

Východoslovenský
BIOPTICKÝ SEMINÁR



***Minisymposium: Pathology of
Melanocytic Lesions-***

Non-melanocytic Mimics of Melanoma

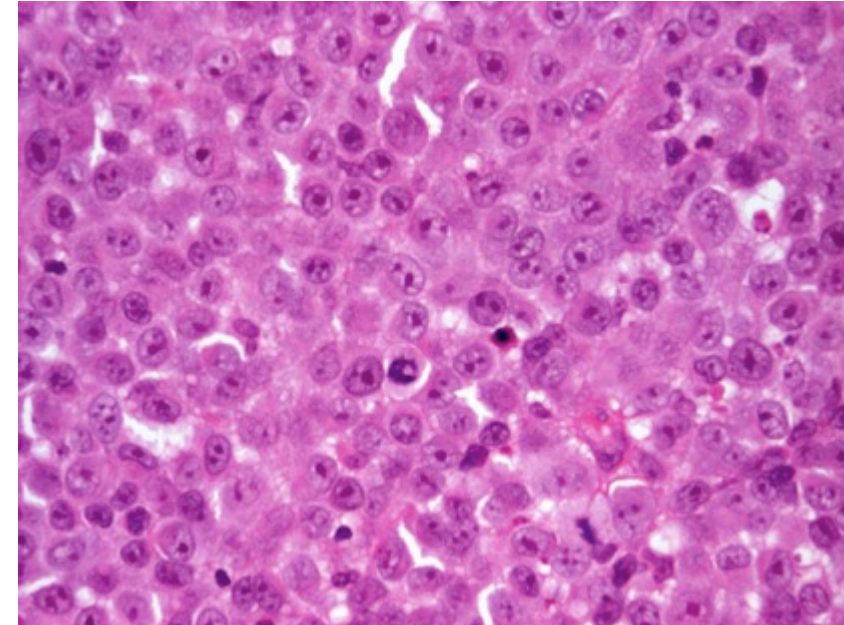
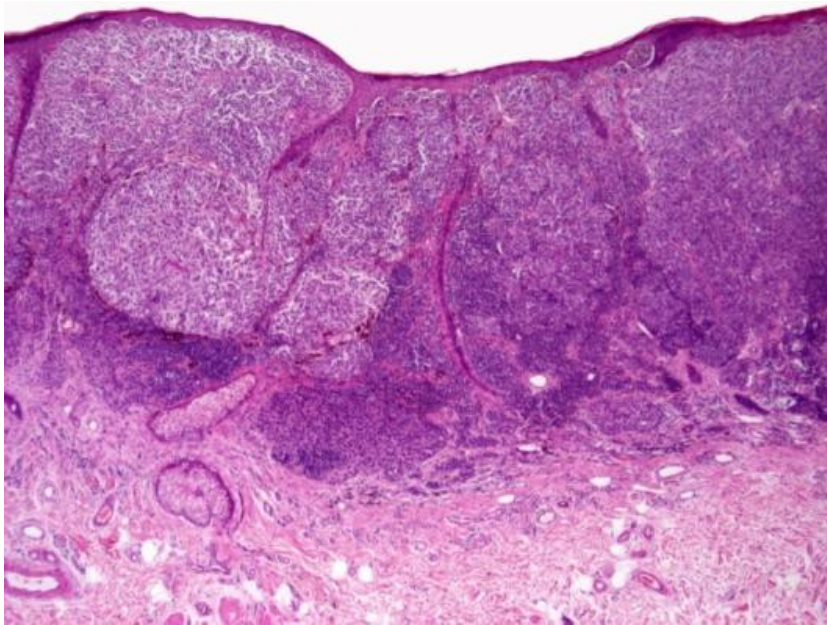
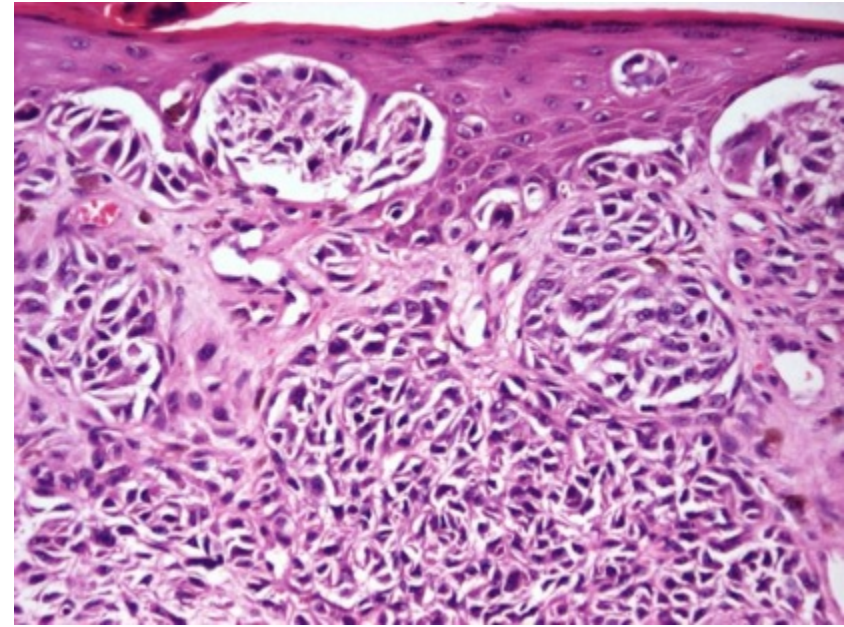
***Thomas Brenn, MD, PhD
Western General Hospital
University of Edinburgh
Scotland***

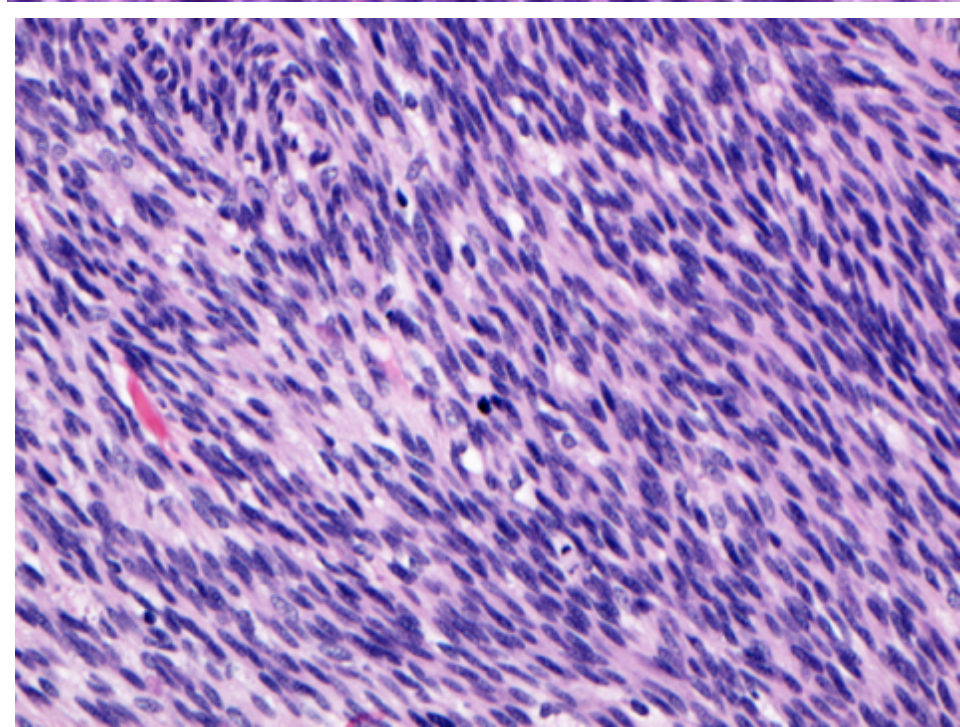
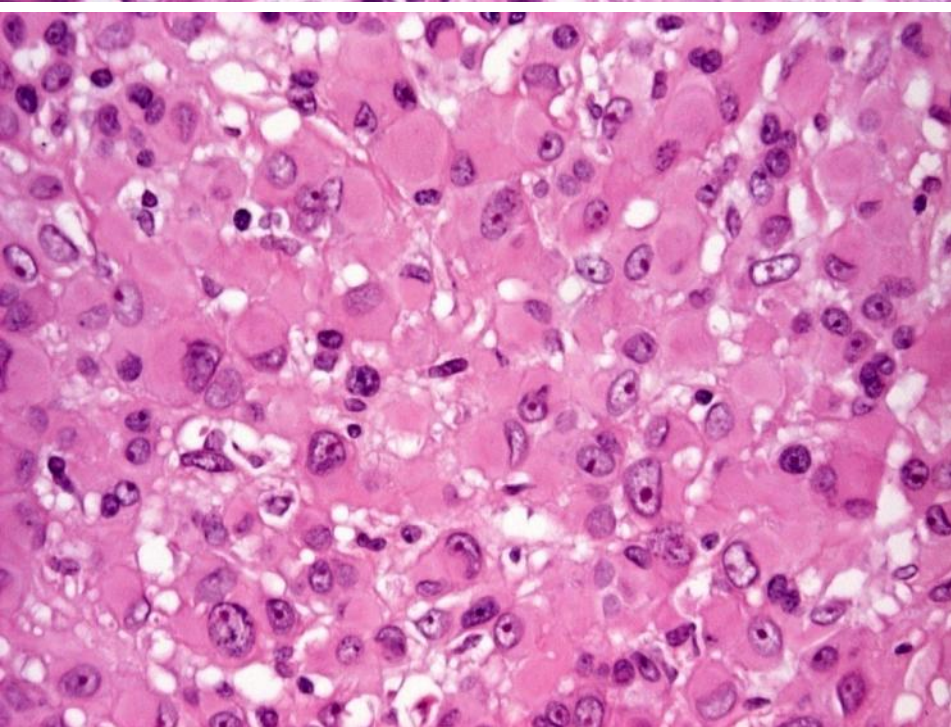
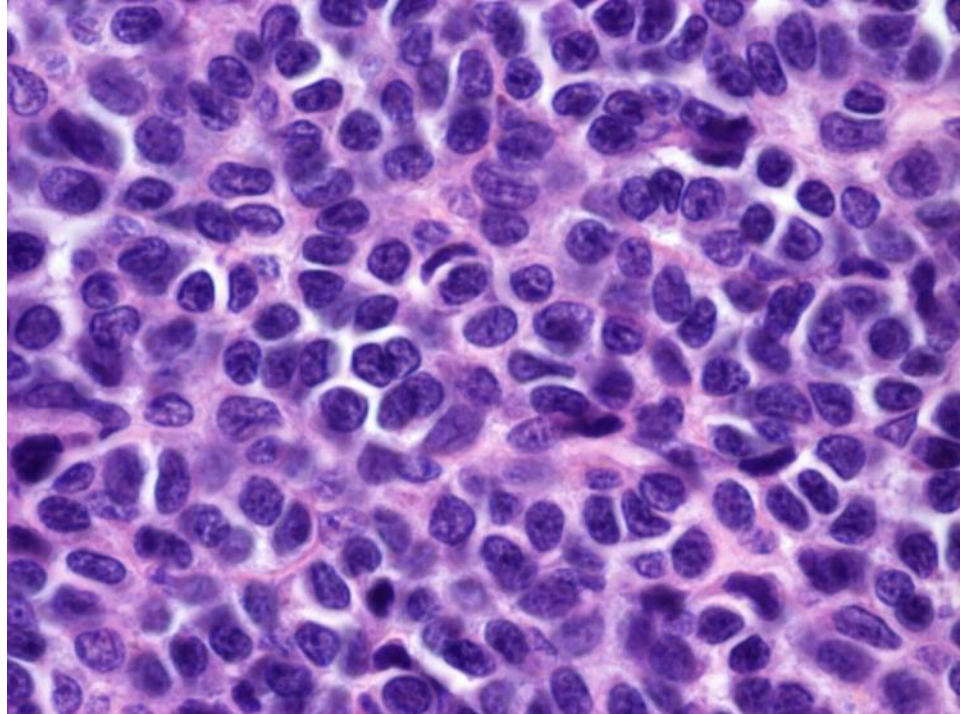
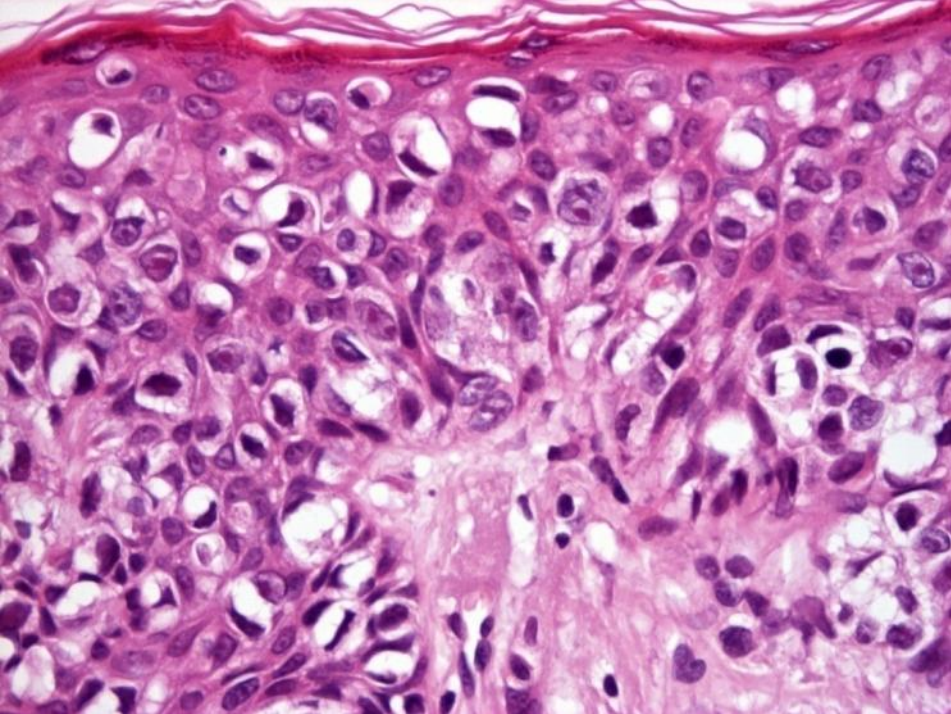


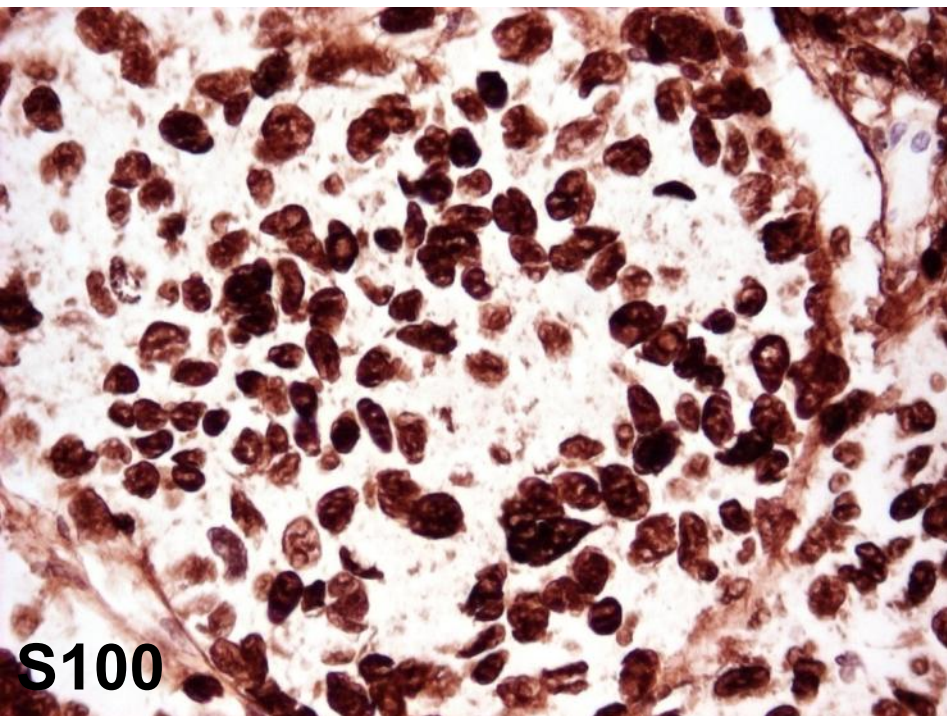
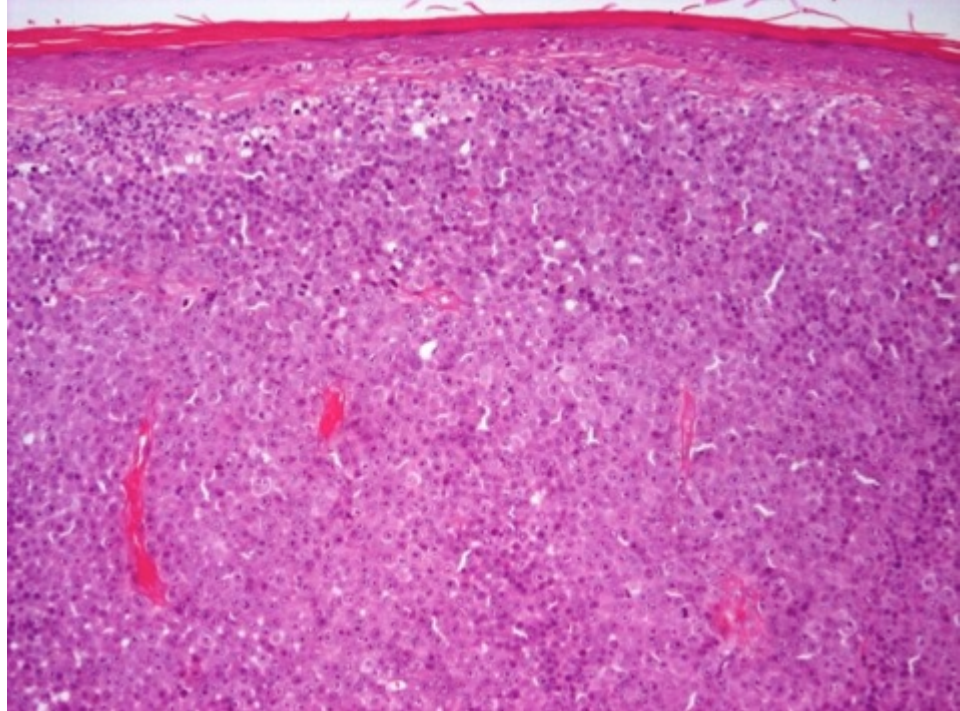
Diagnosis of Melanoma



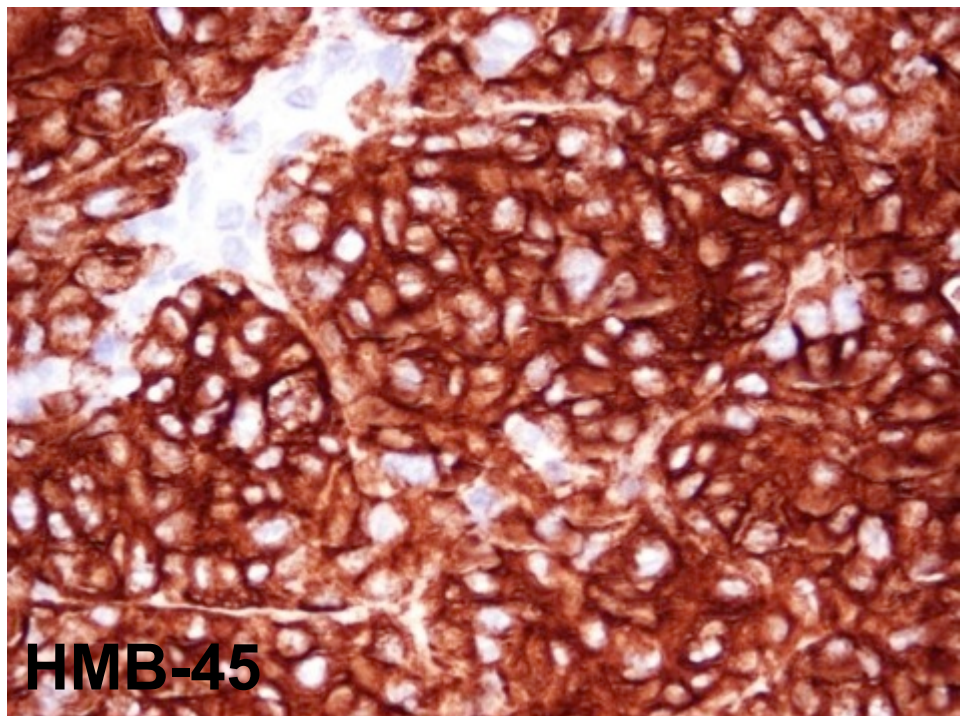
Rigel et al: Cancer of the Skin © 2005 Elsevier Inc.







S100



HMB-45

Non-Melanocytic Mimics of Melanoma

-Introduction-

- **Broad spectrum of benign as well as malignant tumours**
 - **Epithelial**
 - **Neuroendocrine**
 - **Mesenchymal**
 - **Haematolymphoid**

Non-Melanocytic Mimics of Melanoma

-Introduction-

- **Distinction is important because of different**
 - **Outcome and behaviour**
 - **Treatment modality**
- **Separation possible in most cases using**
 - **Clinical presentation**
 - **Histological features**
 - **Immunohistochemistry**

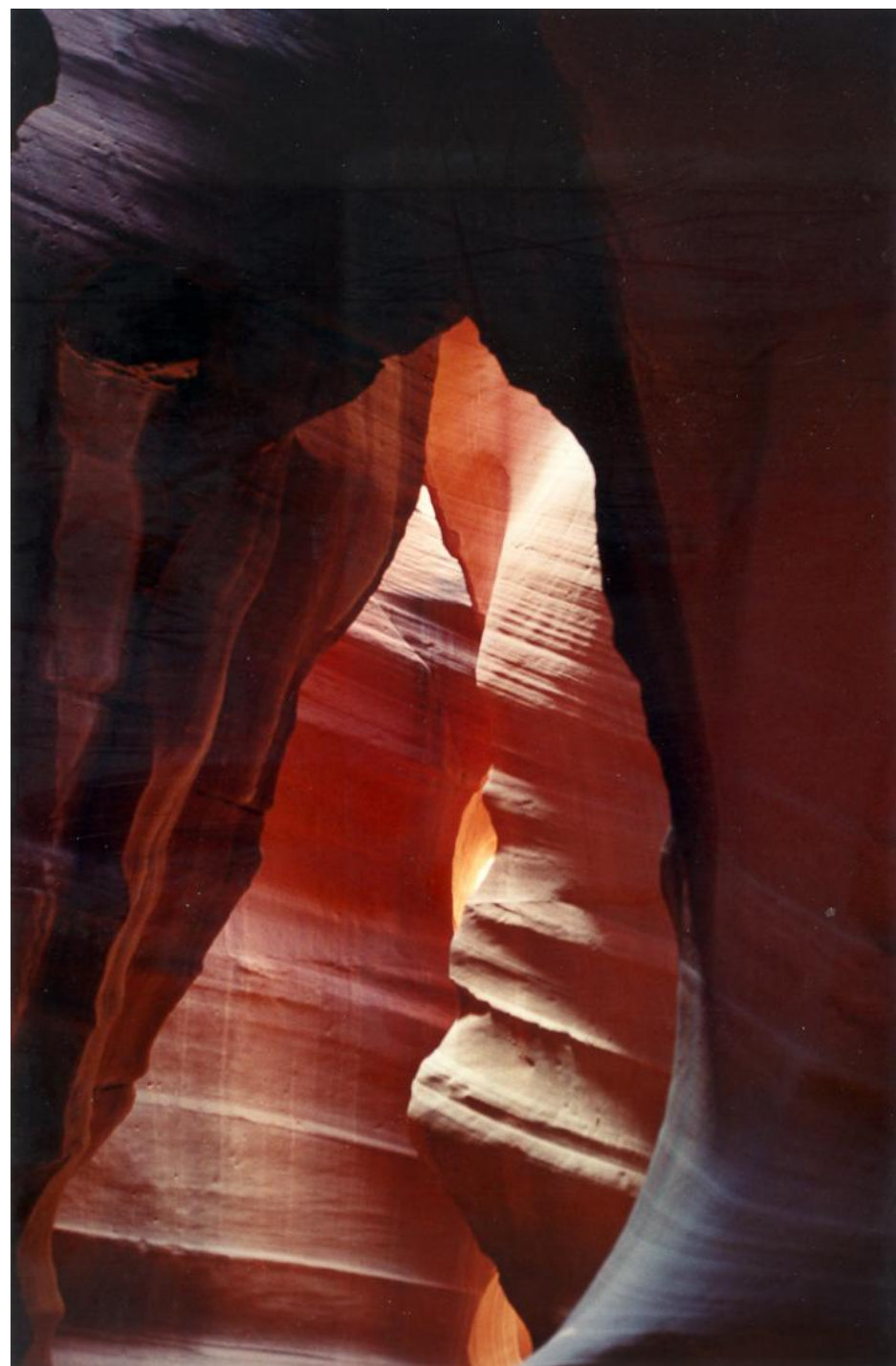
In situ component

Small cell

Epithelioid cell

**Spindle cell/
desmoplastic**

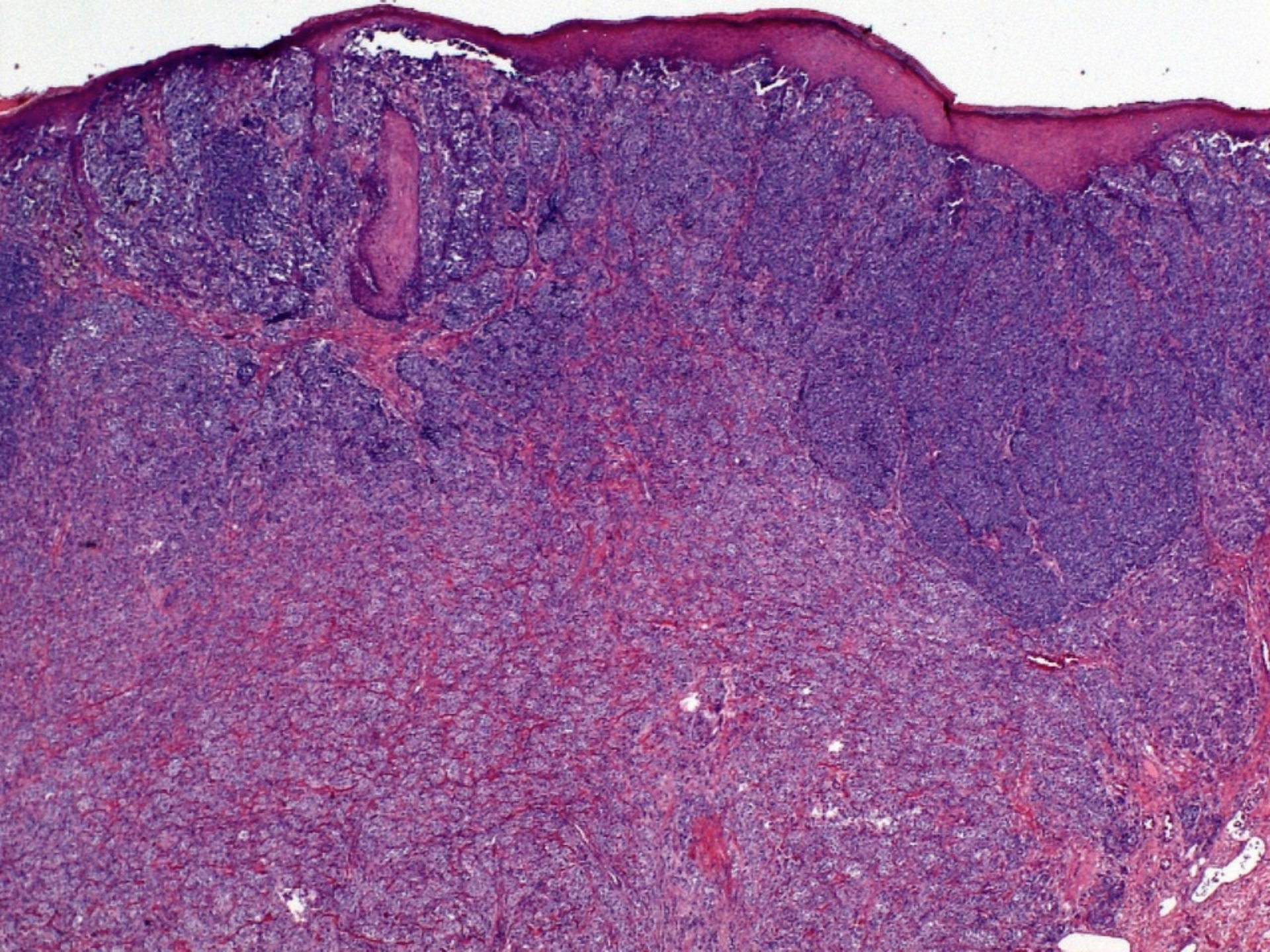
S100-positivity

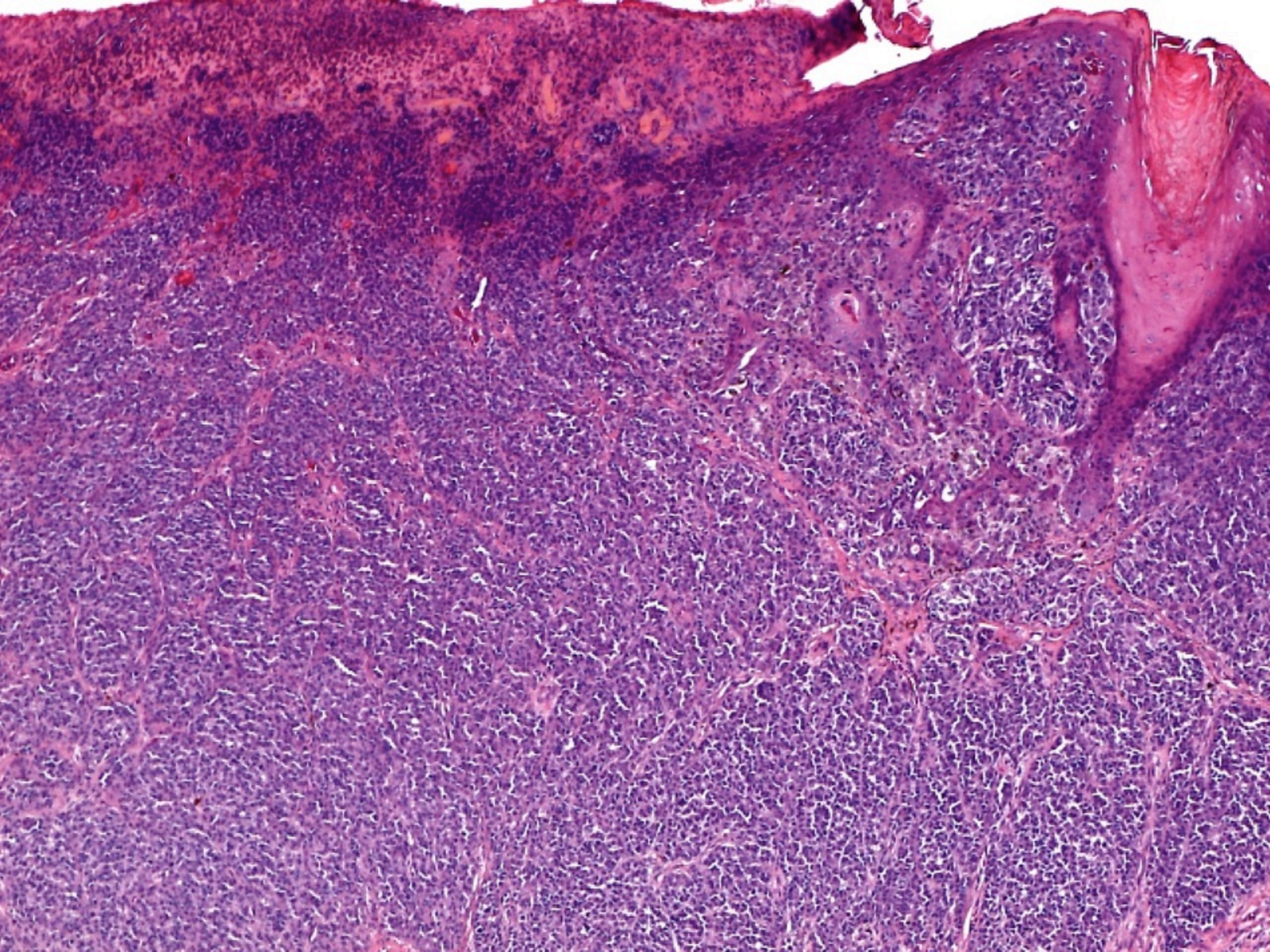


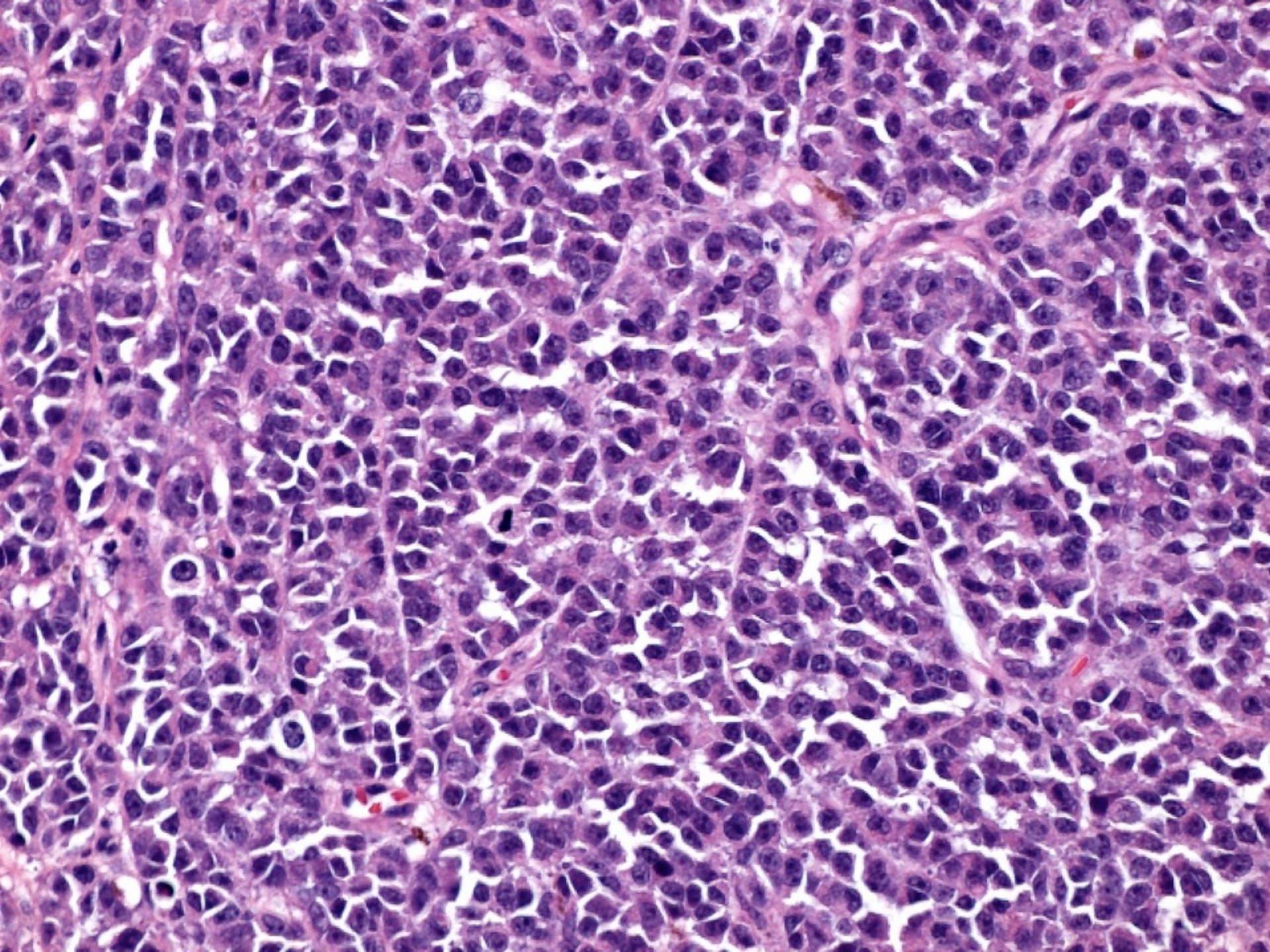
Case 1

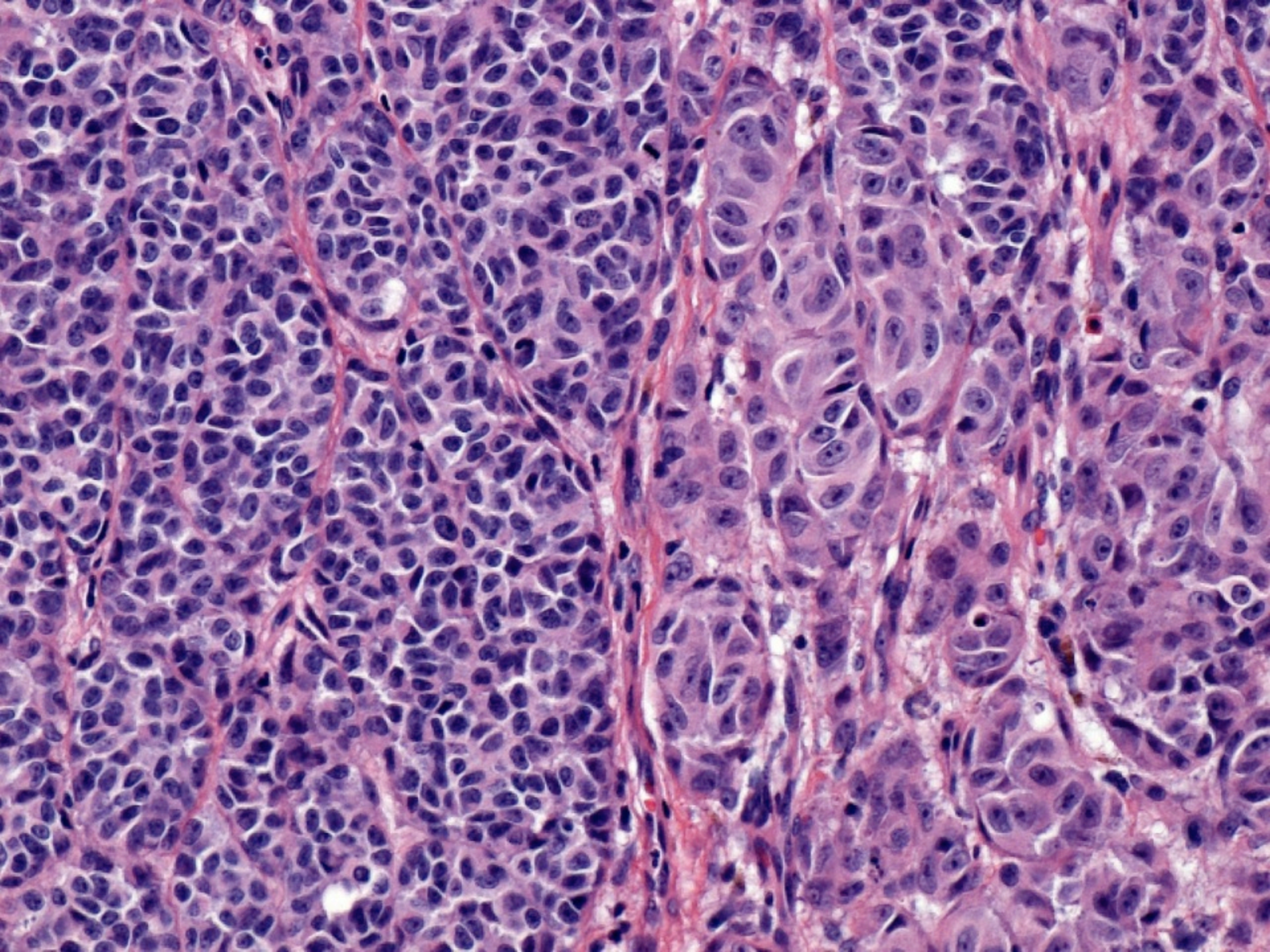
Case History

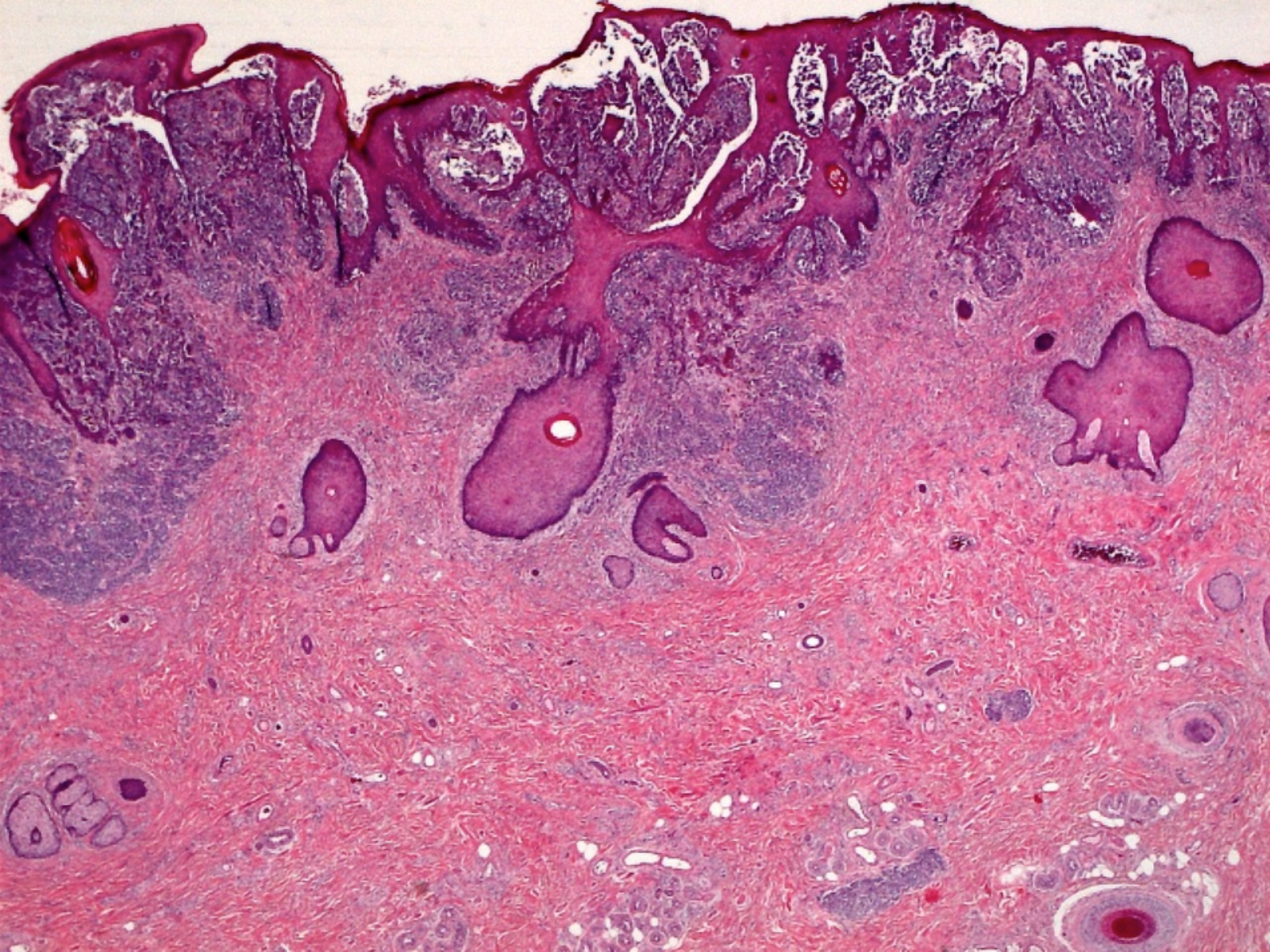
- 80 year old female
- PMH of CLL
- Pigmented tumour on vulva with surrounding erythema and perineal thickening

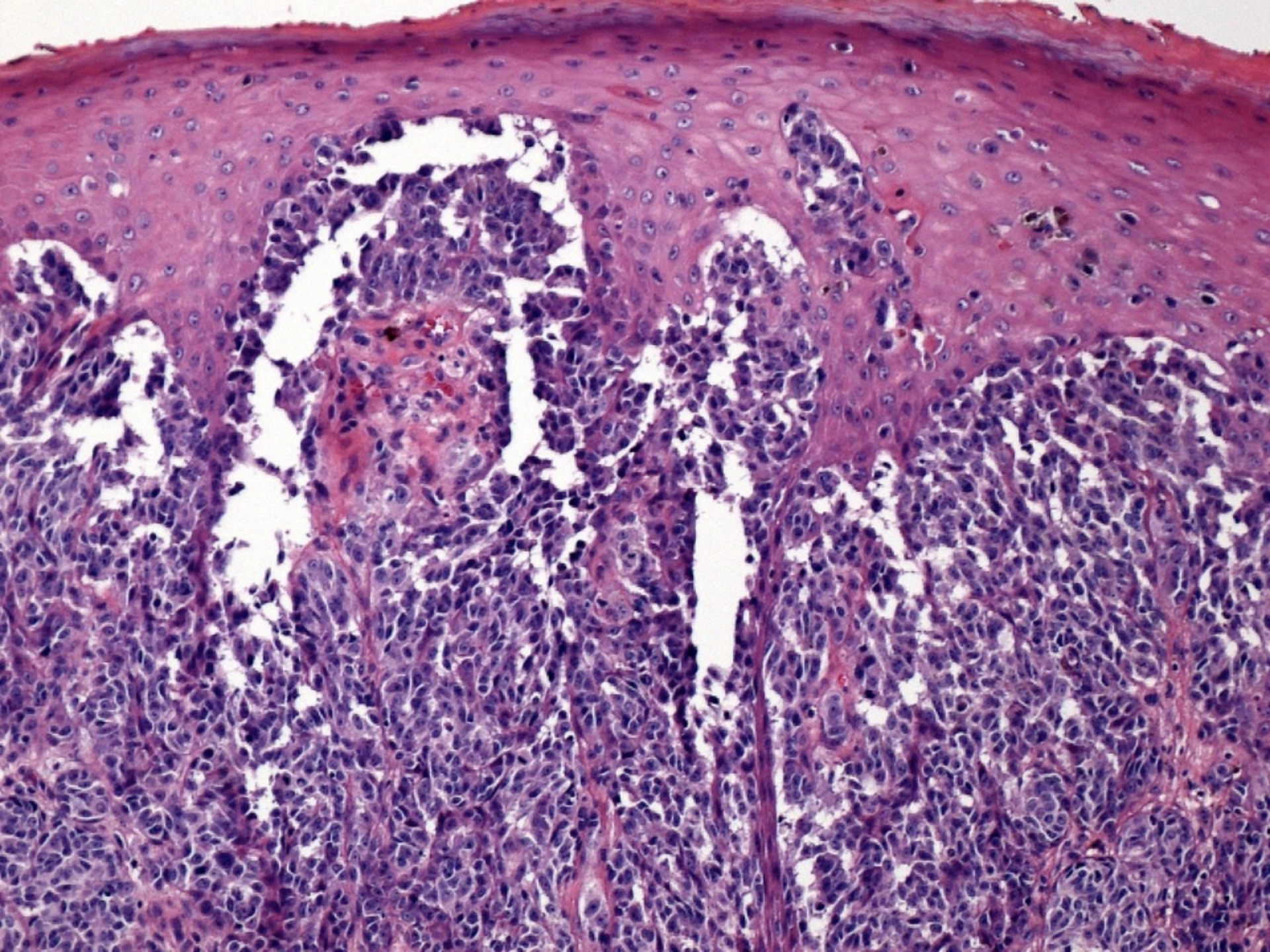


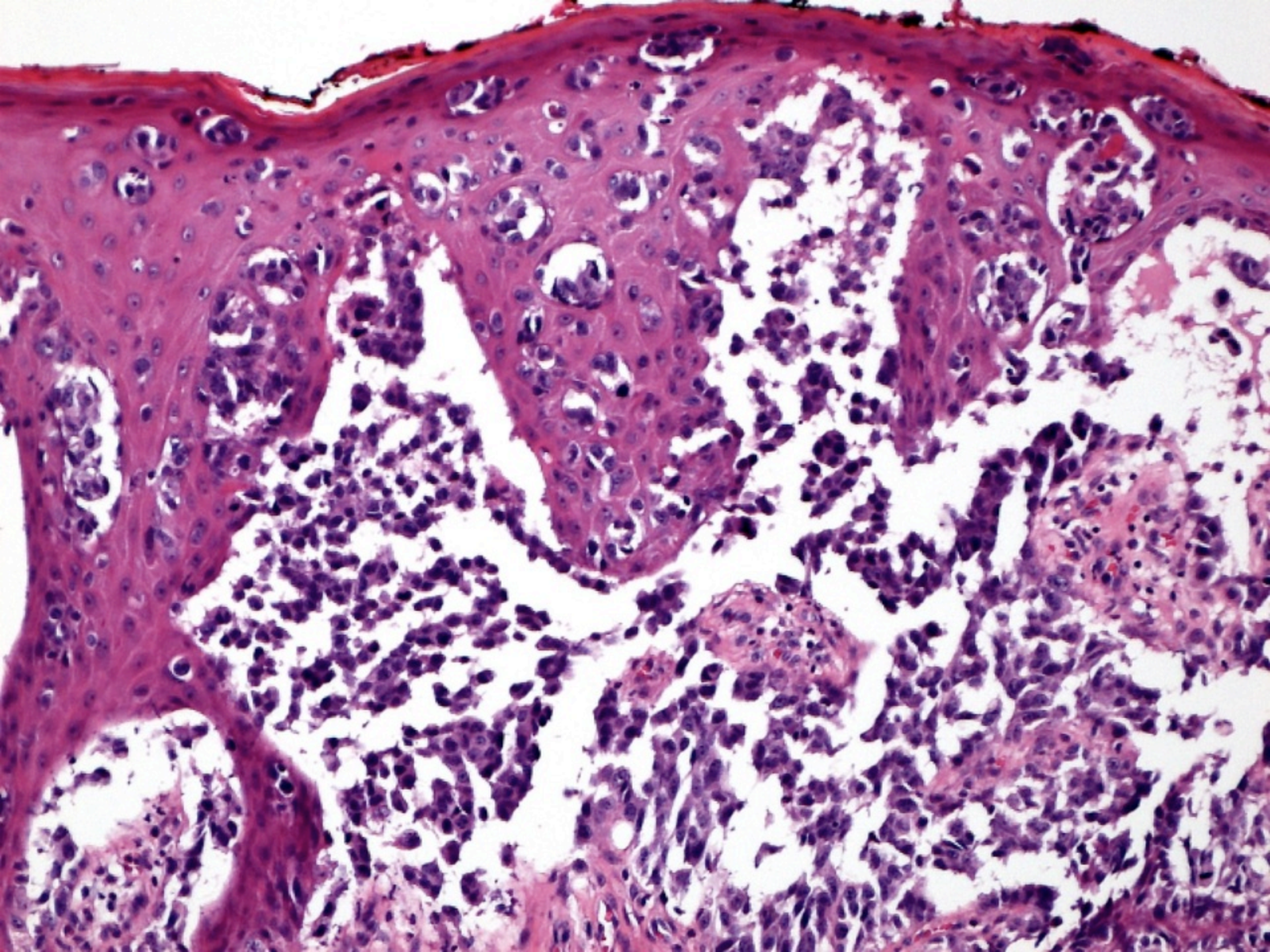


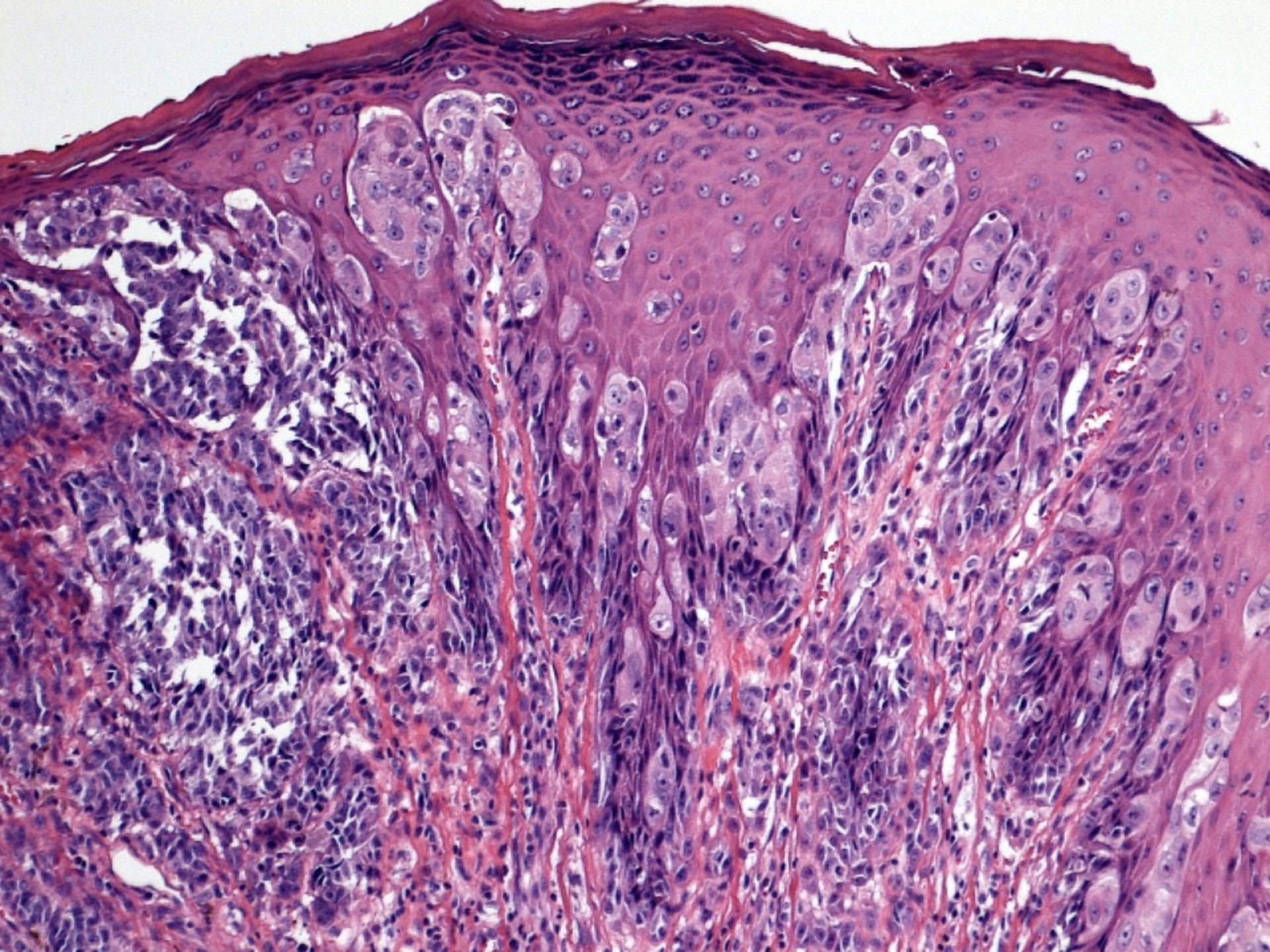


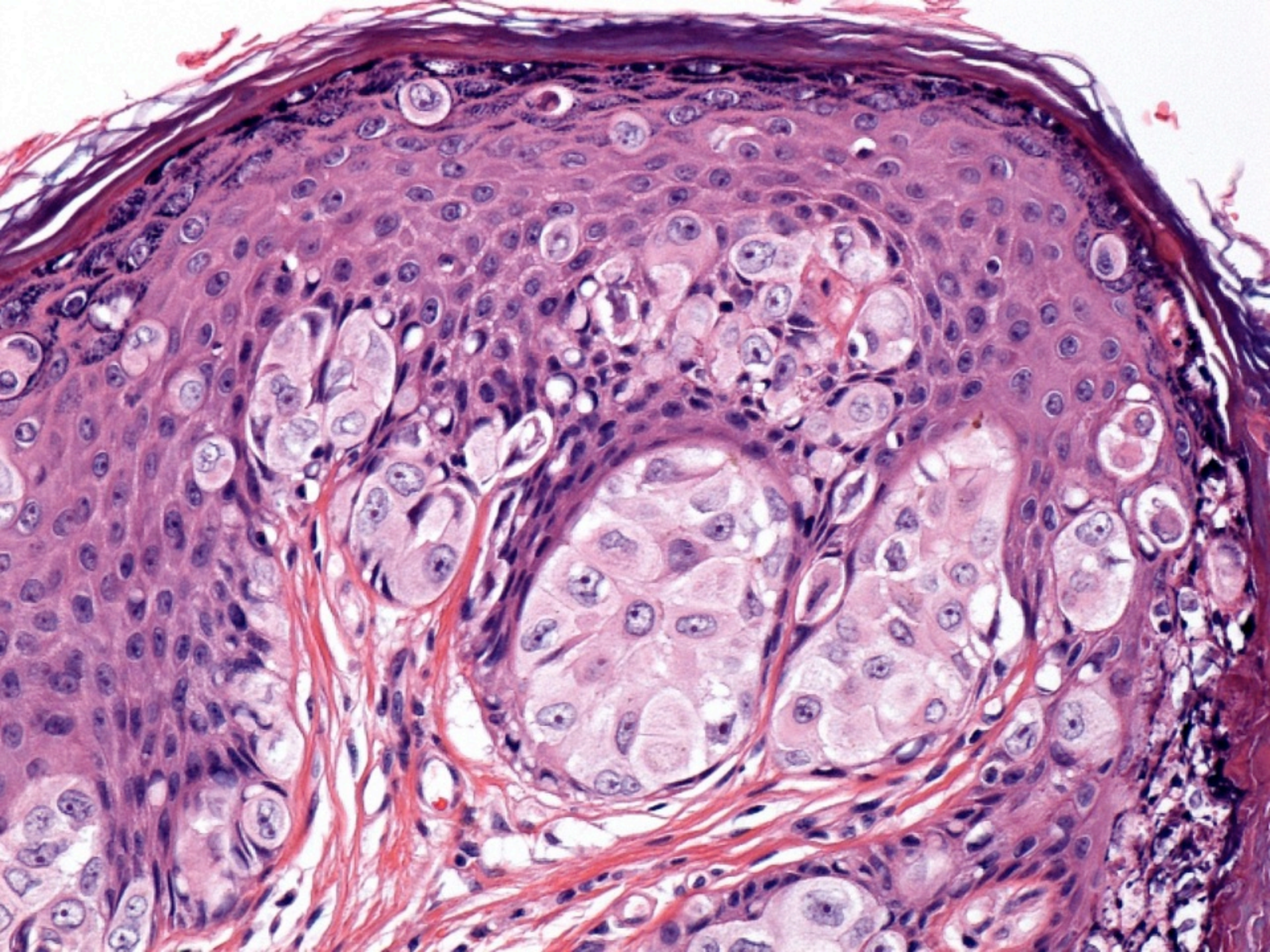




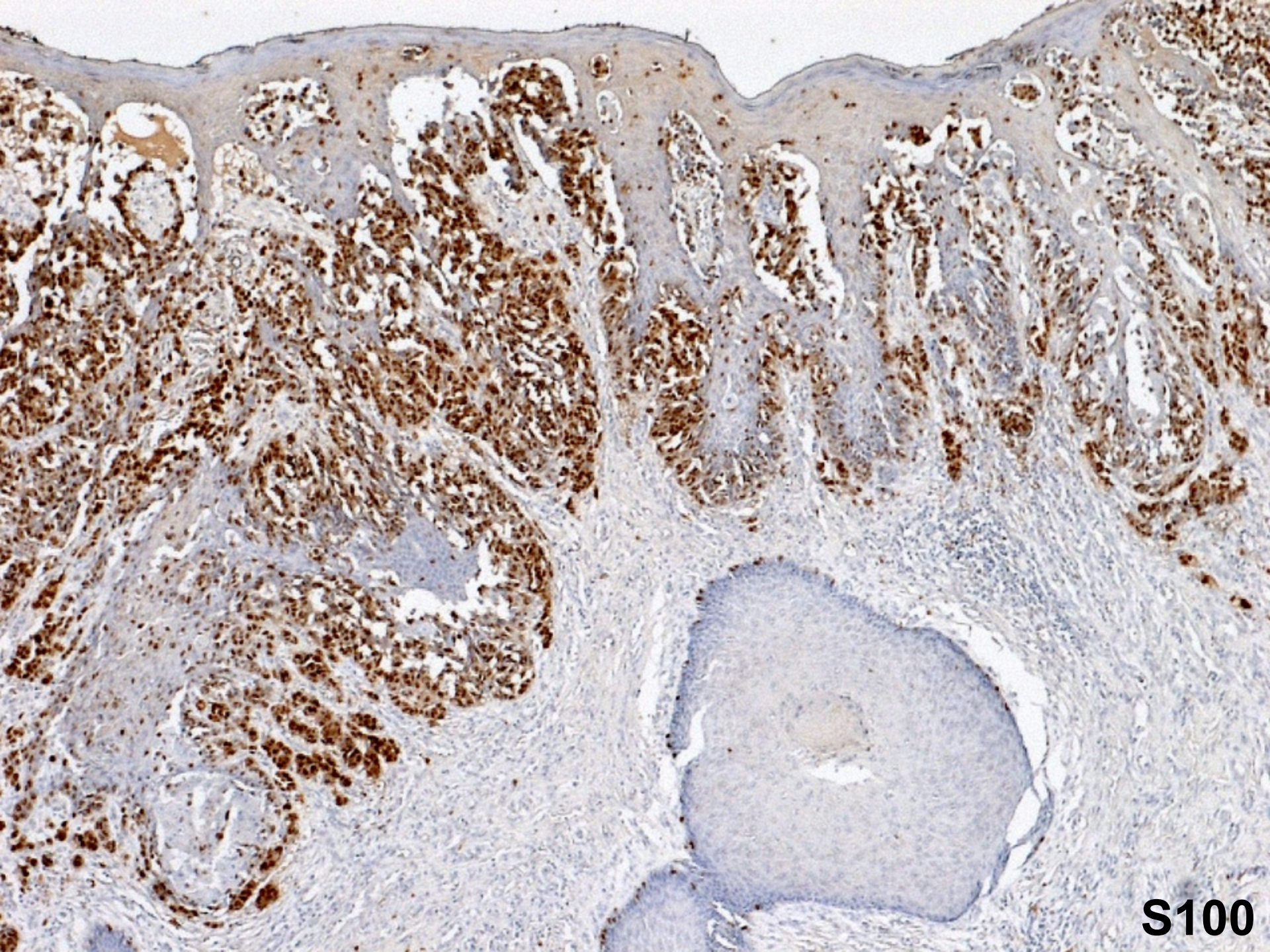




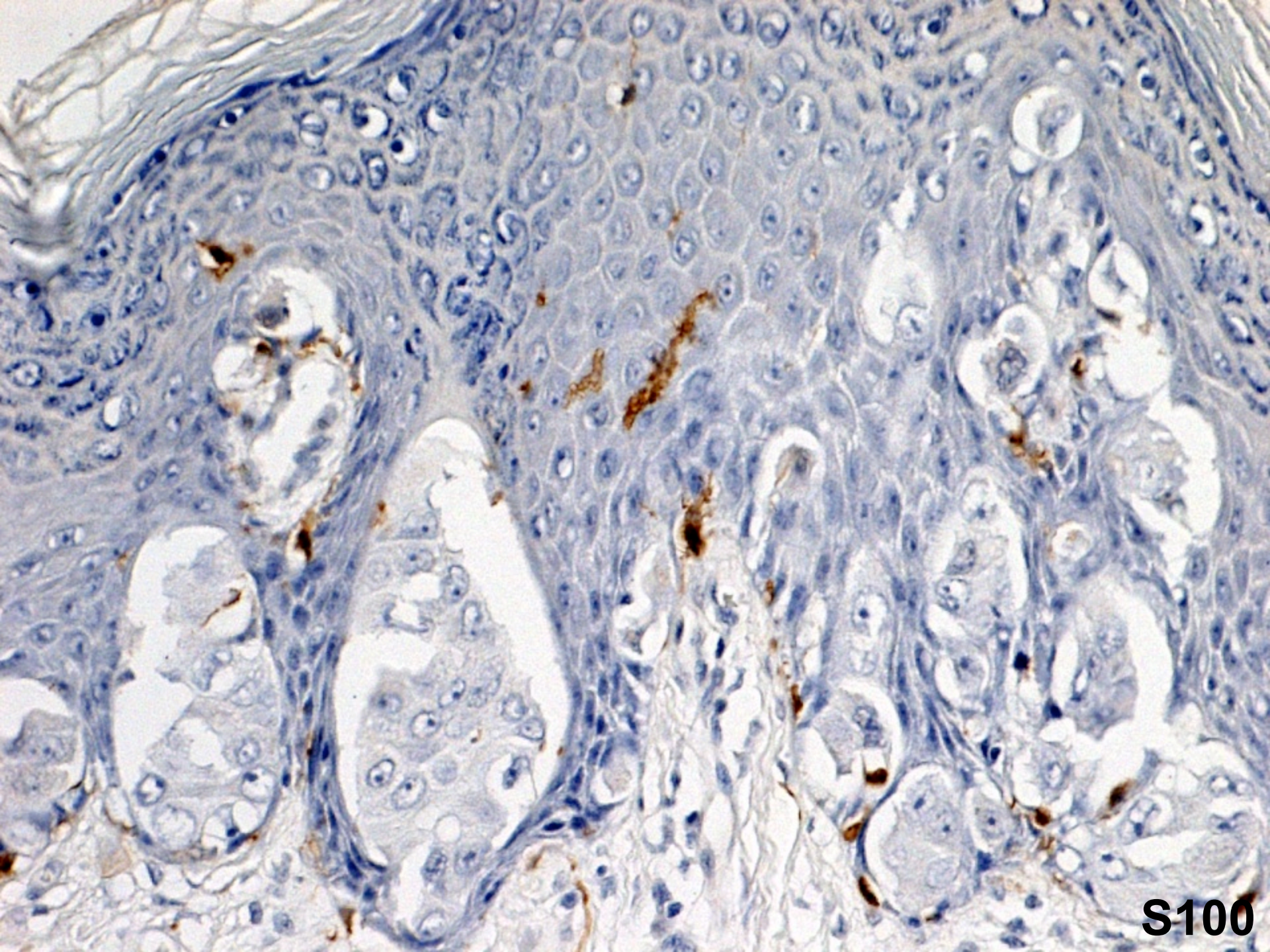




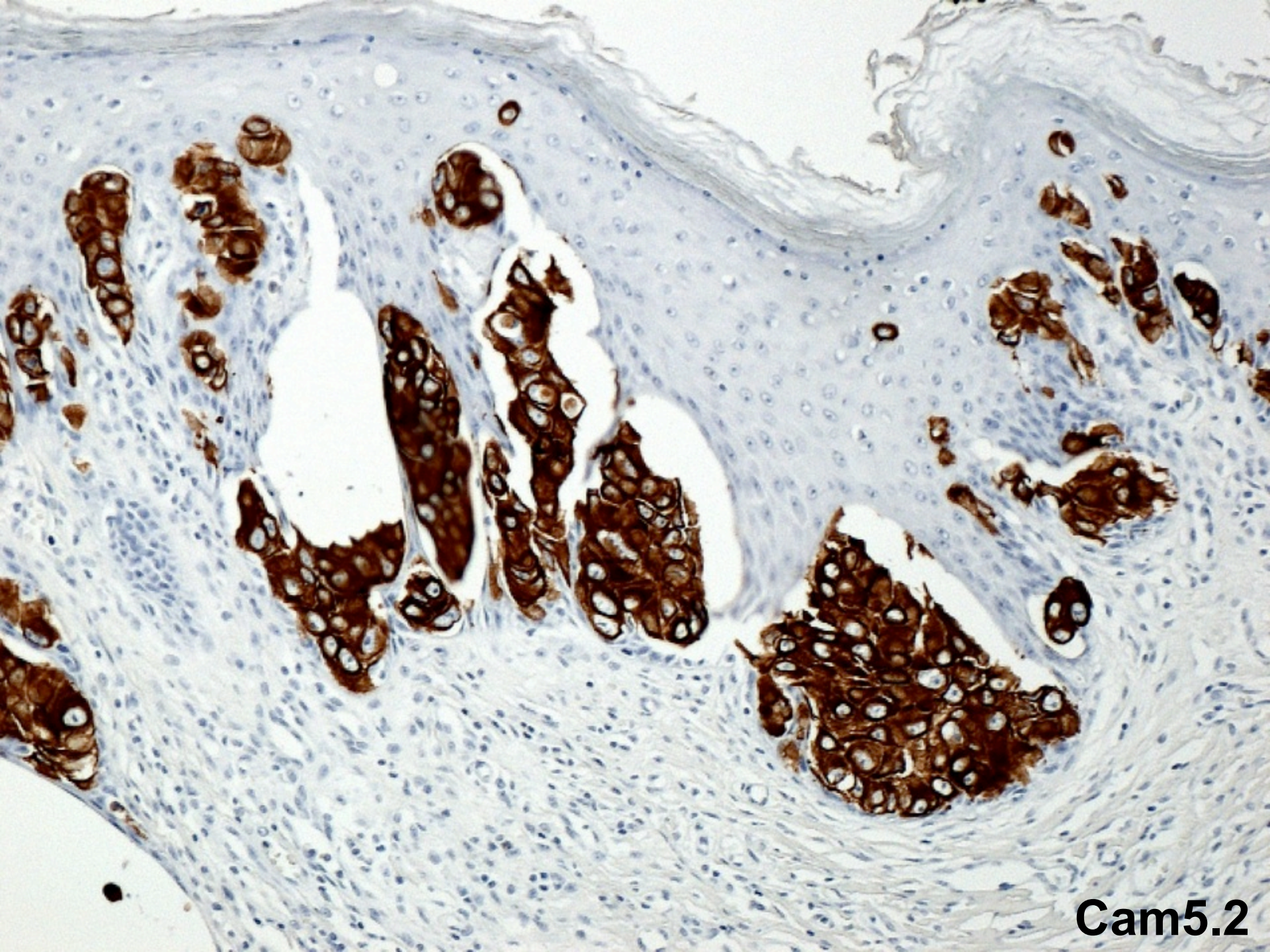
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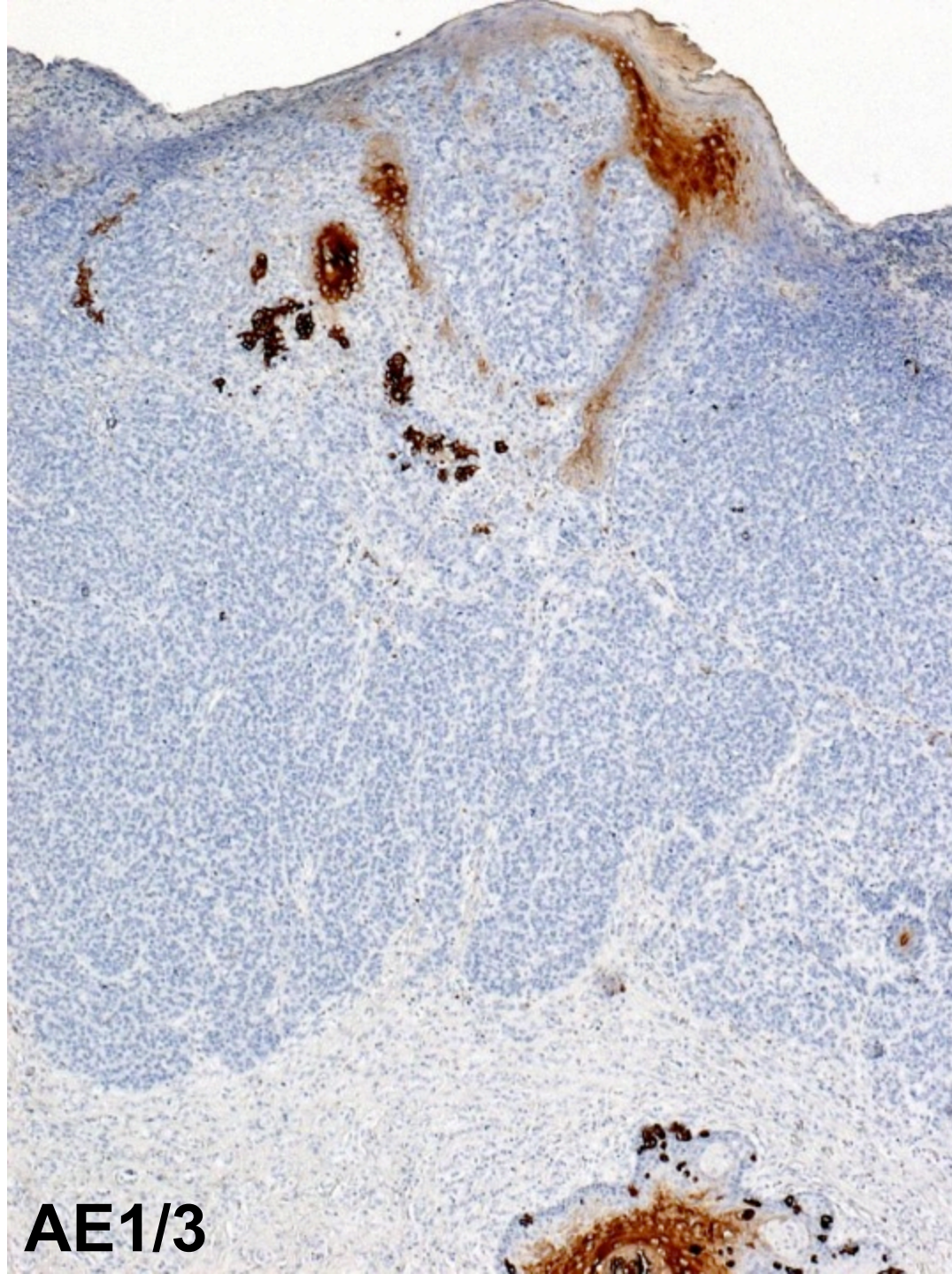


S100



S100





AE1/3

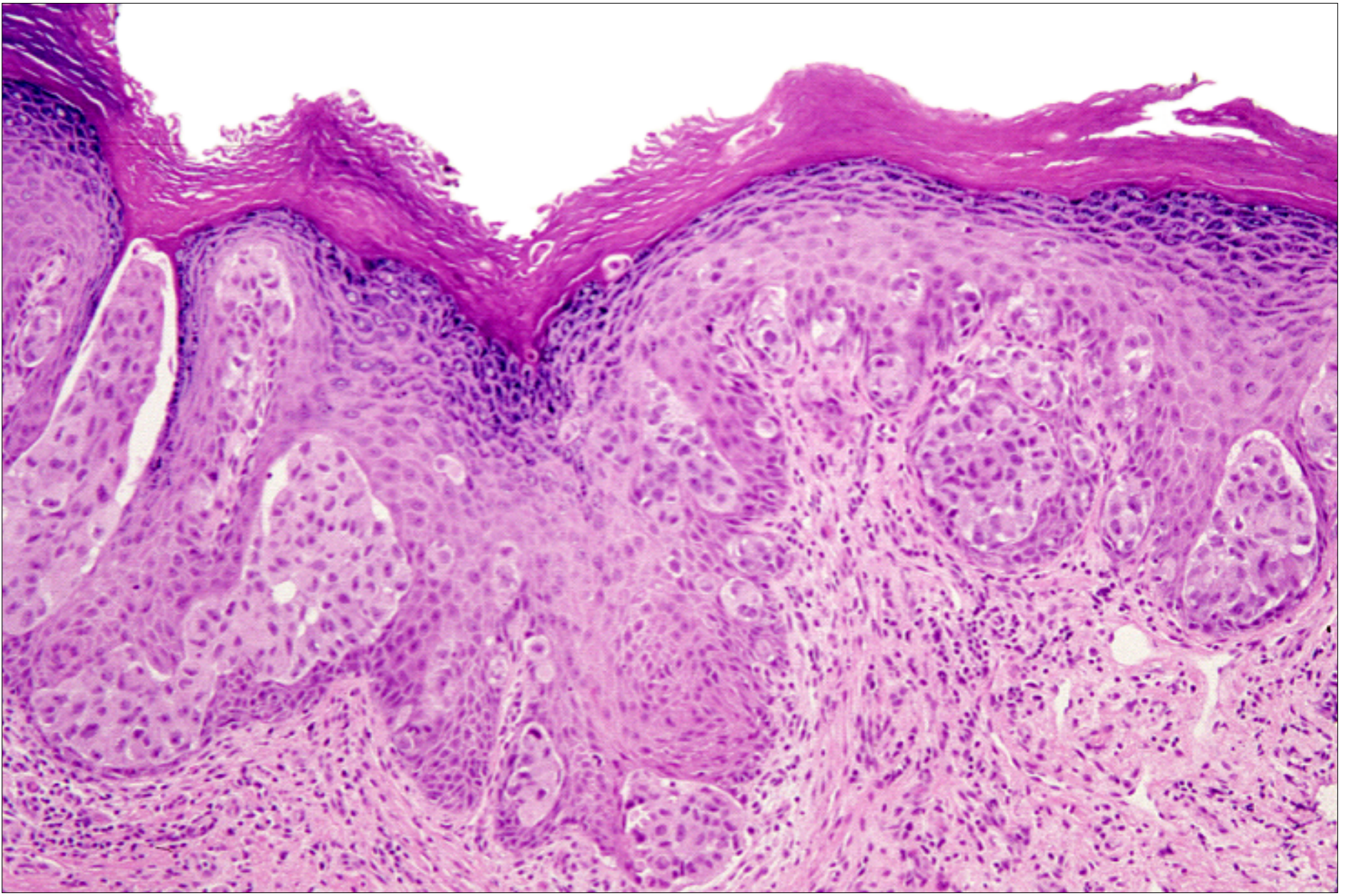
Diagnosis Case 1:

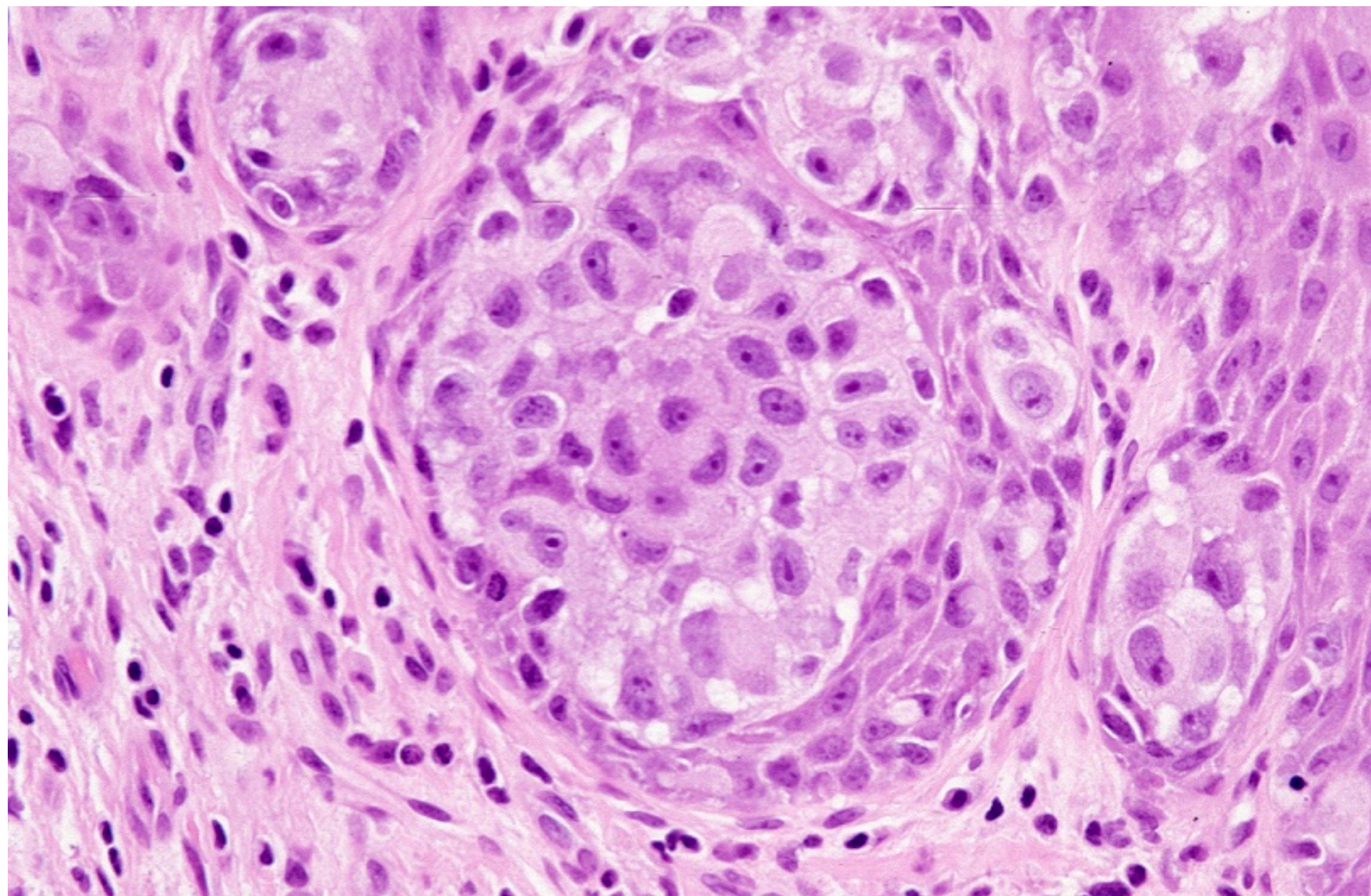
**Extramammary Paget disease and
invasive melanoma**

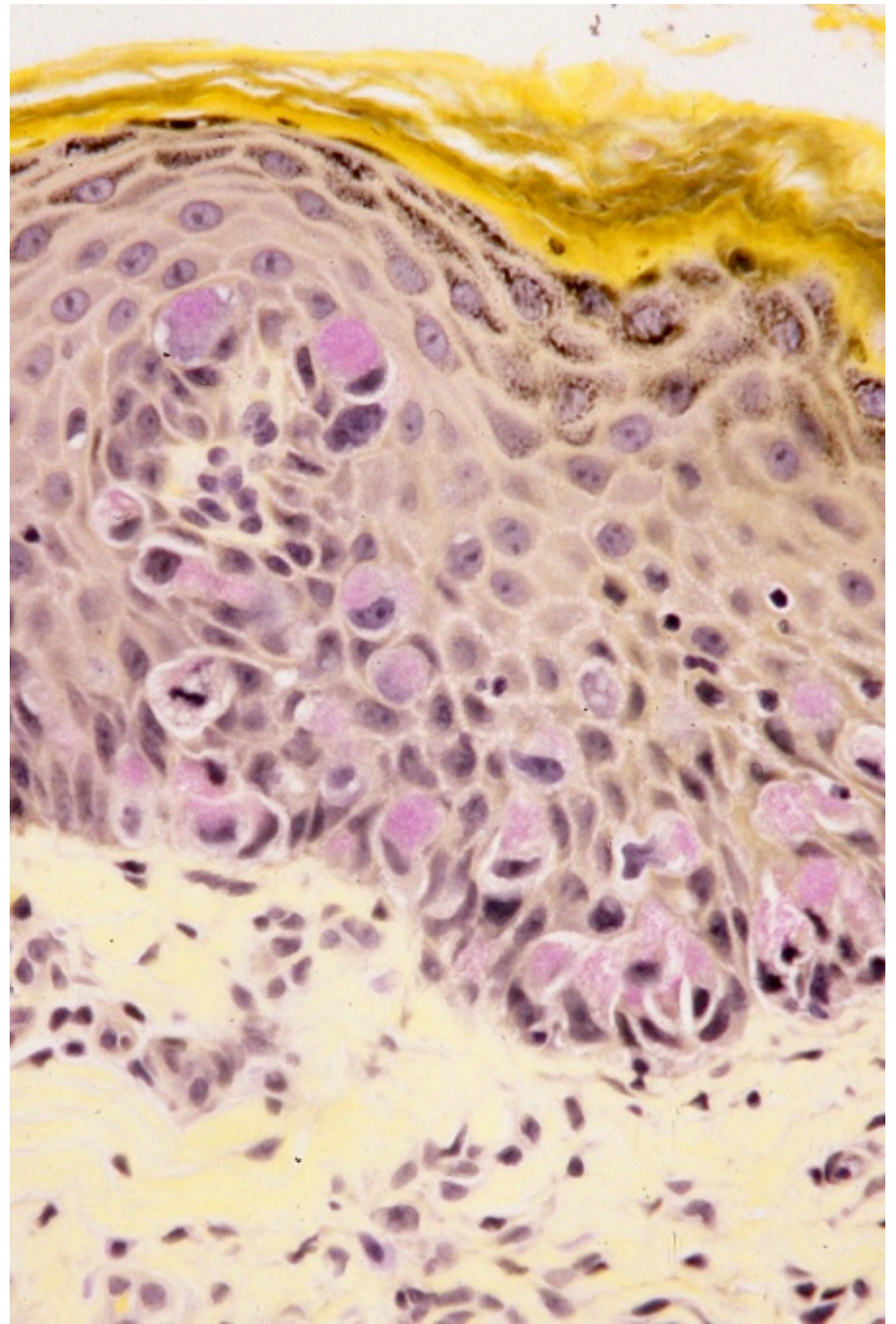
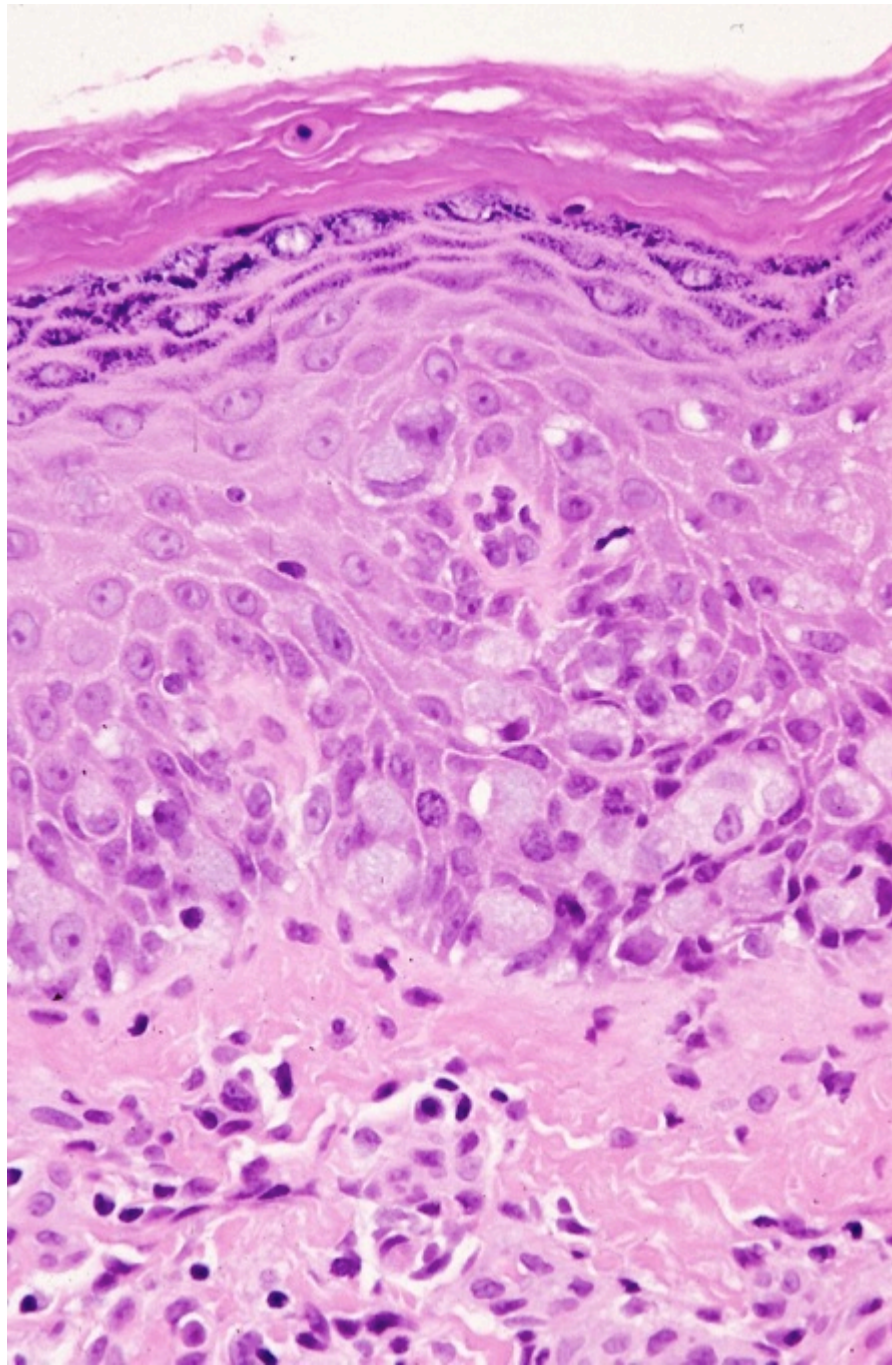
Extramammary Paget Disease

