Correlations, morphologic and genomic

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Depts. of Pathology and Dermatology

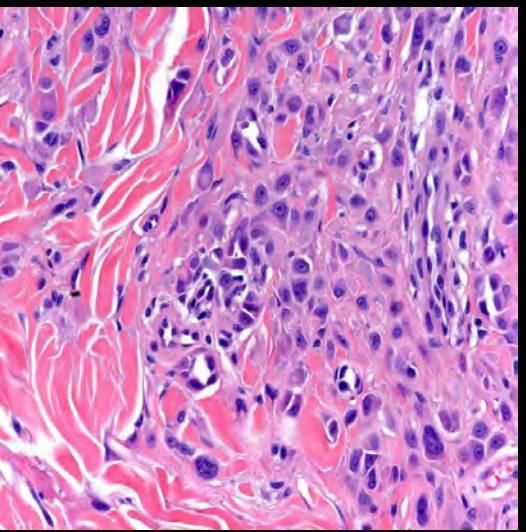
University of California, San Francisco

K=2
K=3
K=4
Shiba Inu
Chow Chow
Akita
Alaskan Malamute
Basenji
Chinese Shar-Pei
Siberian Husky
Afghan Hound
Saluki
Tibetan Terrier
Lhasa Apso
Samoyed
Pekingese
Shih Tzu
Irish Wolfhound
Saint Bernard
Greyhound
Belgain Sheepdog
Belgian Tervuren
Borzoi
Collie
Shetland Sheepdog
Pug
Komondor
Whippet
Standard Poodle
Bichon Frise
Keeshond
Manchester Terrier
Norwegian Elkhound
Kuvasz
Great Dane
Welsh Springer Spaniel
Doberman Pinscher
Standard Schnauzer
Italian Greyhound
Old English Sheepdog
American Water Spaniel
Miniature Schnauzer
Australian Terrier
English Cocker Spaniel
Irish Setter
West Highland White Terrier
Pointer
Basset Hound
Cavalier King Charles Spaniel
Giant Schnauzer
Pharaoh Hound
Golden Retriever
Beagle
Bloodhound
Airedale Terrier
American Cocker Spaniel
American Hairless Terrier
Chesapeake Bay Retriever
Cairn Terrier
Portuguese Water Dog
German Shorthaired Pointer
Border Collie
Bedlington Terrier
Clumber Spaniel
Ibizan Hound
Rhodesian Ridgeback
Dachshund
Australian Shepherd
Chihuahua
Kerry Blue Terrier
Schipperke
Irish Terrier
Flat Coated Retriever
Soft Coated Wheaten Terrier
Pomeranian
Labrador Retriever
Presa Canario
Rottweiler
Bullmastiff
Newfoundland
German Shepherd Dog
French Bulldog
Miniature Bull Terrier
Bulldog
Boxer
Mastiff
Bernese Mountain Dog
Greater Swiss Mountain Dog
Asian/Ancient
Herding
Hunting
Mastiff

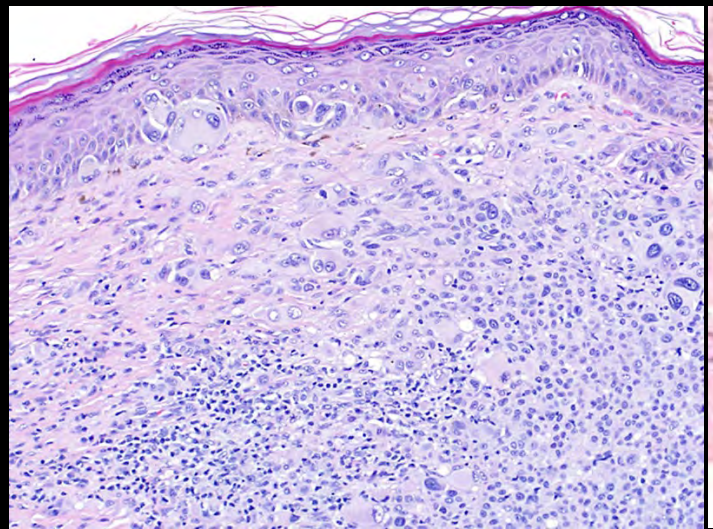
Great expectations!

- Testing will clearly show benign vs. malignant
- Distinctive histomorphology-molecular correlations

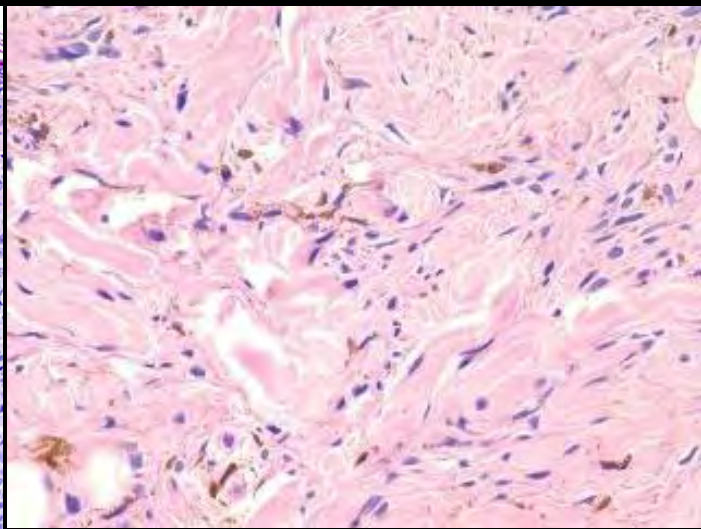
HRAS
Spitz



BAP1oma



GNAQ/
GNA11
blue



The 2018 World Health Organization Classification of Cutaneous, Mucosal, and Uveal Melanoma

Detailed Analysis of 9 Distinct Subtypes Defined by Their Evolutionary Pathway

David E. Elder, MB ChB, FRCPA; Boris C. Bastian, MD, PhD; Ian A. Cree, MB ChB, PhD, FRCPath; Daniela Massi, MD, PhD; Richard A. Scolyer, MD, FRCPA, FRCPath

TABLE 2 | The WHO 2018 classification of melanoma according to pathways.

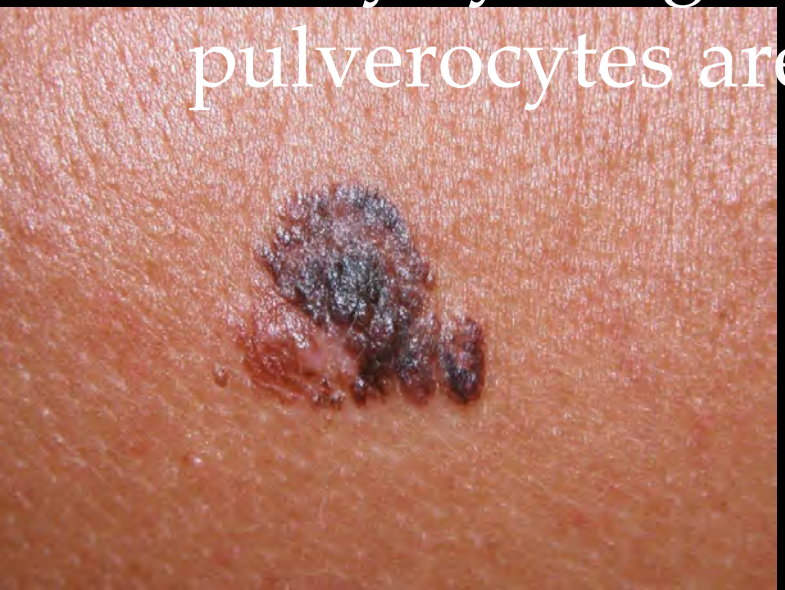
Relationship with sun exposure/sun damage	Pathway n.	Subtype	Genetic hallmarks
Melanomas arising in sun-exposed skin	1	*Low-CSD melanoma/superficial spreading melanoma*	High frequency of *BRAF* p.V600 mutations (7–9)
	2	*High-CSD melanoma (including lentigo maligna melanoma and high-CSD nodular melanoma)*	Predominating mutually exclusive *NF1*, *NRAS*, other *BRAF* (non-p.V600E), and perhaps *KIT* mutations (7–9)
	3	*Desmoplastic melanoma*	Recurrent inactivating *NF1* mutations, *NFKBIE* promoter mutations, and several different activating mutations in the MAPK pathway (*e.g.*: *MAP2K1*) (9–11)
Melanomas arising at sun-shielded sites or without known etiological associations with UV radiation exposure	4	*Malignant Spitz tumor (Spitz melanoma)*	Mutations in *HRAS* and kinase fusions in *ROS1*, *NTRK1*, *NTRK3*, *ALK*, *BRAF*, *MET*, and *RET*; *CDKN2A* homozygous deletion, *TERT* promoter mutations and *MAP3K8* fusions/truncating mutations only in aggressive or lethal variants (7, 12–15)
	5	*Acral melanoma (including nodular melanoma in acral skin)*	Multiple amplifications of *CCND1*, *KIT*, and *TERT*; mutations of *BRAF*, *NRAS*, and *KIT*; kinase fusions of *ALK* or *RET* in a few cases (7, 8)
	6	*Mucosal melanoma*	Numerous copy number and structural variations; uncommonly, *KIT* and *NRAS* mutations (16)
	7	*Melanoma arising in congenital nevus*	In large to giant congenital nevi: *NRAS* mutation; in small to medium-sized congenital nevi, *BRAF* mutations (17, 18)
	8	*Melanoma arising in blue nevus*	Initiating mutations in the Gαq signalling pathway (*GNAQ*, *GNA11*, *CYSLTR2*, *PLCB4*); monosomy 3 (associated with loss of *BAP1*) and chromosome 8q gains in aggressive cases; additional secondary copy number aberrations in *SF3B1* and *EIF1AX* (7, 19)
	9	*Uveal melanoma*	Mutually exclusive mutations in the Gαq pathway (*GNAQ*, *GNA11*, *PLCB4*, *CYSLTR2*); *BAP1*, *SF3B1*, and *EIF1AX* mutations during progression (16)

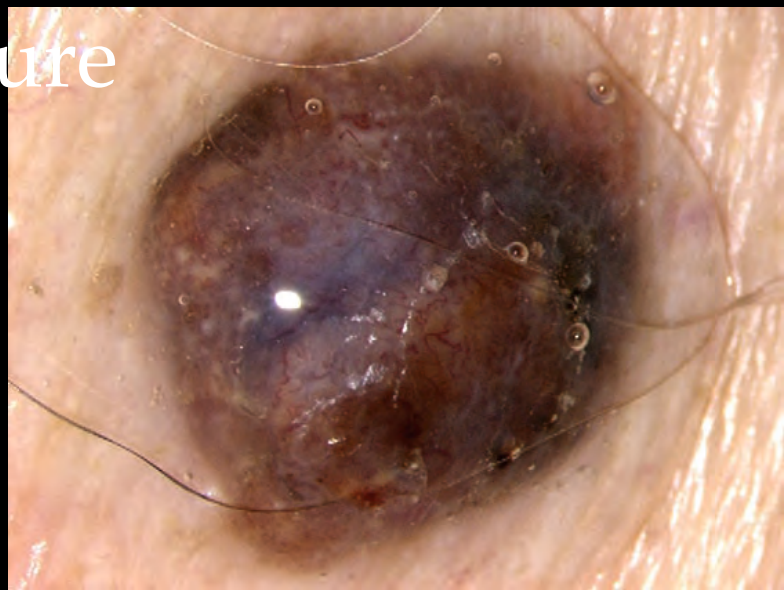
Within each molecular lineage

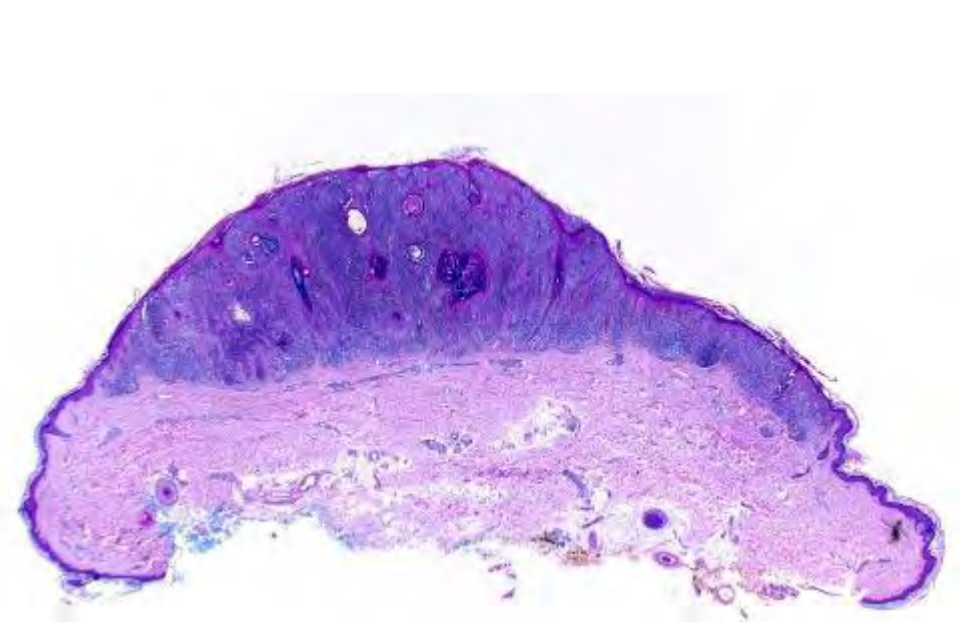
- Benign nevus, one pathogenic mutation
- Melanocytoma (intermediate grade lesion), usually two genomic events, limited copy number changes, spread to local nodes only
- Melanoma, ? 2 to 3 or more pathogenic mutations, spread to and beyond nodes, or hematogenous spread
- 1, 2 and 3 genomic events is the current paradigm, but multiomics is largely un-explored

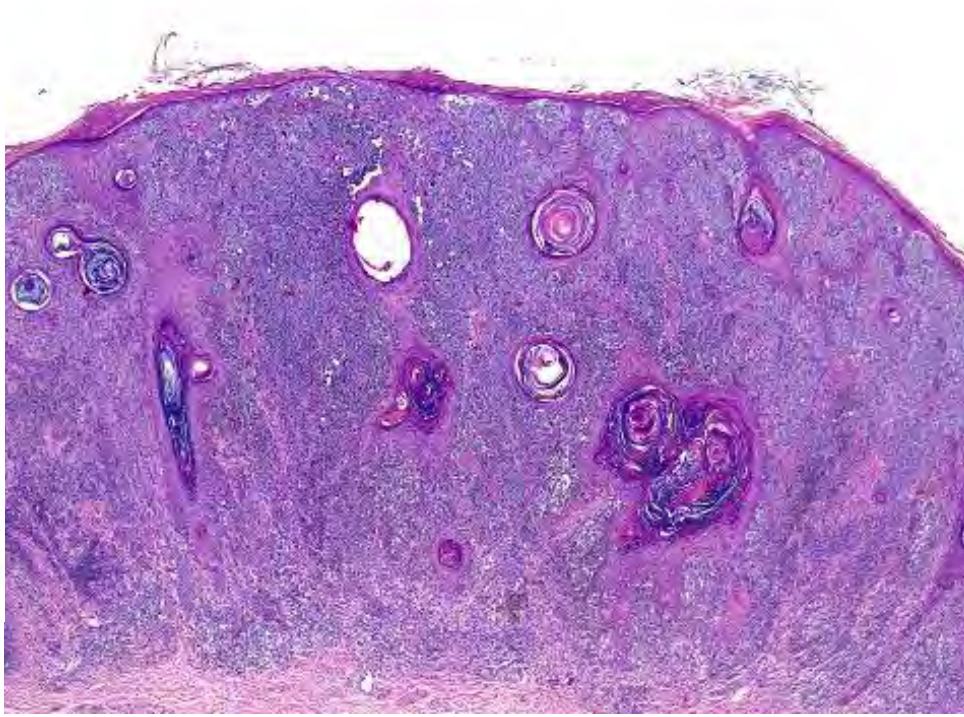
Pathway 1- Low CSD melanoma

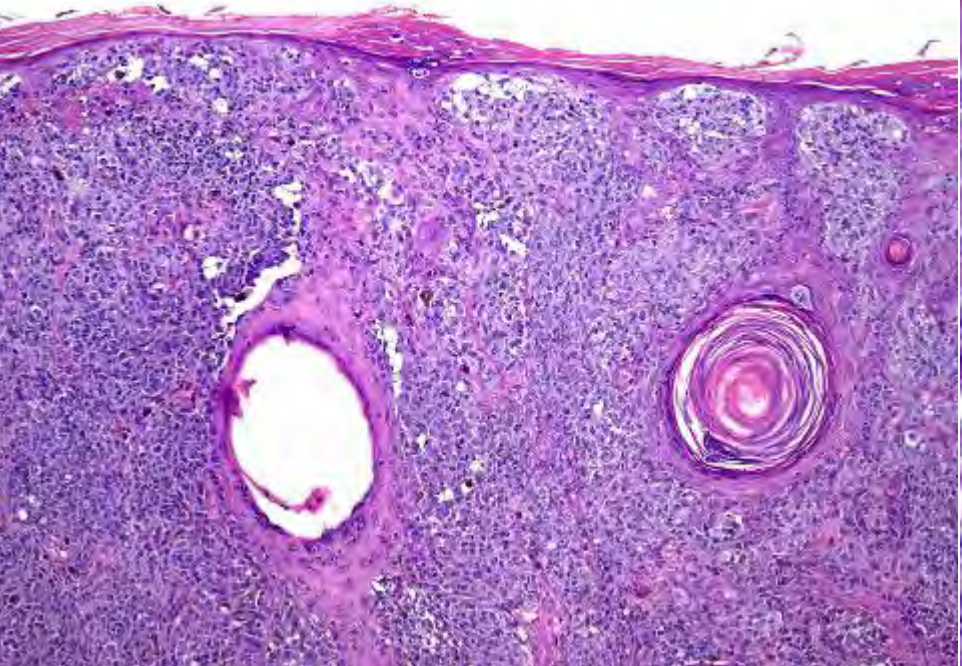
- Mostly BRAF V600E
- Mostly 40-60 year olds
- Mostly superficial spreading/nodular melanoma in Clark's classification
- Many cytologic appearances, but pulverocytes are a signature

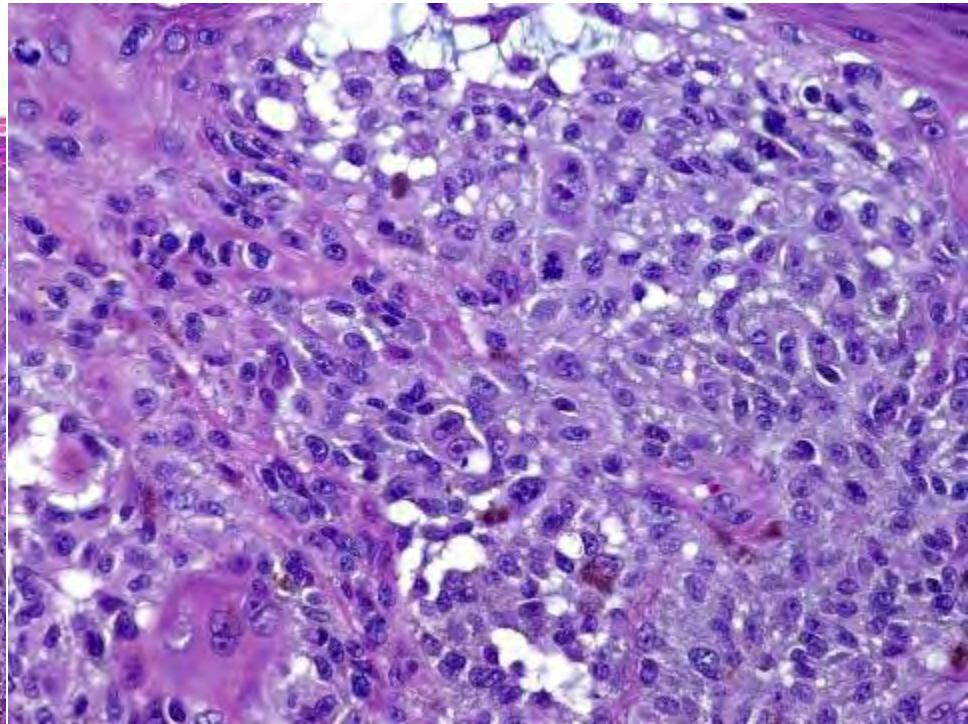


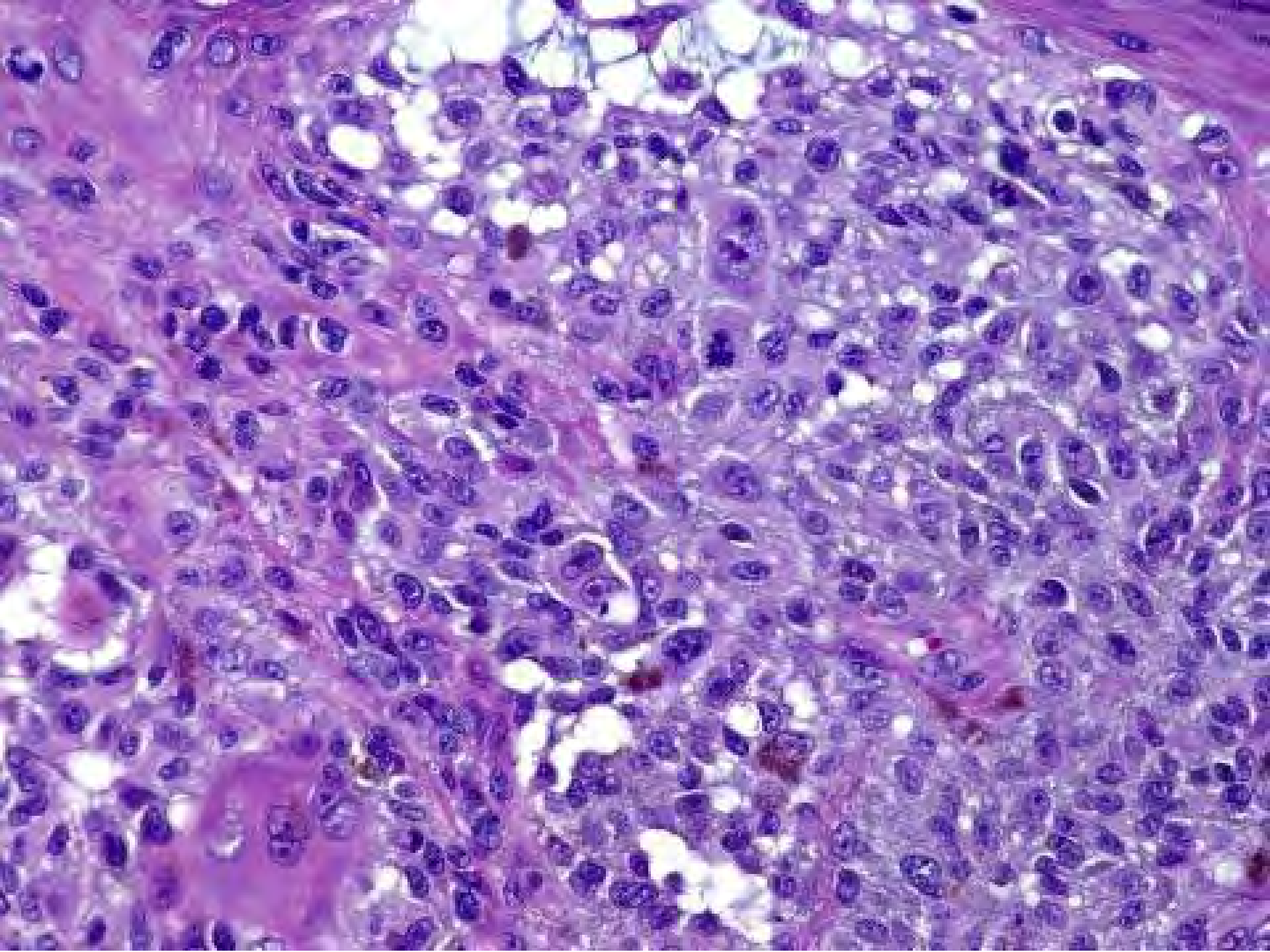


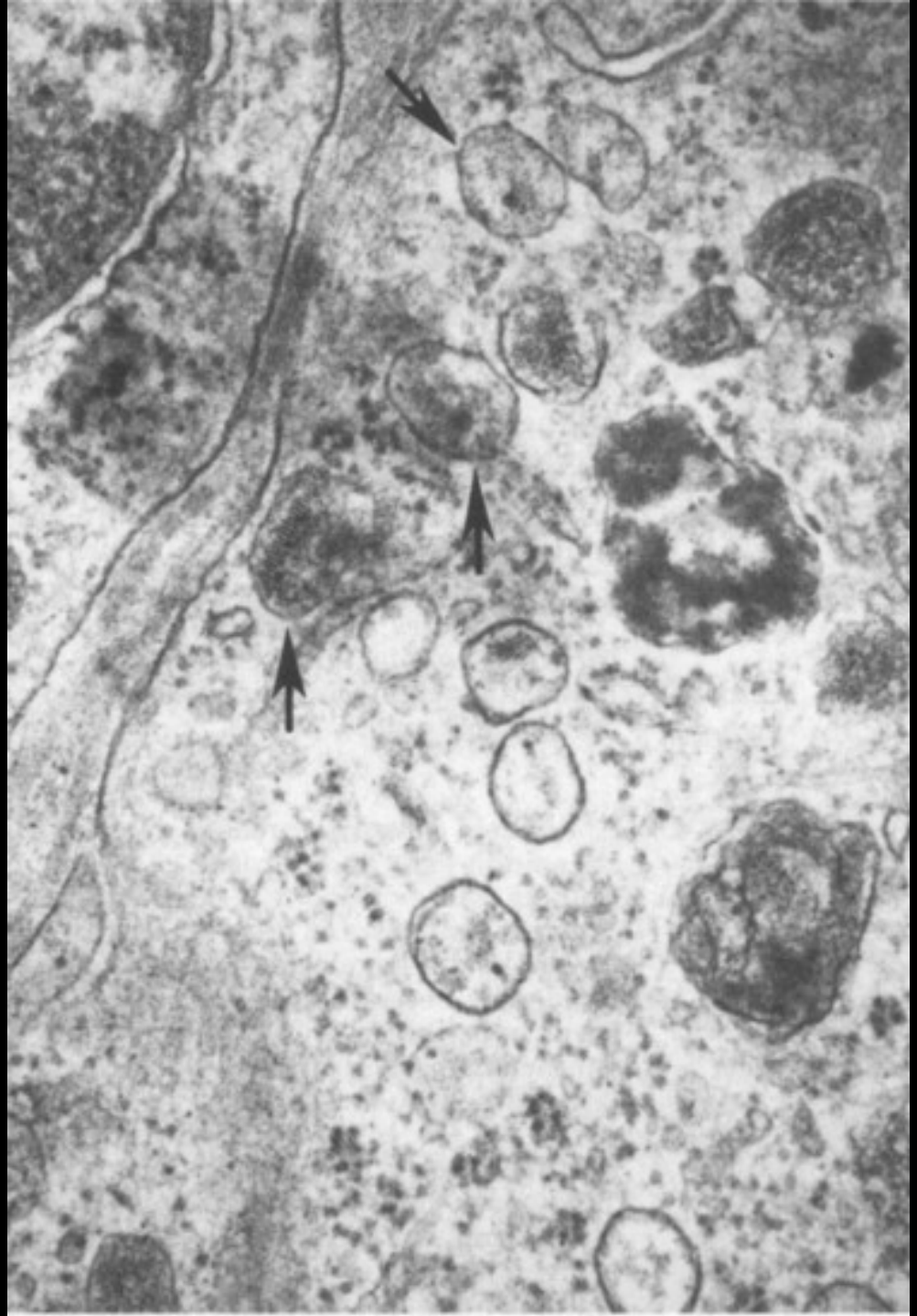


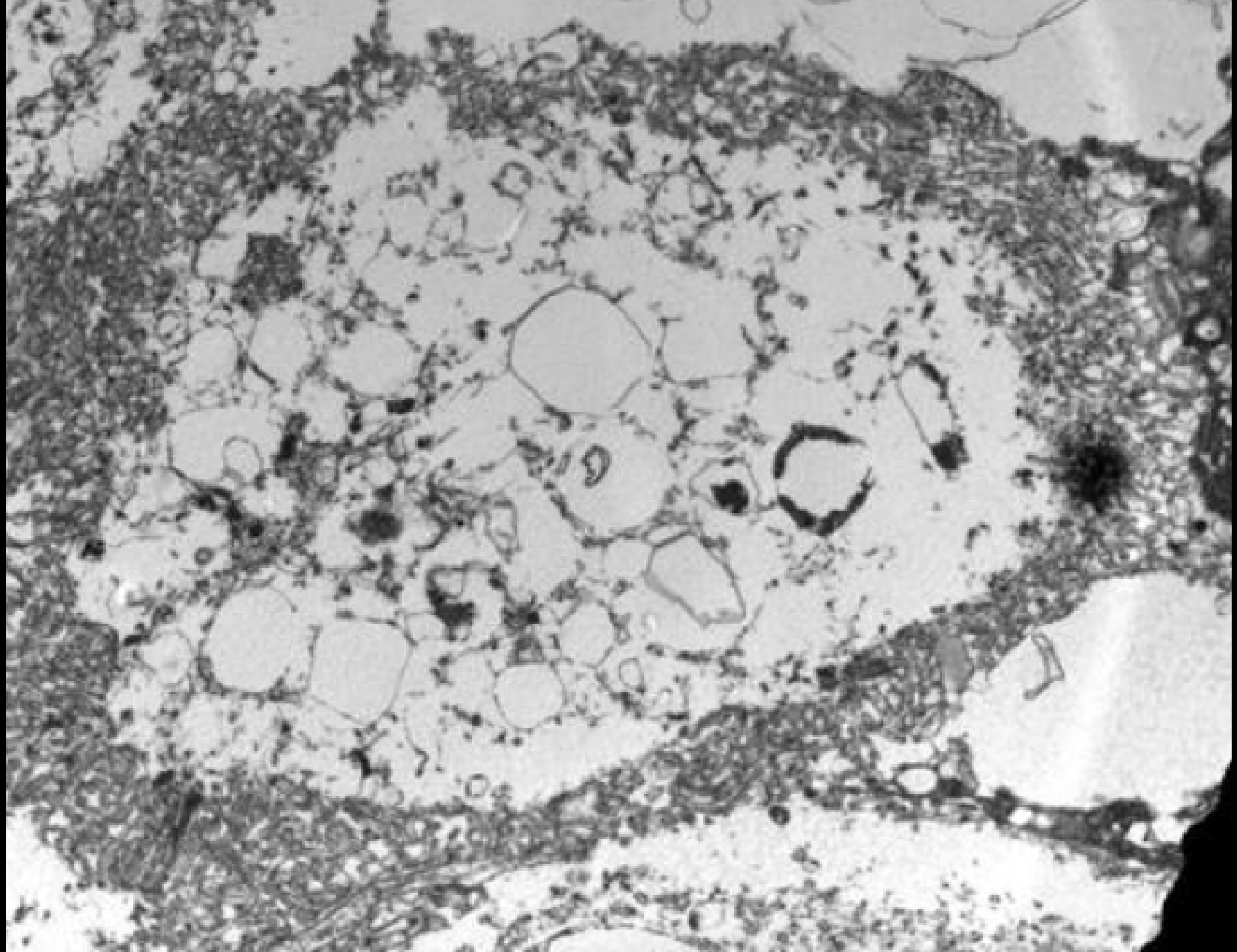






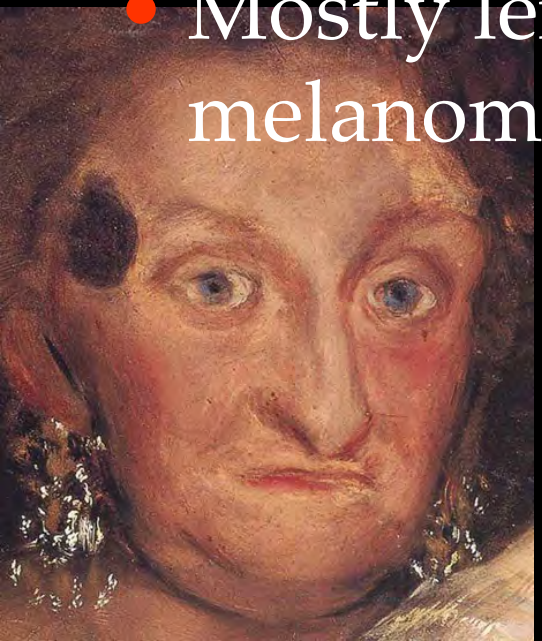


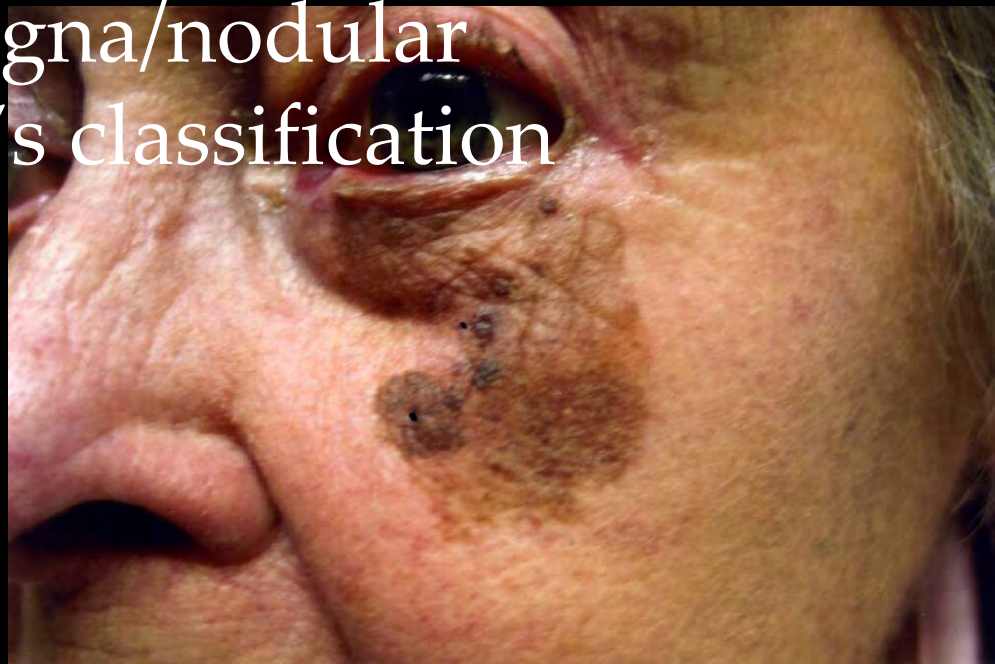


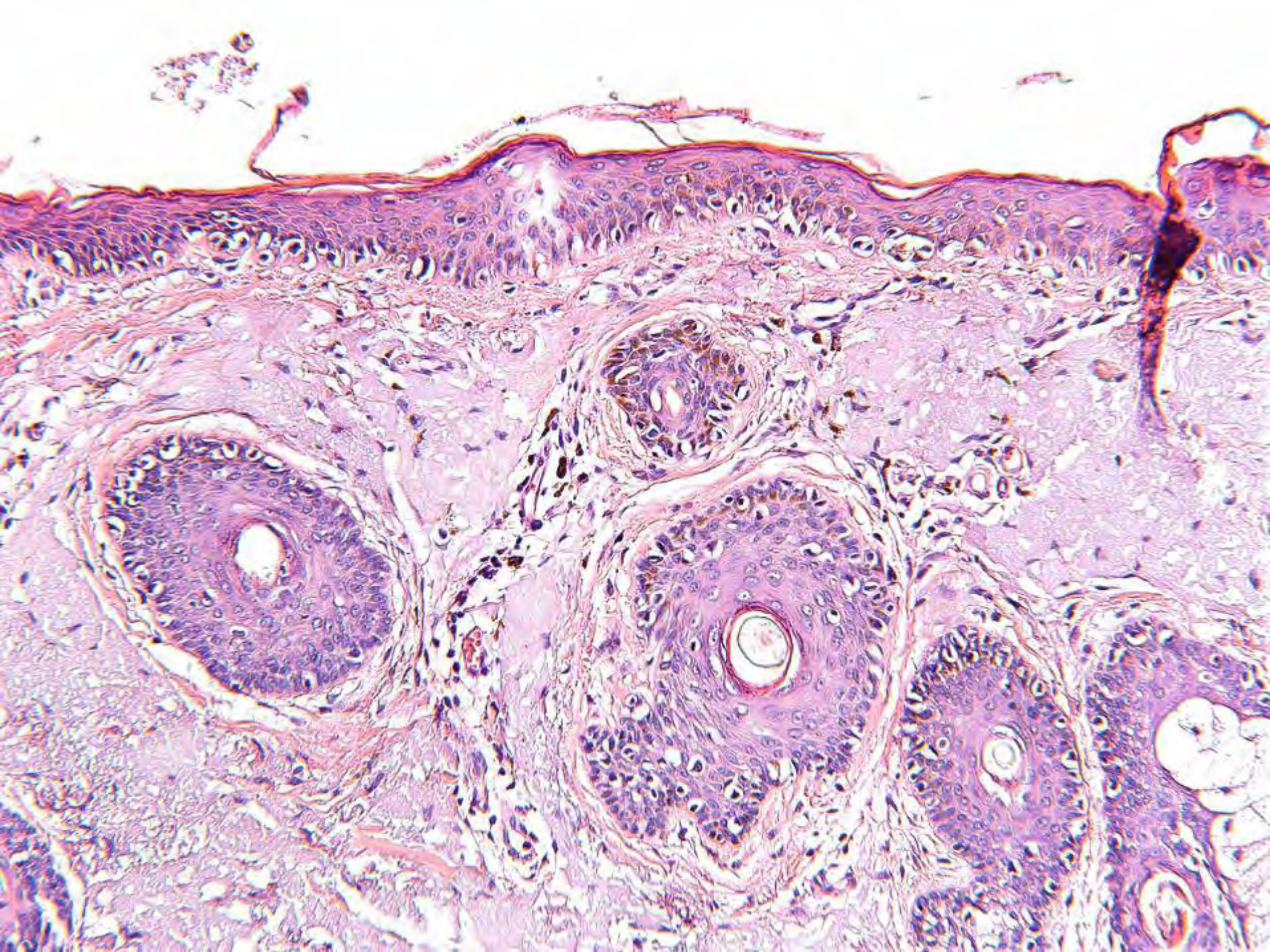


Pathway 2- High CSD melanoma

- Mostly NRAS, NF1, BRAF V600 non-E
- Mostly >60 year olds (younger w. altitude, tanning beds, equatorial, DNA repair mutations)
- Mostly lentigo maligna/nodular melanoma in Clark's classification

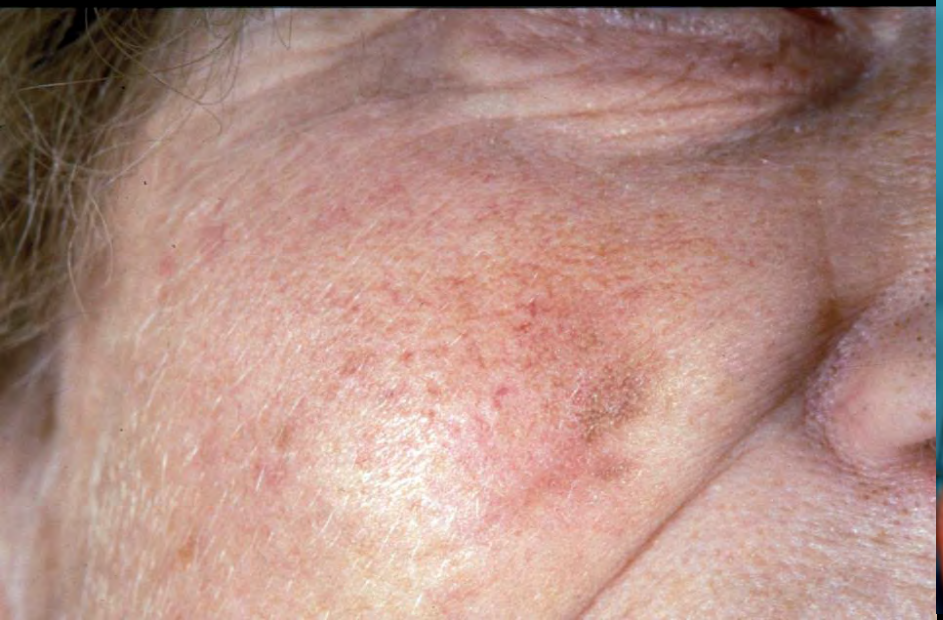


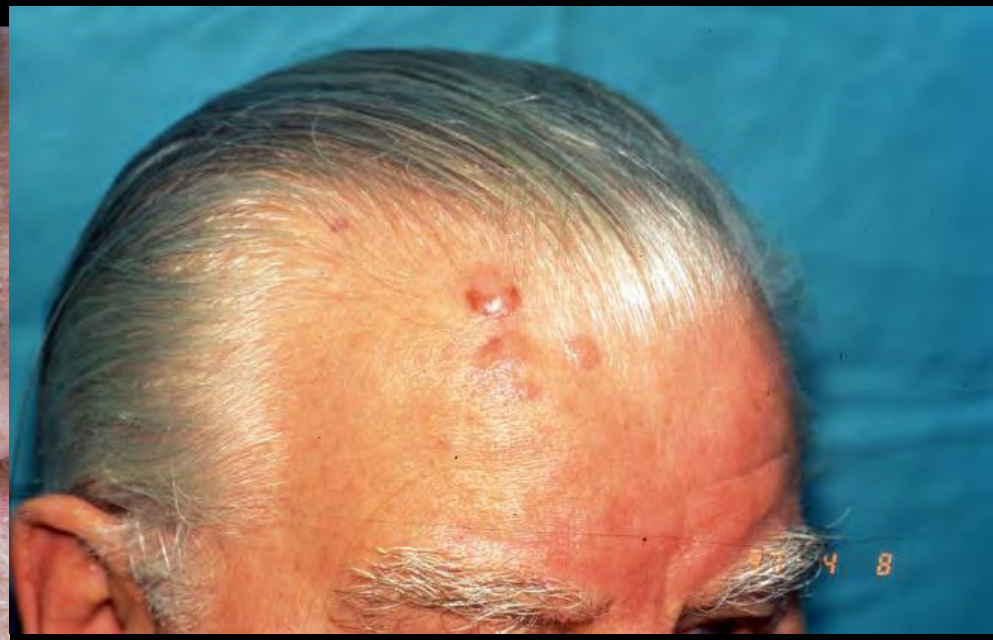


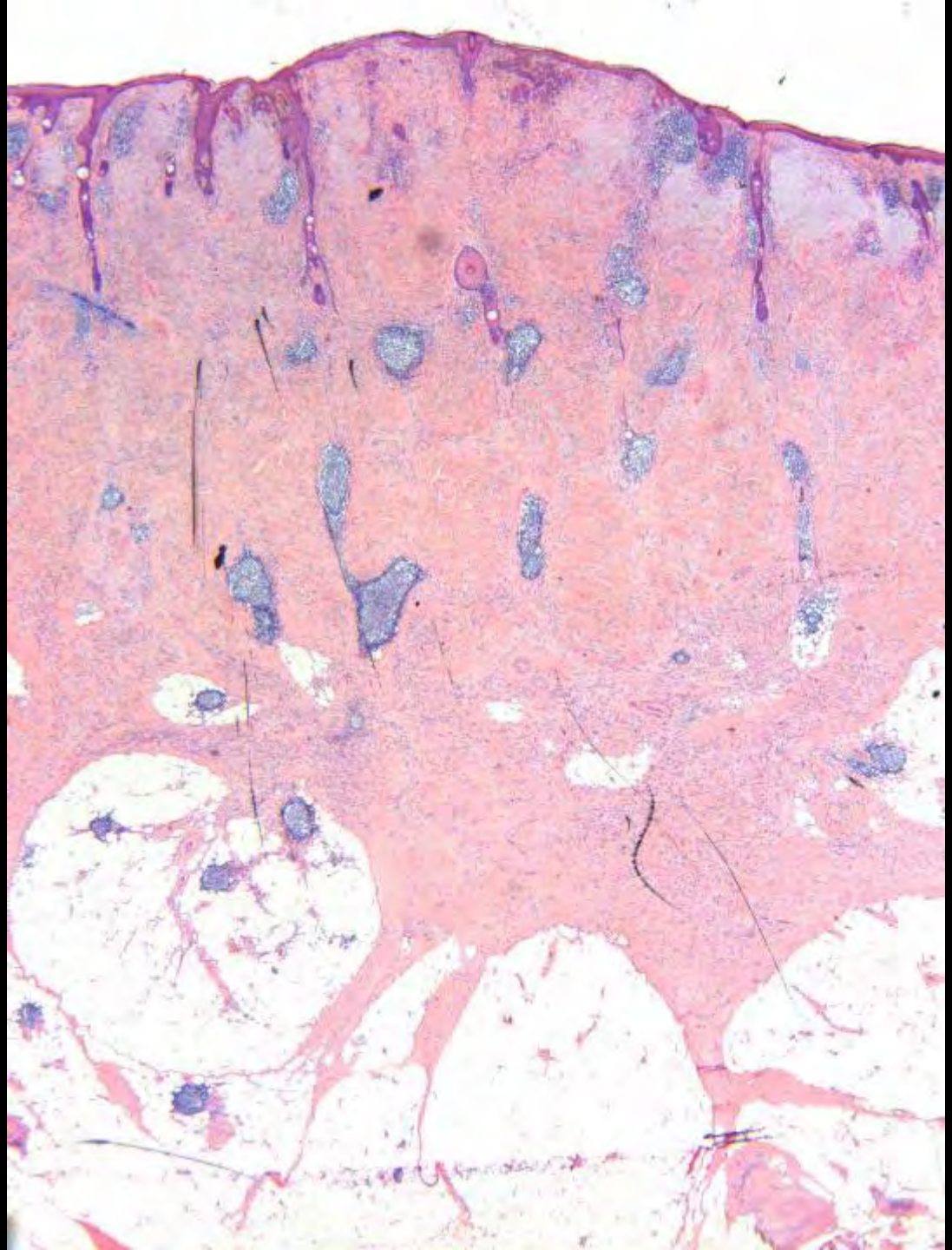


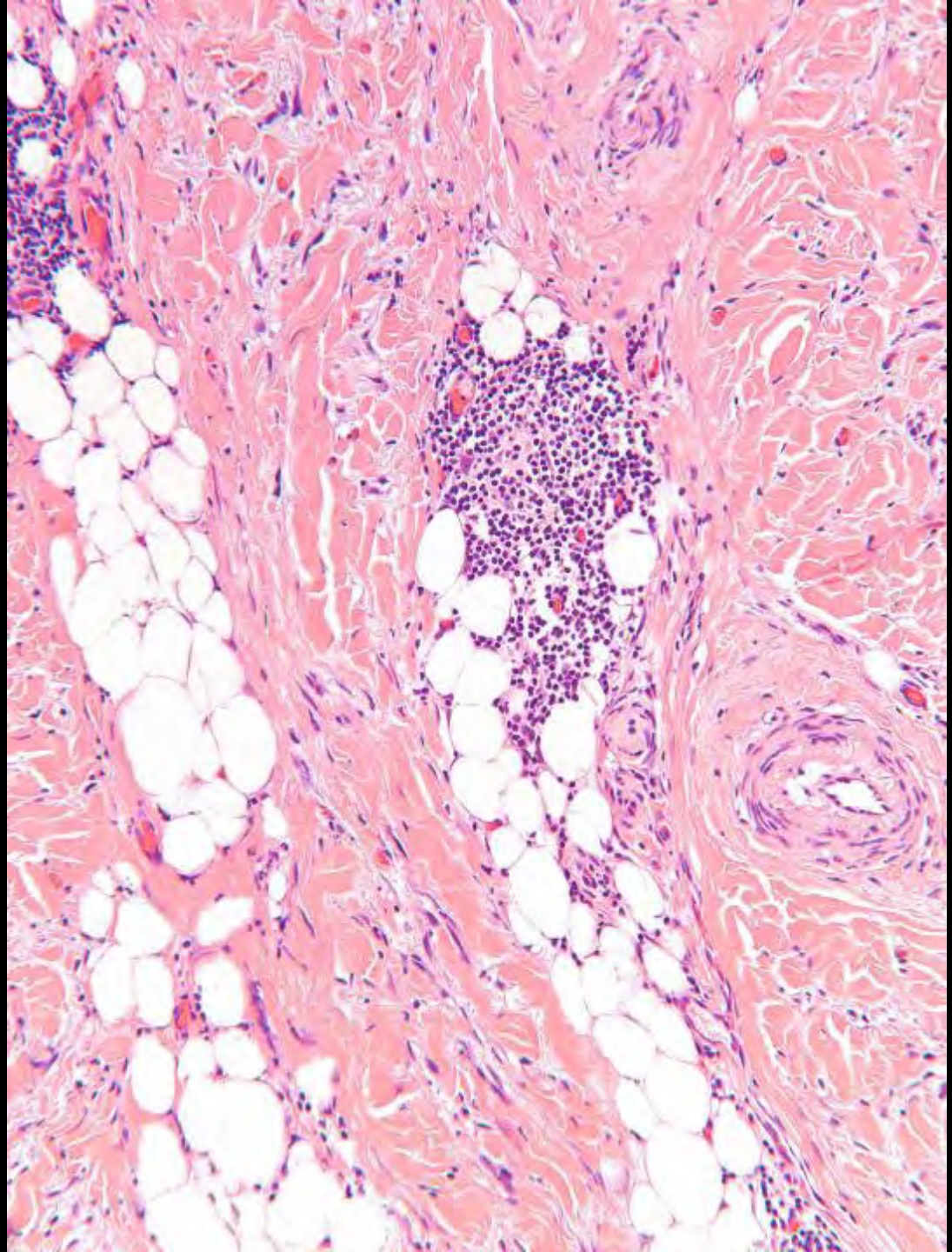
Pathway 3- Desmoplastic melanoma

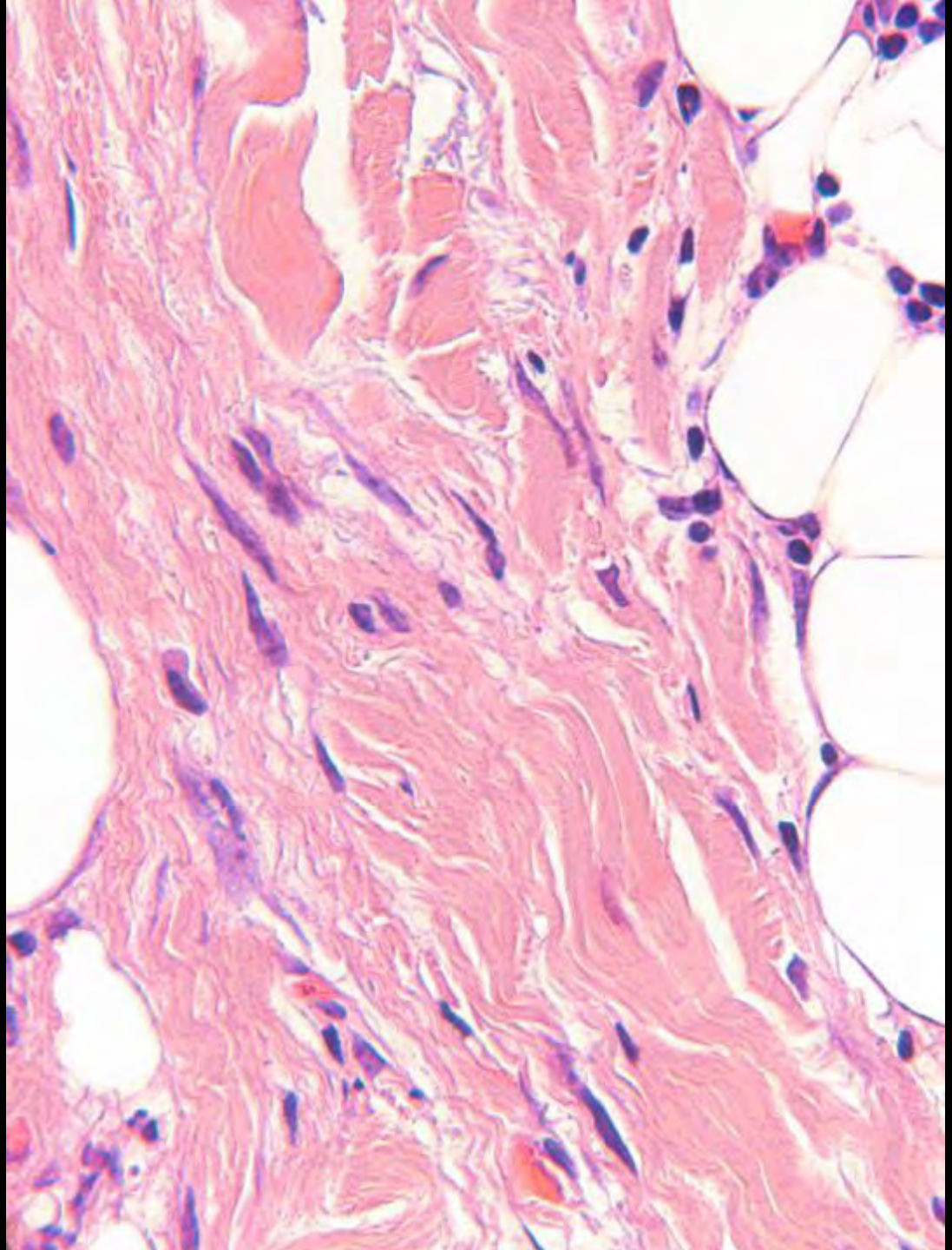
- Mostly NF1, NFkBIE promoter
- High mutational burden, low number of chromosomal copy number changes
- Rarely Melan-A or HMB45 positive

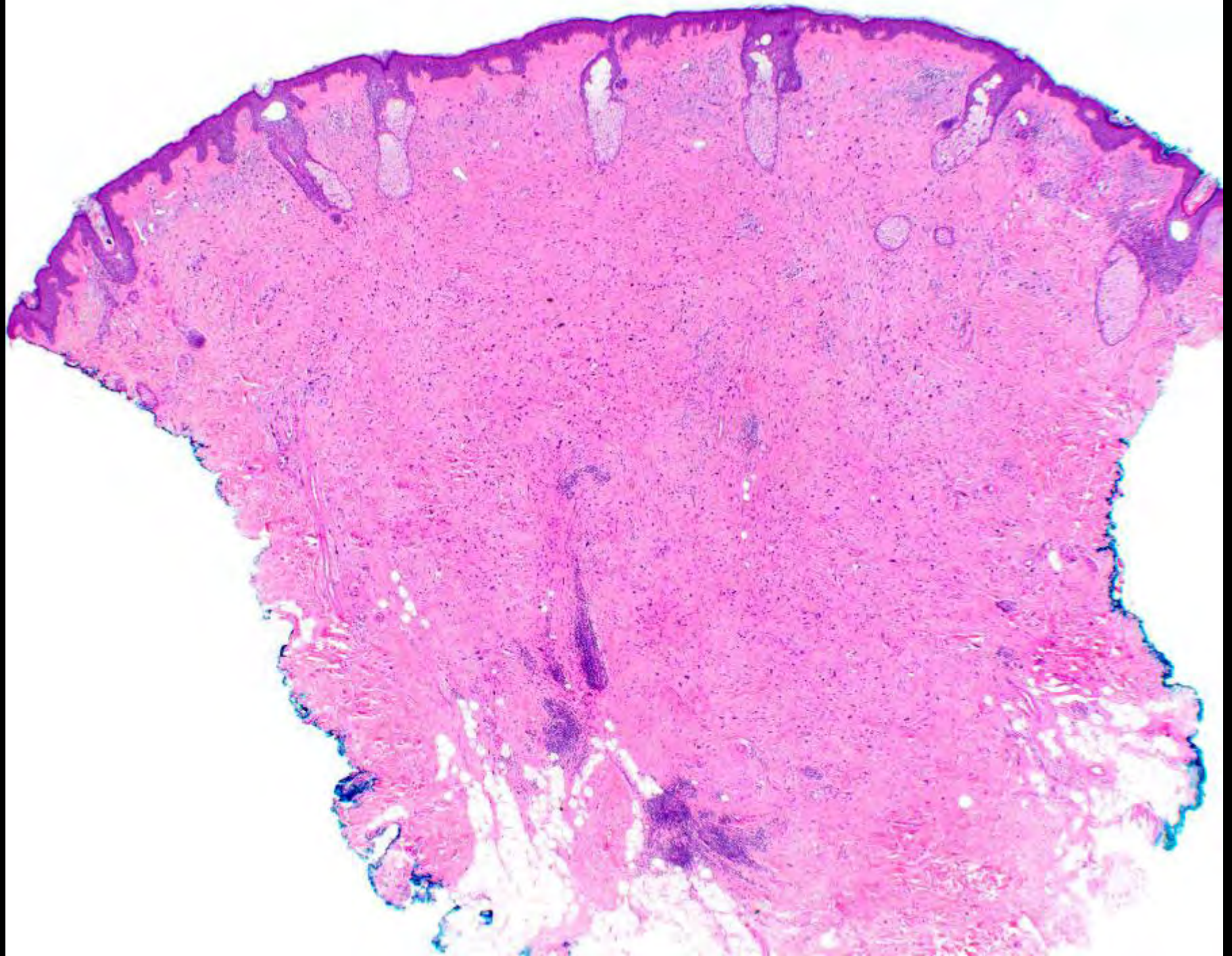


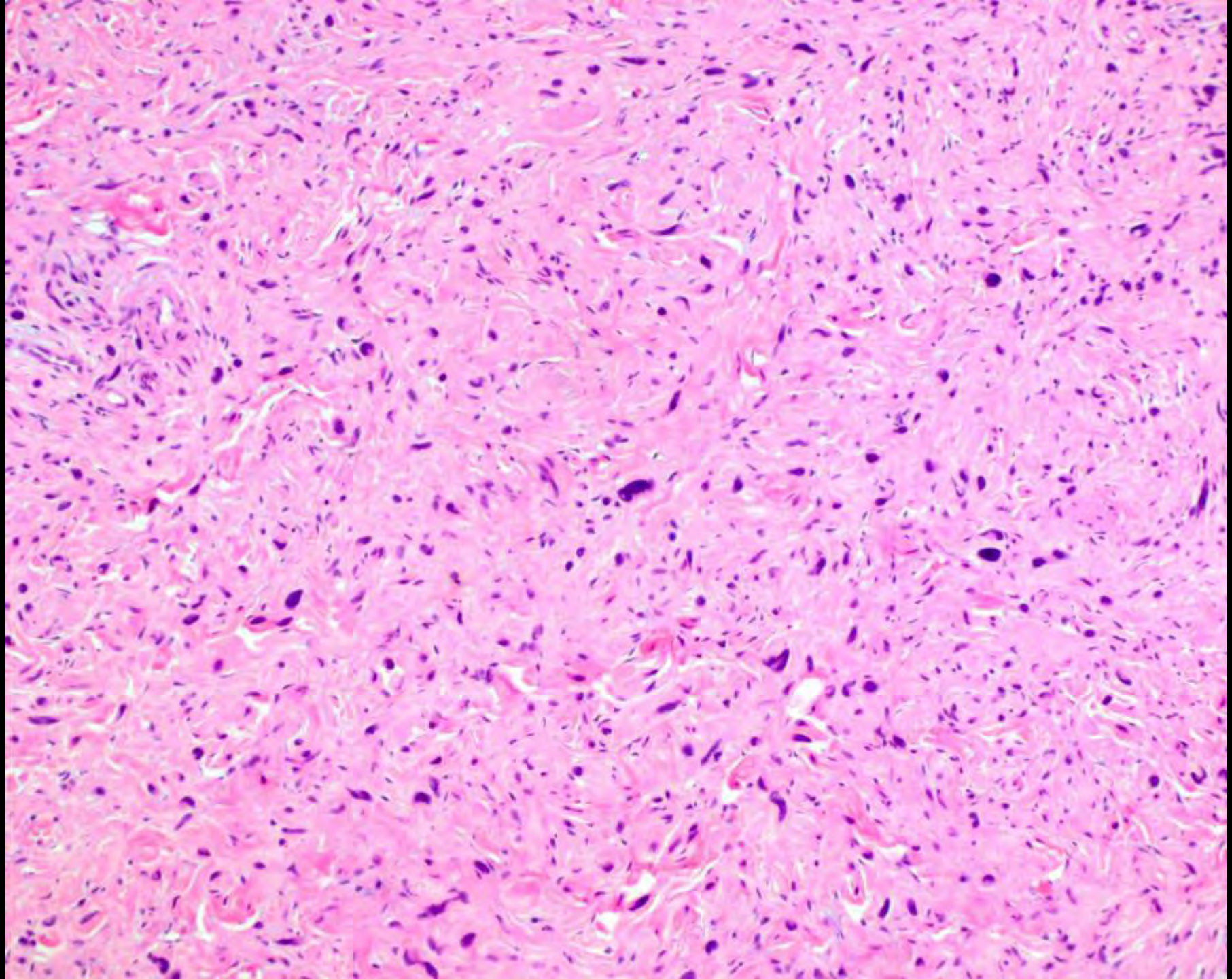


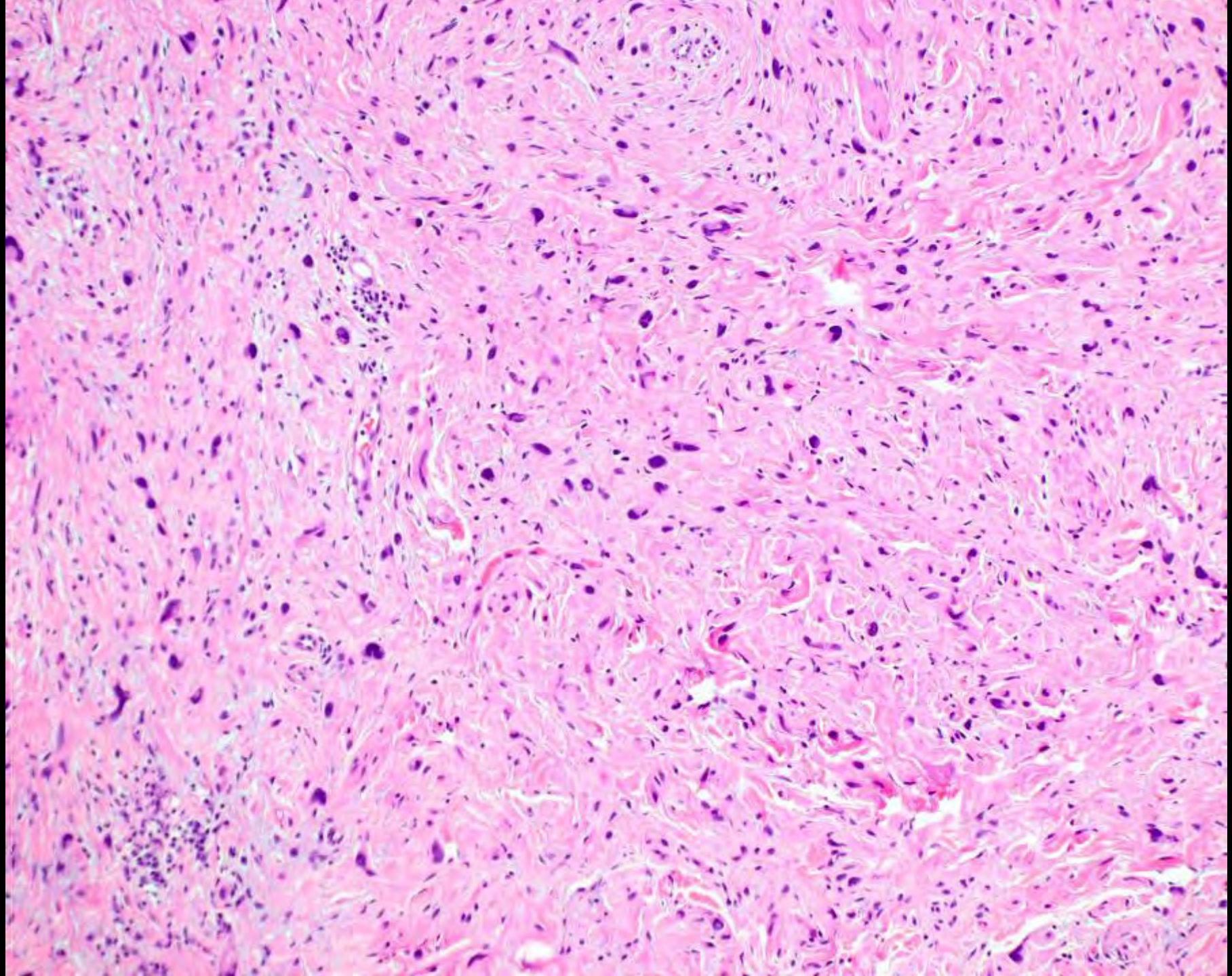


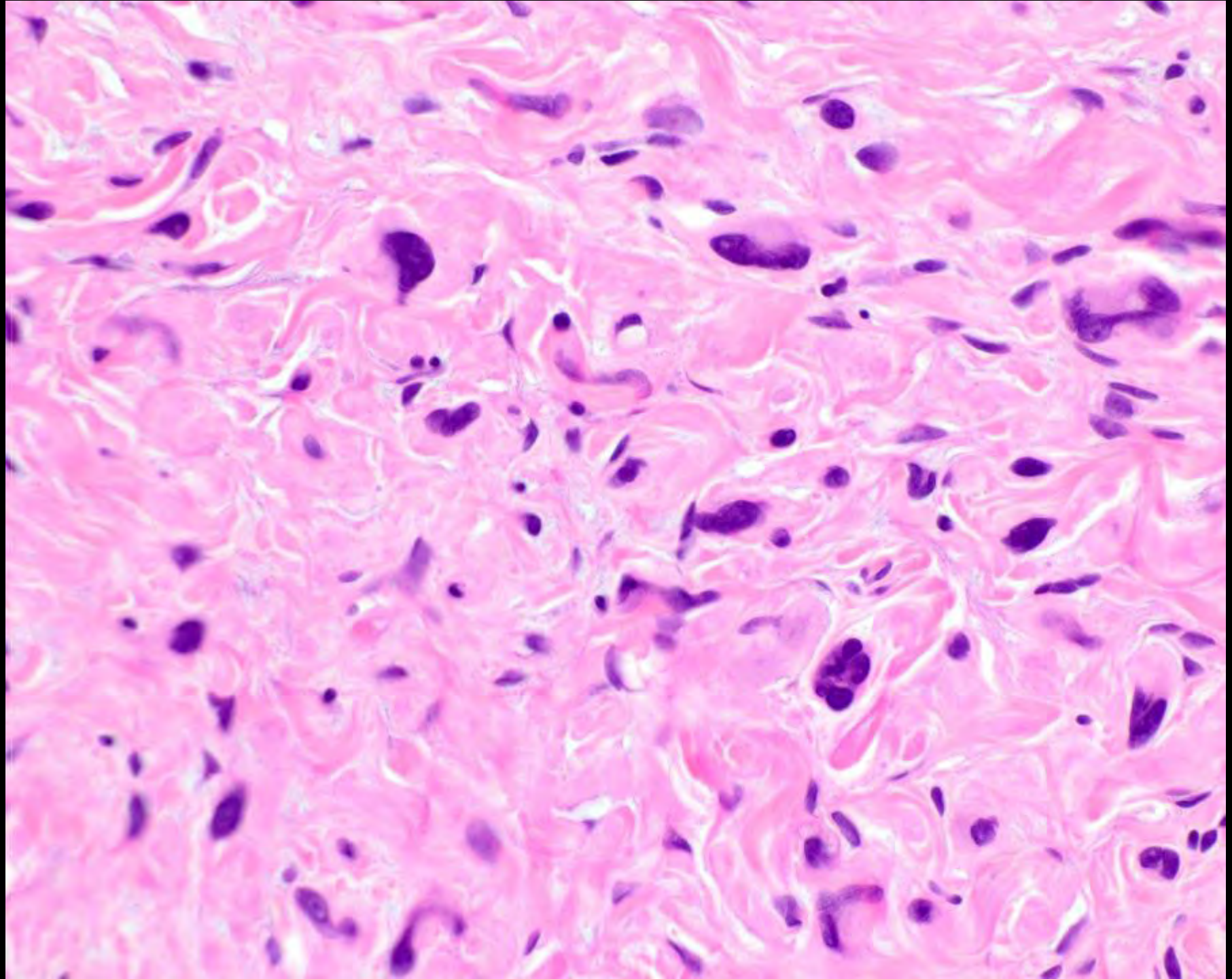


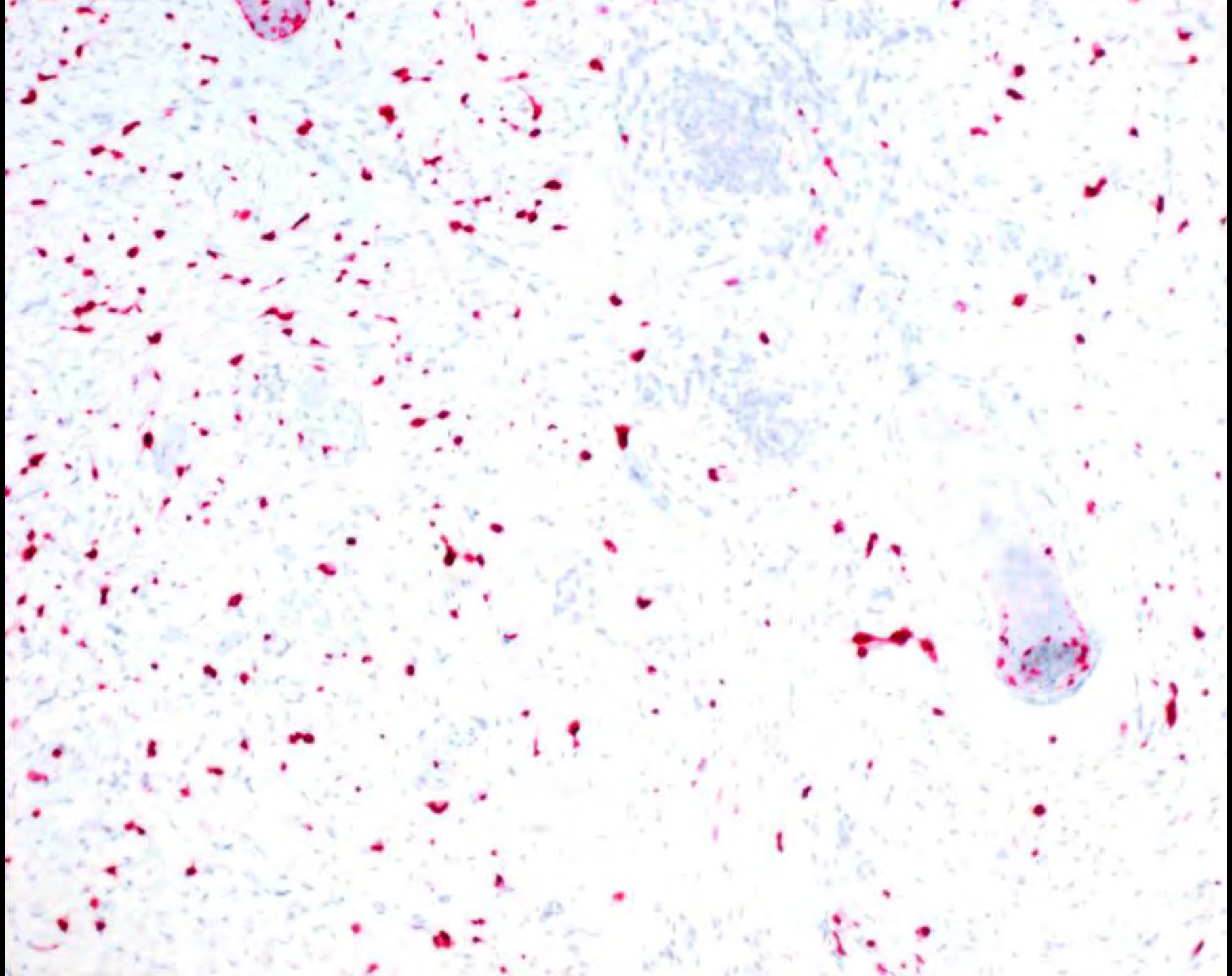




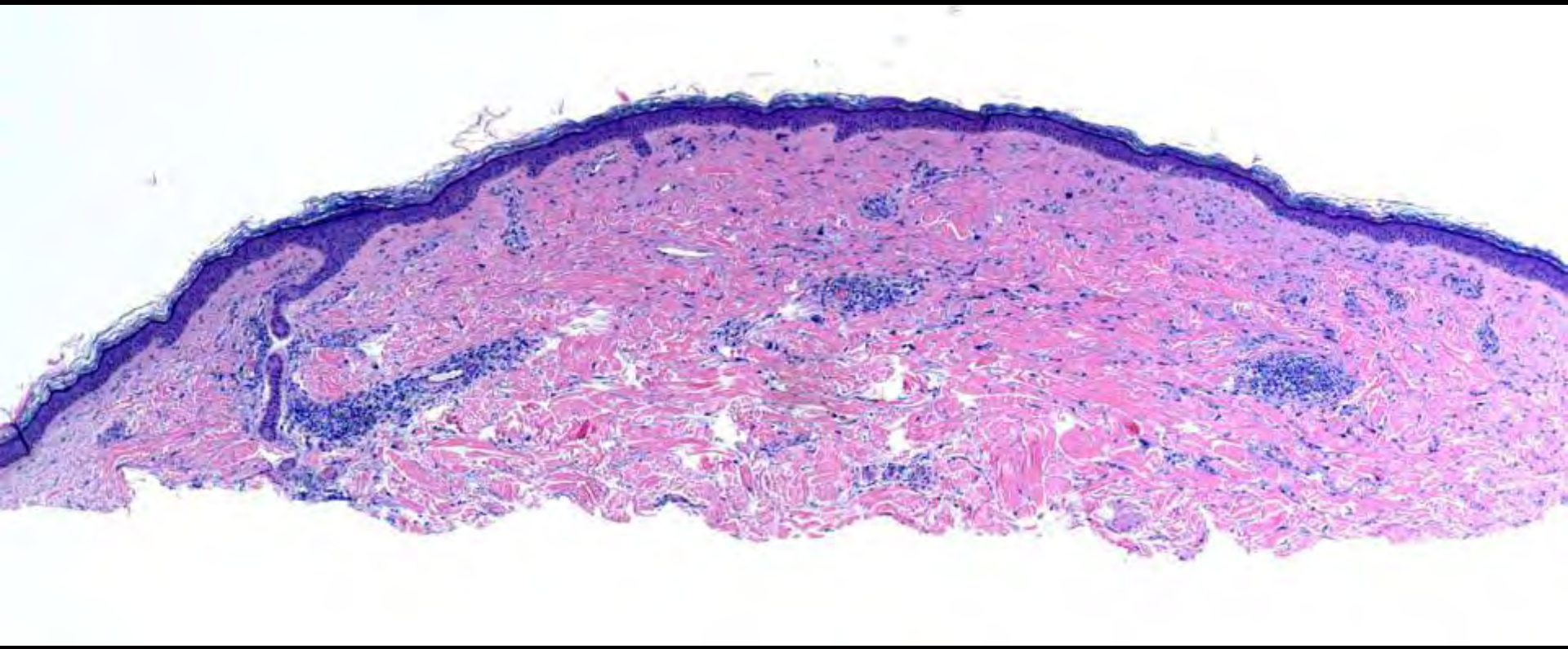


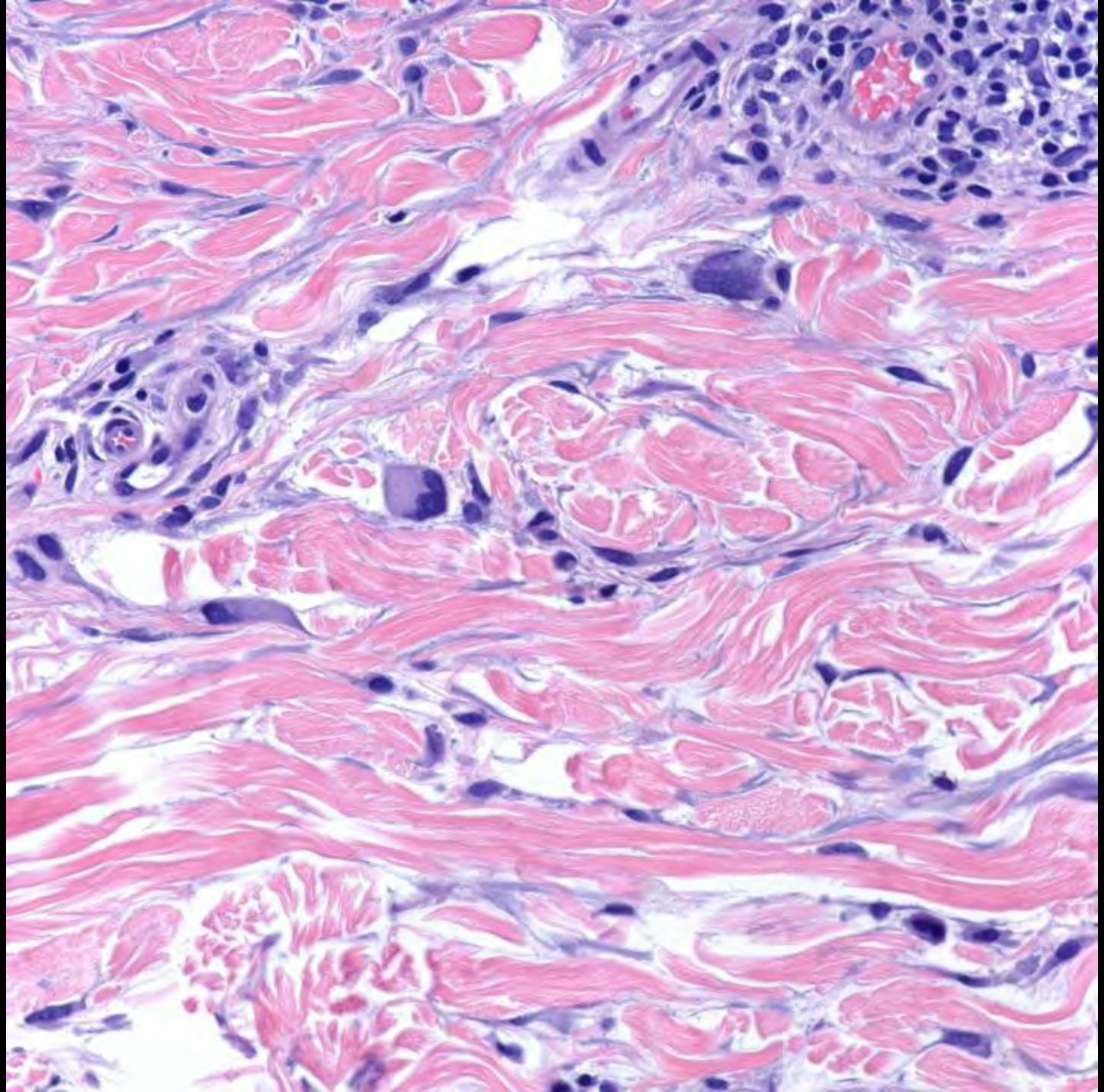


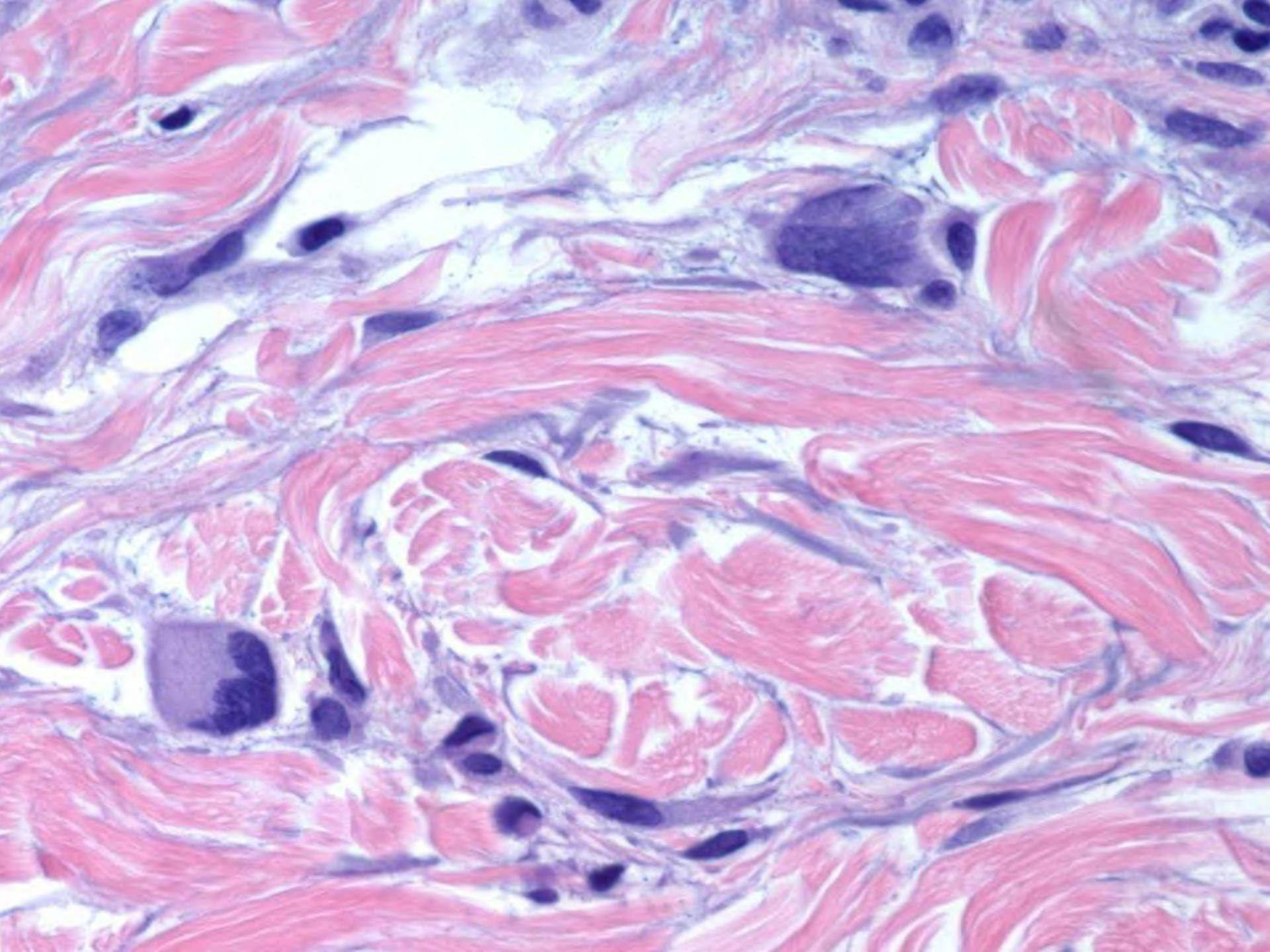




Anonymous consultant's diagnosis- myxoid pleomorphic fibroma with SOX10 positive cells, based in part on Rb negative immunostain







