

Case presentations n°16-18

Paris Melanoma Meeting 2024

Arnaud de la Fouchardière MD, PhD

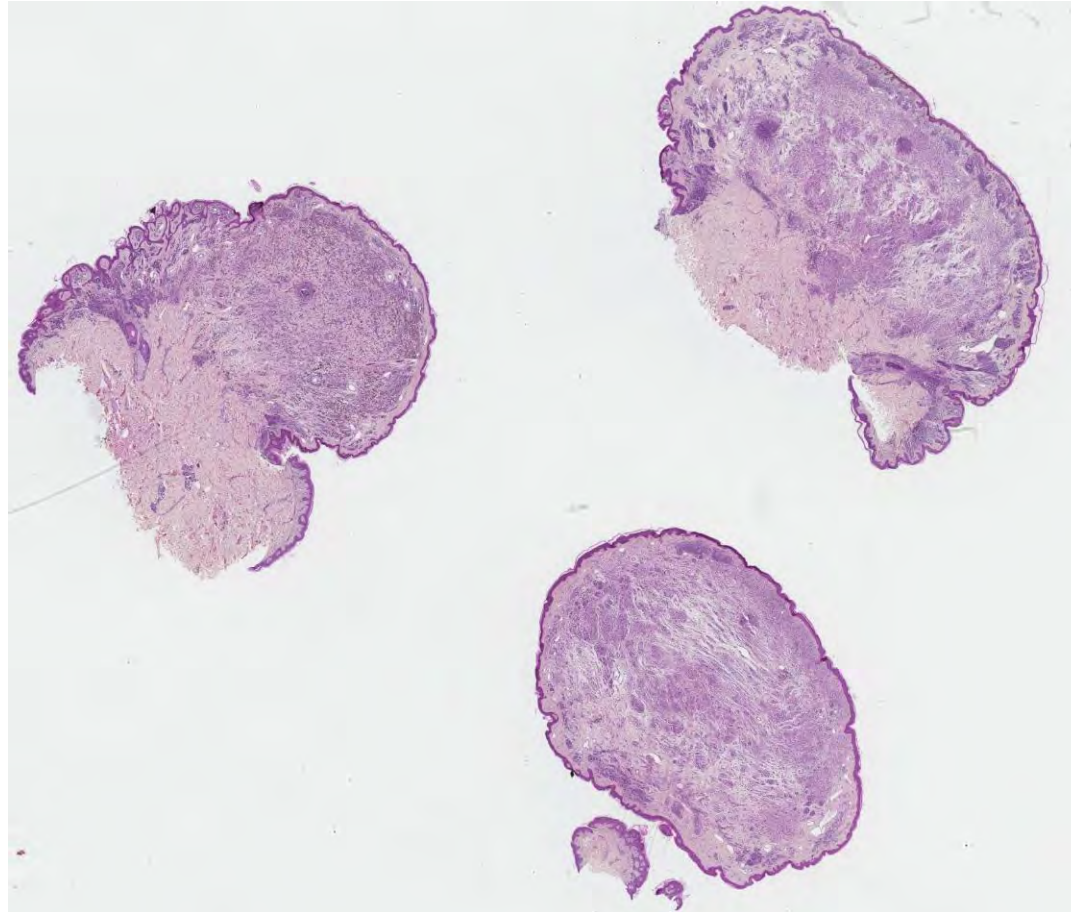
Département de Biopathologie

Centre de Lutte contre le cancer Léon Bérard

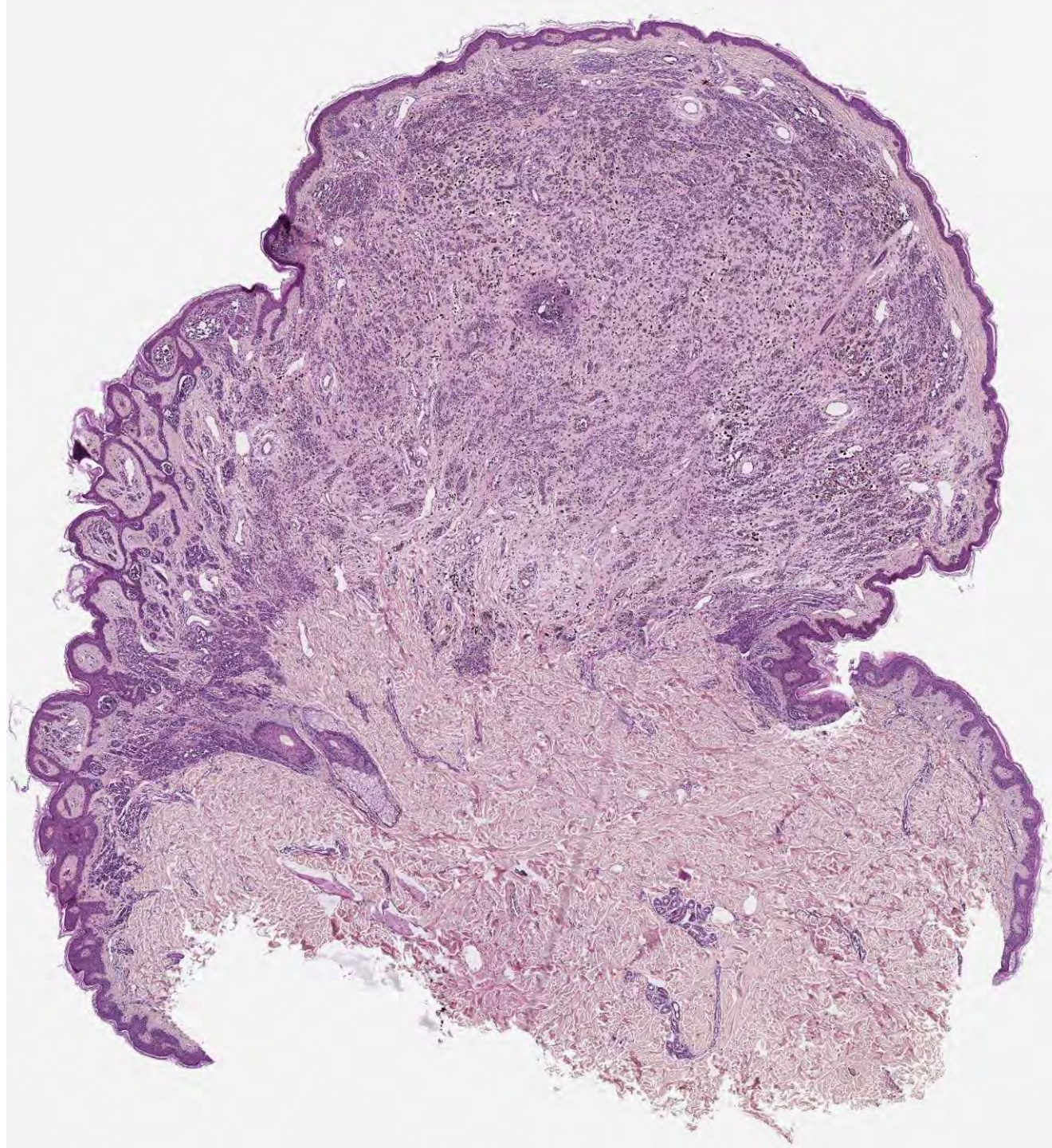
Lyon, FRANCE



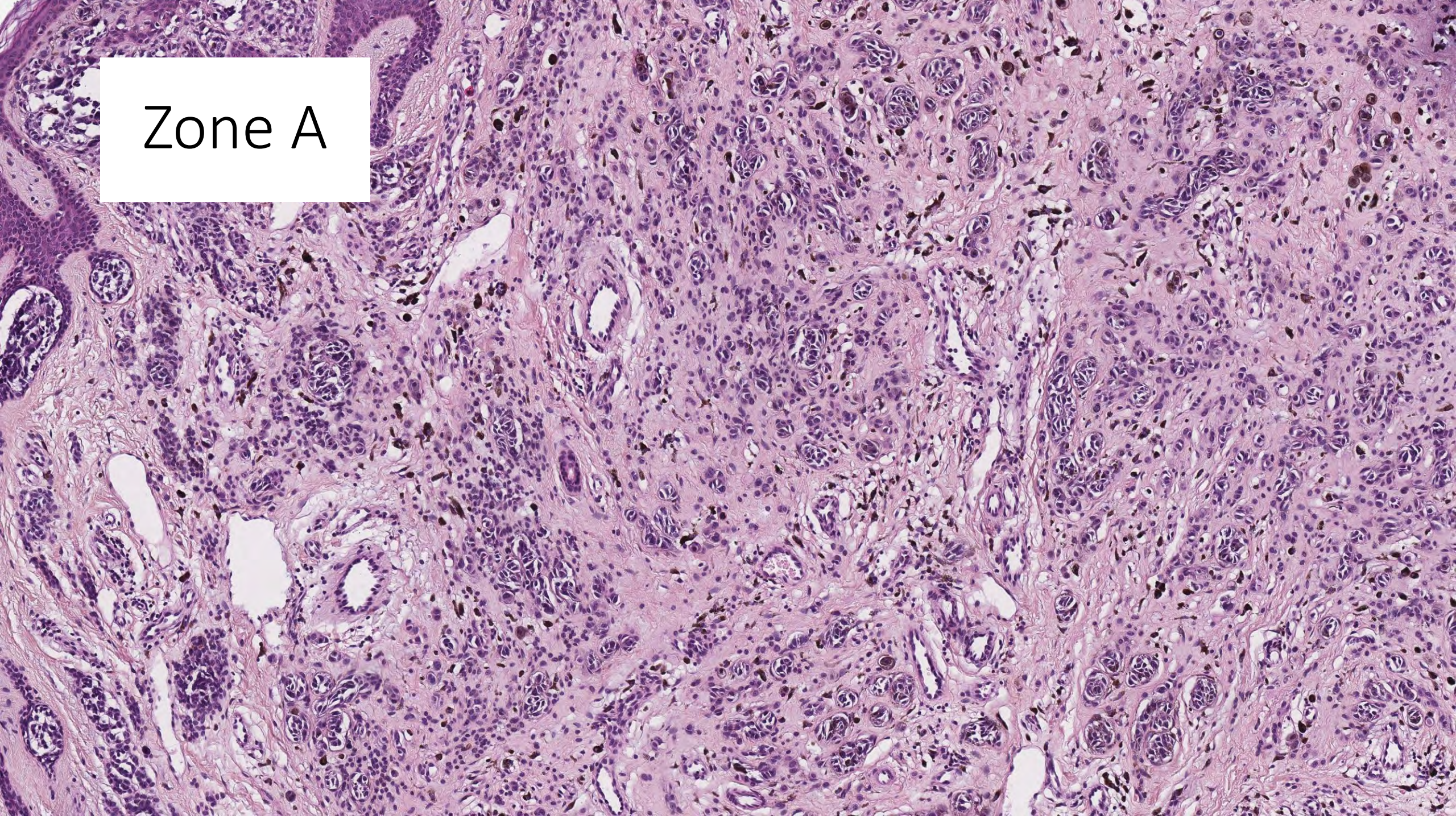
Case N°16 F19 mid-dorsal region



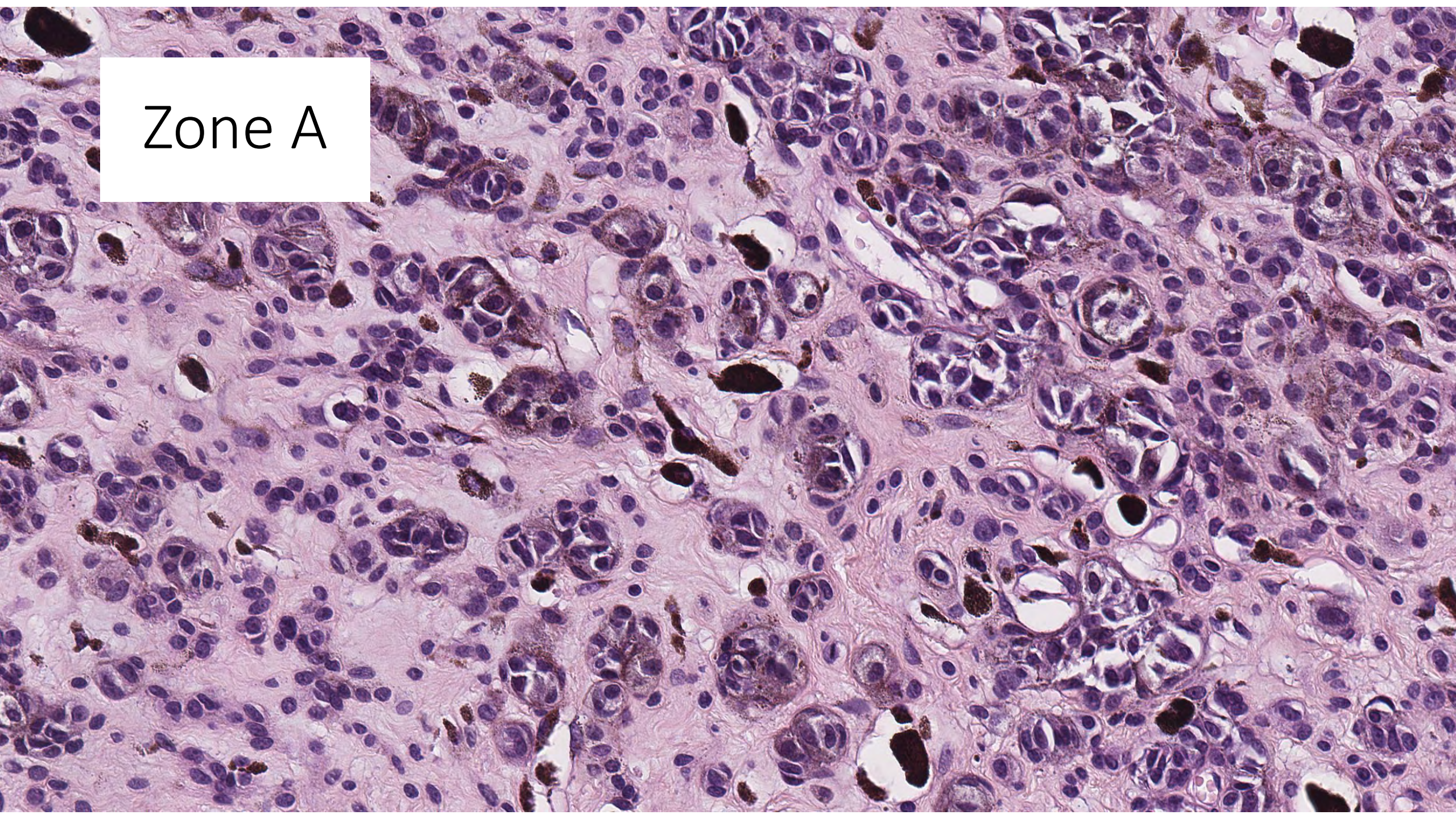
Zone A



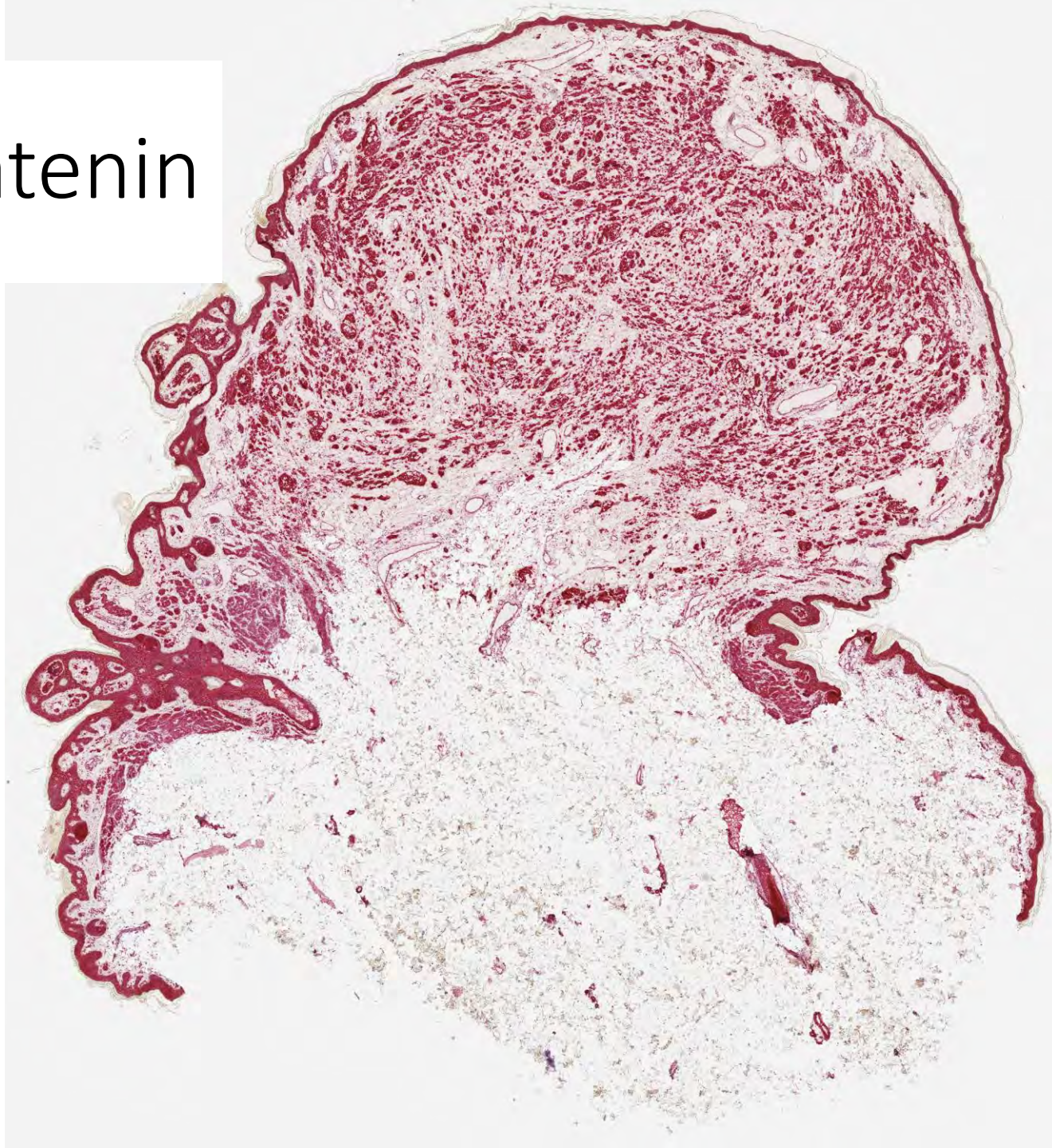
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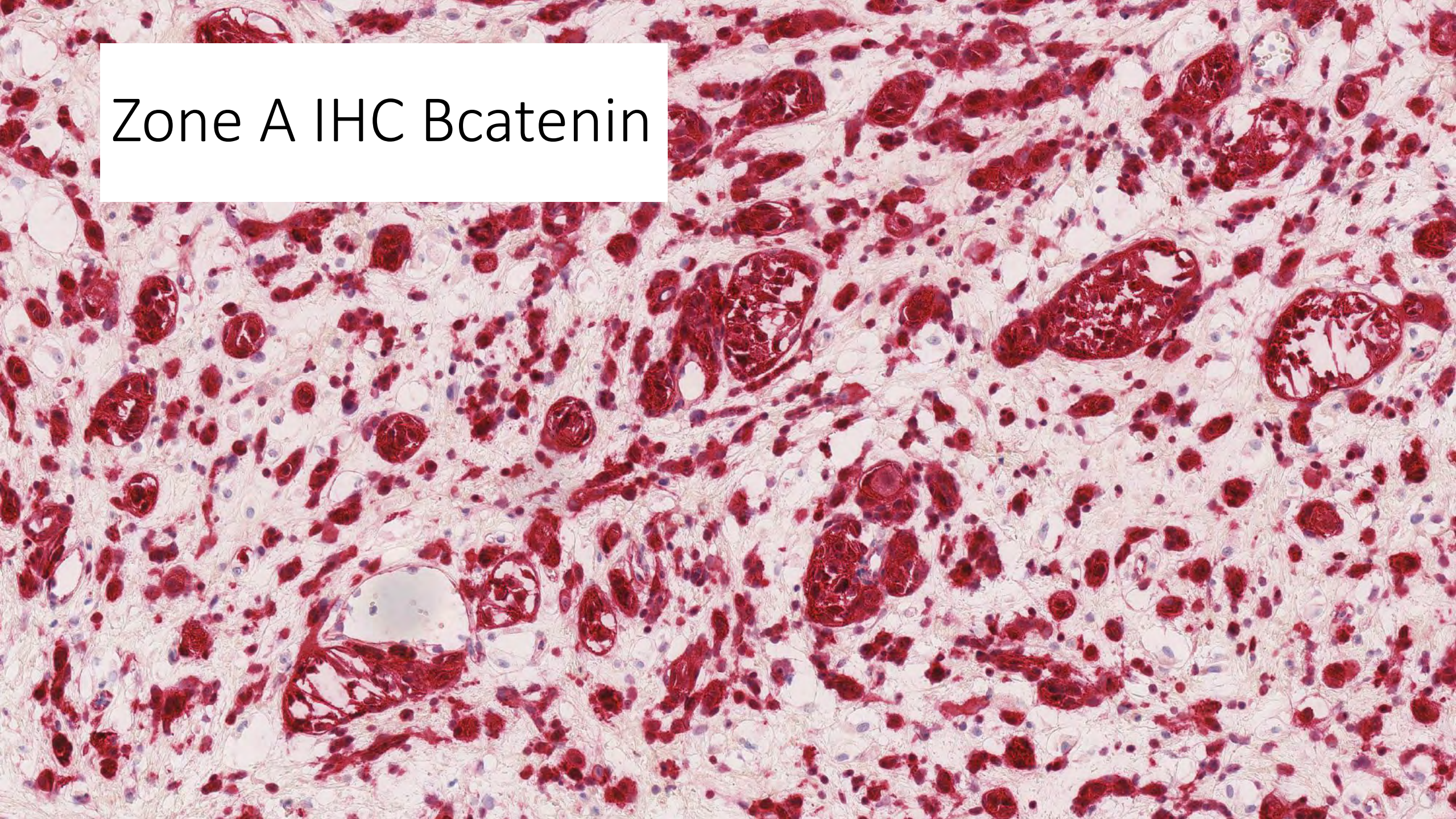
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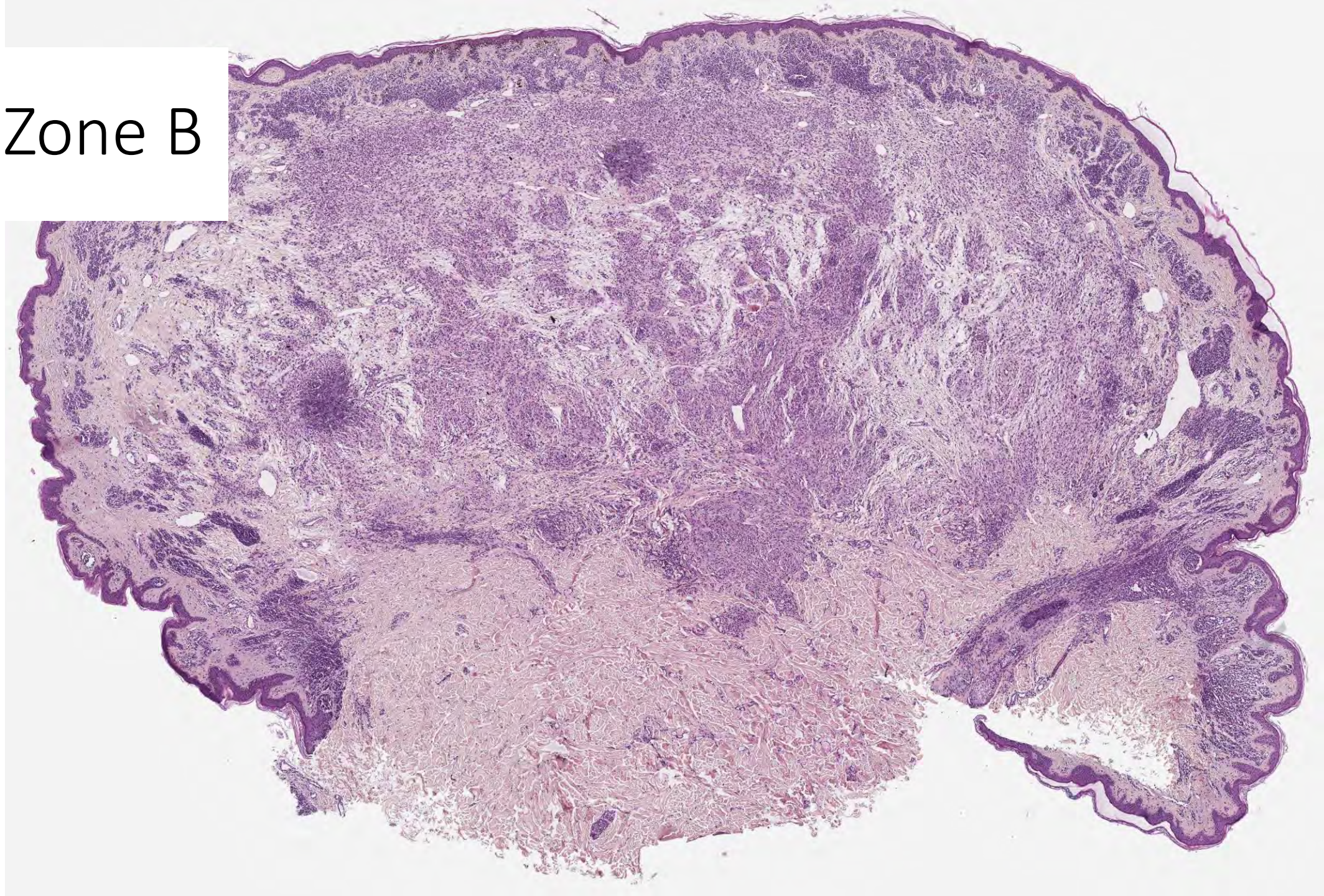
Zone A IHC Bcatenin



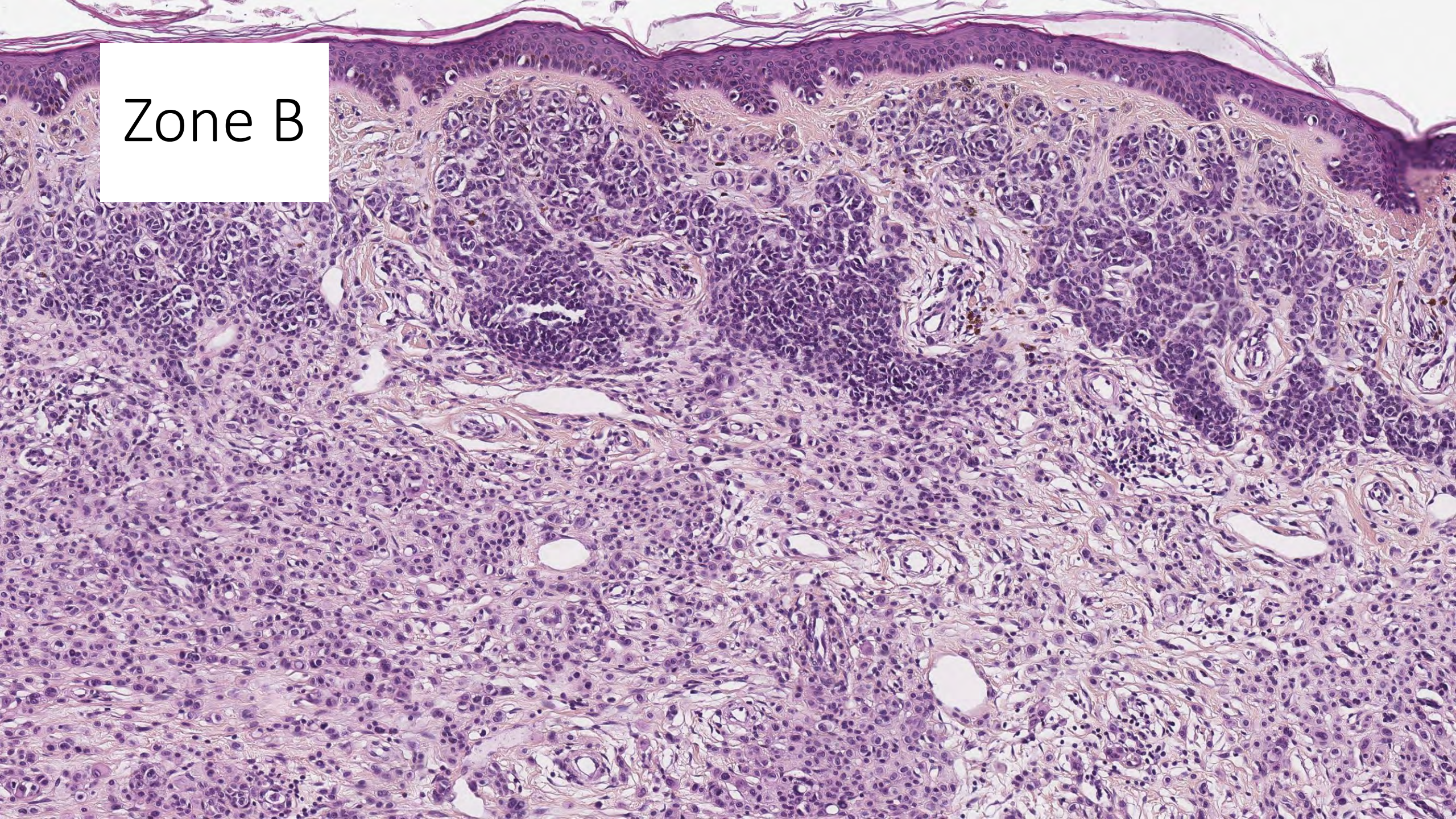
Zone A IHC Bcatenin



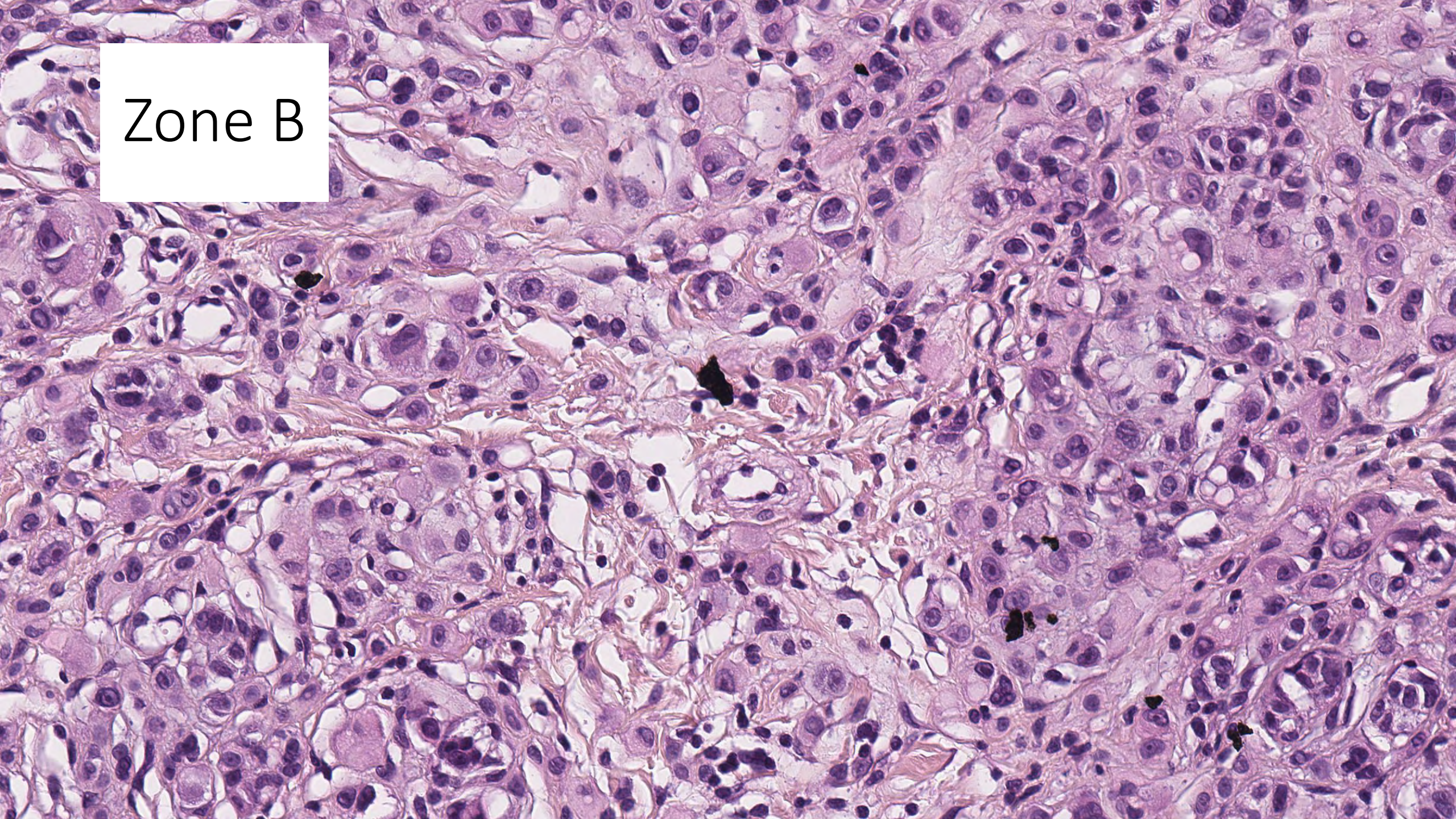
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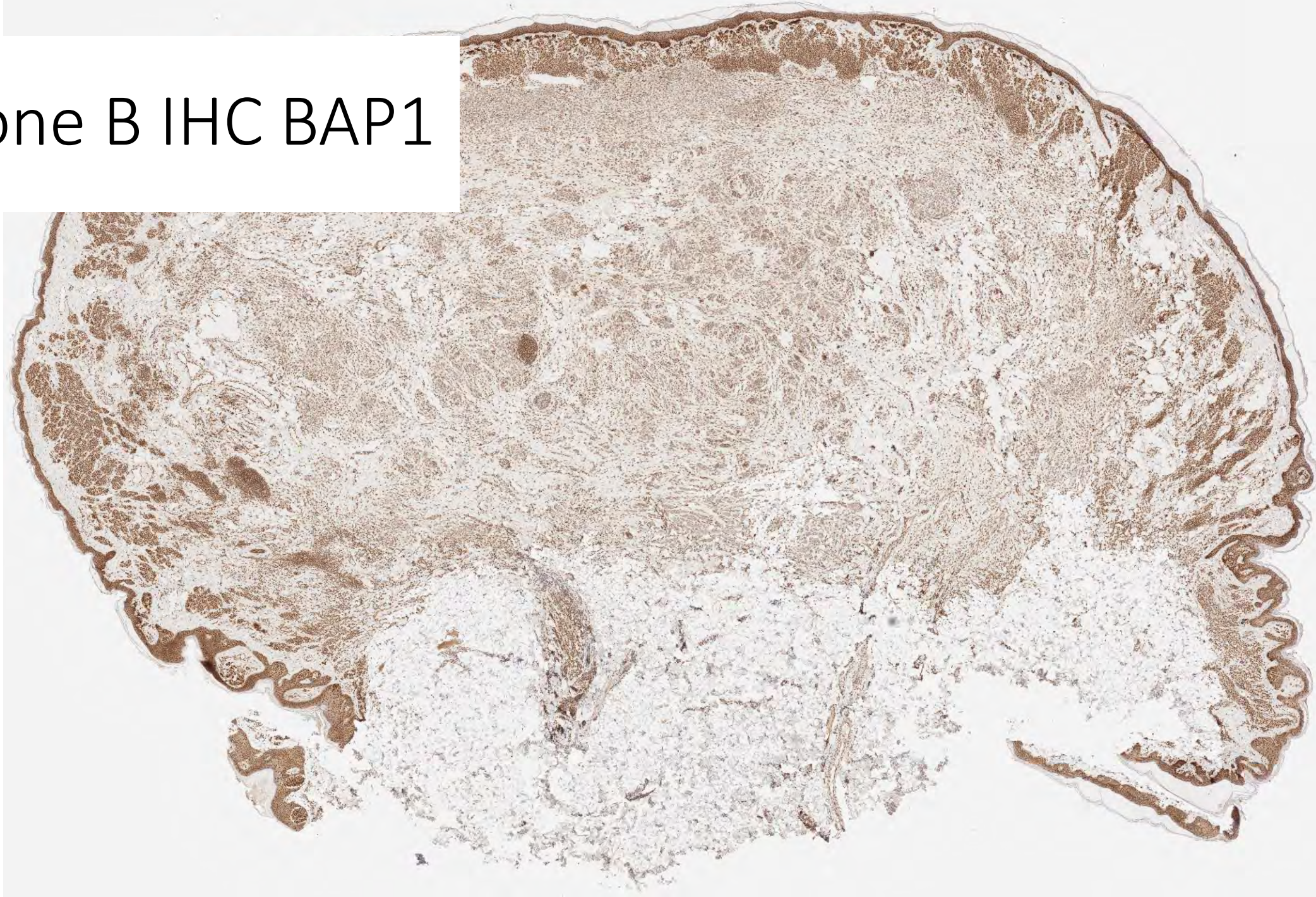
Zone B



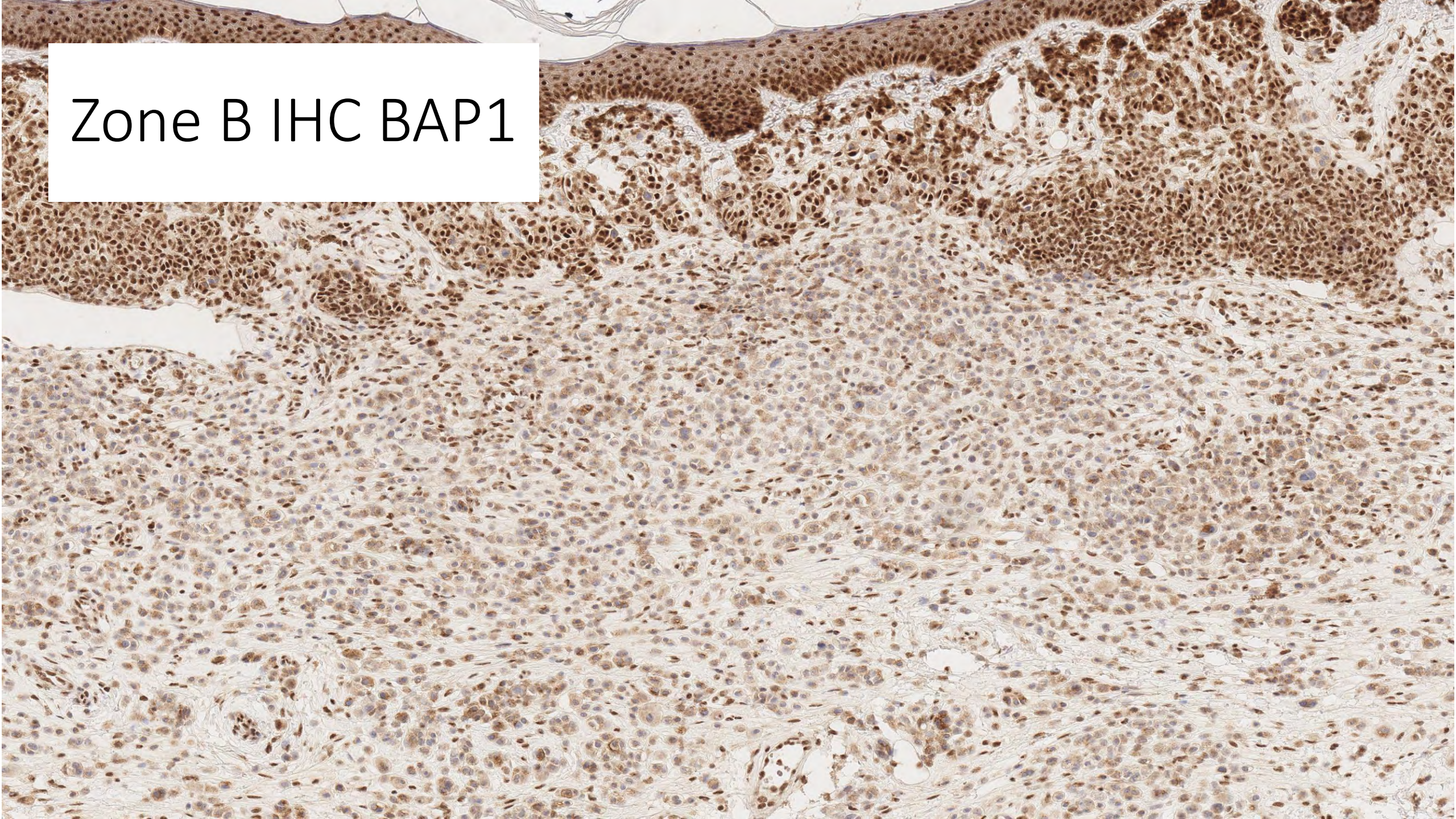
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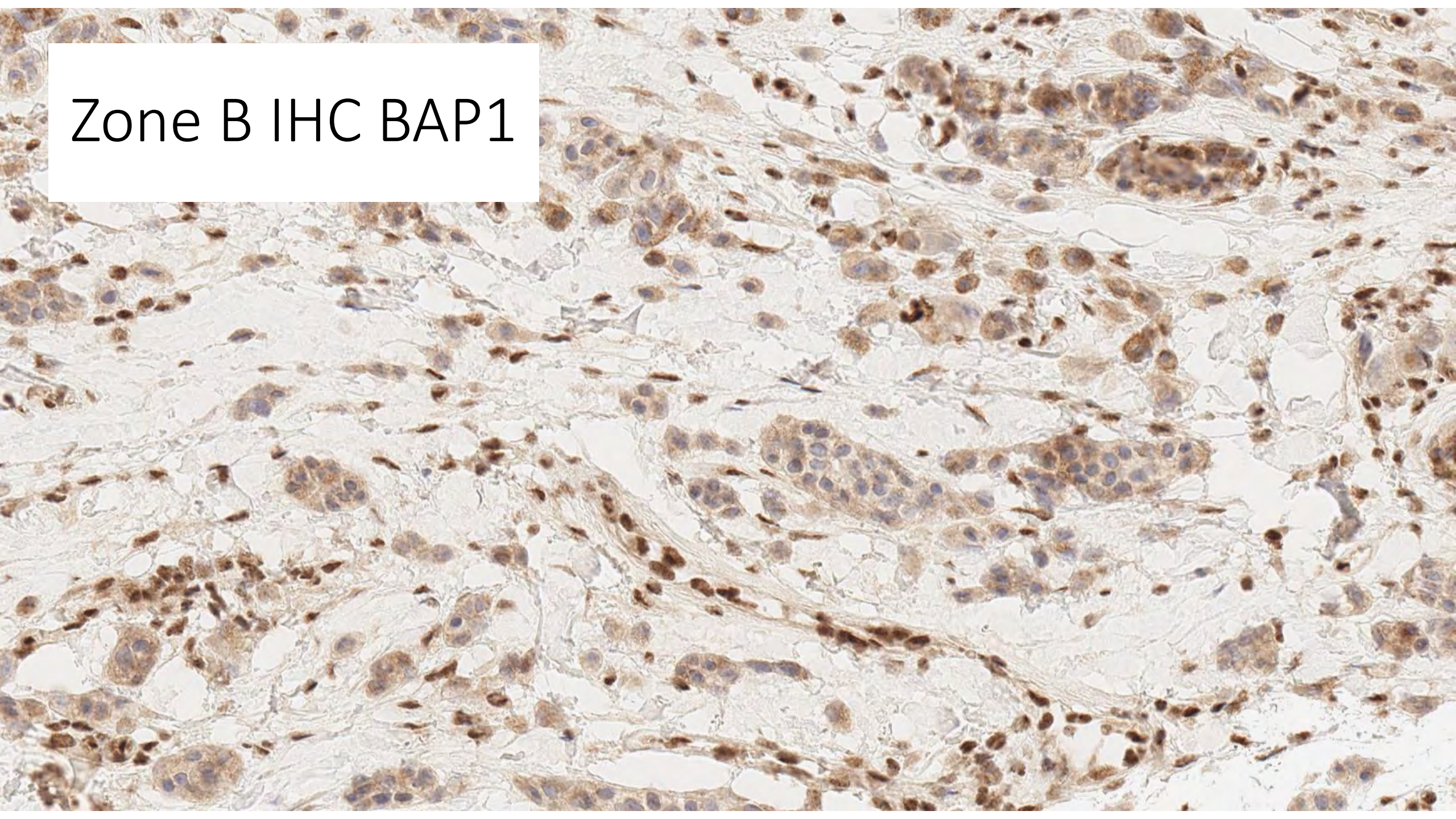
Zone B IHC BAP1



Zone B IHC BAP1



Zone B IHC BAP1



Final diagnosis

- Tri-phenotypic nevus (WAM + BIM ex-nevus)

- Tri-phenotypic nevus (Common nevus + WNT-activated clone + BAP1 inactivated clone)

Pathology. 2018 Oct;50(6):691-693. doi: 10.1016/j.pathol.2018.04.004. Epub 2018 Aug 16.