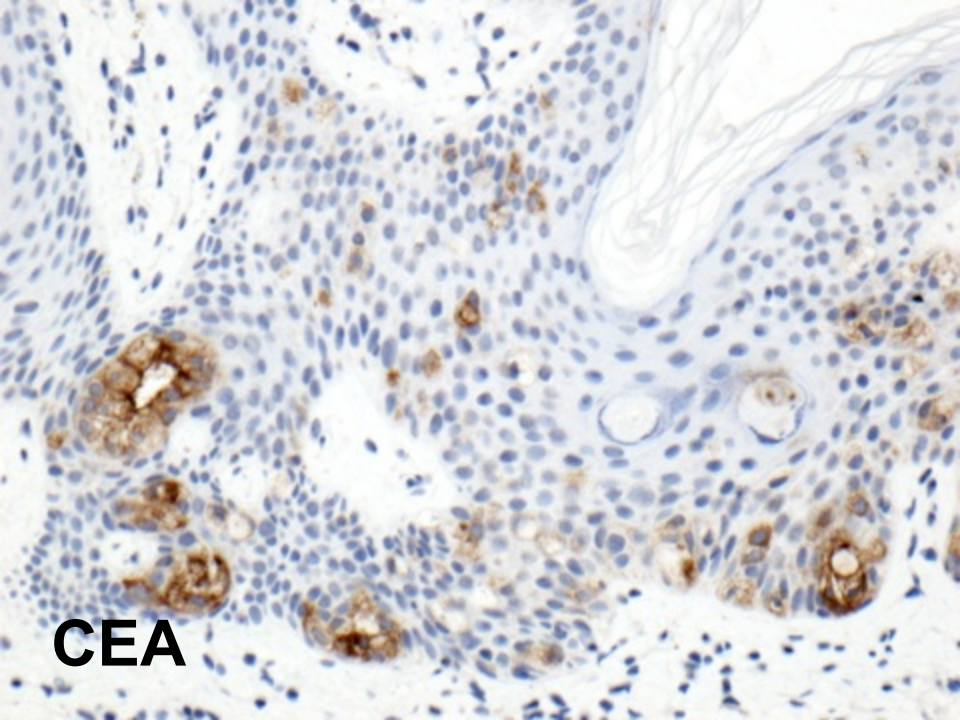
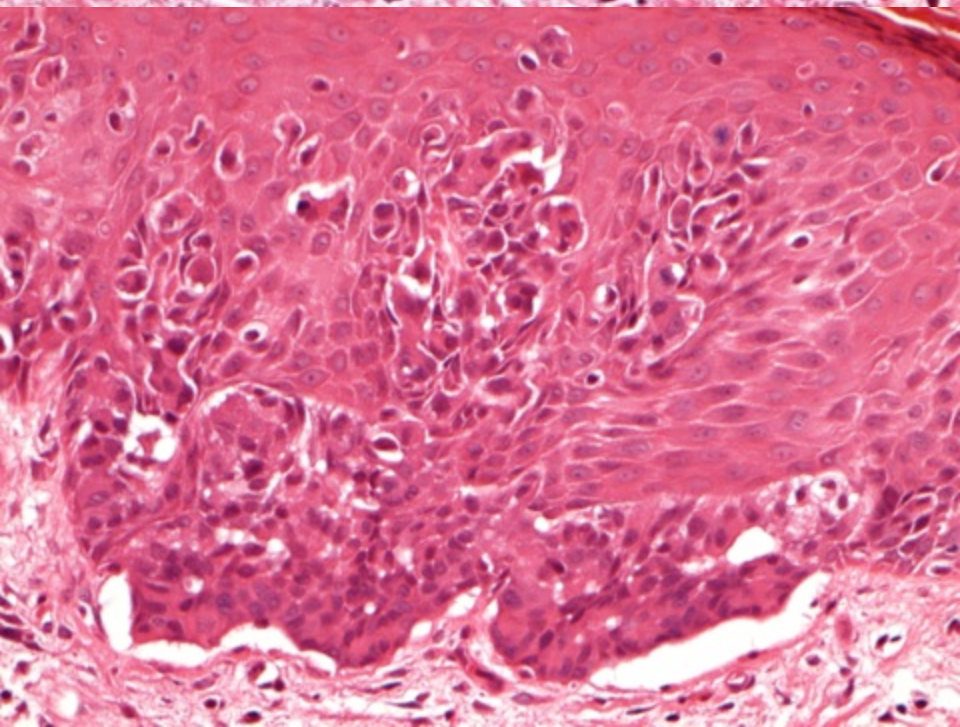
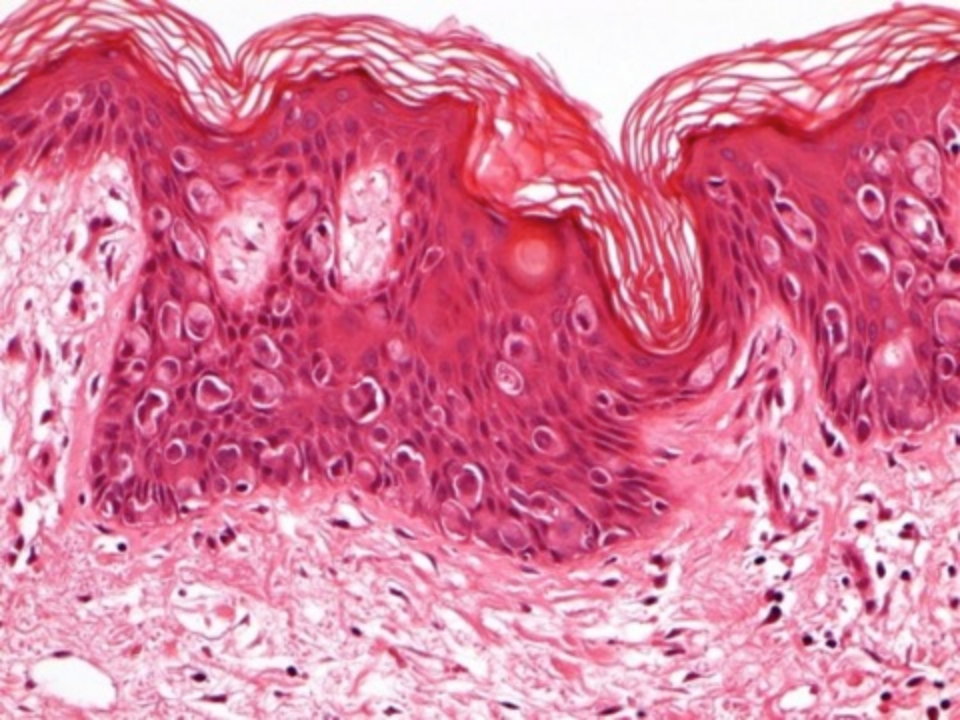
-Clinical-

- **Rare tumour**
- **Scaly plaques resembling eczema**
- **Occasionally pigmented**
- **Pruritus**
- **Anogenital area**
- **Elderly adults**
- **Female predominance**

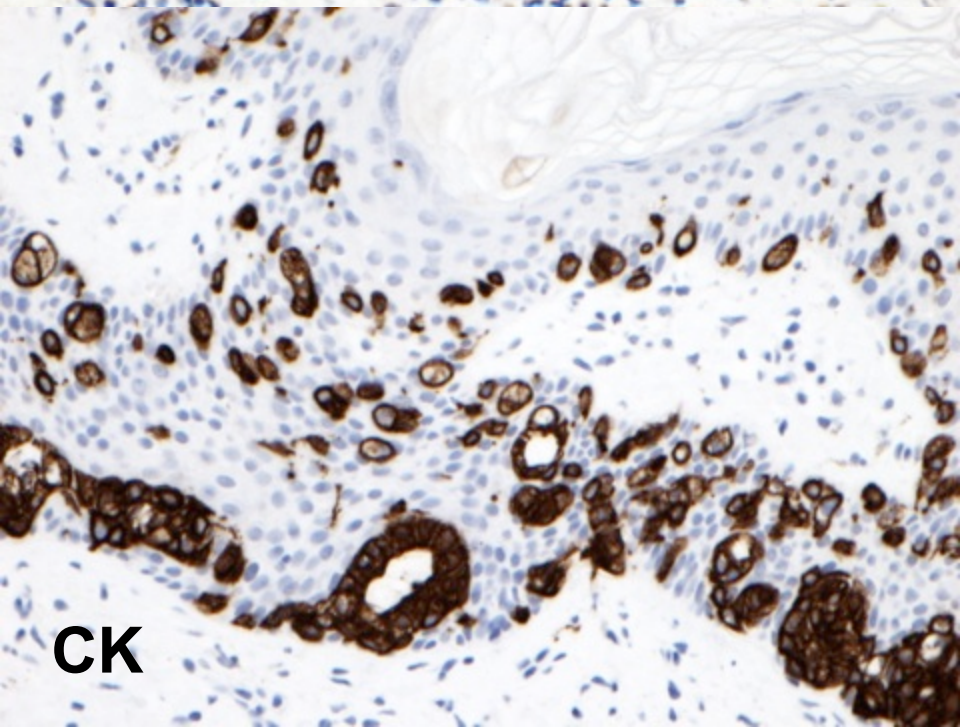




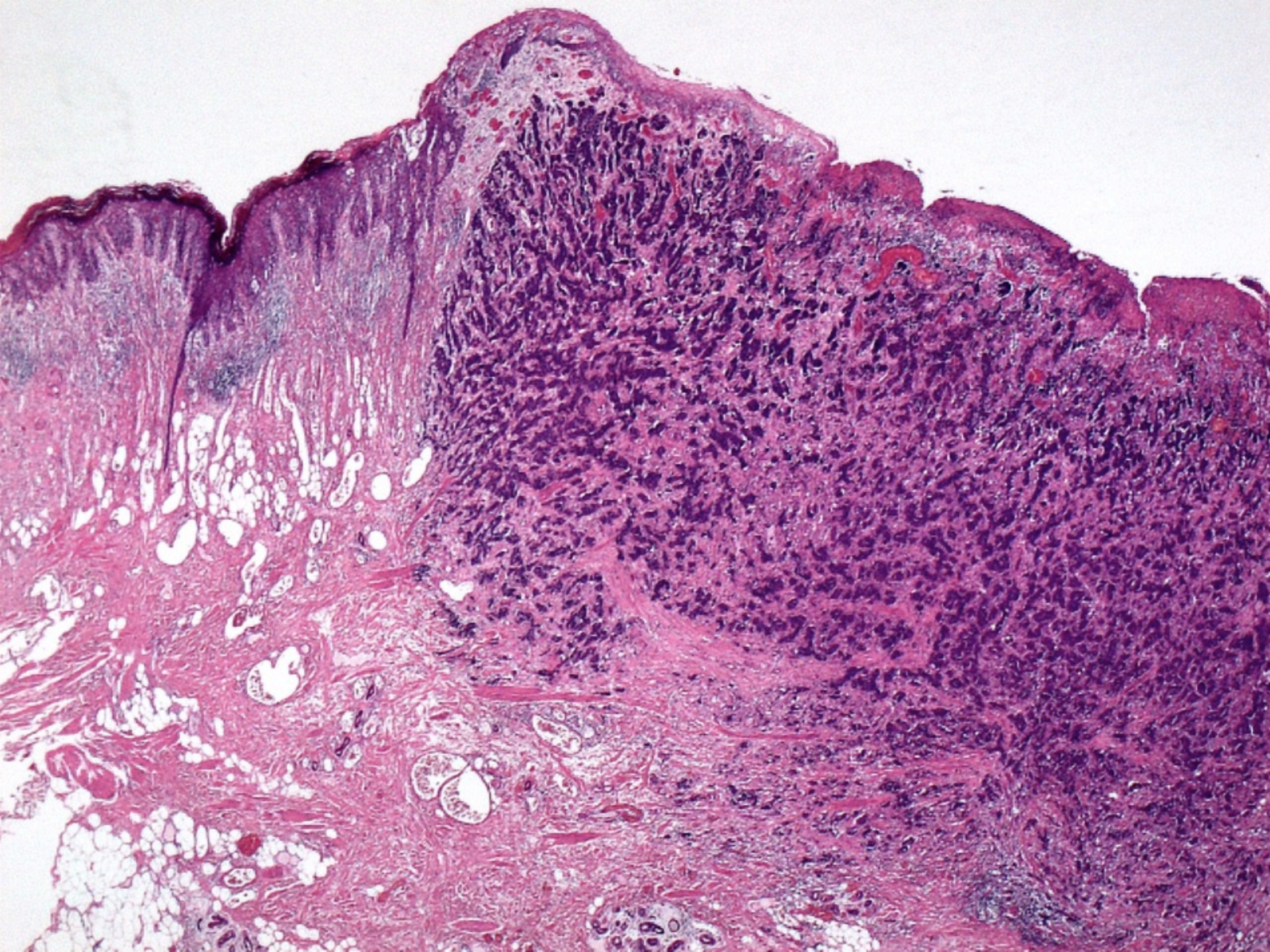


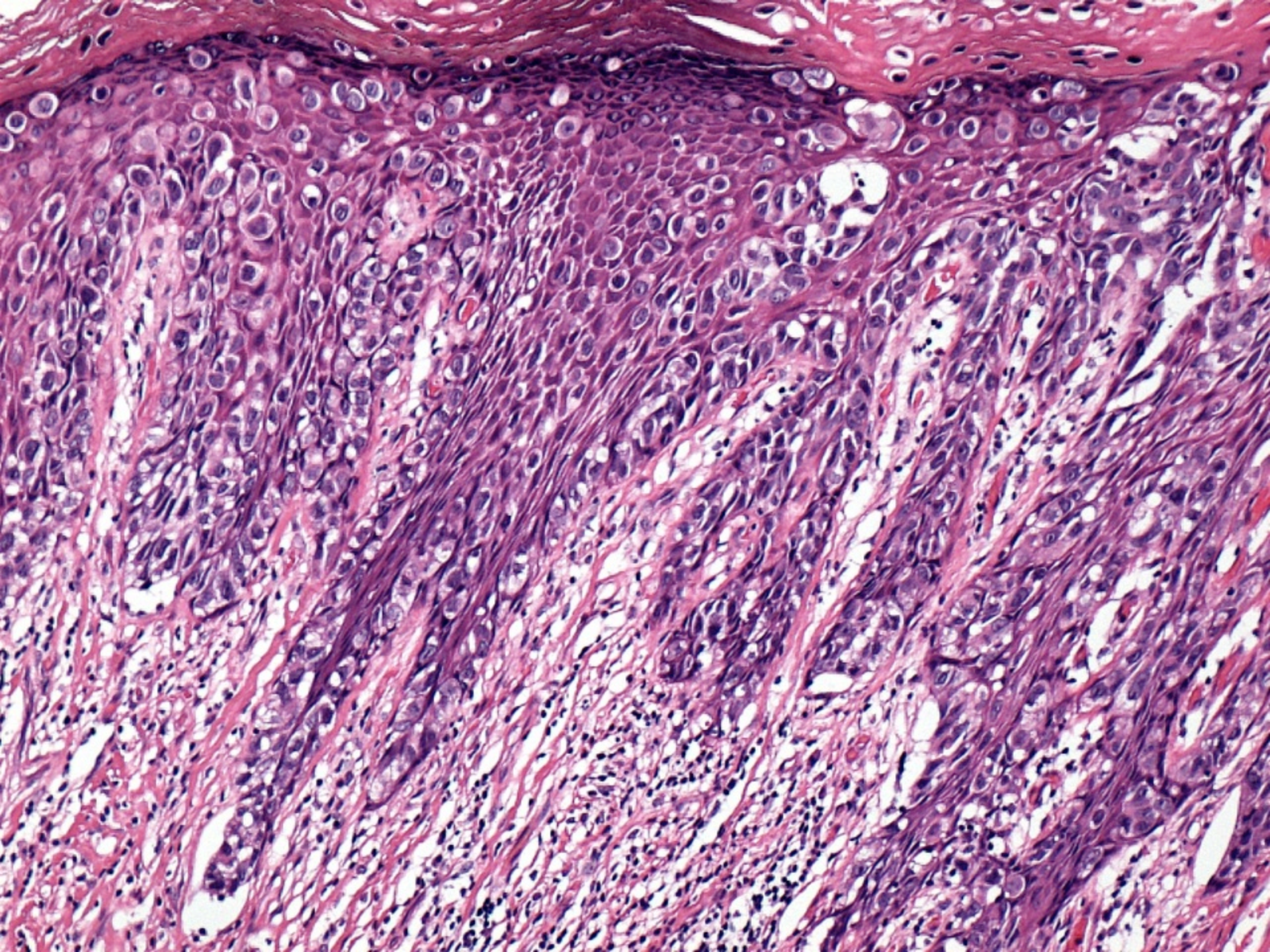


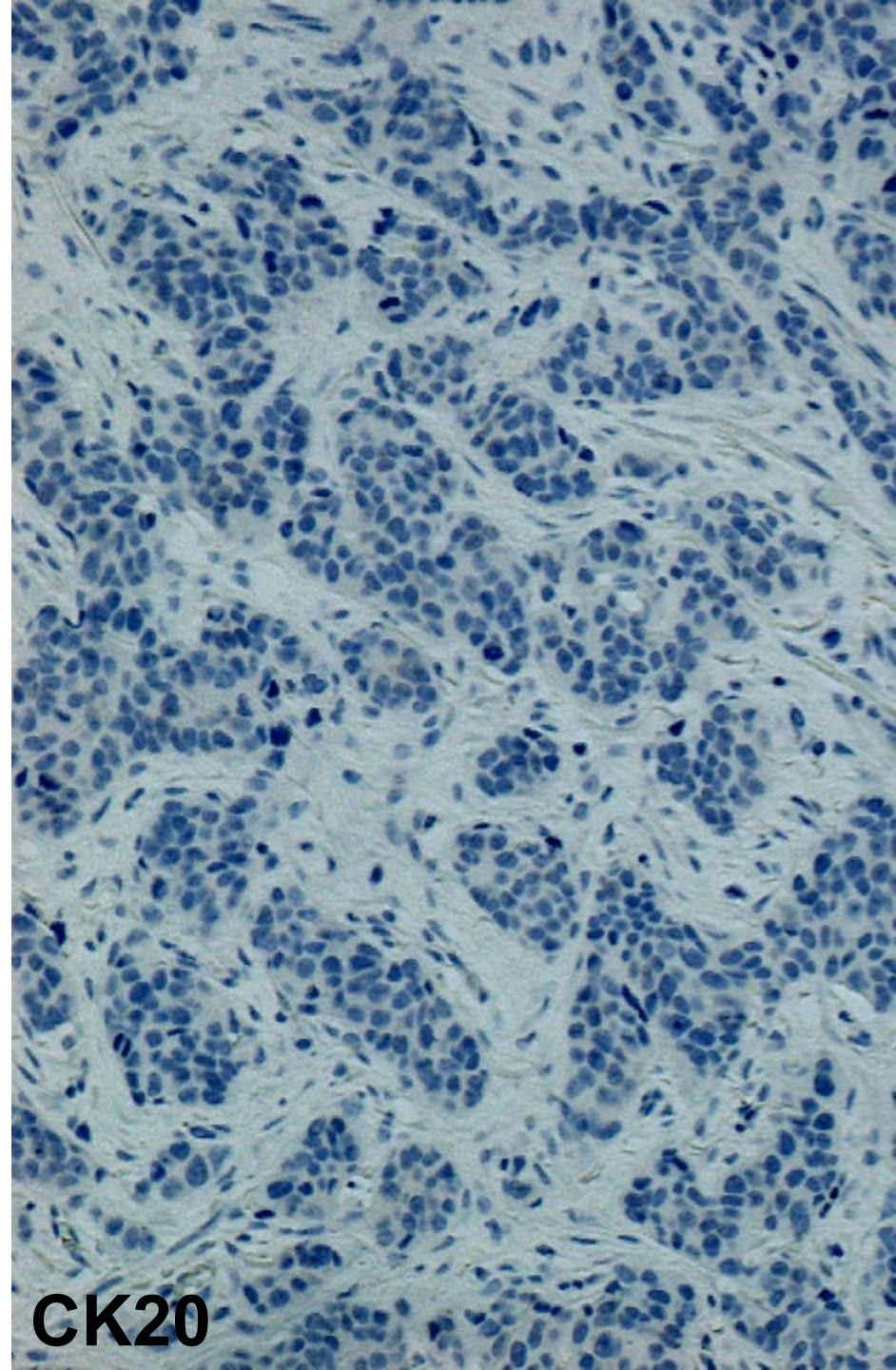
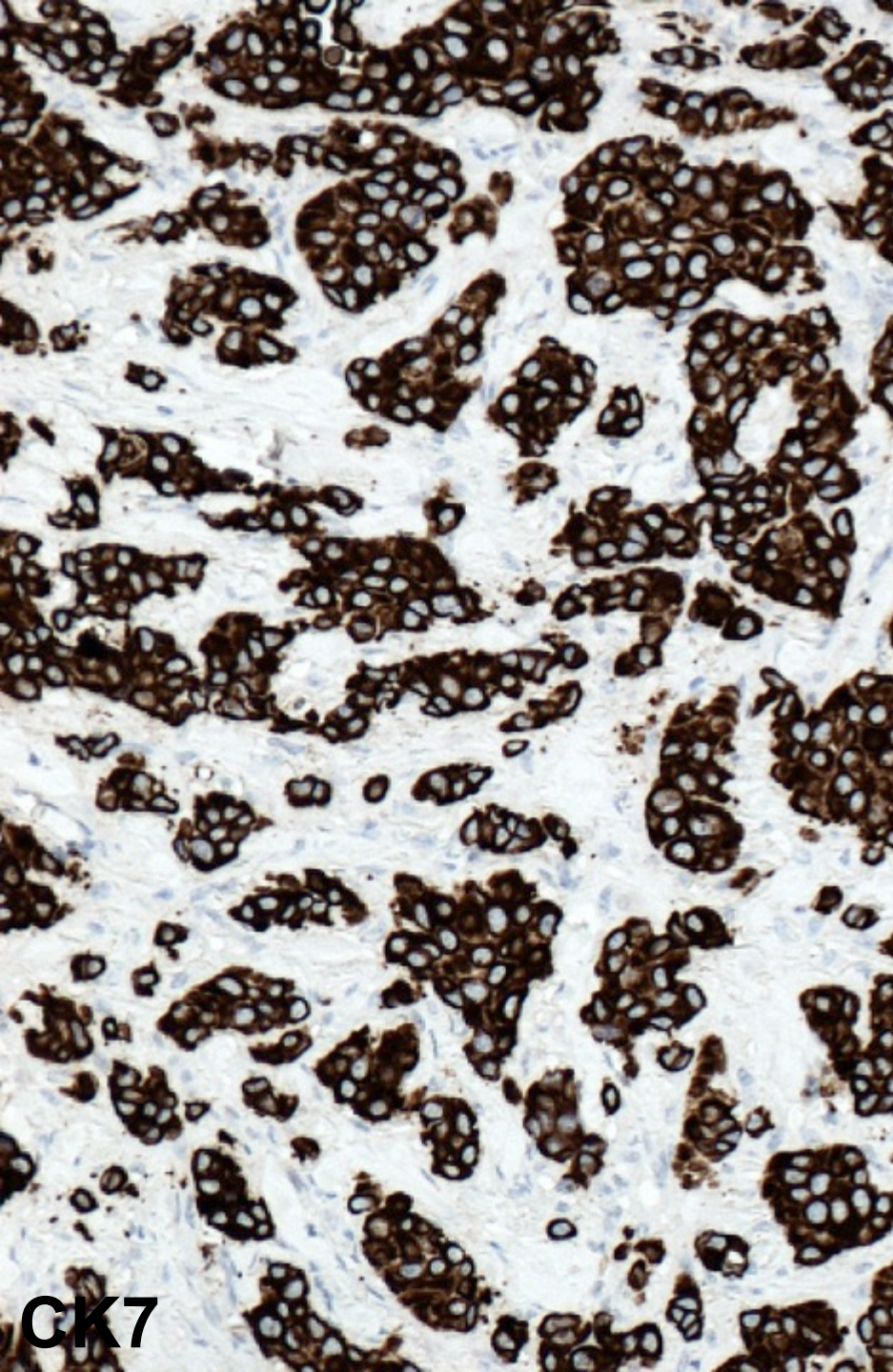
CEA



CK



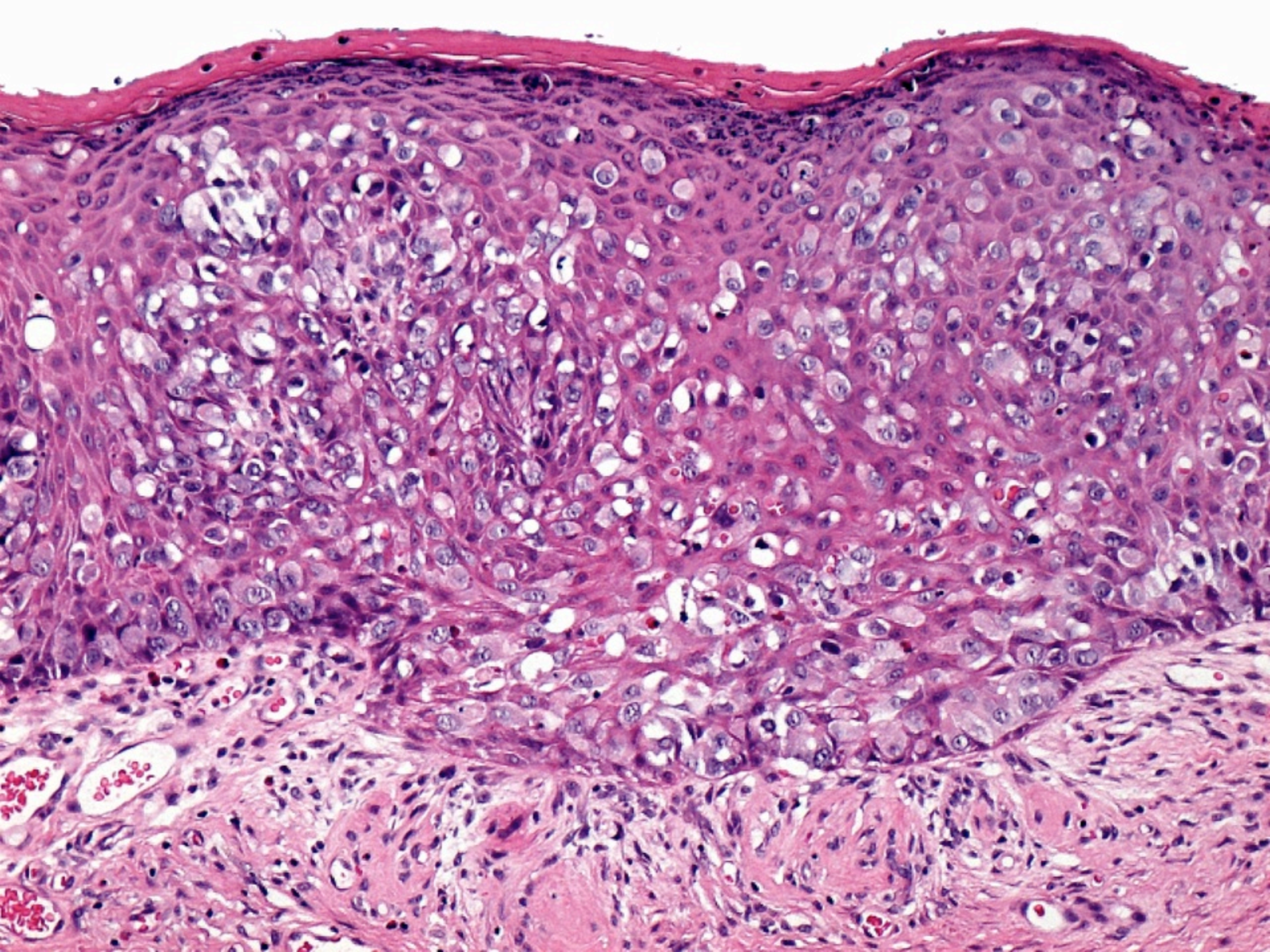


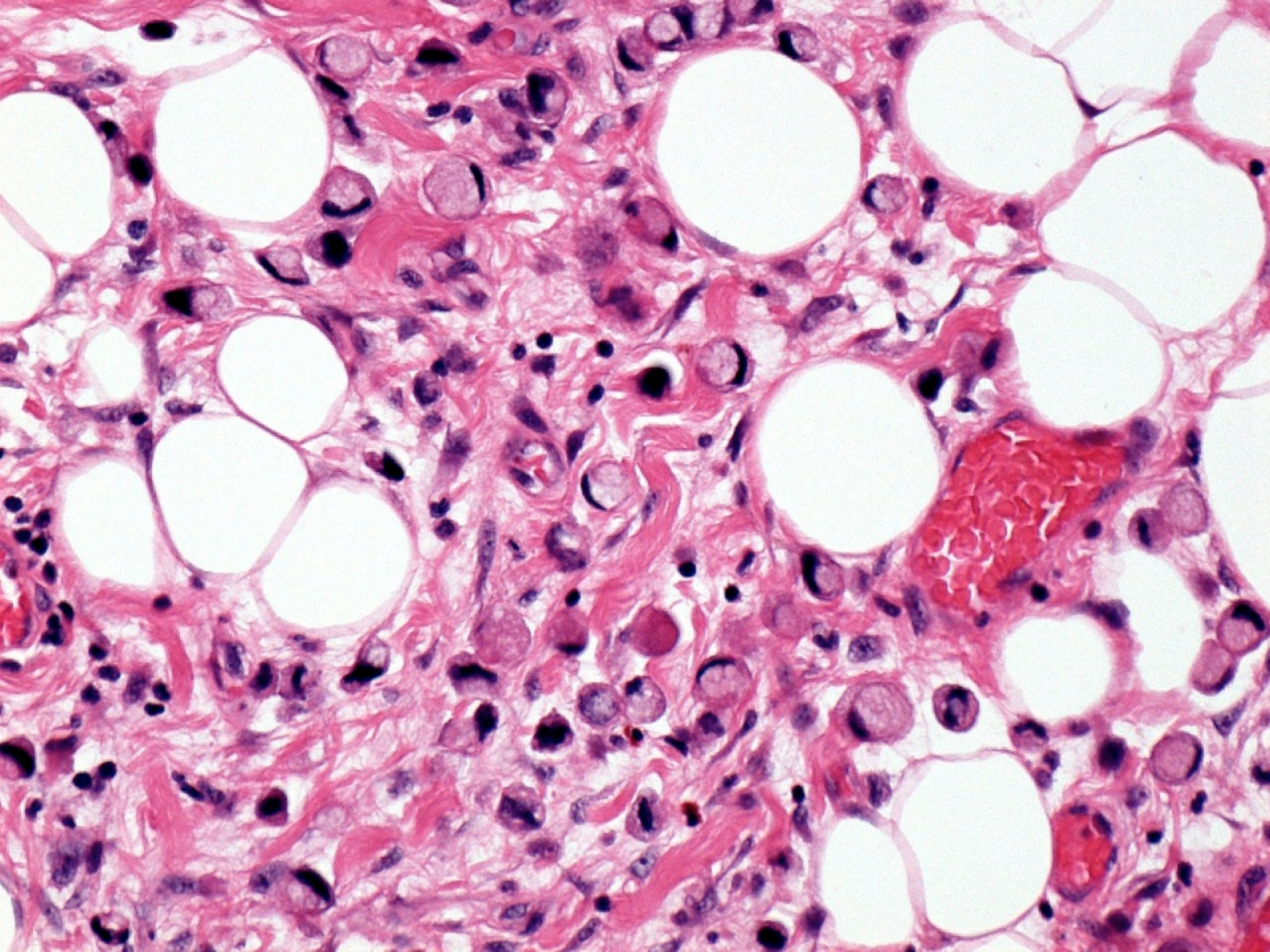


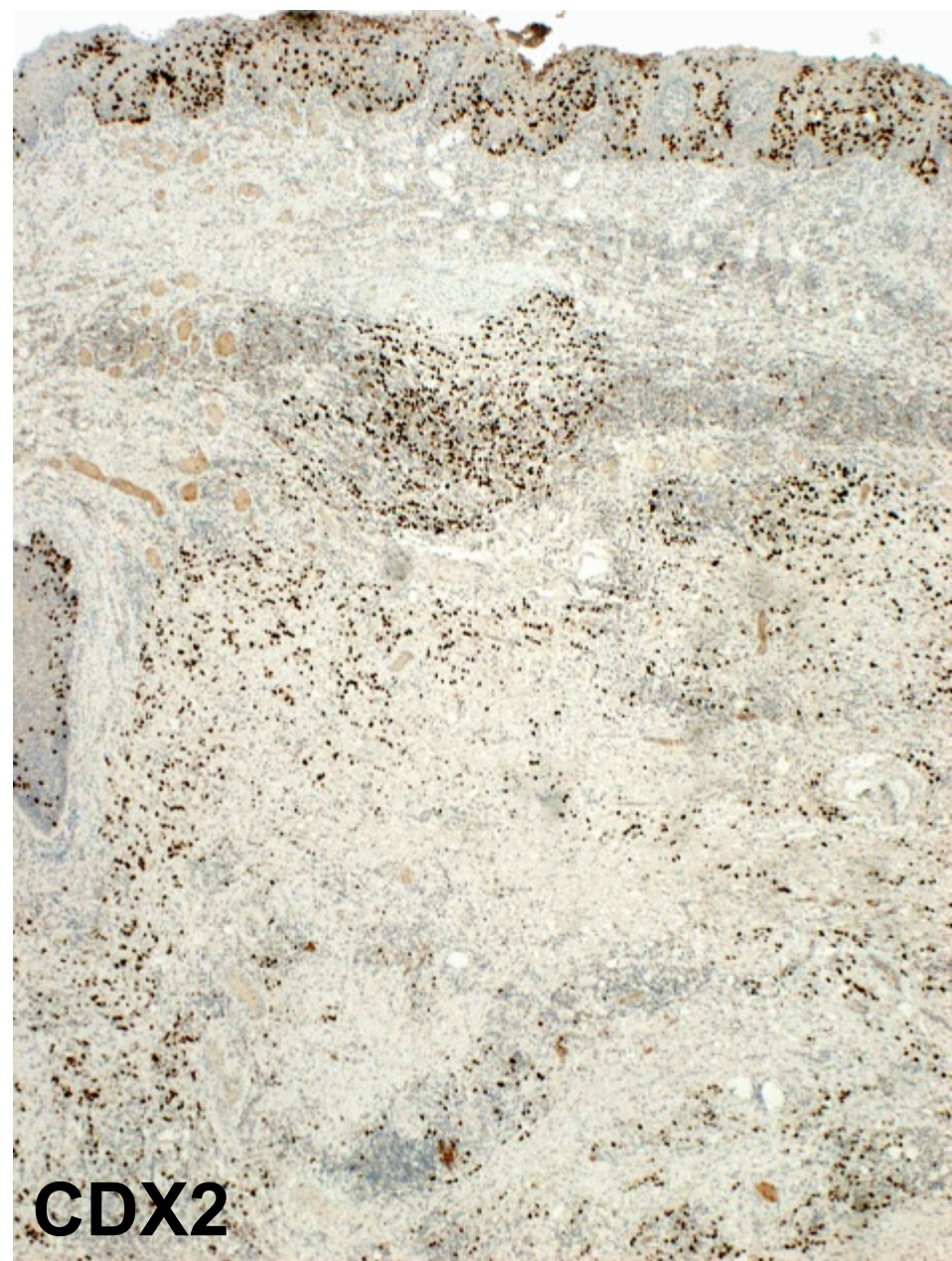
Extramammary Paget Disease

-Prognosis-

- **In situ adenocarcinoma with possibility of invasion**
- **Prognosis:**
 - **High local recurrence rate: ~40%**
 - **Development of invasive adeno-ca. in 10%**
 - **Risk for metastatic disease**
- **Primary cutaneous vs. secondary with underlying malignancy**
- **Majority are primary to skin**







Extramammary Paget Disease

-Summary-

- **Significant clinical and histological overlap**

BUT

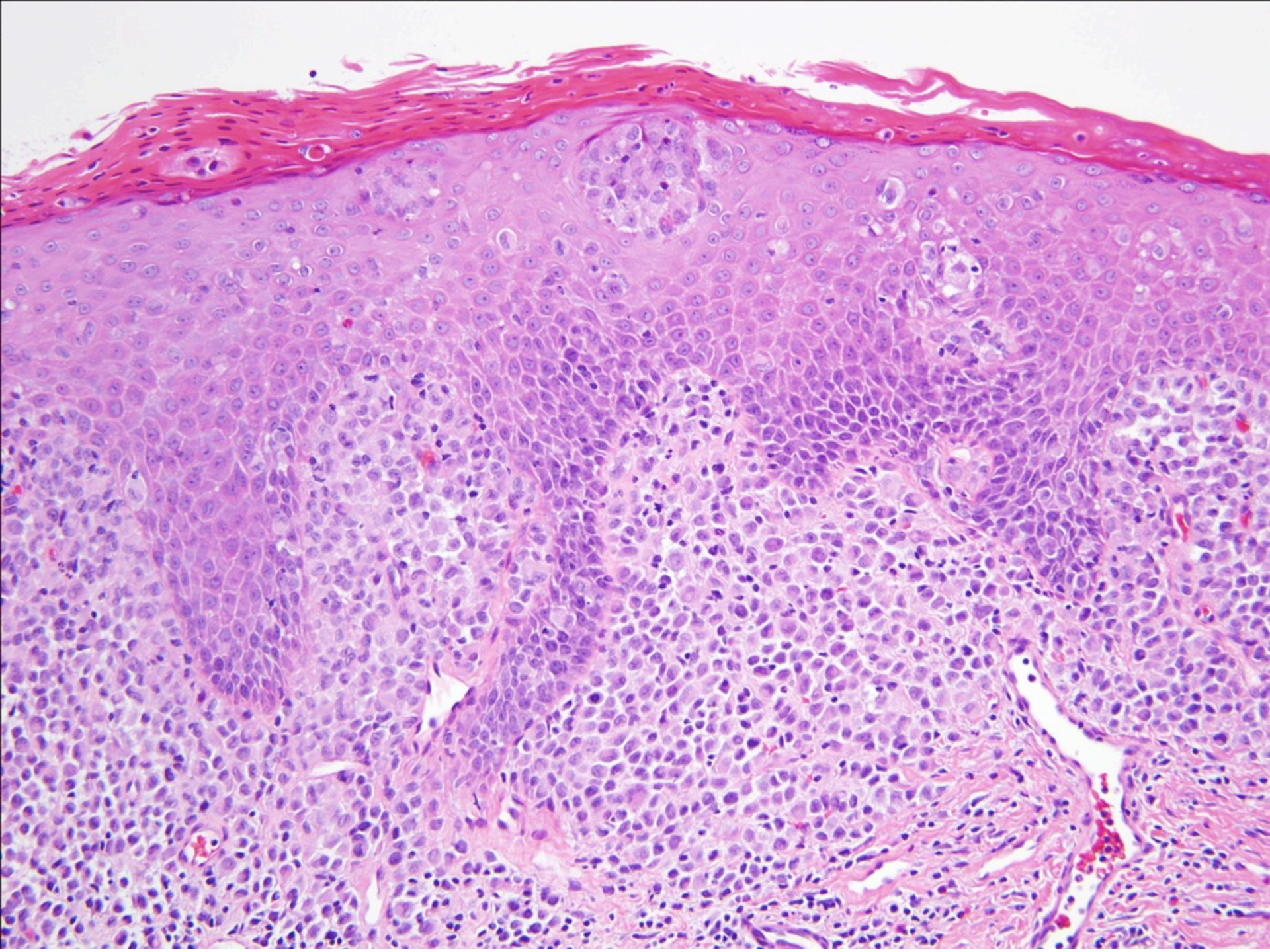
- **Clinical presentation as scaly plaque**
- **Identification of glandular component**
- **Visualization of mucin**
- **Immunohistochemistry (S100-, keratin+)**

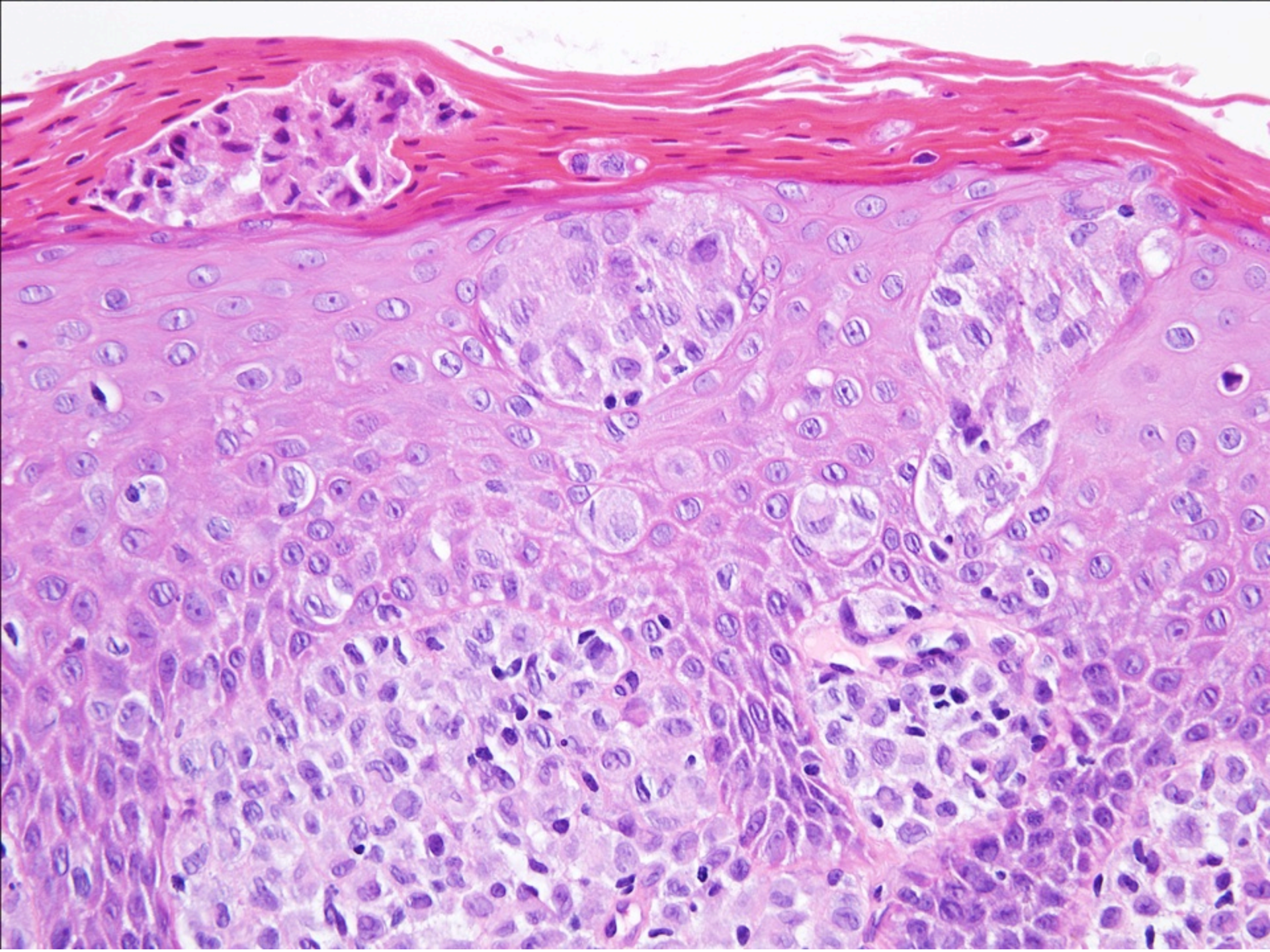
Exclude underlying malignancy!

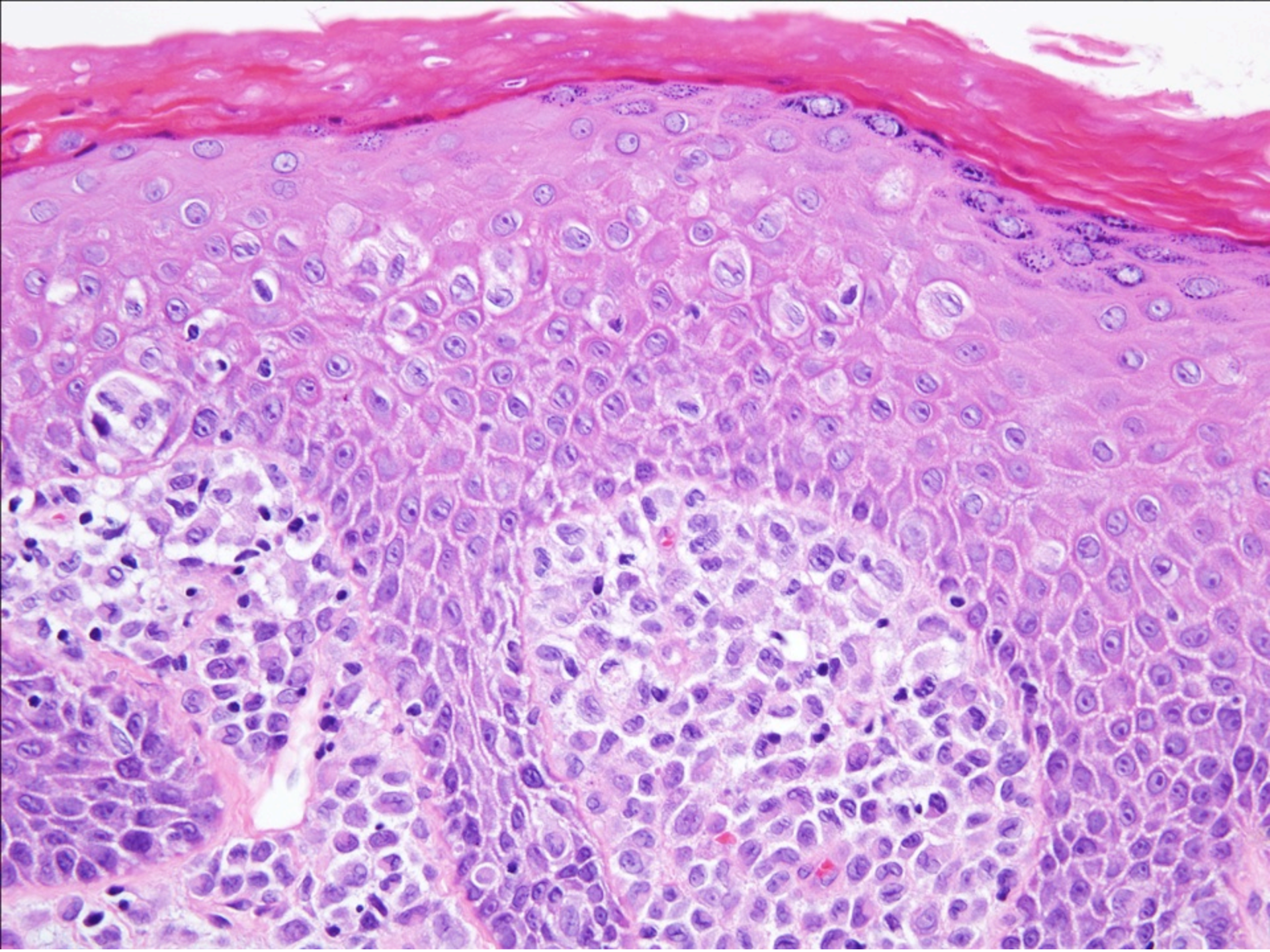
Langerhans Cell Histiocytosis

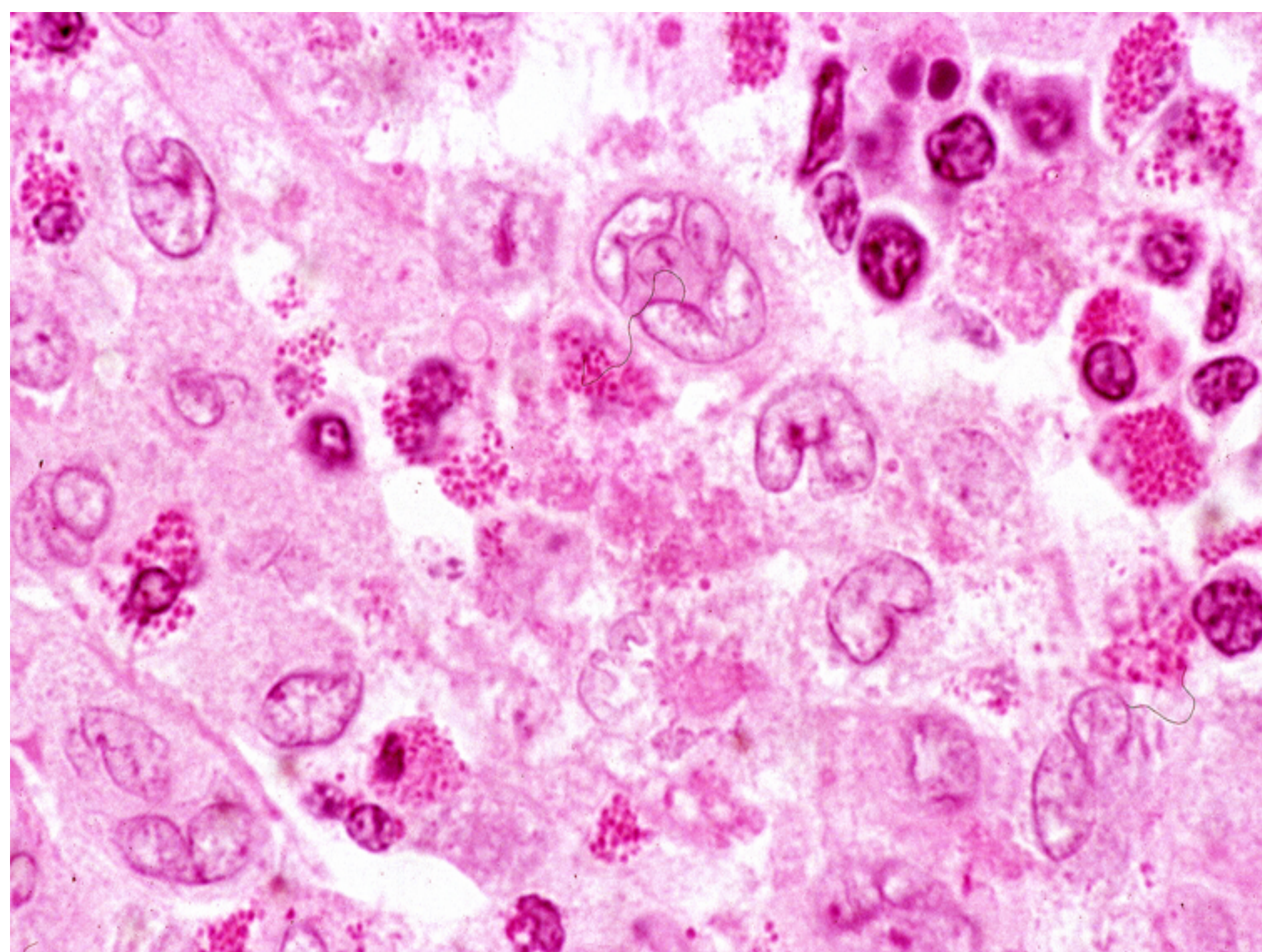
-Clinical-

- **Rare disease**
- **Variable clinical presentation**
- **Childhood-adolescence-adulthood**
- **Skin manifestation:**
Multiple crusted papules

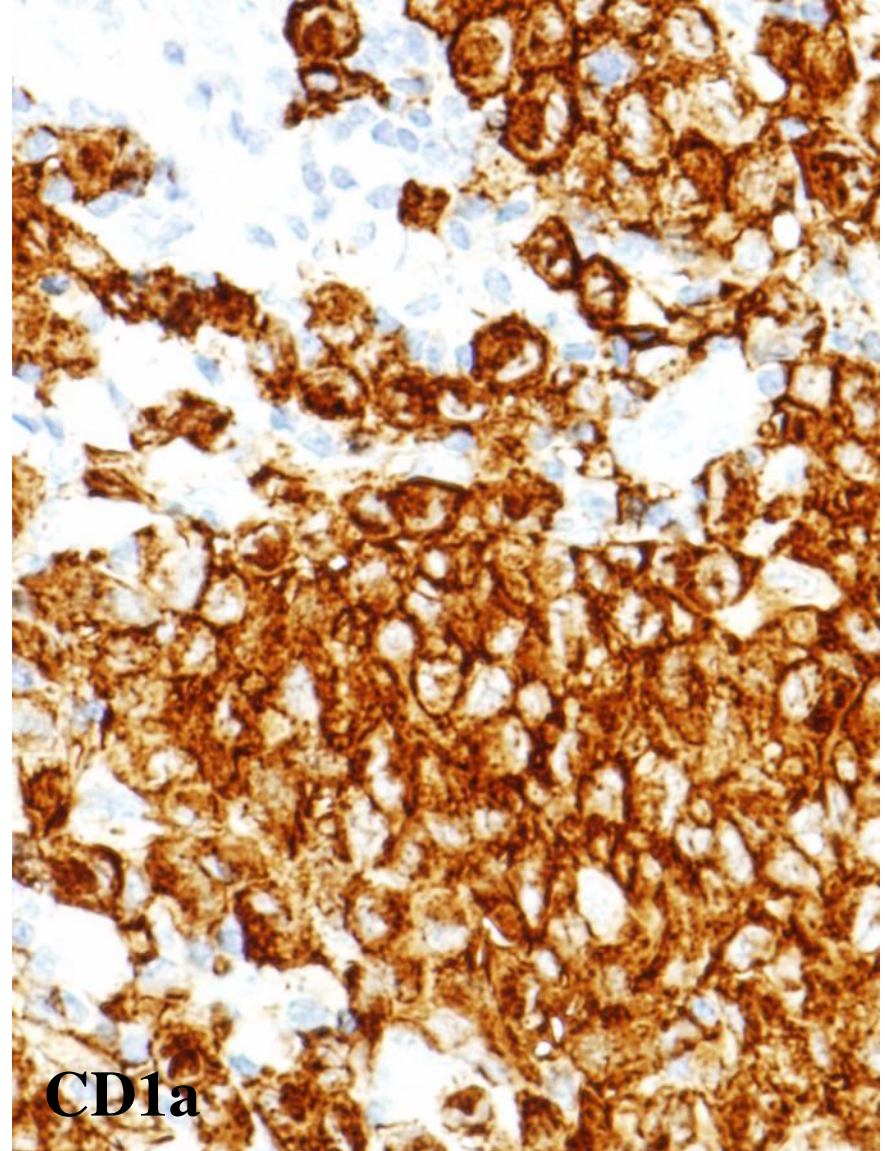
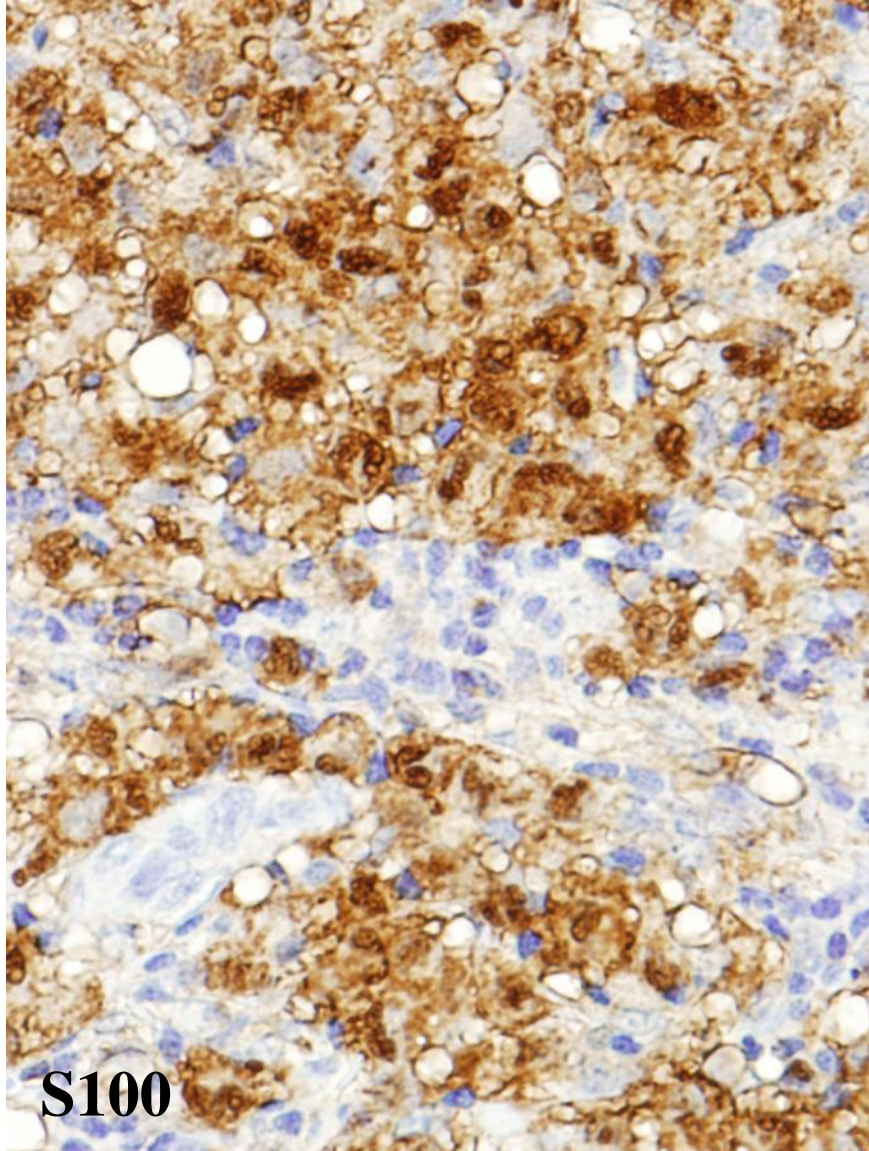




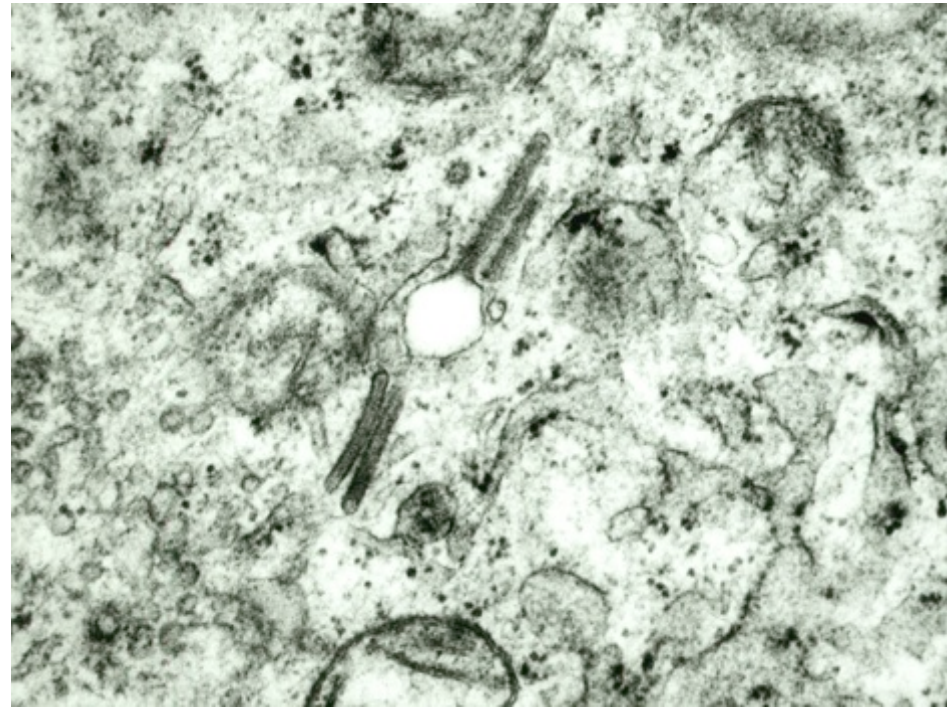
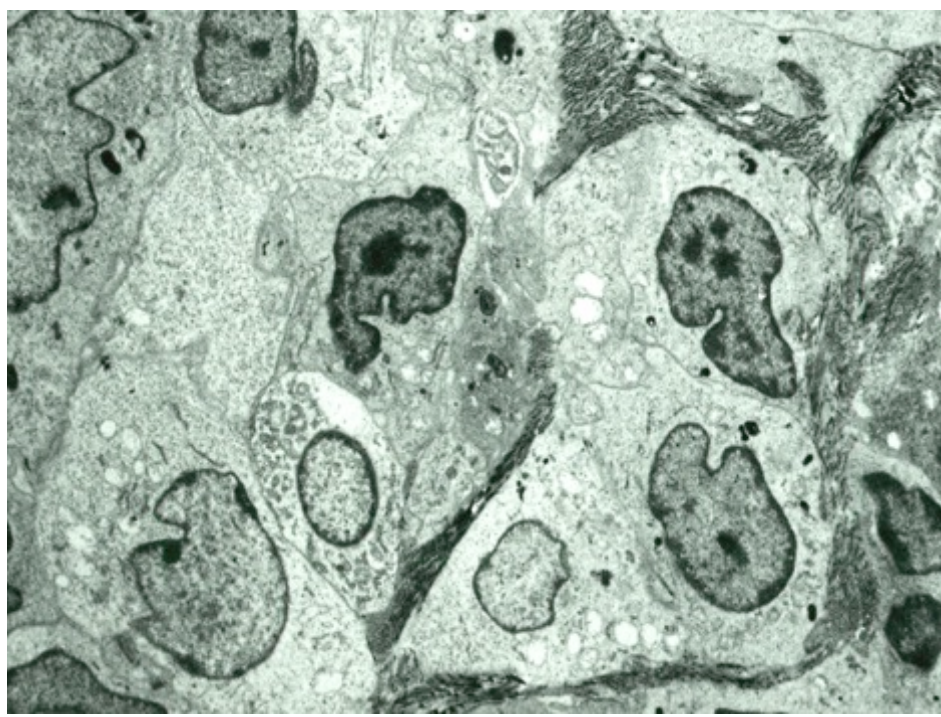




Immunohistochemistry-LCH



Electron Microscopy-LCH



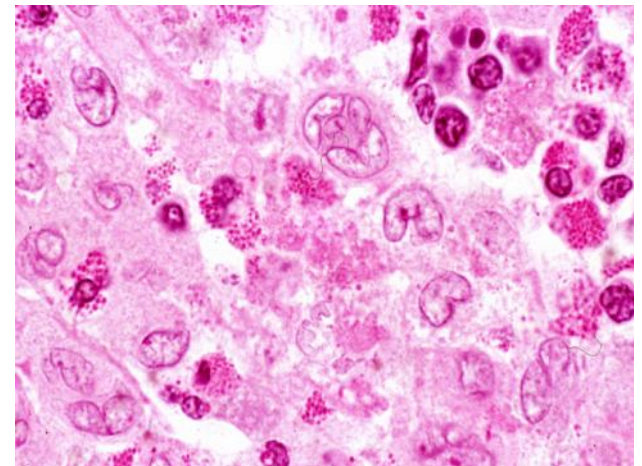
Langerhans Cell Histiocytosis

-Summary-

Significant morphological and immunohistochemical overlap

BUT:

- Different clinical presentation
- Classical cytology
- Positivity for CD1a and langerin
- Characteristic EM findings



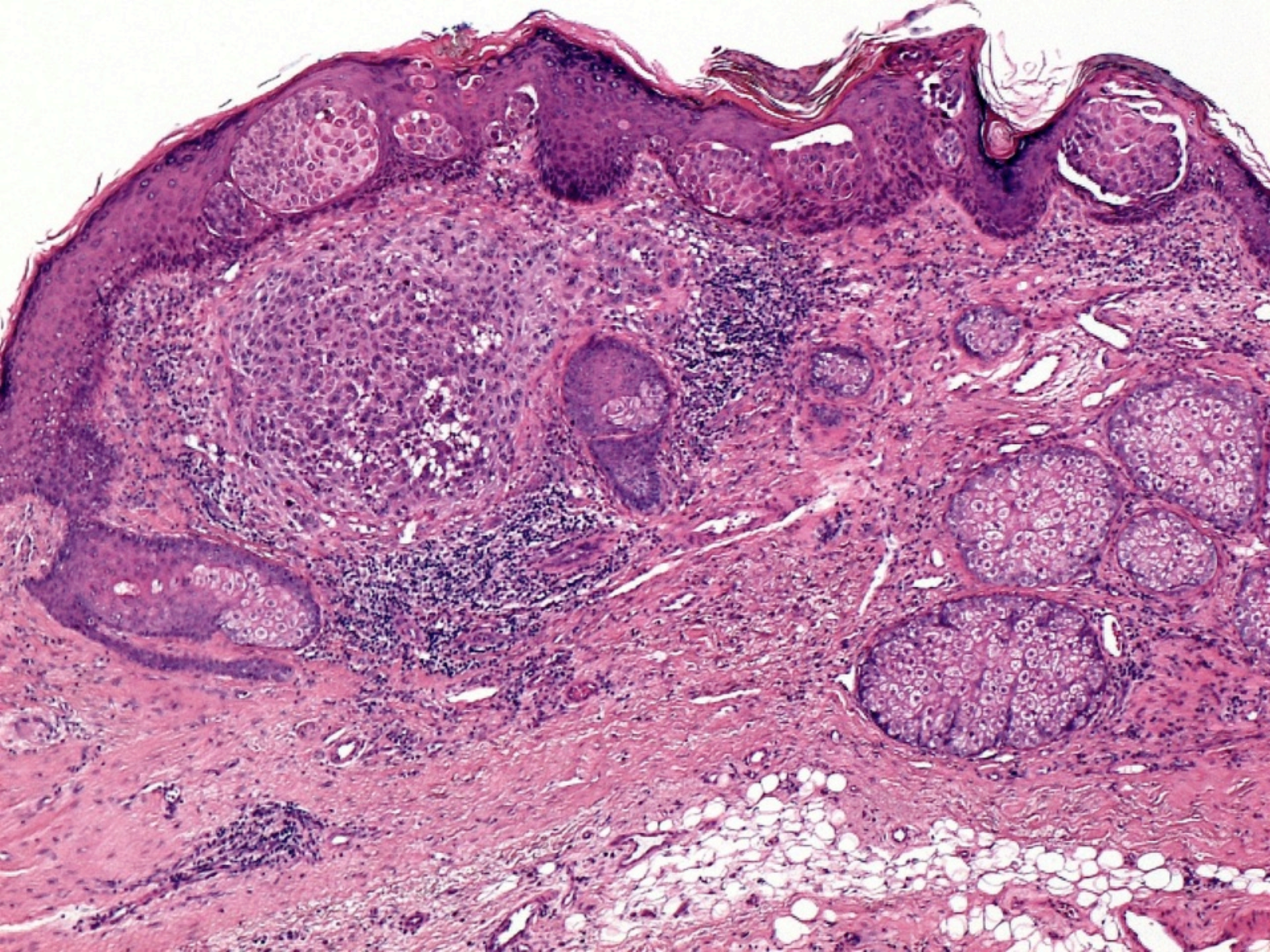
Epidermal Tumours

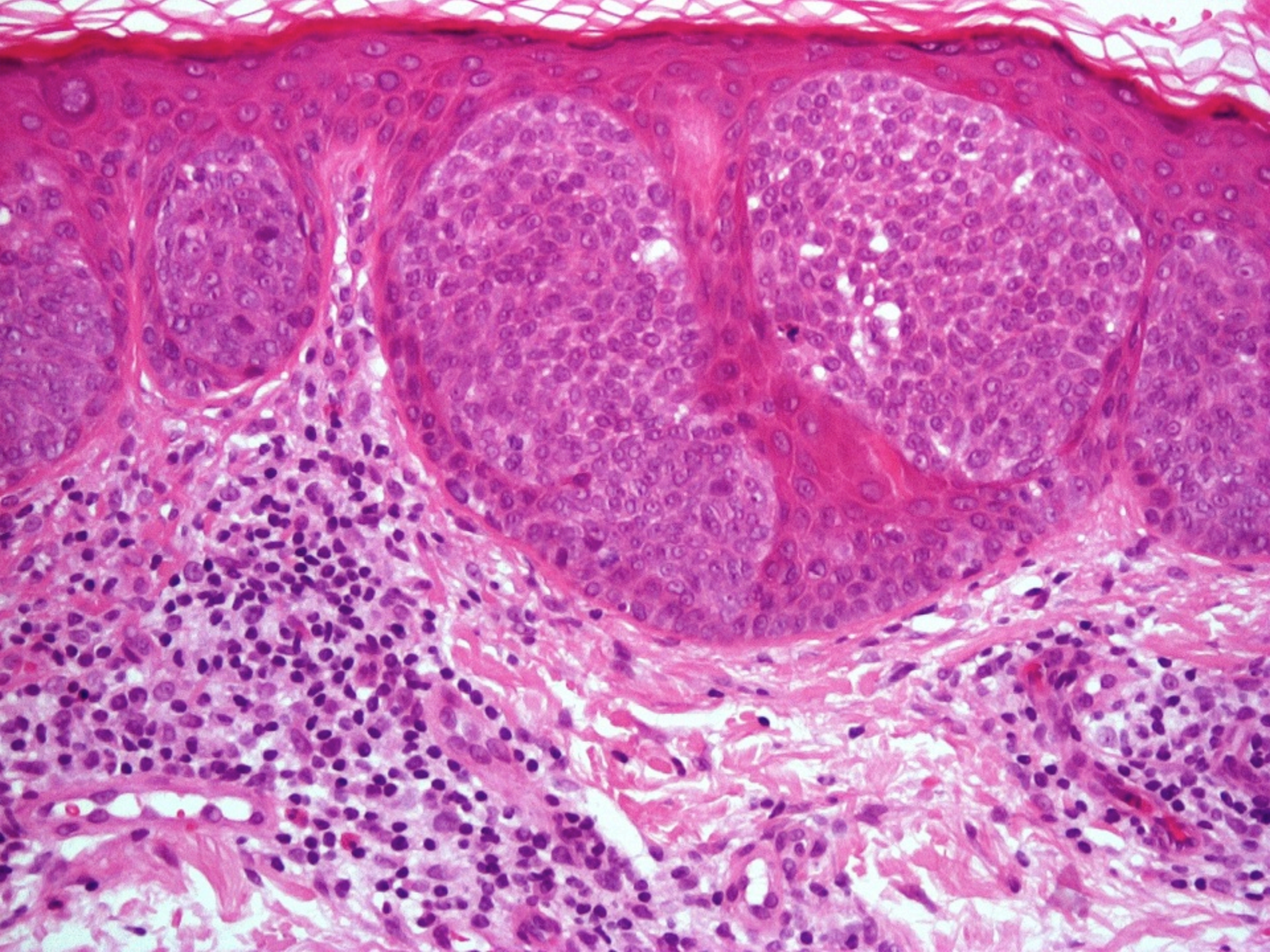
- **Squamous Cell Carcinoma in situ**
- **Solar Lentigo**
- **Pigmented and Clonal Seborrhoeic Keratosis**
- **Pigmented Actinic Keratosis**

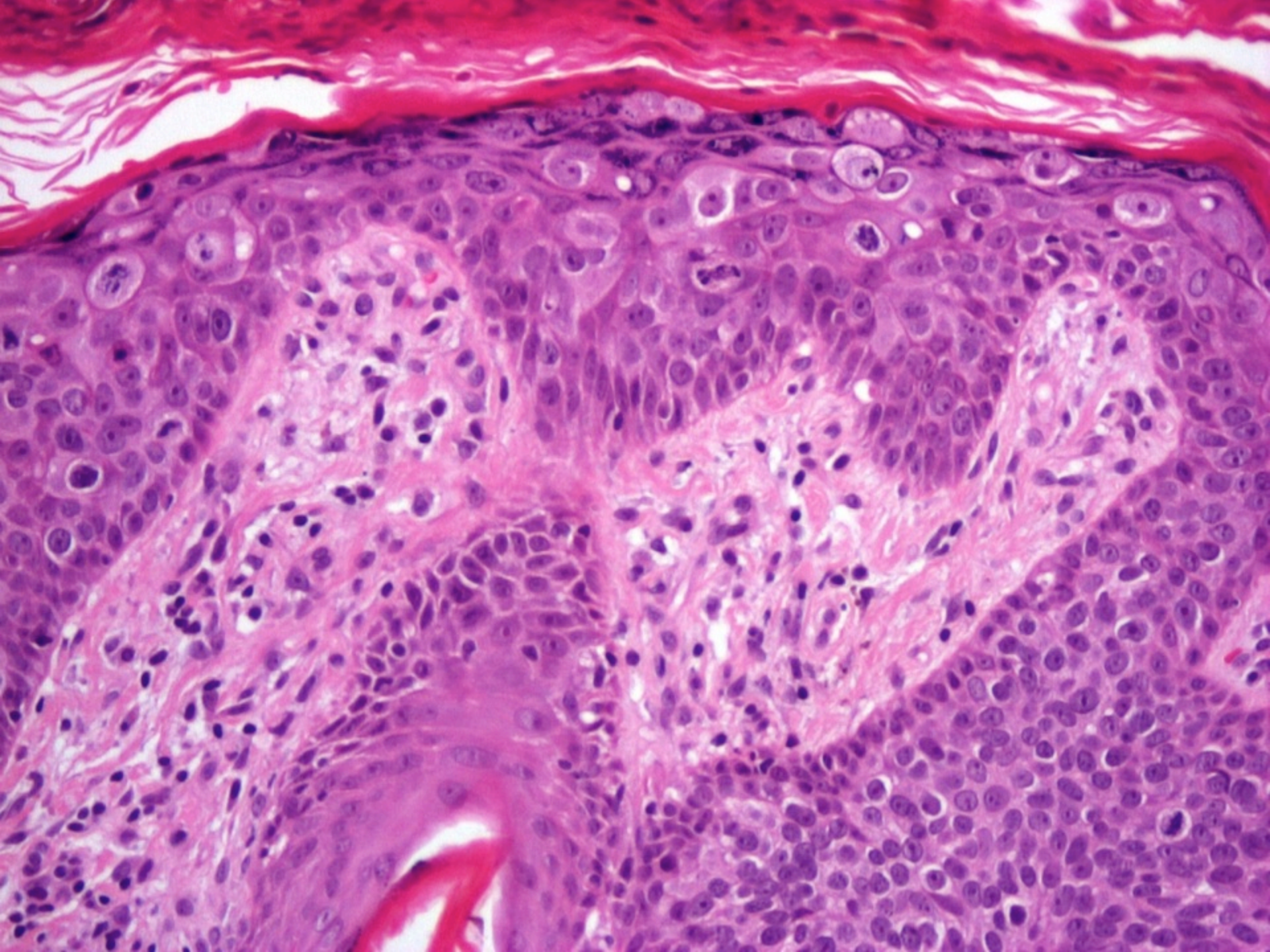
Squamous Cell Carcinoma In Situ

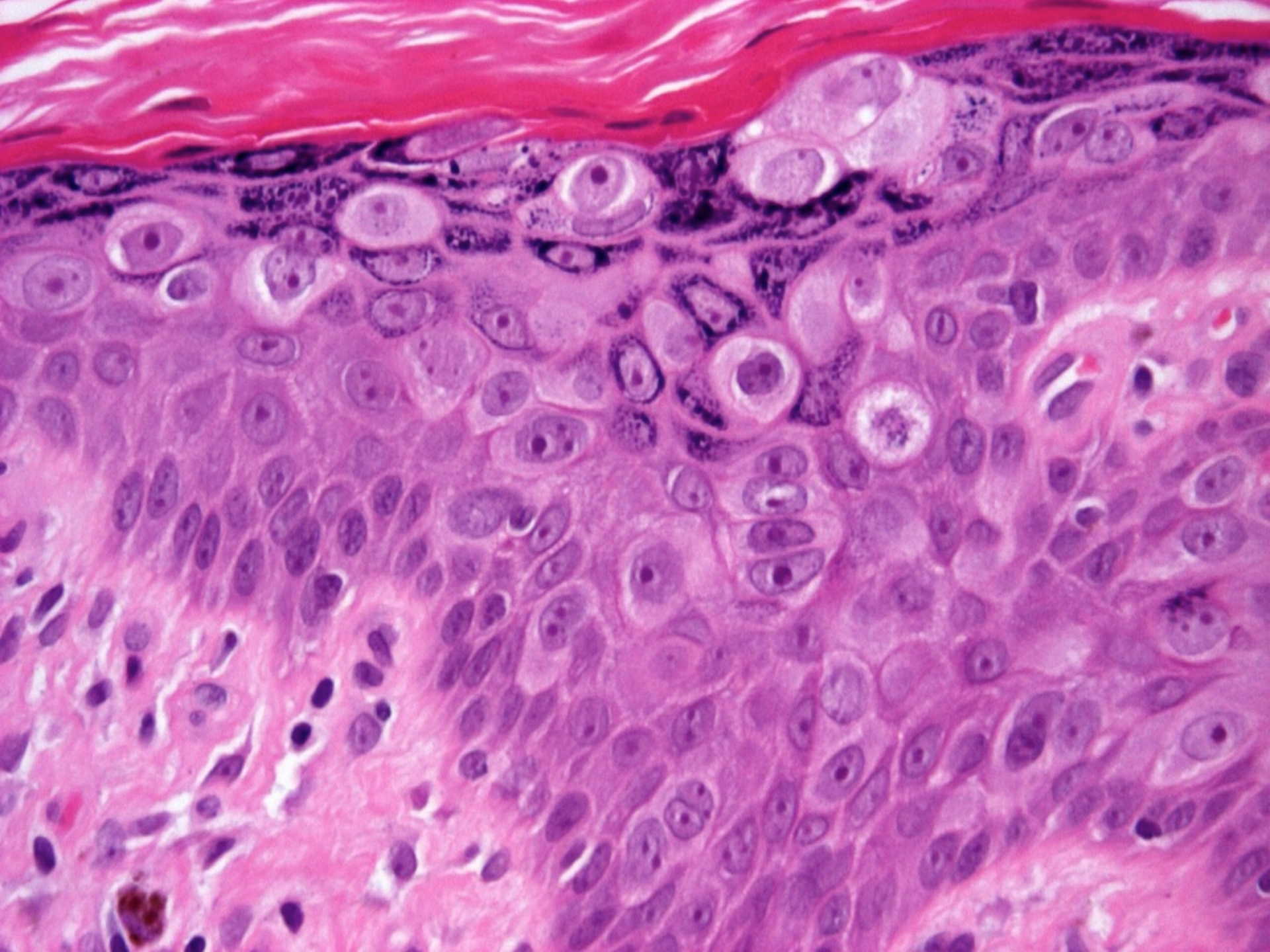
-Clinical-

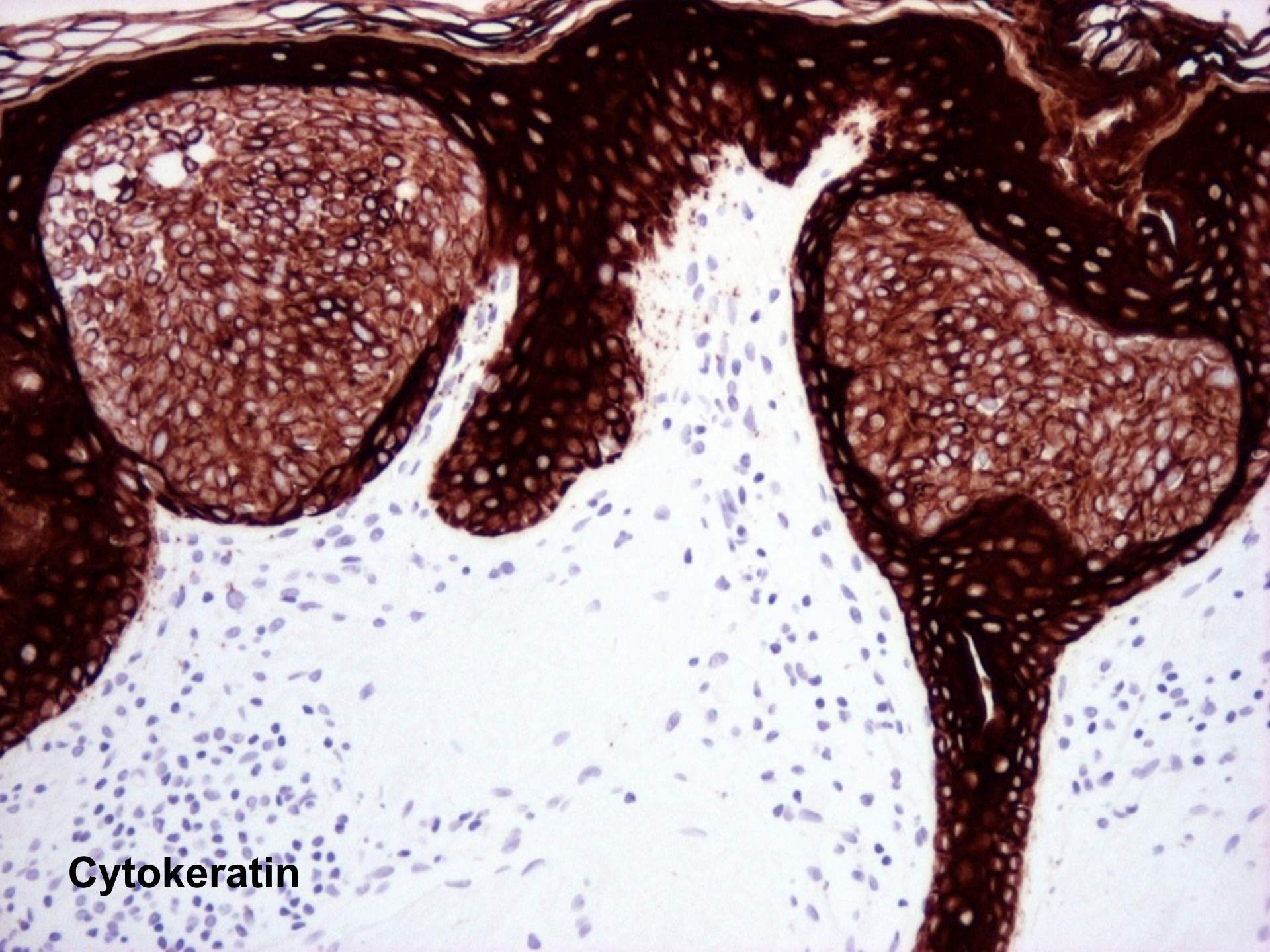
- **Erythematous plaques**
- **Potentially pigmented**
- **Sun-damaged skin**
- **Head and neck, hands**
- **Elderly adults**
- **Fair complexion**











Cytokeratin

Other Keratinocytic Neoplasms

-Clinical-

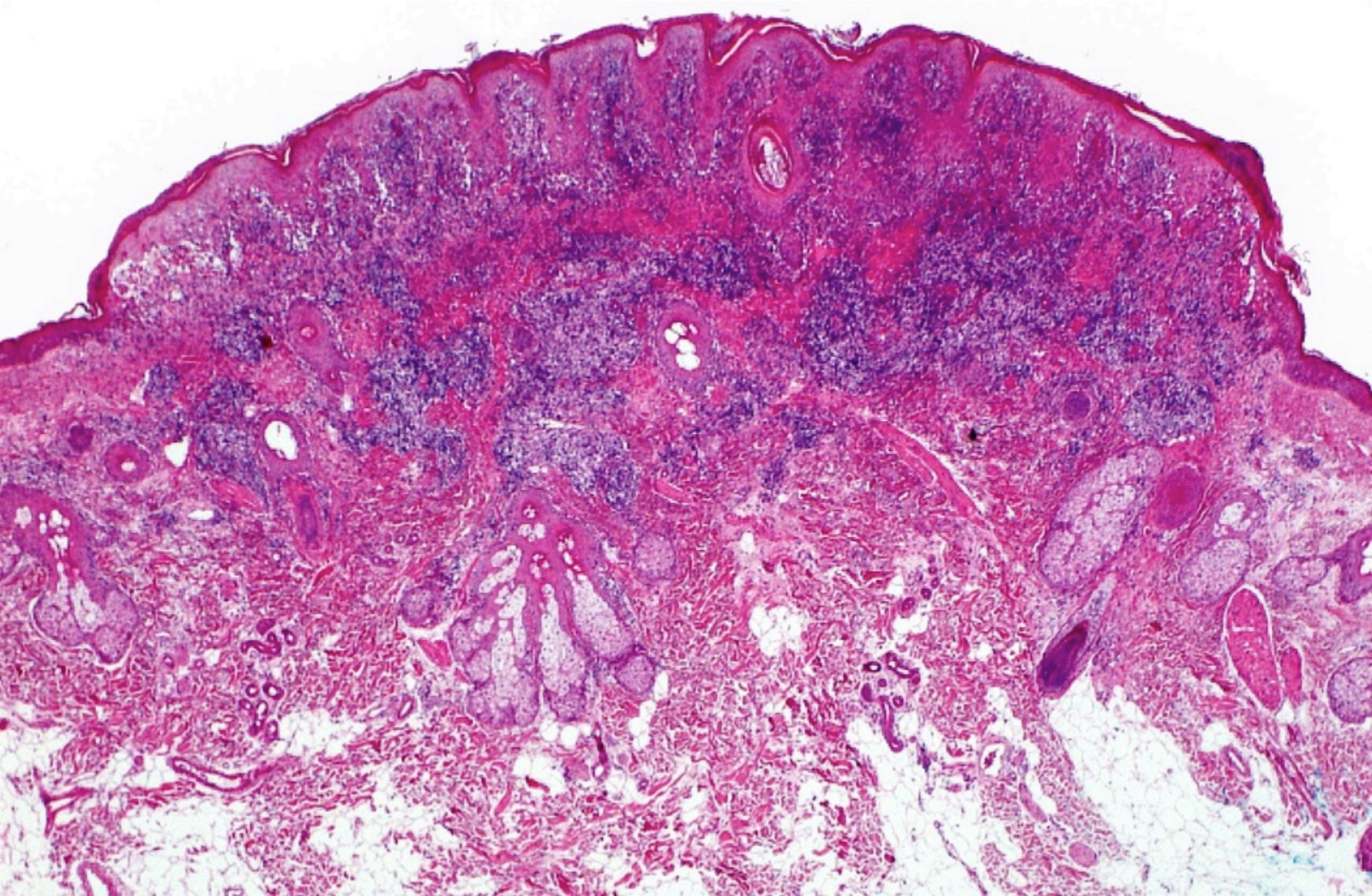
Presentation on sun-exposed / sun-damaged skin

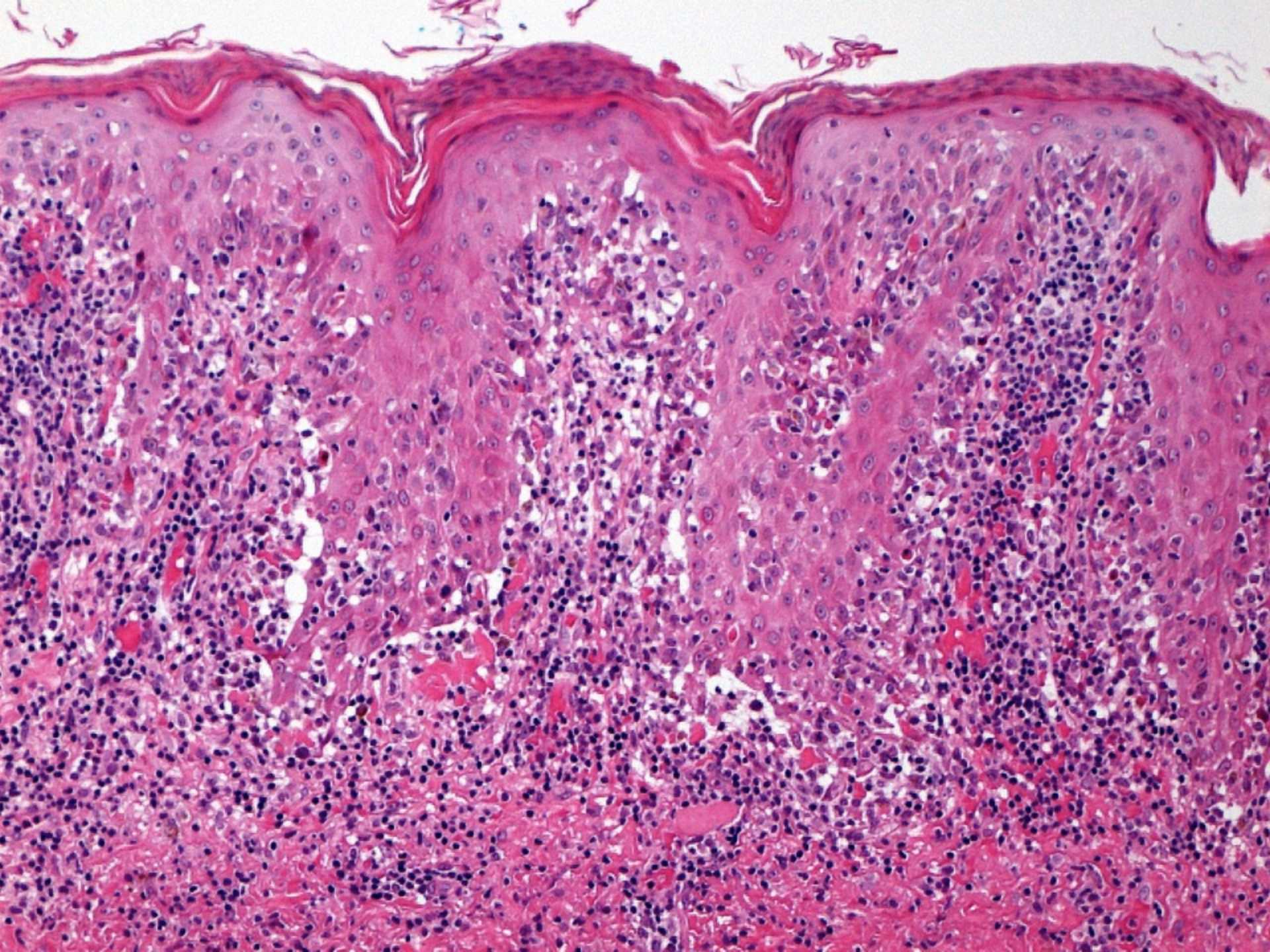
Elderly adulthood

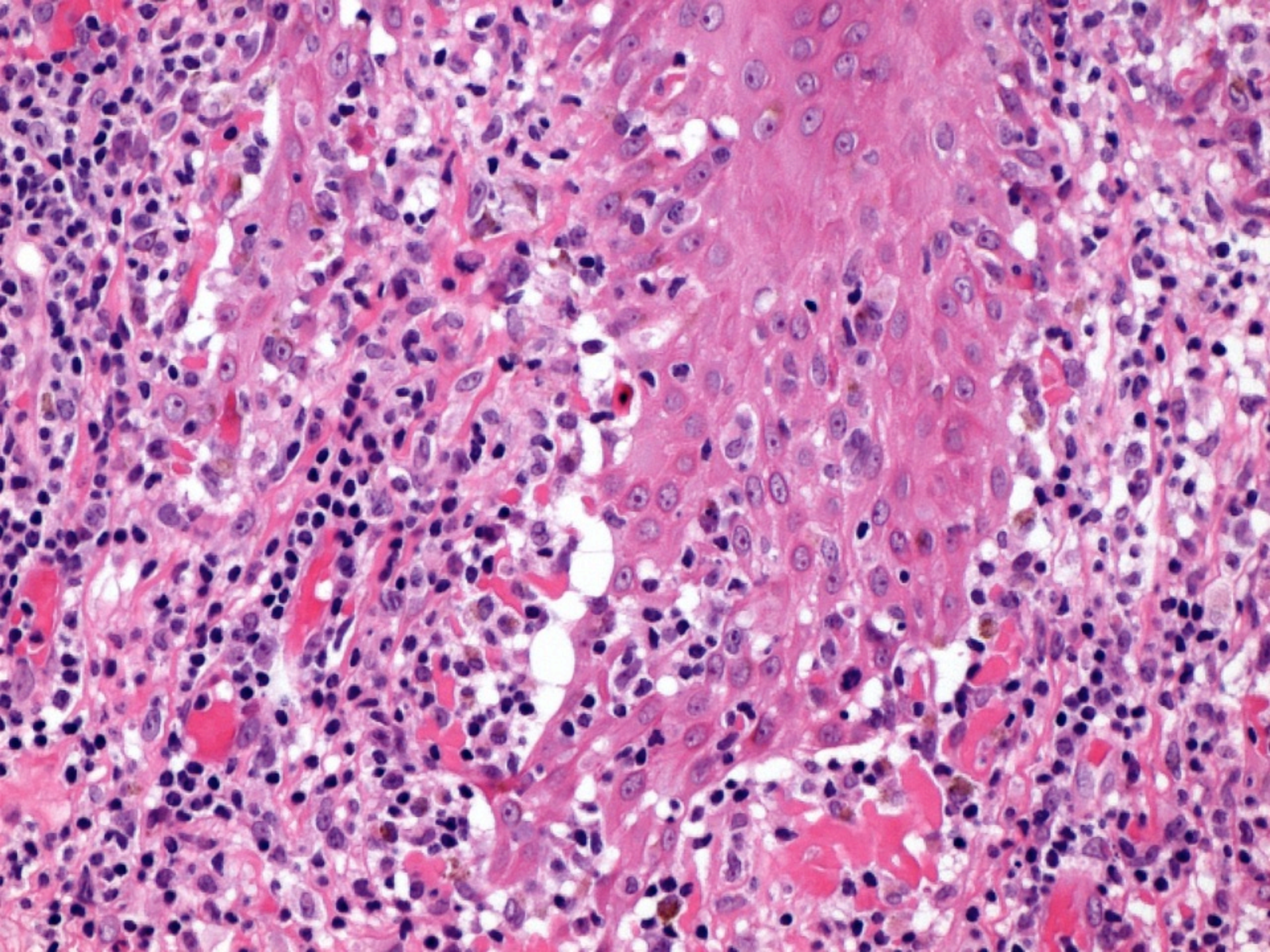
Fair skinned individuals

Often clinically pigmented and clinical distinction from melanoma (i.e. lentigo maligna) difficult