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ORIGINAL ARTICLE

Loss of retinoblastoma in pleomorphic fibroma: An immunohistochemical and genomic analysis

Brian Hinds[1,2] | Alfredo D. Agulló Pérez[3] | Philip E. LeBoit[1,2] | Timothy H. McCalmont[1,2] | Jeffrey P. North[1,2]

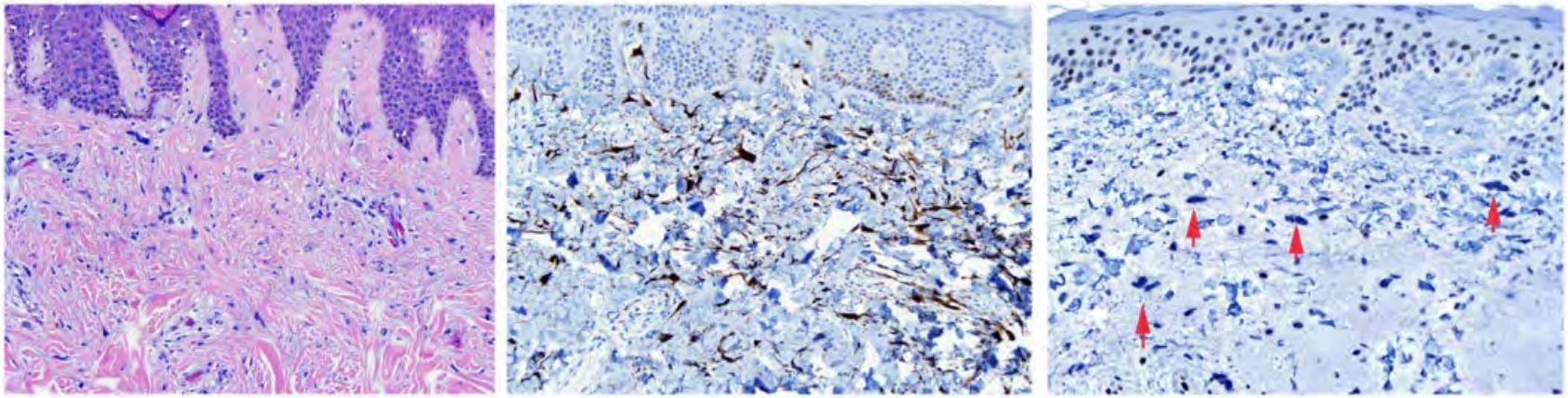
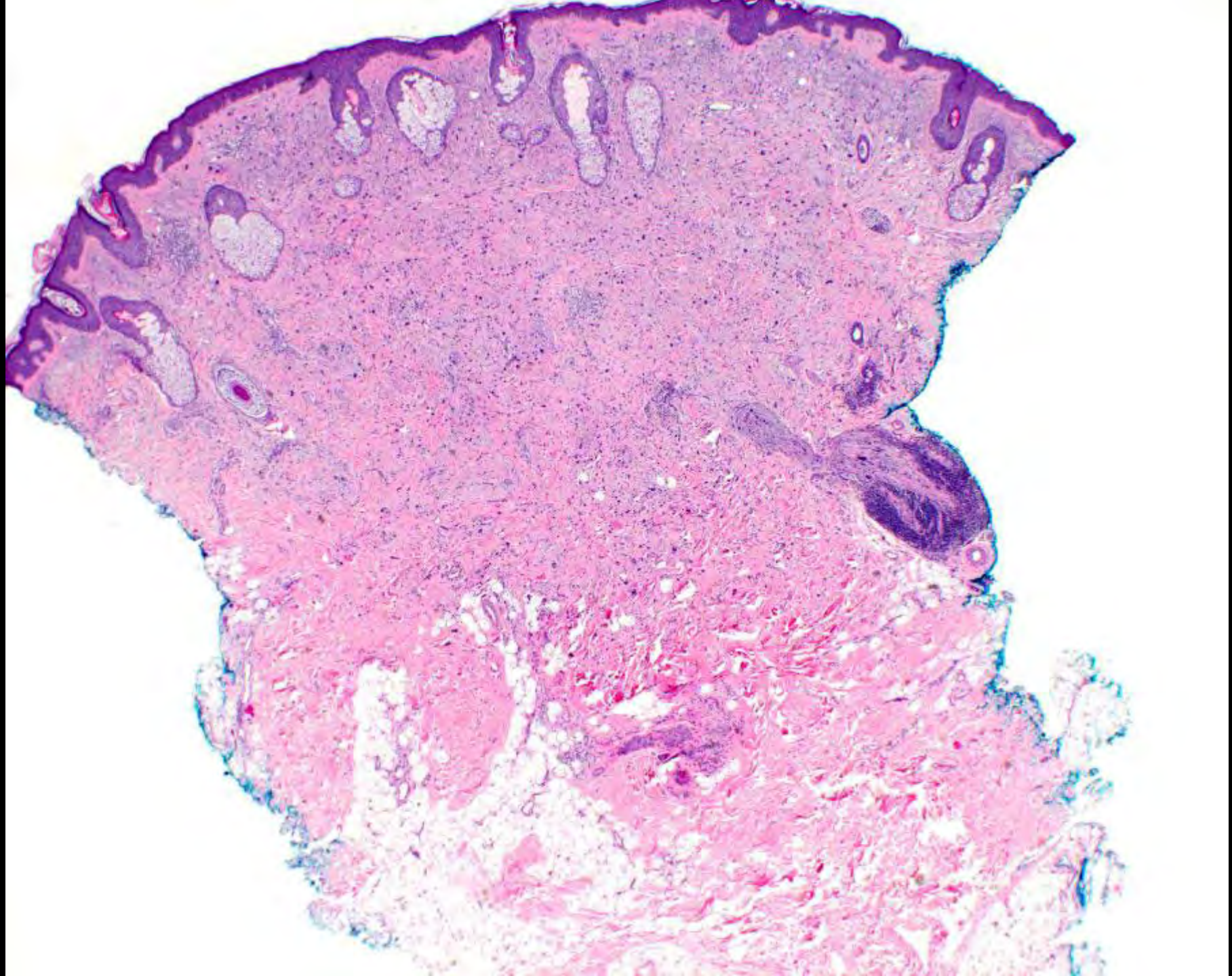
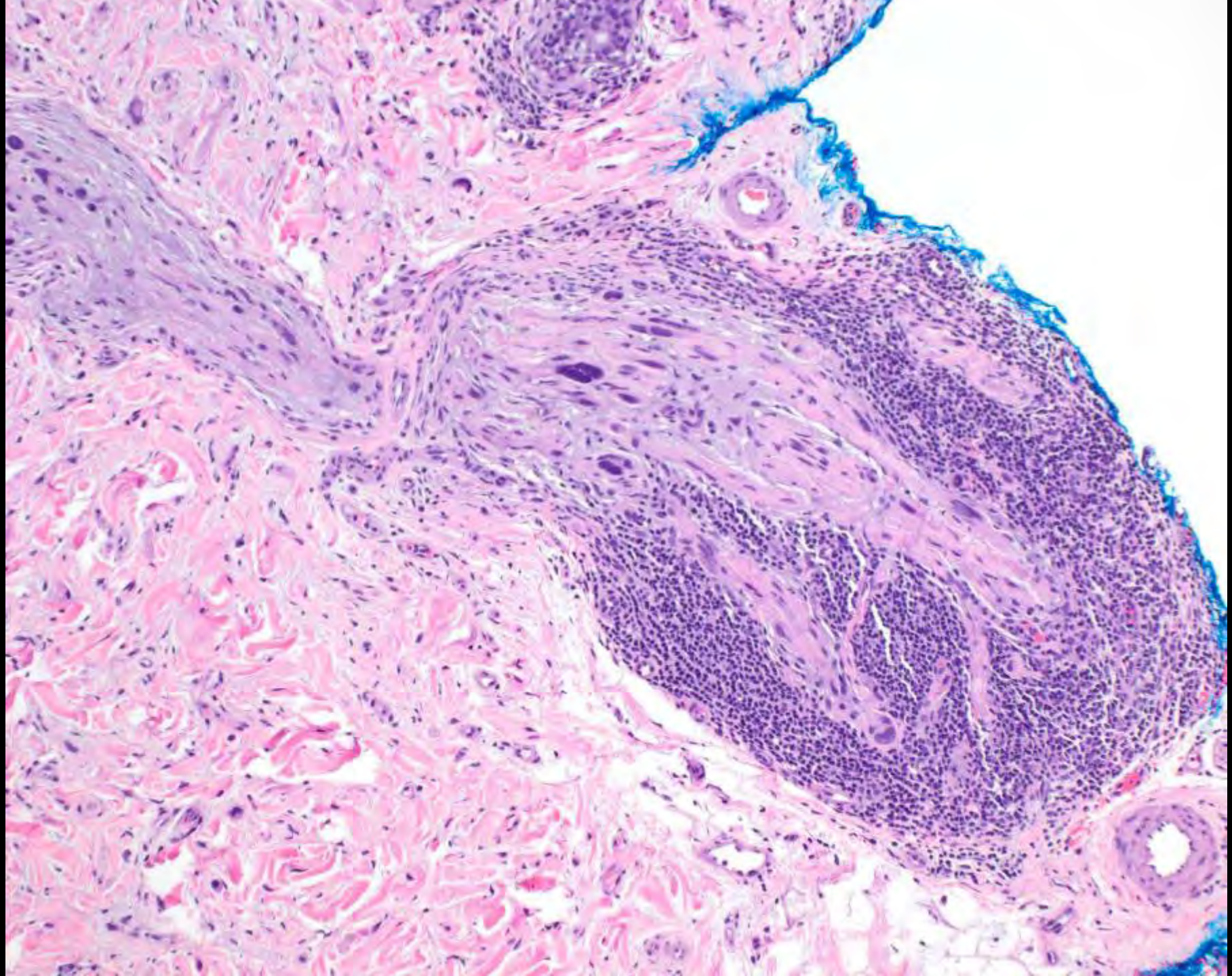
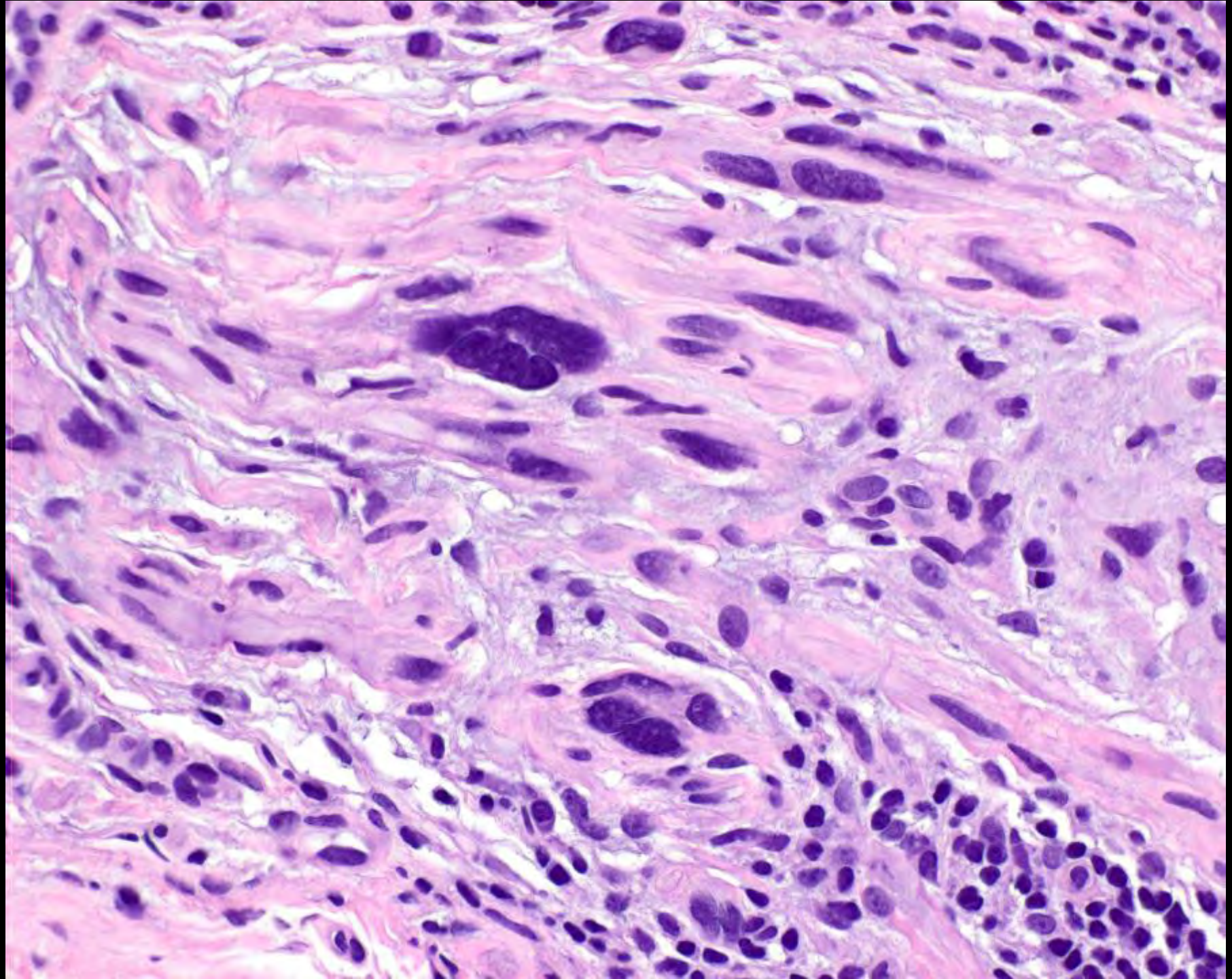
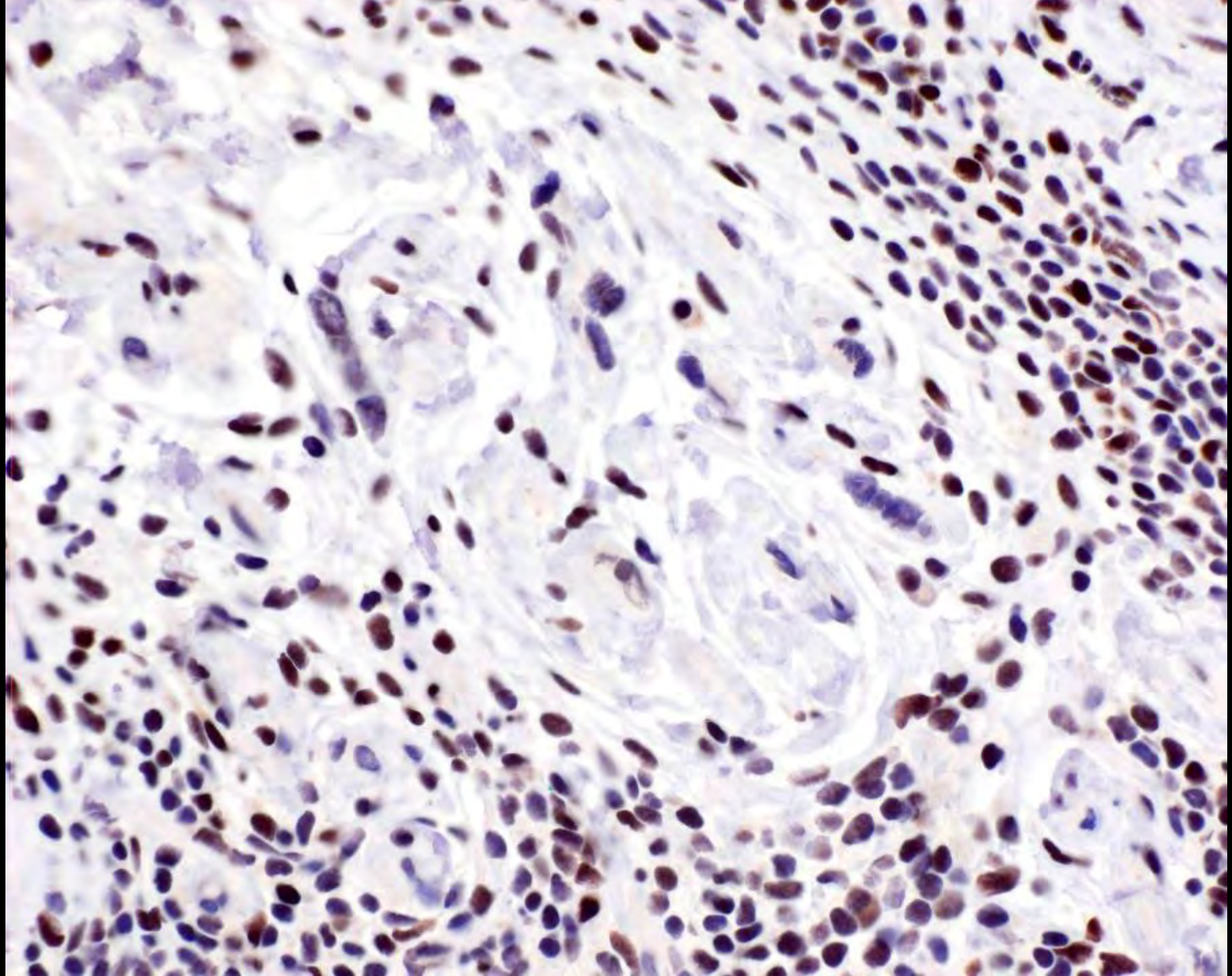


FIGURE 5 Immunostaining of pleomorphic fibroma (PF). Typical histopathologic features of PF with a fibroblastic spindle cell proliferation with scattered multinucleated cells and cells with large, pleomorphic nuclei (A, H&E ×200). Both the small spindled cells and large pleomorphic and multinucleated cells stain positively for p16 (B, p16 ×200). Rb staining is negative in the neoplastic cells, which is easiest to appreciate in the large cells (red arrows) and positive in the overlying epidermis and non-neoplastic dermal cells (C, Rb ×200)









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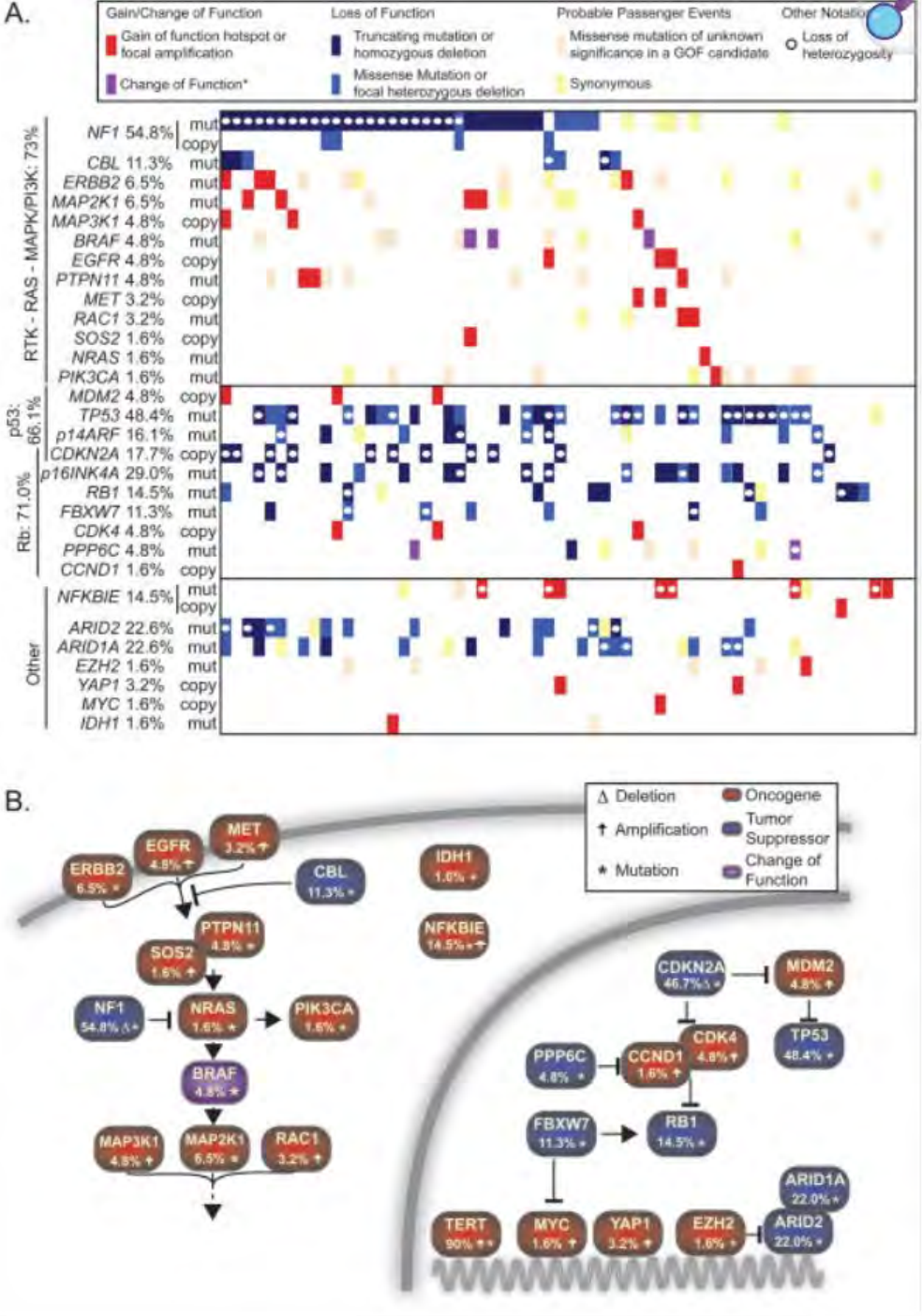
Exome sequencing of desmoplastic melanoma identifies recurrent NFKBIE promoter mutations and diverse activating mutations in the MAPK pathway

A. Hunter Shain[1,2,3], **Maria Garrido**[1,2,3], **Thomas Botton**[1,2,3], **Eric Talevich**[1,2,3], **Iwei Yeh**[1,2,3], **J. Zachary Sanborn**[4], **Jongsuk Chung**[5], **Nicholas J. Wang**[6,7], **Hojabr Kakavand**[8,9], **Graham J. Mann**[8,9], **John F. Thompson**[8,9,10], **Thomas Wiesner**[11], **Ritu Roy**[2], **Adam B. Olshen**[2,12], **Alexander Gagnon**[1,2,3], **Joe W. Gray**[6,7], **Nam Huh**[5], **Joe S. Hur**[13], **Klaus J. Busam**[14], **Richard A. Scolyer**[8,9,10], **Raymond J. Cho**[3,16], **Rajmohan Murali**[14,15,16], and **Boris C. Bastian**[1,2,3,16]


A.
Gain/Change of Function
Gain of function hotspot or focal amplification
Change of Function*
Loss of Function
Truncating mutation or homozygous deletion
Missense Mutation or focal heterozygous deletion
Probable Passenger Events
Missense mutation of unknown significance in a GOF candidate
Synonymous
Other Notation
Loss of heterozygosity
RTK - RAS - MAPK/PI3K: 73%
NF1 54.8% mut copy
CBL 11.3% mut
ERBB2 6.5% mut
MAP2K1 6.5% mut
MAP3K1 4.8% copy
BRAF 4.8% mut
EGFR 4.8% copy
PTPN11 4.8% mut
MET 3.2% copy
RAC1 3.2% mut
SOS2 1.6% copy
NRAS 1.6% mut
PIK3CA 1.6% mut
p53: 66.1%
MDM2 4.8% copy
TP53 48.4% mut
p14ARF 16.1% mut
CDKN2A 17.7% copy
Rb: 71.0%
p16INK4A 29.0% mut
RB1 14.5% mut
FBXW7 11.3% mut
CDK4 4.8% copy
PPP6C 4.8% mut
CCND1 1.6% copy
Other
NFKBIE 14.5% mut copy
ARID2 22.6% mut
ARID1A 22.6% mut
EZH2 1.6% mut
YAP1 3.2% copy
MYC 1.6% copy
IDH1 1.6% mut
B.
Δ Deletion
Amplification
Mutation
Oncogene
Tumor Suppressor
Change of Function
MET 3.2%
EGFR 4.8%
ERBB2 6.5%
CBL 11.3%
IDH1 1.6%
NFKBIE 14.5%
PTPN11 4.8%
SOS2 1.6%
NF1 54.8%
NRAS 1.6%
PIK3CA 1.6%
BRAF 4.8%
MAP3K1 4.8%
MAP2K1 6.5%
RAC1 3.2%
CDKN2A 46.7%
MDM2 4.8%
CDK4 4.8%
TP53 48.4%
PPP6C 4.8%
CCND1 1.6%
FBXW7 11.3%
RB1 14.5%
ARID1A 22.0%
ARID2 22.0%
TERT 90%
MYC 1.6%
YAP1 3.2%
EZH2 1.6%

Retinoblastoma gene alterations in DMM

- Pathway disrupted by mutations in ~70%
- Includes RB1/CDK4/CCND1/CDKN2A
- High overall mutation rate in DMMs, so driver vs. passenger status not known
- Overall, Rb mutations in only 4% of MMs

Pathway 4- Spitz melanoma

- RTK and STK gene fusions, HRAS, MAP3K8 fusions/rearrangements
- Mostly <30 year olds ?
- A subset of spitzoid melanoma

Spitz melanoma

- Spitz lineage initiating event
- Additional progression events (homozygous loss of CDKN2A, mutations in hTERT, CDK4, p53, etc.)
- Spread beyond local lymph nodes, but prognosis seems better than classic melanoma

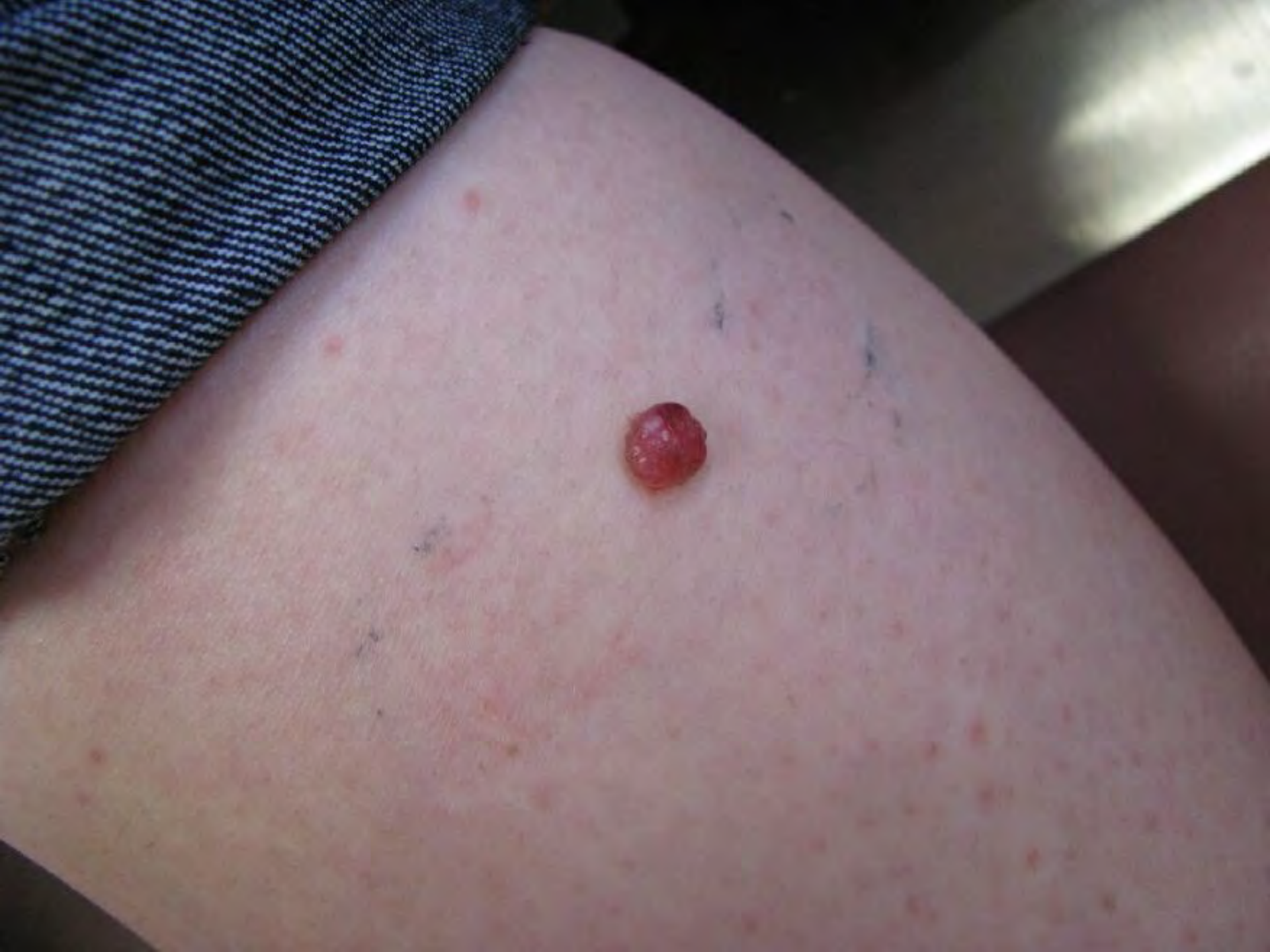
Mod Pathol. 2020 June ; 33(6): 1122–1134. doi:10.1038/s41379-019-0445-z.

Spitz Melanoma is a Distinct Subset of Spitzoid Melanoma

Shyam Raghavan, MD[1], Sandra Peternel, MD[2,3], Thaddeus W. Mully, MD[2], Jeffrey P. North, MD[2], Laura B. Pincus, MD[2], Philip E. LeBoit, MD[2], Timothy H. McCalmont, MD[2], Boris C. Bastian, MD, PhD[2], Iwei Yeh, MD, PhD[2]

Spitz melanoma

- Doesn't obey the ABCDE rules
- Mono-hued papules, nodules, plaques.
- Affects racial groups equally
- Little relationship to sun exposure
- Only a few begin in pre-existent nevi (conventional or Spitz)



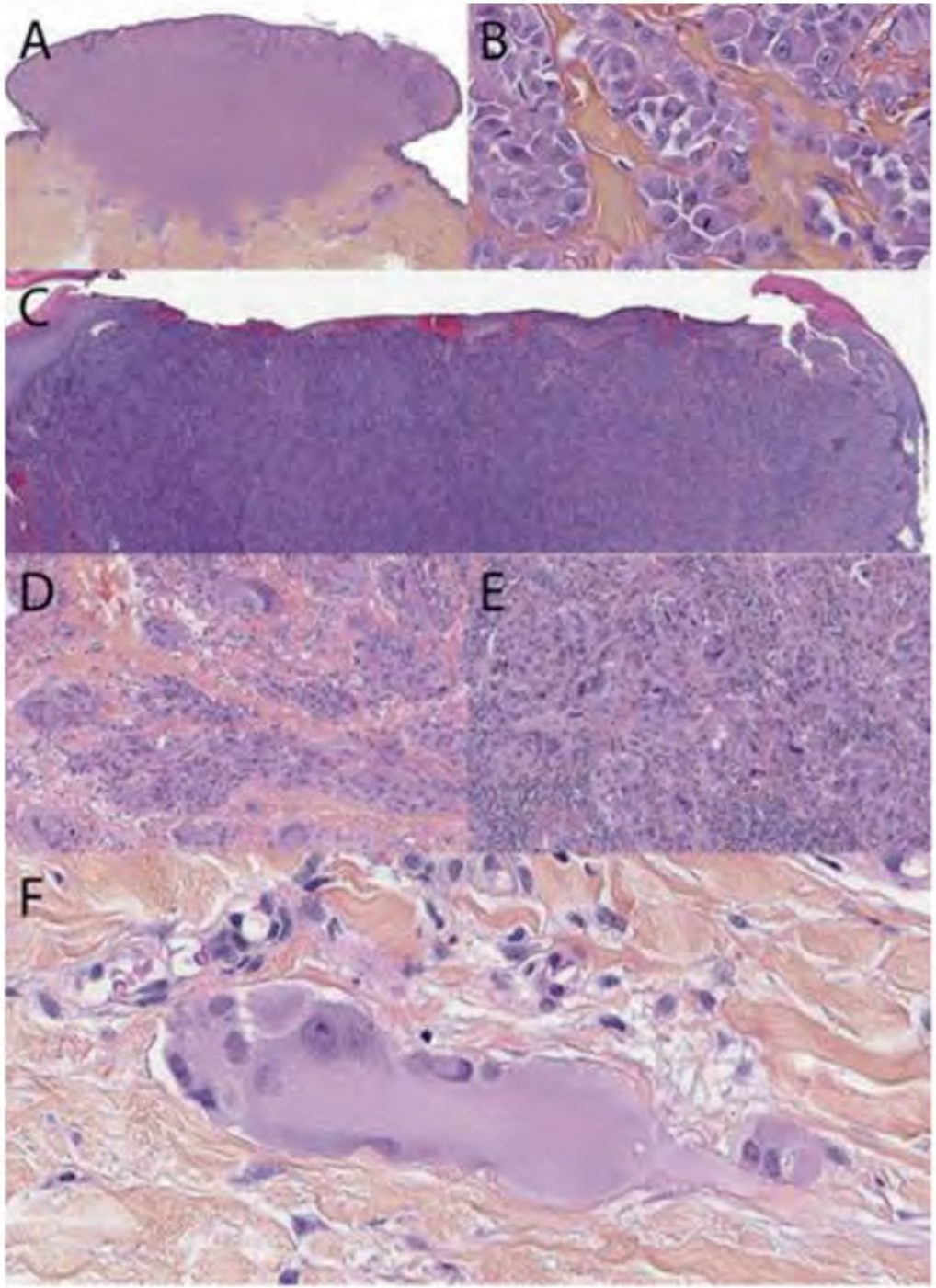
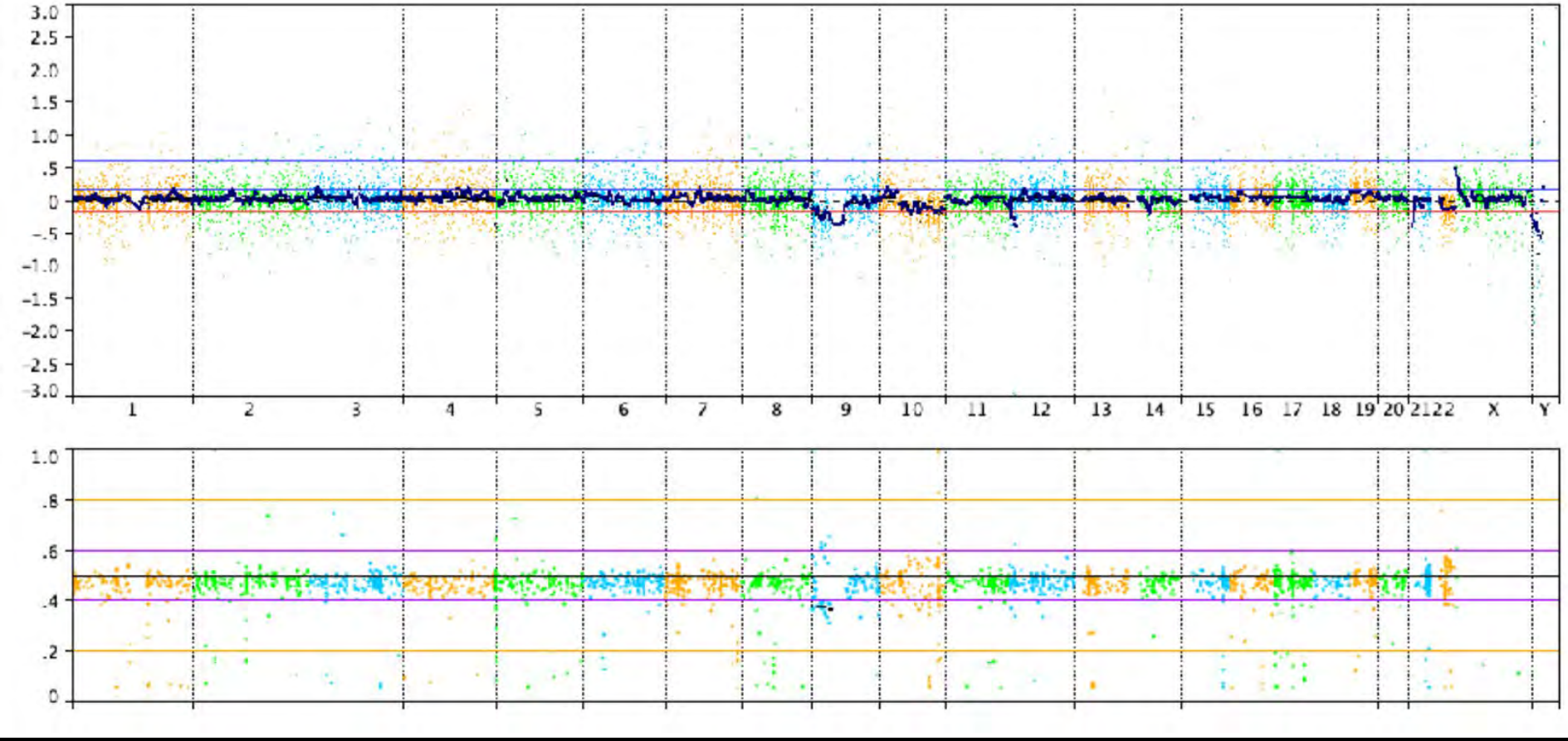


Fig. 4 Malignant Spitz tumors with *MAP3K8* fusion. **a** Large exophytic, wedge-shaped proliferation infiltrating deeply into the dermis. **b** Close-up view of **a**. Large epithelioid, unpigmented melanocytes with scattered mitotic figures. **c** Exophytic, mainly dermal proliferation with broad superficial ulceration. Cellular sheets and fascicles of large spindled melanocytes. **d–f** High-power detail of multiple large multinucleated melanocytes reaching up to 200 microns in size in **f**

18 year old male, left knee

- MAP3K8 fusion
- missense V126D mutation of CDKN2A
- loss of the wild-type allele on chr. 9p, loss involving chr. 10
- inactivating mutation in PTEN


3.0
2.5
2.0
1.5
1.0
.5
0
-.5
-1.0
-1.5
-2.0
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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 X Y
1.0
.8
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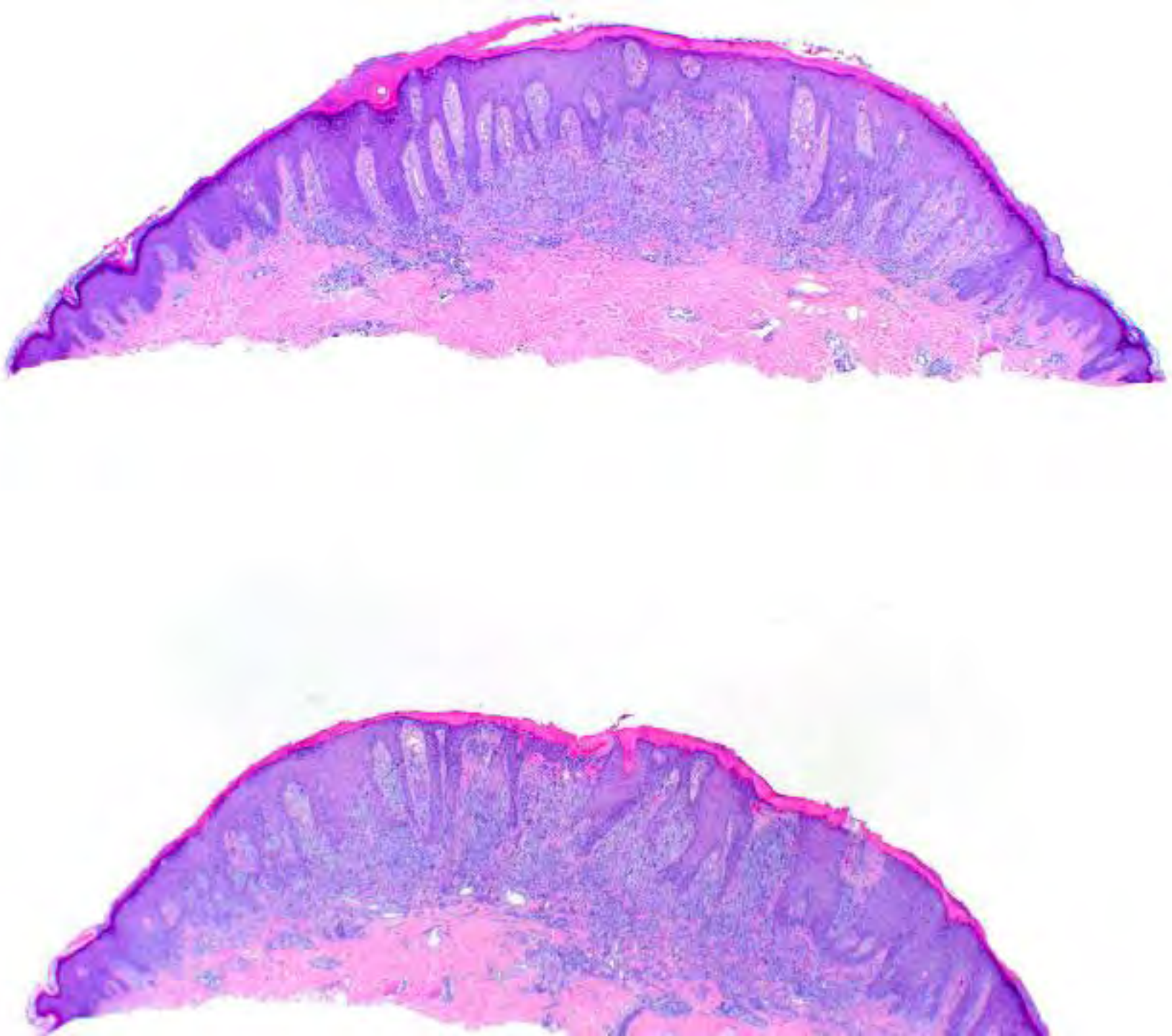
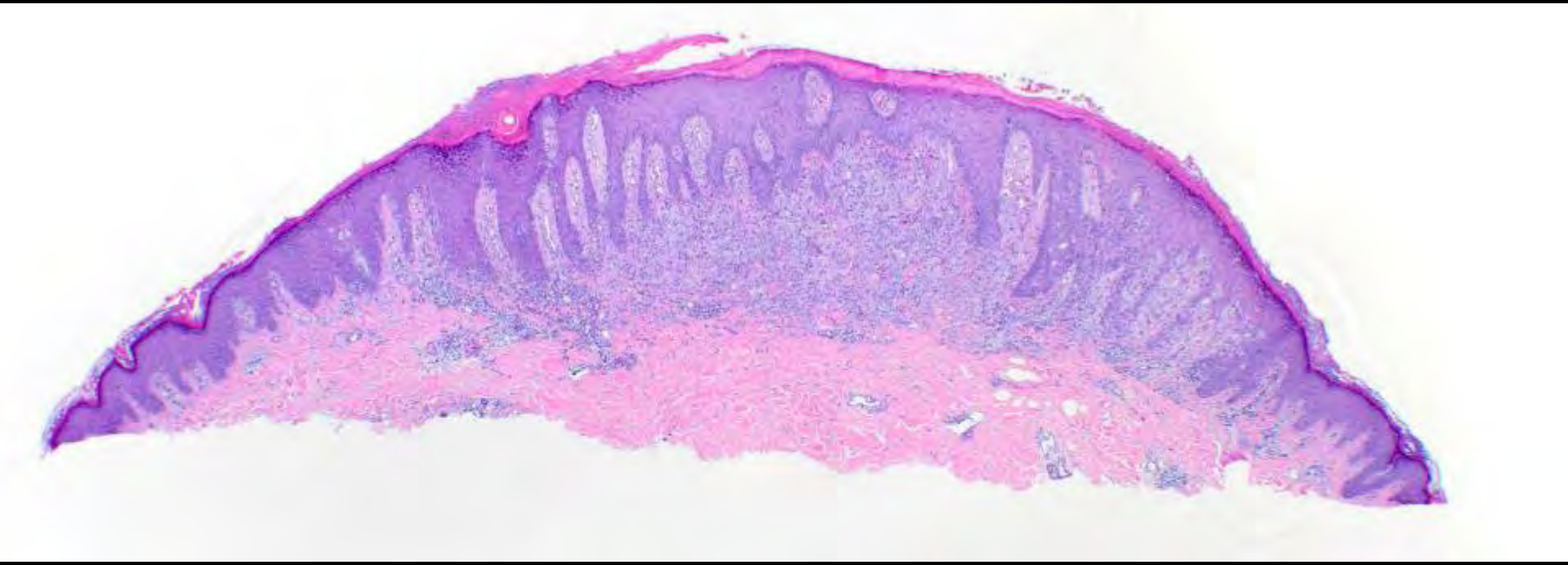
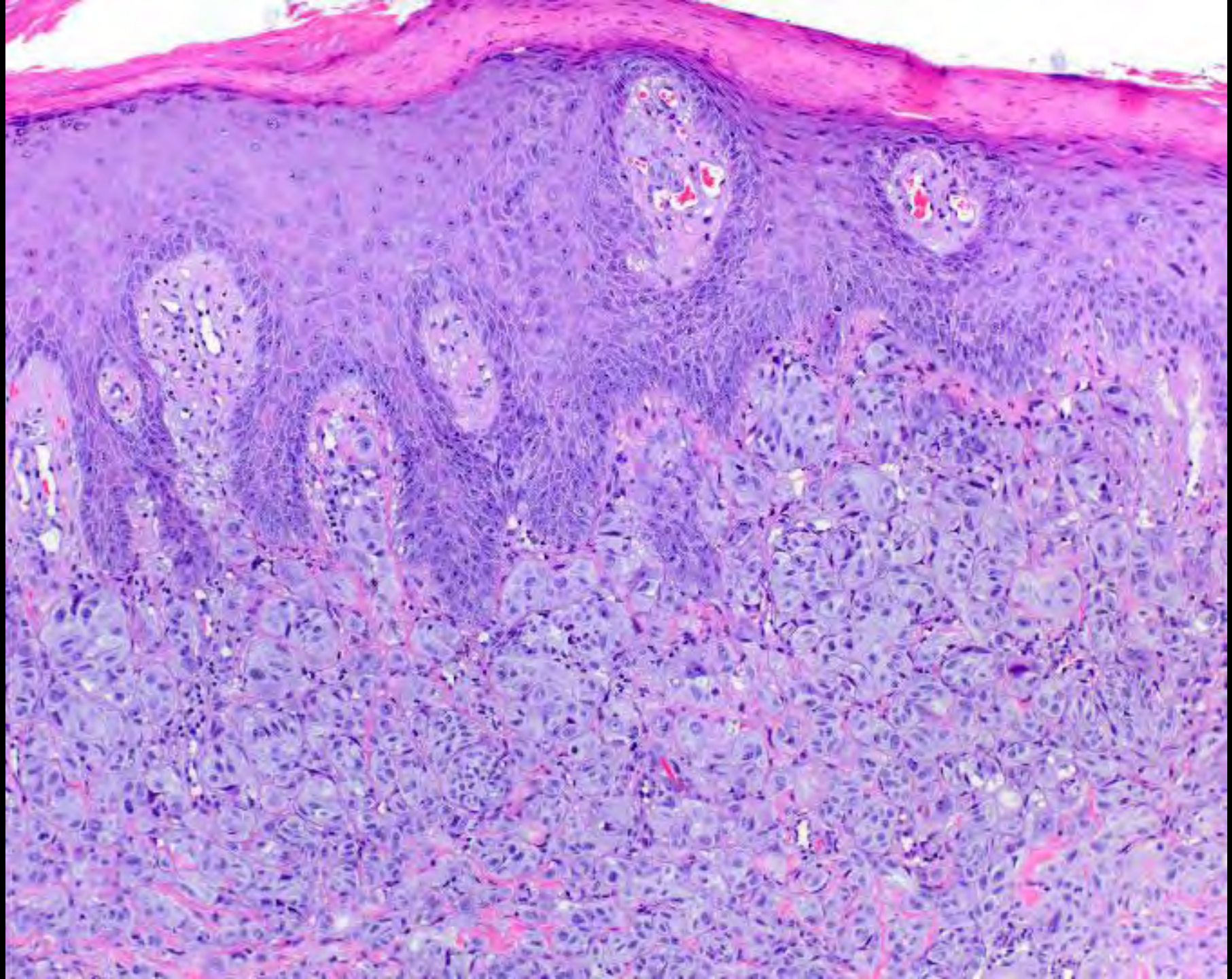
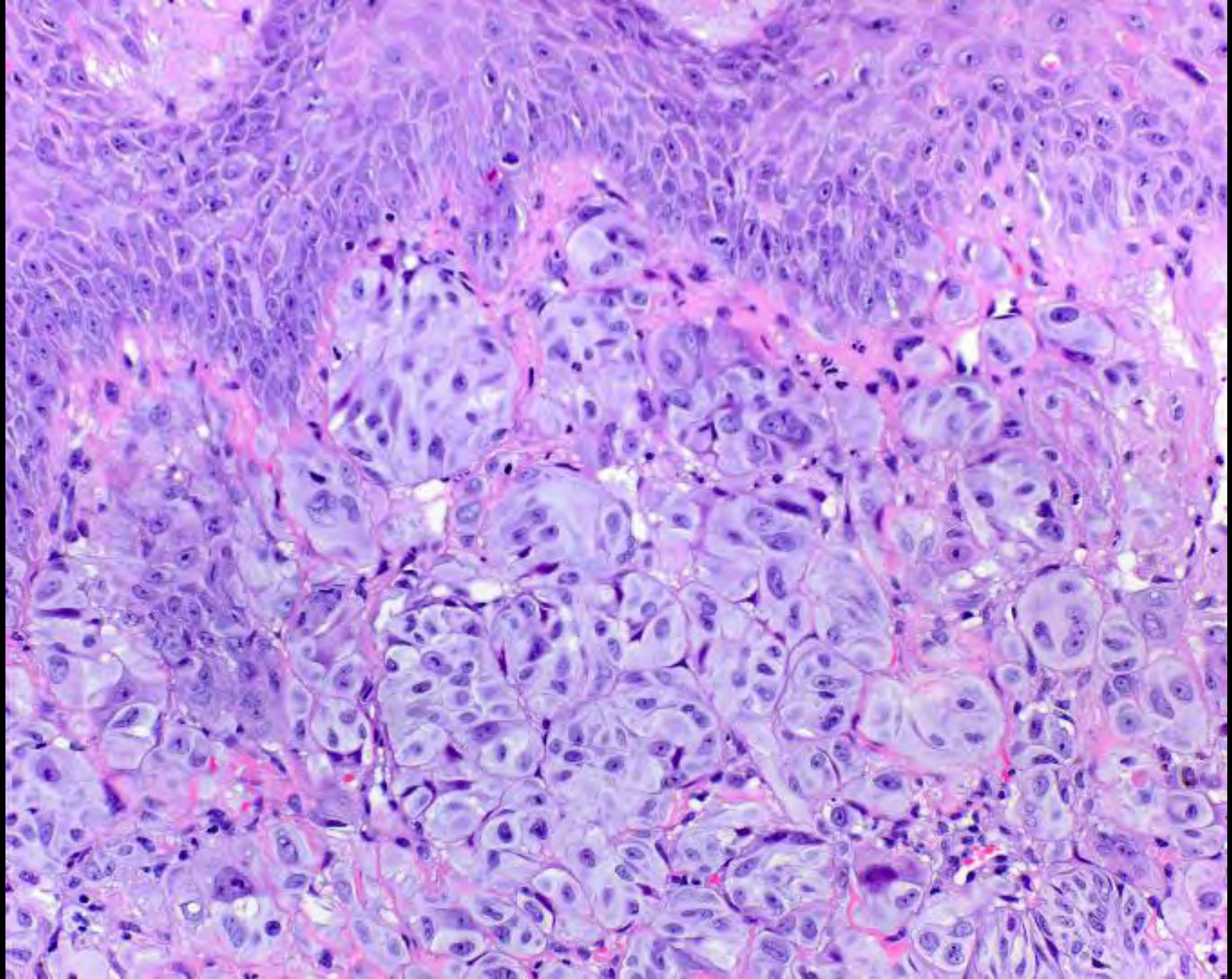
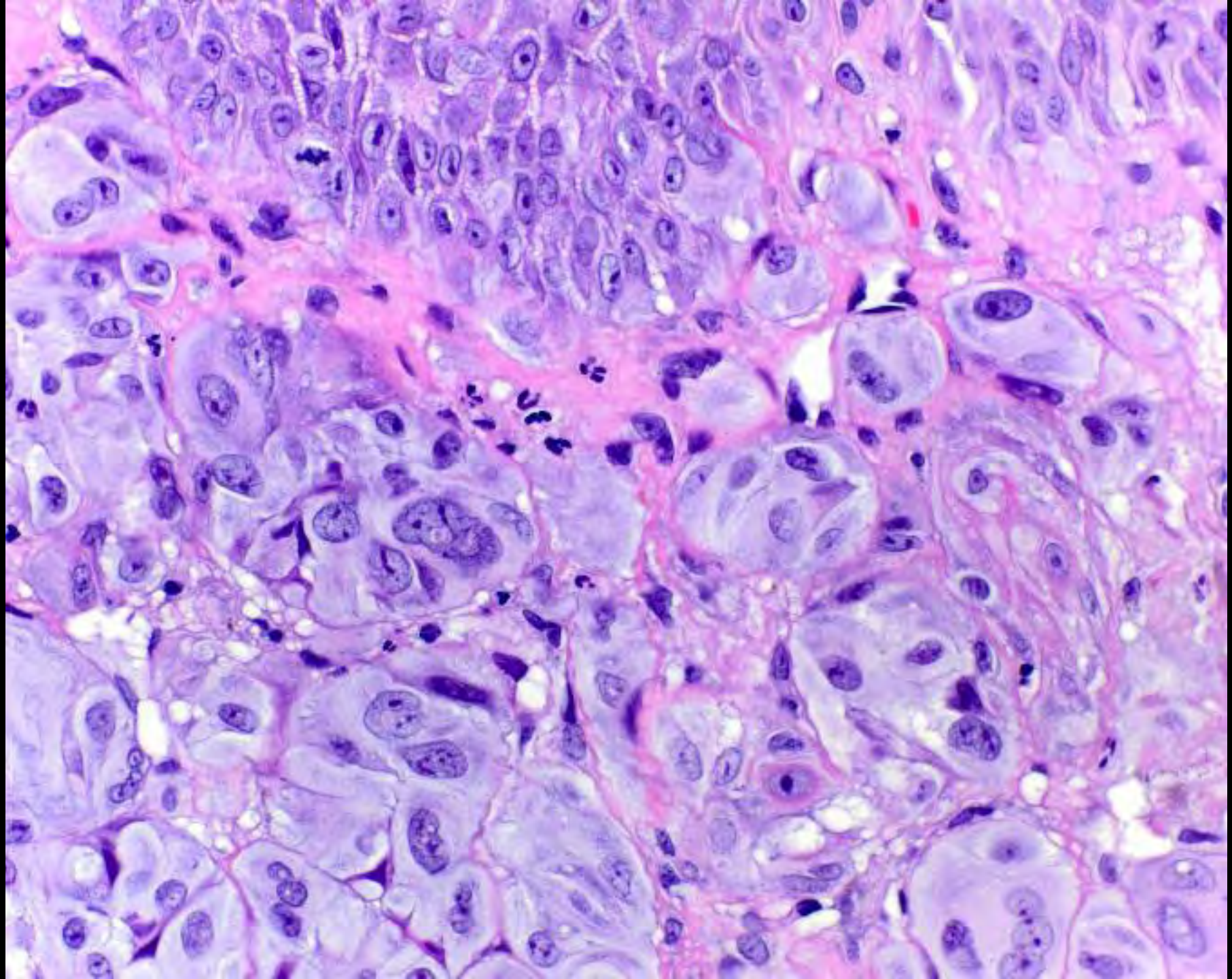
.4
.2
0

