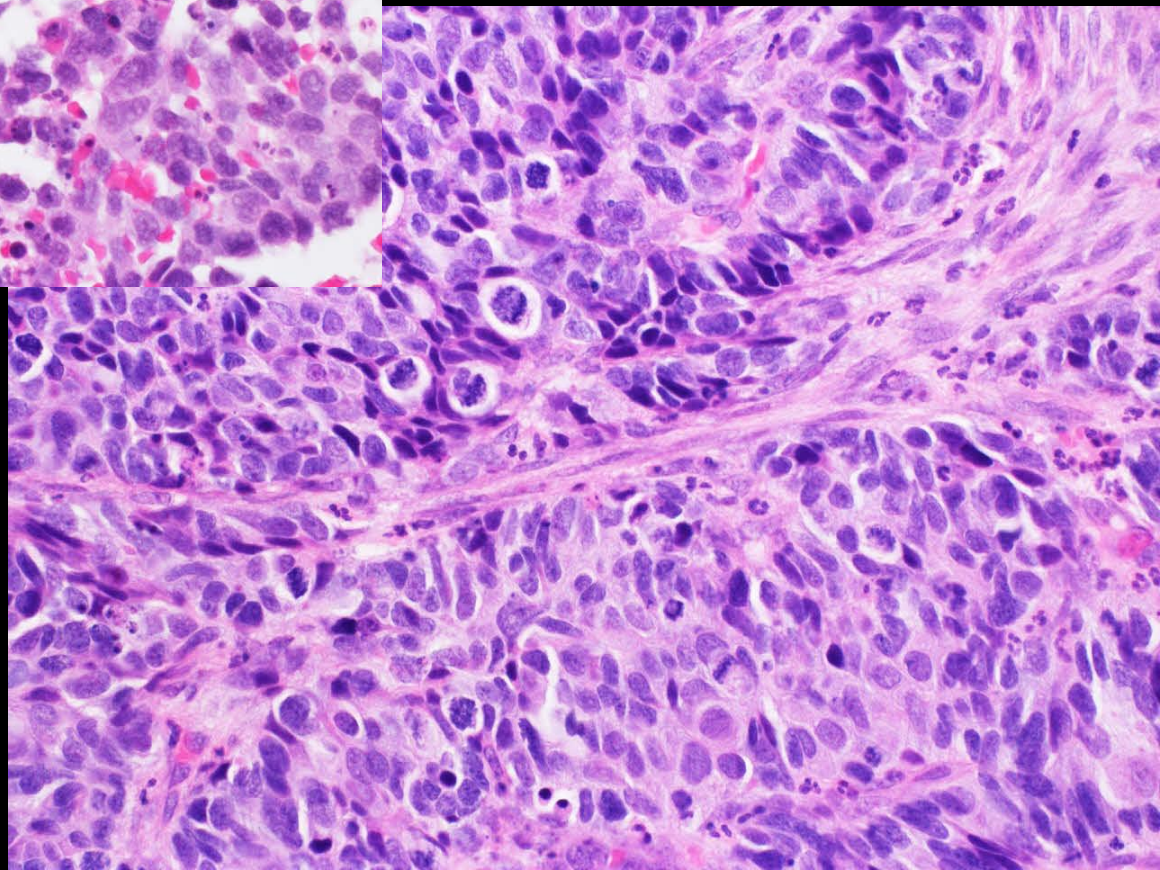
- Female aged 33 years
  - Irregular frequent bleeding
  - Never had a cervical smear
  - Fungating mass seen at cervix

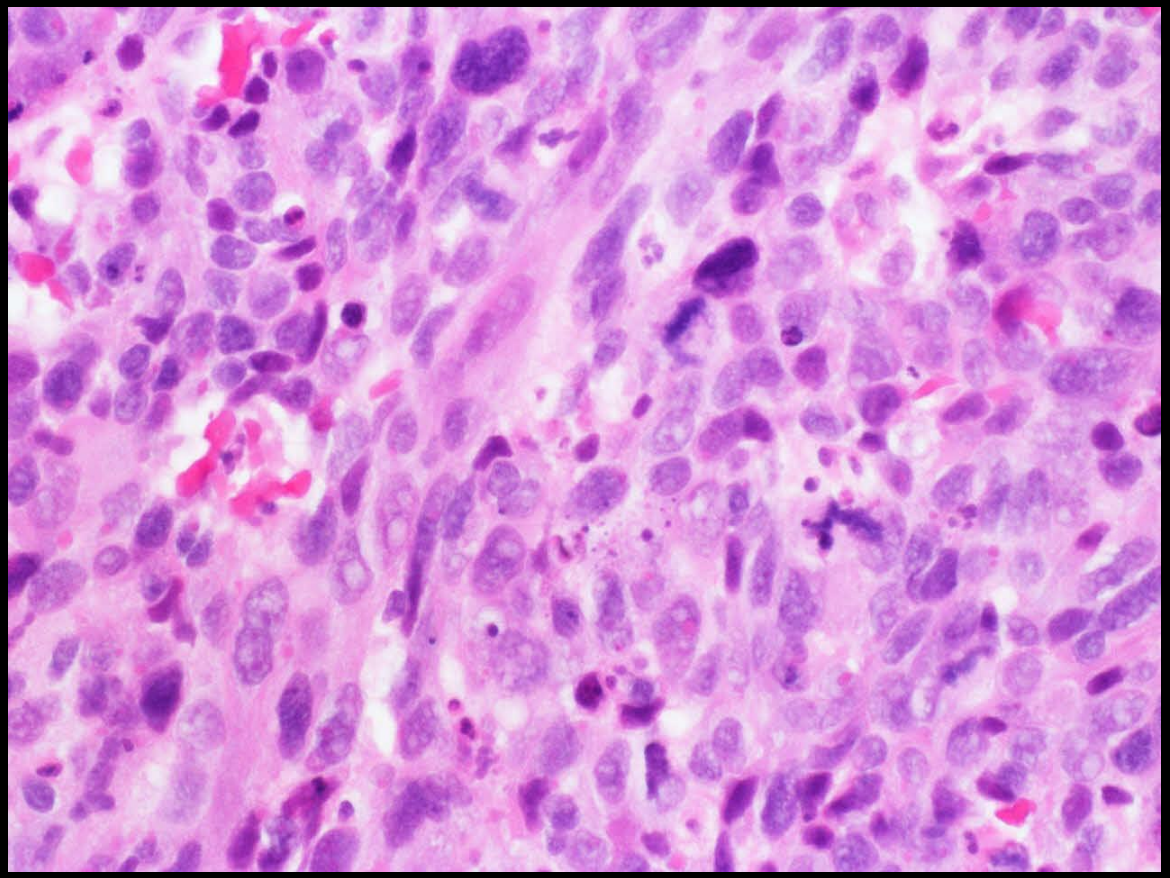
# Cervical Biopsies





x400

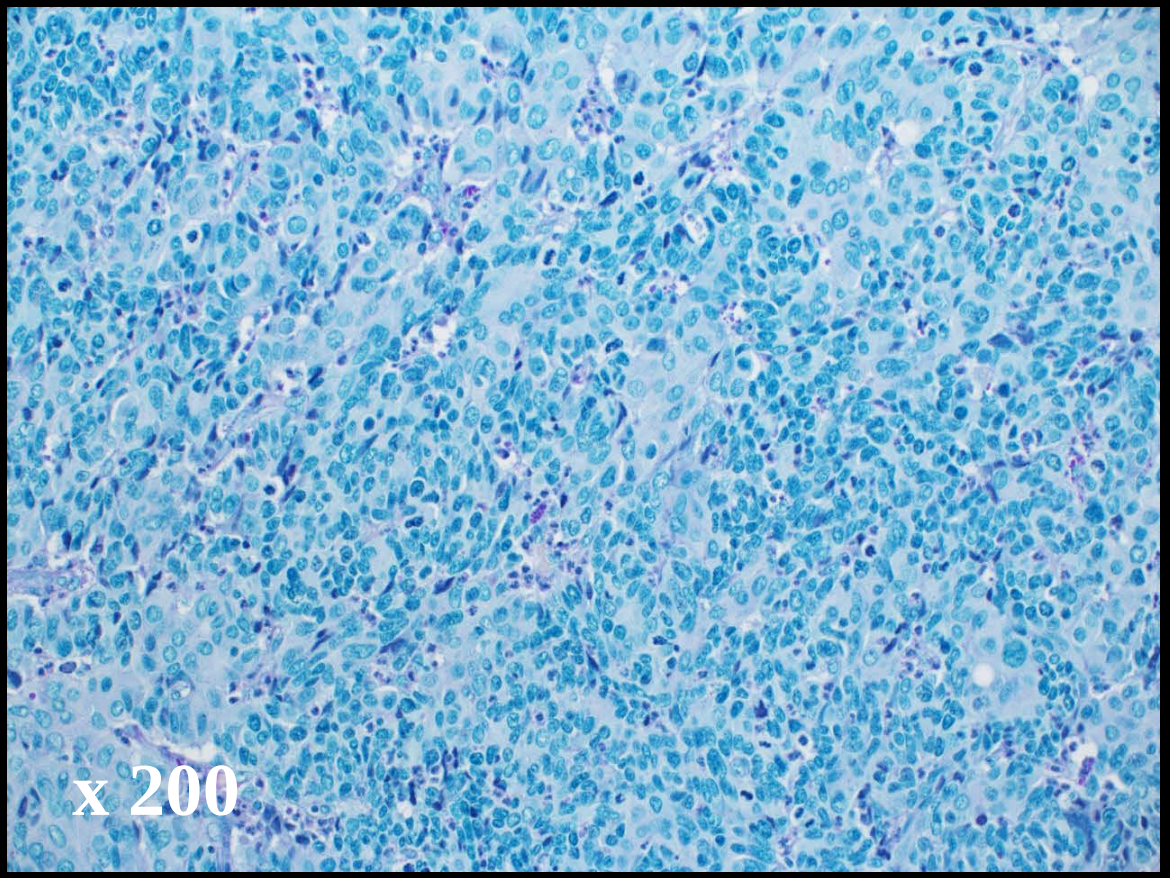




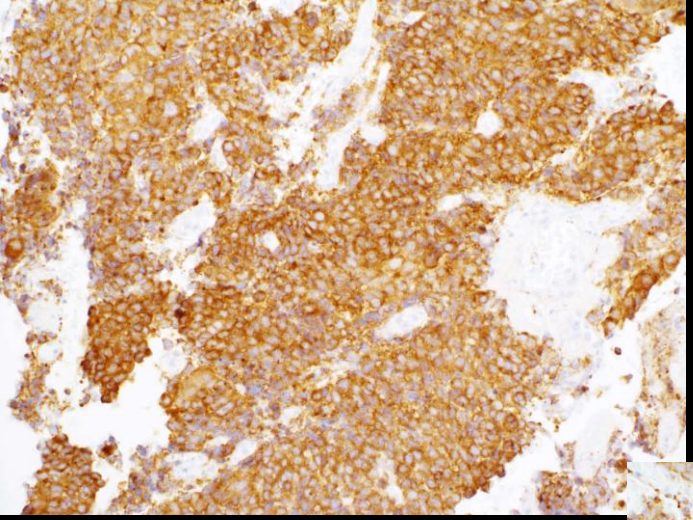
x600

Large pleomorphic and basophilic cells with stippled chromatin admixed with eosinophilic cells, some of which look ‘squamoid’ in appearance.  No true glandular spaces and ABPASD for mucin negative.