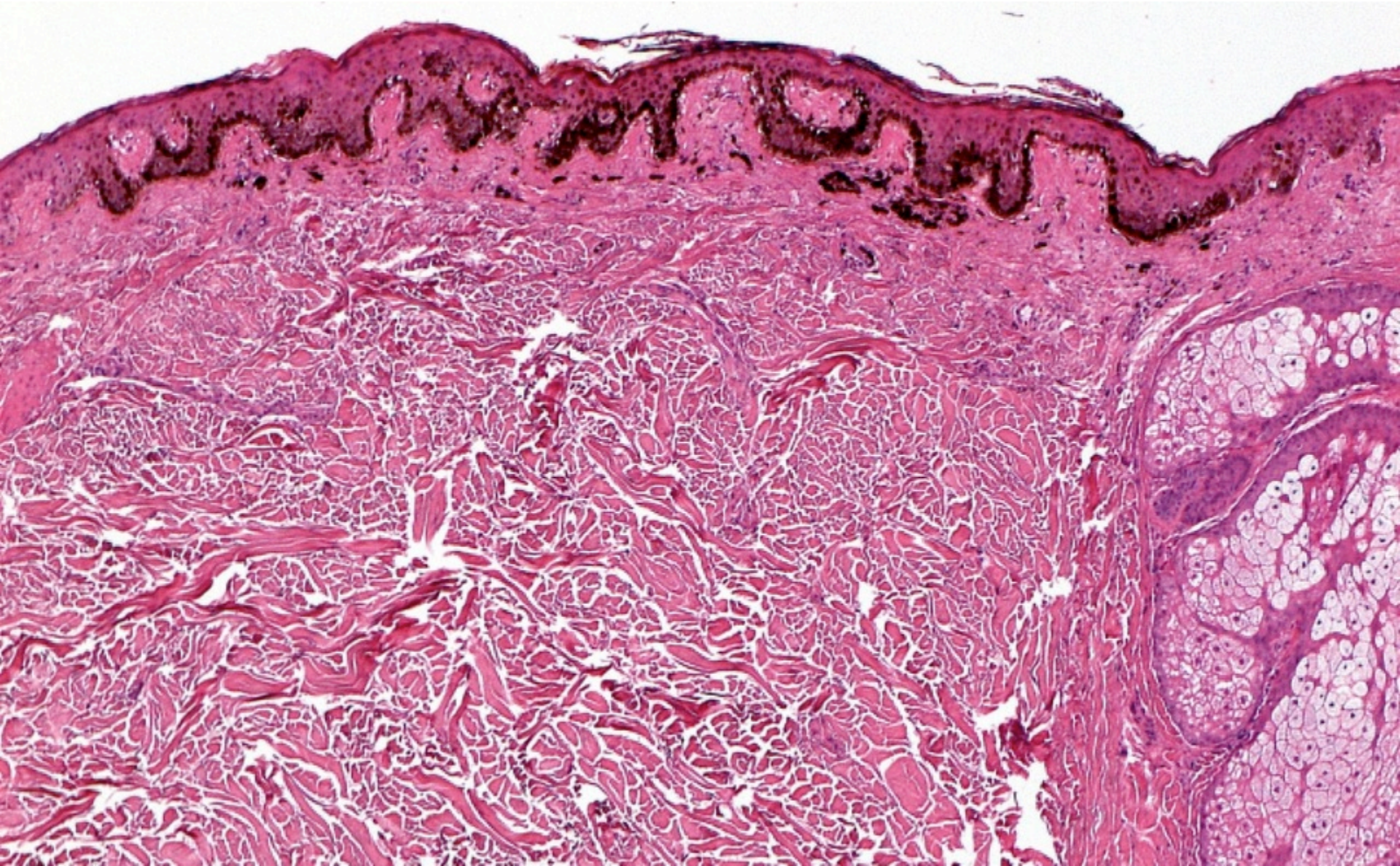
Lichenoid Keratosis

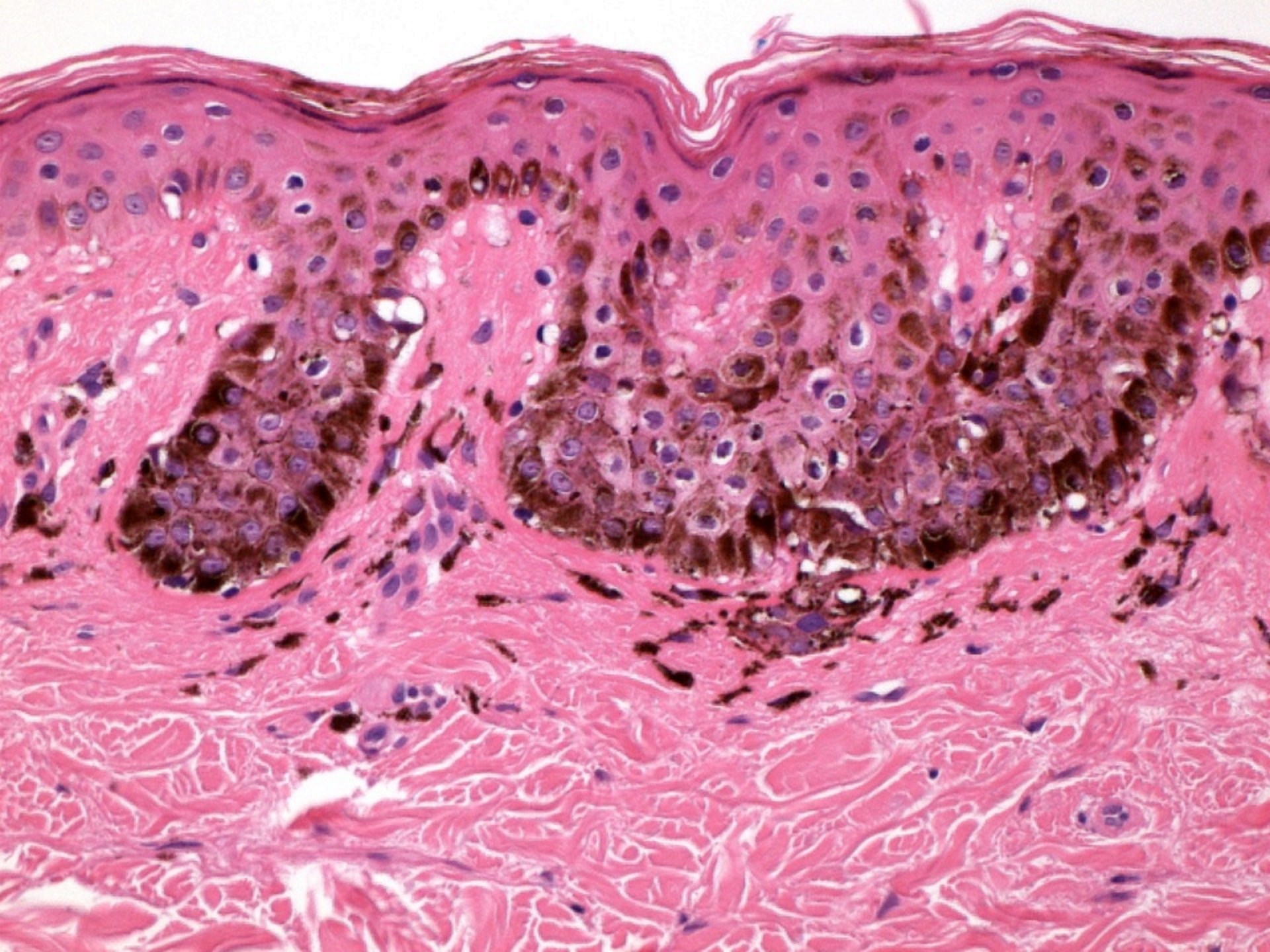


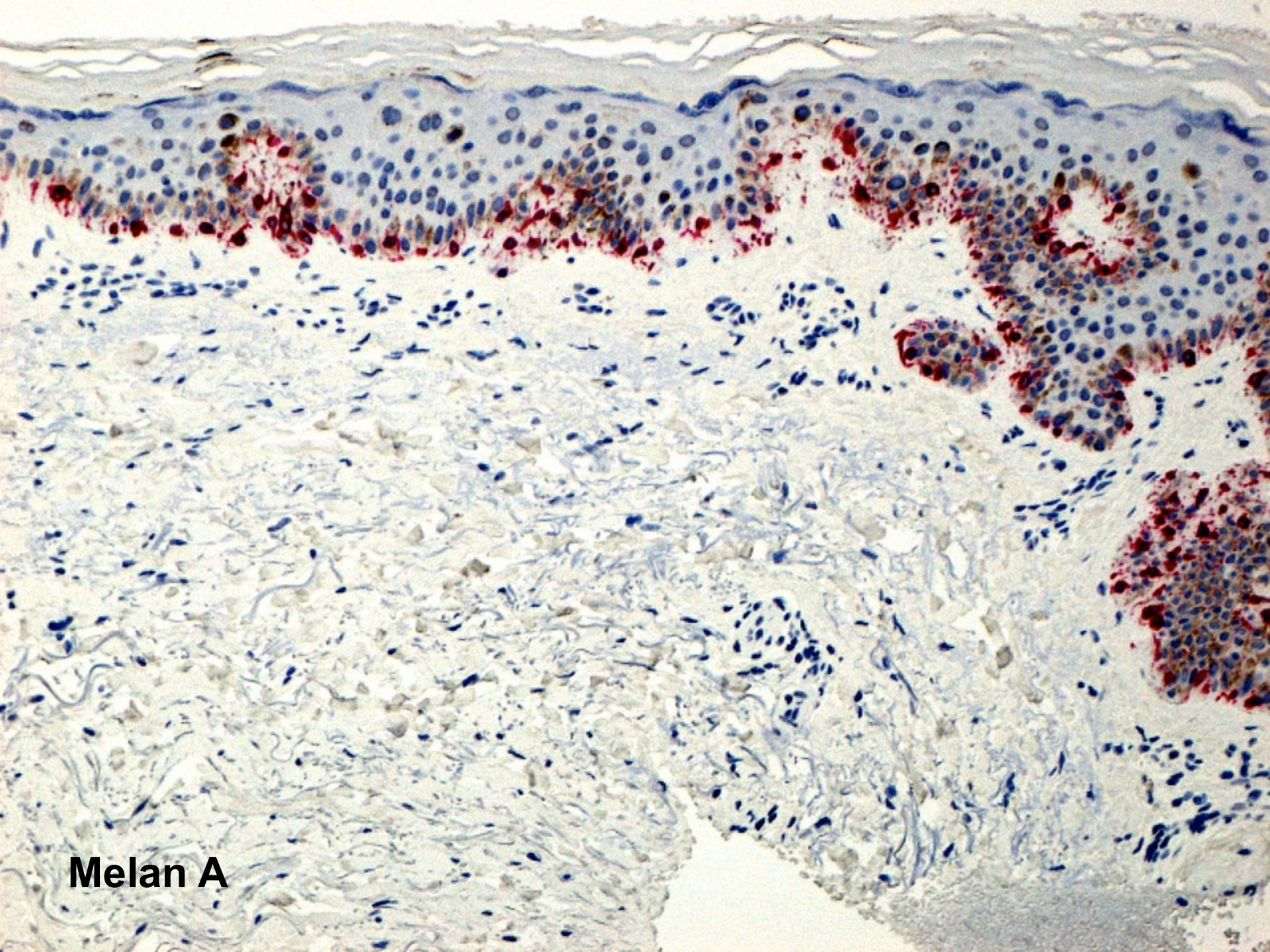




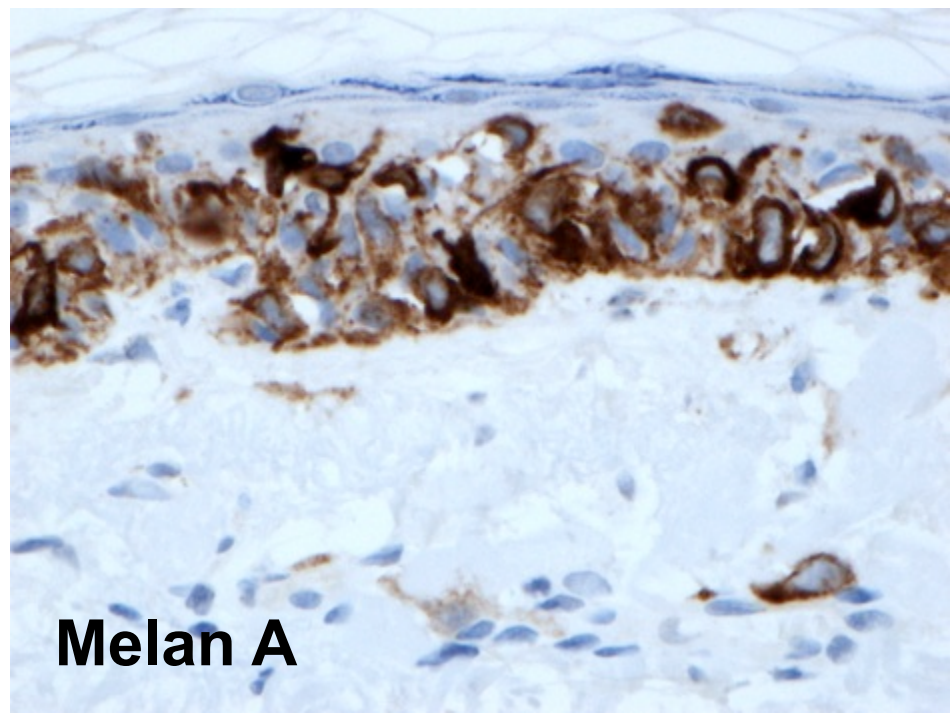
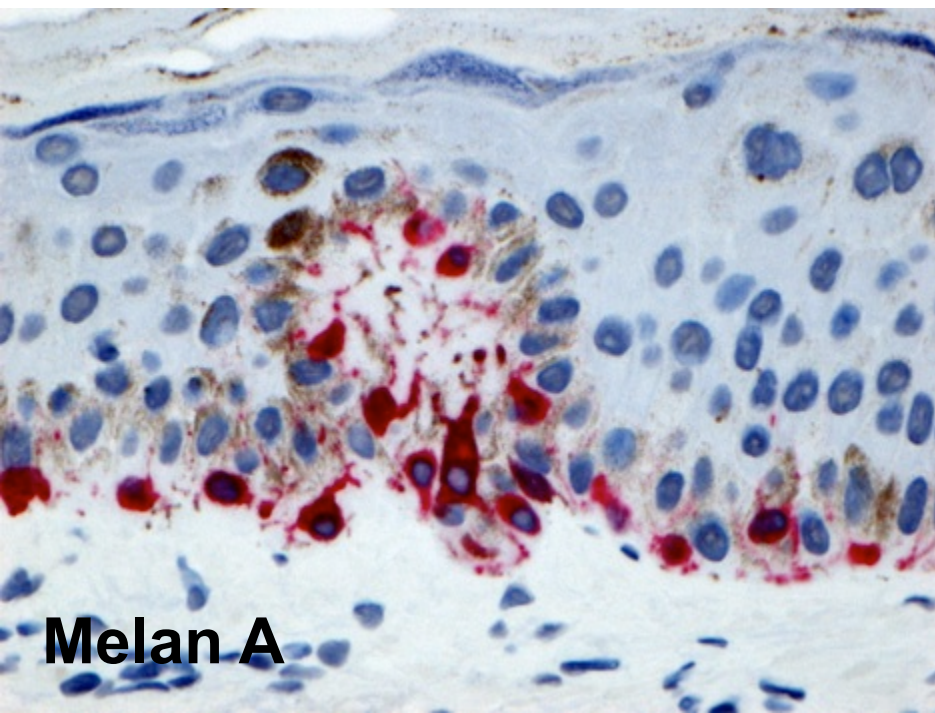
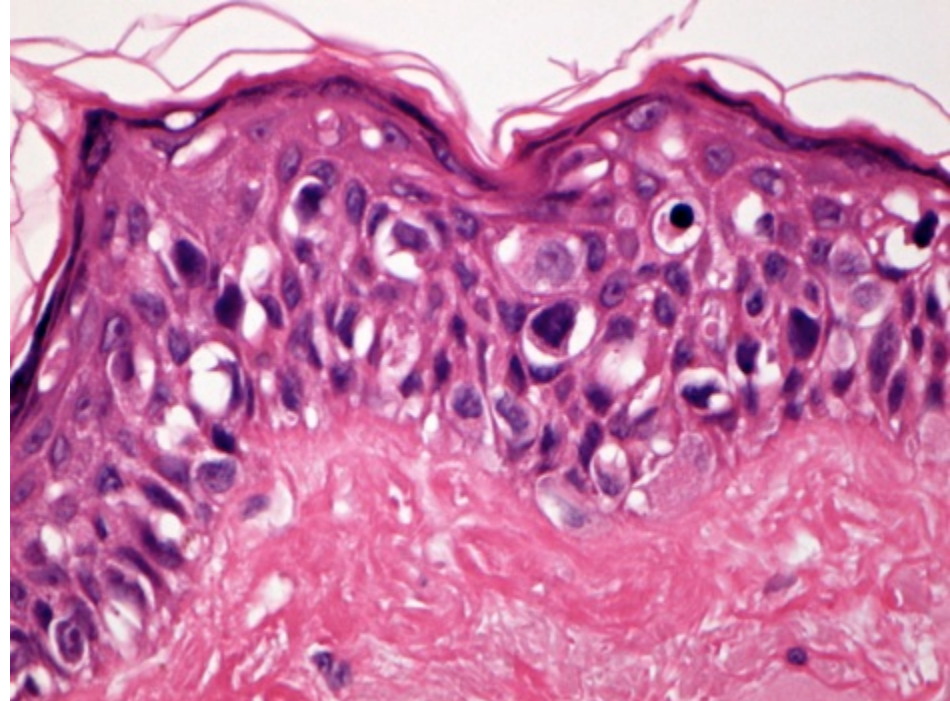
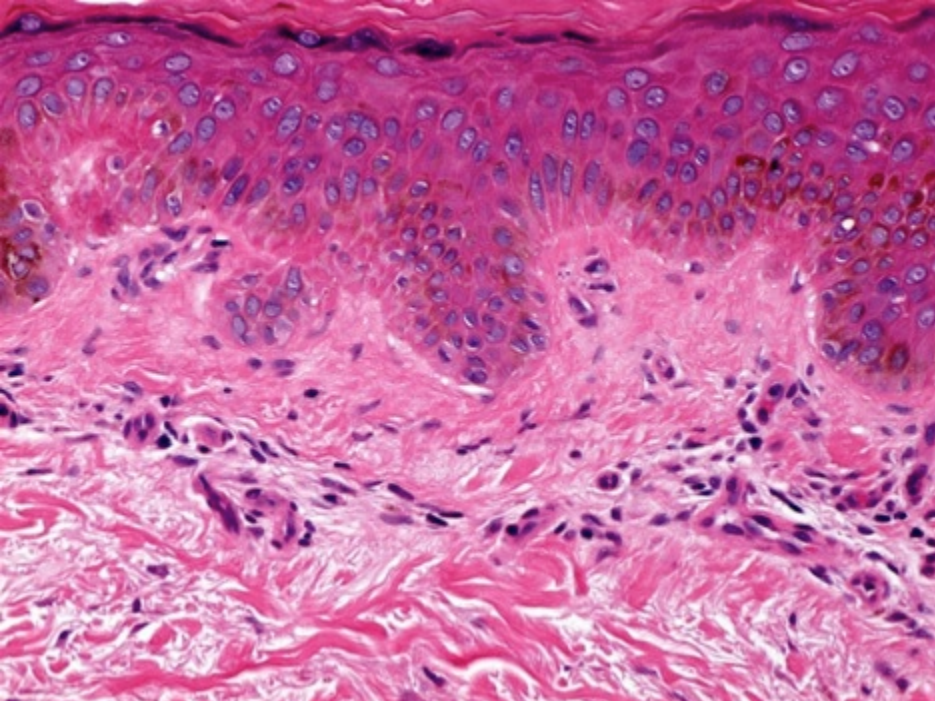
Solar Lentigo



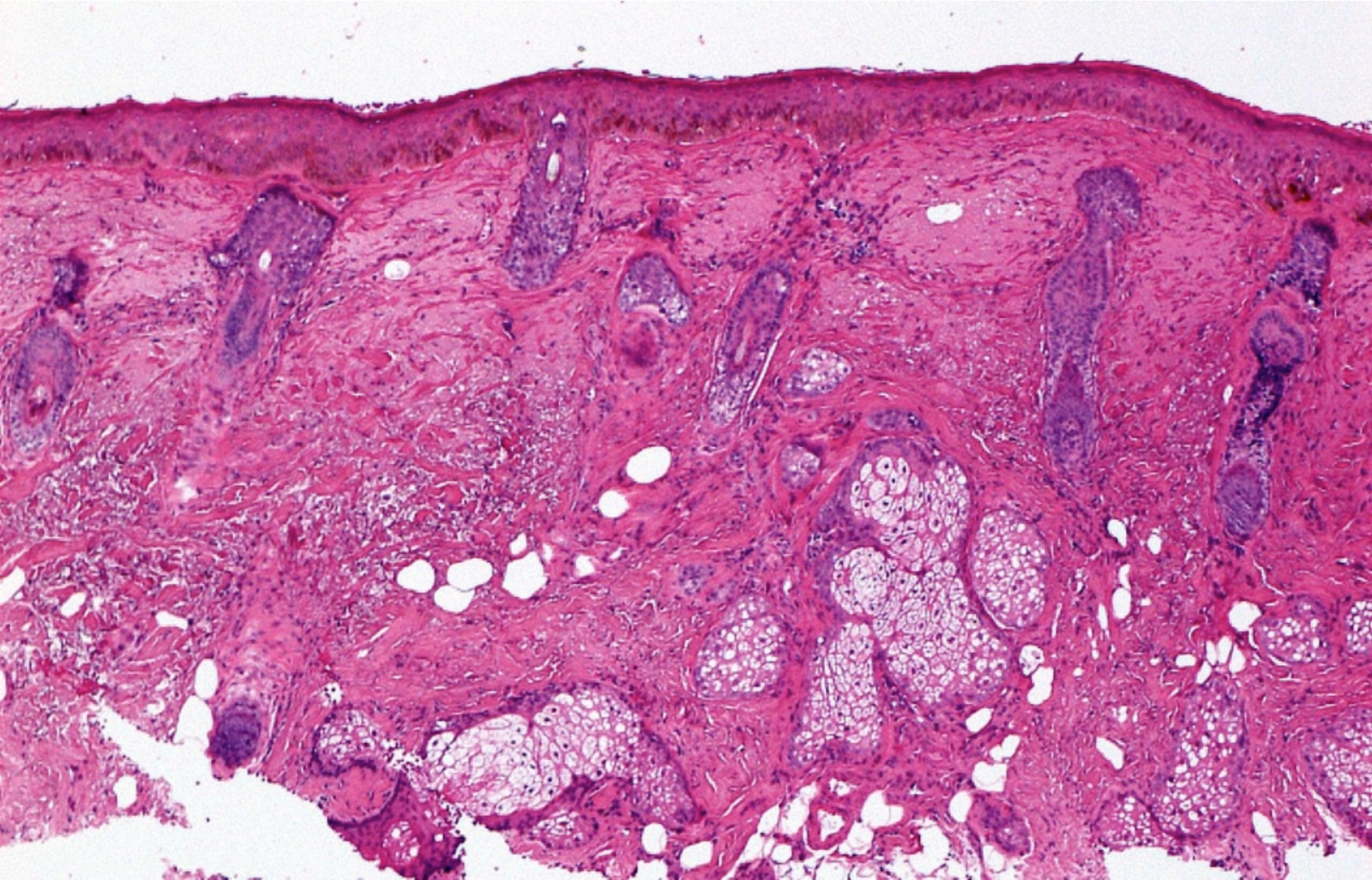


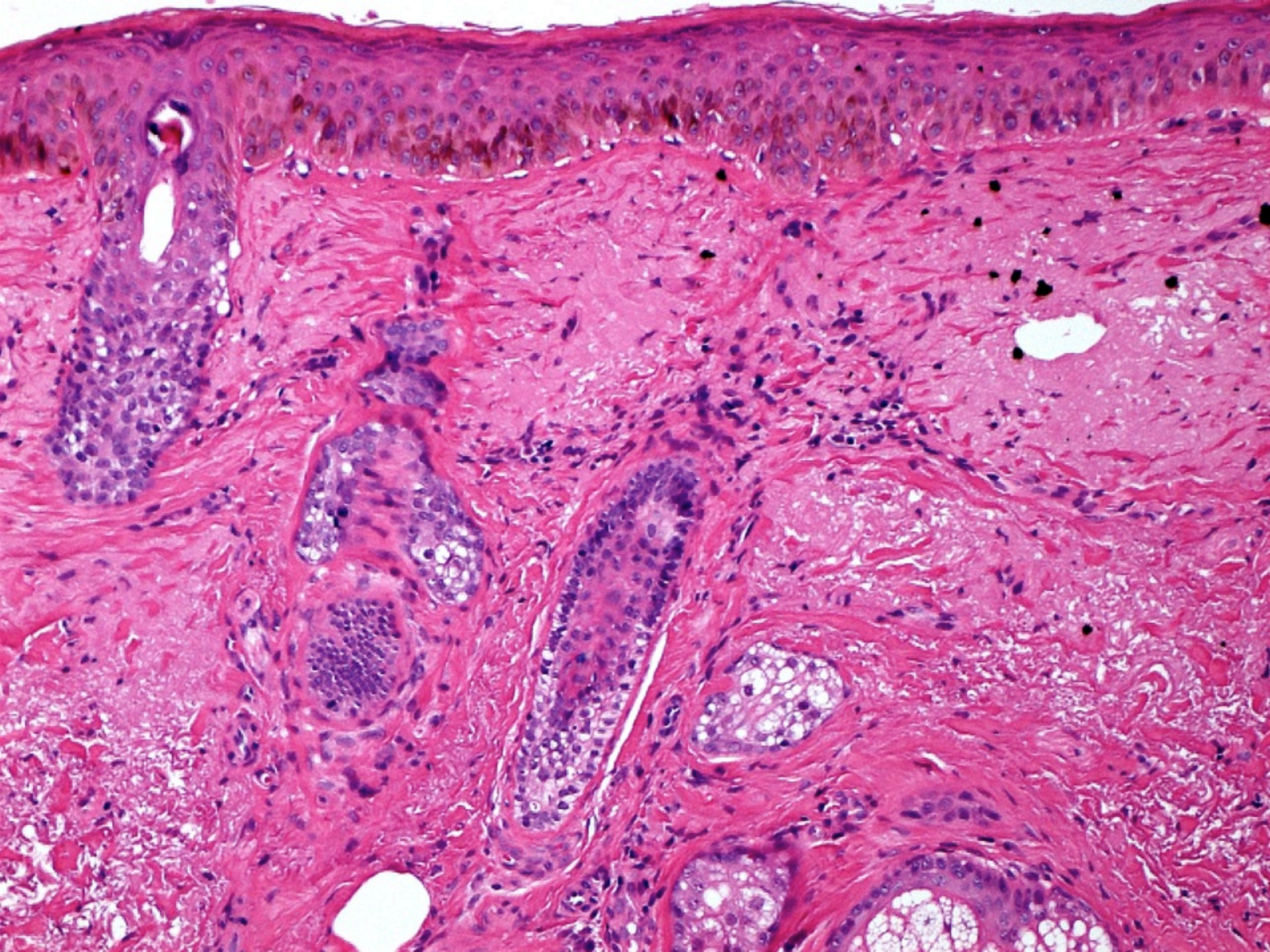


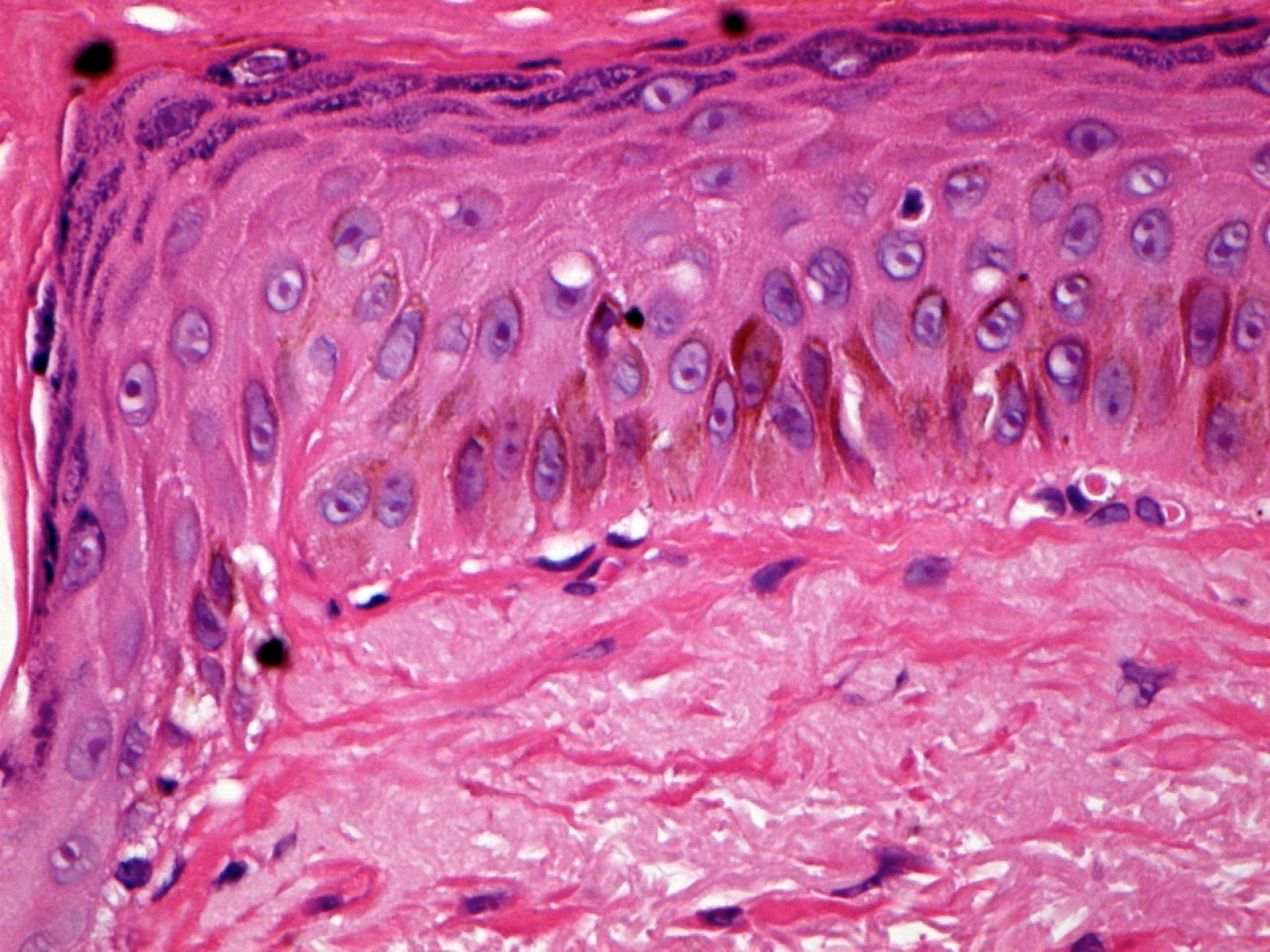
Melan A

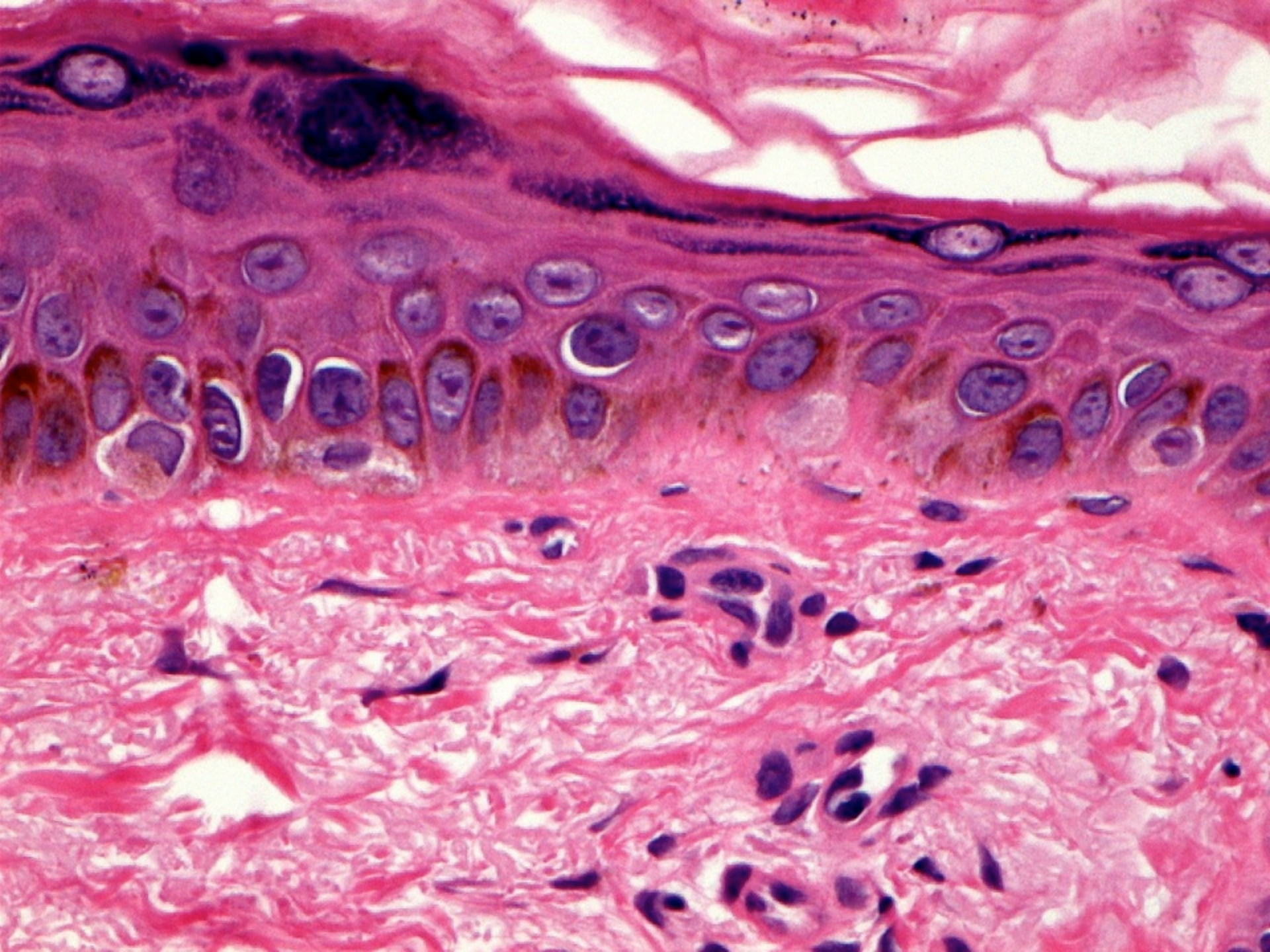


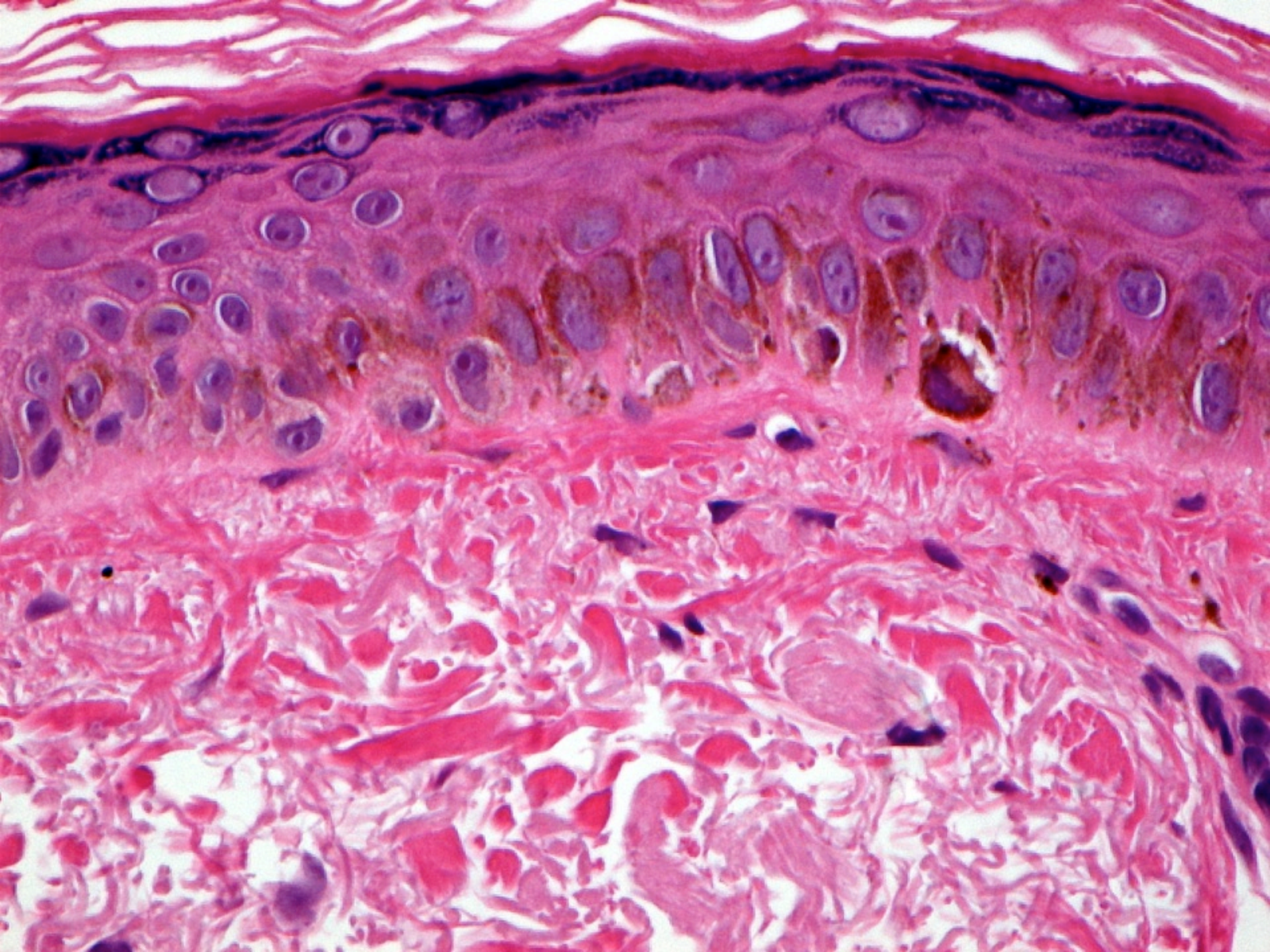
Pigmented Actinic Keratosis

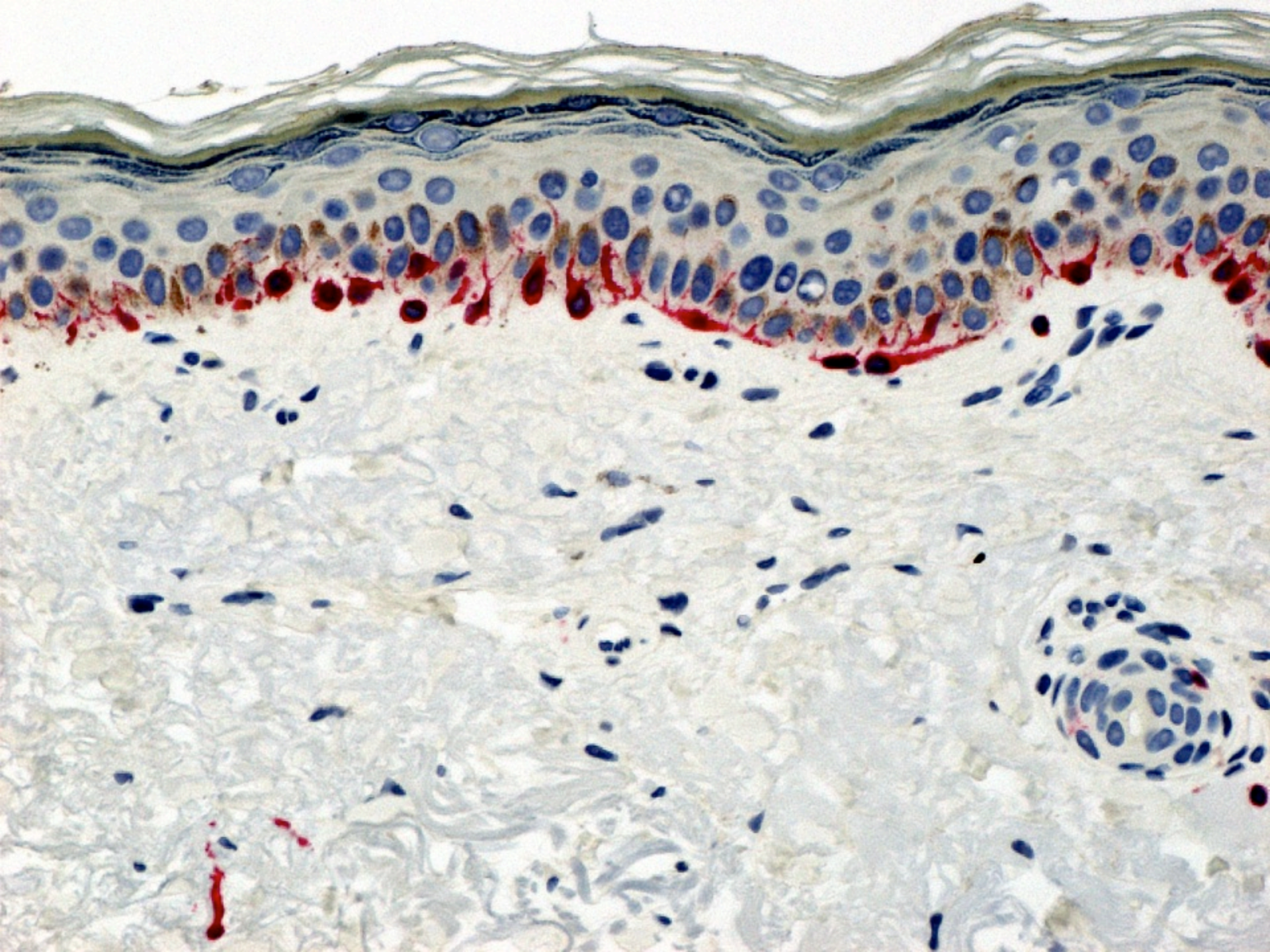


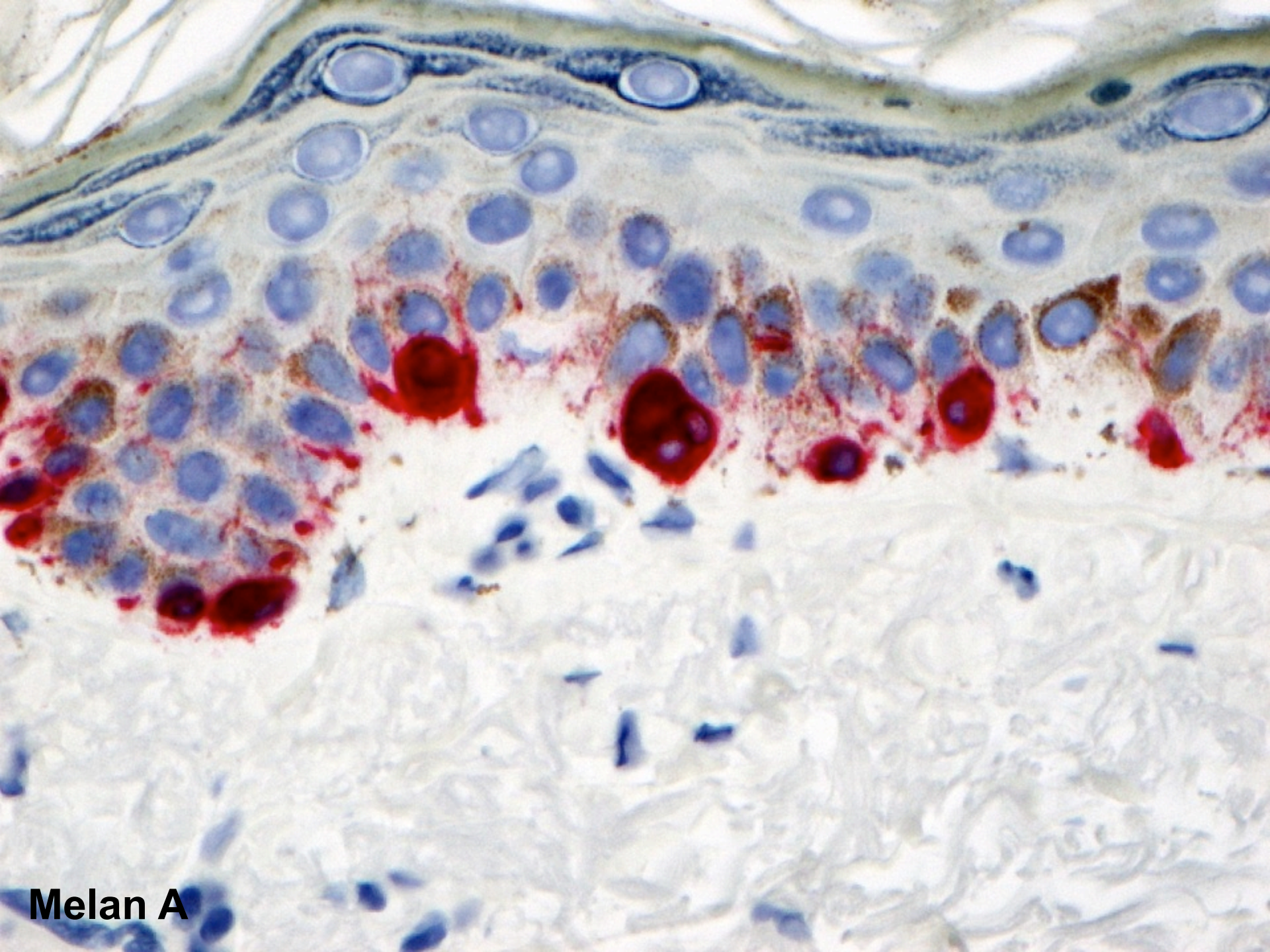












Melan A

Pigmented Actinic Keratosis

-Summary-

- **Significant clinical overlap and histological distinction challenging**

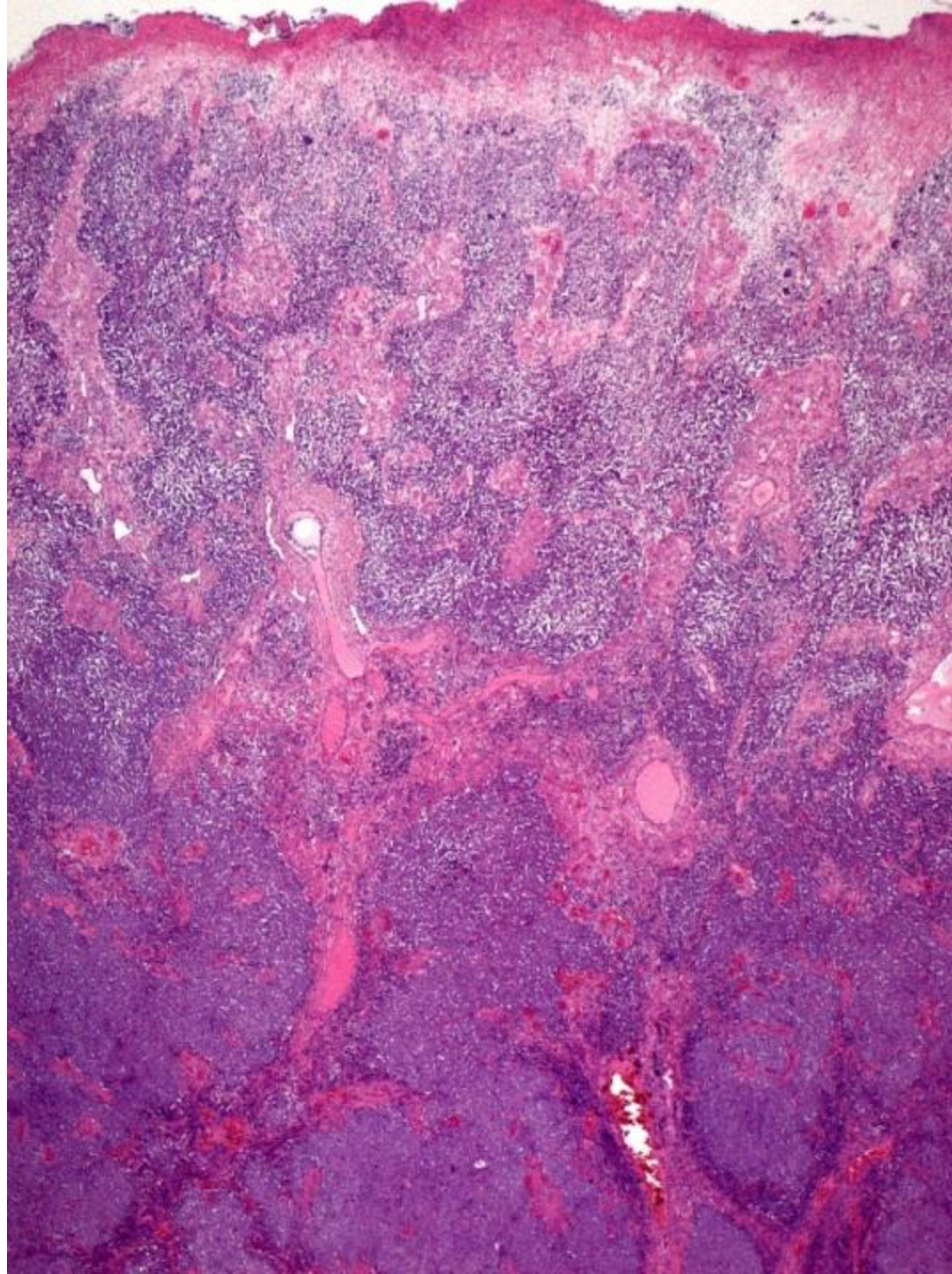
BUT

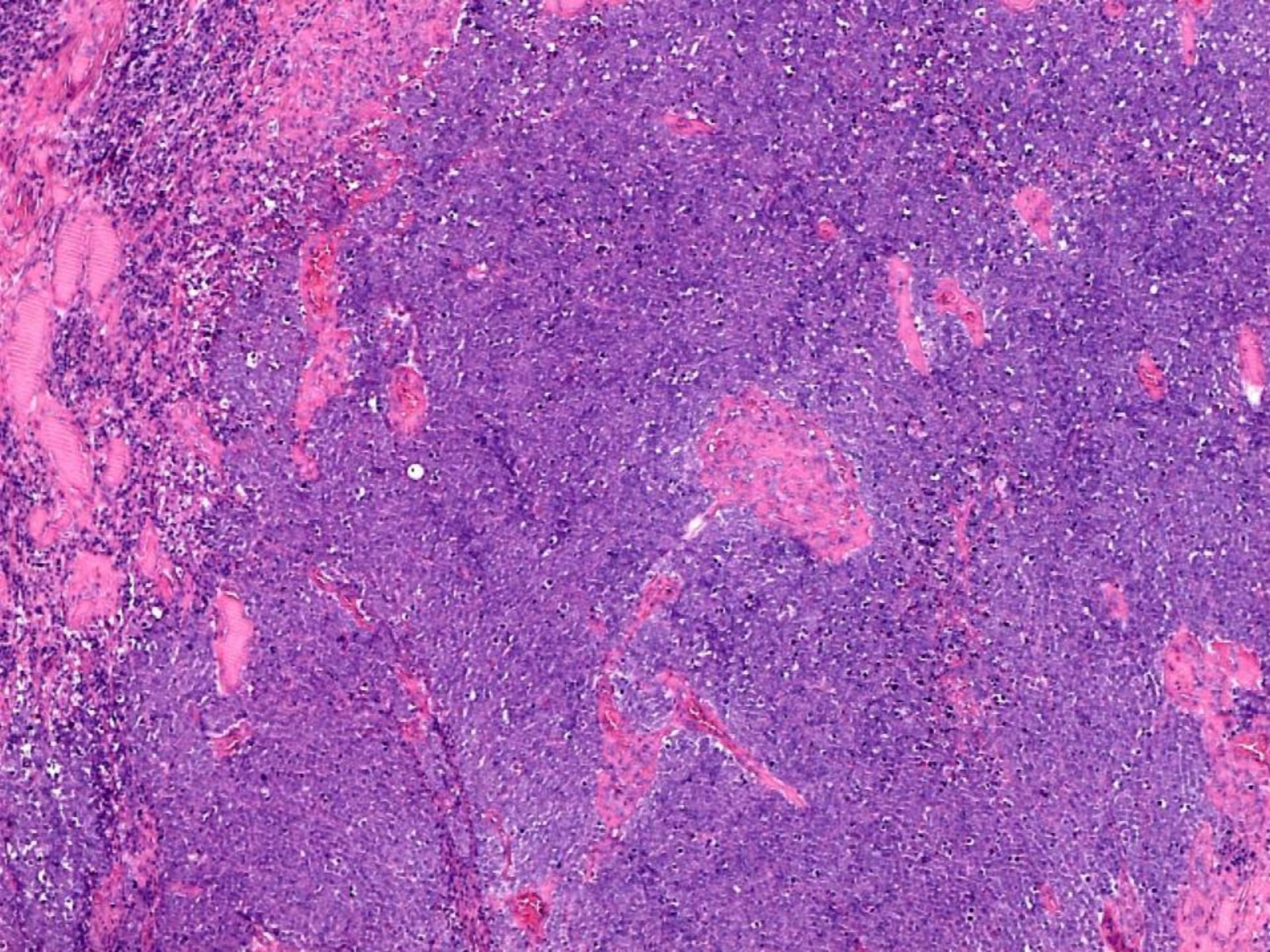
- **Red Melan A immunohistochemistry often helpful**
- **Repeat biopsy may be necessary especially if clinical concern for LM**

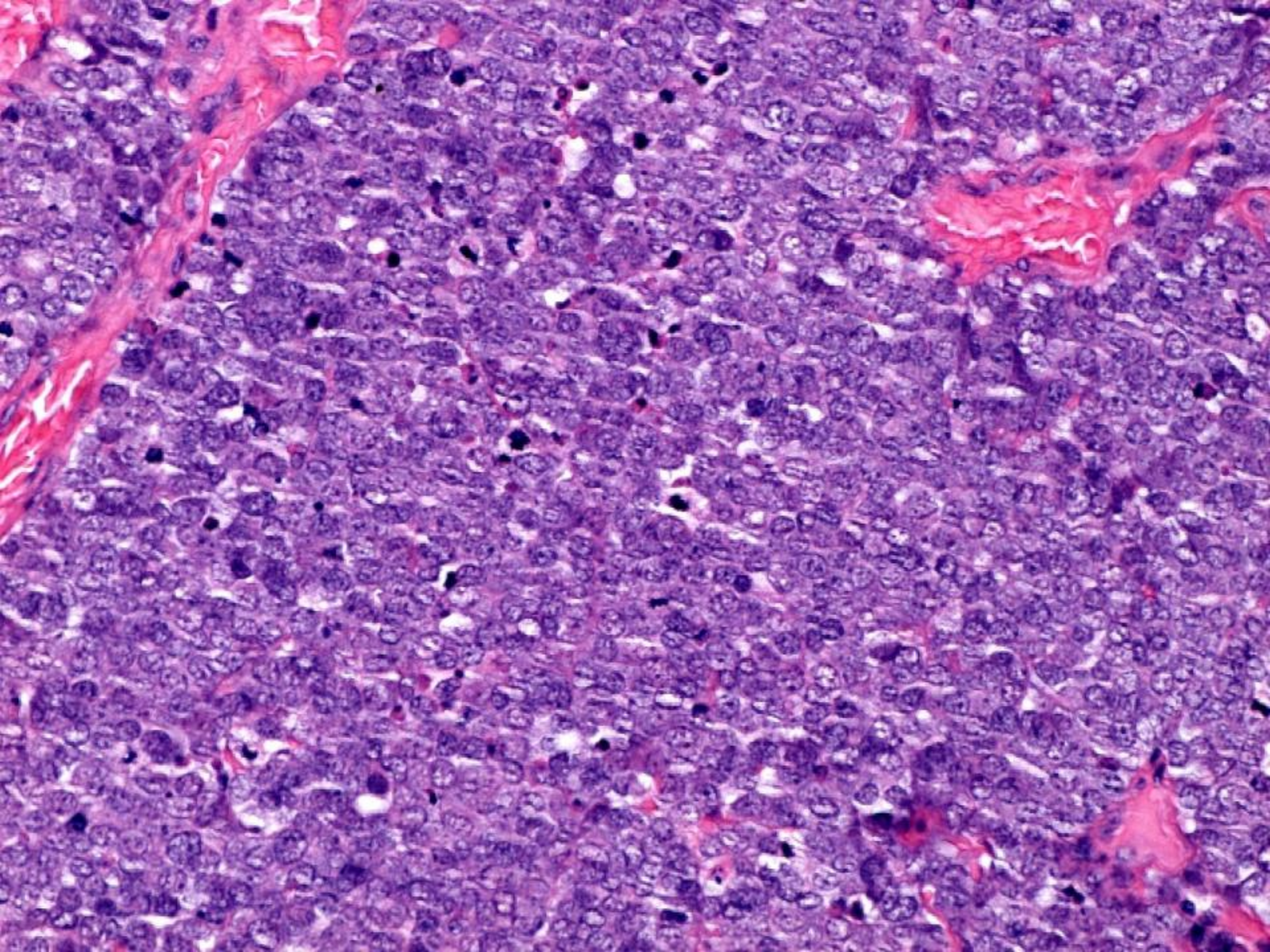
Merkel Cell Carcinoma

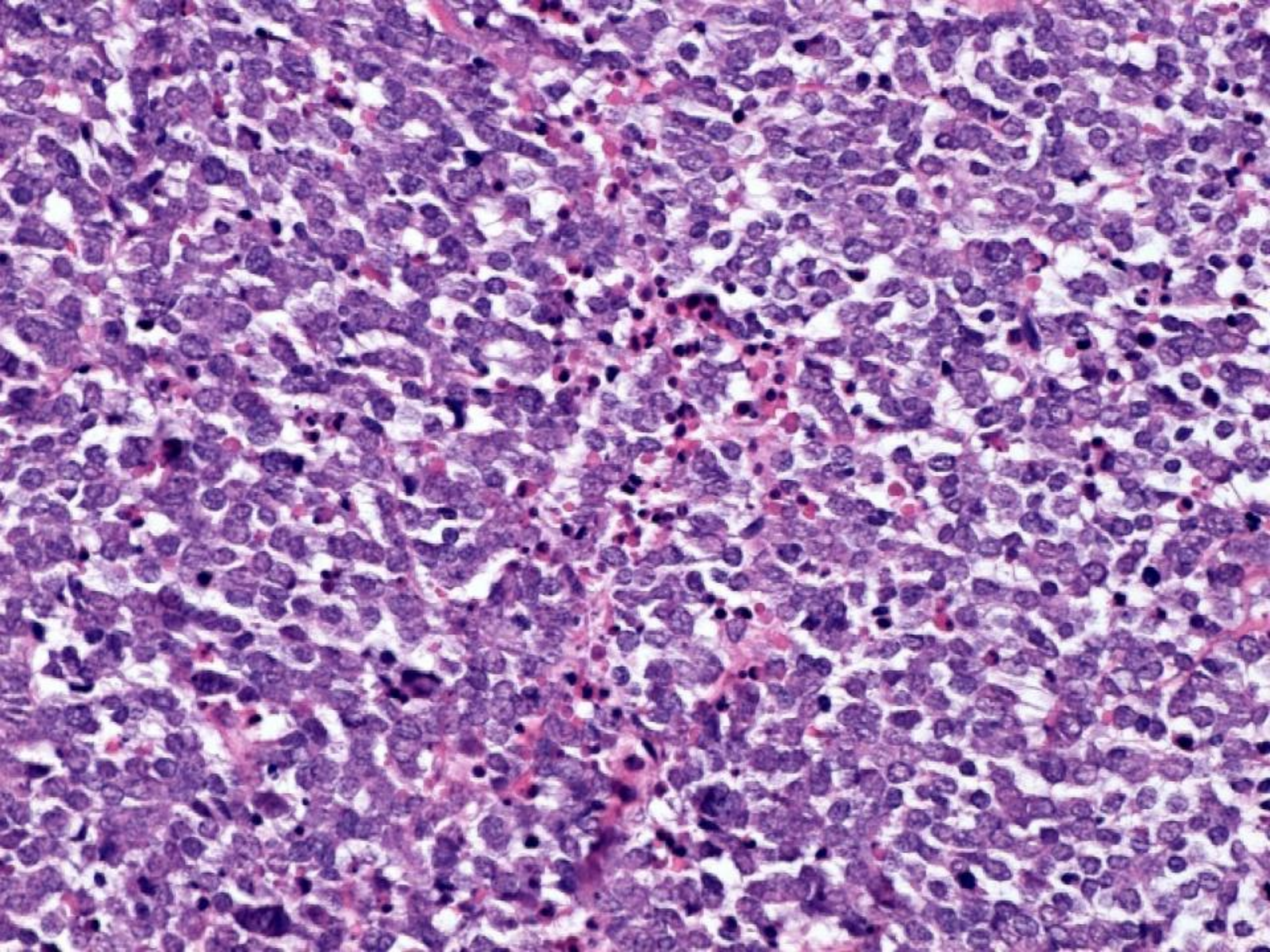
-Clinical-

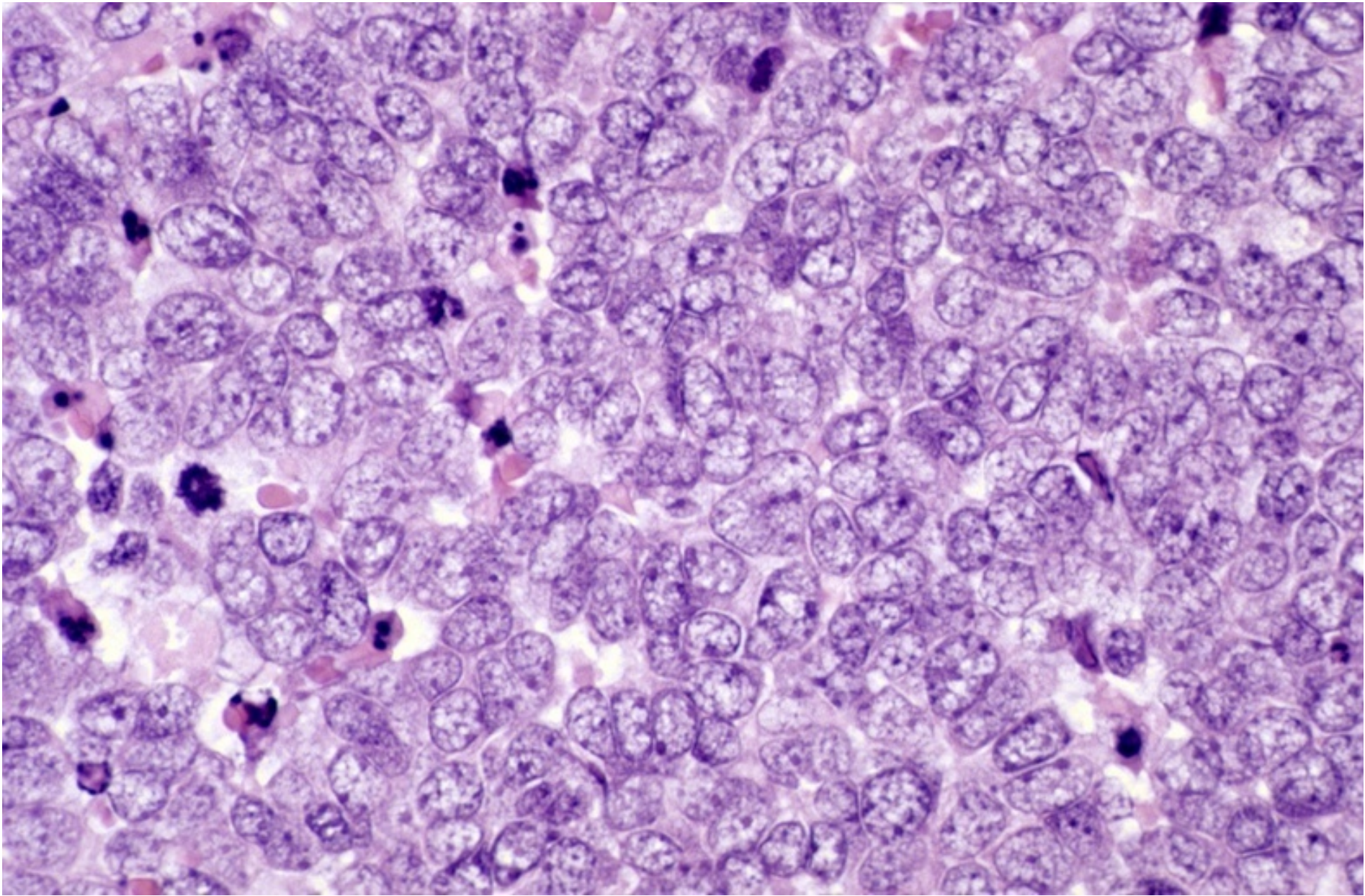
- **Rare but aggressive neoplasm**
- **Elderly Caucasians
(0.23/100.000)**
- **Male predominance**
- **Small papules/nodules
(<2cm)**
- **Sun-exposed skin**
- **Head and neck area > extremities**
- **Rarely on sun-protected and mucosal sites**

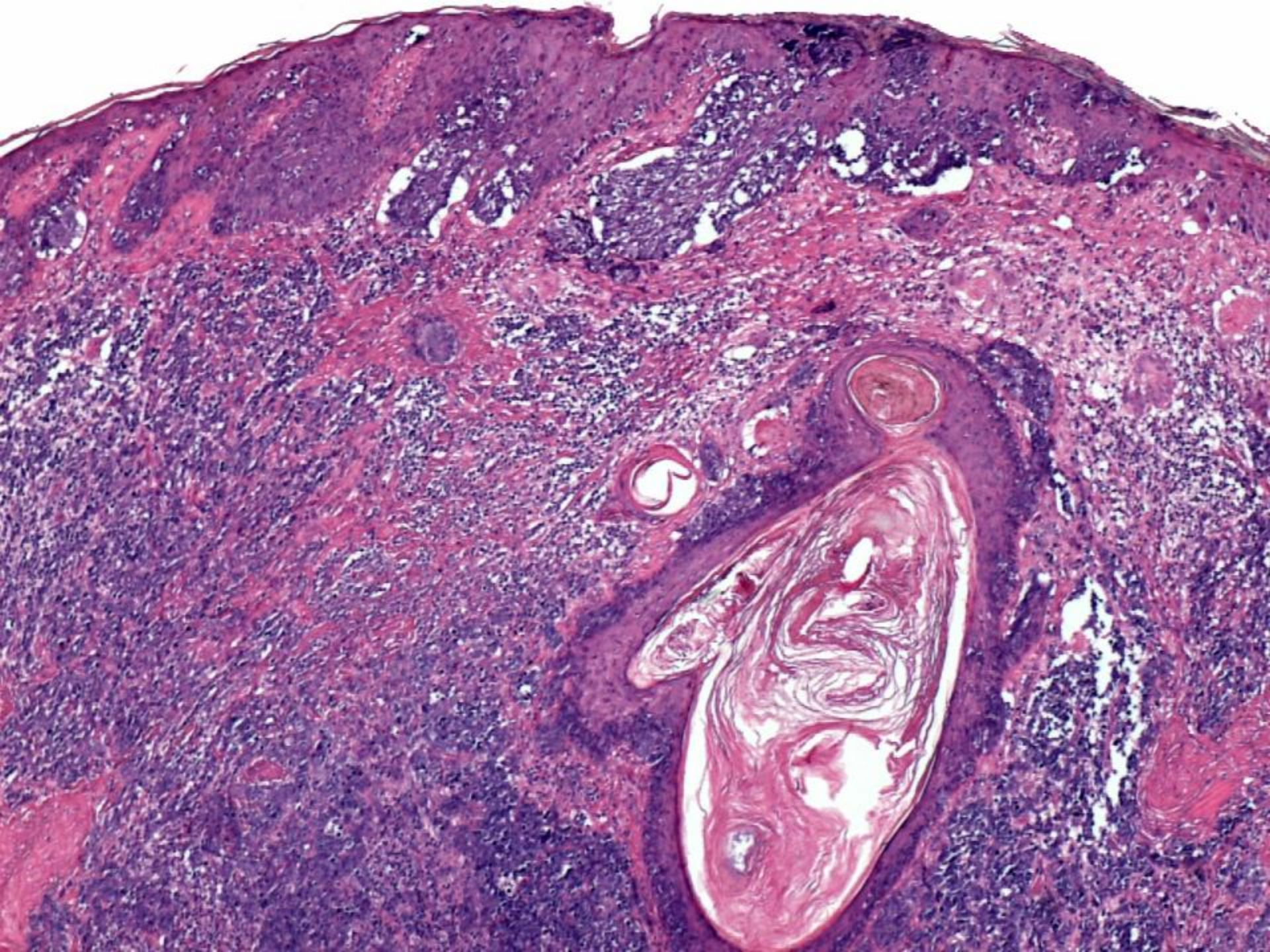


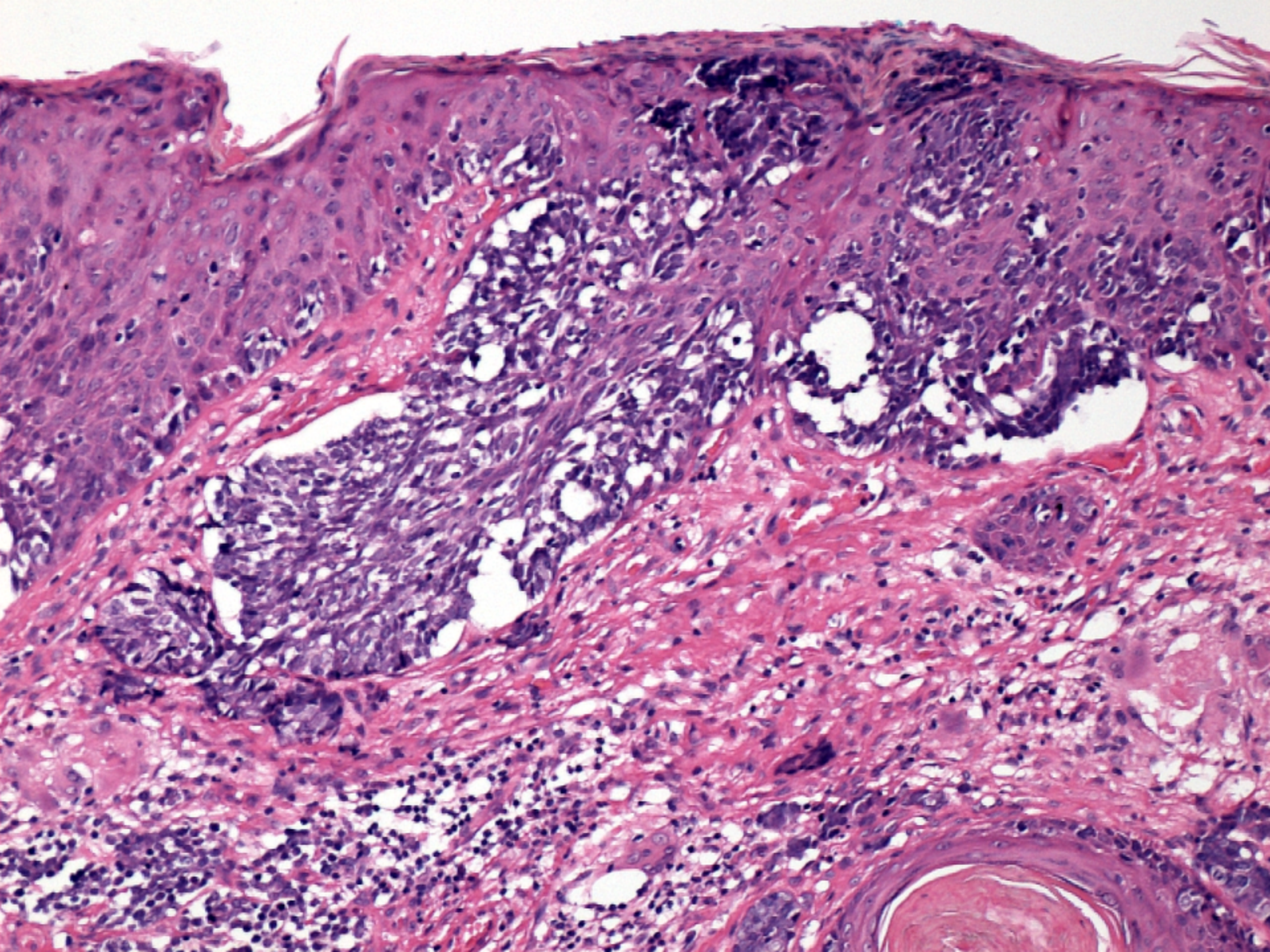




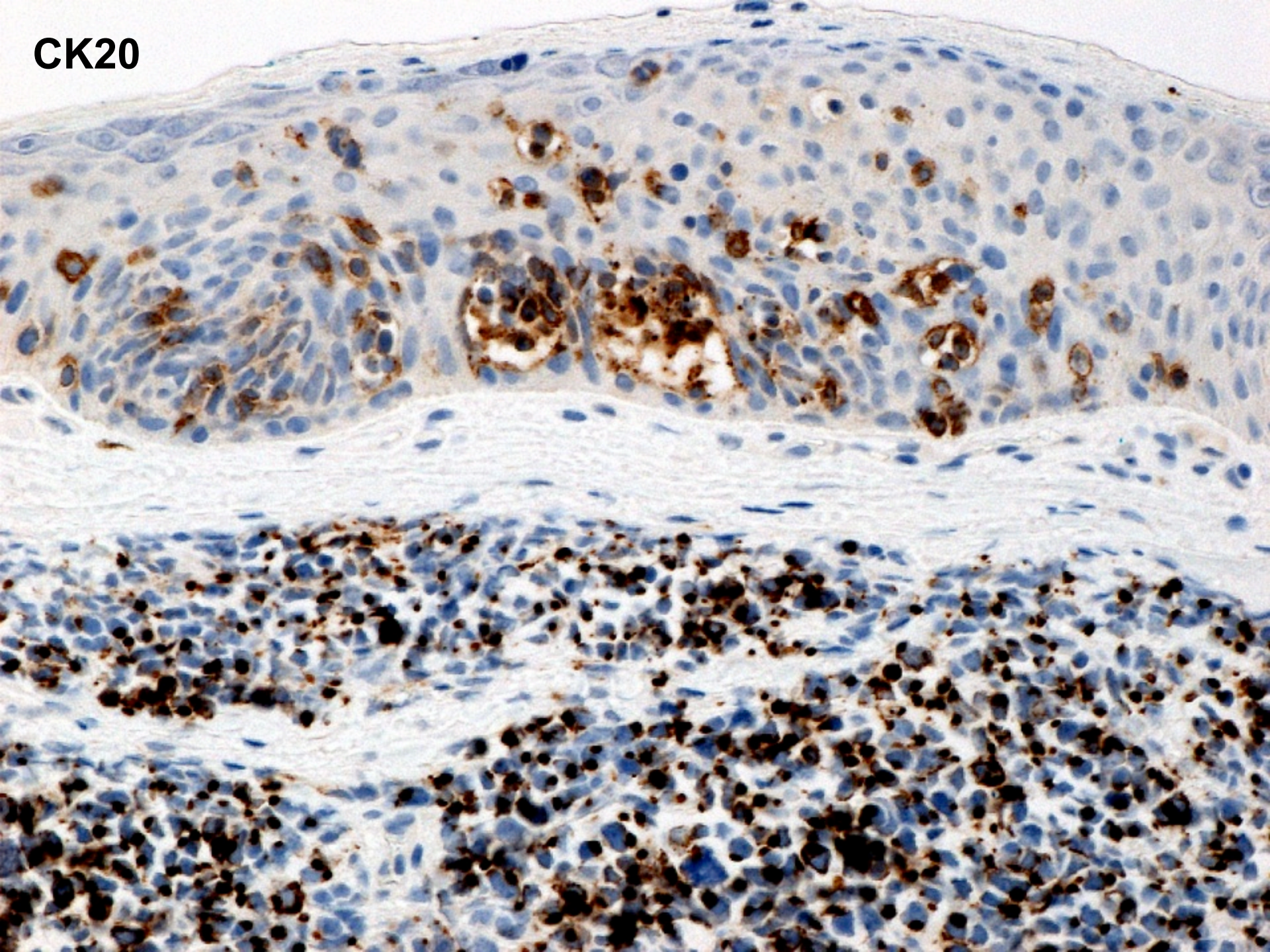


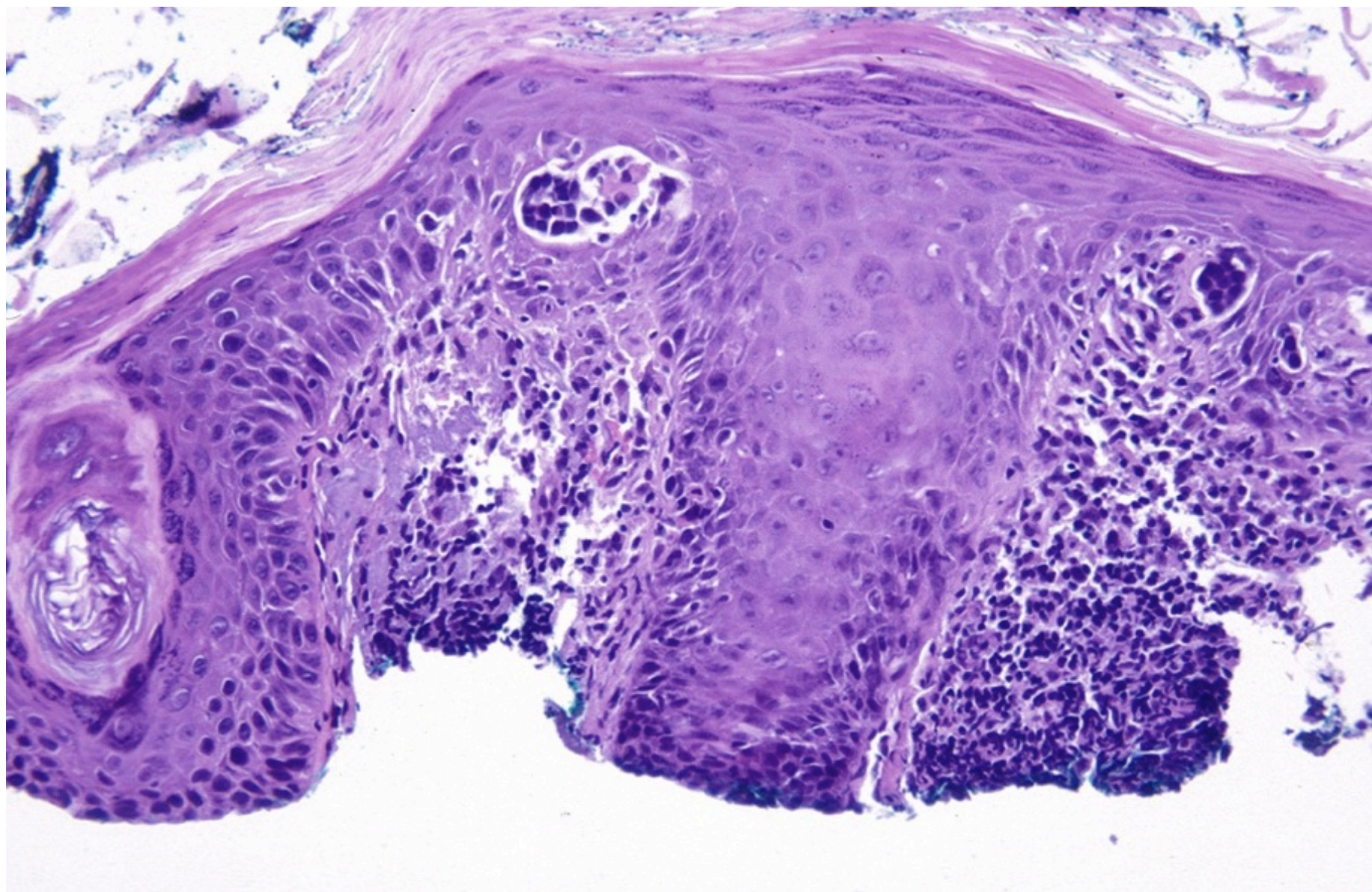


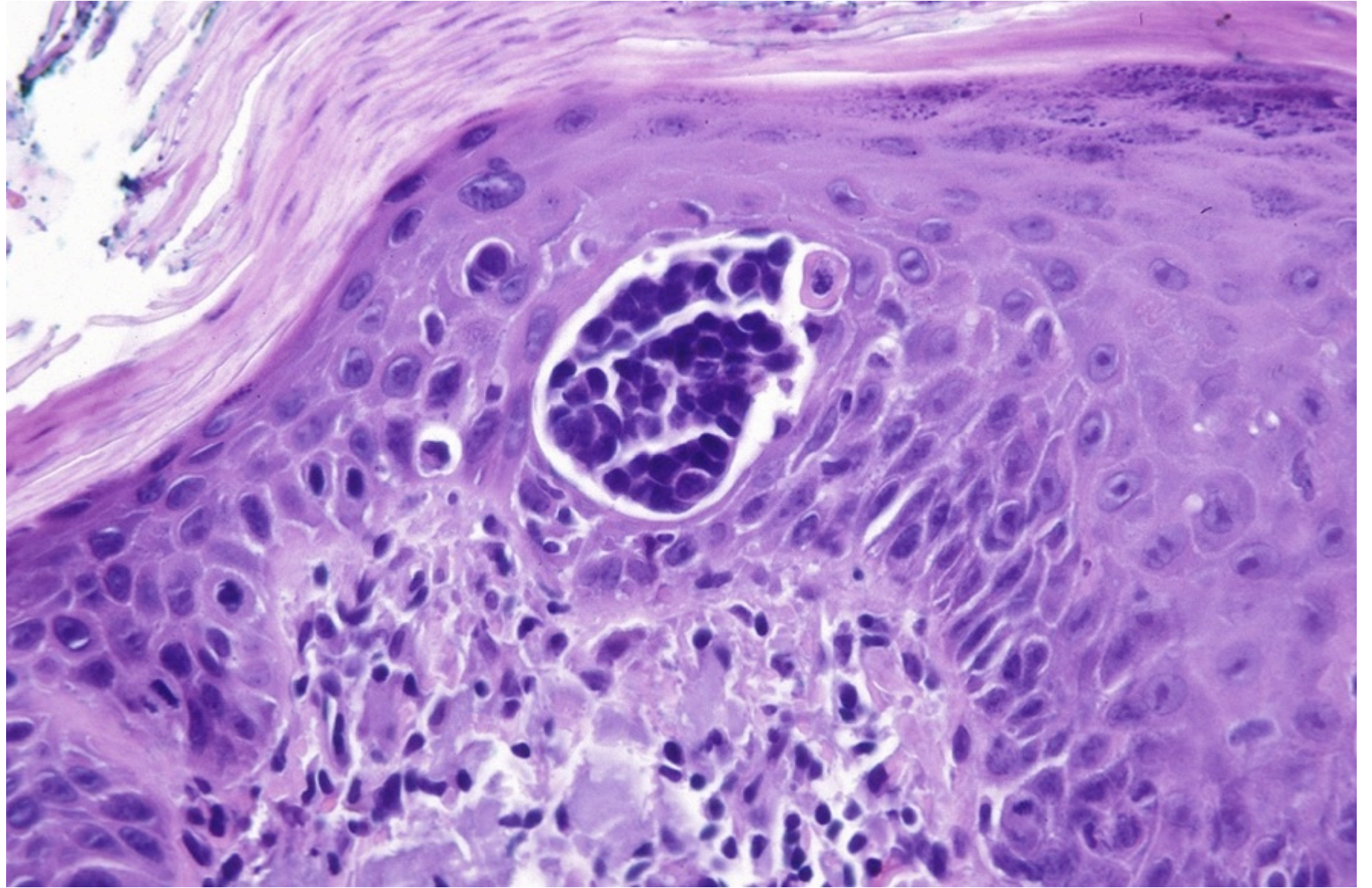




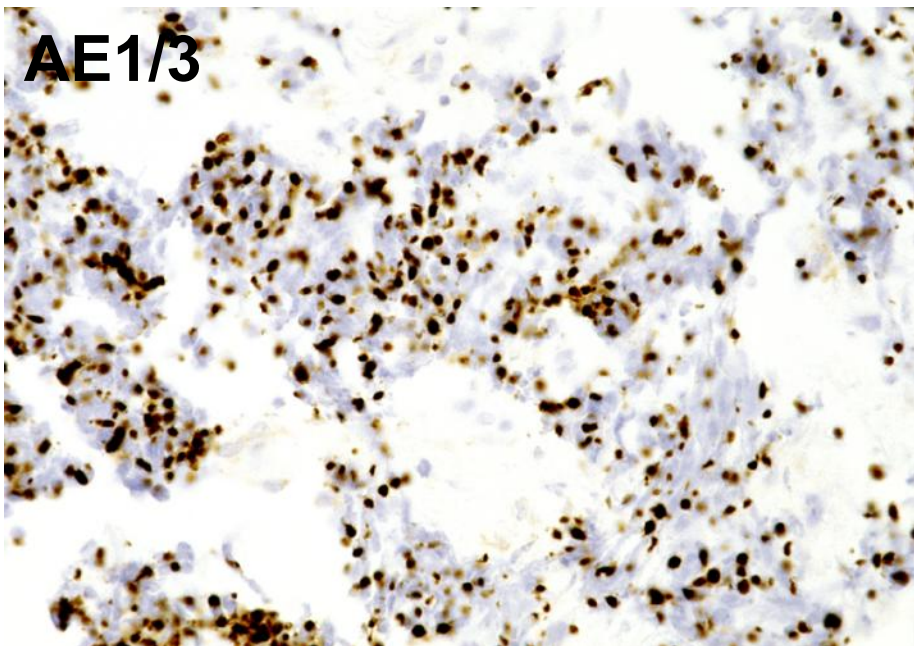
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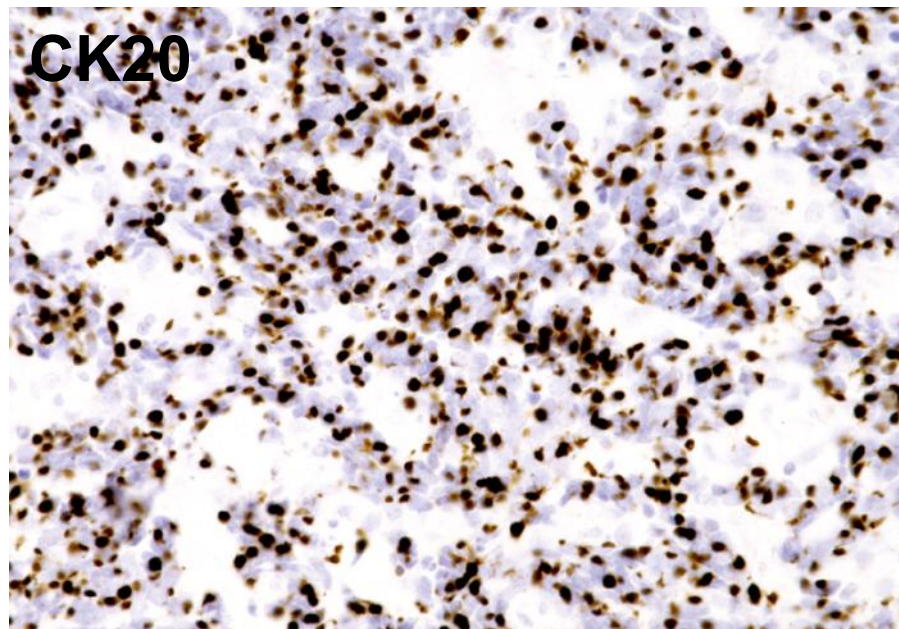




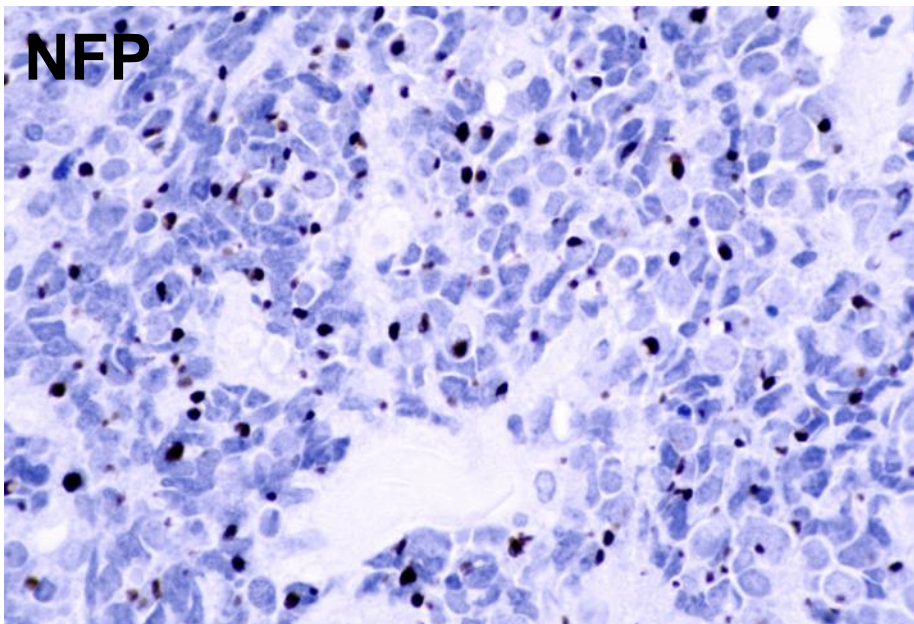
AE1/3



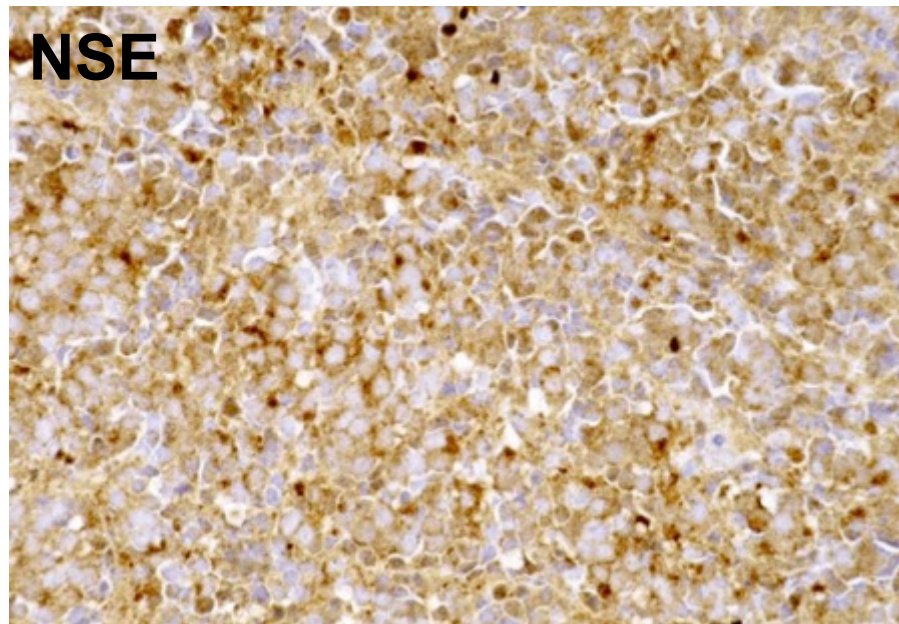
CK20



NFP



NSE



Merkel Cell Carcinoma

-Prognosis-

- Aggressive clinical course
- Local recurrence 40%
- Loco-regional metastasis 60%
- Distant metastasis 40%
 - Liver, bone, lung and brain
- 3-year survival 55%
- Favorable prognostic factors:
 - Small tumor size <2cm
 - Female gender
 - Head and neck location