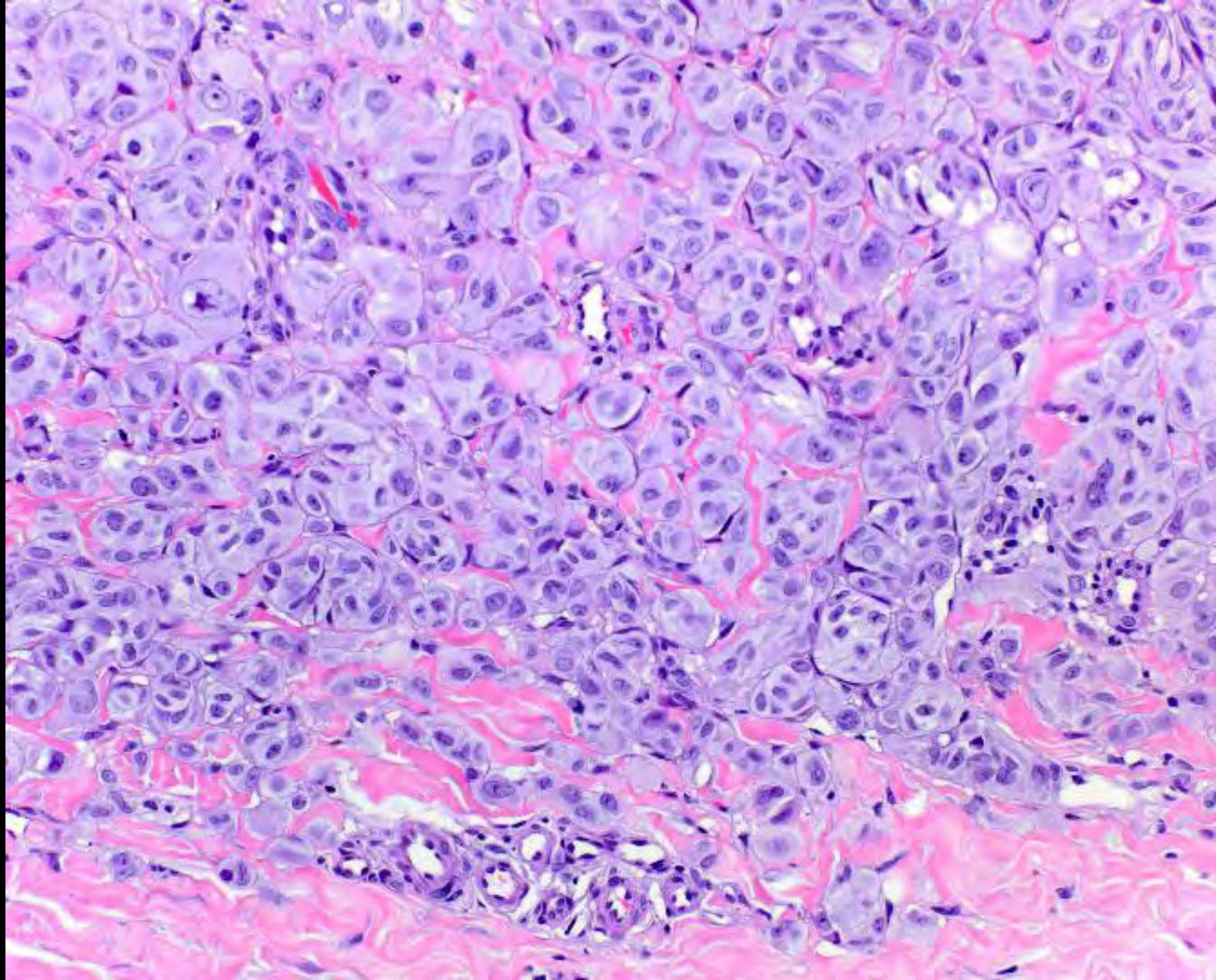


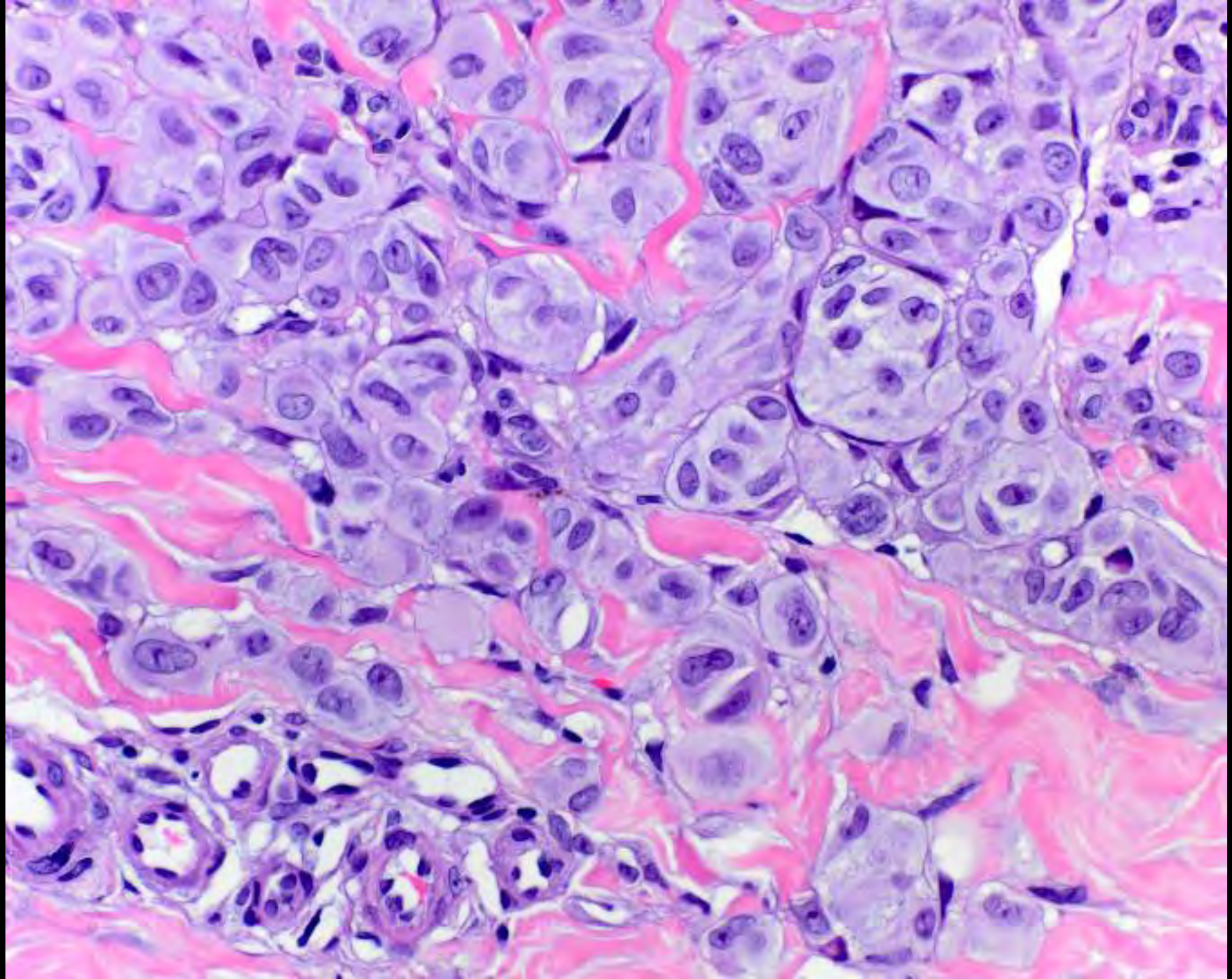


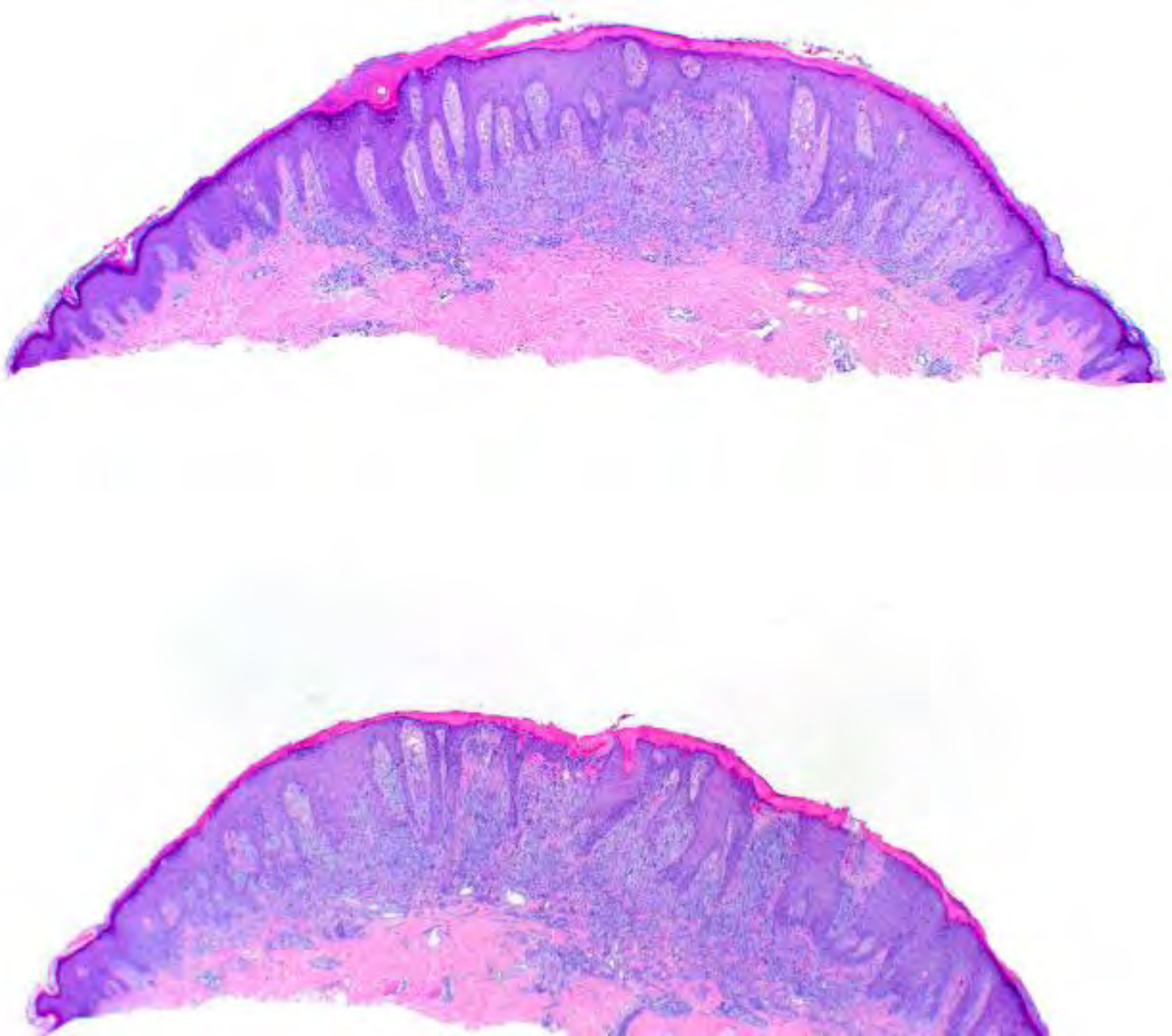


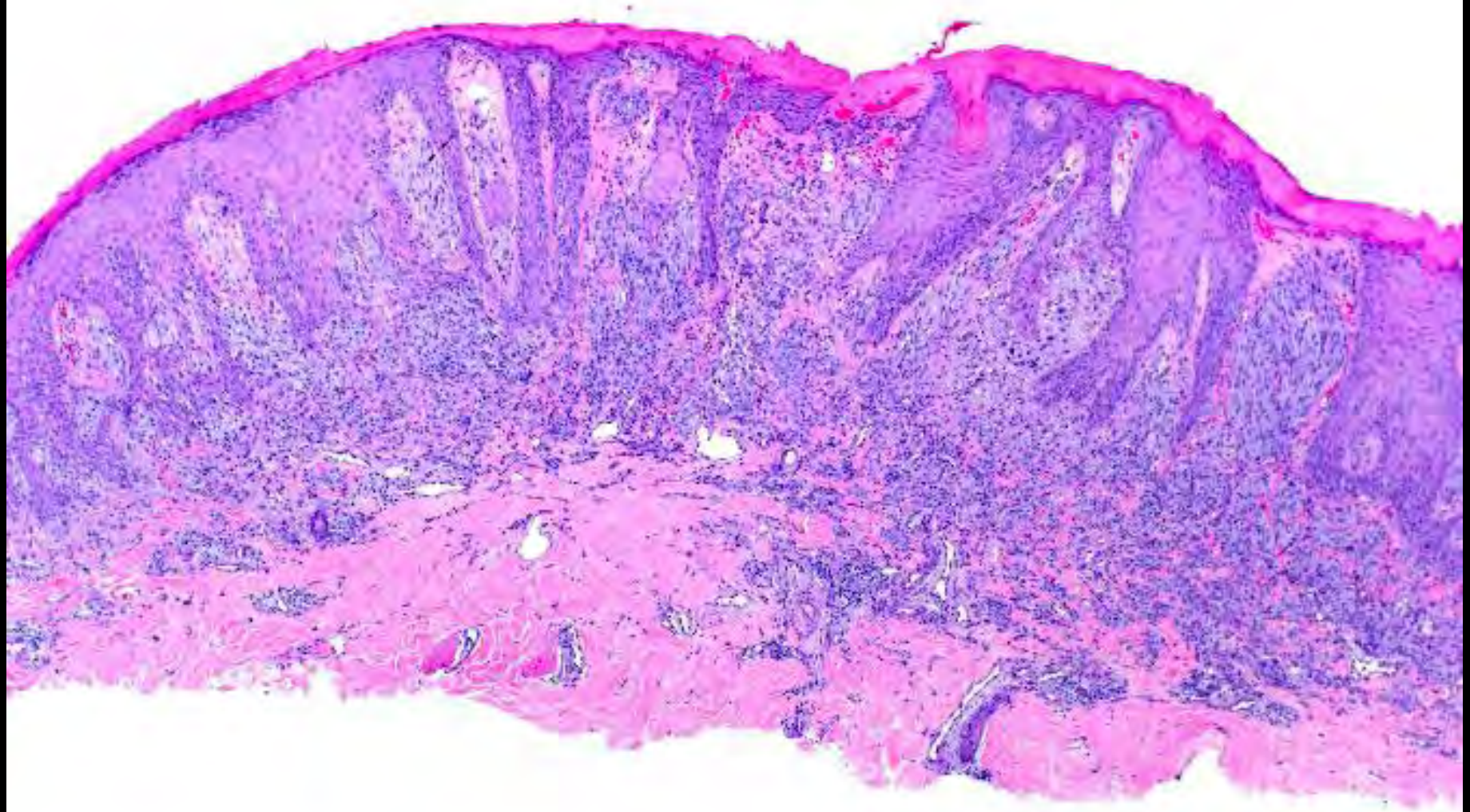


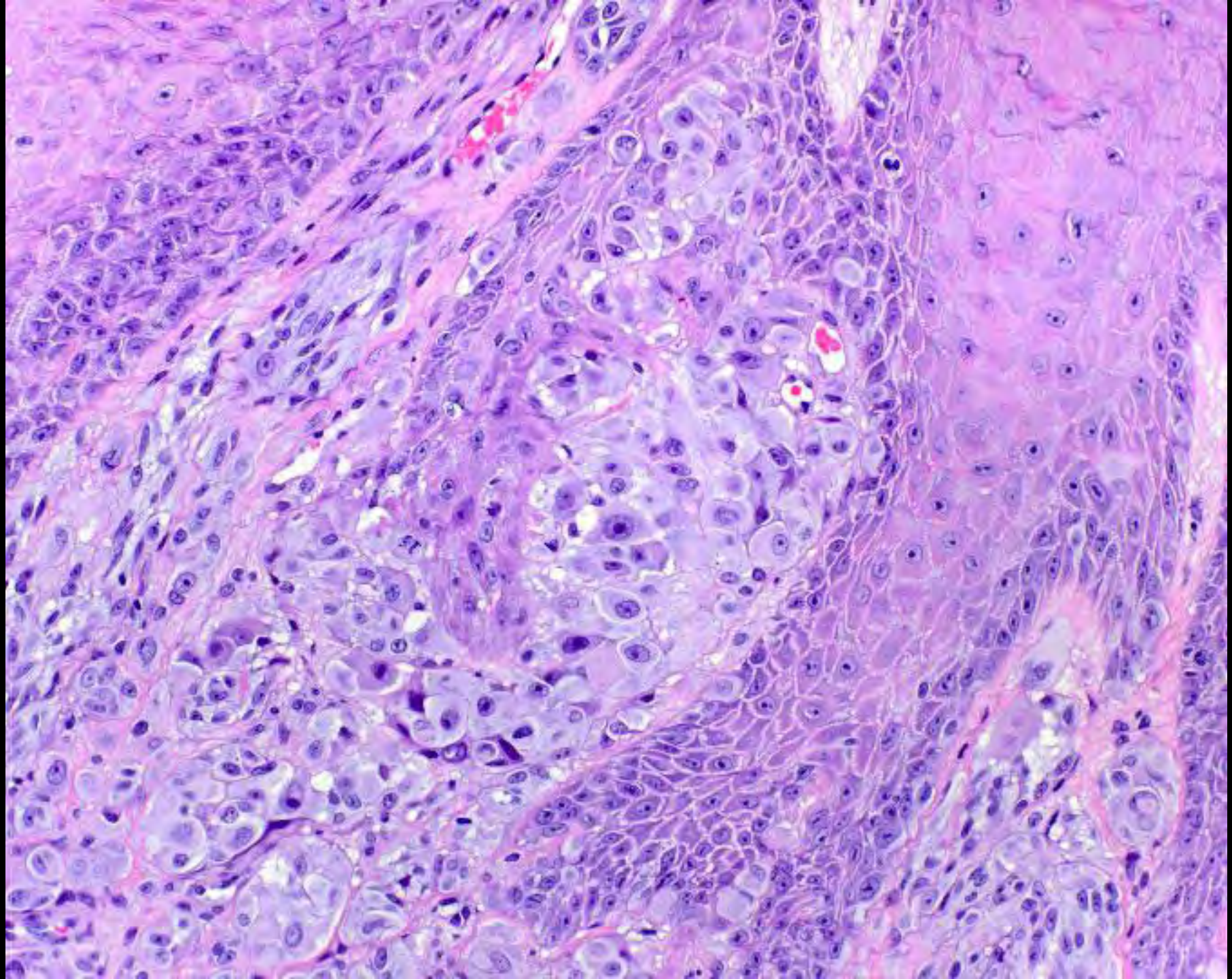


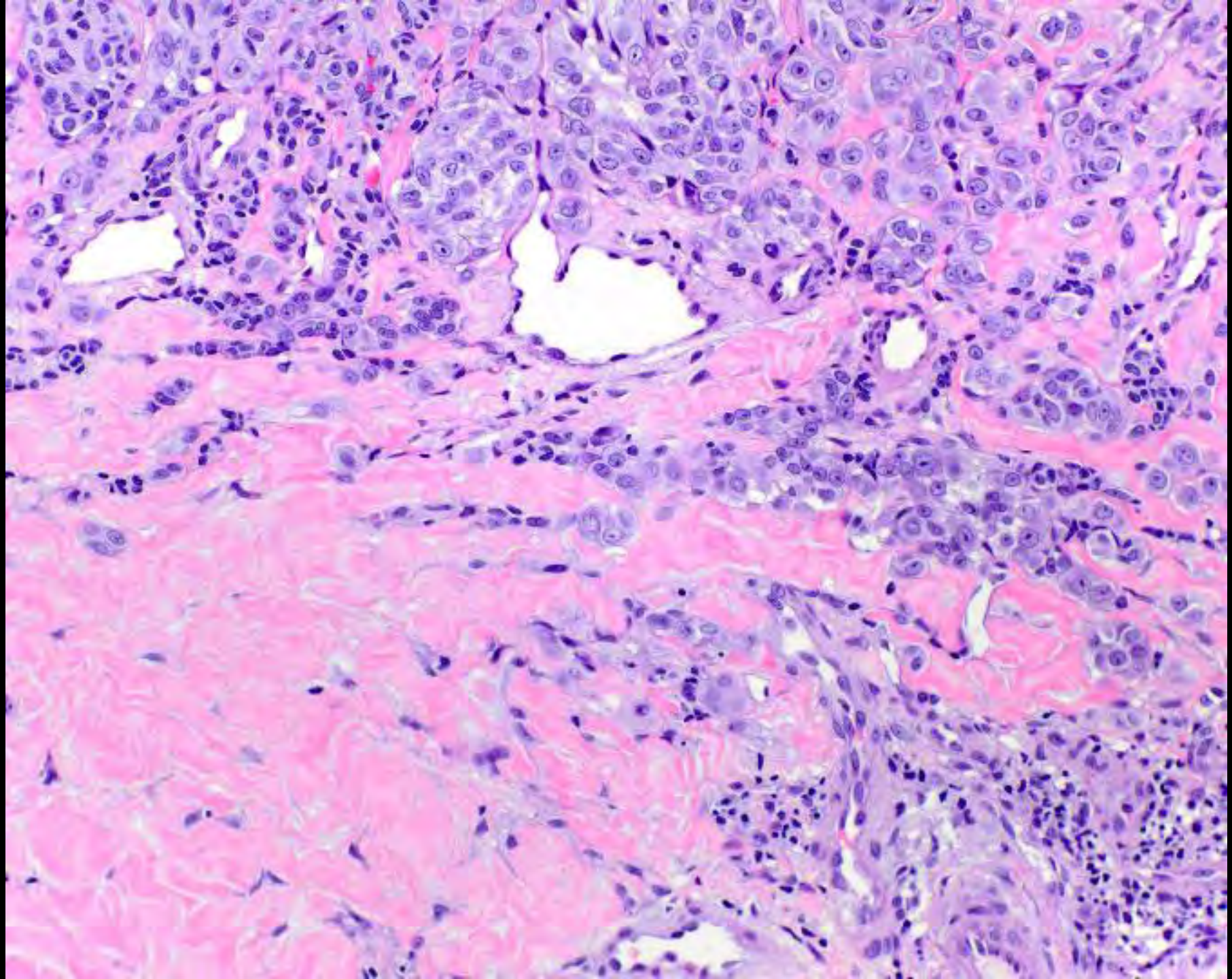




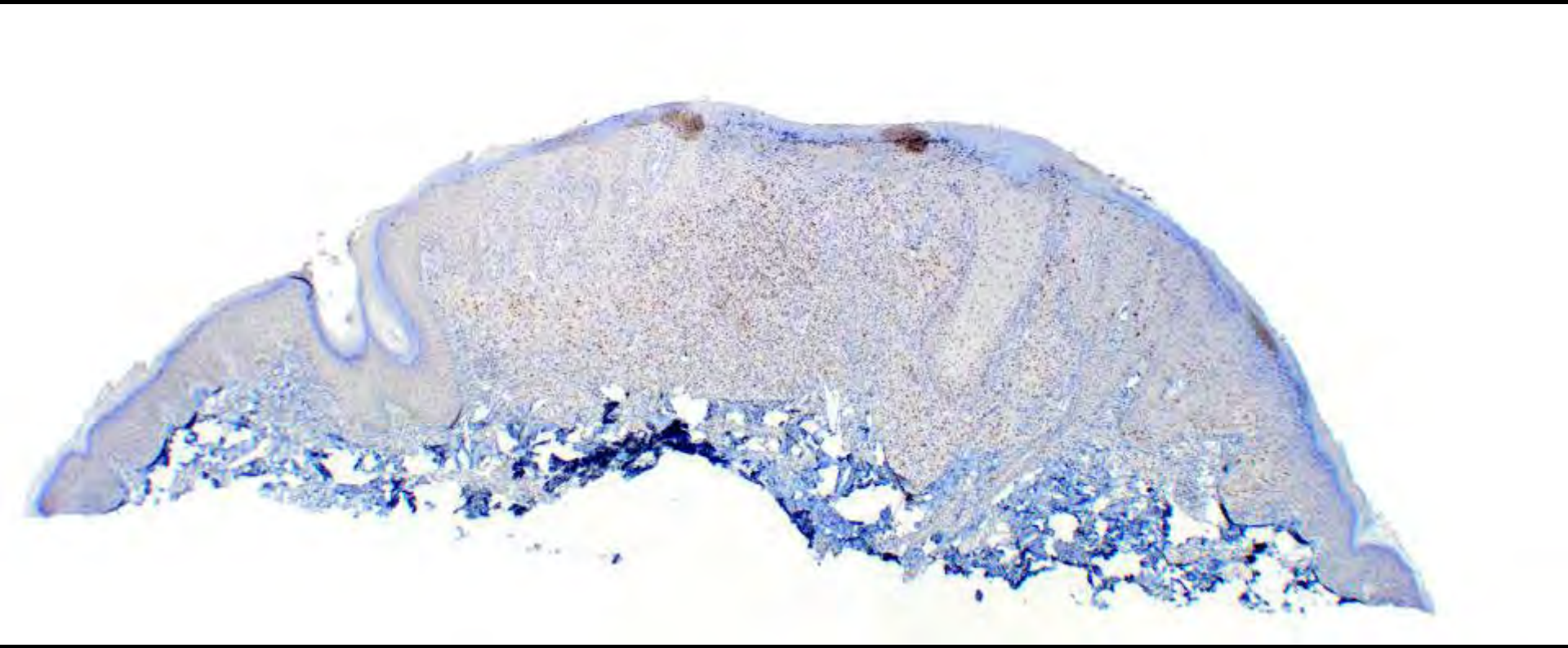


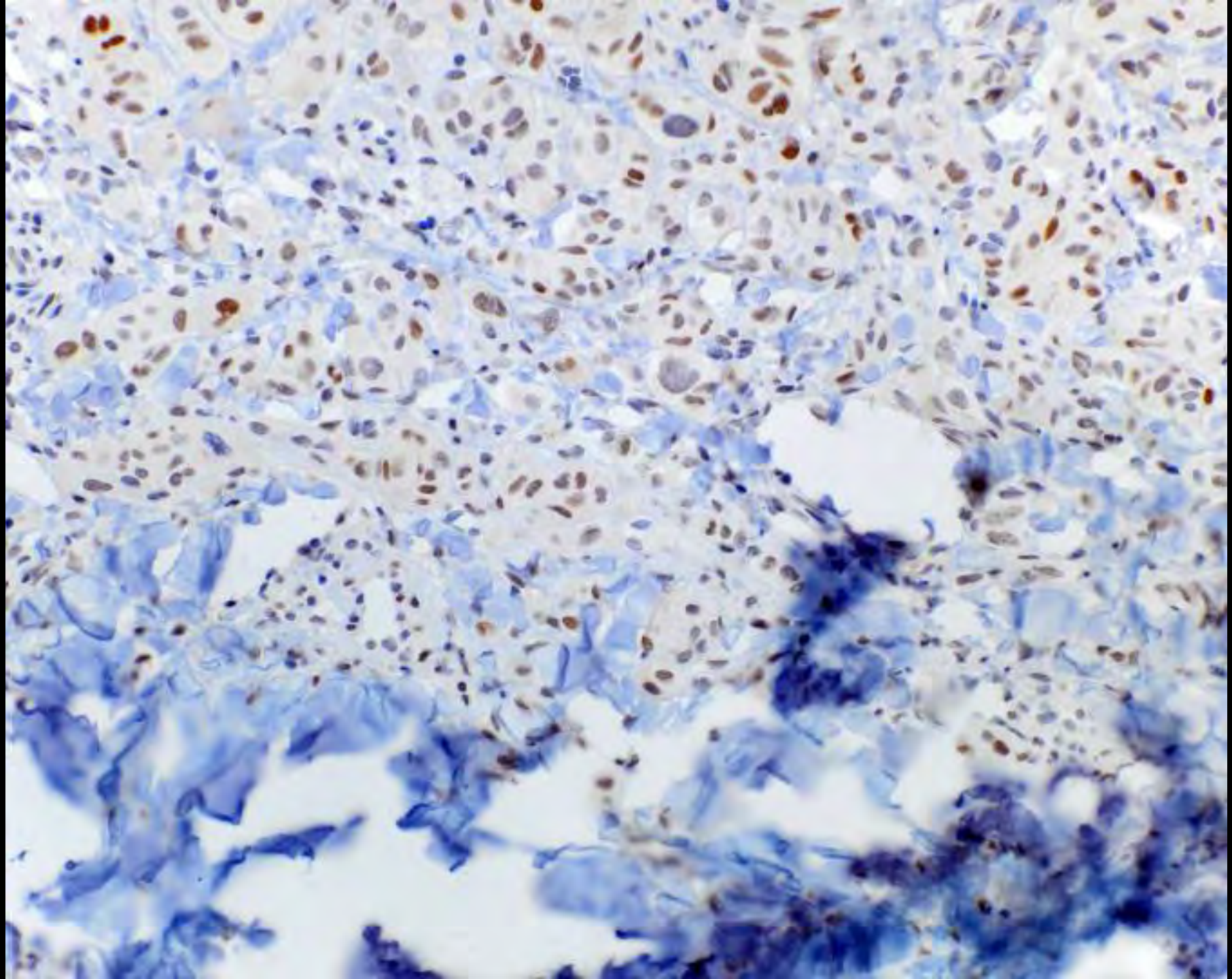




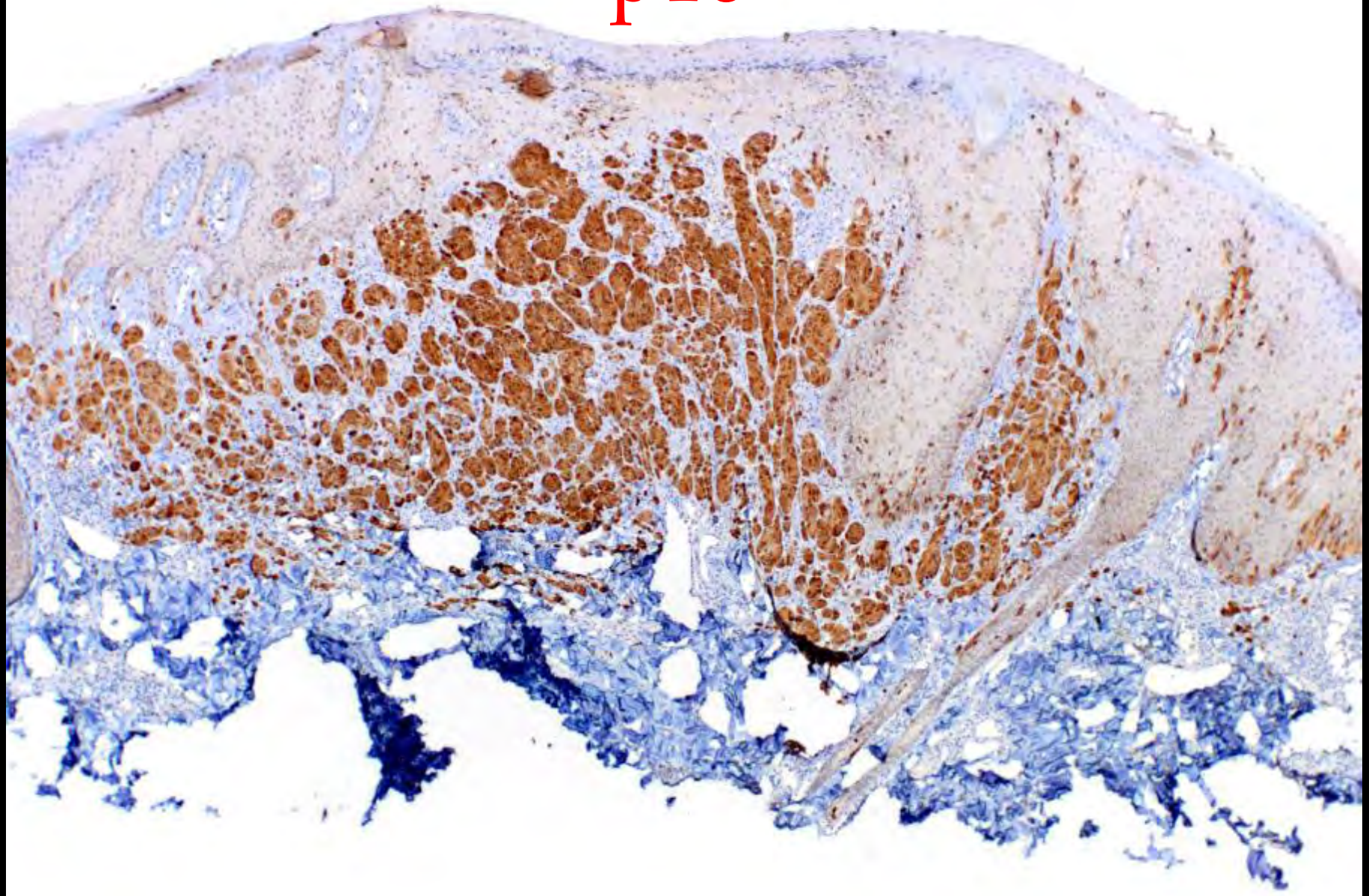


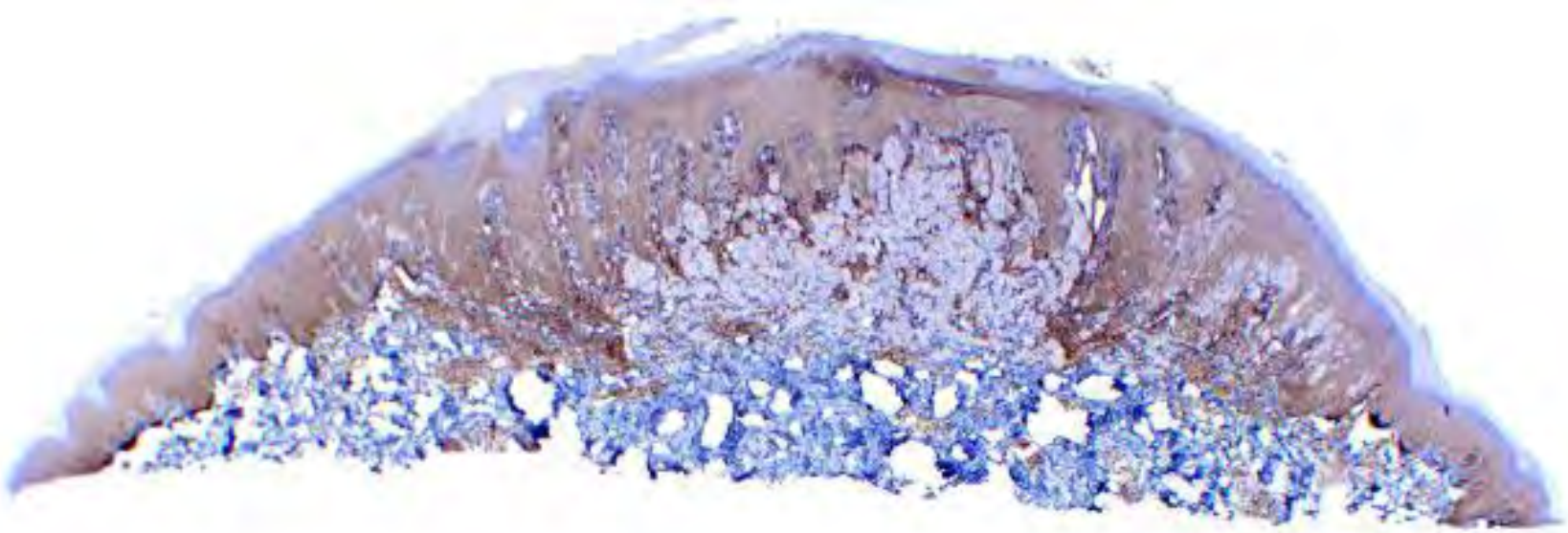
PRAME



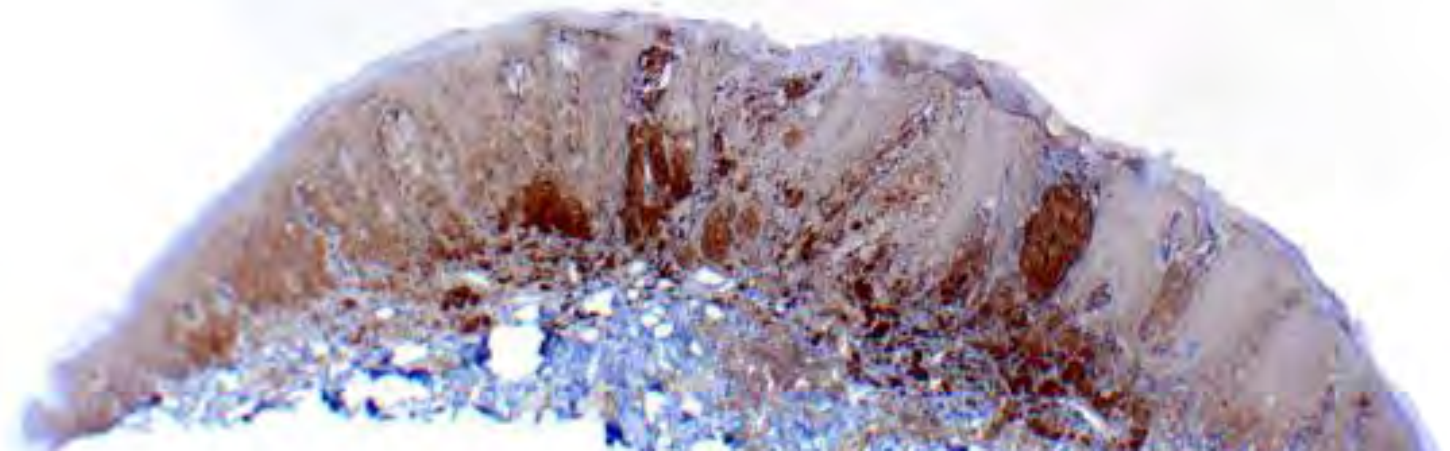


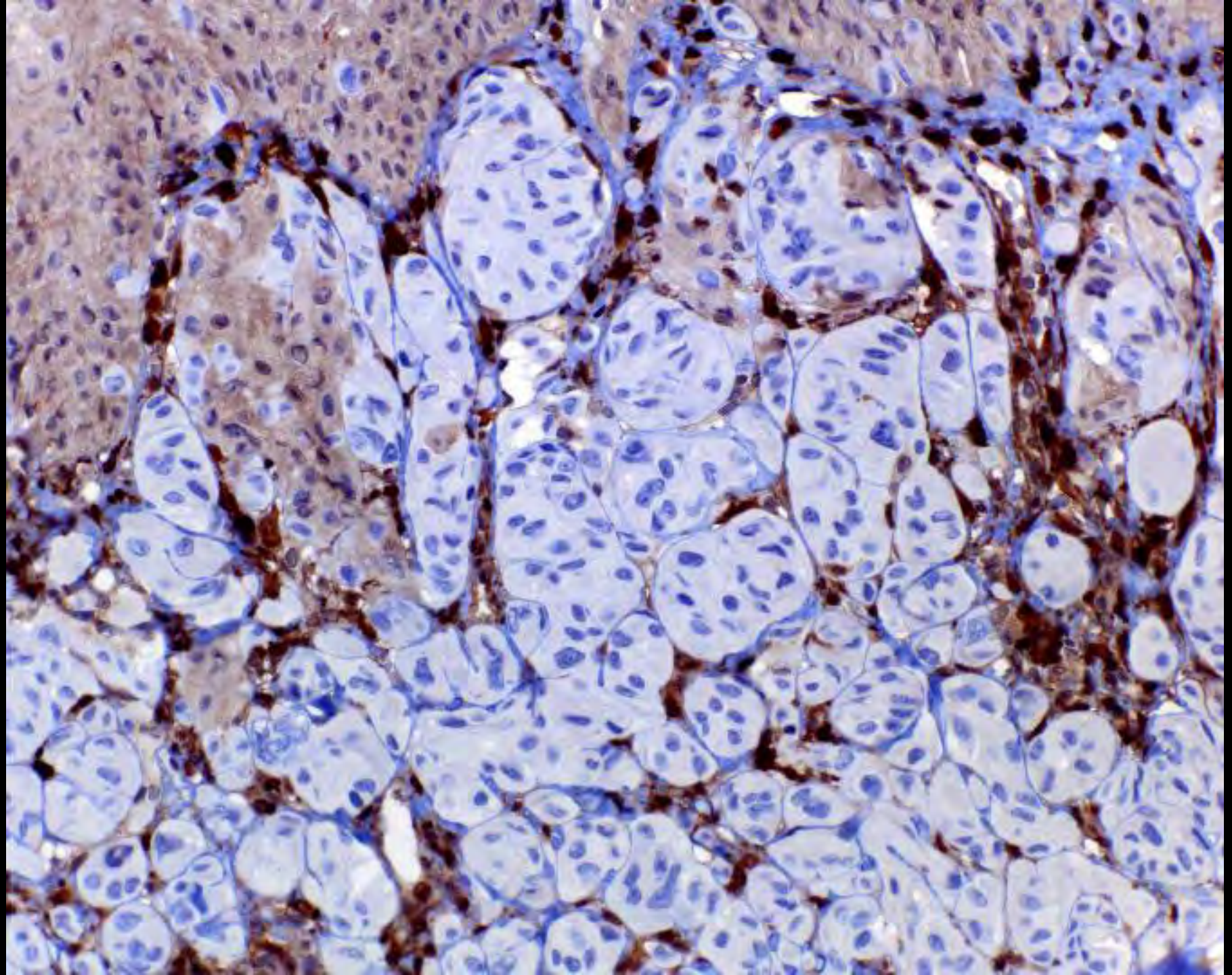
p16

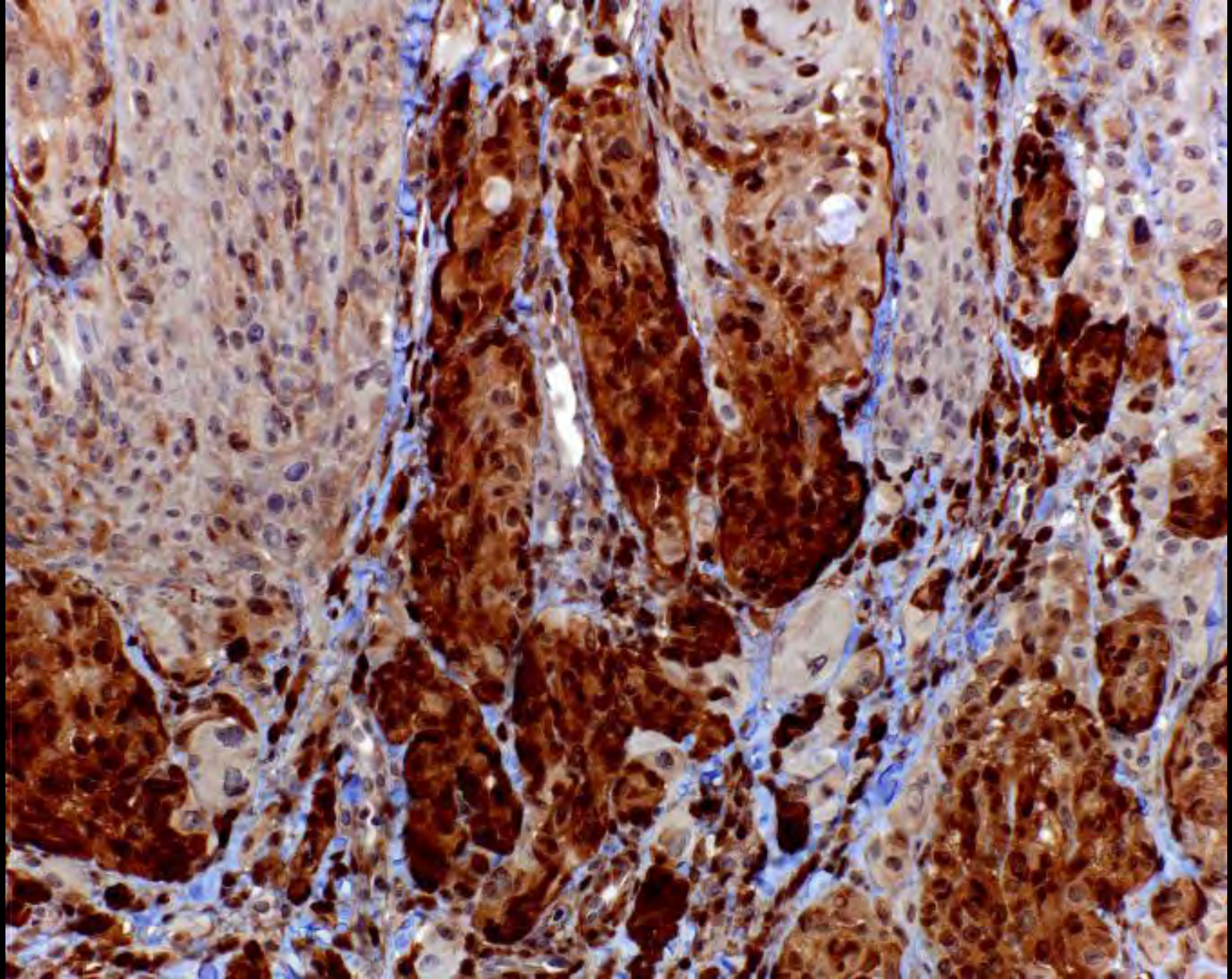




PTEN








ὀστρακισμός
• BRAF mutated, morphologically Spitzoid tumors
• BAP1 inactivated melanocytic tumors
• BLITZ tumors

BRAF Mutated and Morphologically Spitzoid Tumors, a Subgroup of Melanocytic Neoplasms Difficult to Distinguish From True Spitz Neoplasms

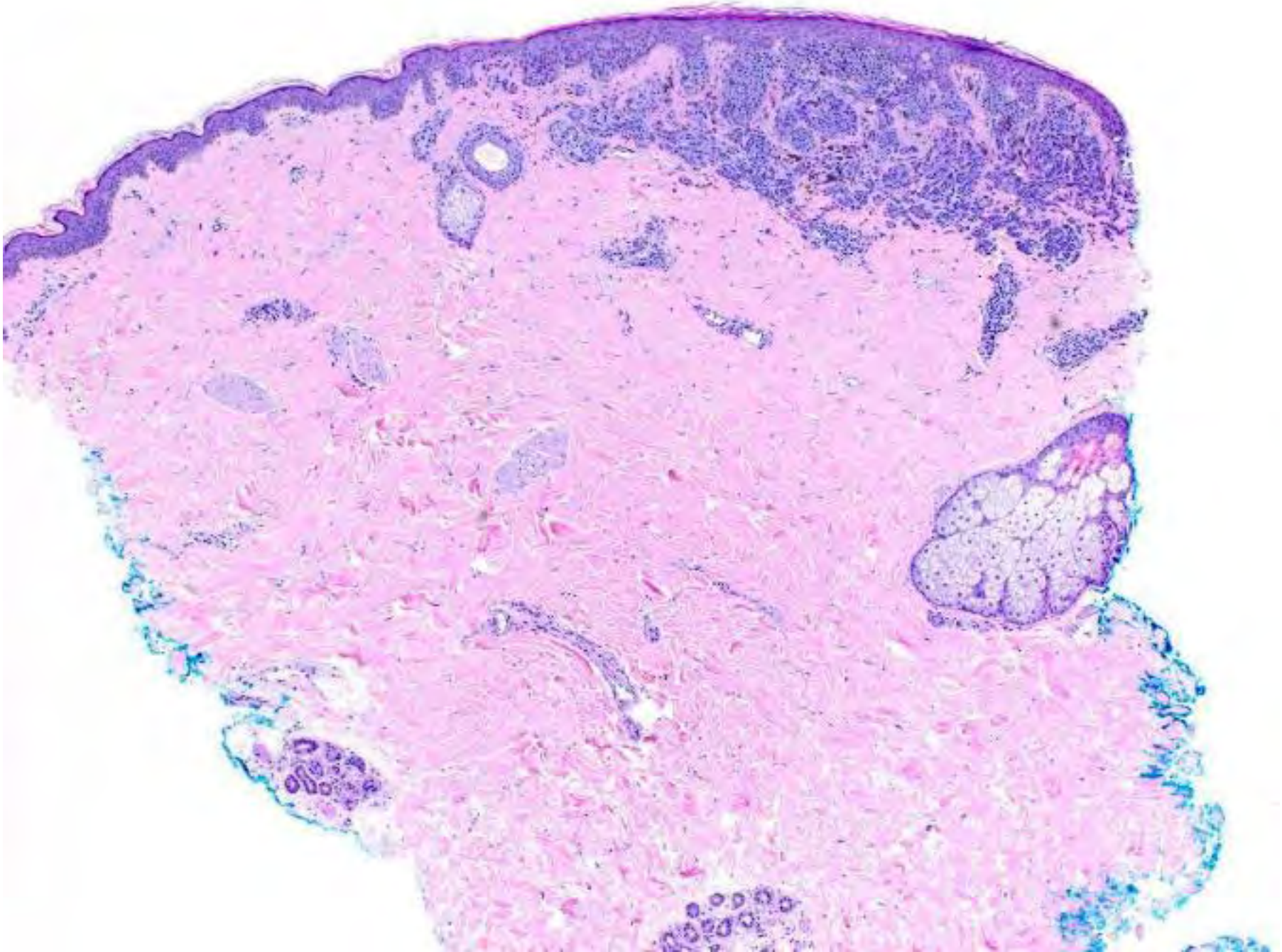
Pedram Gerami, MD, Alice Chen, BA,* Natasha Sharma, MS,* Pragi Patel, BS,* Michael Hagstrom, BA,* Pranav Kancherla, HS,* Tara Geraminejad, HS,* Shantel Olivares, BA,* Asok Biswas, MD,† Marcus Bosenberg, MD, PhD,‡ Klaus J. Busam, MD,§ Arnaud de La Fouchardière, MD, PhD,‖ Lyn M. Duncan, MD,¶ David E. Elder, MBChB,# Jennifer Ko, MD, PhD,** Gilles Landman, MD,†† Alexander J. Lazar, MD, PhD,‡‡ Lori Lowe, MD,§§ Daniela Massi, MD, PhD,‖‖ Daniela Mihic-Probst, MD,¶¶ Douglas C. Parker, MD,## Richard A. Scolyer, MD,***†††‡‡‡ Christopher R. Shea, MD,§§§ Artur Zembowicz, MD, PhD,‖‖‖ Sook Jung Yun, MD, PhD,¶¶¶ Willeke A.M. Blokx, MD,### and Raymond L. Barnhill, MD*****

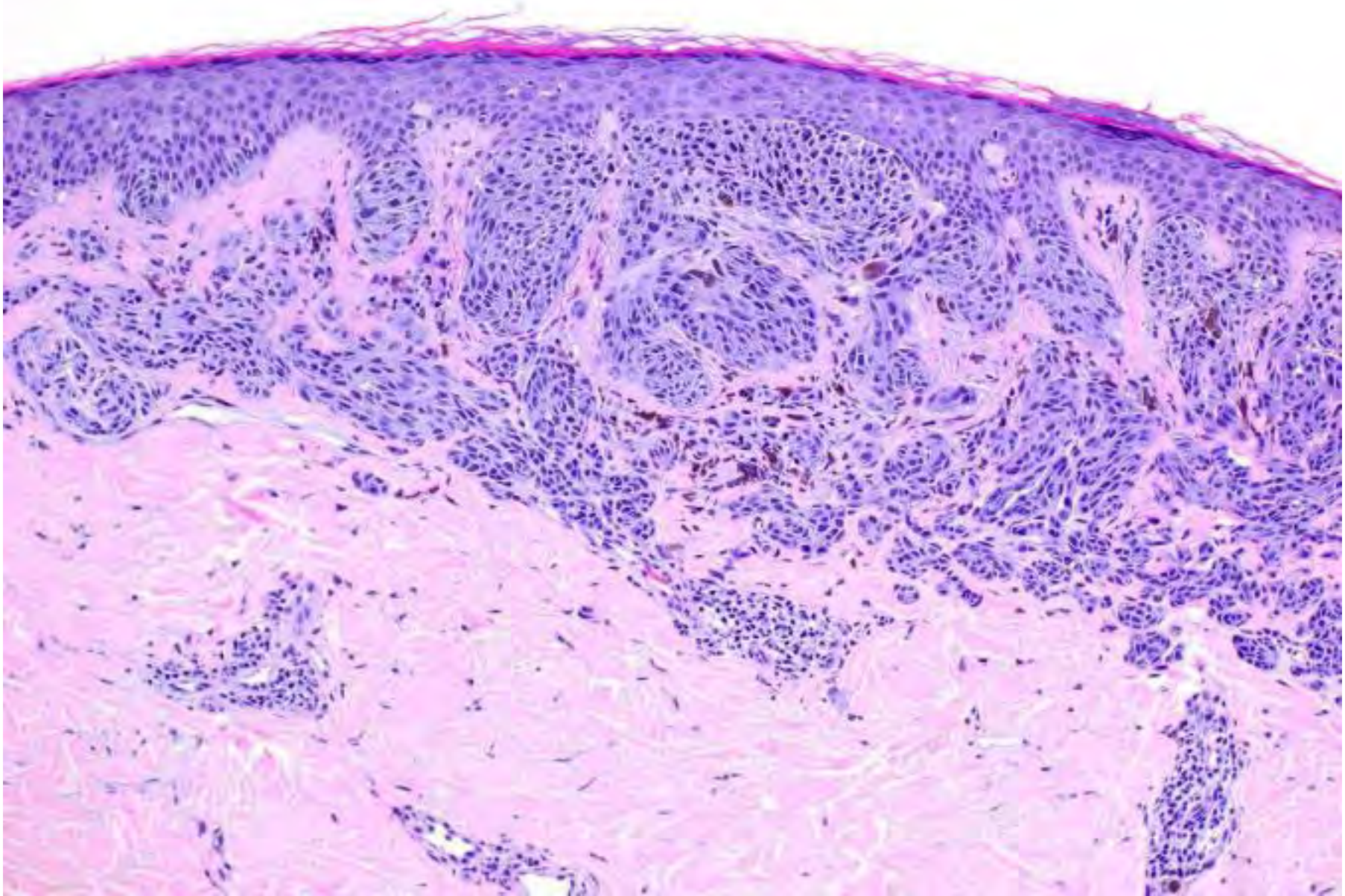
(*Am J Surg Pathol* 2024;48:538–545)

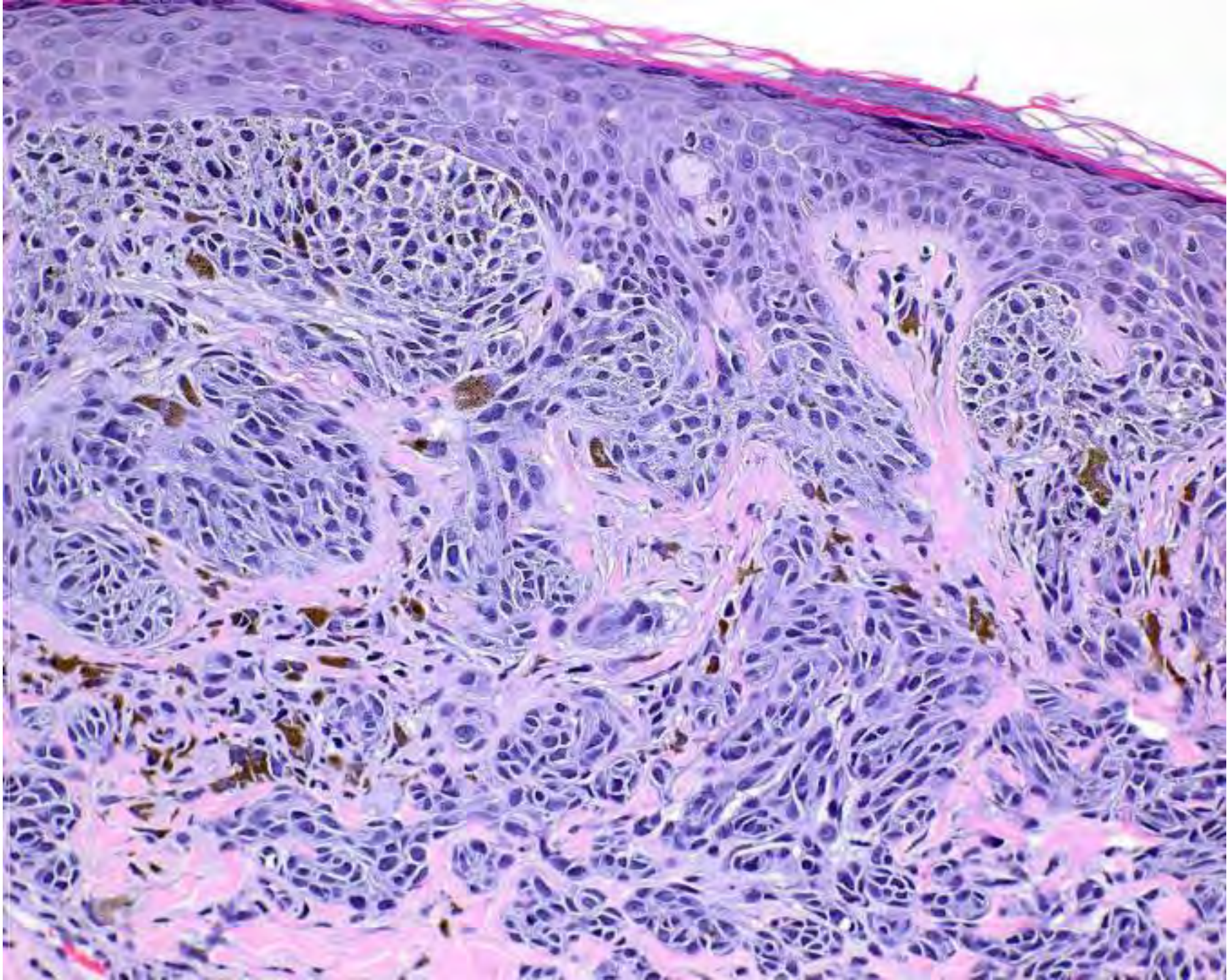
BRAF Mutated Spitz nevus

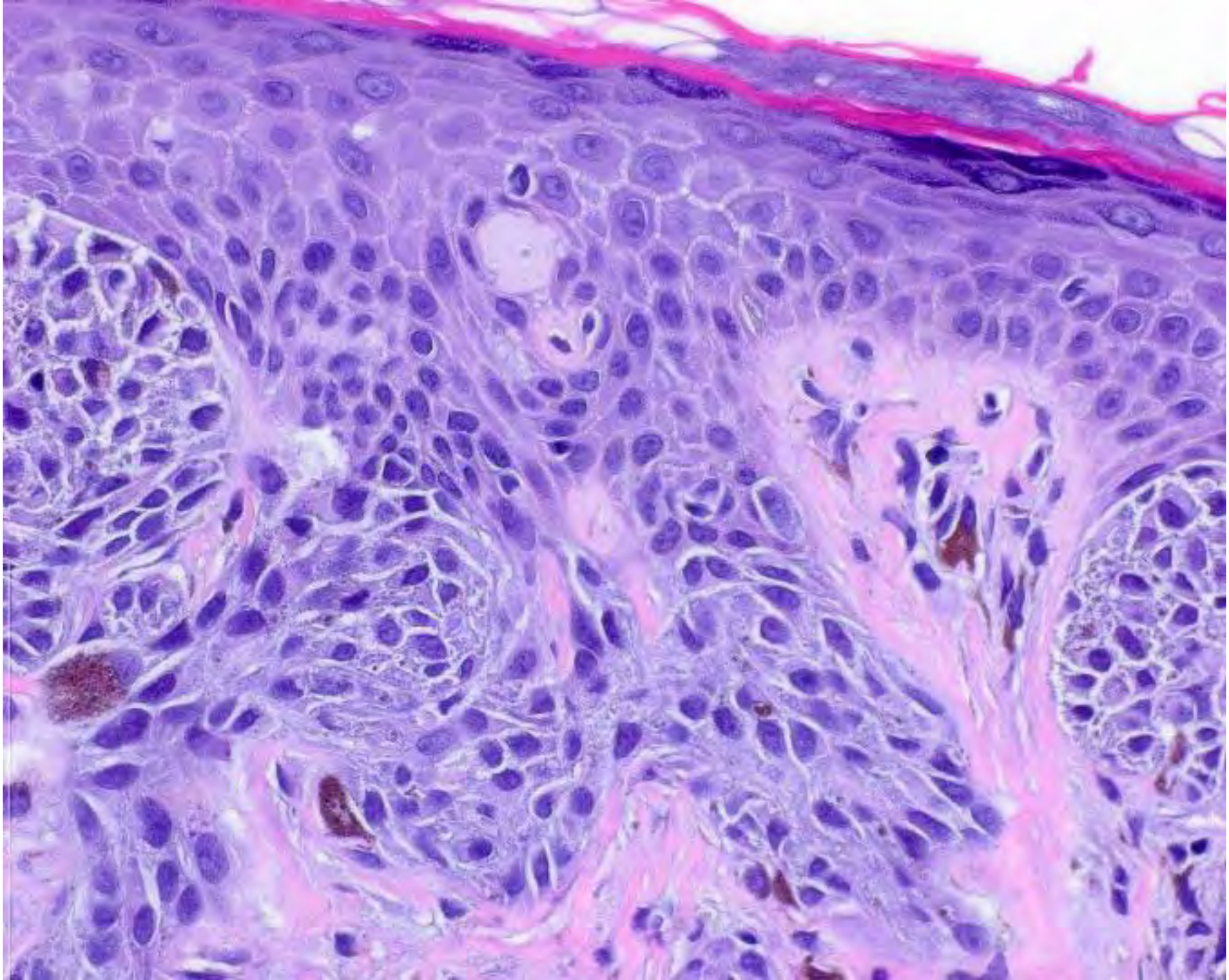
- Often on thighs
- Kamino bodies present, but small
- No component of common nevus
- Pulverocytes absent or few
- Classic Spitz cells (homogeneous cytoplasm, clefts)
- No or few additional mutations, copy number changes in limited data

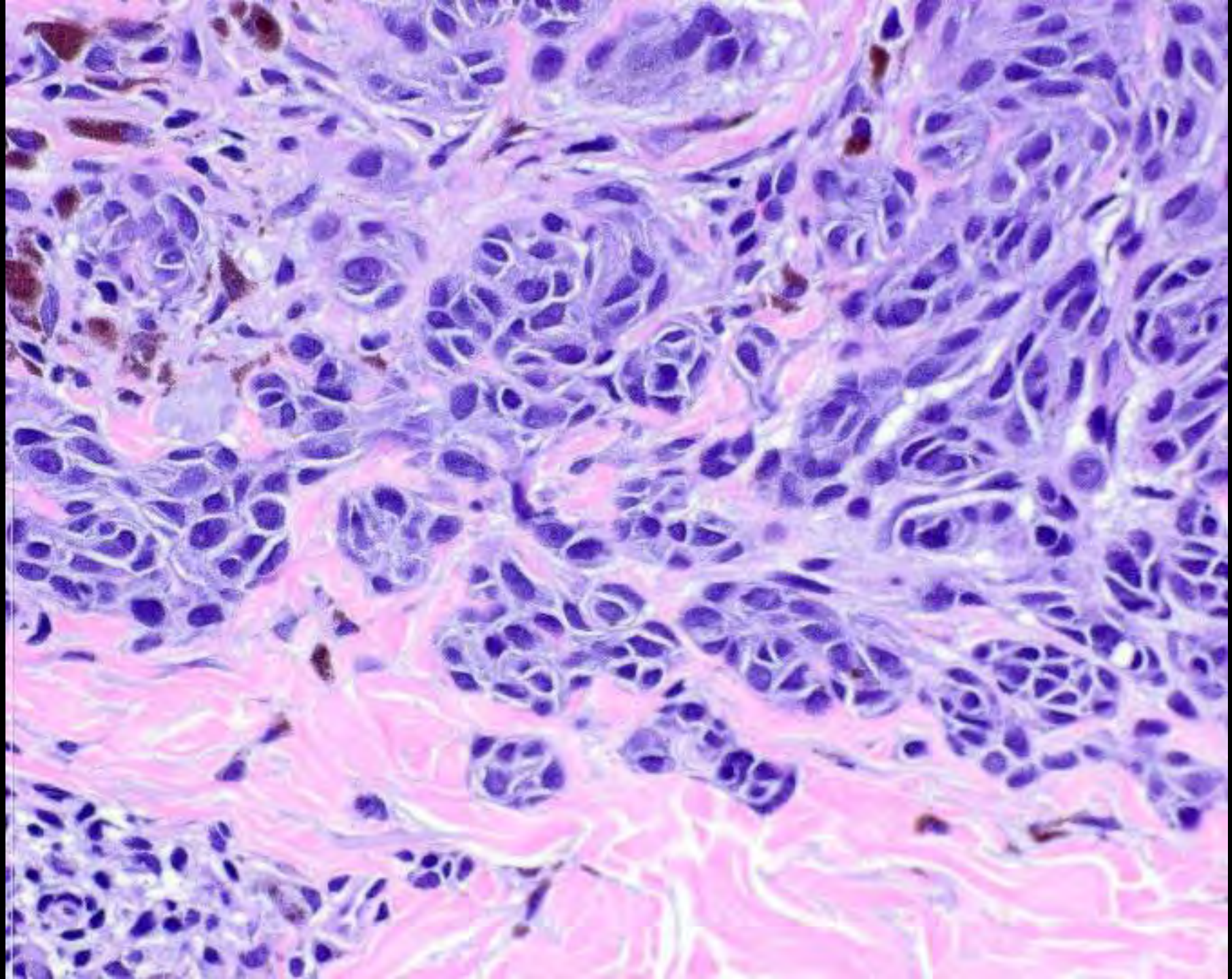
- Currently, I am concerned about genomic instability > WHO approved Spitz nevus but WHO knows….



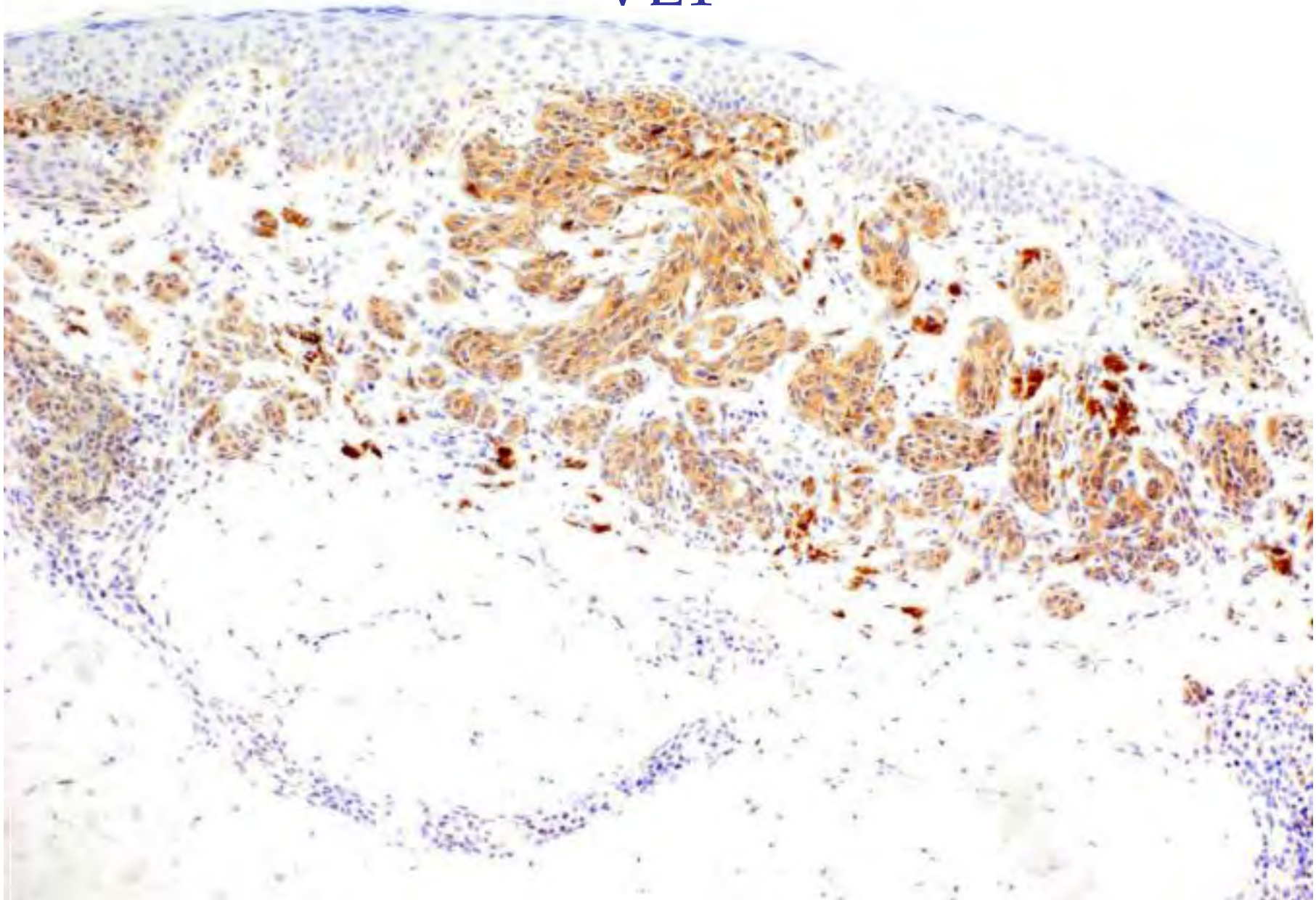








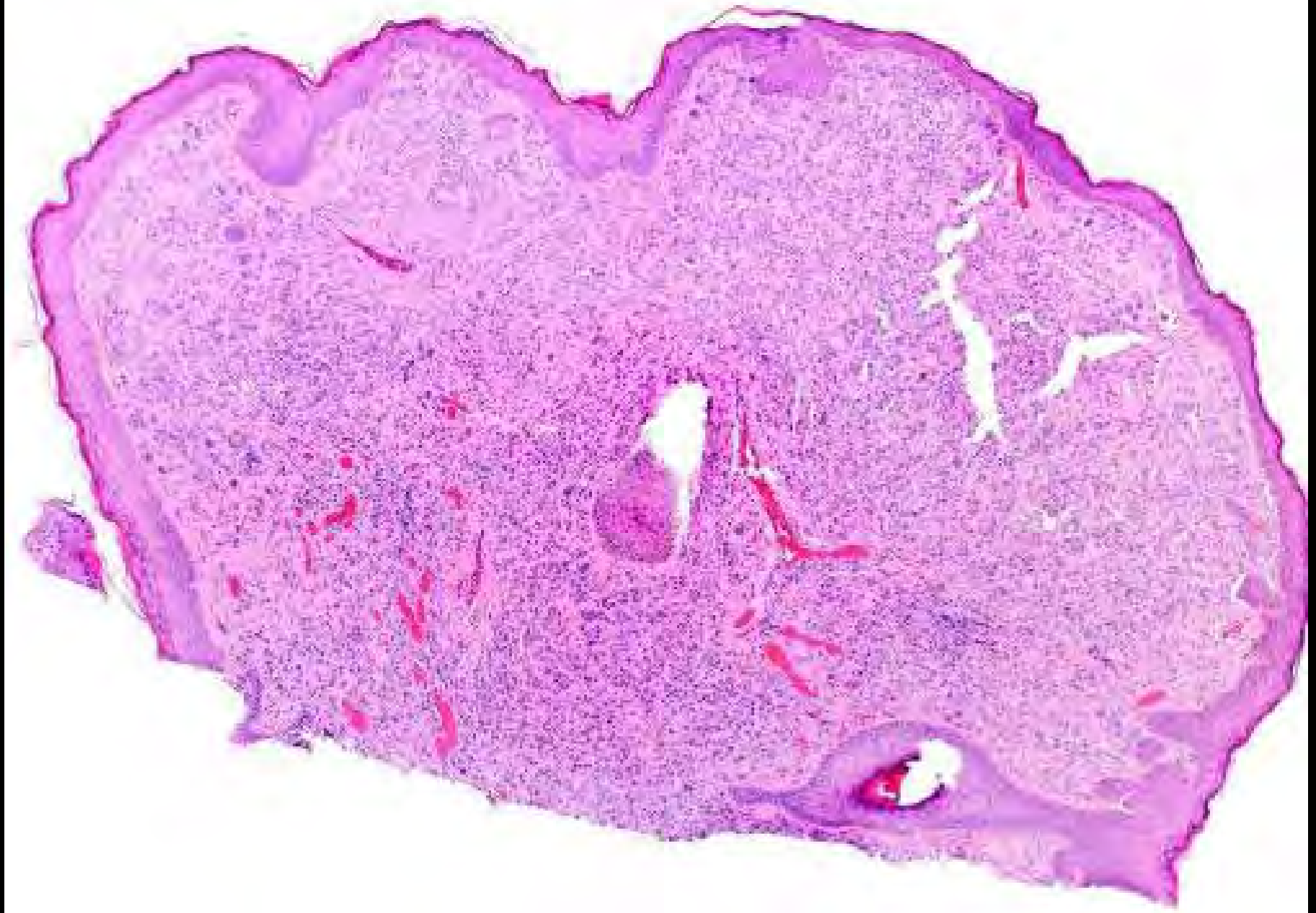
VE1

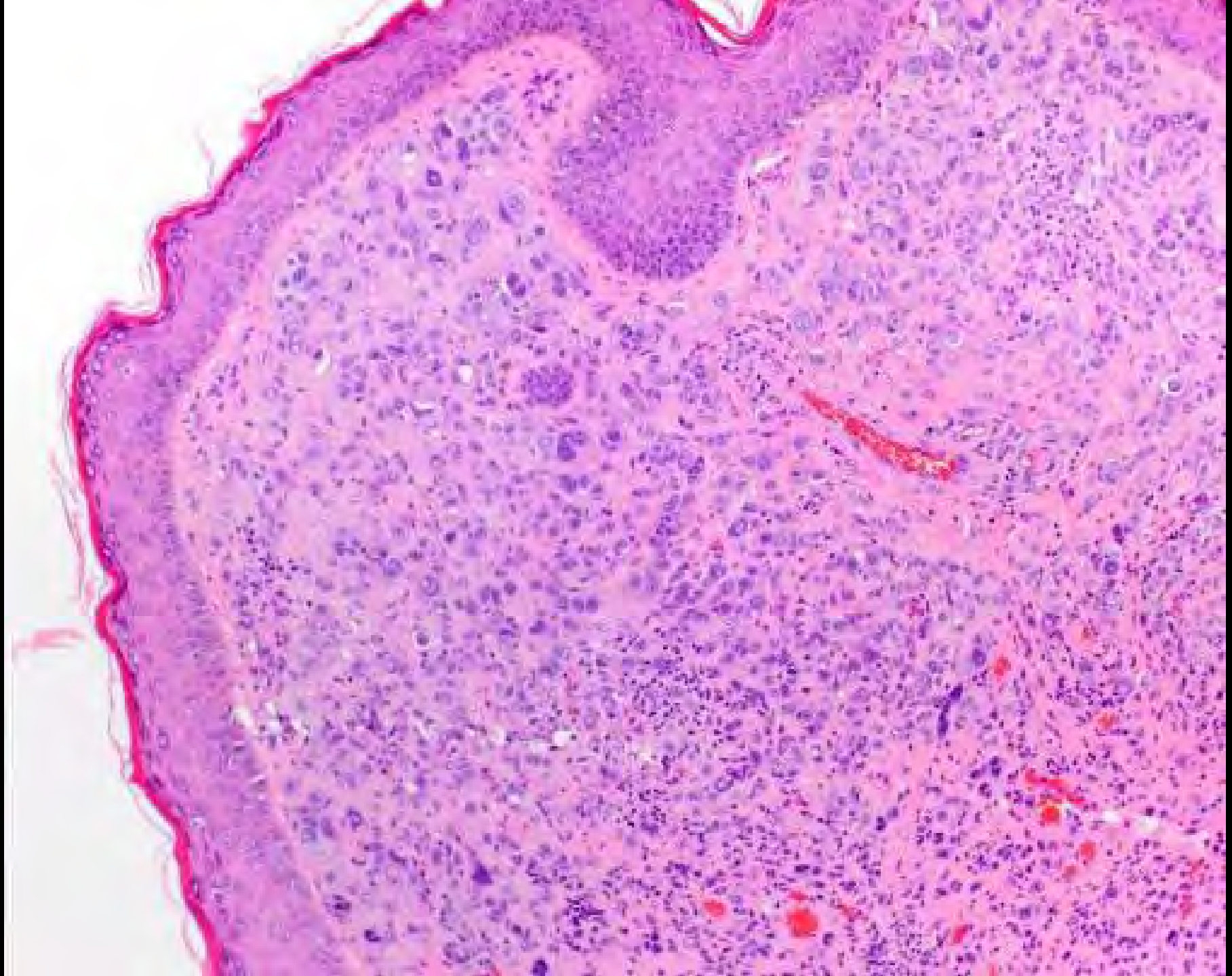


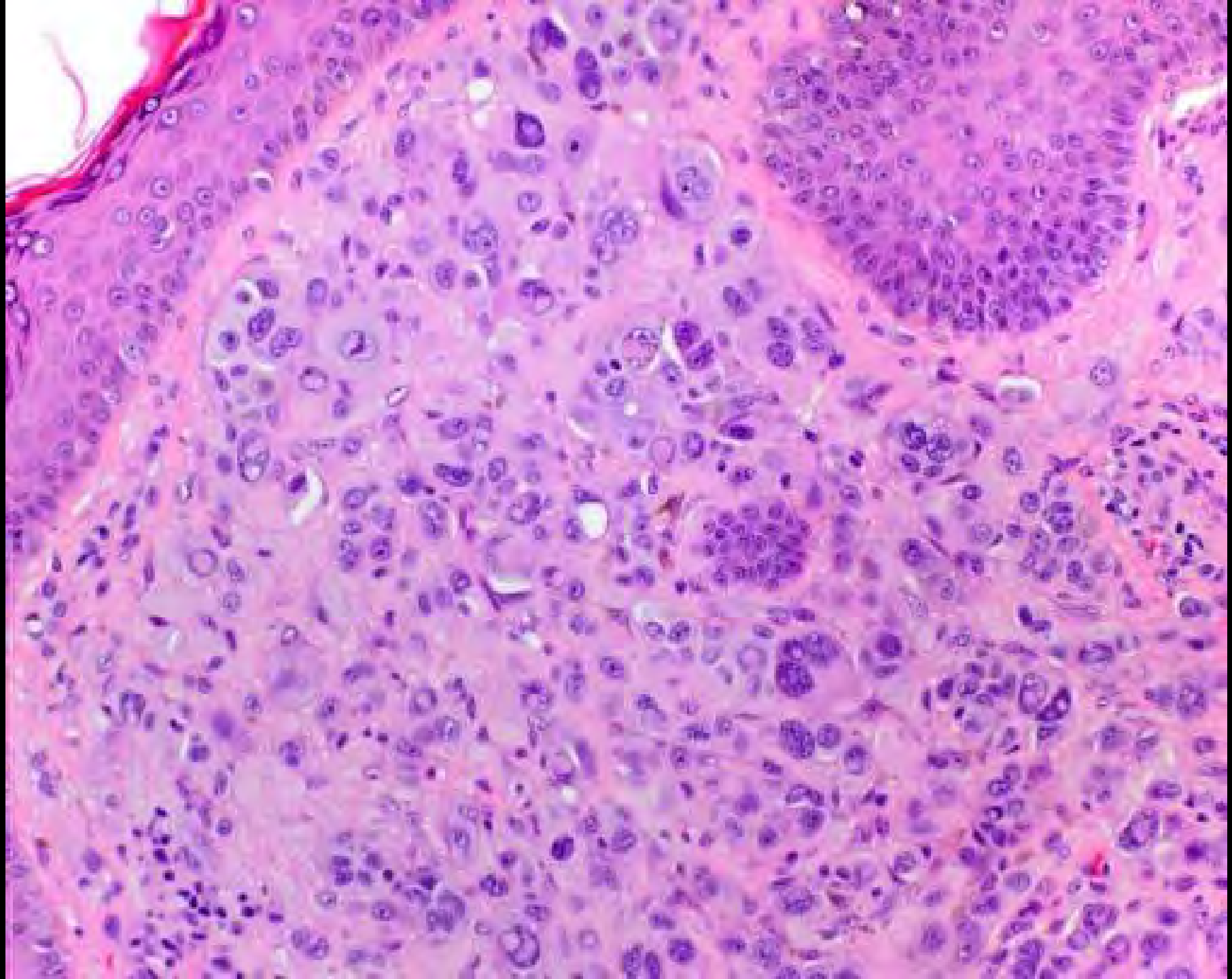
11 year old girl

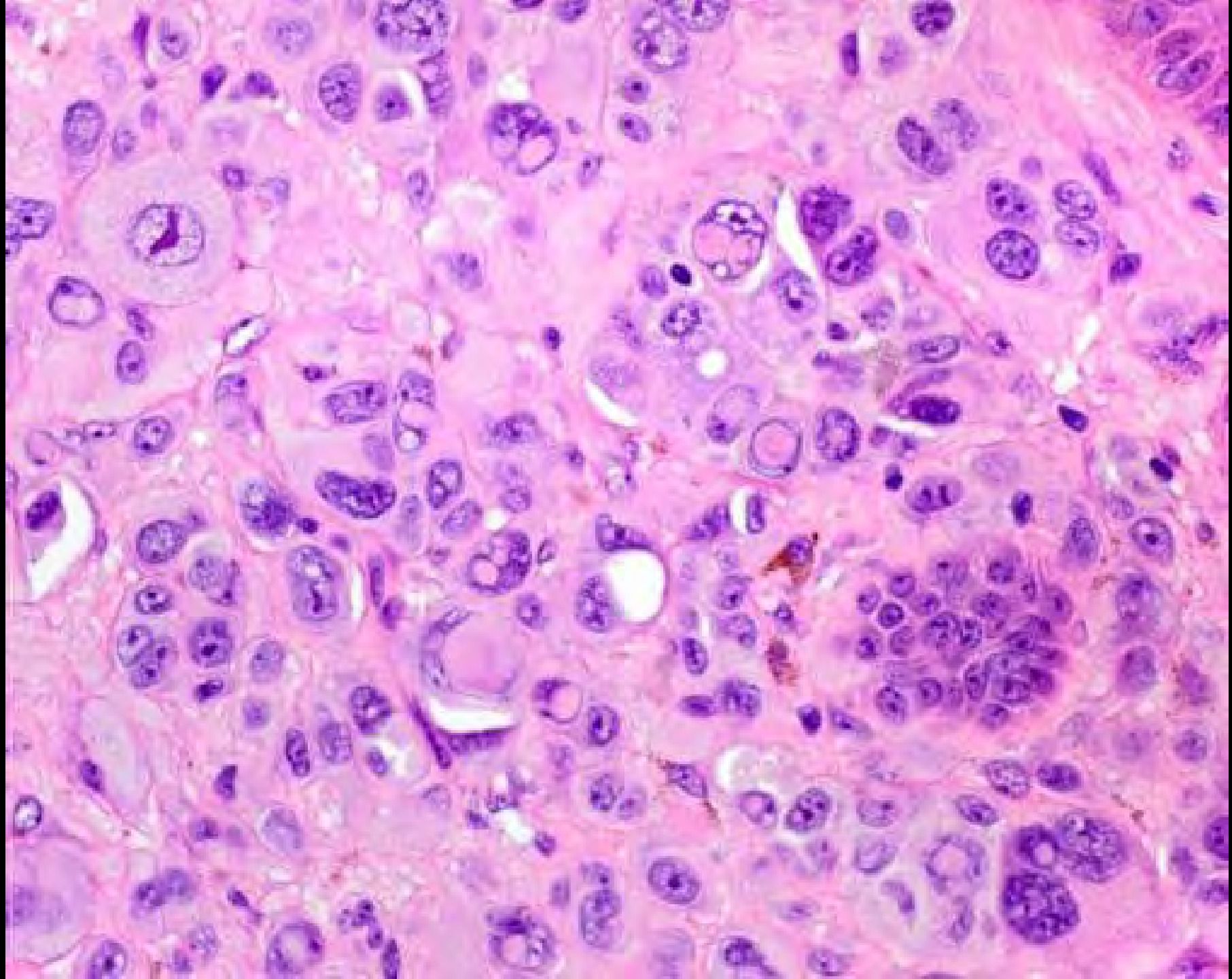
11 year old girl

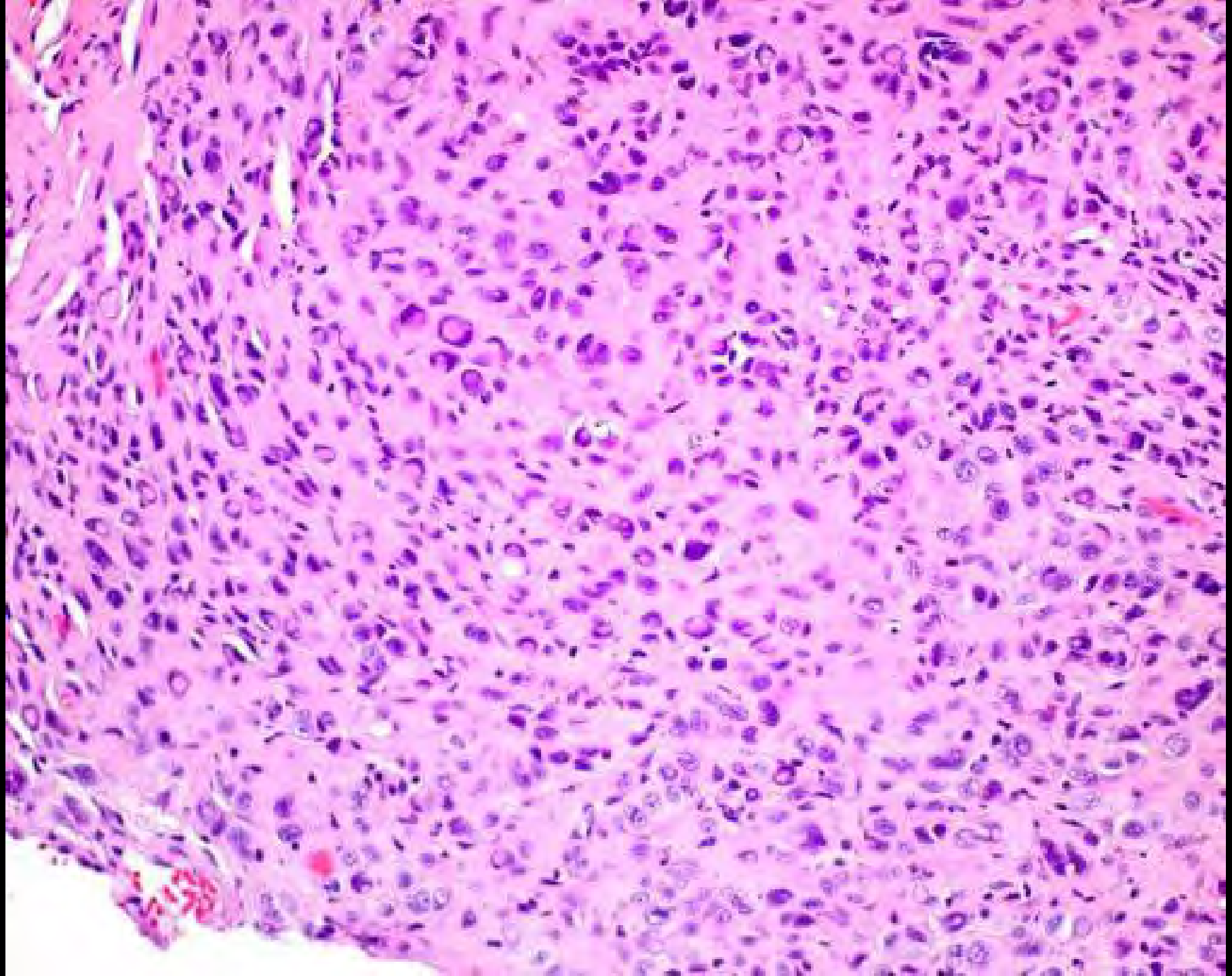
- BRAF V600E
- Deep deletion, CDKN2A,B
- Loss of chr. 18