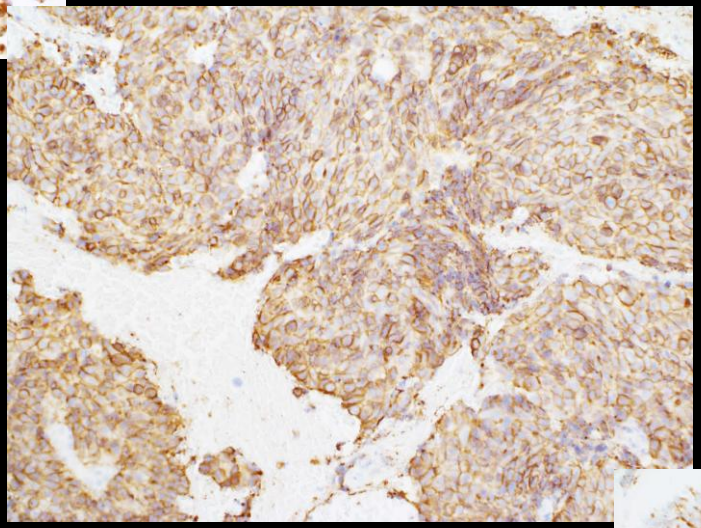
**ABPASD**



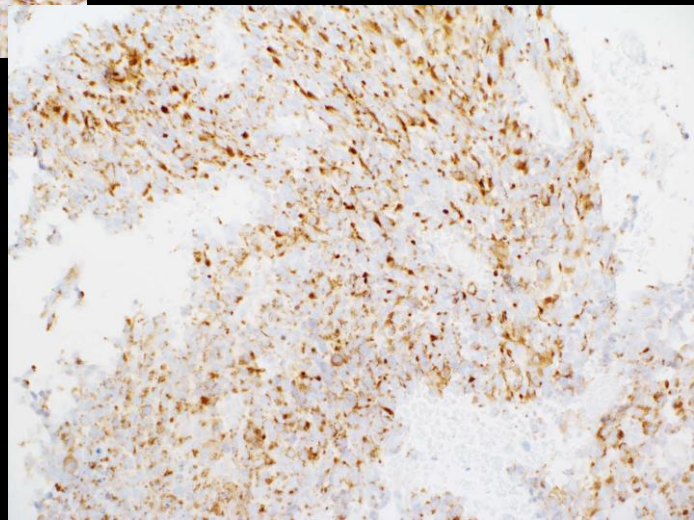

**Squamous markers CK5/6 and p63 NEGATIVE**



Synaptophysin

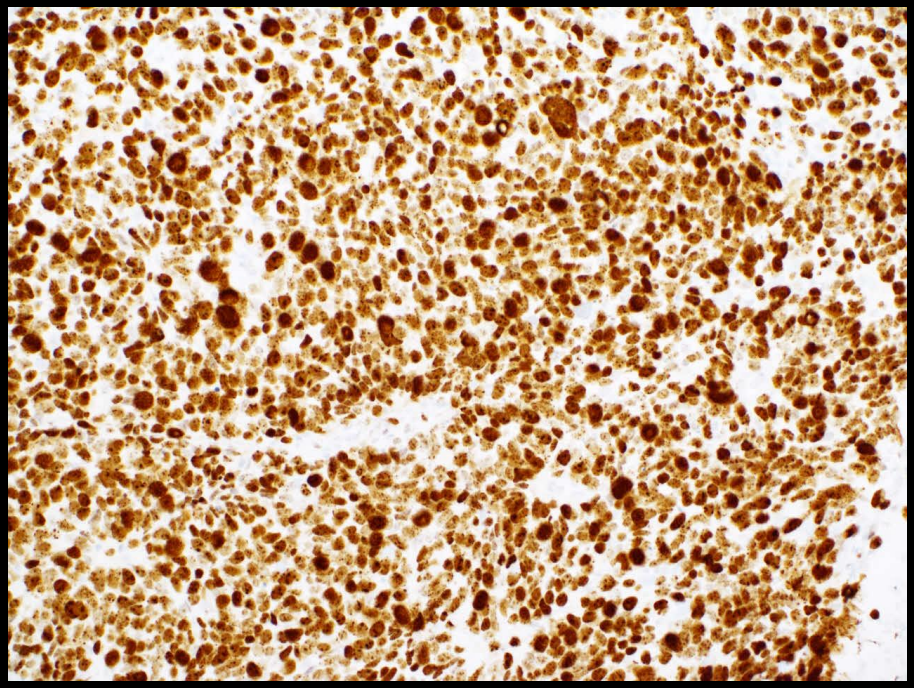


CD56

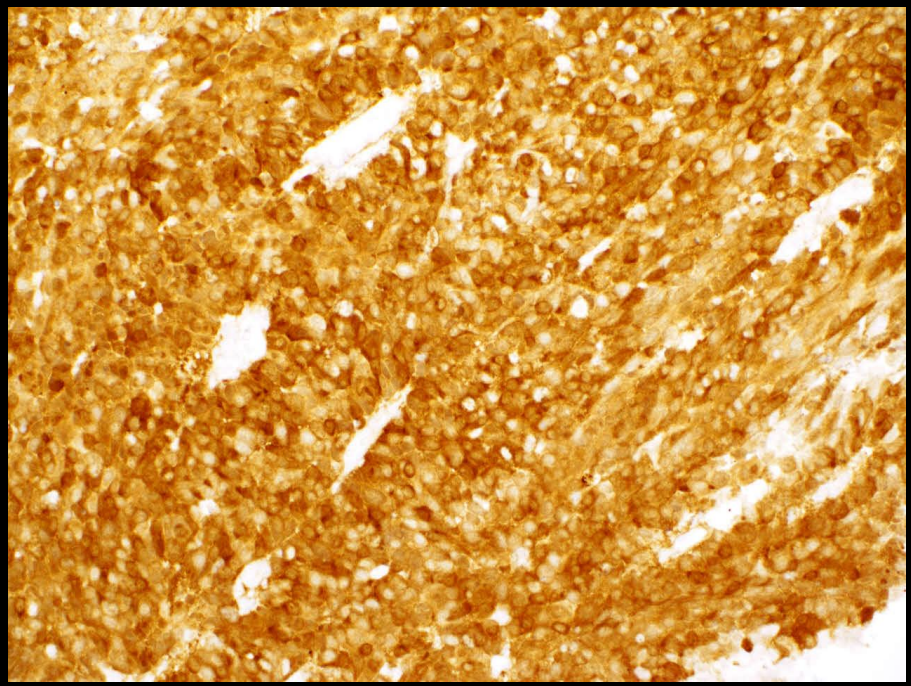


Chromogranin

x 200

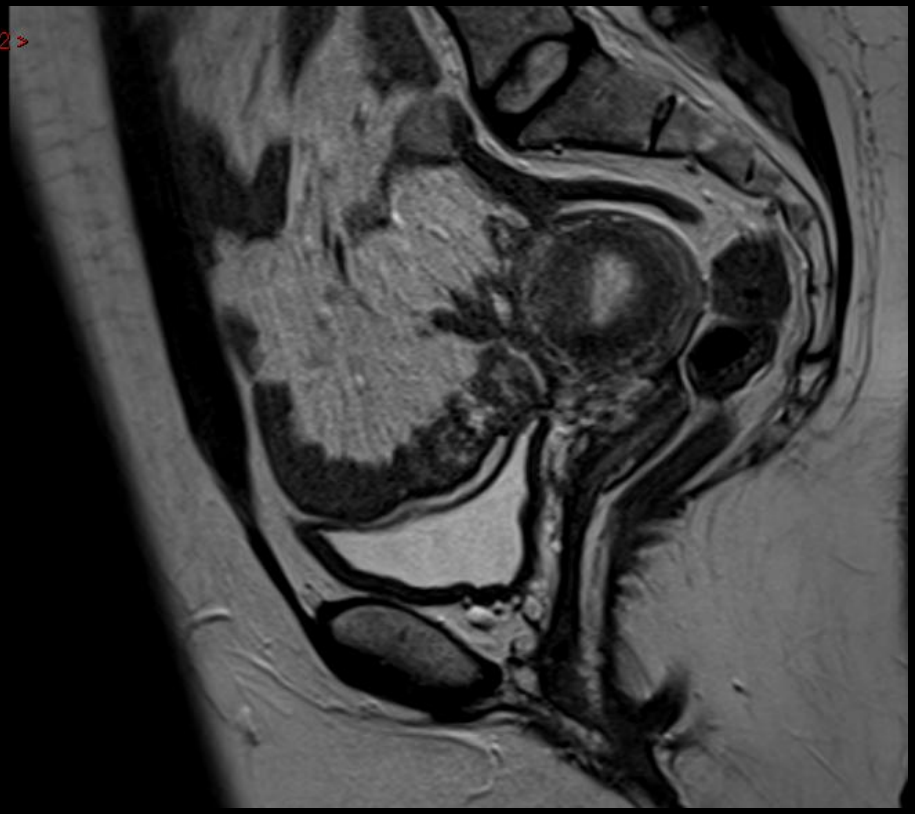


Ki67

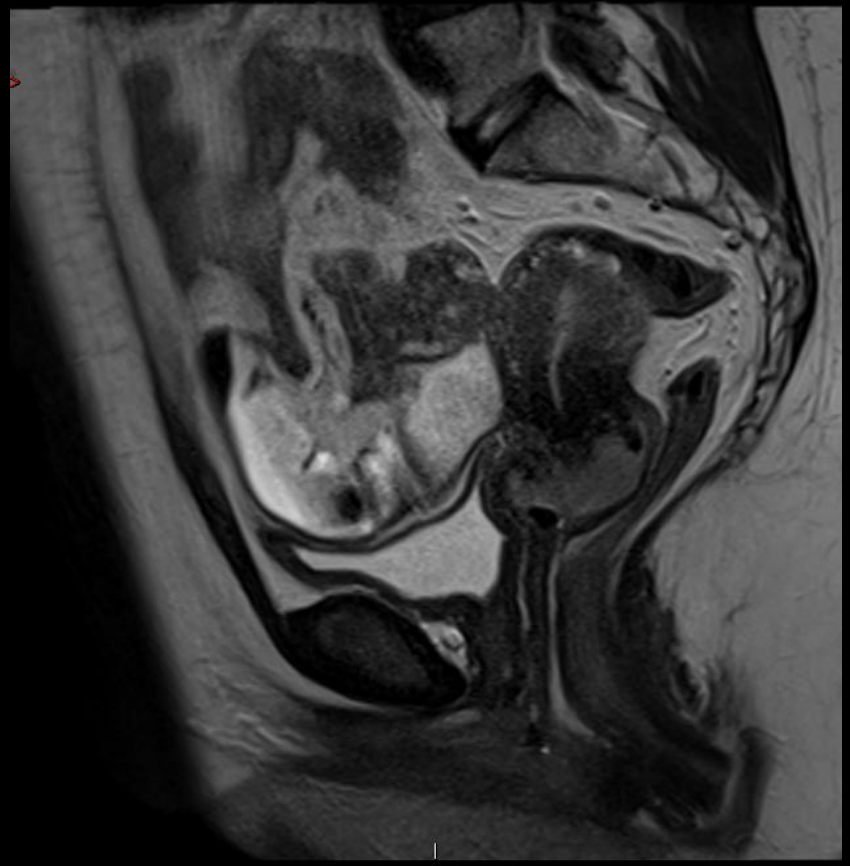


x 200

p16



MRI - 6cm ectocervical tumour extending into vagina



# Case E2

- Biopsy Diagnosis:
  - Large cell neuroendocrine carcinoma
  - Combined poorly differentiated squamous cell carcinoma and large cell neuroendocrine carcinoma was considered but no definite evidence of squamous differentiation on the biopsy

# Case E2

- Treated with neoadjuvant chemotherapy (Carboplatin/Etoposide) and subsequently underwent a radical hysterectomy, bilateral salpingo-oophrectomy and pelvic node clearance
  - FIGO Stage IIB mixed adenocarcinoma and large cell neuroendocrine carcinoma with CIN 3 in ectocervix with LVSI and involvement of the vagina
  - Tumour showed little response to chemotherapy
  - Post operative radiotherapy

# Case E2

- Responses: 92 in total
  - 25– Cervical Small Cell Carcinoma
  - 20 – Large Cell Neuroendocrine Carcinoma
  - 19 – Neuroendocrine Carcinoma
  - 18 - Poorly Differentiated Neuroendocrine Carcinoma

# Case E2

- Other responses :
    - 3 – Poorly Differentiated Squamous Cell Carcinoma with Neuroendocrine Differentiation
    - 1 -Neuroendocrine Carcinoma (small and large cell)
    - 1 -Small Cell Carcinoma with Squamous Component
    - 1 -Neuroendocrine Carcinoma and Squamous Cell Carcinoma
    - 1 -Undifferentiated Neuroendocrine Carcinoma
    - 1 -Neuroendocrine Tumour
    - 1 -Neuroendocrine Tumour/Neuroendocrine Carcinoma
    - 1 -Neuroendocrine Carcinoma vs Poorly Differentiate SCC with NE Differentiation

# Case E2

- Large Cell Neuroendocrine Carcinoma
  - Organoid, trabecular, cord-like or sheet-like growth
  - Tumour cells larger than small cell carcinoma with abundant eosinophilic cytoplasm
  - Large nuclei, prominent nucleoli, and high mitotic rate
  - Geographic necrosis may be seen

# Case E2

- Differential diagnosis of Large Cell Neuroendocrine Carcinoma
  - Small Cell Neuroendocrine Carcinoma
  - Mixed Neuroendocrine Carcinoma and Squamous Cell Carcinoma/Adenocarcinoma
  - Poorly Differentiated Squamous Cell Carcinoma
  - Poorly Differentiated Adenocarcinoma
  - Undifferentiated Carcinoma
  - Atypical Carcinoid
  - Malignant Melanoma

# Case E2

- Discussion
  - Can coexist with a non-neuroendocrine carcinoma
  - HPV 16 and 18 implicated as aetiological agents
  - Aggressive behavior
  - Small cell carcinoma of the cervix and LCNEC of cervix behave and are therefore treated similarly – MULTIMODAL treatment
  - Poor five year survival (Stage 1 – 42%, Stage II – 19%, Stage III – 10% and Stage IV – 23% [McCusker et al, Gyn Onc, 2003, **88**(3):p.241-50]

# Case E2

- Learning points
  - Nice example of a rare tumour
  - Biopsies not always fully representative of the entire tumour