Merkel Cell Carcinoma

-Summary-

Significant clinical and histological overlap

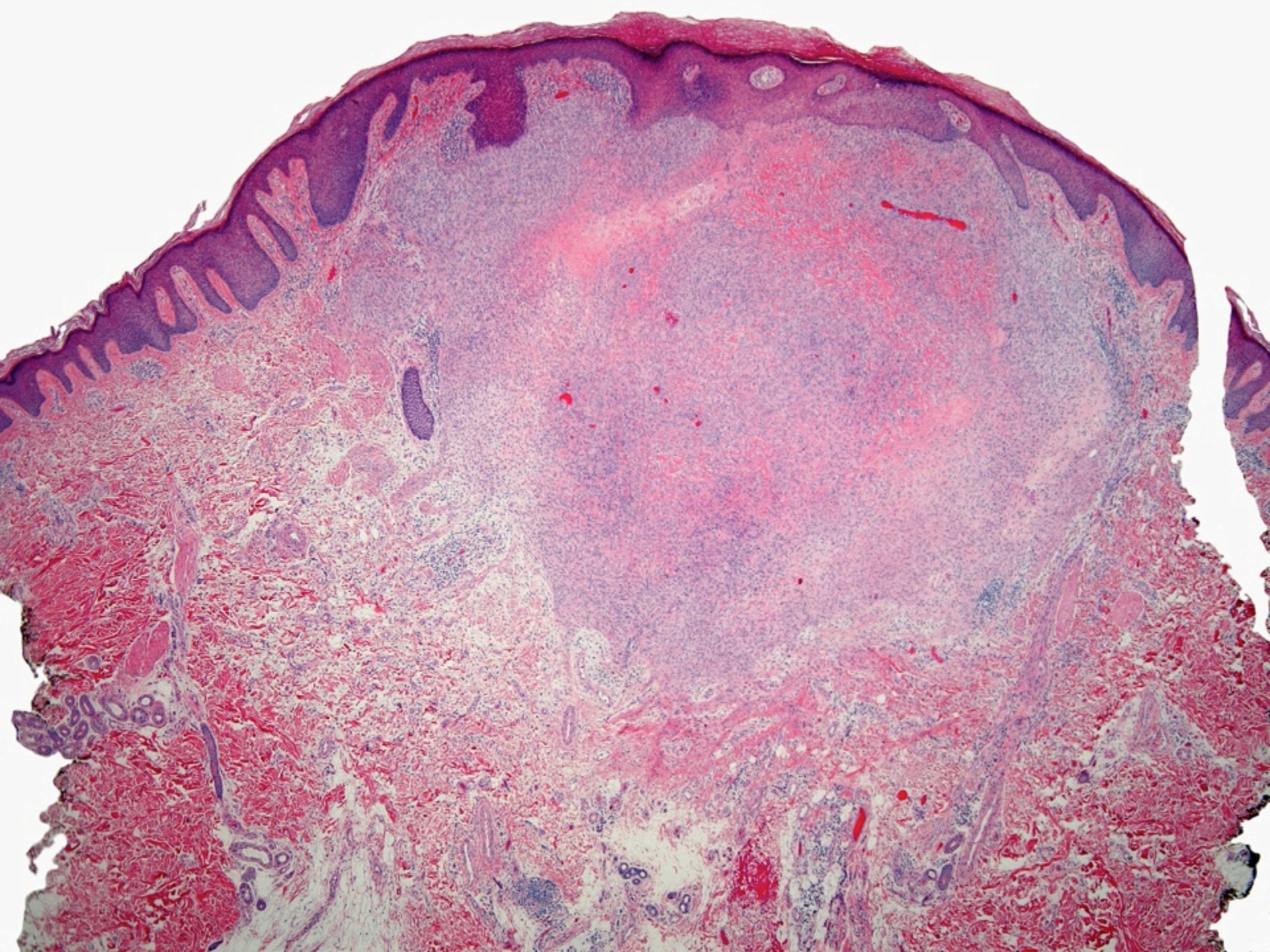
BUT:

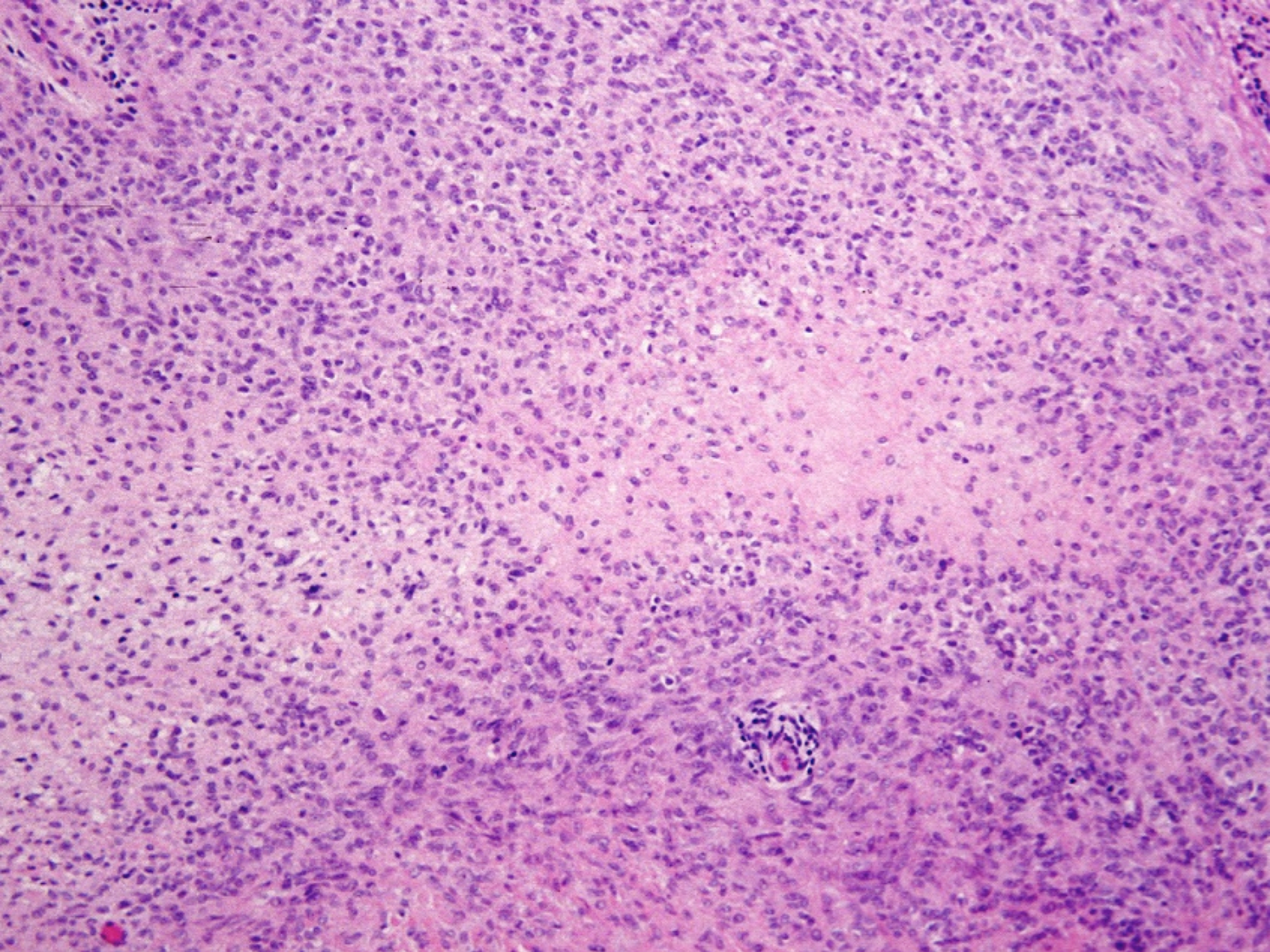
- **Immunohistochemistry:**
 - **S100-negative**
 - **Cytokeratin-positive (ck20+, ck7-)**

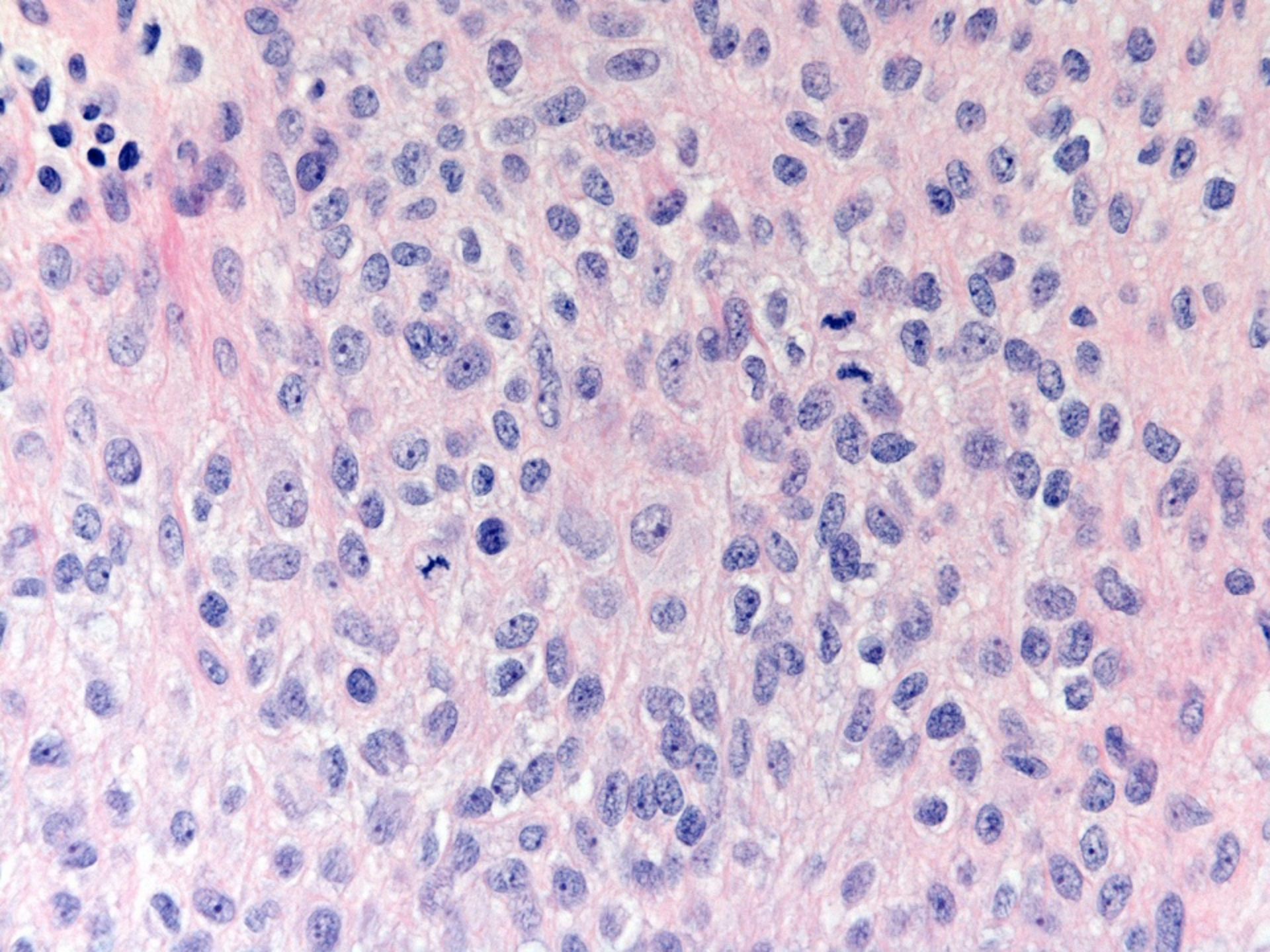
Case 2

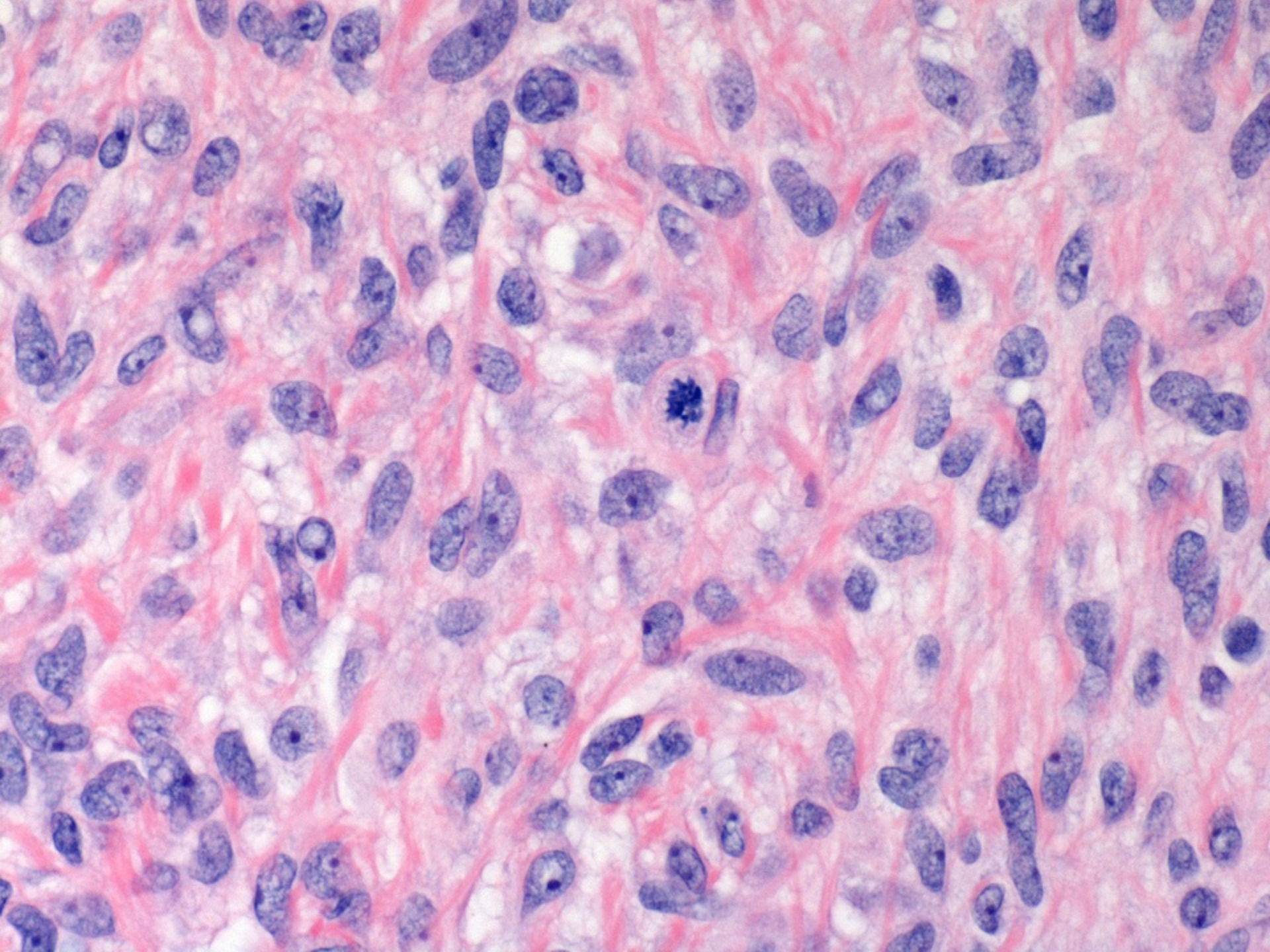
Case History

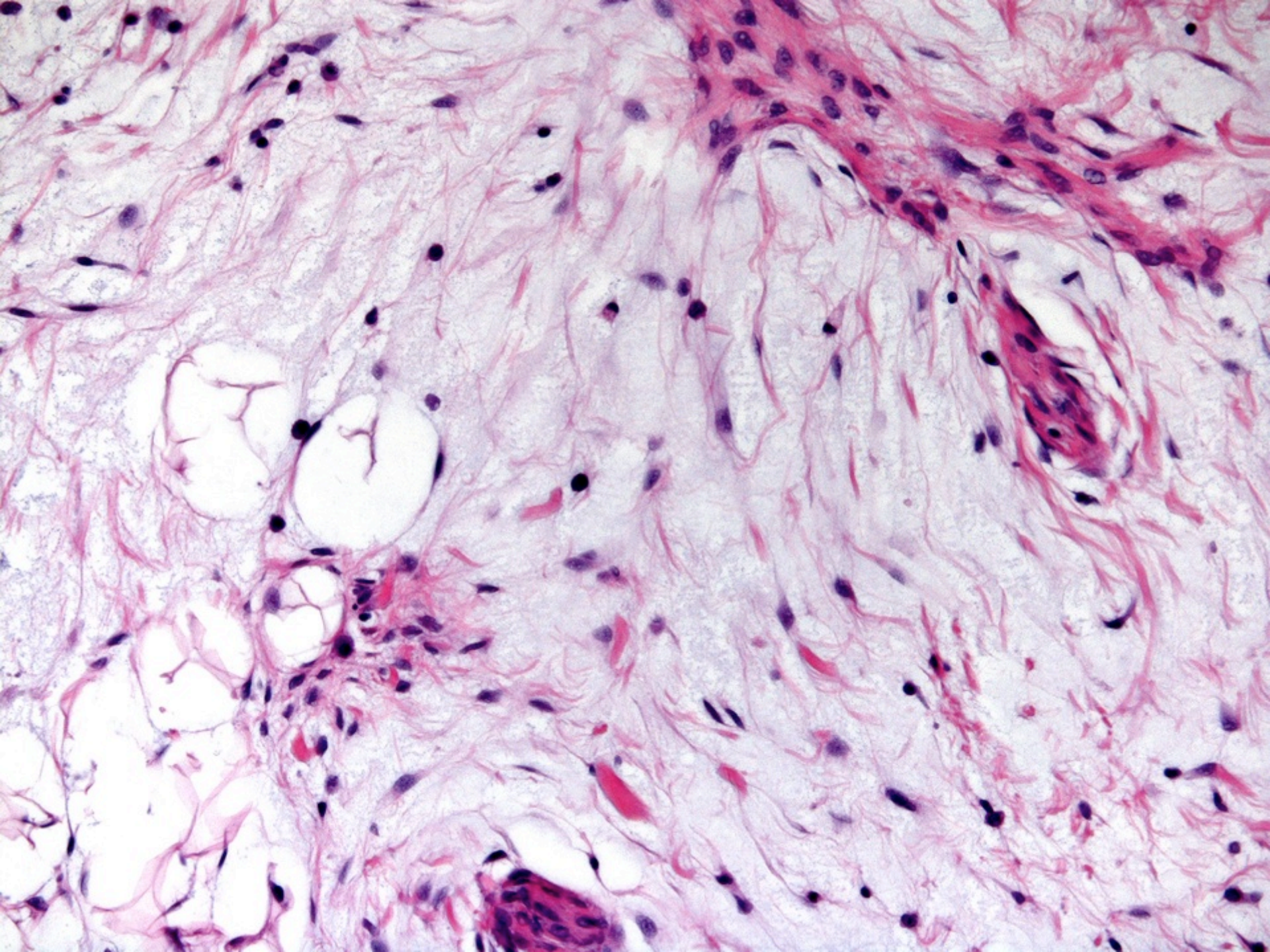
- 42 year old male
- Pigmented lesion on the leg
- ?dysplastic naevus

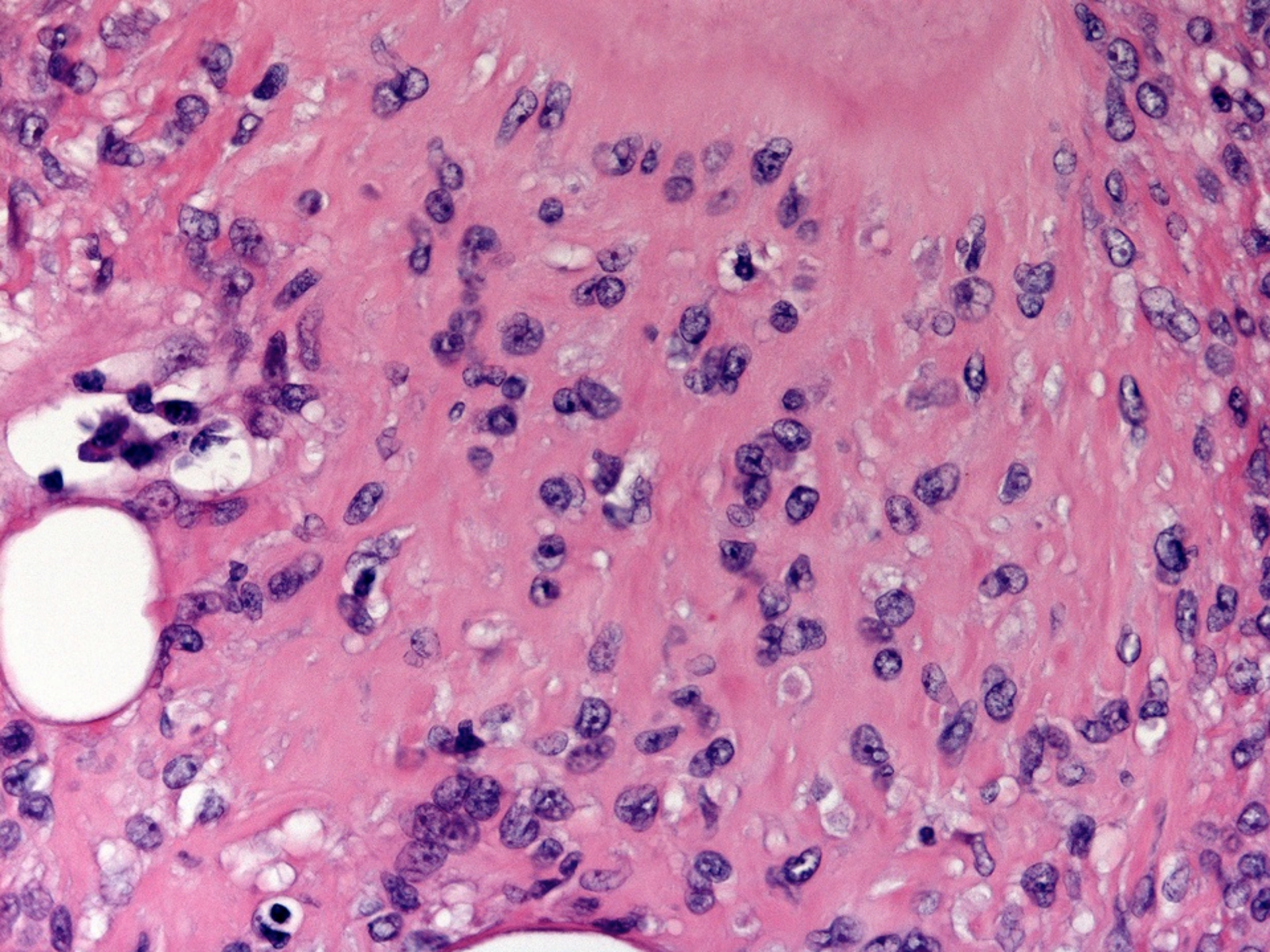




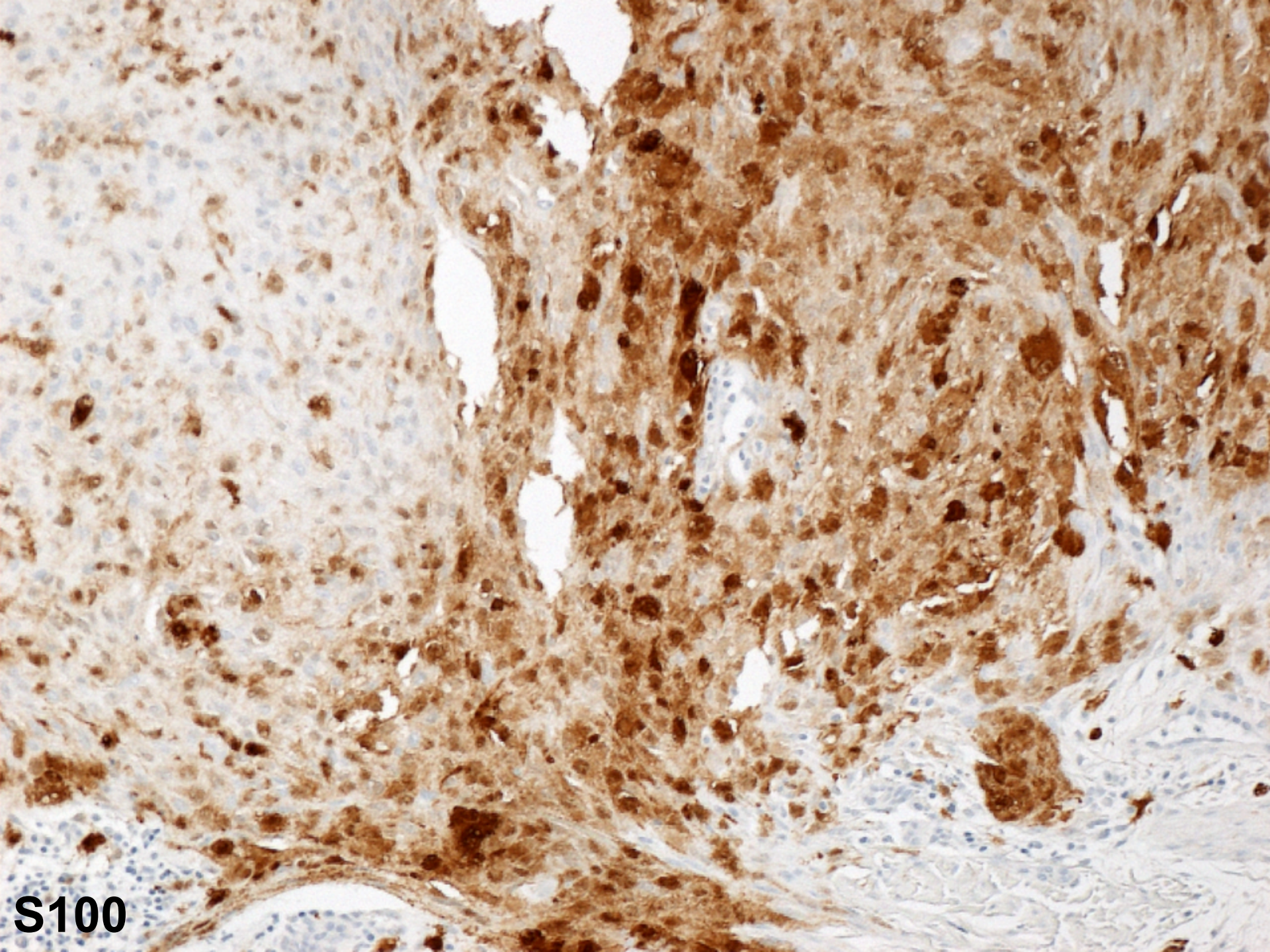




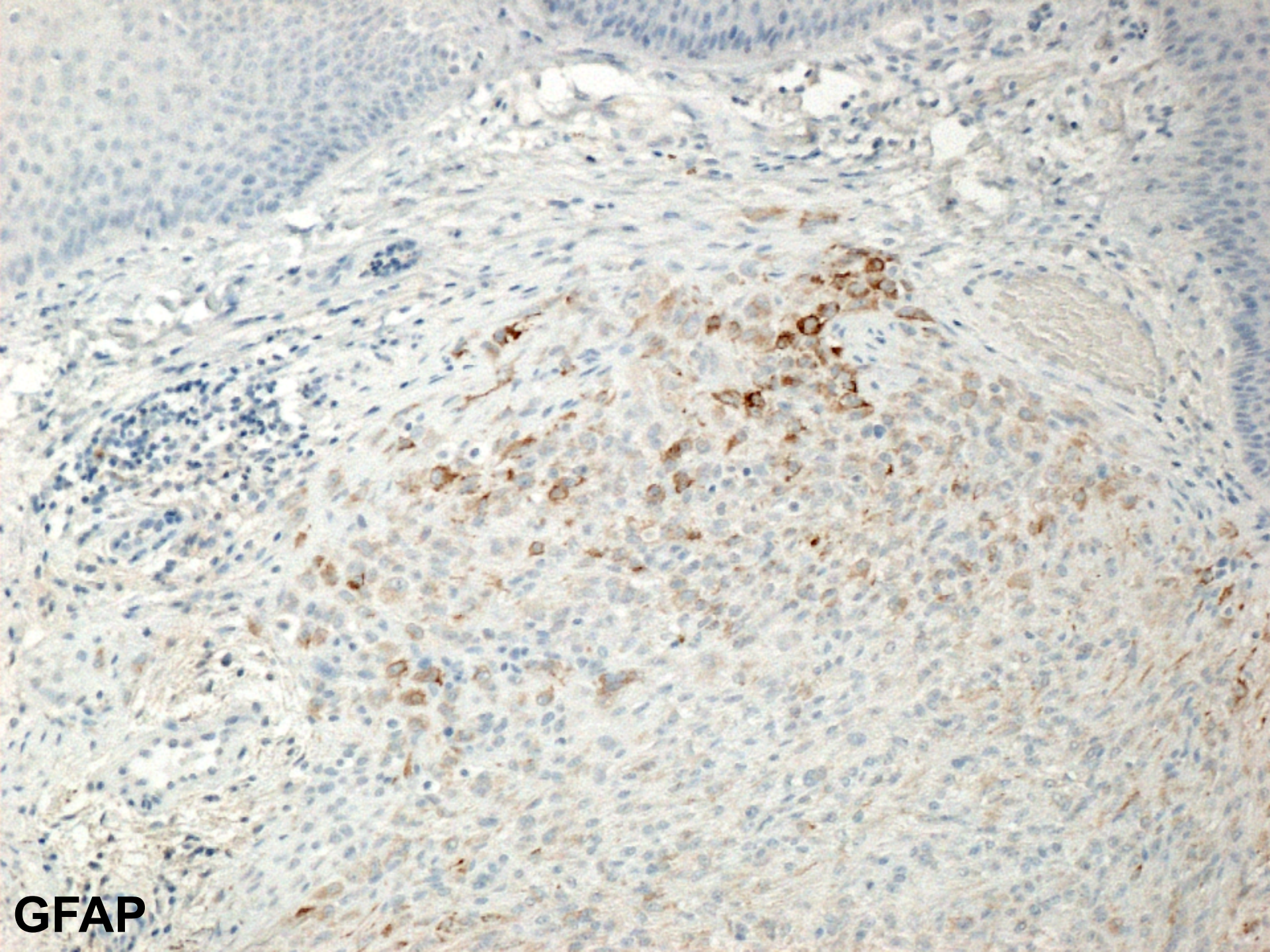




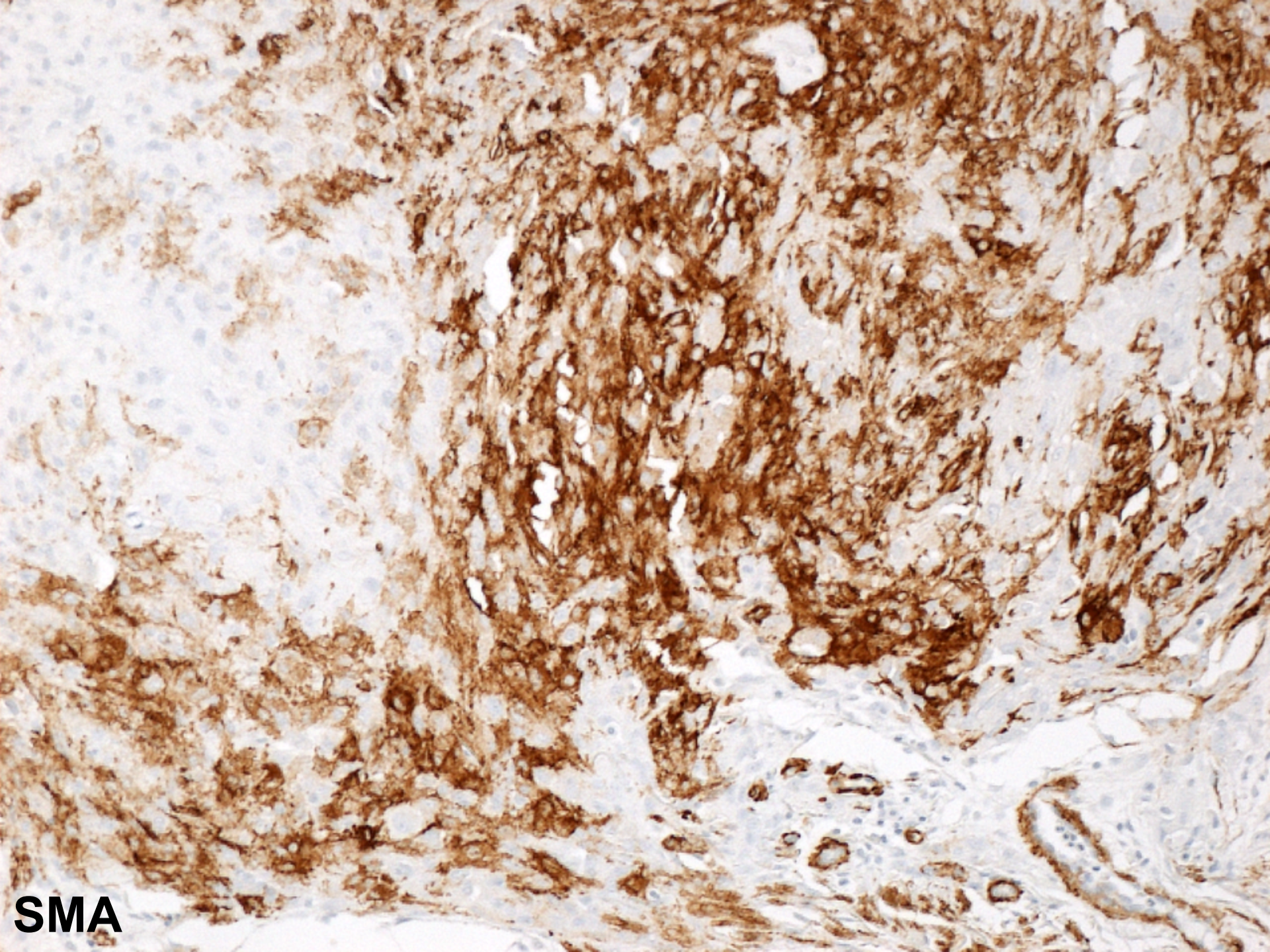
Diagnosis Case 2:



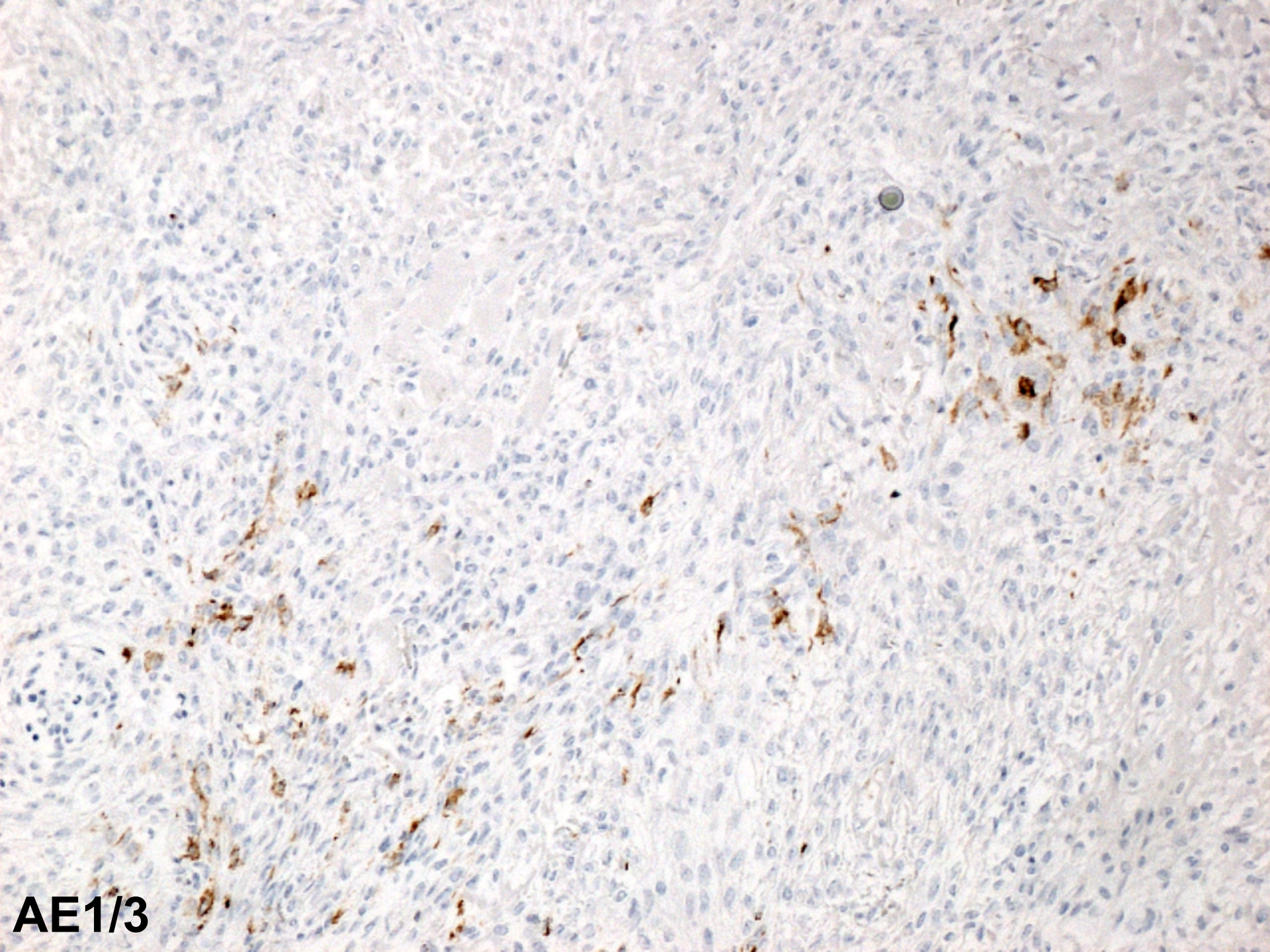
S100



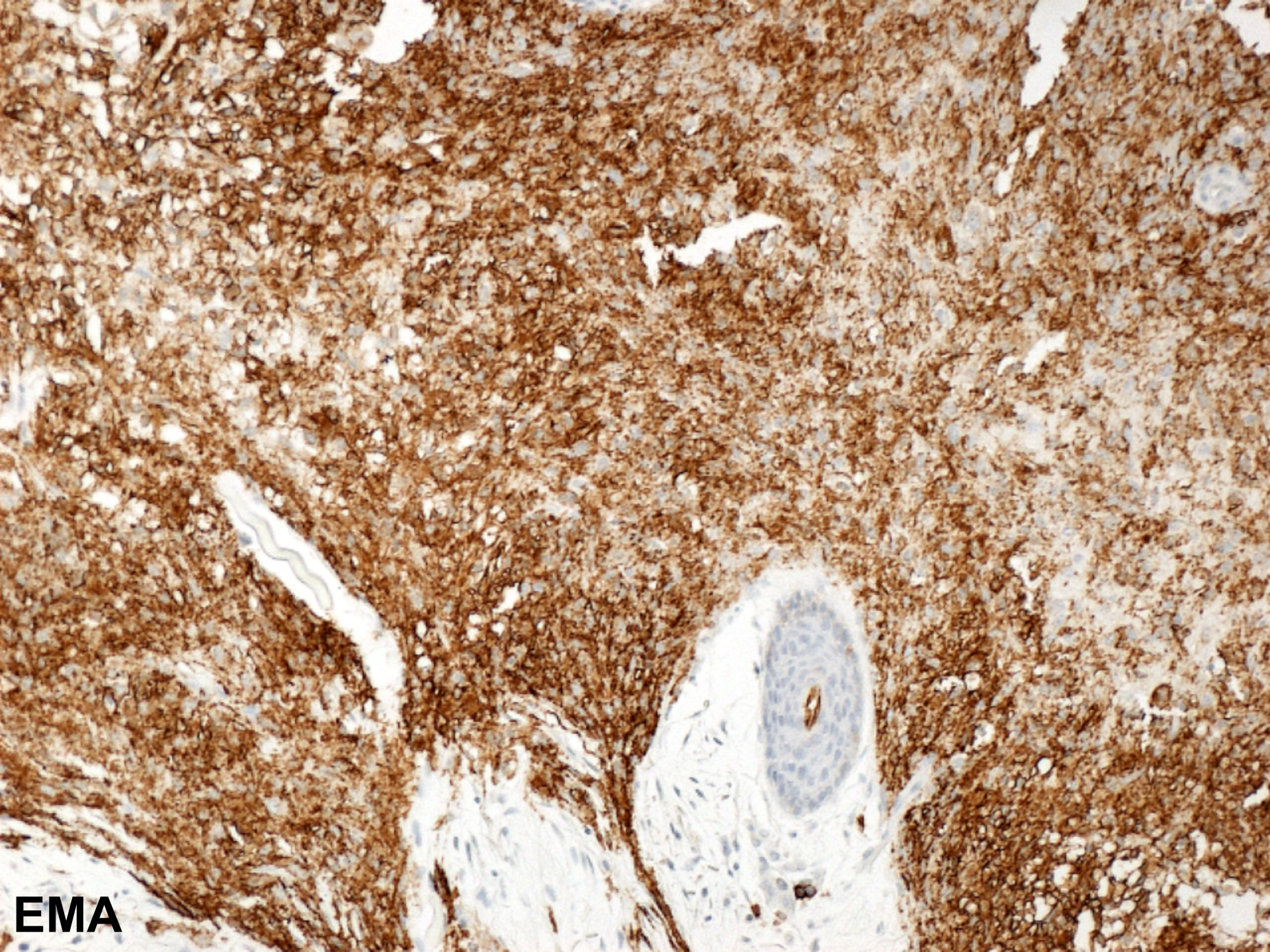
GFAP



SMA



AE1/3



EMA

Diagnosis Case 2:

Cutaneous myoepithelioma

Cutaneous Myoepithelioma

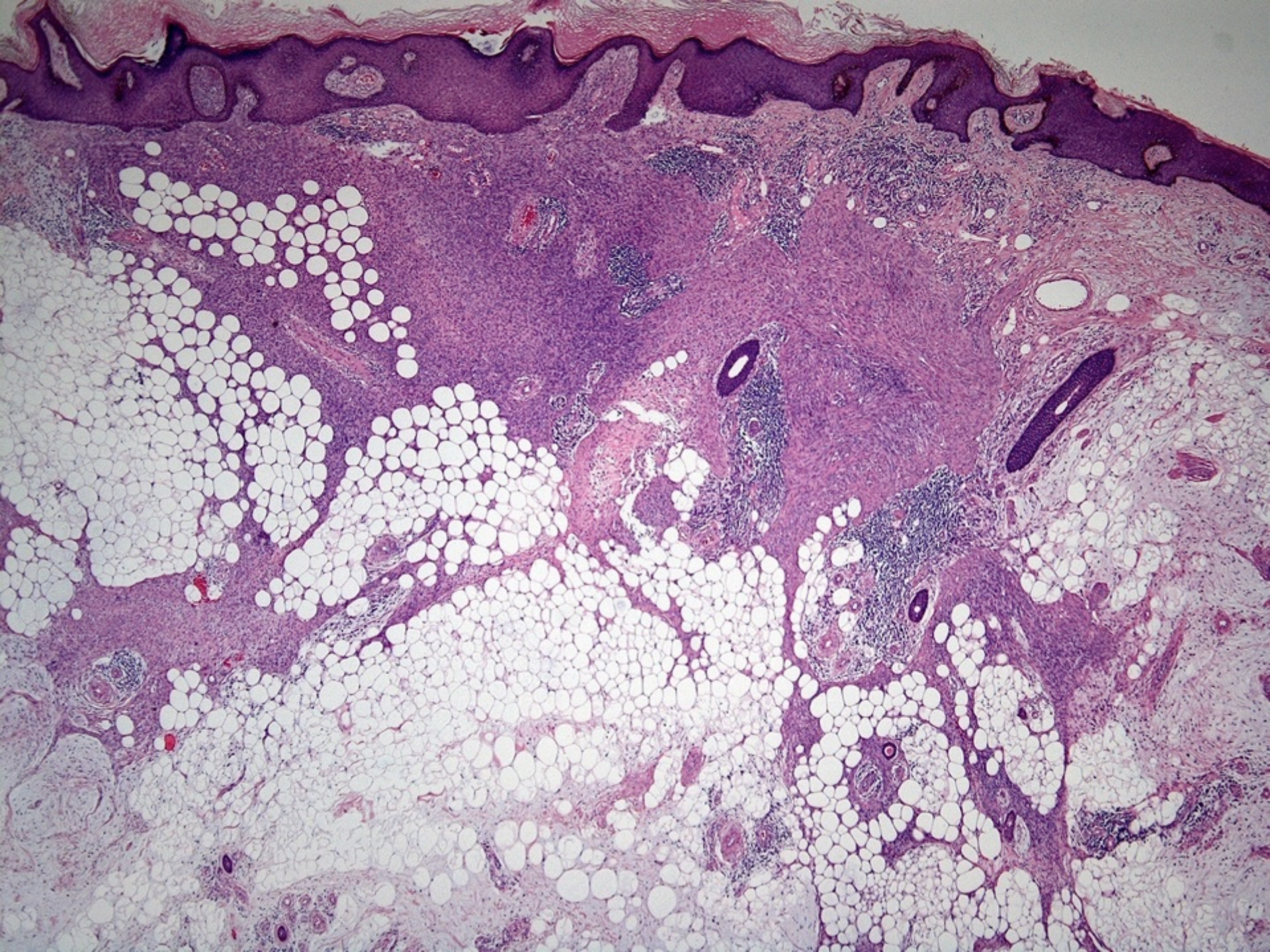
-Clinical-

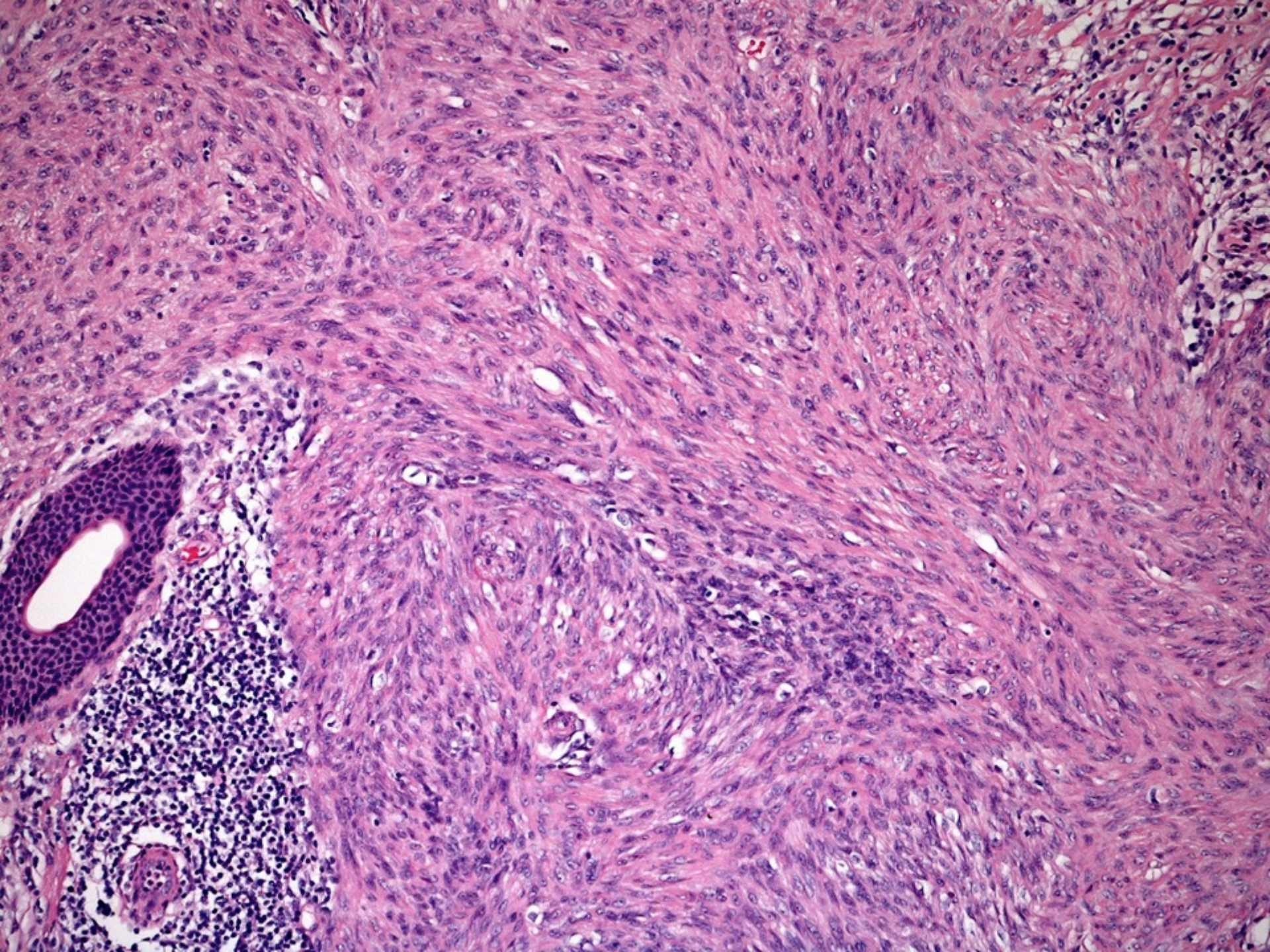
- **Nodules of 1-2 cm**
- **Young adults**
- **Male predominance**
- **Predilection for extremities**
- **Also present in soft tissue and rarely bone and visceral sites**

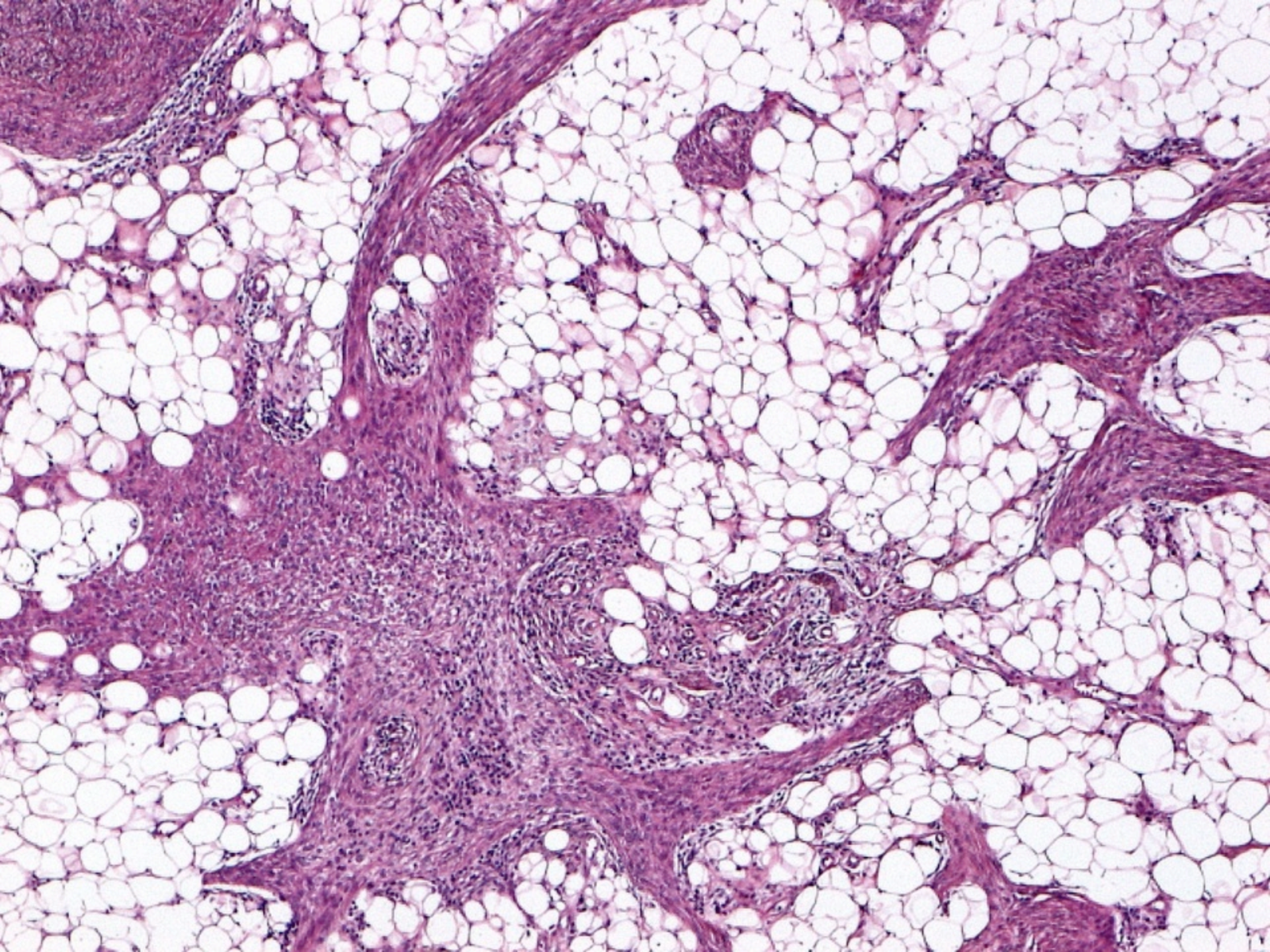
Mentzel T et al 2003 J Cutan Pathol; 30: 294-302.

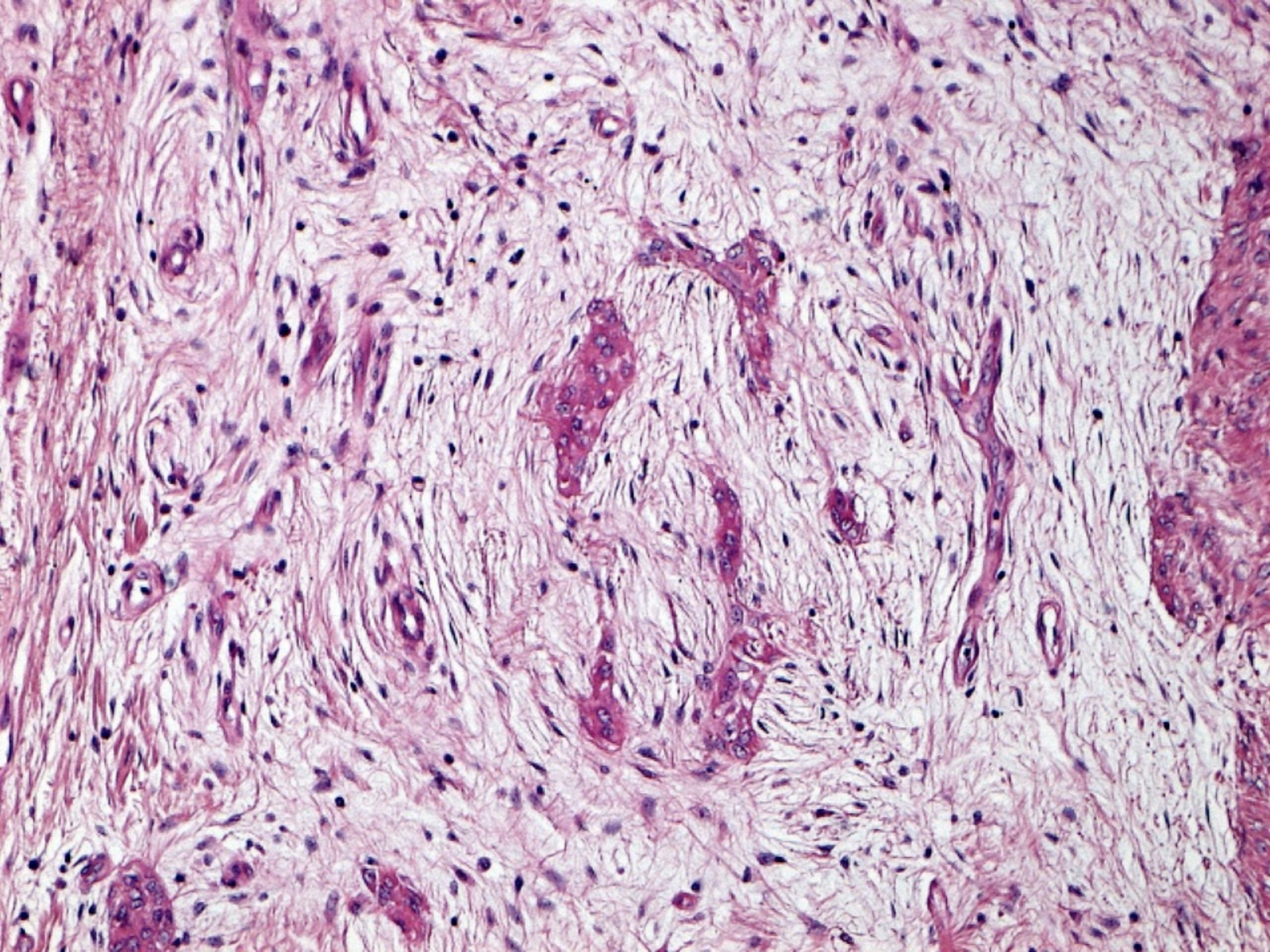
Hornick JL and Fletcher CF 2004 Hum Pathol; 35: 14-24.

Jo VV et al 2013 Am J Surg Pathol; 37: 710-718.

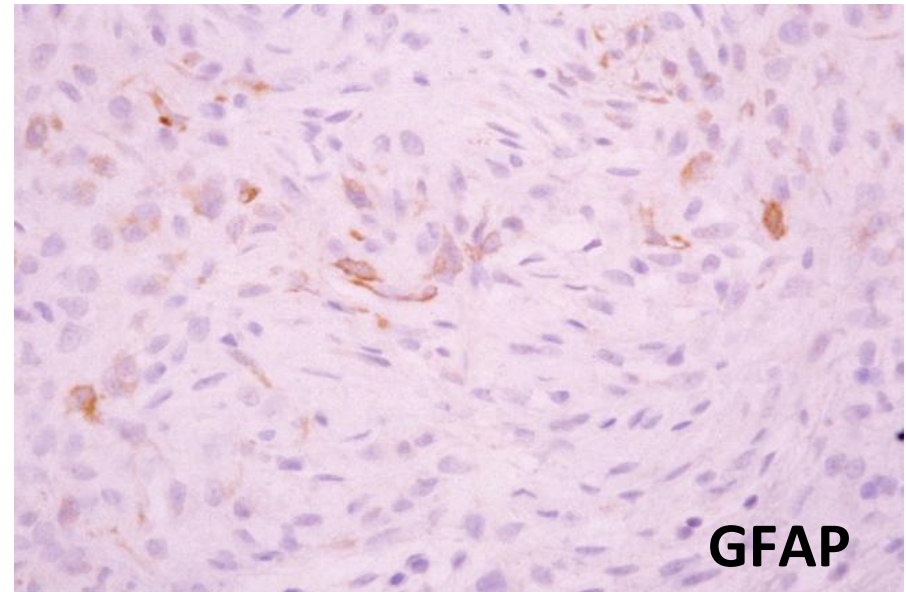
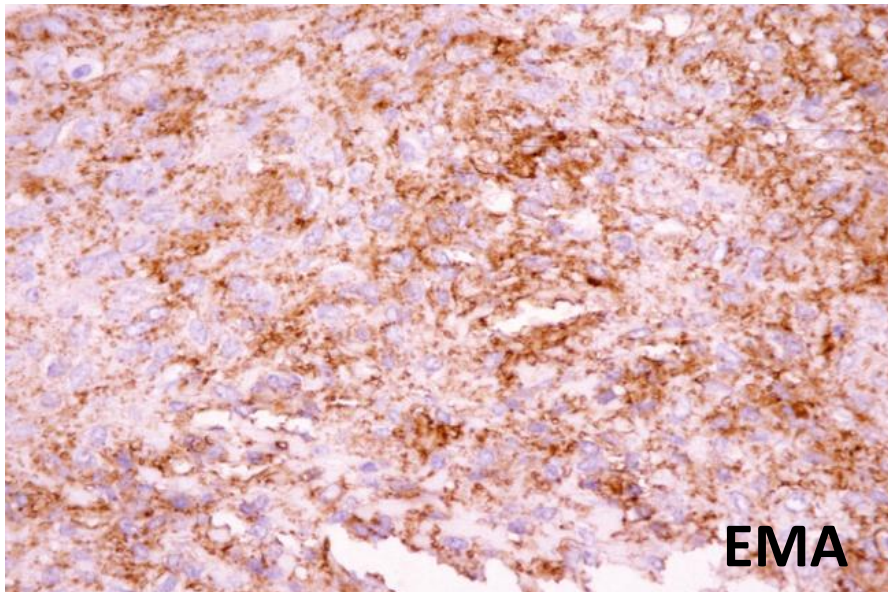
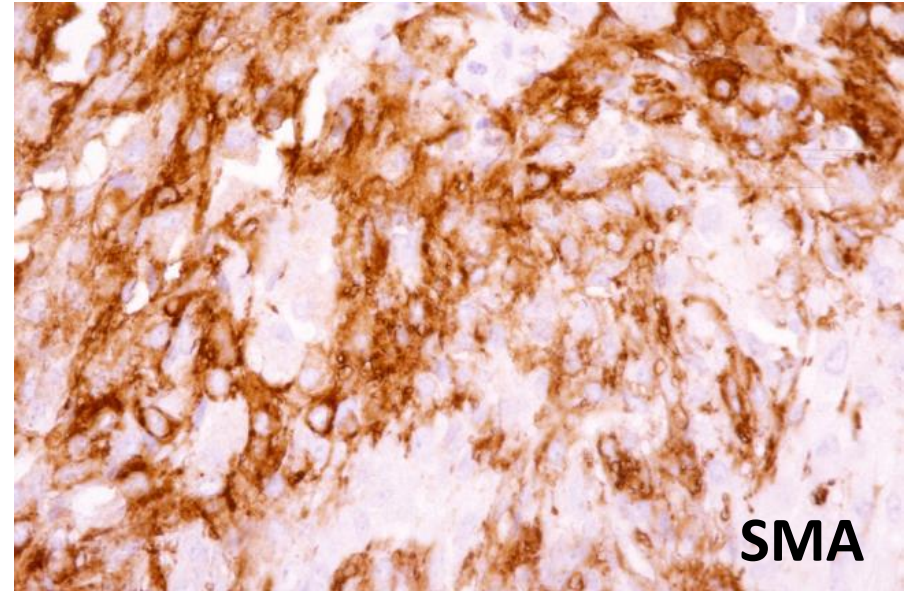
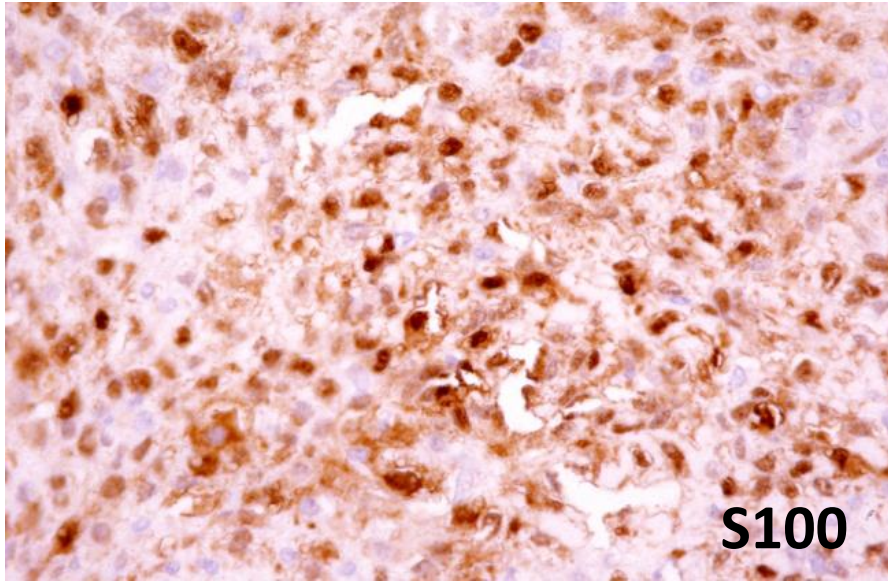


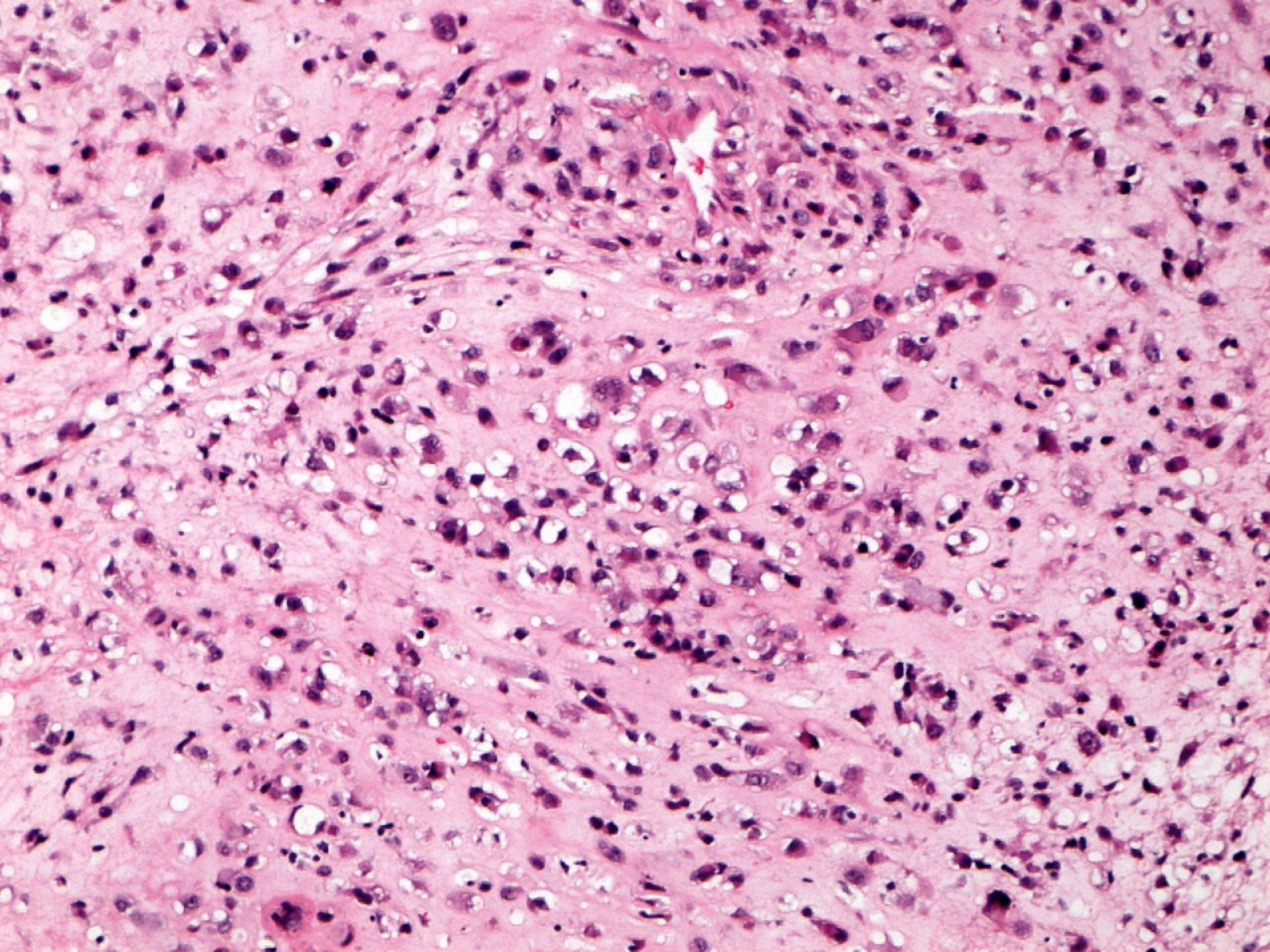


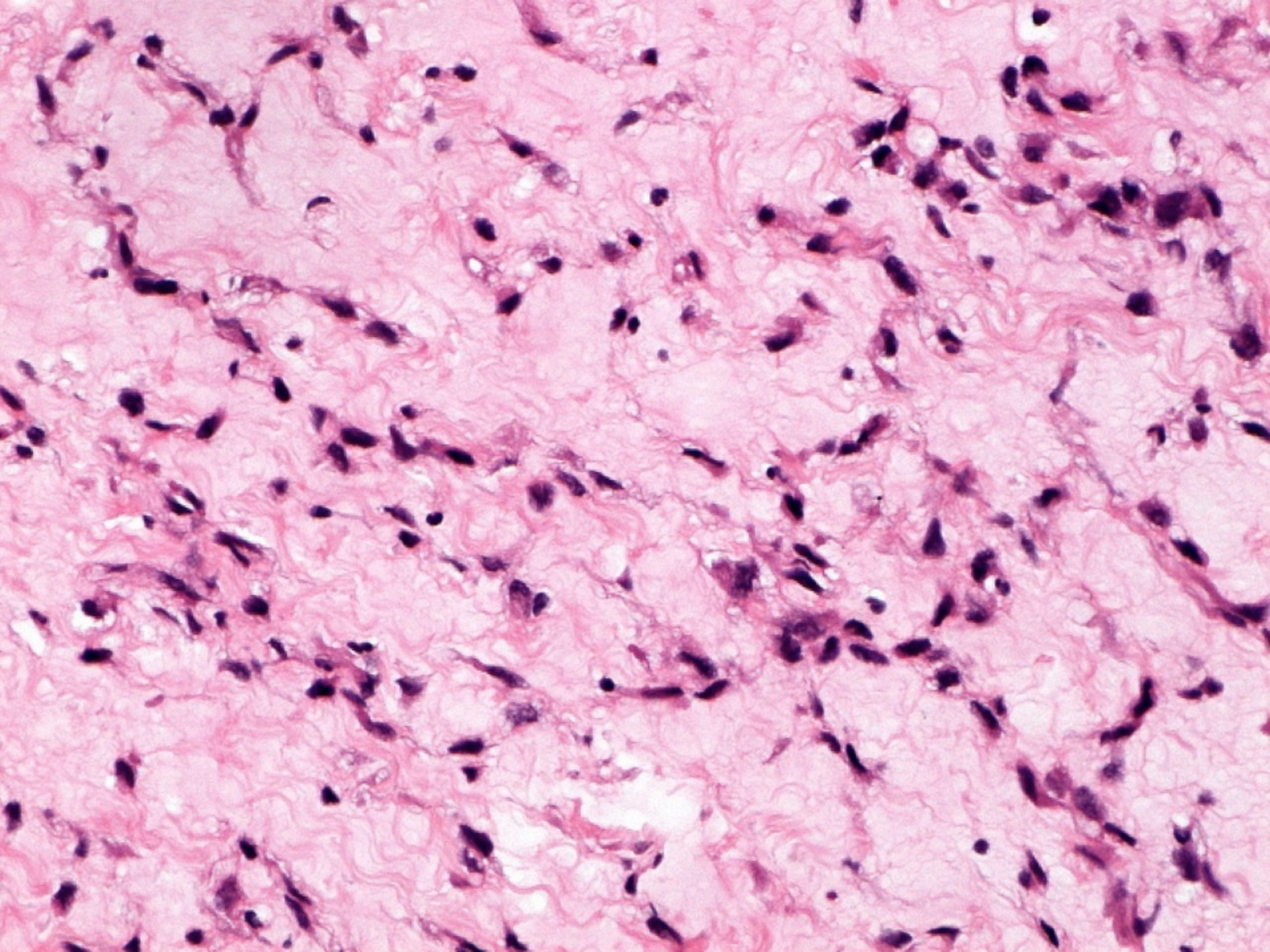


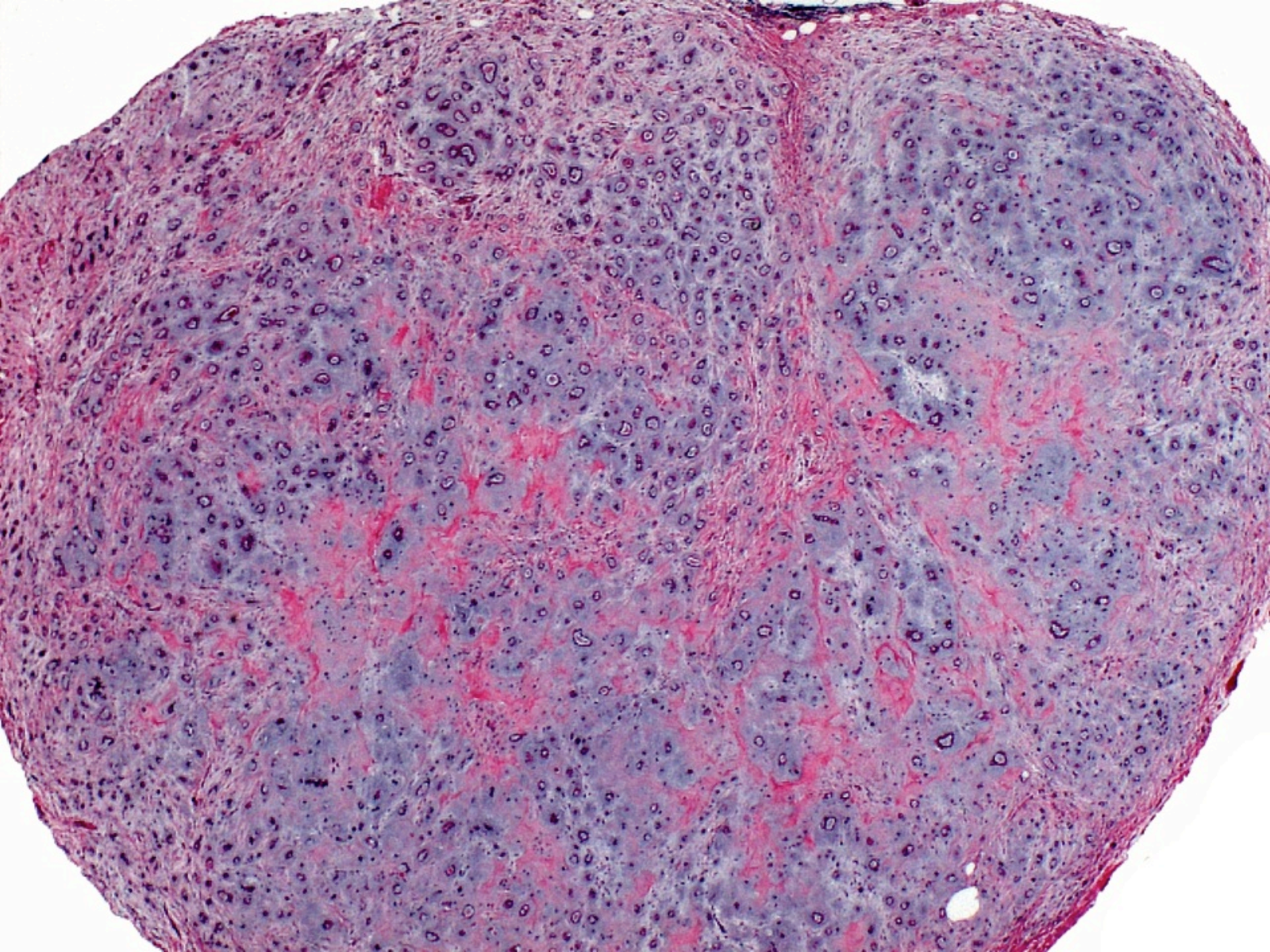


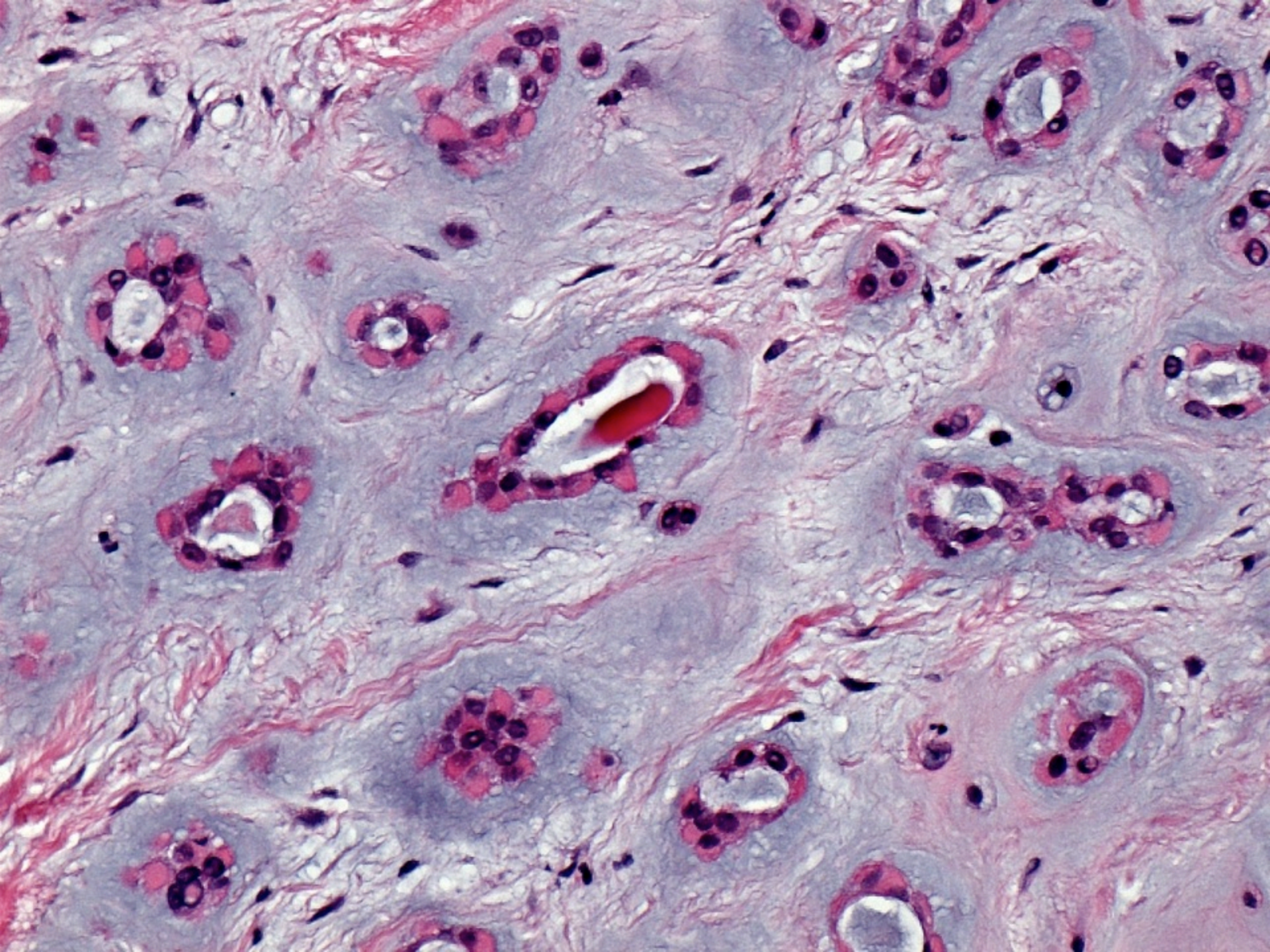
Immunohistochemistry

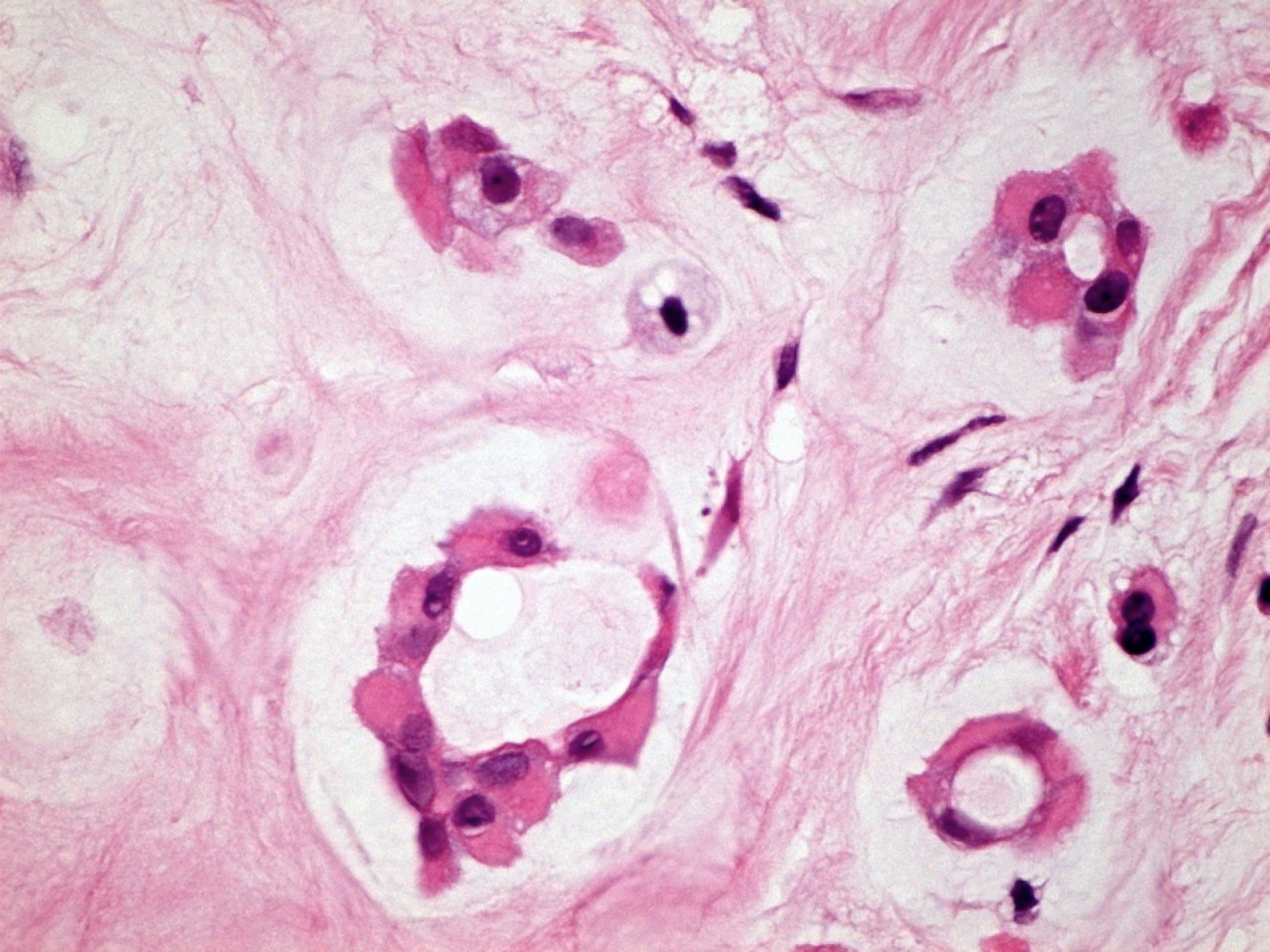


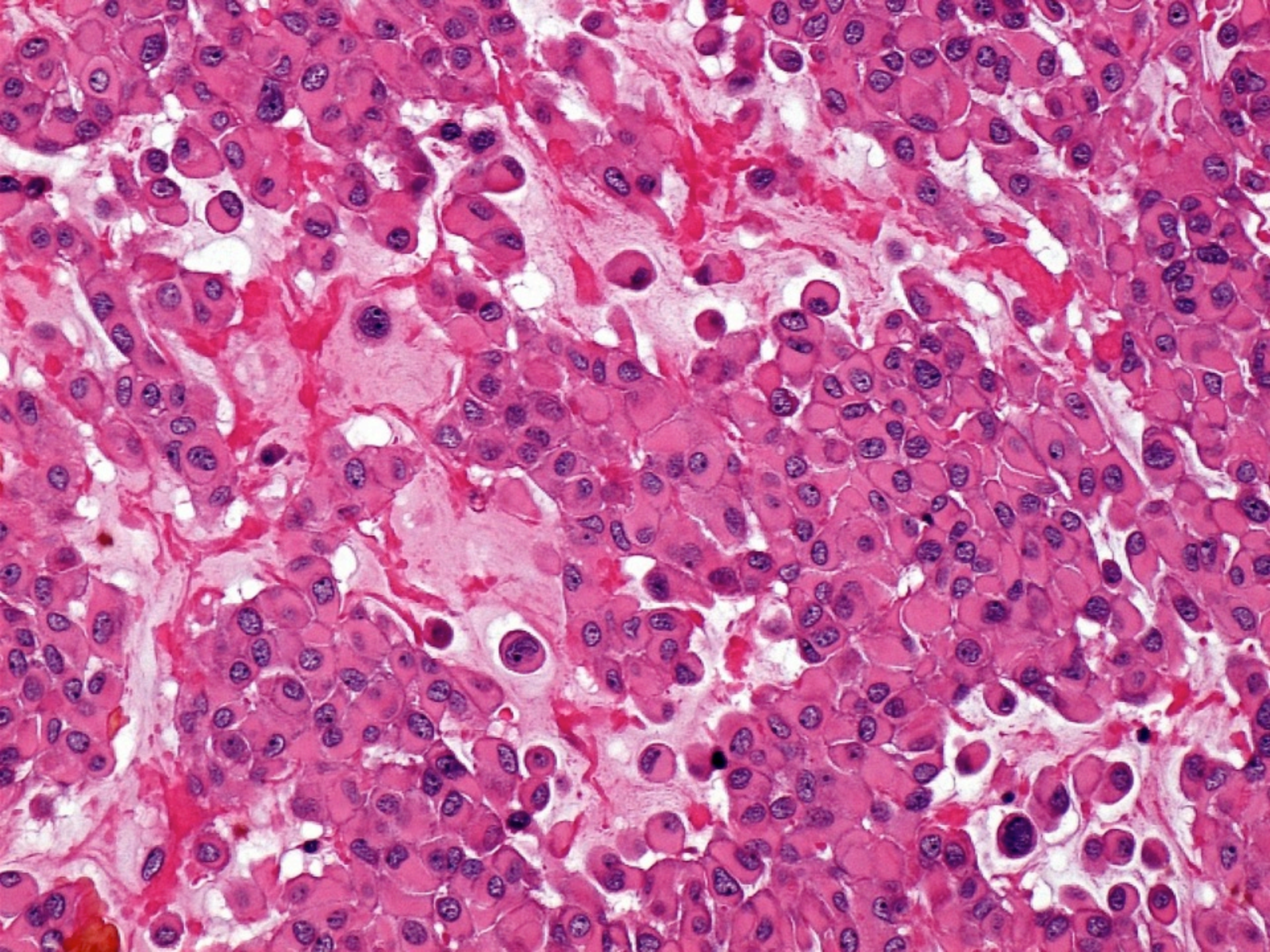




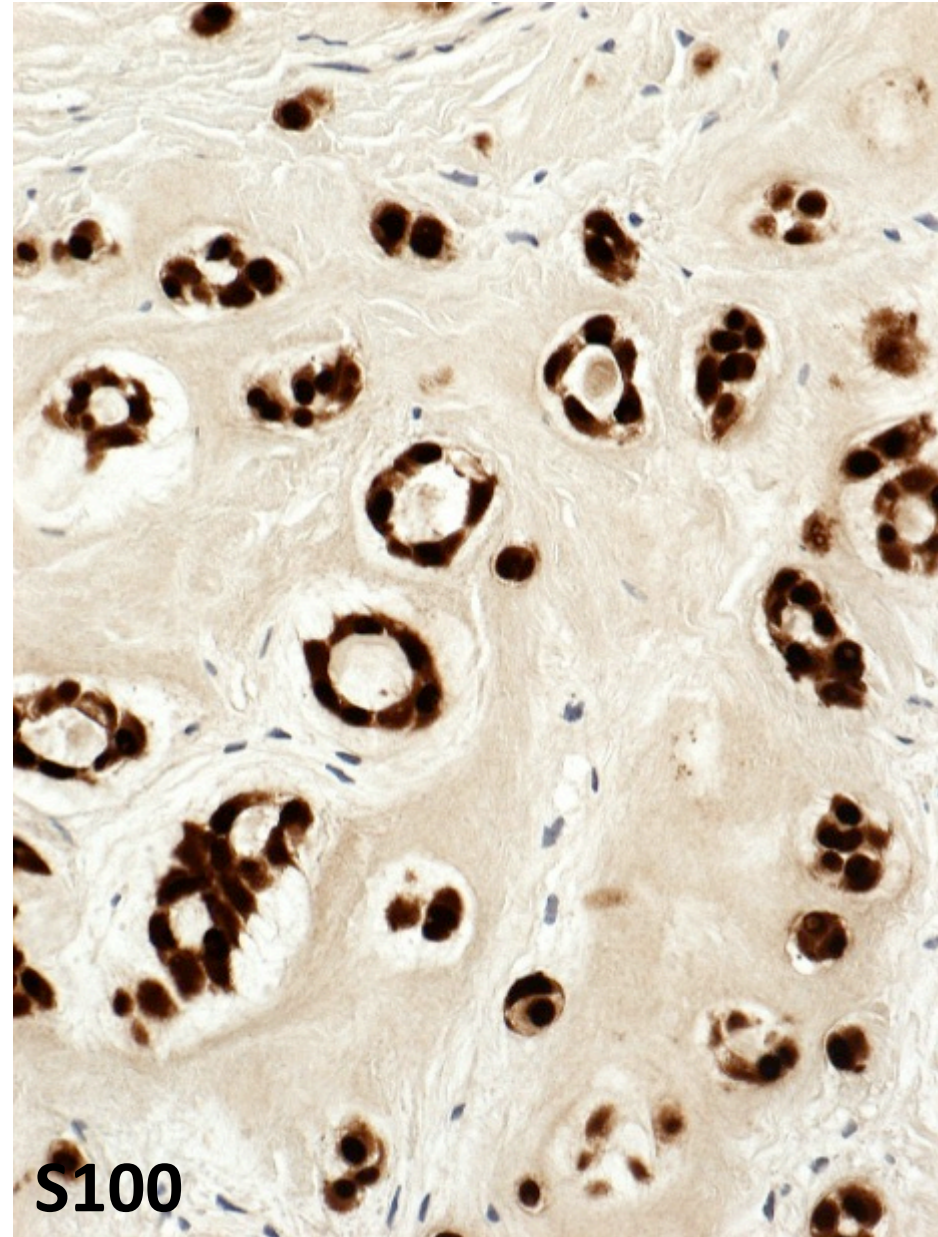
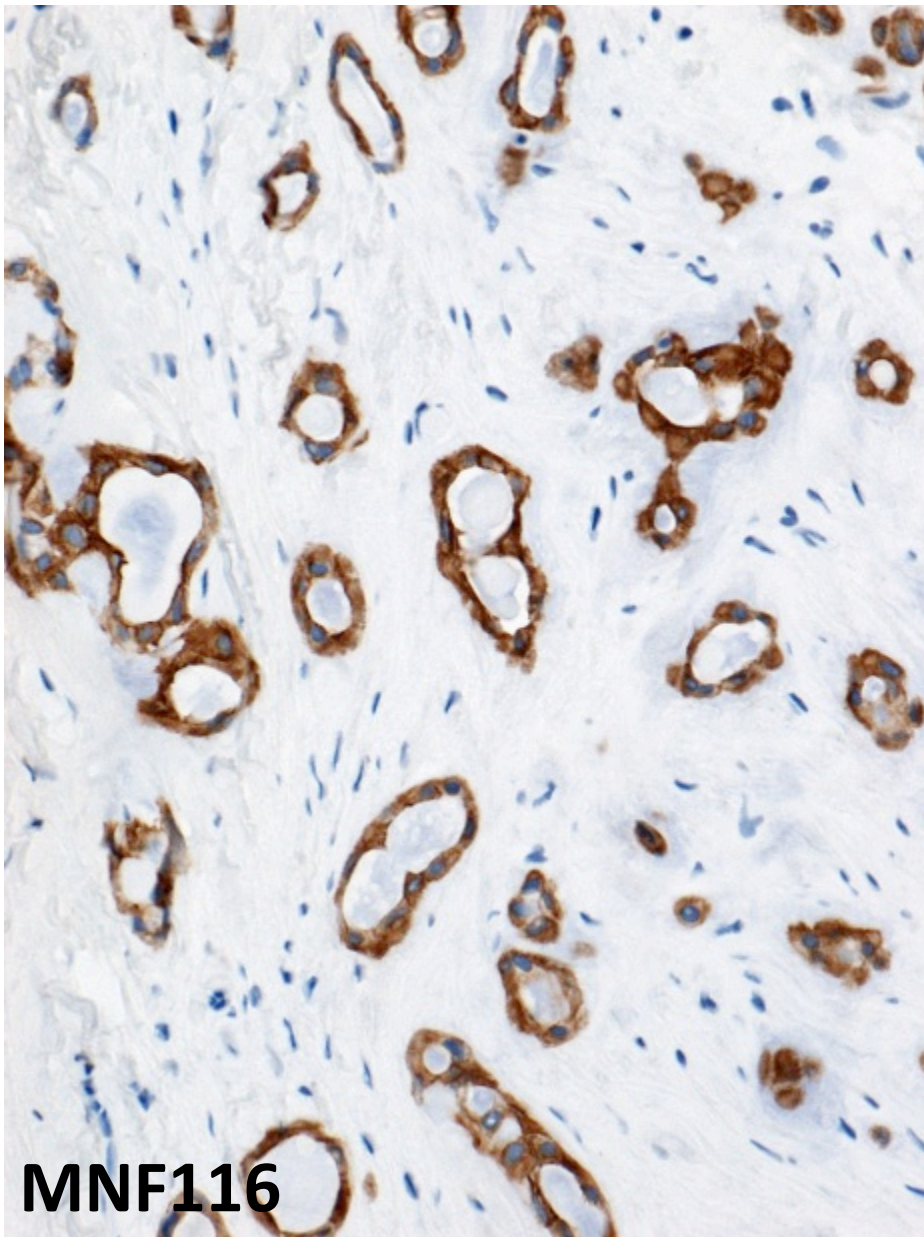








Immunohistochemistry



MNF116

S100

Myoepithelioma of Skin and Soft Tissues

-Cytogenetics-

- High rate of EWSR1 gene rearrangement (45%)
- Especially deep tumours and those lacking duct differentiation
- EWSR1-POU5F1 analogous to cutaneous hidradenoma and salivary gland tumours (mucoepidermoid carcinoma)
- PLAG-1 rearrangement in tumours showing duct differentiation analogous to pleomorphic adenoma of salivary gland

Antonescu, CR et al. Genes, Chromosomes & Cancer. 2010 ; 49: 1114-1124.