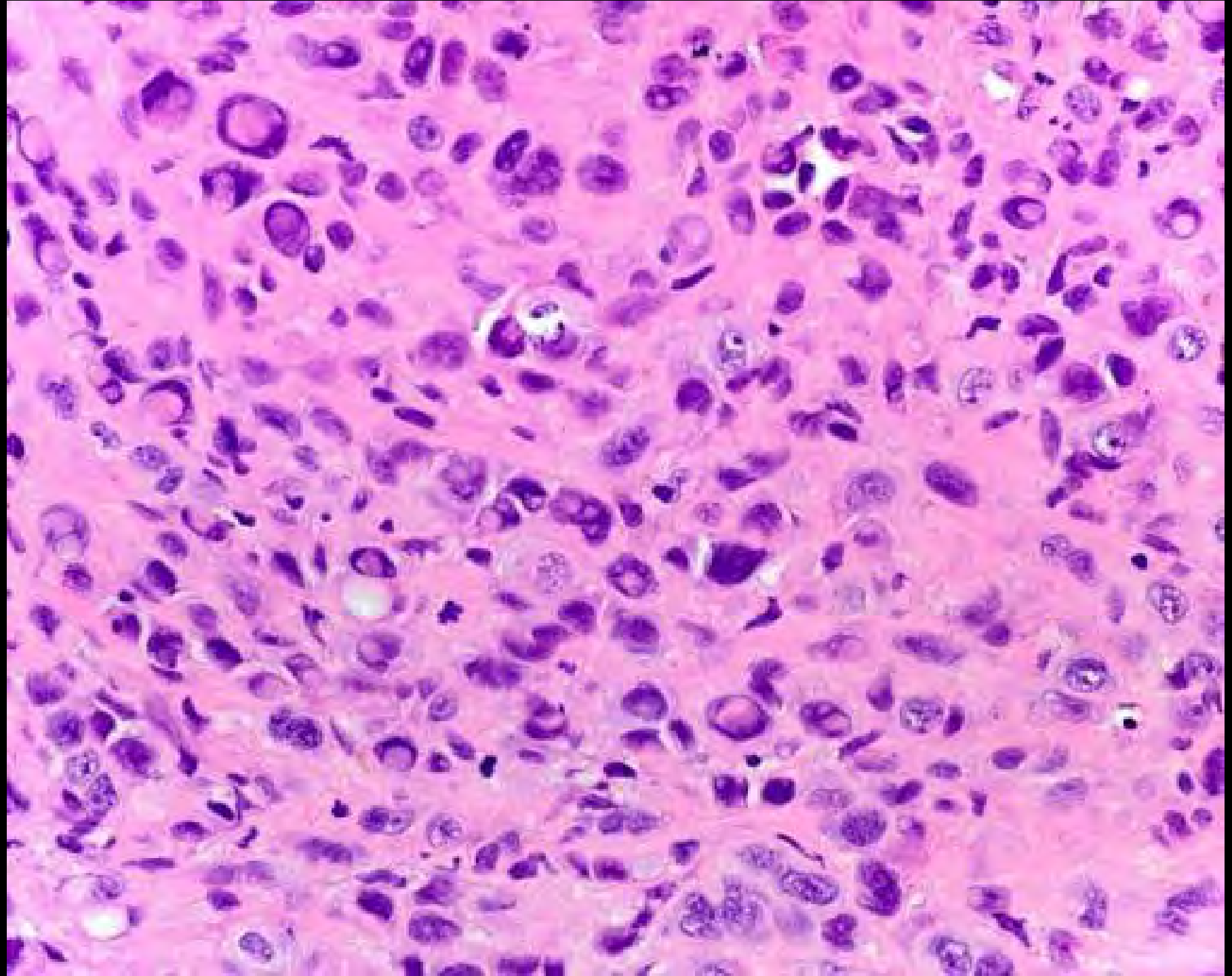




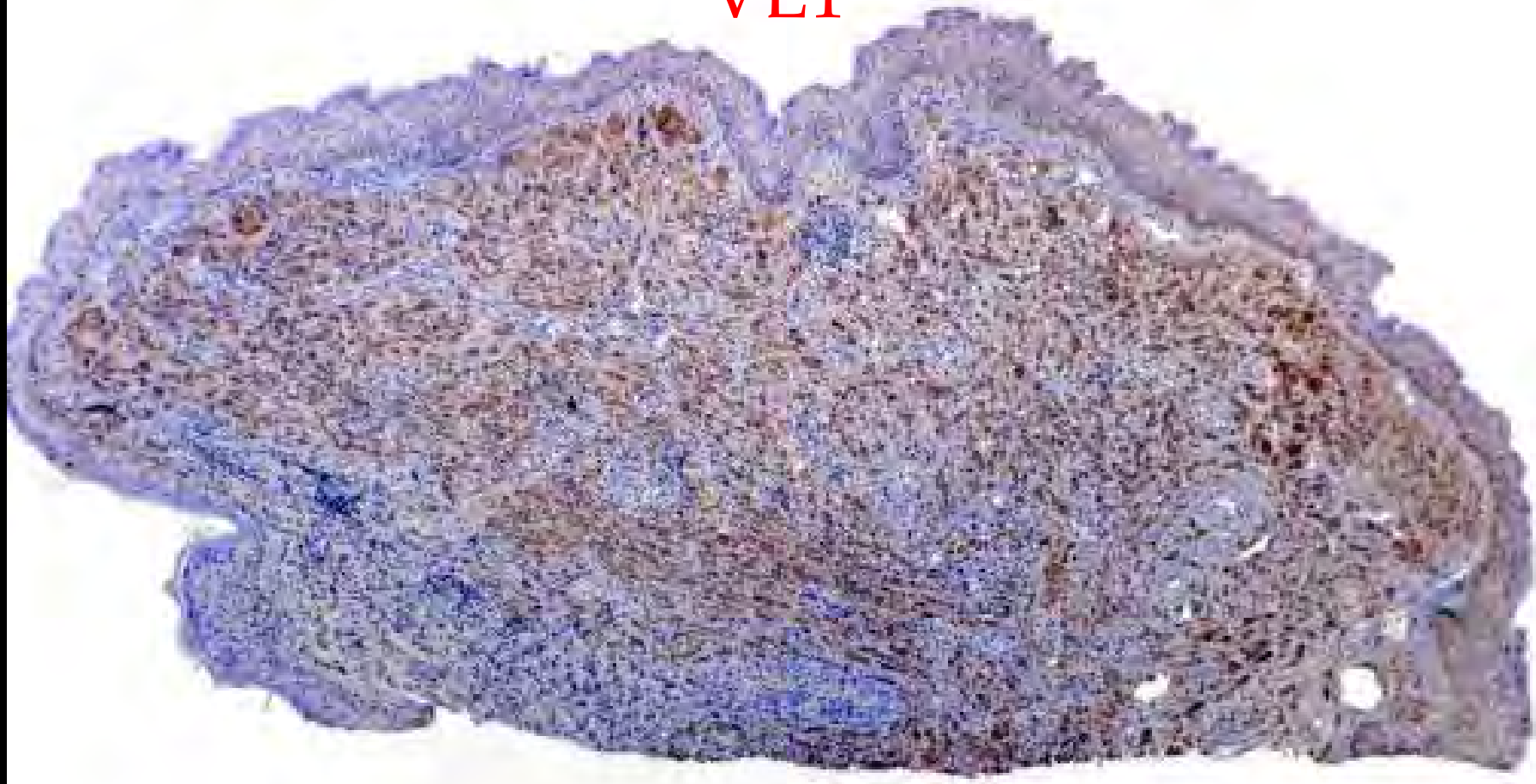


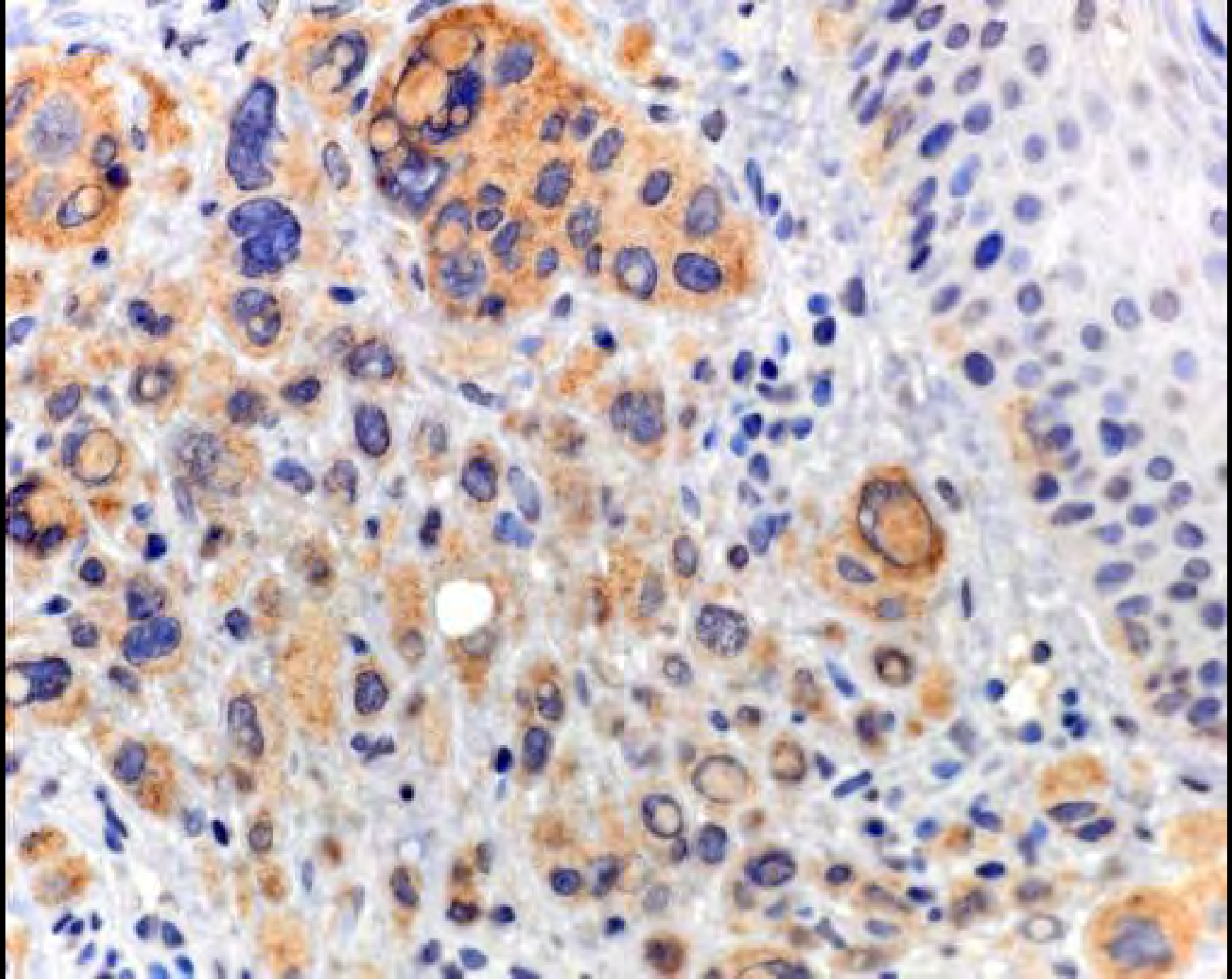


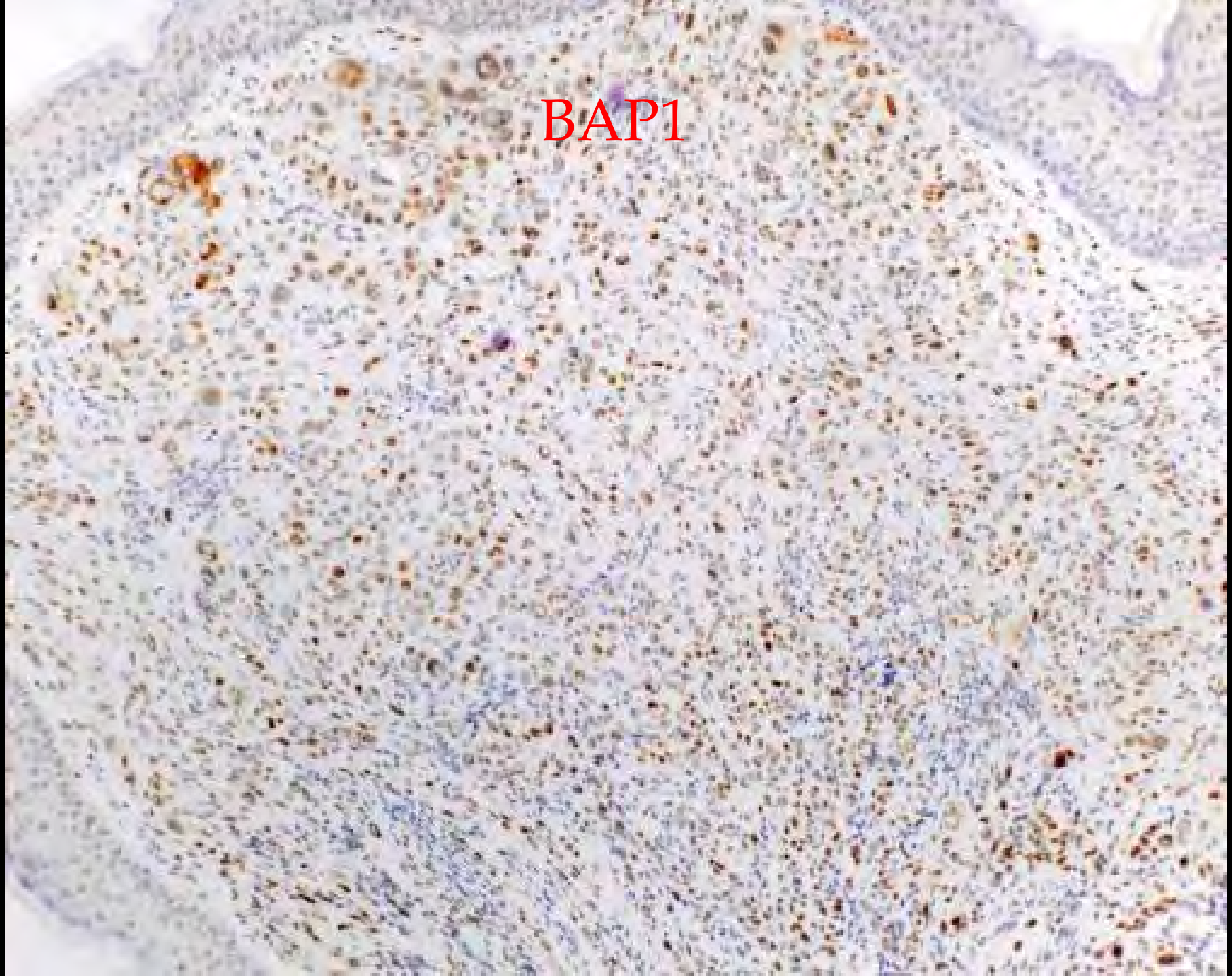


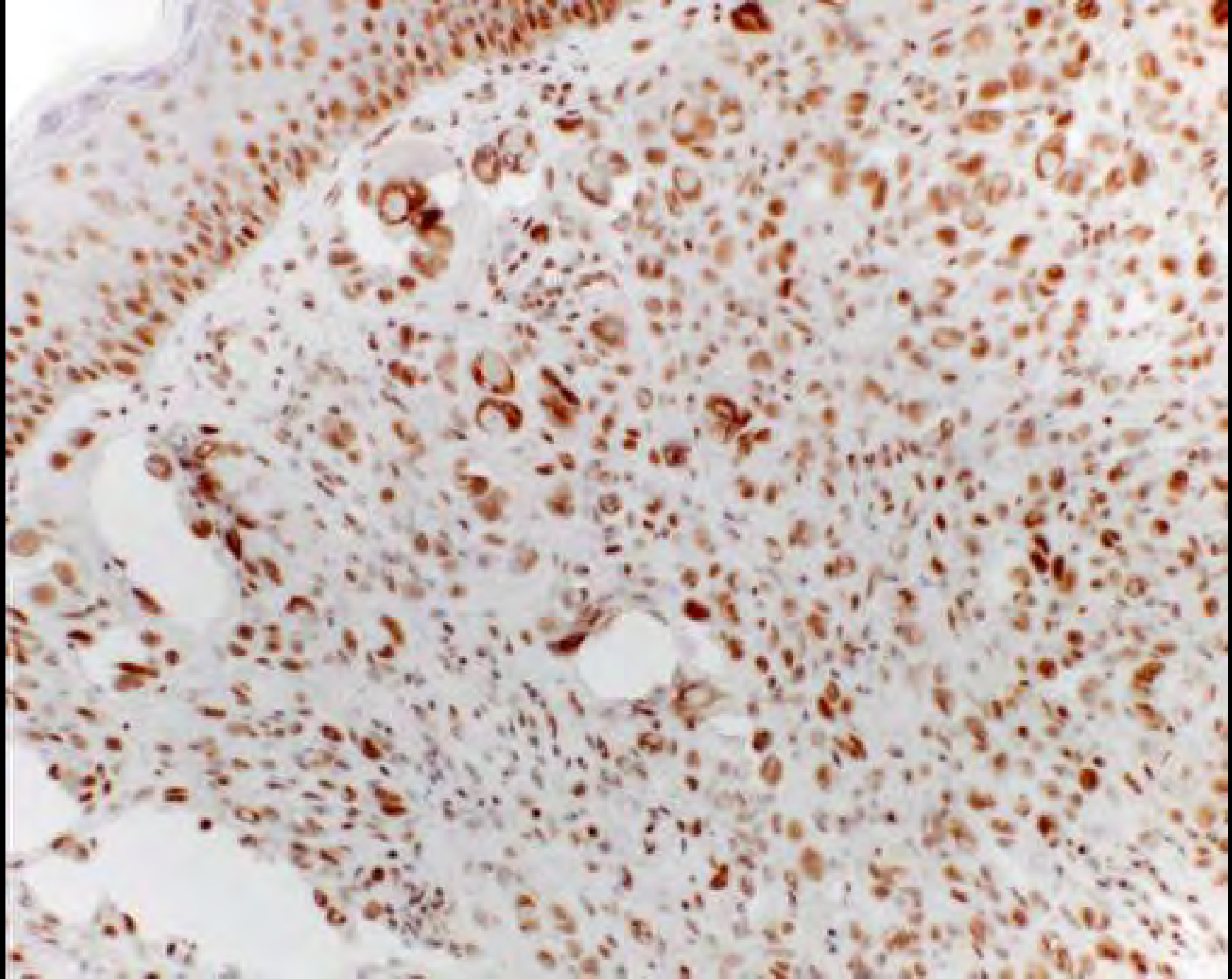


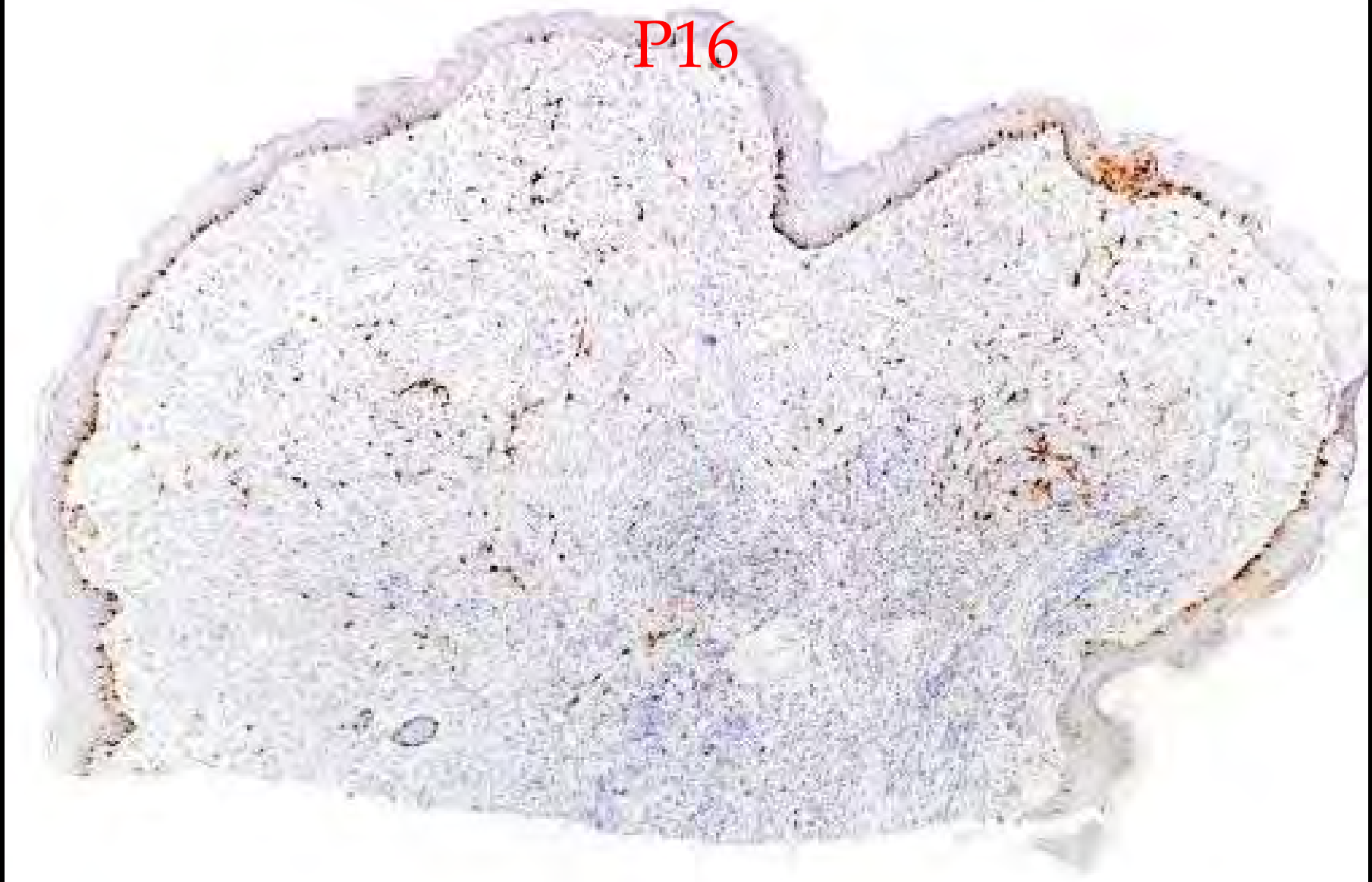
VE1

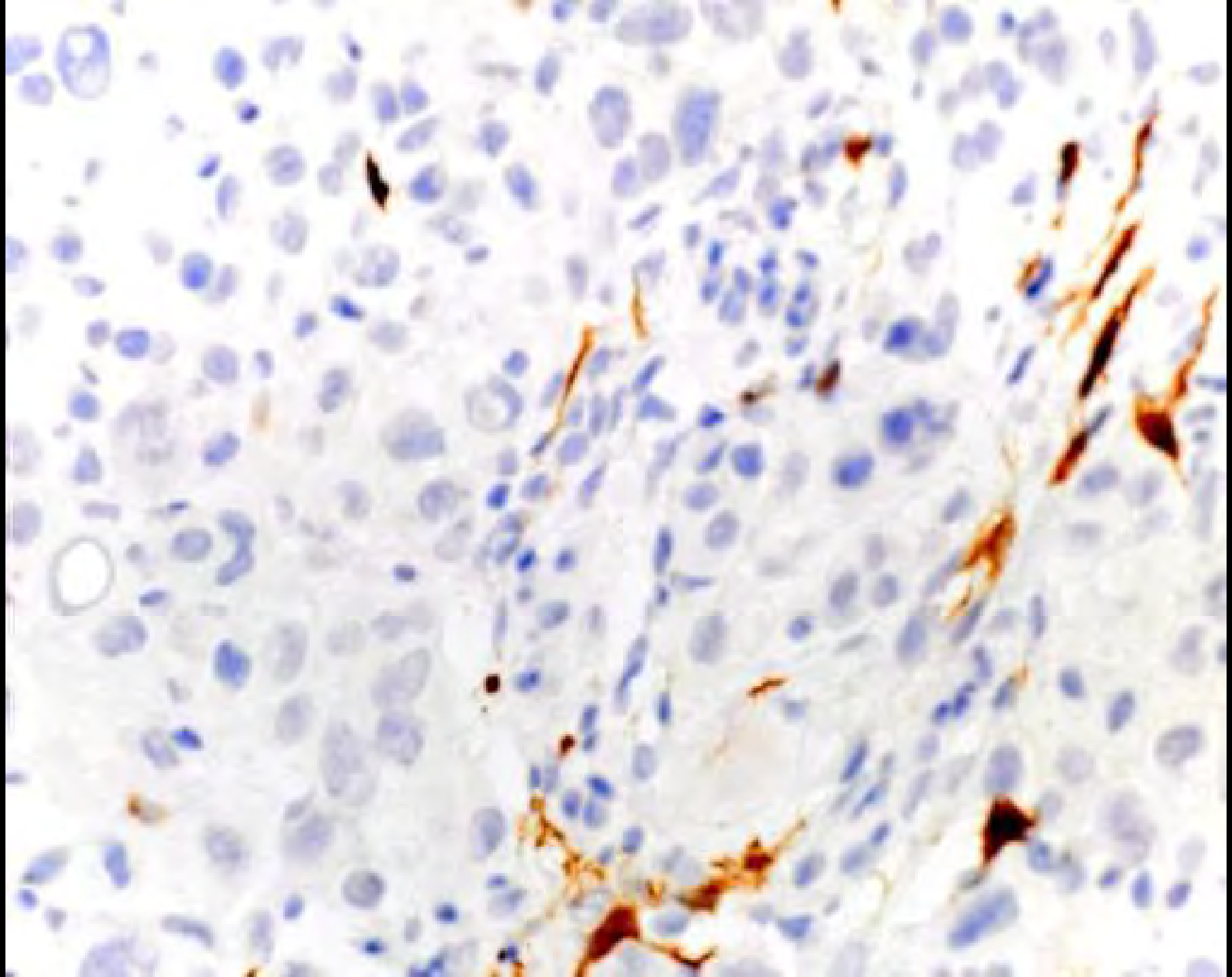





BAP1

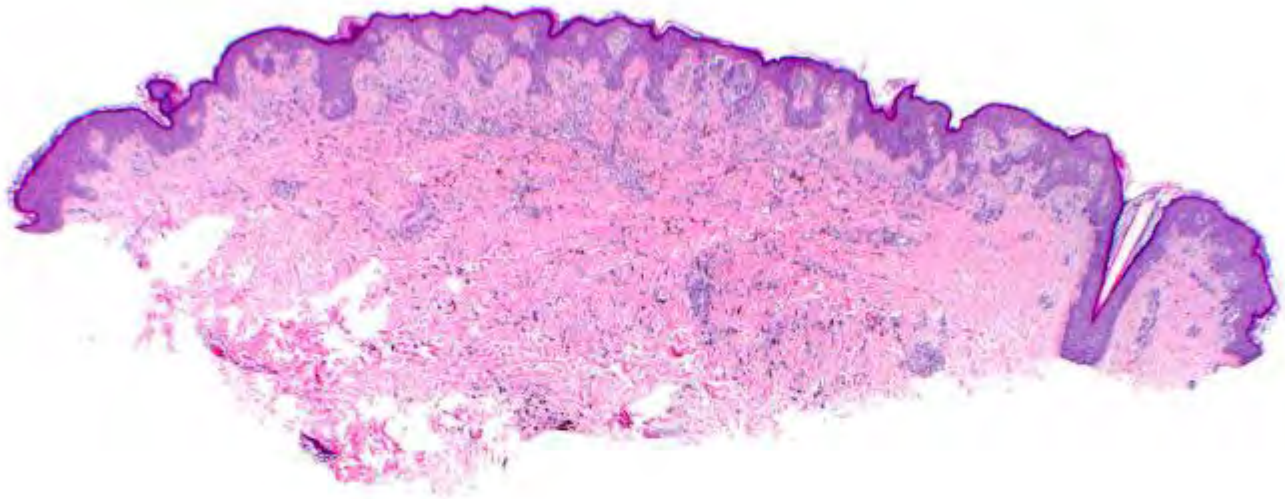


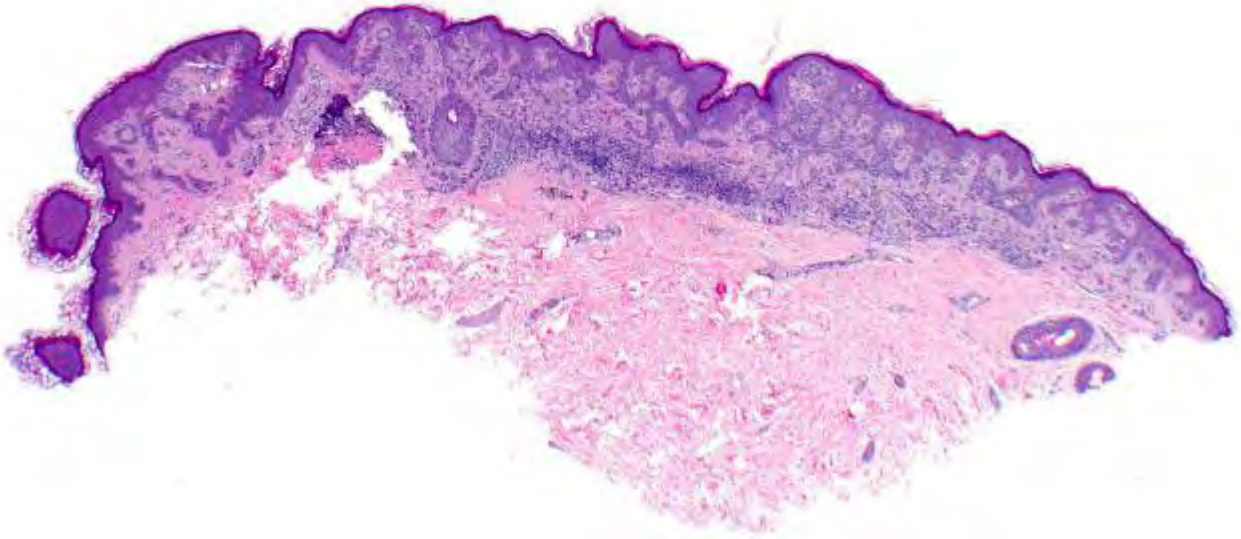

P16

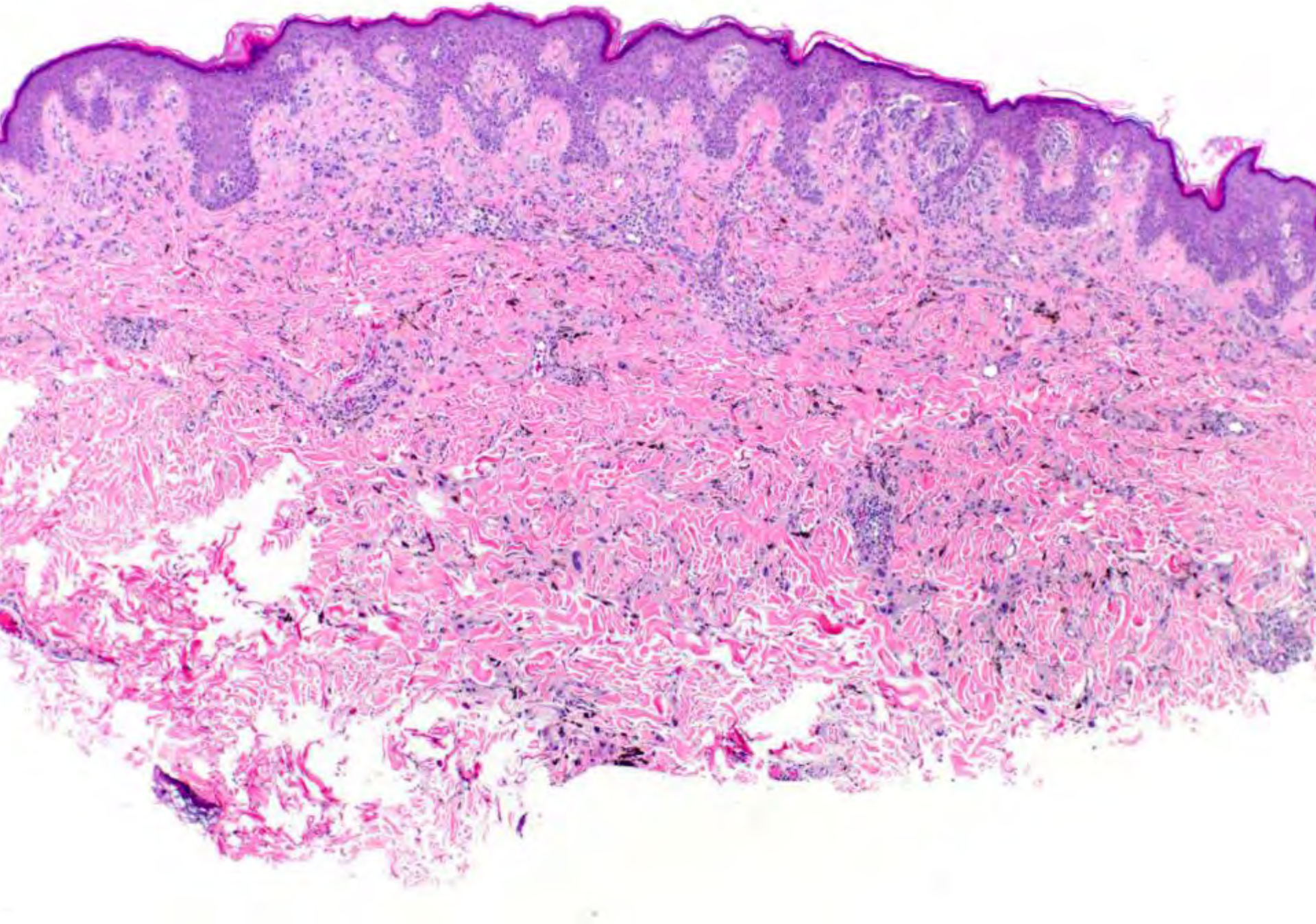


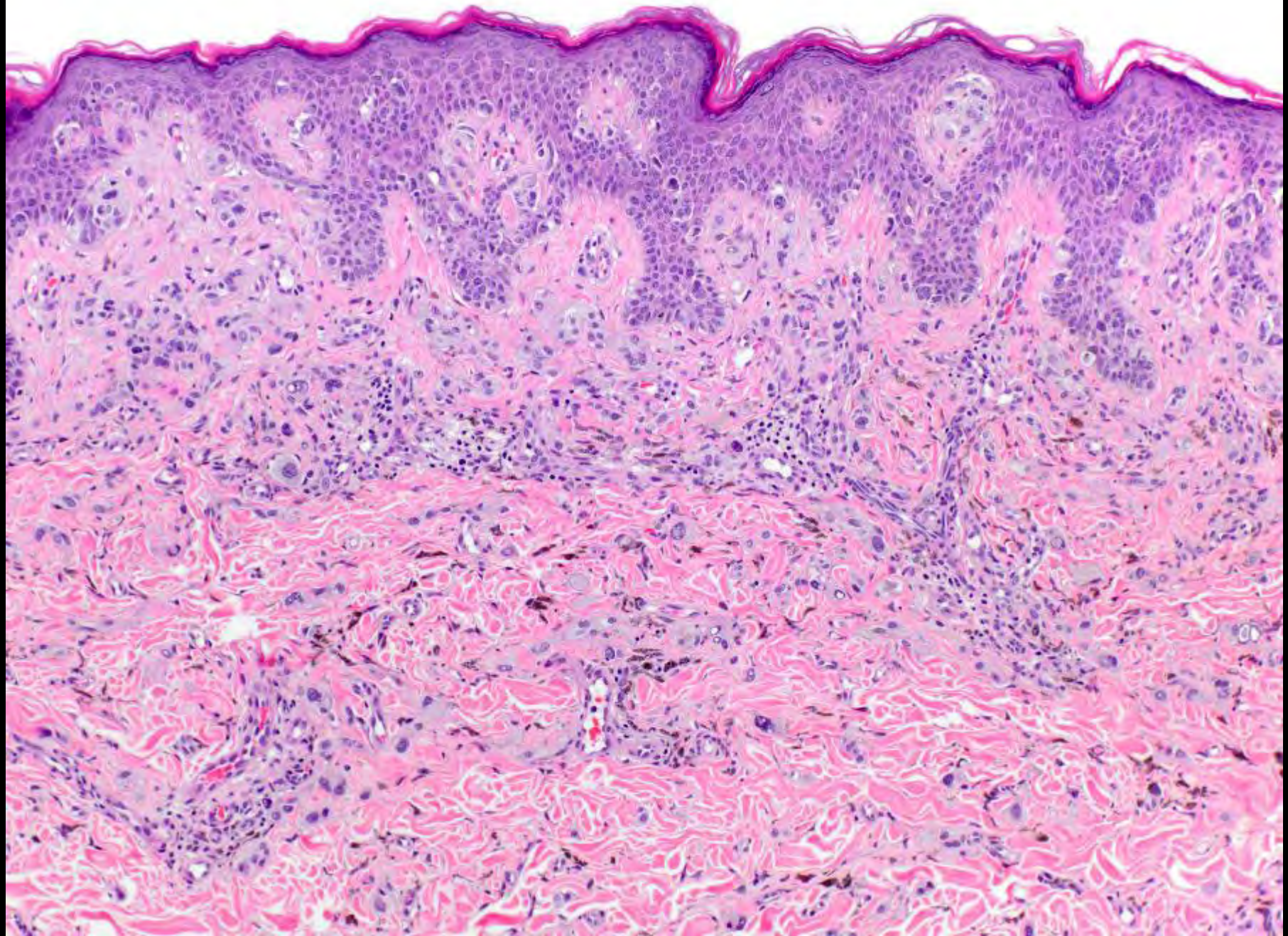
20 year old woman, inner thigh

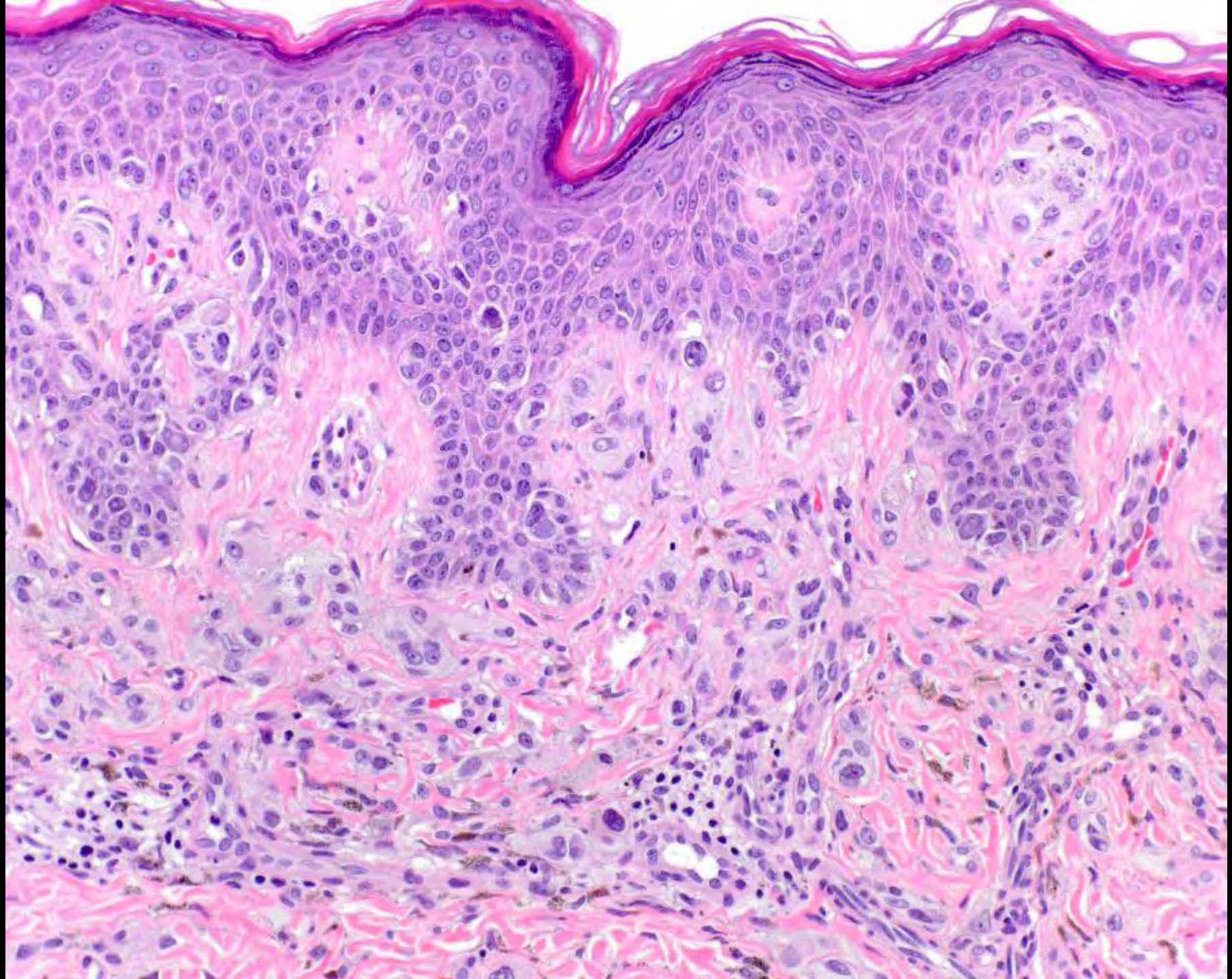
- BRAF V600E initiating mutation,
- mutations were present in the DNA repair gene ATM
- and in CDKN2A, which codes for p16

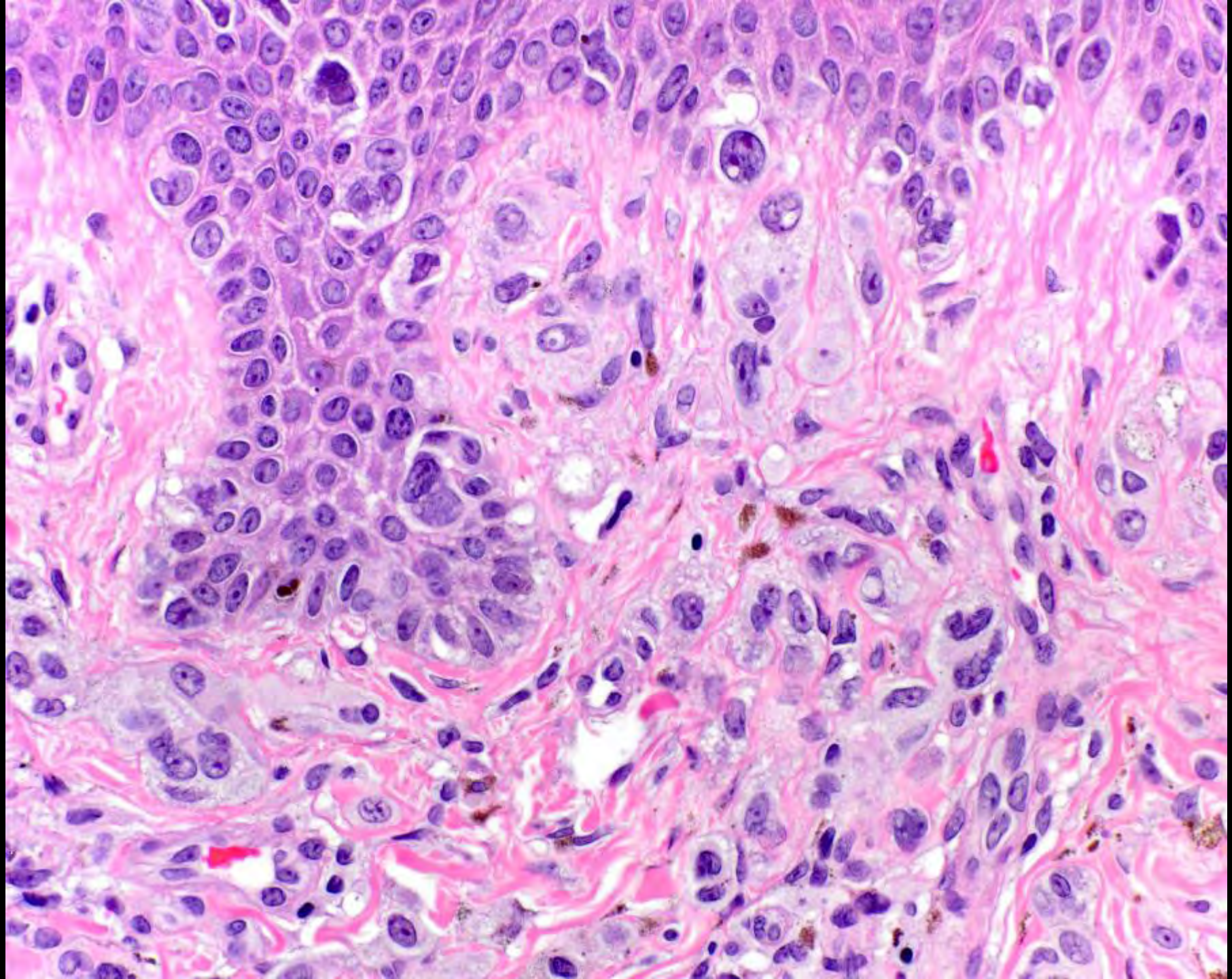


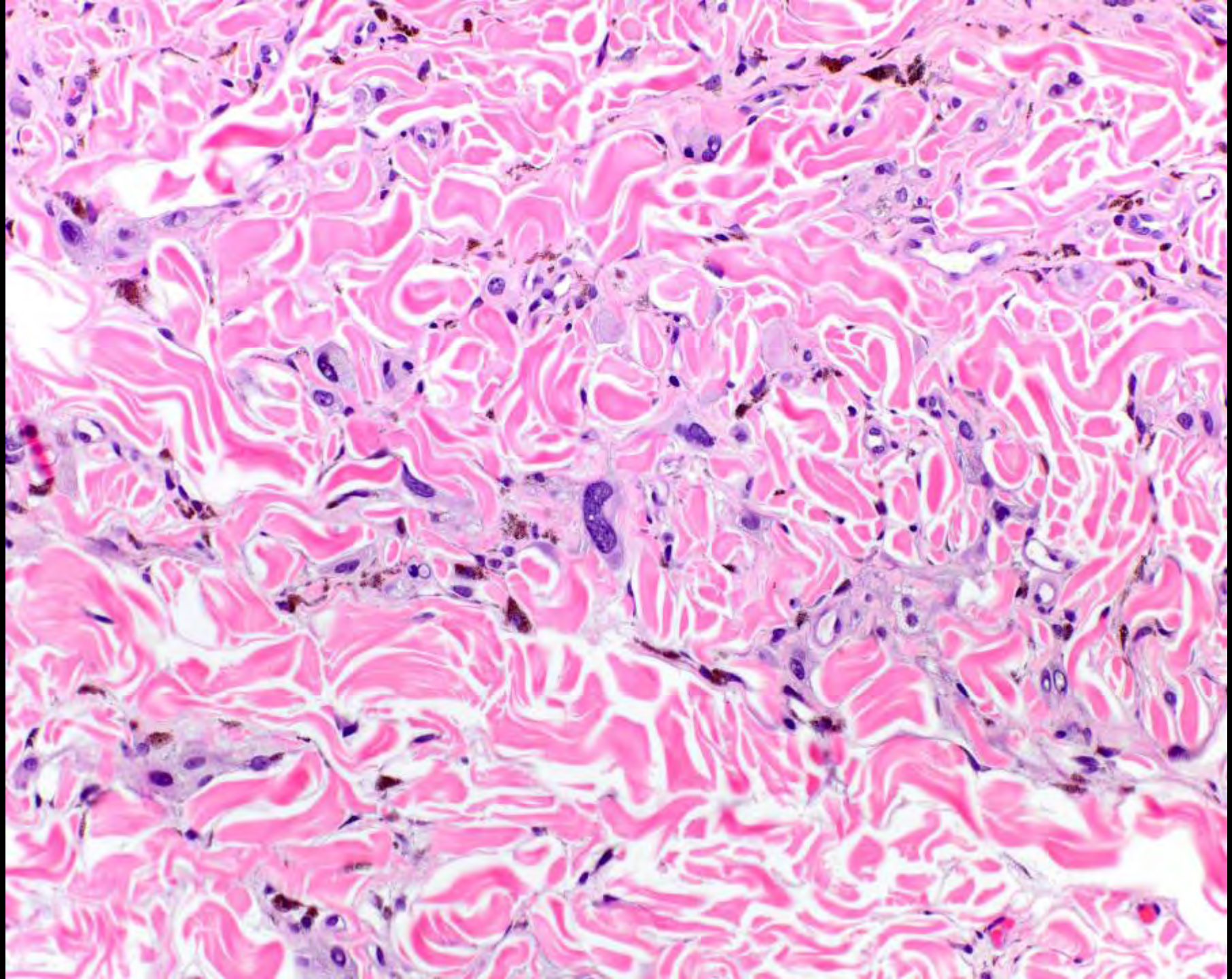


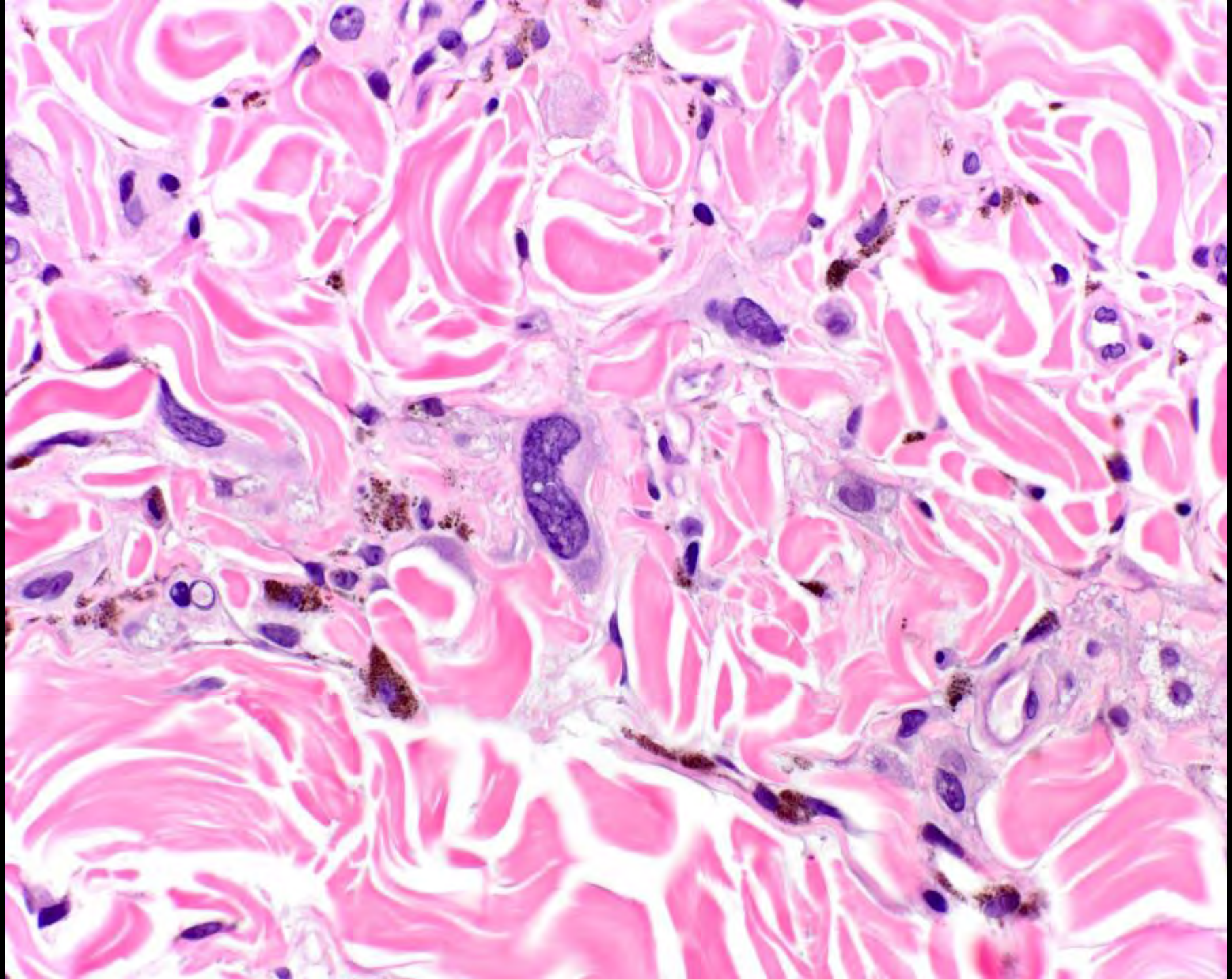


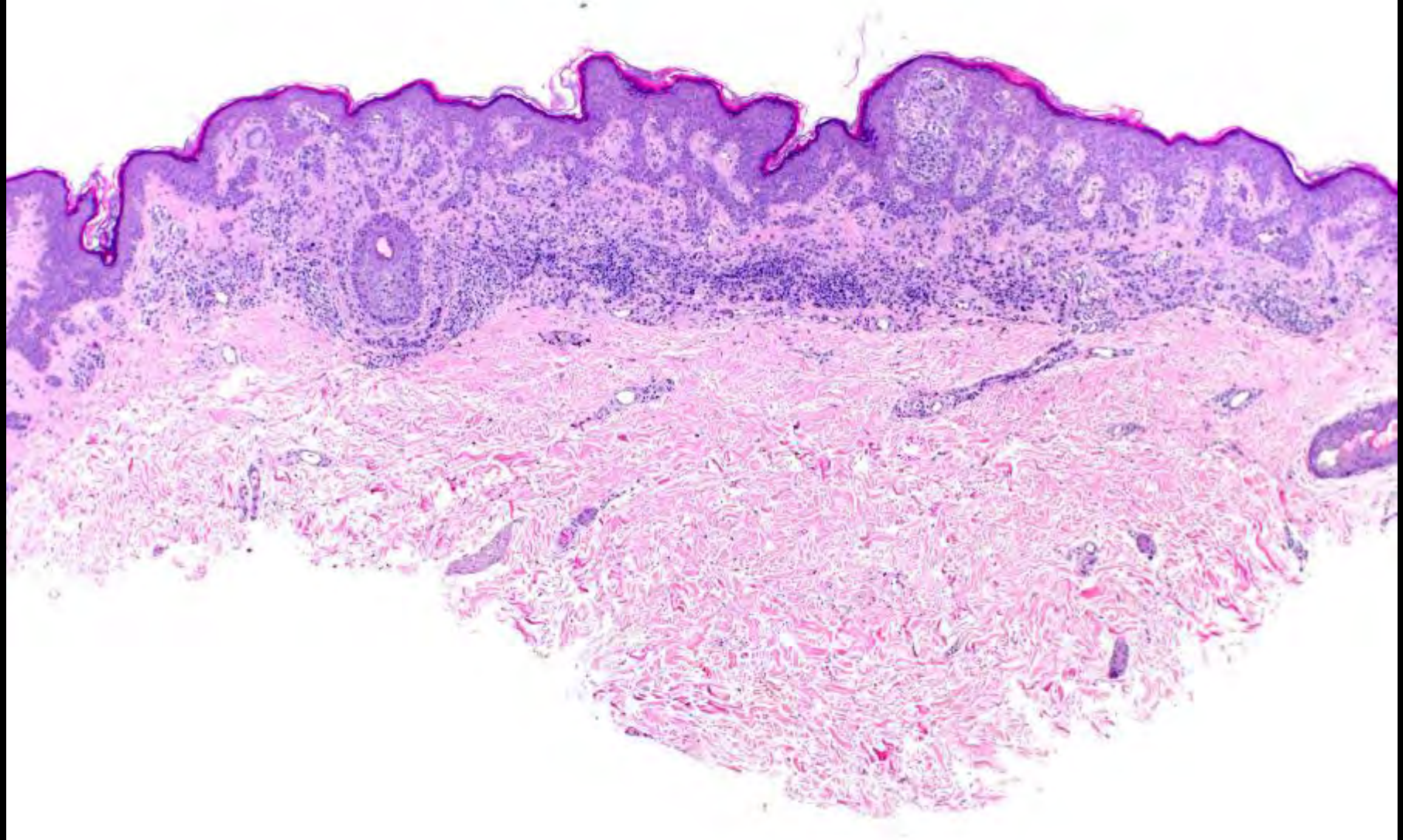


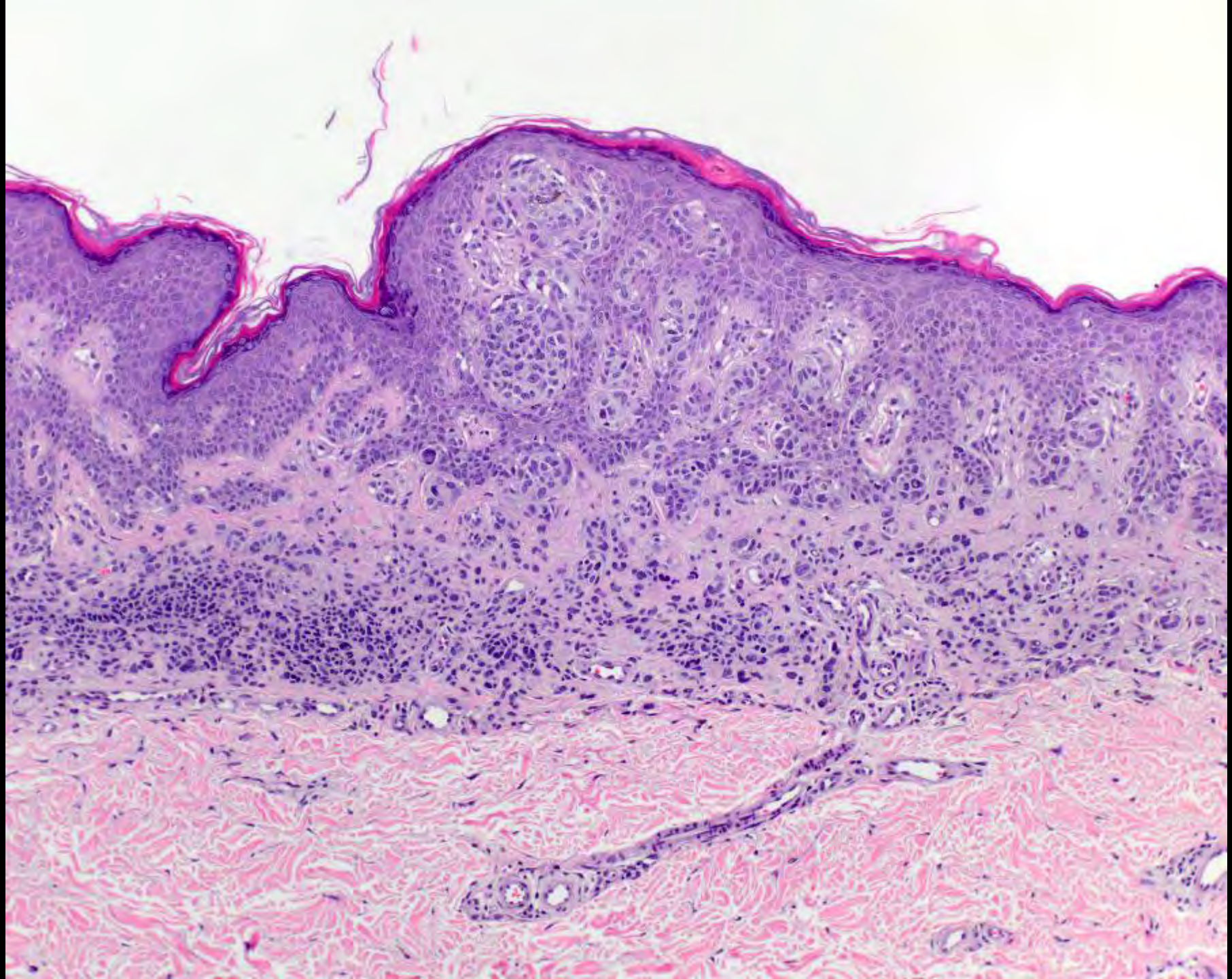


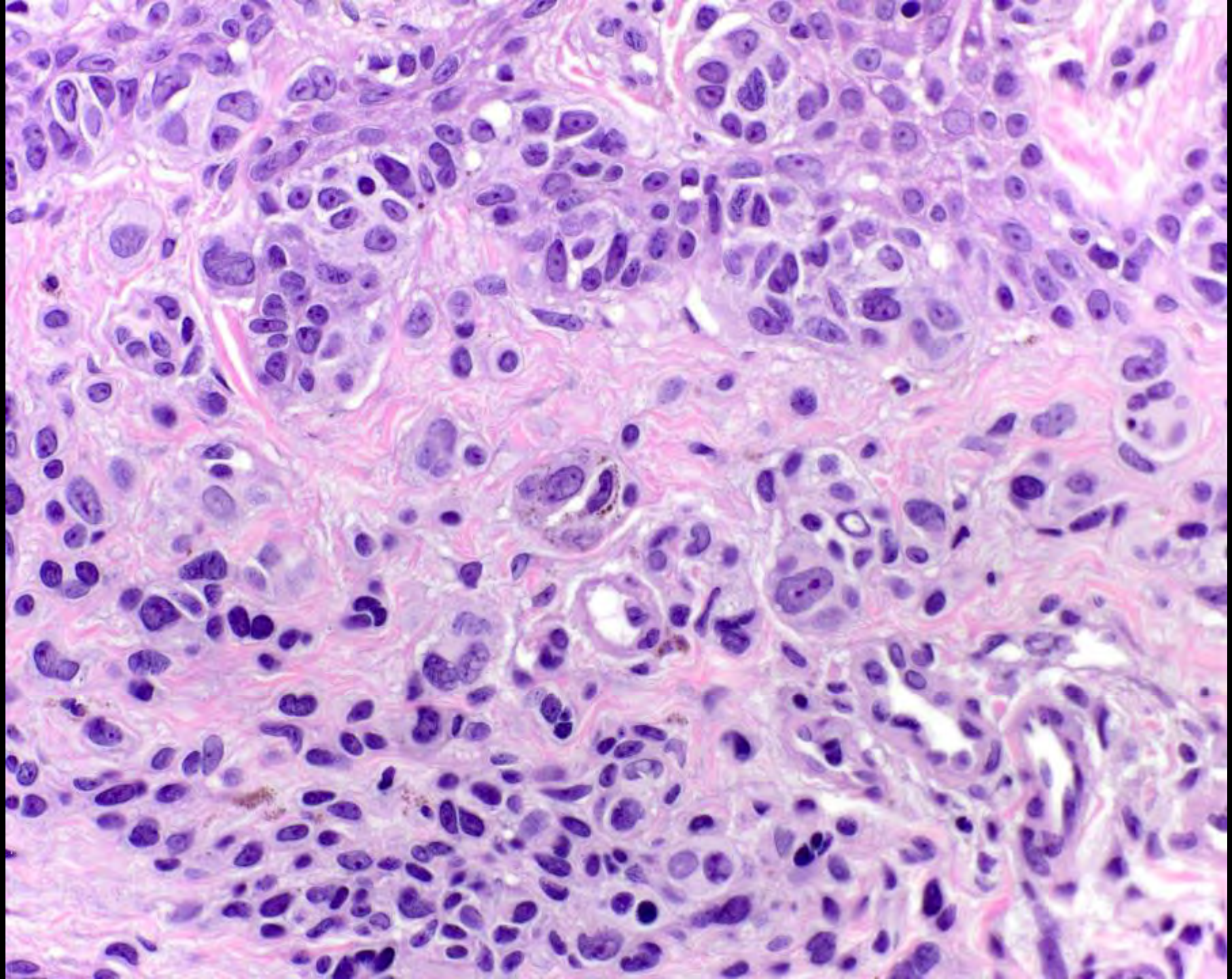


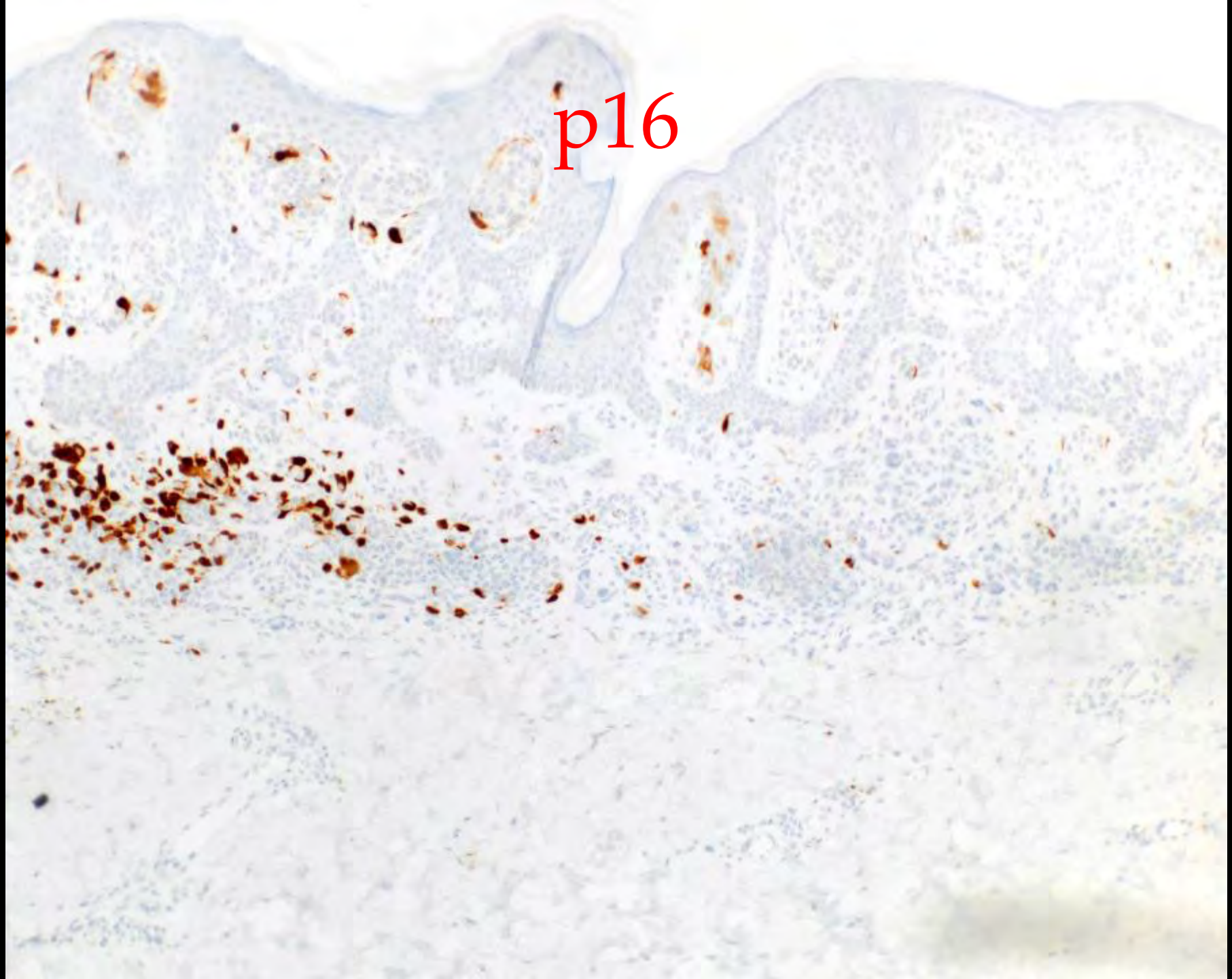








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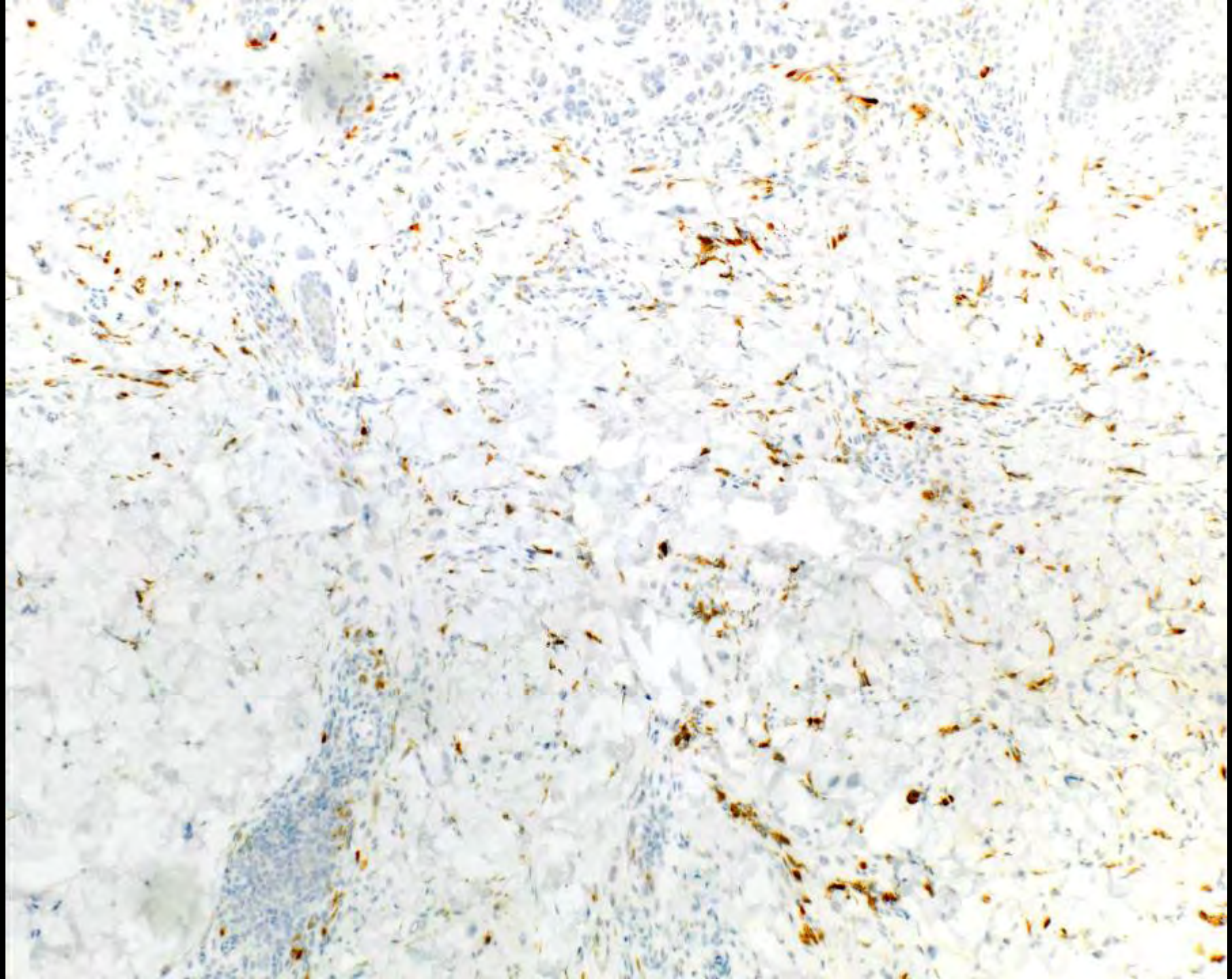
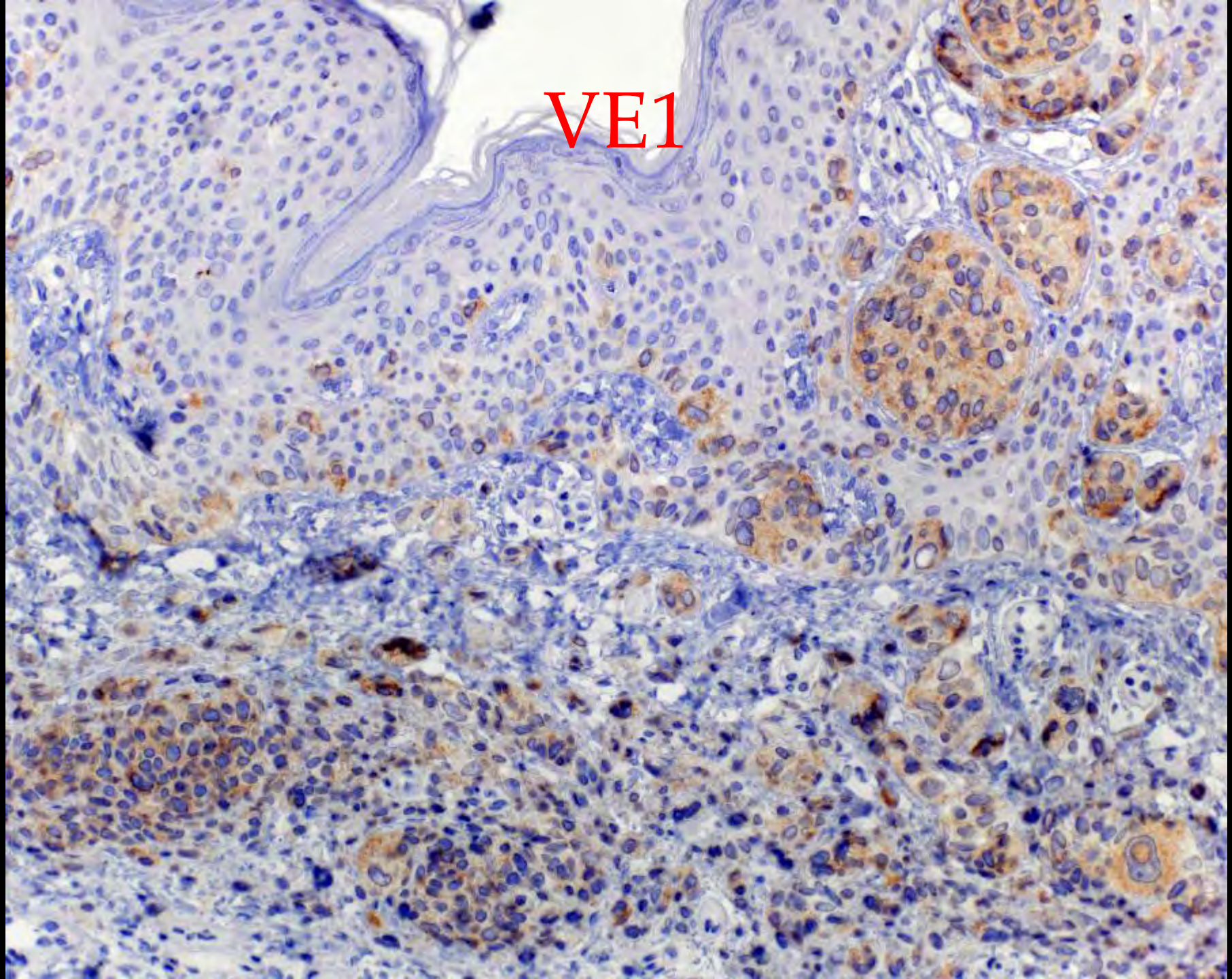



VE1

What's missing?