# Scotland and Northern Ireland EQA Scheme

## Circulation 46

Special Educational Cases E3 and E4

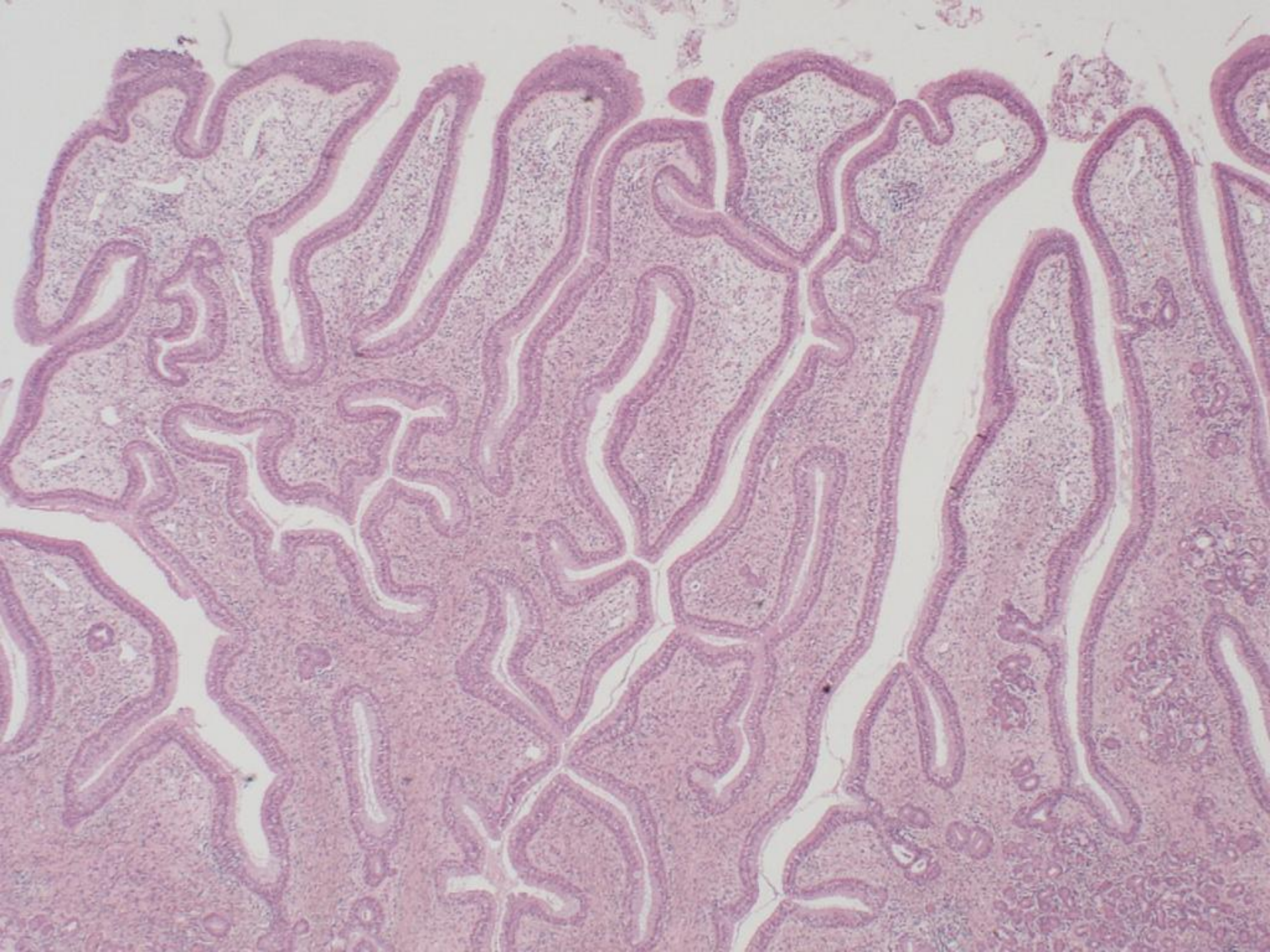
*Presented by Dr A Chapman*

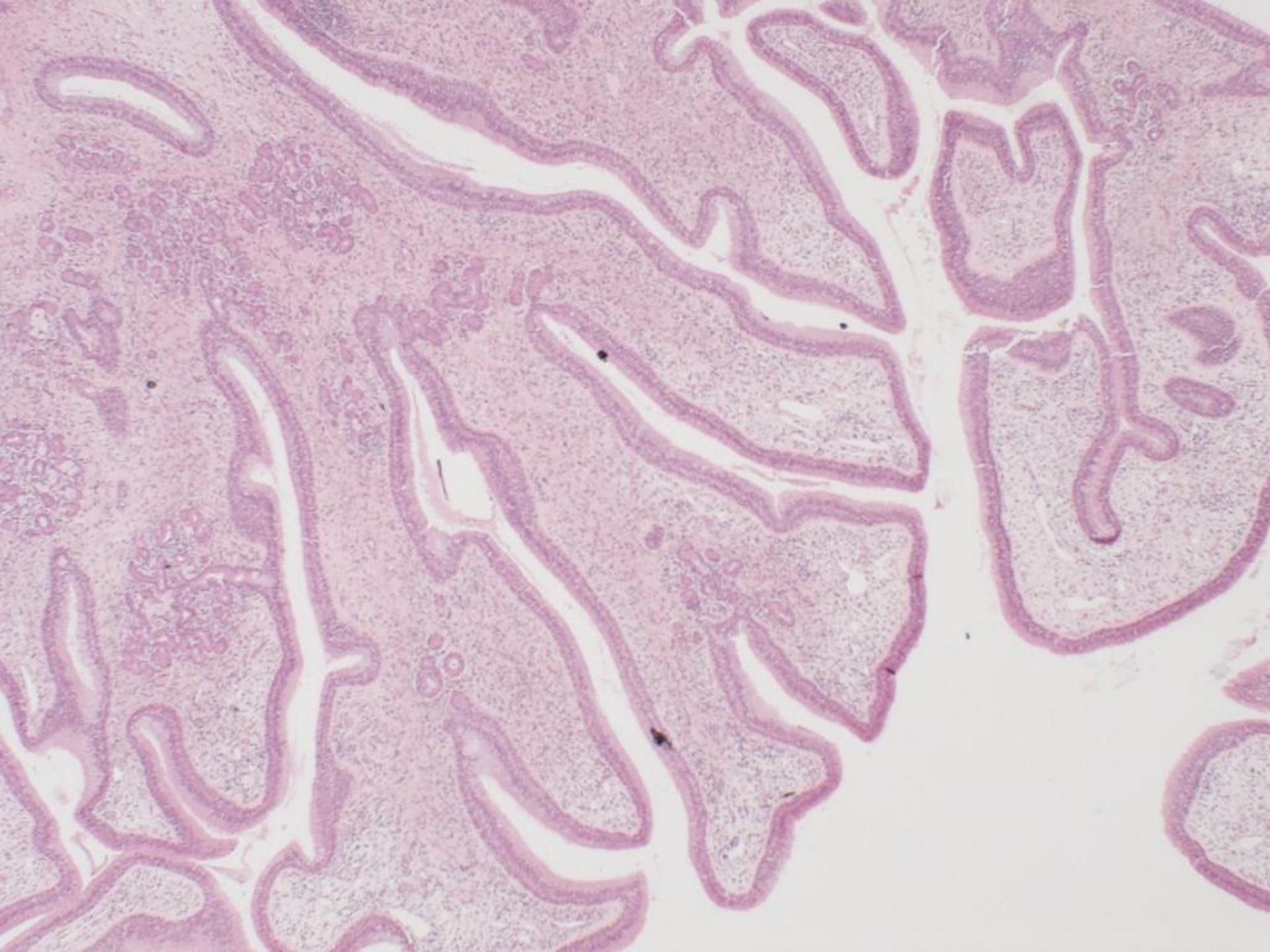
# Case E3

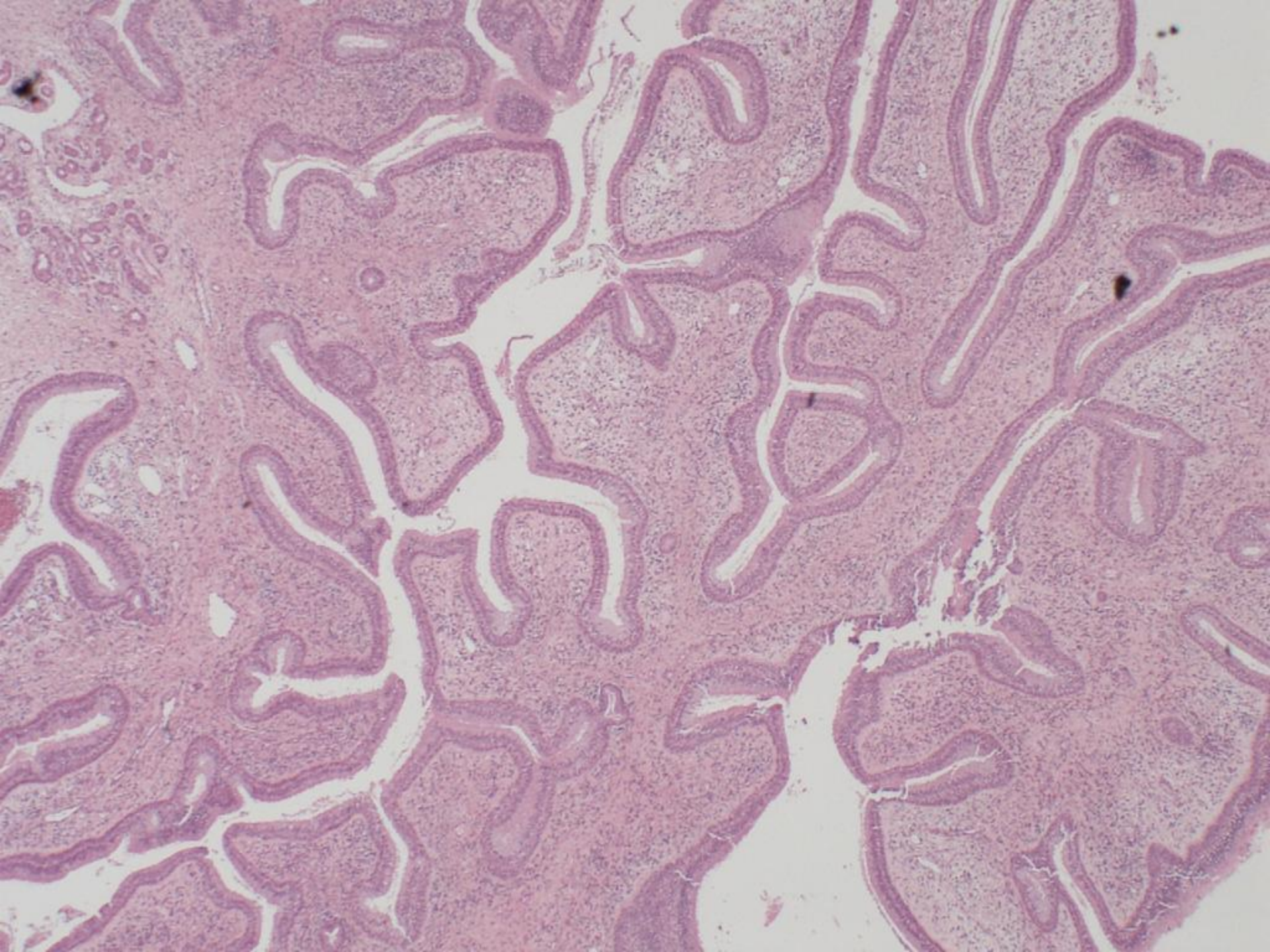
- Female 66 years

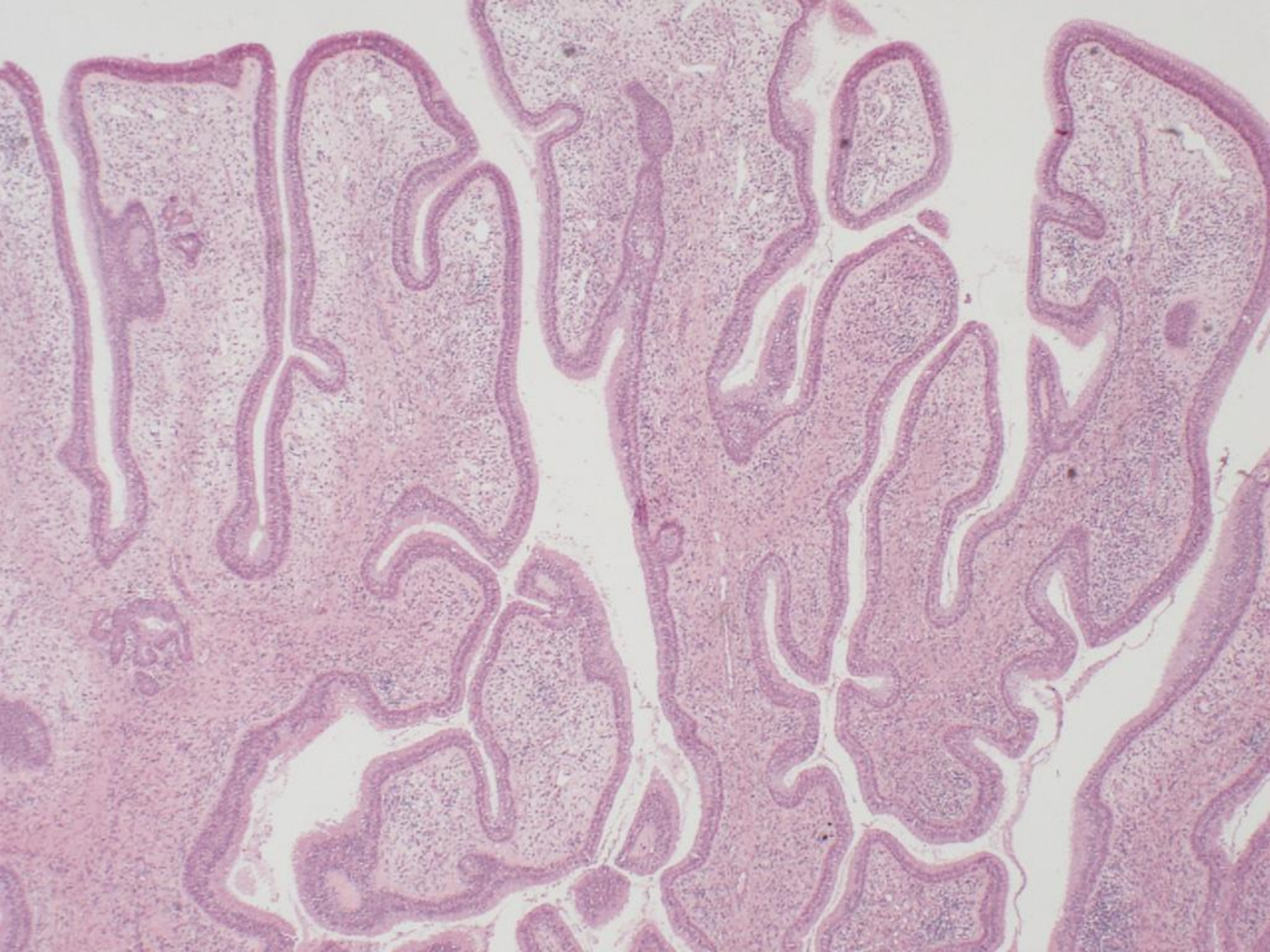
  Polyp right posterior nasal septum

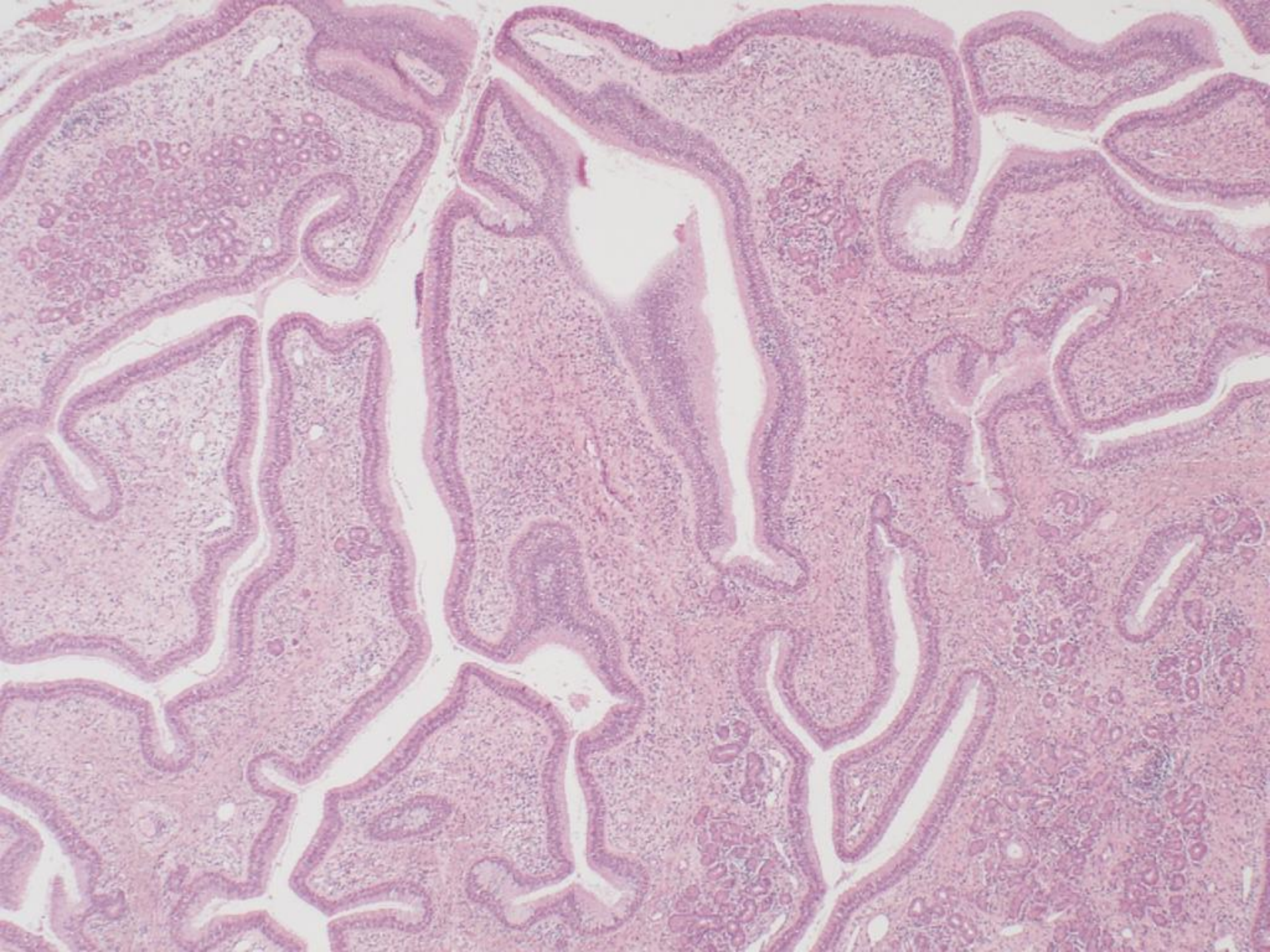
  Presented with 10 month history of nasal obstruction; mass extended from nasal cavity towards nasopharynx; received was a tan-coloured polypoid mass, 30 x 18 x 8mm.