Tri-phenotypic naevus: a case report.

Cellier L¹, Jacquemus J¹, Youssef-Provençal N², Houlier A¹, de la Fouchardiere A³.

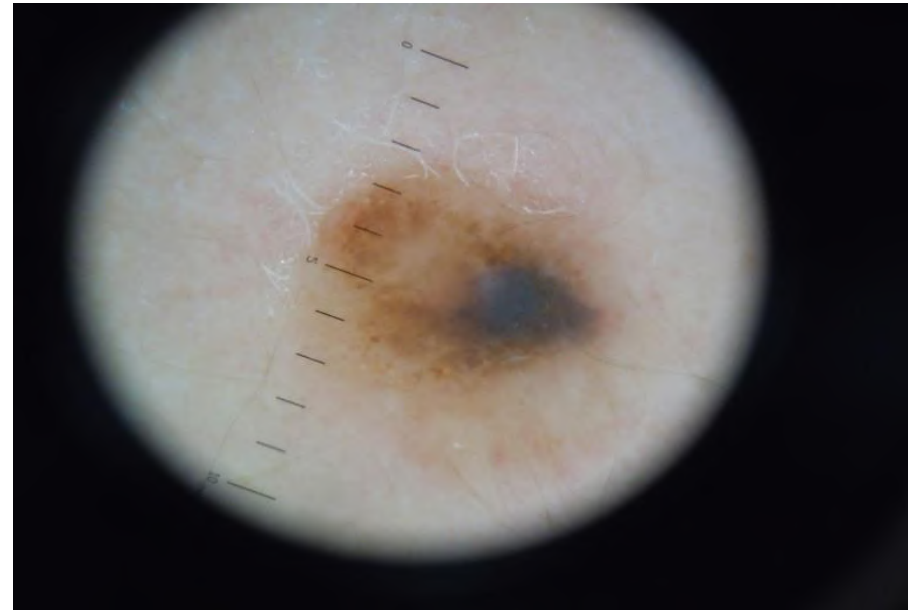
 **Author information**

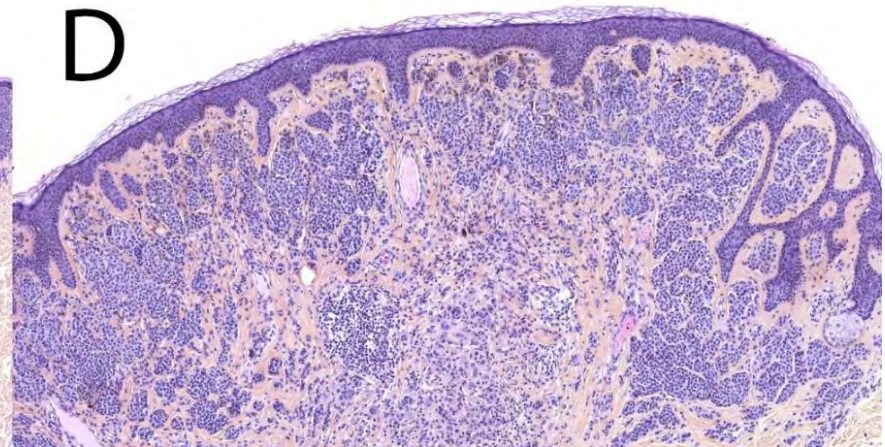
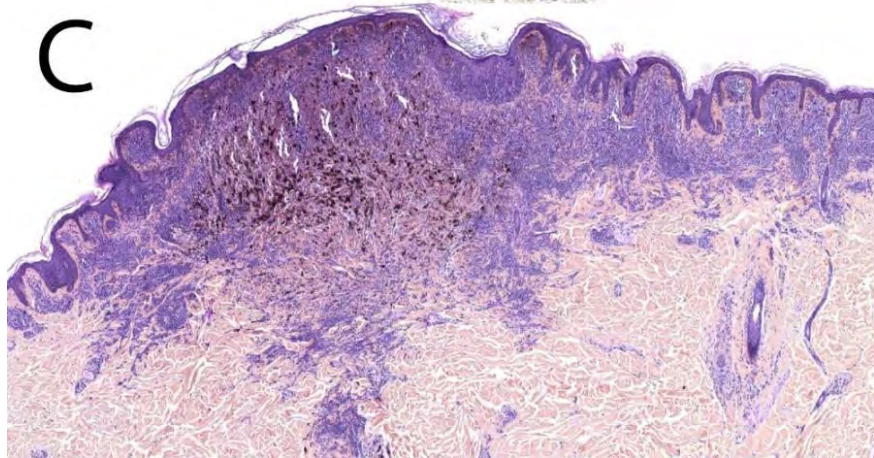
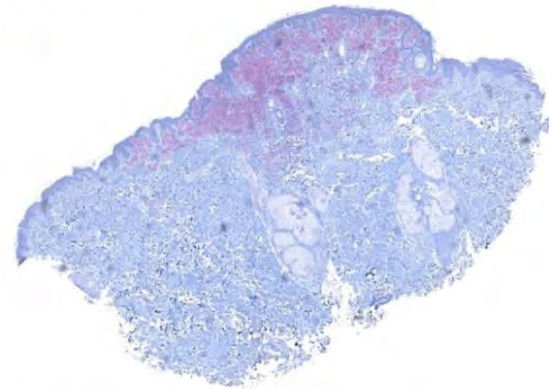
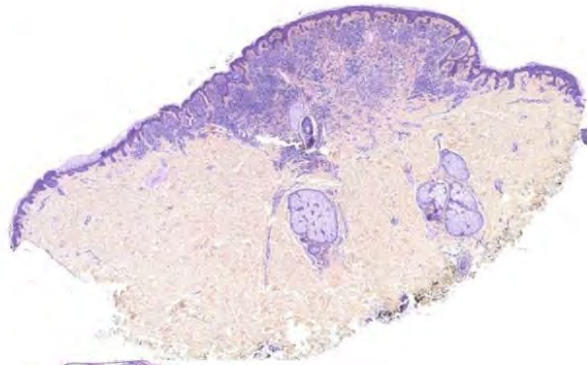
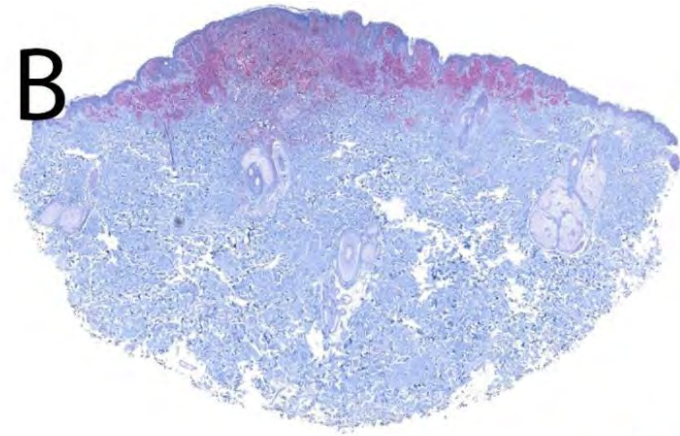
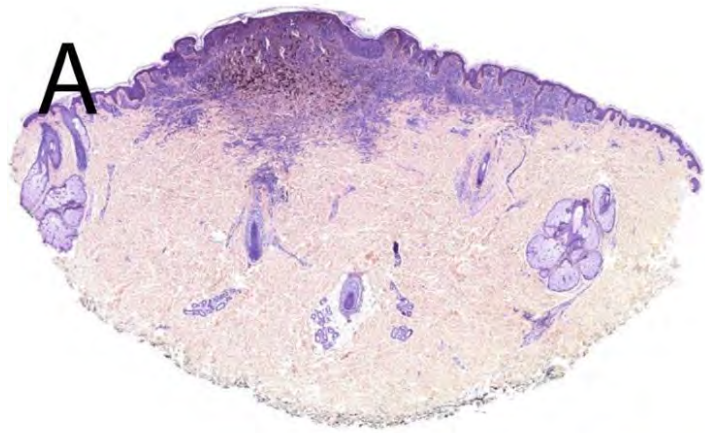
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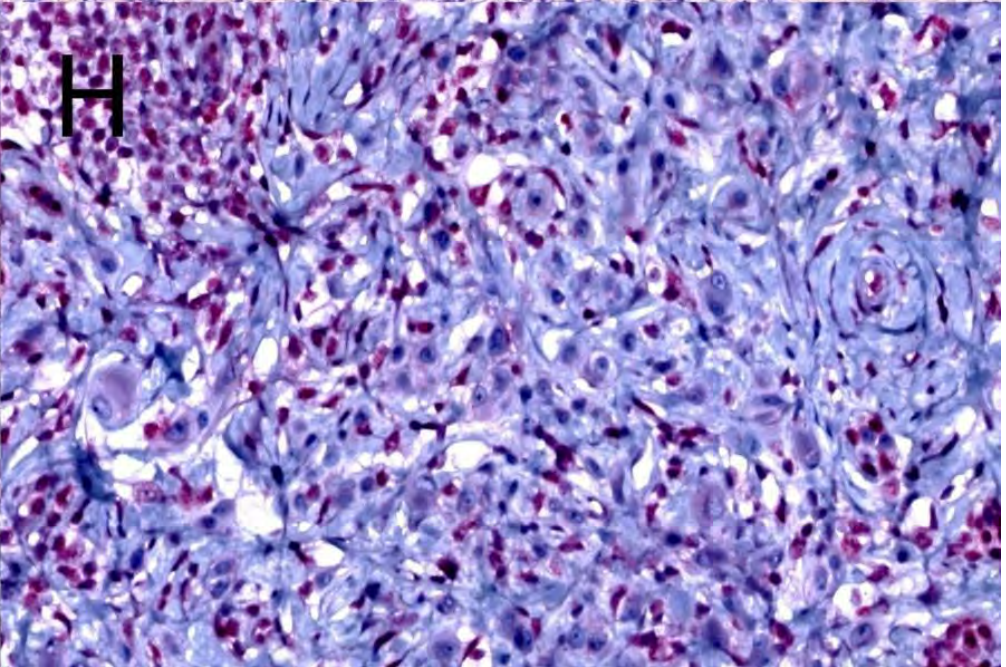
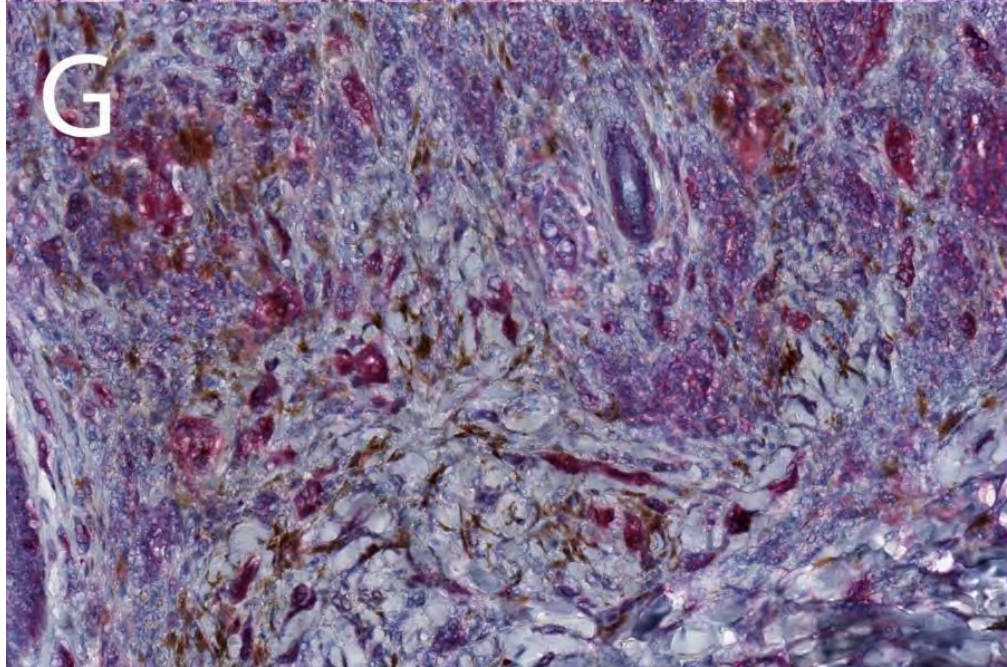
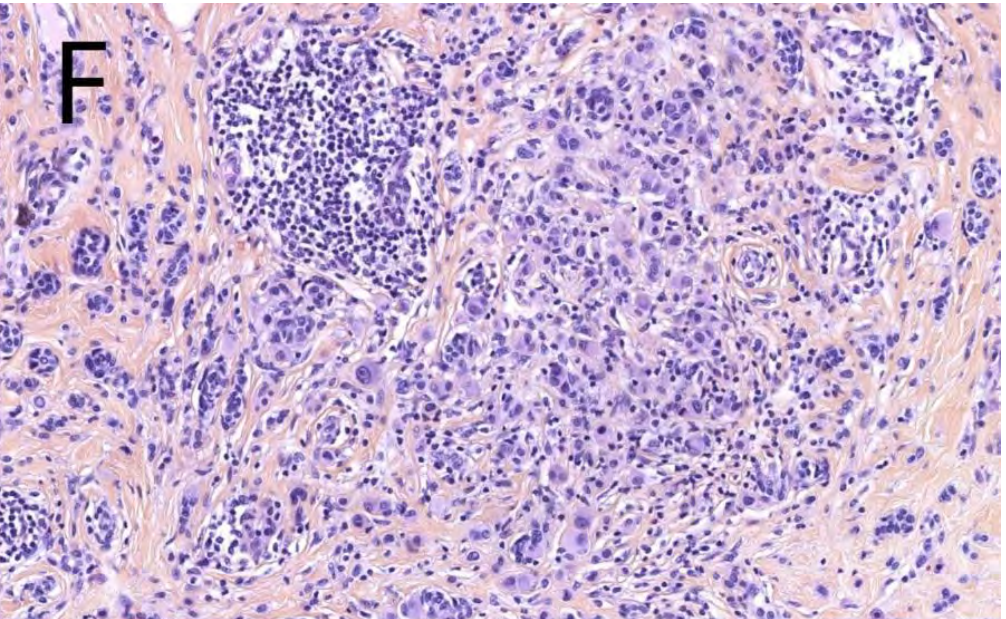
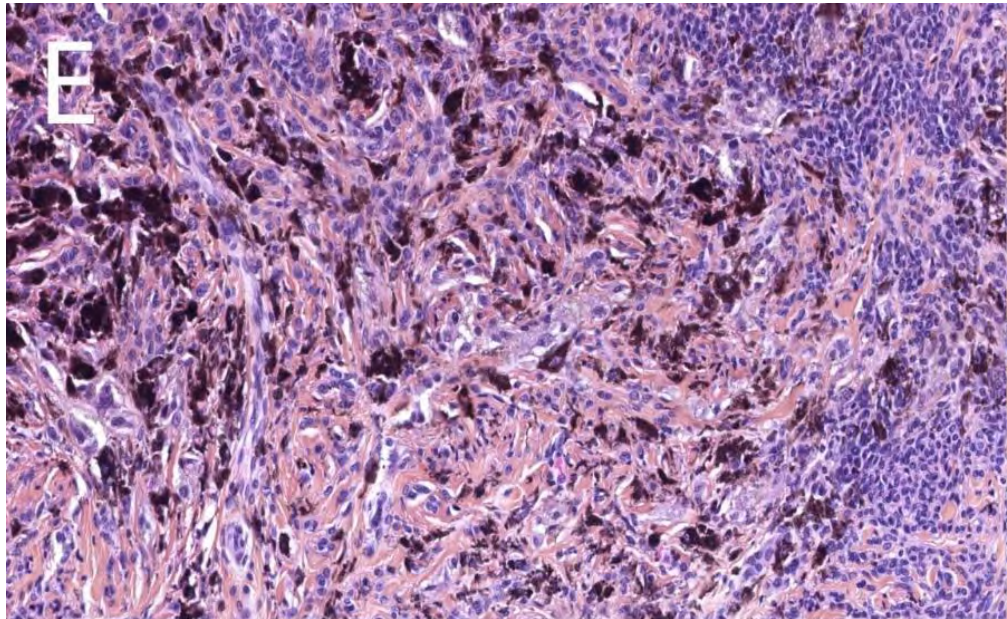
Double combined nevus



- F, 19 yo
- Lesion on the back

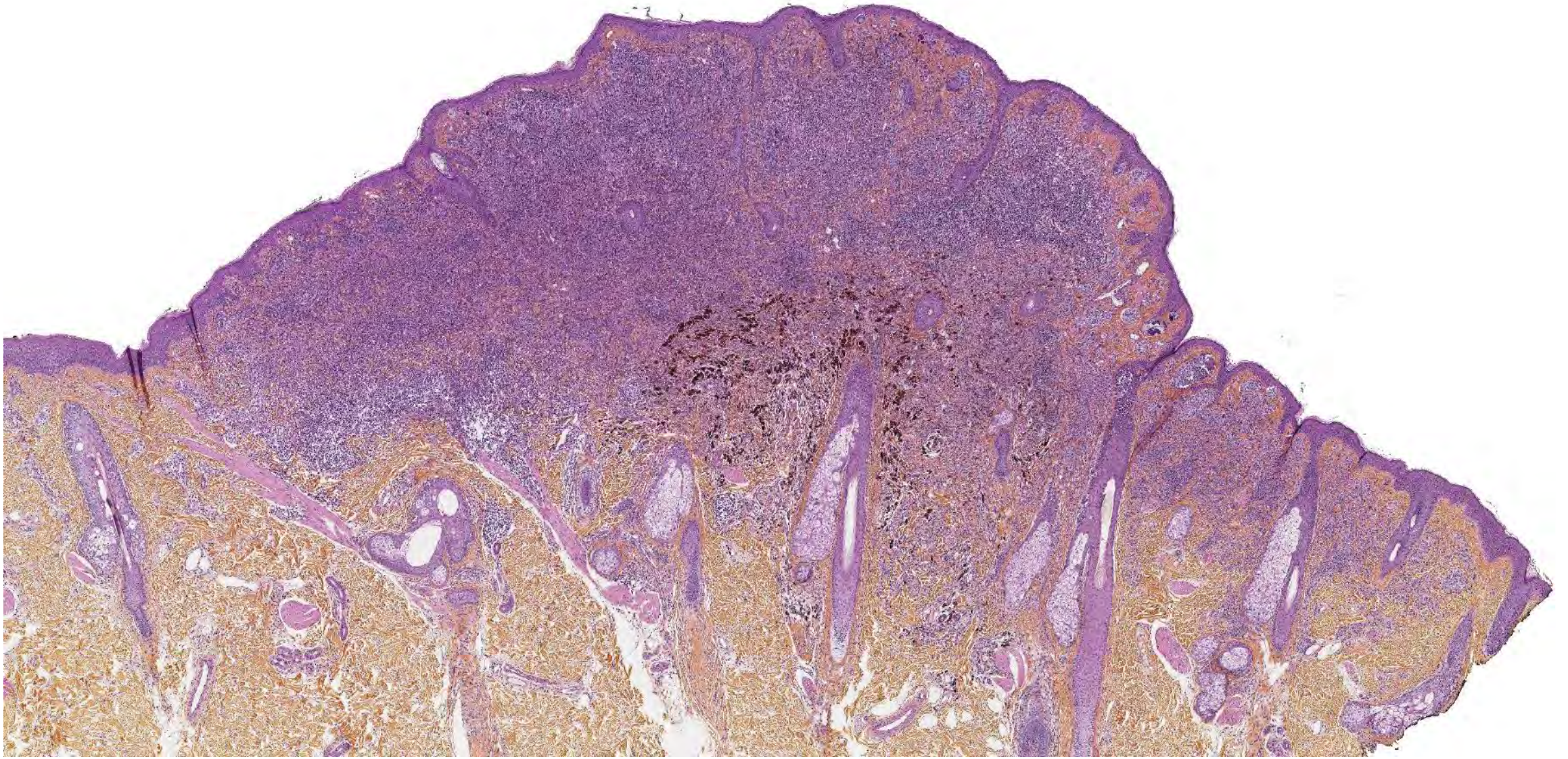


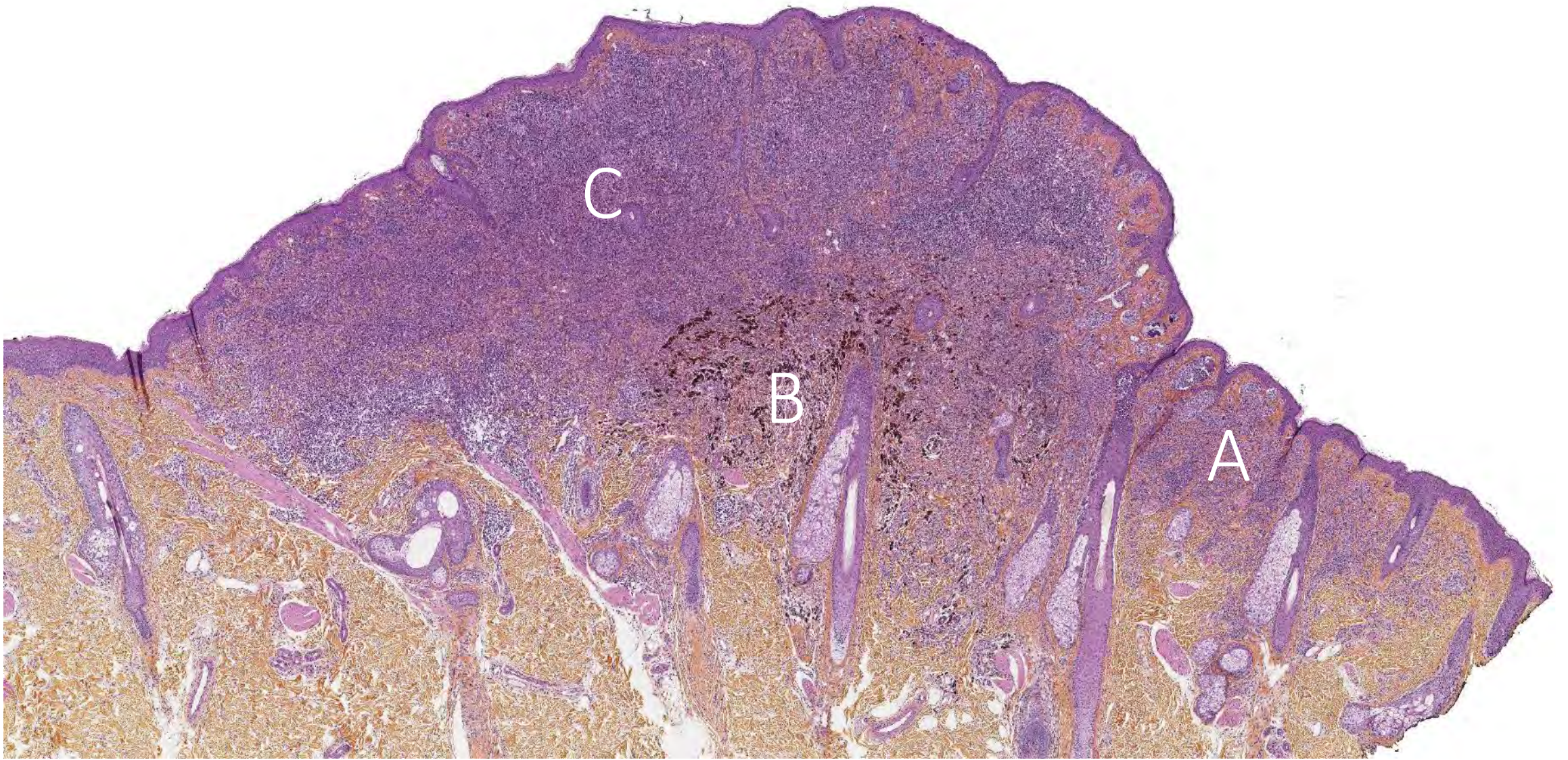




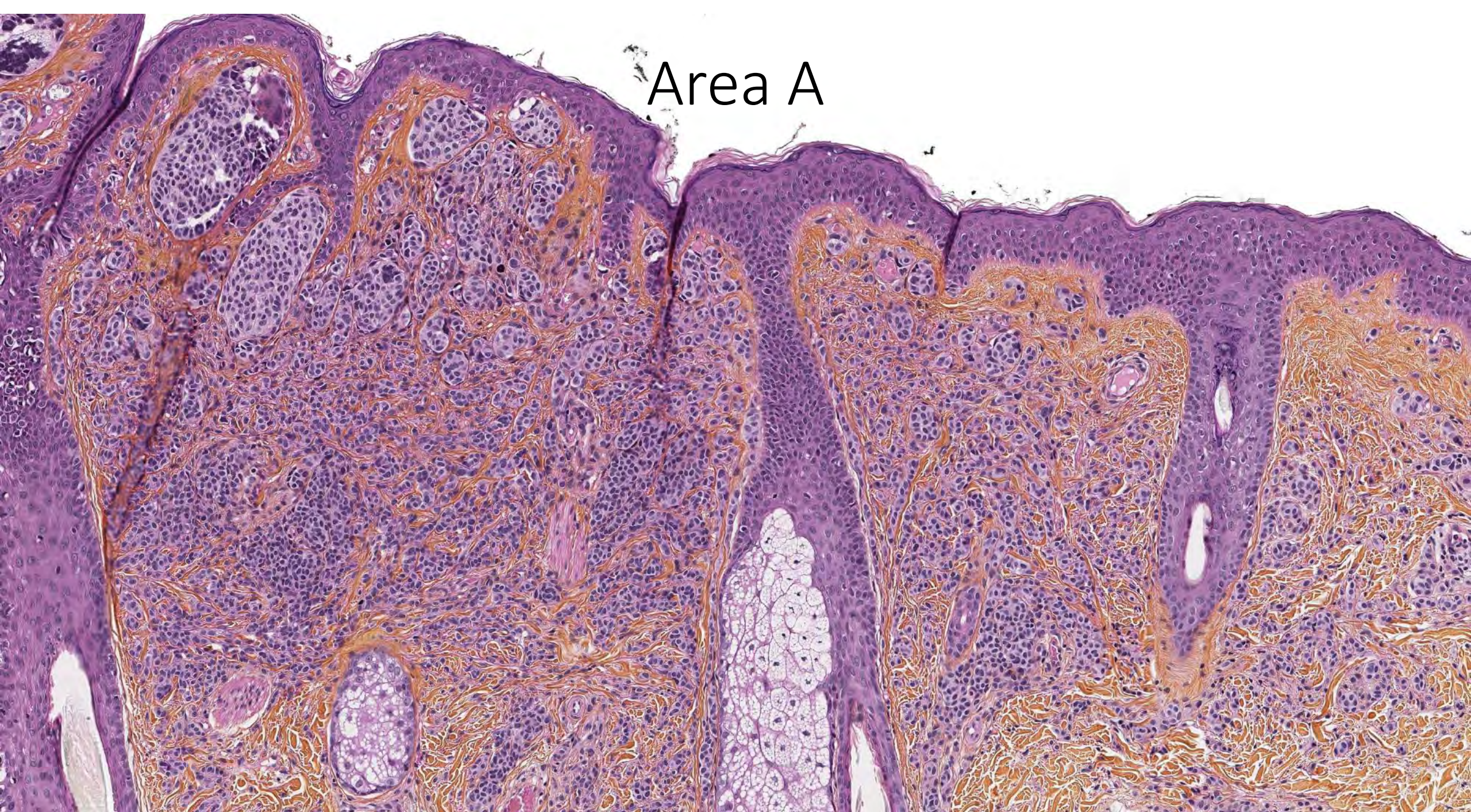
Tri-phenotypic nevus (Common + WNT-activated + BAP1 inactivated)