Different cells of origin:

1. Melanoblasts vs. basilar melanocytes
2. Topographic differences between melanocytes

Kerl H, Soyer HP, Cerroni L, Wolf IH, Ackerman AB.
Ancient melanocytic nevus.
Semin Diagn Pathol. 1998 Aug;15(3):210-5.
PubMed PMID: 9711671.

Ancient nevus, Kerl et al. 1998

- Mostly on the face of older persons.
- Dome-shaped, skin-colored or reddish brown papule, with features of Miescher's nevus.
- Exoendophytic, mostly intradermal proliferations of two populations of melanocytes
- The large melanocytes may resemble those of epithelioid Spitz's nevus.
- A few mitotic figures may be present
- The epidermis usually is uninvolved
- Degenerative changes include thrombi, hemorrhage, pseudoangiomatous changes, thick rims of sclerosis around dilated venules, fibrosis, and mucin.

One patient had metastases

ORIGINAL STUDY

Ancient Melanocytic Nevus: A Simulator of Malignant Melanoma

Helmut Kerl, MD, Ingrid H. Wolf, MD,* Katrin Kerl, MD,† Lorenzo Cerroni, MD,* Heinz Kutzner, MD,‡ and Zsolt B. Argenyi, MD§*

Kerl H, Wolf IH, Kerl K, Cerroni L, Kutzner H, Argenyi ZB.
Ancient melanocytic nevus: a simulator of malignant melanoma.
Am J Dermatopathol. 2011 Apr;33(2):127-30.

Criteria for ancient nevus- Kerl et al.

Exo-endophytic intradermal nodule

No junctional component

Two populations of melanocytes: large atypical melanocytes and small "nevoid" melanocytes

Degenerative changes often with vascular component

Few mitotic figures sometimes

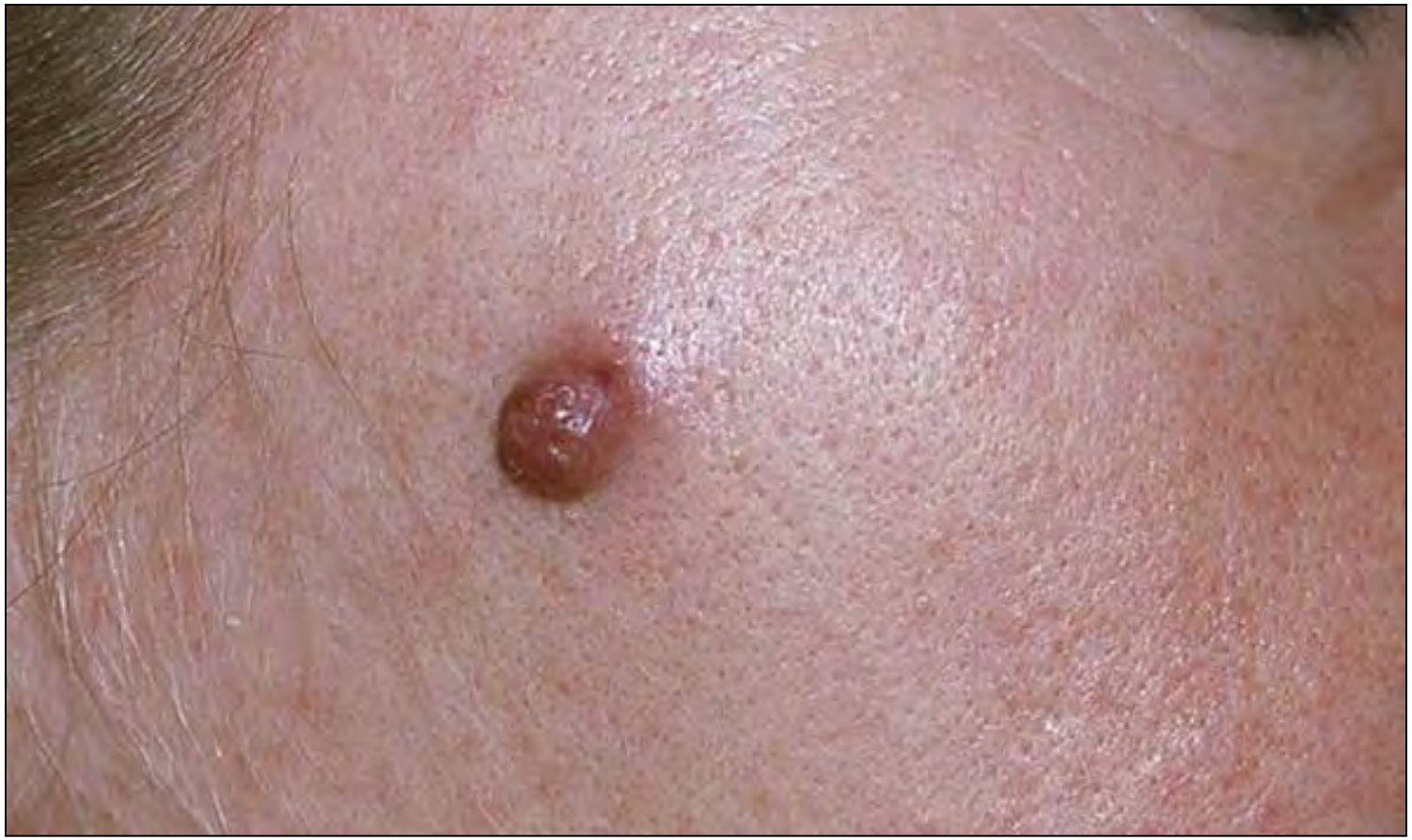
TABLE 3. Dermal Melanoma—Histopathologic Features

Absence of epidermal/junctional component (serial sections recommended).
Large nodules with sheets of melanocytes
Striking atypical melanocytes
Mitoses frequent (>3 per slide). High proliferation rate
Usually no degenerative changes, except necrosis
Continuity between nevus cells and melanoma cells
Plasma cells, lymphocytes, and melanin at base

TABLE 1. Ancient Melanocytic Nevus—Clinical Data

Patient Number	Sex	Age (yr)	Location	Follow-up (yr)
1	F	60	Face	8
2	M	62	Trunk	14
3	F	50	Upper arm	13
4	M	71	Trunk	6
5	F	79	Face	9
6	F	43	Trunk	5
7	F	36	Face	6
8	M	38	Upper leg	5
9	F	75	Face	5
10	F	40	Trunk	17
11	M	44	Trunk	17
12	M	20	Trunk	16
13	F	52	Lower arm	16

FIGURE 1



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American Journal of Dermatopathology. 33(2):127-130, April 2011.DOI: 10.1097/IAE.0b013e31817f7b58

FIGURE 1 . Ancient melanocytic nevus. Exophytic reddish brown nodule.

FIGURE 2

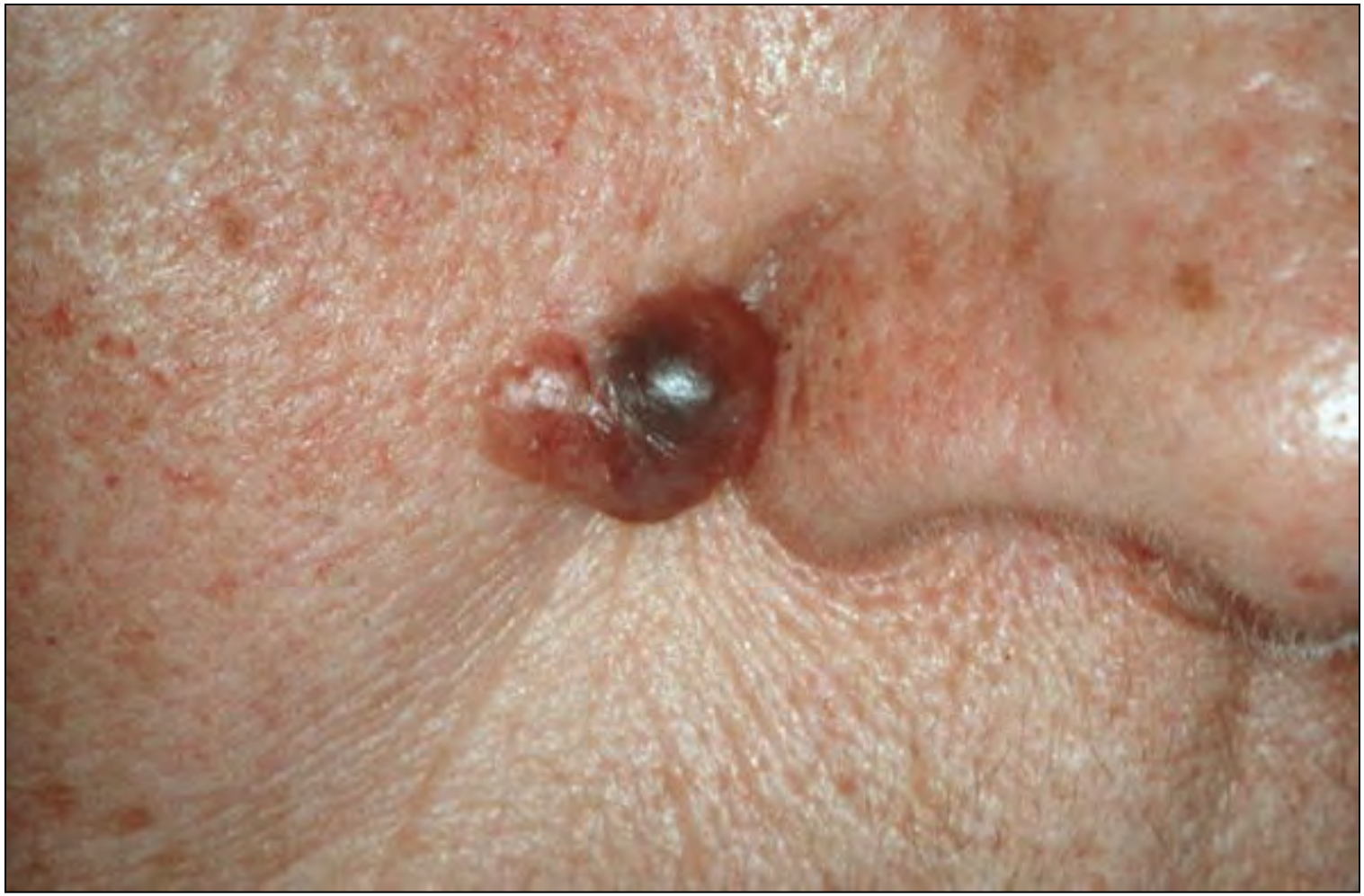

FIGURE 2 . Ancient melanocytic nevus. Dome-shaped asymmetric brownish tumor with a bluish cast.

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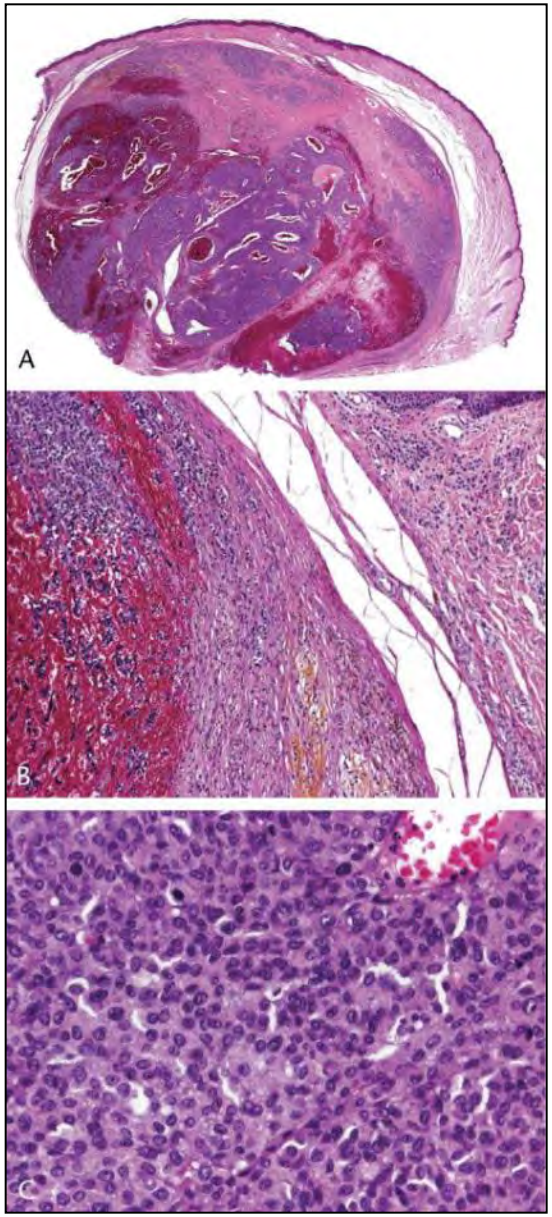
FIGURE 4



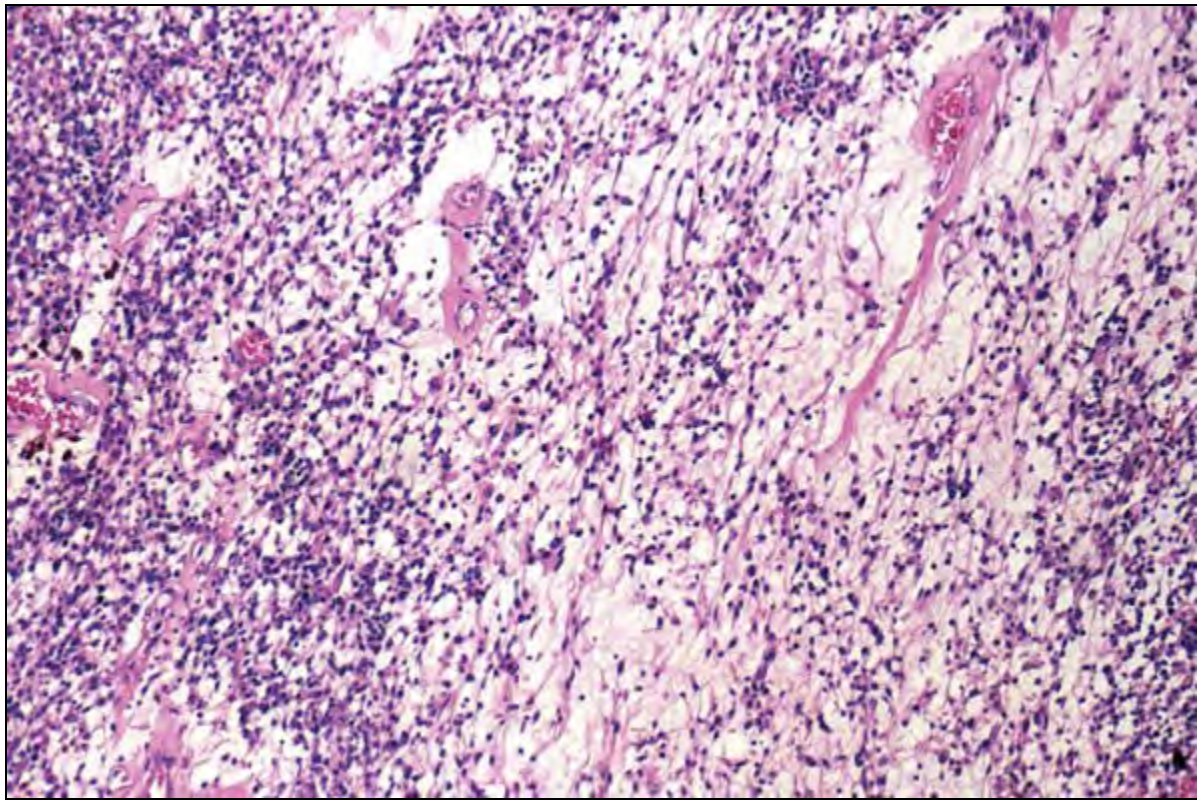


FIGURE 5 . Ancient melanocytic nevus. Mucinous areas with spindle cells.

FIGURE 4 . Ancient melanocytic nevus. (Patient No. 5) A, Exo-endophytic tumor with 2 cell populations and degenerative stromal changes. The epidermis is spared. B, Two populations of melanocytes: small monomorphous ones in a "congenital" pattern and large melanocytes within an area of hemorrhage. C, Large melanocytes with pleomorphic nuclei. Note high cellularity. Courtesy: Sander (Hamburg) and Flaig (Munich).

FIGURE 6

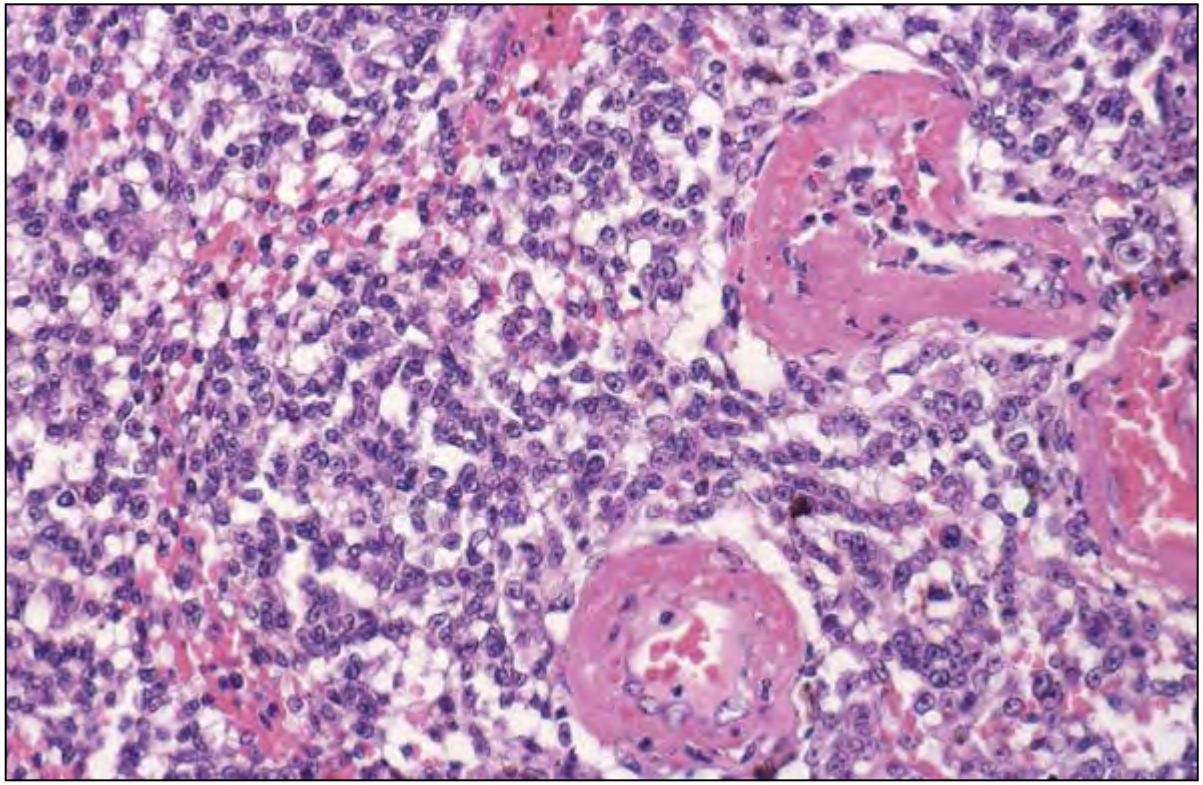


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FIGURE 6 . Ancient melanocytic nevus. Rims of sclerosis around vessels (hyaline angiopathy).

FIGURE 7

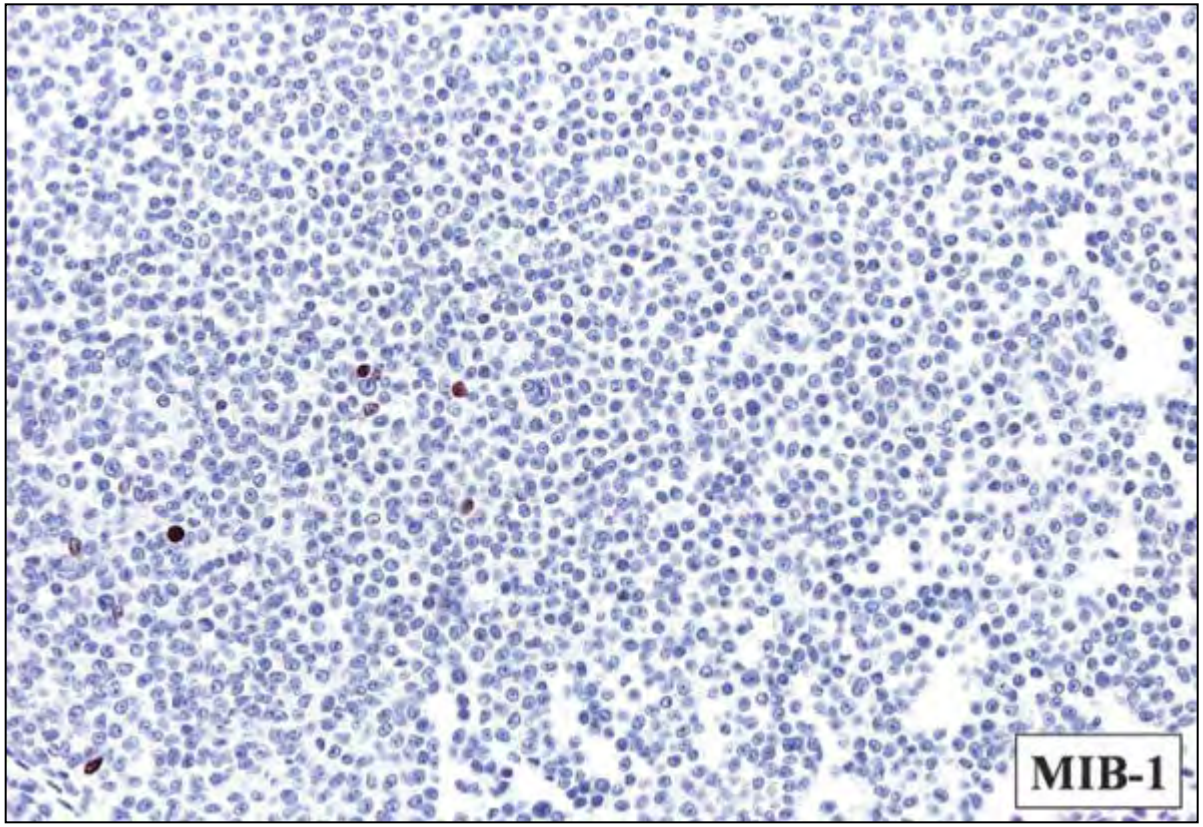

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FIGURE 7 . Ancient melanocytic nevus. A nodule composed of large pleomorphic melanocytes reveals a low proliferation rate. MIB-1.

TABLE 3

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FIGURE 8

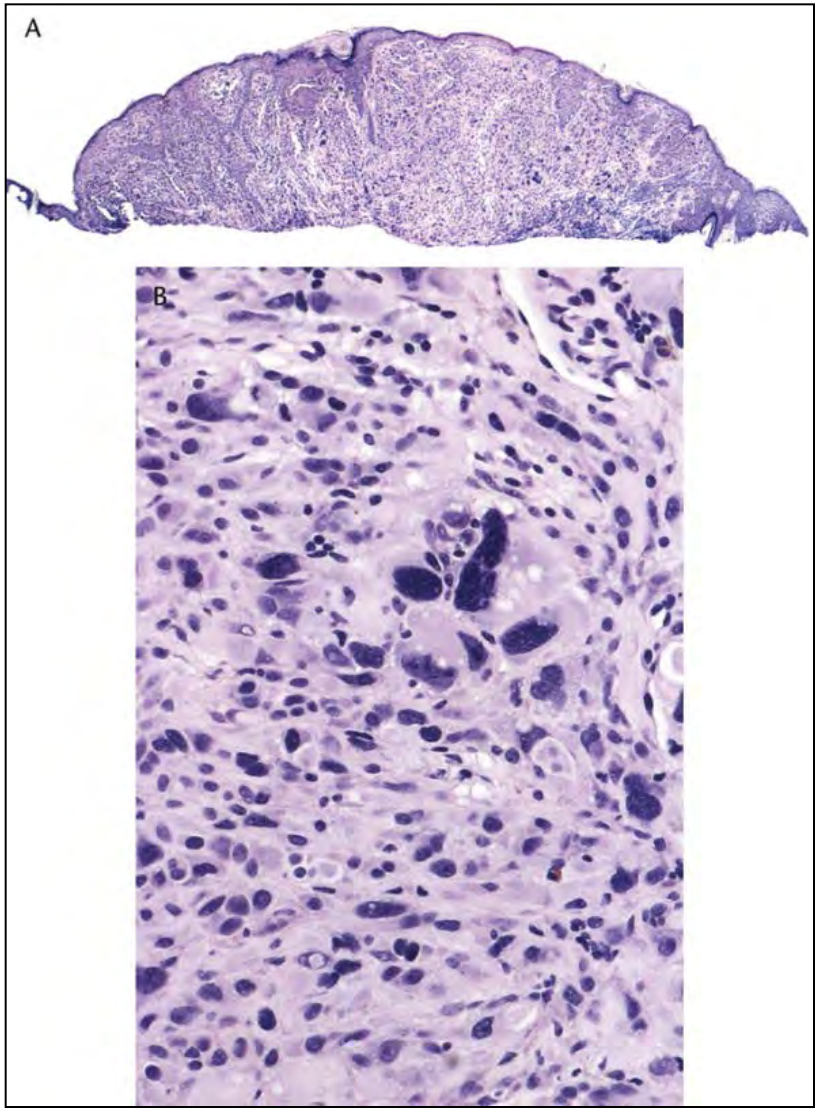

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FIGURE 8 . A, B, "Bizarre" nevus. Large and pleomorphic cells with prominent chromatin clumping (monster cells). This melanocytic nevus is different from AN.

ORIGINAL ARTICLE

''Ancient'' Blue Nevi (Cellular Blue Nevi With Degenerative Stromal Changes)

Lorenzo Cerroni, MD, Riccardo G. Borroni, MD,*† Cesare Massone, MD,* and Helmut Kerl, MD**

(*Am J Dermatopathol* 2008;30:1–5)

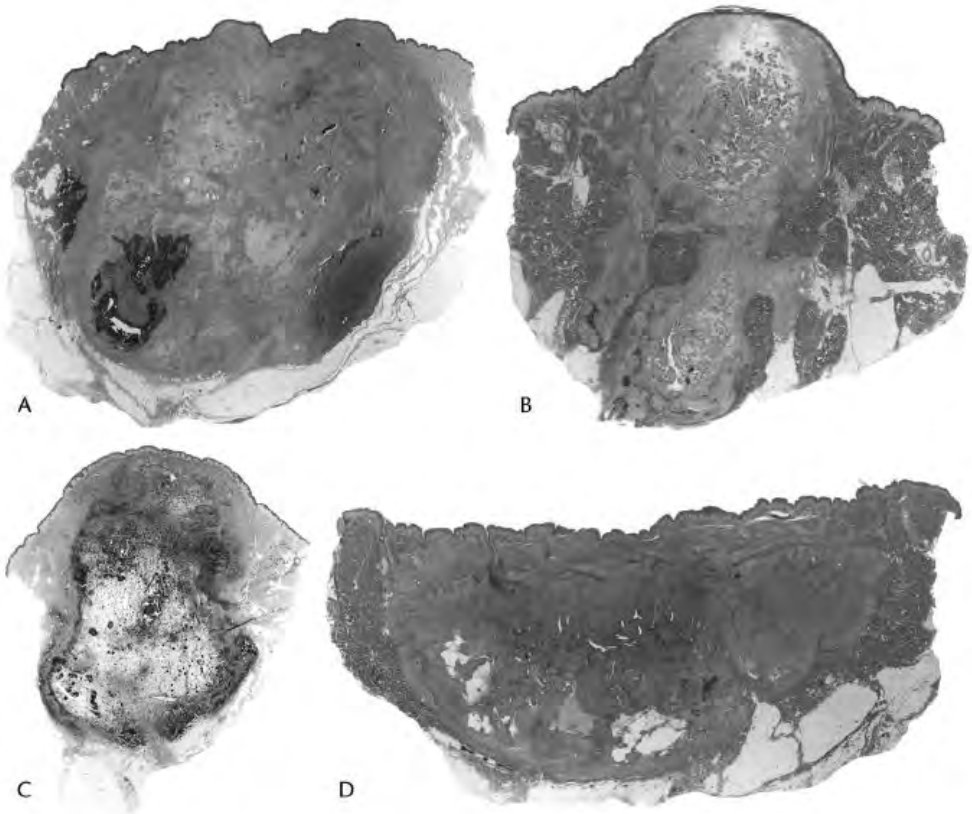


FIGURE 1. Overall architecture of ancient blue nevi with features of cellular blue nevus (neuronevus Masson): A, case 1; B, case 2; C, case 3; D, case 4.

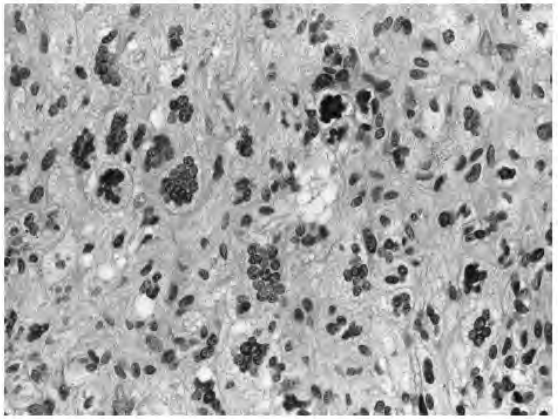


FIGURE 2. Prominent presence of multinucleated melanocytes (case 1).

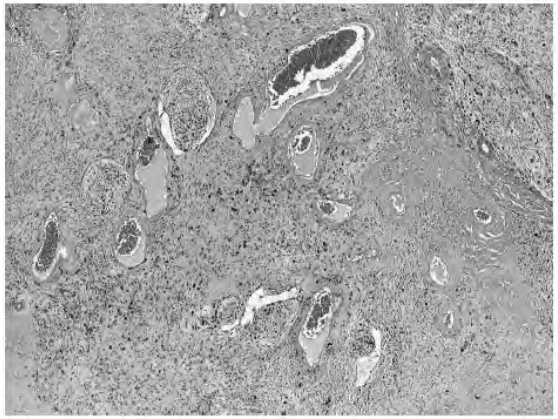
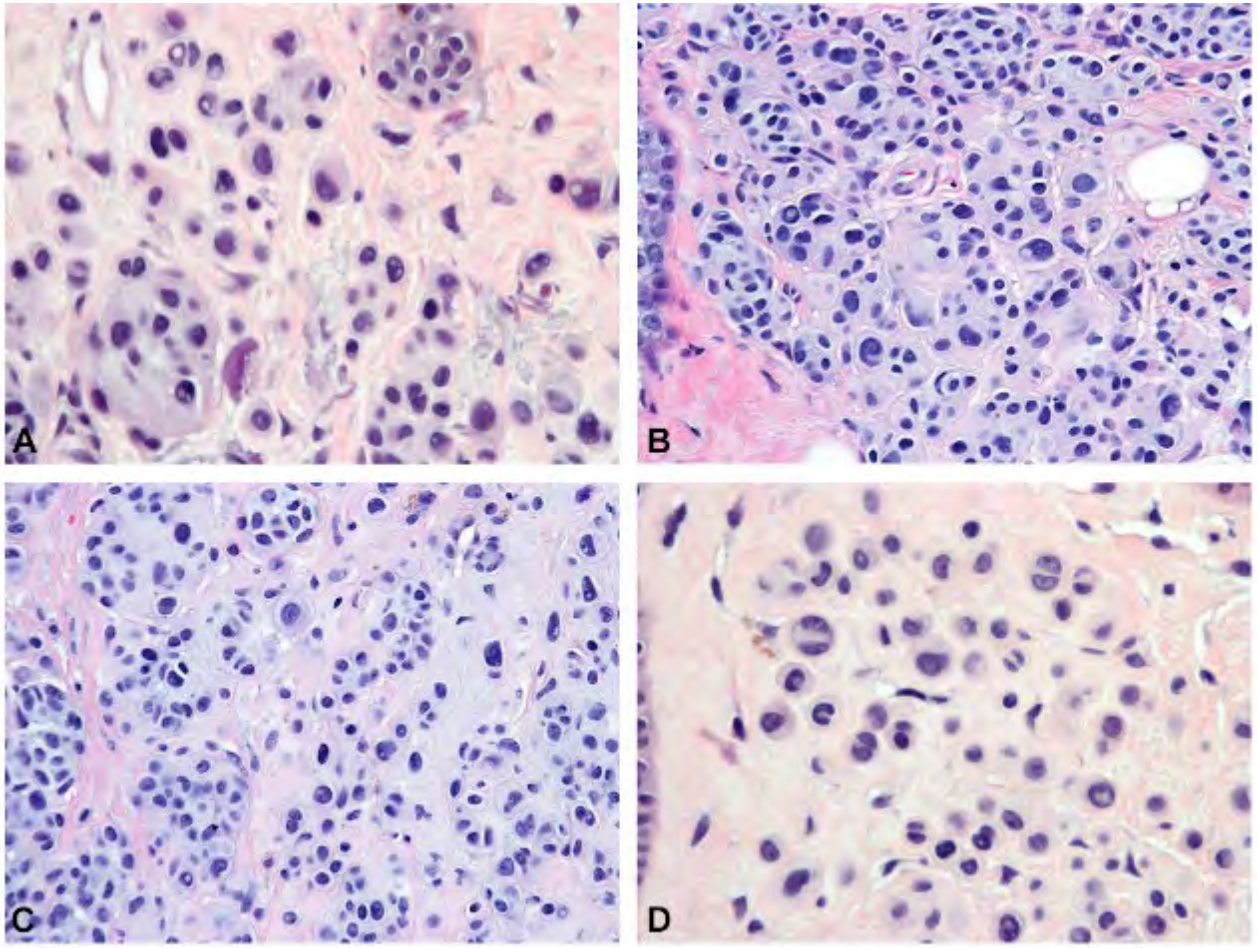


FIGURE 4. Pseudoangiomatous pattern (case 1).

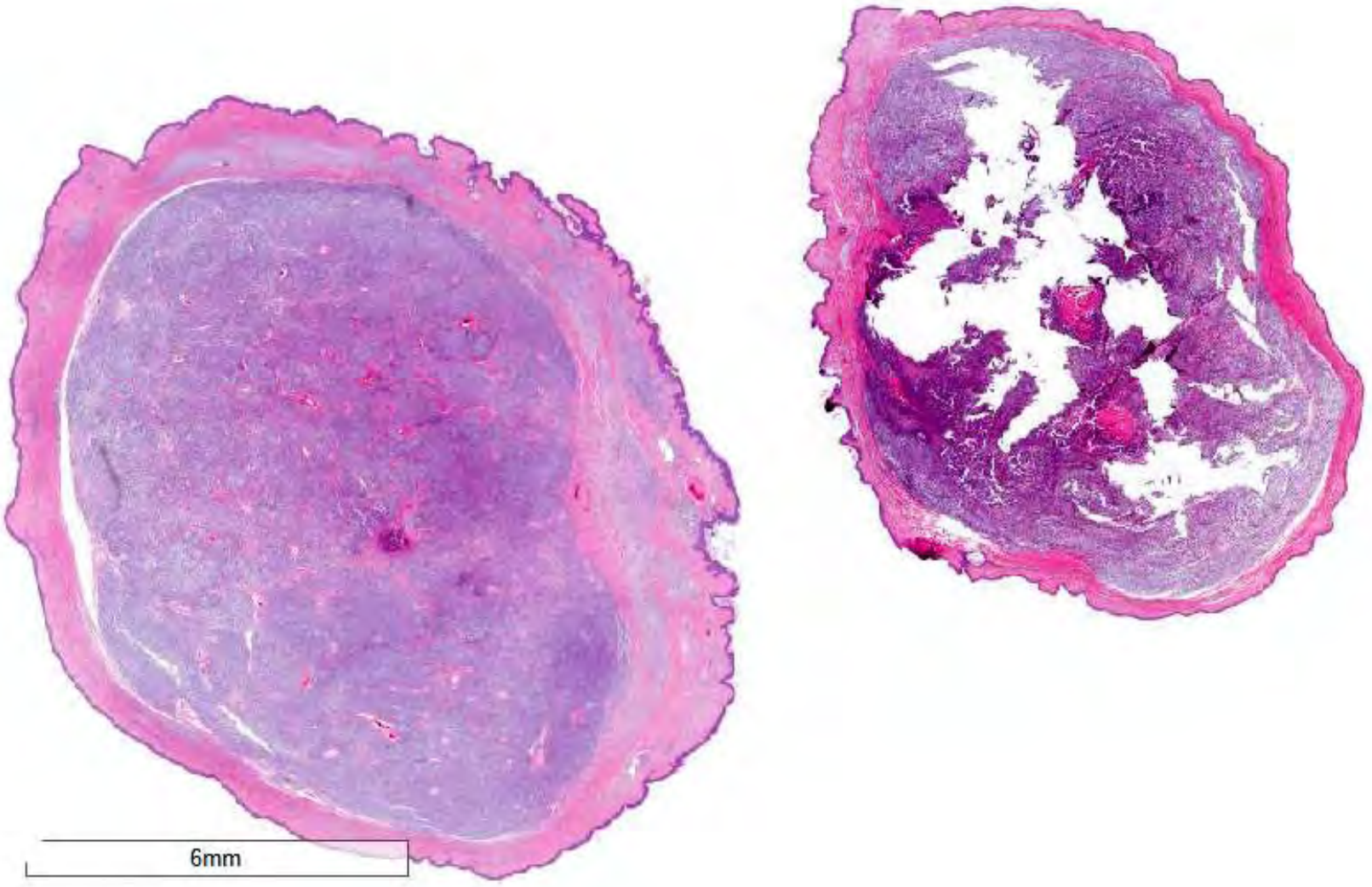
Intradermal nevi with atypical nuclei in the elderly: The senescent nevus

Alan S. Boyd, MD,[a,b] Sheau-Chiann Chen, PhD,[c] and Yu Shyr, PhD[c]
Nashville, Tennessee



UCSF series Case 1

- Red-brown papule on face, 38 year old woman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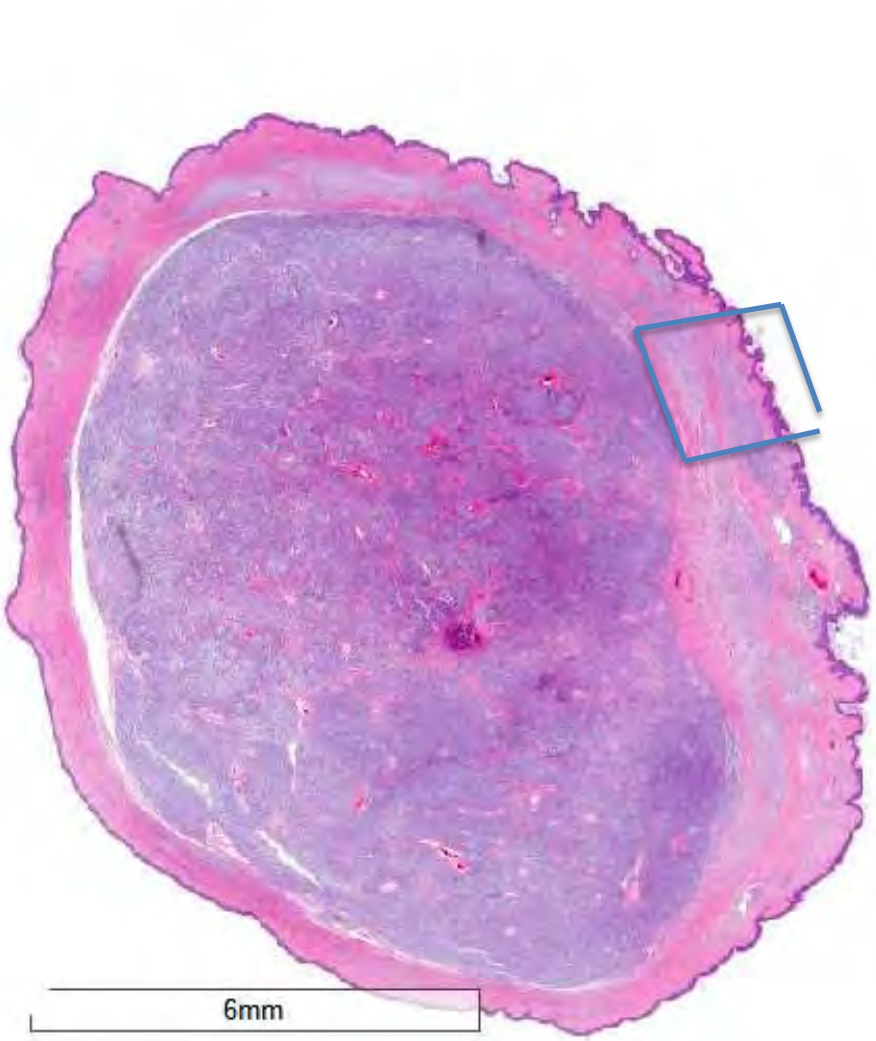
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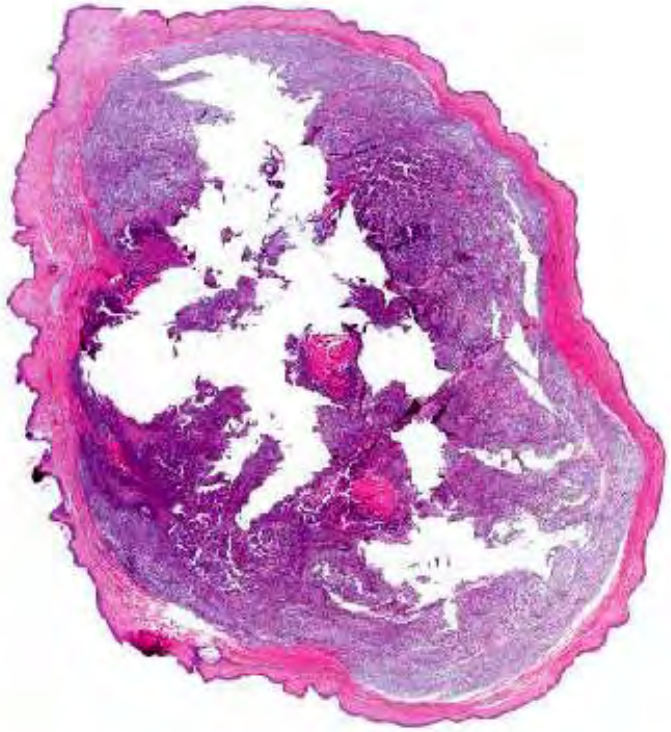

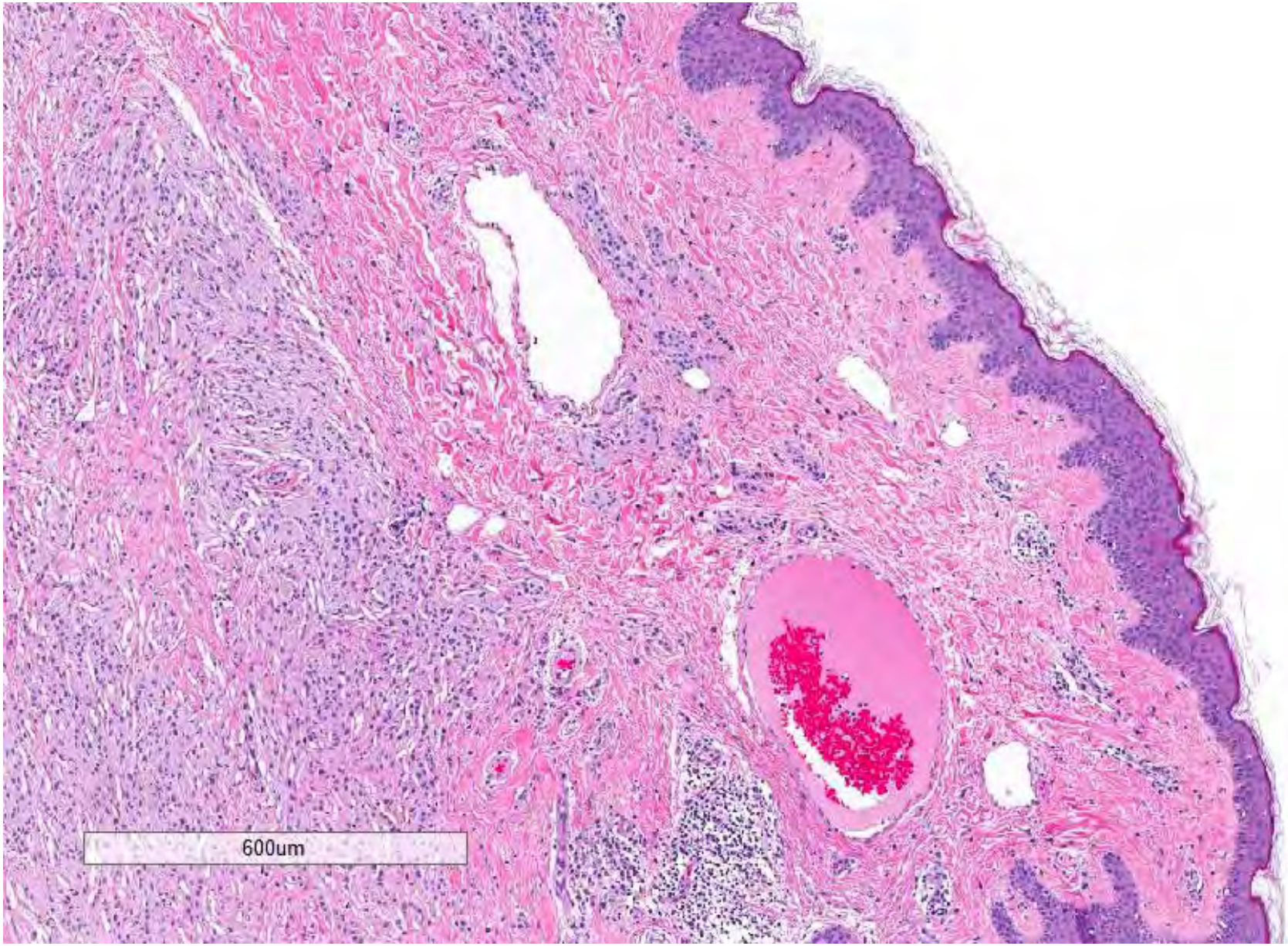
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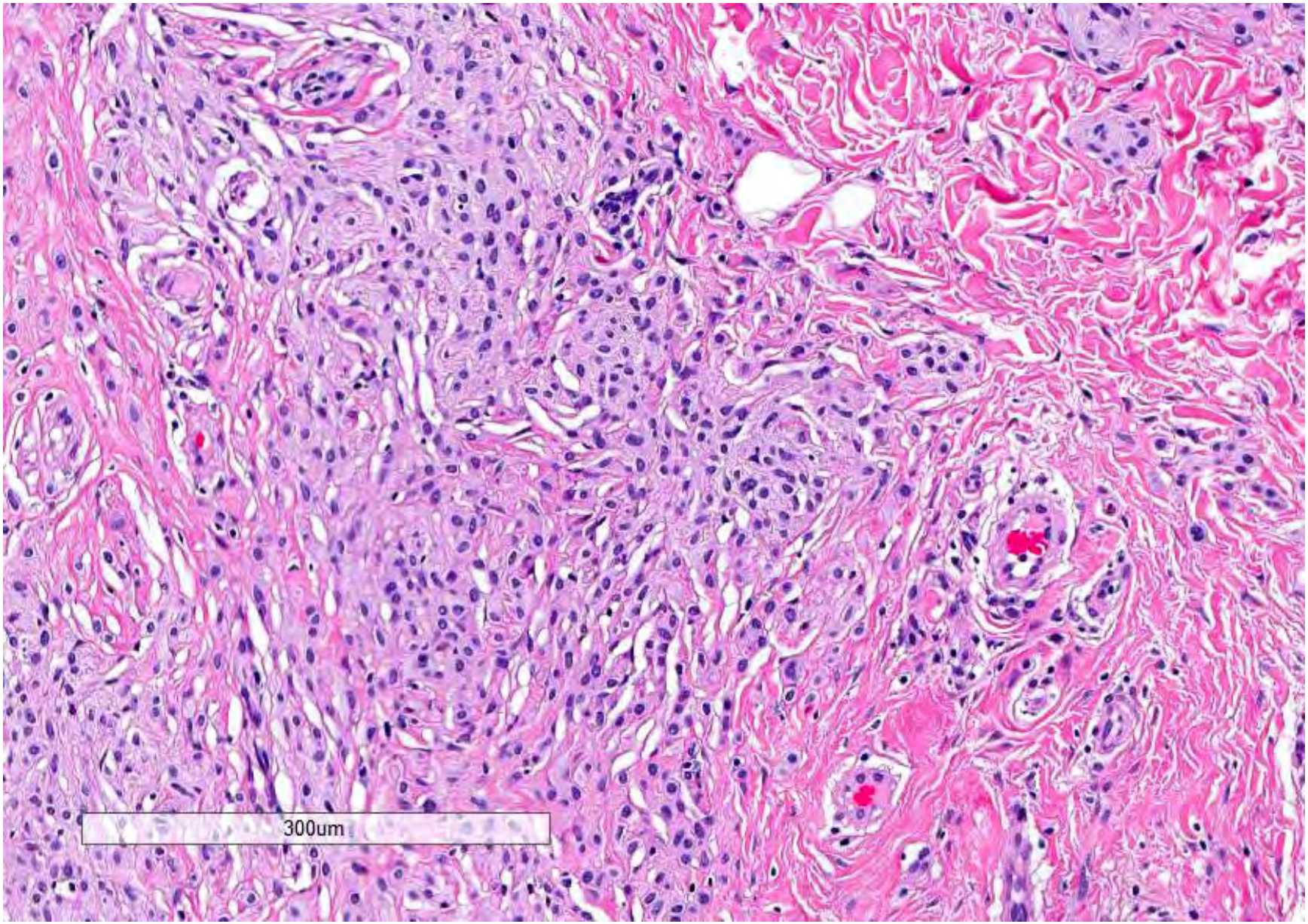
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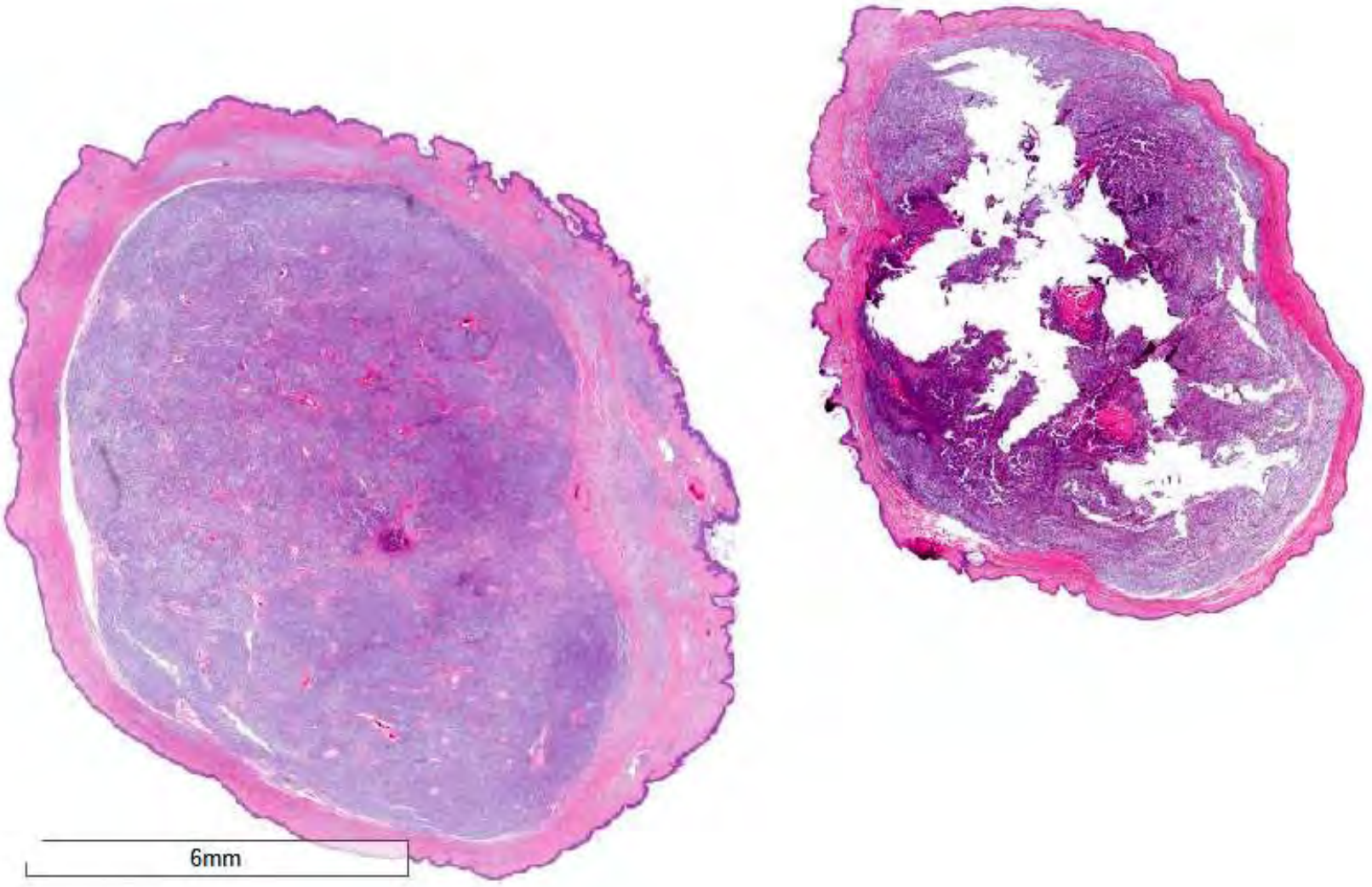
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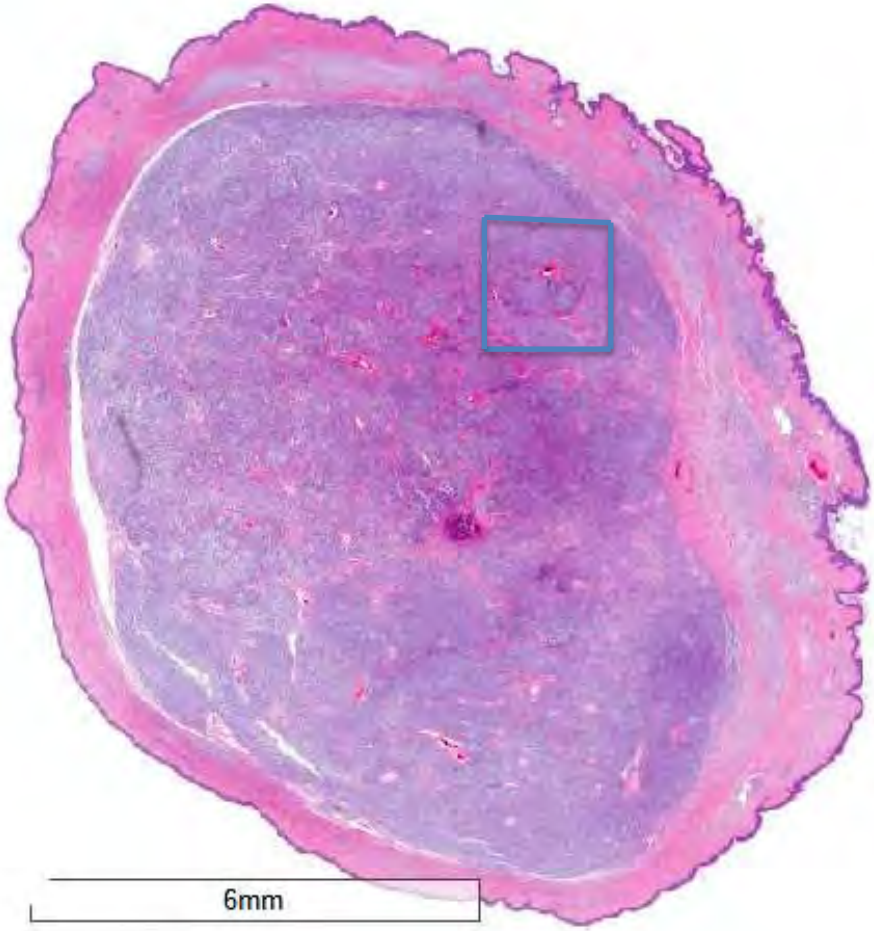
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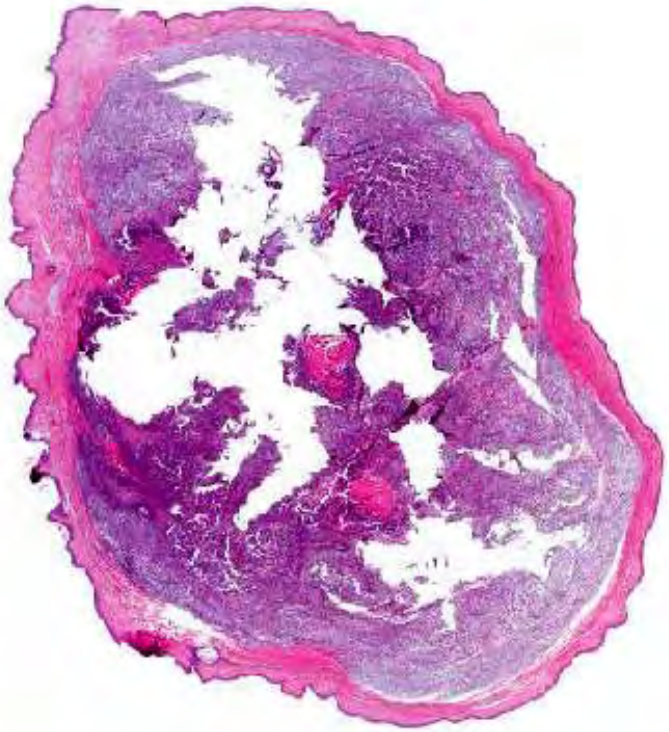

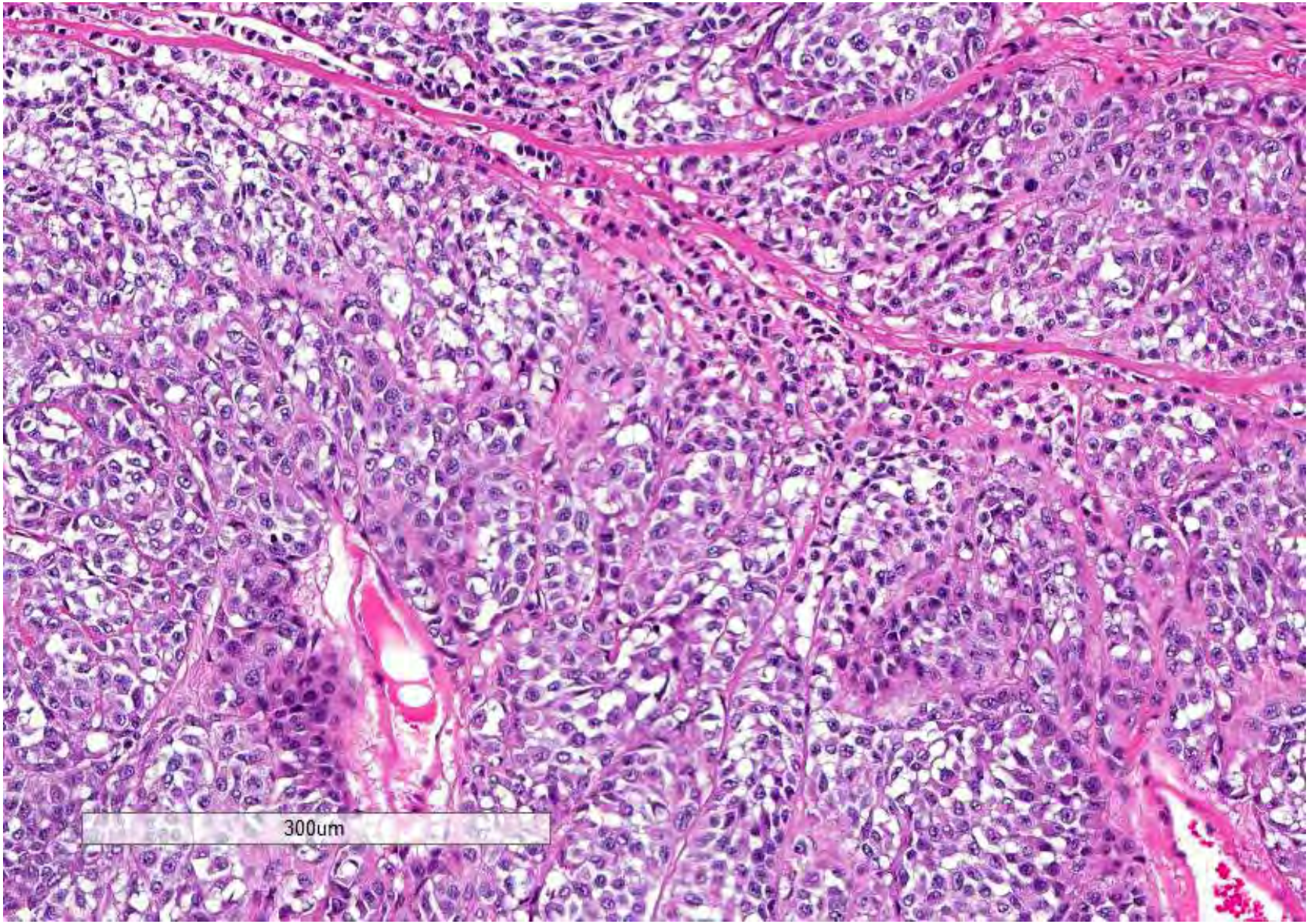
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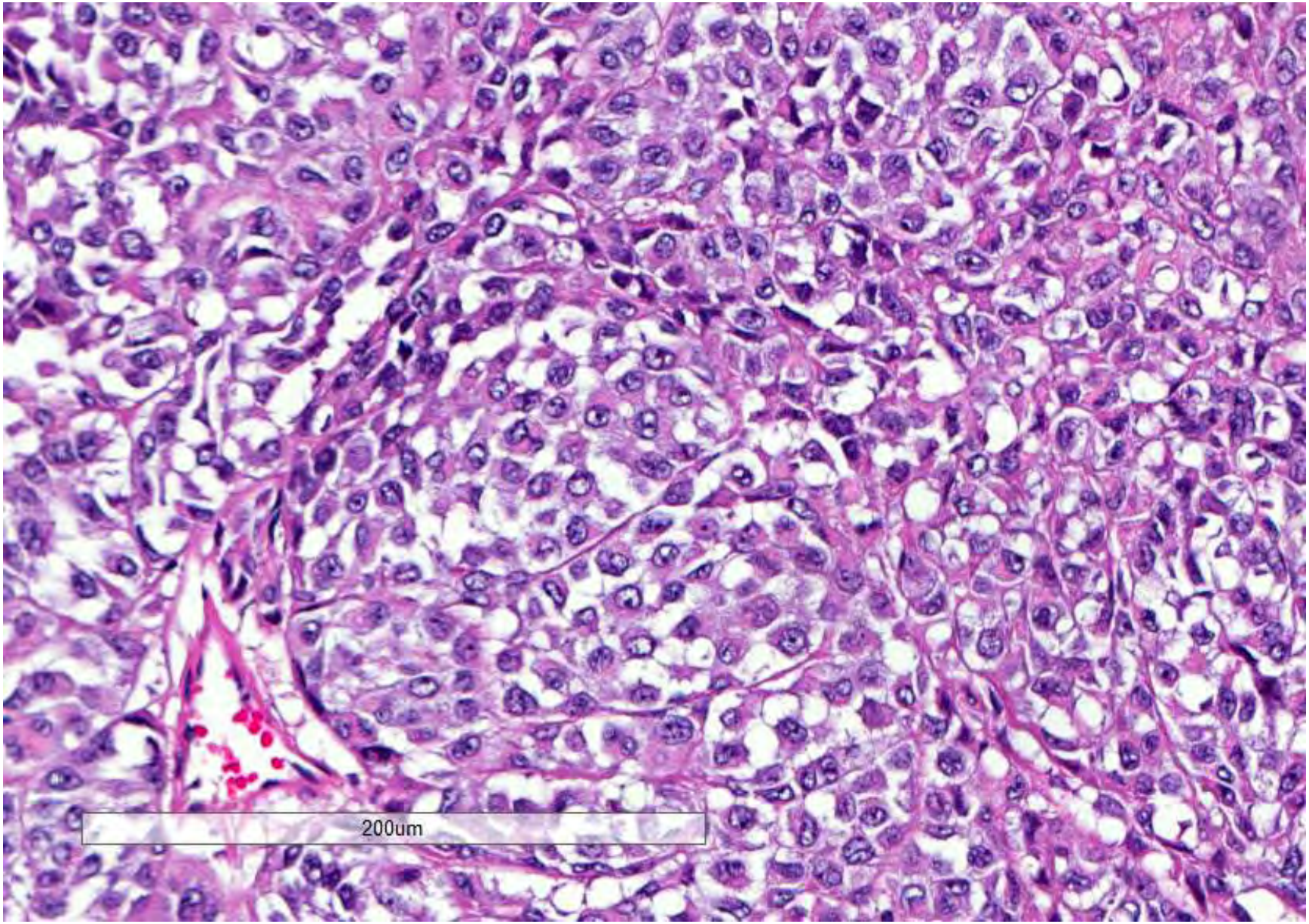
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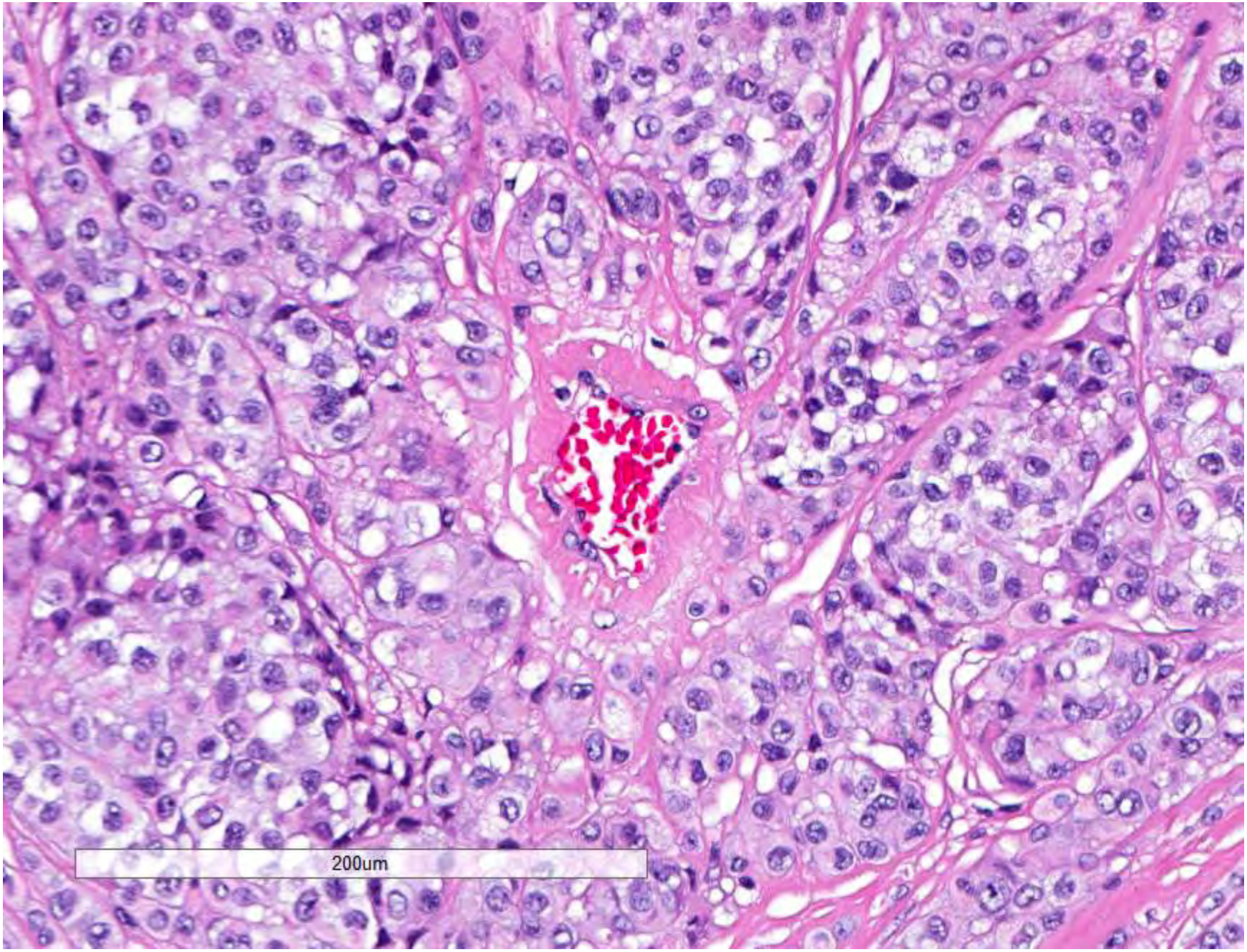
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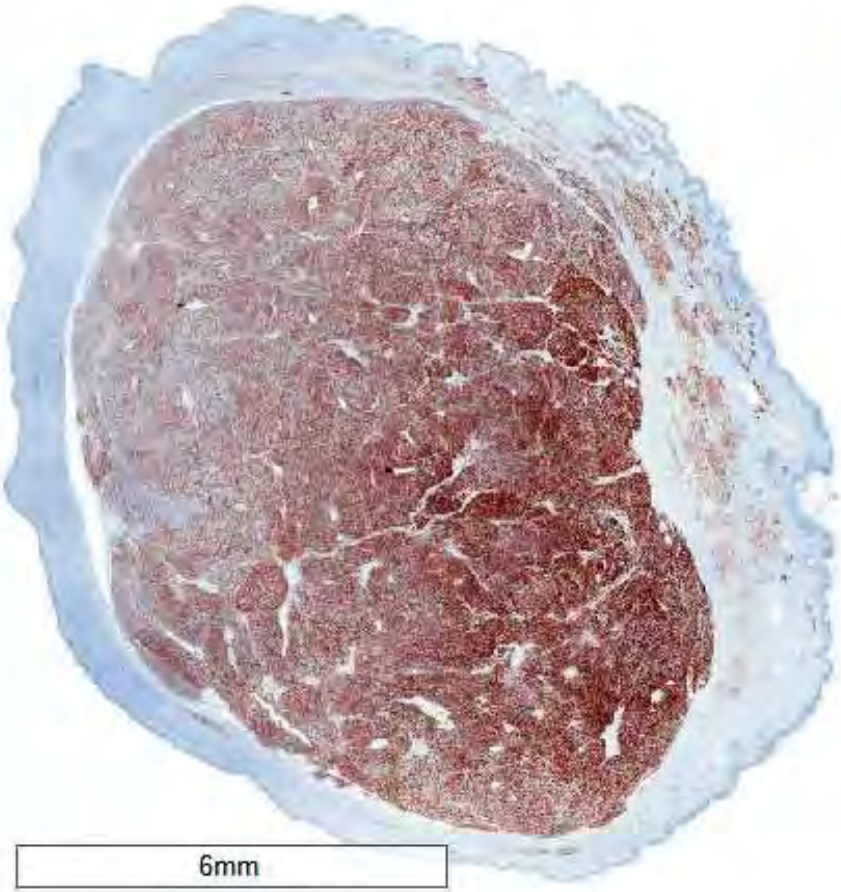