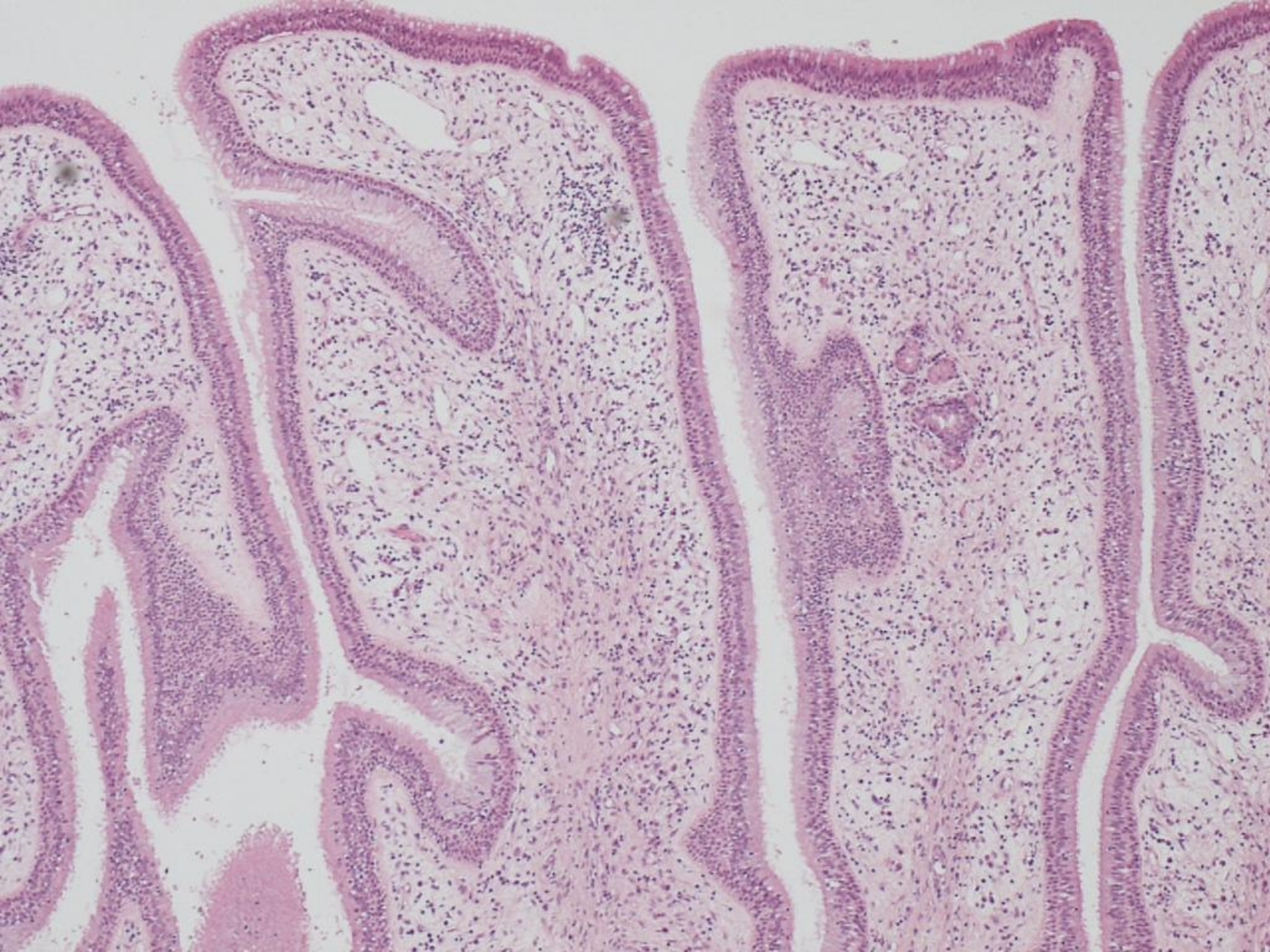


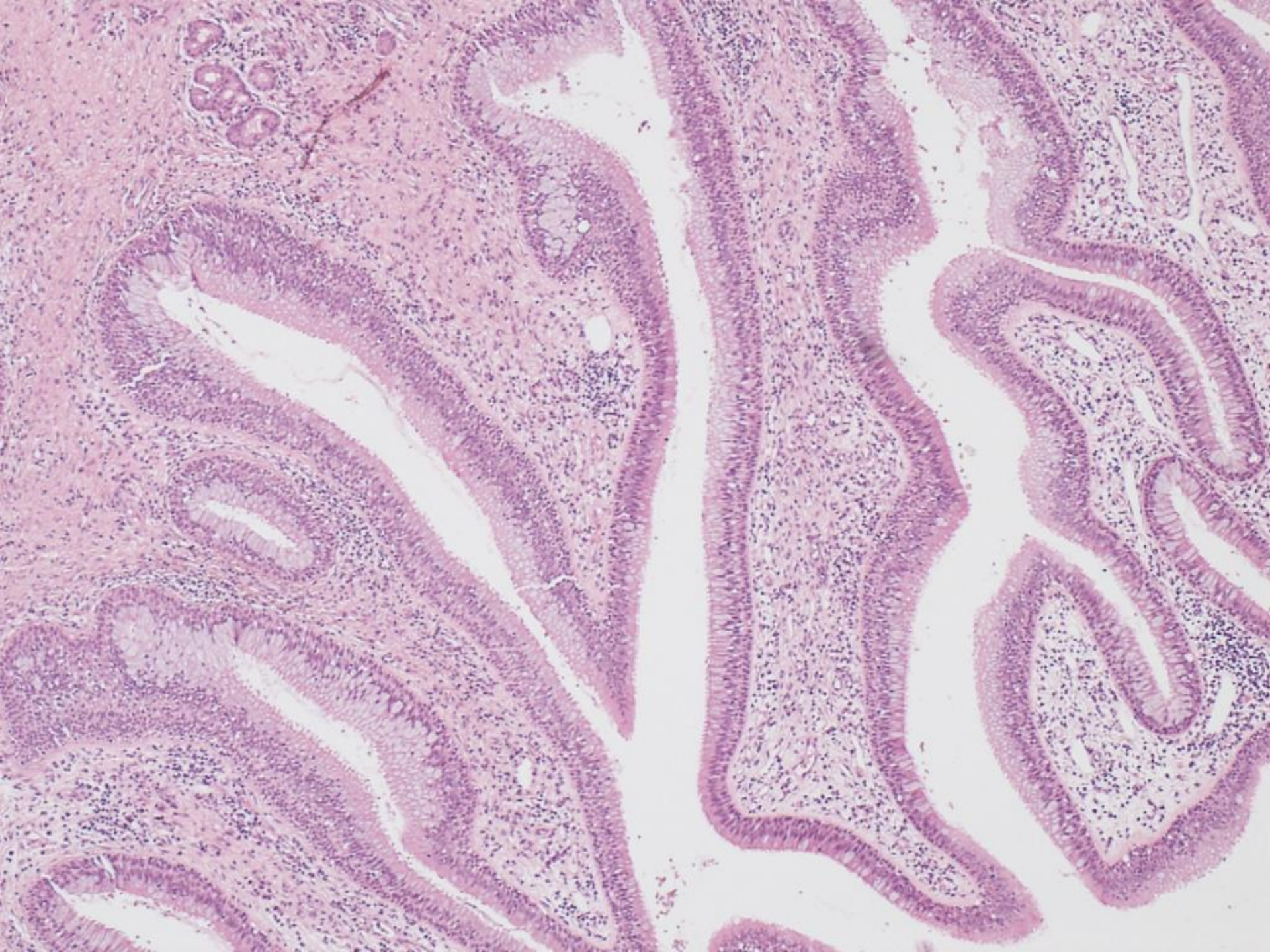


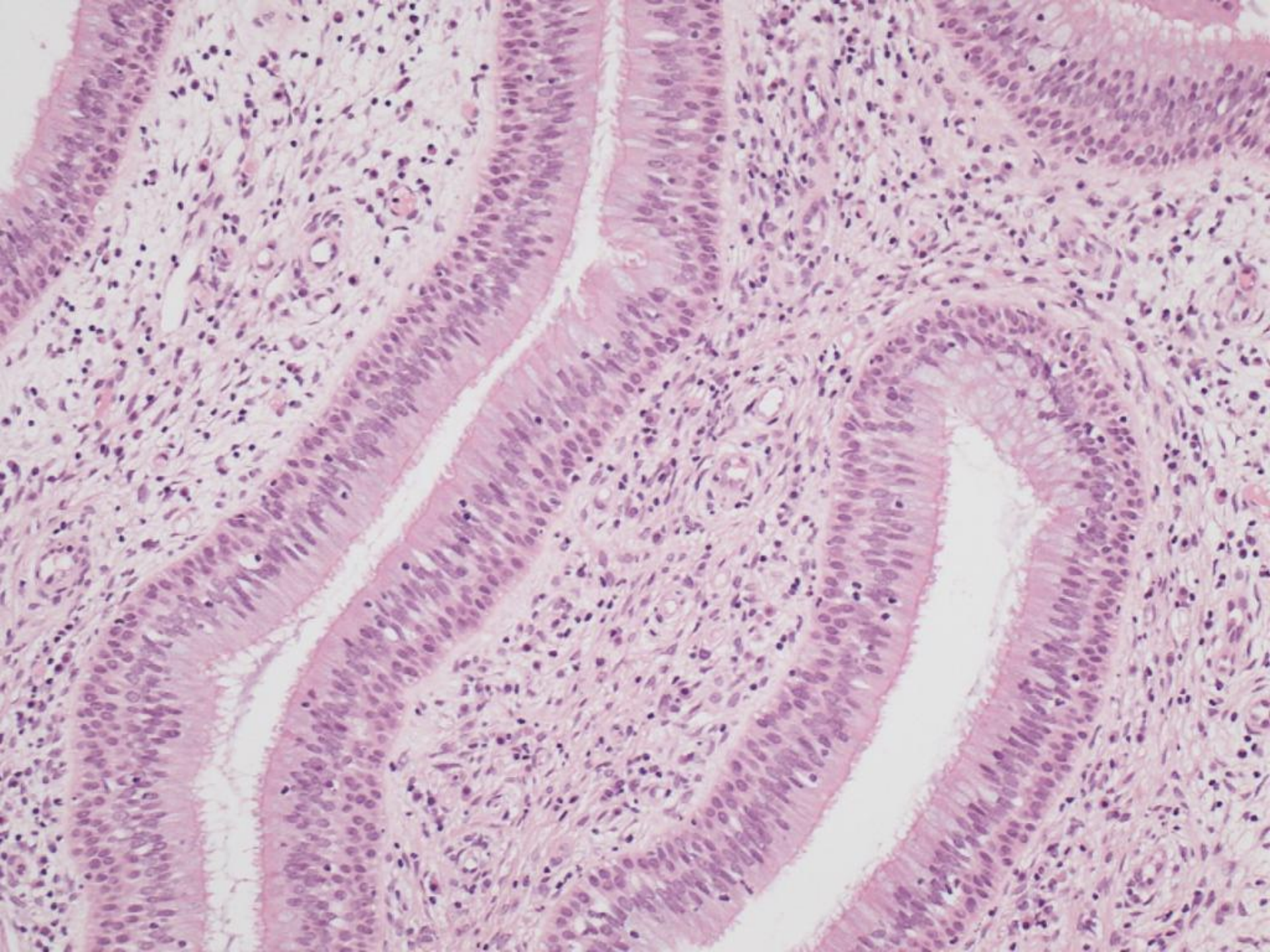


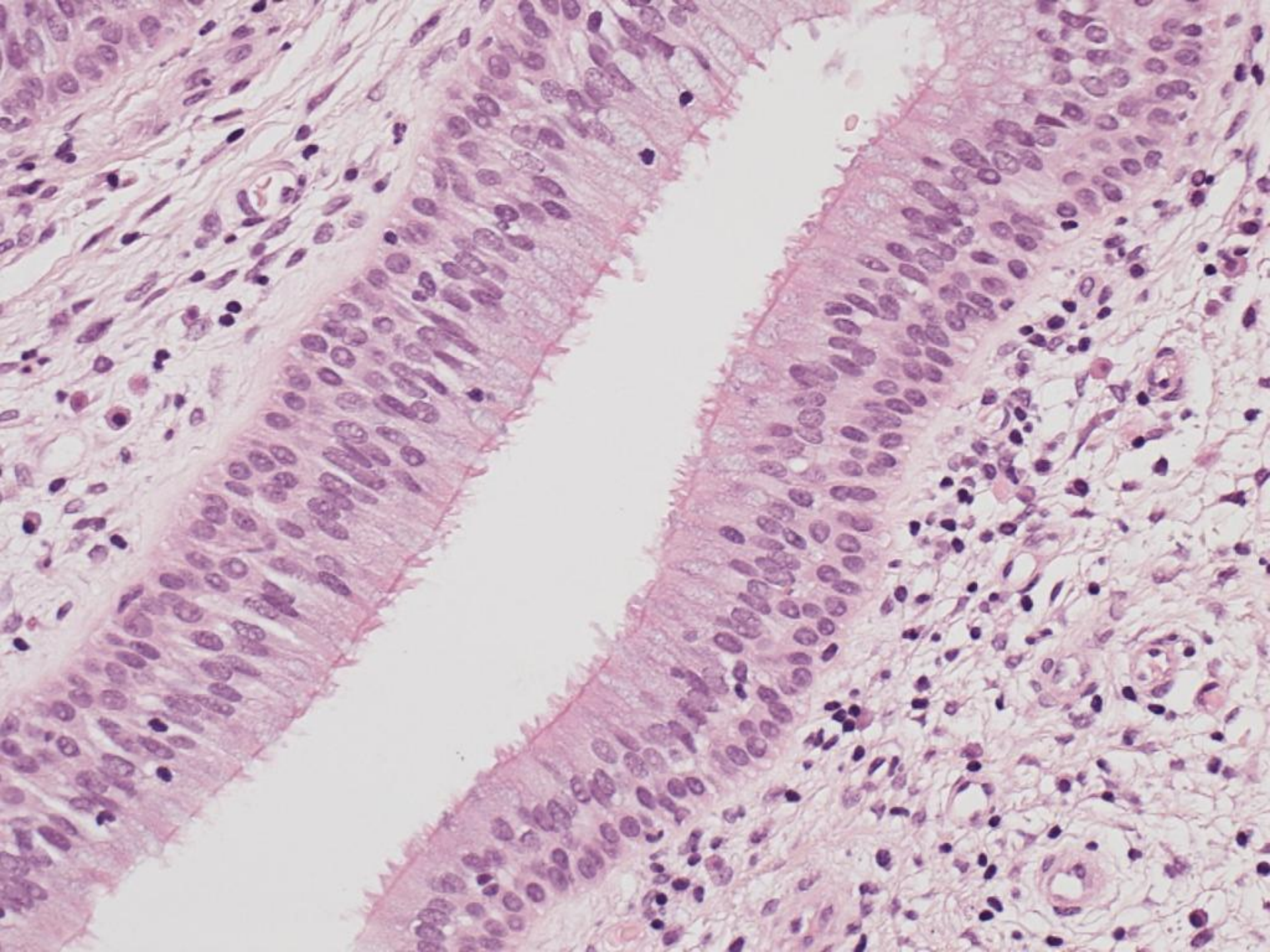


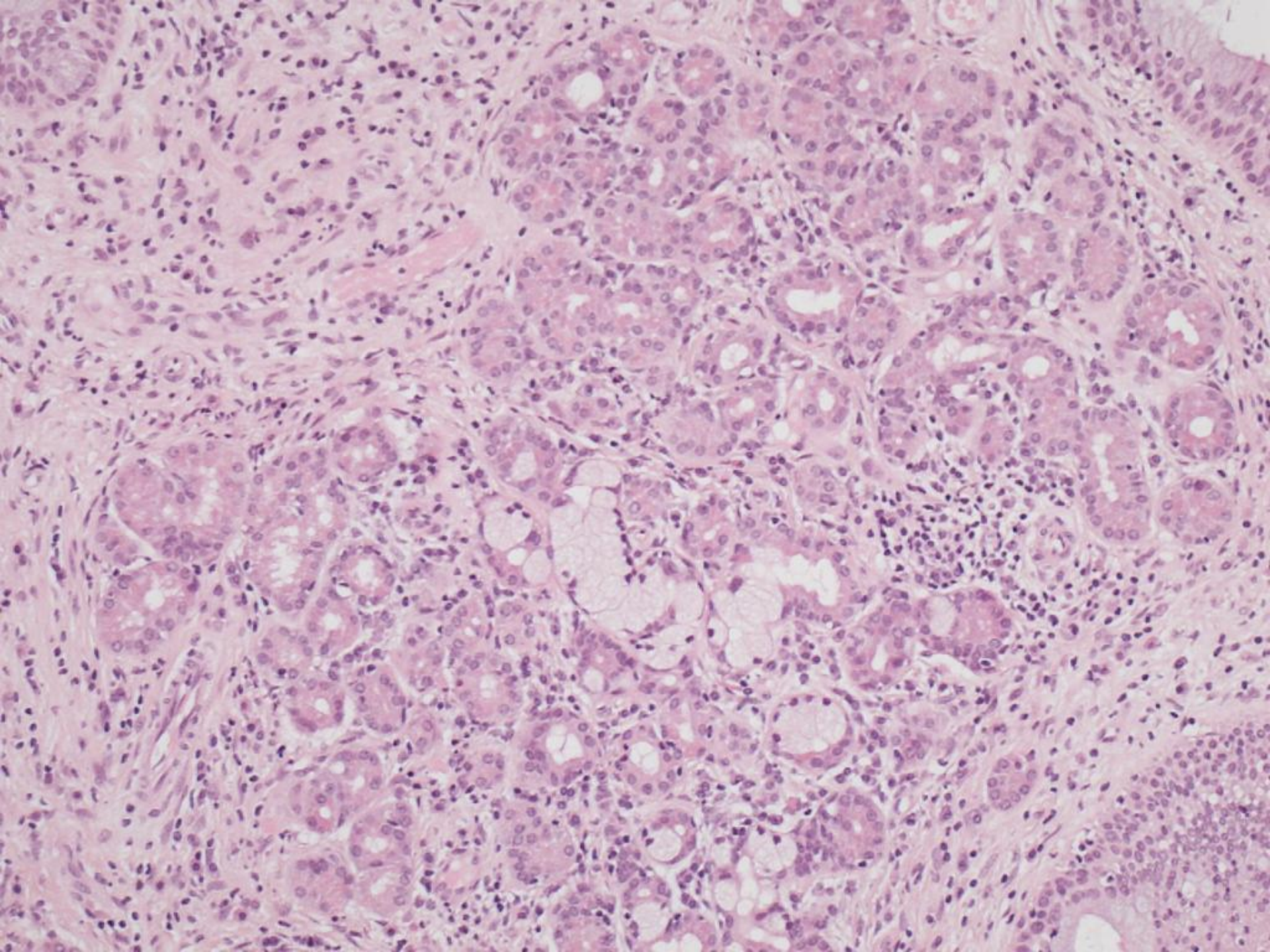


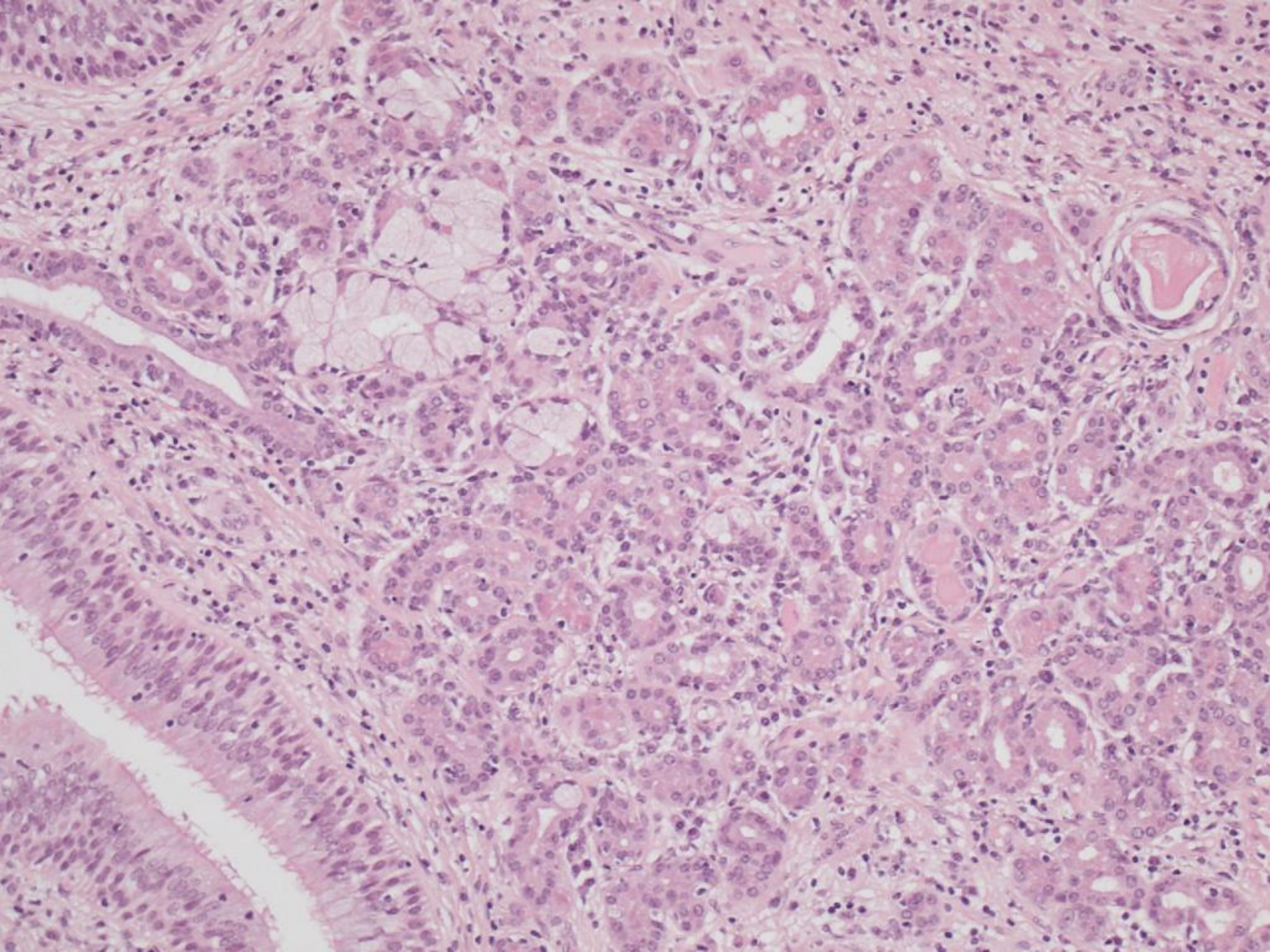


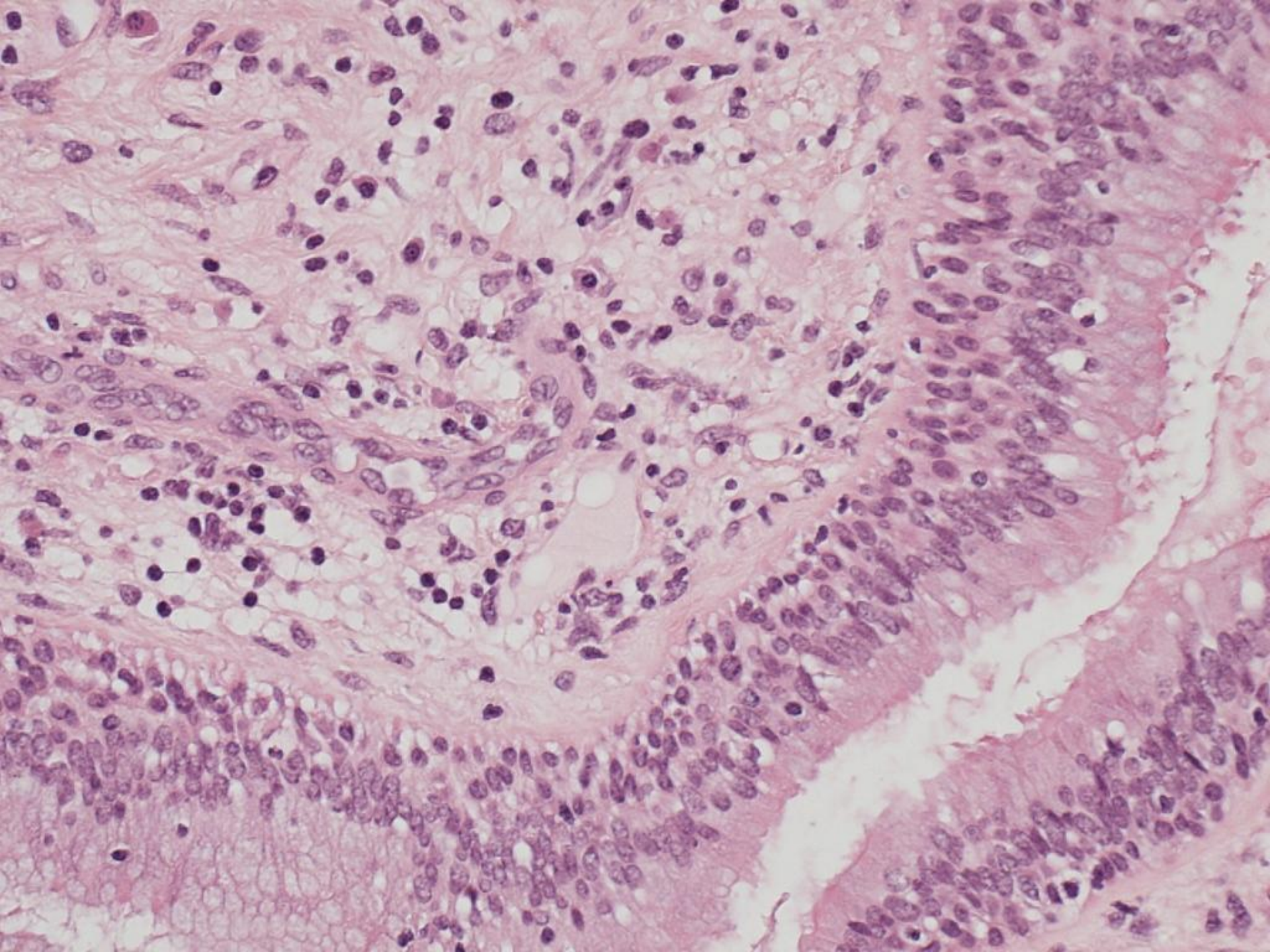












# Case E3

- Diagnosis:

  Respiratory Epithelial Adenomatoid Hamartoma (REAH)

# Case E3

- 90 Responses:
  - 34+3 – Respiratory Epithelial Adenomatoid Hamartoma (REAH)
  - 5+1 – seromucinous hamartoma
  - 2 – seromucinous hamartoma vs REAH
  - 2 – considered REAH but insufficiently thickened basement membrane
  - 6 – included “hamartoma”

# Case E3

- 90 Responses:
  - 9 – benign nasal/septal polyp
  - 8 – inflammatory (nasal septal/sinonasal) polyp
  - 7 – sinonasal/nasal papilloma
  - 6 – Schneiderian papilloma/polyp
  - 6 – seromucinous polyp, fungiform nasal papilloma, benign reactive, cylindrical cell papilloma, polypoid hyperplasia in chronic rhinosinusitis, Papillary Sail – Adenoma (a form of duct papilloma)
  - 1 – Respiratory Epithelial Adenomatoid Carcinoma

# Case E3

- Differential diagnosis
  - Seromucinous hamartoma - ?a spectrum
  - Inflammatory sinonasal polyp, inverted papilloma, low grade sinonasal adenocarcinoma

# Case E3

- Discussion
  - Invaginated and tubular architecture with fewer discrete glands (but clearly arising in direct continuity with the surface epithelium)
  - Periglandular stromal hyalinization is not prominent ?related to less glandular architecture
  - “Stromal hyalinization may be prominent but is not seen in all cases” Wenig & Heffner, Fitzhugh & Mirani
  - Mild inflammation but architecture too complex for inflammatory polyp
  - Pre-existing seromucinous glands present; no haphazard proliferation of glands lined by single epithelial layer (seromucinous hamartoma)
  - All lined by benign respiratory epithelium; no transitional/squamous epithelium with microcysts and neutrophils (inverted papilloma); no evidence of atypia or malignancy
  - Immunohistochemistry…..

# Case E3

- Learning points
  - Uncommon lesion
  - First described in 1995 (Wenig BM & Heffner DK)
  - Hamartomatous lesion – complete excision usually curative: awareness is important to avoid overdiagnosis and unnecessary surgical treatment