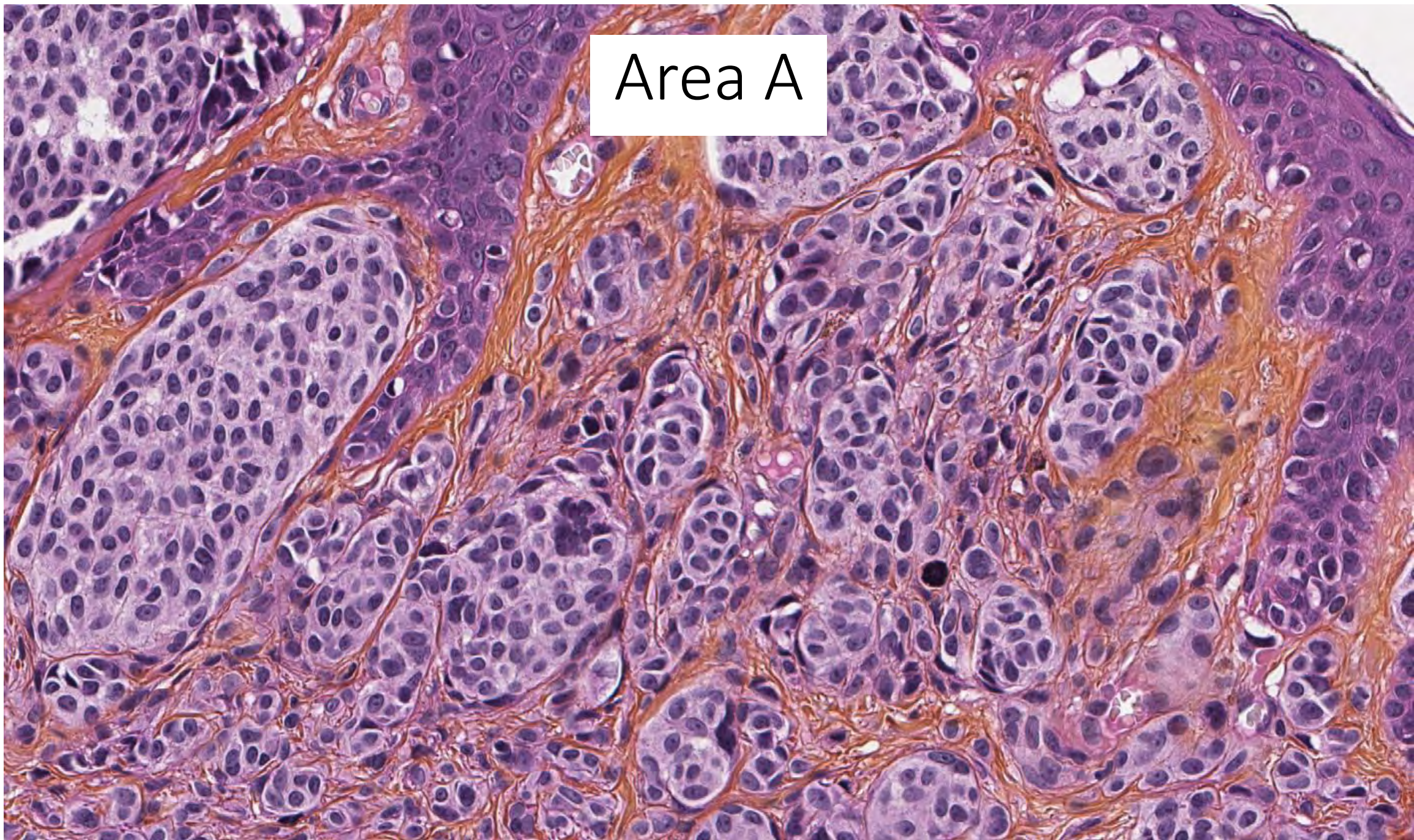




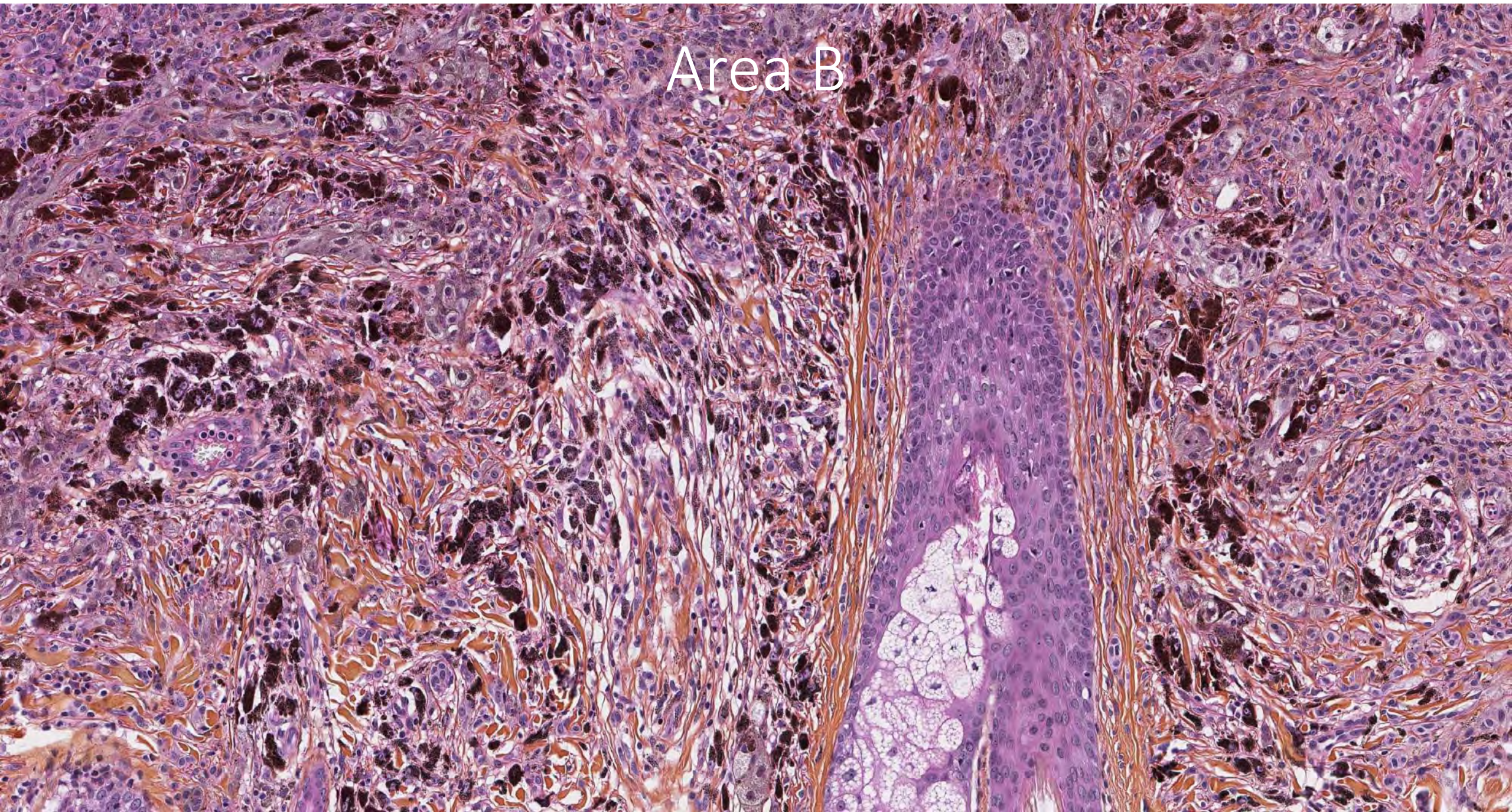
Area A



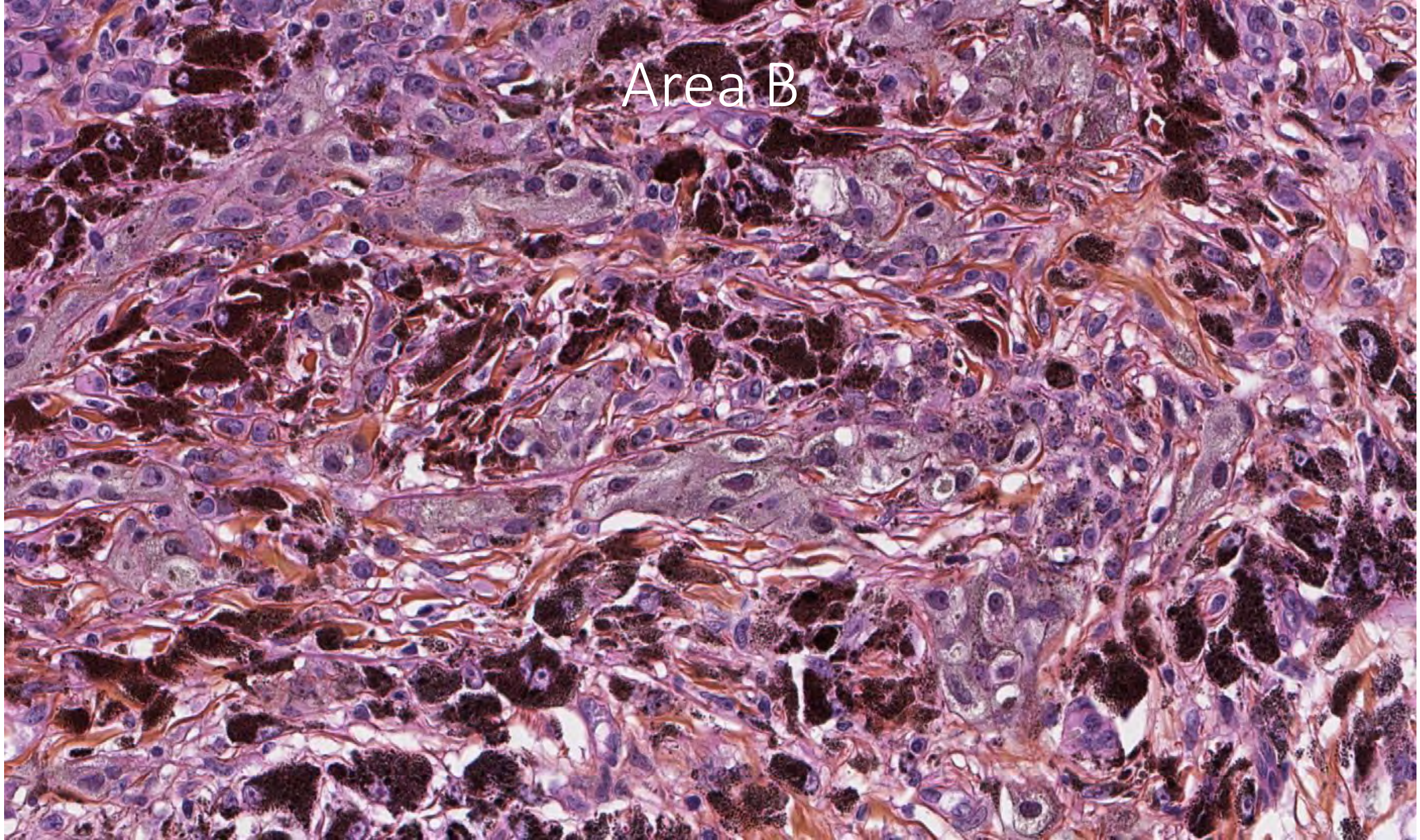
Area A



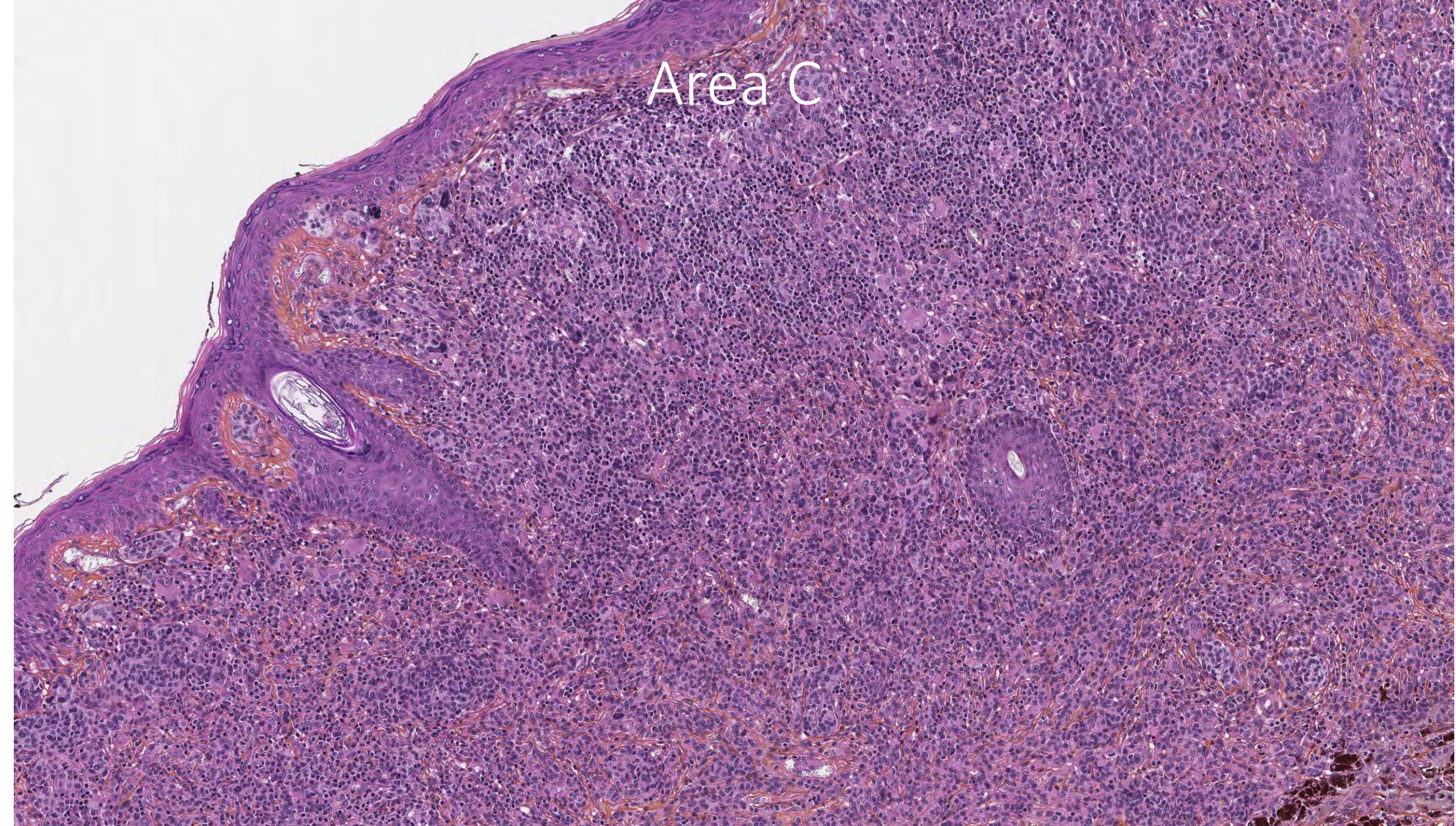
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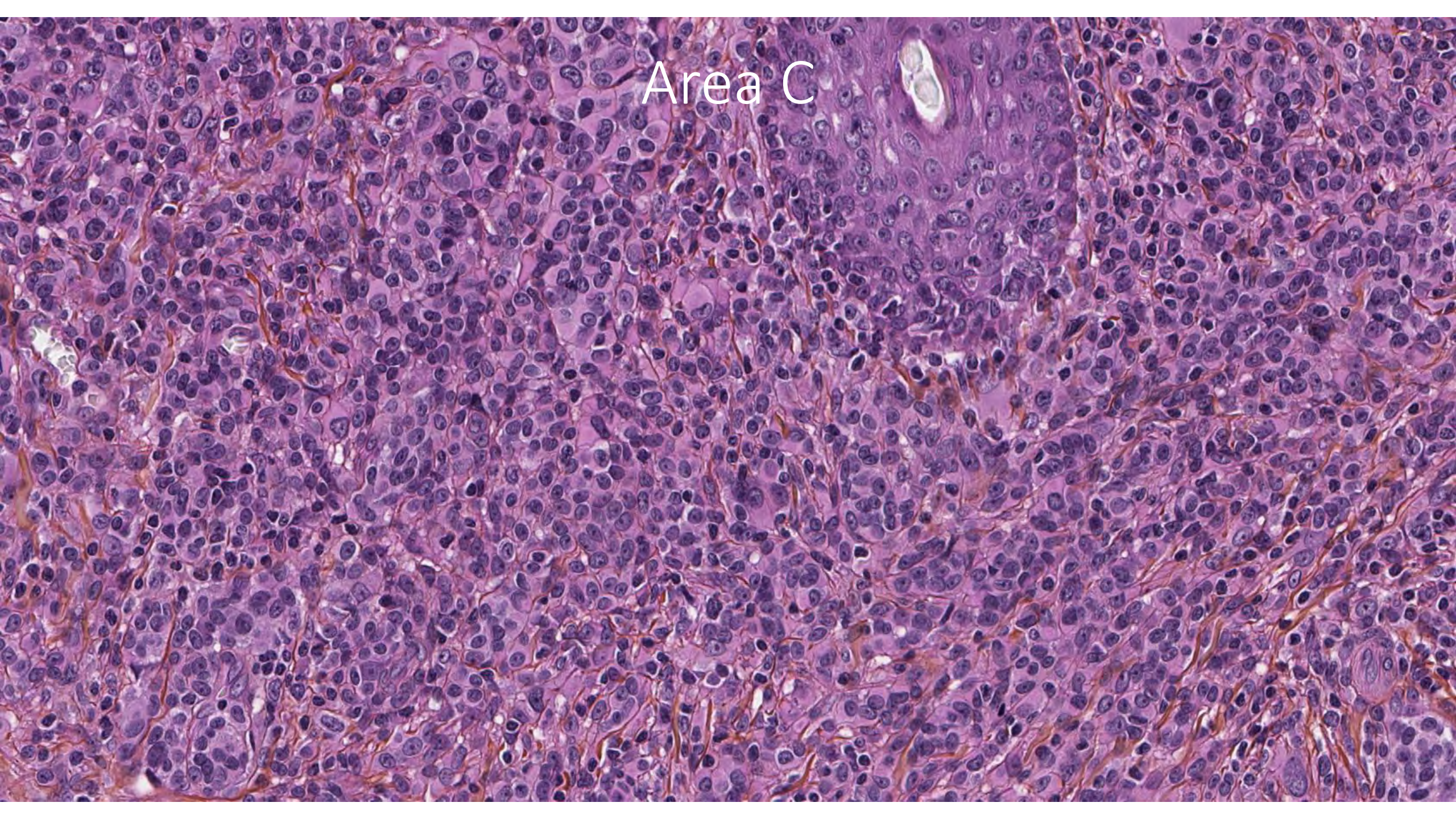
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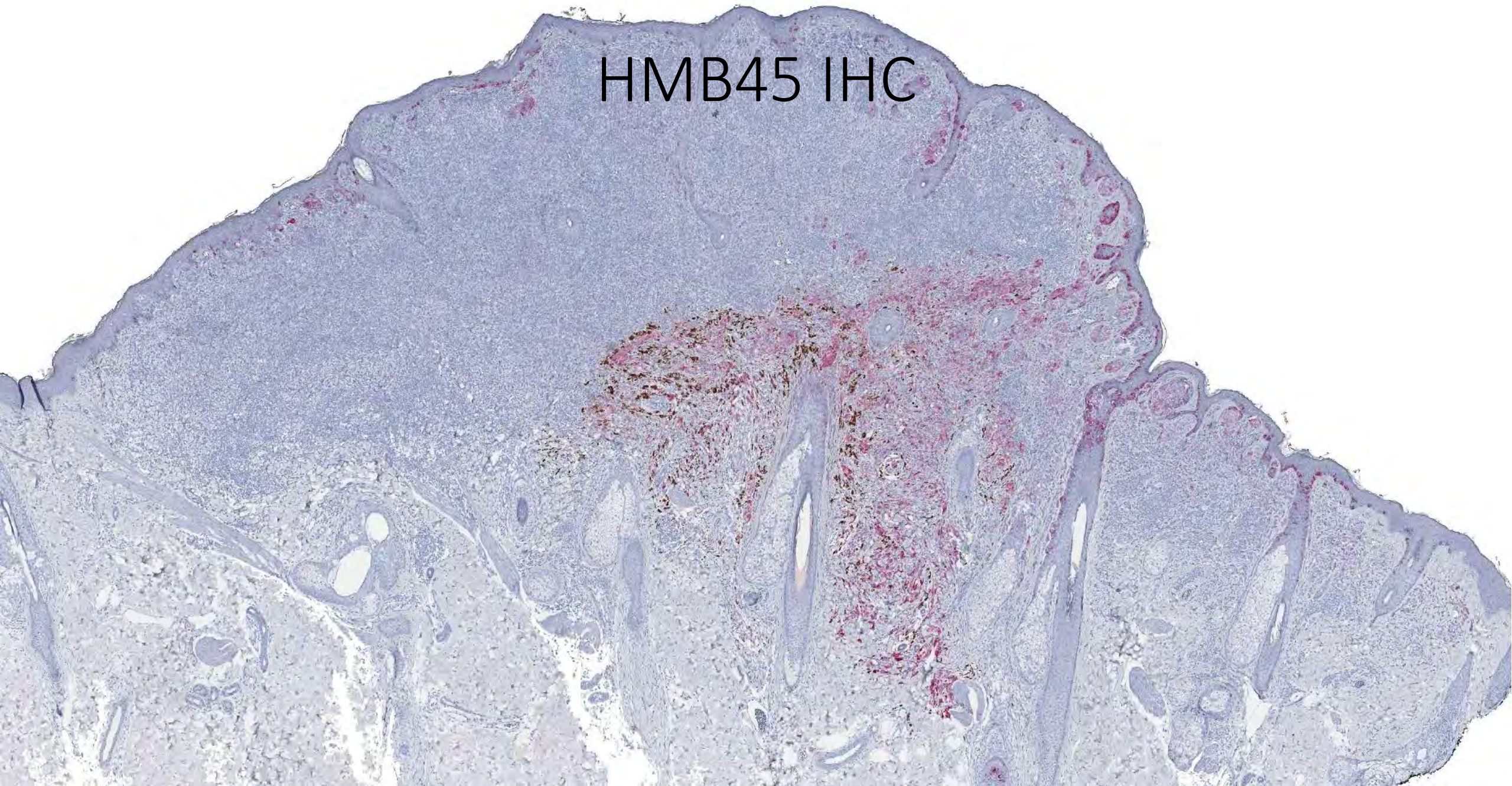
Area C



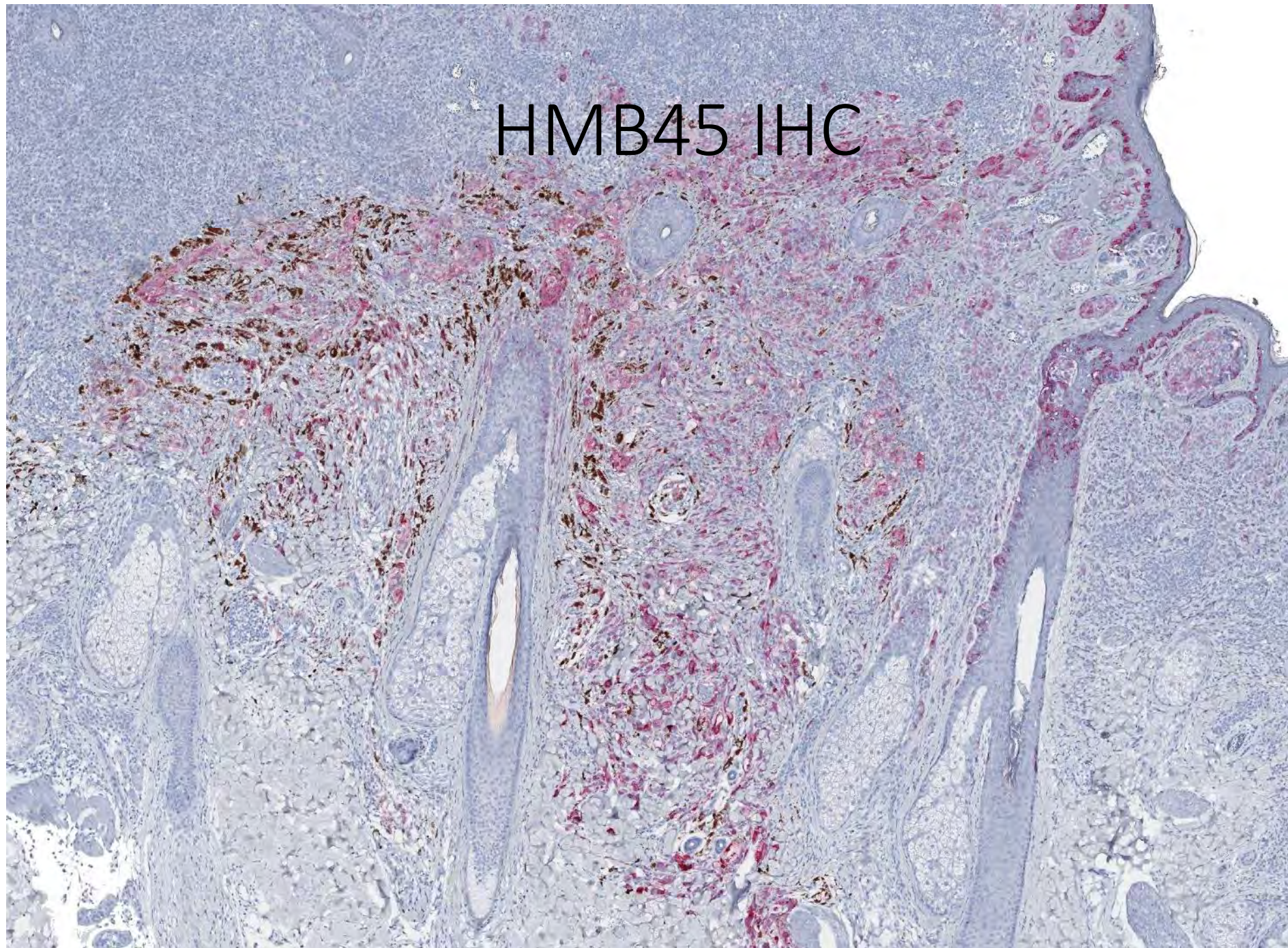
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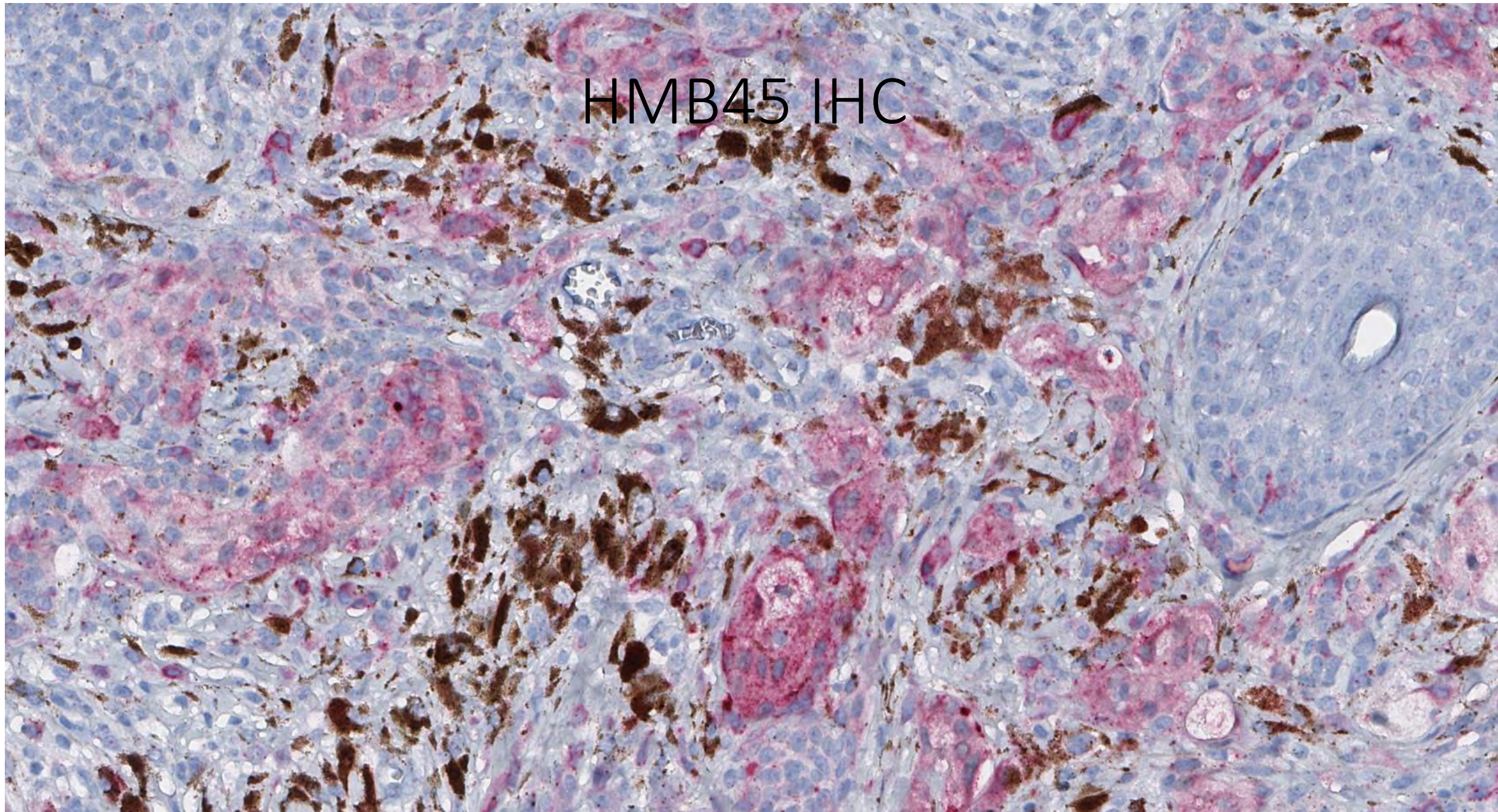
HMB45 IHC