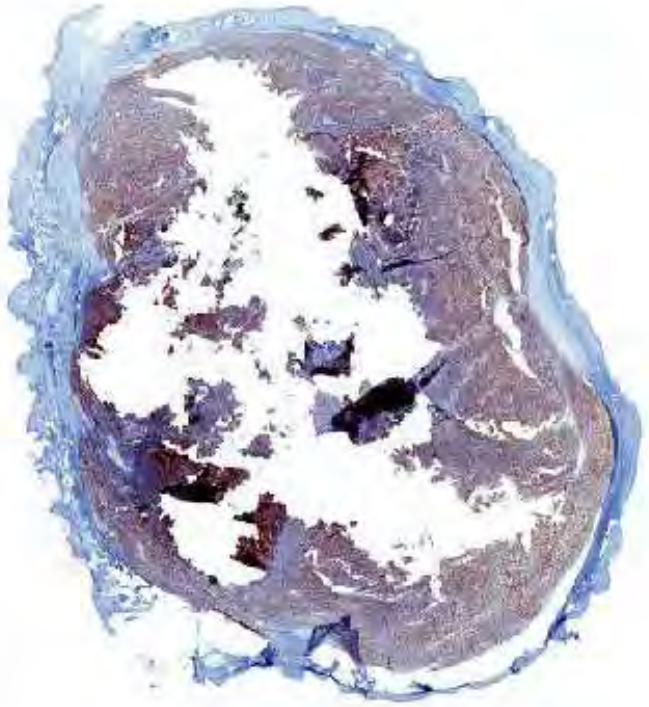

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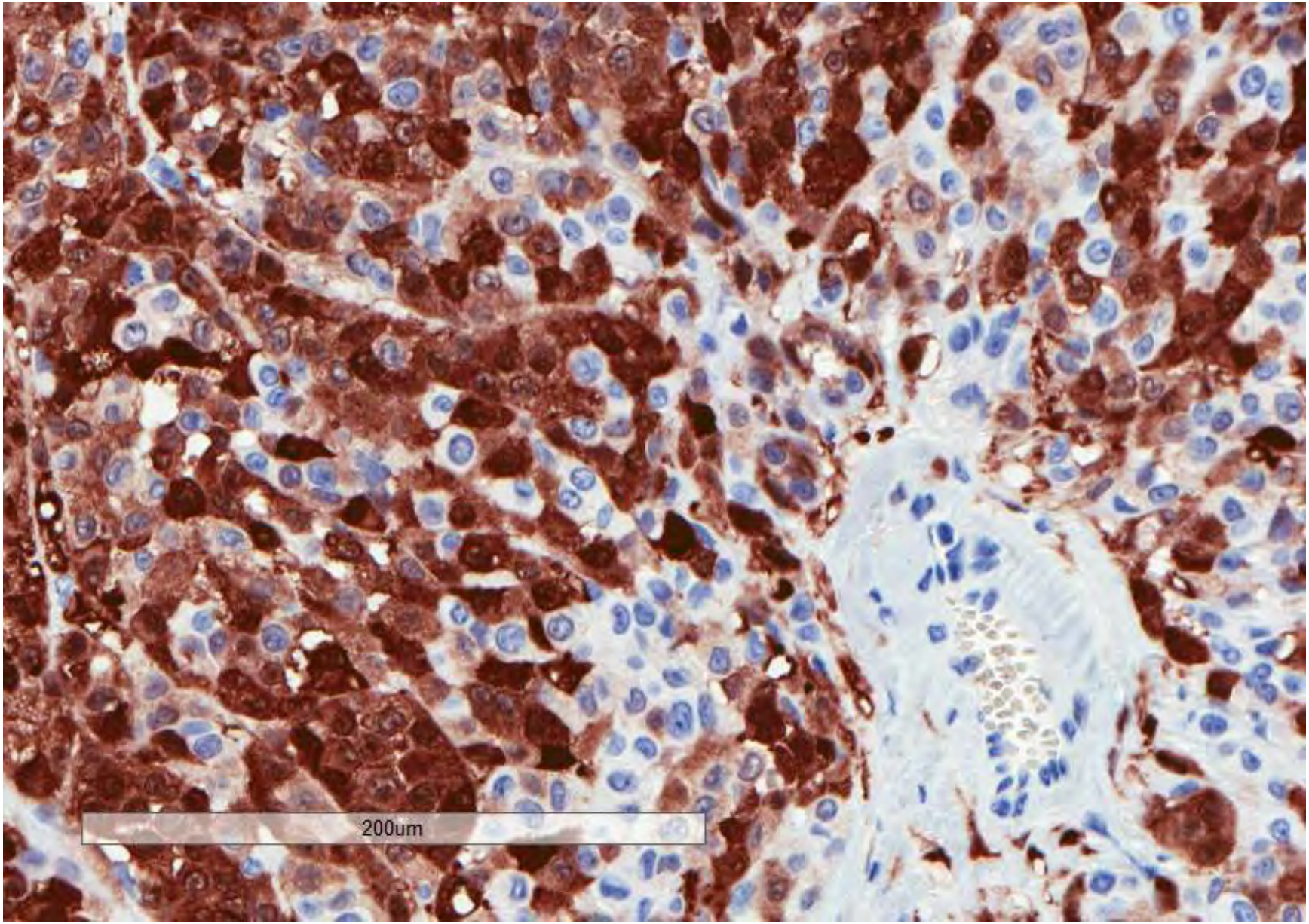
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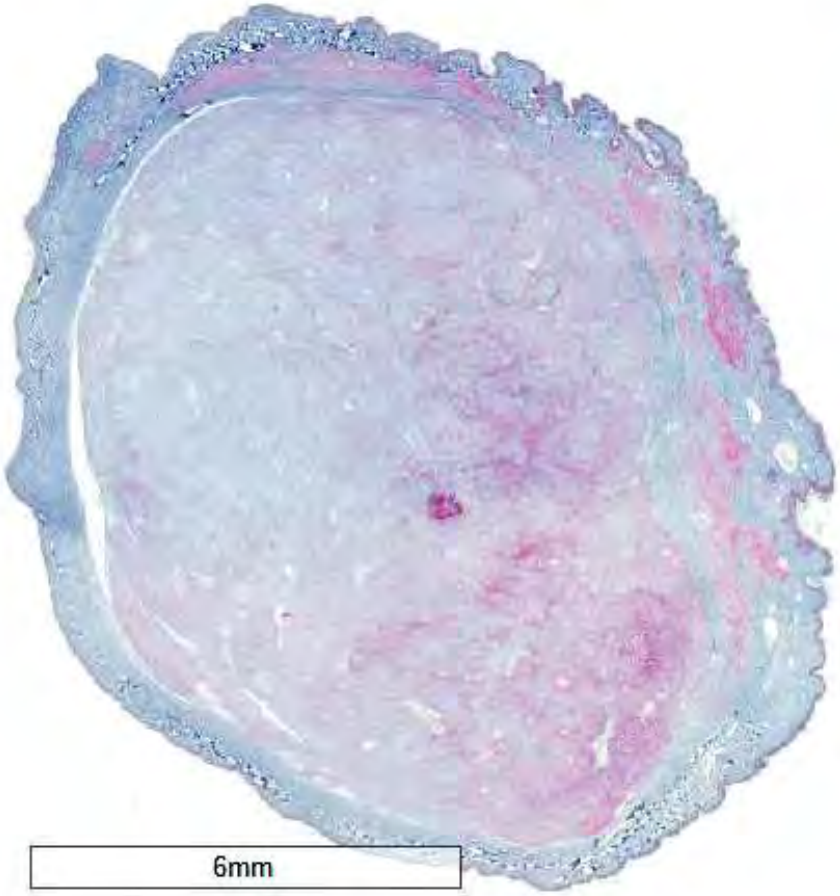

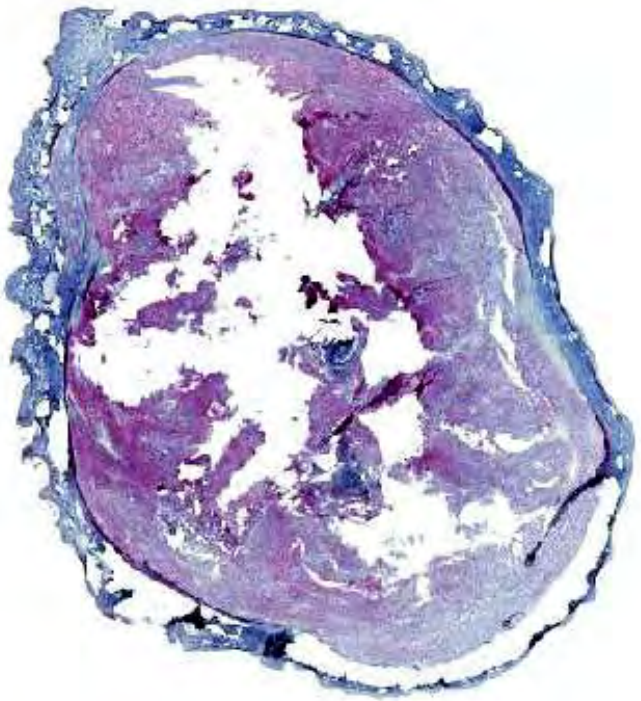

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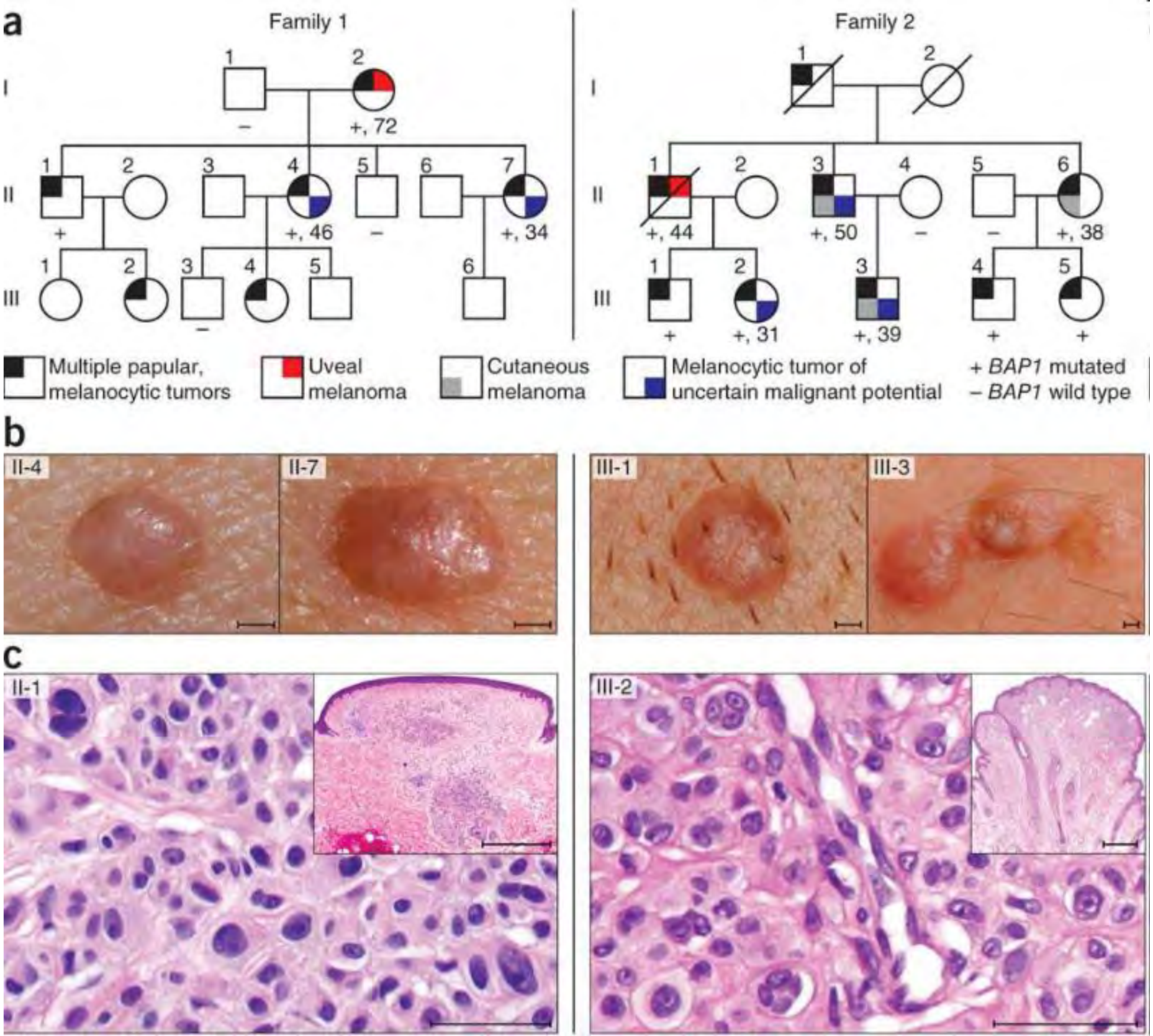
a
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Multiple papular, melanocytic tumors
Uveal melanoma
Cutaneous melanoma
Melanocytic tumor of uncertain malignant potential
+ BAP1 mutated
– BAP1 wild type
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II-7
III-1
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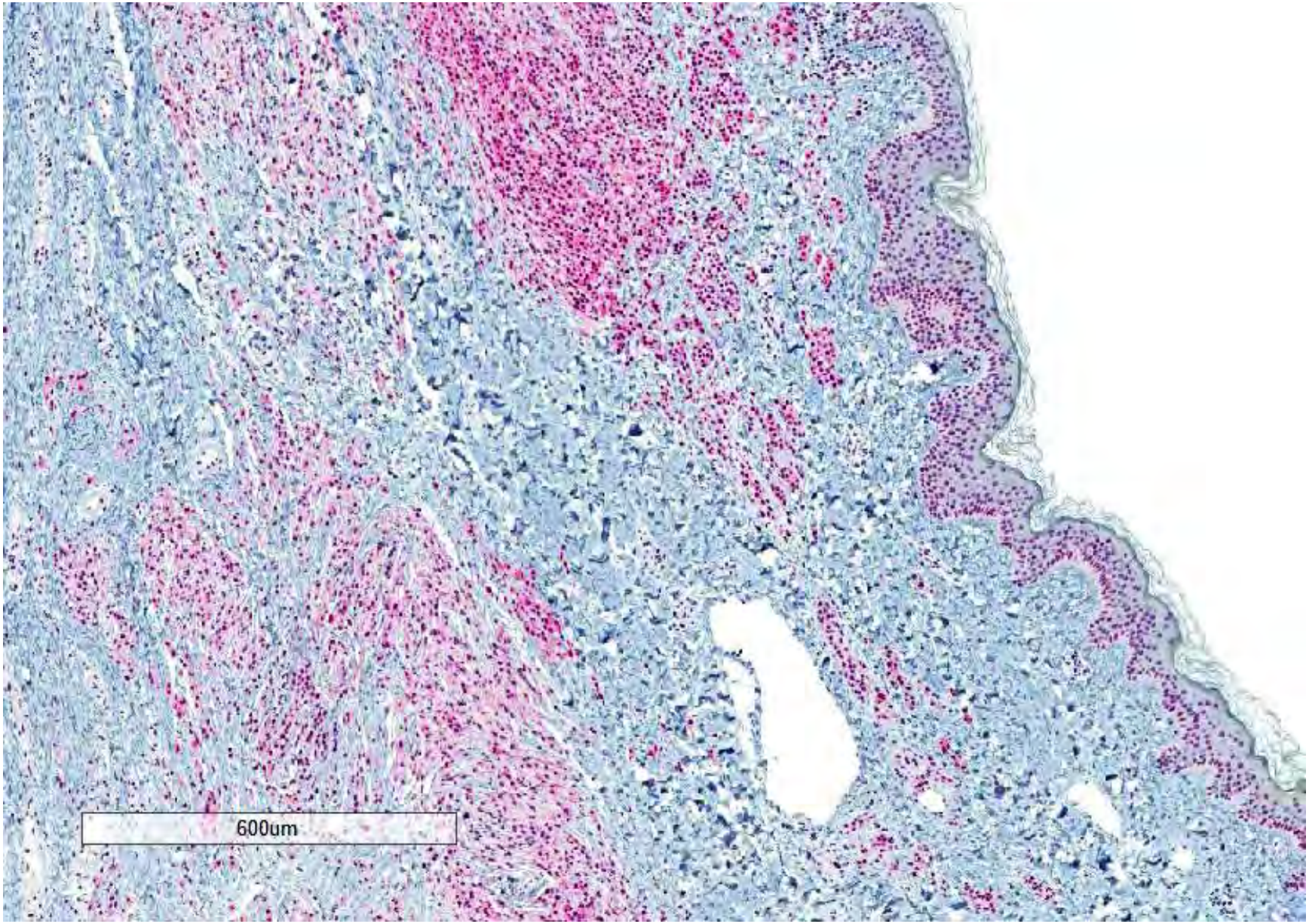
III-2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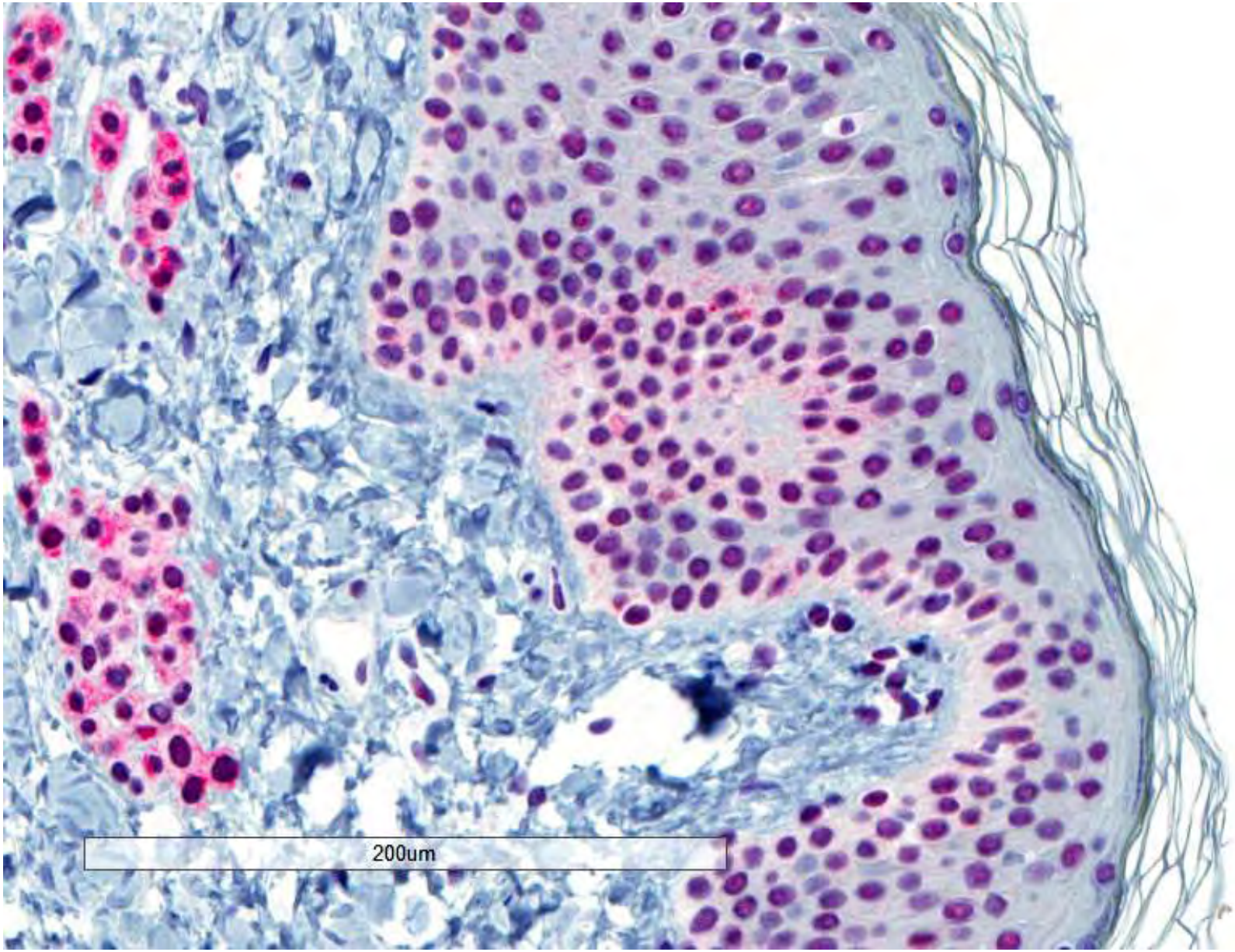
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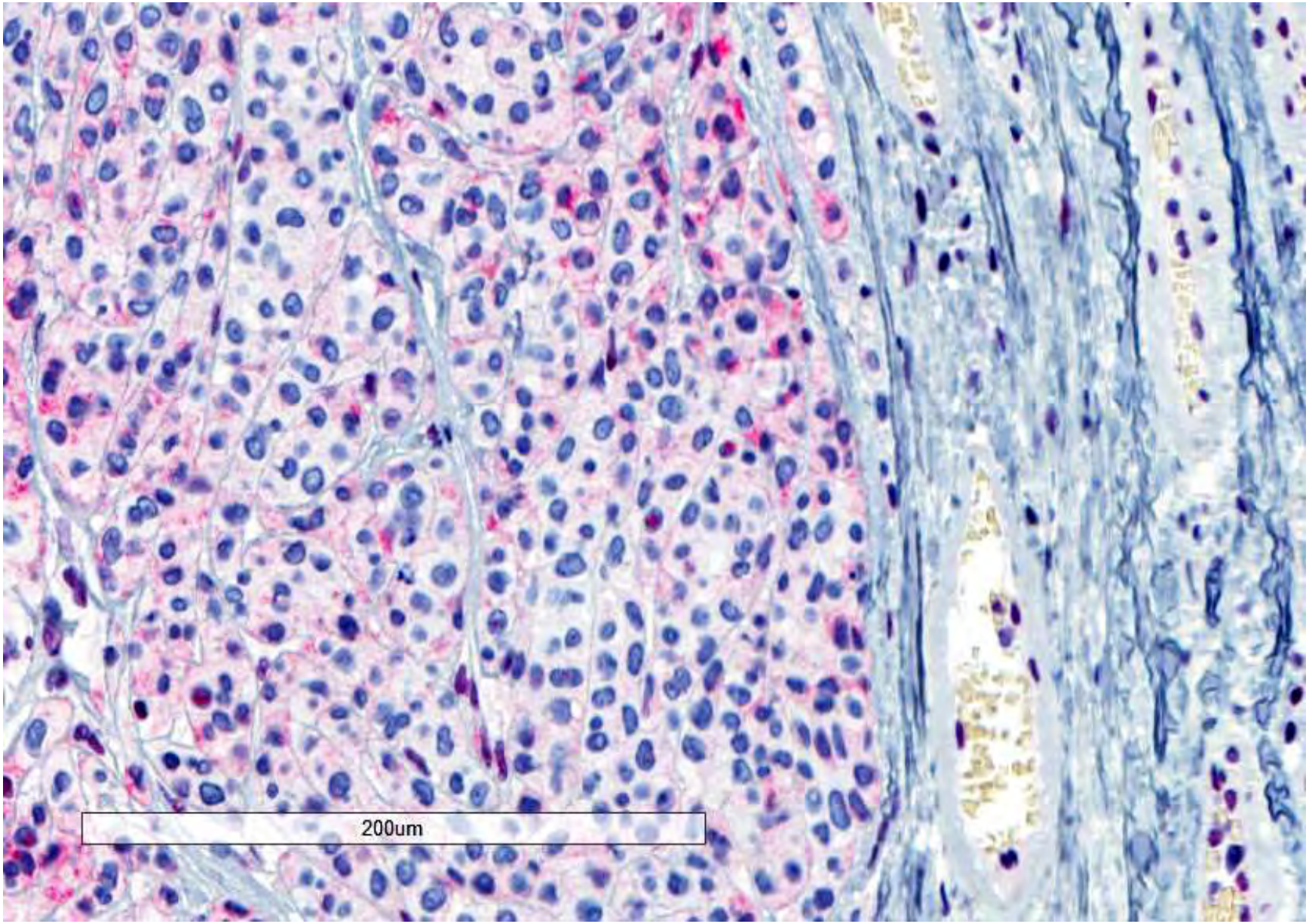
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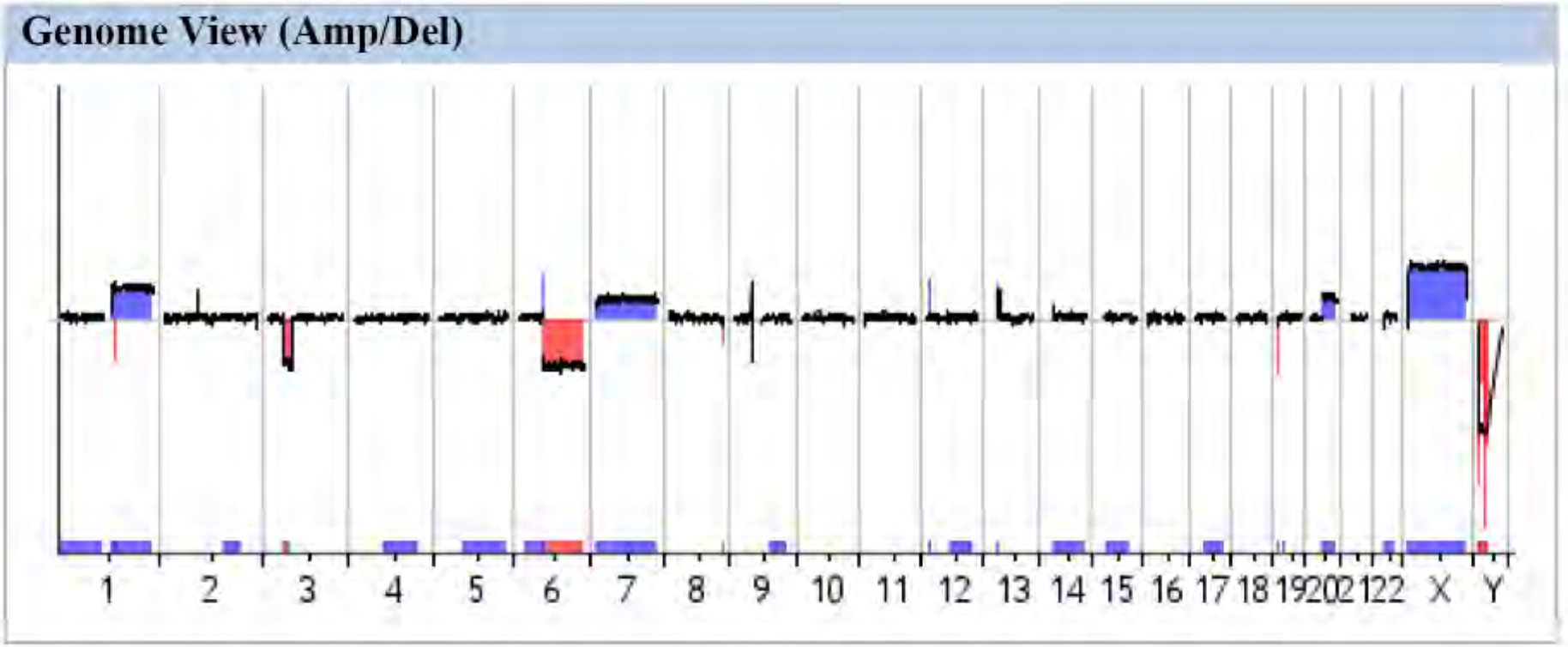
Genome View (Amp/Del)
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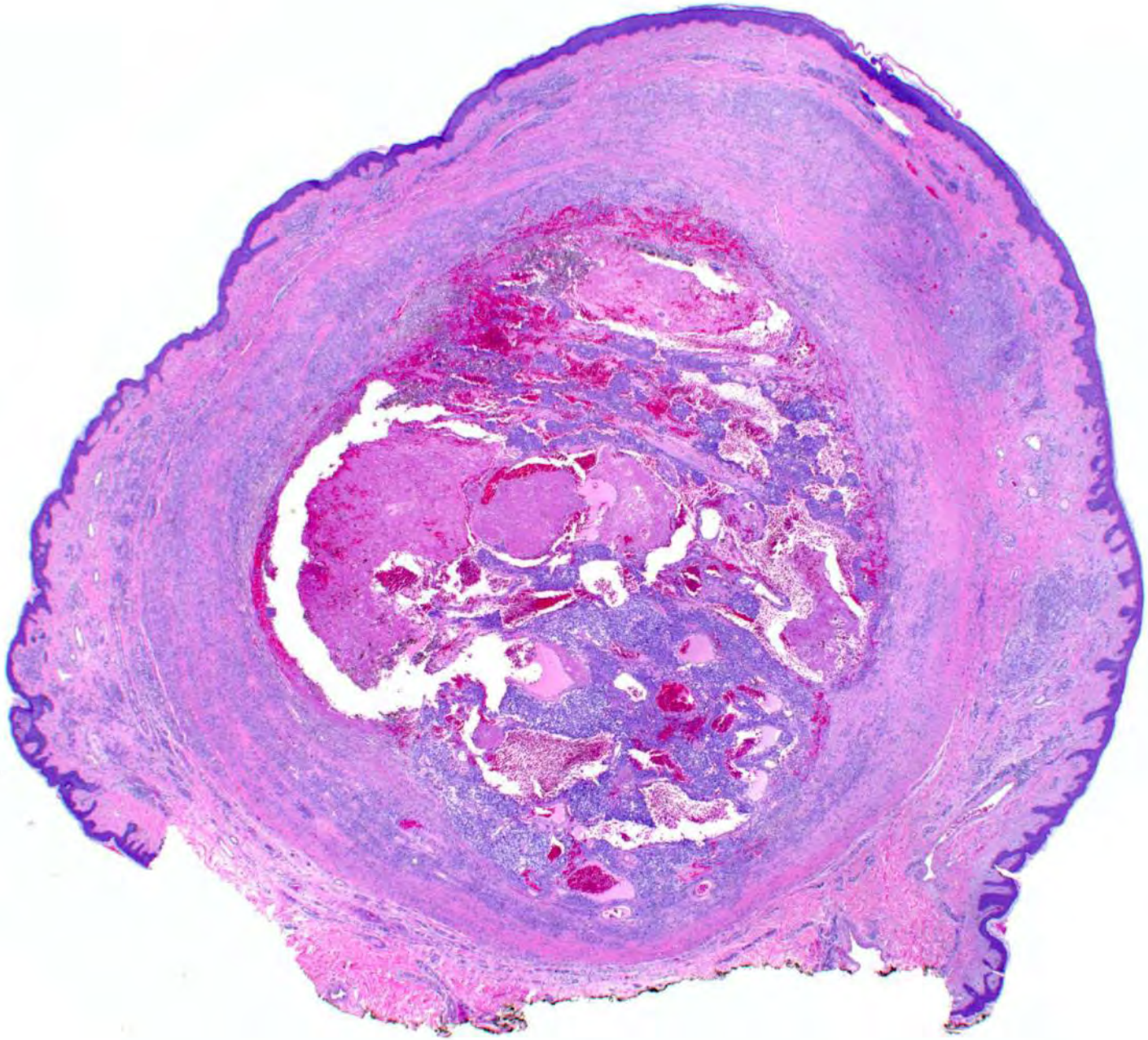
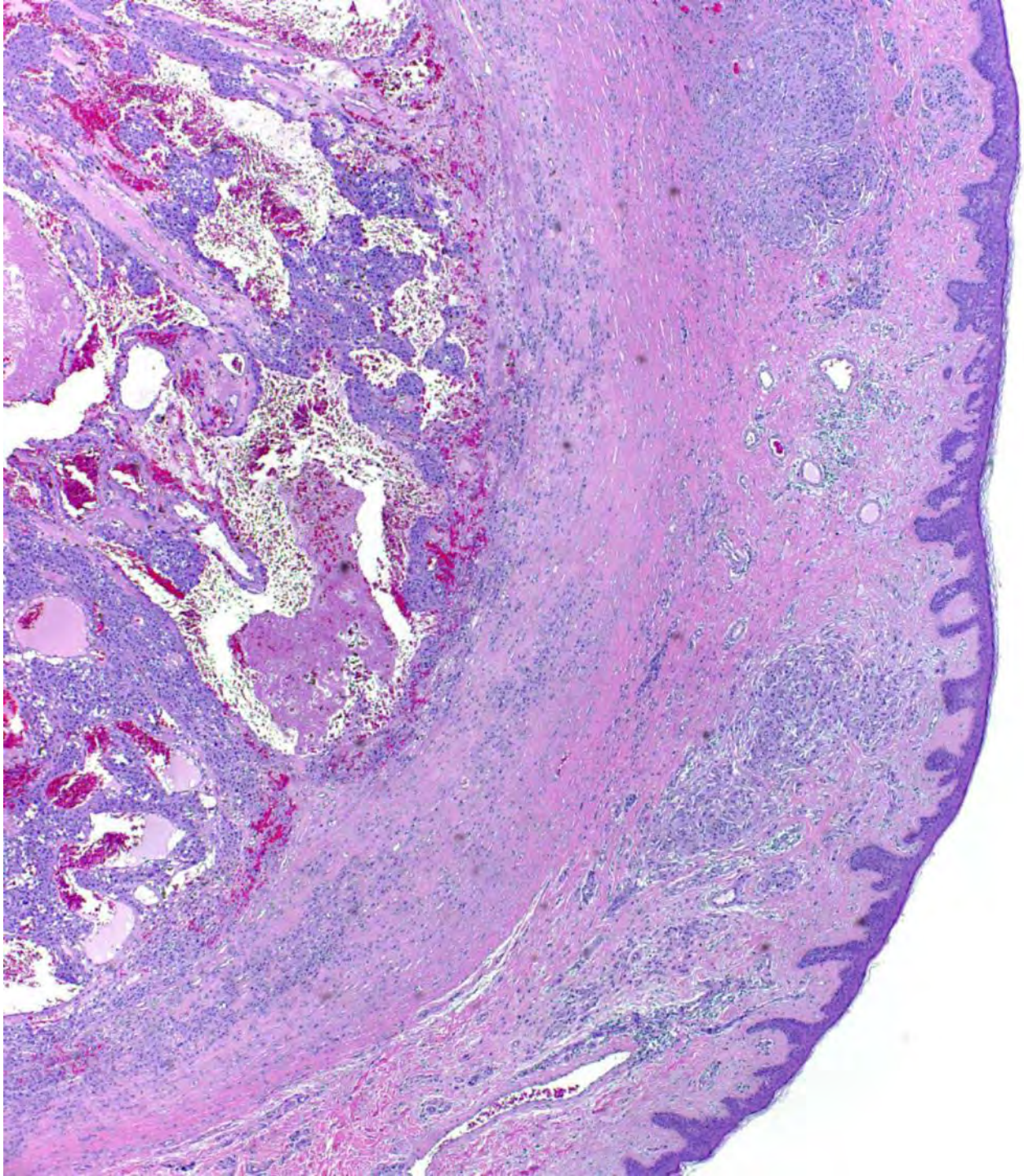
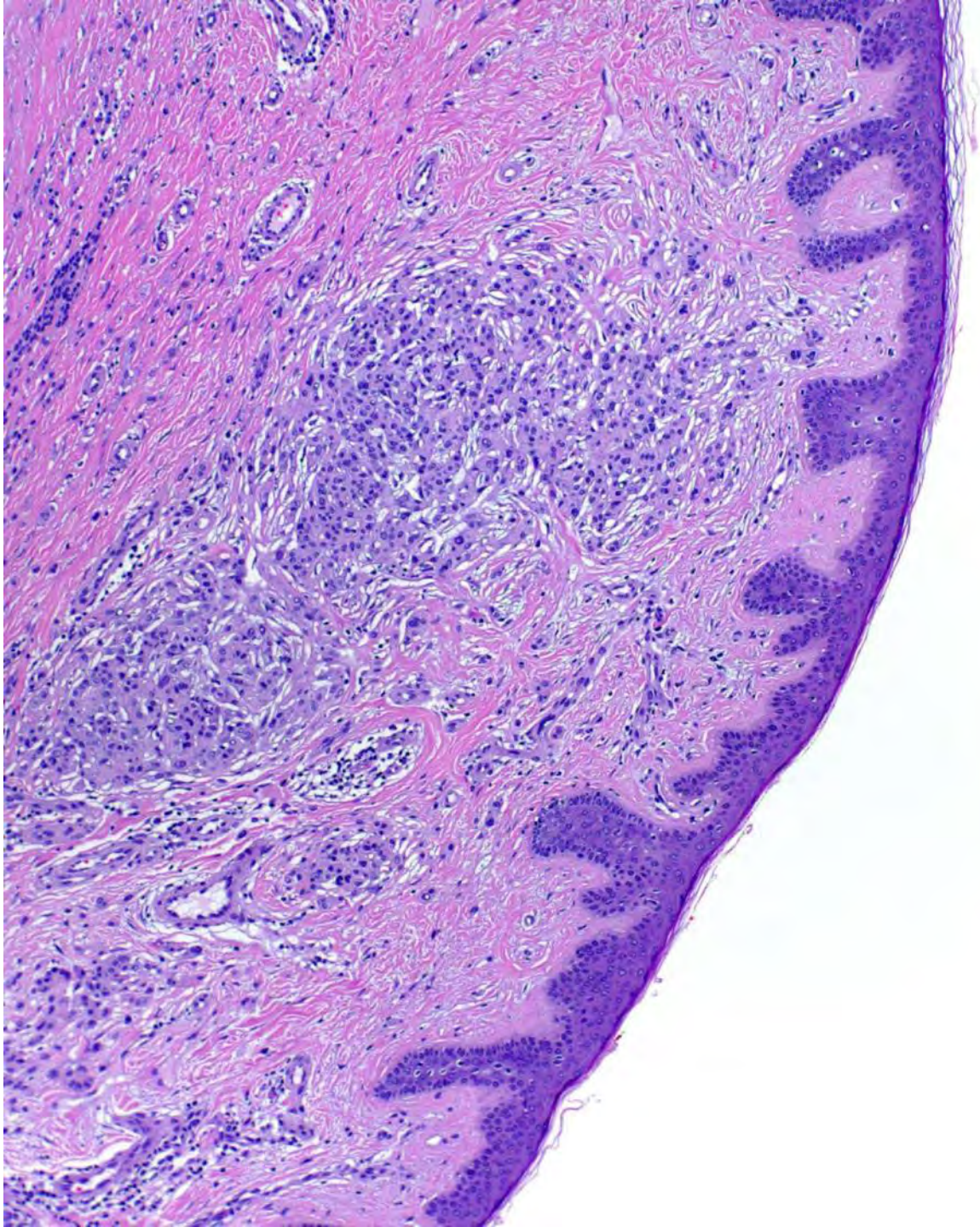
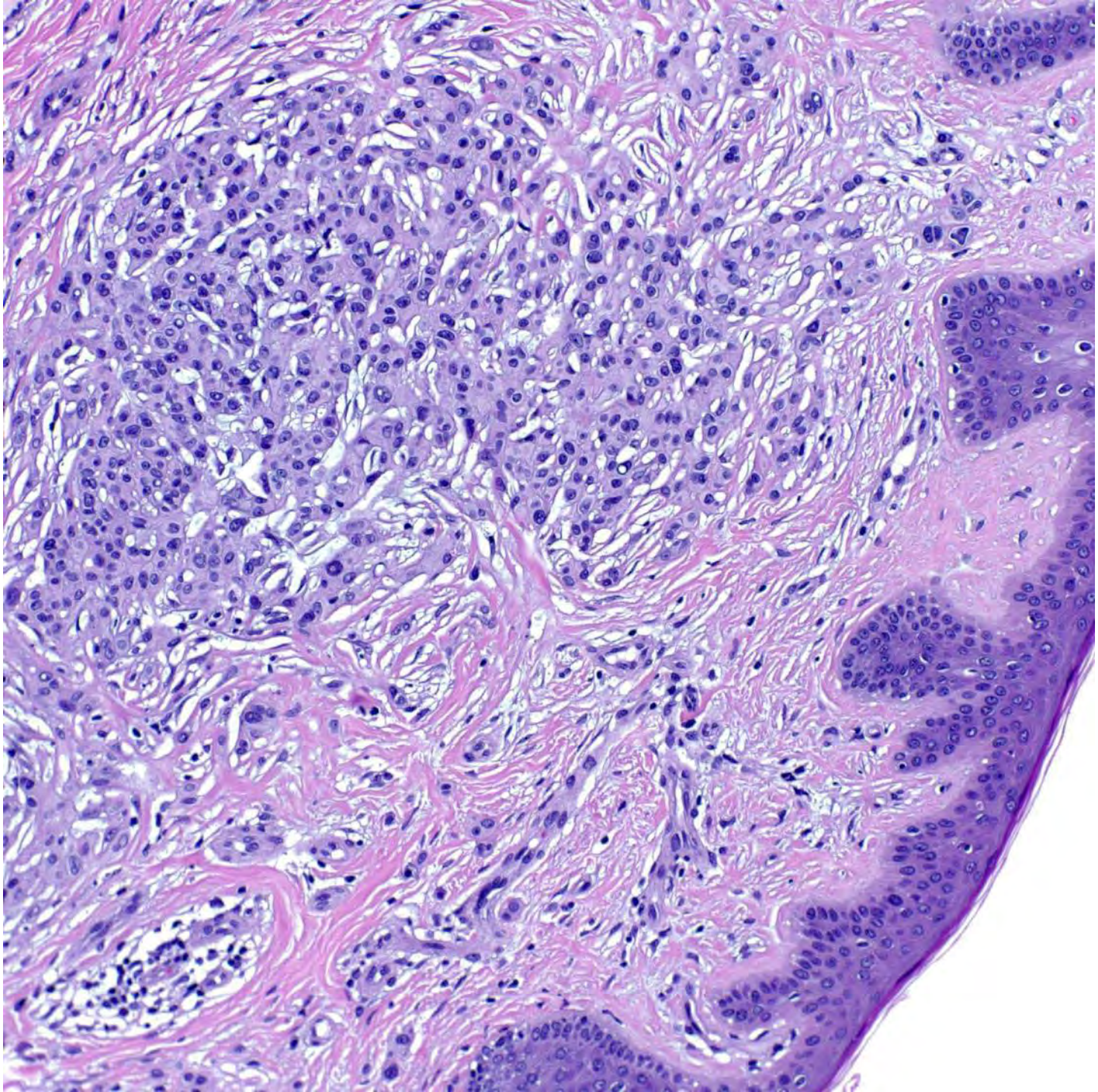
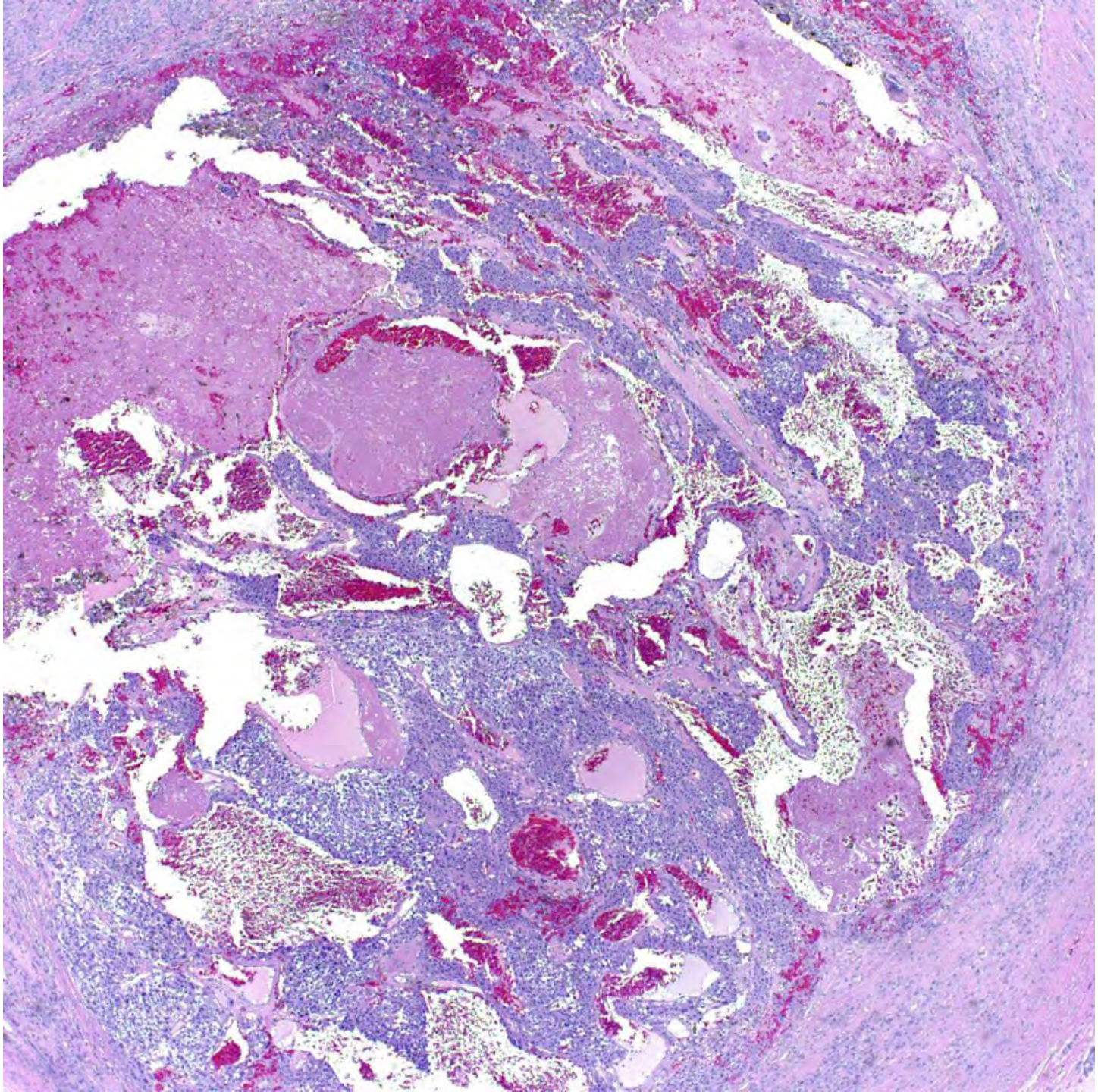
- 42 year old male
- Left anterior shoulder lesion
- History of many dysplastic nevi

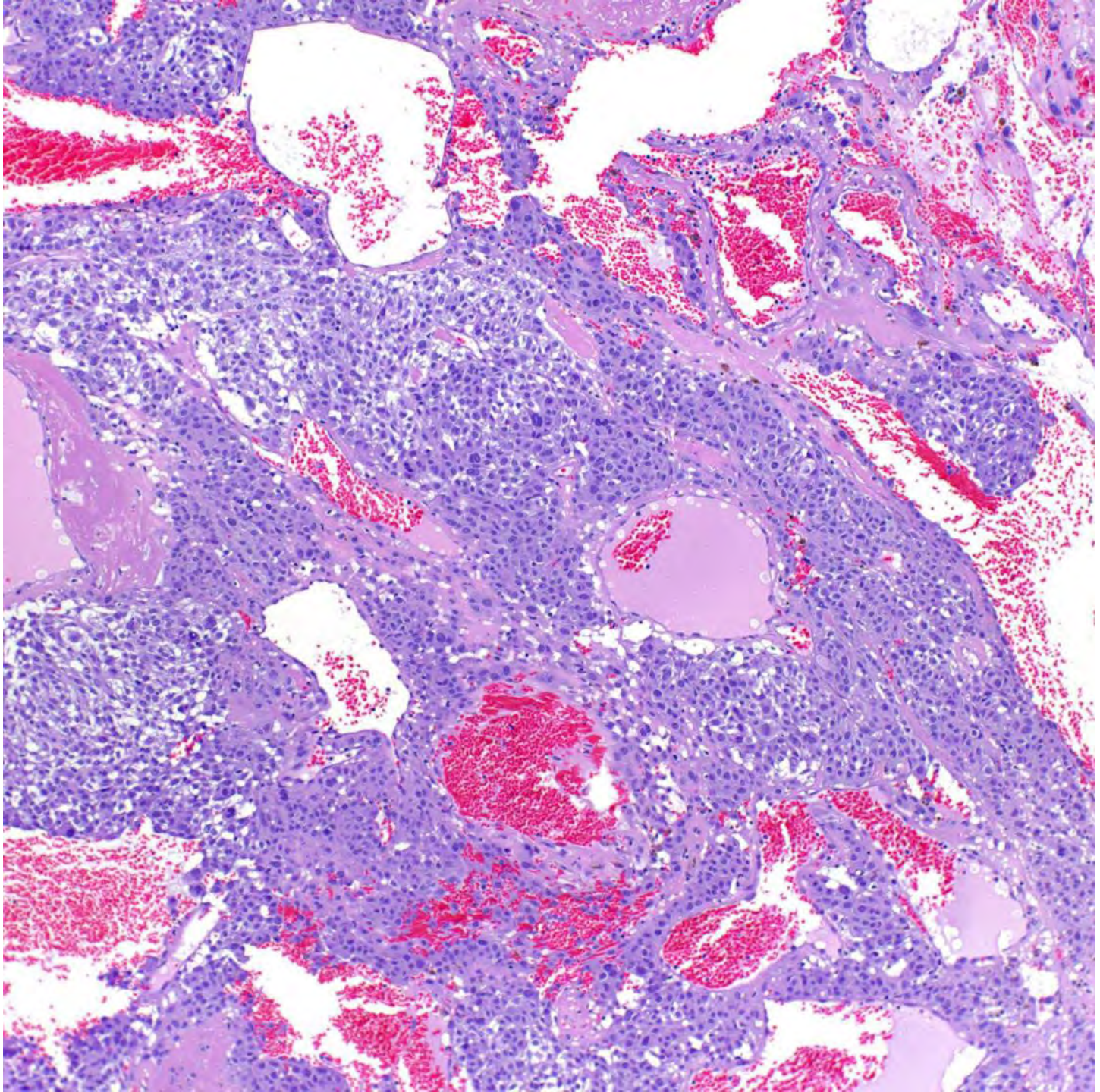


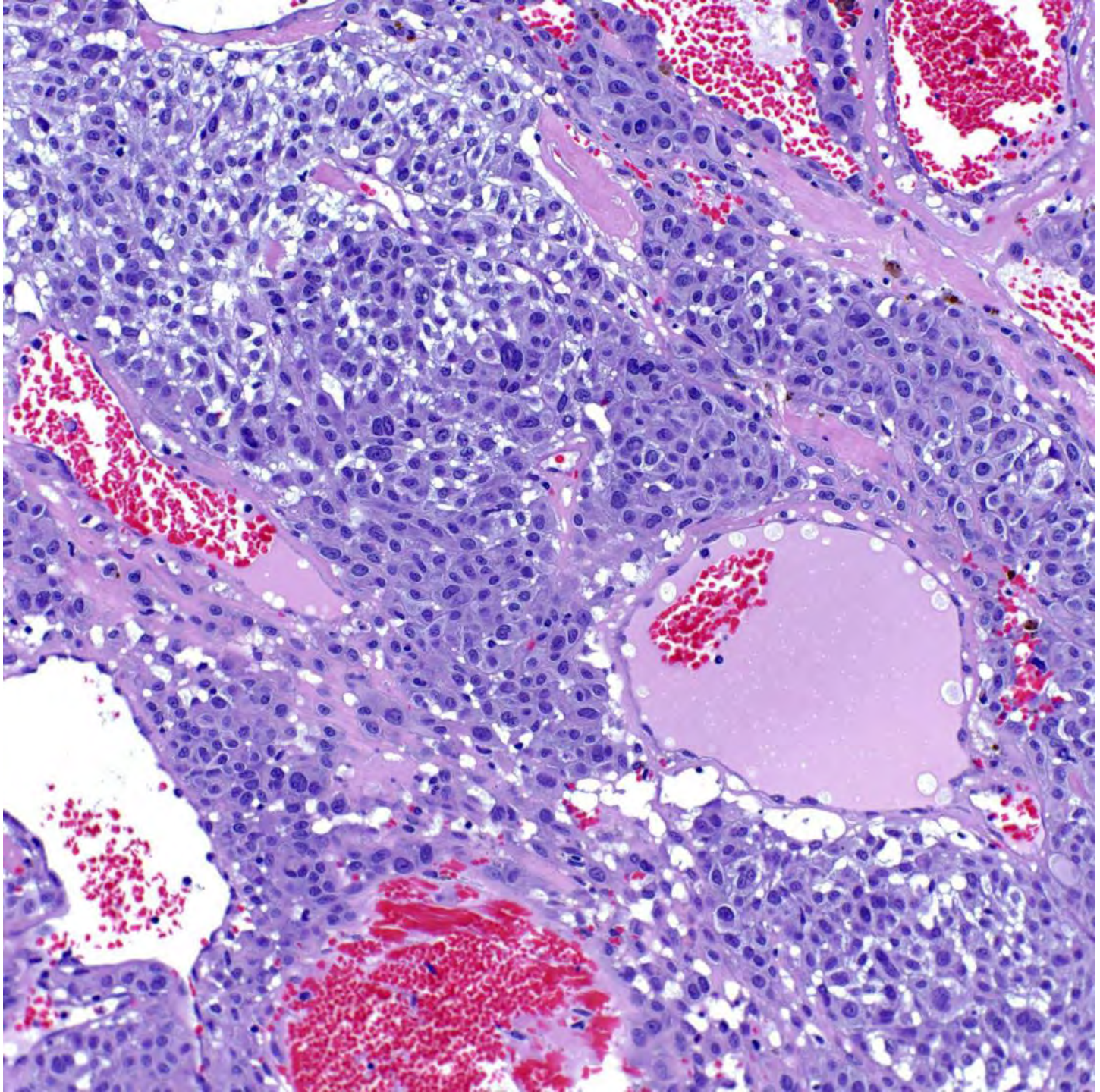


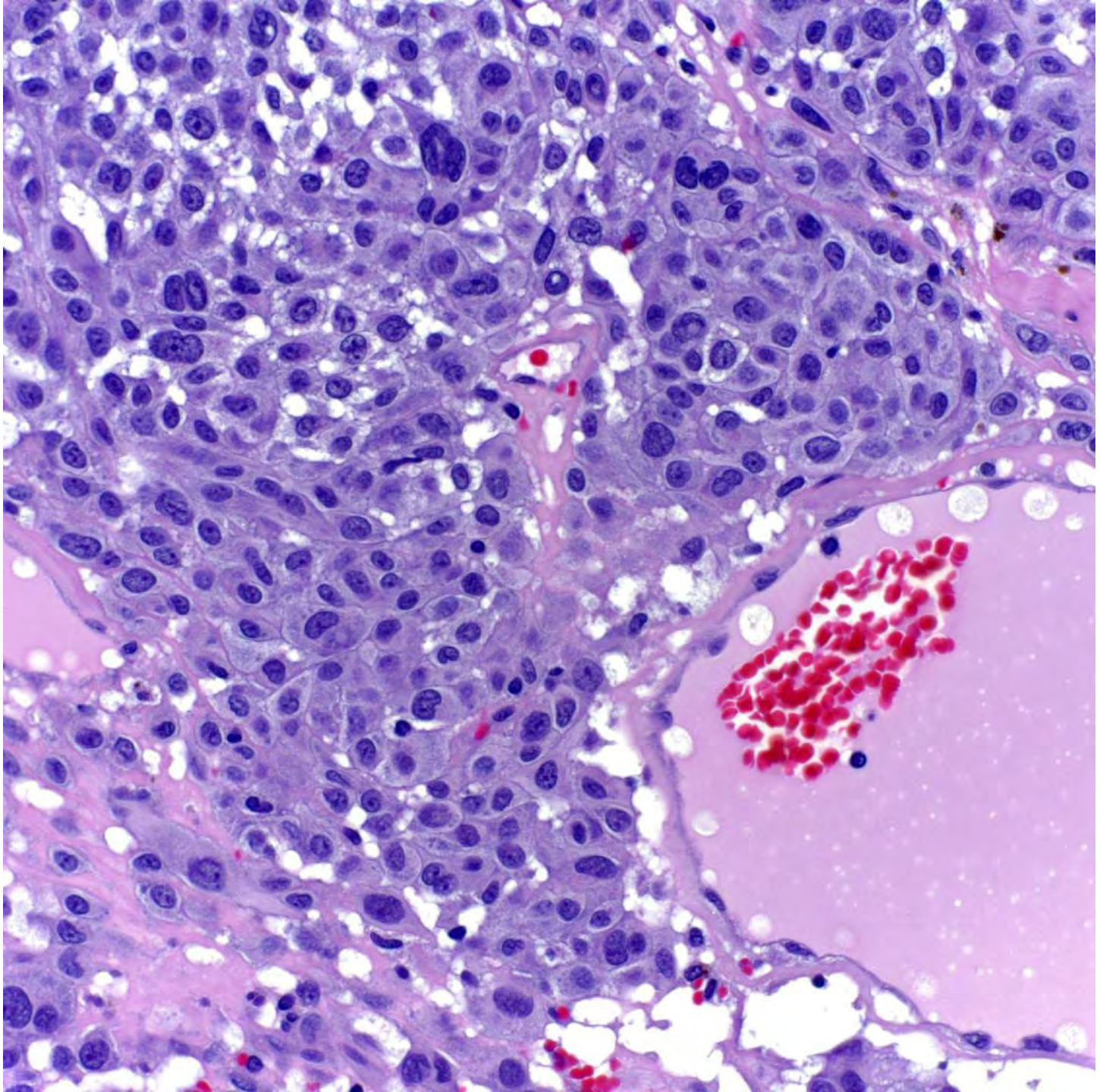












Results by CGH

Loss of chr. 9, loss of interstitial area on 3p including BAP-1

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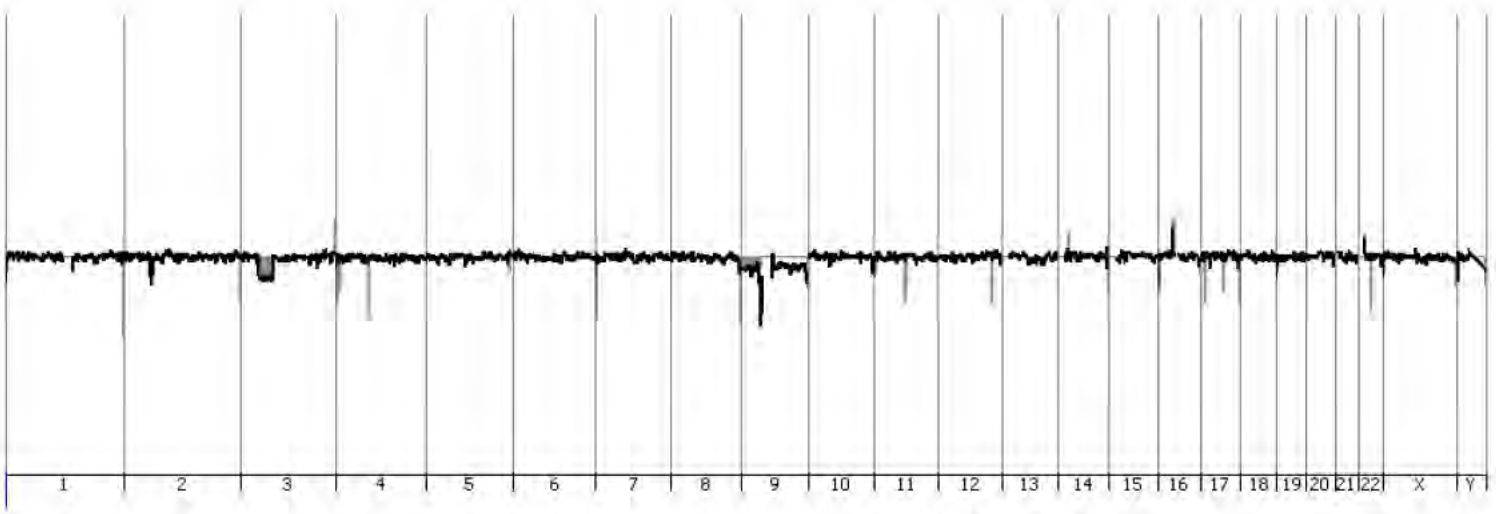
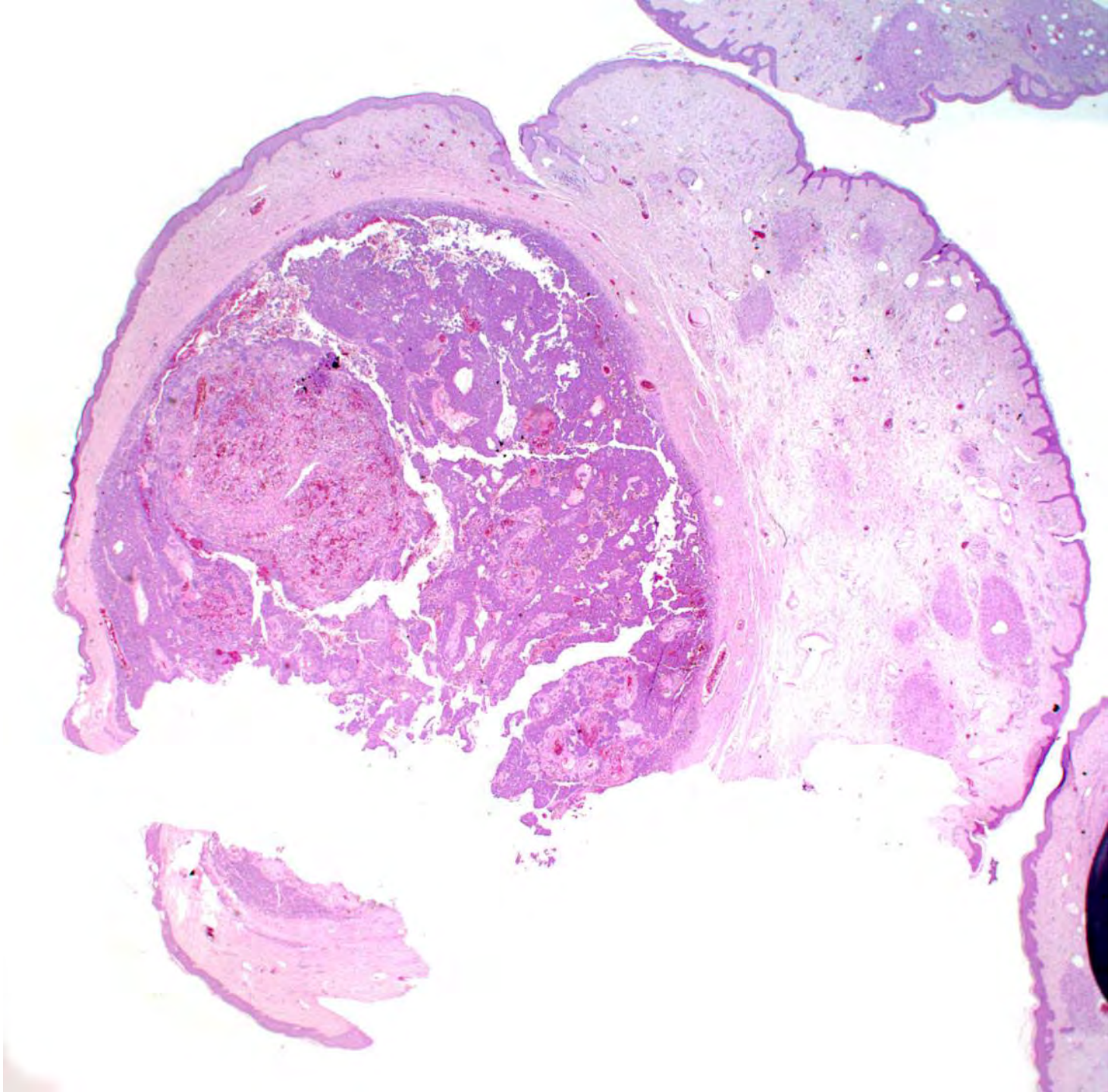
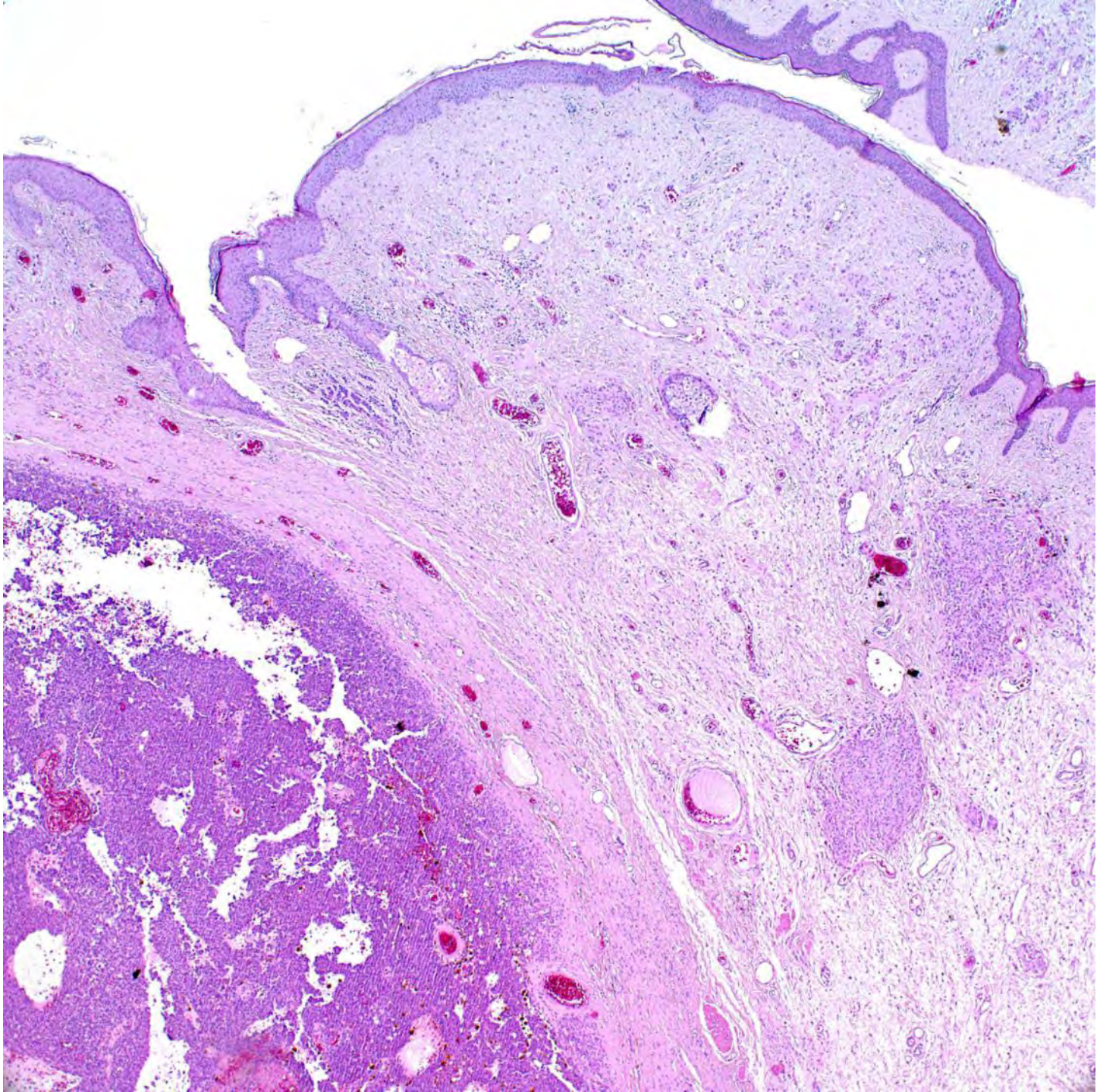
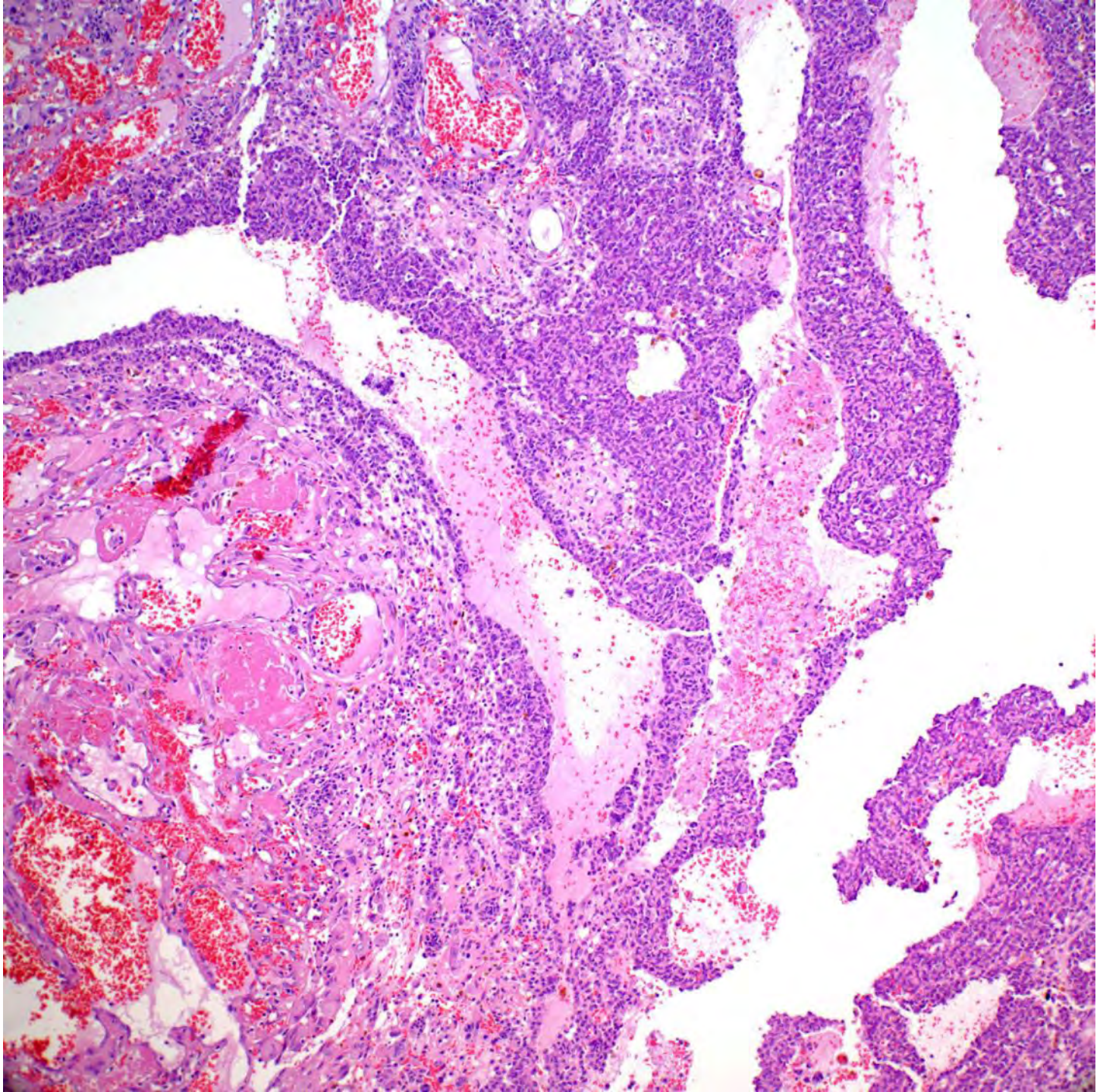
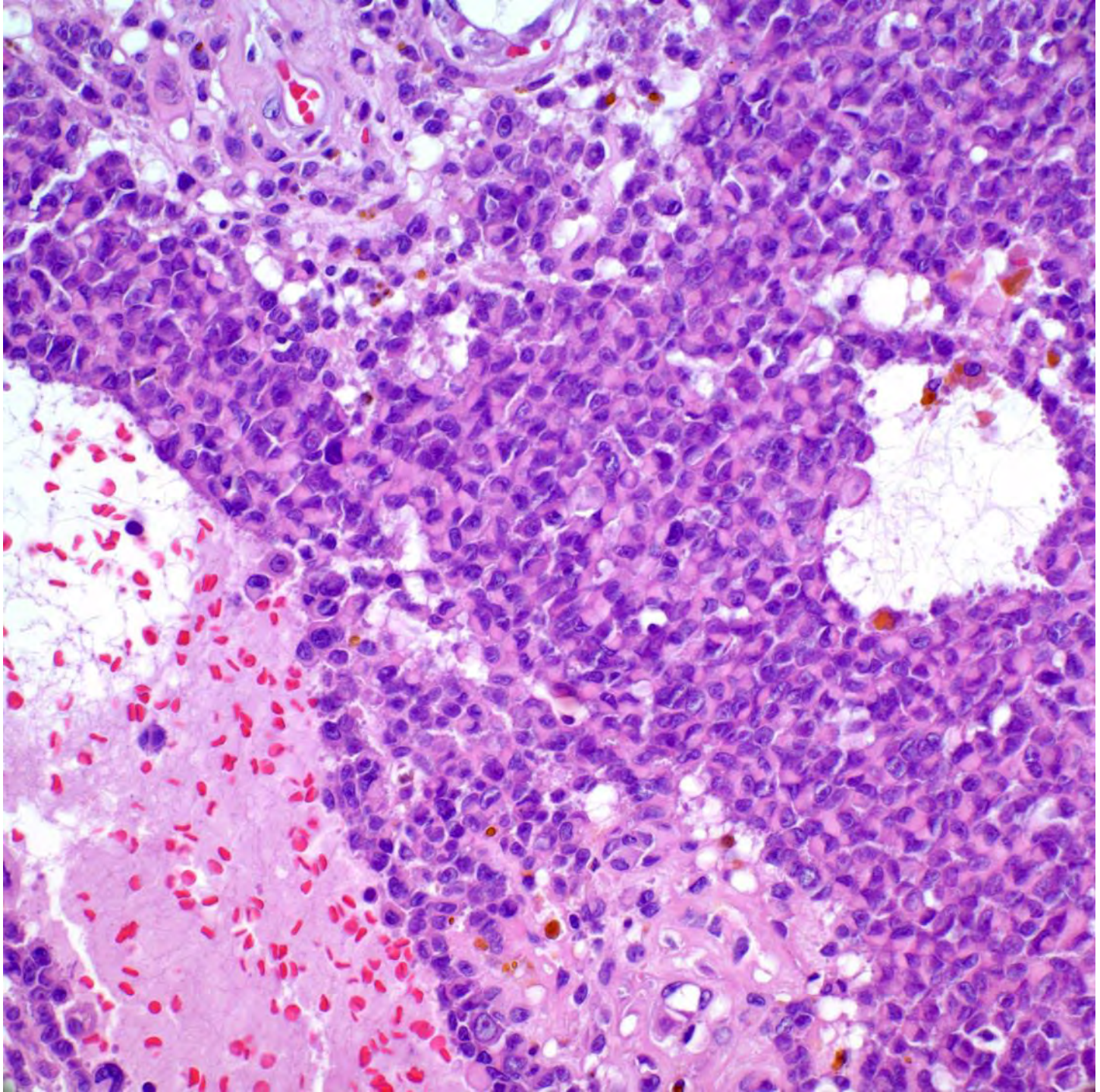