Bahrami A, et al. Genes Chromosomes Cancer. 2012 Feb;51(2):140-8.

Jo VV et al 2013 Am J Surg Pathol; 37: 710-718.

Cutaneous Myoepithelioma

-Prognosis-

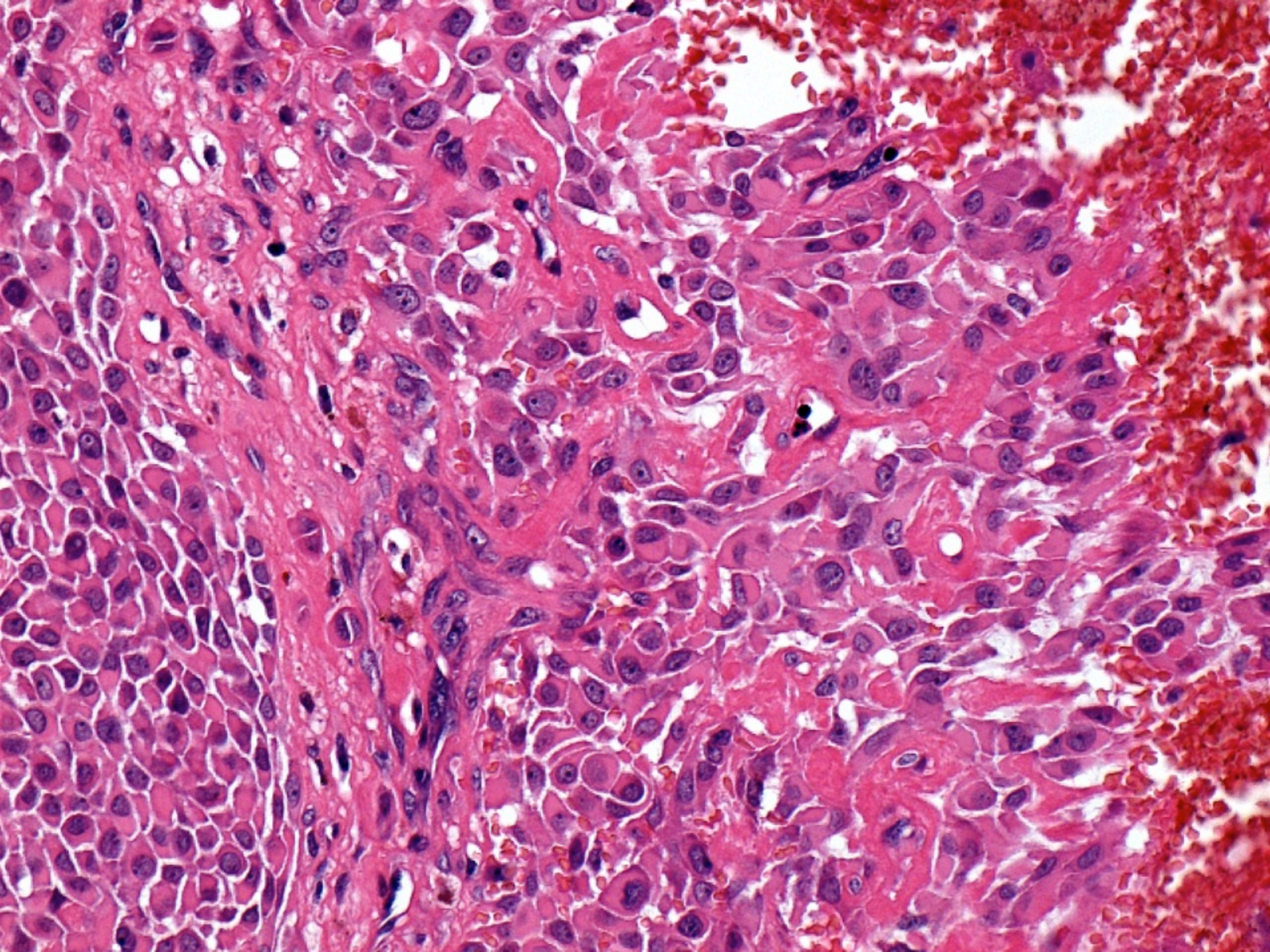
- Potential for local recurrence
- LN metastasis exceedingly rare
- So far no death from disease
- No predictive morphological features

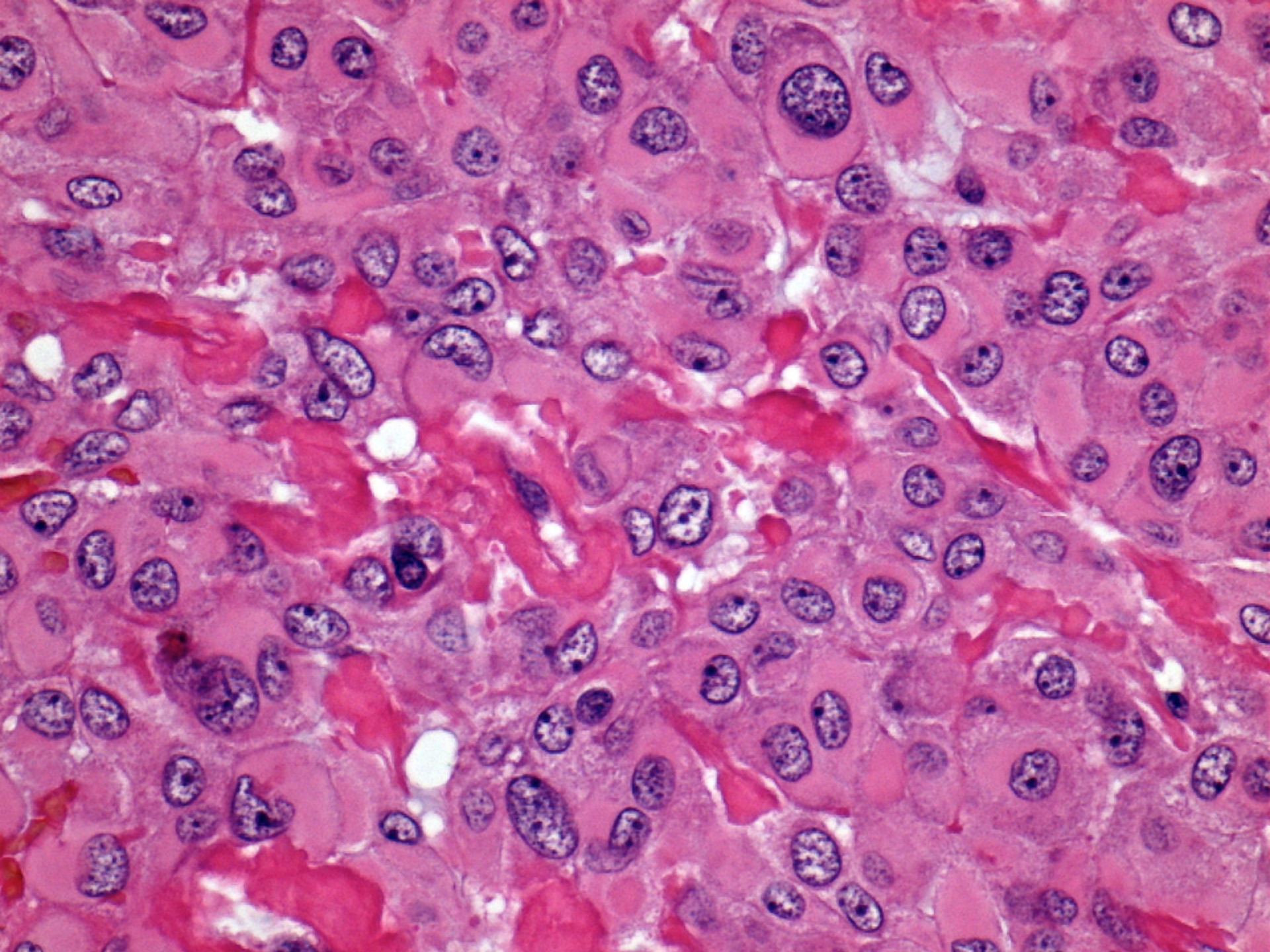
Soft Tissue Myoepithelioma

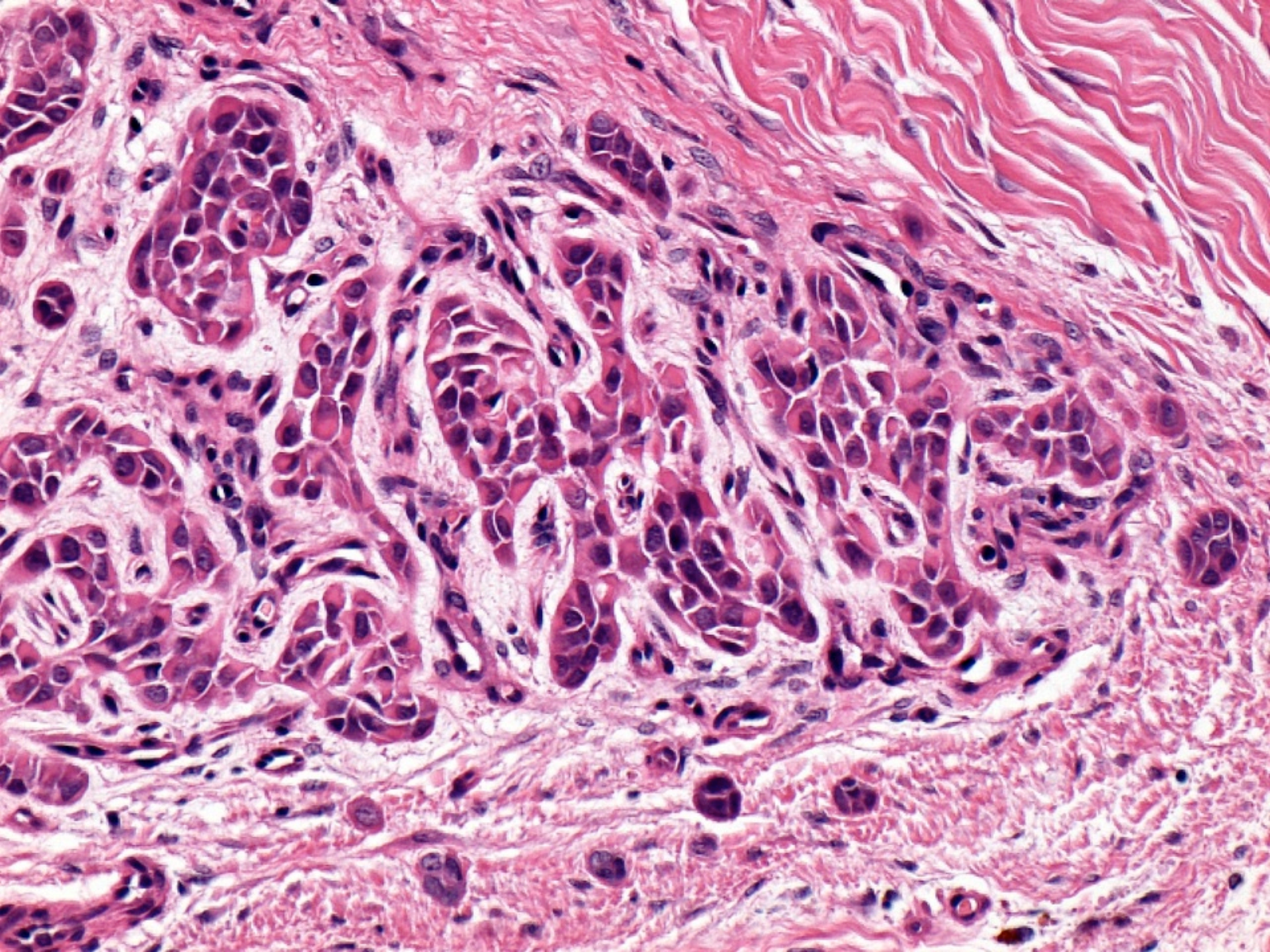
-Prognosis-

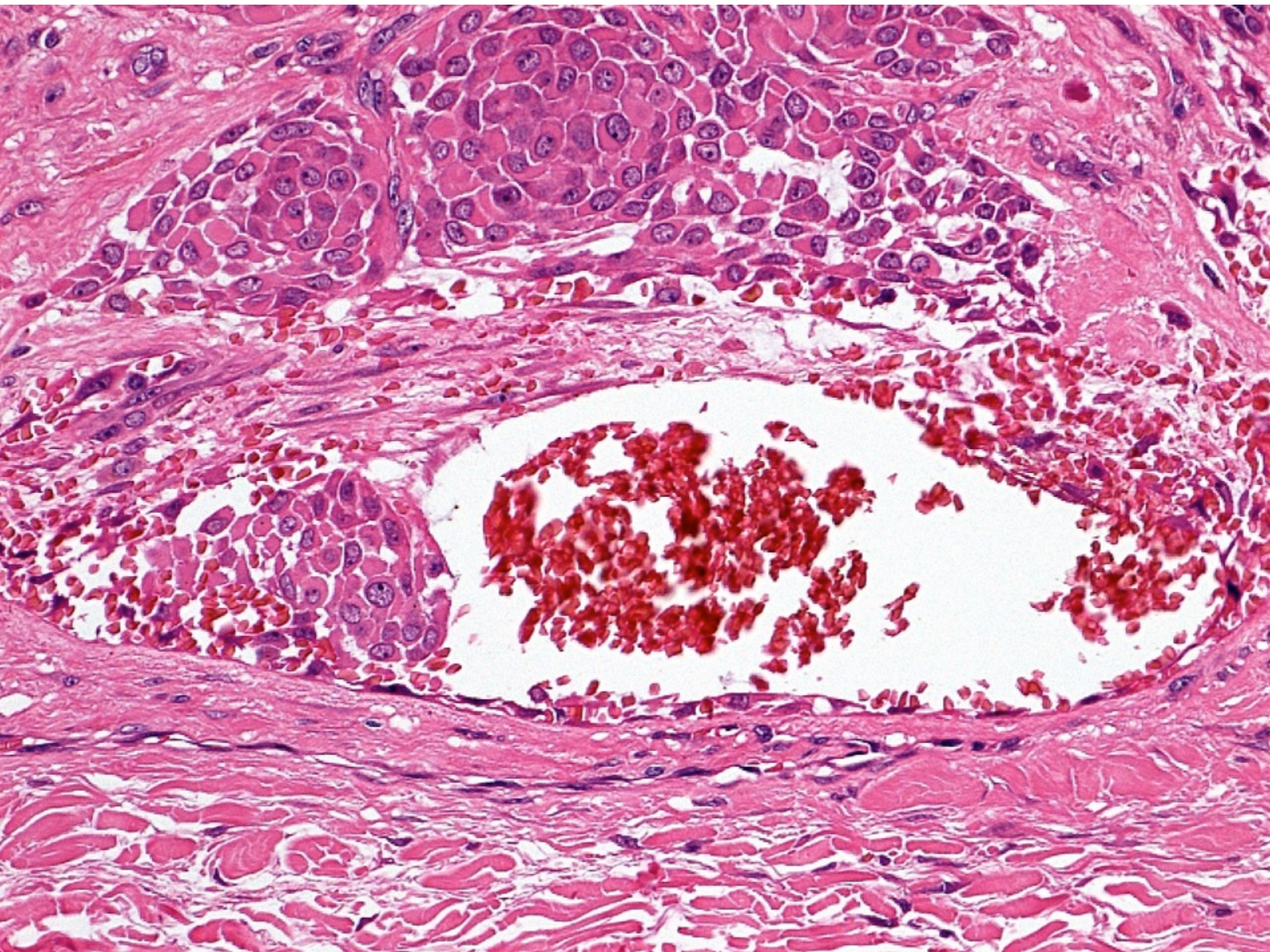
- Potential for local recurrence
- Distant metastasis and associated mortality in cases with cytological features of malignancy (myoepithelial carcinoma)

Hornick JL and Fletcher CF 2003 Am J Surg Pathol; 27: 1183-1196.

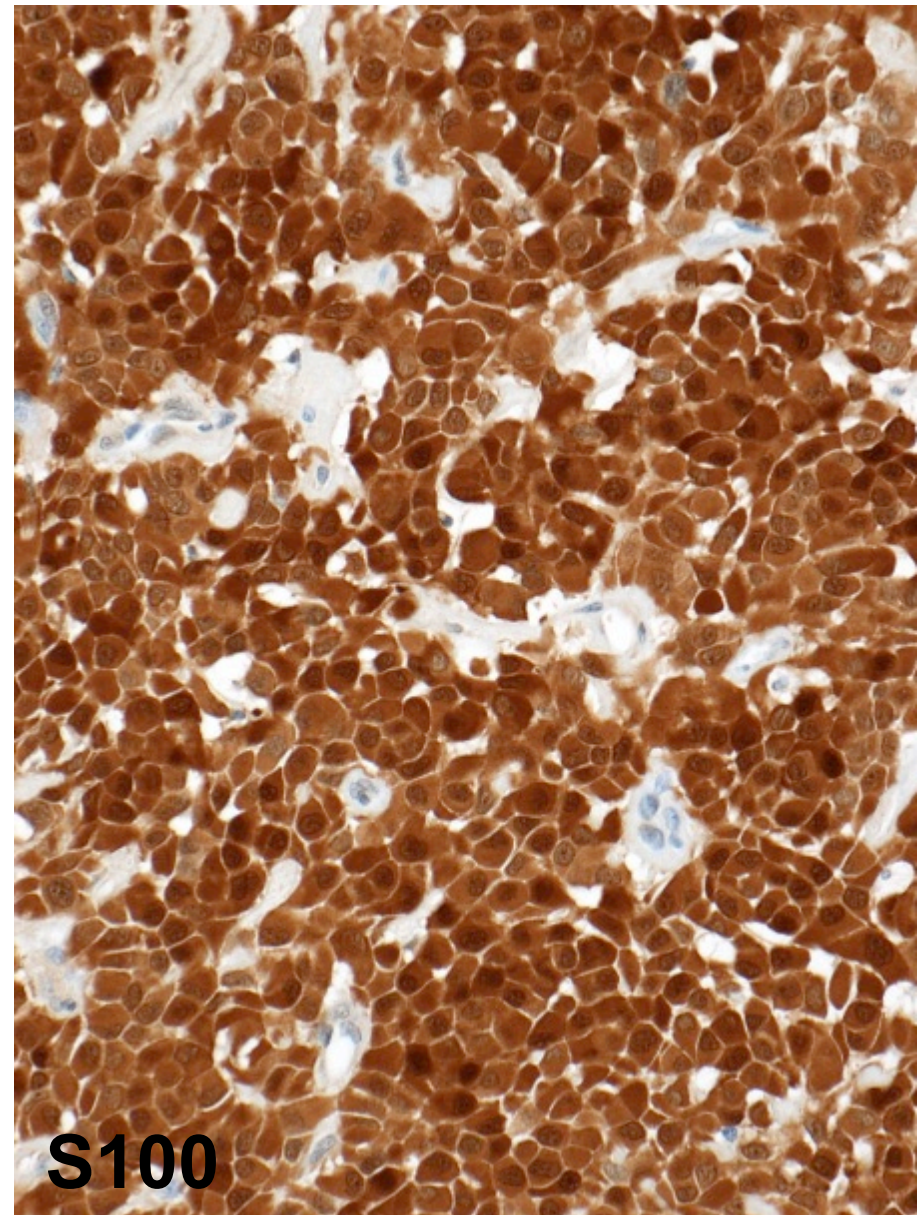
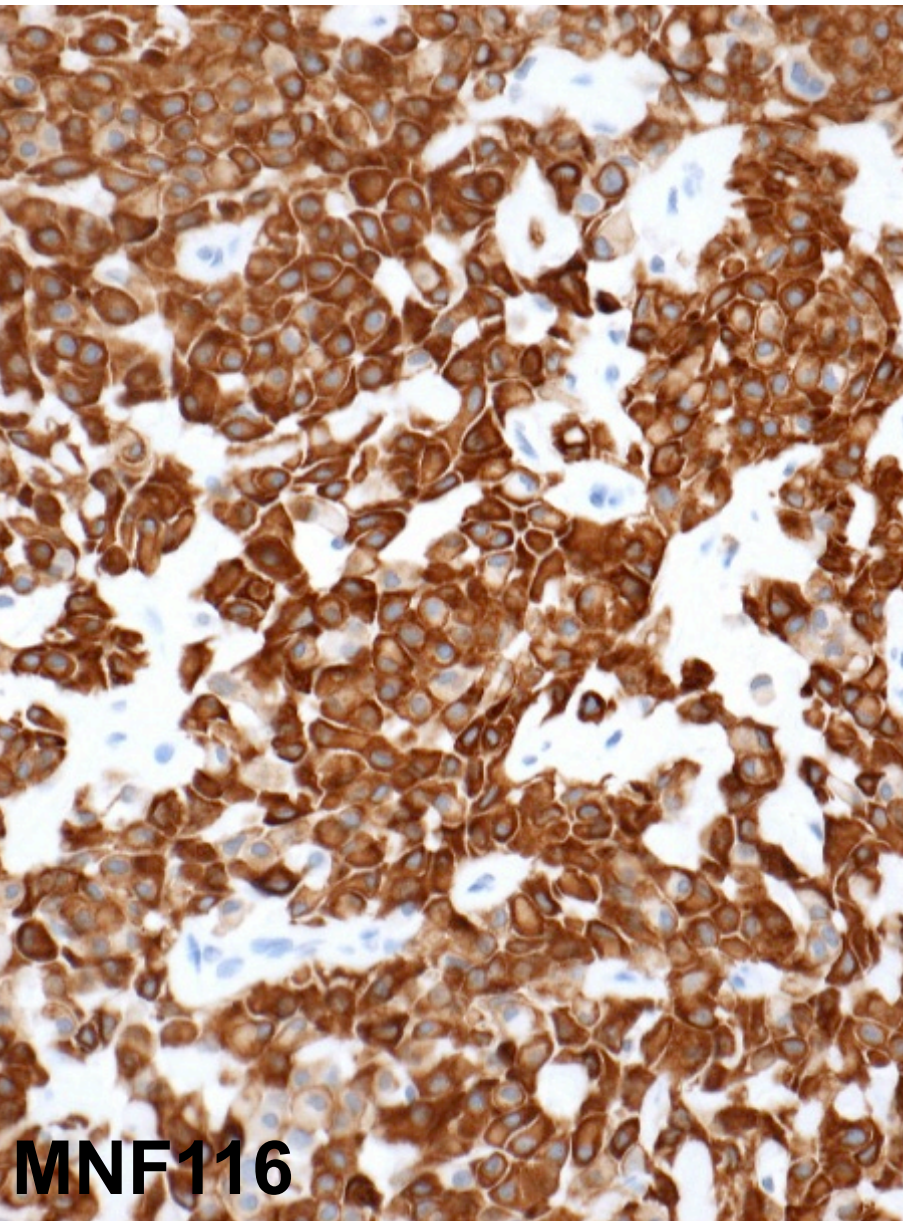








Immunohistochemistry



Cutaneous Myoepithelioma

-Summary-

Significant clinical, histological and immunohistochemical overlap

BUT:

- **Subtle morphological clues**
- **Immunohistochemistry:**
 - **Melan A and HMB45 negative**
 - **EMA or Cytokeratin-positive**

Cellular Neurothekeoma

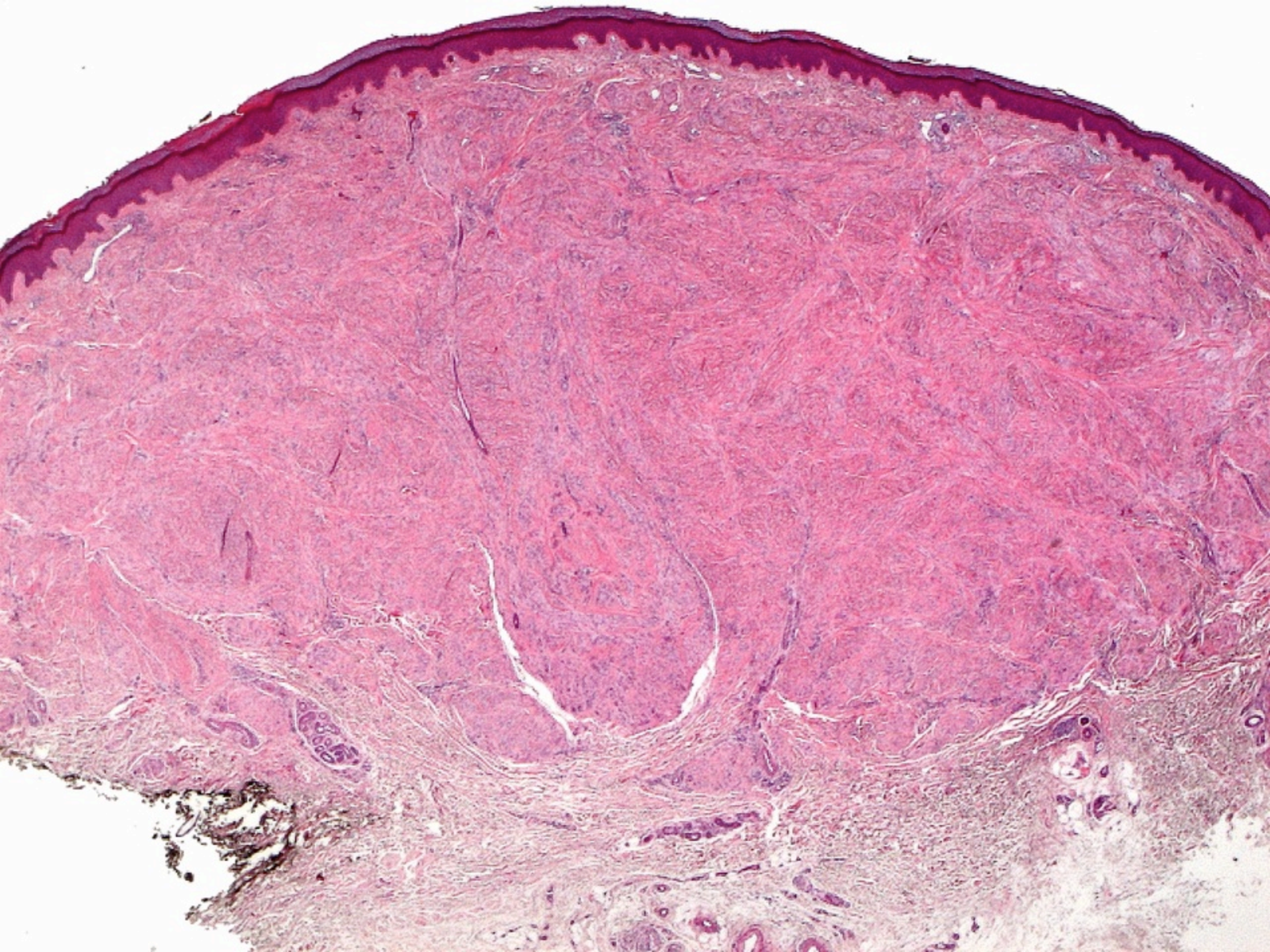
-Clinical-

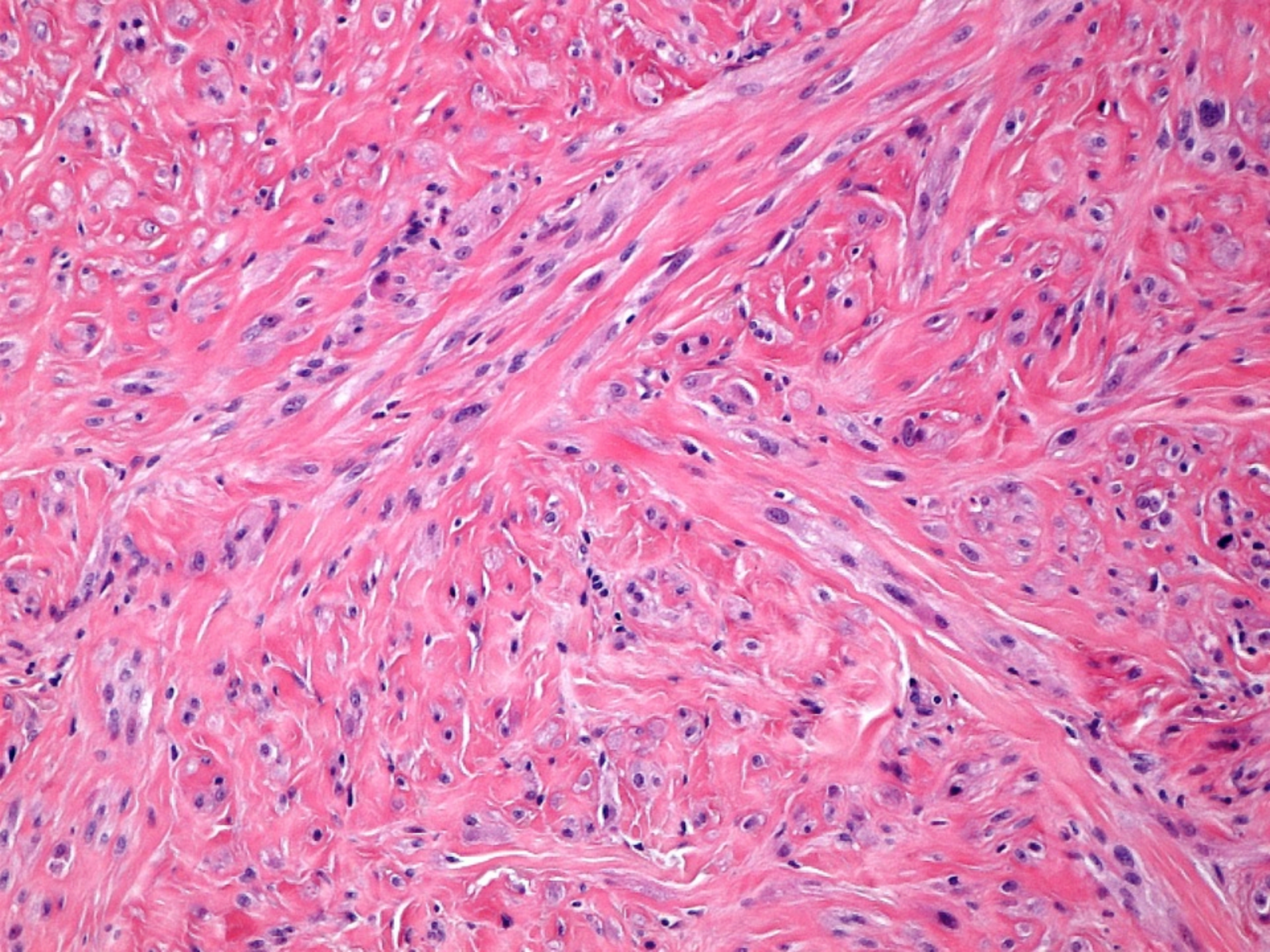
- Papules and small nodules
- Young patients; 1st to 3rd decade
- Female predilection
- Upper half of body; head and neck, shoulder region
- Clinical: cyst, DF

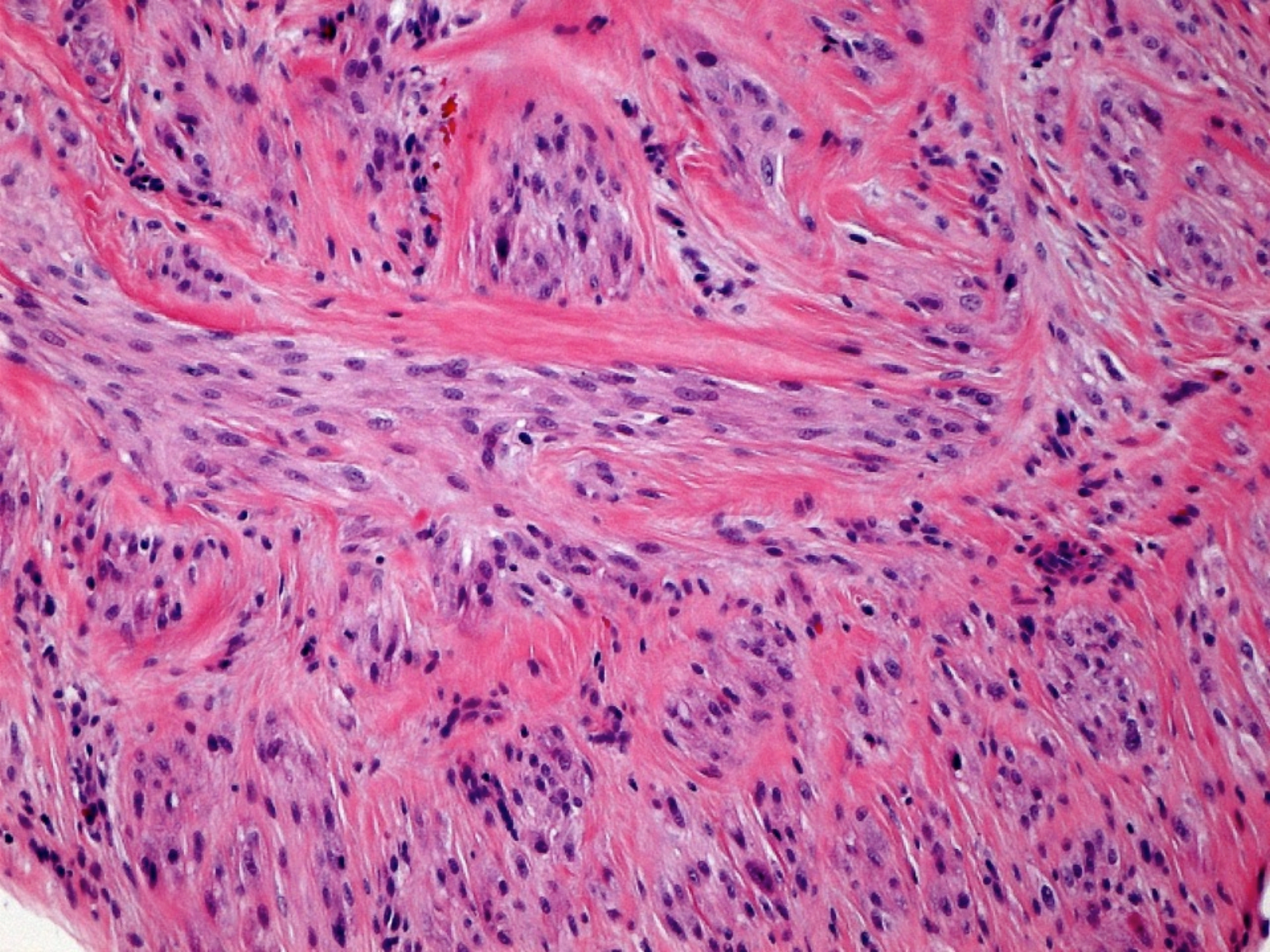
Hornick JL, Fletcher CD. 2007 Am J Surg Pathol; 31(3): 329-40.

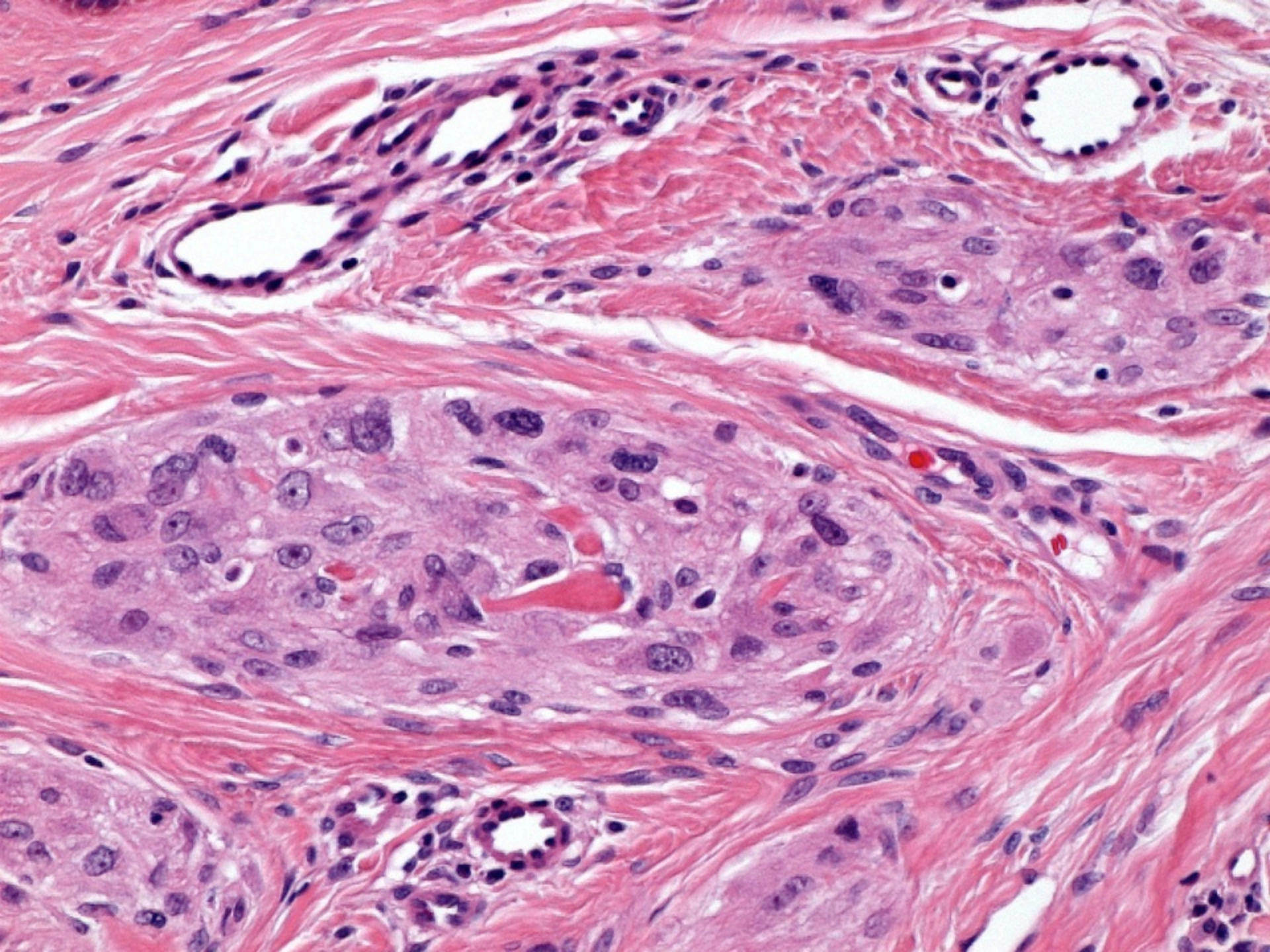
Fetsch JF et al. 2007 Am J Surg Pathol; 31(7): 1103-14.

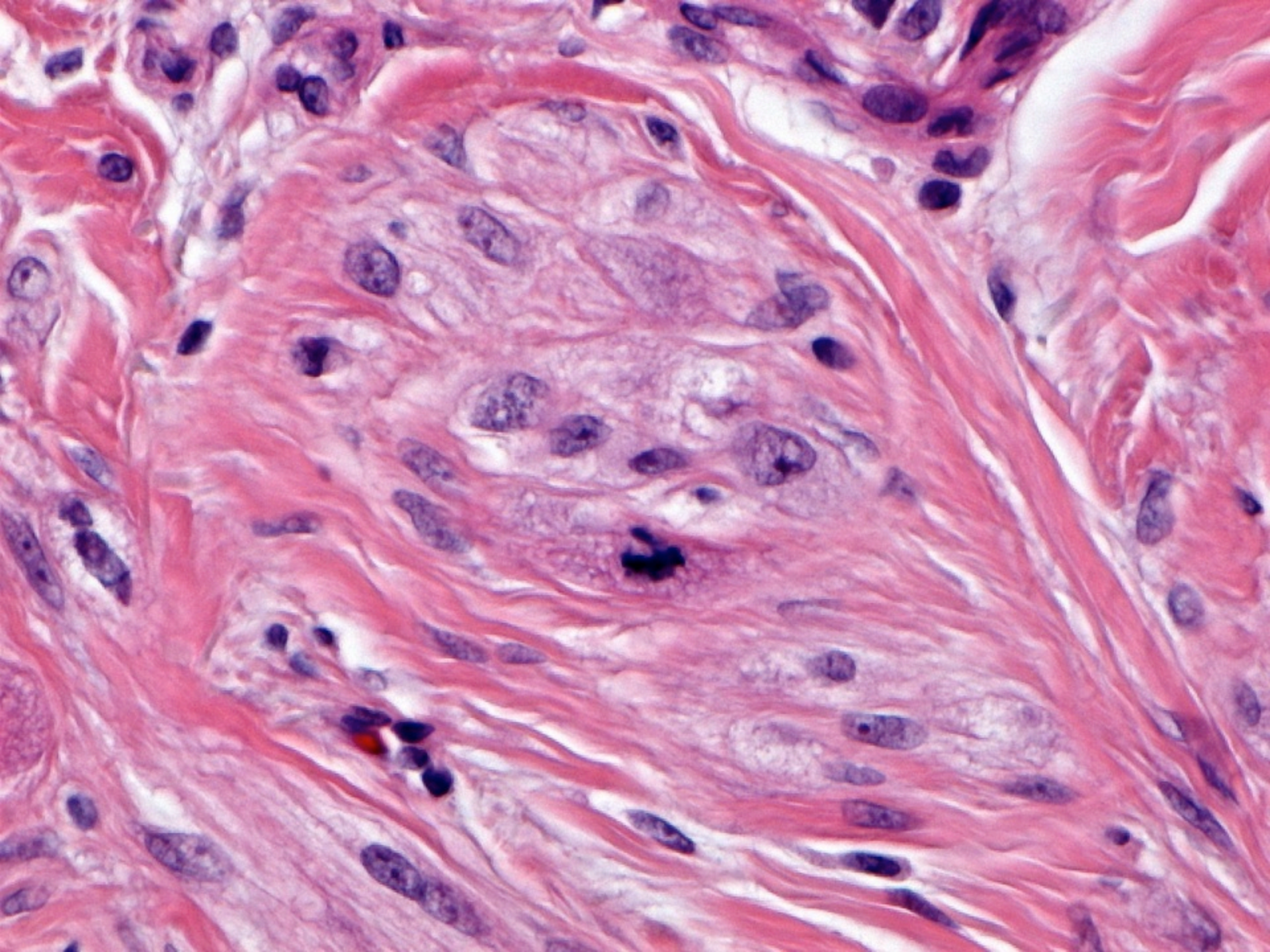
Laskin WB, Fetsch JF, Miettinen M. 2000 Hum Pathol; 31(10): 1230-41.

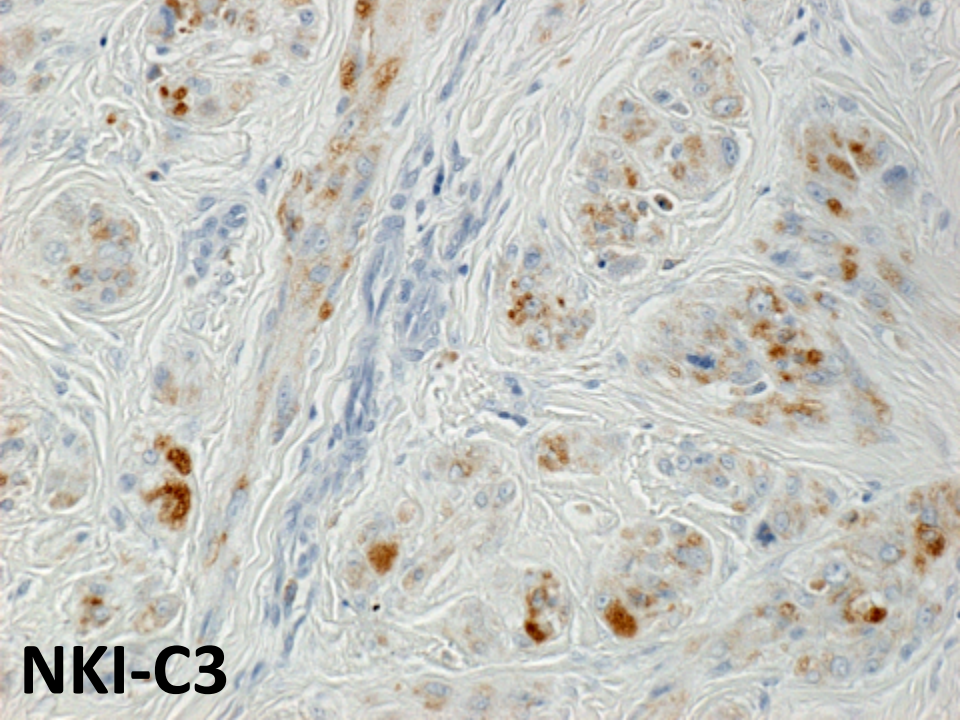
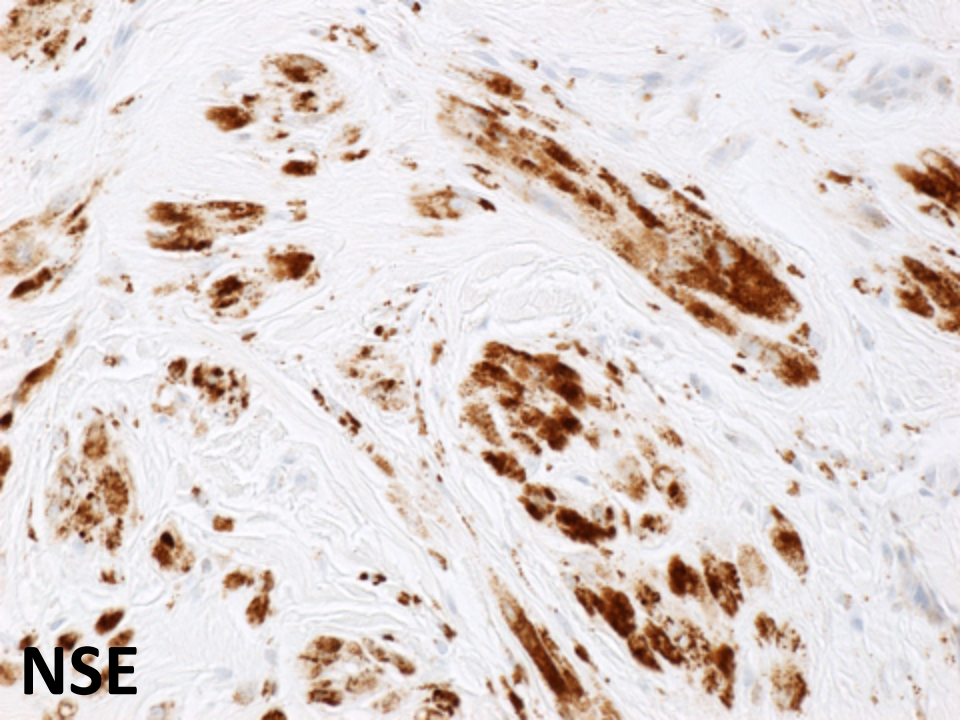
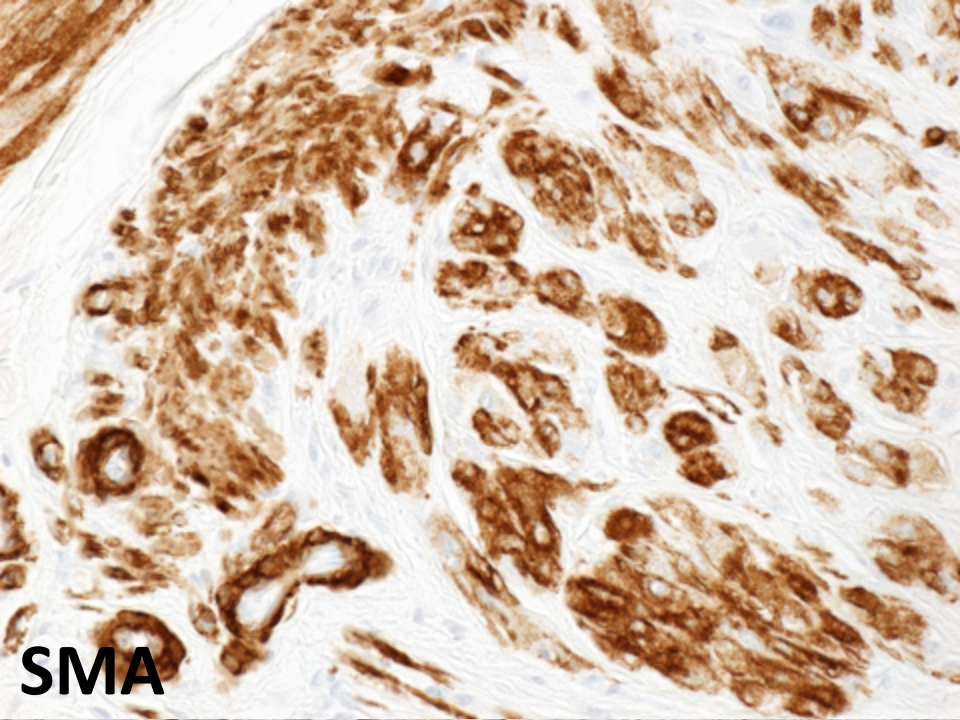
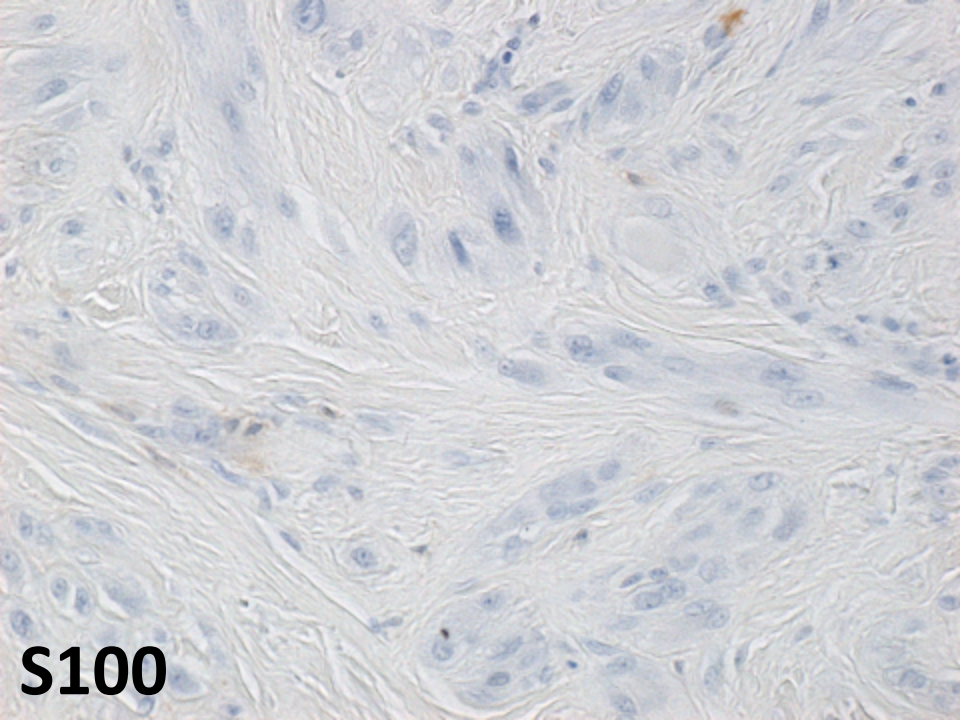






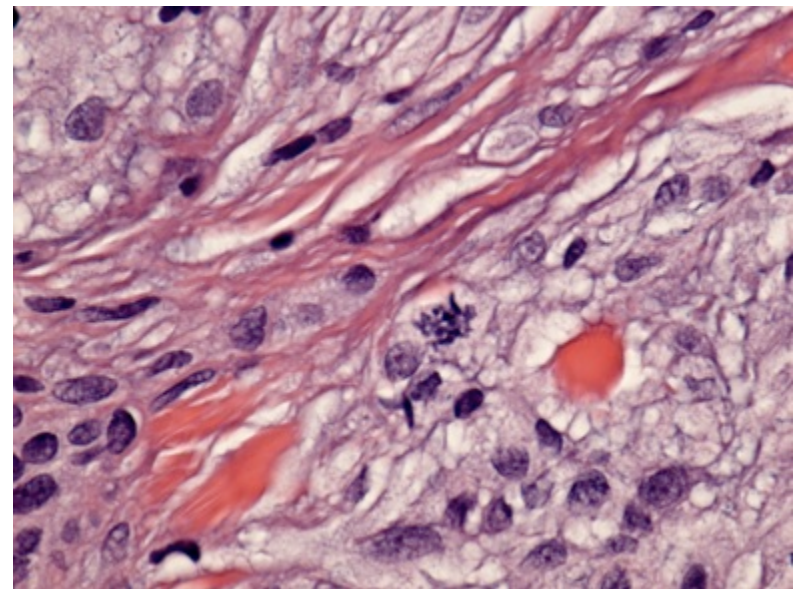
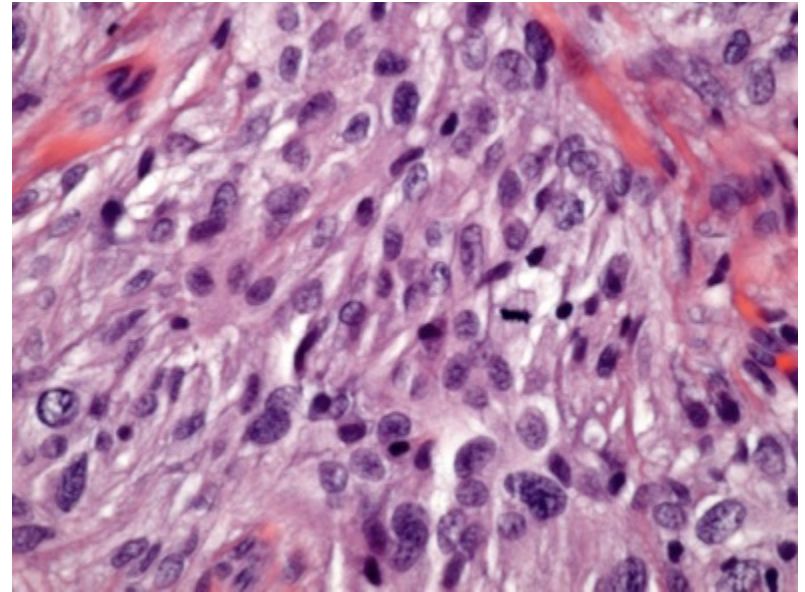






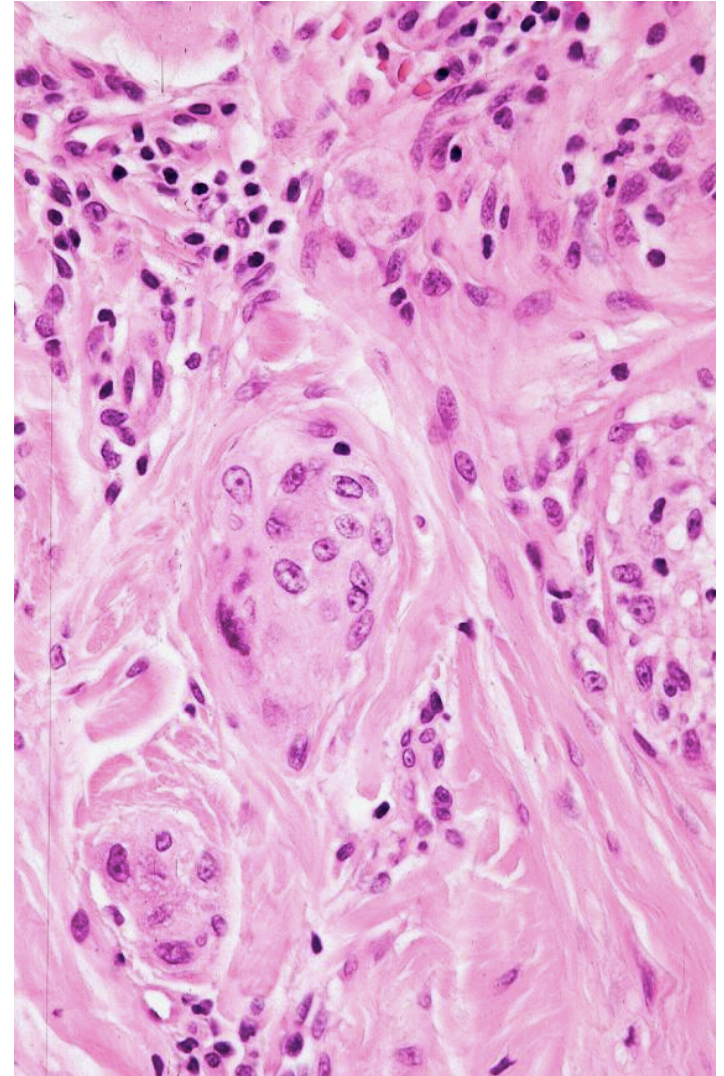
Atypical Cellular Neurothekeoma

- Large size (up to 6 cm)
- Extension into subcutaneous tissue
- Infiltrative borders
- High mitotic rate
- Marked cytologic atypia



Cellular Neurothekeoma

- **Benign behaviour**
- **Rare local recurrence**
- **No adverse outcome in large series**
- **Atypical features not associated with poor prognosis**
- **Unrelated to Dermal Nerve Sheath Myxoma**



Dermal Nerve Sheath Myxoma vs “Neurothekeoma”

DNSM and cellular neurothekeoma separate and distinct entities!

DNSM – true Schwann cell neoplasm

Cellular neurothekeoma – line of differentiation unknown

Cellular neurothekeoma may show stromal myxoid change

Hornick JL, Fletcher CD. 2007 Am J Surg Pathol; 31(3): 329-40.

Fetsch JF et al. 2007 Am J Surg Pathol; 31(7): 1103-14.

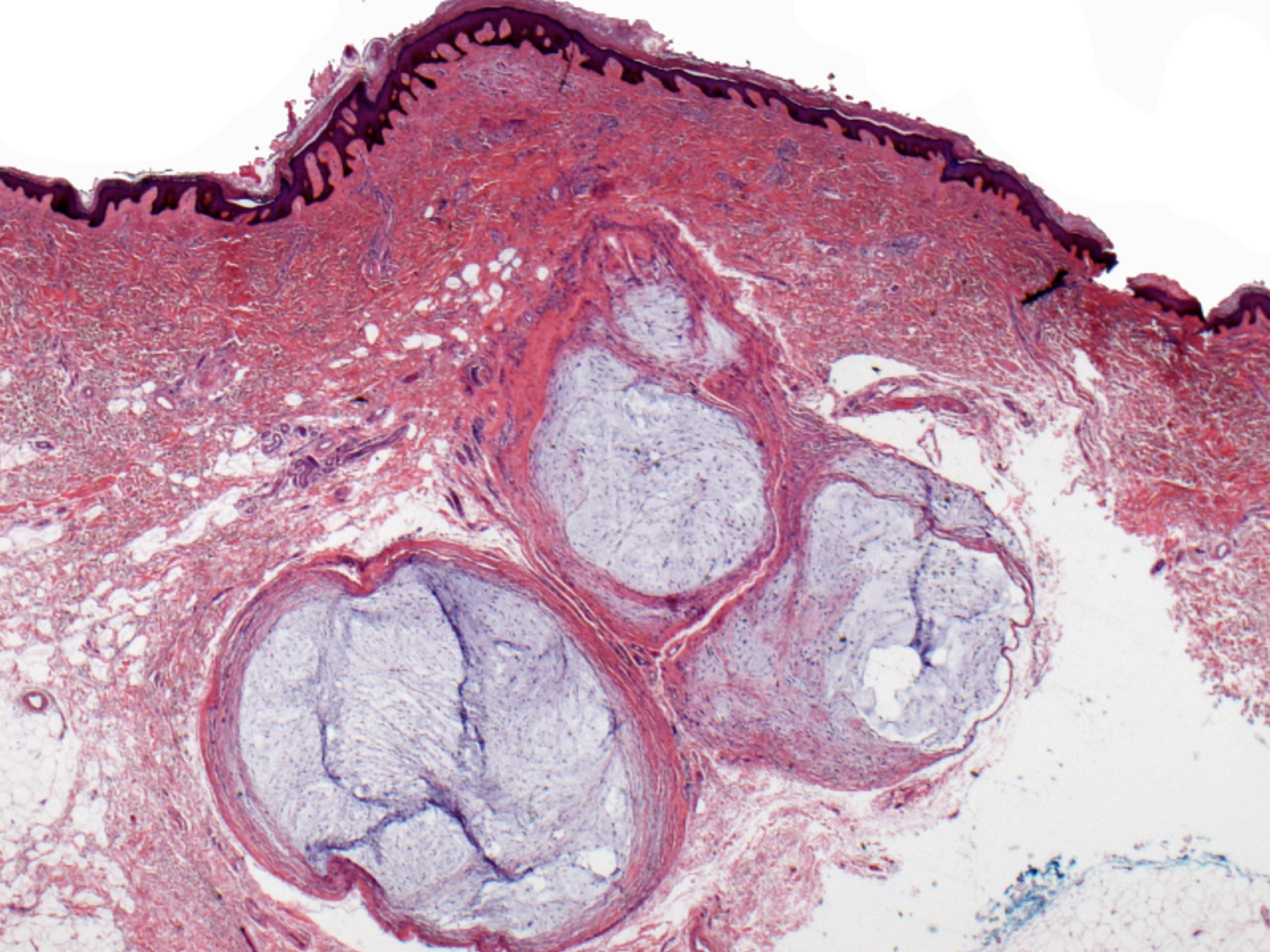
Laskin WB, Fetsch JF, Miettinen M. 2000 Hum Pathol; 31(10): 1230-41.

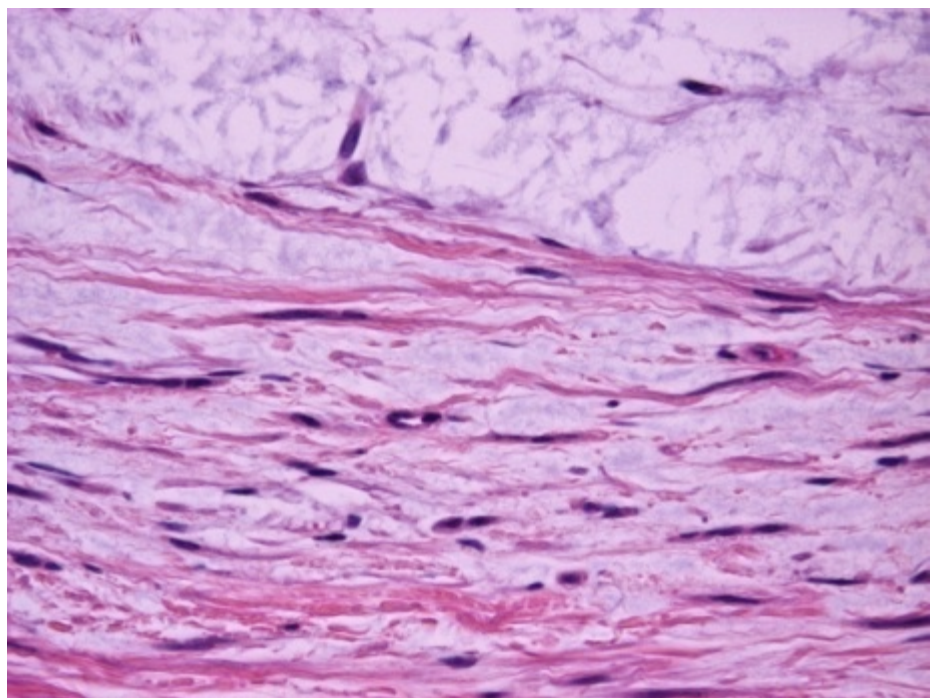
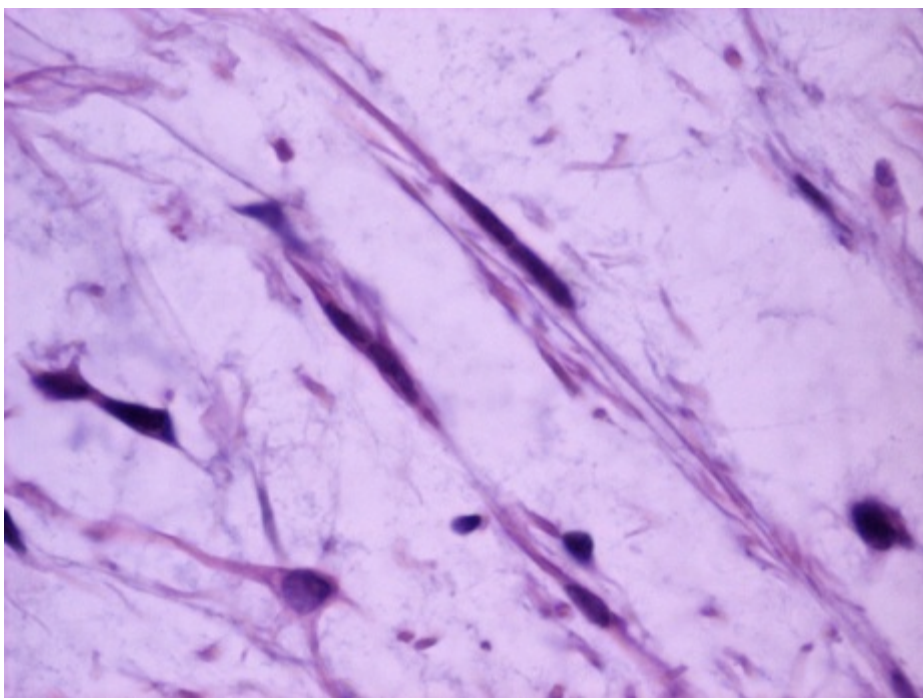
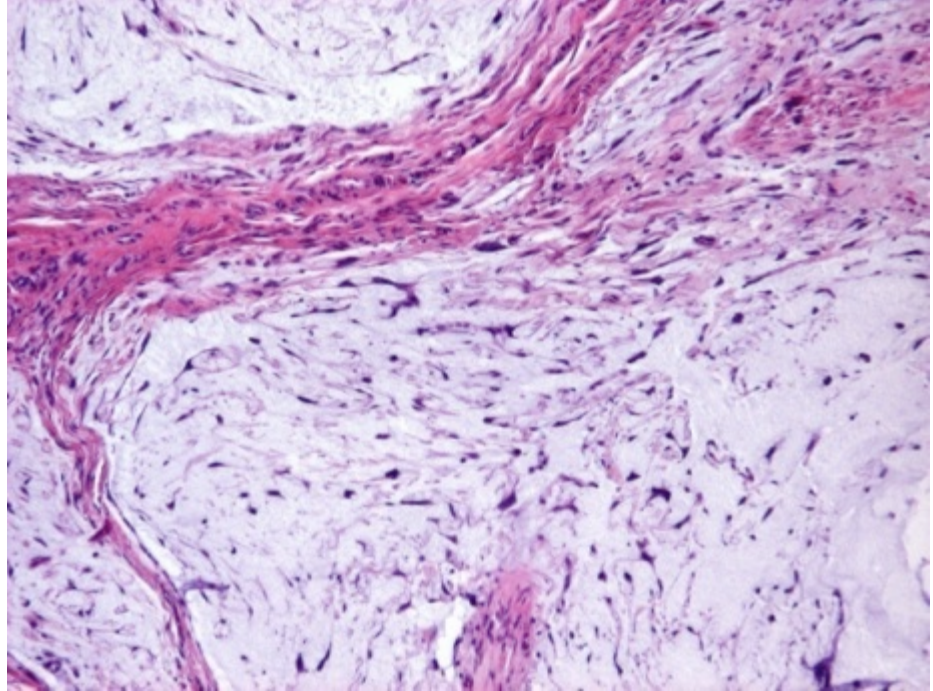
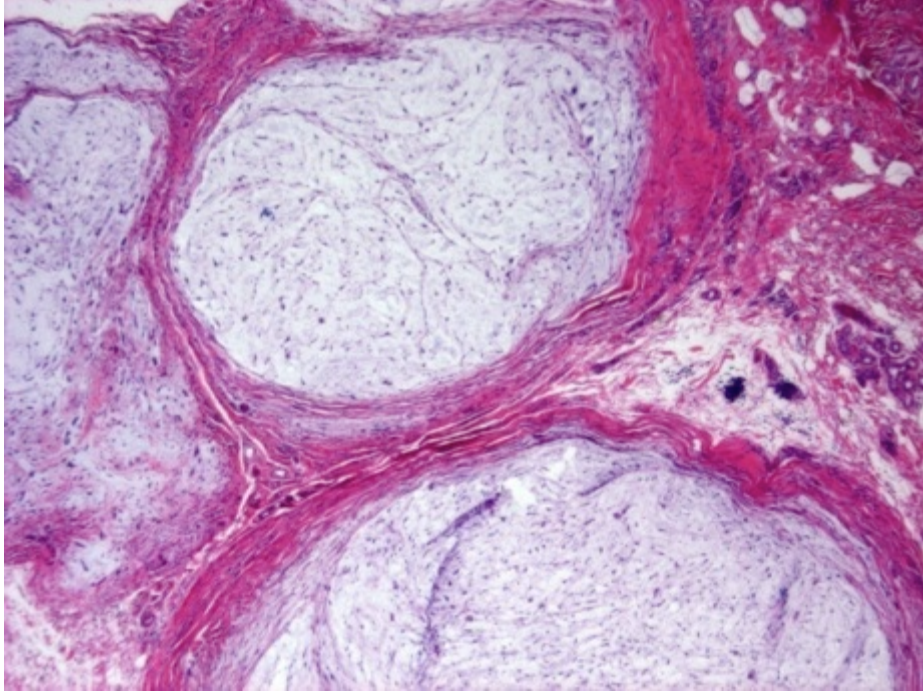
Sheth, S et al 2011 Modern Pathology; 24: 343-354.

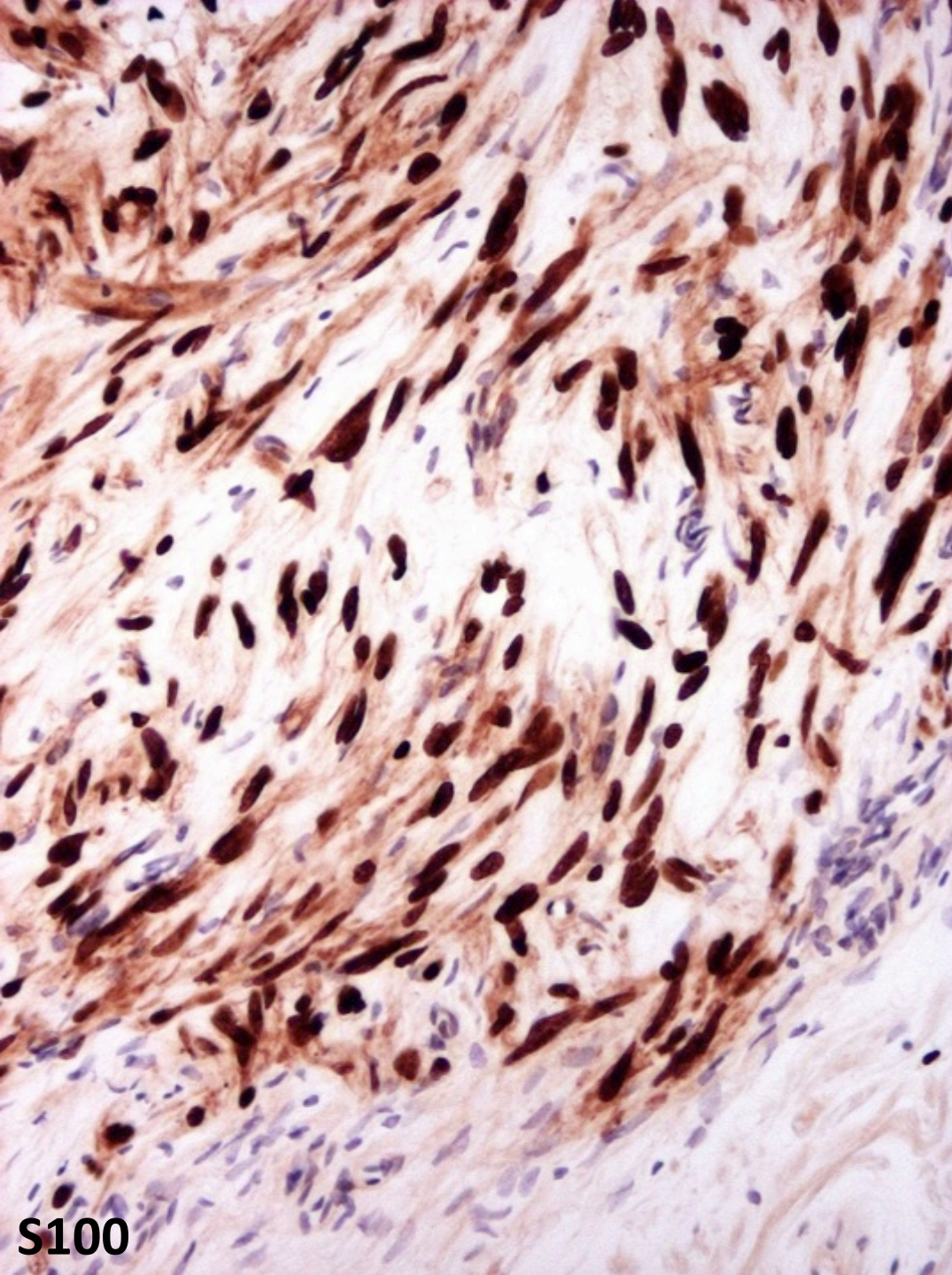
Dermal Nerve Sheath Myxoma

-Clinical-

- **Young to middle aged adults**
- **Distal extremities, fingers**
- **High local recurrence rate ~50%**







DNSM

-Immunohistochemistry-

Also positive:

GFAP

EMA

S100

Cellular Neurothekeoma

-Summary-

Significant clinical and histological overlap

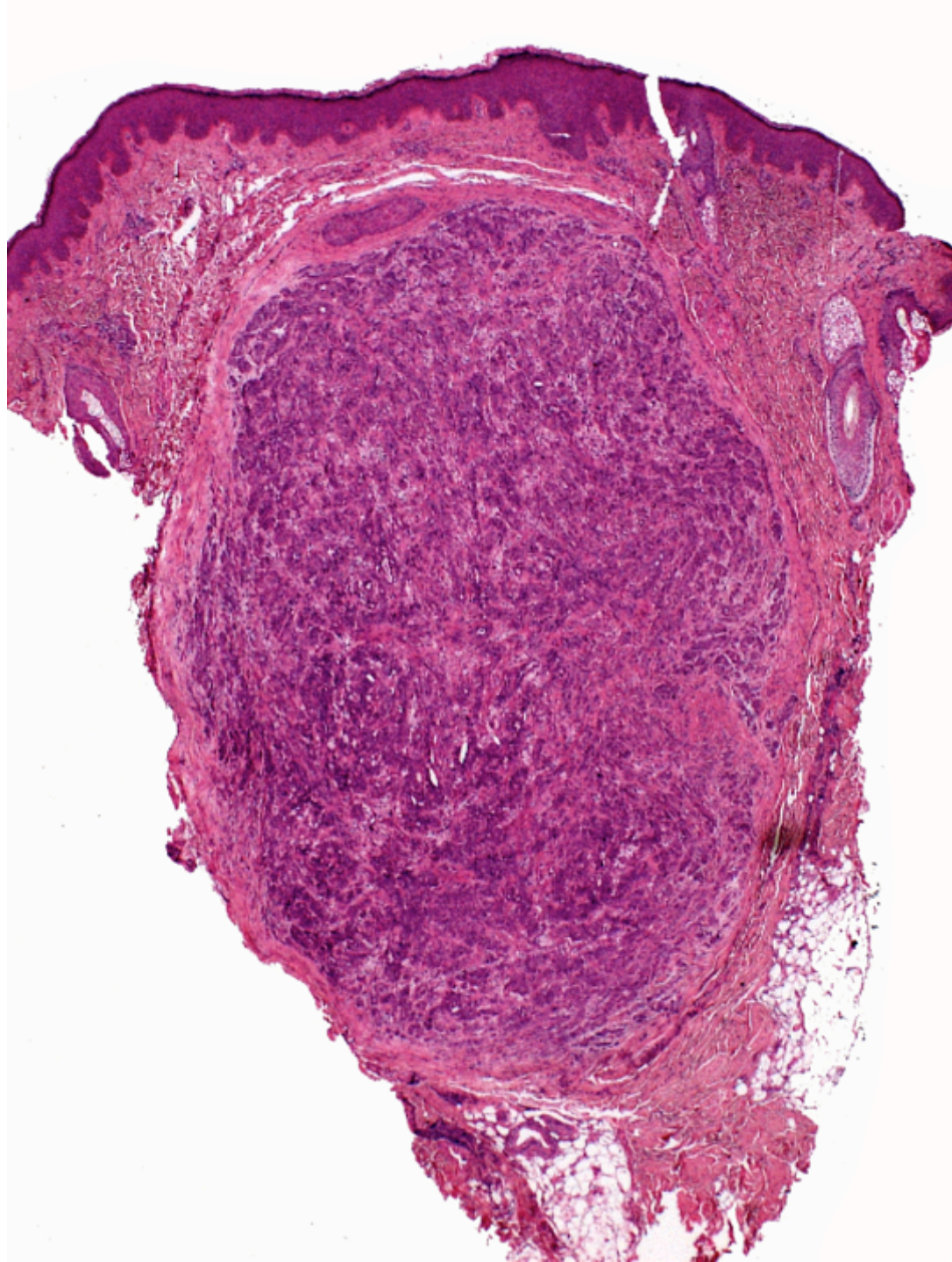
BUT:

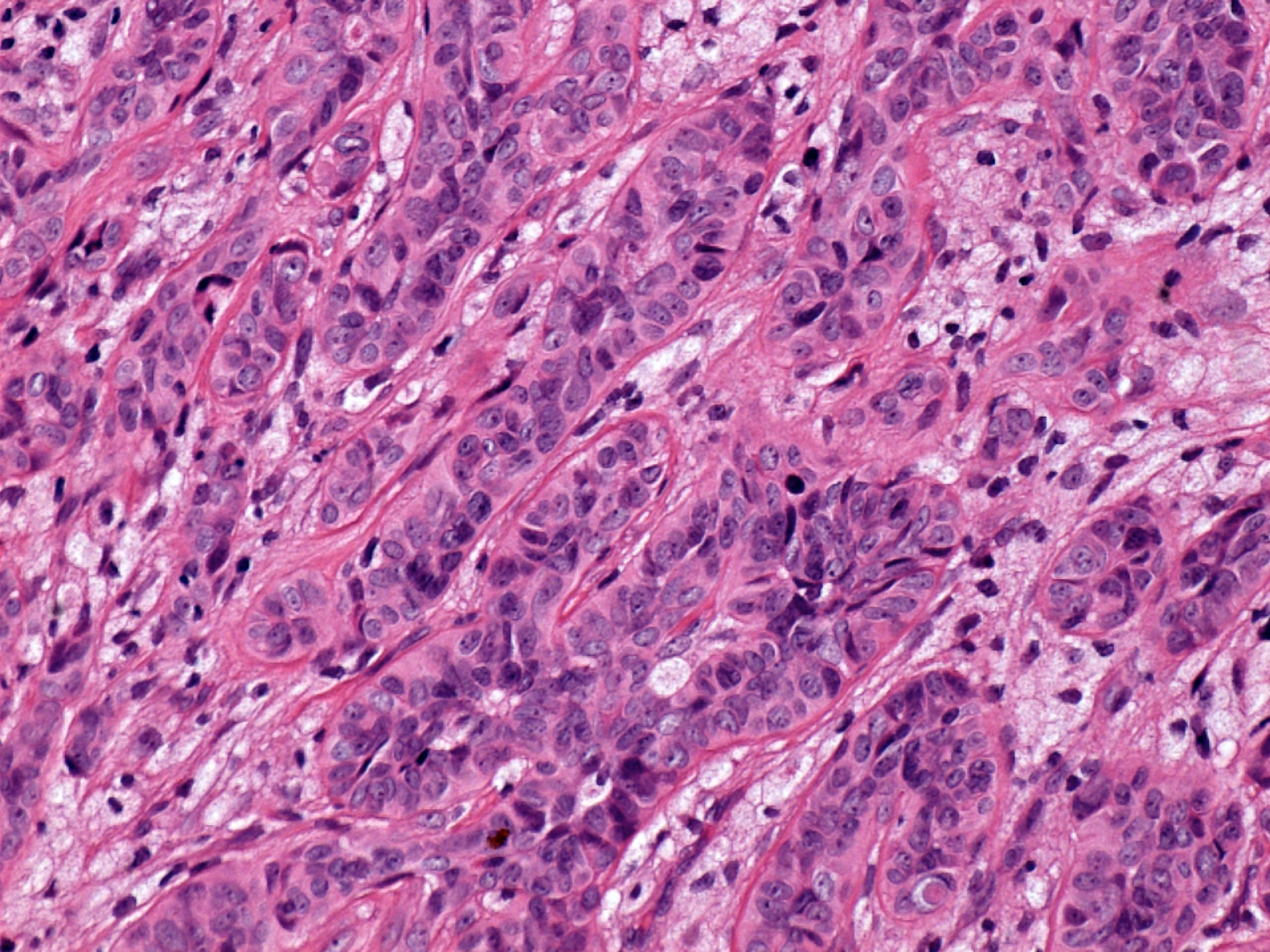
- **Immunohistochemistry:**
 - **S100-negative**