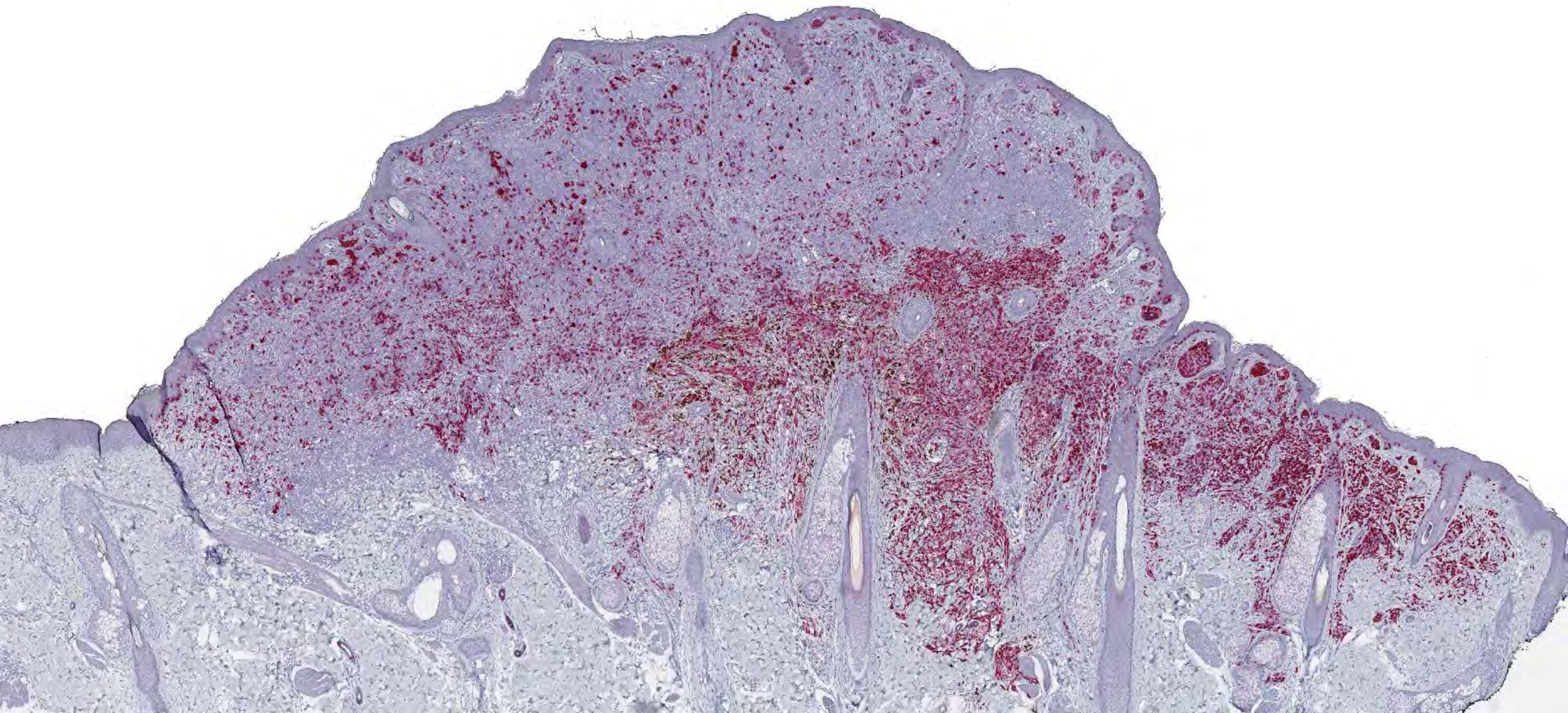
HMB45 IHC



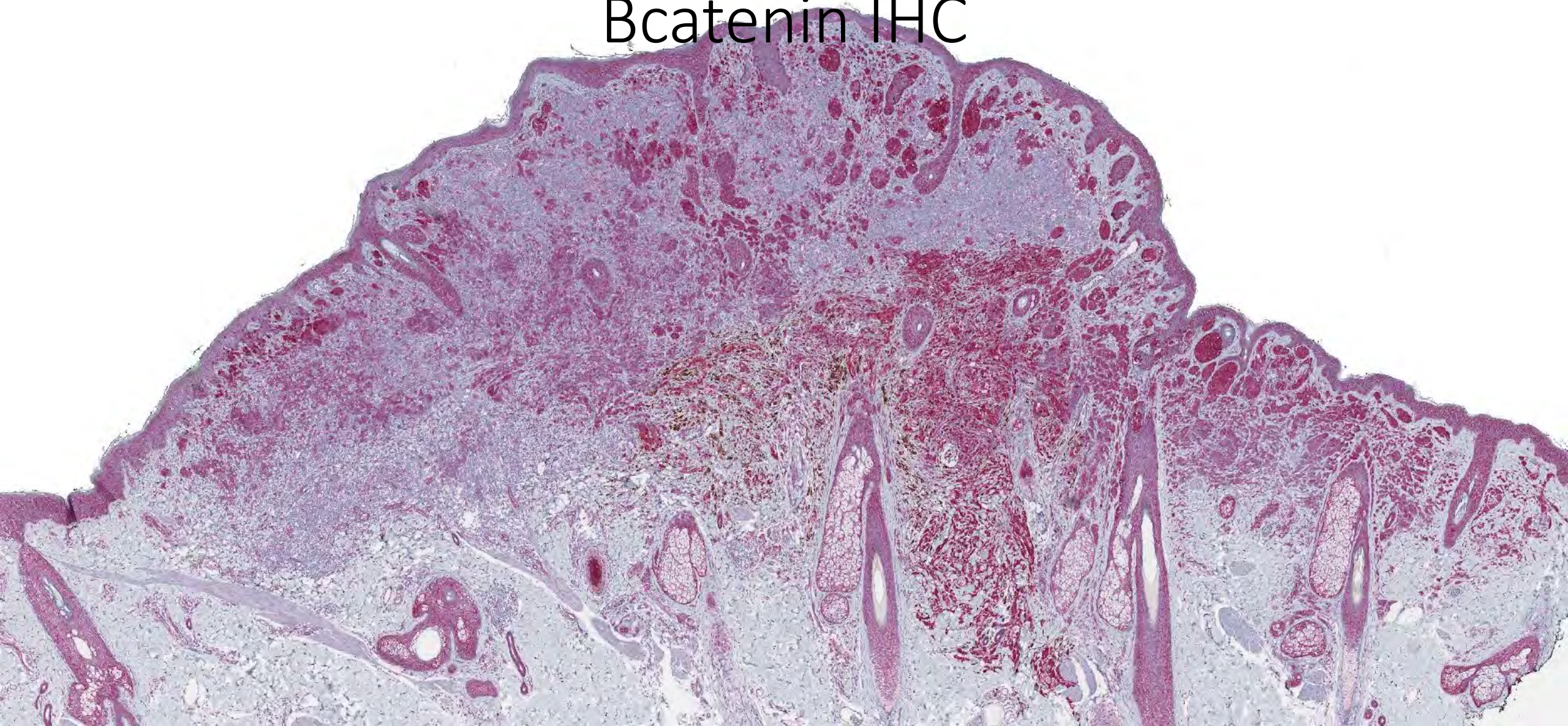
HMB45 IHC



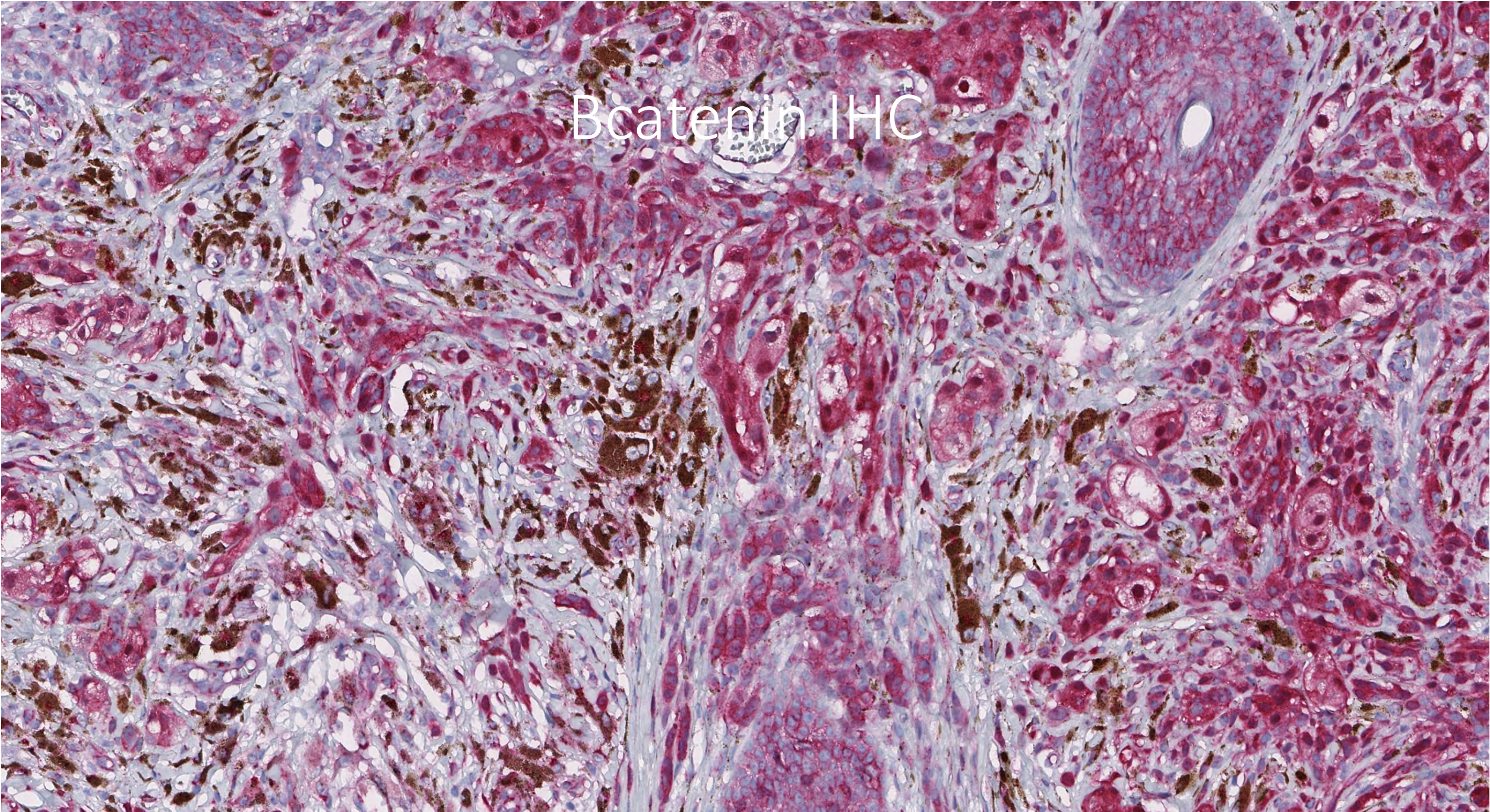
p16 IHC



Bcatenin IHC



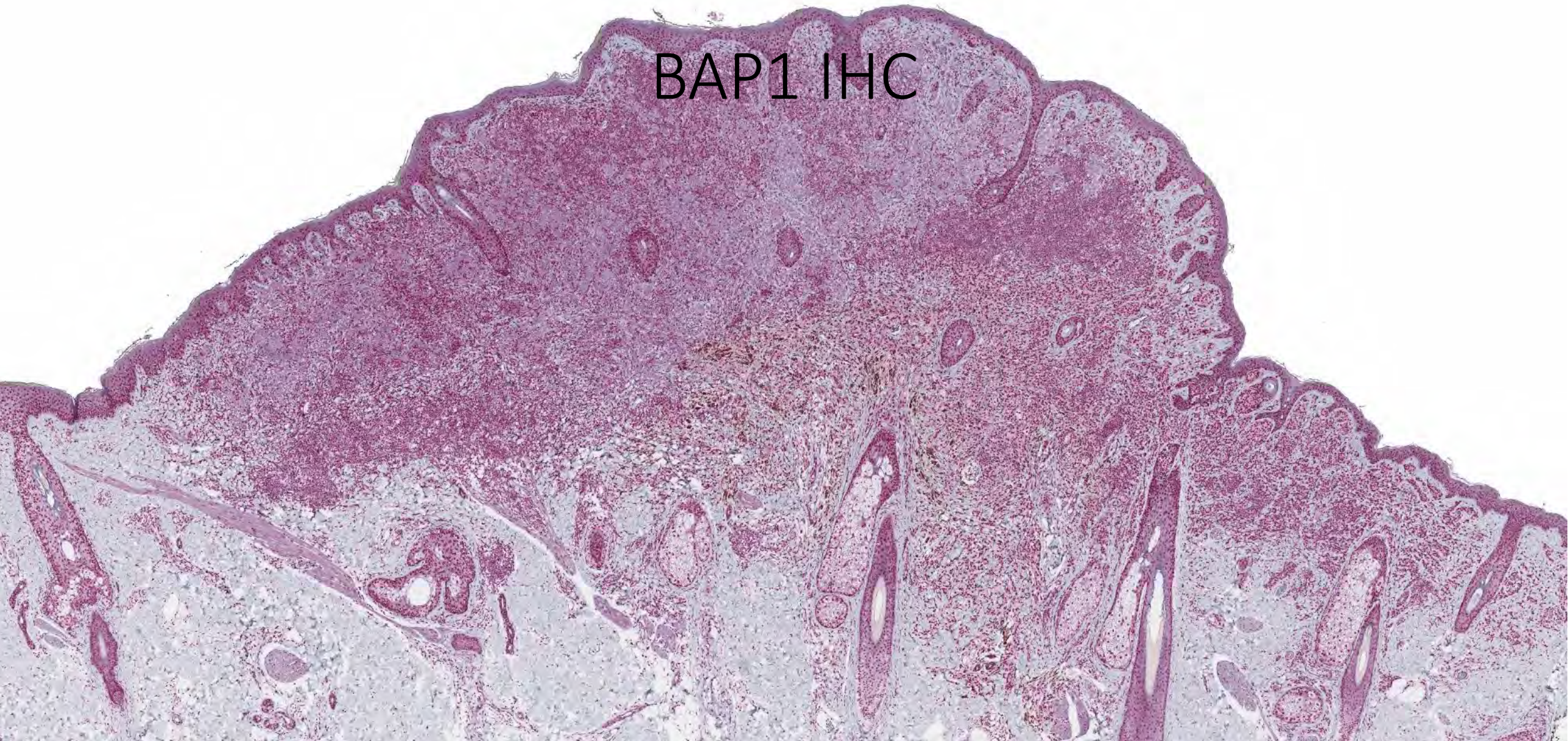
βcatenin IHC



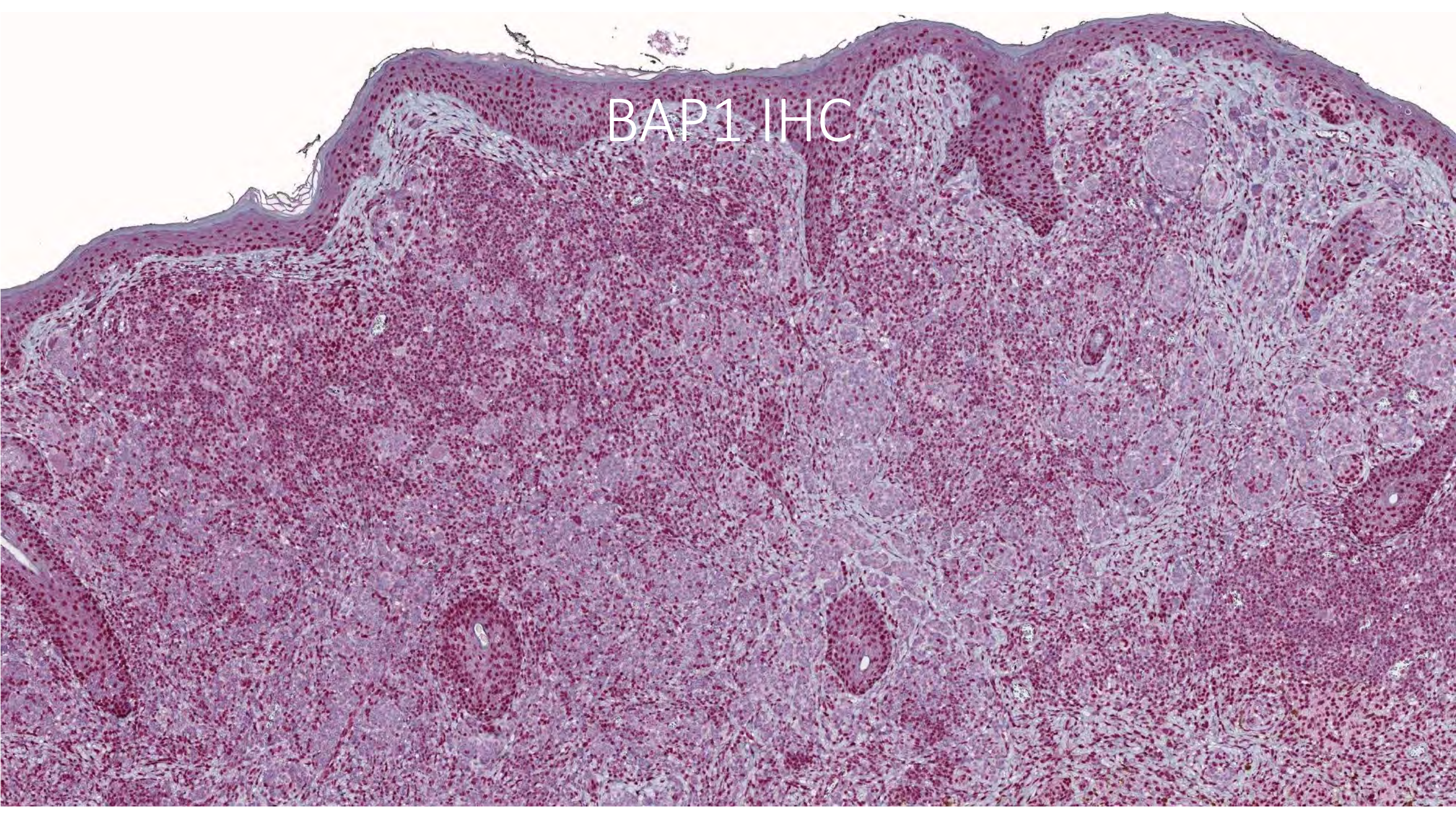
BRAF V600E IHC



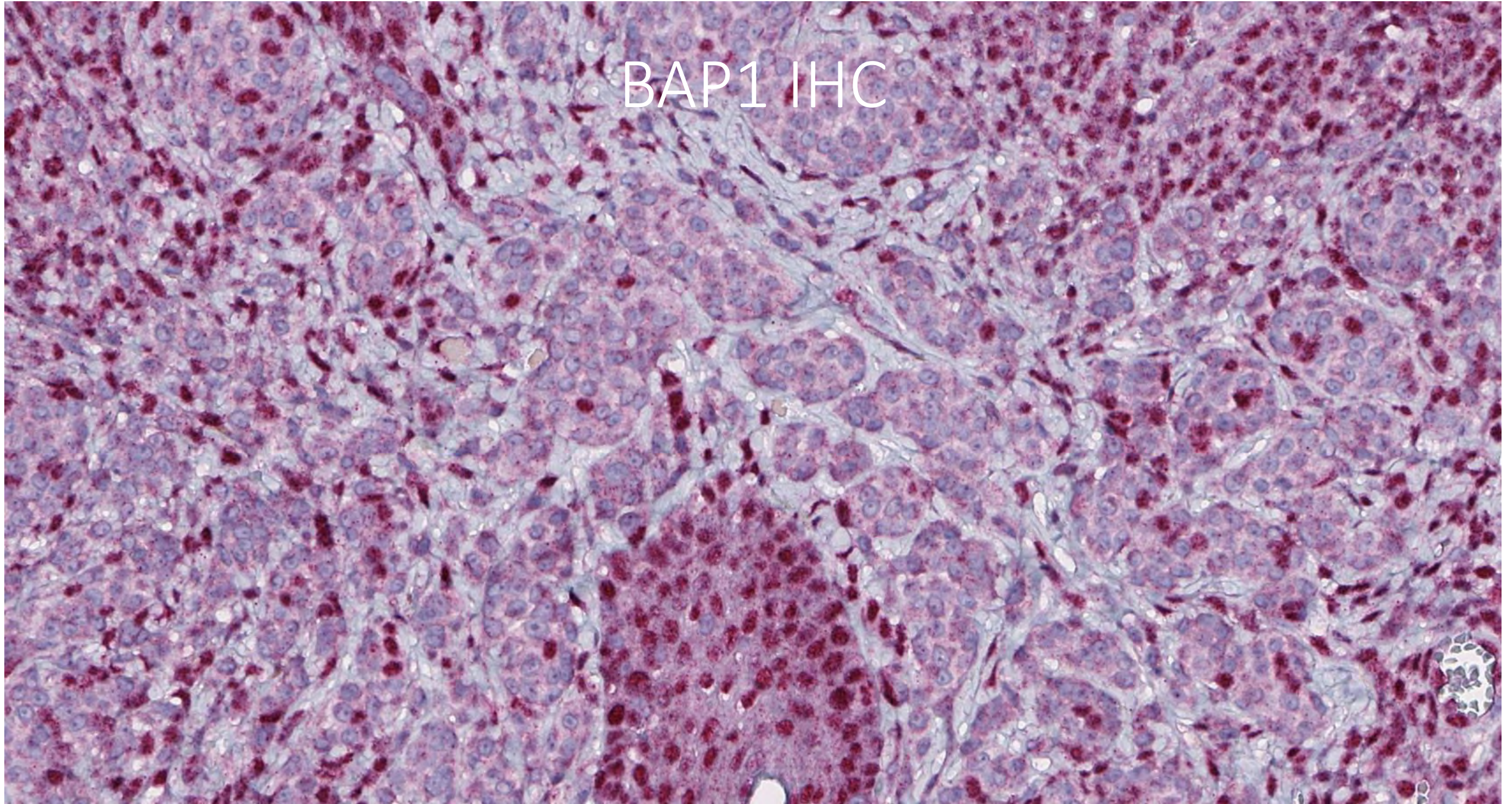
BAP1 IHC



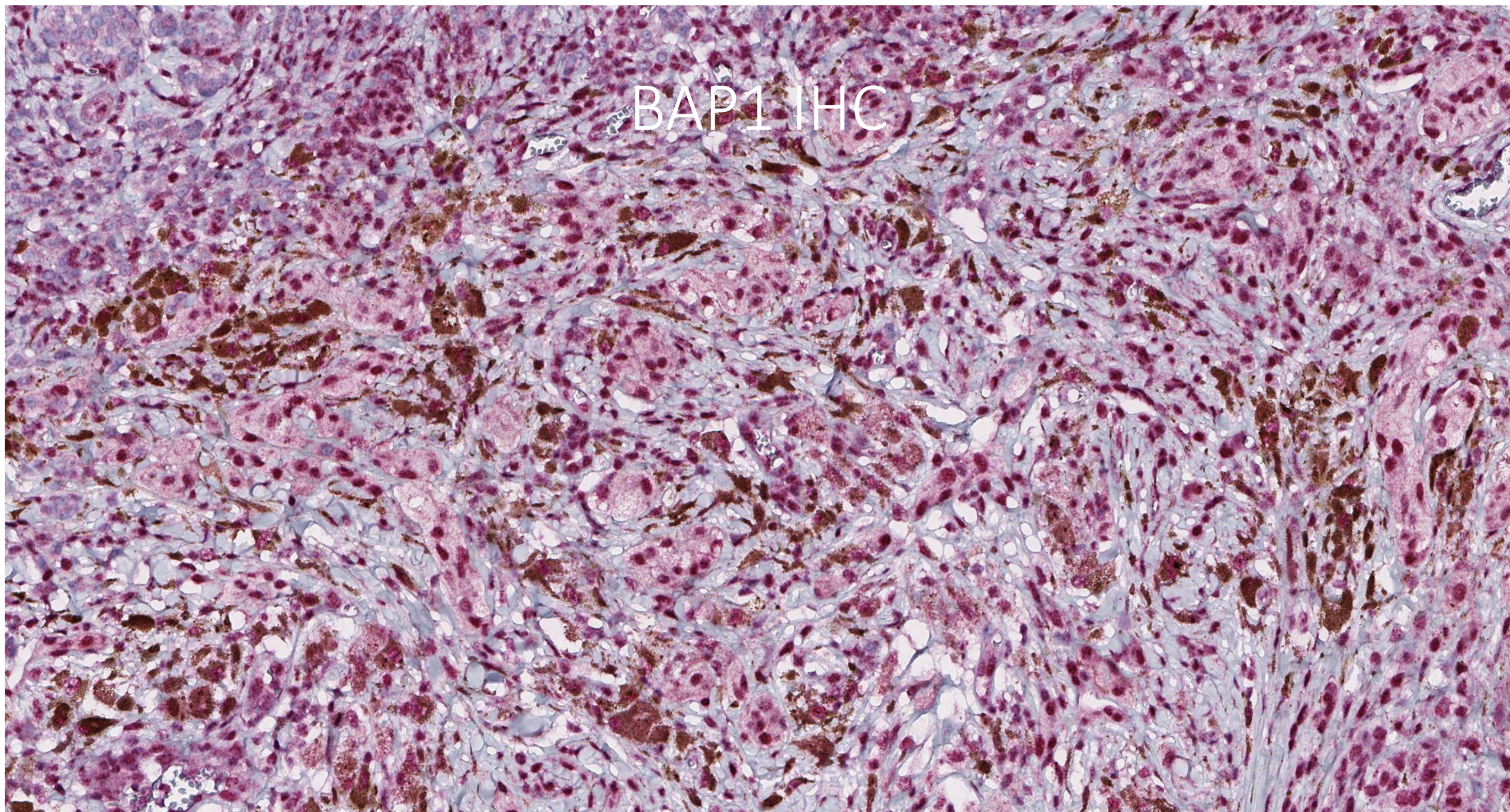
BAP1 IHC

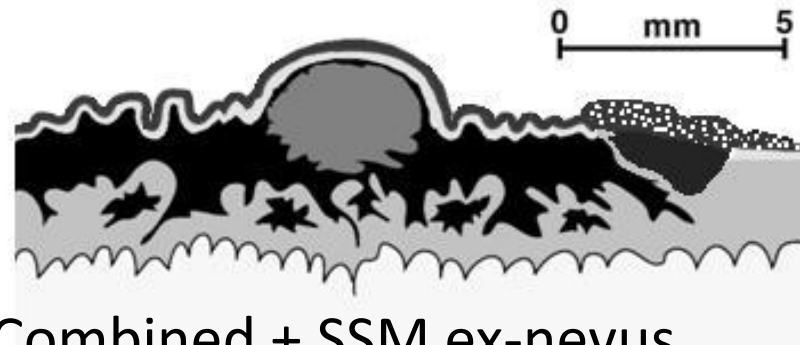


BAP1 IHC

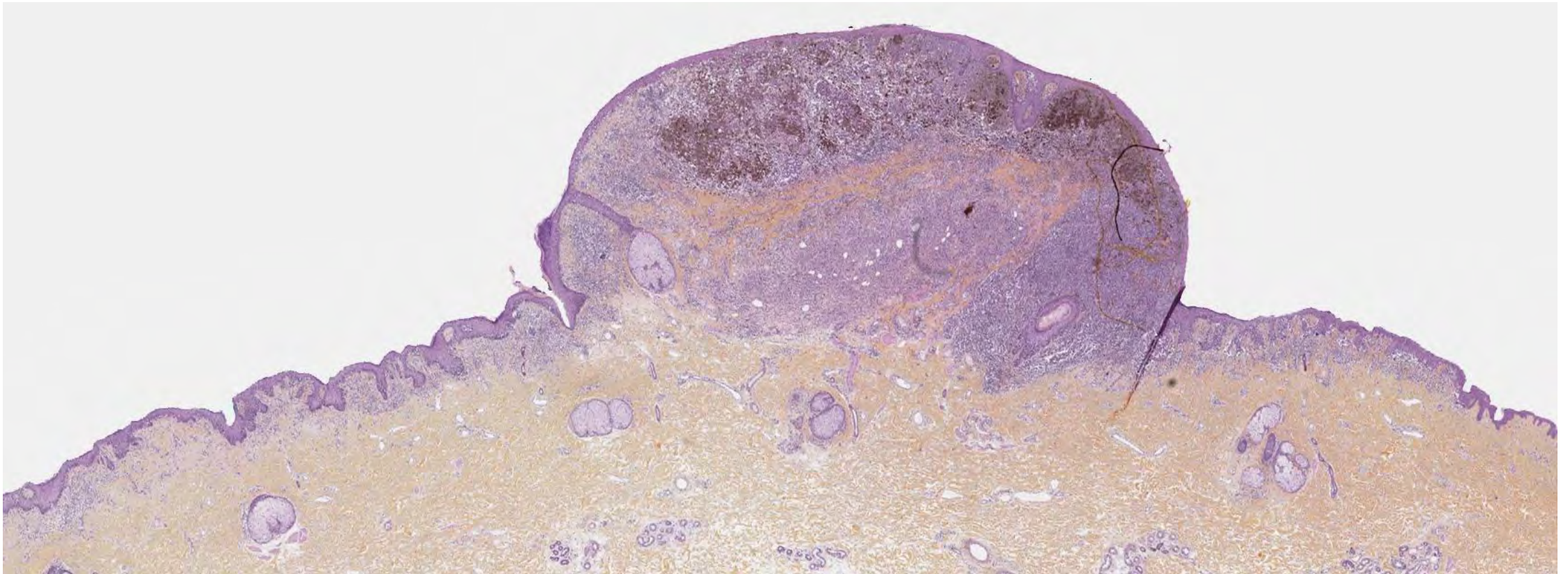


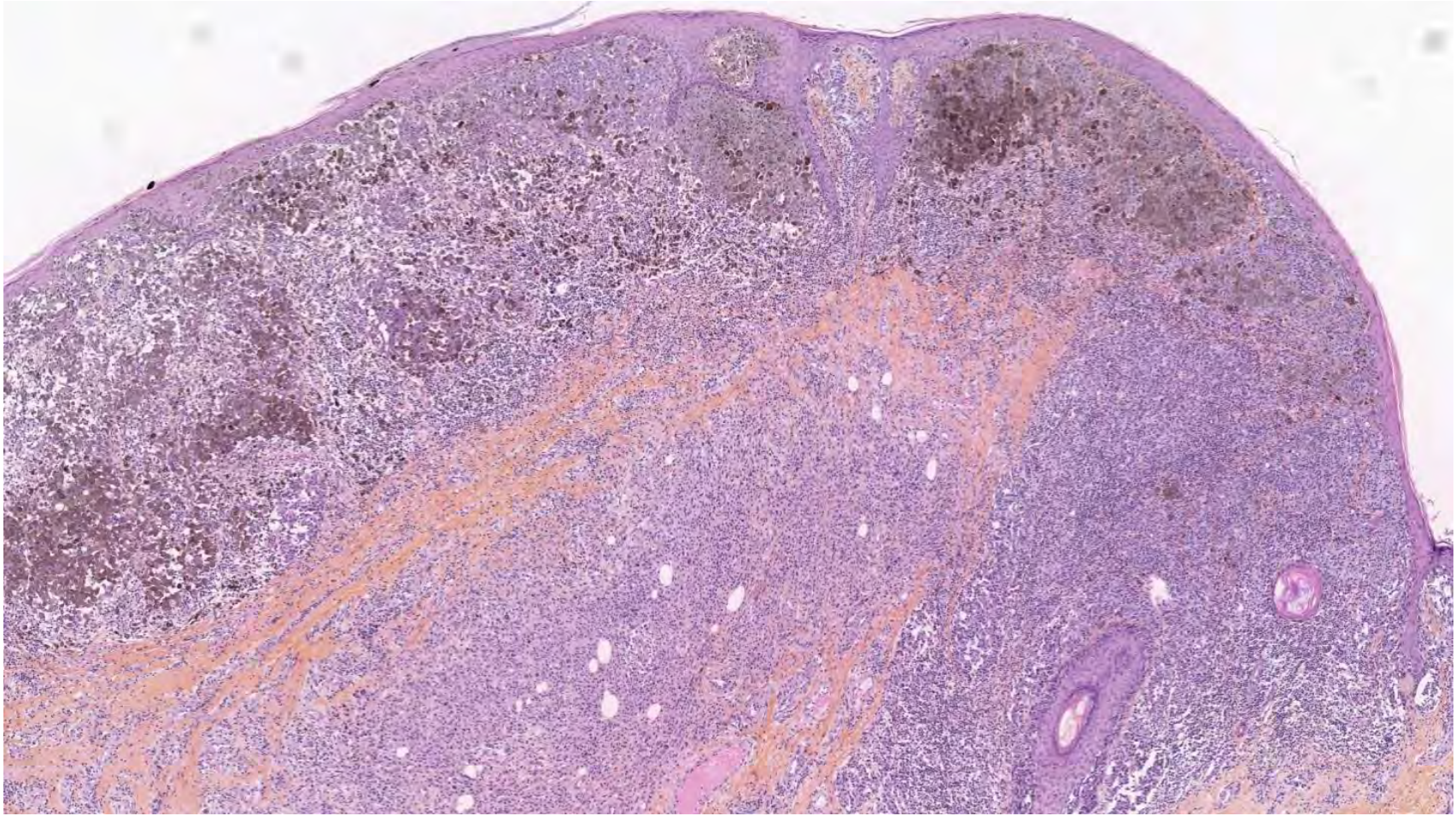
BAP1 IHC

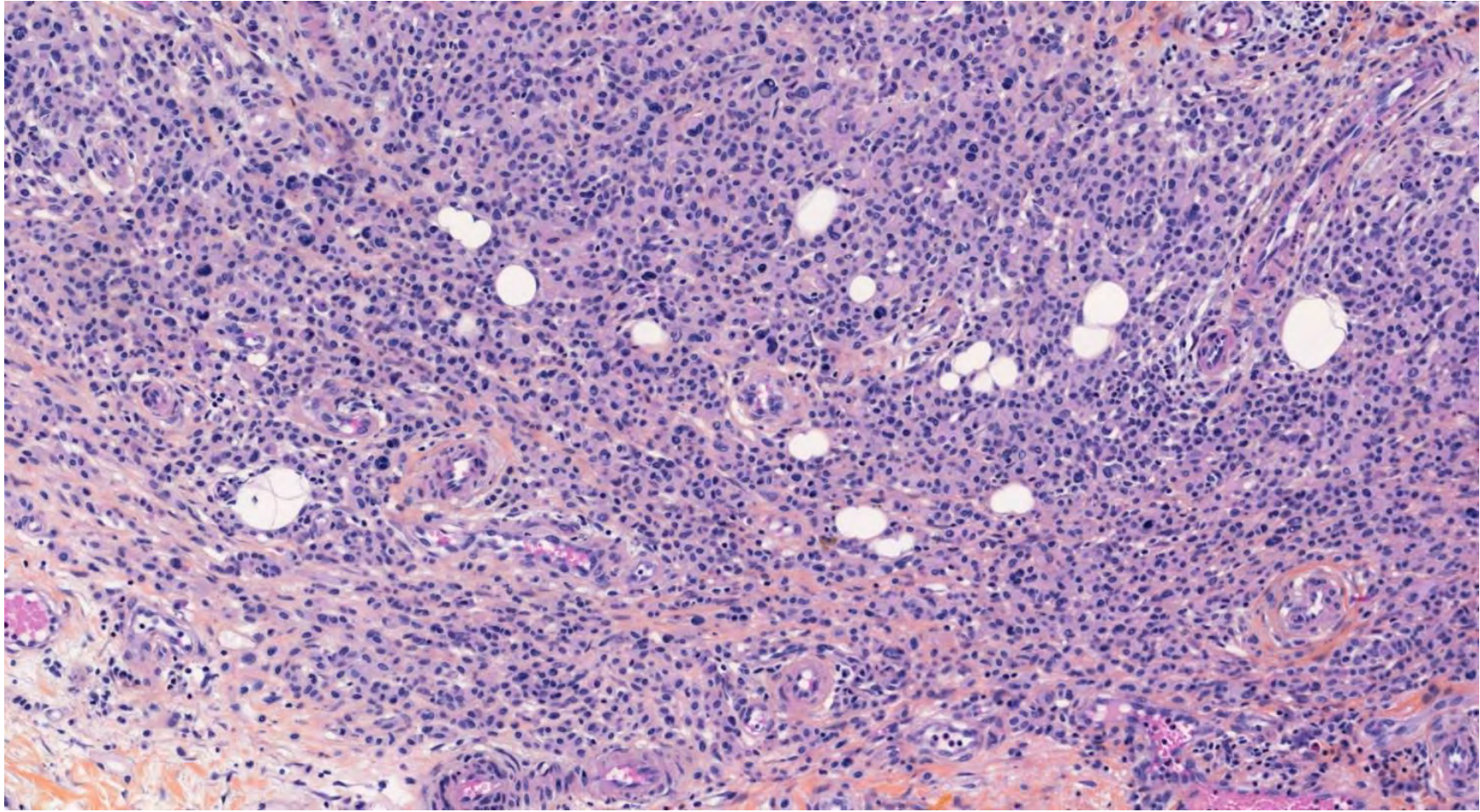


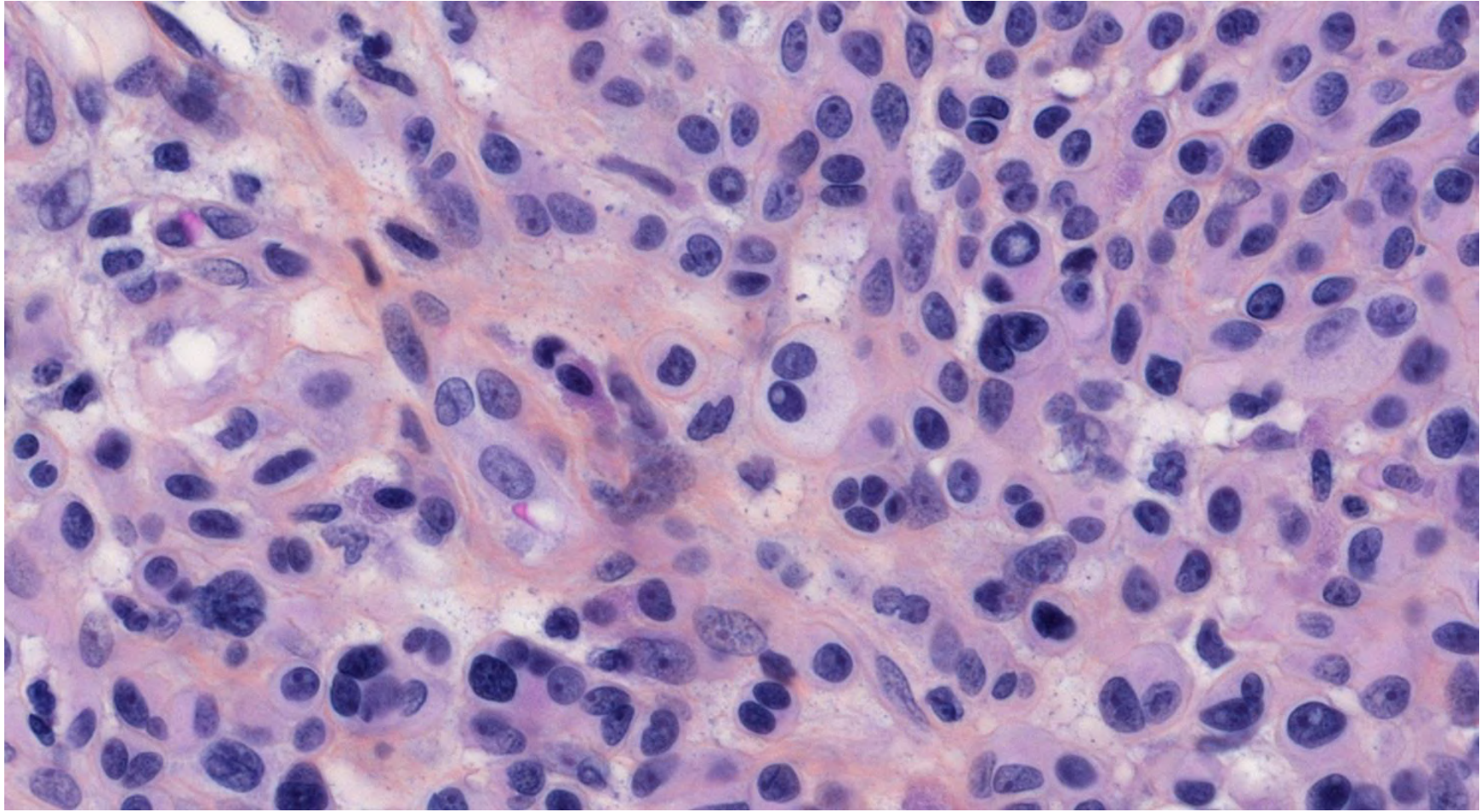


Combined + SSM ex-nevus

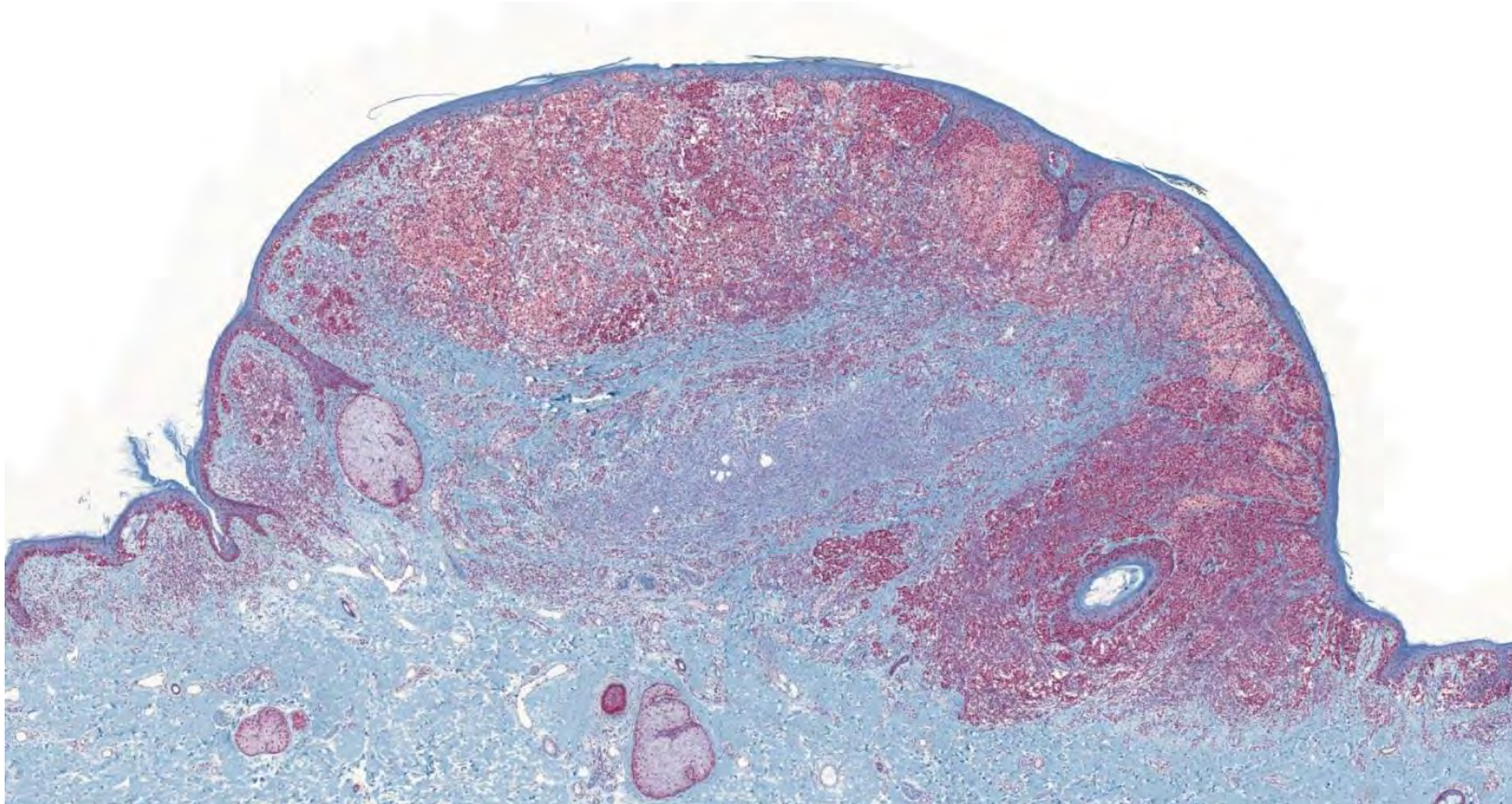




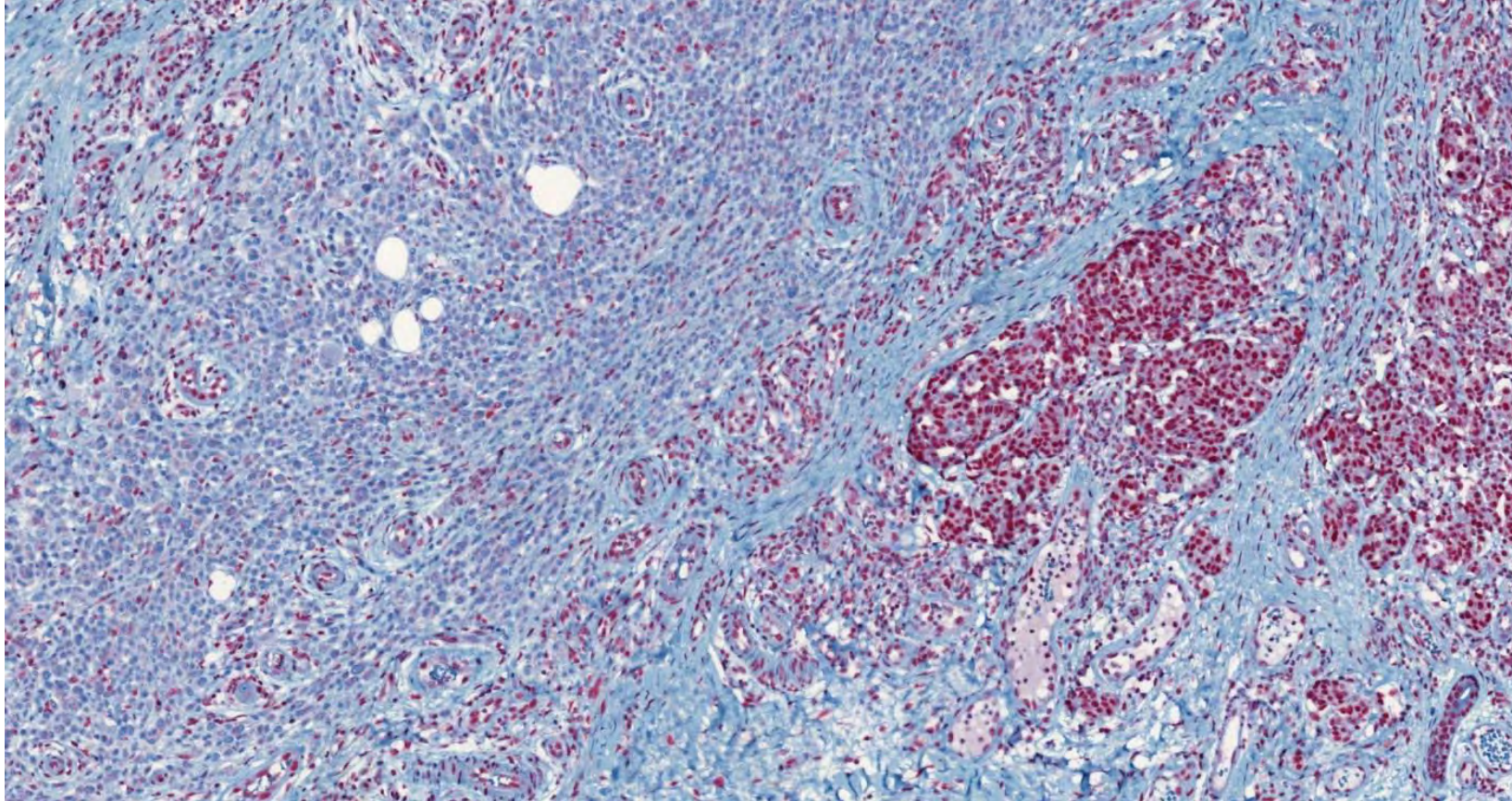




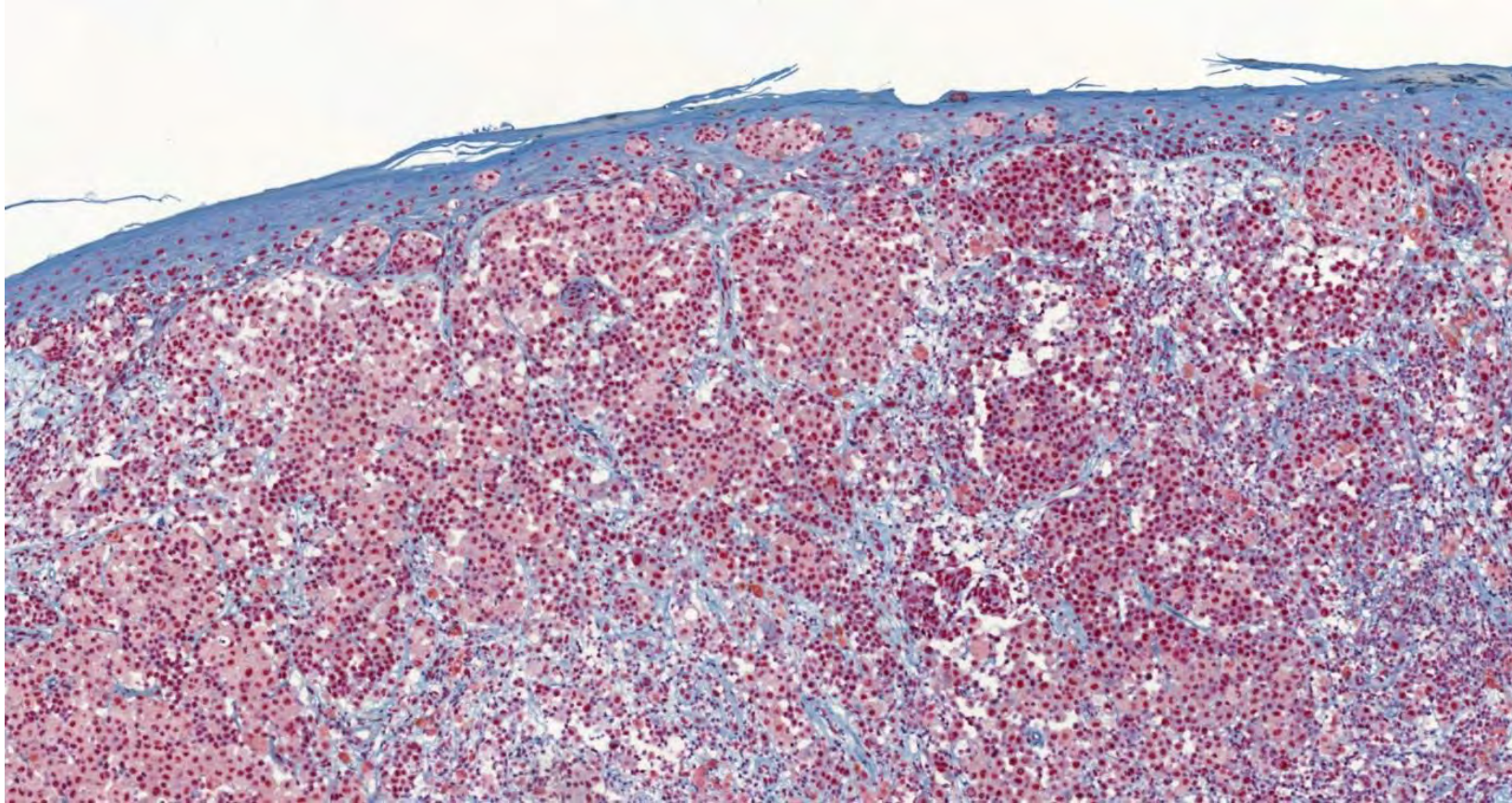
BAP1 IHC



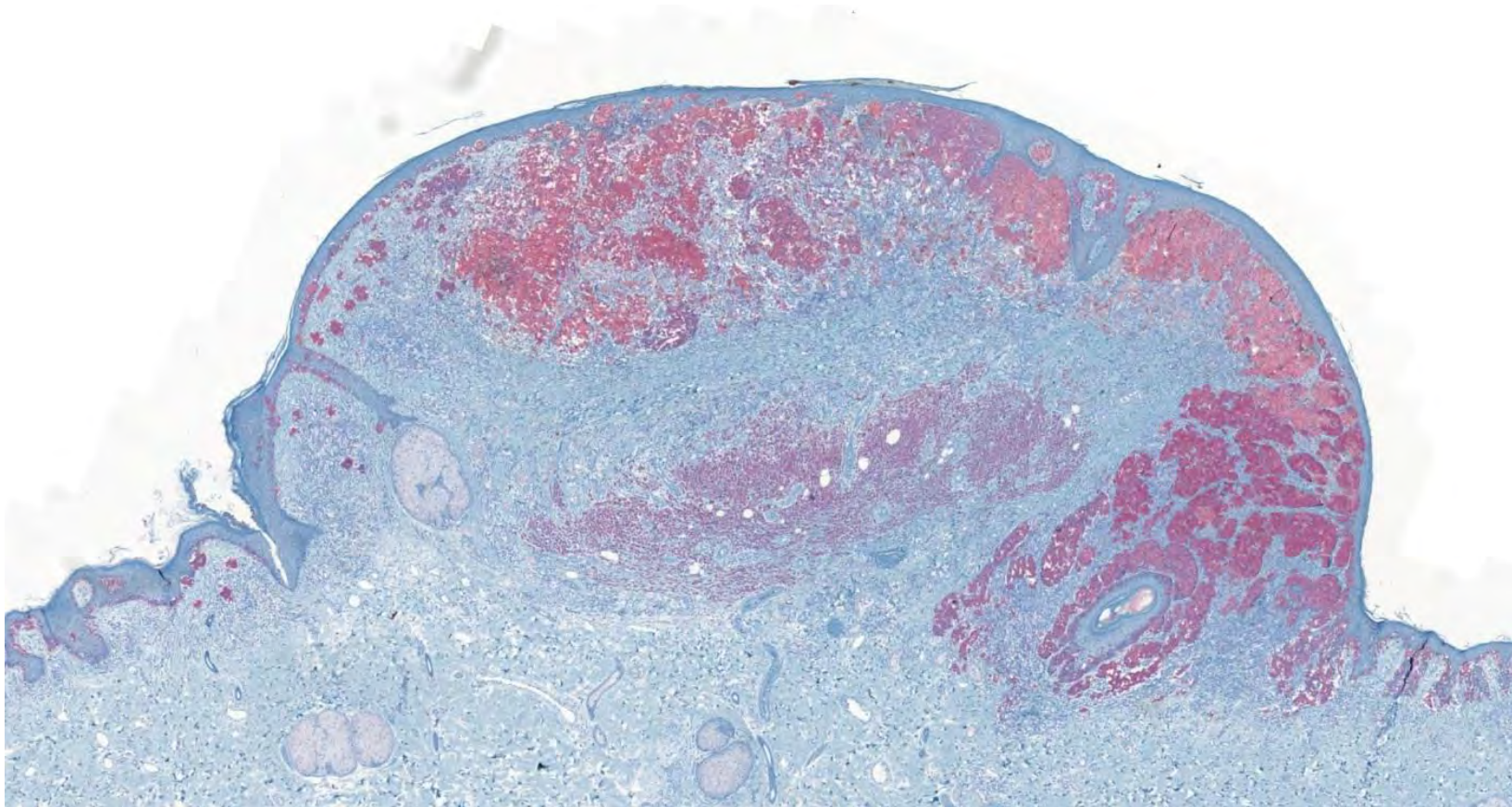
BAP1 IHC



BAP1 IHC



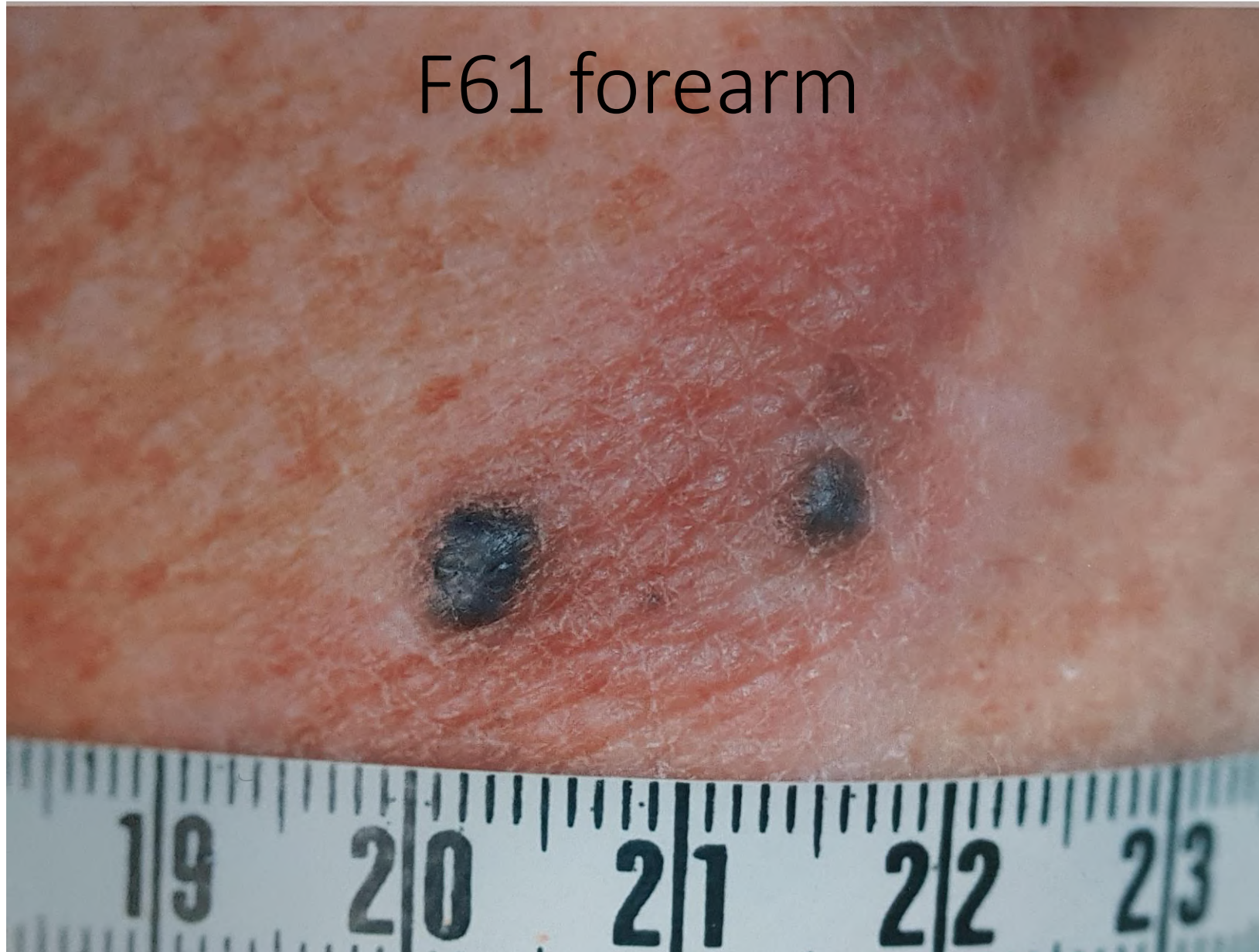
BRAF IHC

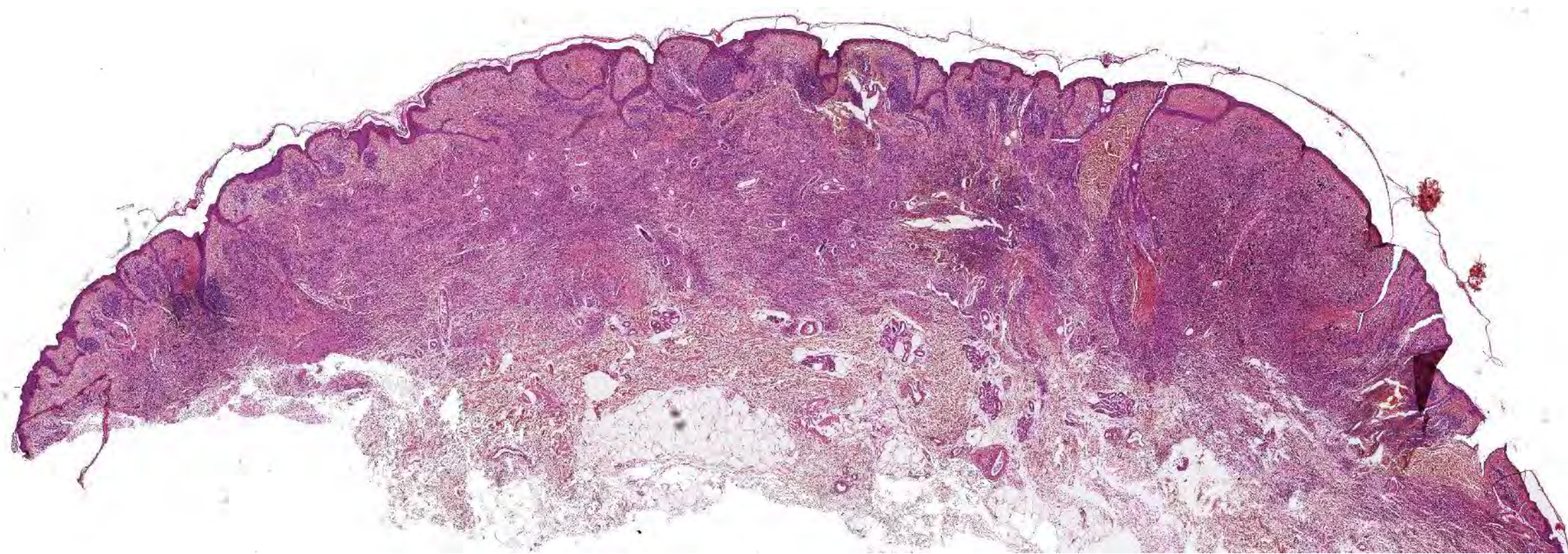


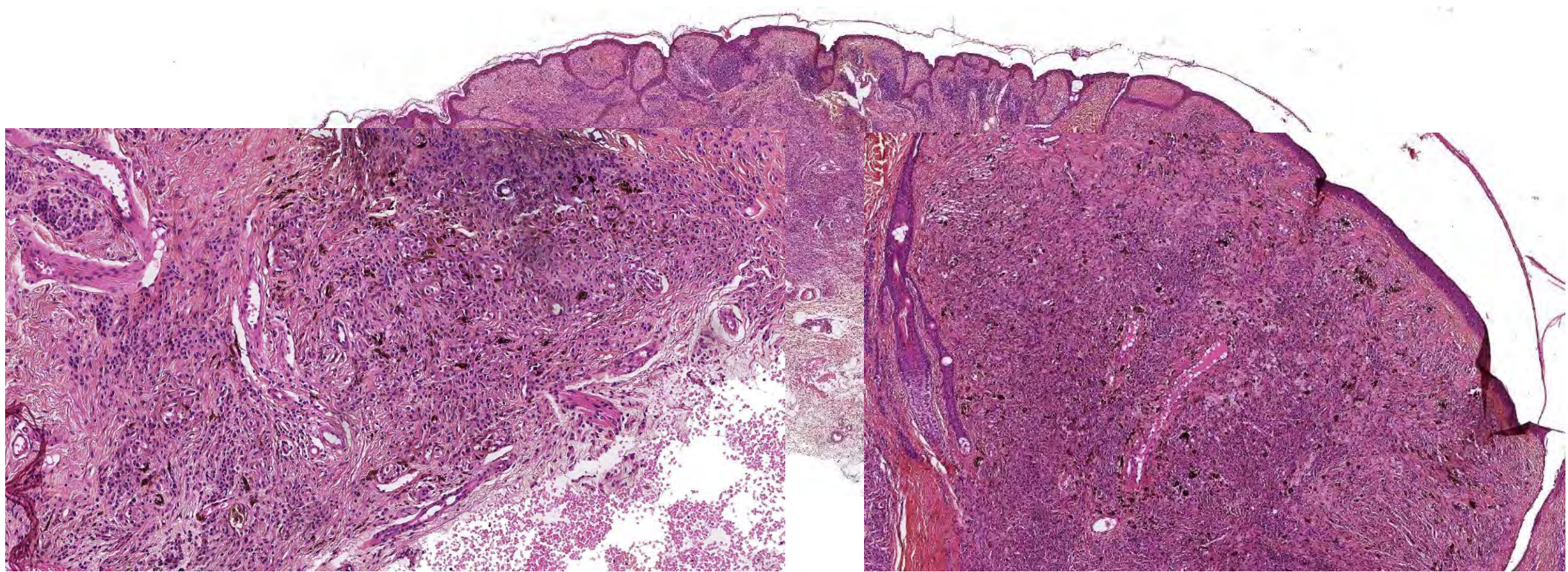