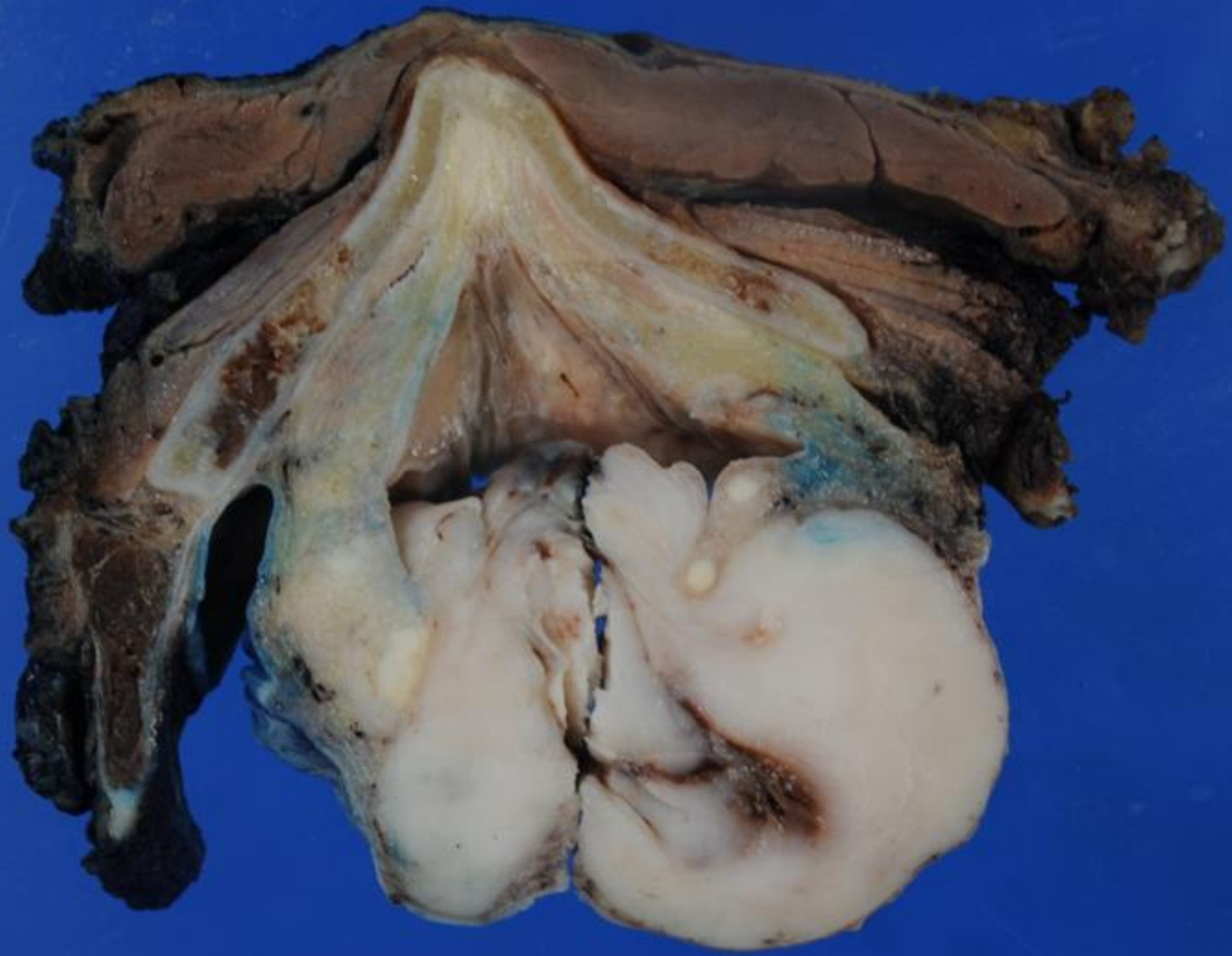
# Case E4

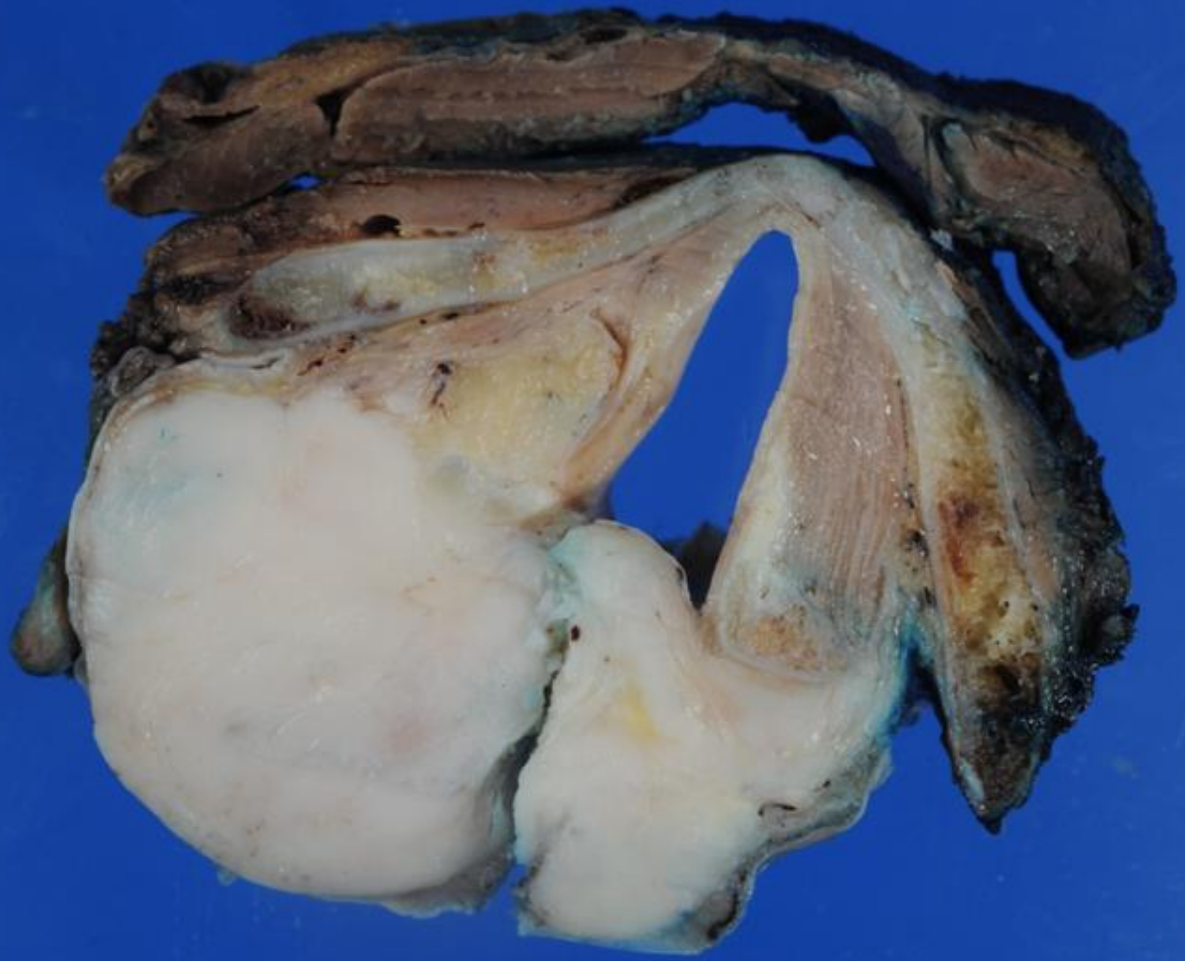
- Male 46 years

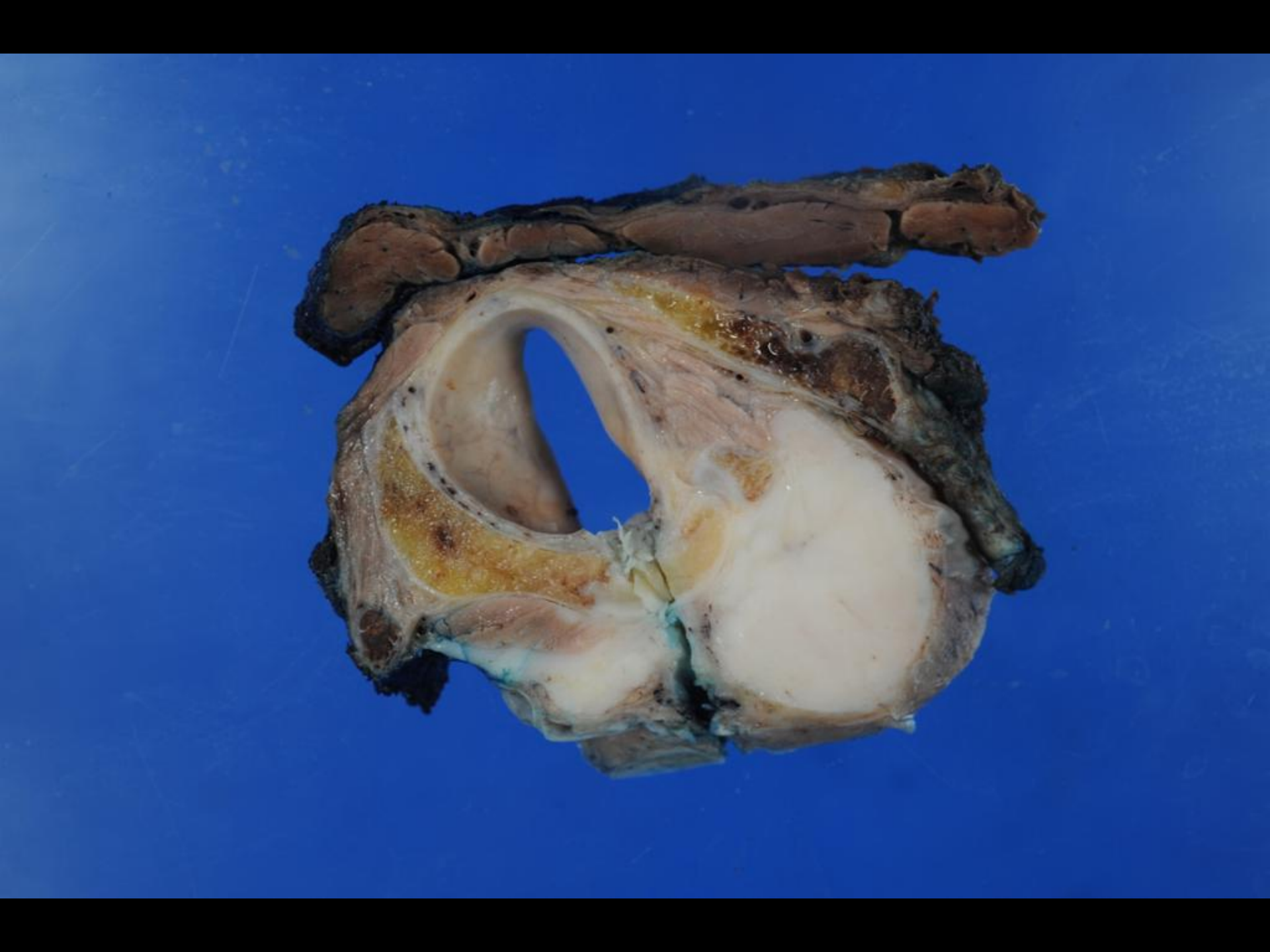
  Total laryngectomy

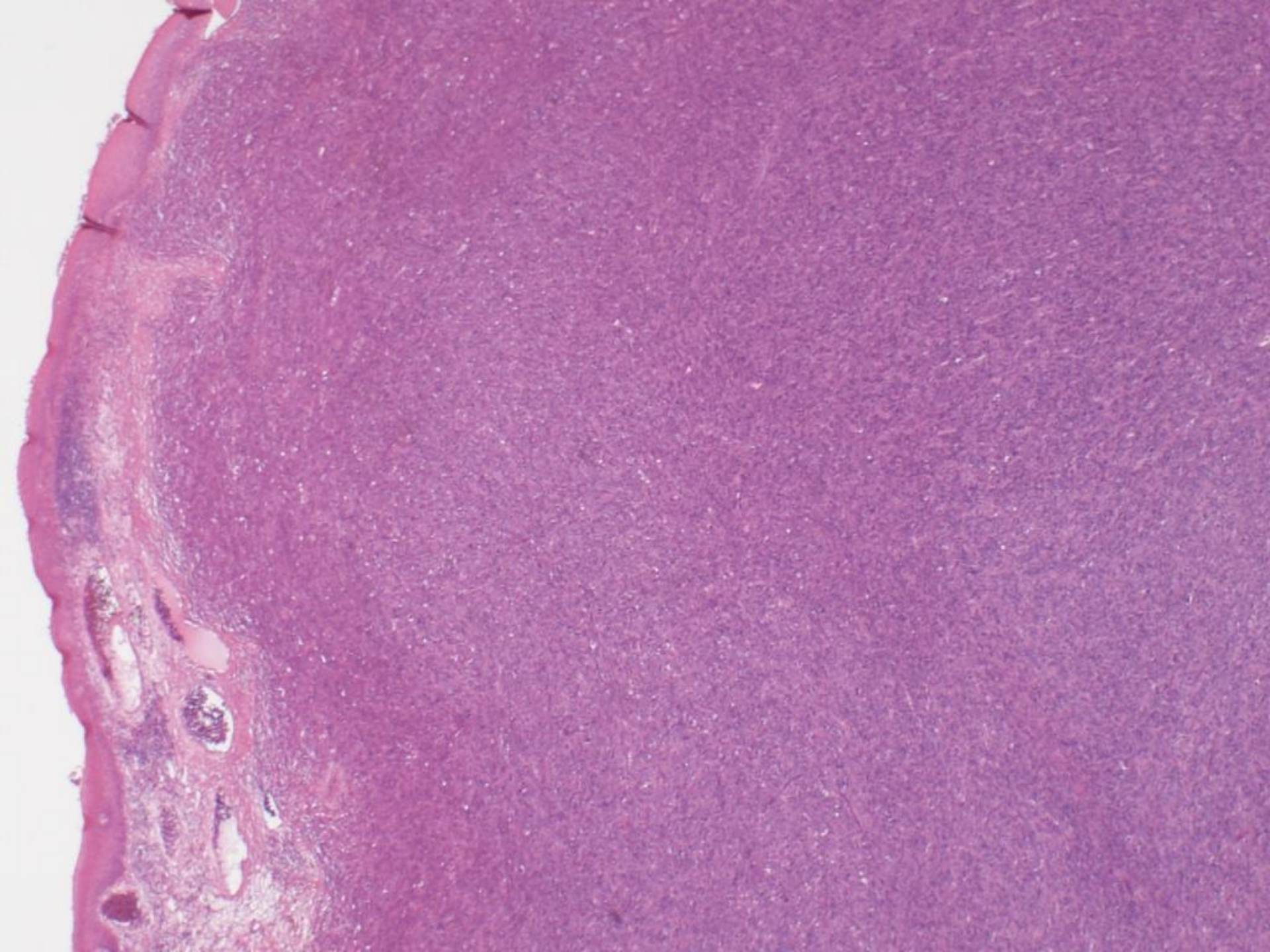
  Large polypoid mass in posterior larynx

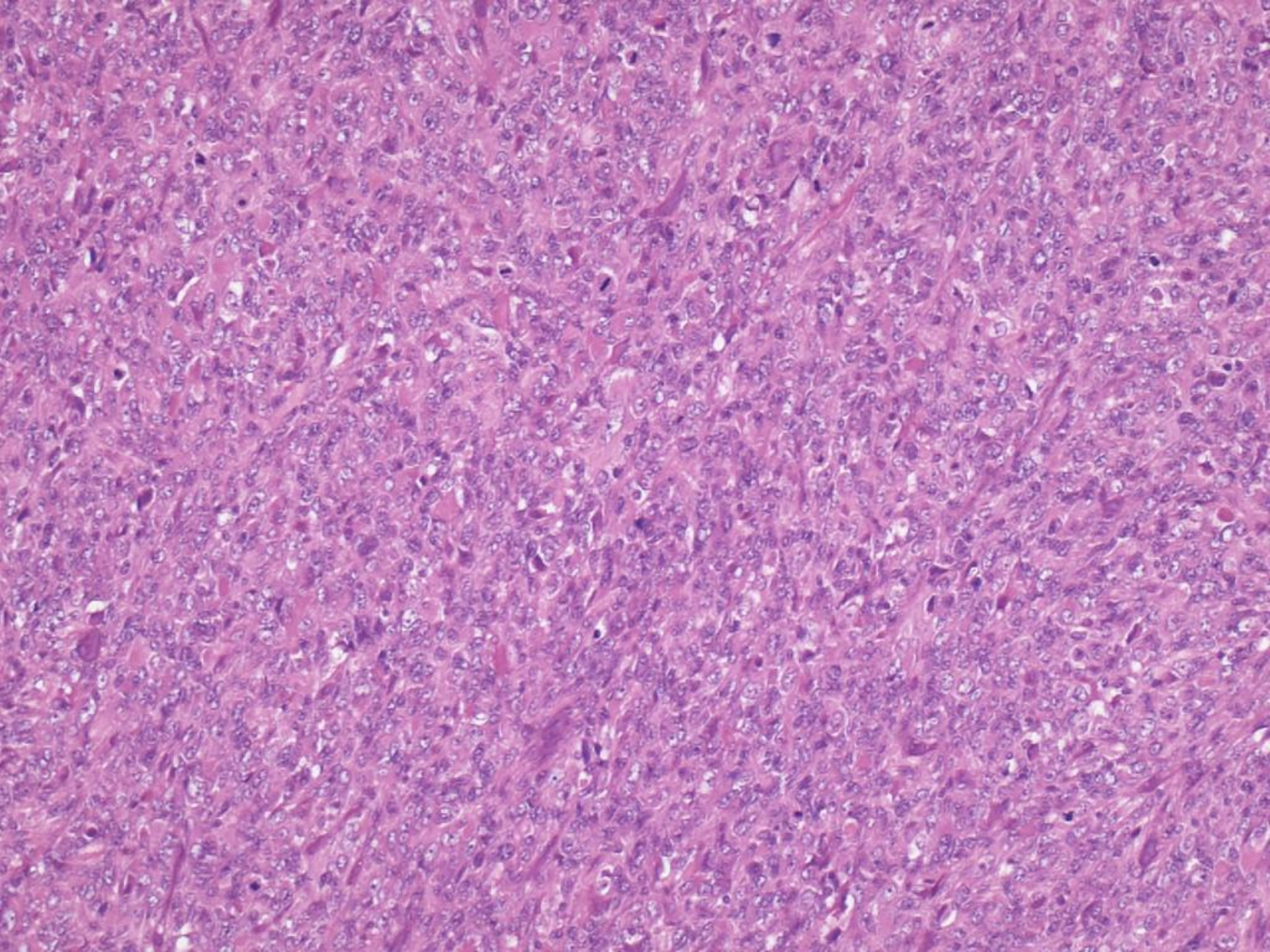
  Polypoid mass, 45 x 28 x 37mm, in the posterior part of the larynx; vocal cords not abnormal; encircled posterior parts of thyroid cartilages, close to arytenoid cartilages and superior aspect of cricoid cartilage