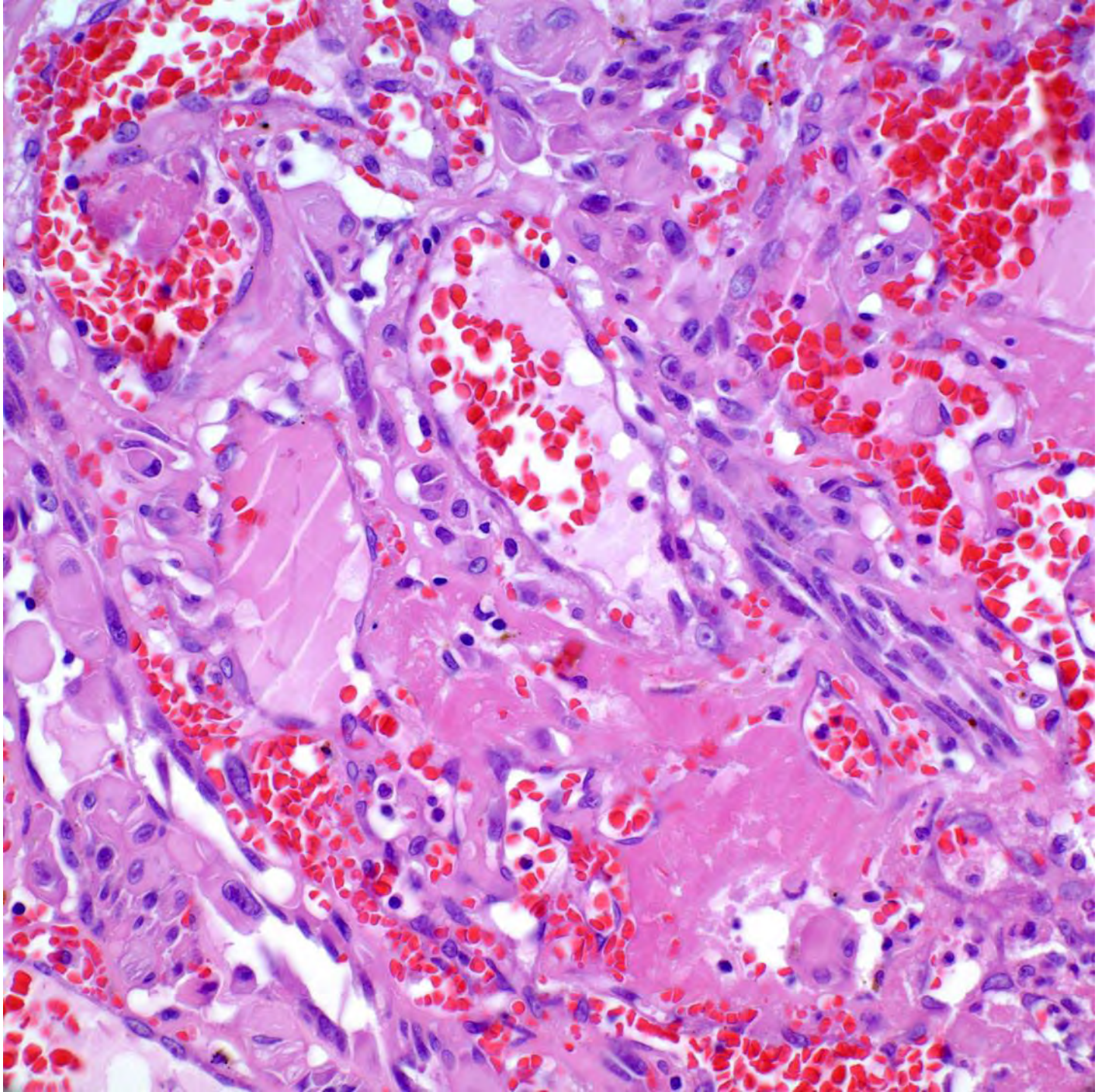
72 year old man, site not known

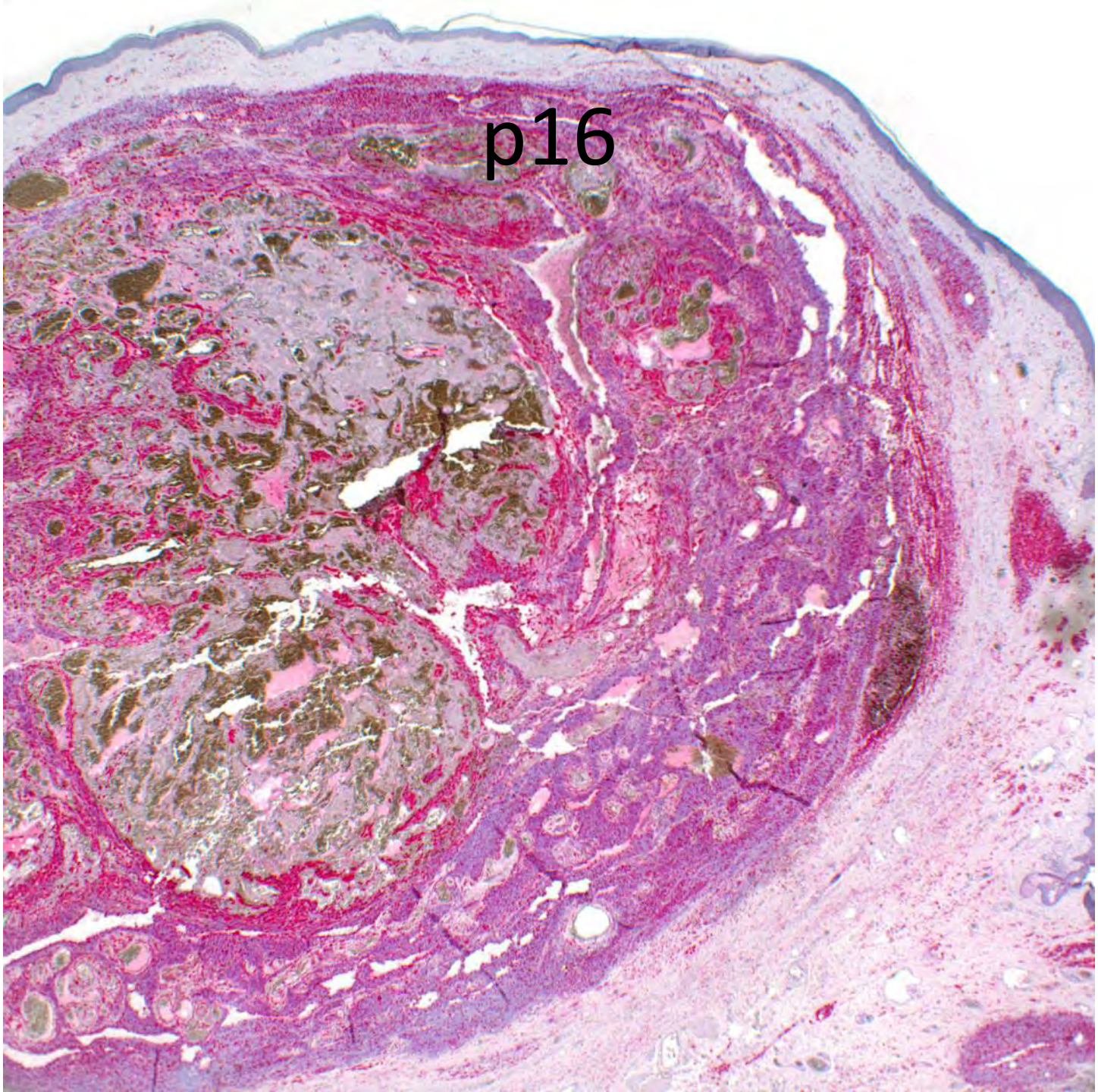








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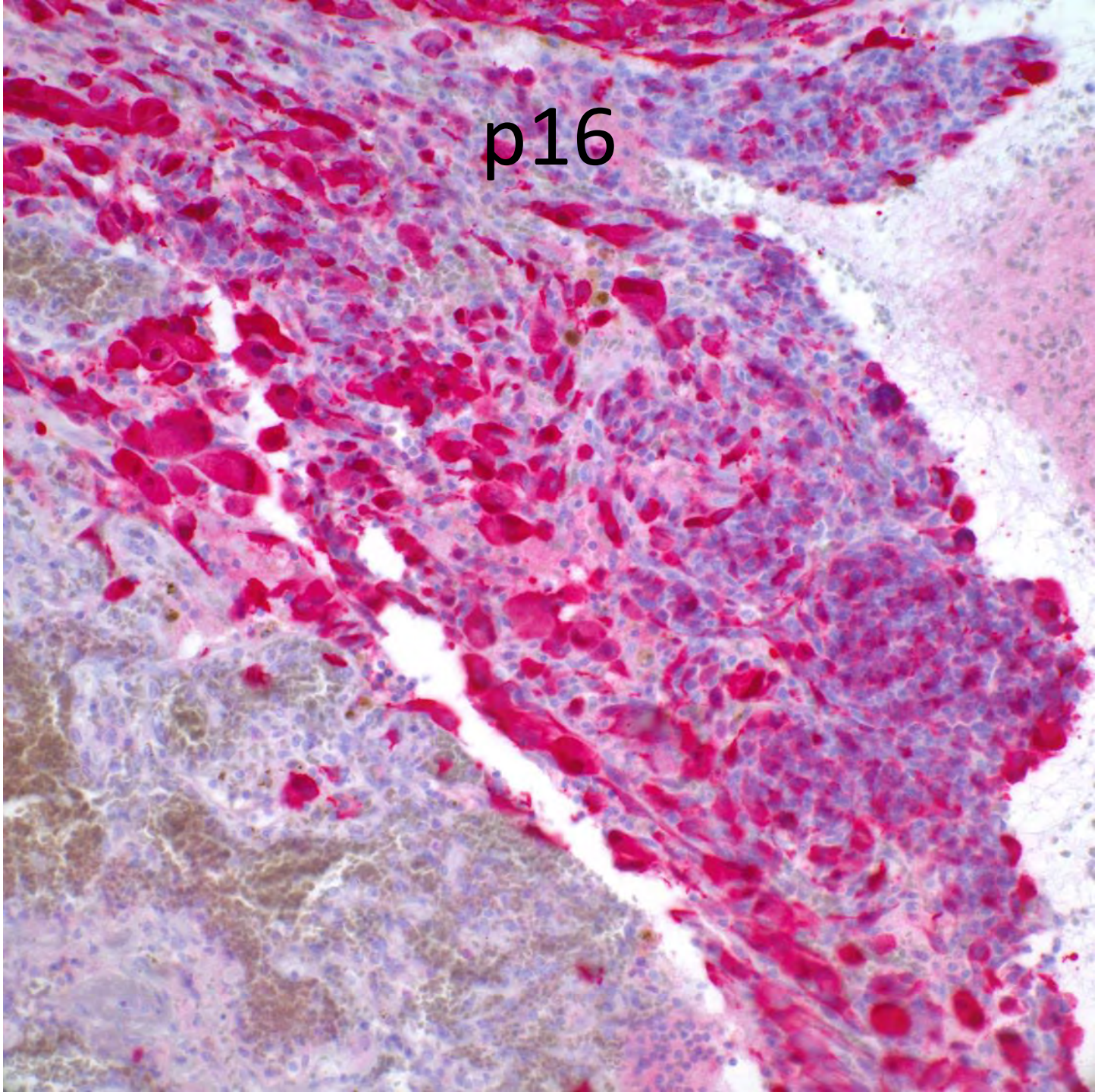
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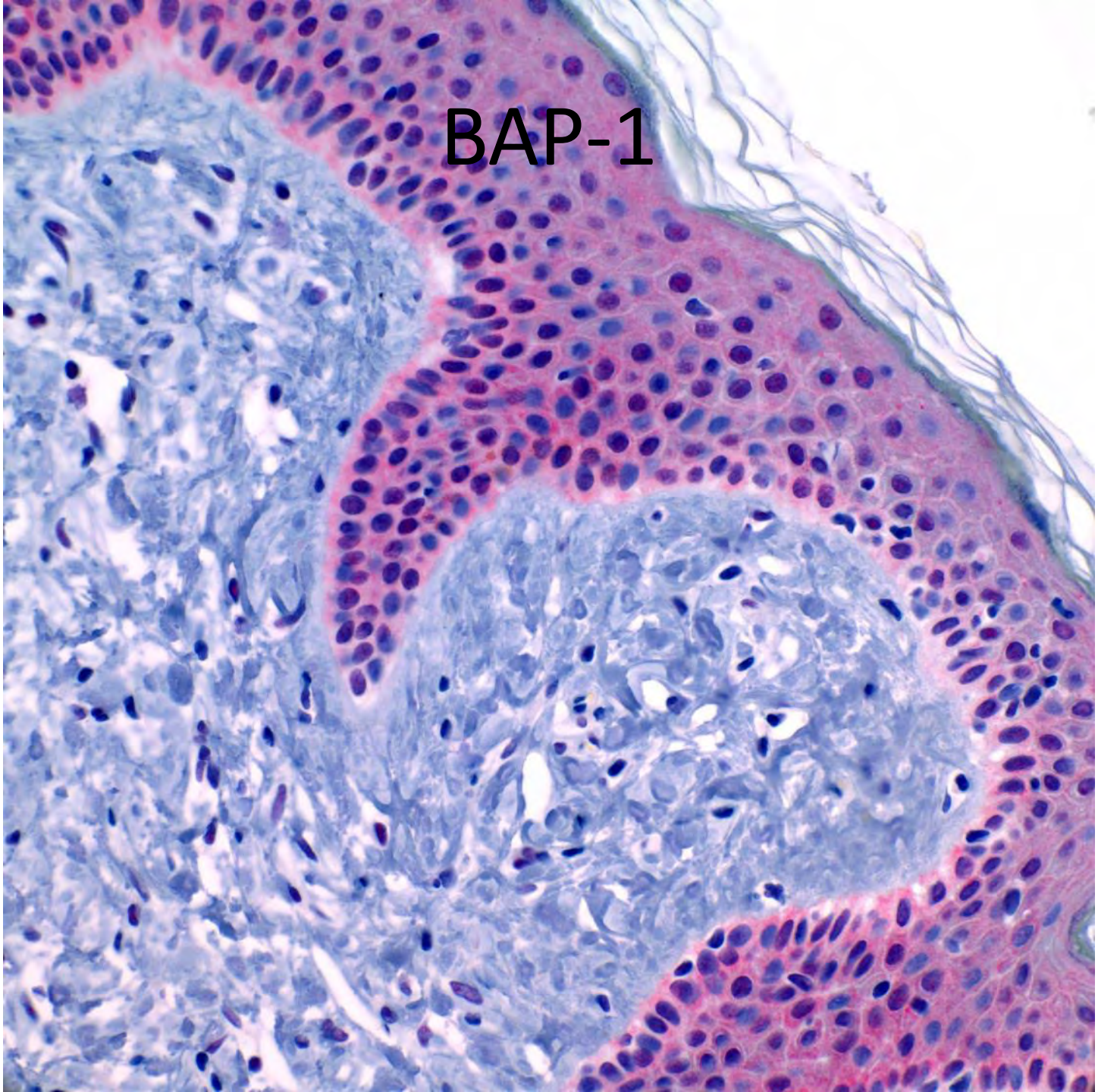
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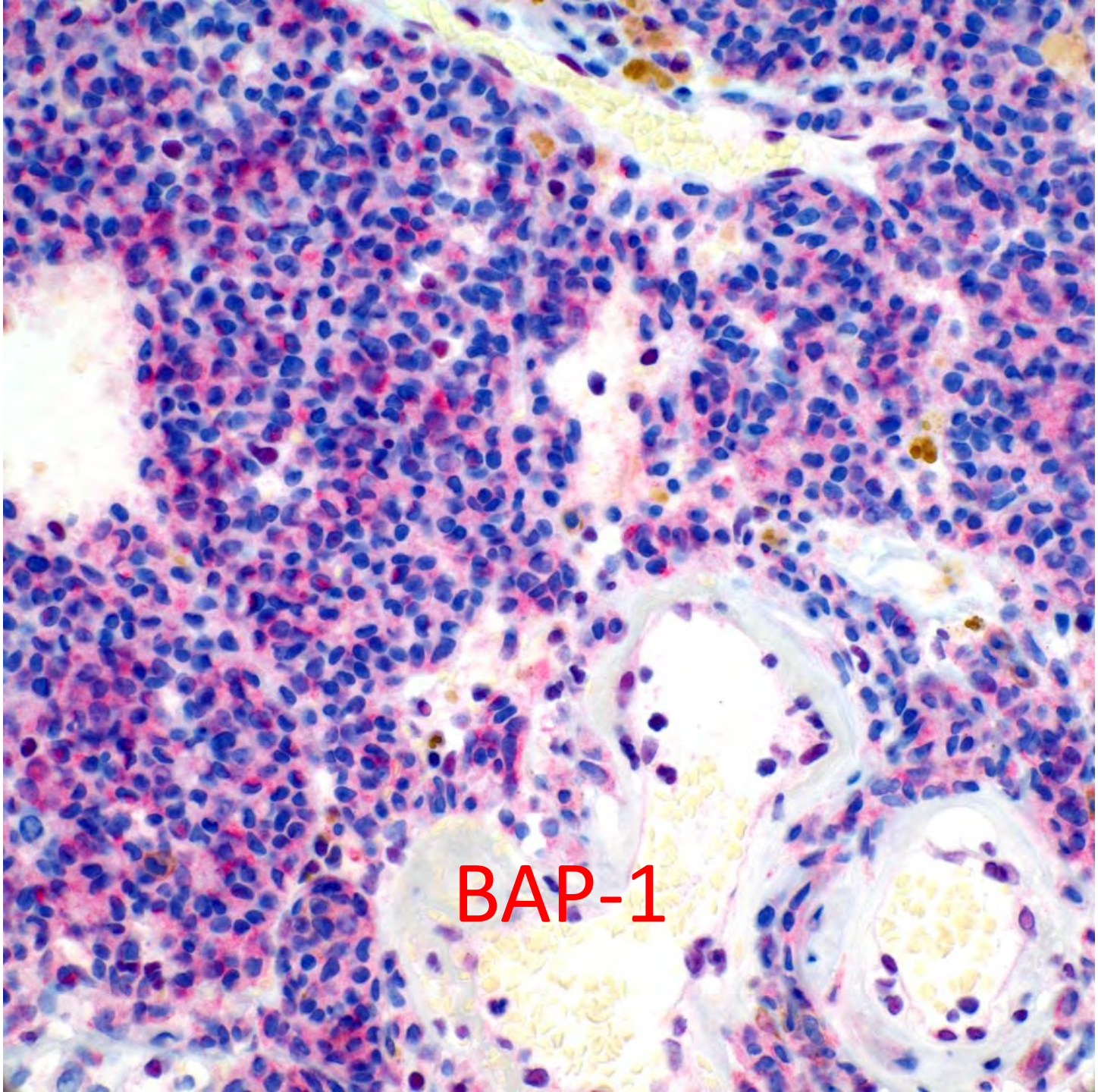
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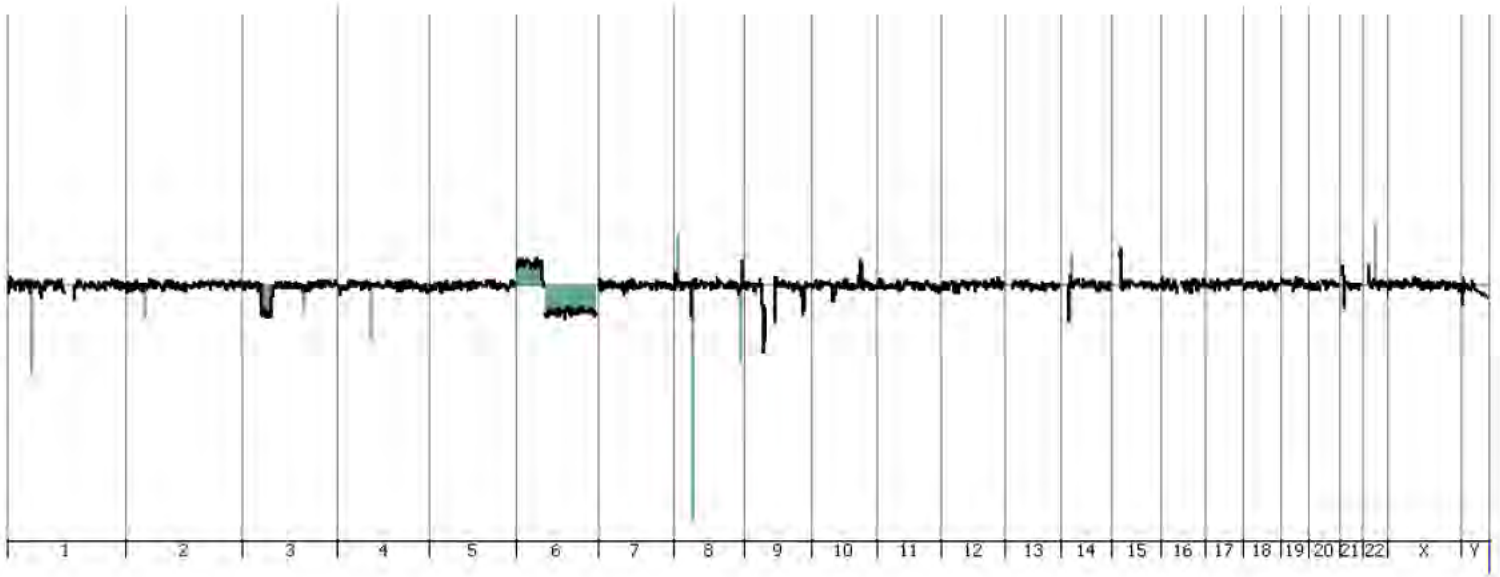

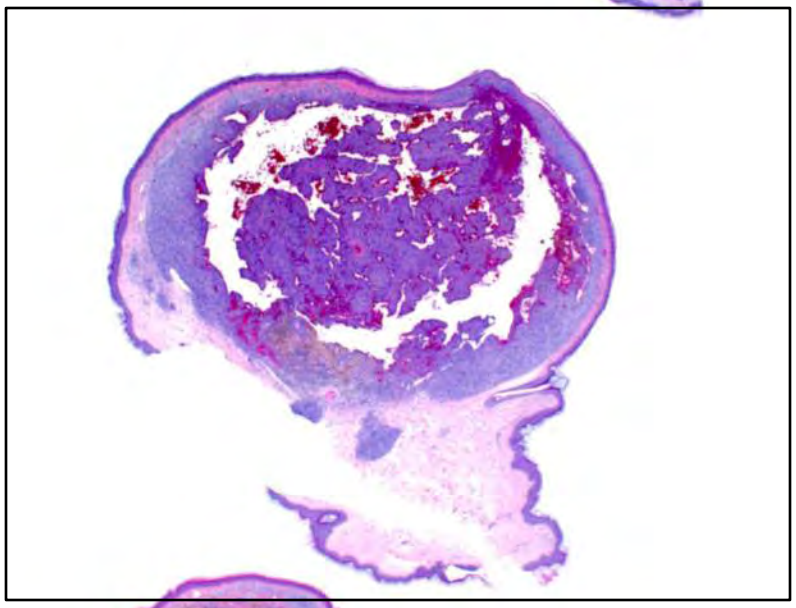

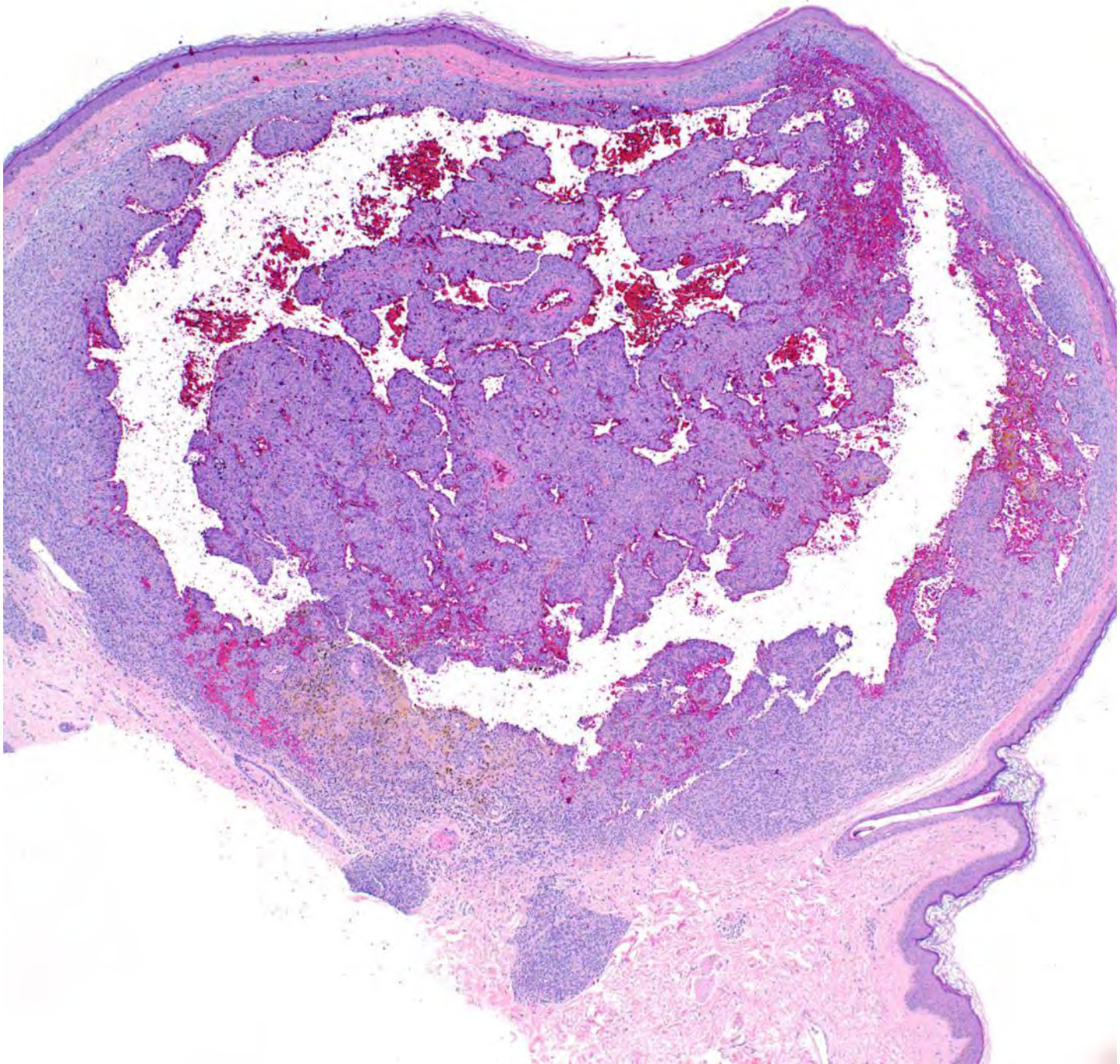

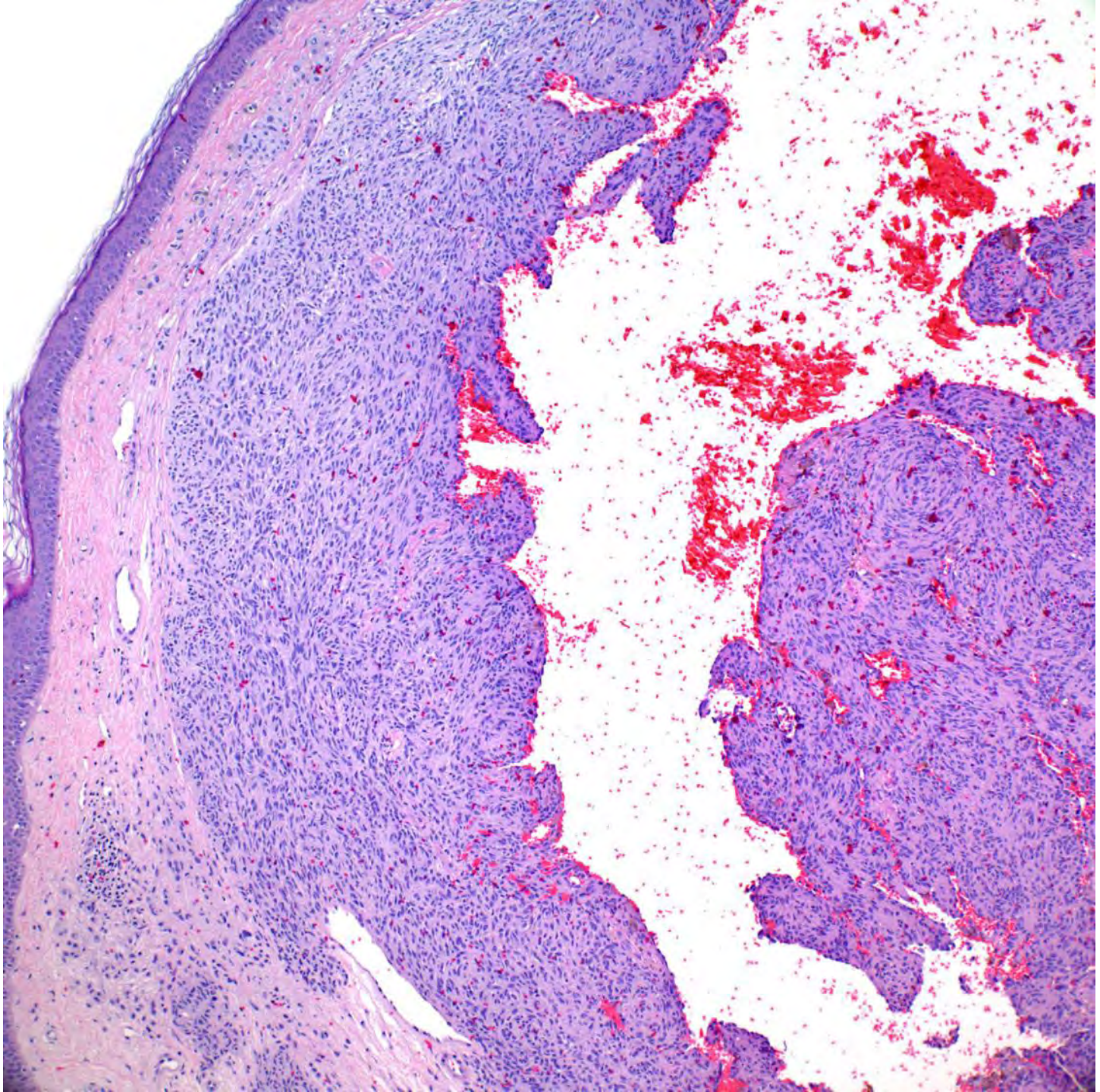

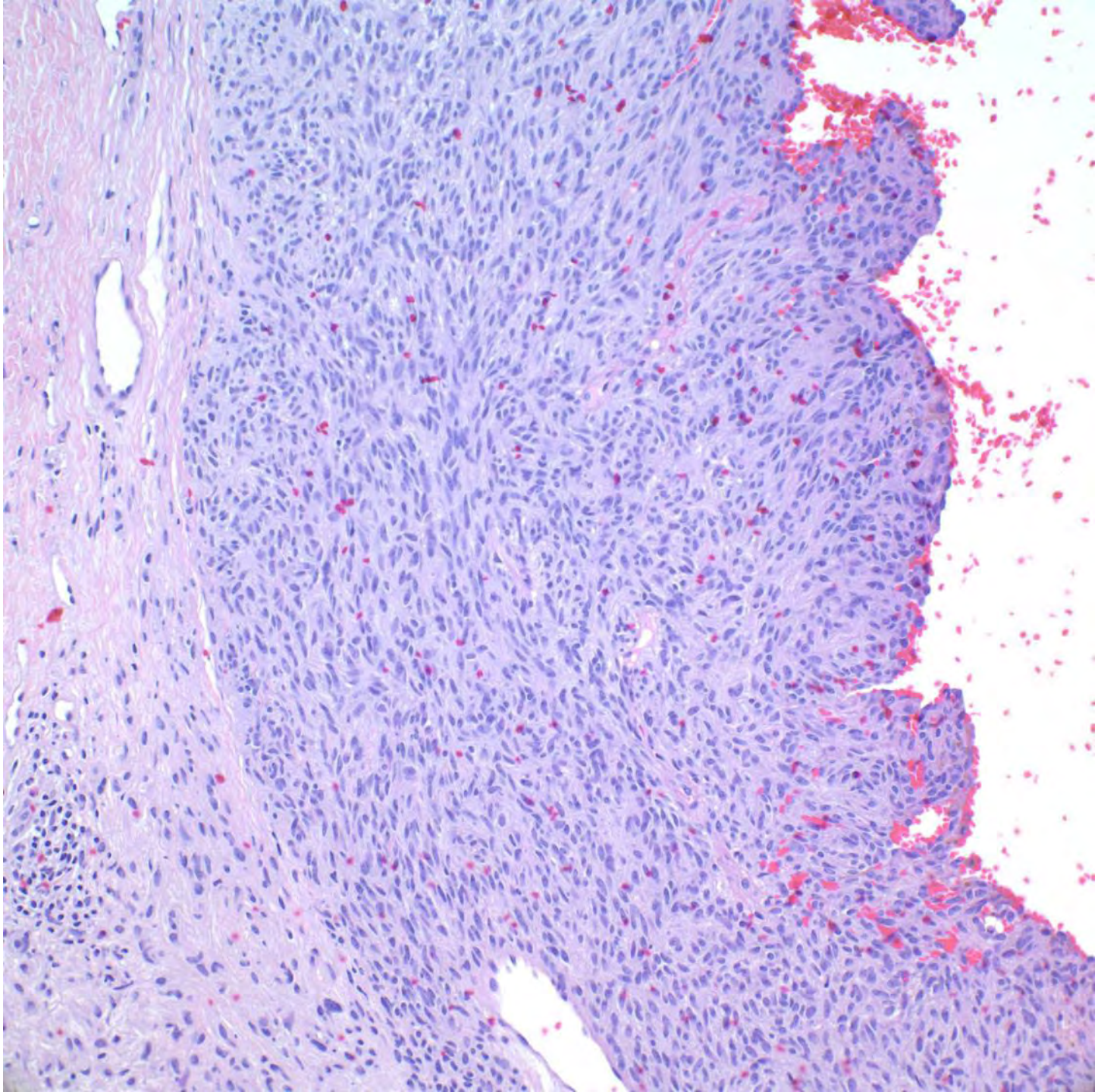

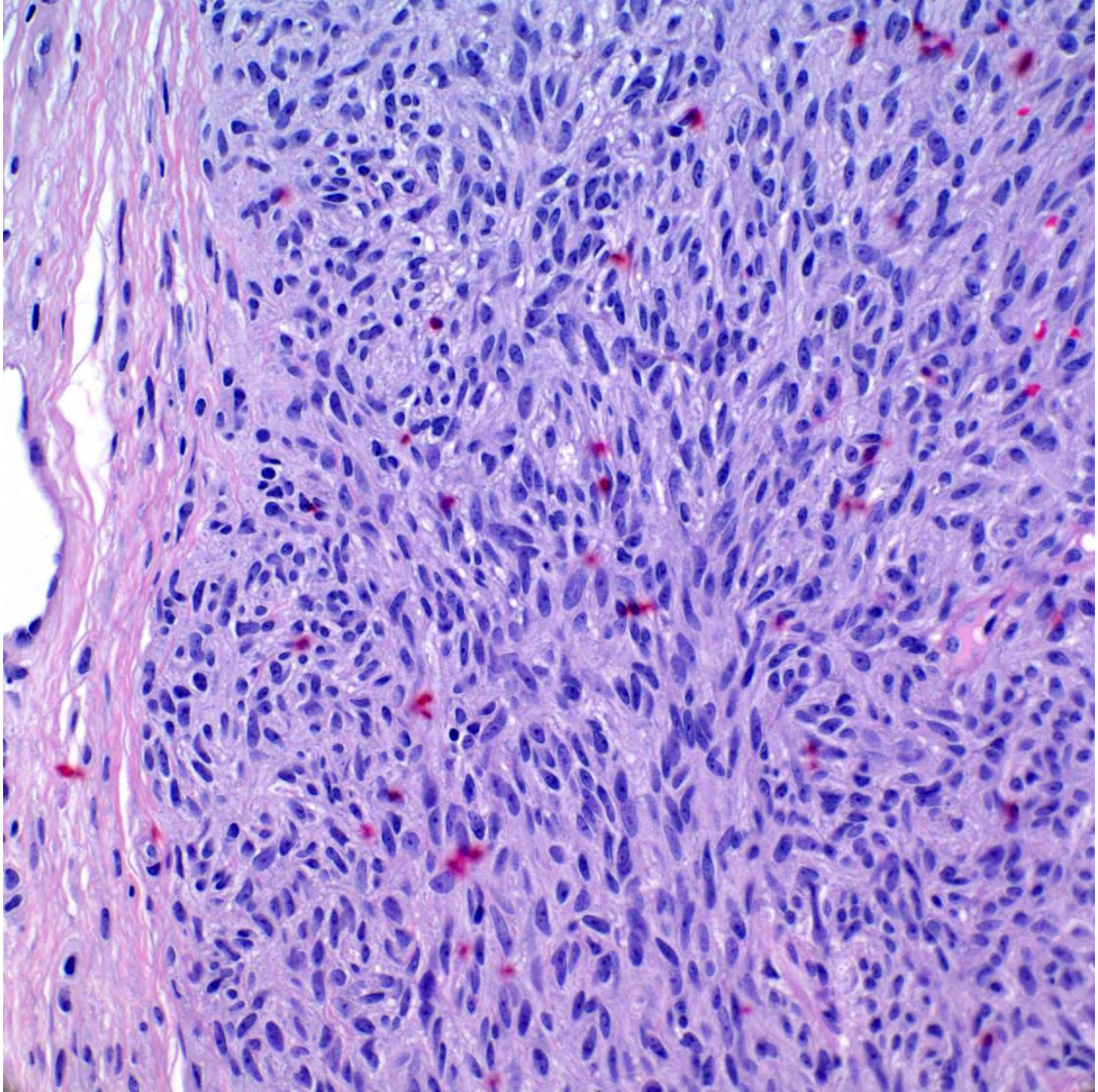

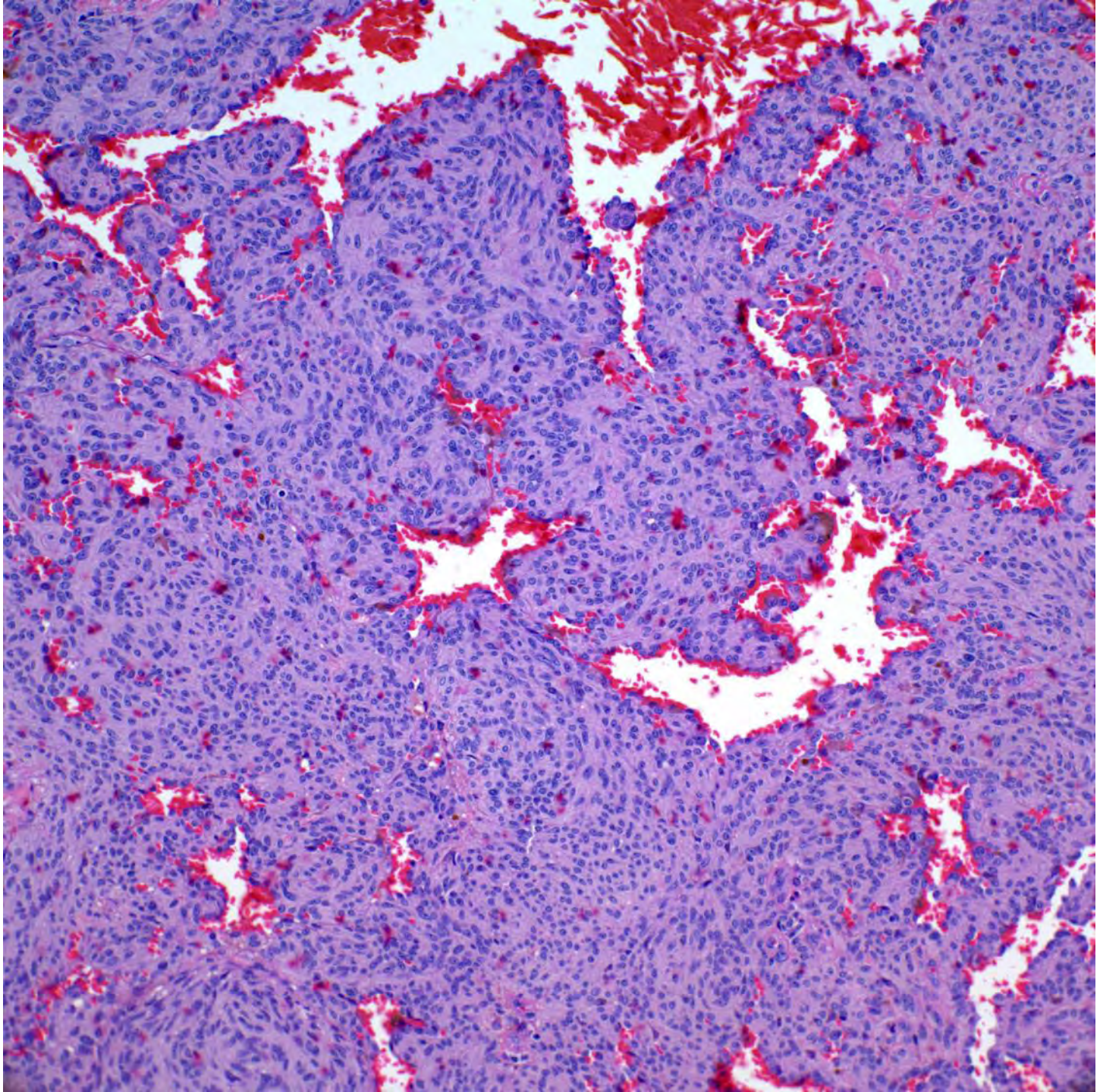

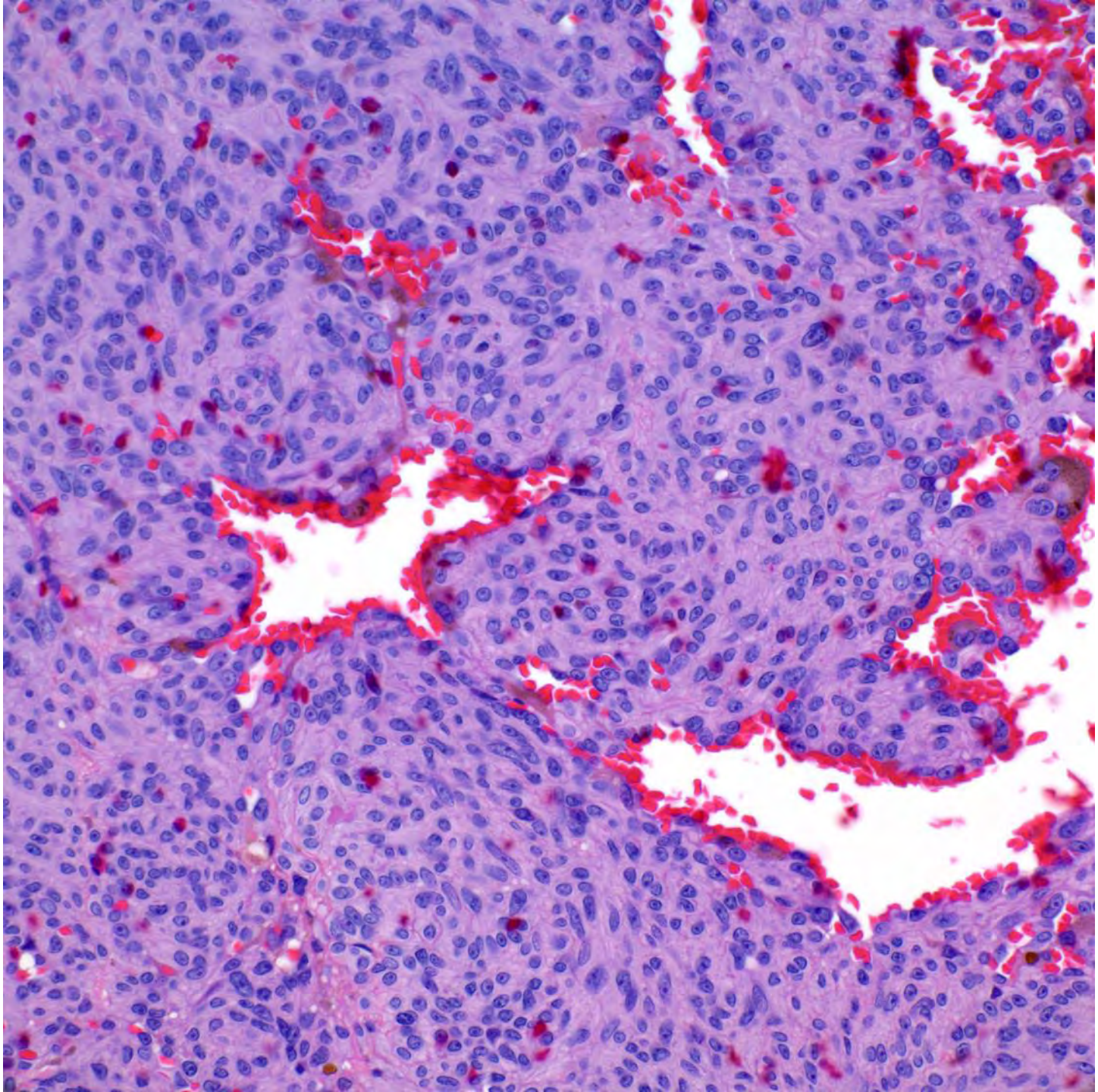

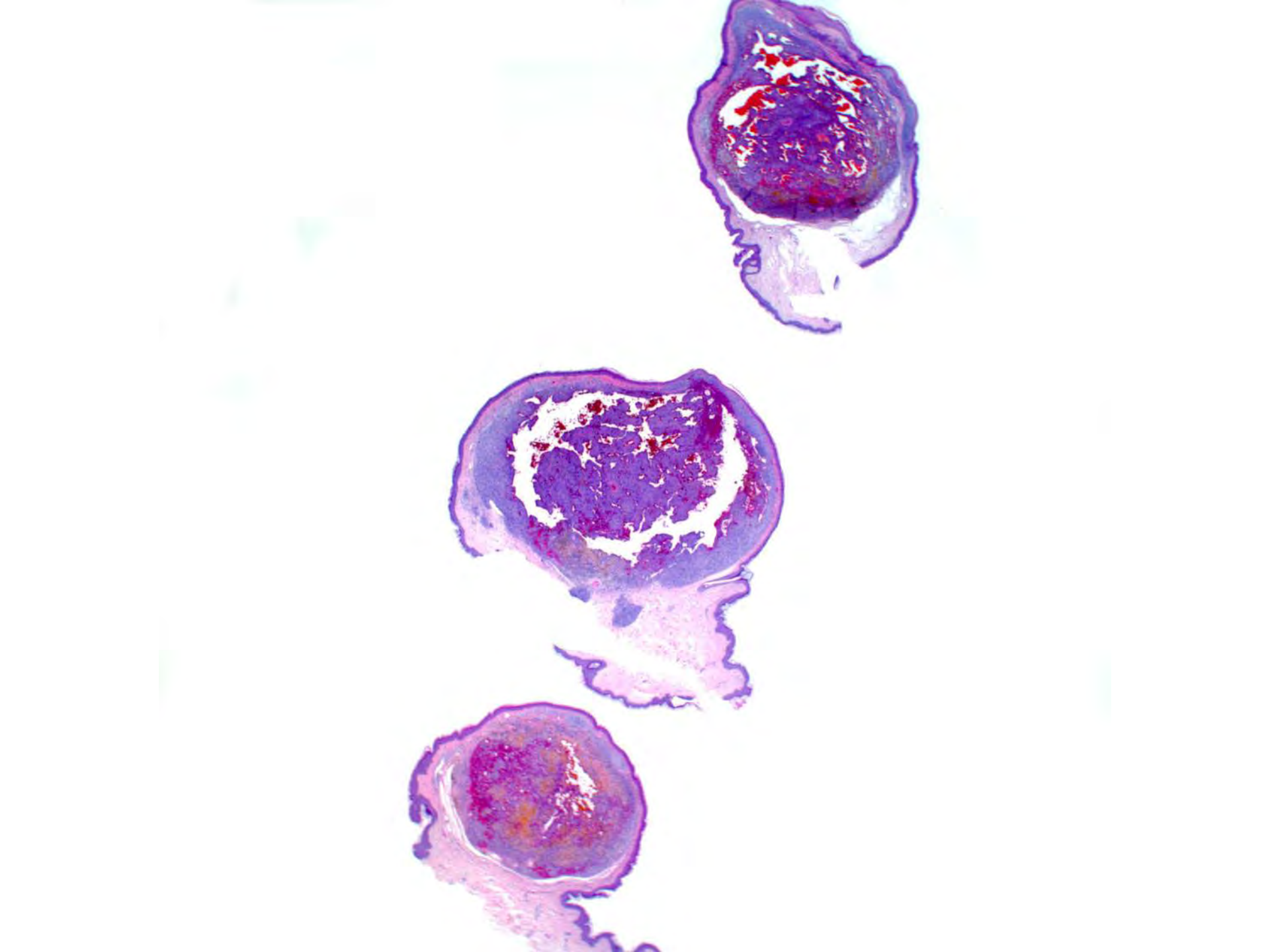

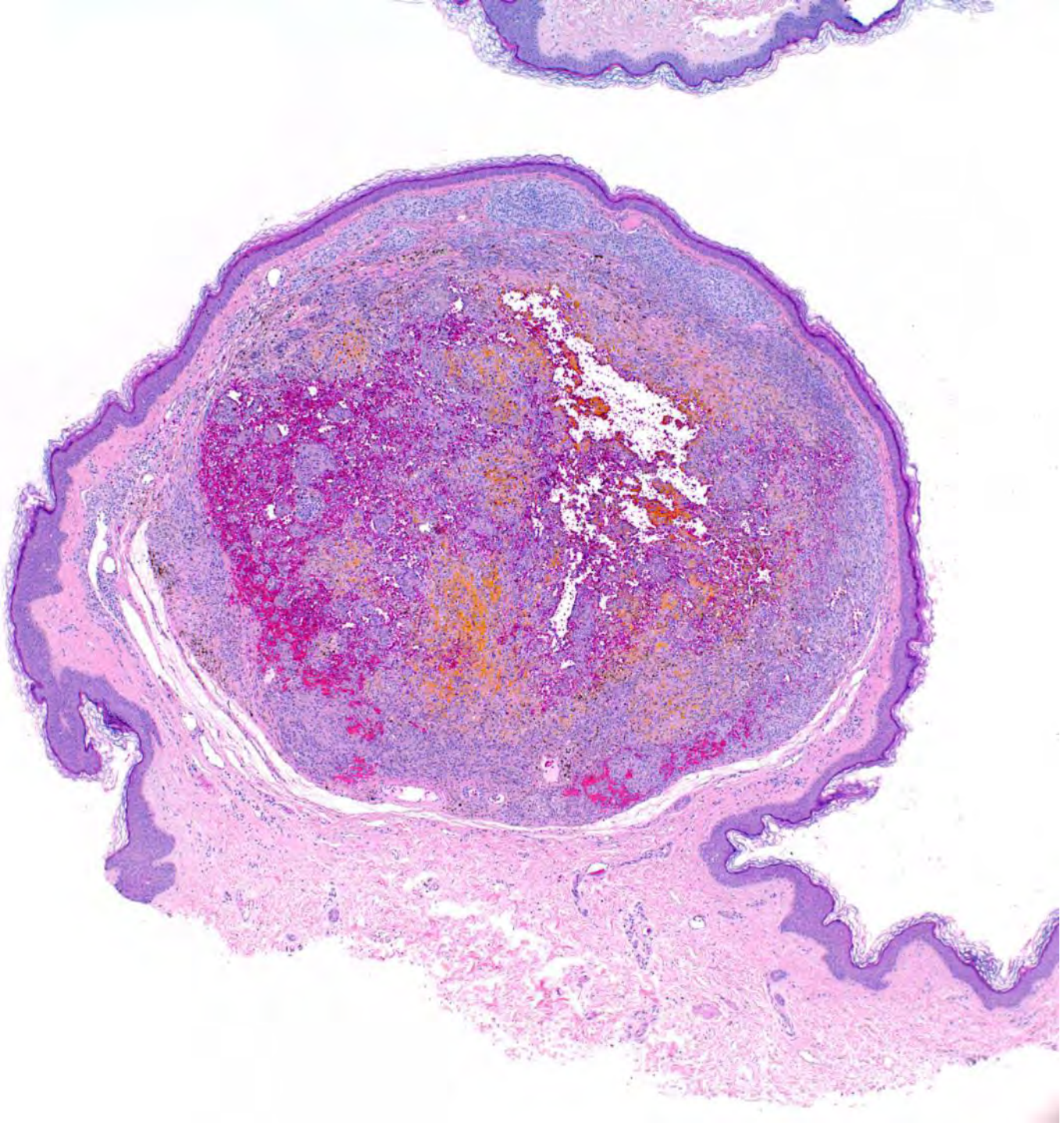

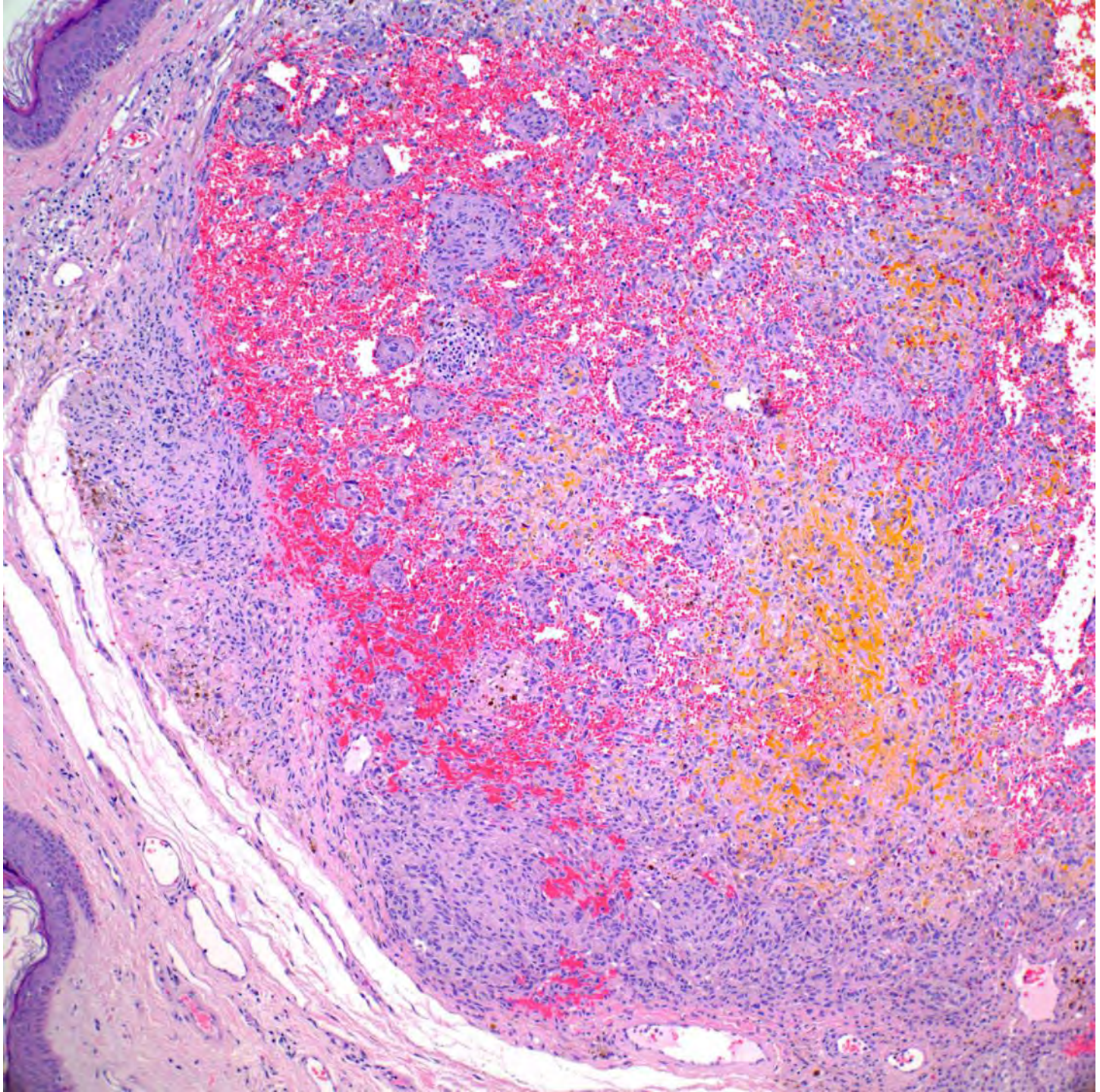

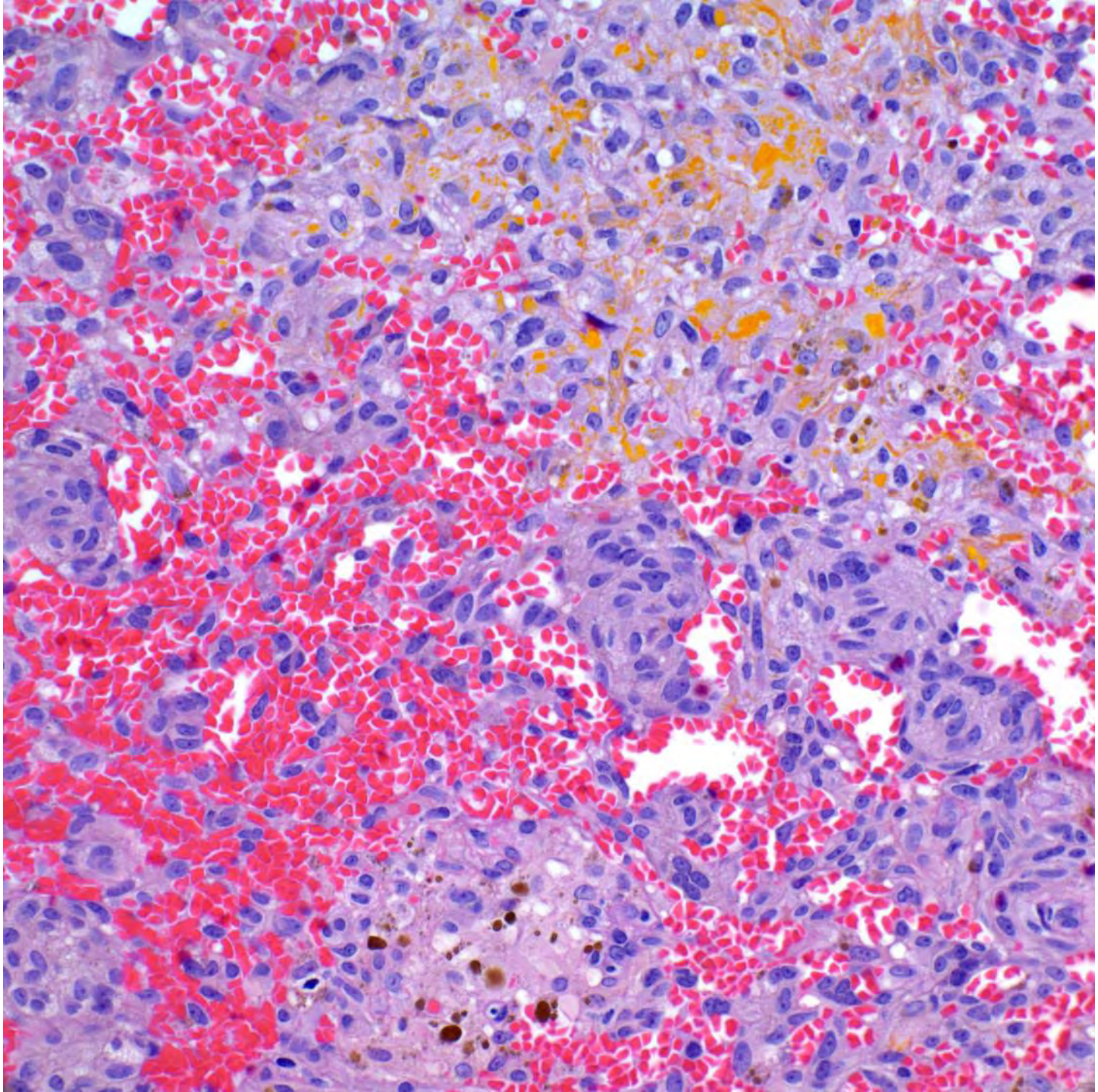

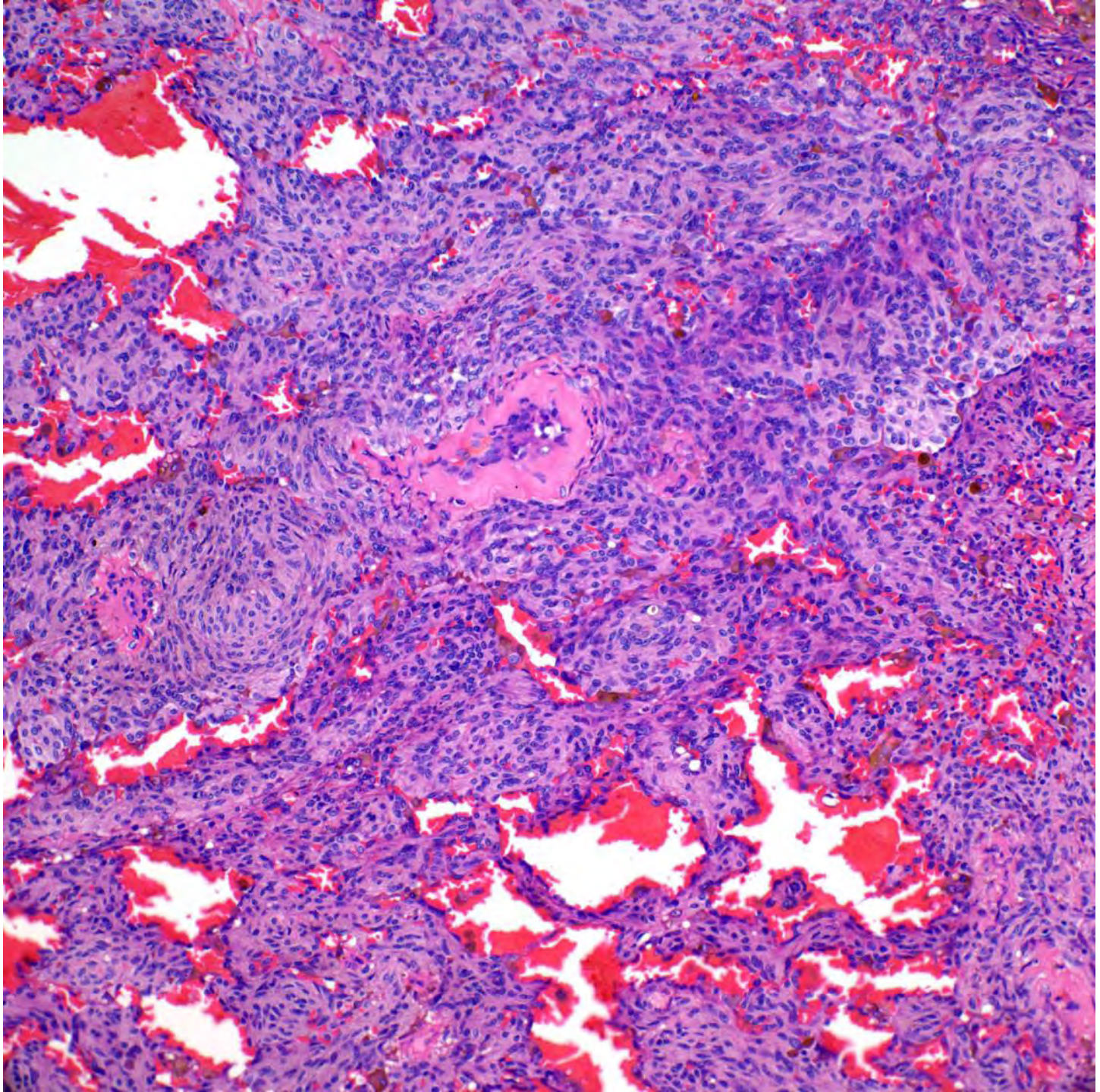

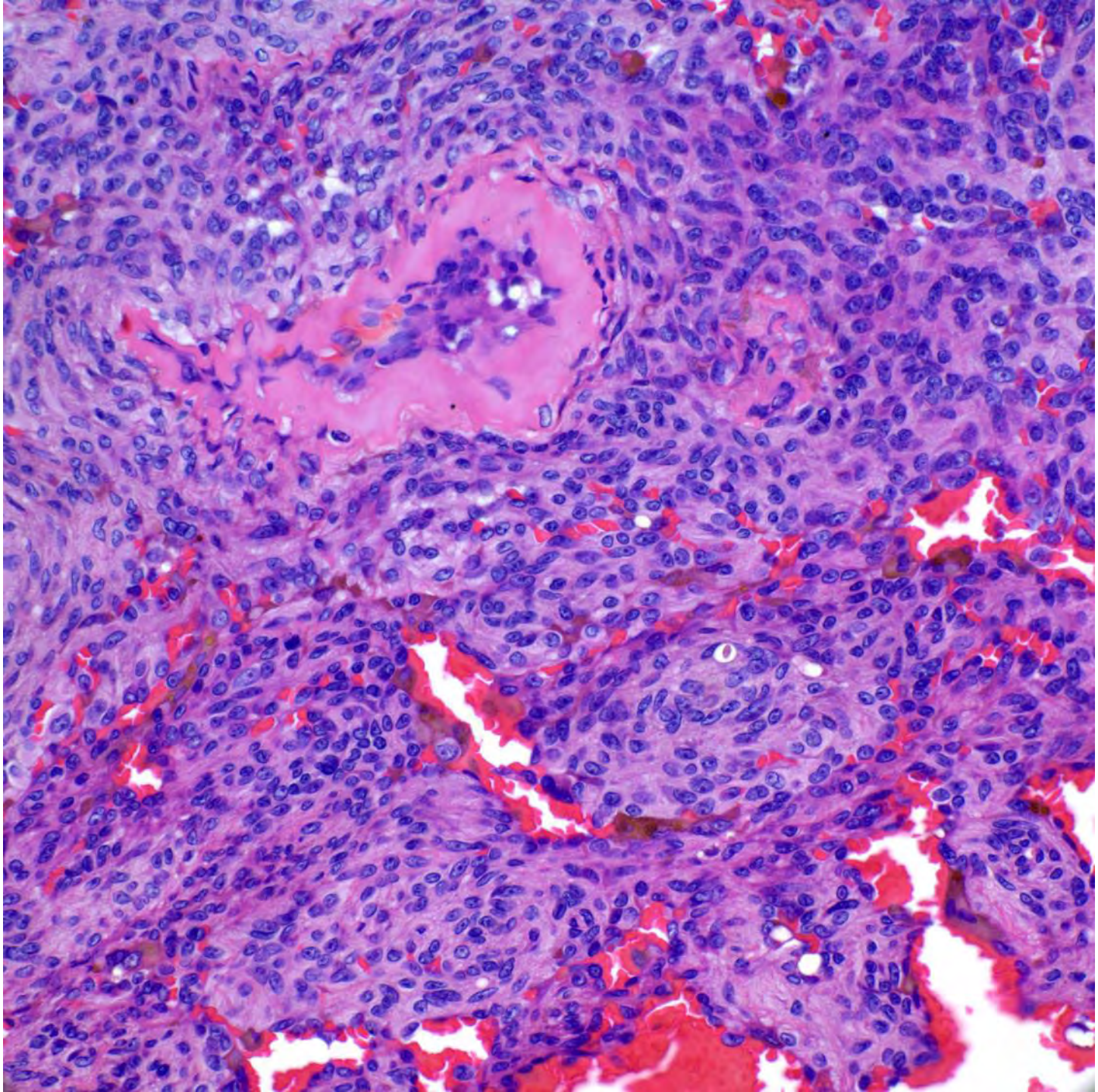

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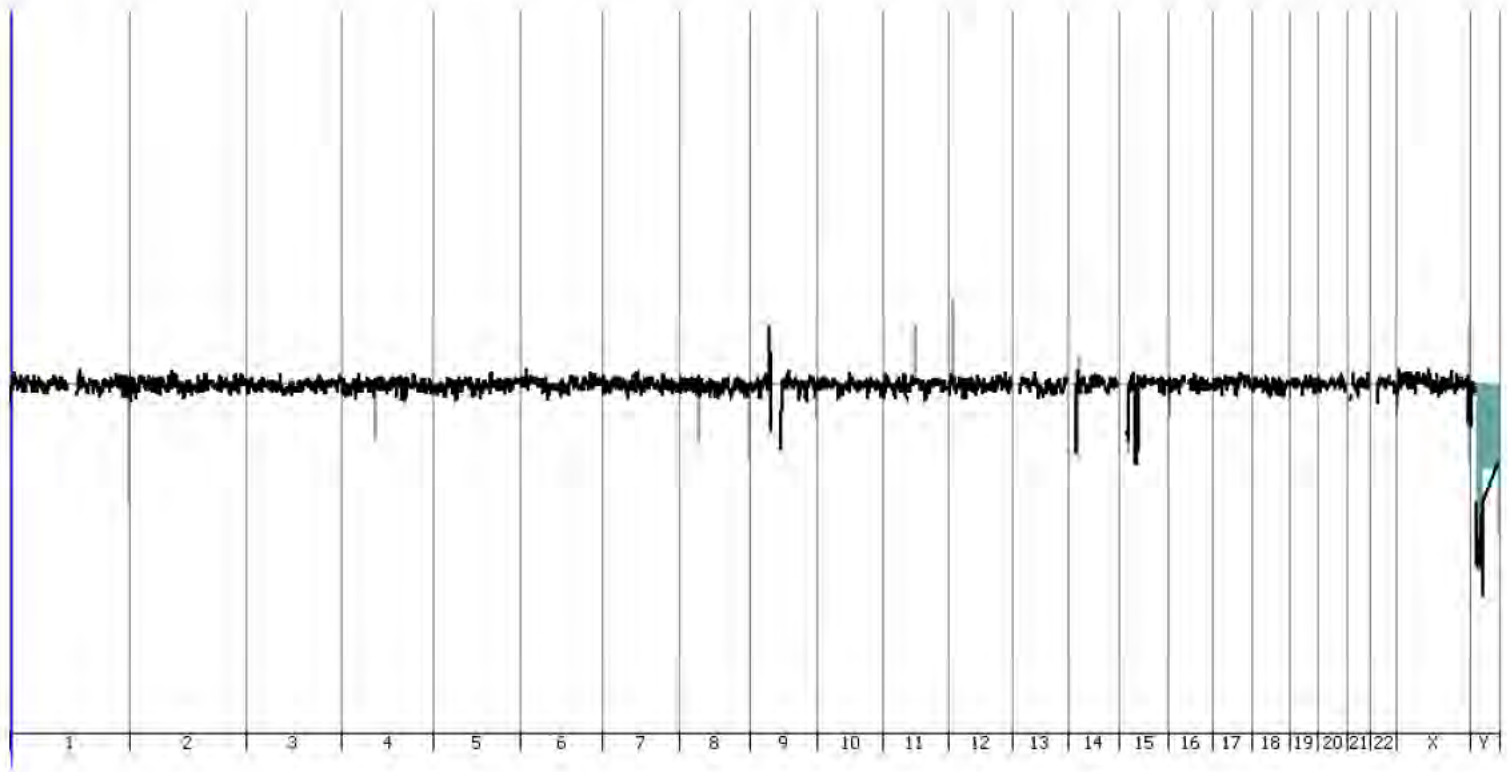
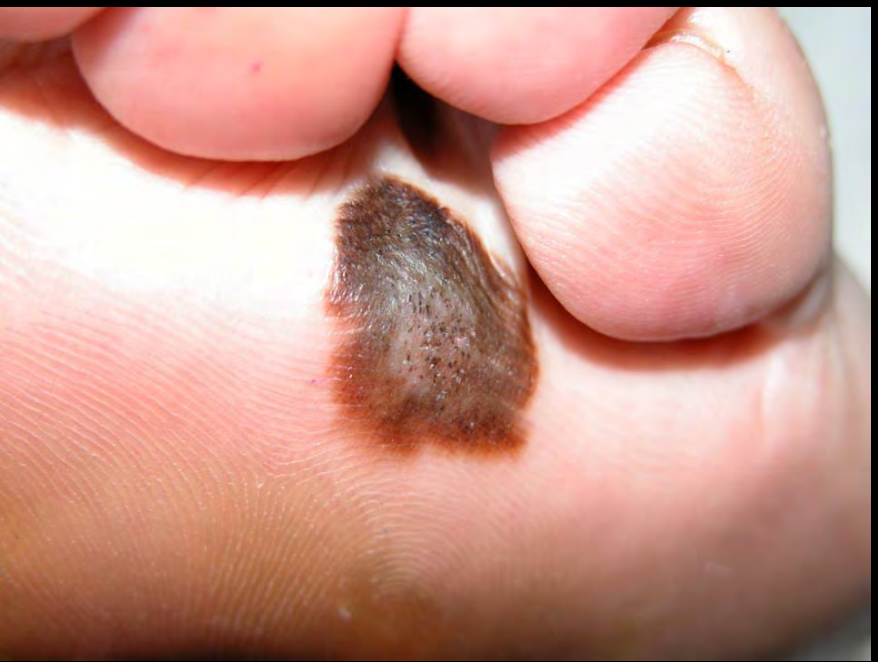