Double combined nevus



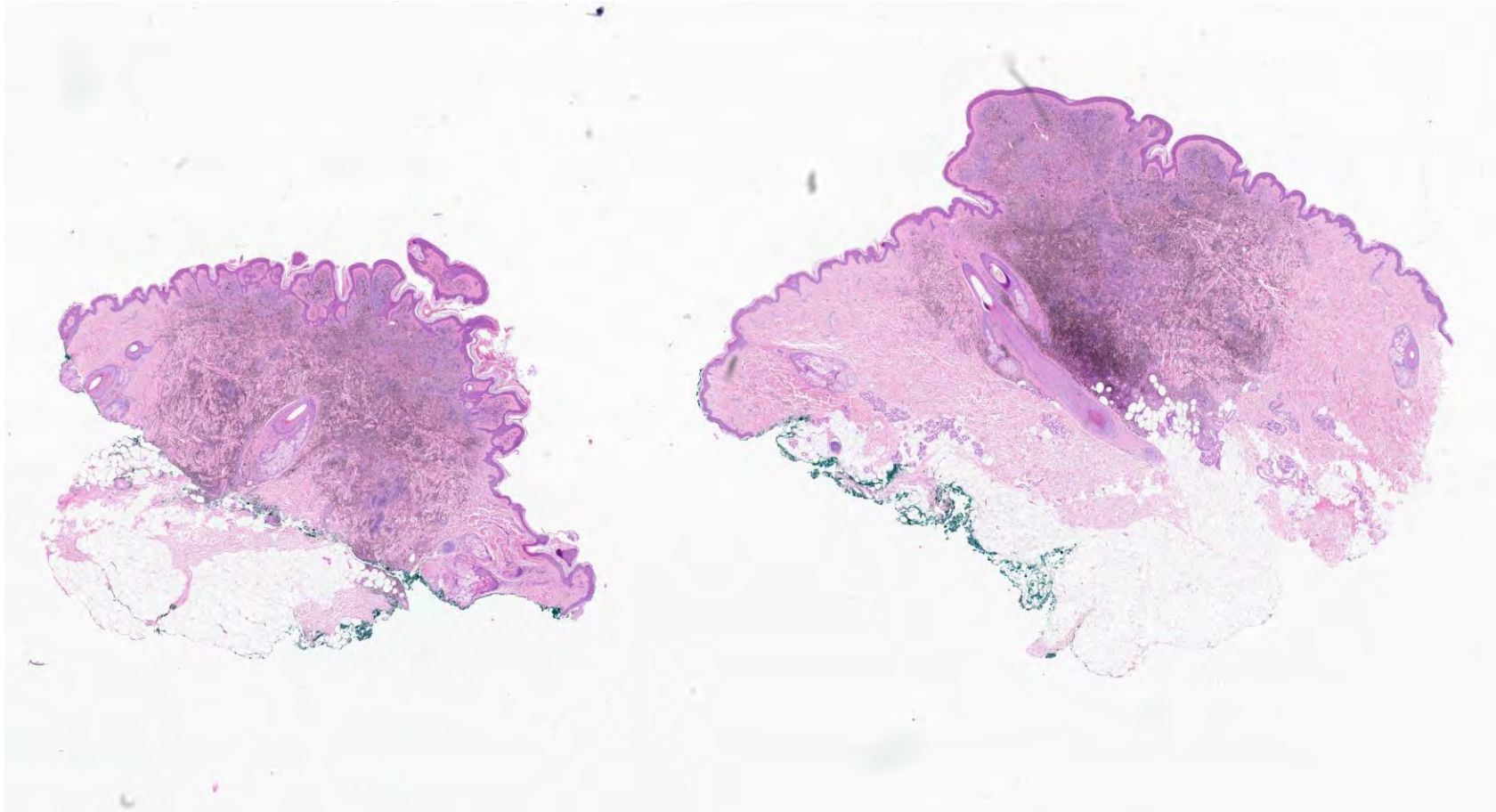
F61 forearm

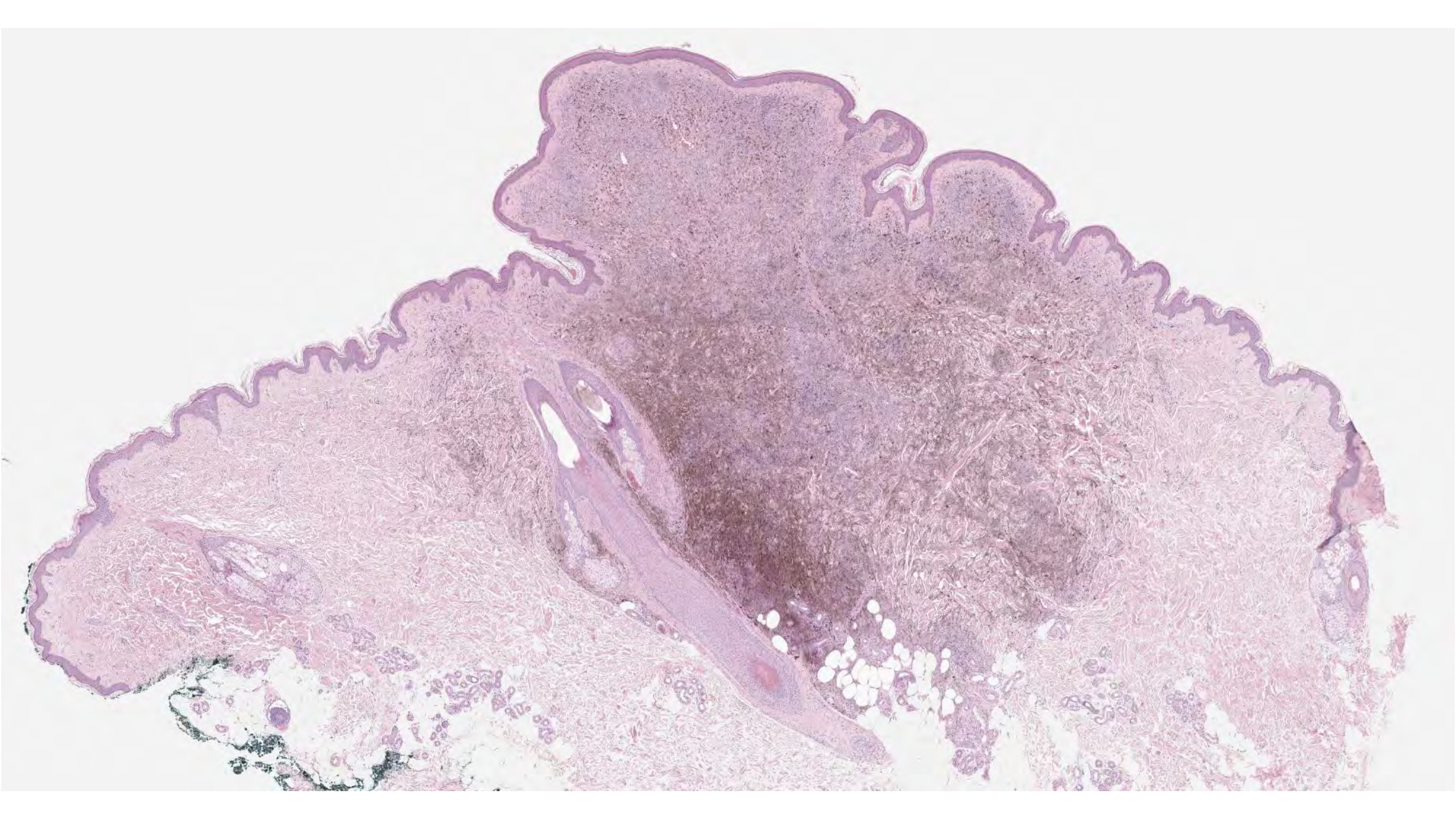


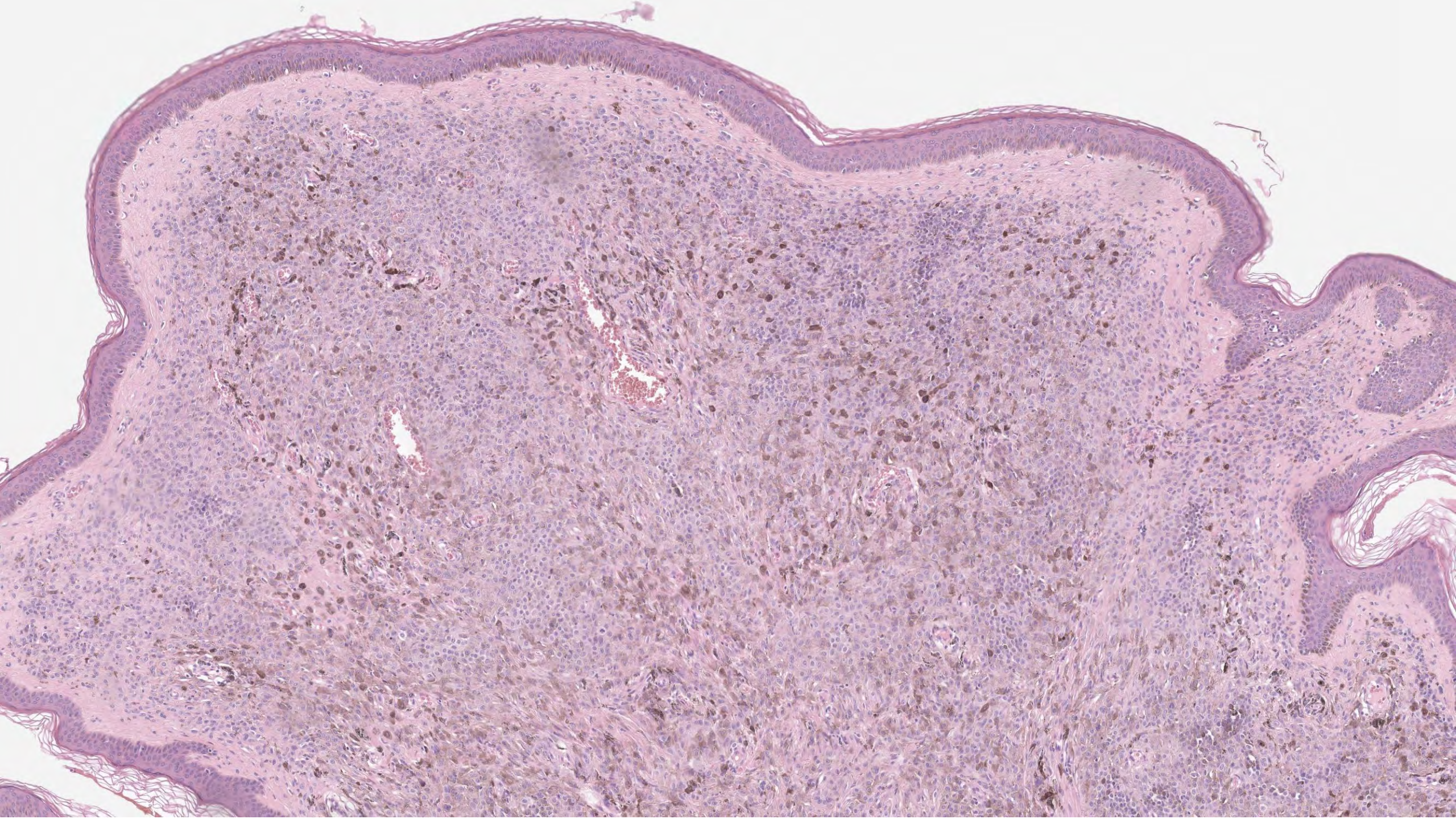


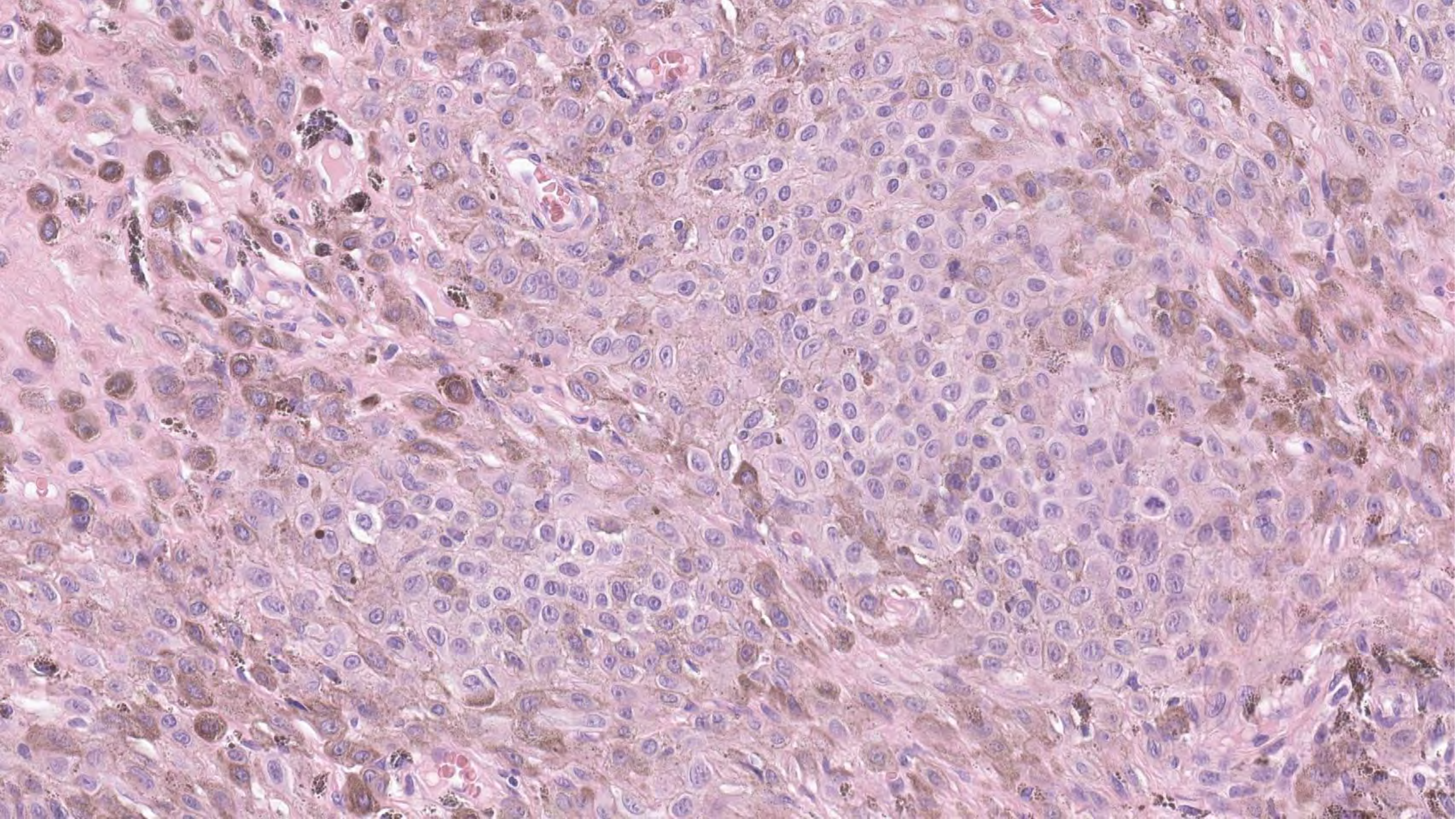


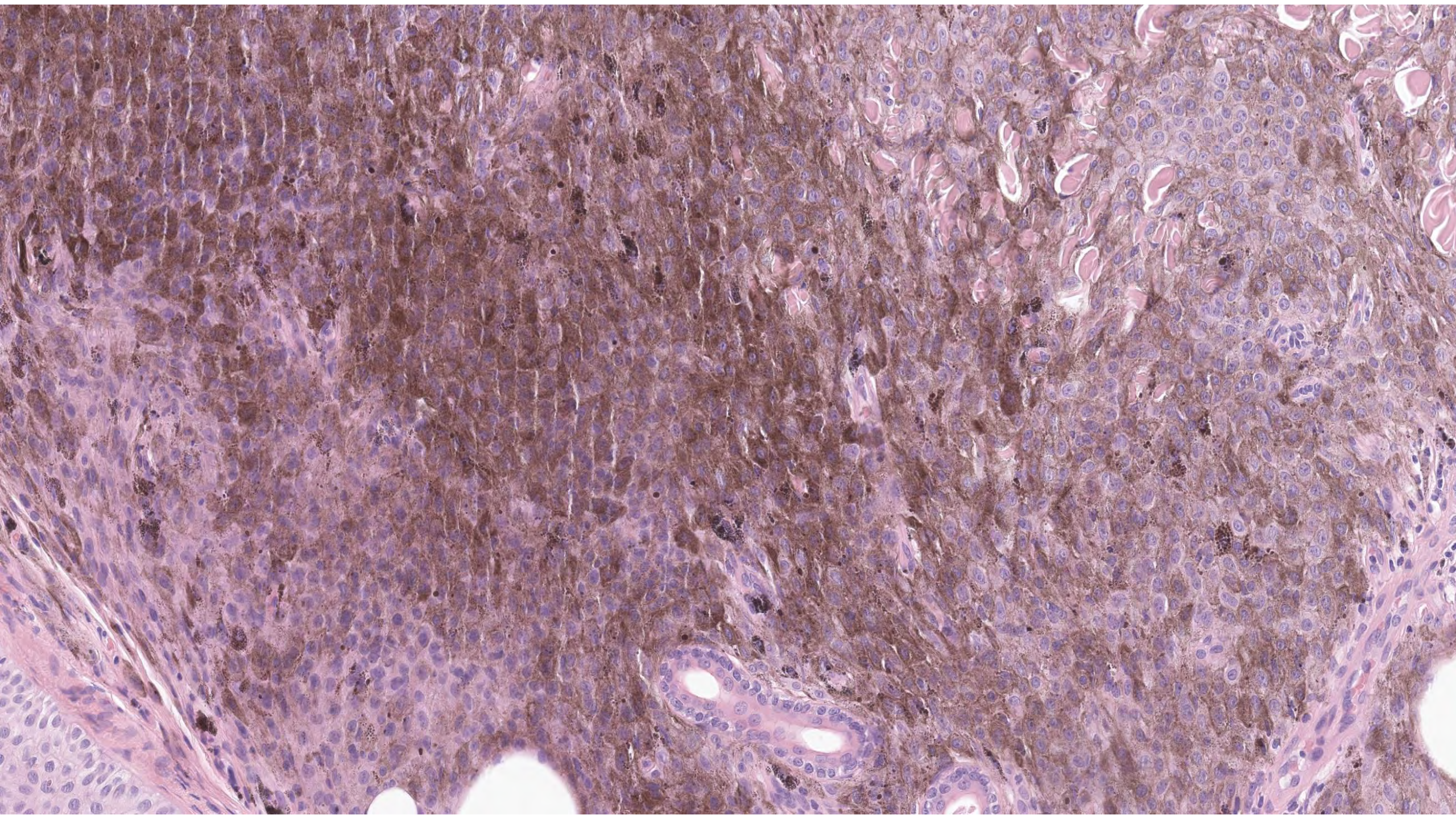
Case N°17 M25 forearm











IHC/Molecular results

- MelanA, Sox10, CCND1 Diffuse
- Bcatenin, BRAF V600E, negative
- P16 positive

Final diagnosis

- Blue nevus with PKC fusion

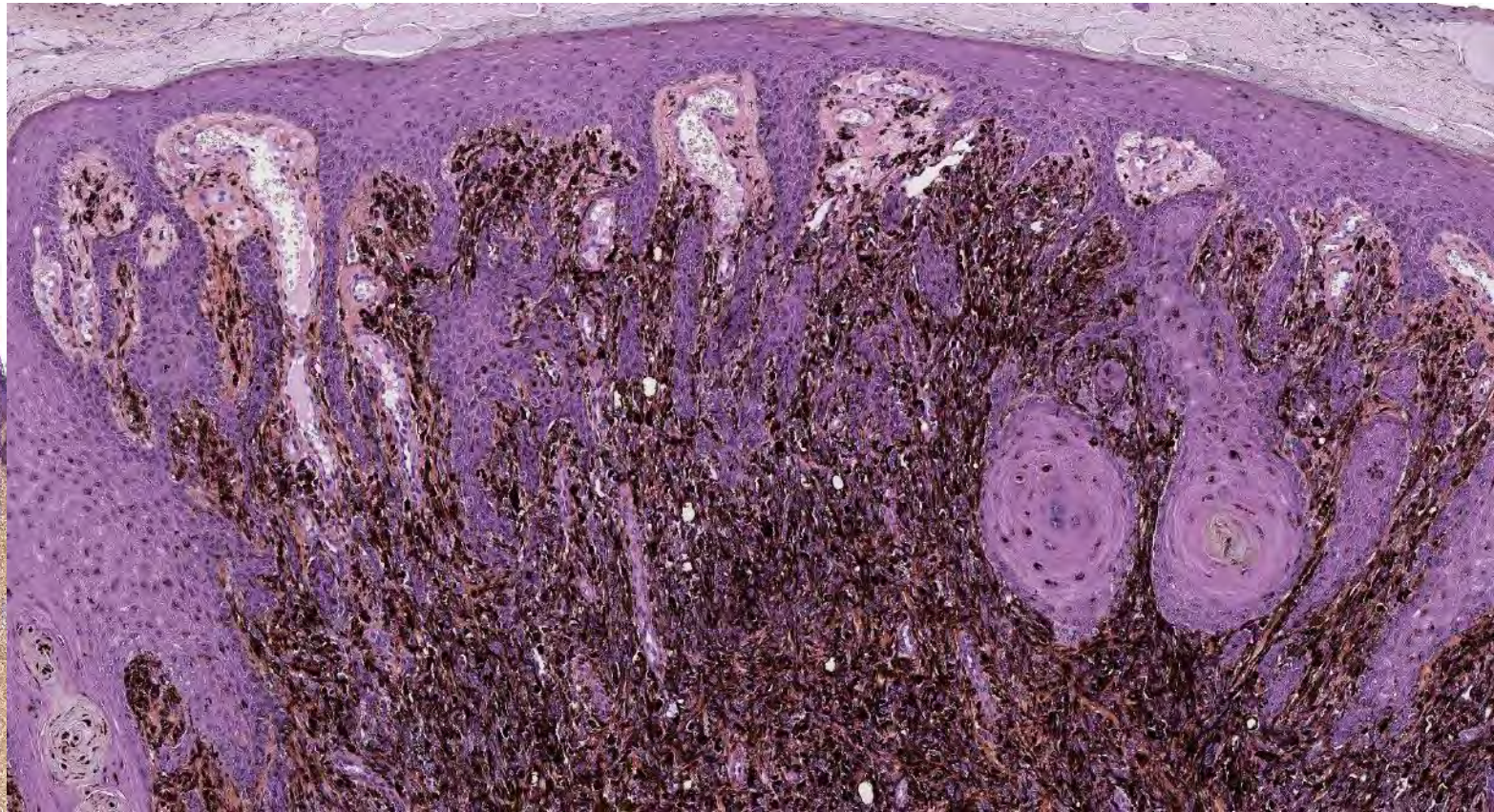
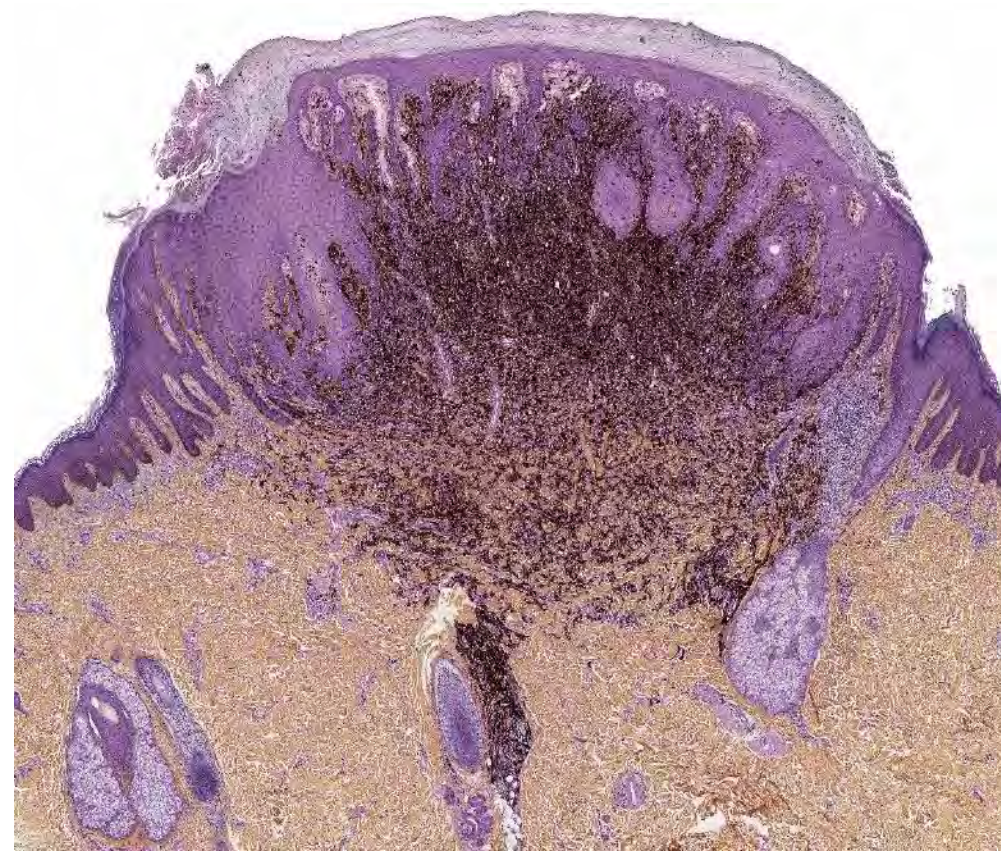
PKC gene fused melanocytic tumors

highly variable morphology

- Junctional PEM-like features
 - Upper dermis horizontal band
 - Dermal combined blue nevus features
 - Smooth muscle hyperplasia
 - Variable pigment load
 - Variable but constant fibrosis
-
- « PEM + Common + Blue » mixture suggests PKC gene fused tumour
 - Can have partial features and/or extreme ends of the spectrums

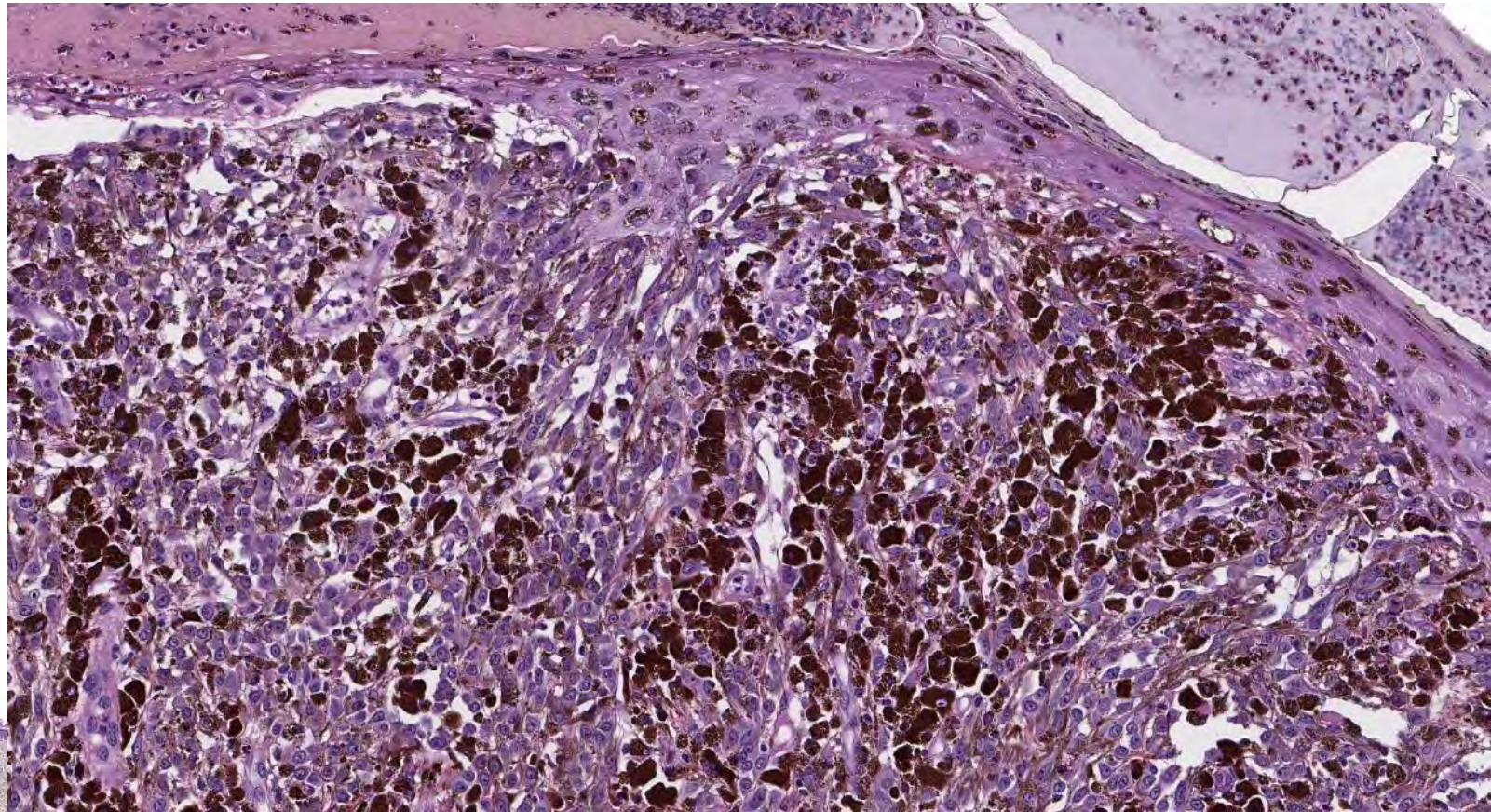
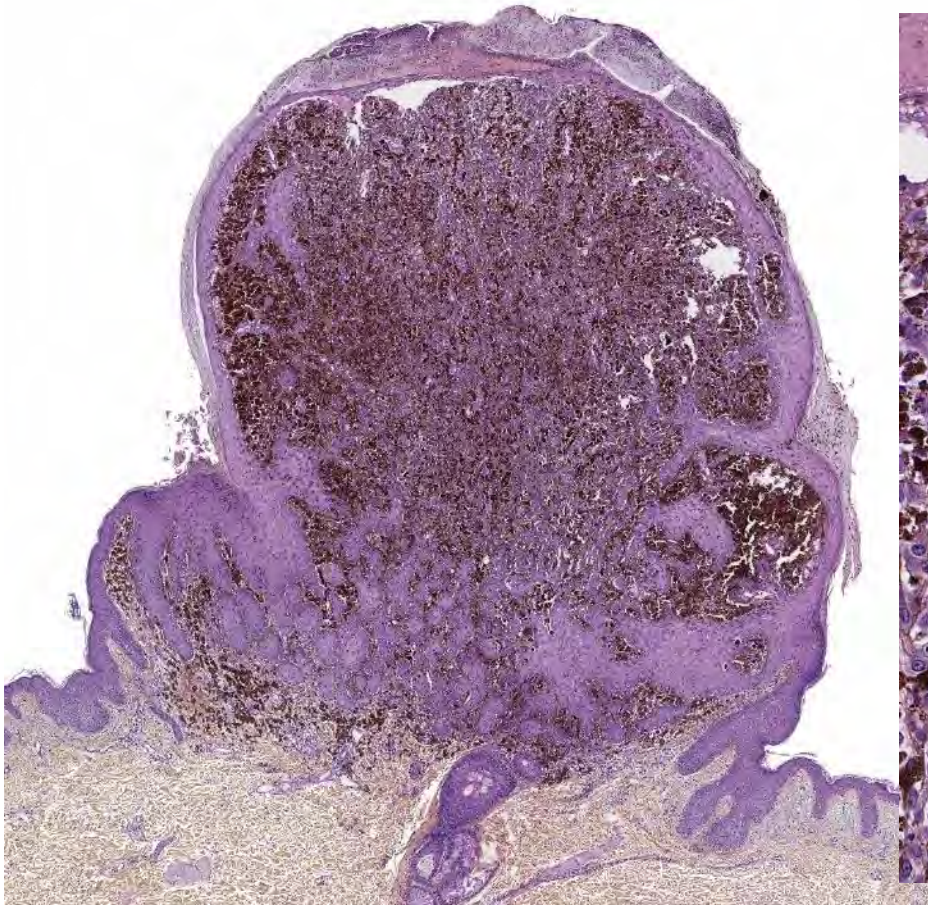
PKC gene fused melanocytic tumors