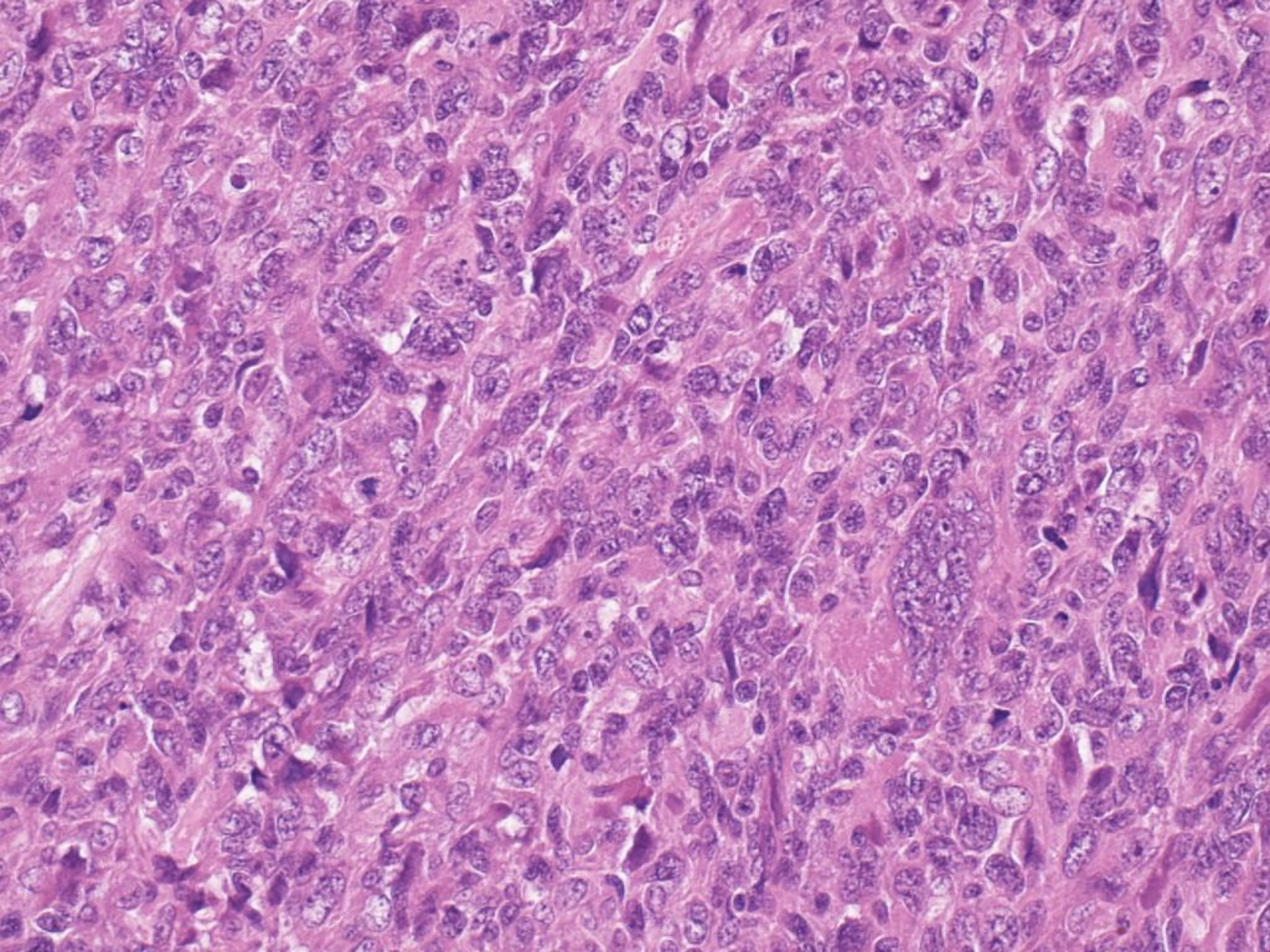


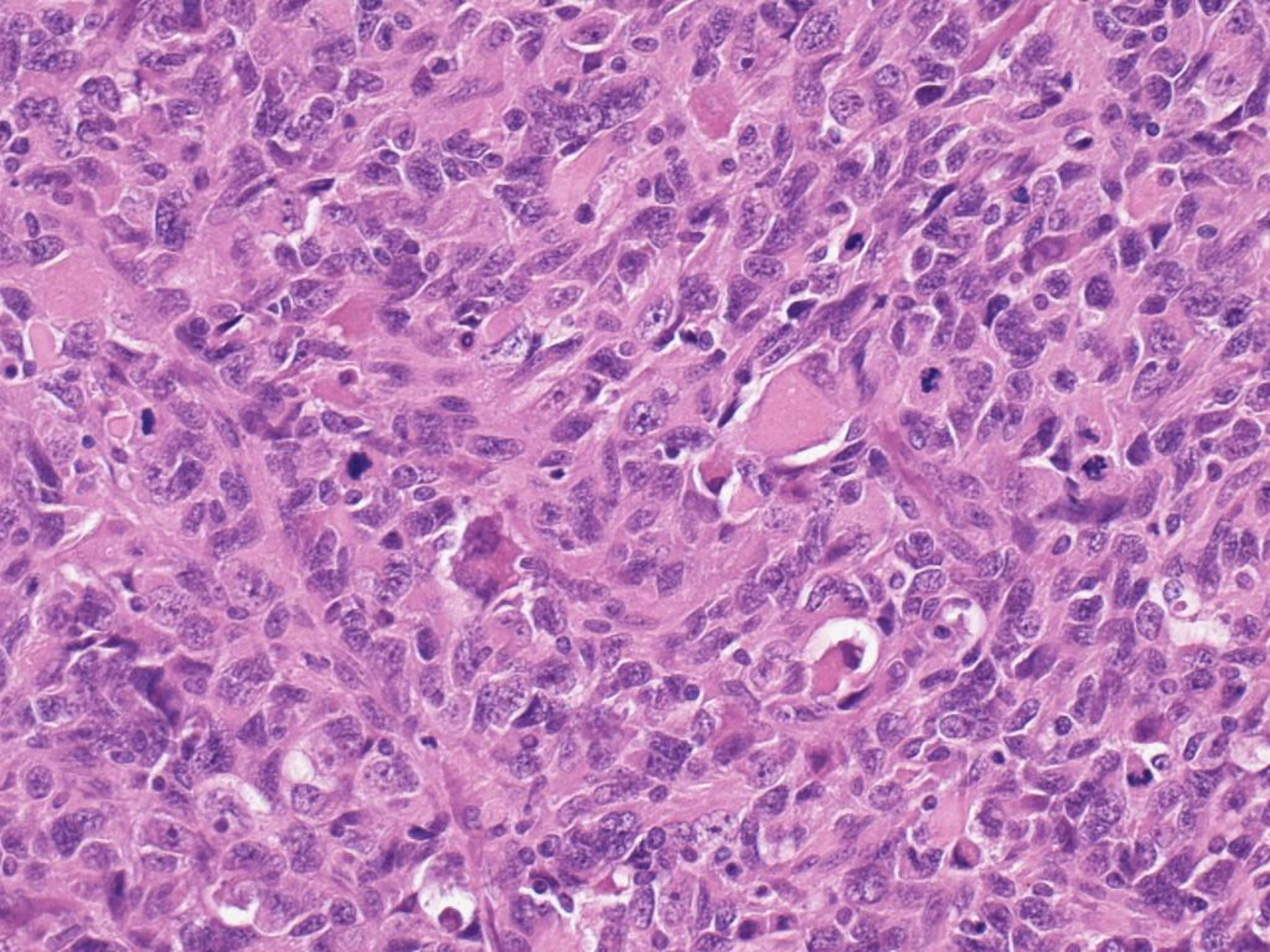


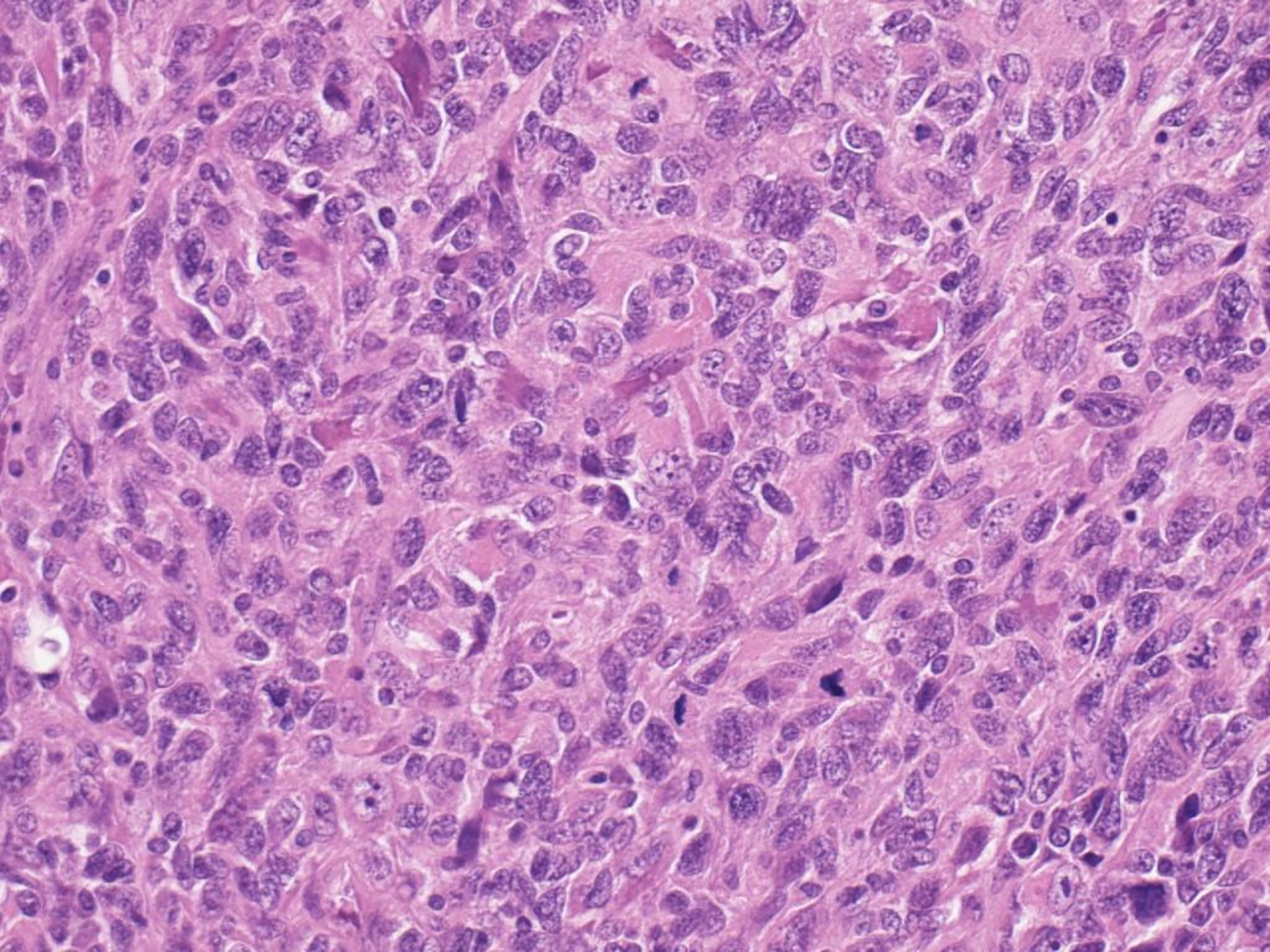


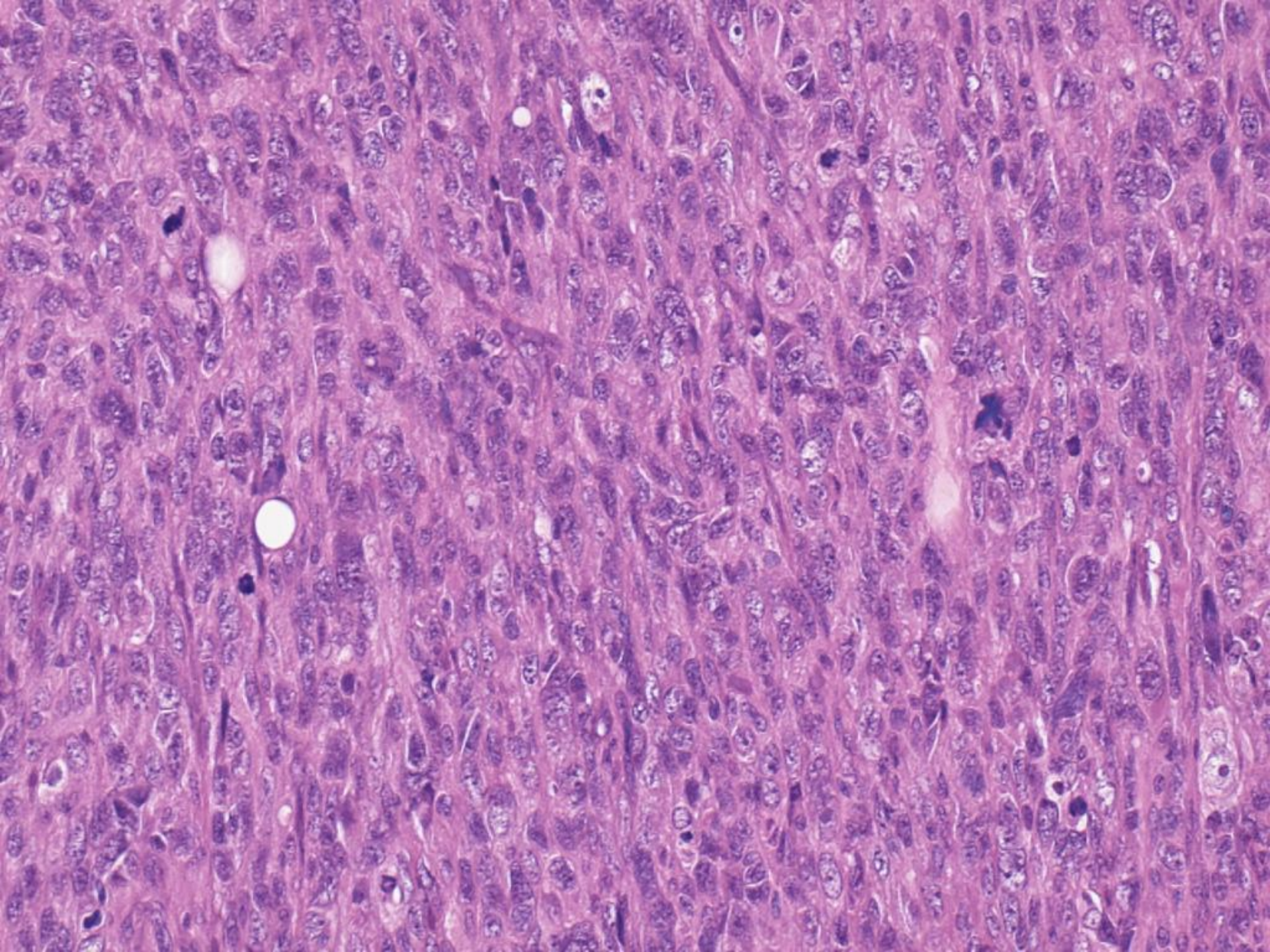


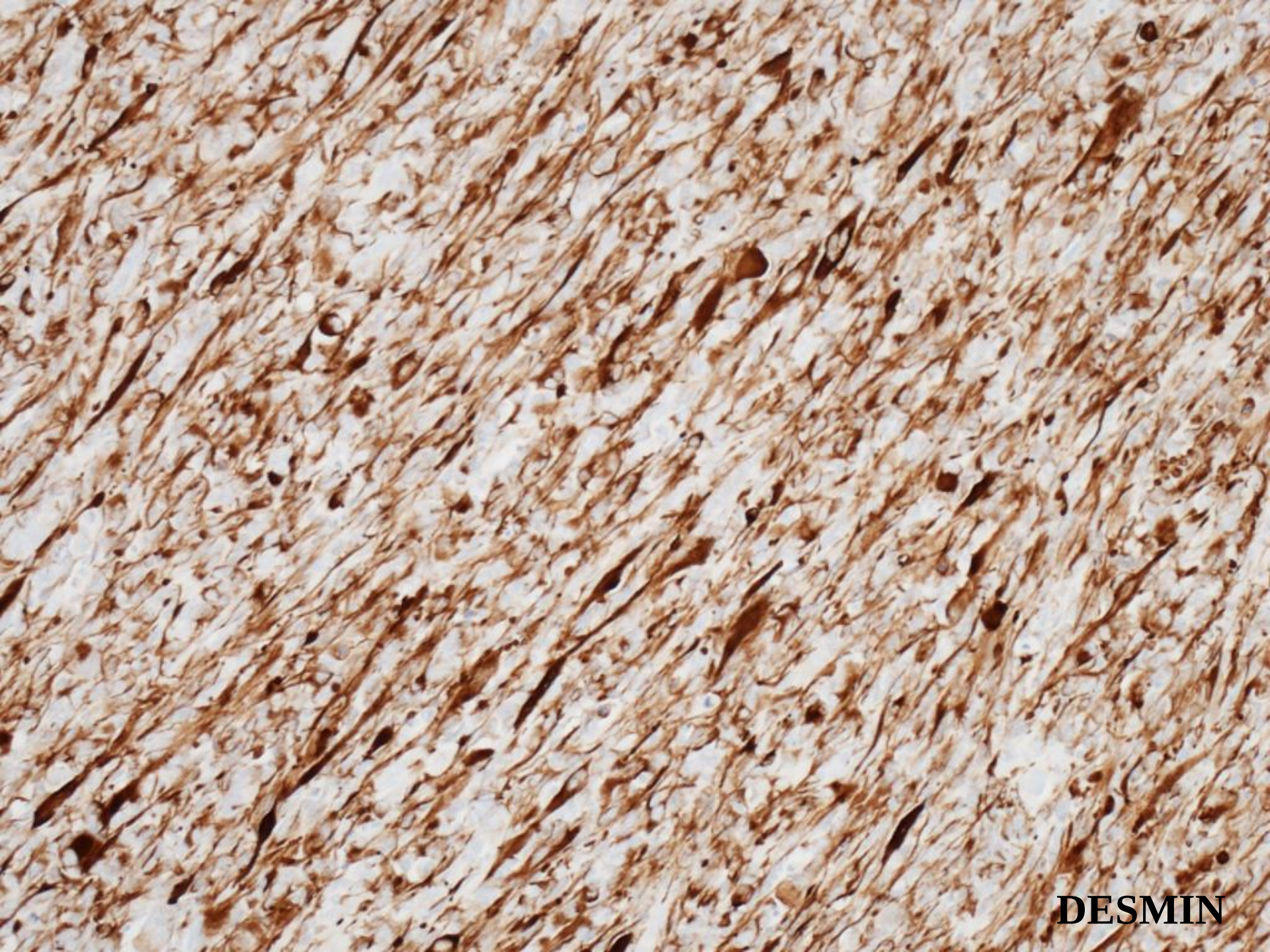


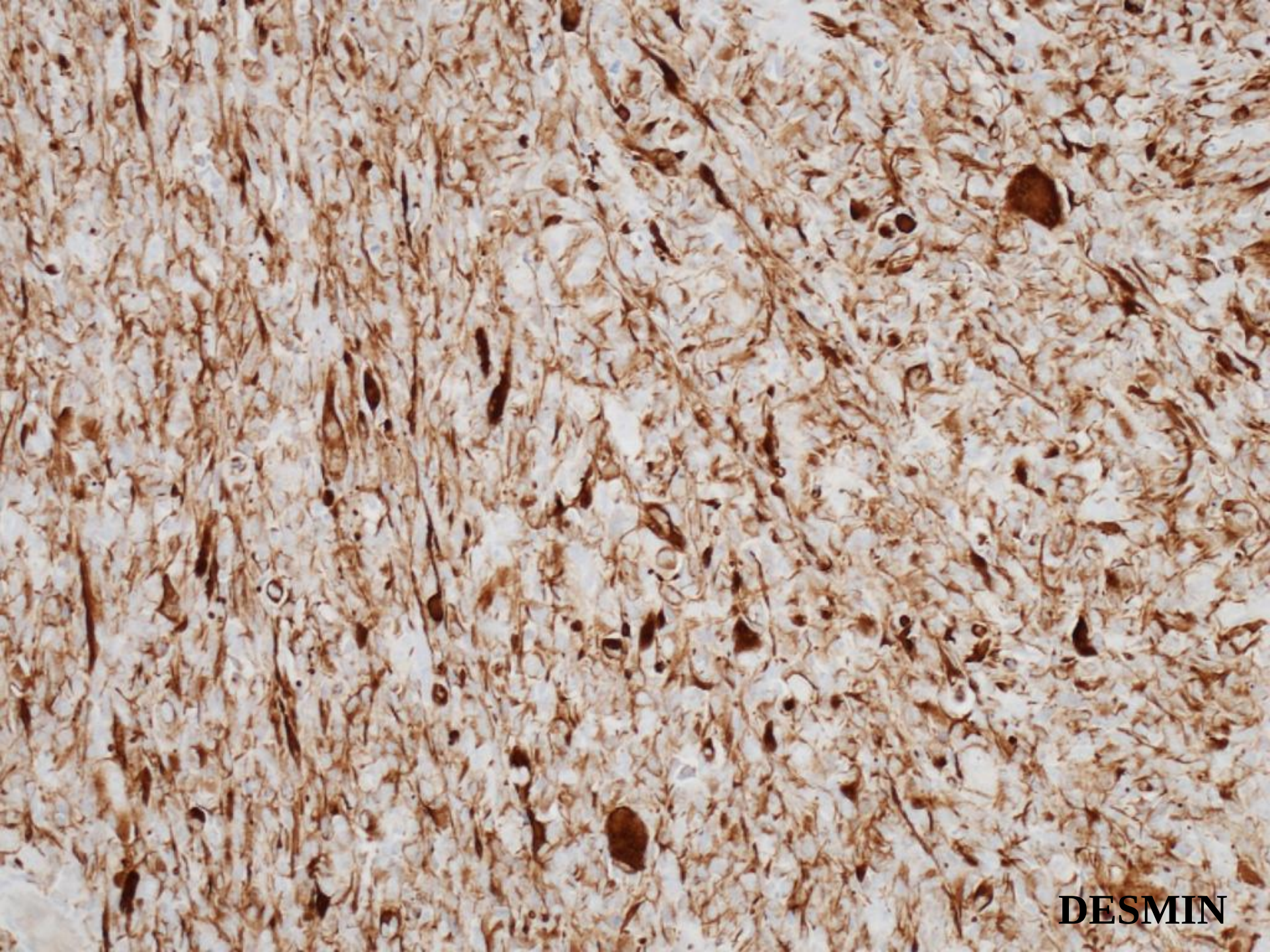


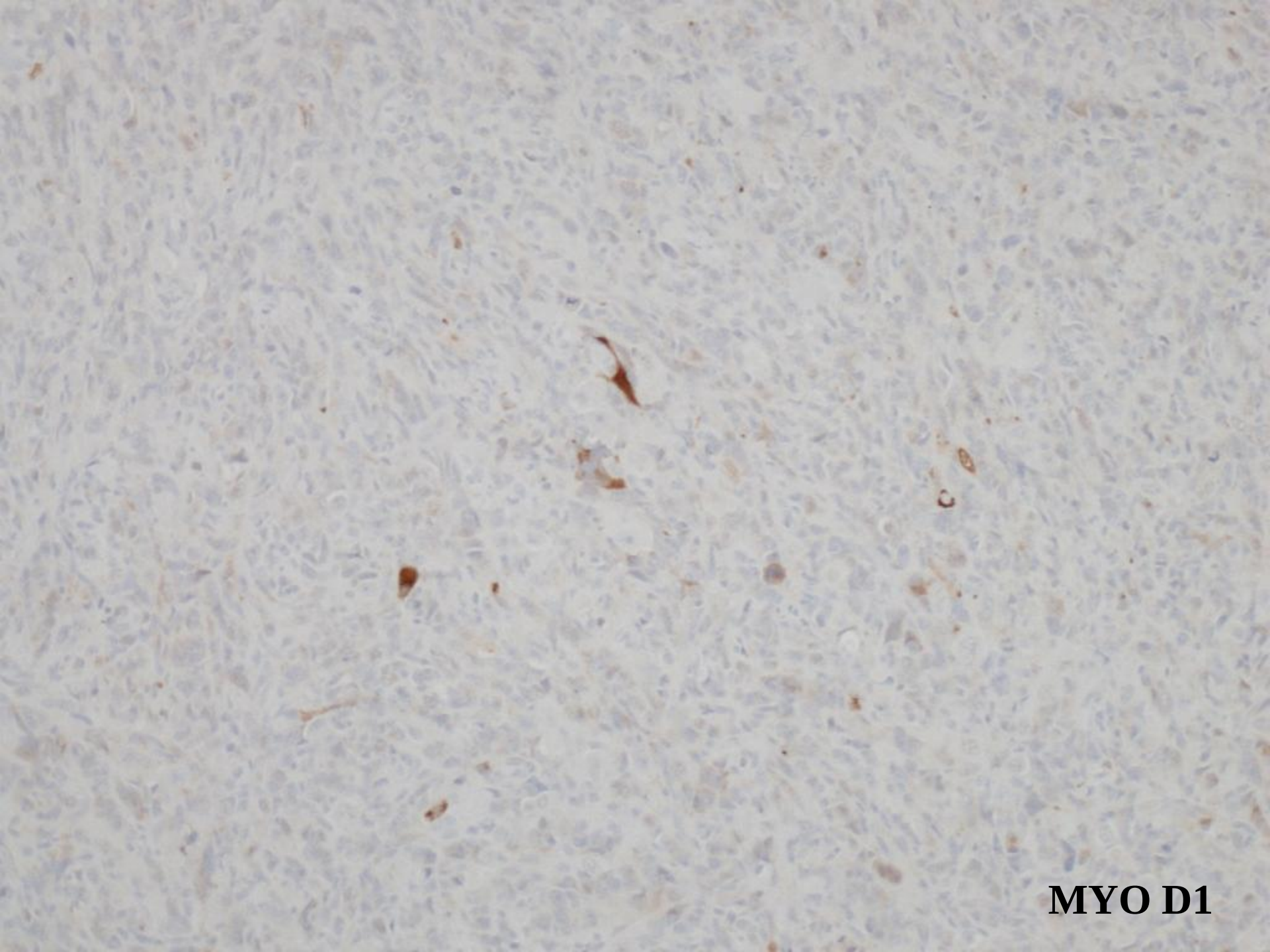


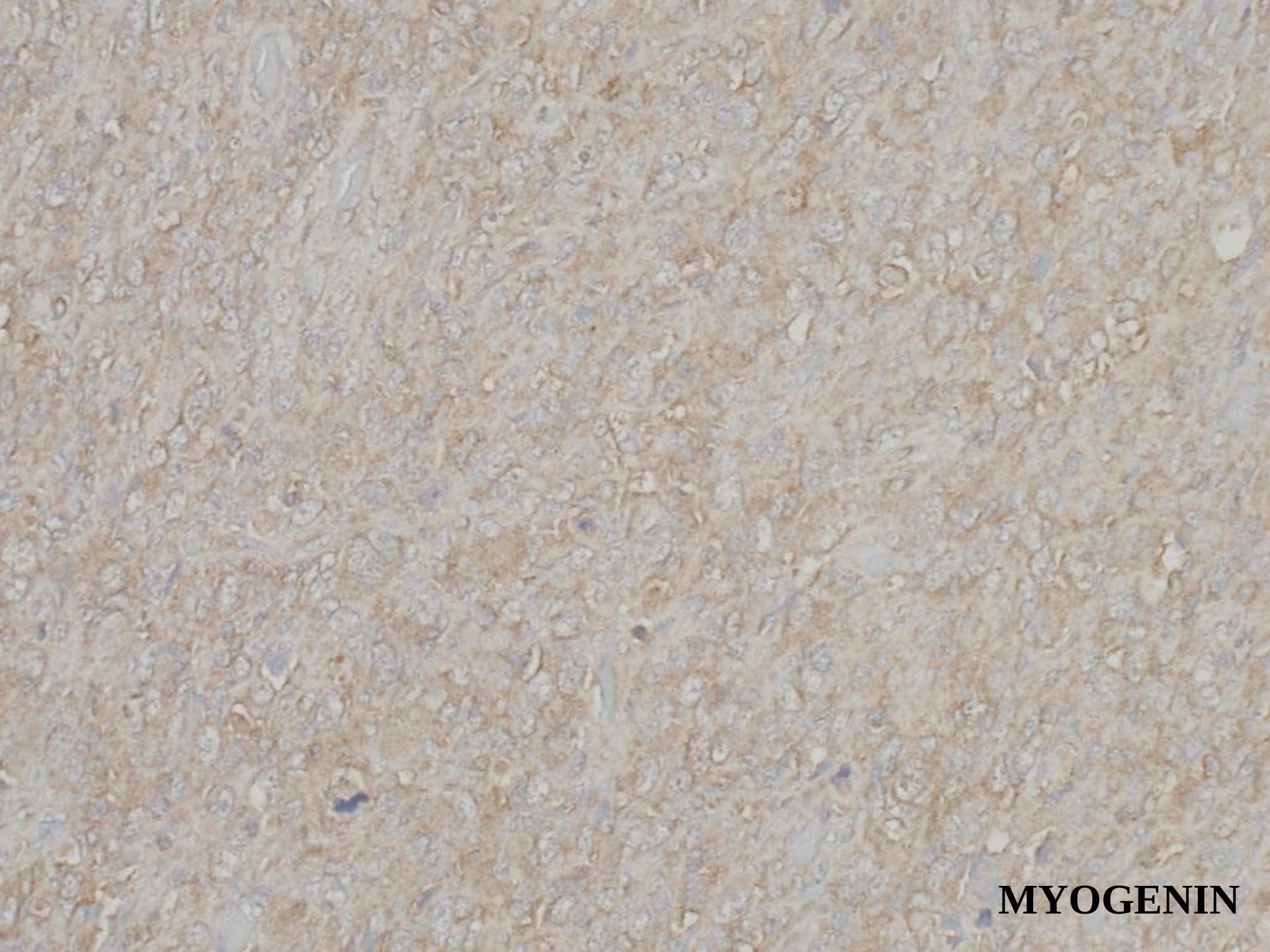





DESMIN


DESMIN


MYO D1


MYOGENIN

# Case E4

- NEGATIVE: smooth muscle actin, CD34, CD31
- Laryngectomy specimen had been decalcified.

- Immunohistochemistry performed on previous arytenoid biopsy containing the same tumour:
- POSITIVE: desmin, myoD1, myogenin, (weakly positive smooth muscle actin)
- NEGATIVE: MNF116, AE1/AE3, p63, S100, CD3, CD20 (mostly negative CD31 and CD34)
- No evidence of a FOXO1 gene rearrangement.

# Case E4

- Diagnosis:

  Pleomorphic rhabdomyosarcoma

# Case E4

- 92 Responses:
    - 12 - rhabdomyosarcoma
    - 1 – pleomorphic rhabdomyosarcoma
    - 12 – included/favoured rhabdomyosarcoma

# Case E4

- 92 Responses:
  - 8 – sarcomatoid/spindle cell carcinoma
  - 3 – leiomyosarcoma
  - 1 – angiosarcoma
  - 1 – melanoma
  - 54 – high grade/poorly differentiated/pleomorphic/anaplastic/spindle cell/giant cell malignancy ?sarcoma ?sarcomatoid carcinoma ?melanoma ?lymphoma ?vasoformative ?synovial sarcoma ?extraskeletal osteosarcoma ?MPNST

  - 28 mentioned immunohistochemistry

# Case E4

- Differential diagnosis
  - Spindle cell/sarcomatoid carcinoma – morphology, squamous dysplasia/differentiation
  - Other sarcomas (also very rare at this site), melanoma, (lymphoma)

# Case E4

- Discussion
  - Rhabdomyosarcoma of the larynx very rare
  - Metastases to larynx also uncommon
  - Not included in most recent WHO classification (discussion limited to specific entities often found in the larynx or that have an important differential diagnostic role)
  - Difficult to stage accurately
  - Poorly documented, all age groups affected, centred around glottic region, ?early presentation -> good prognosis?
  - This patient is alive 20 months post laryngectomy but has pulmonary, mediastinal and left parapharyngeal metastases

# Case E4

- Learning points
  - Very rare tumour but does occur in the larynx
  - Diagnosis starts with morphology and assessment of squamous dysplasia/differentiation but needs appropriate immunohistochemistry