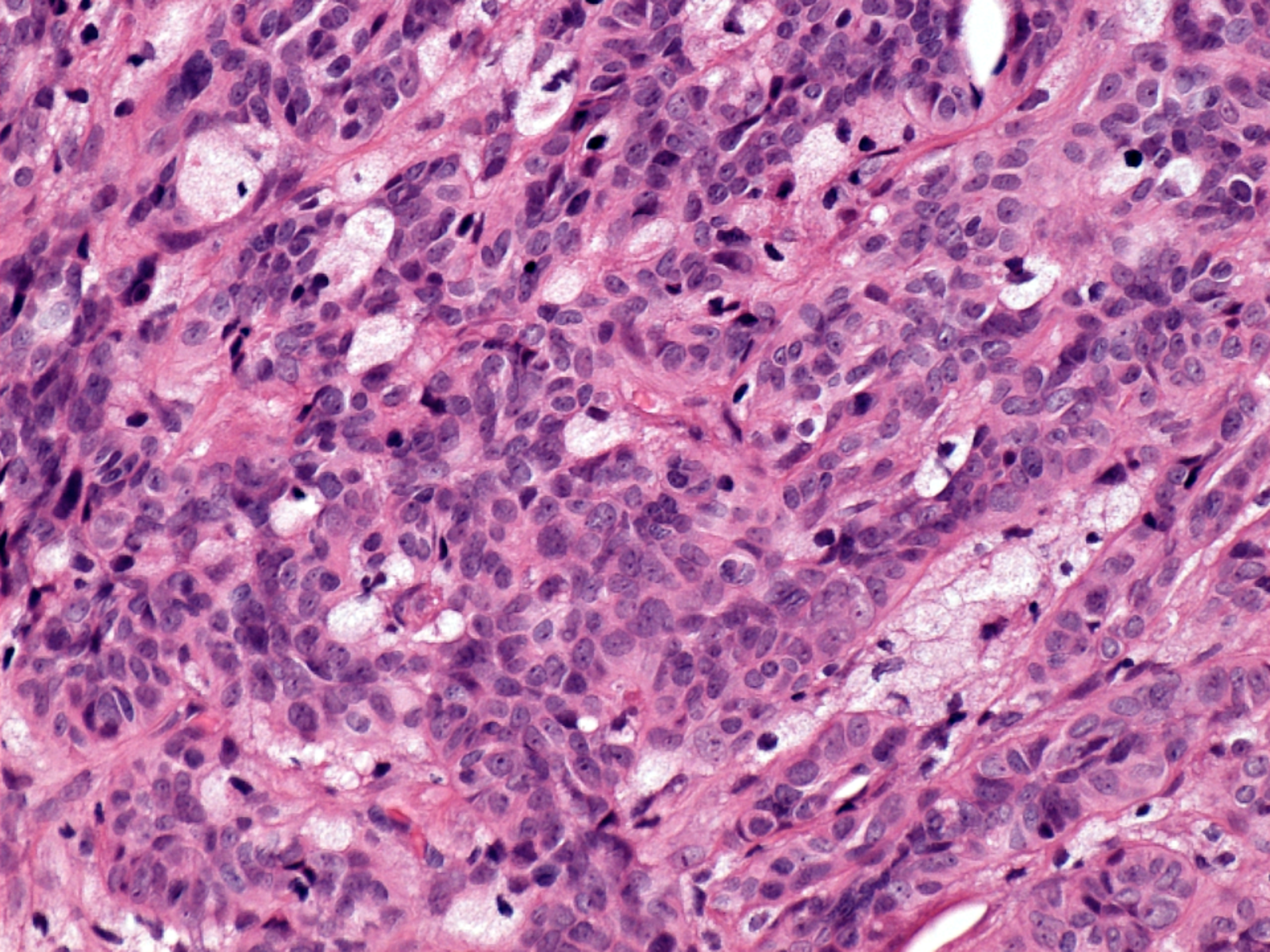
Epithelioid Schwannoma

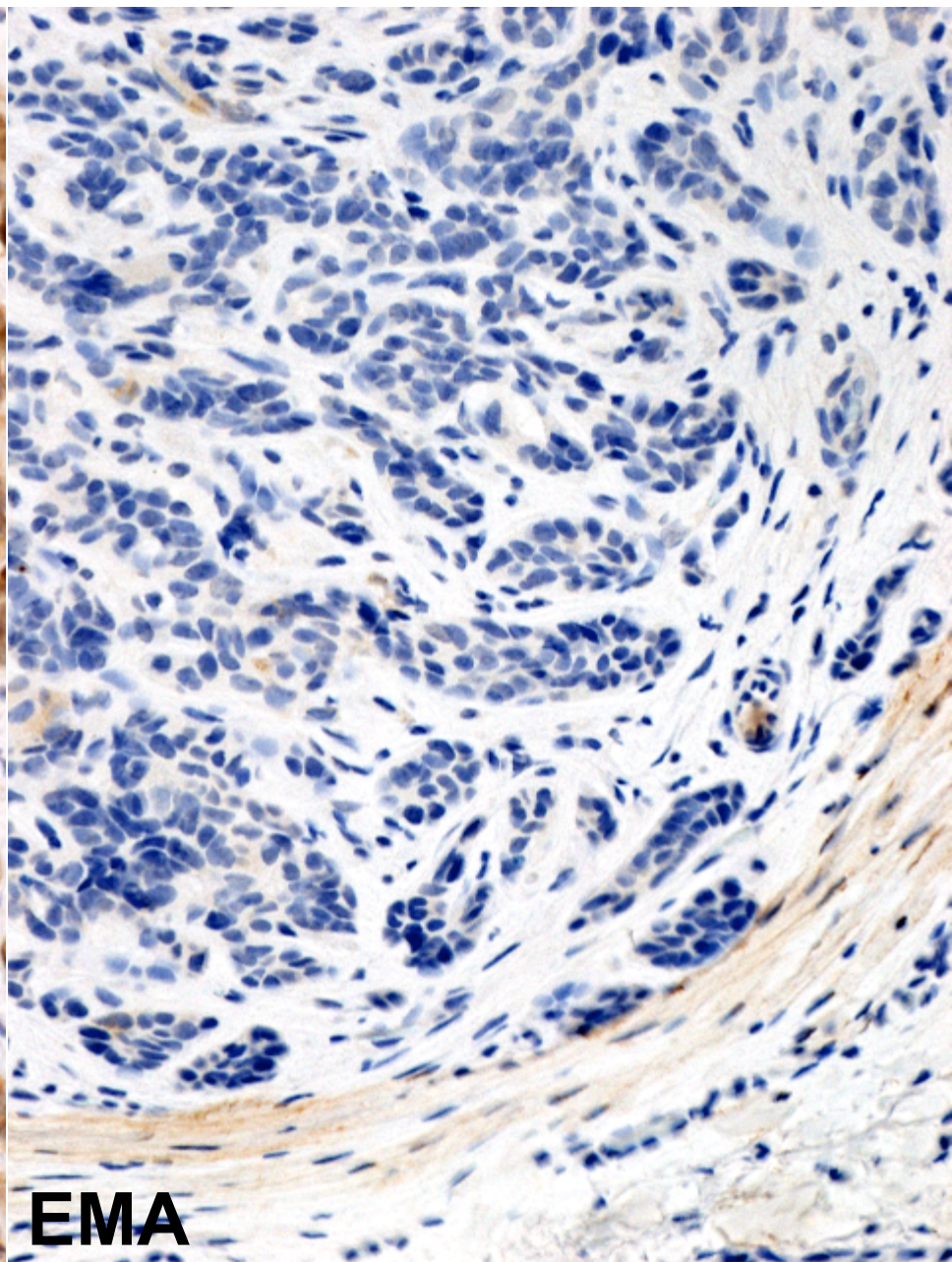
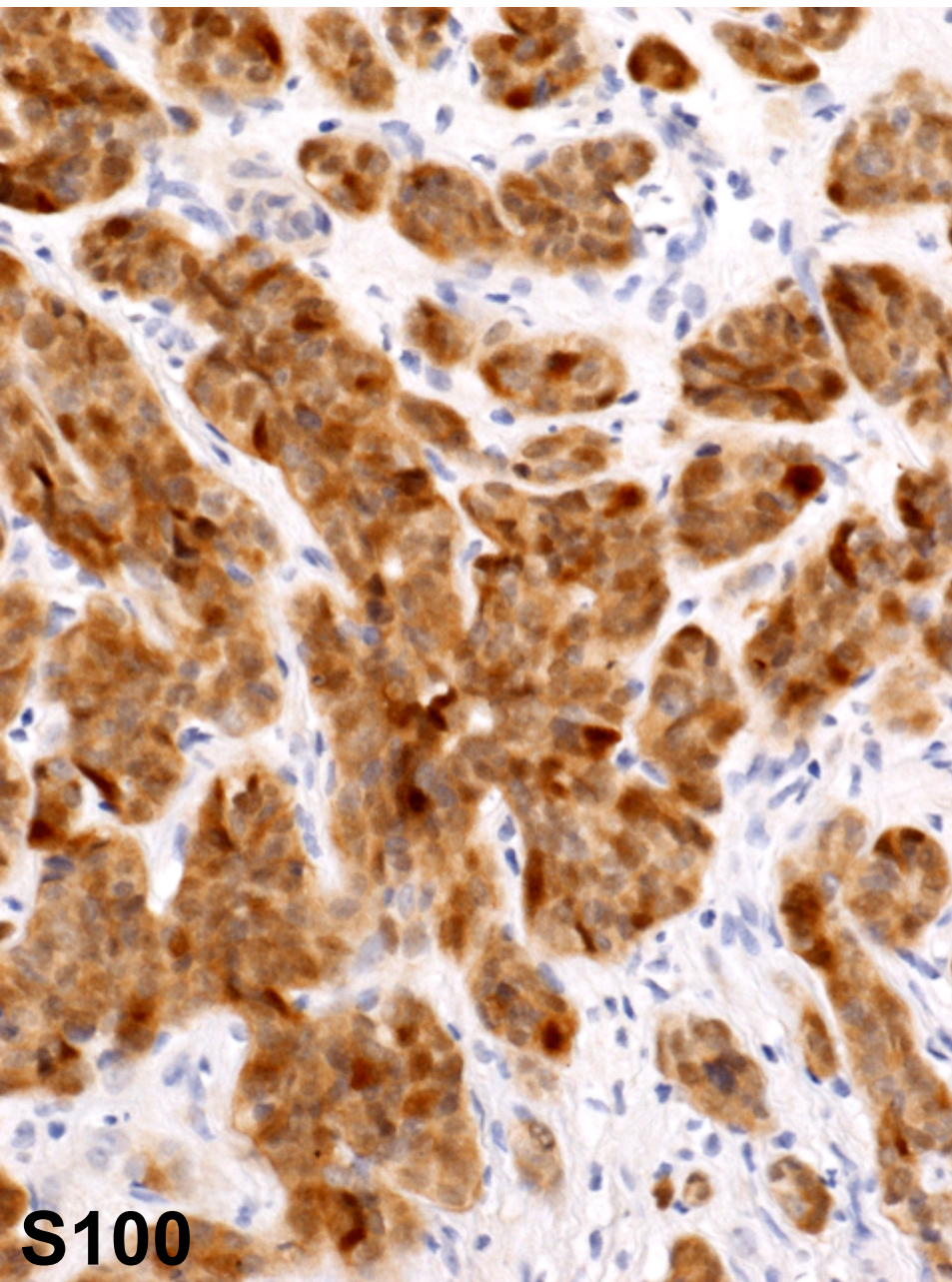
-Variants-

- **Rare subtype**
- **Most commonly affecting skin and subcutis**
- **Middle aged adults, female predominance**
- **Painless nodule, 0.5-3 cm**
- **Extremities**
- **Entirely benign behaviour**





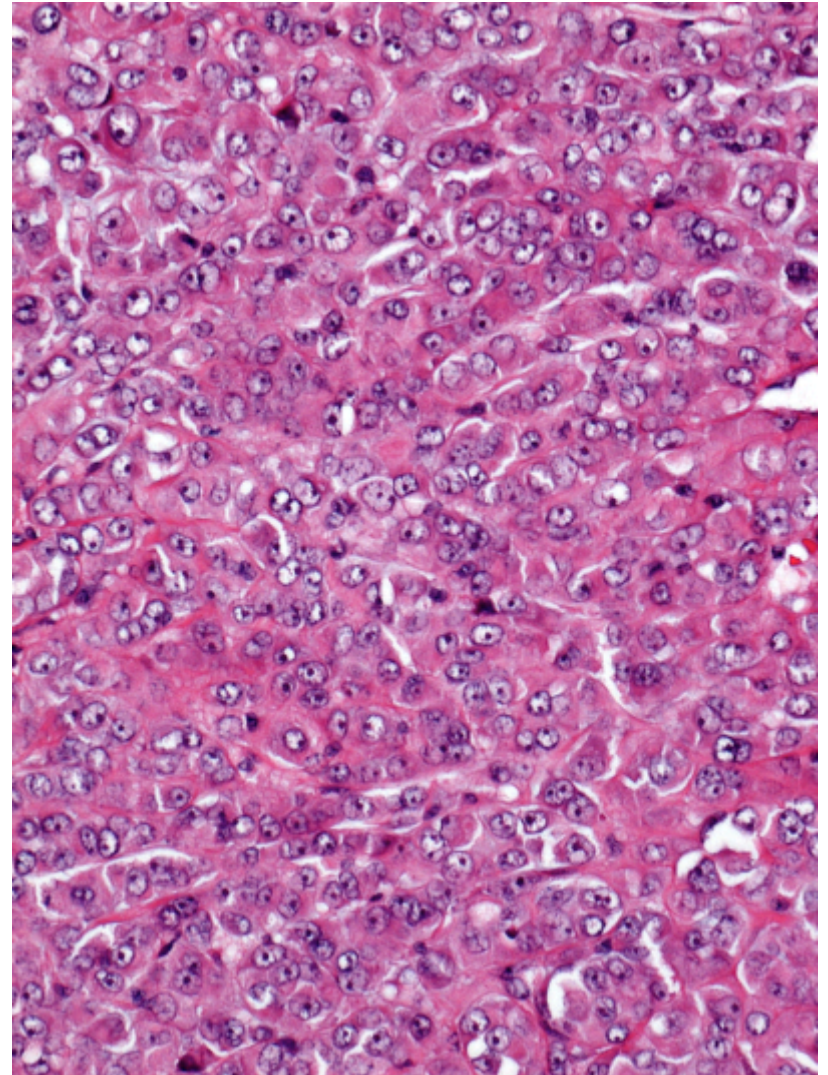




Epithelioid Schwannoma

-DDx-

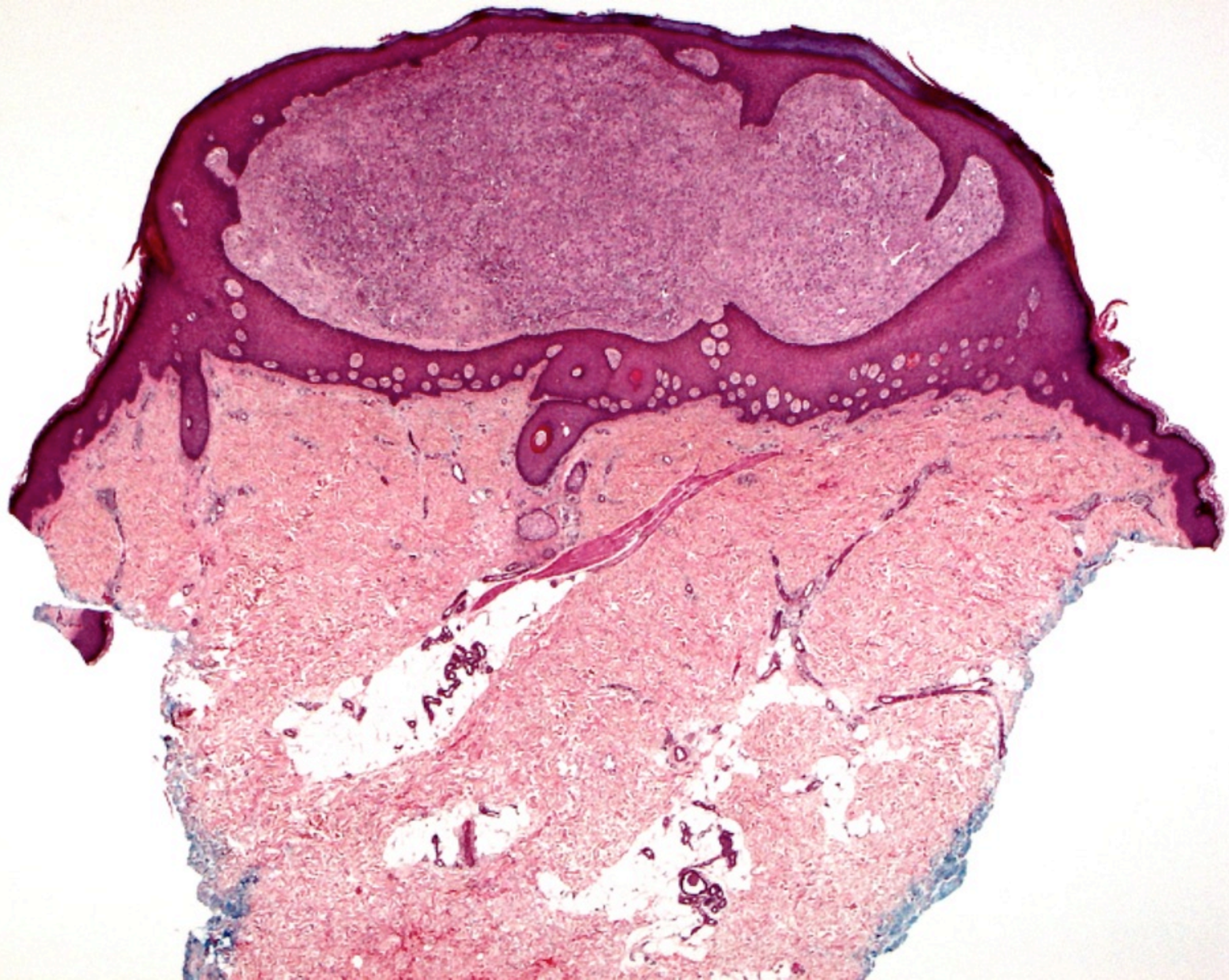
- Epithelioid MPNST
- Myoepithelioma
- Metastatic Melanoma

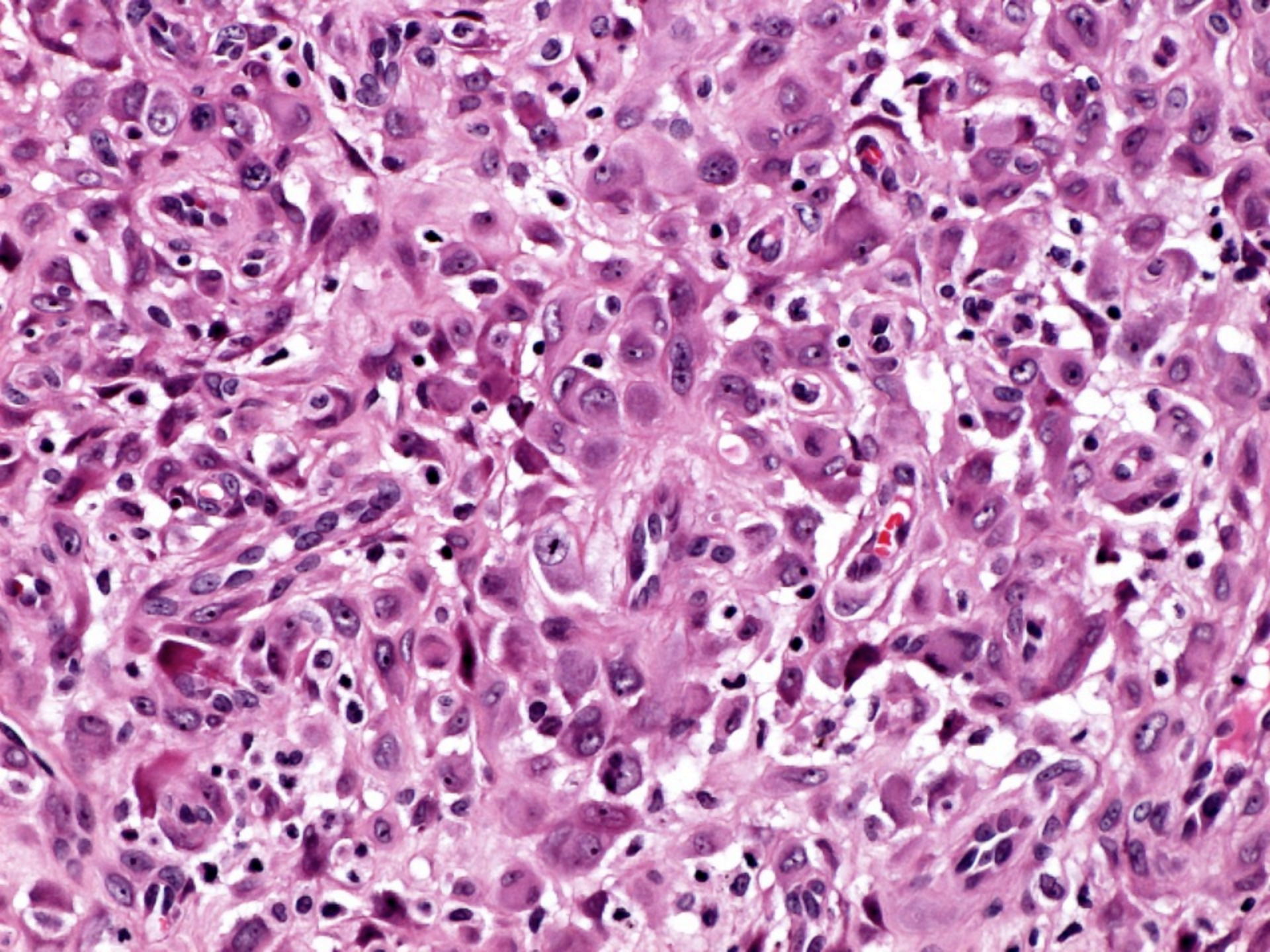


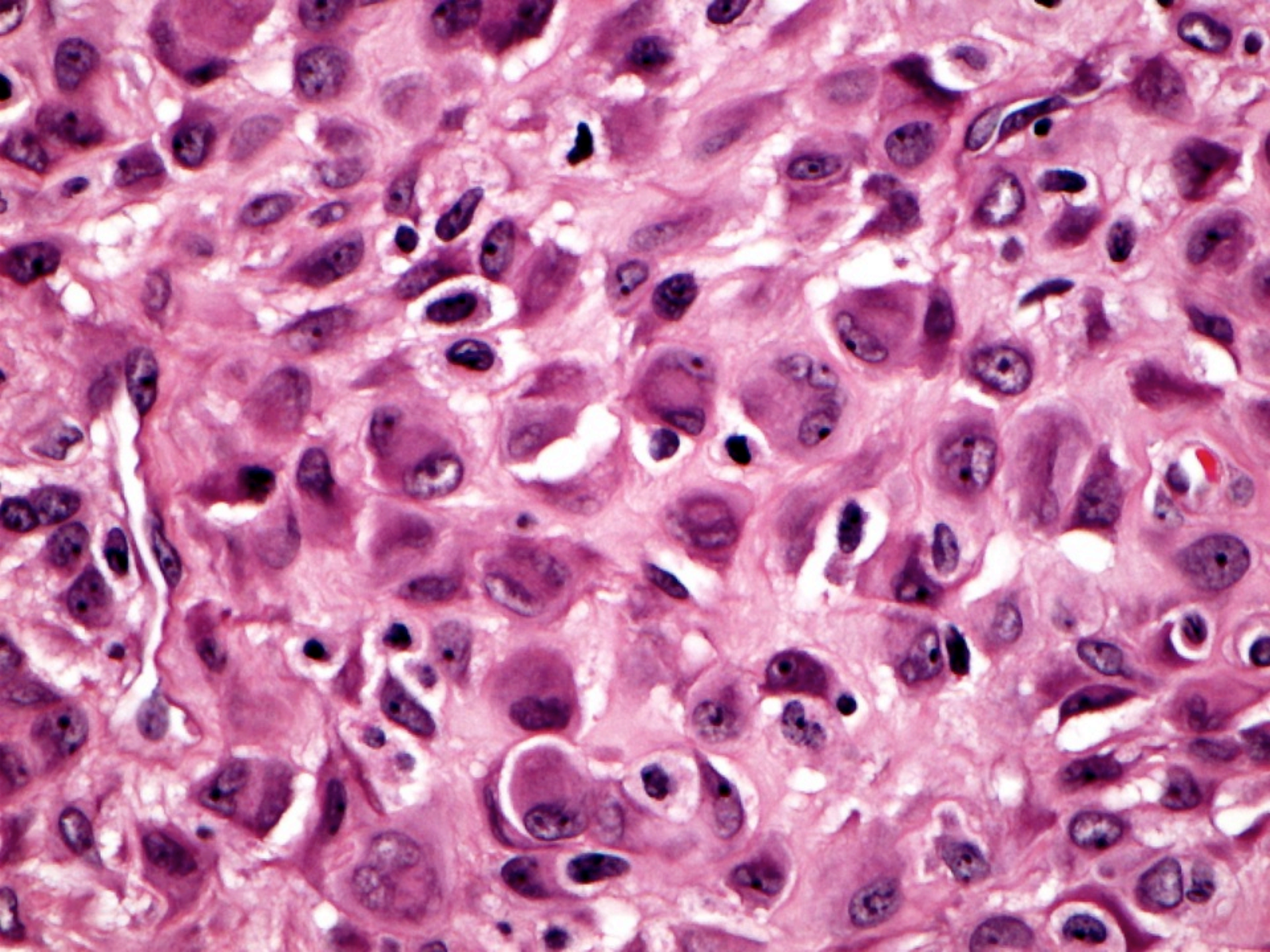
Epithelioid Fibrous Histiocytoma

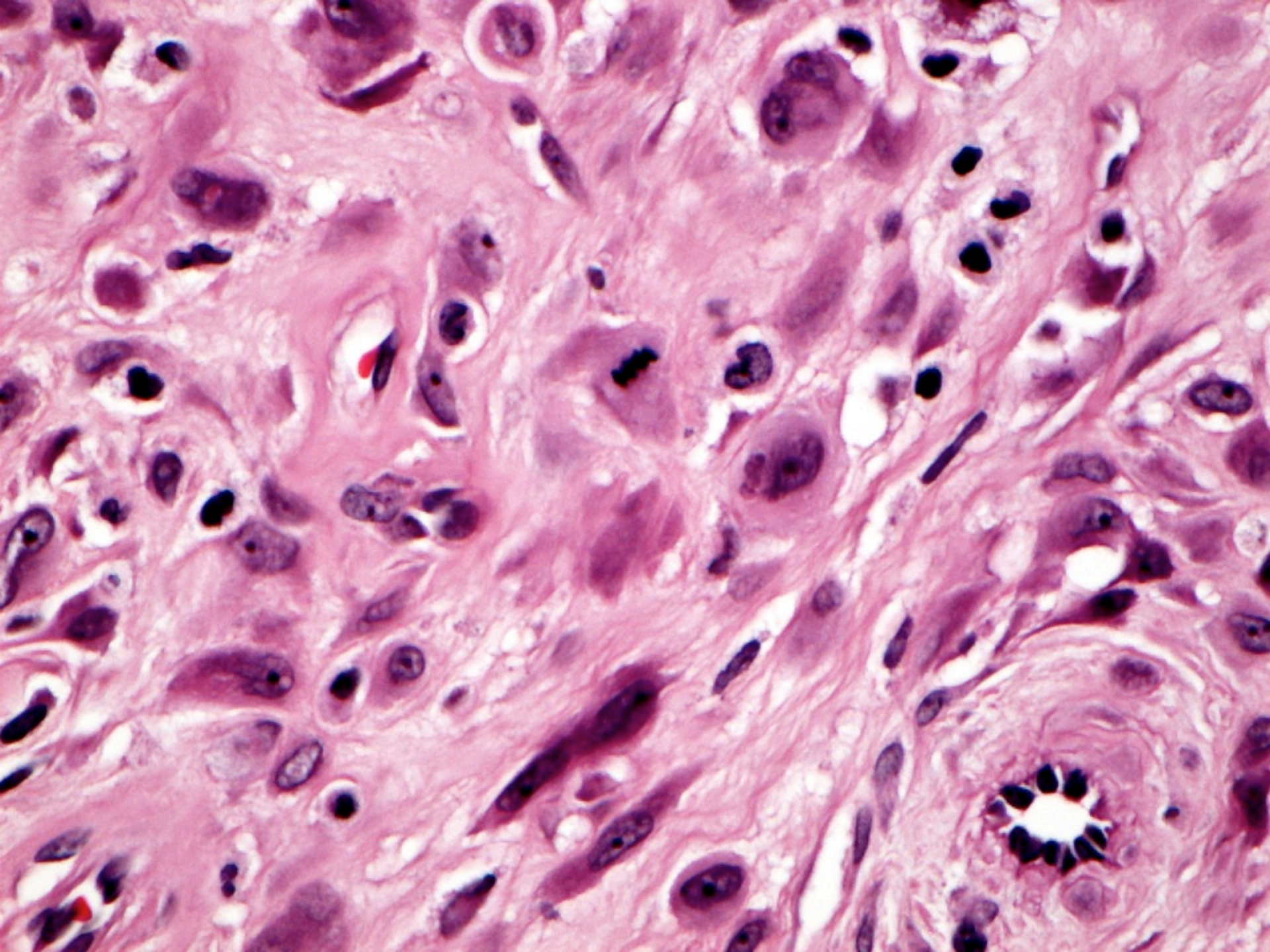
-Overview-

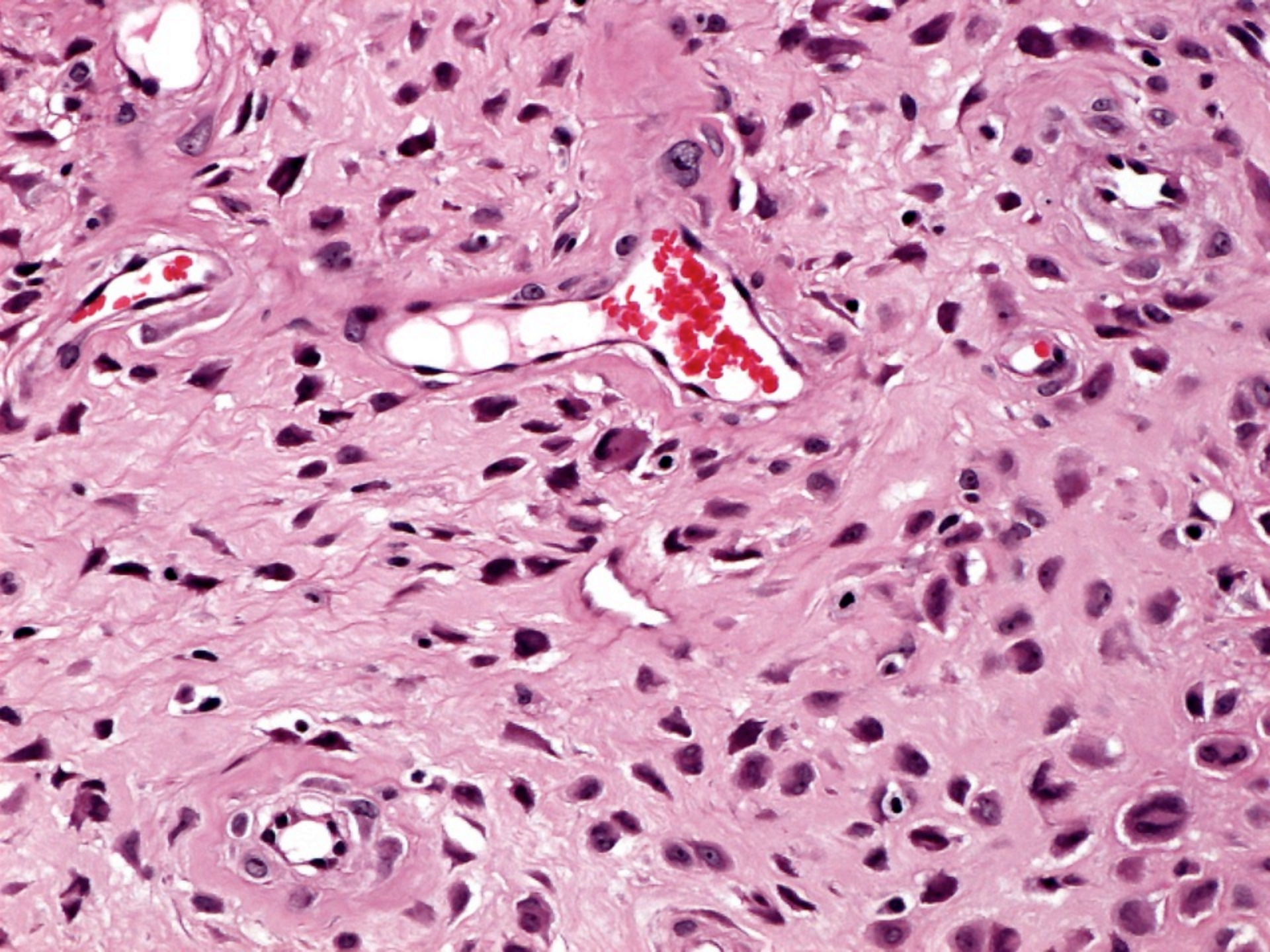
- **Uncommon tumor type**
- **Uncertain relationship to conventional cutaneous FH**
- **Young to middle-aged adults**
- **Predilection for trunk and extremities**
- **Usually polypoid**
- **Benign – rarely recur**

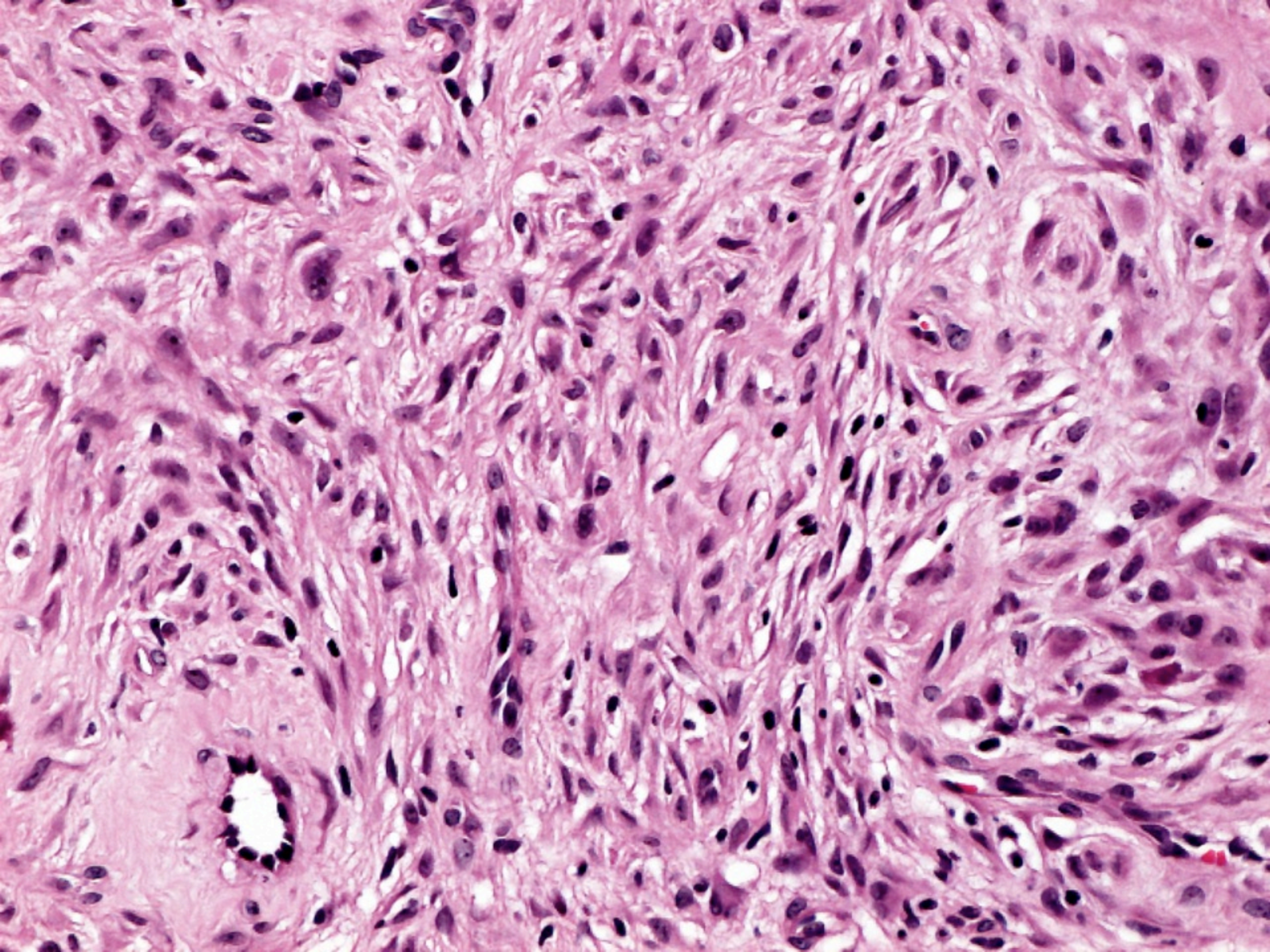


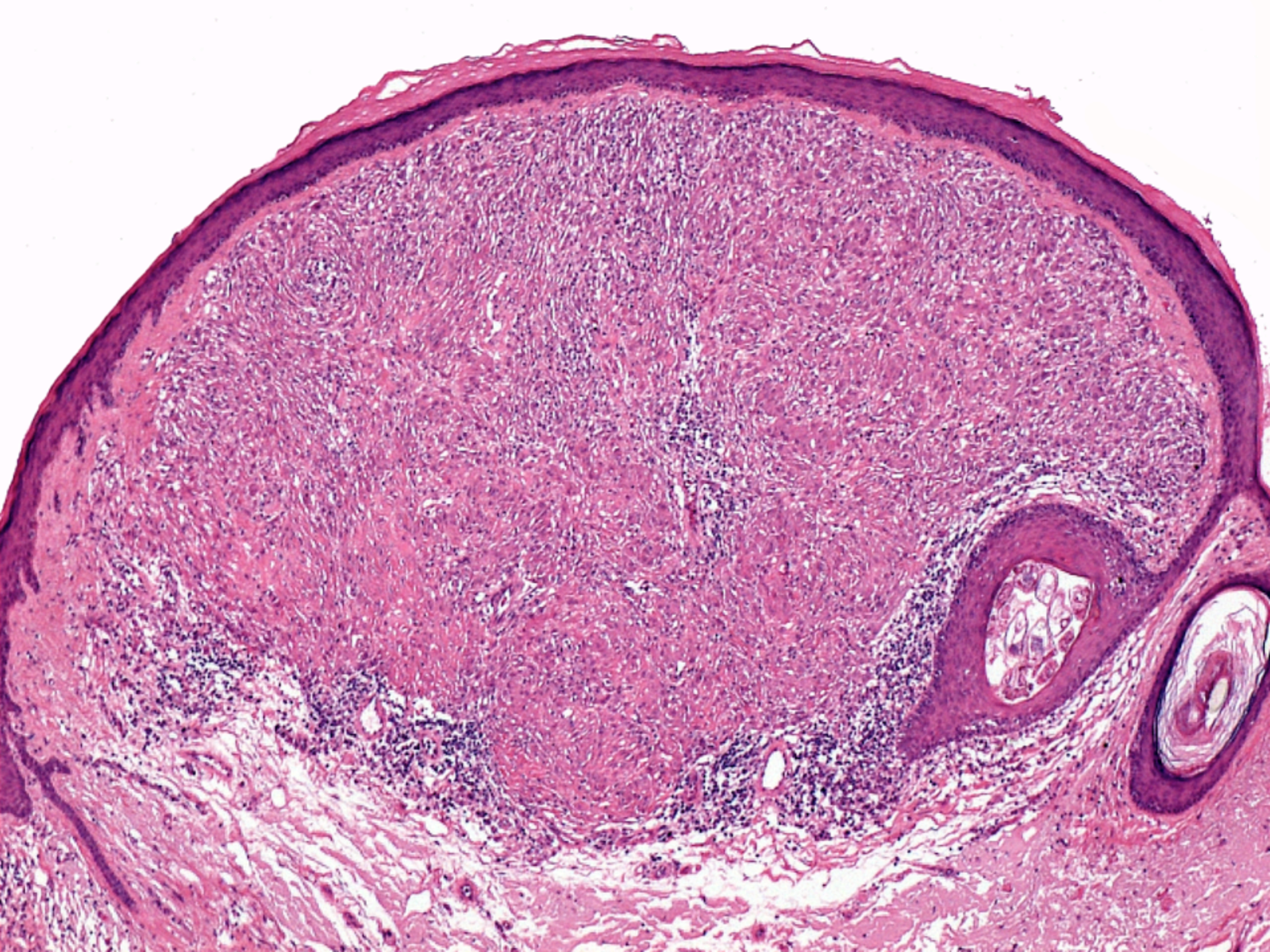


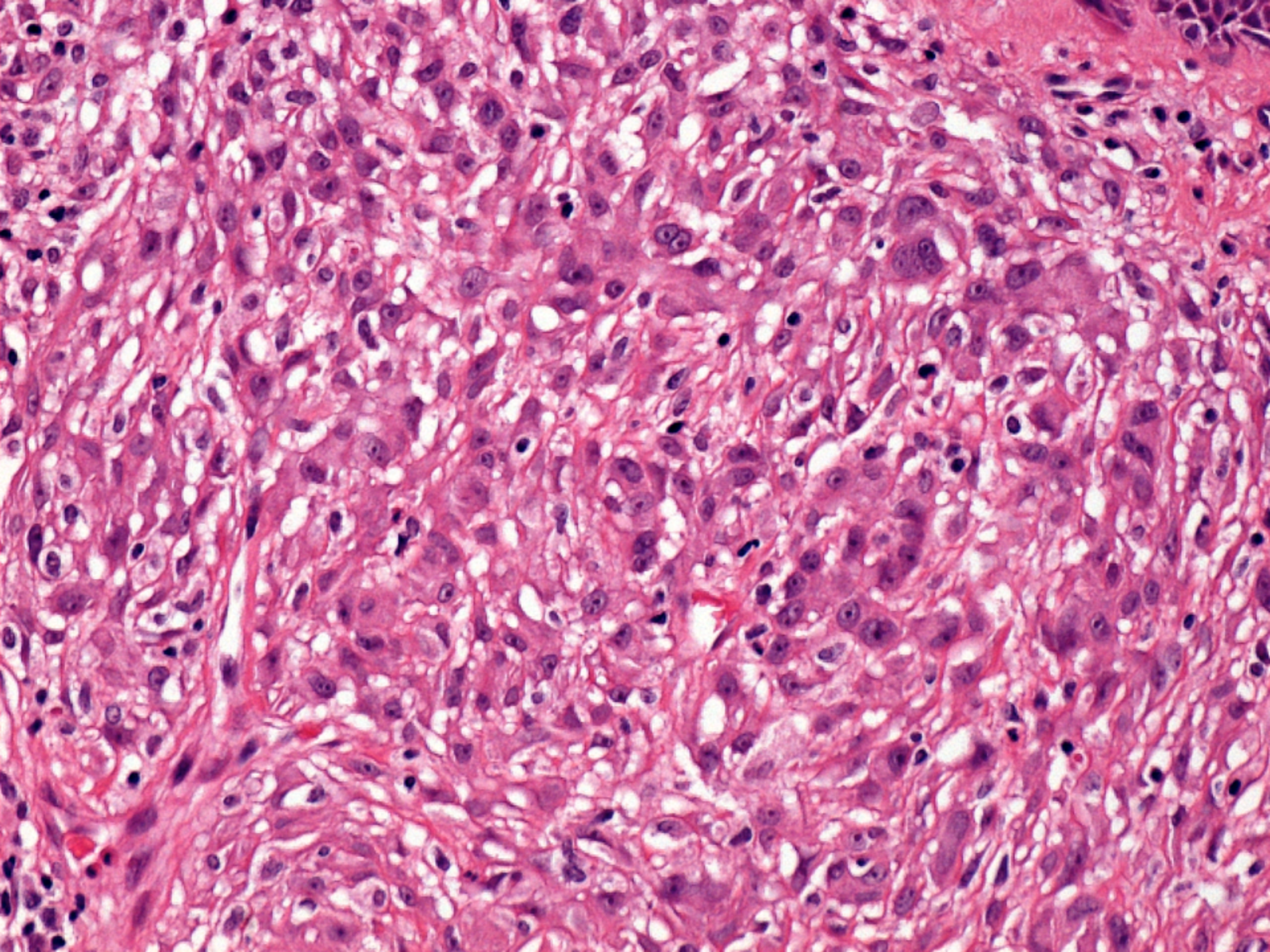


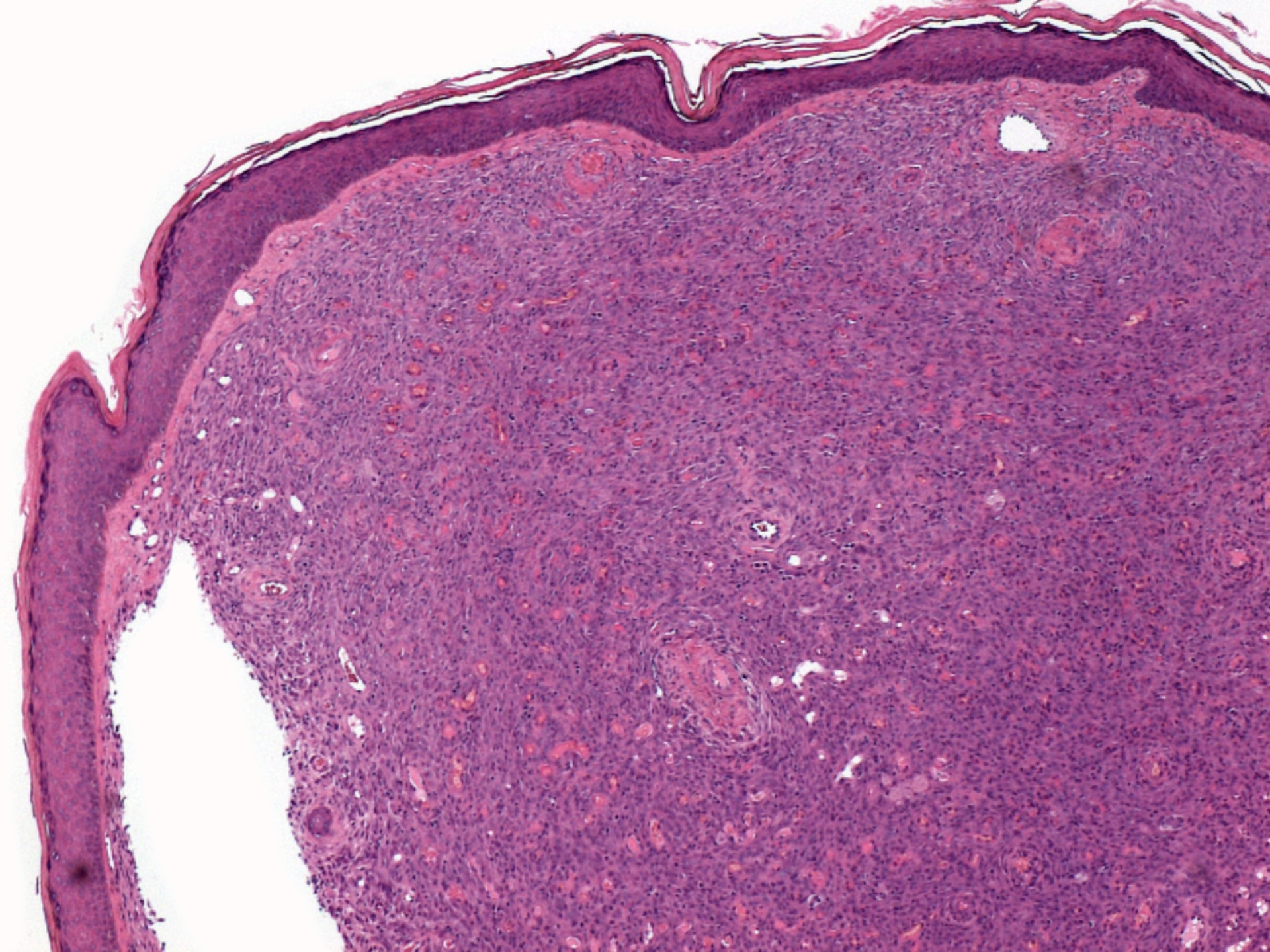


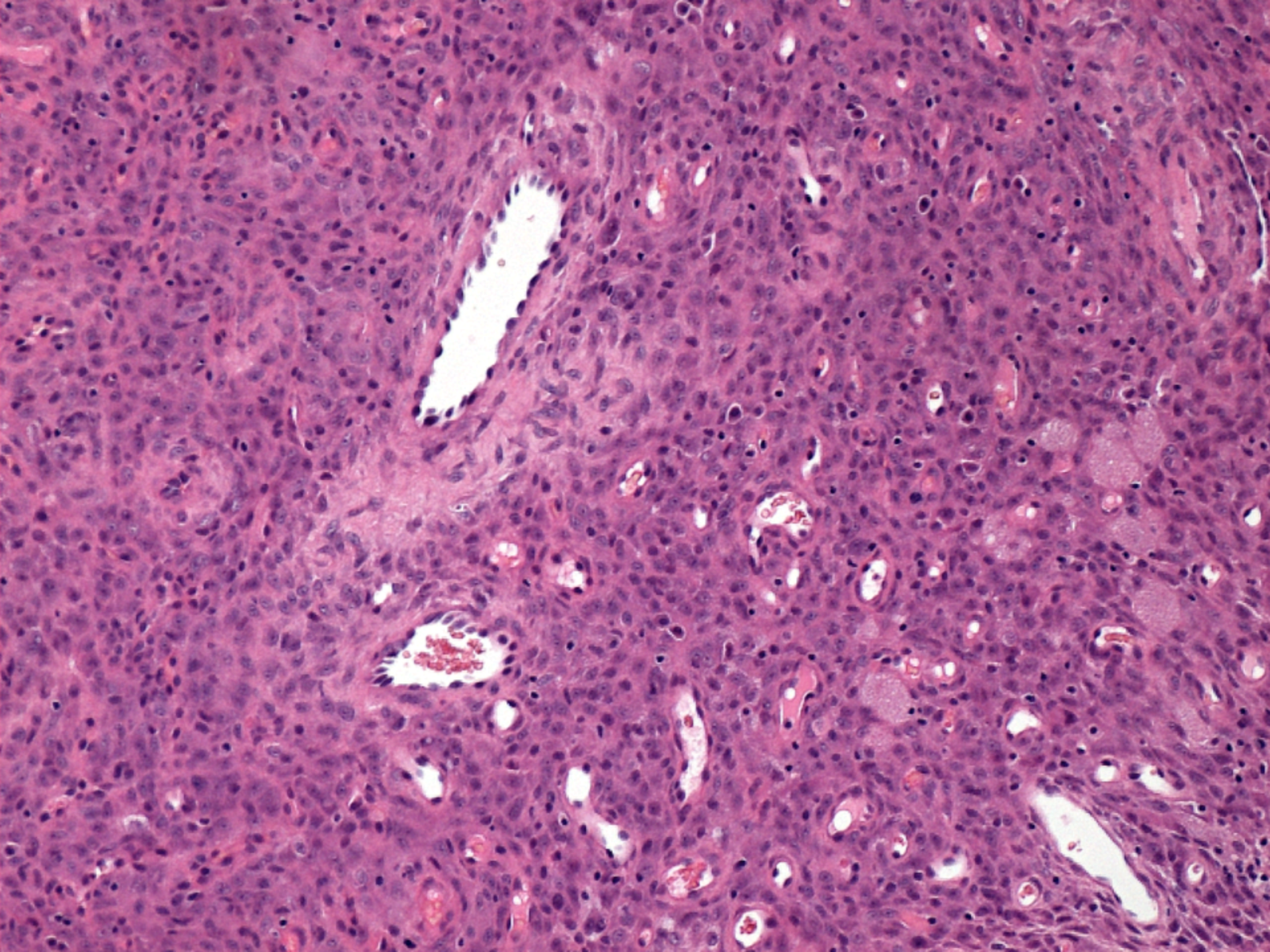


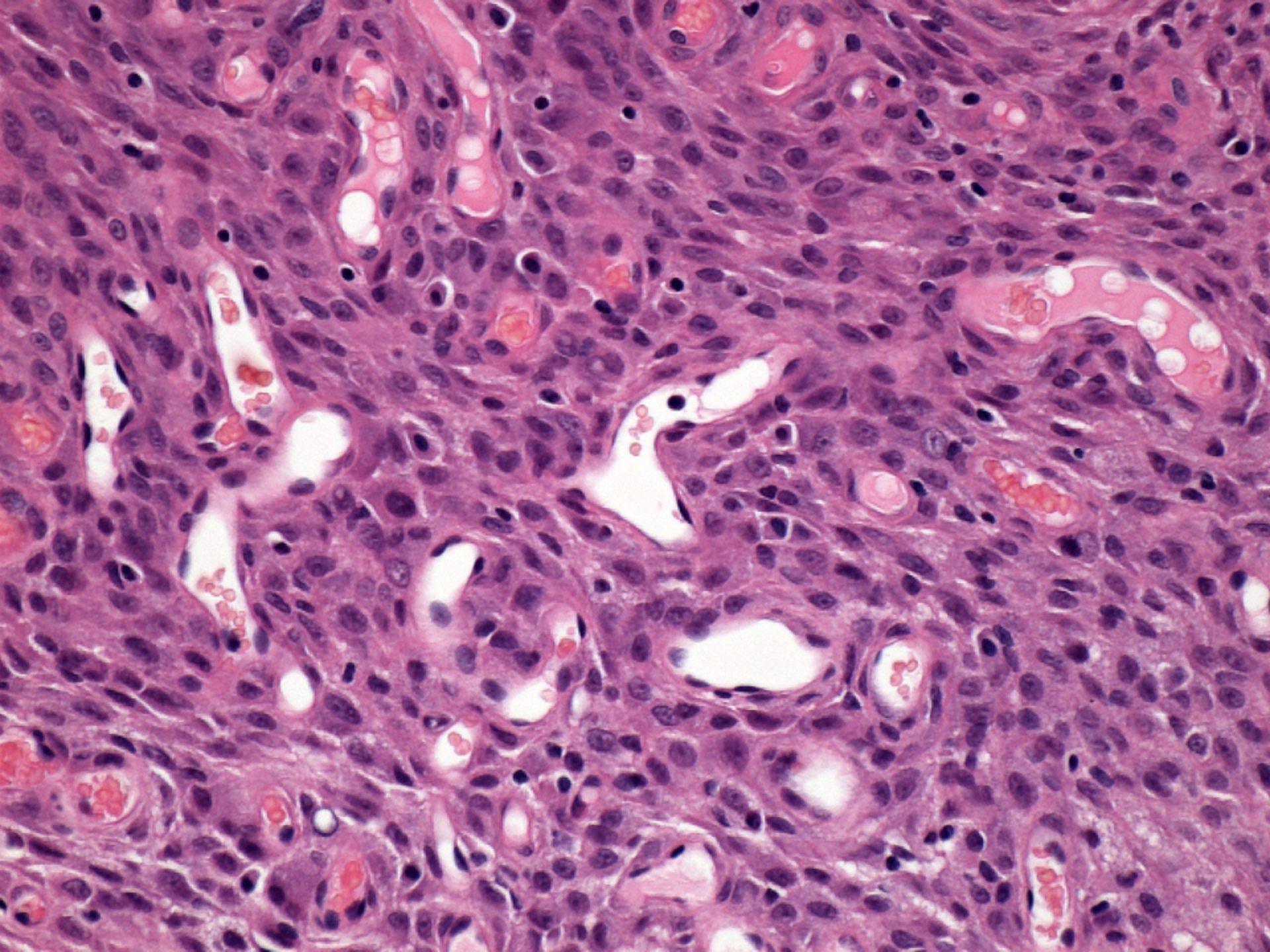






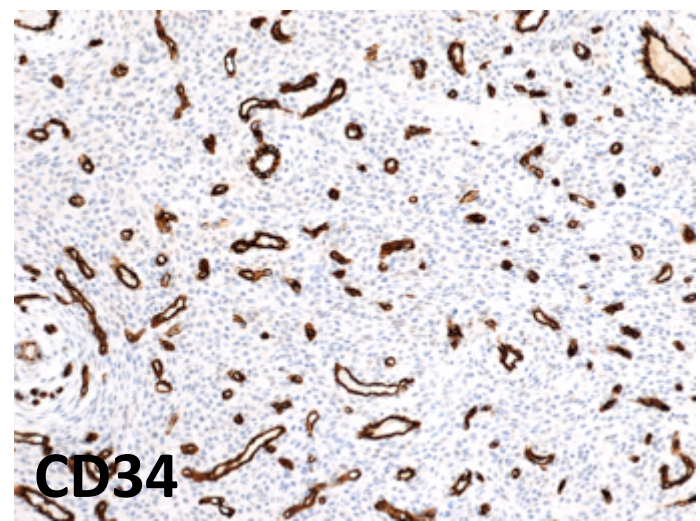
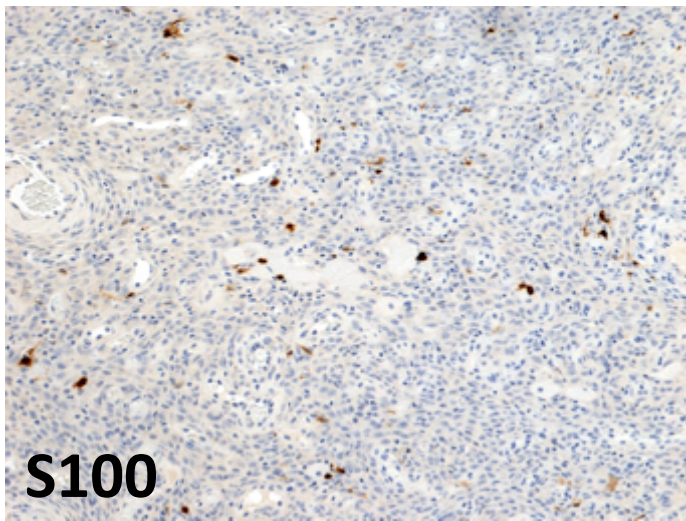
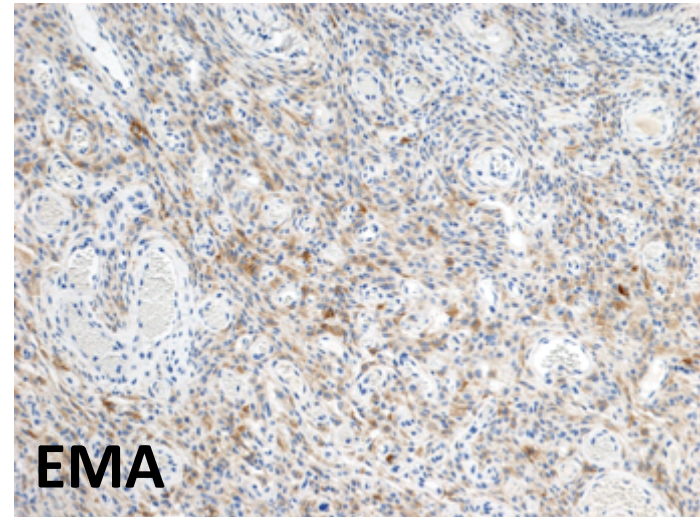
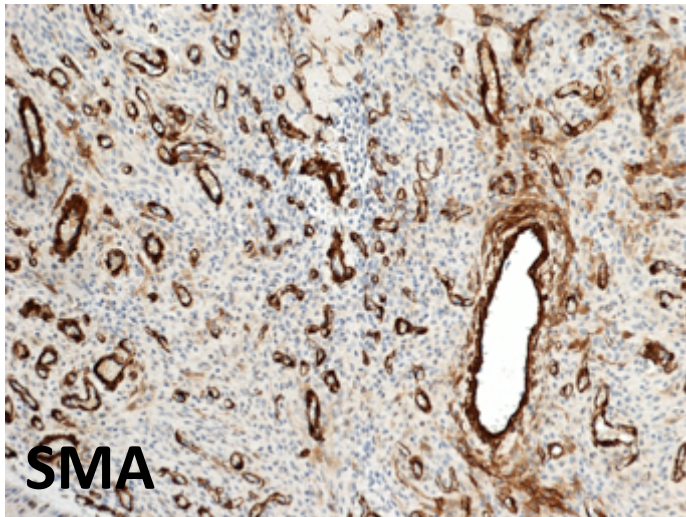






Epithelioid Fibrous Histiocytoma

-Immunohistochemistry-



Epithelioid Fibrous Histiocytoma

-Summary-

- Many morphologic similarities, especially with Spitz naevus

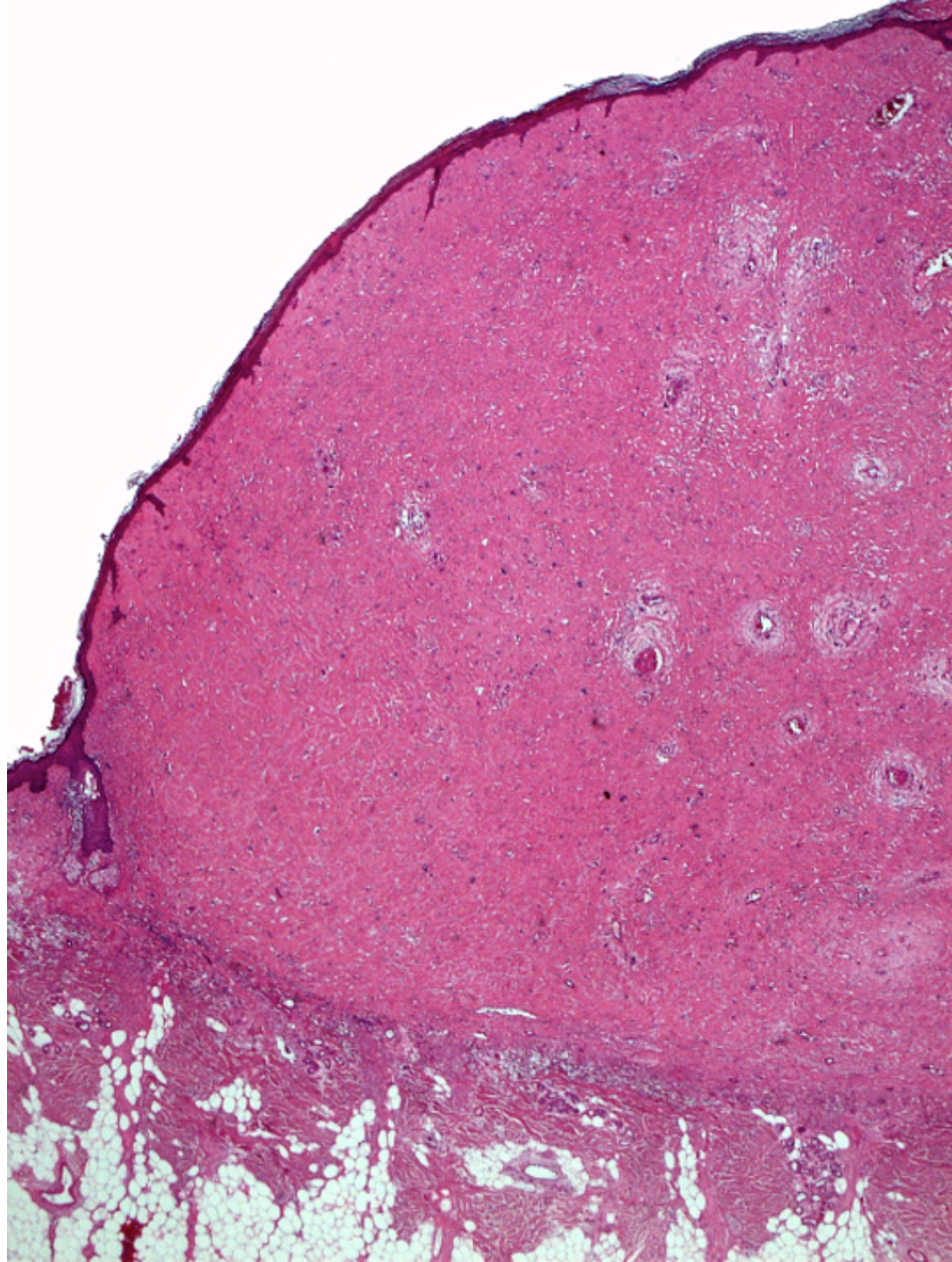
BUT:

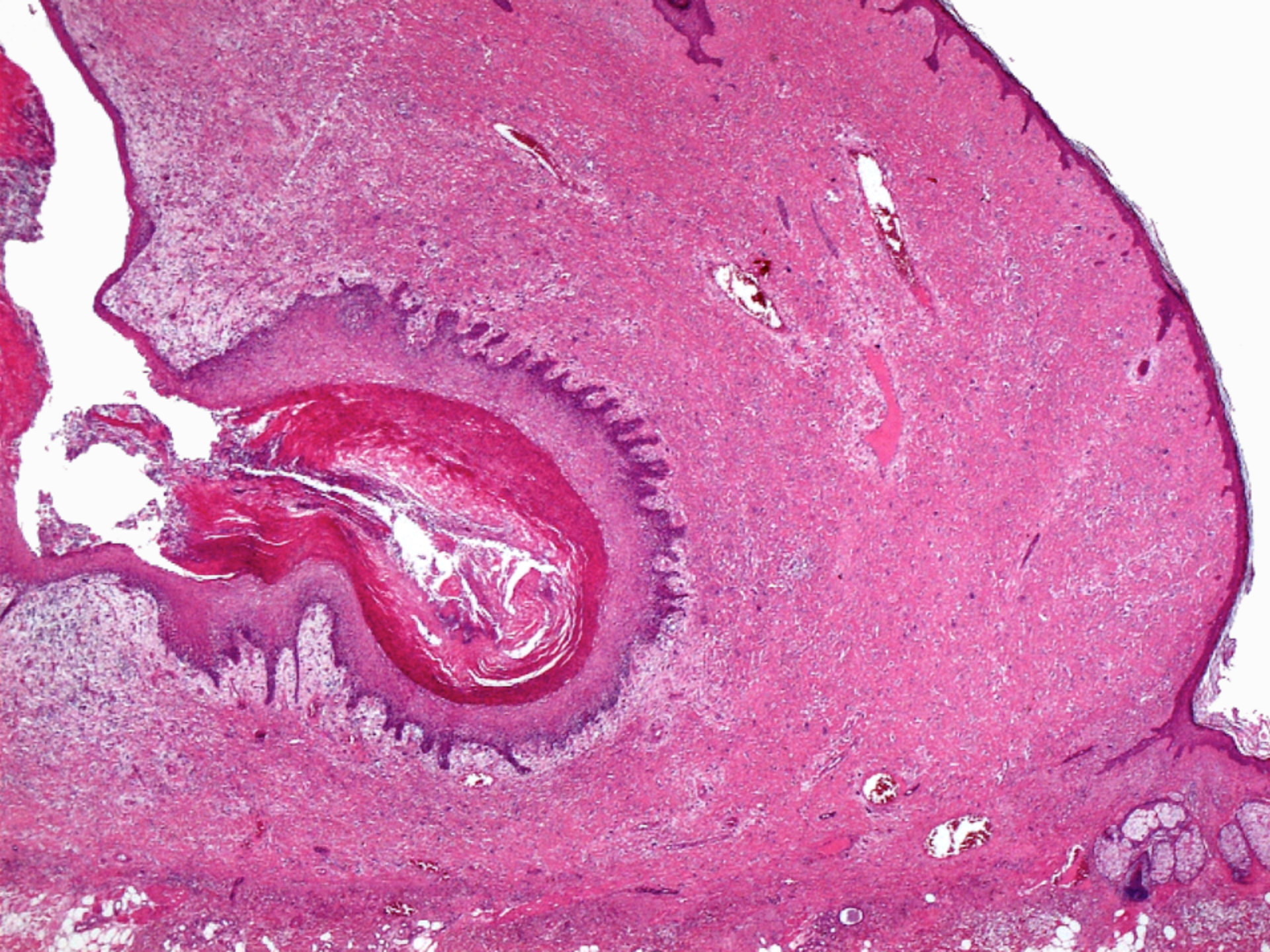
- Morphologic clues:
 - Polypoid
 - Well-circumscribed, +/- collarette
 - Binucleated cells
- Immunohistochemistry:
 - Negative for S100, second-line melanoma markers

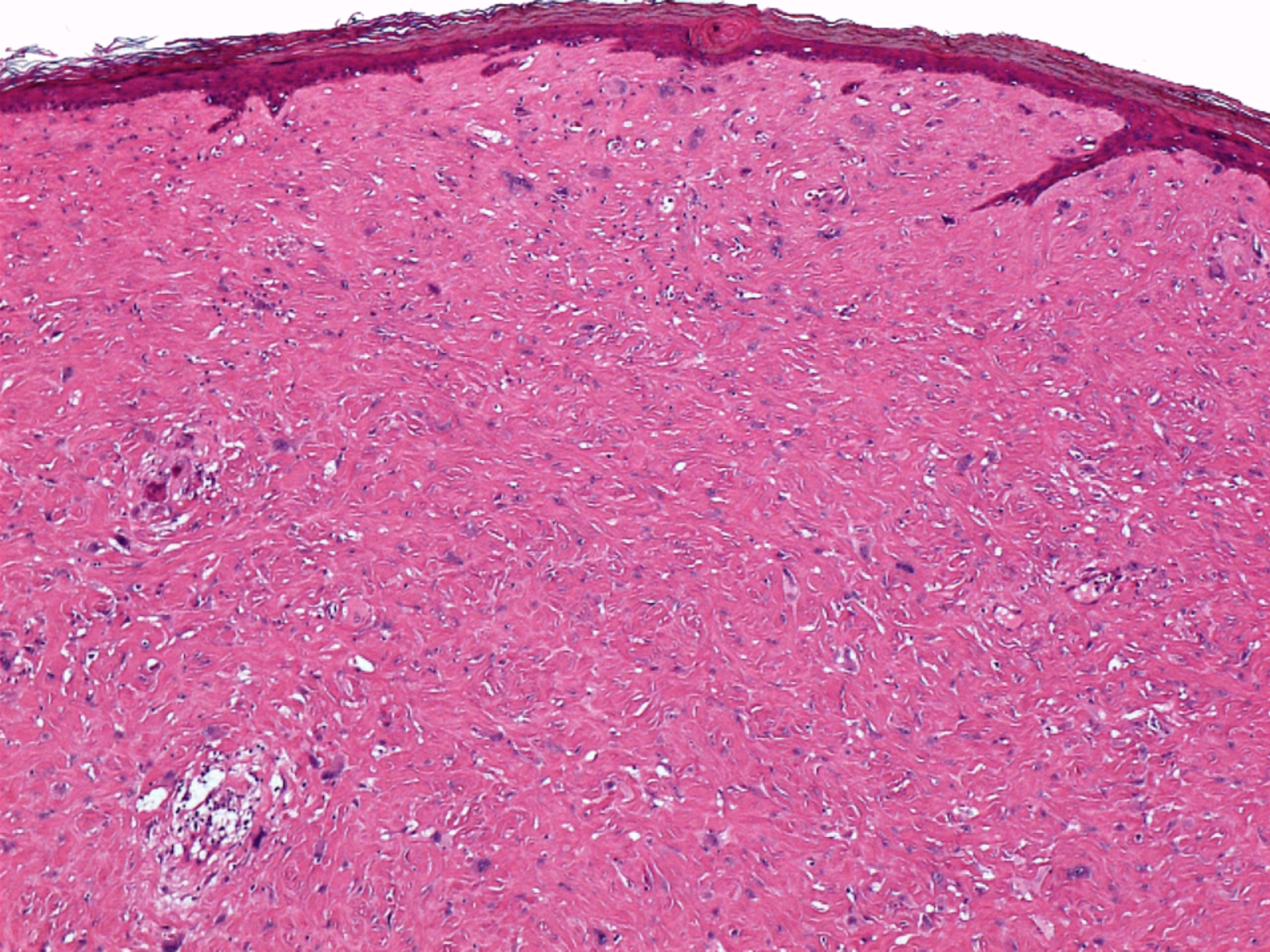
Case 3

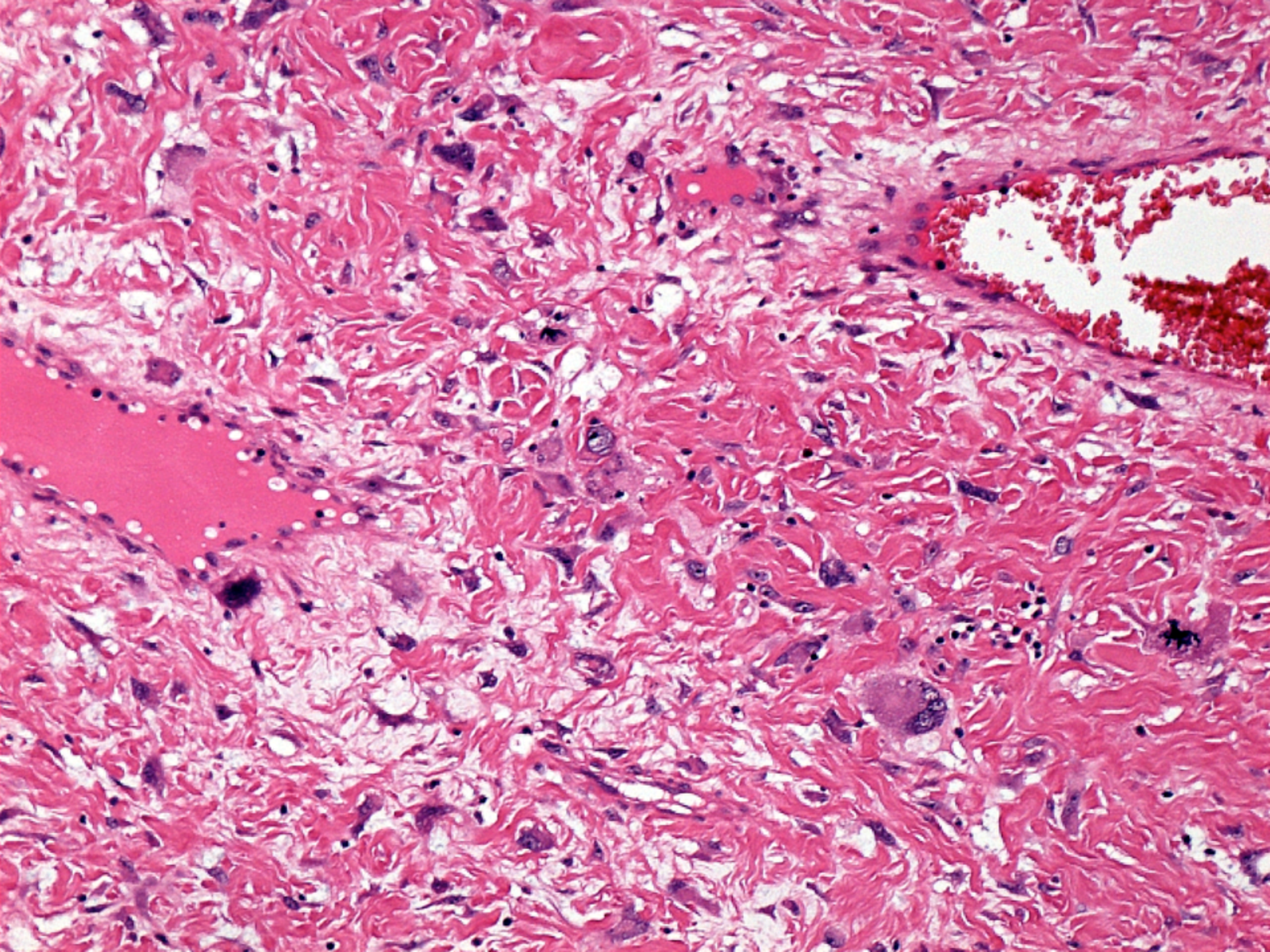
Case History

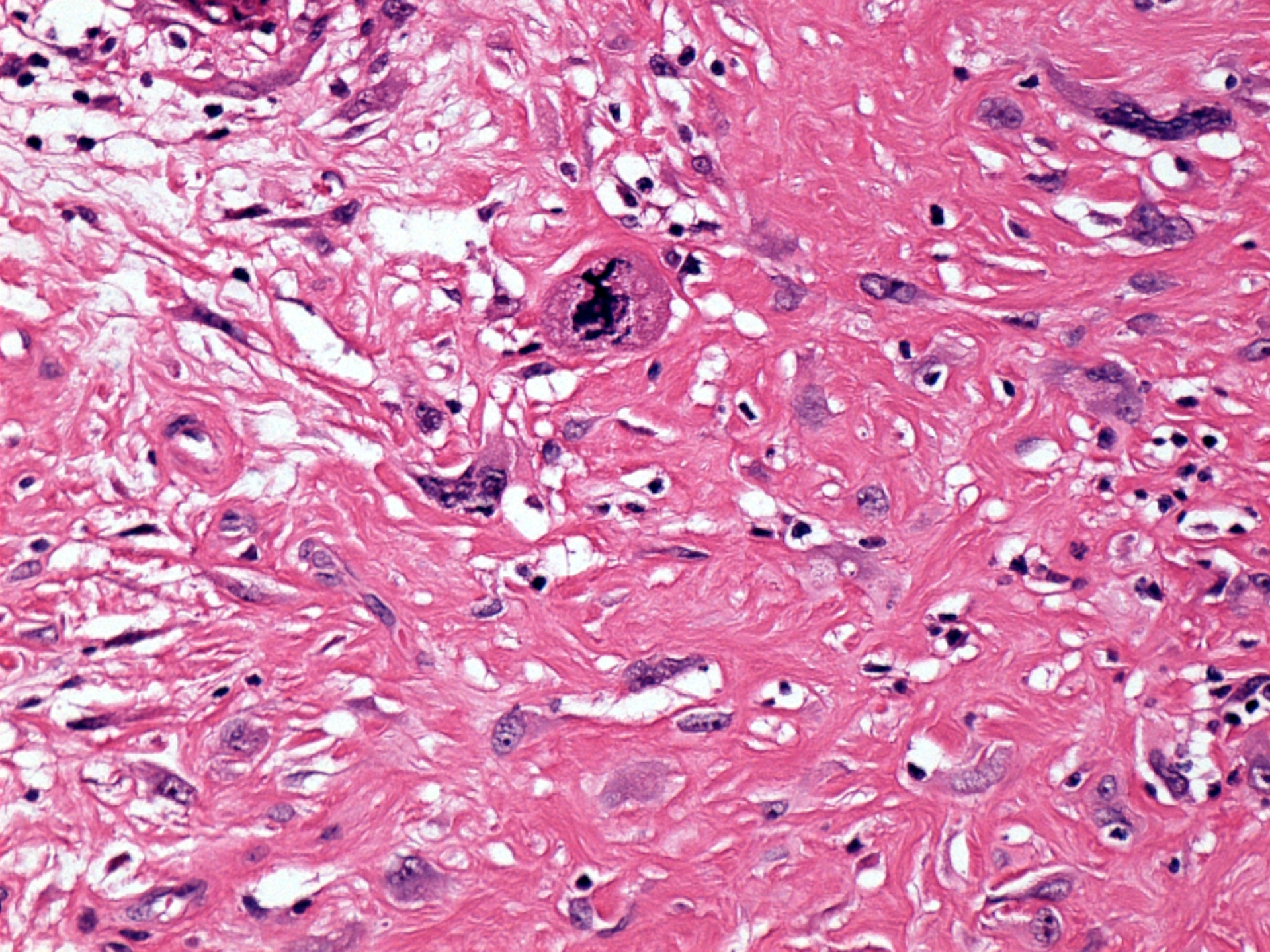
- 85 year old male
- Rapidly growing tumour
- On the scalp

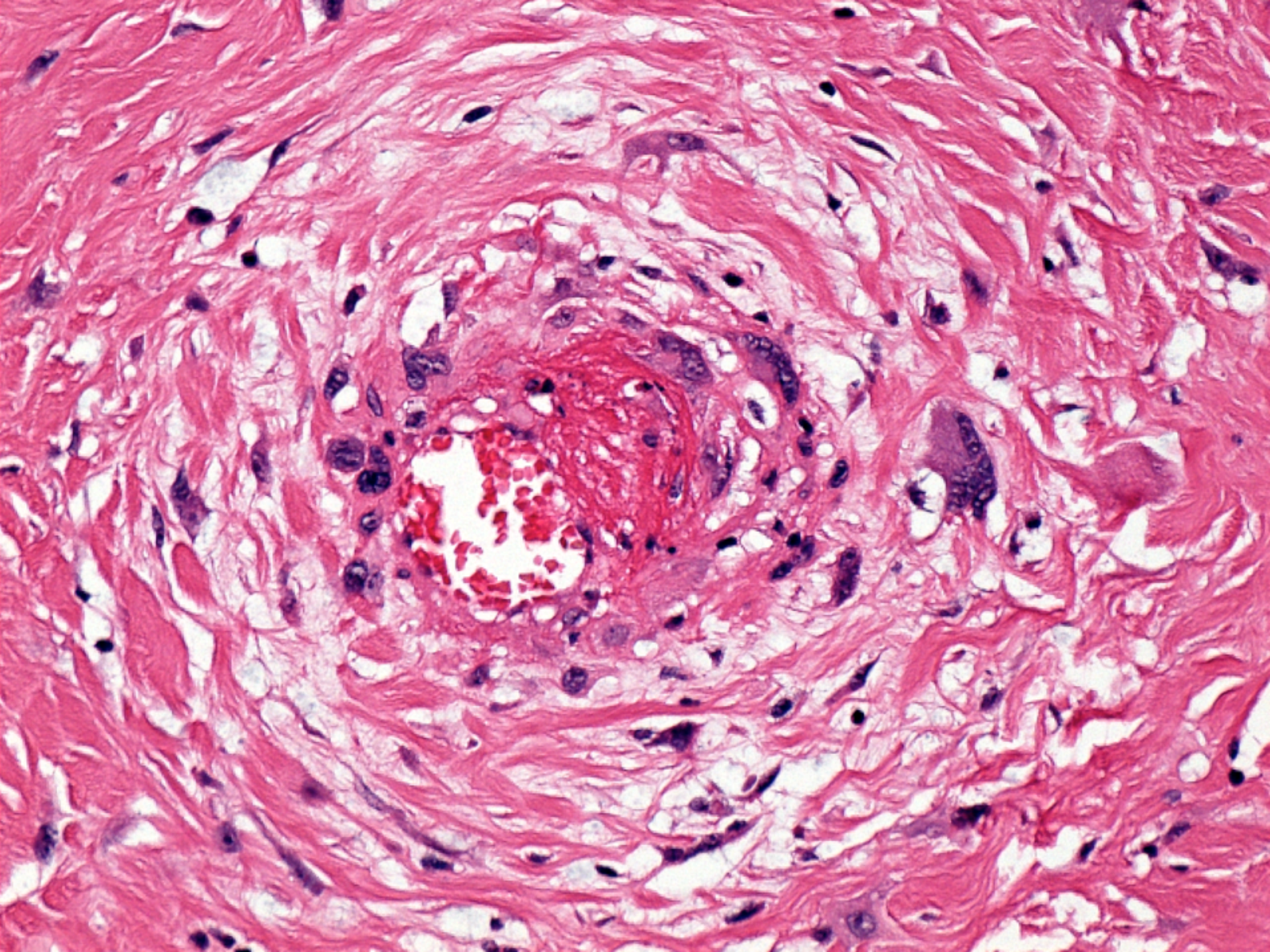


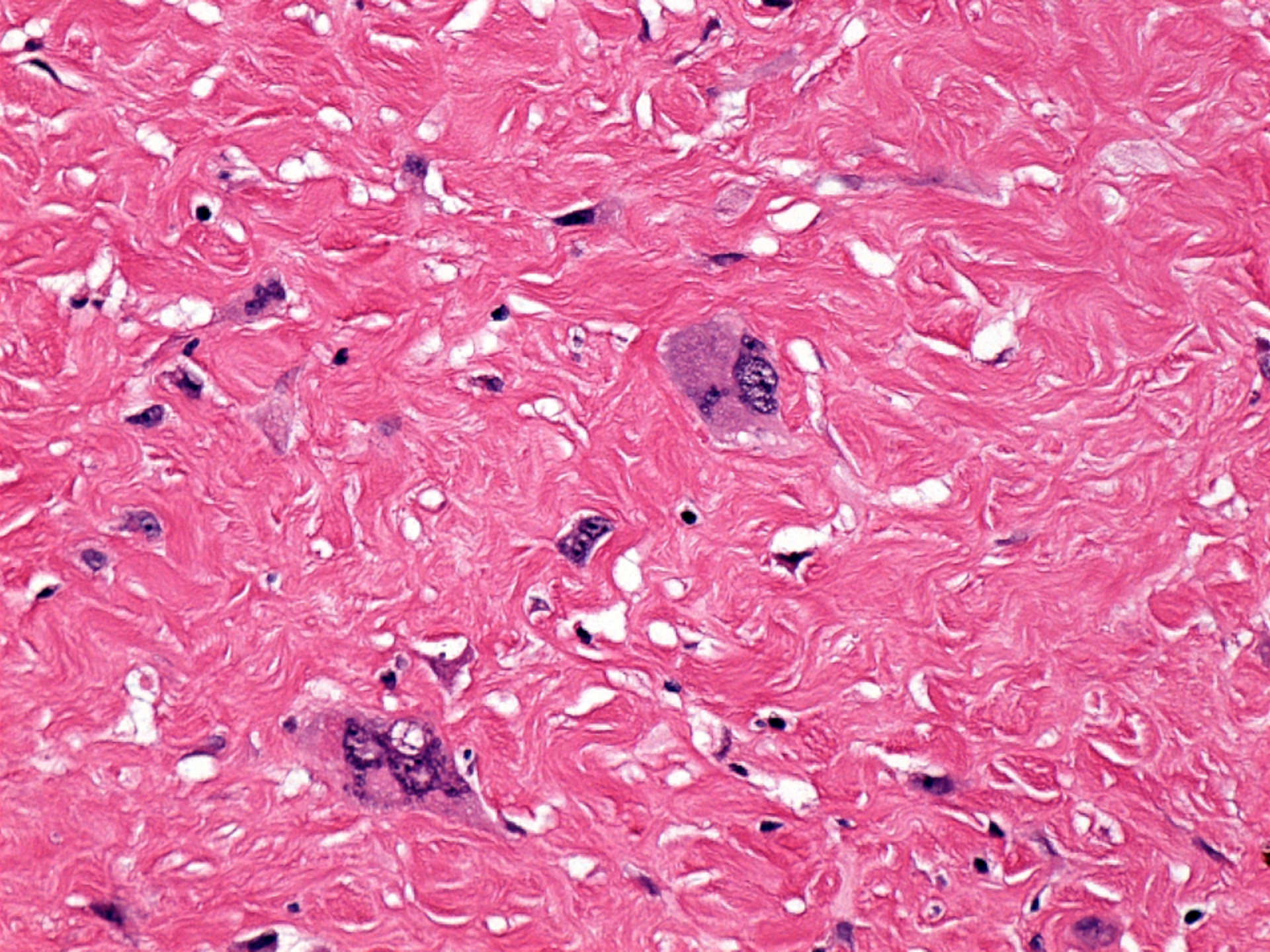


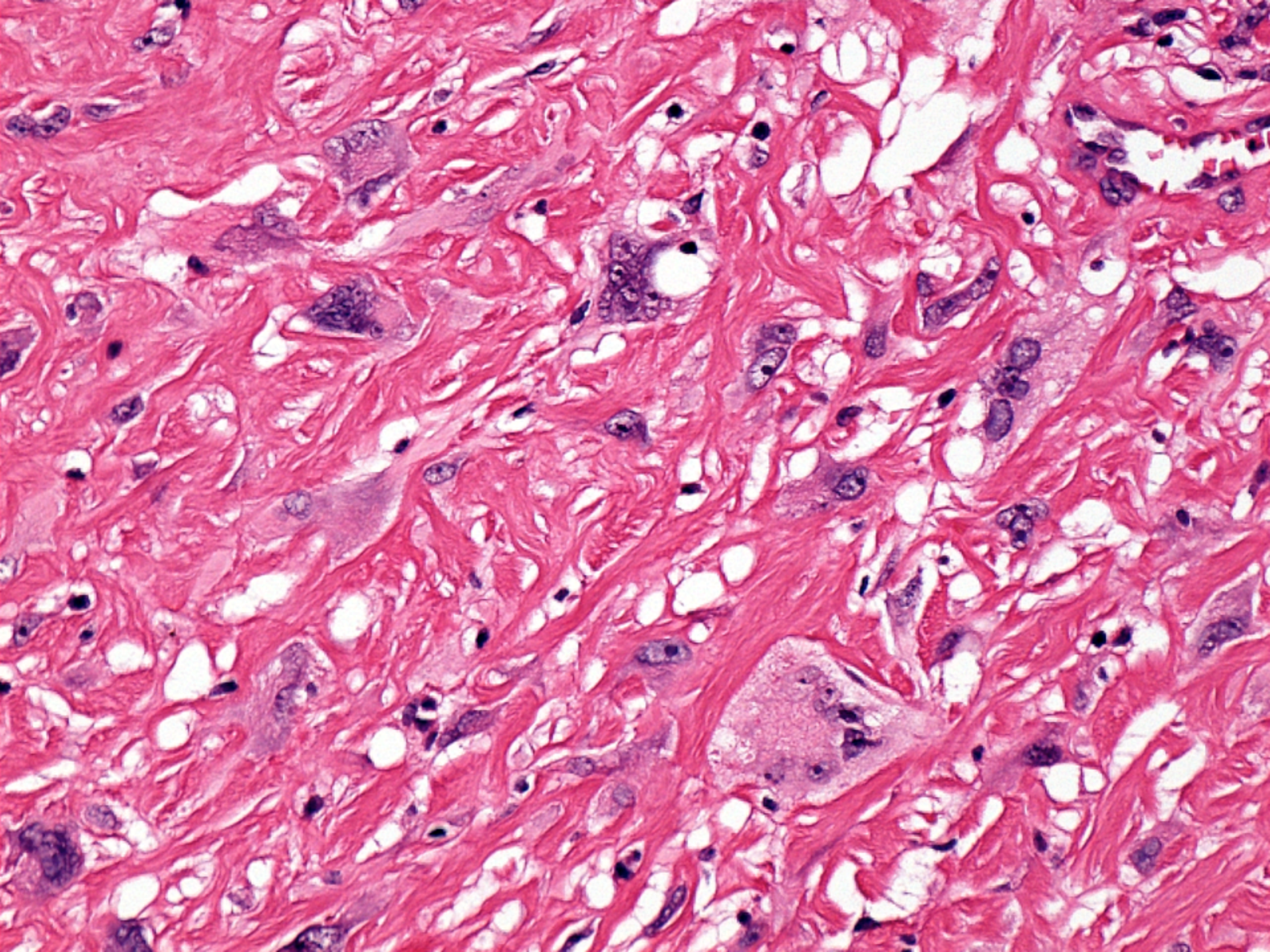


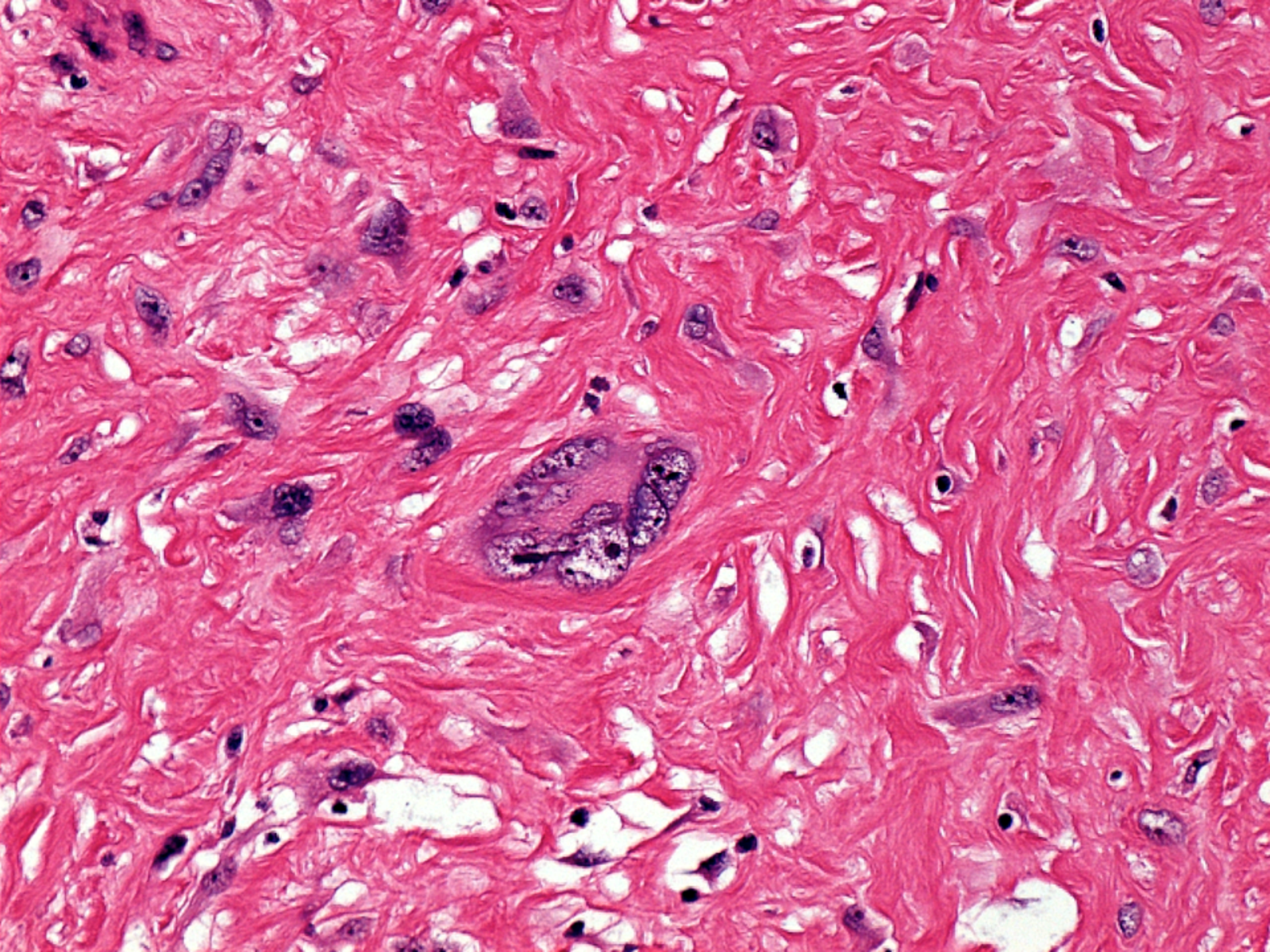


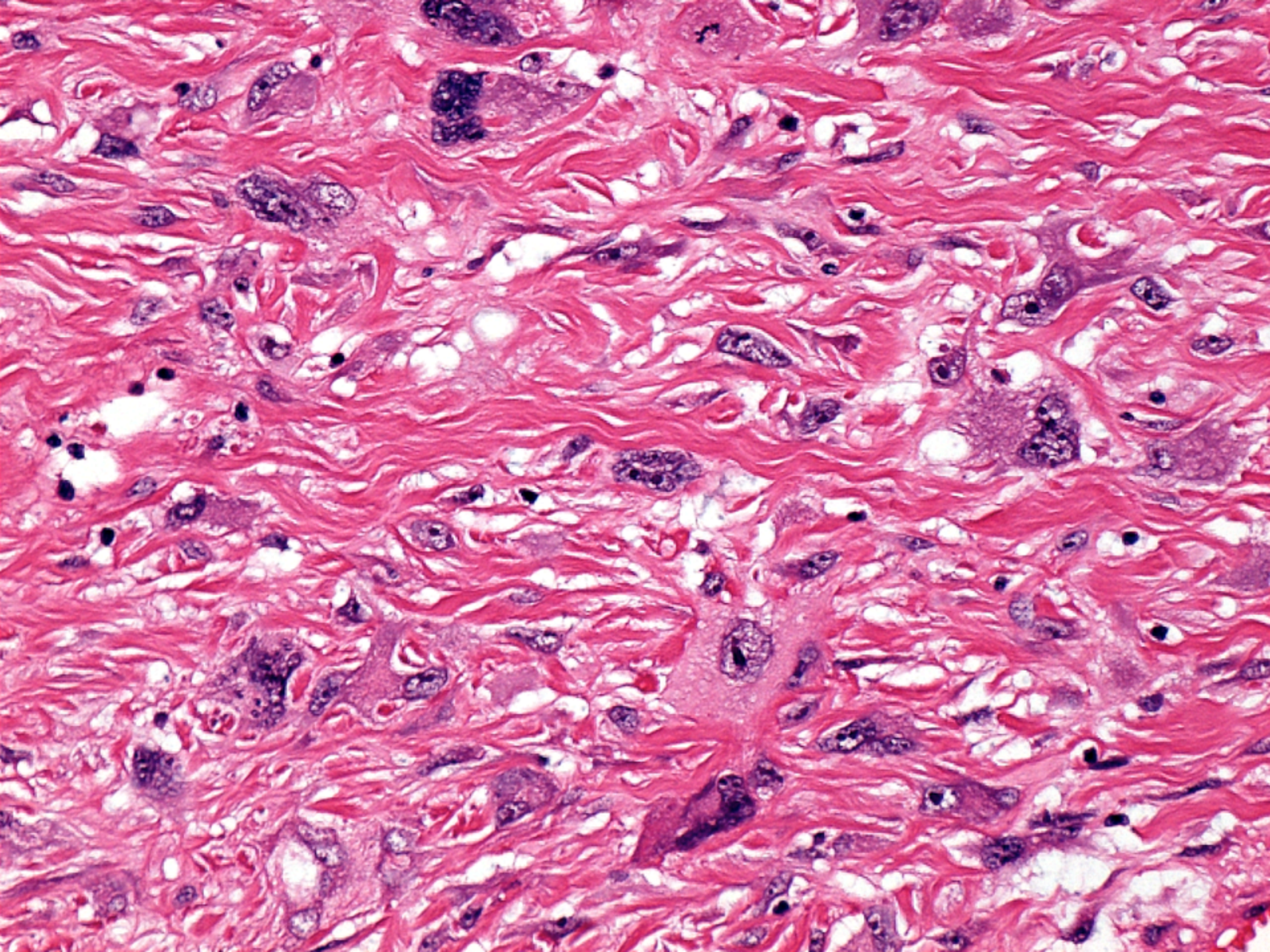












Diagnosis Case 3:

Case 3

-Immunohistochemistry-

Positive

- CD68
- CD10
- SMA

Negative

- AE1/3, MNF116
- Cam5.2, CK5/6
- EMA
- P63
- S100
- Melan A
- Desmin
- CD34, CD31

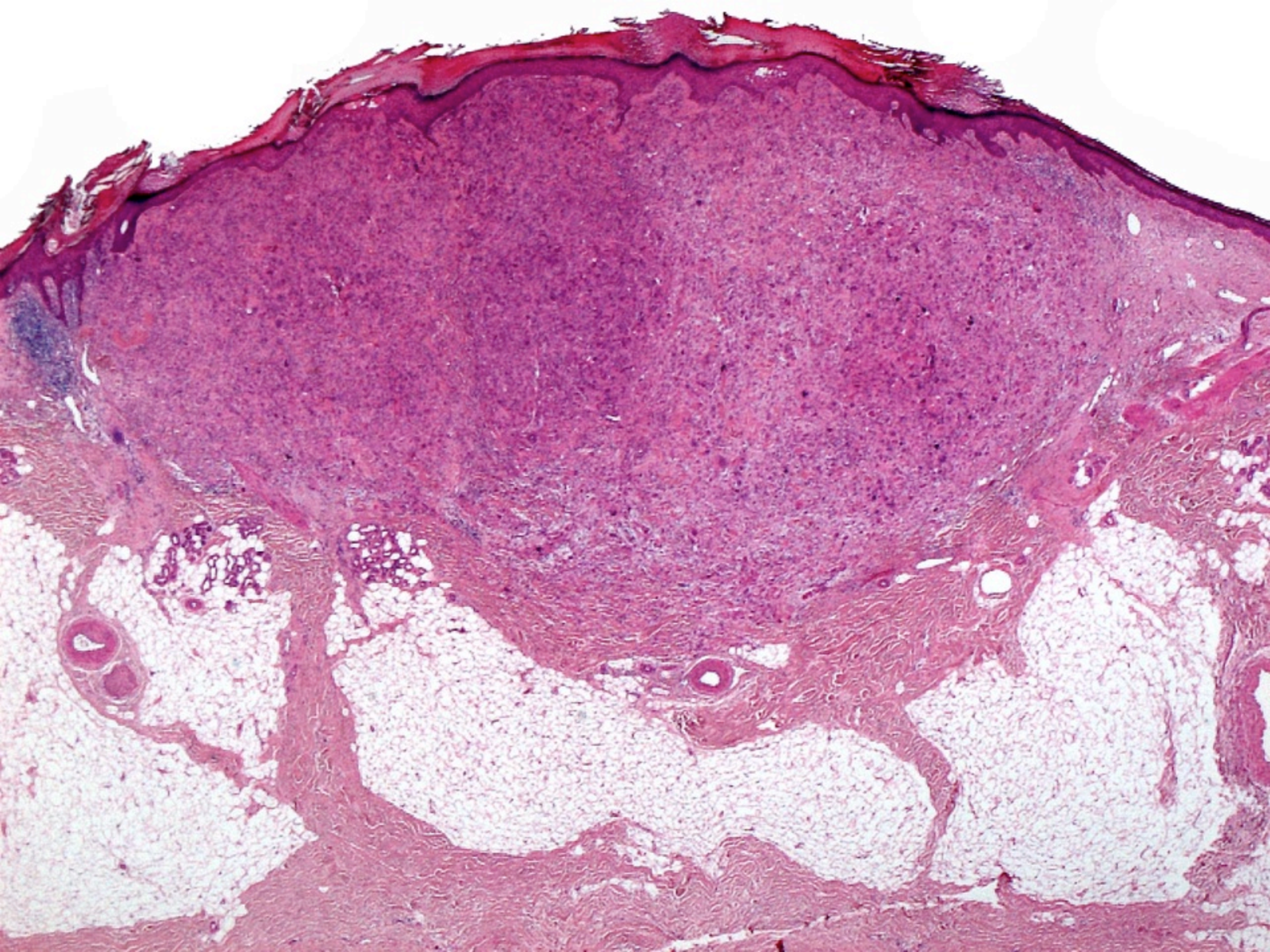
Diagnosis Case 3:

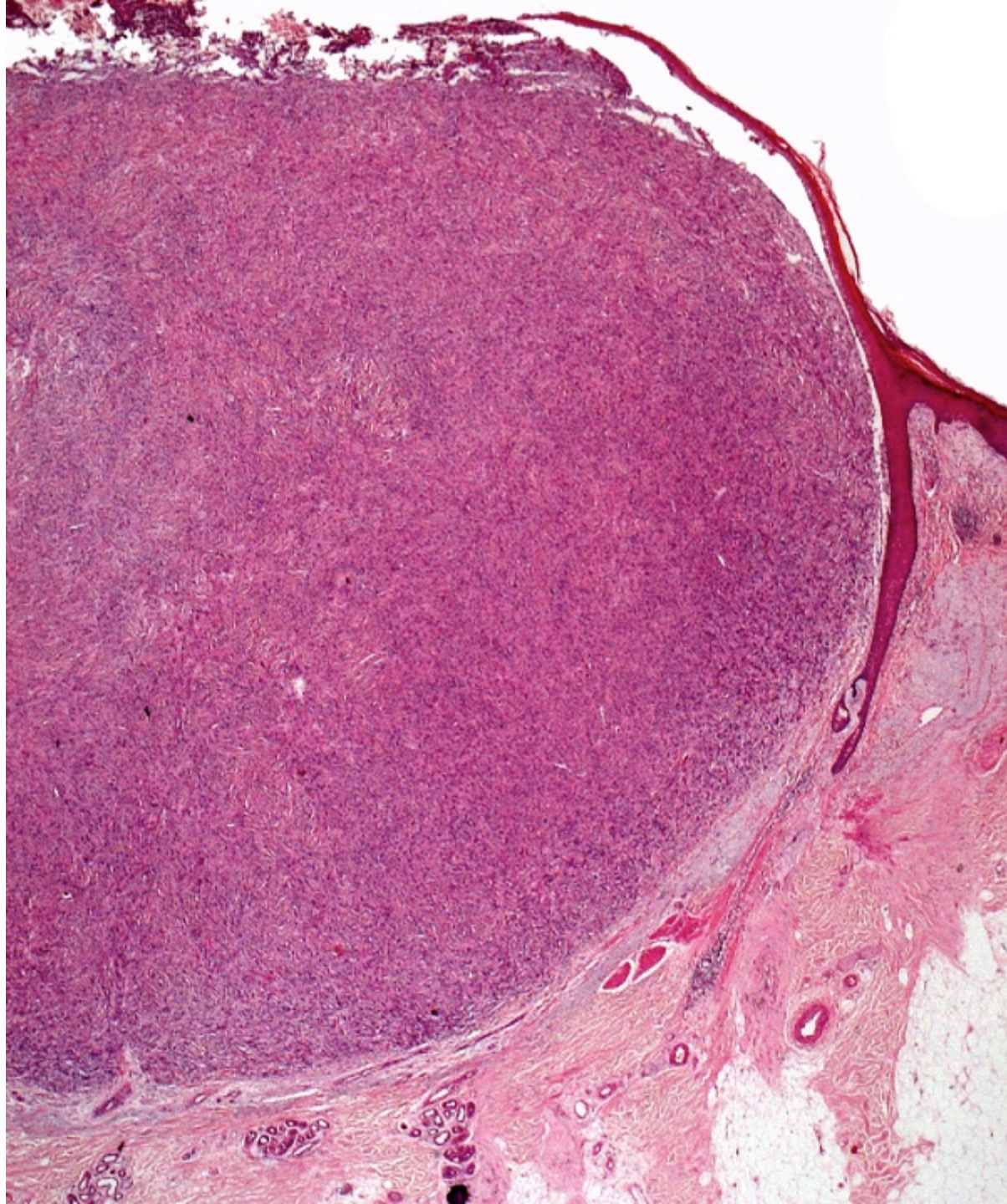
Atypical fibroxanthoma

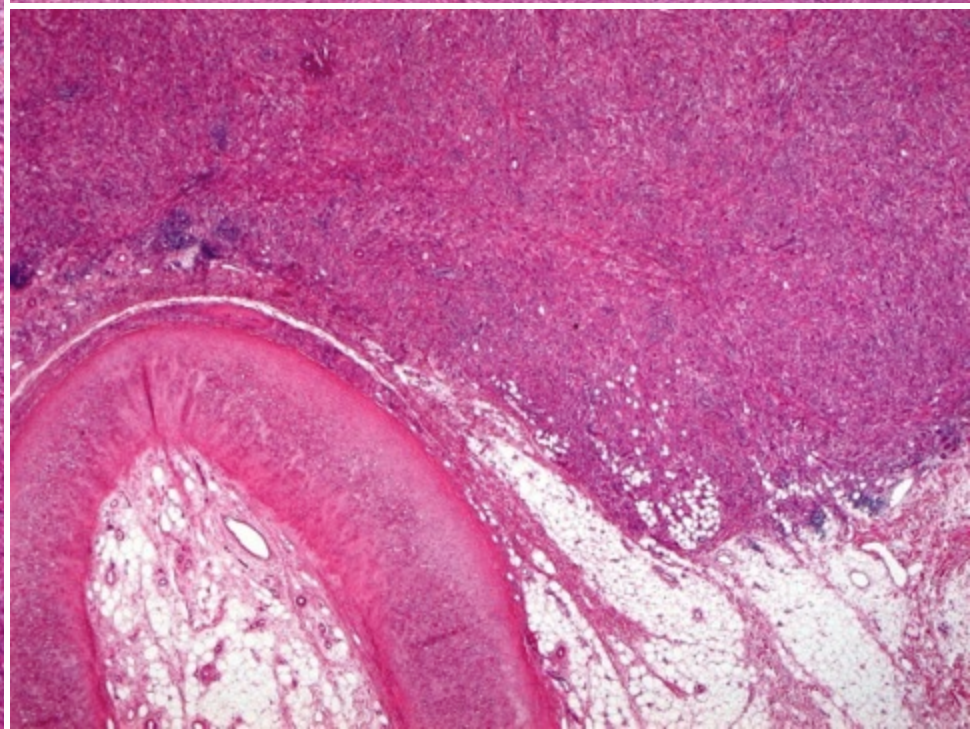
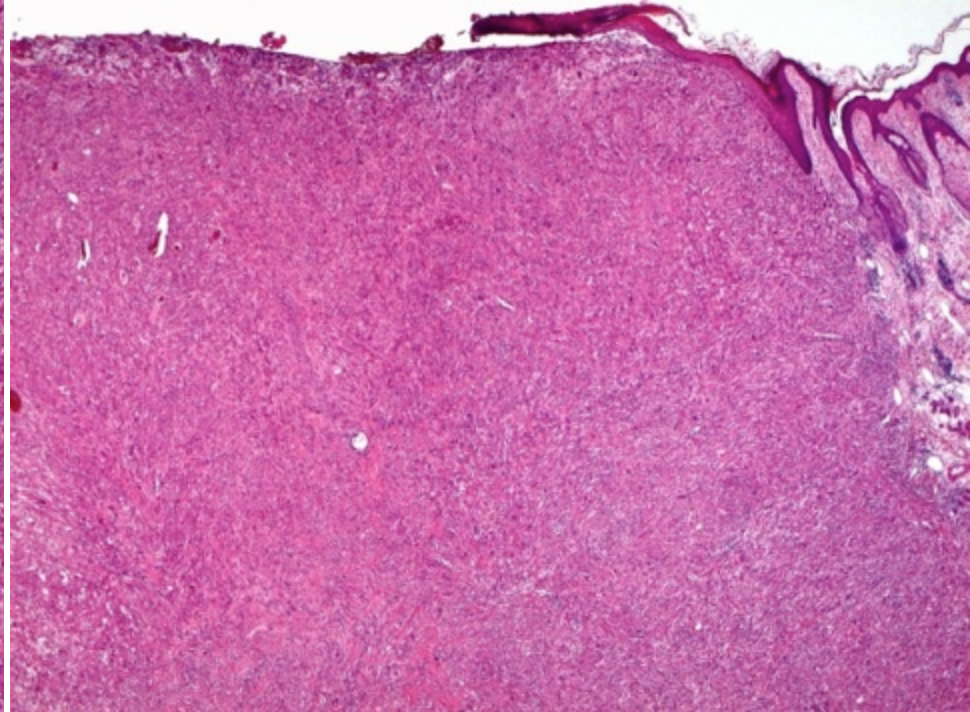
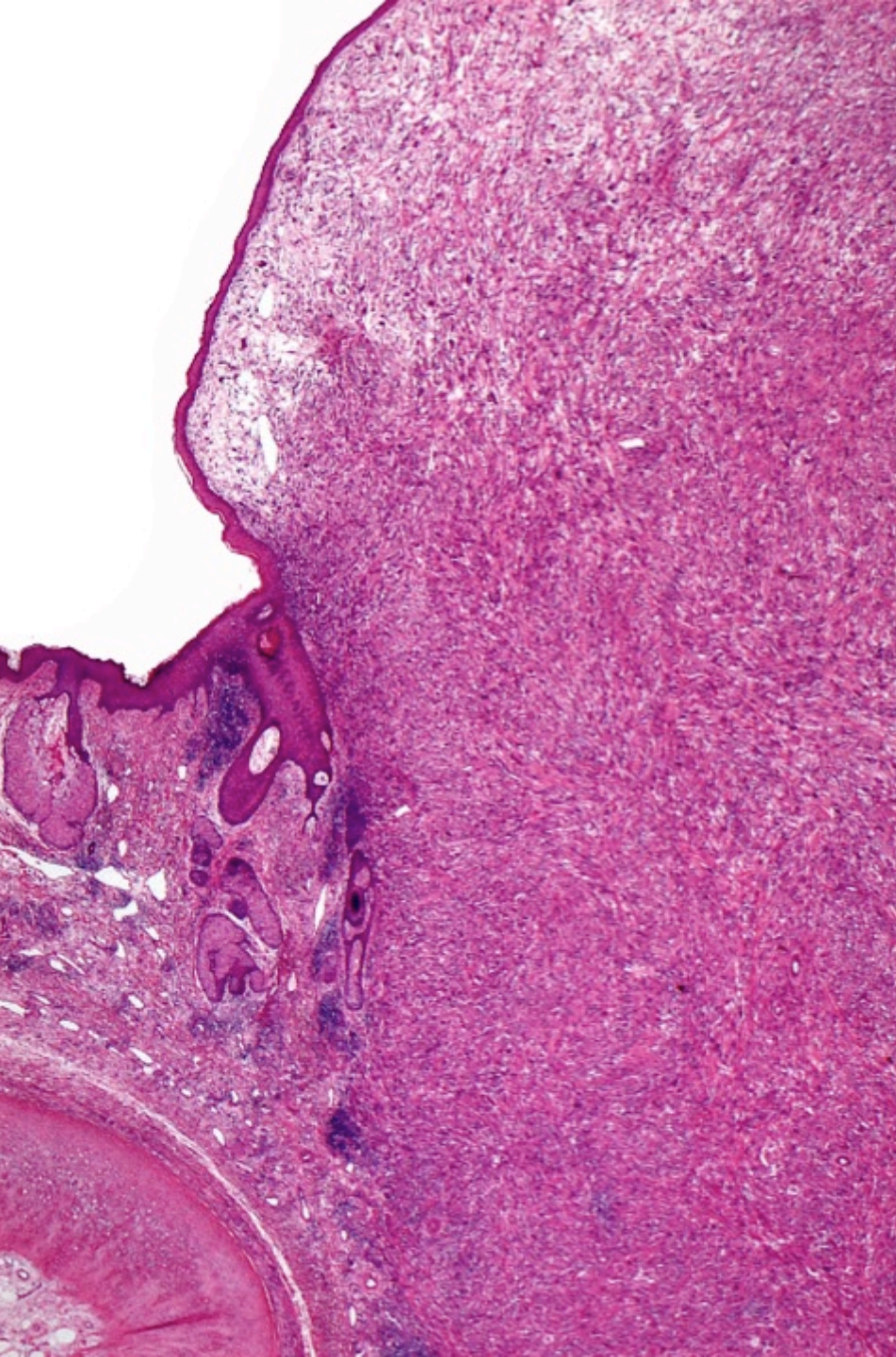
Atypical Fibroxanthoma

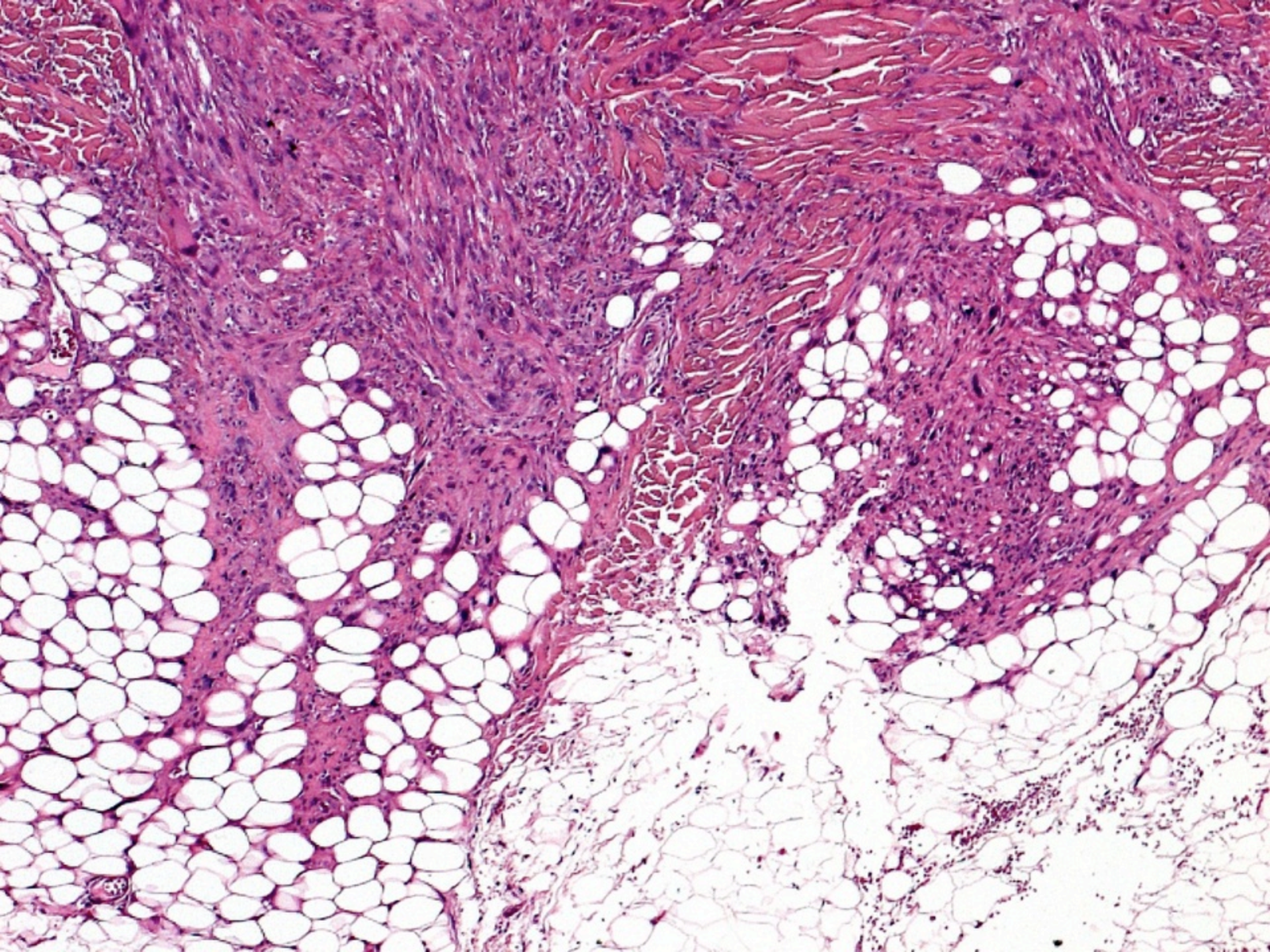
-Clinical-

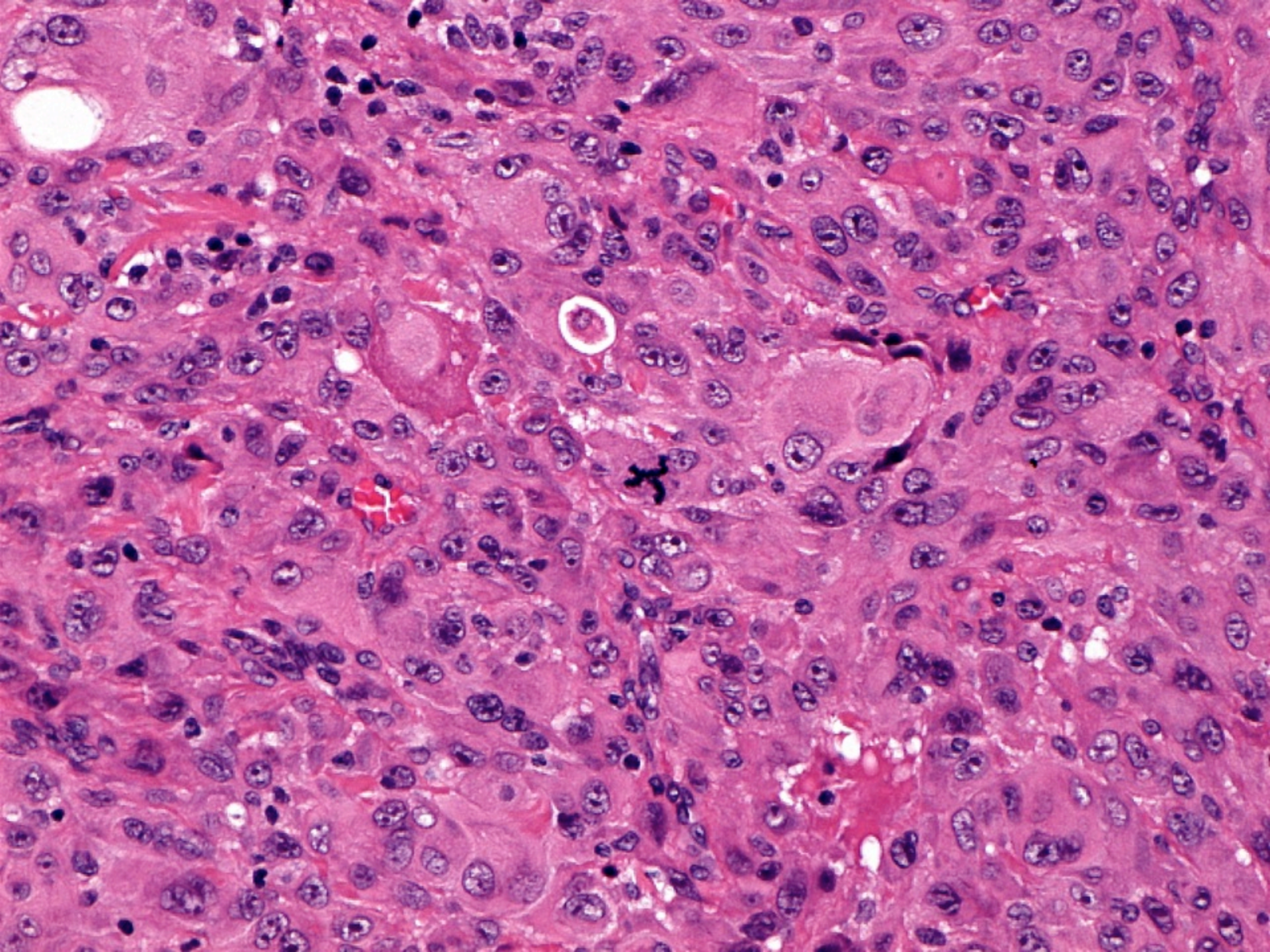
- **Rapidly growing, exophytic/polypoid tumor**
- **~1-2cm, centrally ulcerated**
- **Sun-damaged skin**
 - **Ear, nose, forehead, cheek**
- **Elderly adults, M>F**
- **Xeroderma pigmentosum**

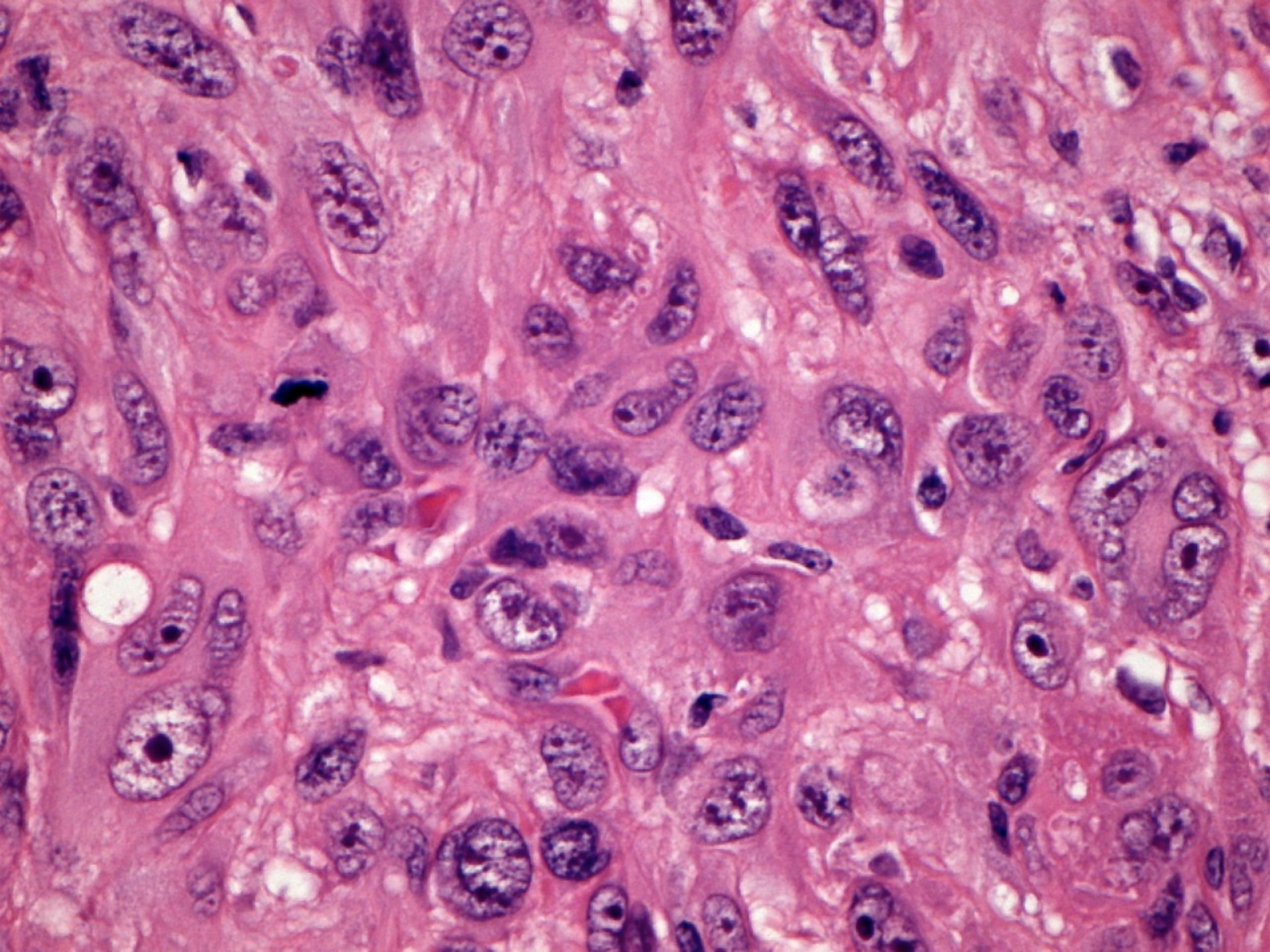


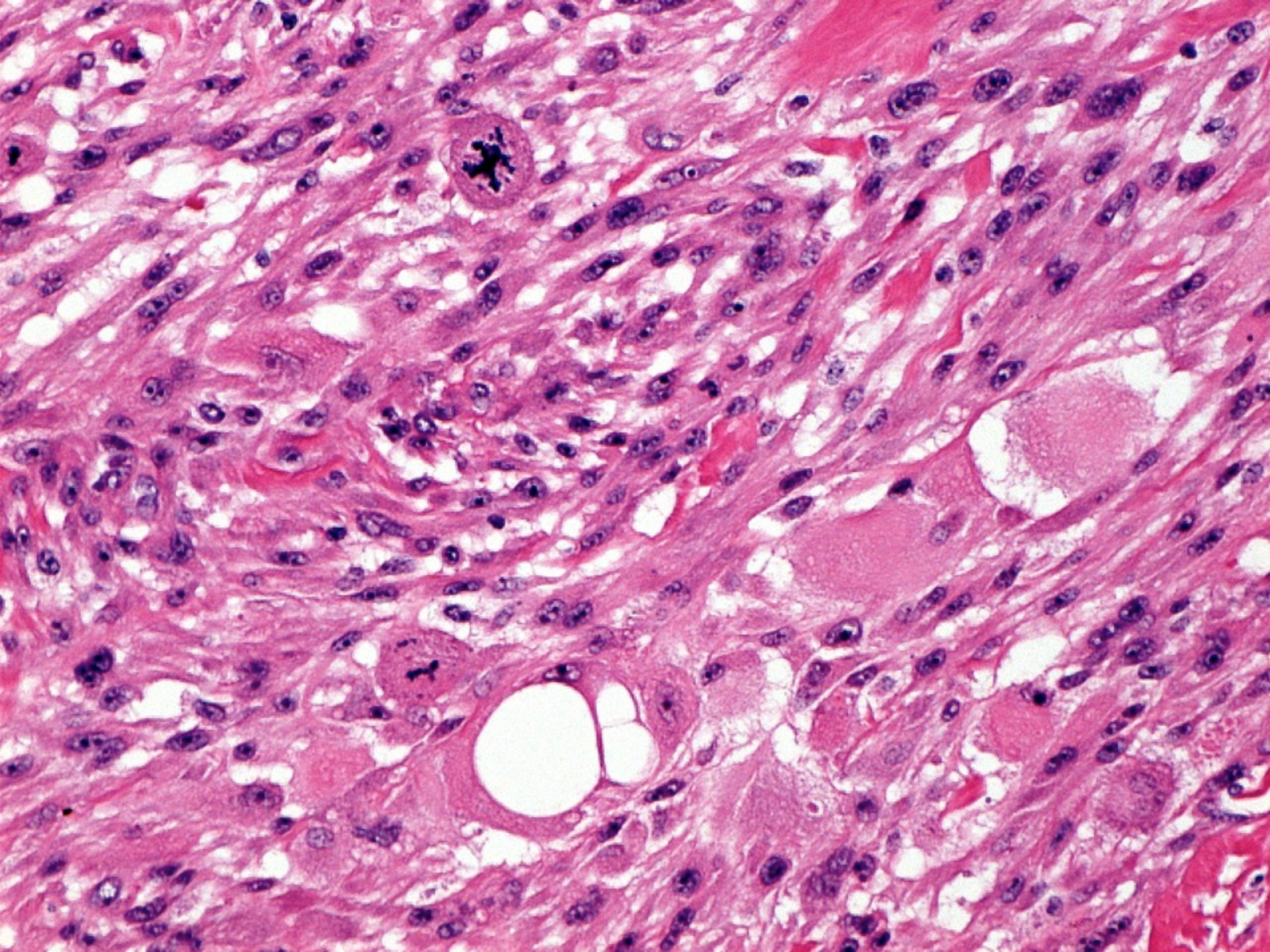


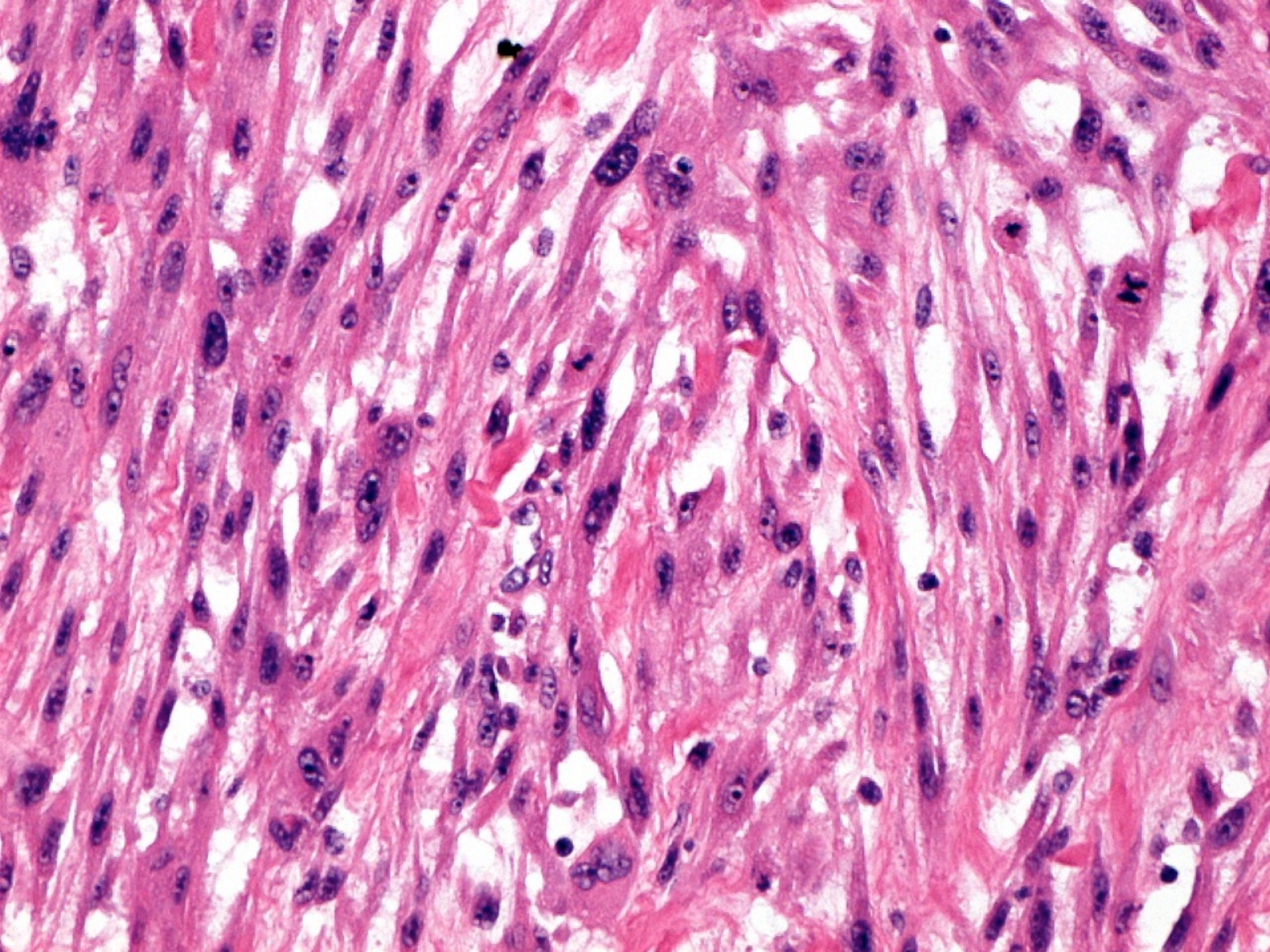


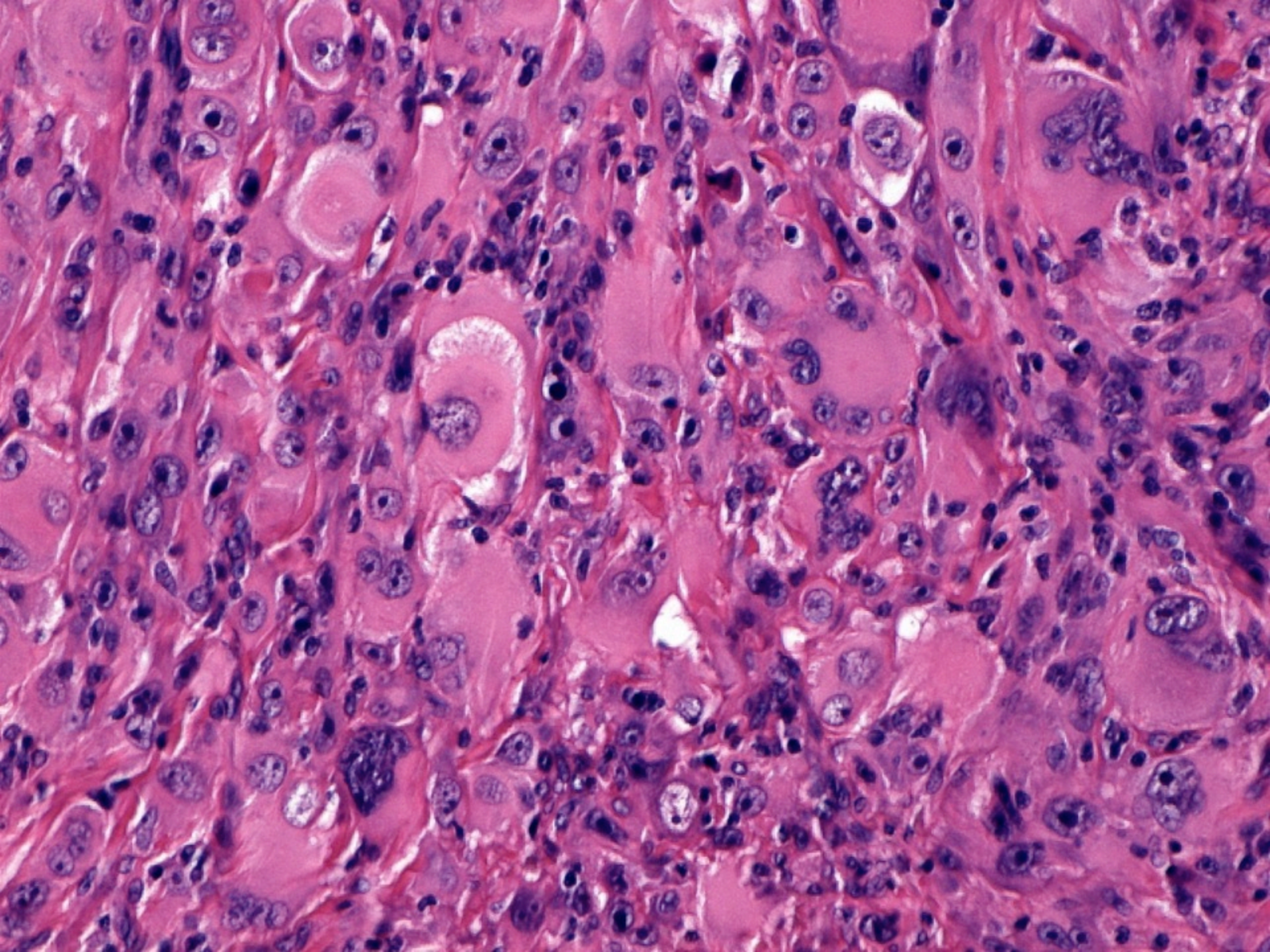


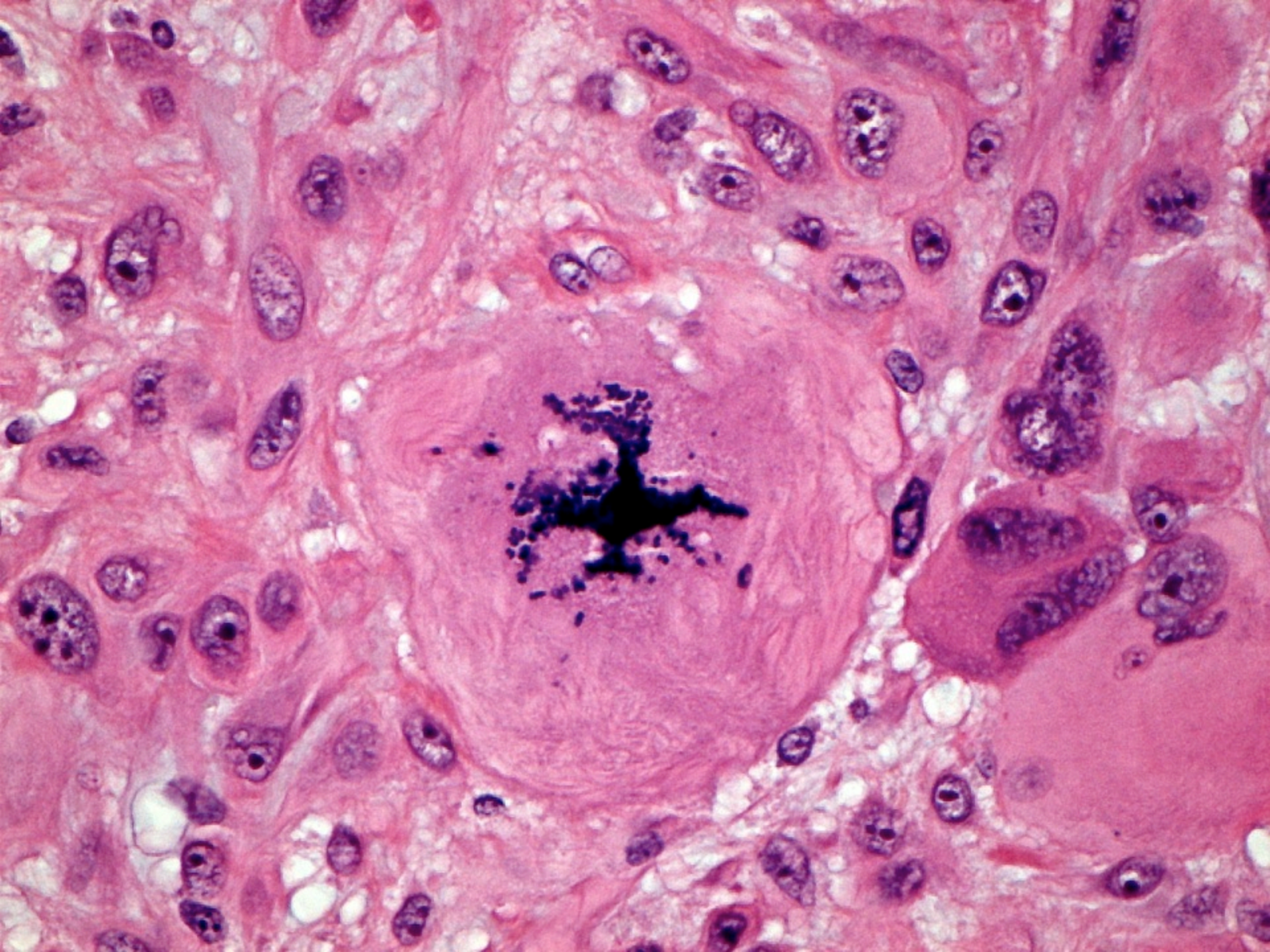








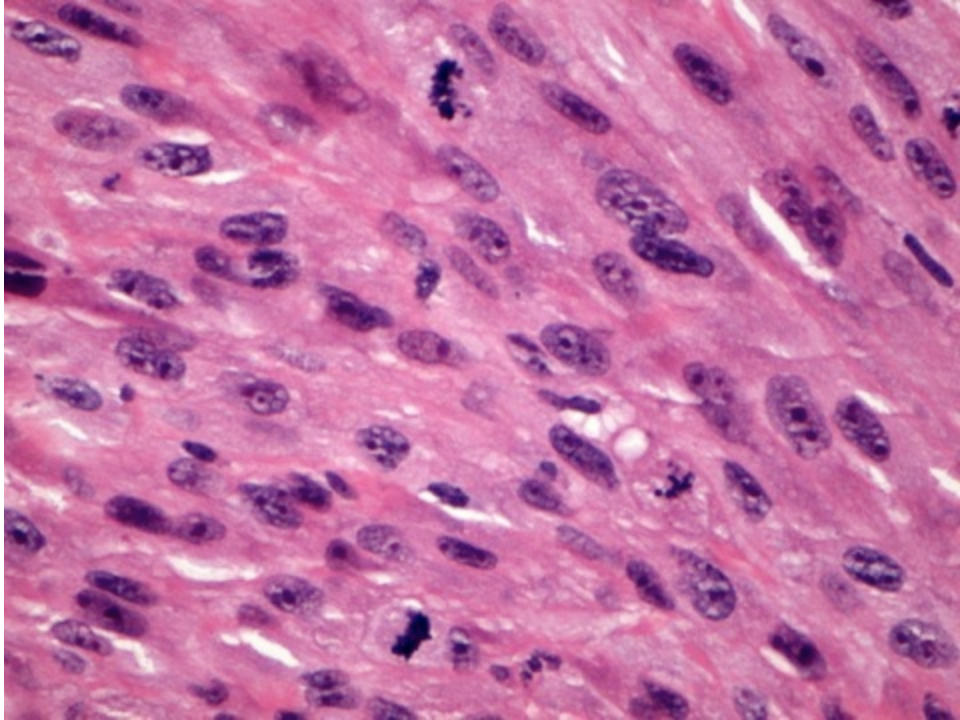
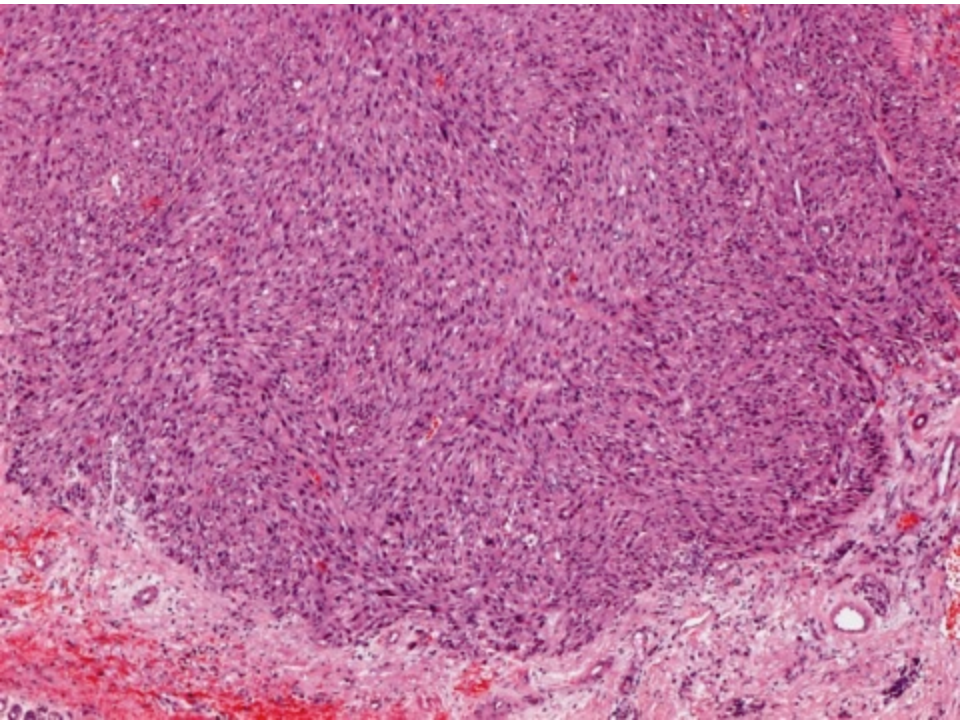
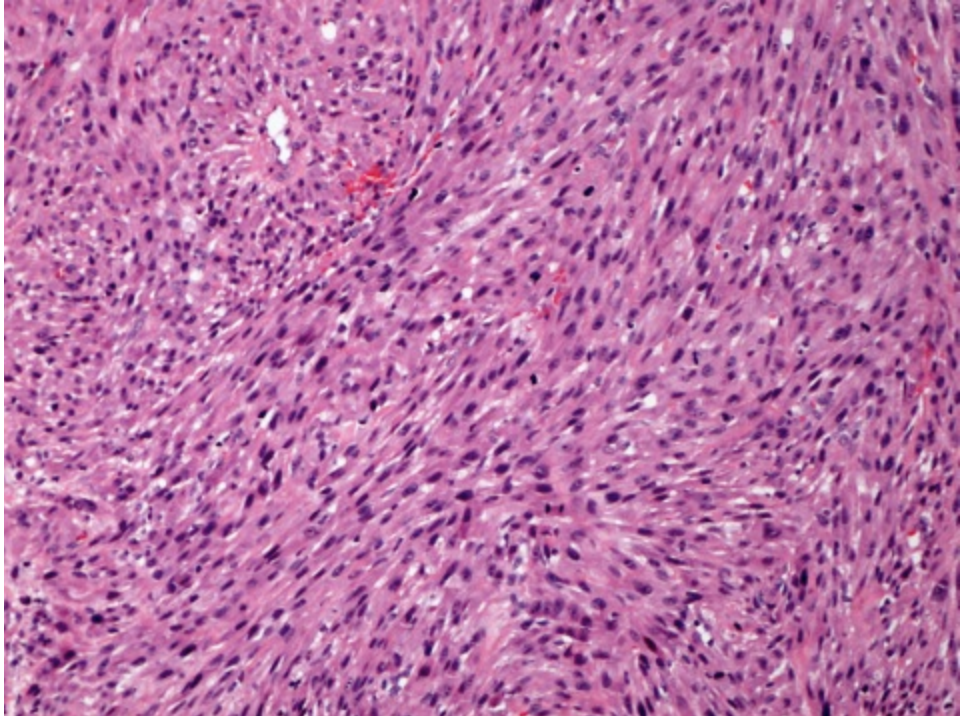
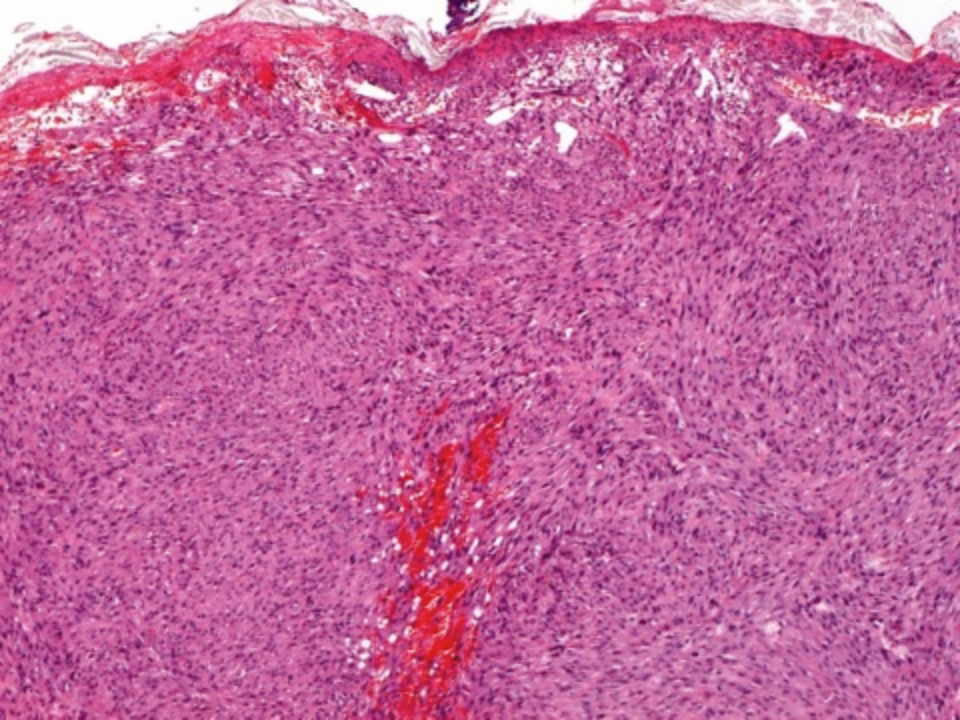


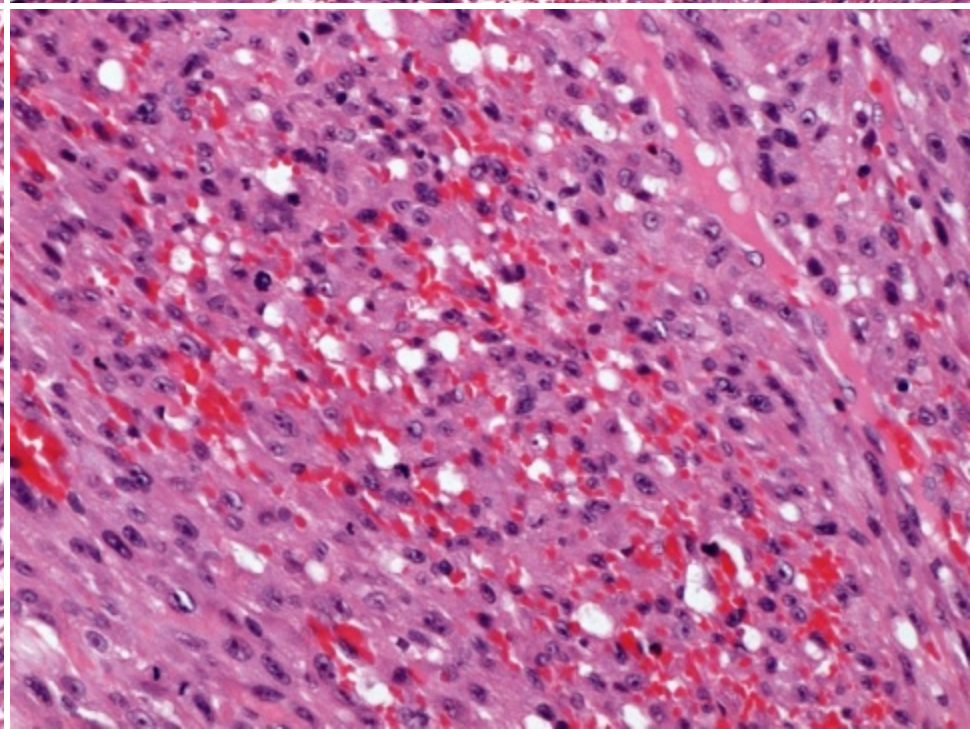
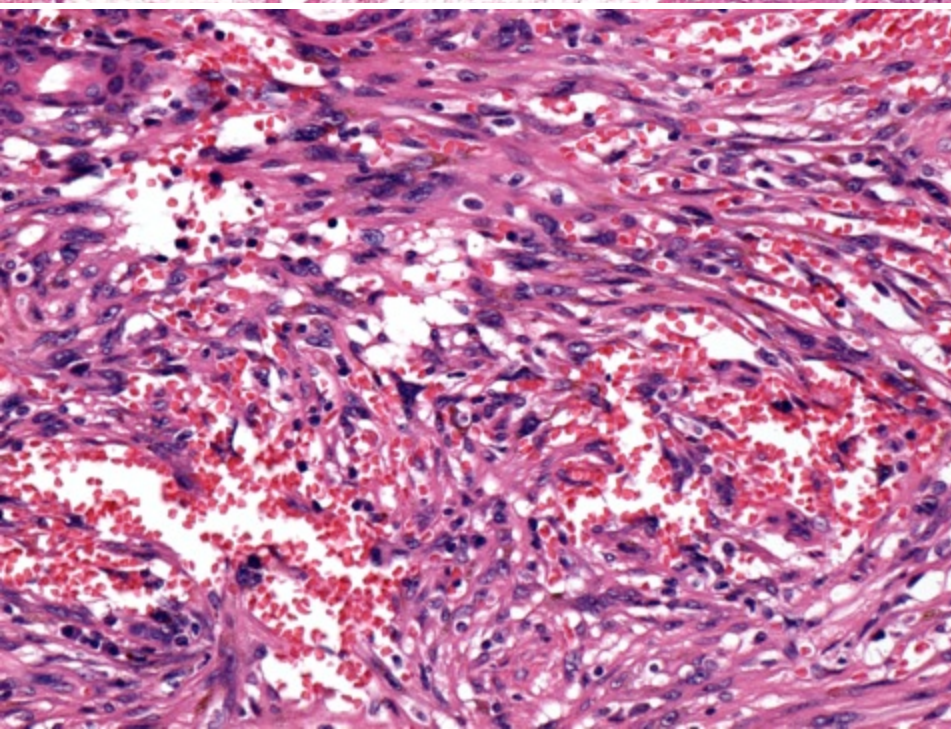
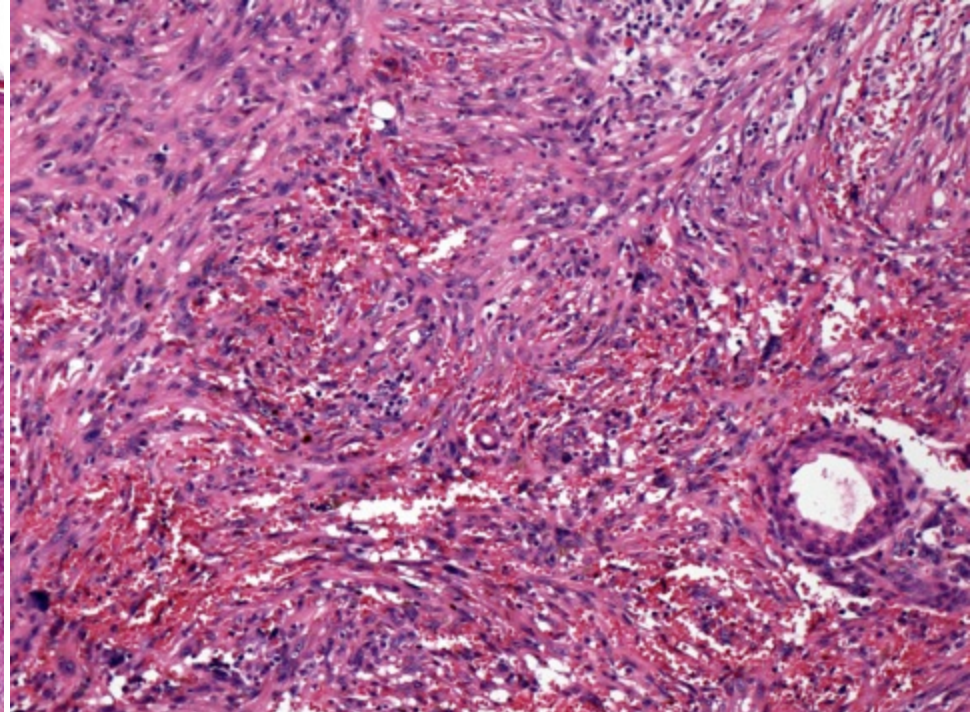
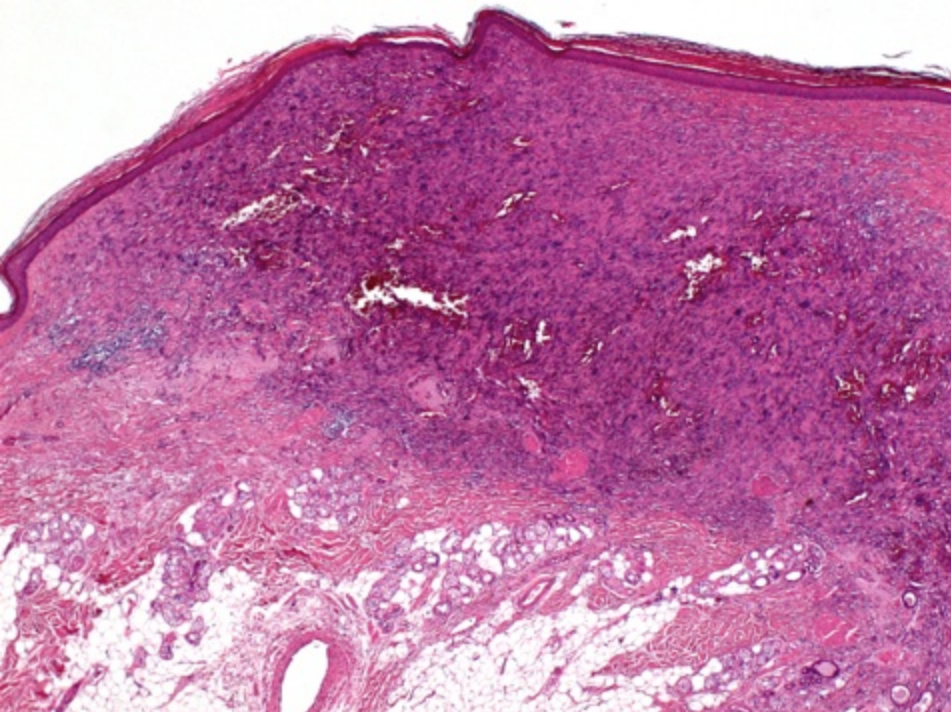


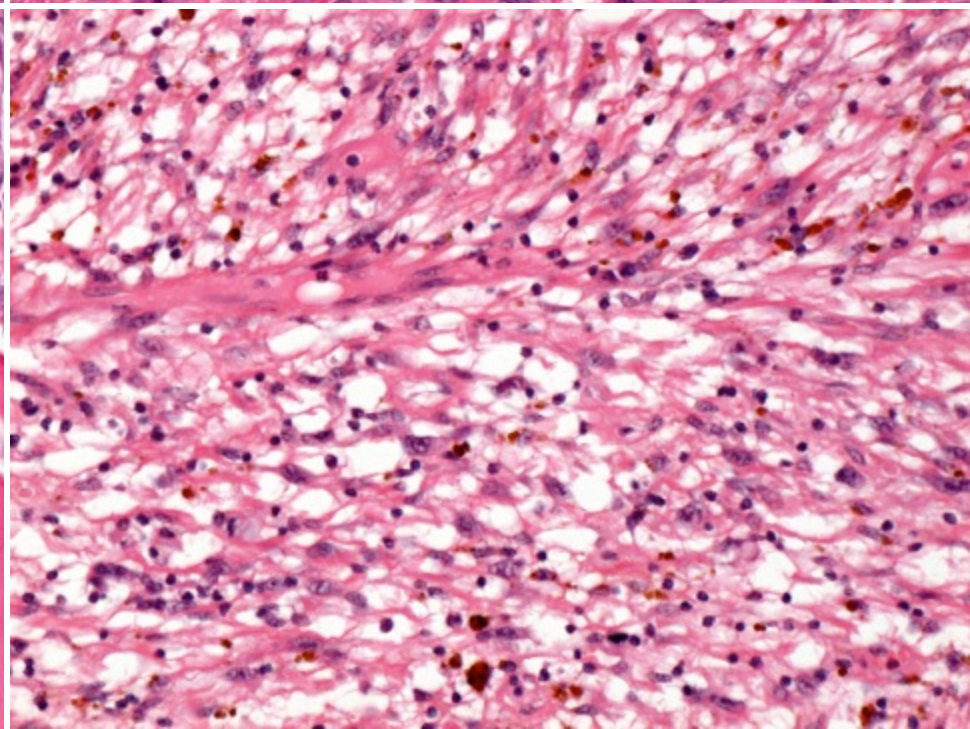
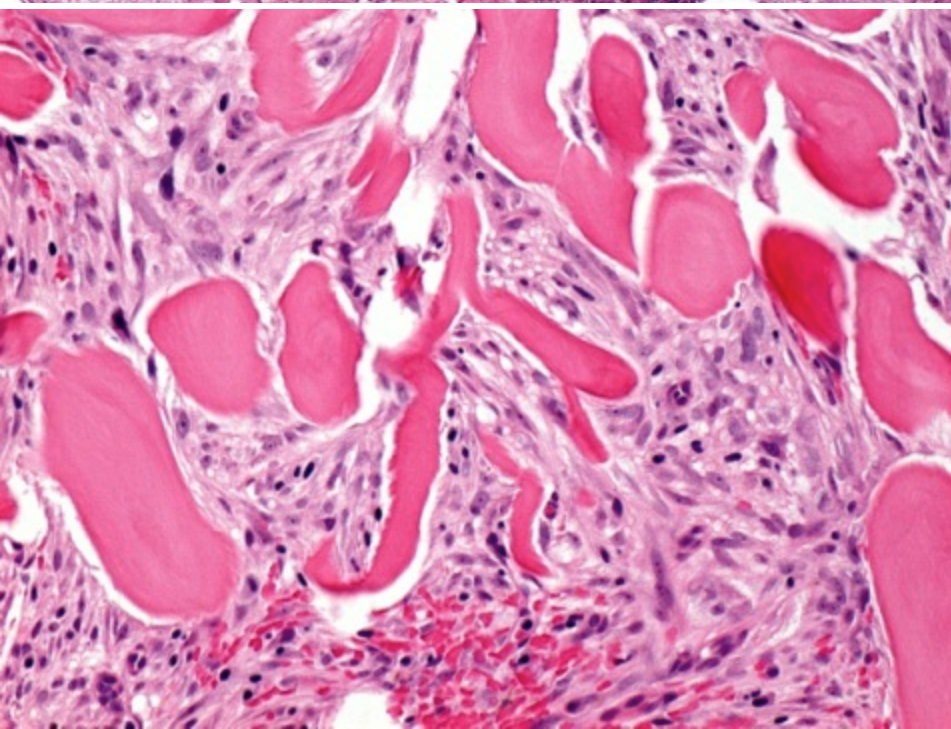
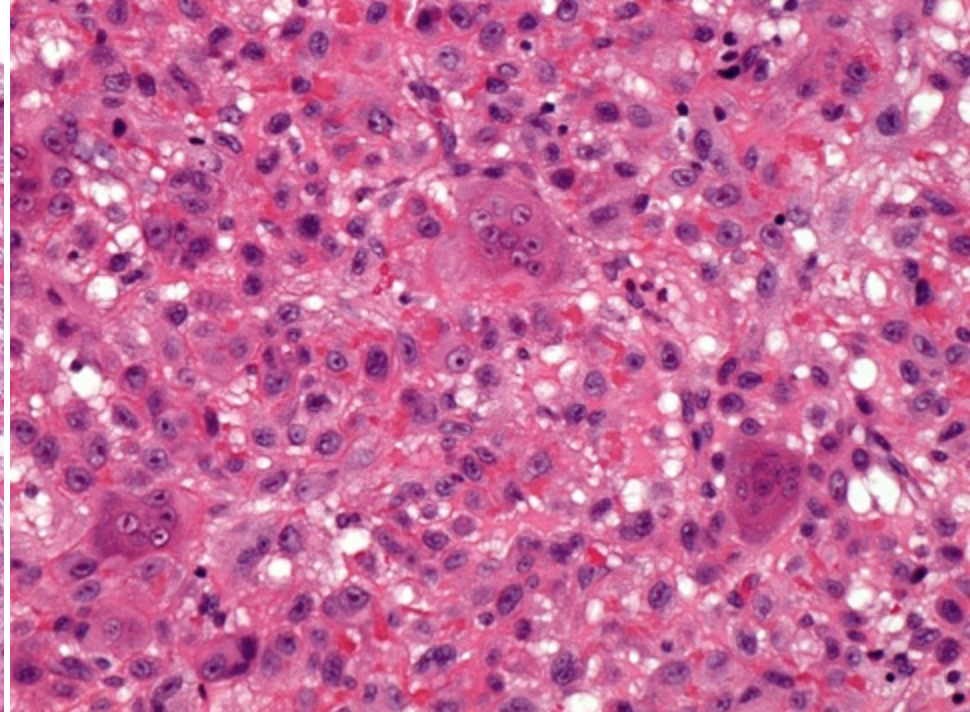
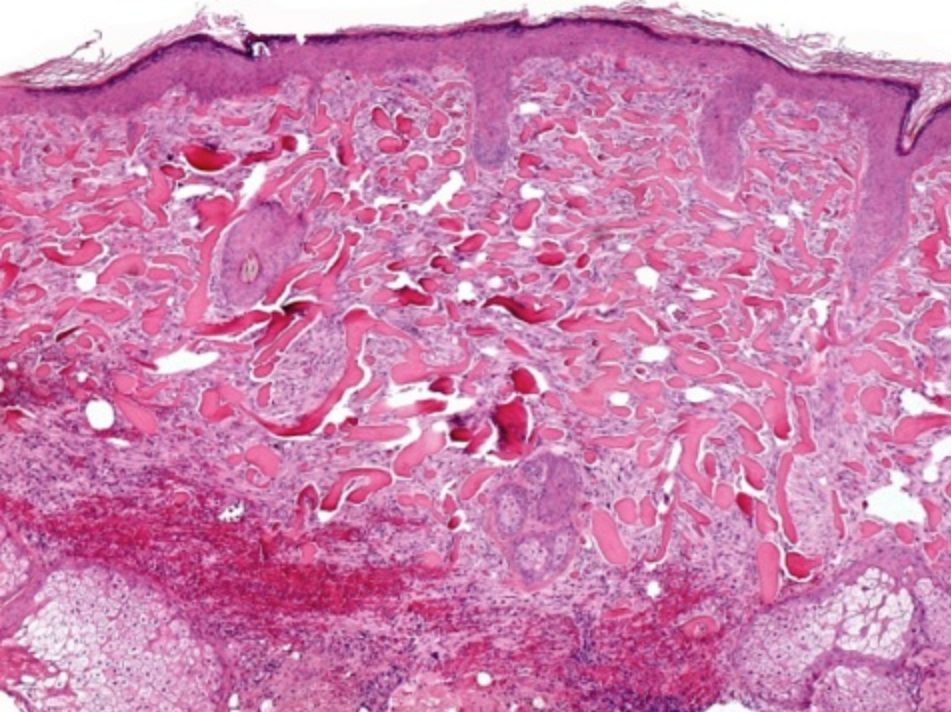
Atypical Fibroxanthoma

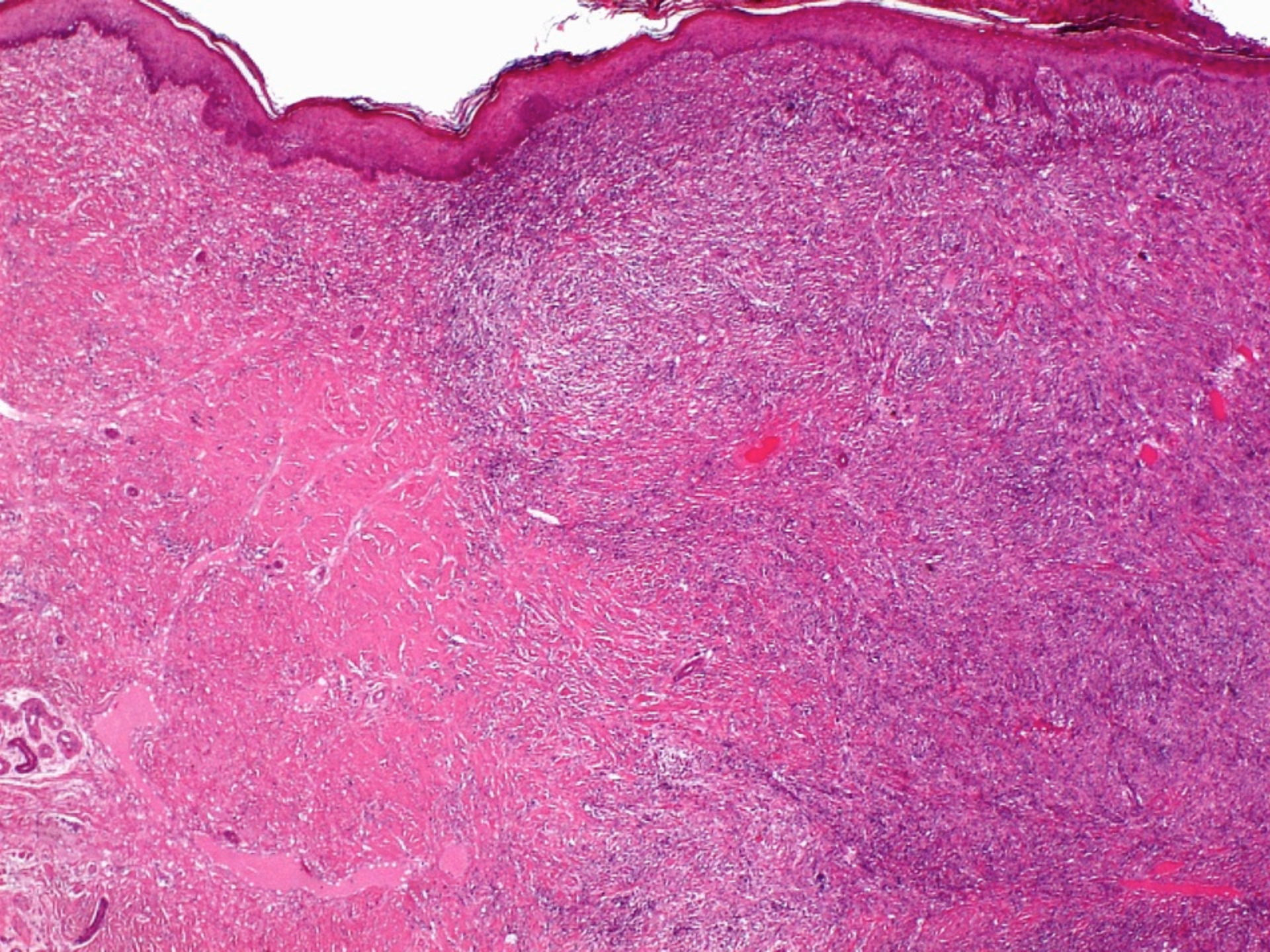
-Morphological Variants-

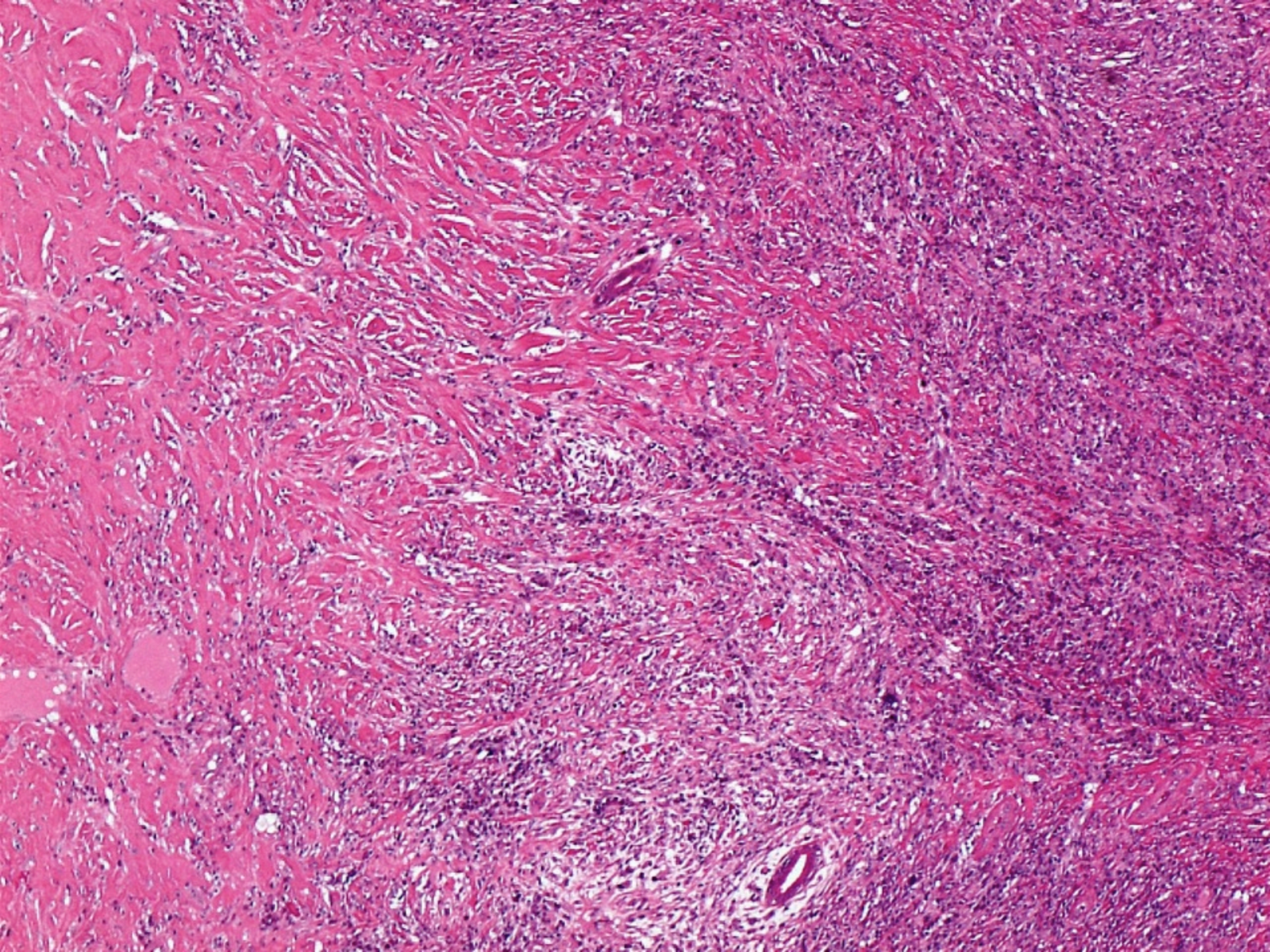
- **Spindle cell**
- **Keloidal**
- **Clear cell**
- **Granular cell**
- **Myxoid**
- **Plaque-like**
- **Pseudoangiomatous**
- **Osteoclast-like giant cells**
- **Regression**











Atypical Fibroxanthoma

-Immunohistochemistry-

Diagnosis of exclusion

No positive discriminatory histological or immunohistochemical features

Negative:

- S100**
- multiple CK, especially HMW-CK**
- Desmin**
- CD34**

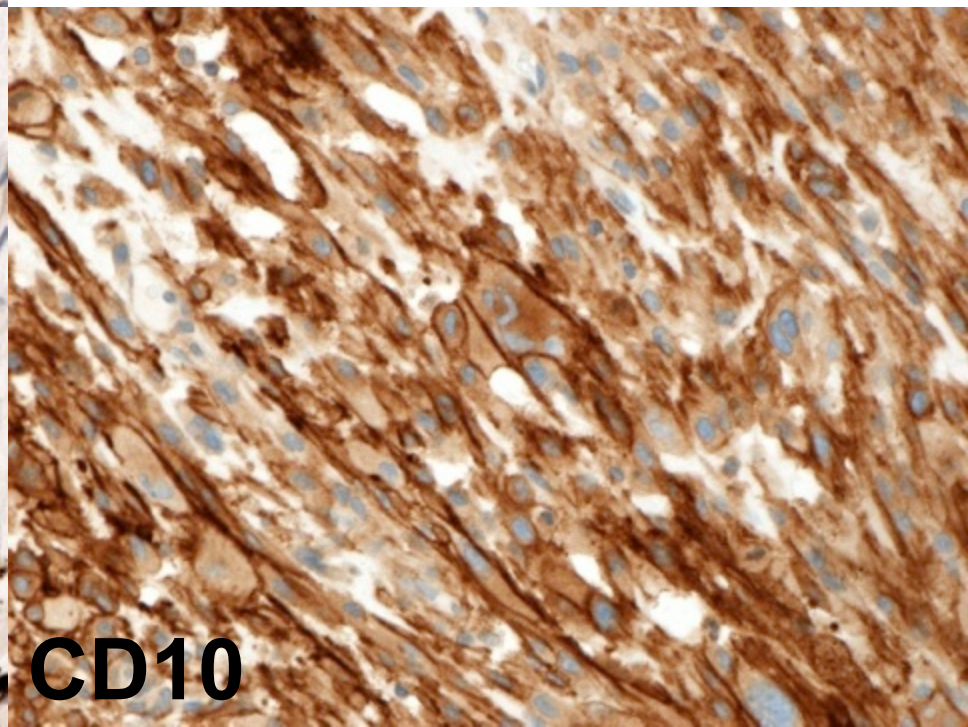
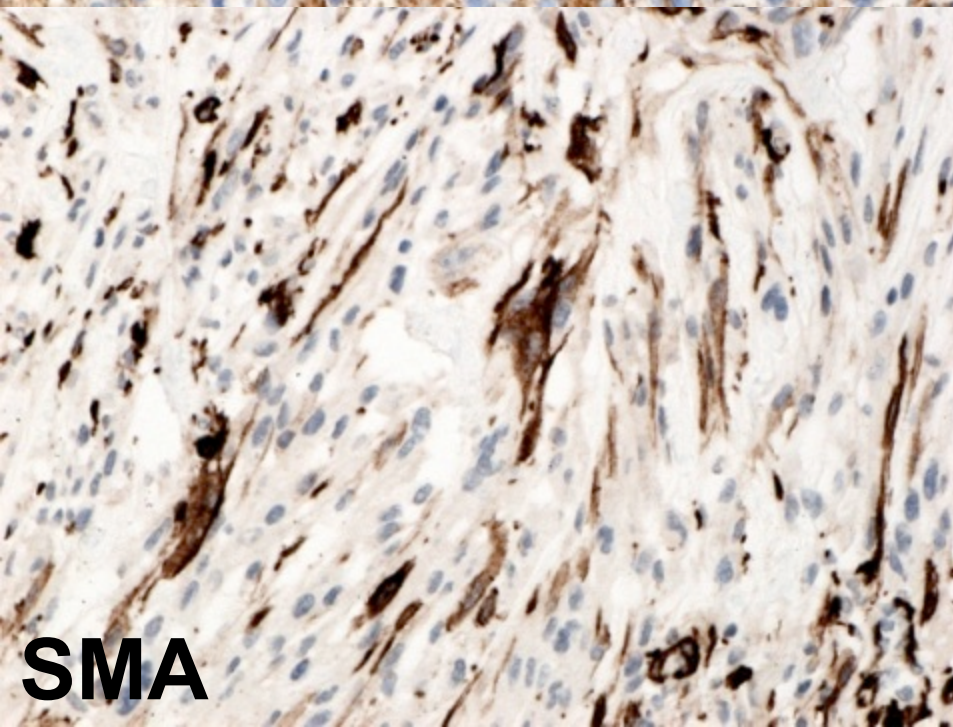
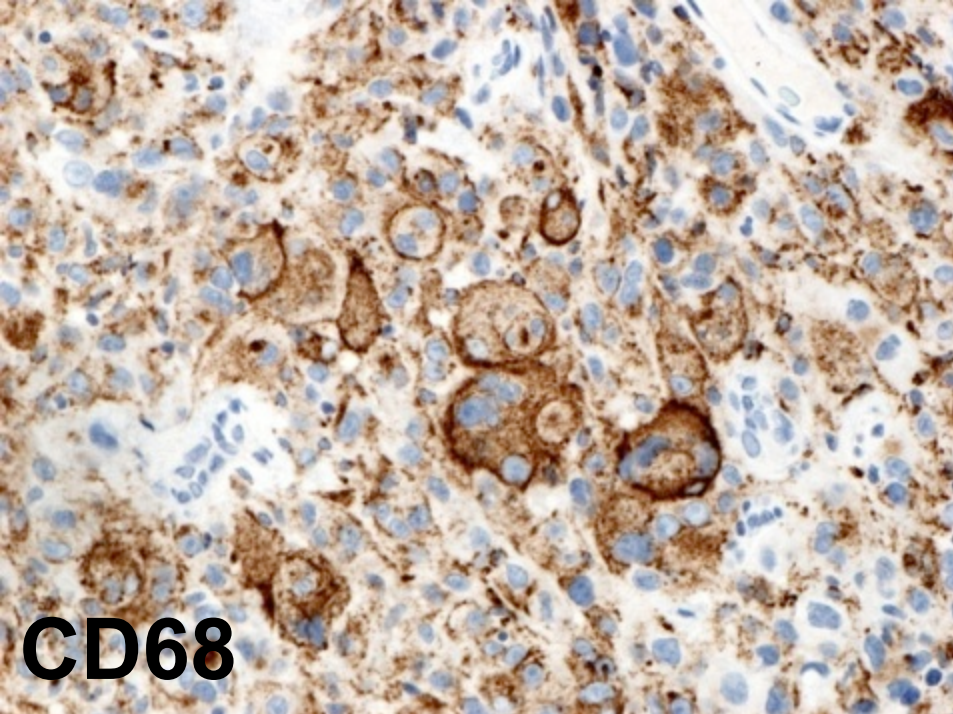
AFX

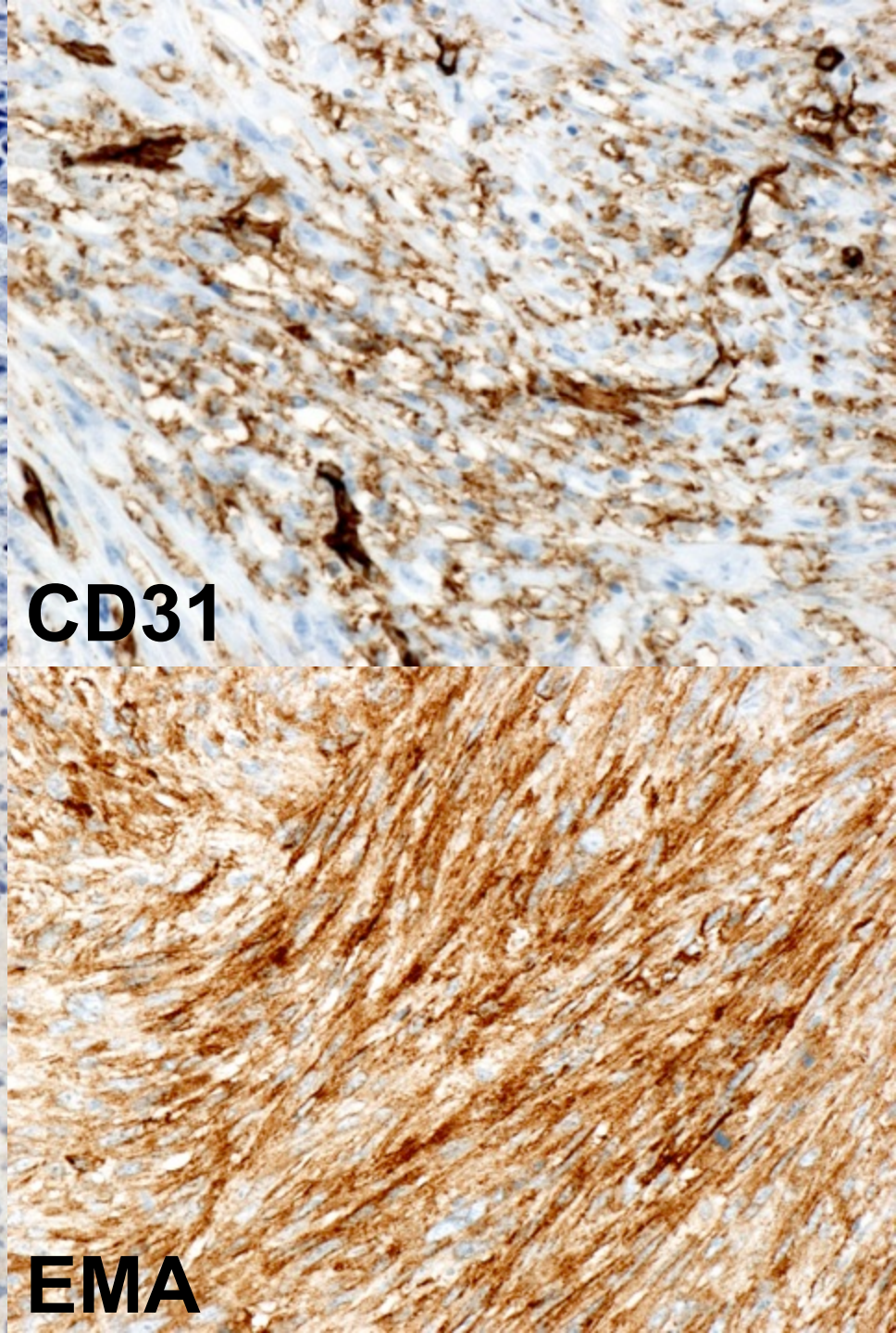
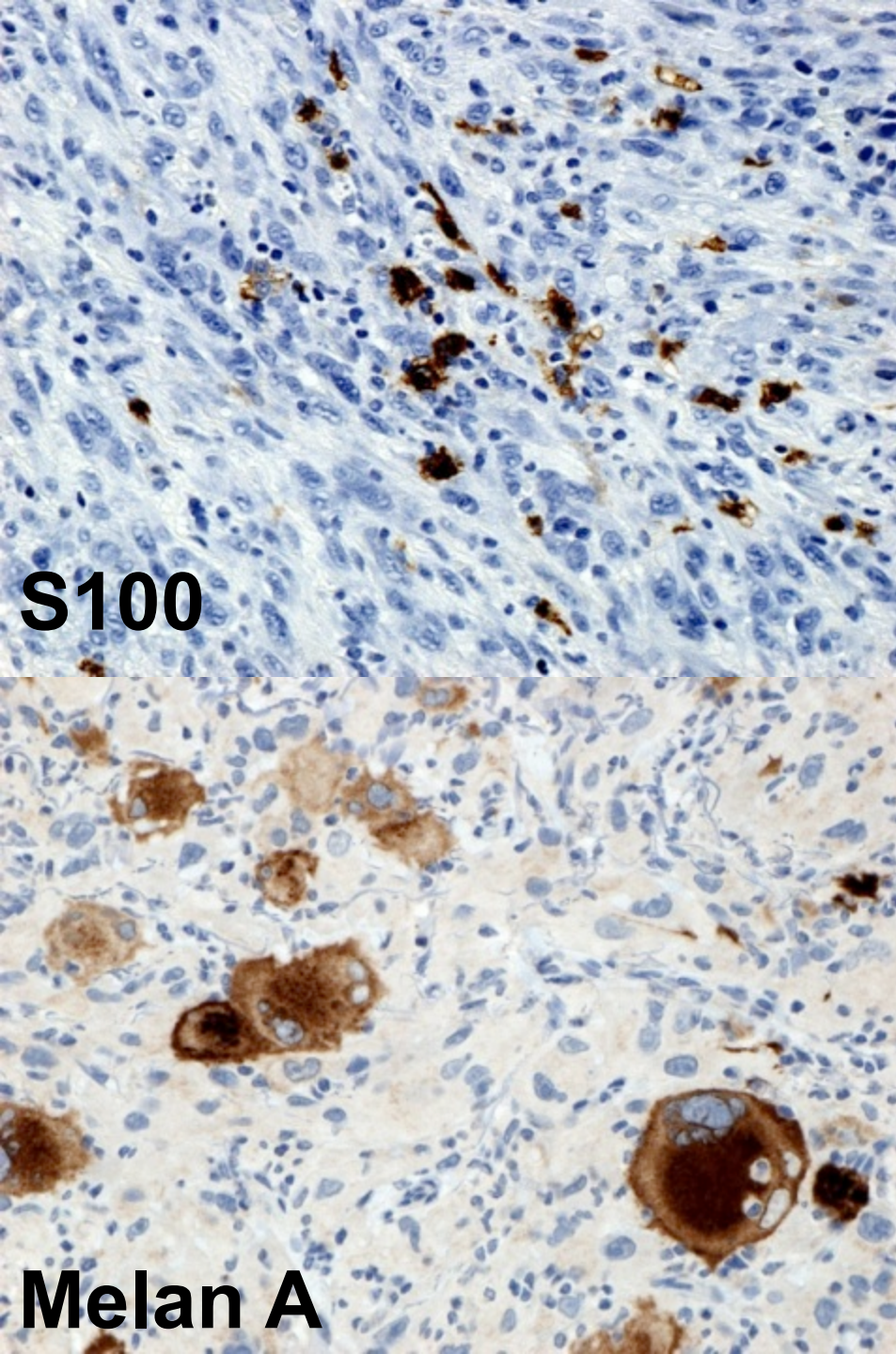
-Immunohistochemistry-