Junctional PEM-like features



PKC gene fused melanocytic tumors

Junctional PEM-like features



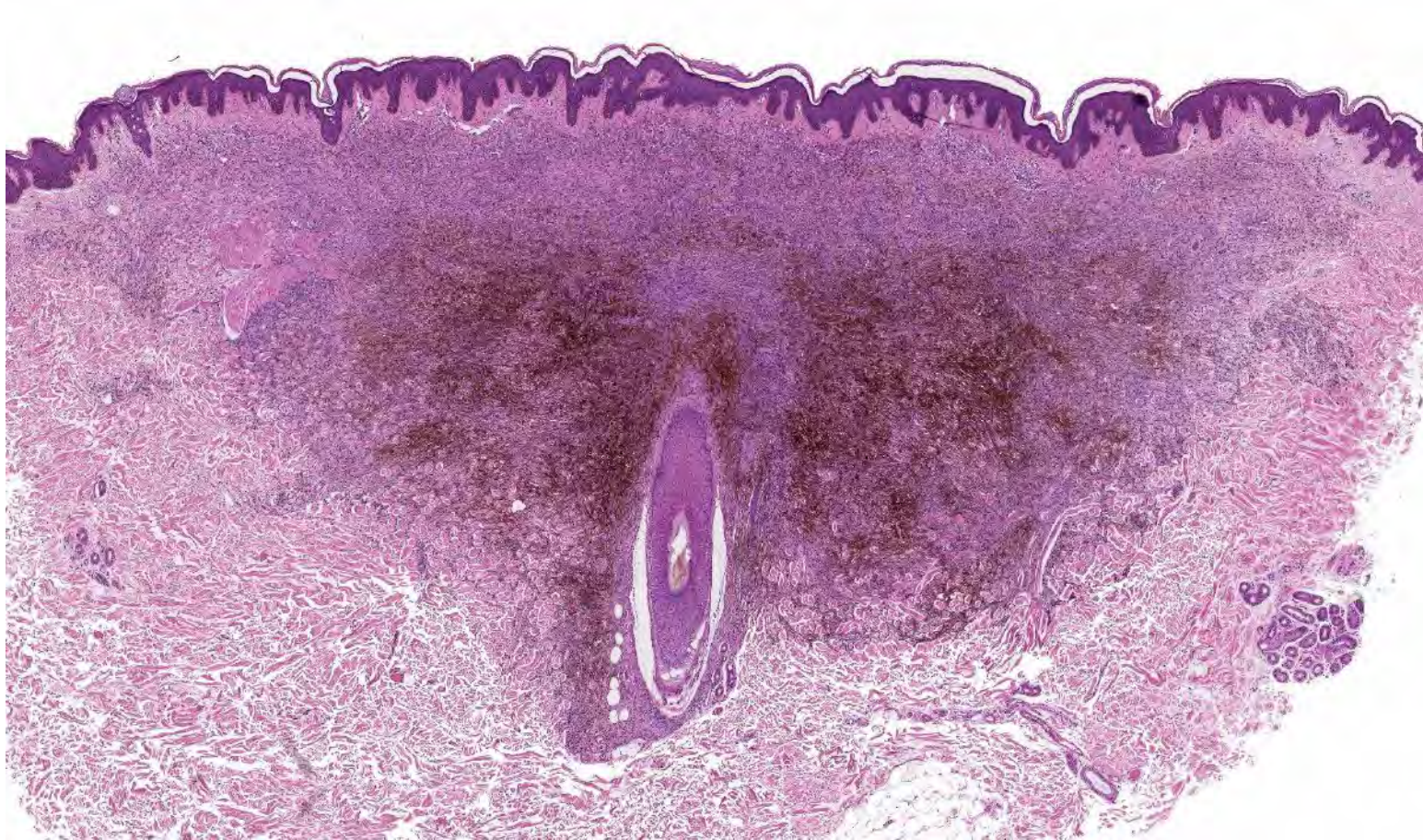
PKC gene fused melanocytic tumors

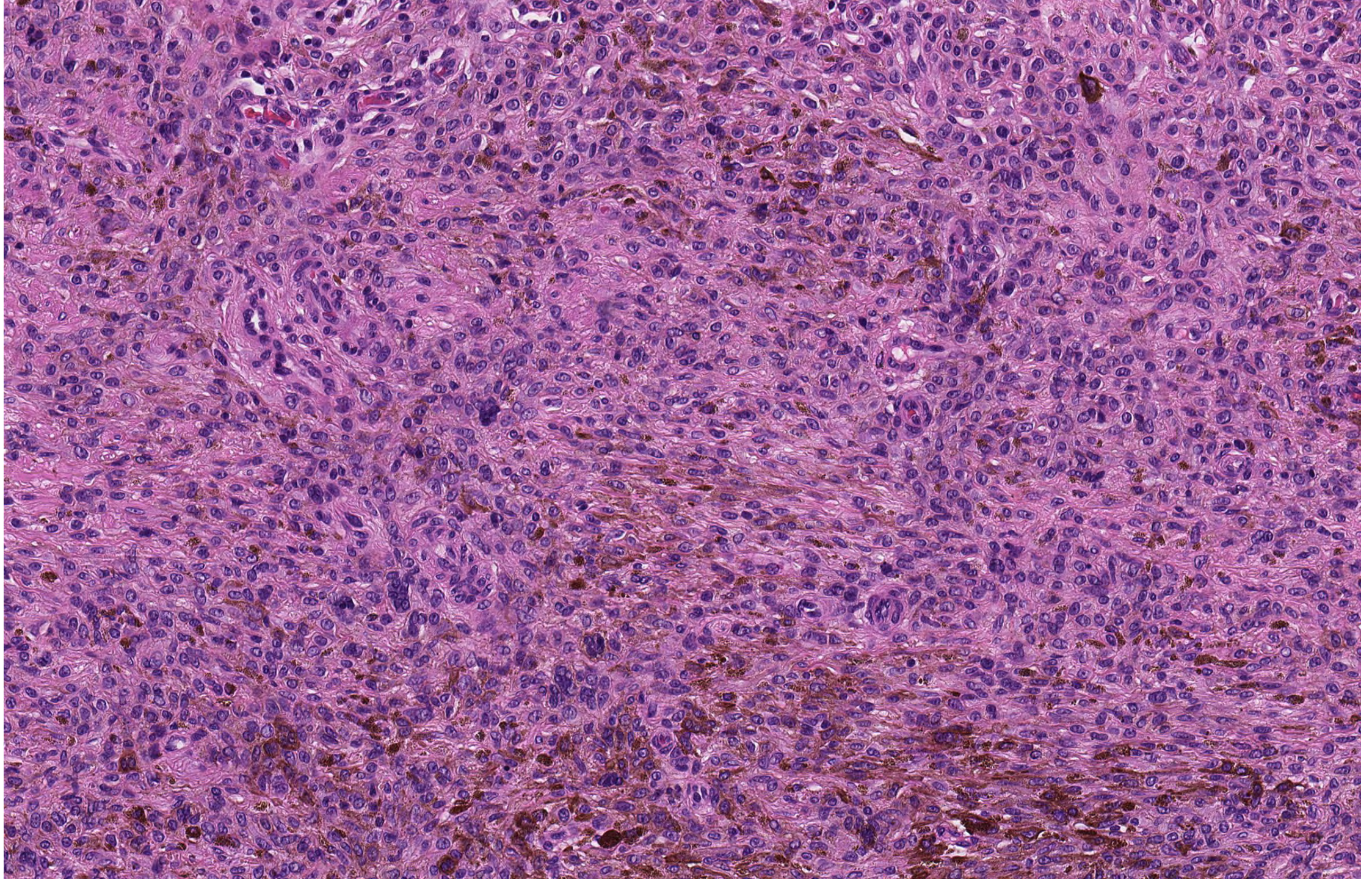
Upper dermis horizontal band

- Horizontal band of nevocytoid melanocytes
- Separated from the epidermis by a grenz zone
- Less pigmented than the rest of the tumor
- Interweaved at the bottom with pigmented dendritic melanocytes

PKC gene fused melanocytic tumors

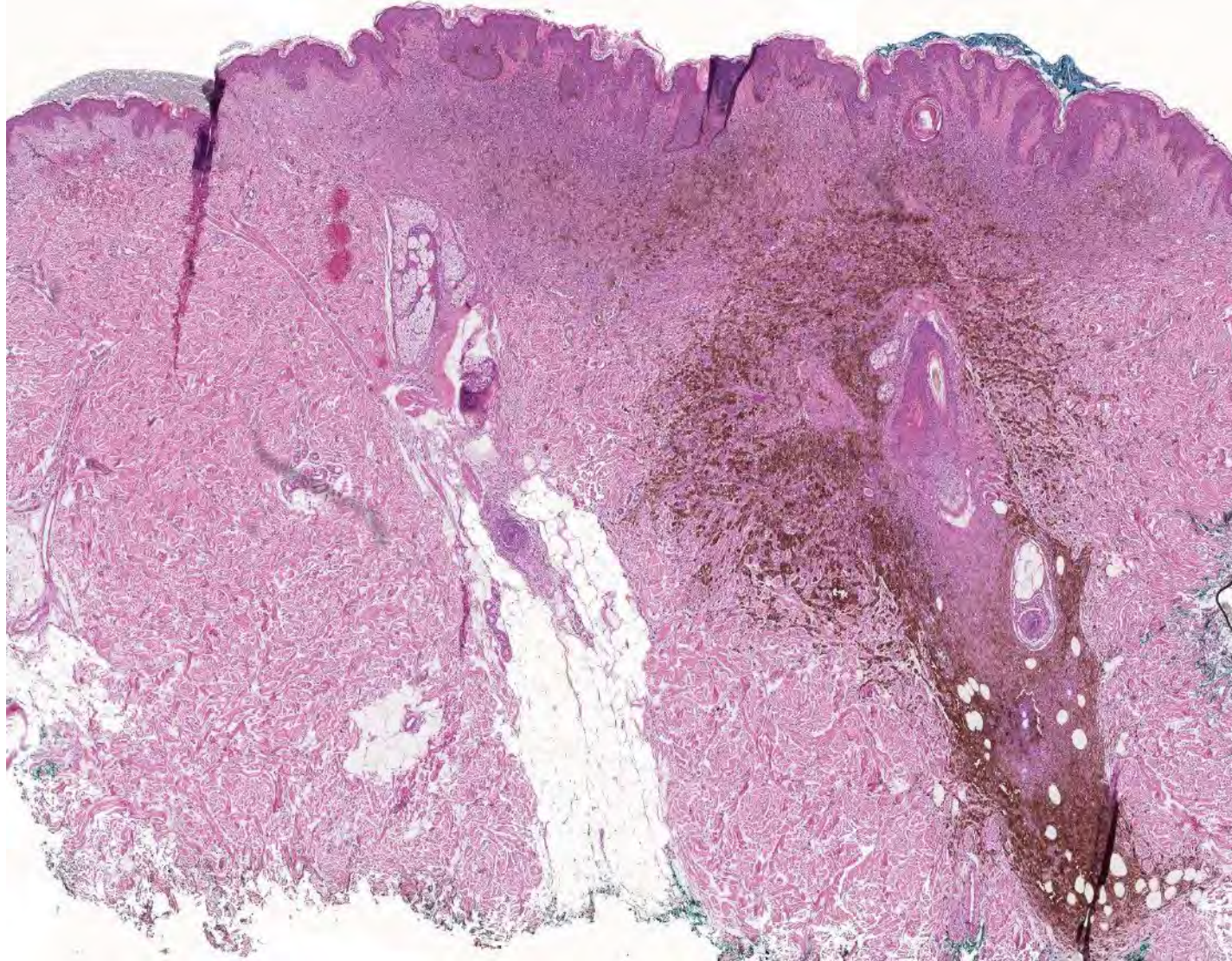
Upper dermis horizontal band





PKC gene fused melanocytic tumors

Upper dermis horizontal band



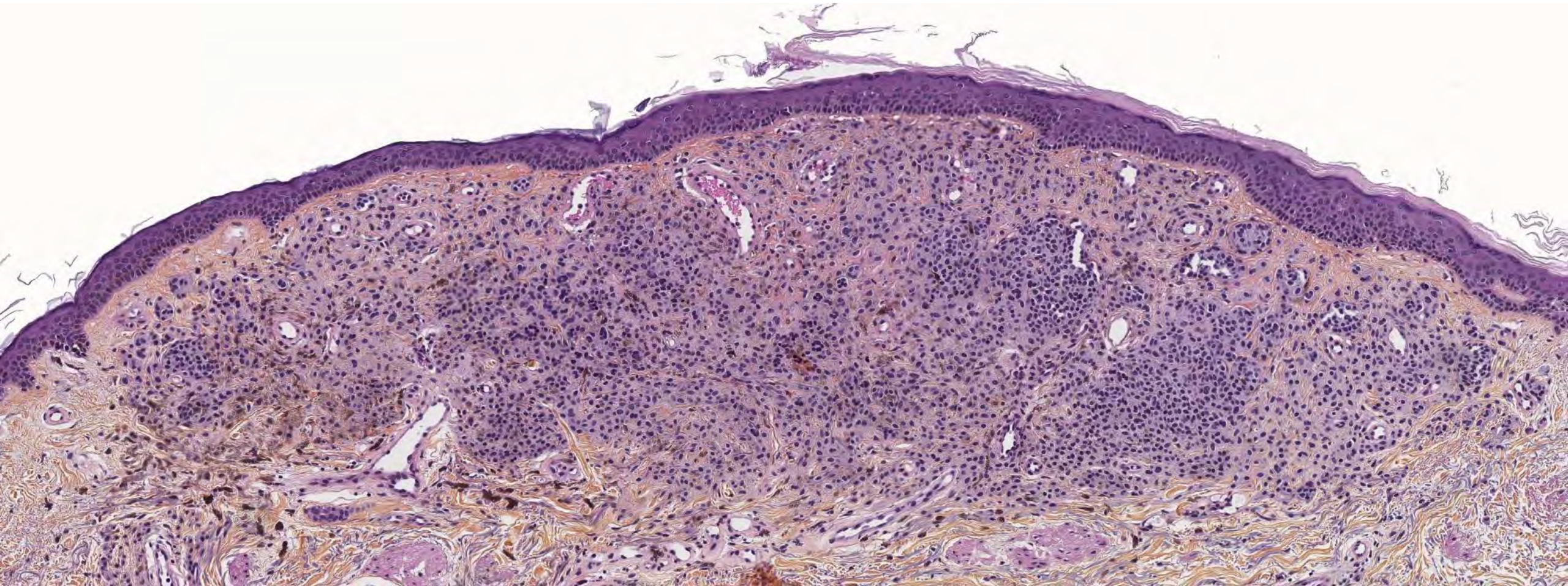
PKC gene fused melanocytic tumors

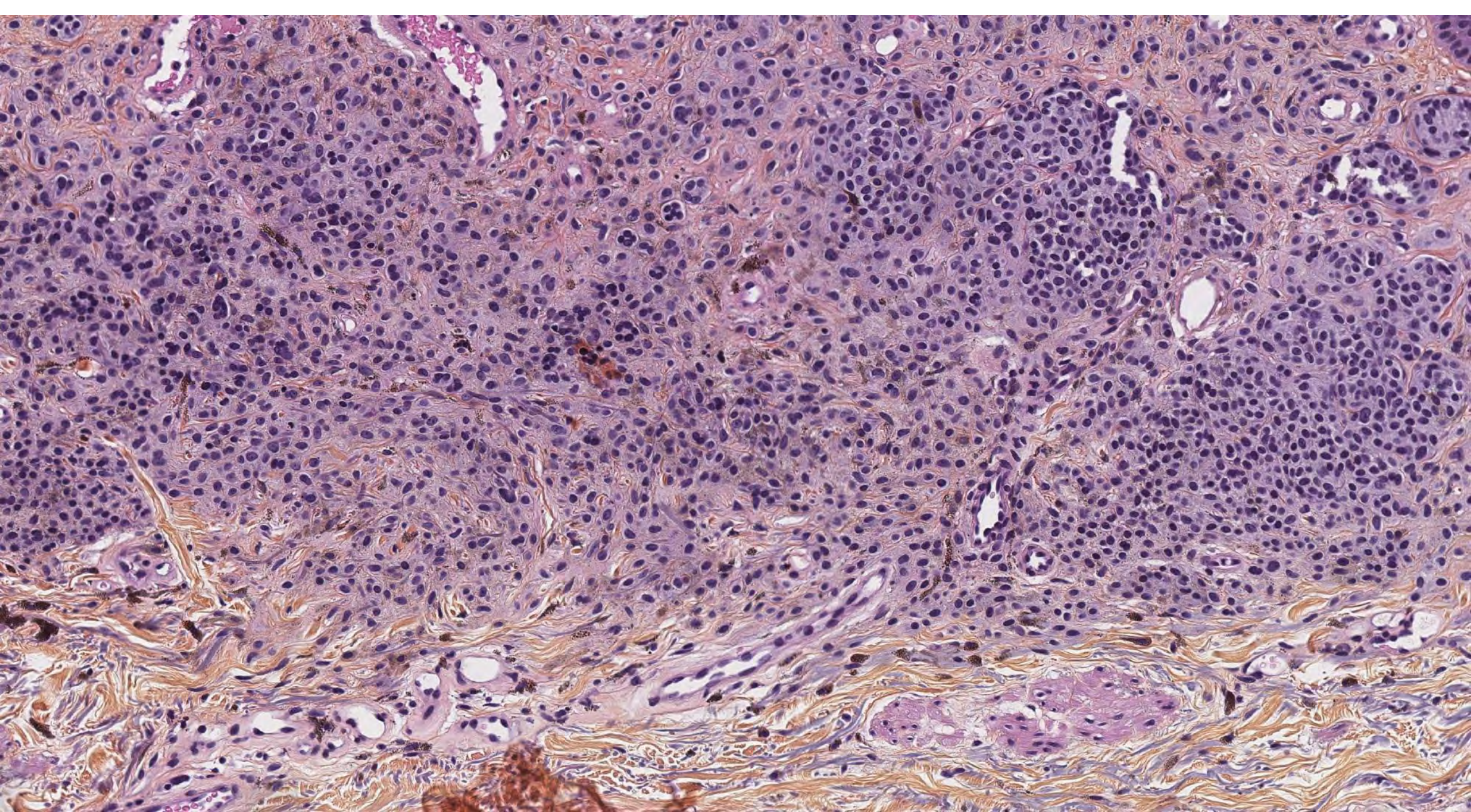
Upper dermis horizontal band



PKC gene fused melanocytic tumors

Almost only the band

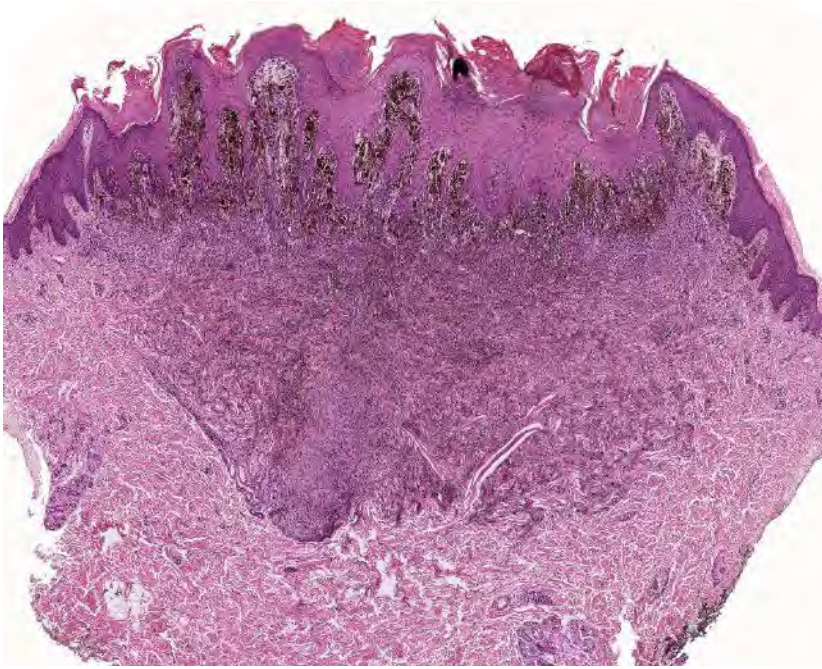




PKC gene fused melanocytic tumors

Junctional PEM-like features

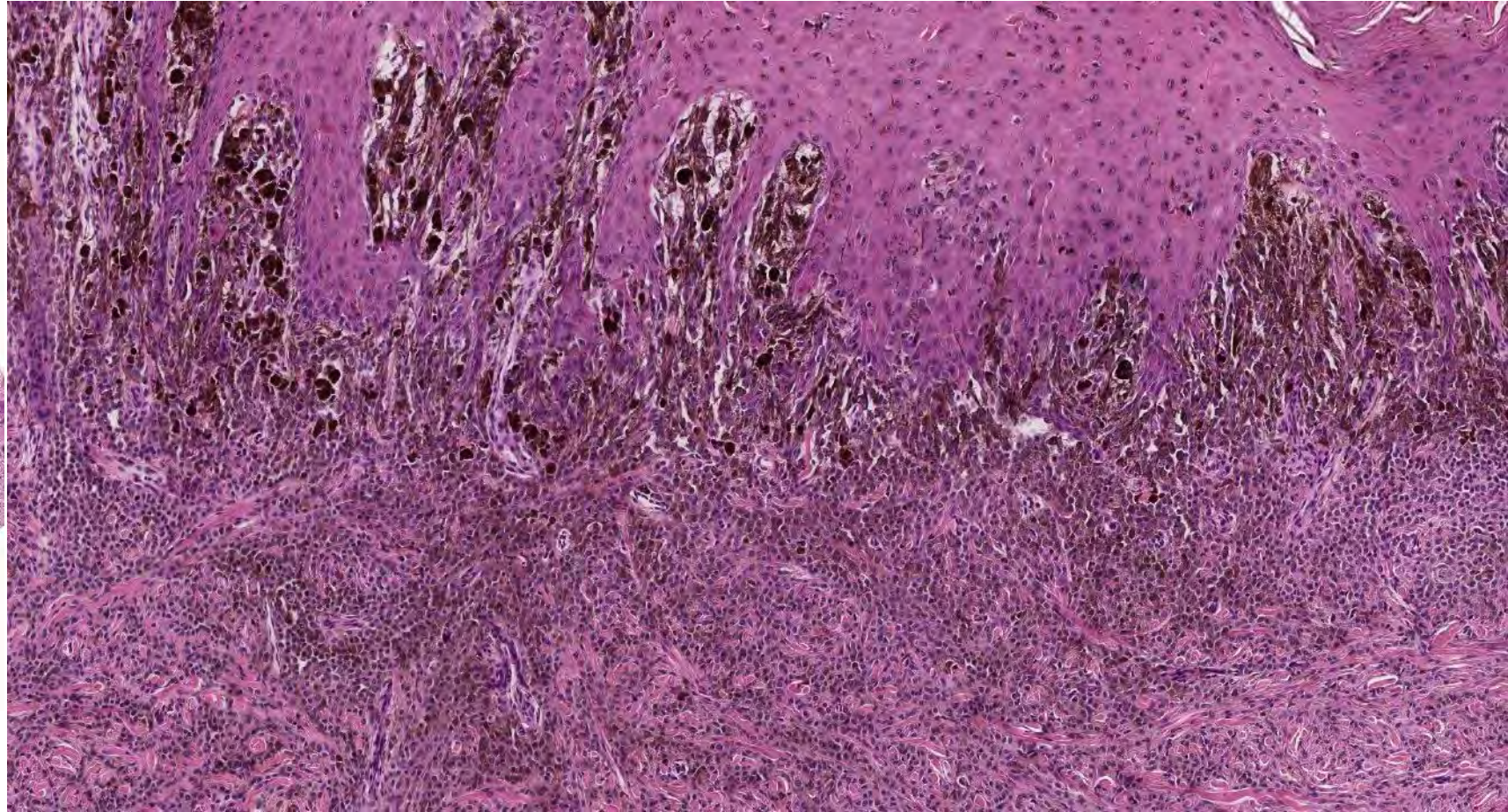
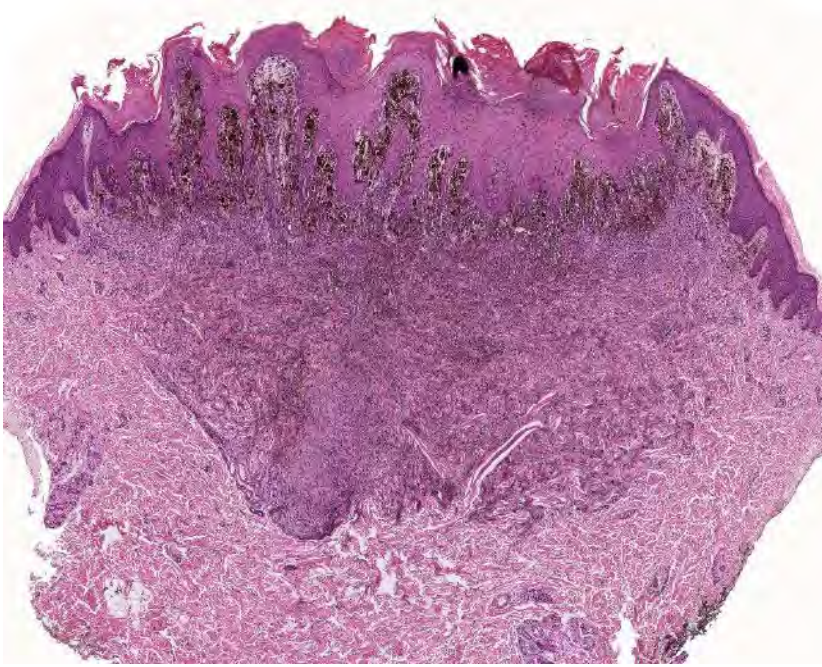
Upper dermis horizontal band



PKC gene fused melanocytic tumors

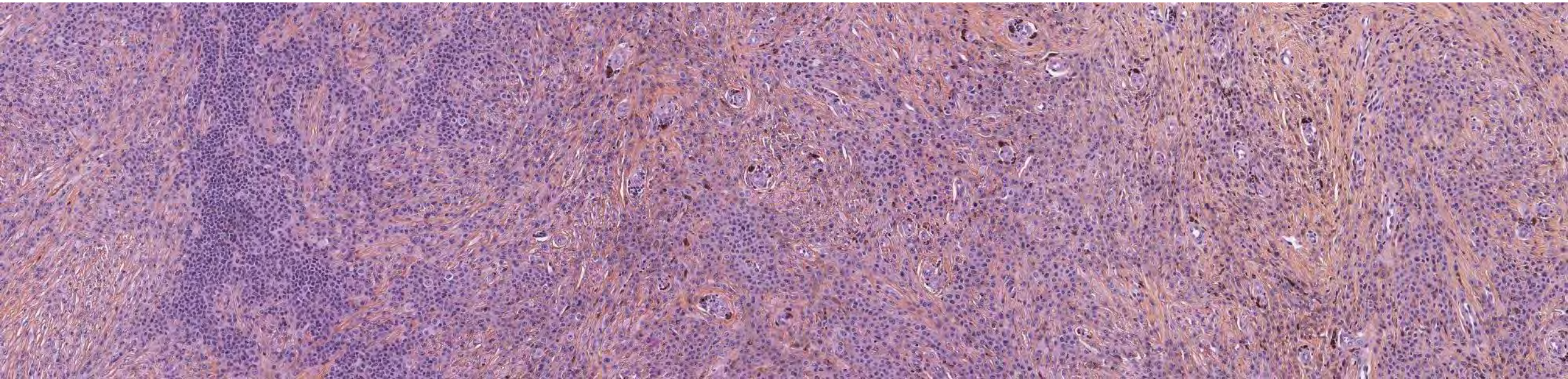
Junctional PEM-like features

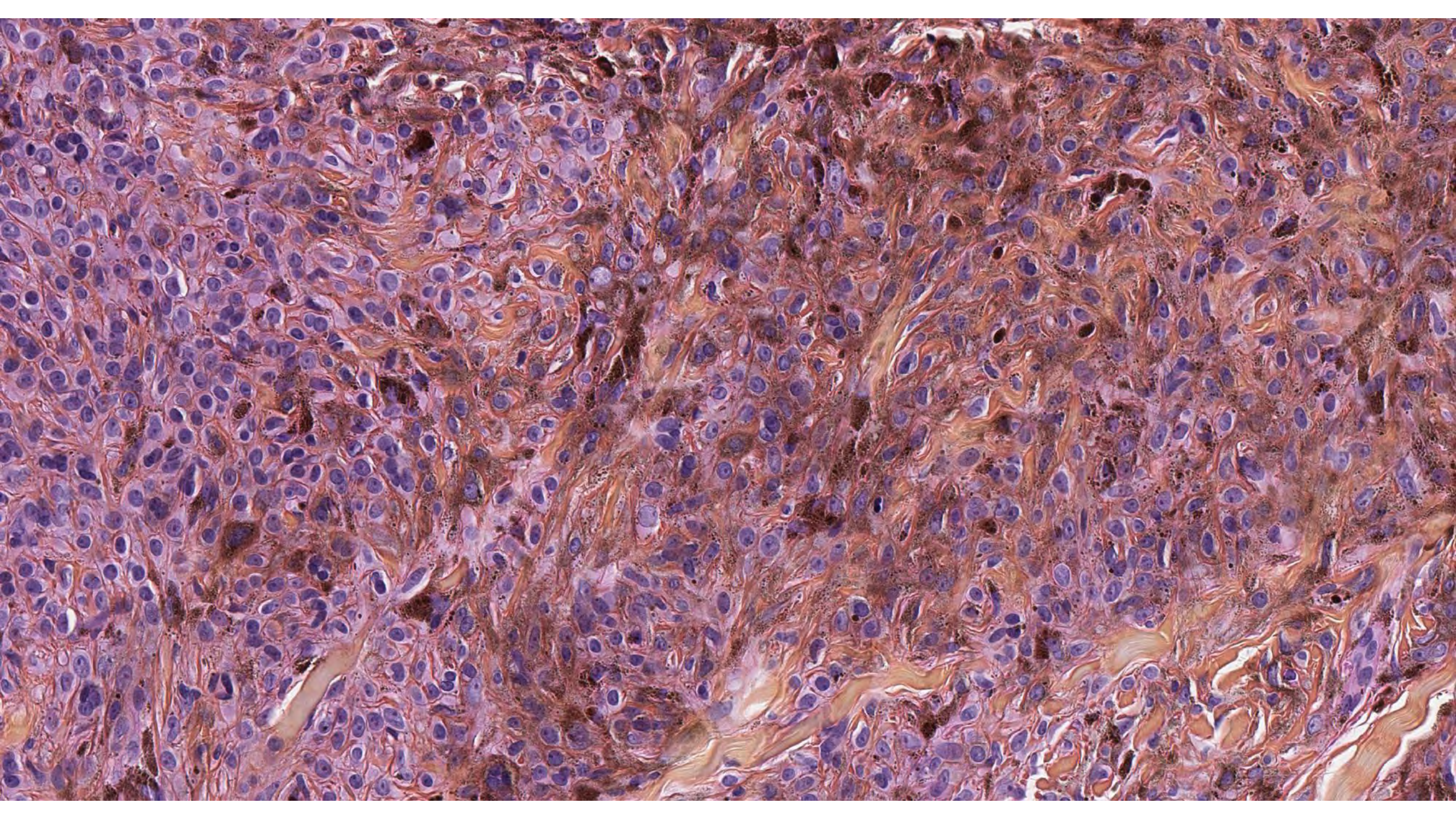
Upper dermis horizontal band

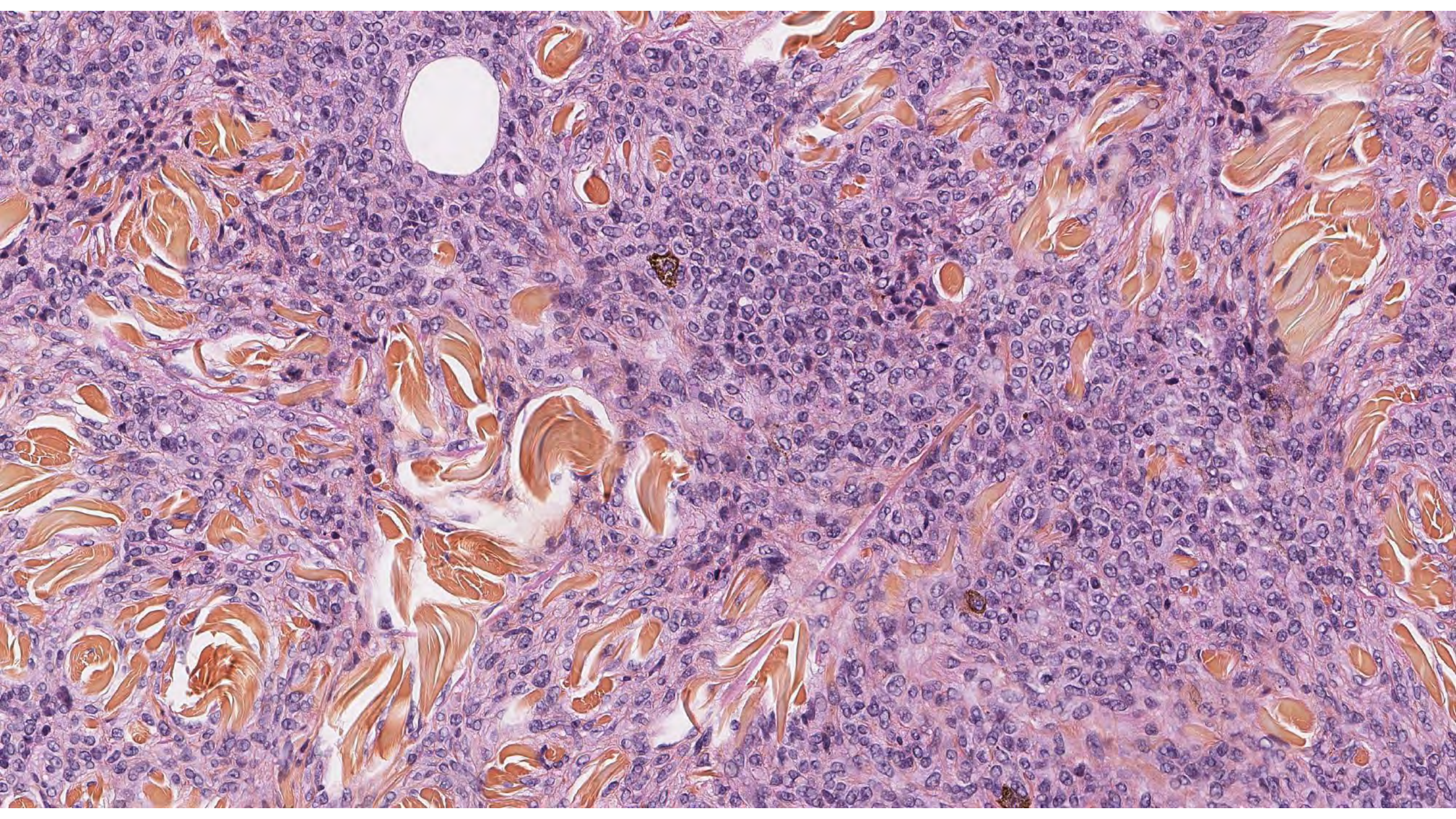


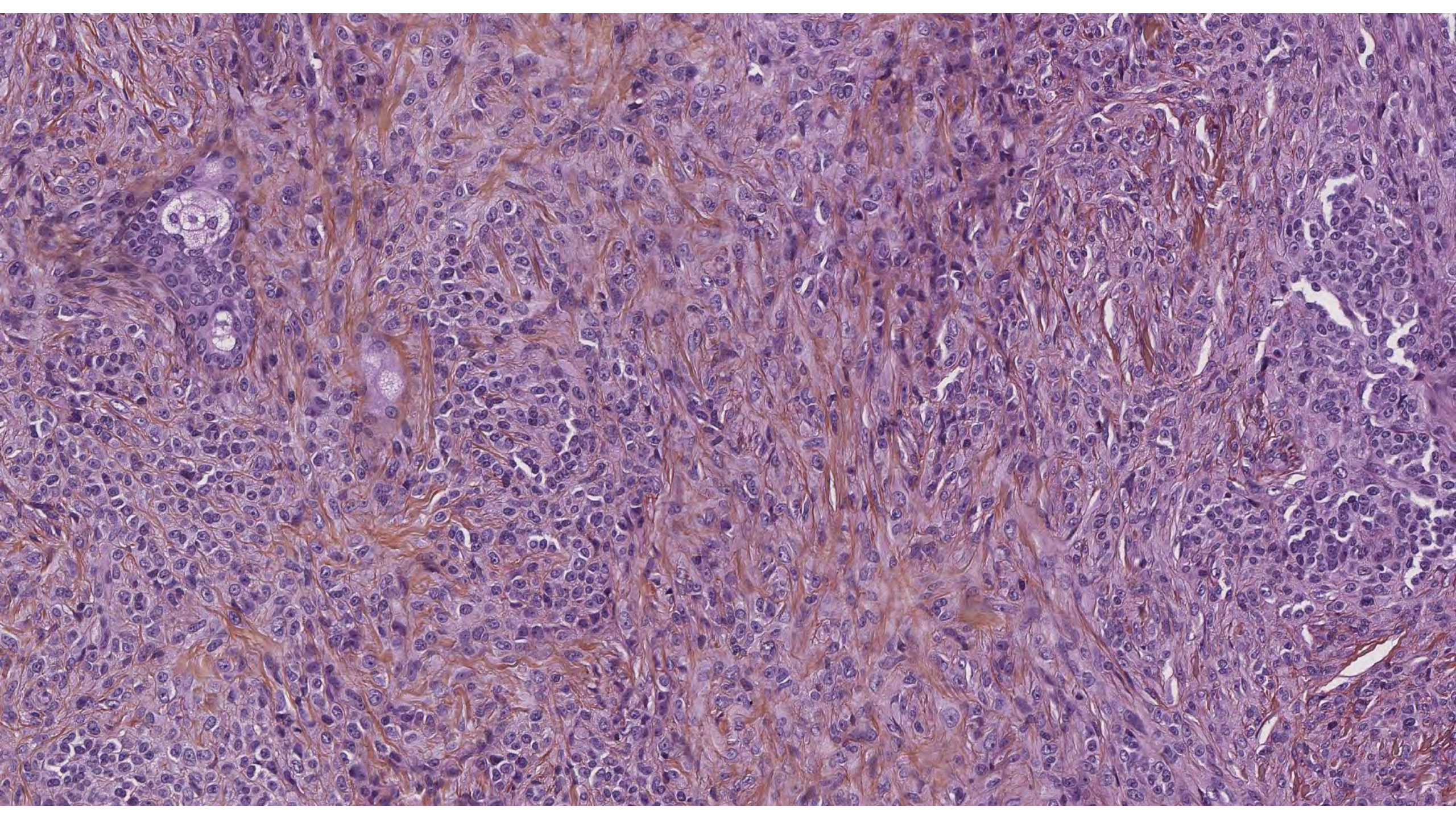
PKC gene fused blue nevus
highly variable morphology
Biphasic architecture (dermis)