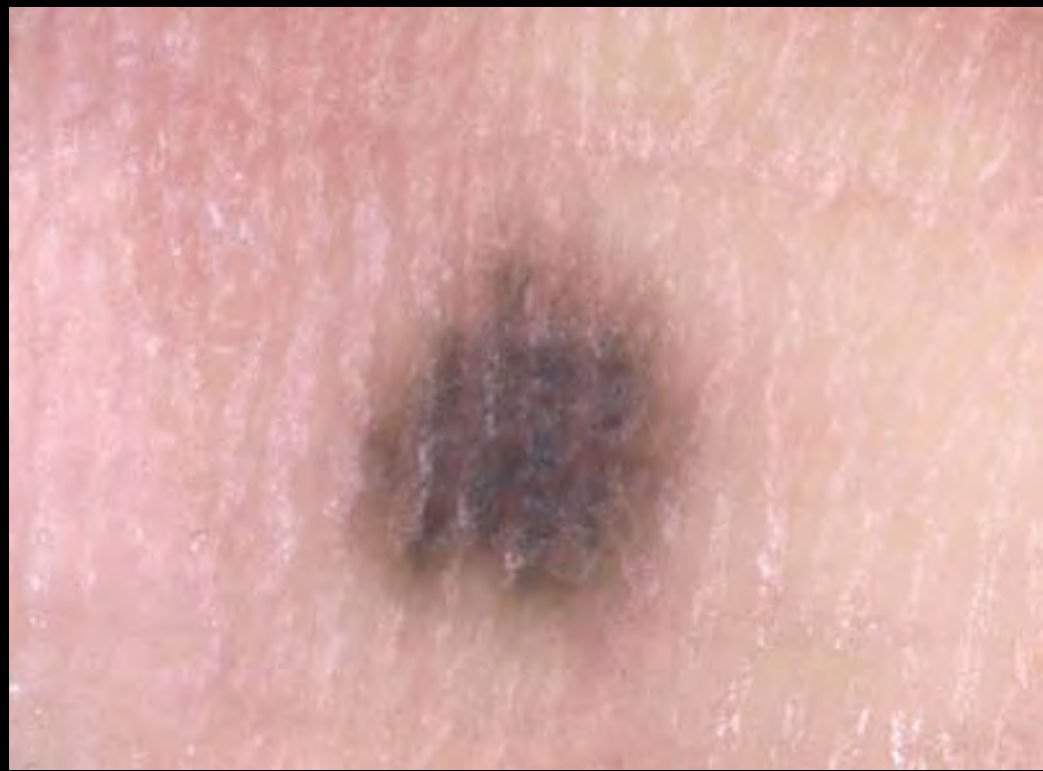
Our cases

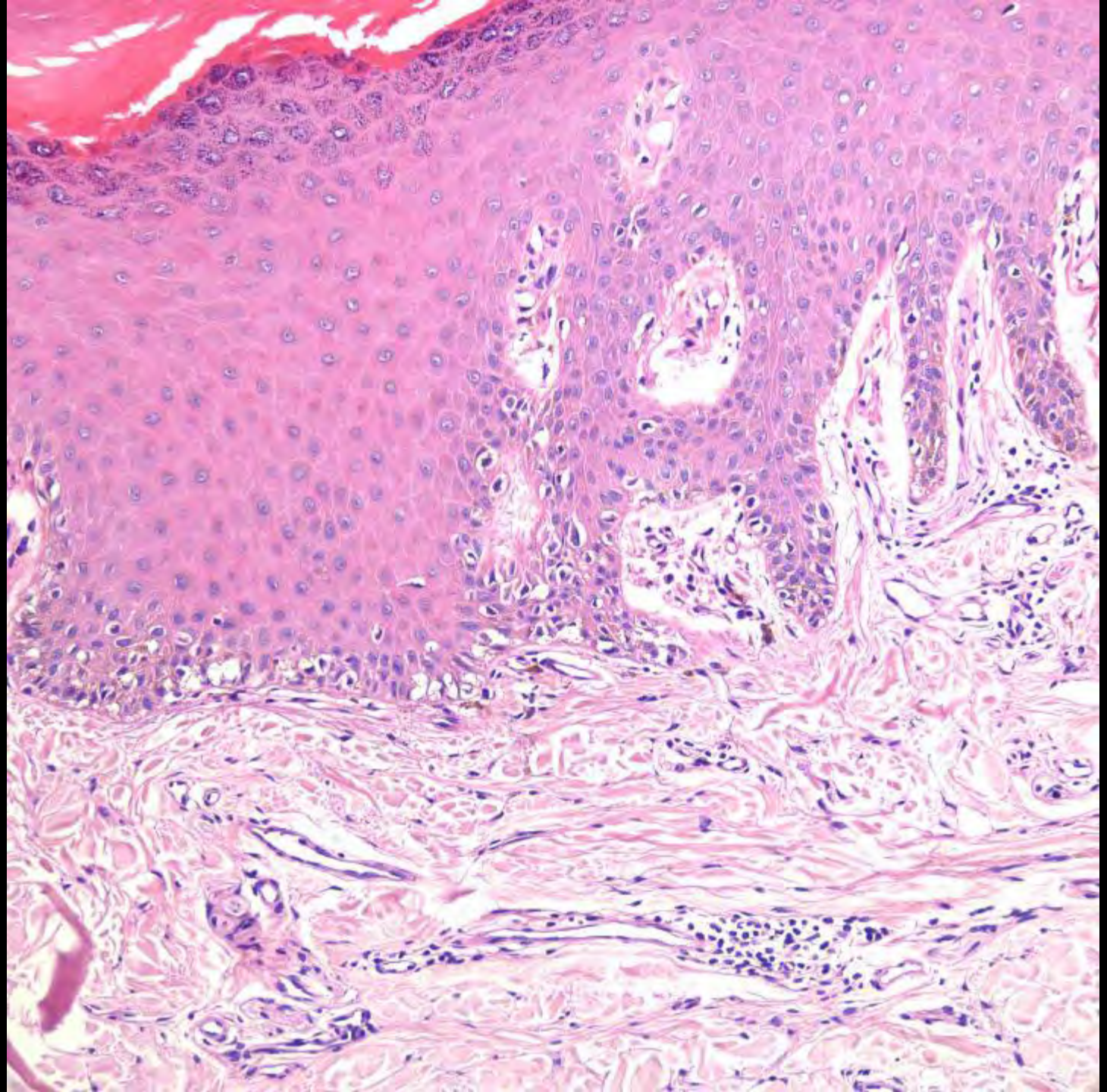
- NGS in 5/6
- BRAF mutated in 5
- hTERT promoter wild type in 5
- BAP1 mutations in 3
- CTNNB1 mutated in 2
- Low numbers of copy number changes in most
- Conclusion: most are melanocytomas, some could be melanomas

Pathway 5- Acral melanoma

- Prevalence similar across racial groups
- Gene amplifications frequent, esp. CCND1, KIT, TERTp, mutations BRAF, NRAS, KIT







Pathway 7- Melanoma ex congenital nevus

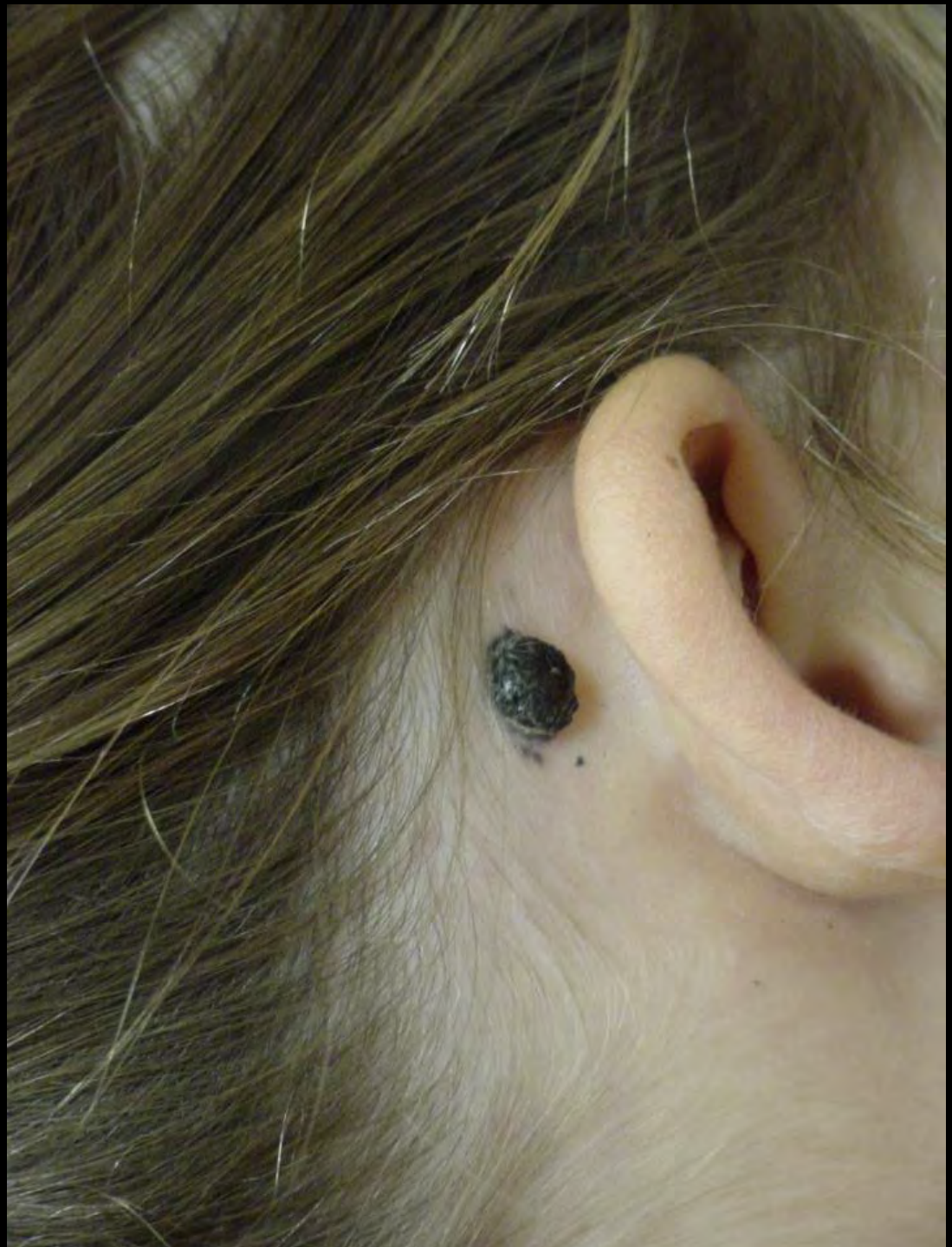
- Prevalence similar across all racial groups
- Mostly in NRAS driven congenital nevi
- Distinction from proliferative nodules still a work-in-progress

Pathway 8- Melanoma ex blue nevus, Blue melanoma

- Prevalence similar across all racial groups
- Initiated by GNAQ, GNA11, CYSLTR2 mutations, PRKC fusions
- Additional mutations in BAP1, SF3B1, EIF1AX
- Gains 6p, 8q, loss 6q
- Remnant of blue nevus

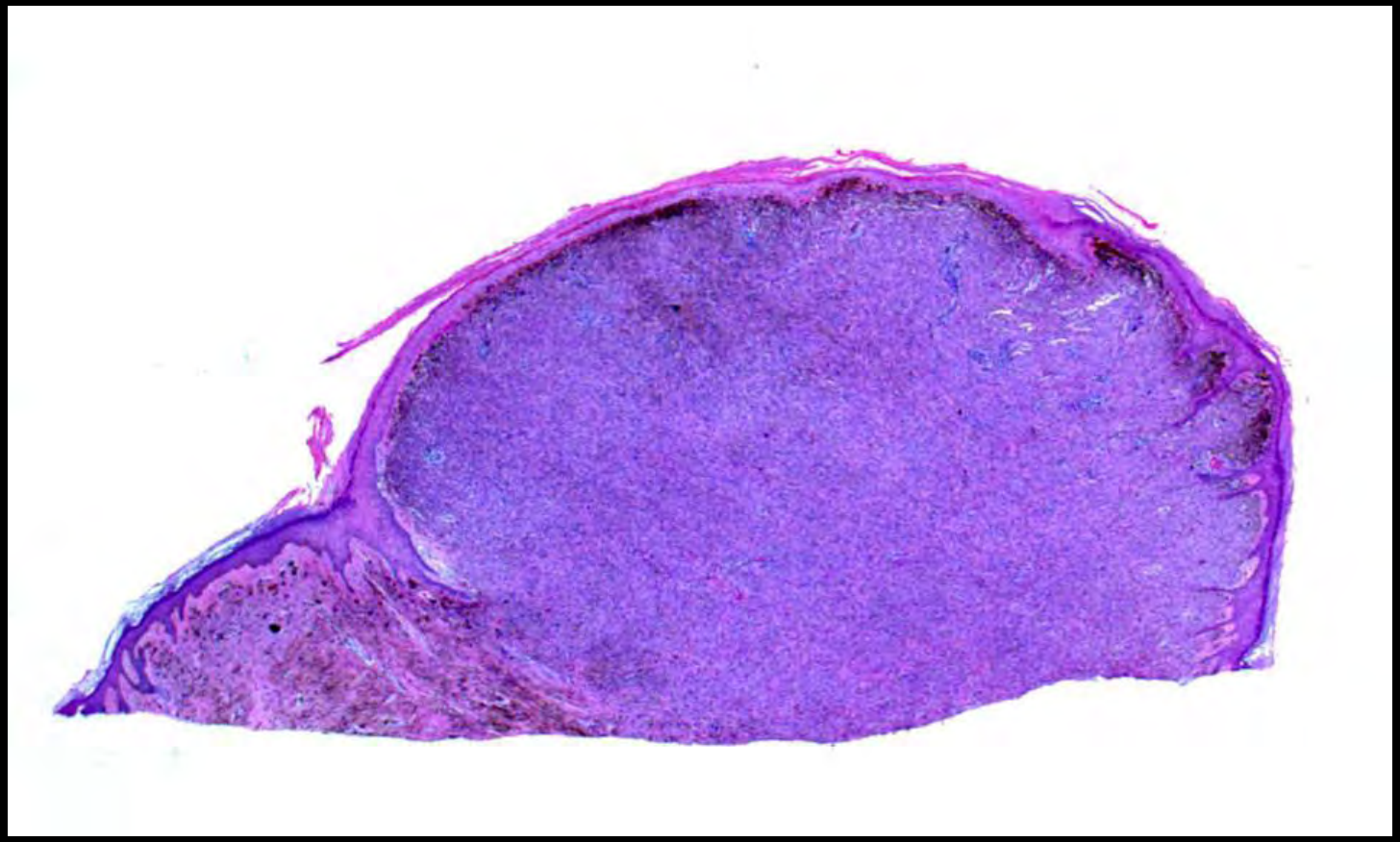
Melanoma ex blue nevus

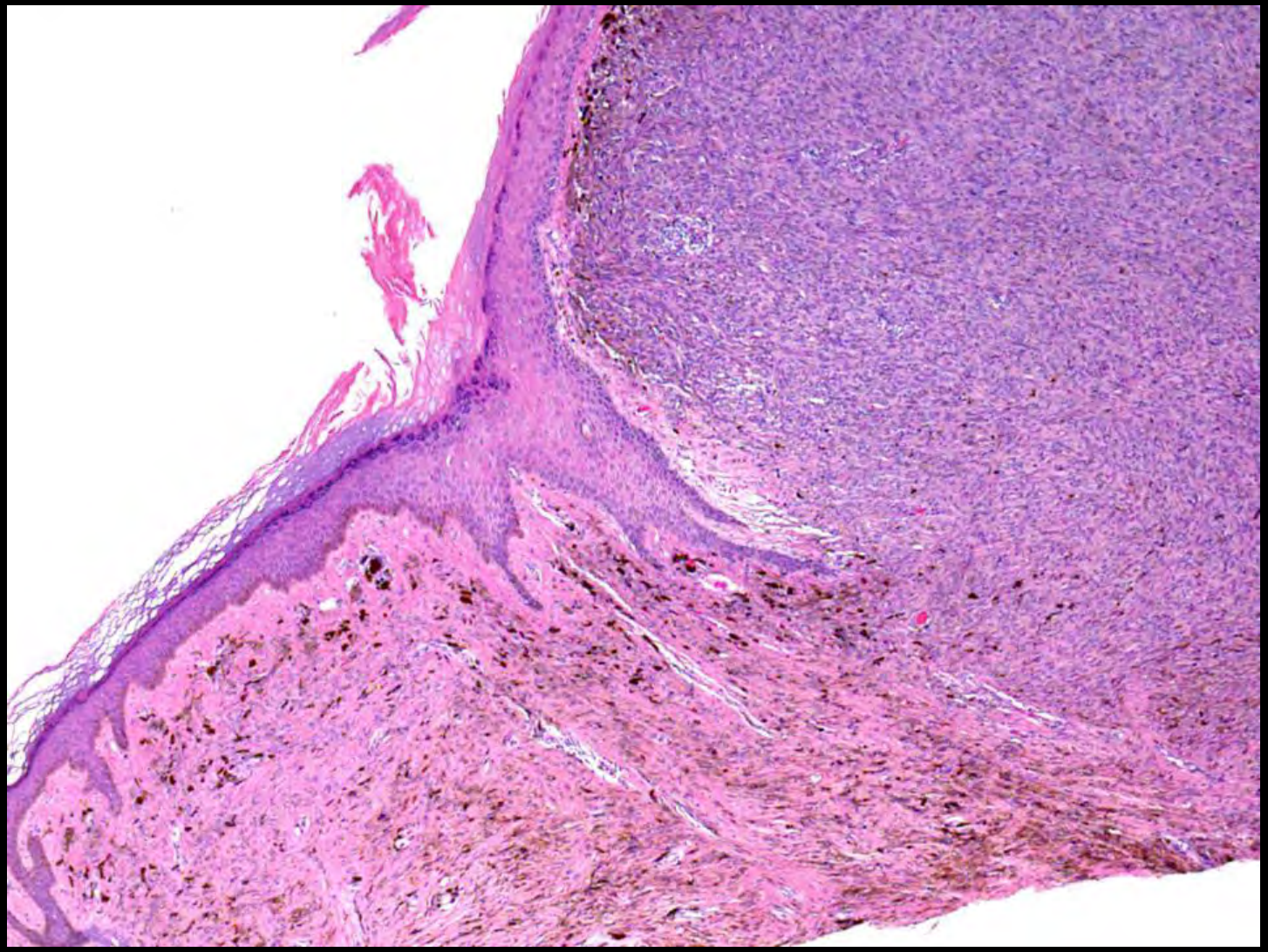
- Melanomas can arise in any type of blue nevus, from "dermal melanocytoses" to cellular blue nevus.
- Often quite thick when first detected, thus having a particularly unfavorable prognosis.
- Present either as change in pre-existent blue nevus, or as a dark brown/black plaque or nodule

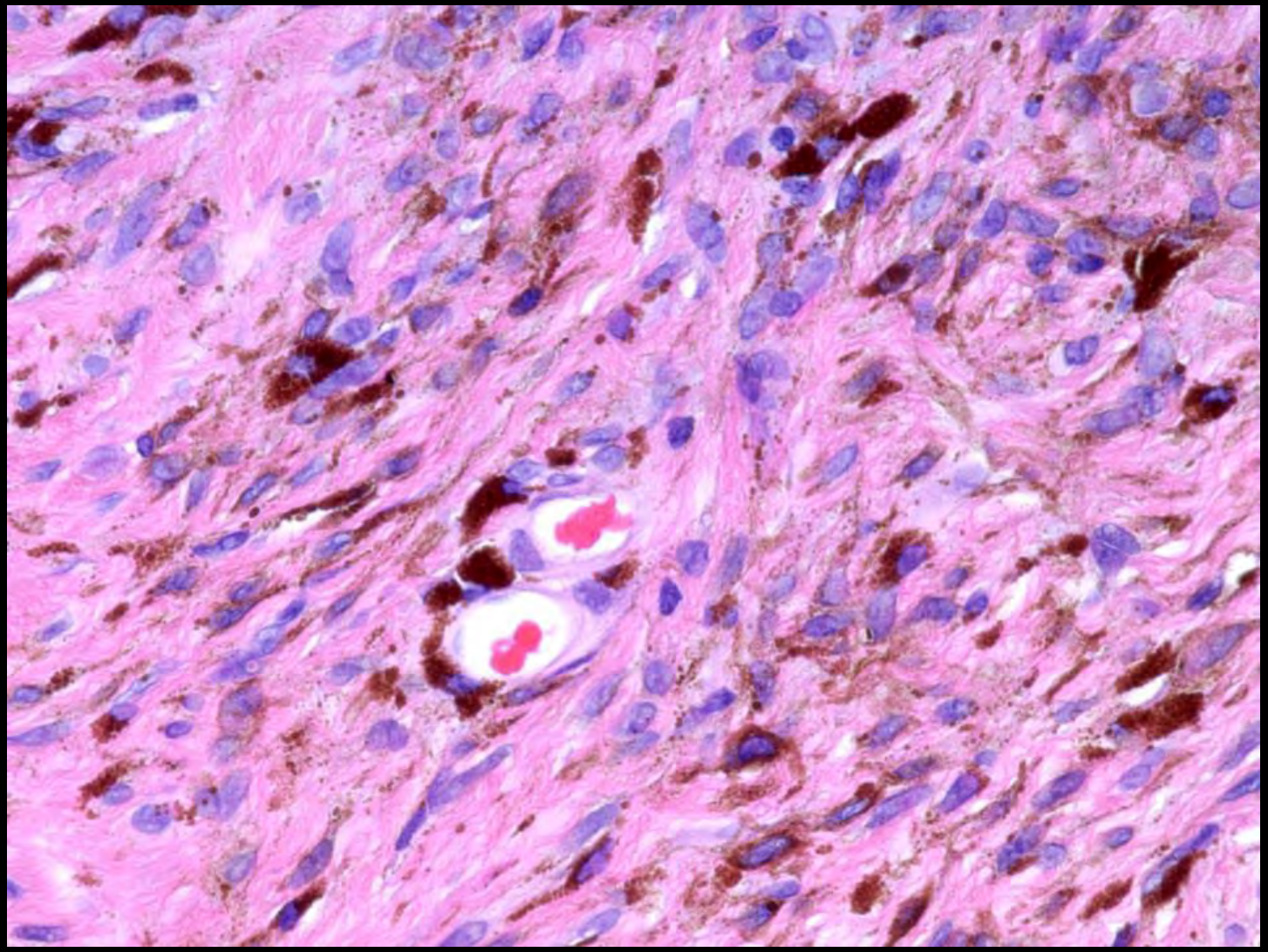


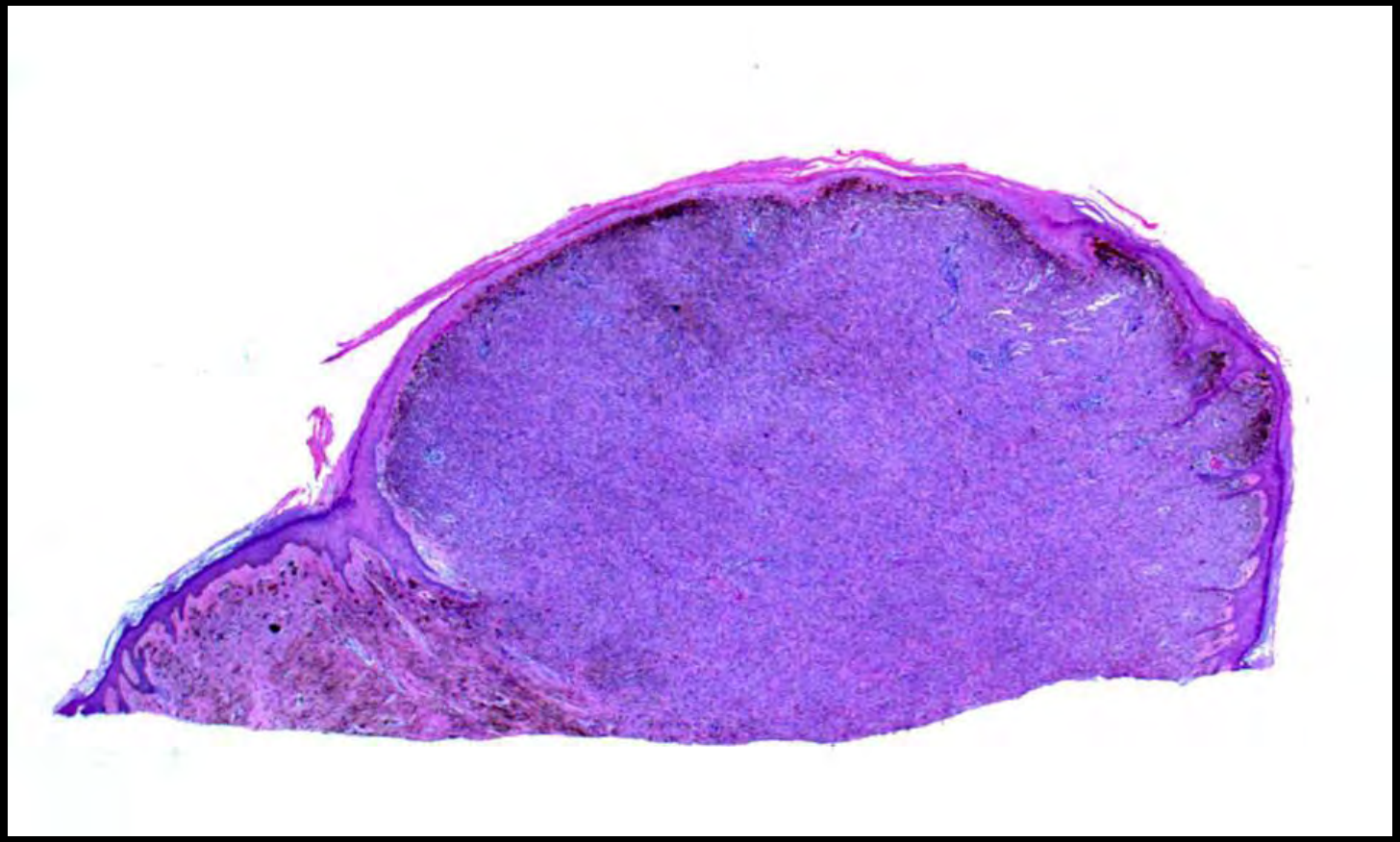
Blue nevic melanoma- histopathologic features

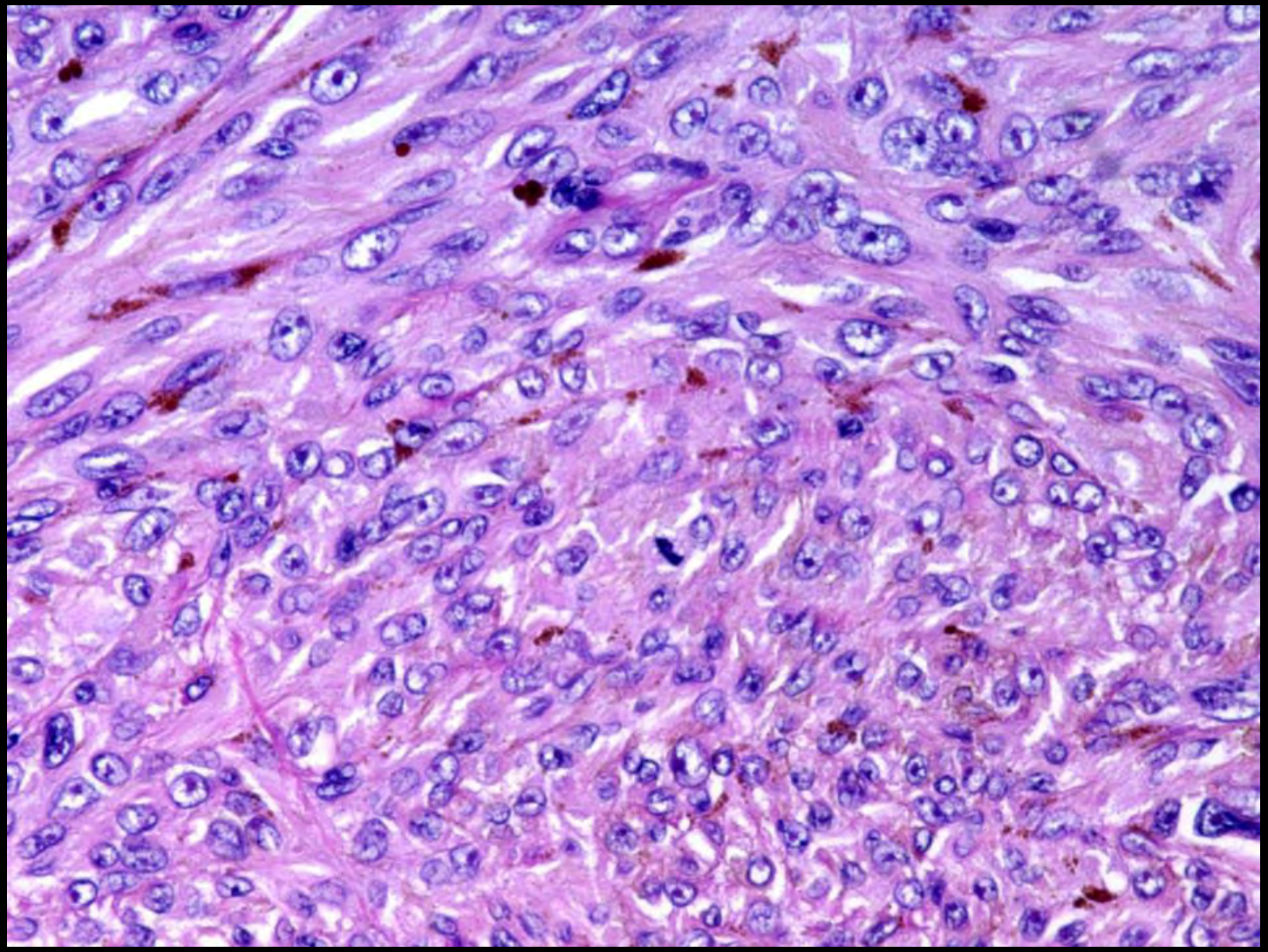
- Most dermally based
- Most ex cellular blue nevus
- Large oval melanocytes with variably pigmented cytoplasm
- Many melanophages
- Cells with large nuclei and large nucleoli, sometimes eosinophilic
- Mitoses, sometimes more than 2/mm2

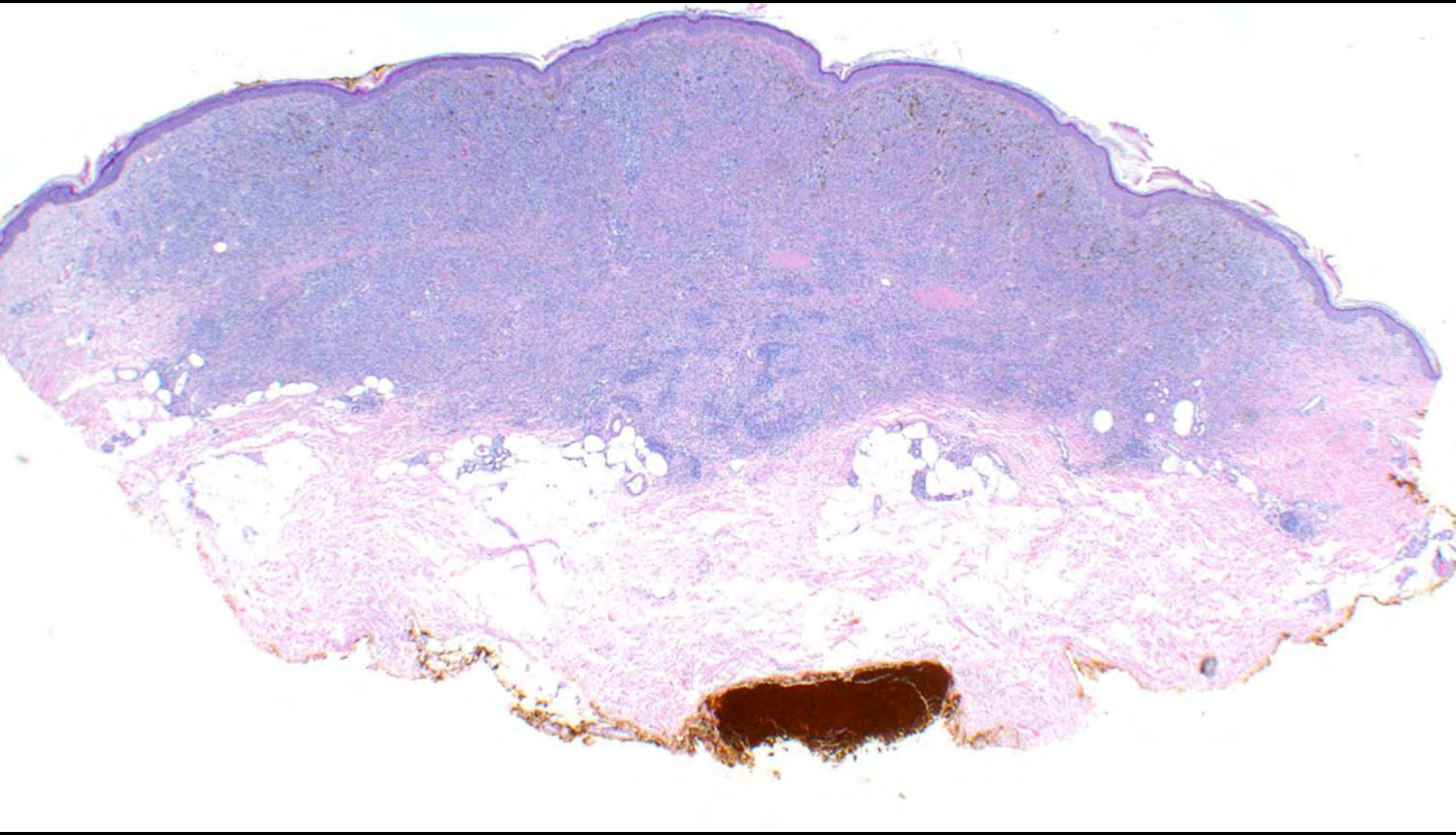


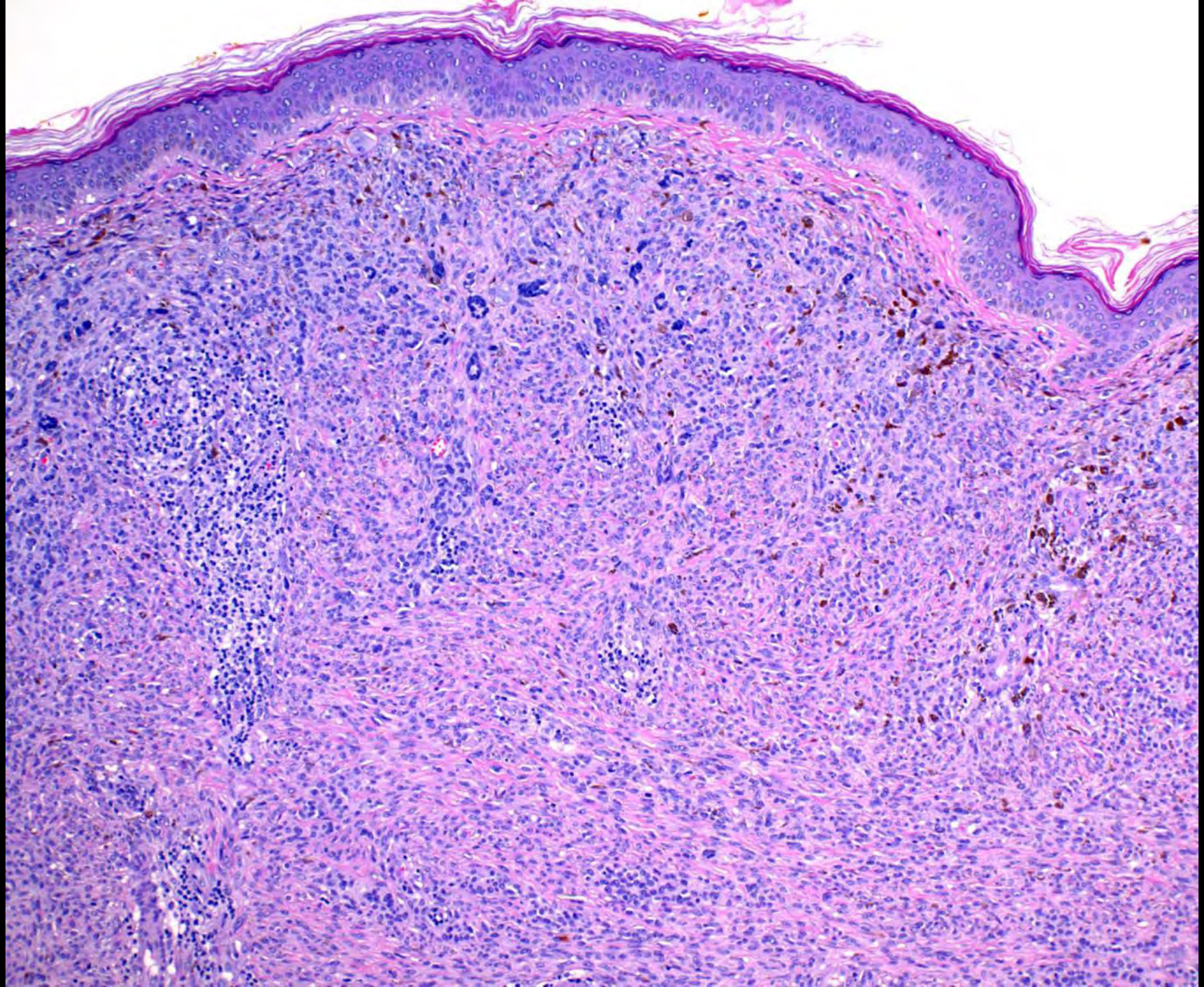


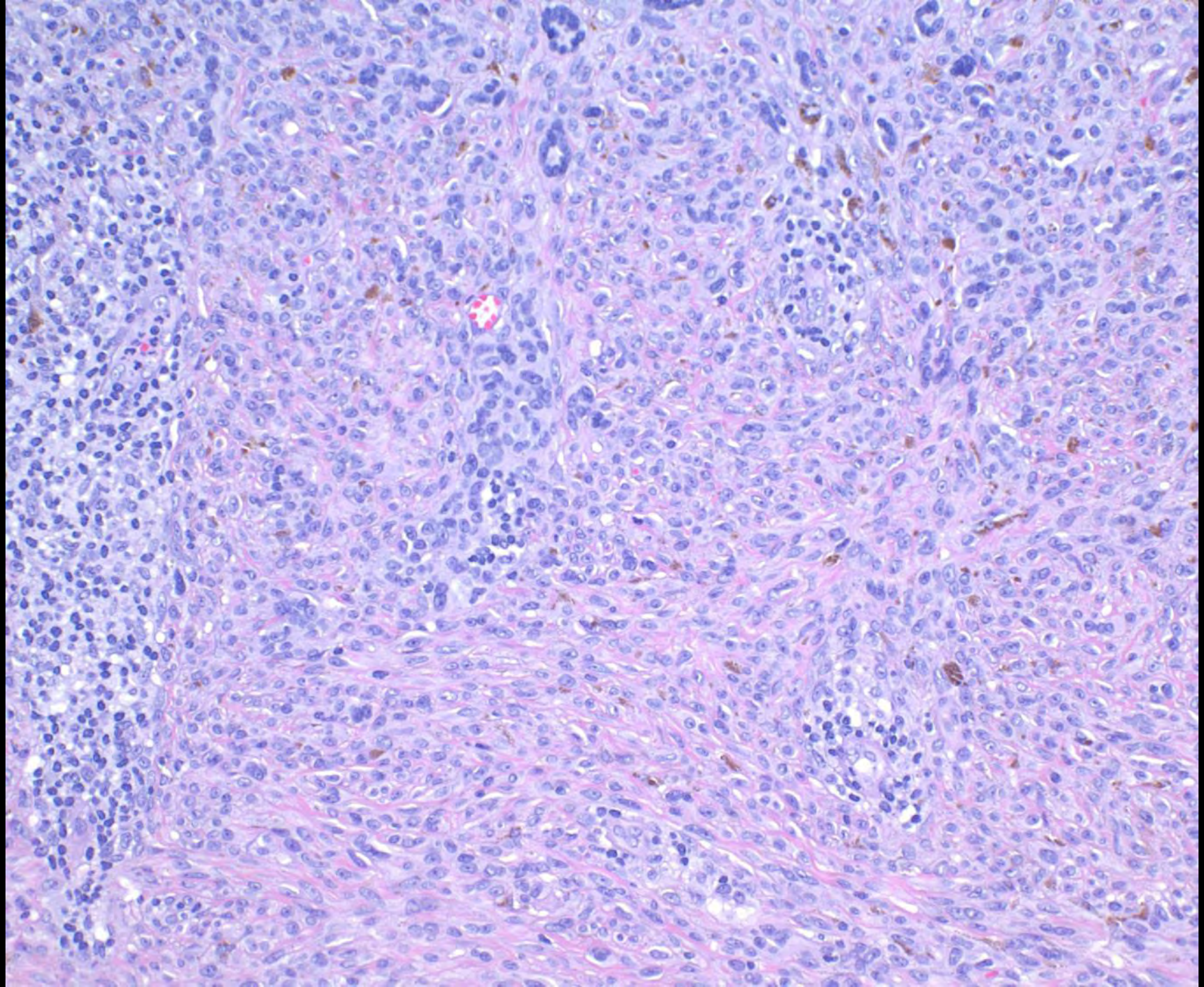


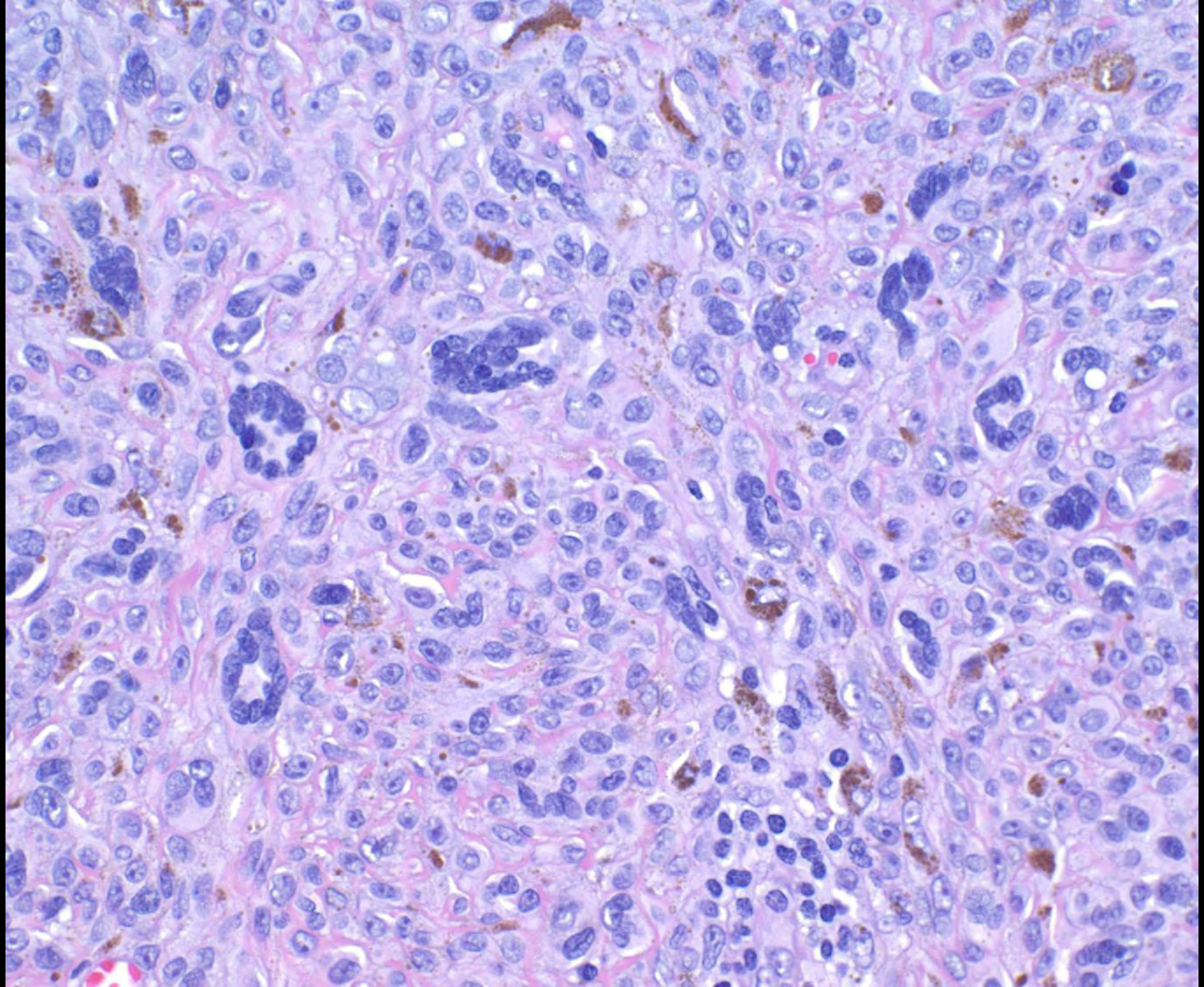


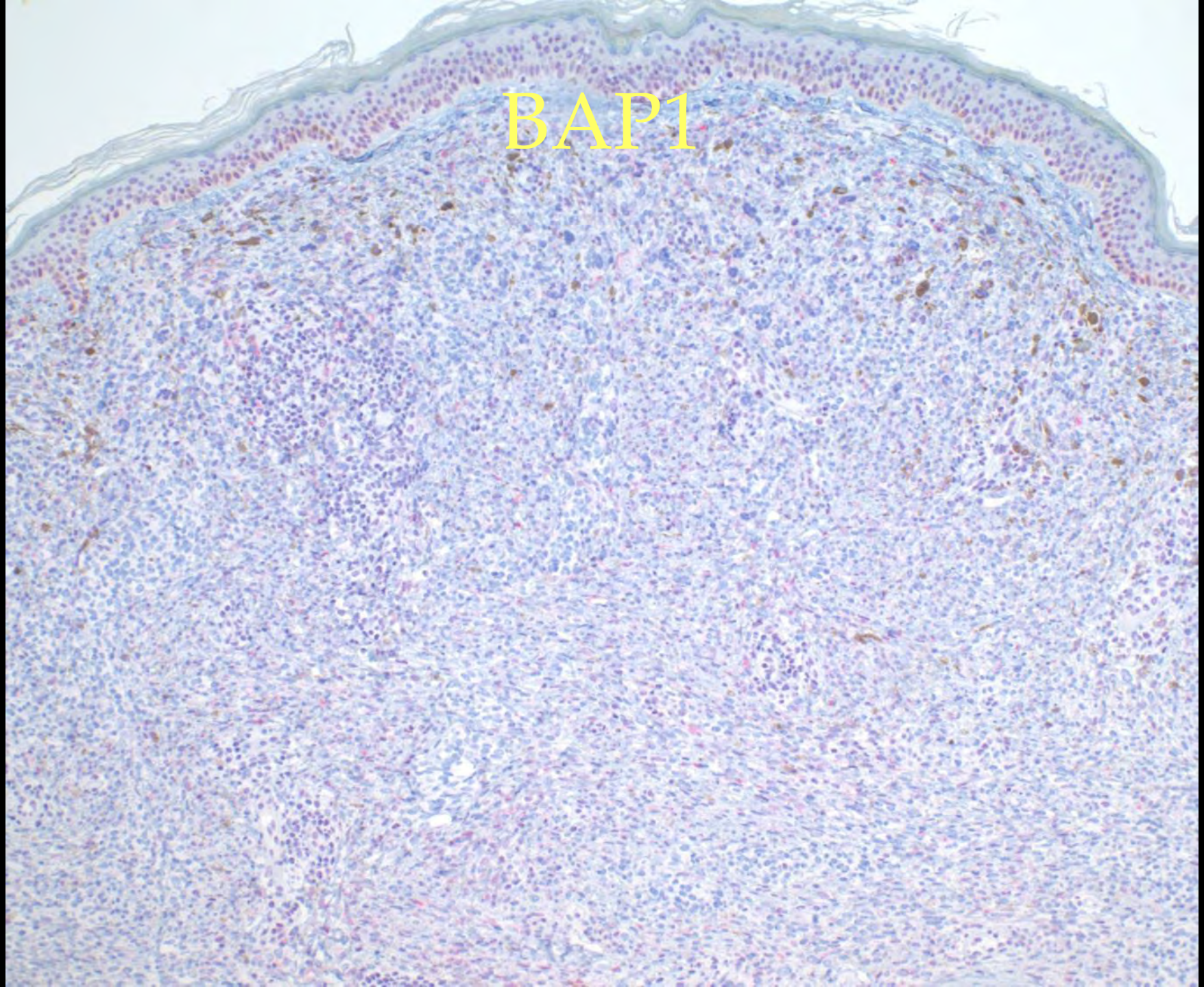


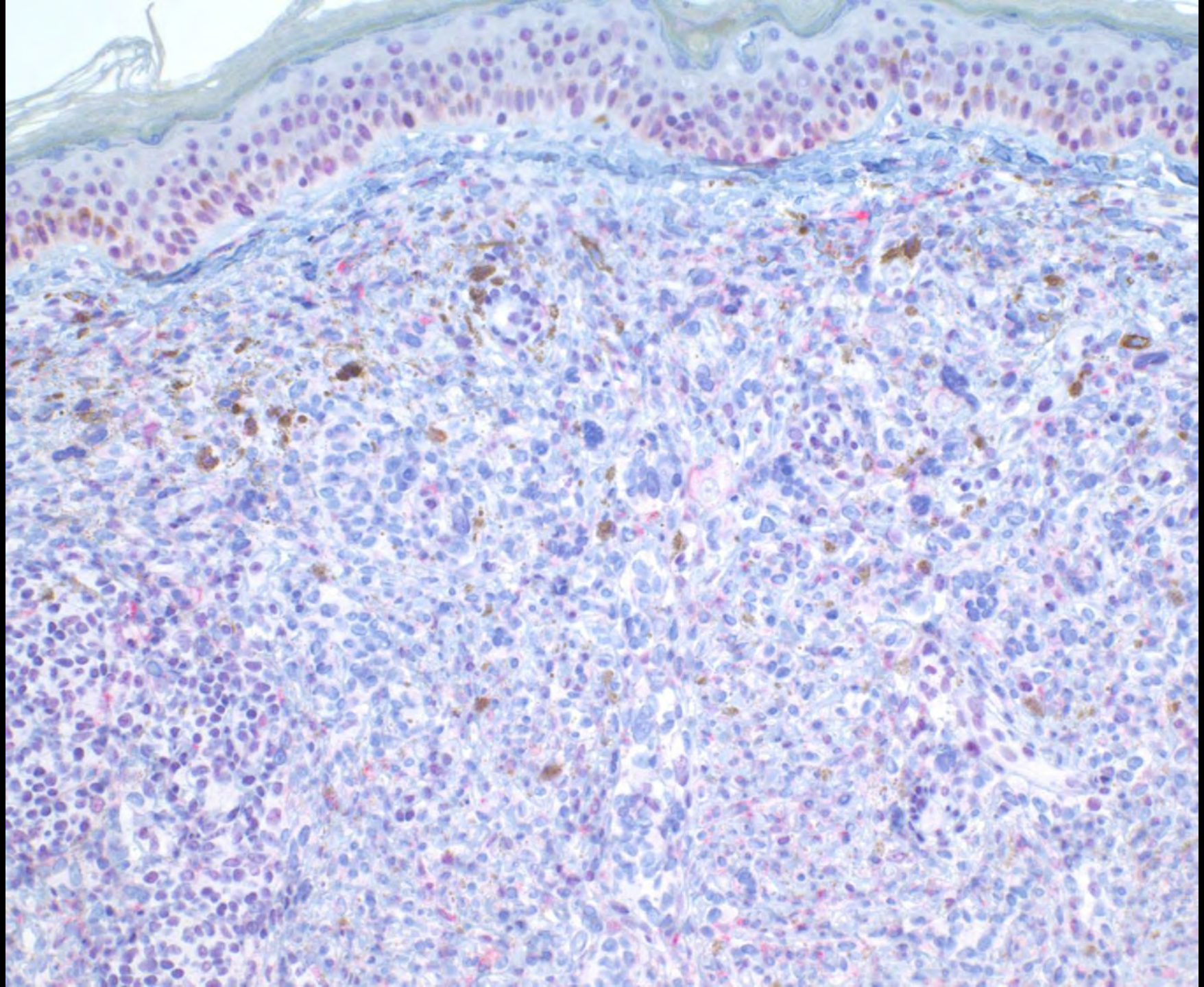


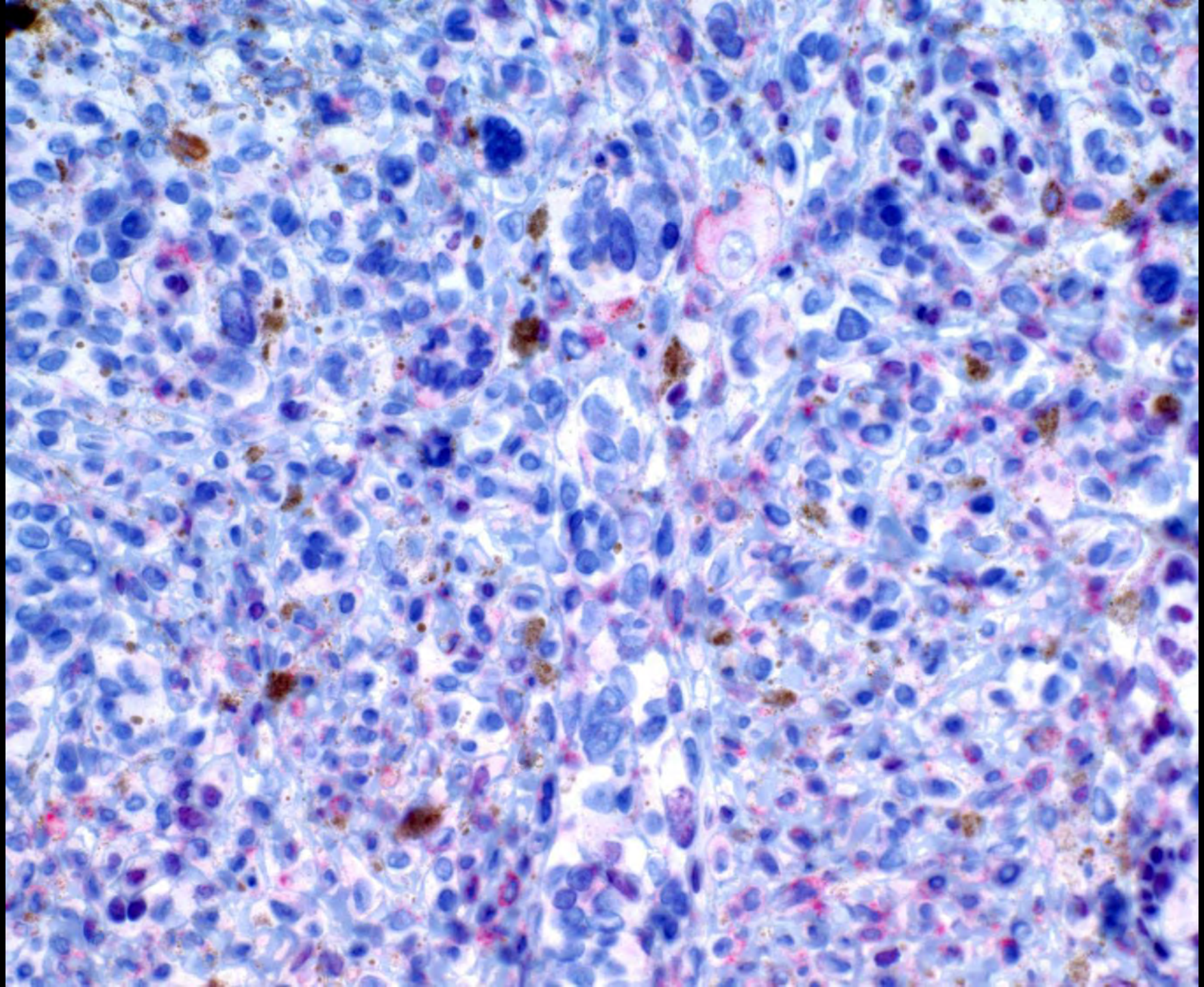







BAP1



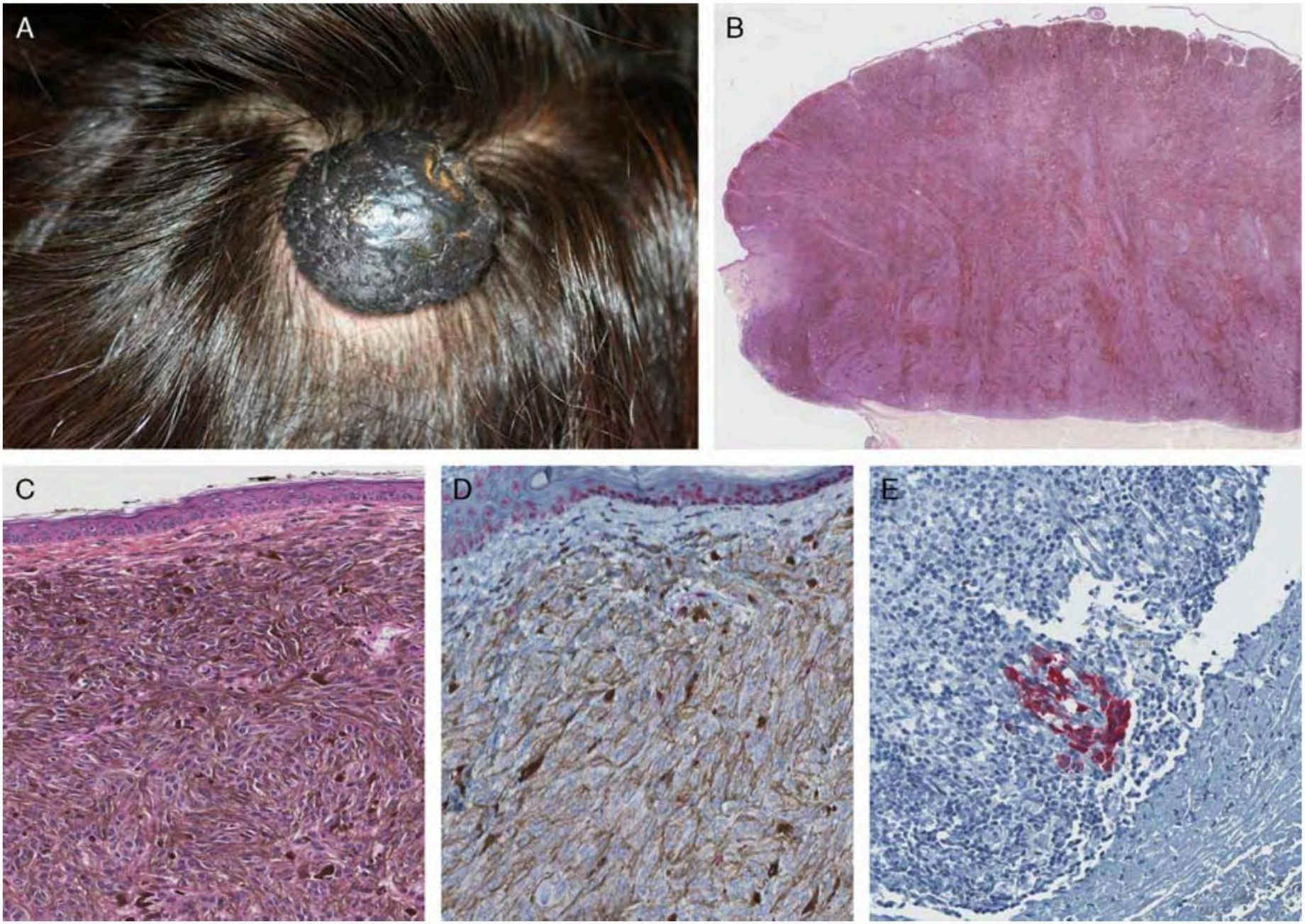


ORIGINAL ARTICLE

Melanomas Associated With Blue Nevi or Mimicking Cellular Blue Nevi

Clinical, Pathologic, and Molecular Study of 11 Cases Displaying a High Frequency of GNA11 Mutations, BAP1 Expression Loss, and a Predilection for the Scalp

Sebastian Costa, MD, Michelle Byrne, MBBS,† Daniel Pissaloux, PhD,* Veronique Haddad, PharmD,* Sandrine Paindavoine, Msc,* Luc Thomas, MD, PhD,‡ Francois Aubin, MD, PhD,§ Thierry Lesimple, MD,‖ Florent Grange, MD, PhD,¶ Bertille Bonniaud, MD,# Laurent Mortier, MD, PhD,** Christine Mateus, MD,†† Brigitte Dreno, MD,‡‡ Brigitte Balme, MD,§§ Beatrice Vergier, MD, PhD,‖‖ and Arnaud de la Fouchardiere, MD, PhD**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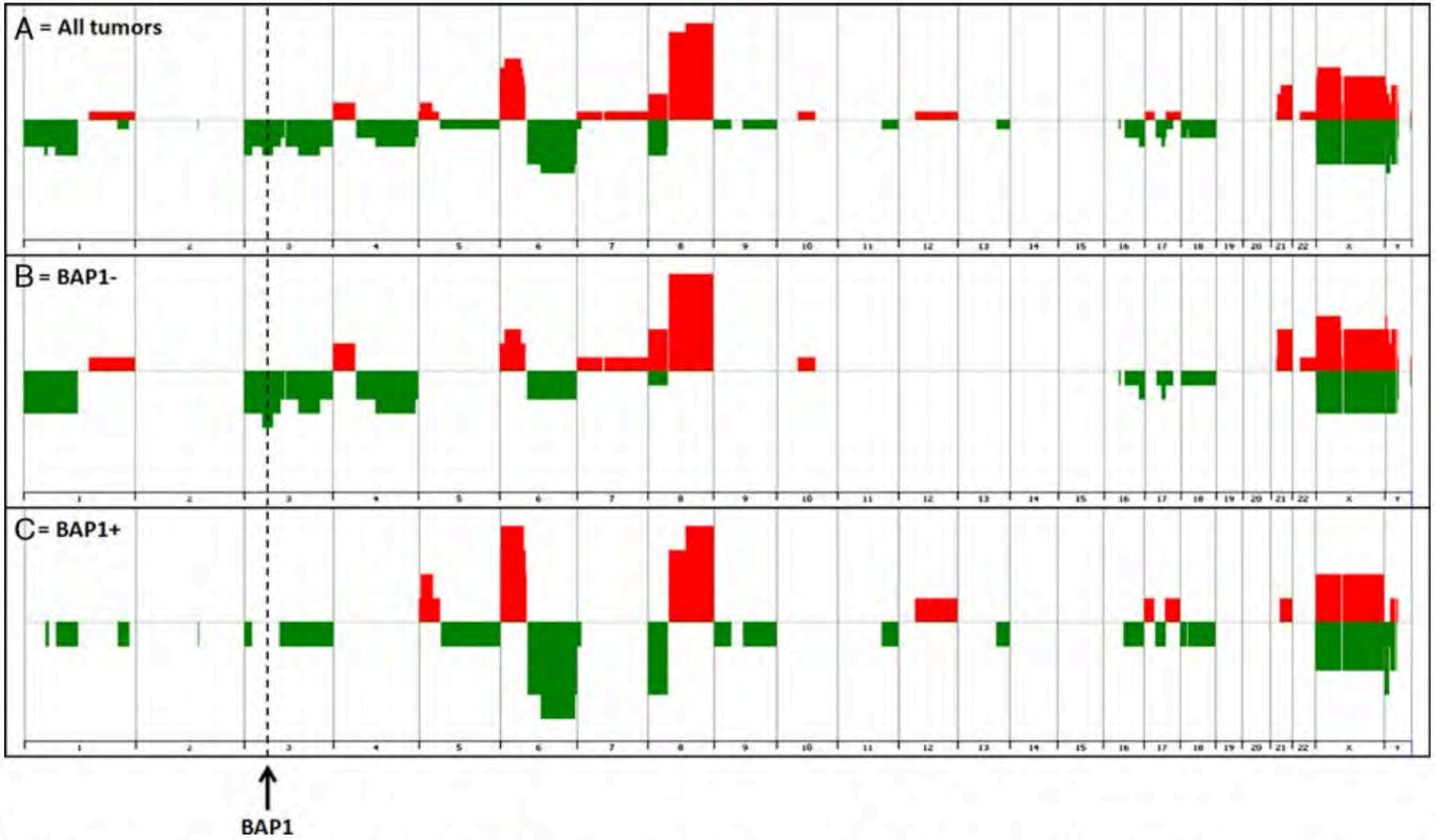

FIGURE 4. Penetrance plots showing recurrent chromosomal alterations in MABN/MMCBN. Red blocks represent chromosome gains; green blocks represent chromosome losses. The amplitude of each abnormality corresponds to its prevalence. A, Penetrance plot summarizing the copy number imbalances per chromosome in all patients. B, Penetrance plot summarizing the copy number imbalances per chromosome in the group of 7 patients with BAP1 IHC loss (BAP1-negative tumors). C, Penetrance plot summarizing the copy number imbalances per chromosome in the group of 4 patients without BAP1 loss (BAP1-positive tumors).

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MODERN PATHOLOGY

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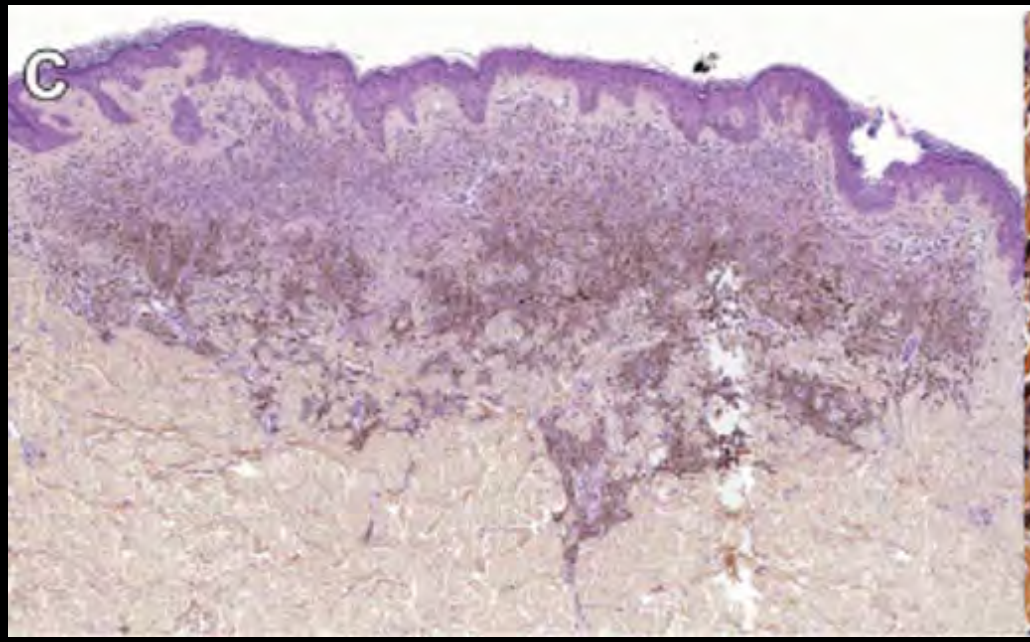
Research Article

Histologic and Genetic Features of 51 Melanocytic Neoplasms with Protein Kinase C Fusion Genes

Arnaud de la Fouchardière[a,b,*], Daniel Pissaloux[a,b], Aurélie Houlier[a], Sandrine Paindavoine[a], Franck Tirode[b], Philip E. LeBoit[c,d], Boris C. Bastian[c,d], Iwei Yeh[c,d]

[a] *Department of Biopathology, Centre Lèon Bérard, Lyon, France;* [b] *Department of Research, University of Lyon, Université Claude Bernard Lyon 1, Cancer Research Centre of Lyon, Lyon, France;* [c] *Department of Dermatology, Helen Diller Family Cancer Center, University of California, San Francisco, San Francisco, California;* [d] *Department of Pathology, Helen Diller Family Cancer Center, University of California, San Francisco, San Francisco, California*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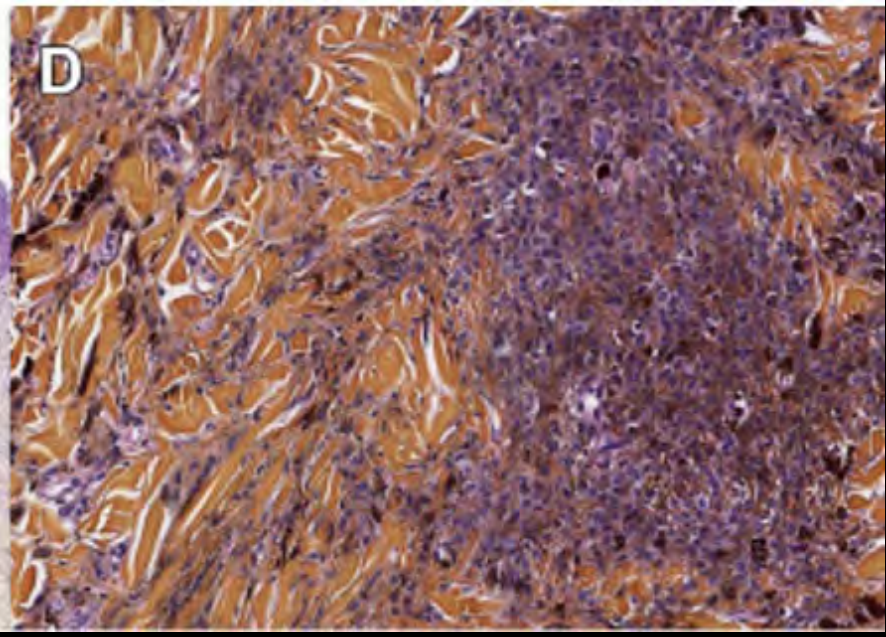
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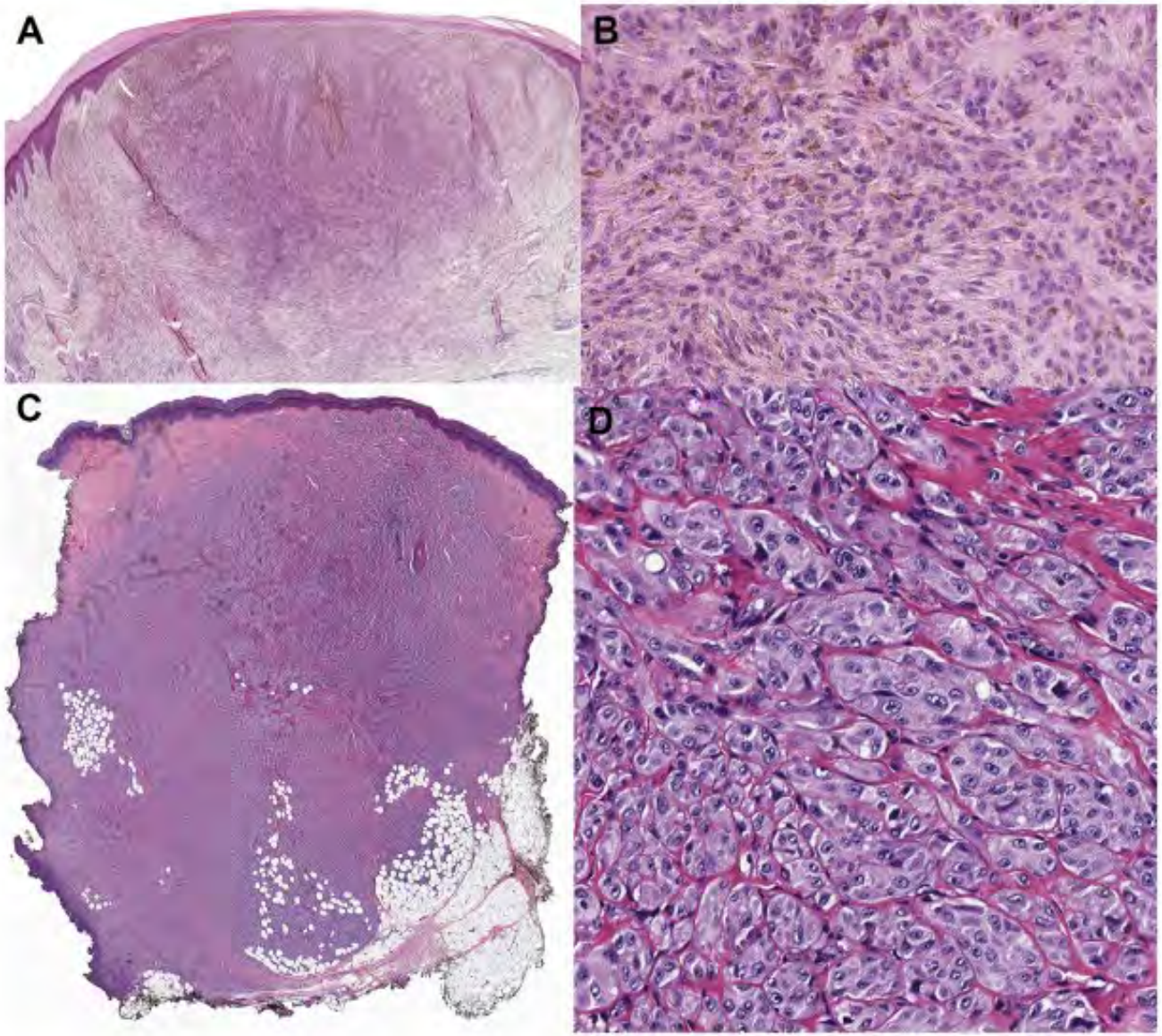

Figure 4.
Histopathology of melanomas with protein kinase C fusion genes. (A) Dense dermal melanocytic proliferation infiltrating the subcutis. (B) Close-up view of panel A, with nests of epithelioid cells within a fibrous background with important cytonuclear atypia and mitotic figures. (C) Mainly dermal melanocytic proliferation with a central sheet-like pattern partially erasing the peripheral biphasic pattern of the pre-existing nevus. (D) Close-up view of panel C, in the central area sheets of nevoid and epithelioid melanocytes with abundant melanin pigment and a fibrous background.