CD99

EMA

Rare p63





Atypical Fibroxanthoma

-Summary-

Diagnosis of exclusion

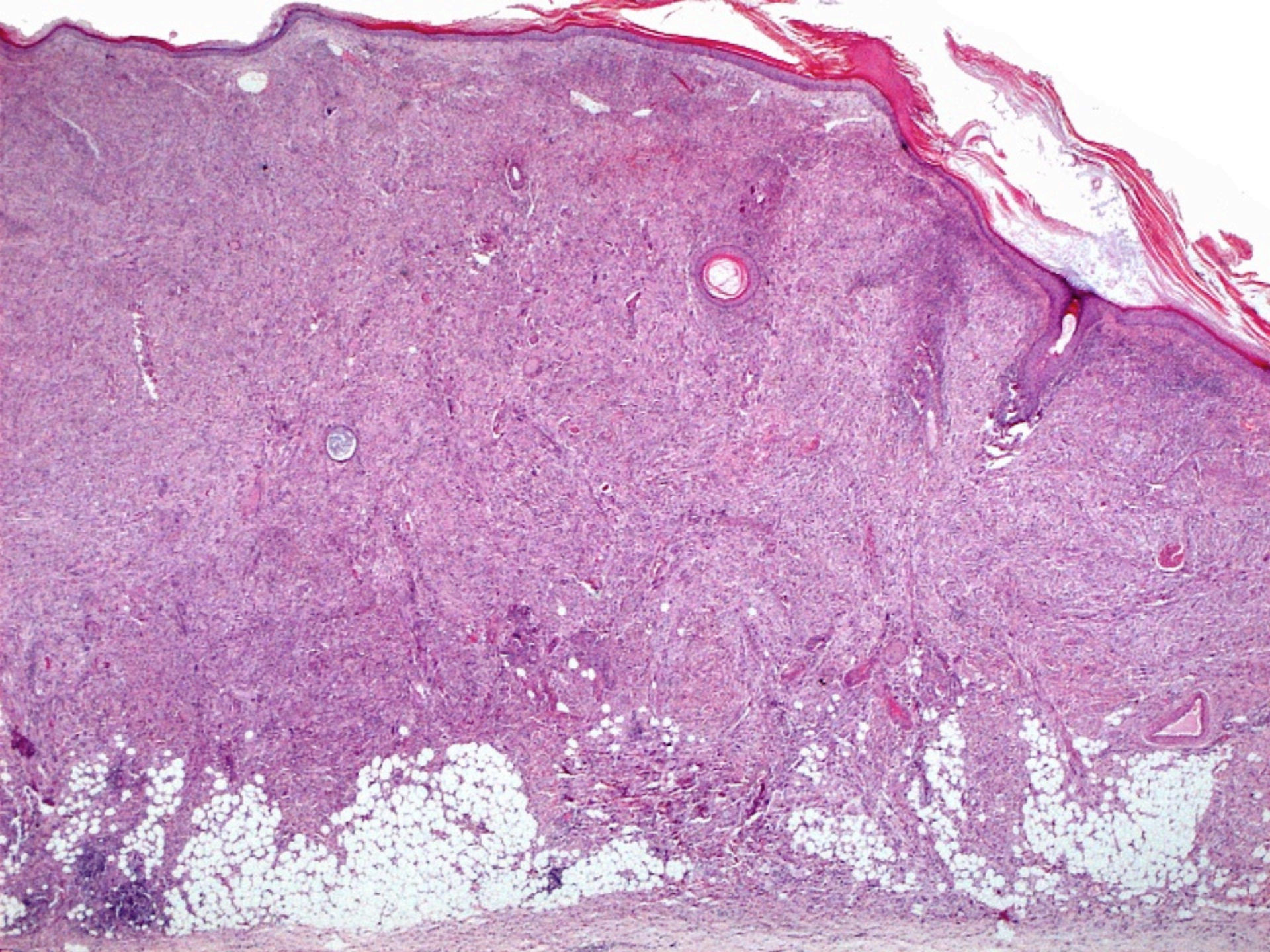
Benign behavior if

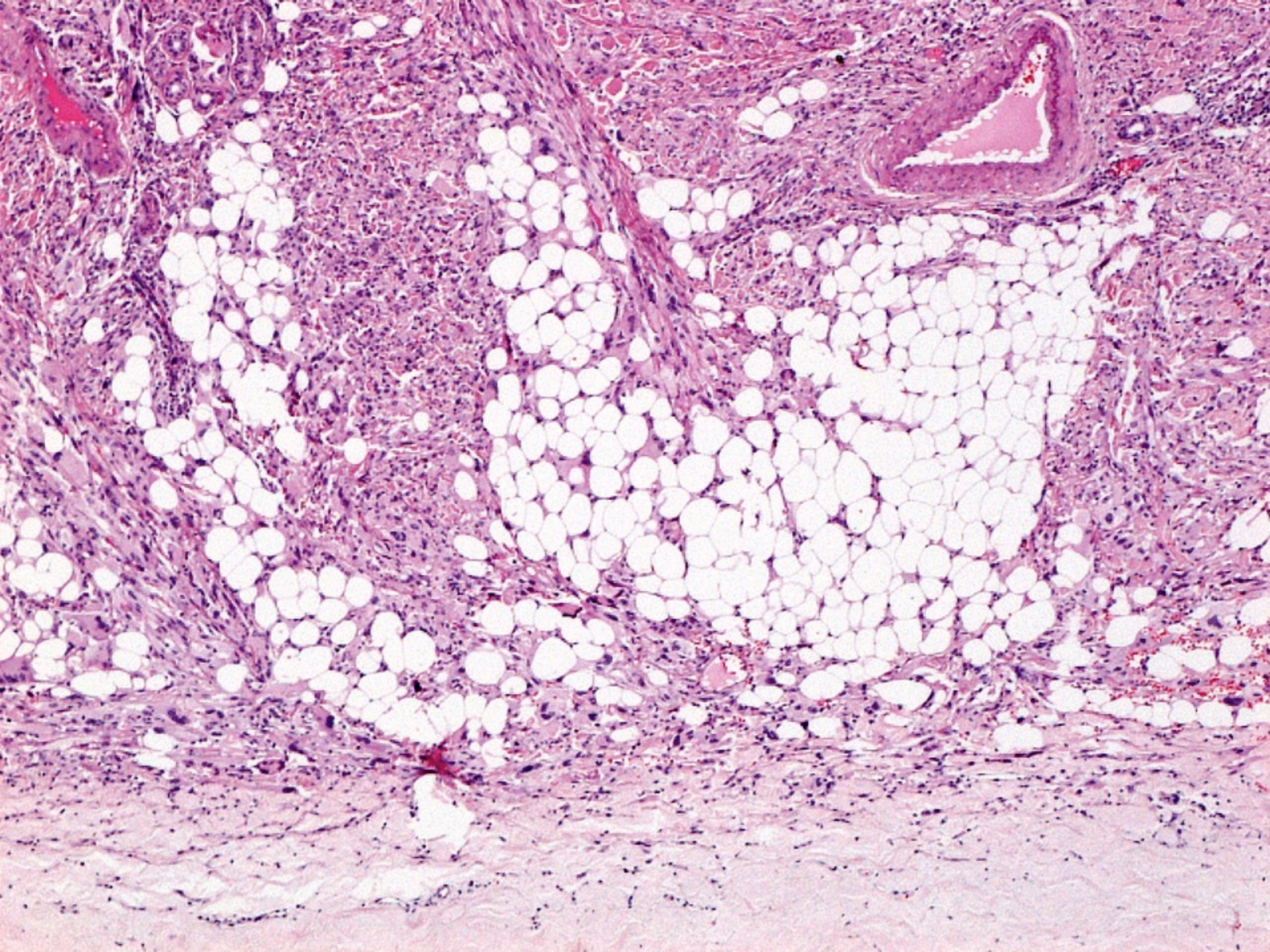
- **Strict diagnostic criteria applied**
- **Absence of:**
 - **Infiltrative growth**
 - **Invasion of subcutis or beyond**
 - **LVI/PNI**
 - **Tumor necrosis**
- **Otherwise regarded as:**
 - **Pleomorphic Dermal Sarcoma, NOS**

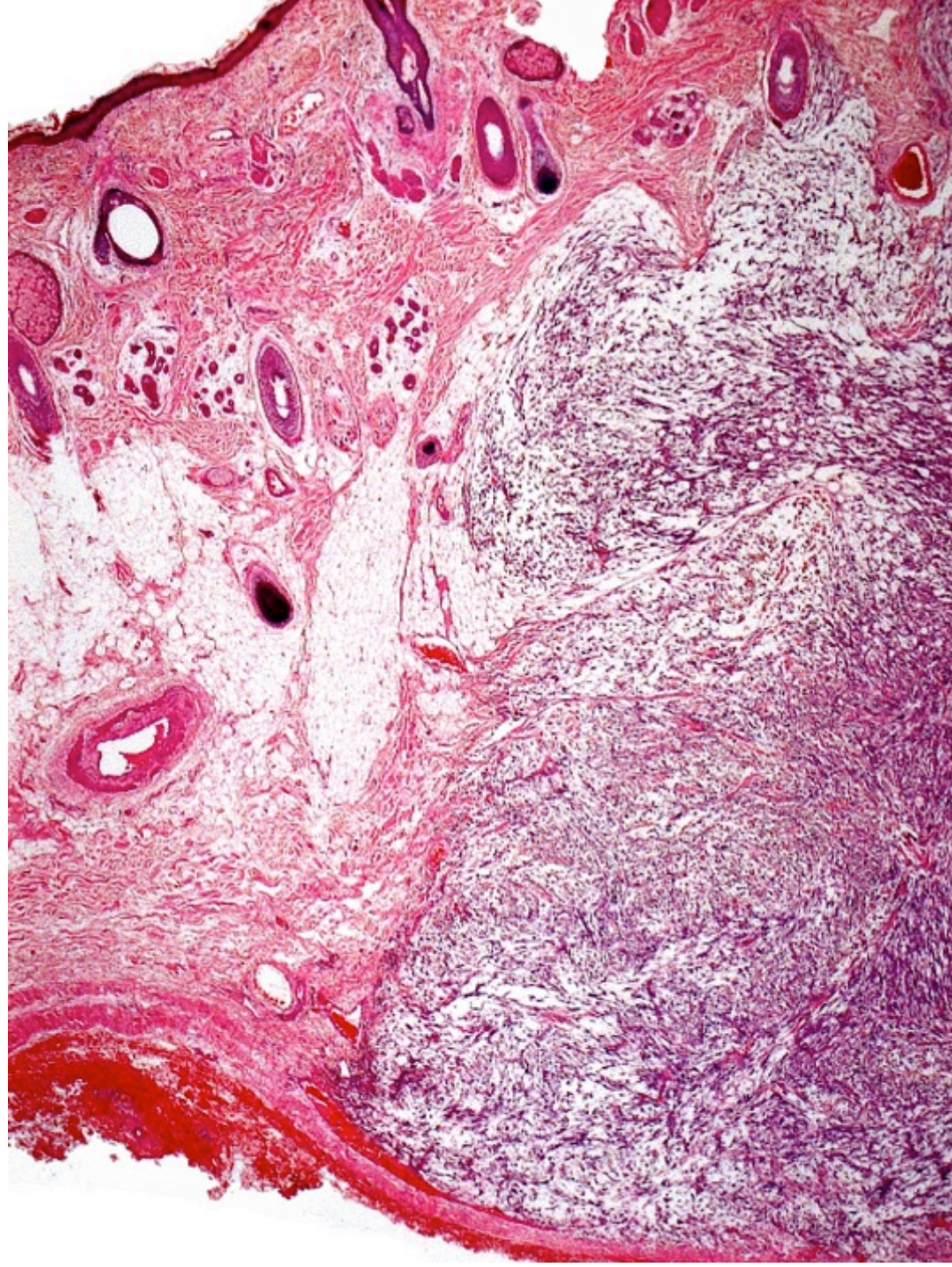
Pleomorphic Dermal Sarcoma

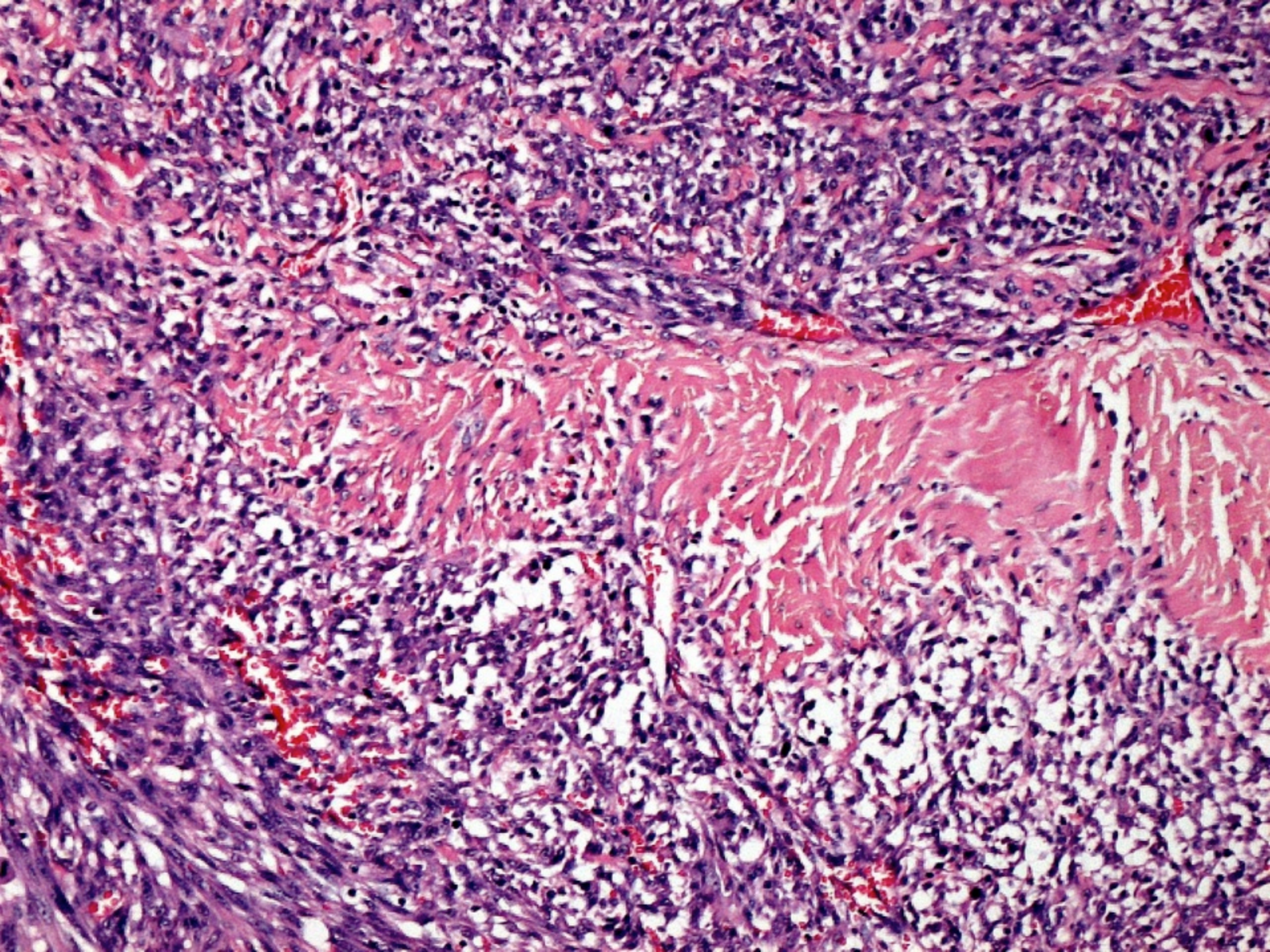
-Clinical Features-

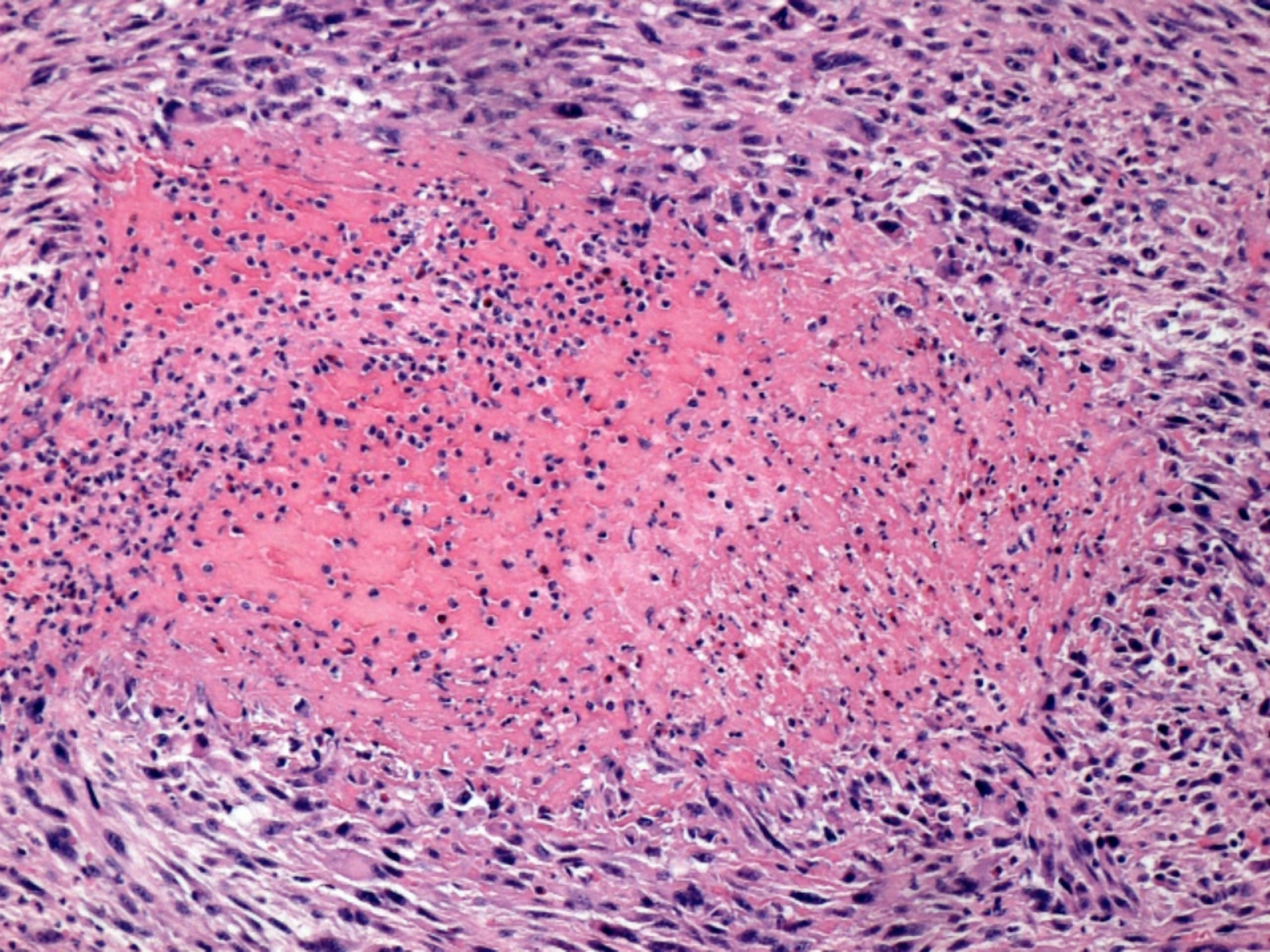
- **Sun-damaged skin**
- **Head and neck; scalp**
- **Elderly**
- **Strong male predilection**
- **Rapid growth**
- **Ulceration and bleeding**
- **2.5 cm median**

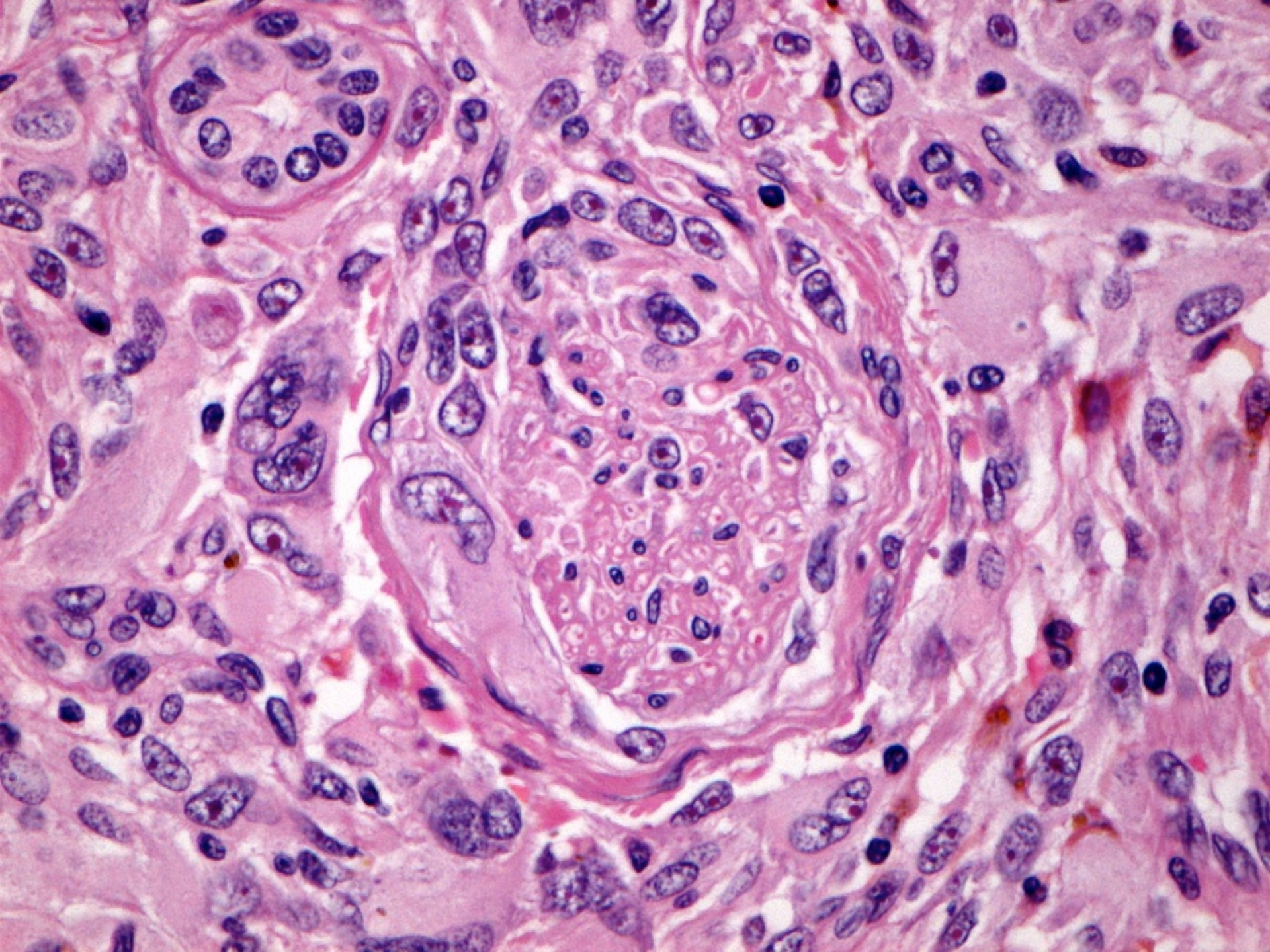


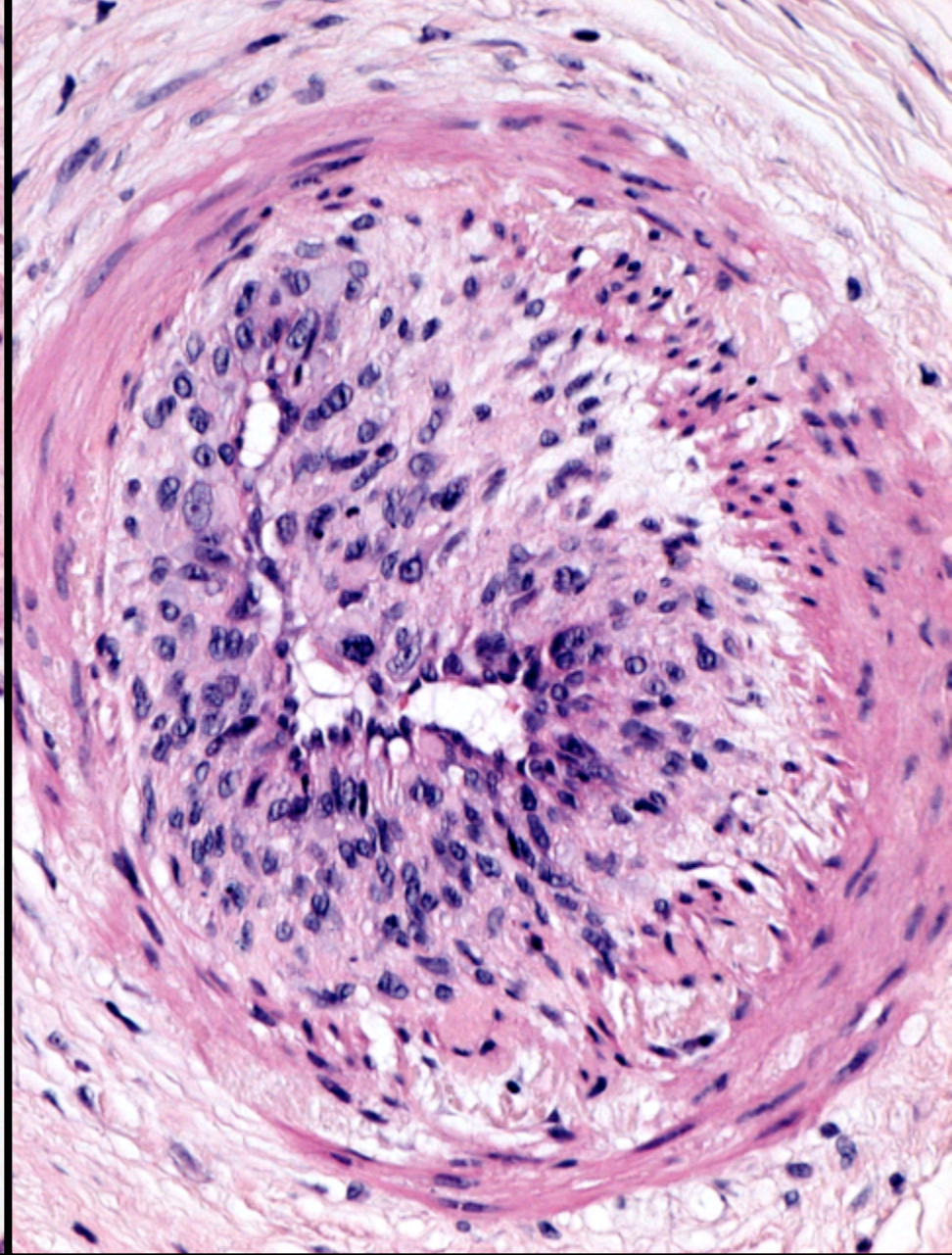
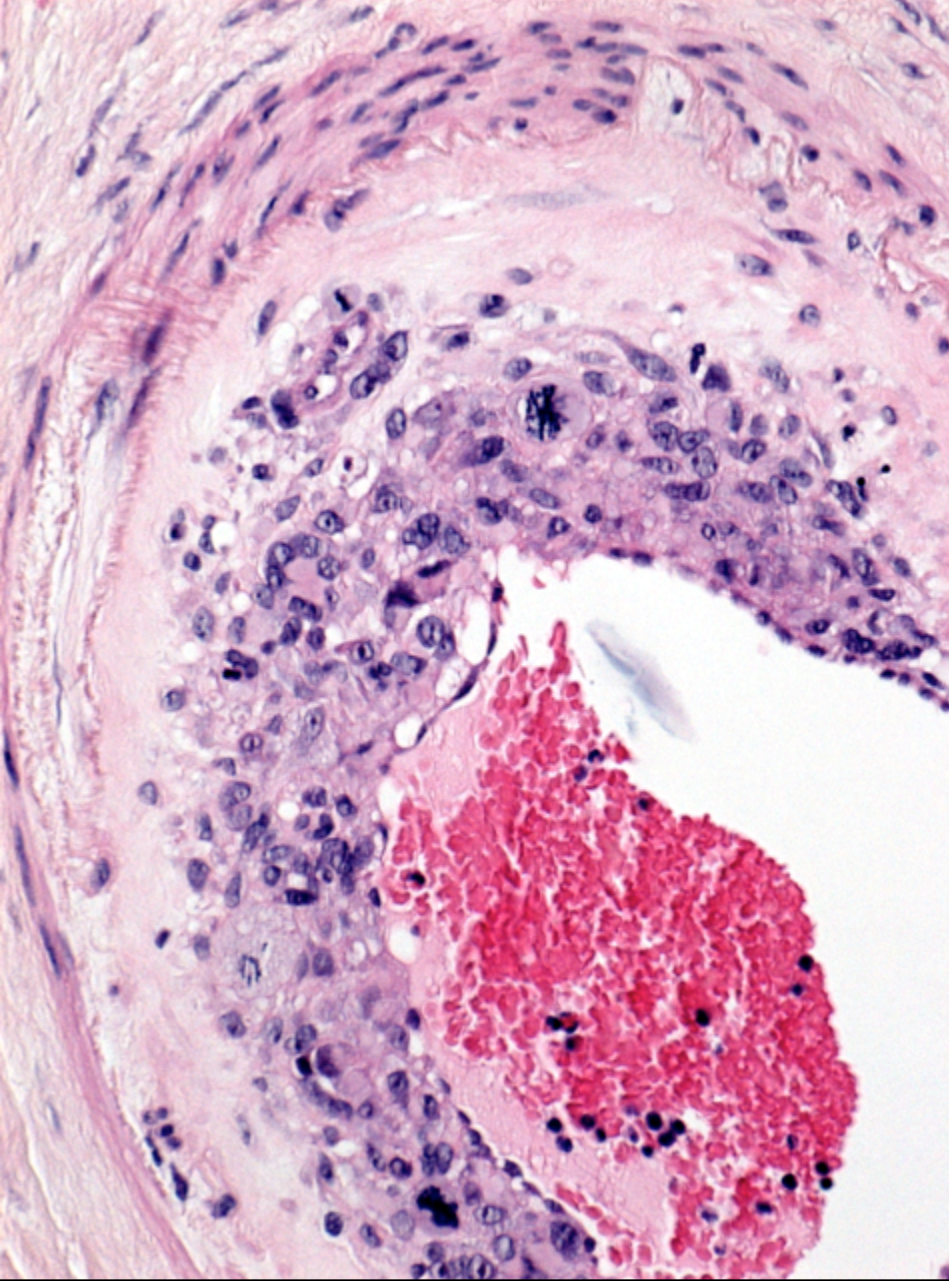


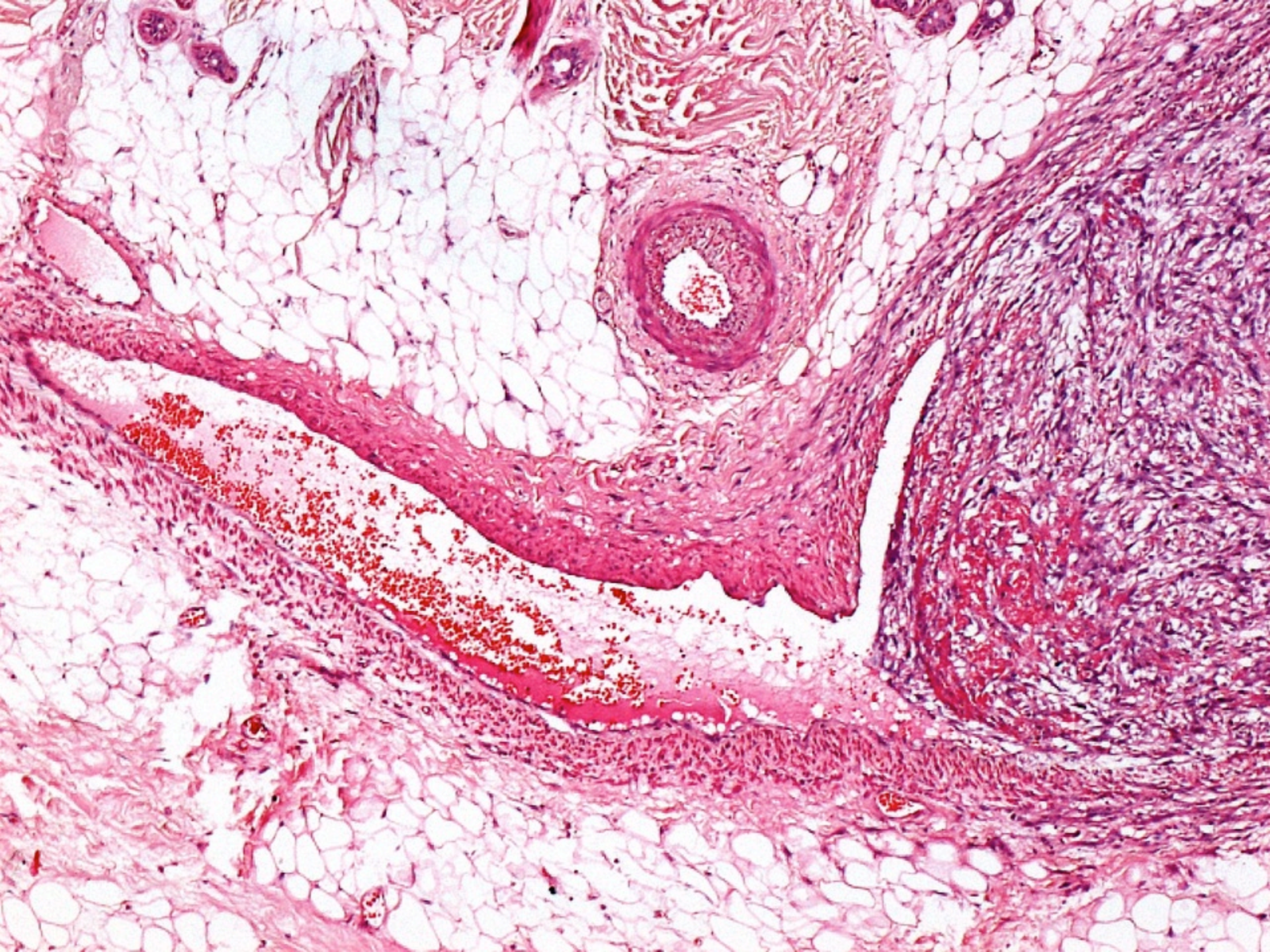


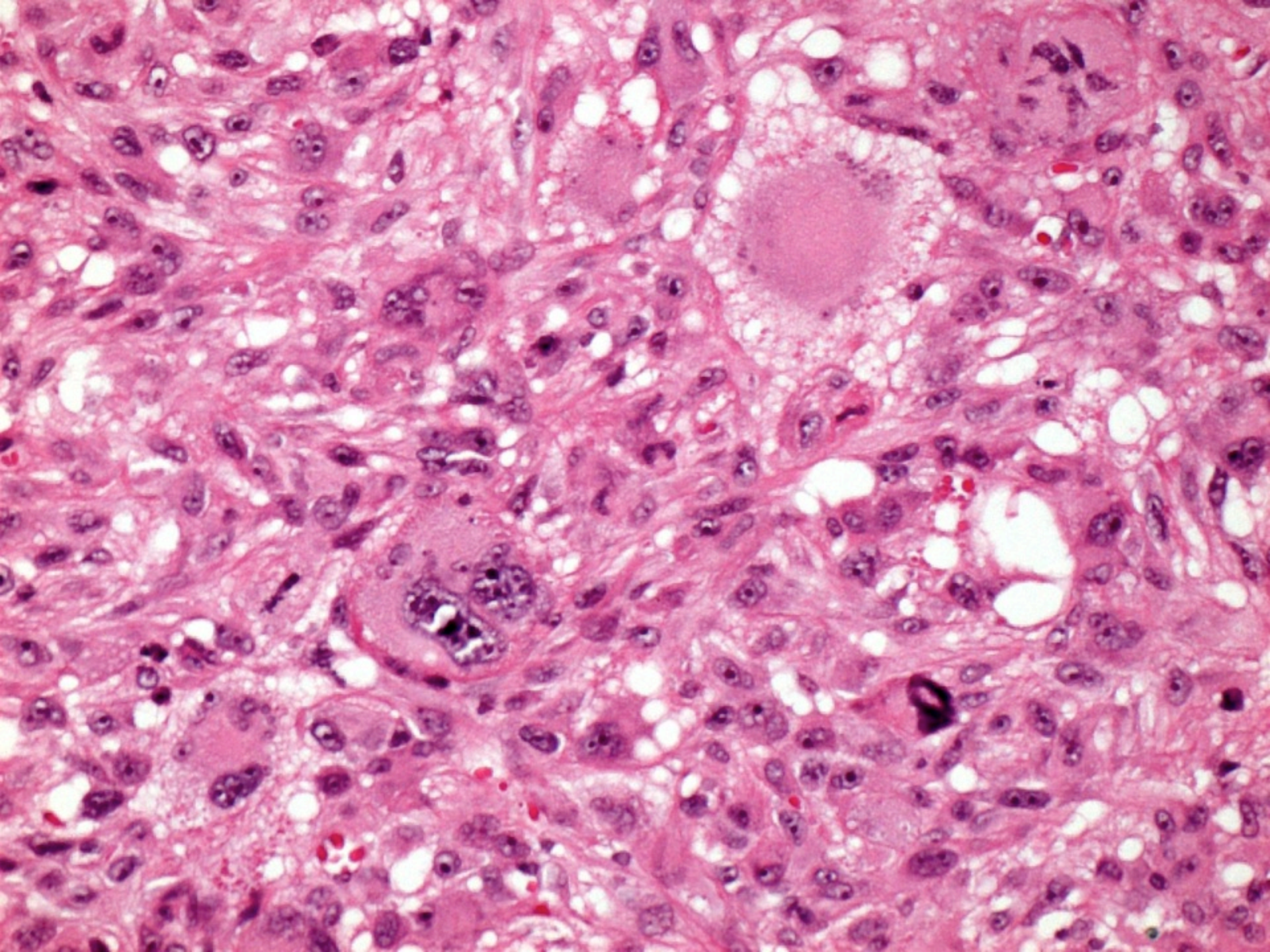


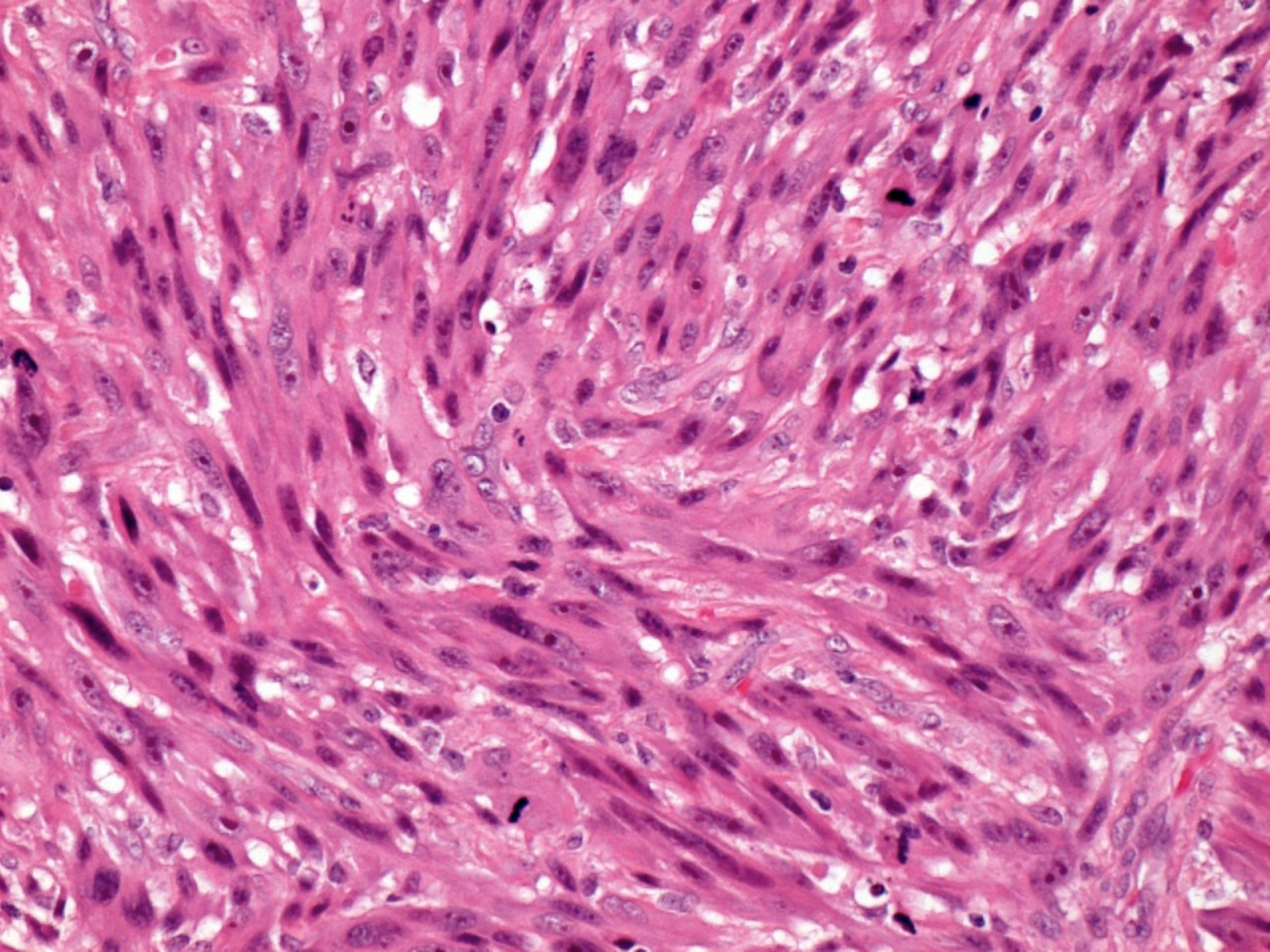


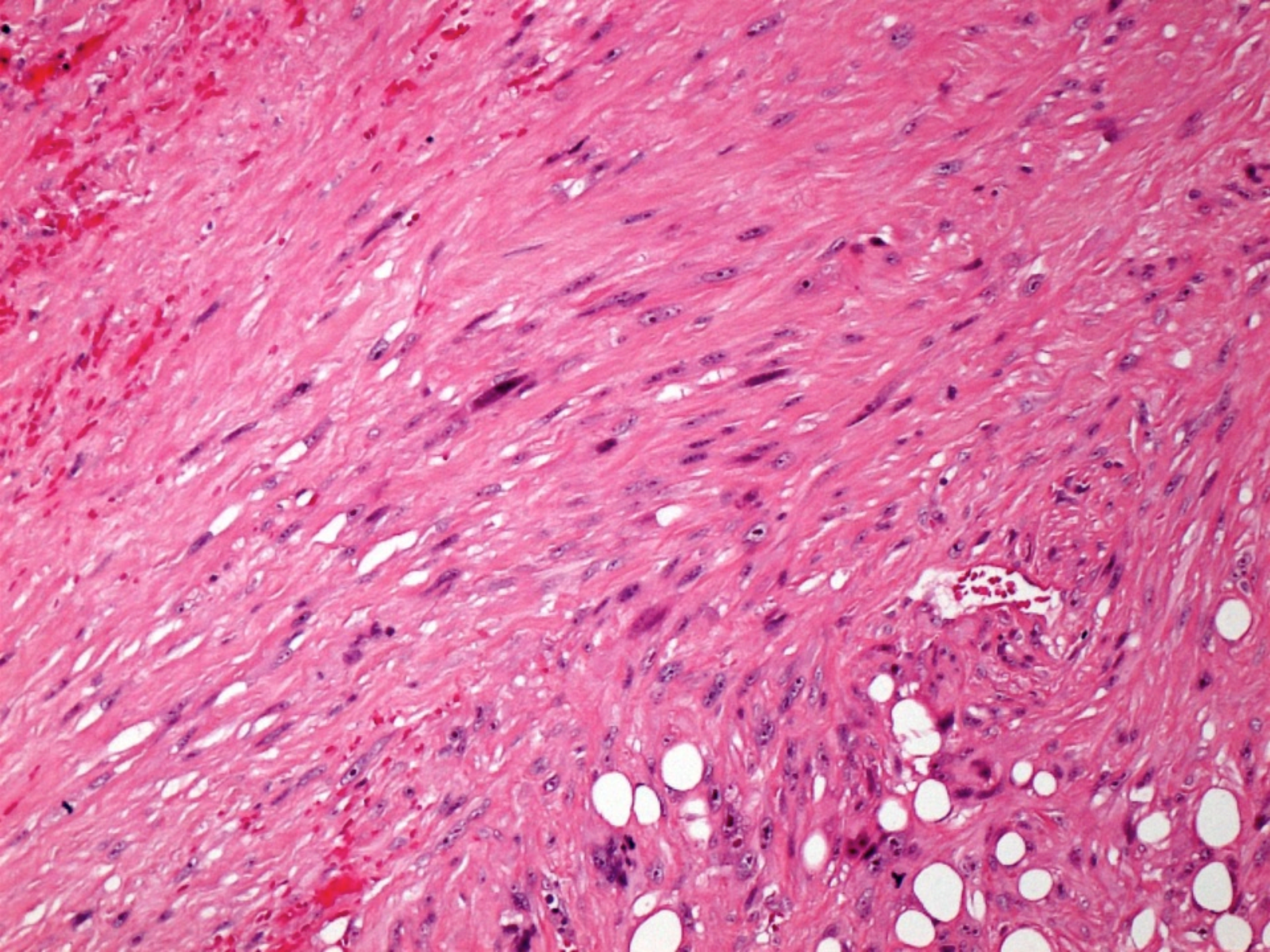


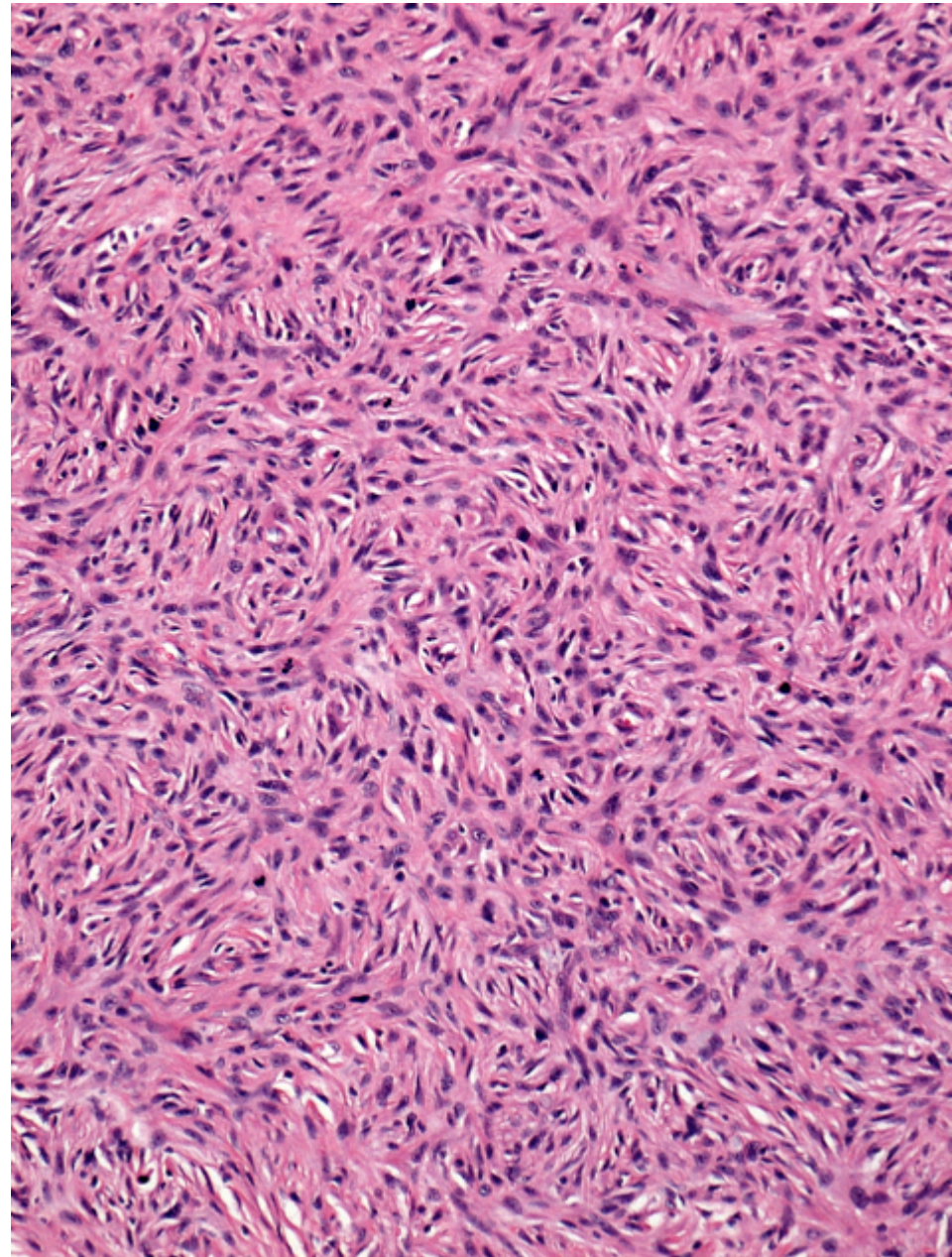
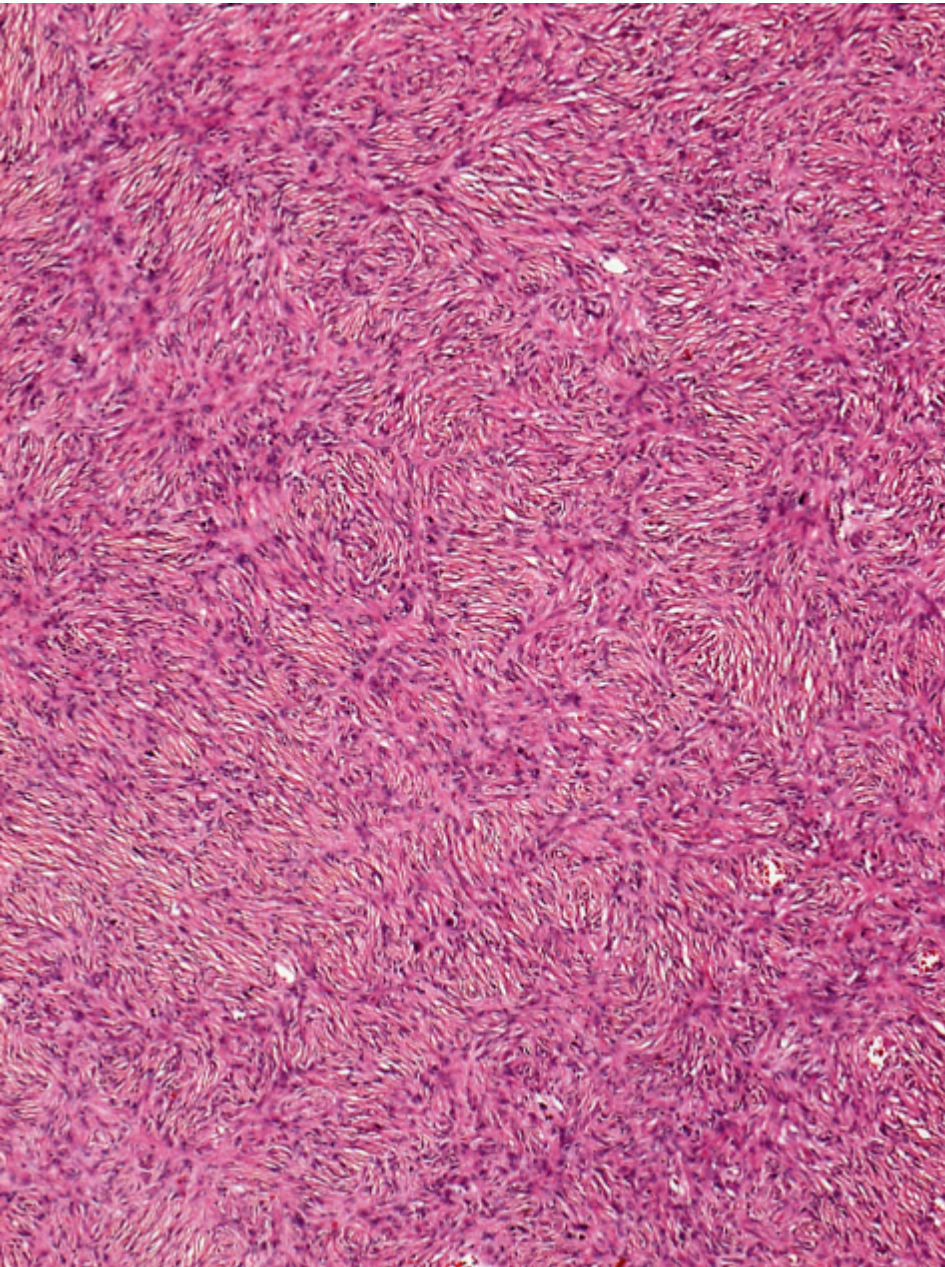


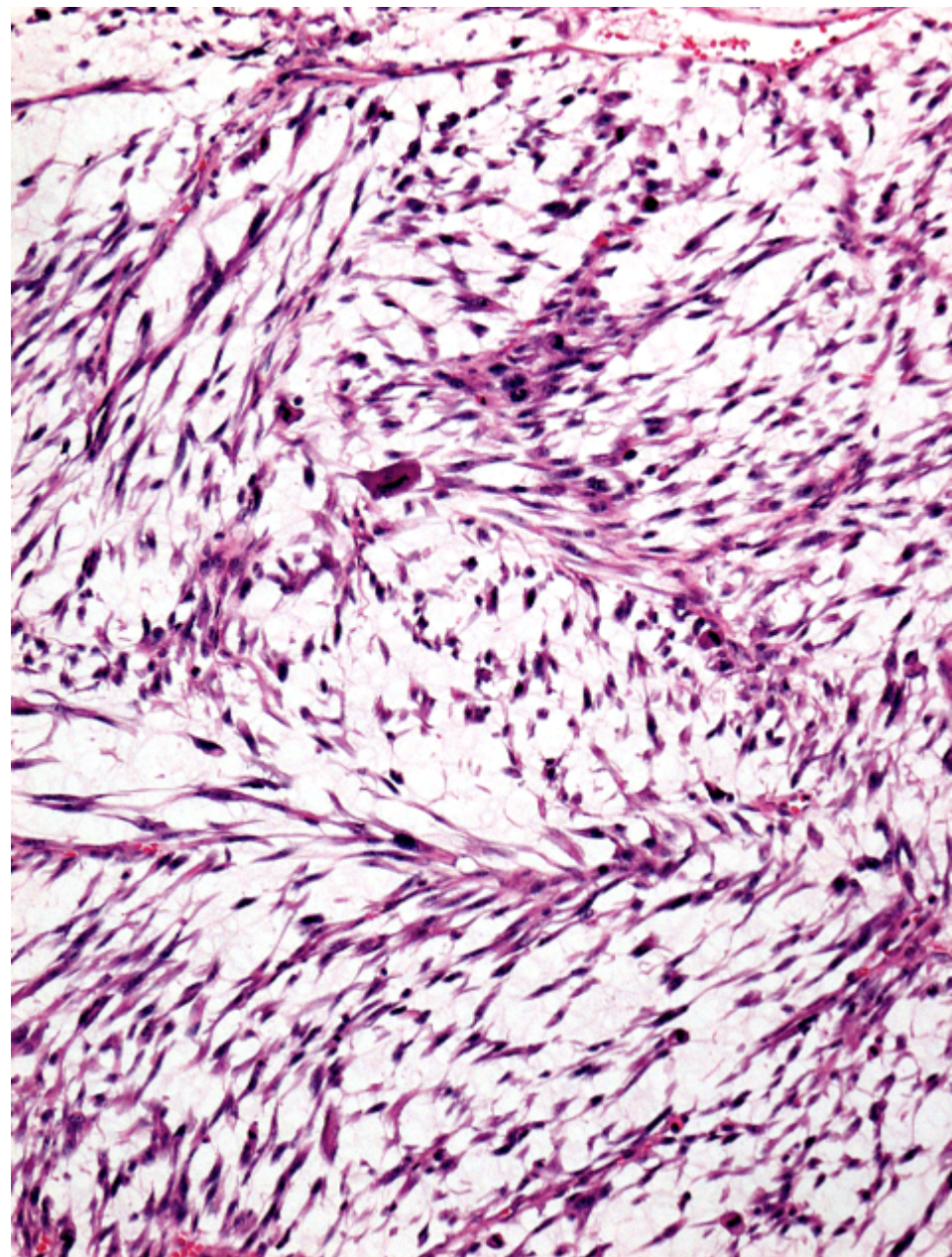
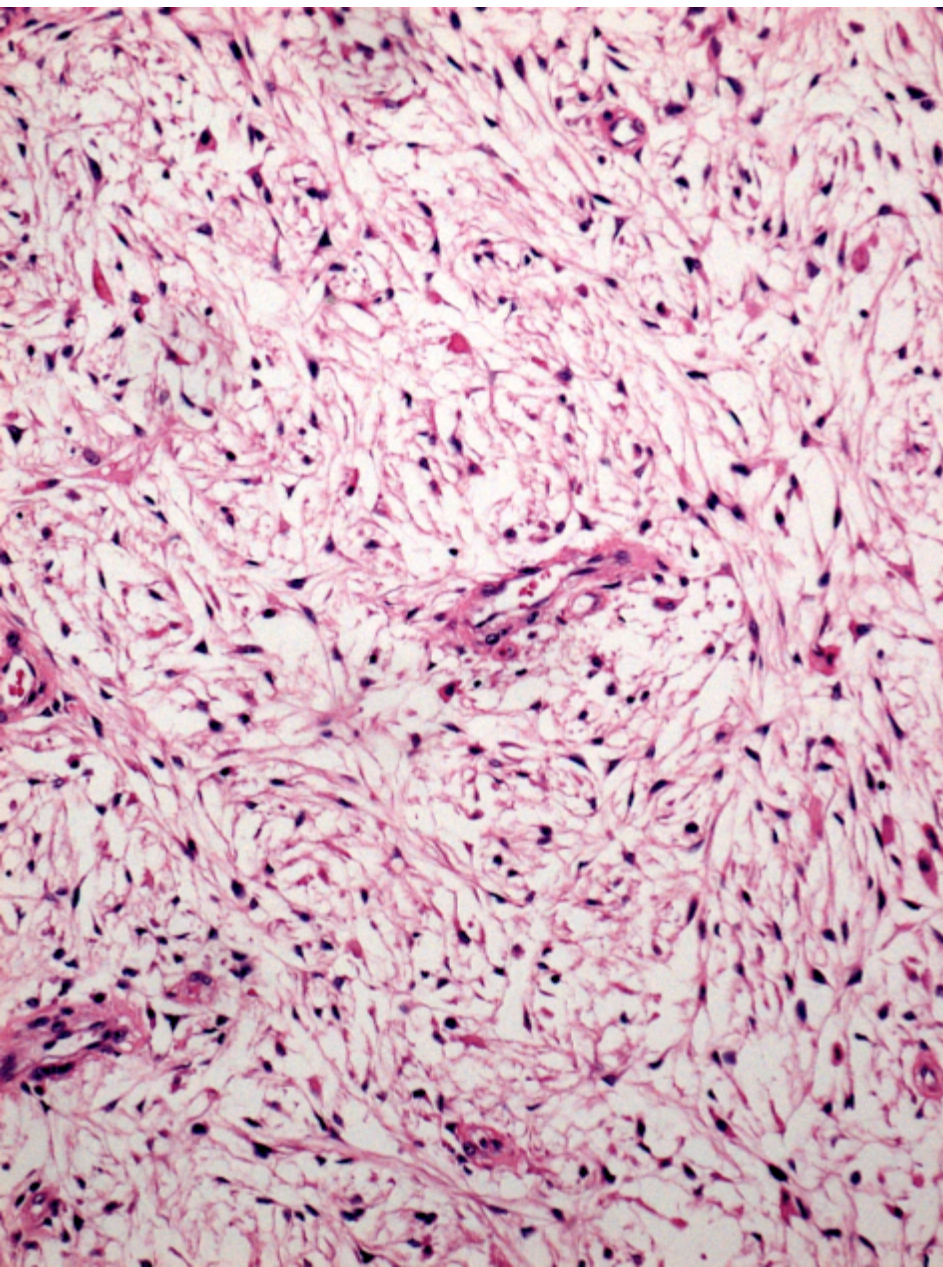


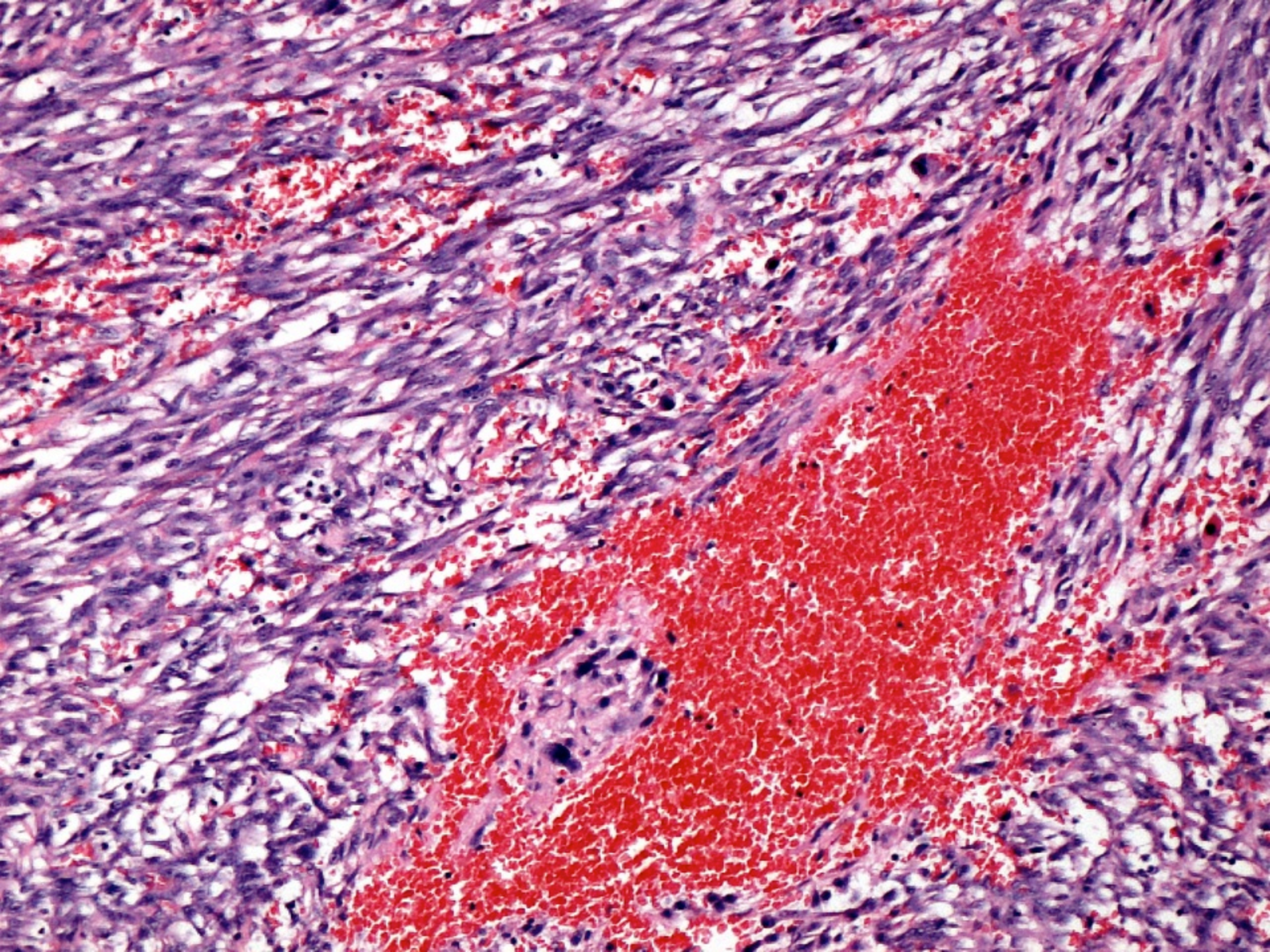












Pleomorphic Dermal Sarcoma

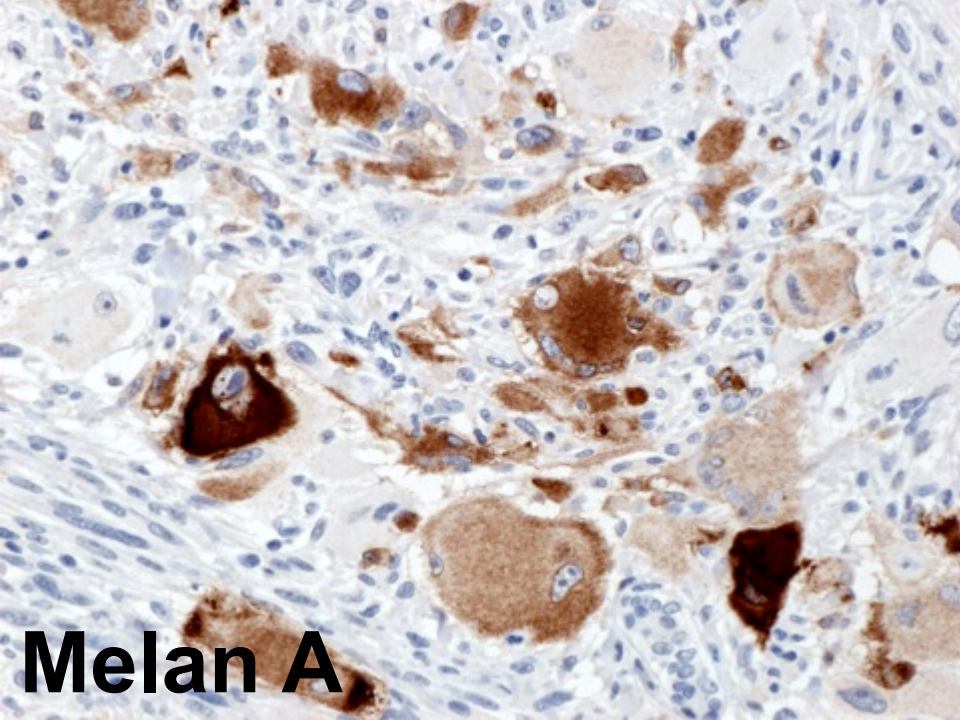
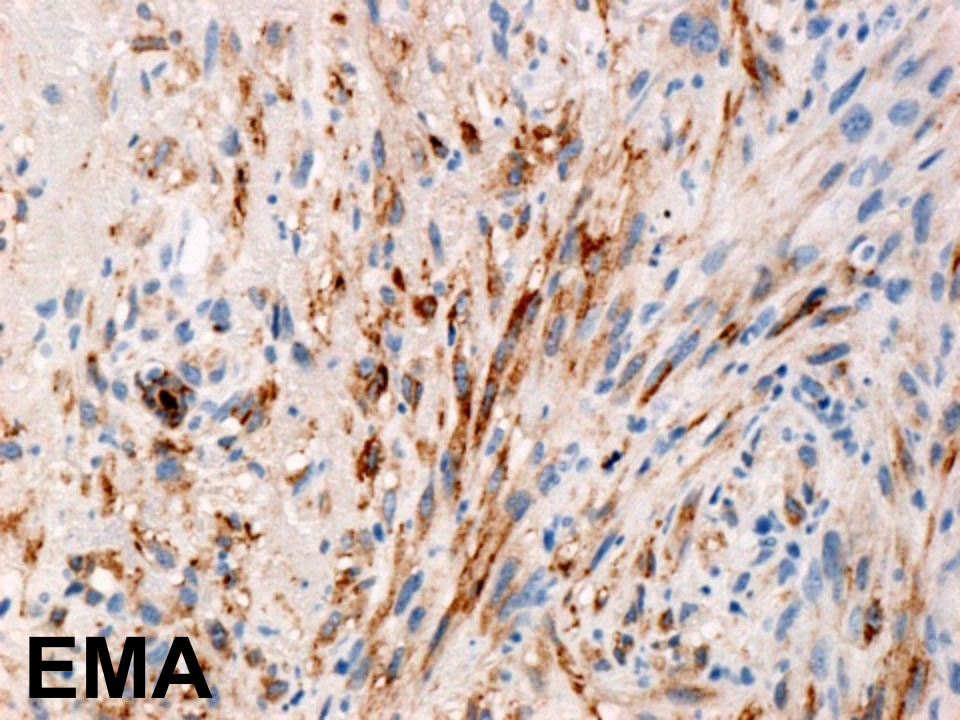
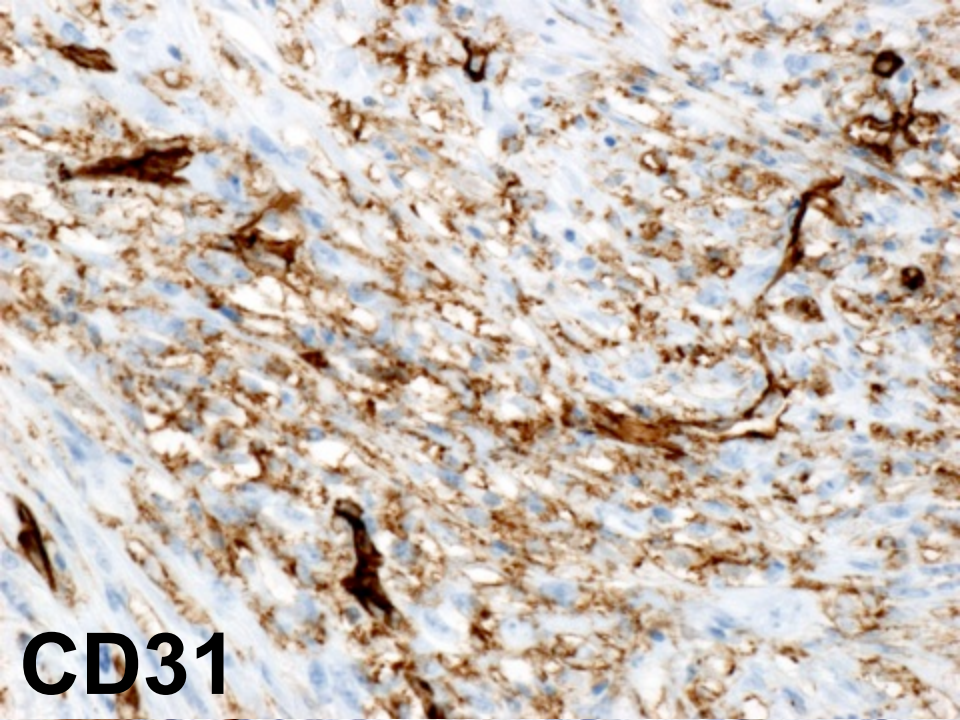
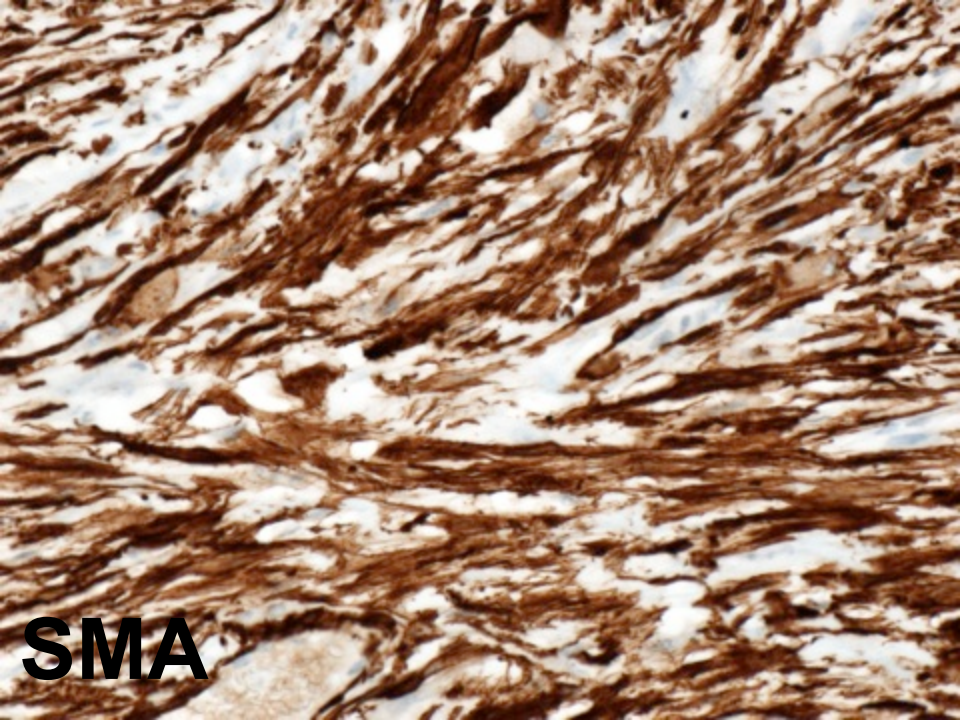
-Immunohistochemistry-

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Negative:

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- multiple CK, especially HMW-CK**
- Desmin**
- CD34**



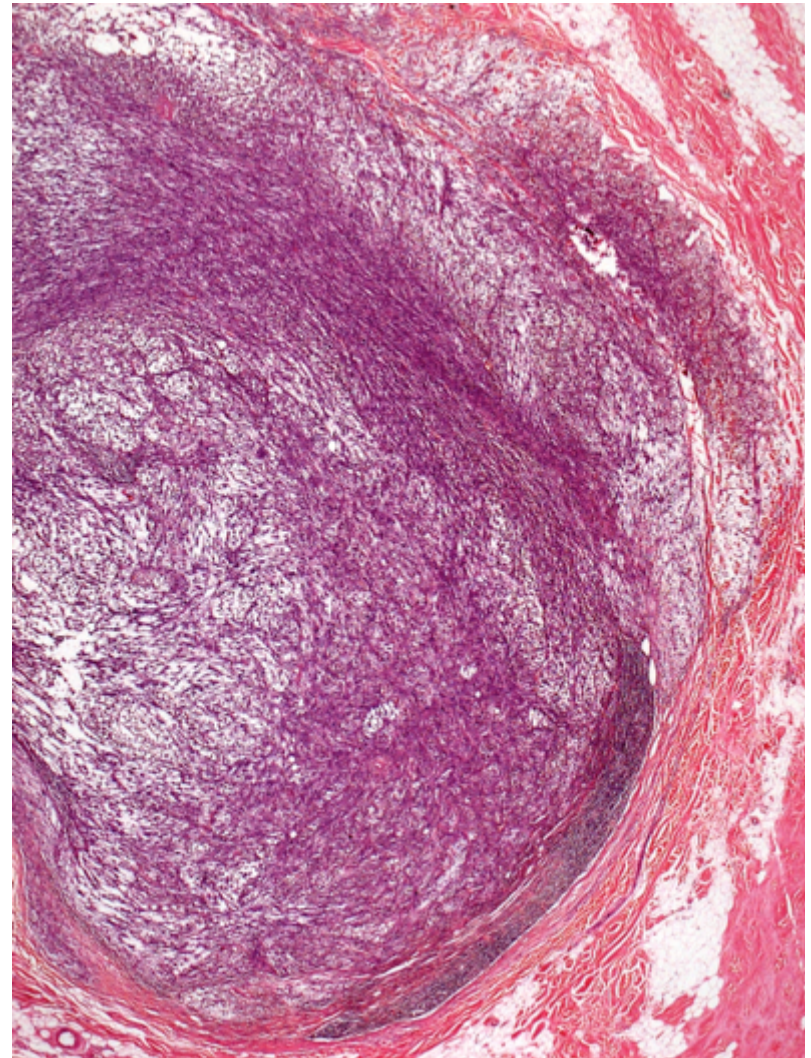
Pleomorphic Dermal Sarcoma

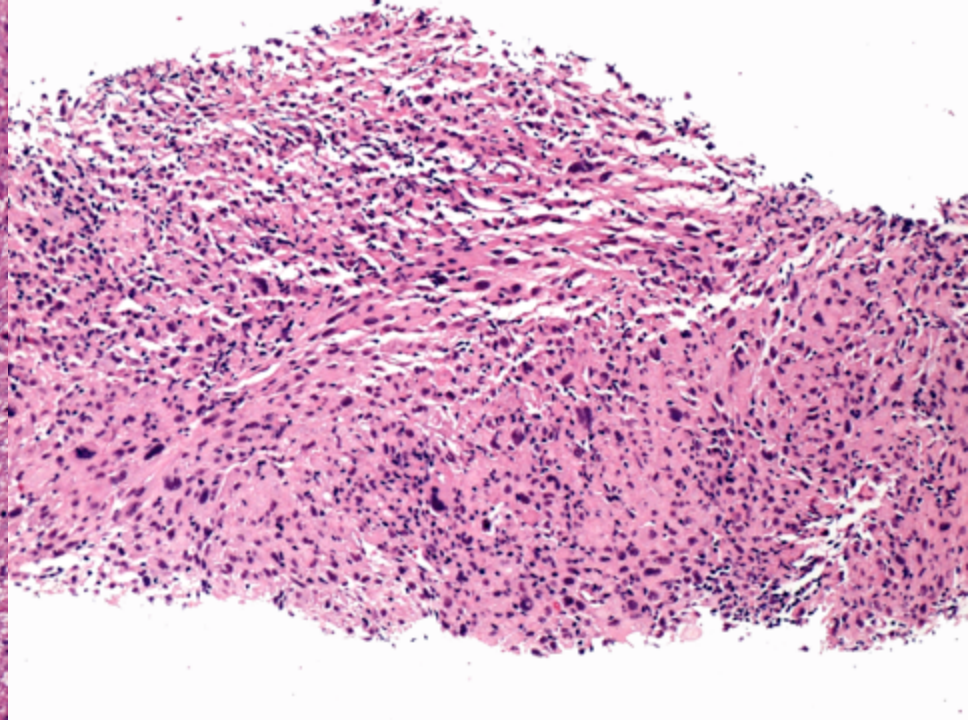
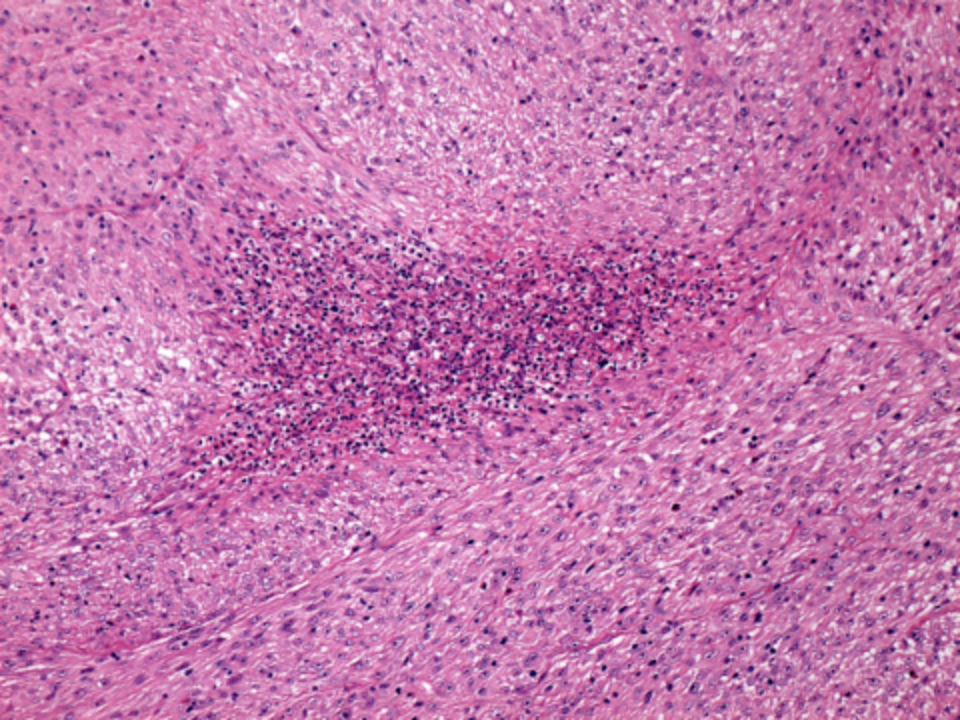
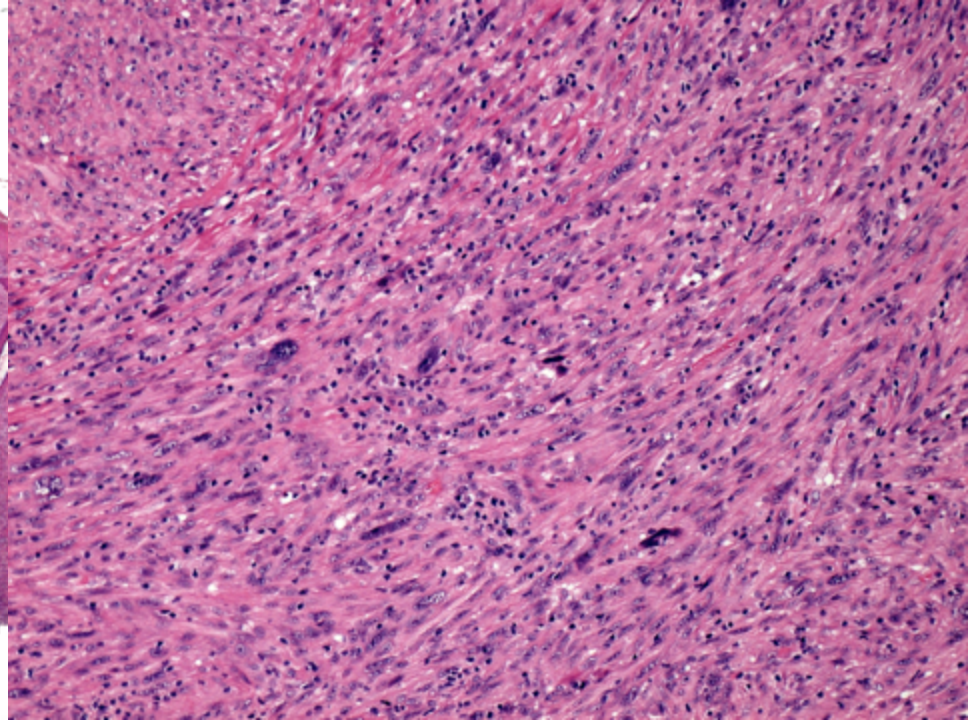
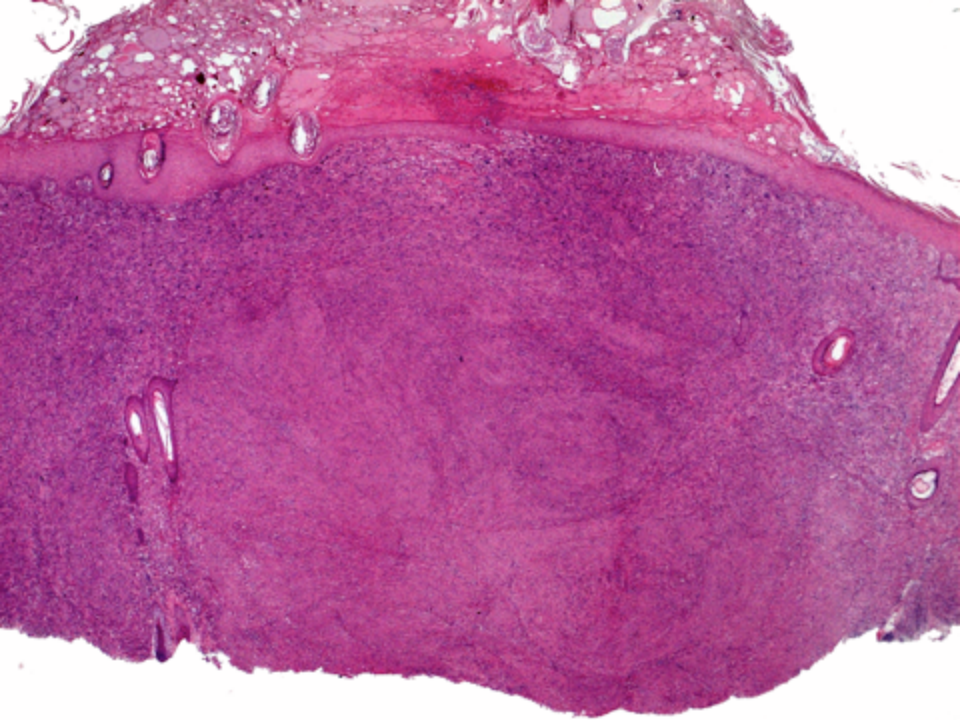
-Prognosis-

**Risk for local recurrence
(30%)**

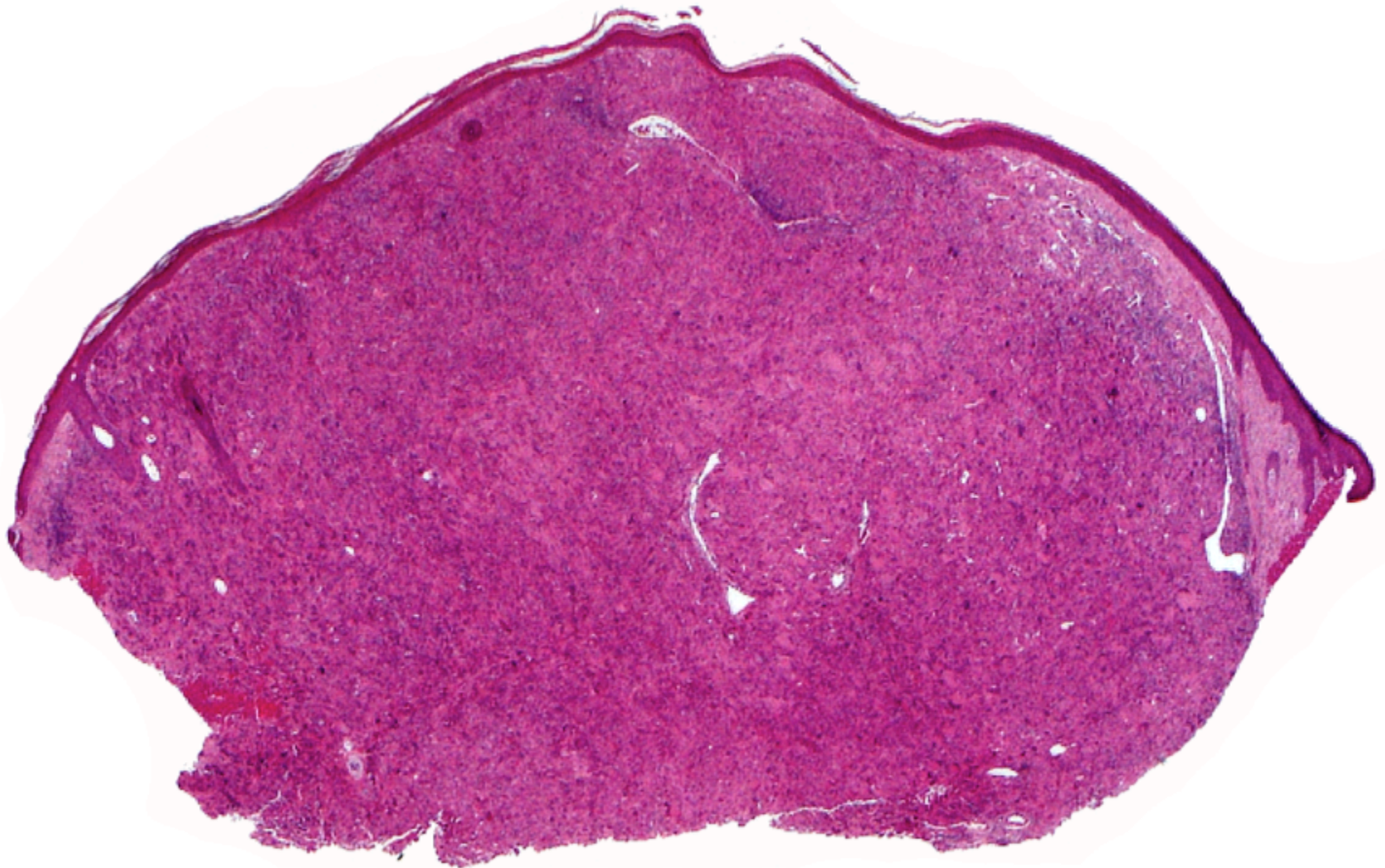
Rare metastasis (10%)

Rare mortality





Atypical Fibroxanthoma / PDS



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