«Combined common nevus + blue» morphology

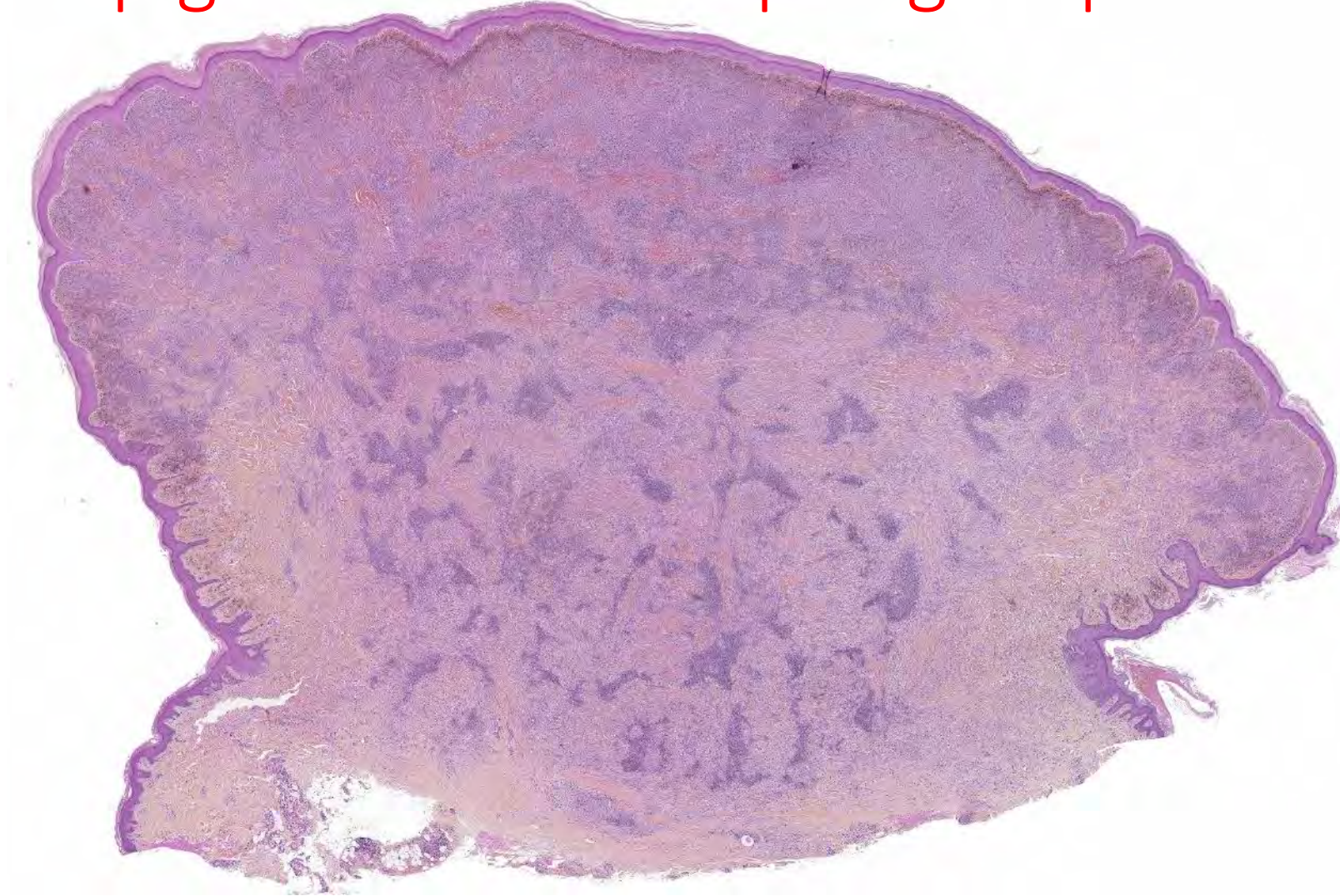


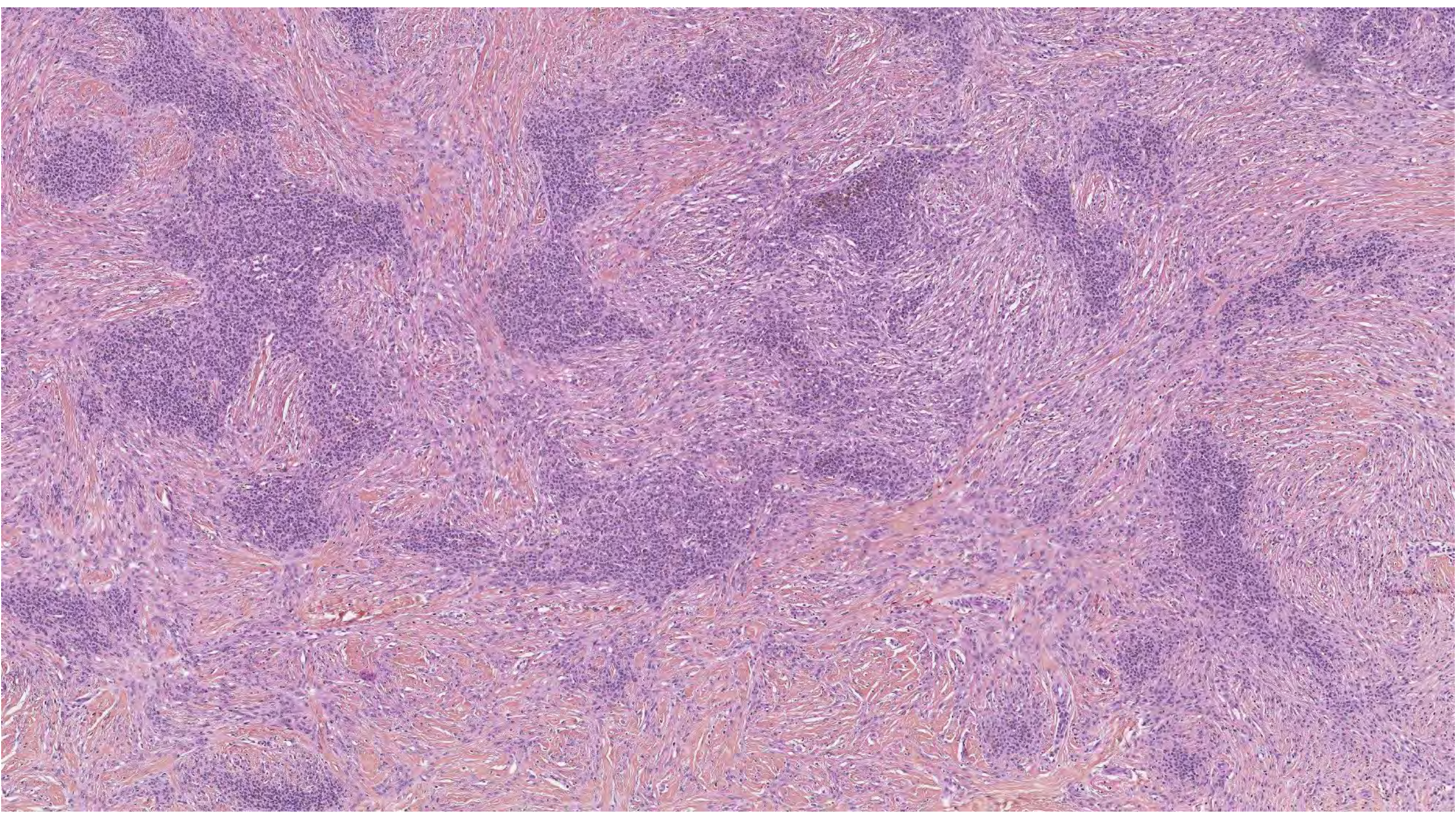


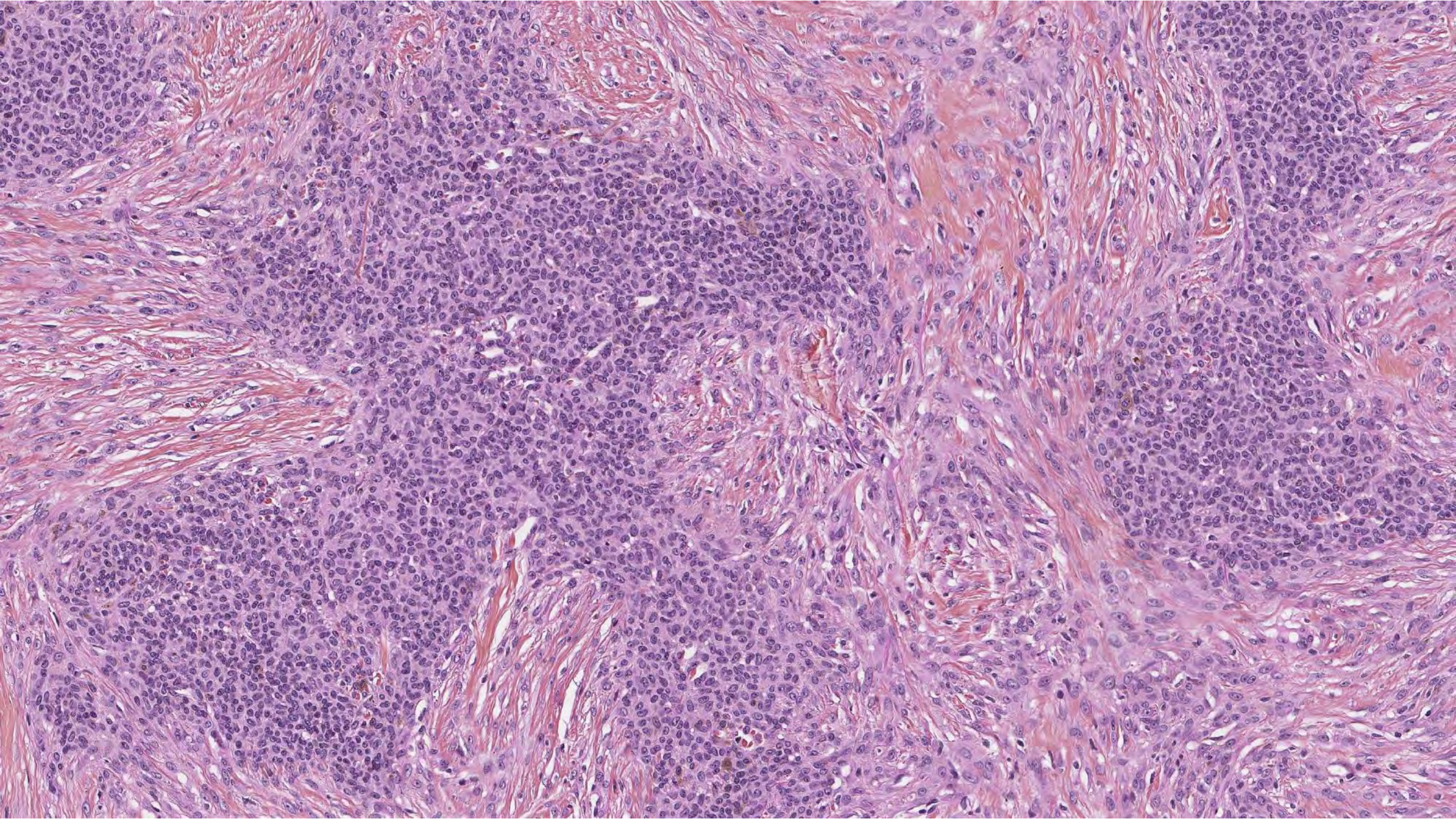




PKC gene fused melanocytic tumors
Band + Biphasic architecture (dermis)
Unpigmented « archipelago » pattern



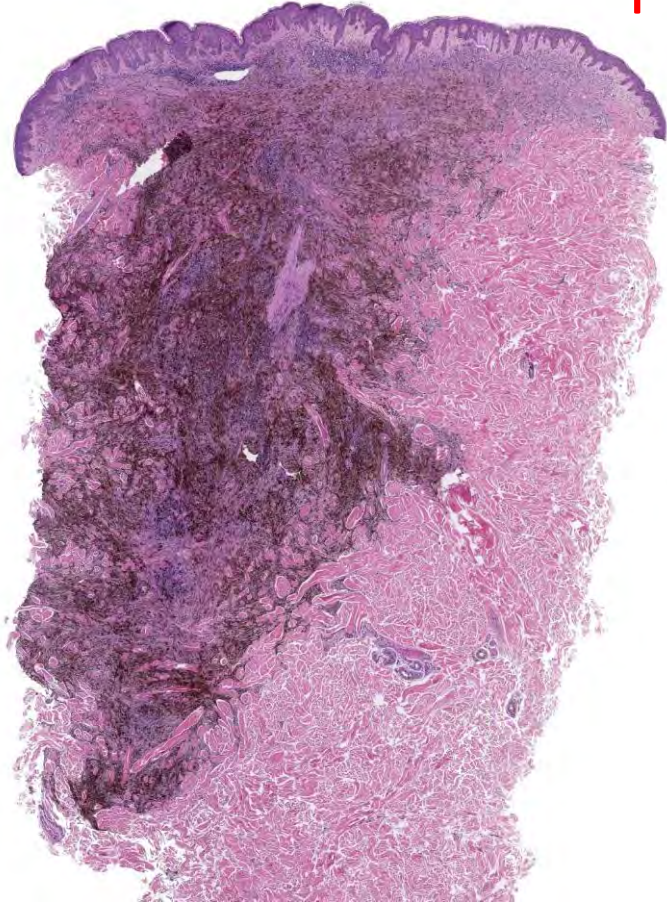




PKC gene fused melanocytic tumors

Upper dermis horizontal band

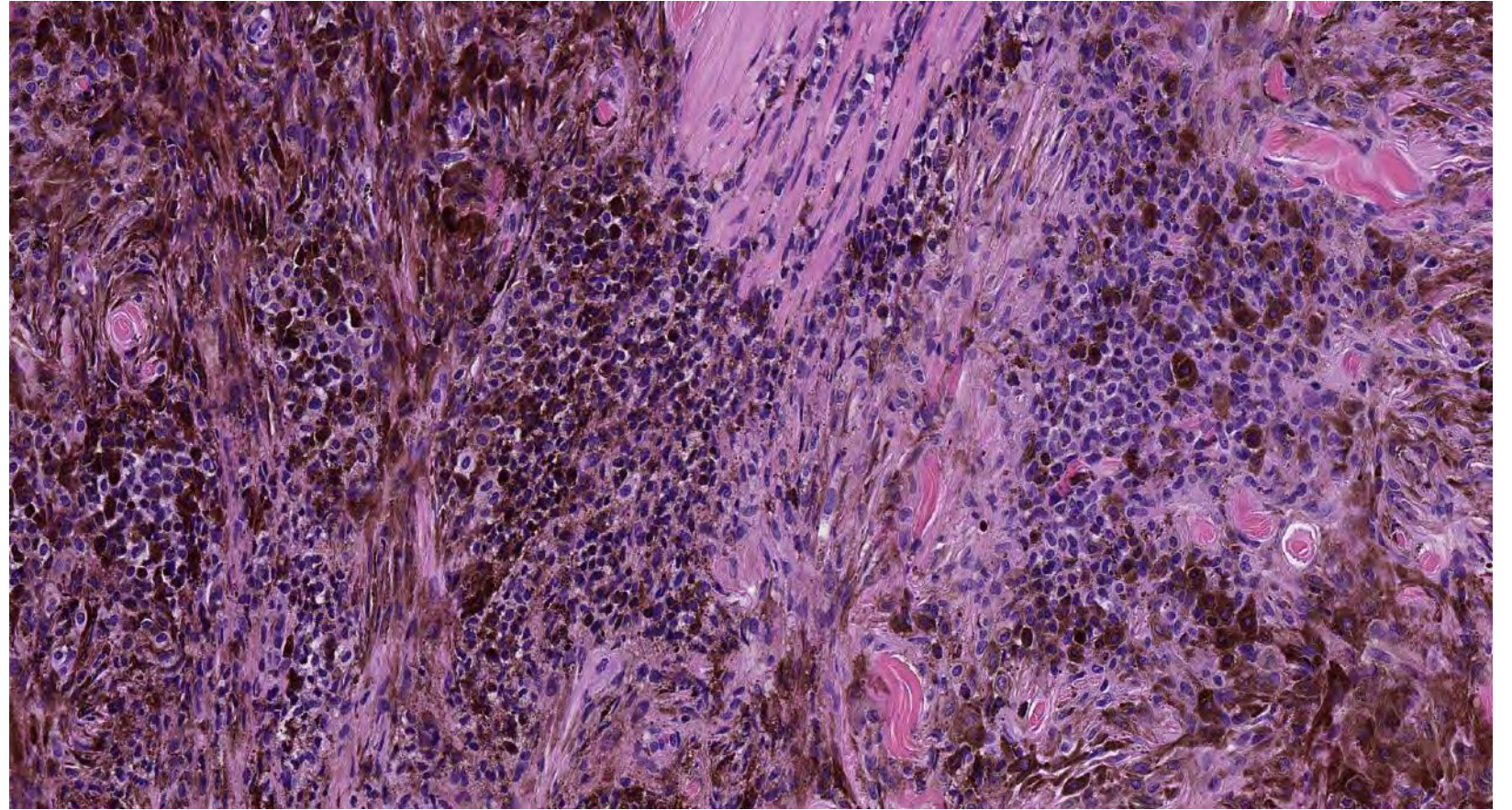
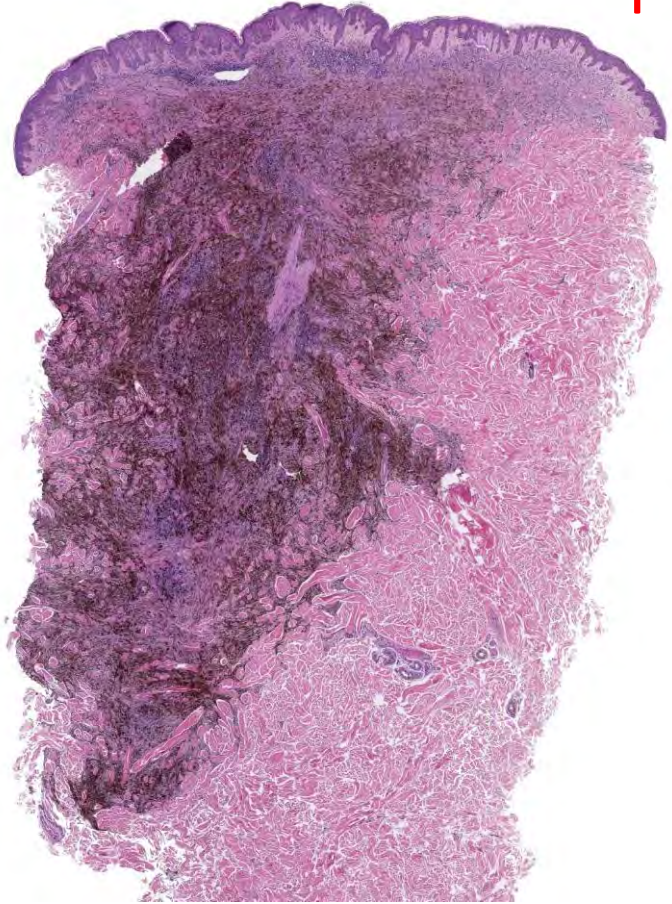
Biphasic architecture (dermis)



PKC gene fused melanocytic tumors

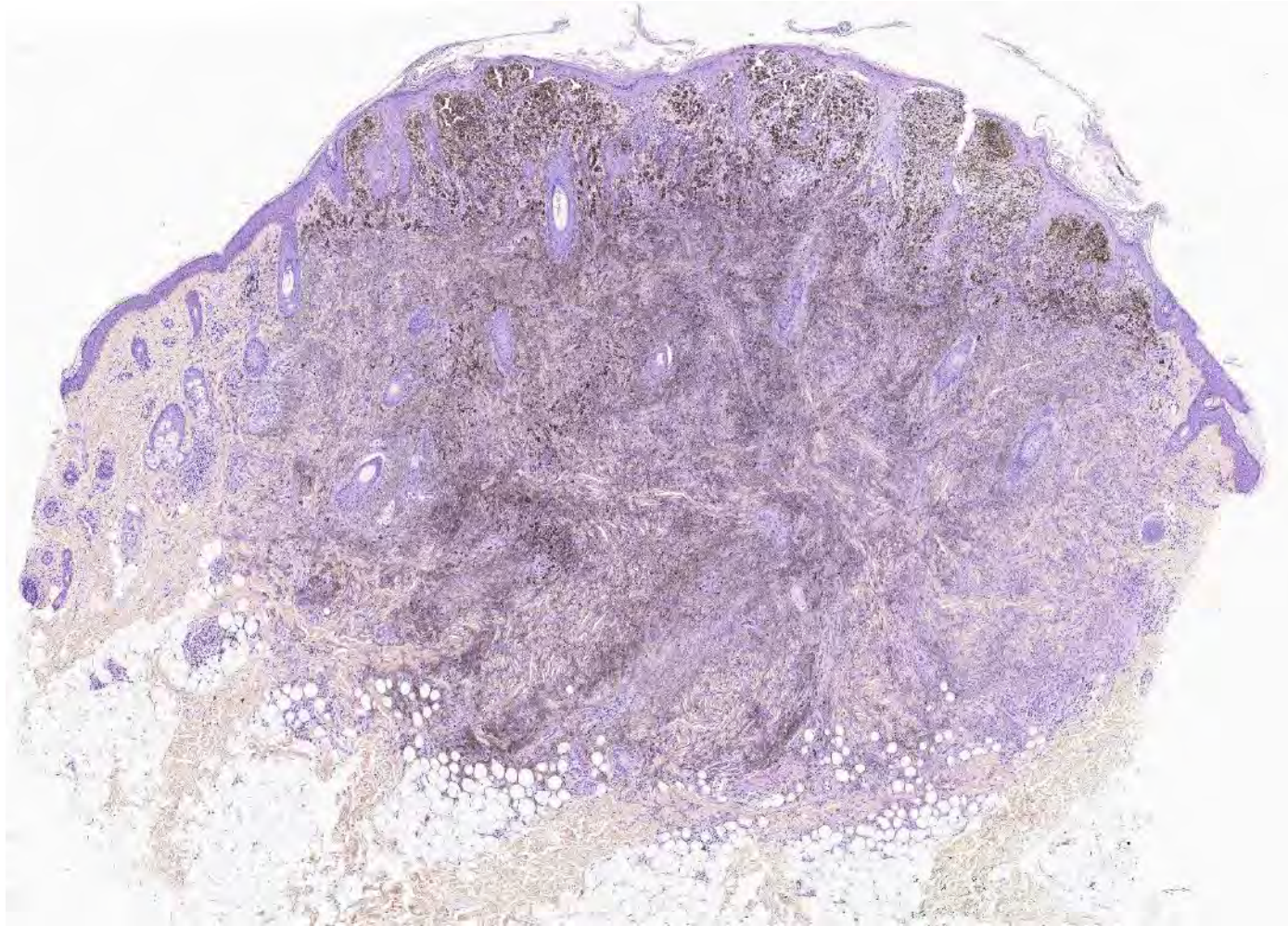
Upper dermis horizontal band

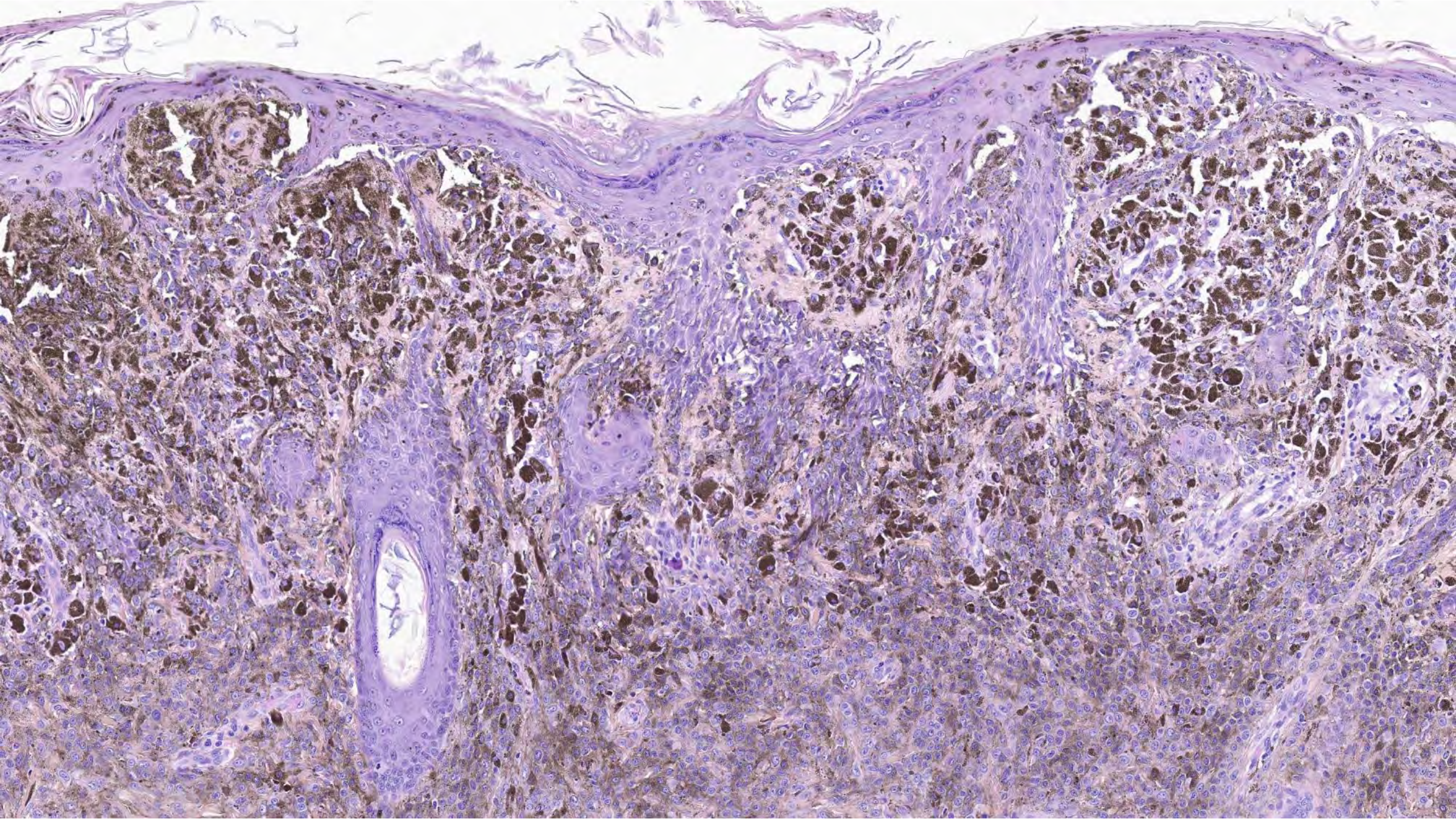
Biphasic architecture (dermis)

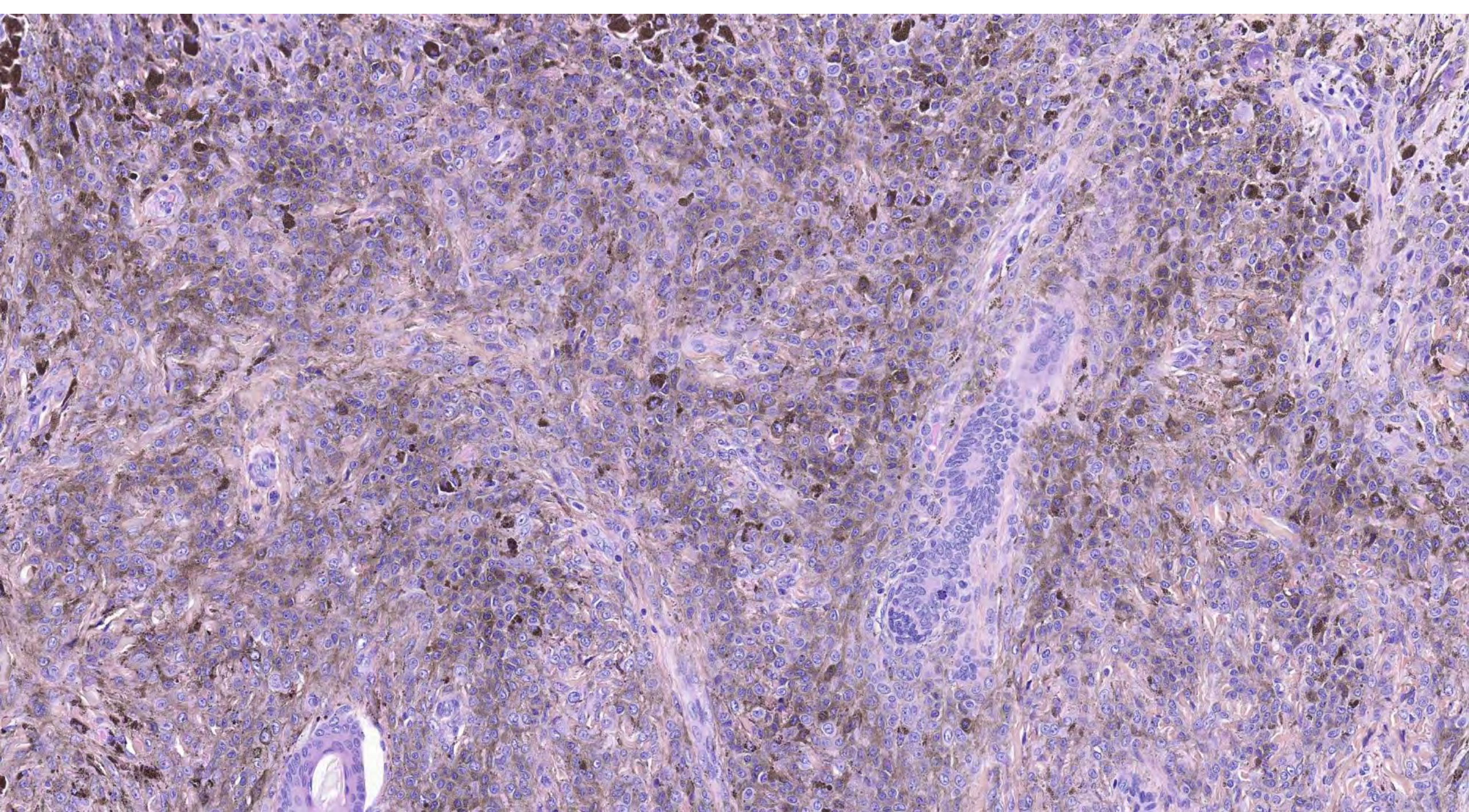


PKC gene fused melanocytic tumors

Junctional PEM-like features
+ Biphasic architecture (dermis)
« combined common + blue »

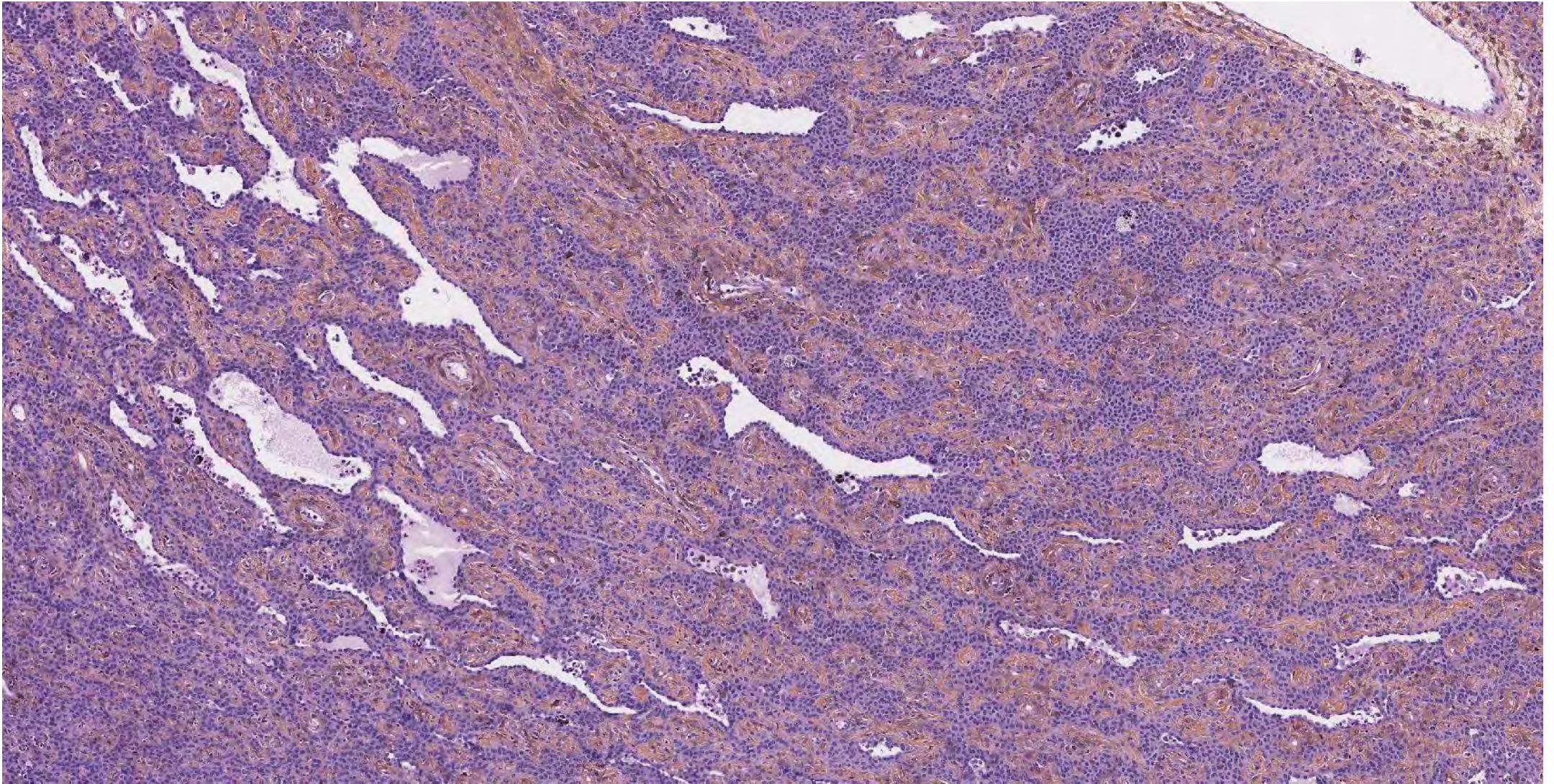






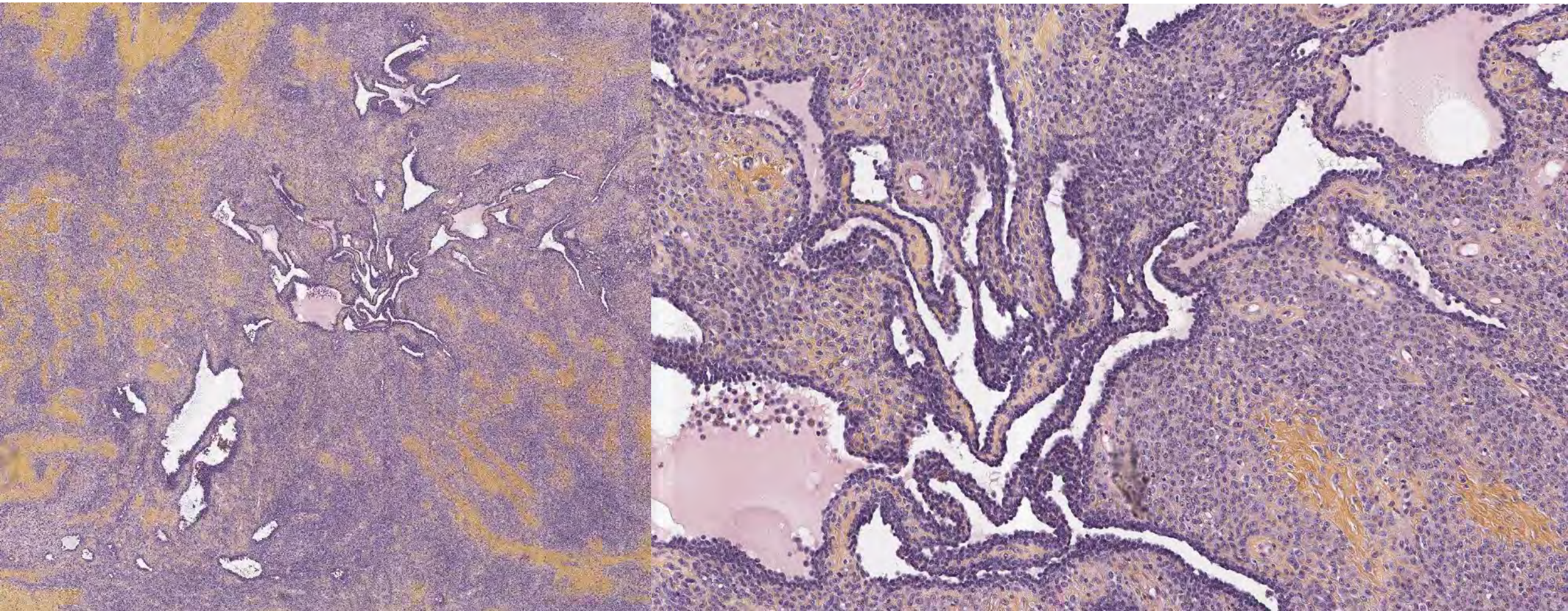
PKC gene fused melanocytic tumors

Pseudo-vascular clefting in cellular areas



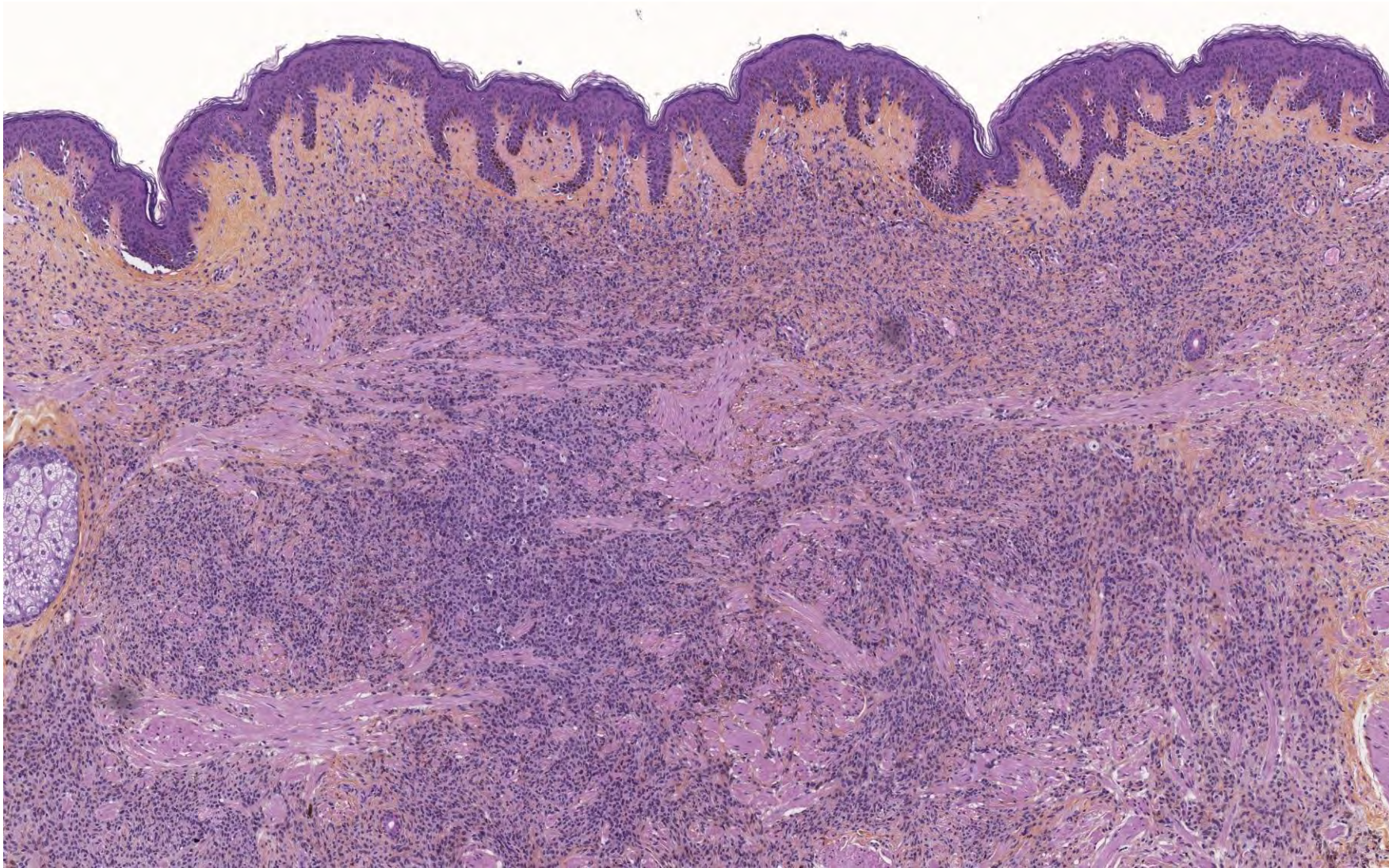
PKC gene fused melanocytic tumors

Pseudo-vascular clefting in cellular areas



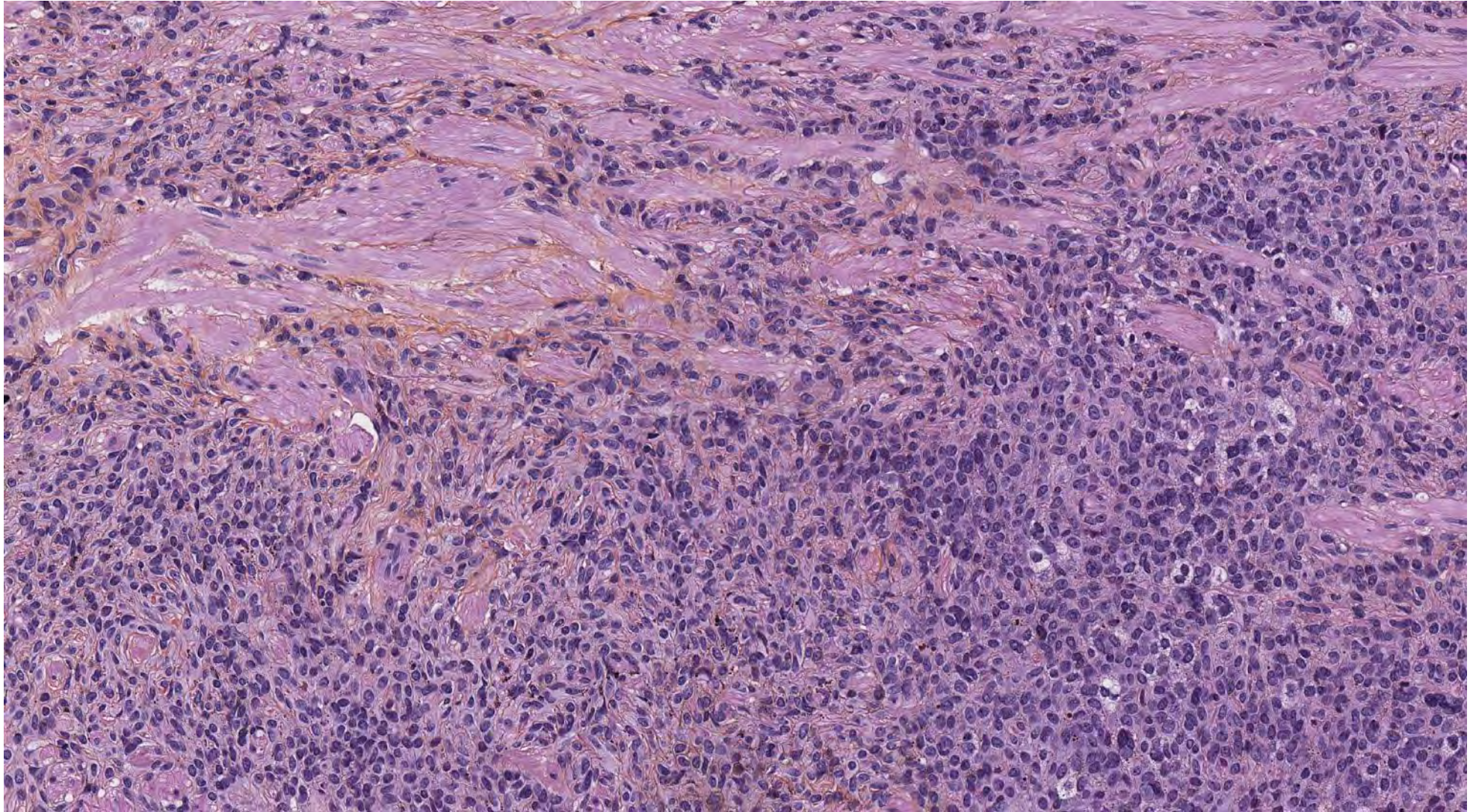
PKC gene fused melanocytic tumors

Smooth muscle hyperplasia



PKC gene fused melanocytic tumors

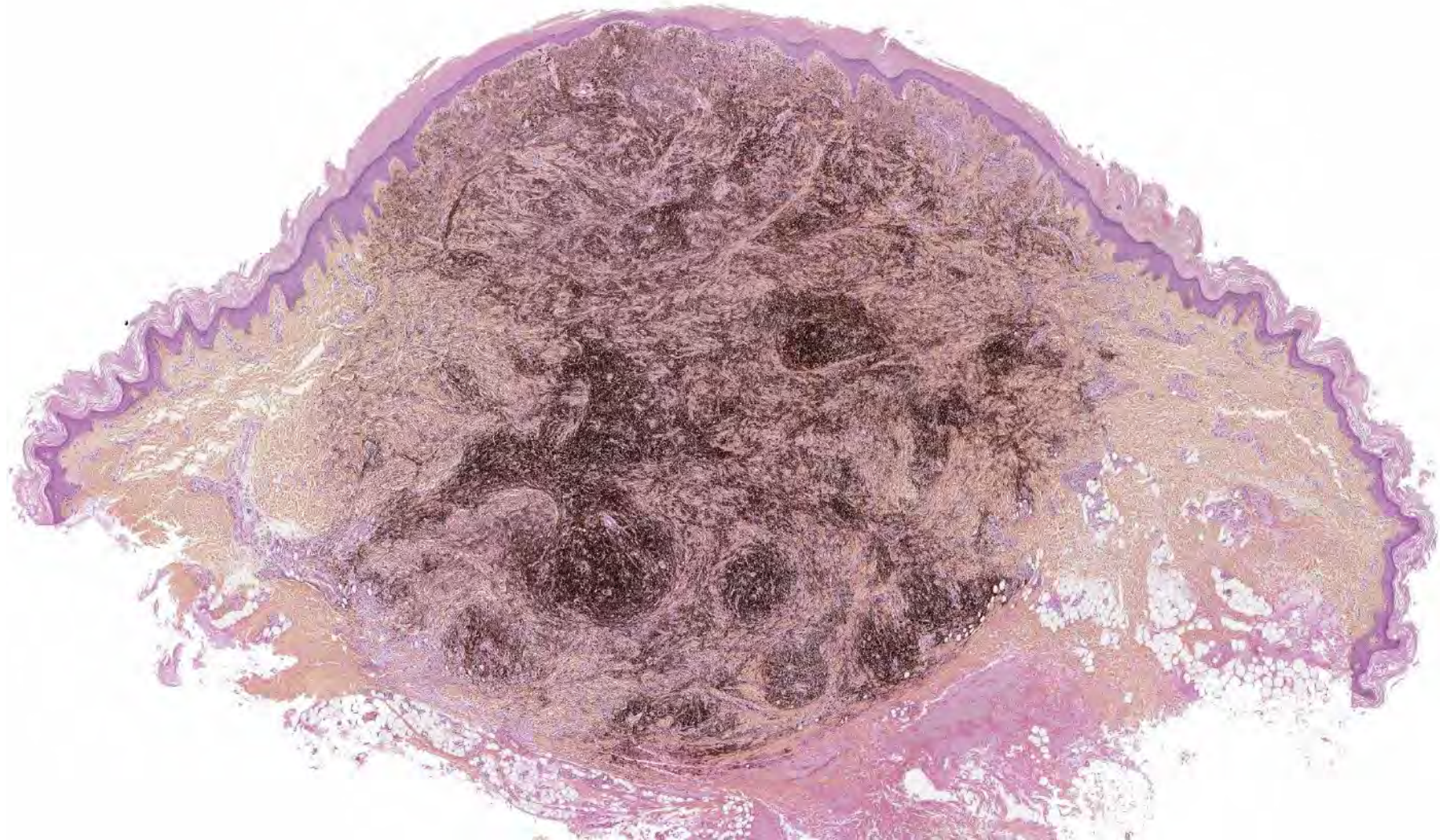
Smooth muscle hyperplasia



PKC gene fused melanocytic tumors

Medium power clues :

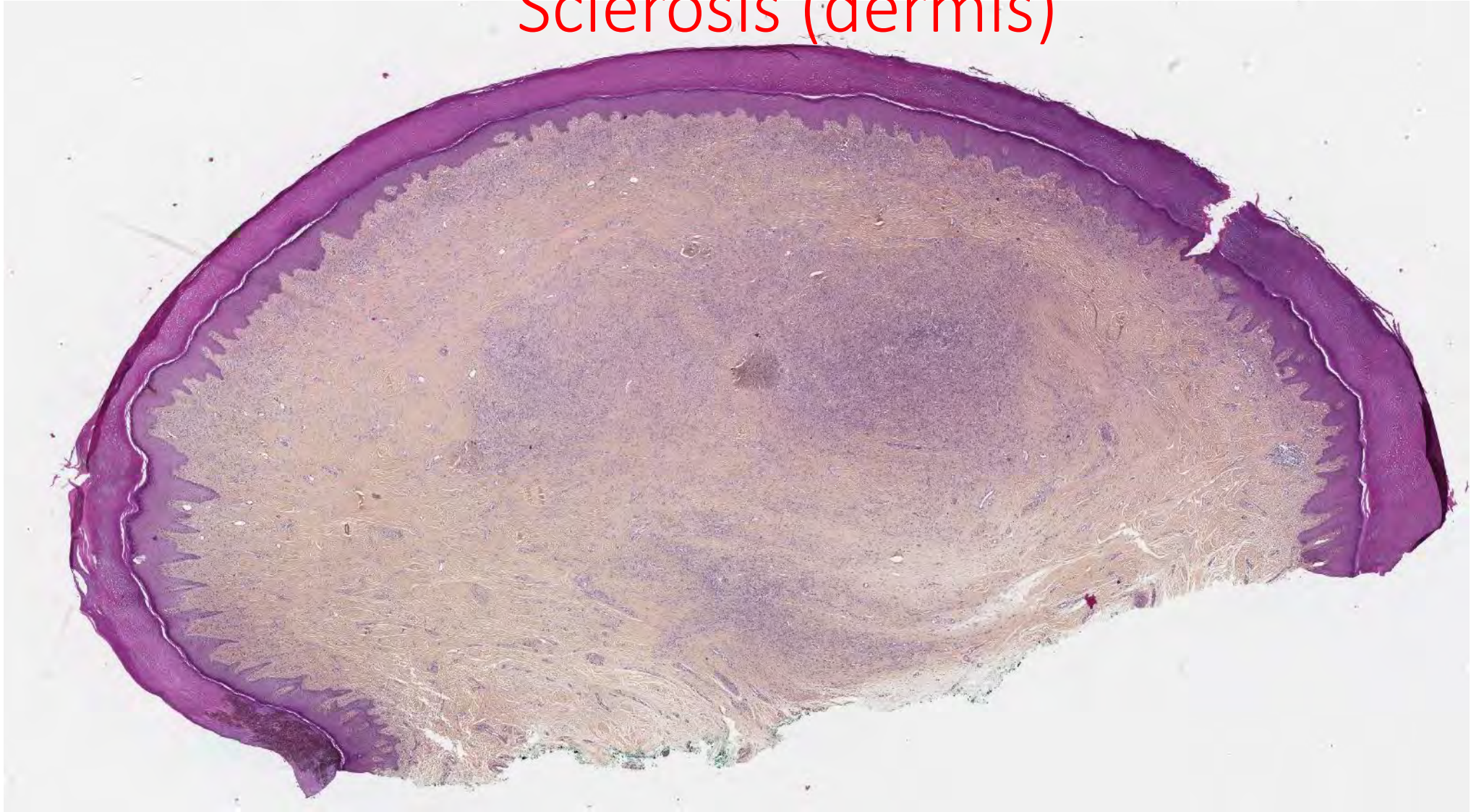
Fibrosis (dermis)



PKC gene fused melanocytic tumors

Medium power clues :

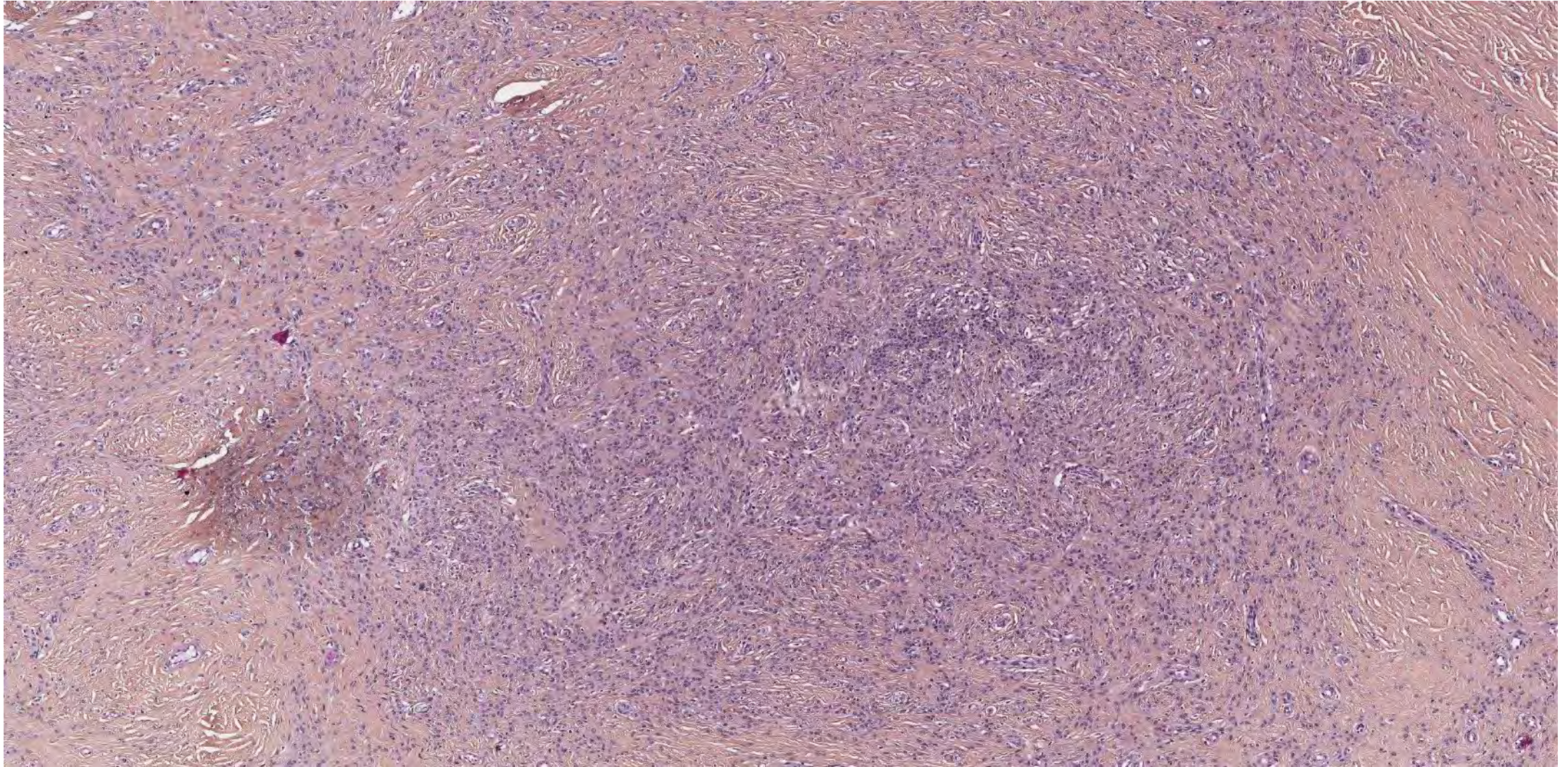
Sclerosis (dermis)



PKC gene fused melanocytic tumors

Medium power clues :

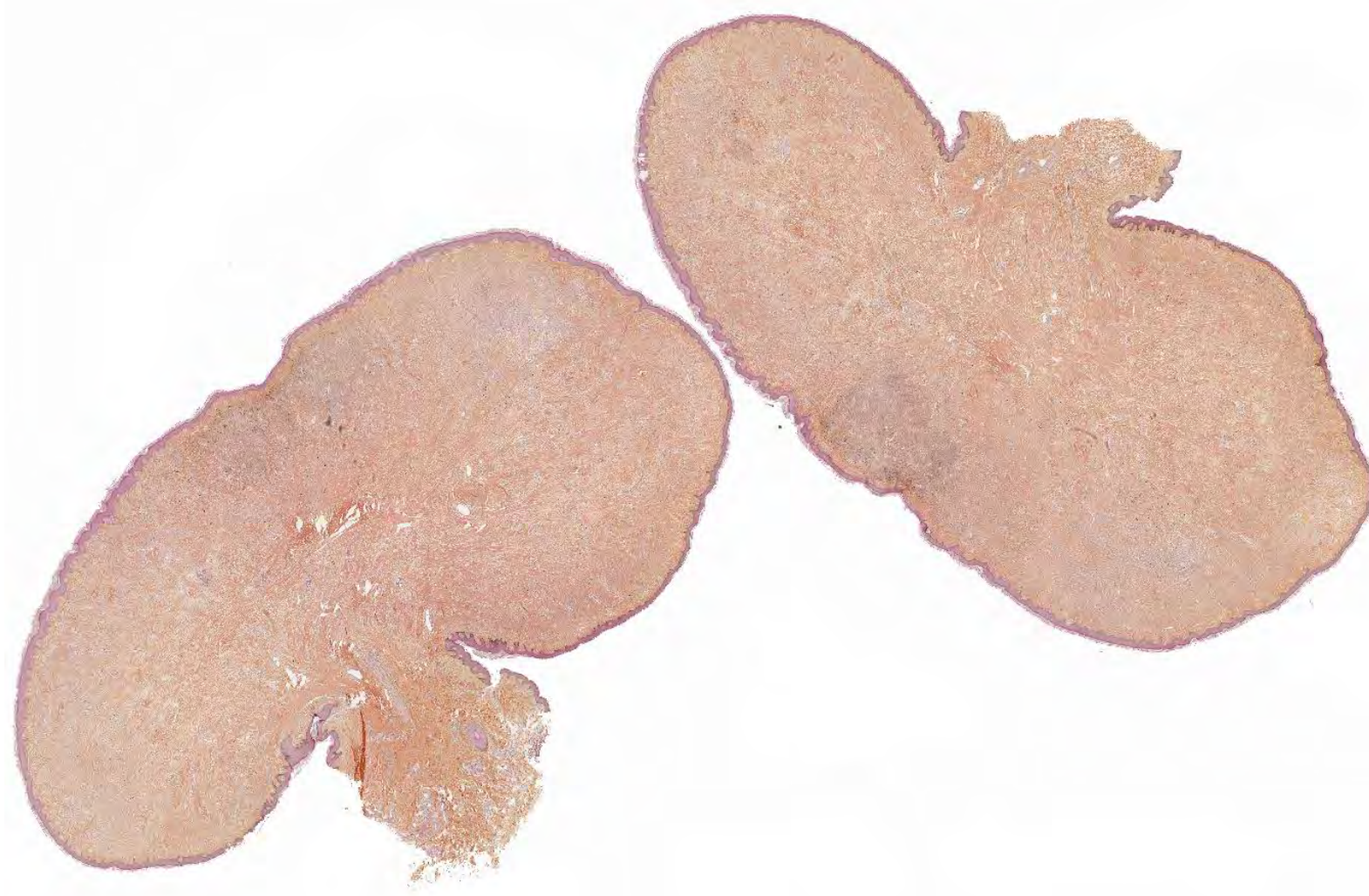
Sclerosis (dermis)



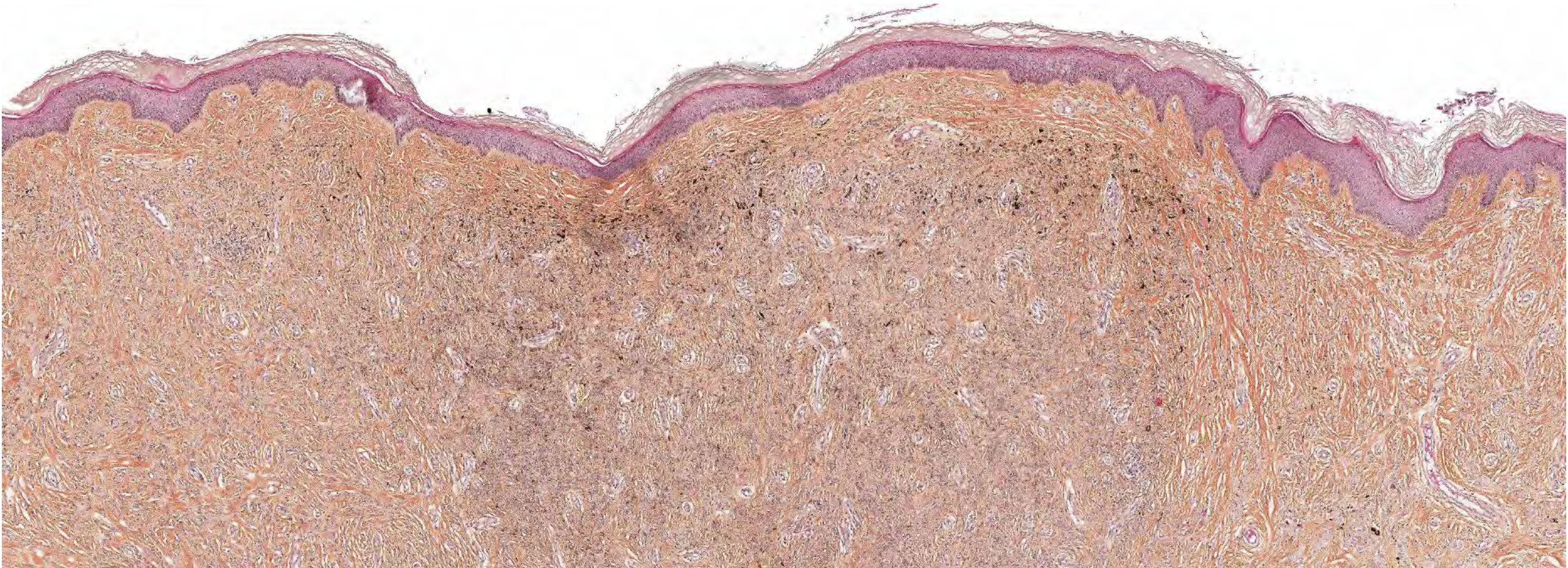
PKC gene fused melanocytic tumors

Medium power clues :

Sclerosis (dermis)



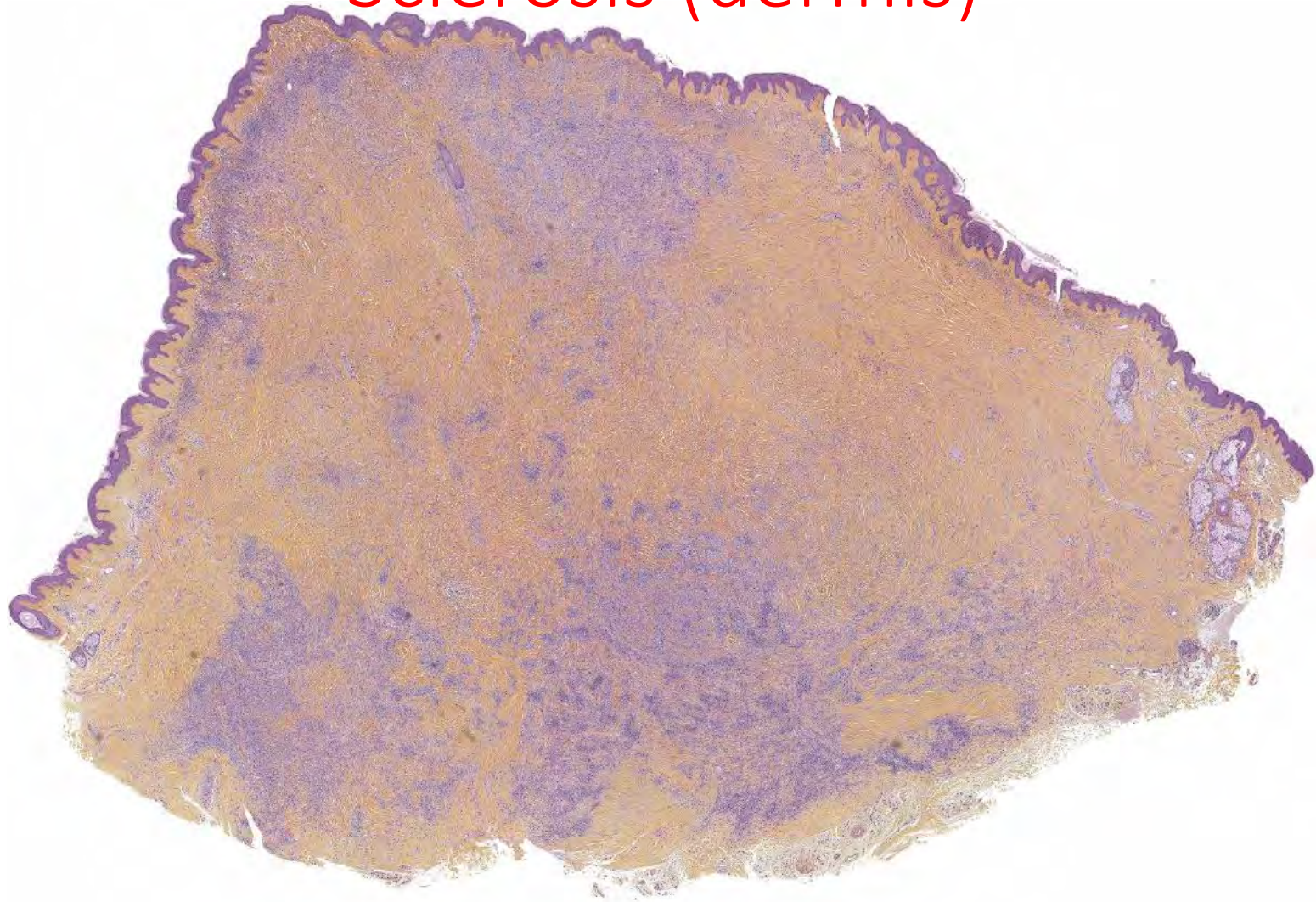
PKC gene fused melanocytic tumors
Medium power clues :
Sclerosis (dermis)



PKC gene fused melanocytic tumors

Medium power clues :

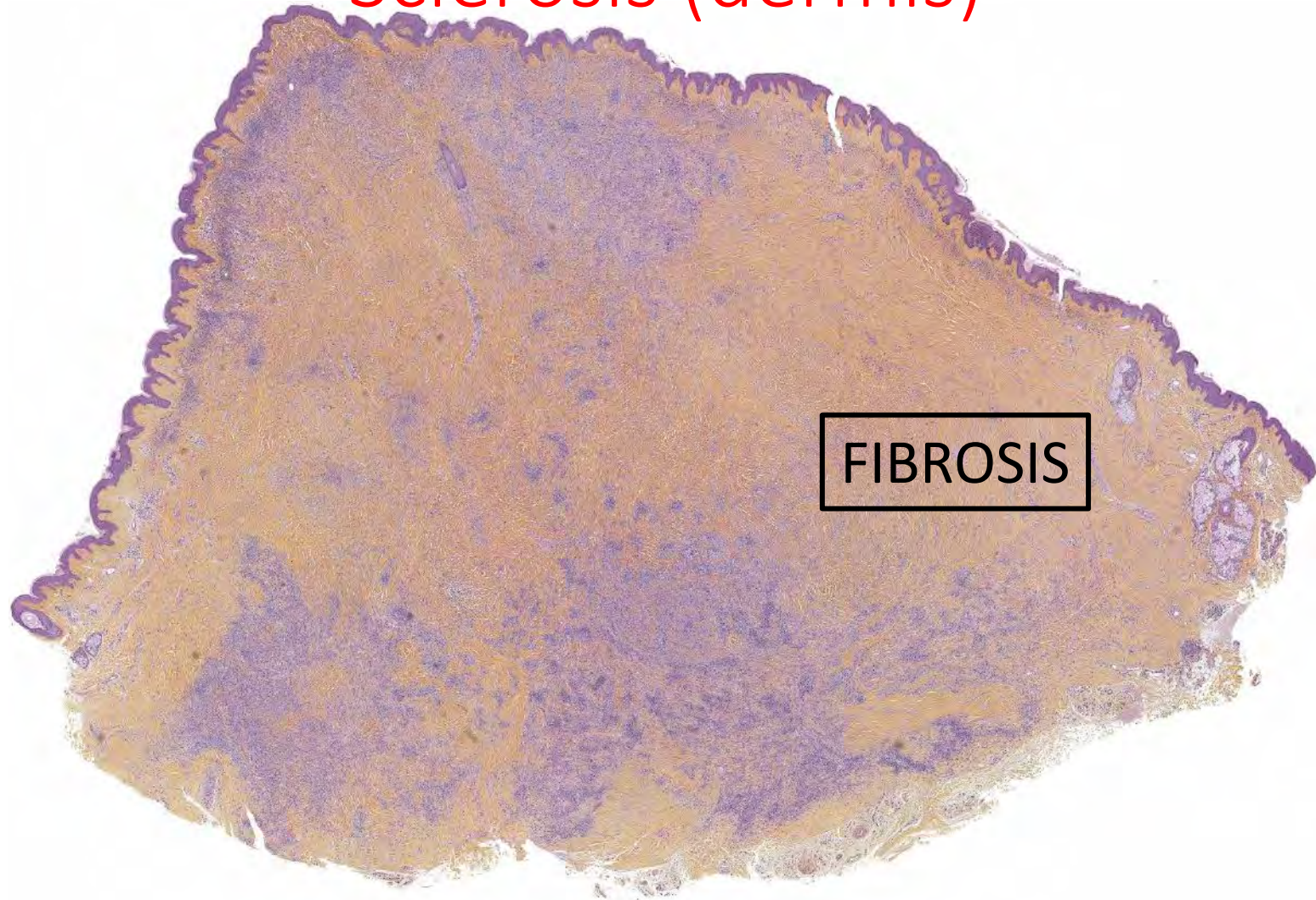
Sclerosis (dermis)



PKC gene fused melanocytic tumors

Medium power clues :

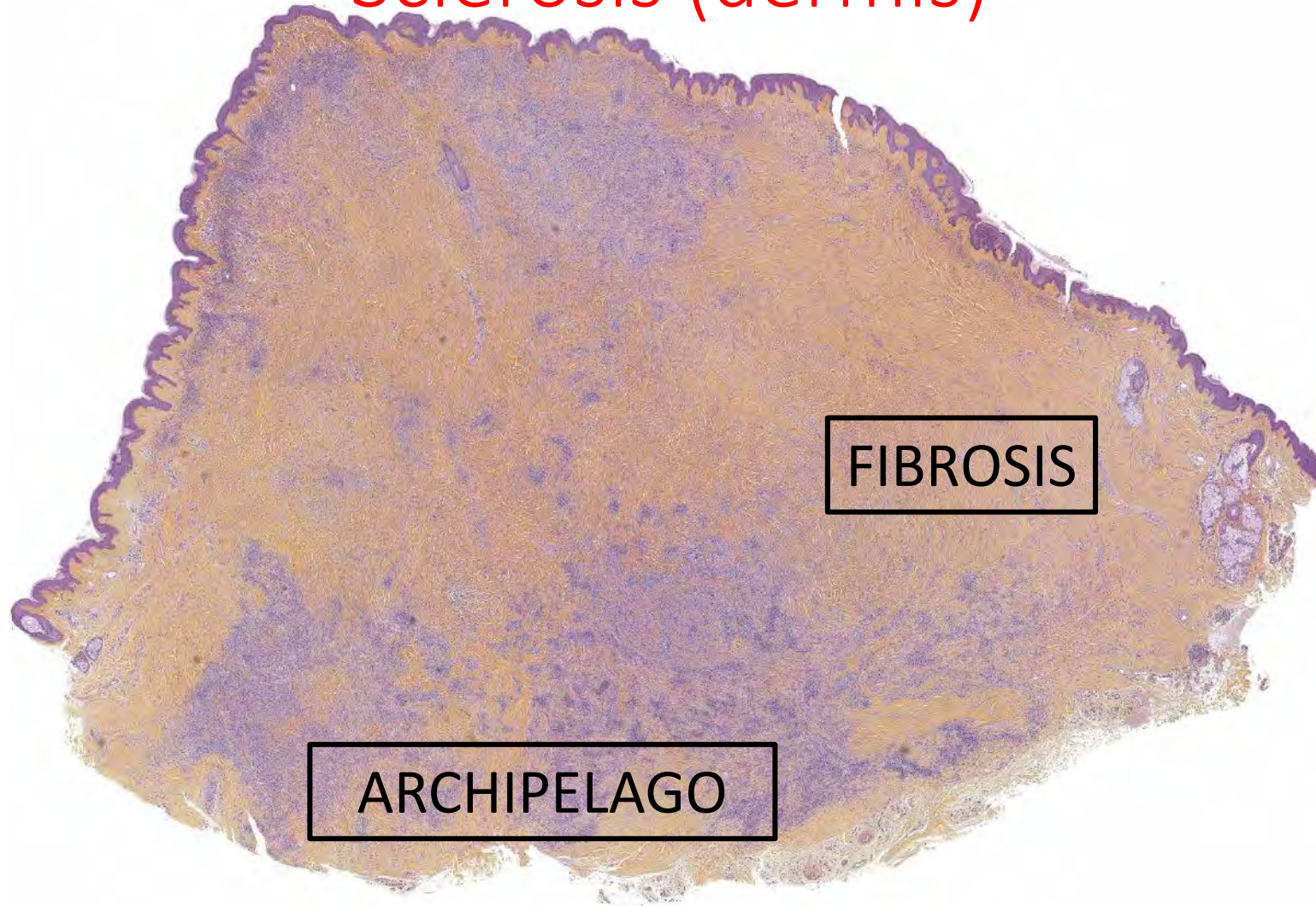
Sclerosis (dermis)



PKC gene fused melanocytic tumors

Medium power clues :

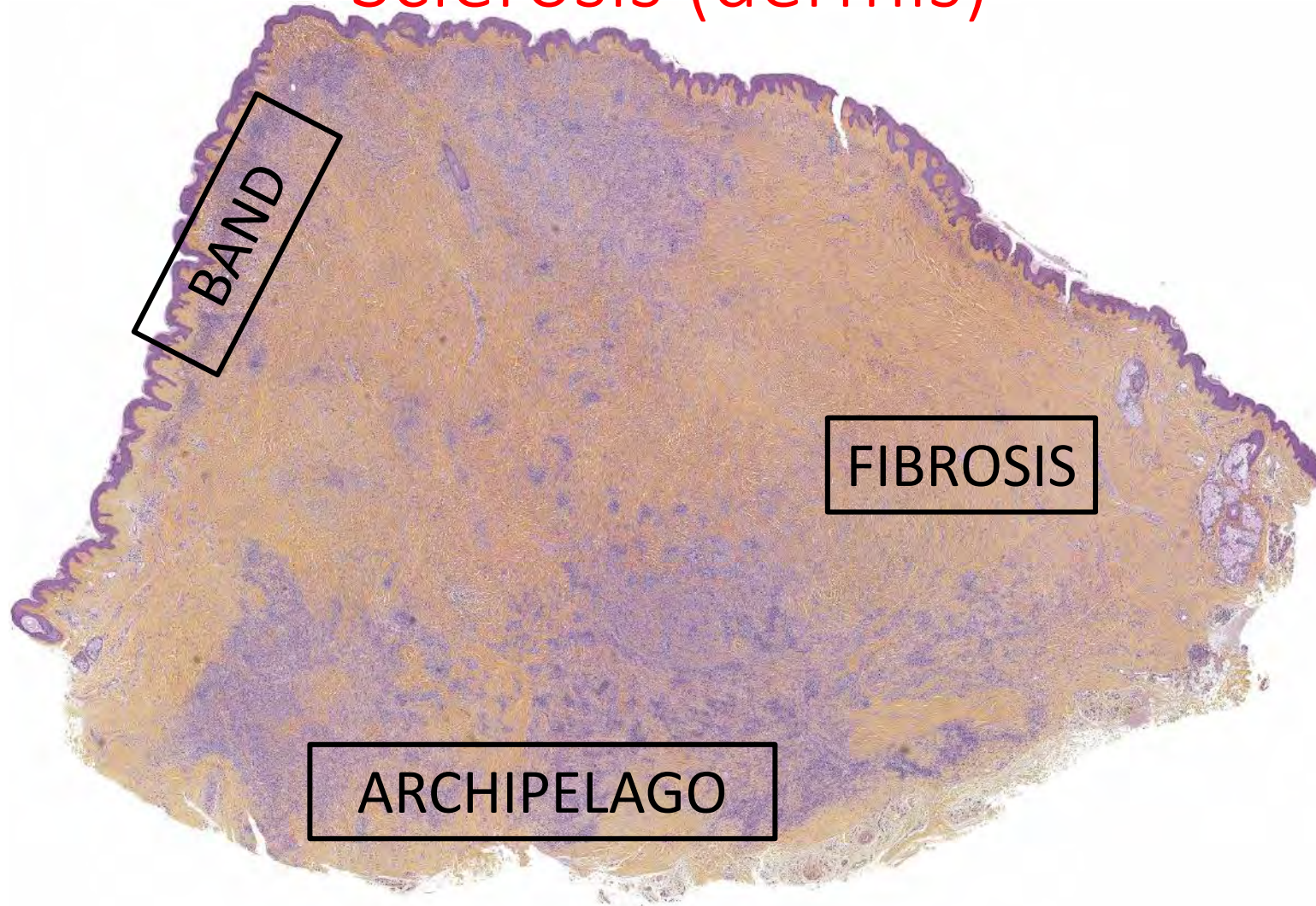
Sclerosis (dermis)



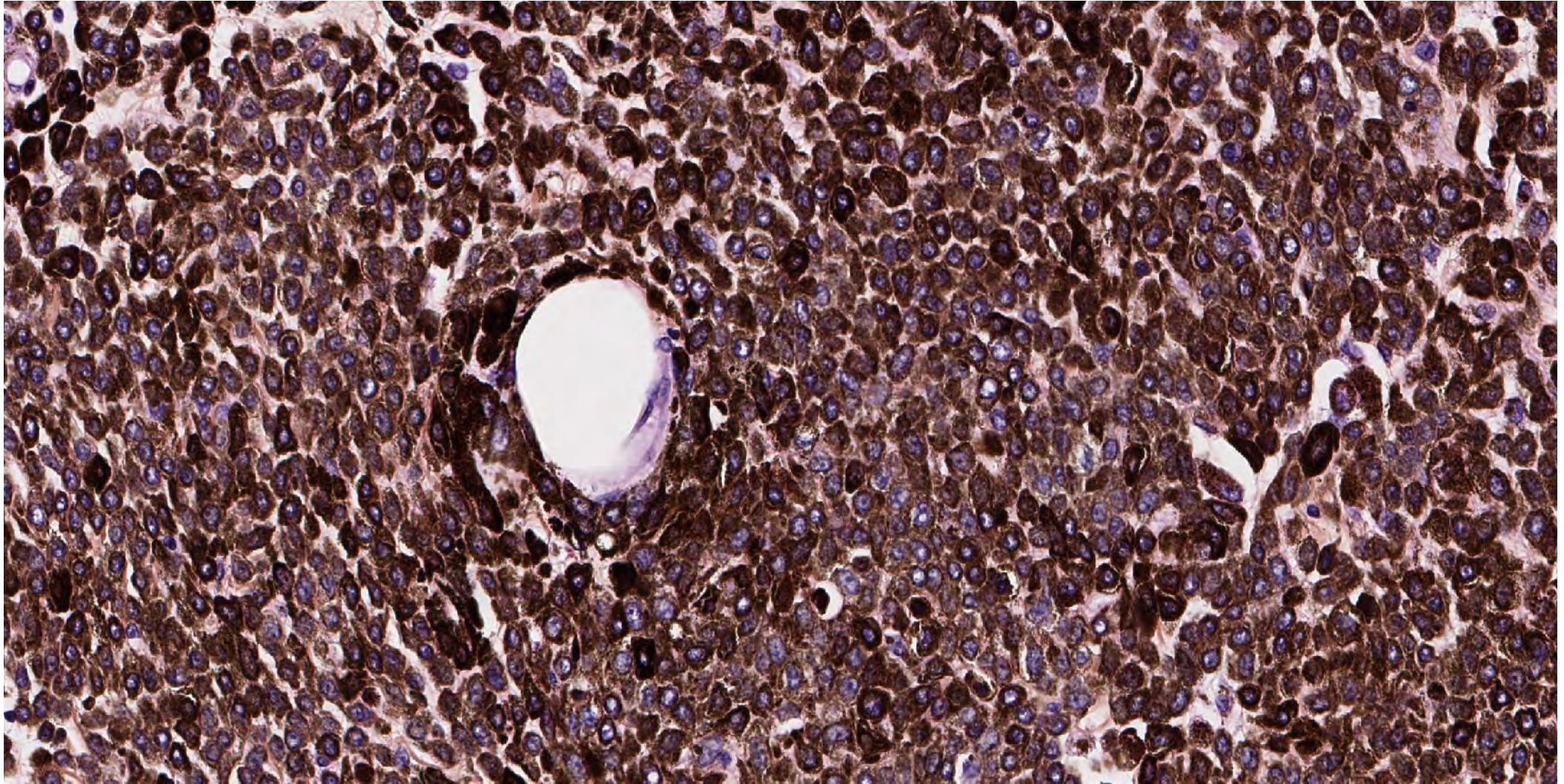
PKC gene fused melanocytic tumors

Medium power clues :

Sclerosis (dermis)

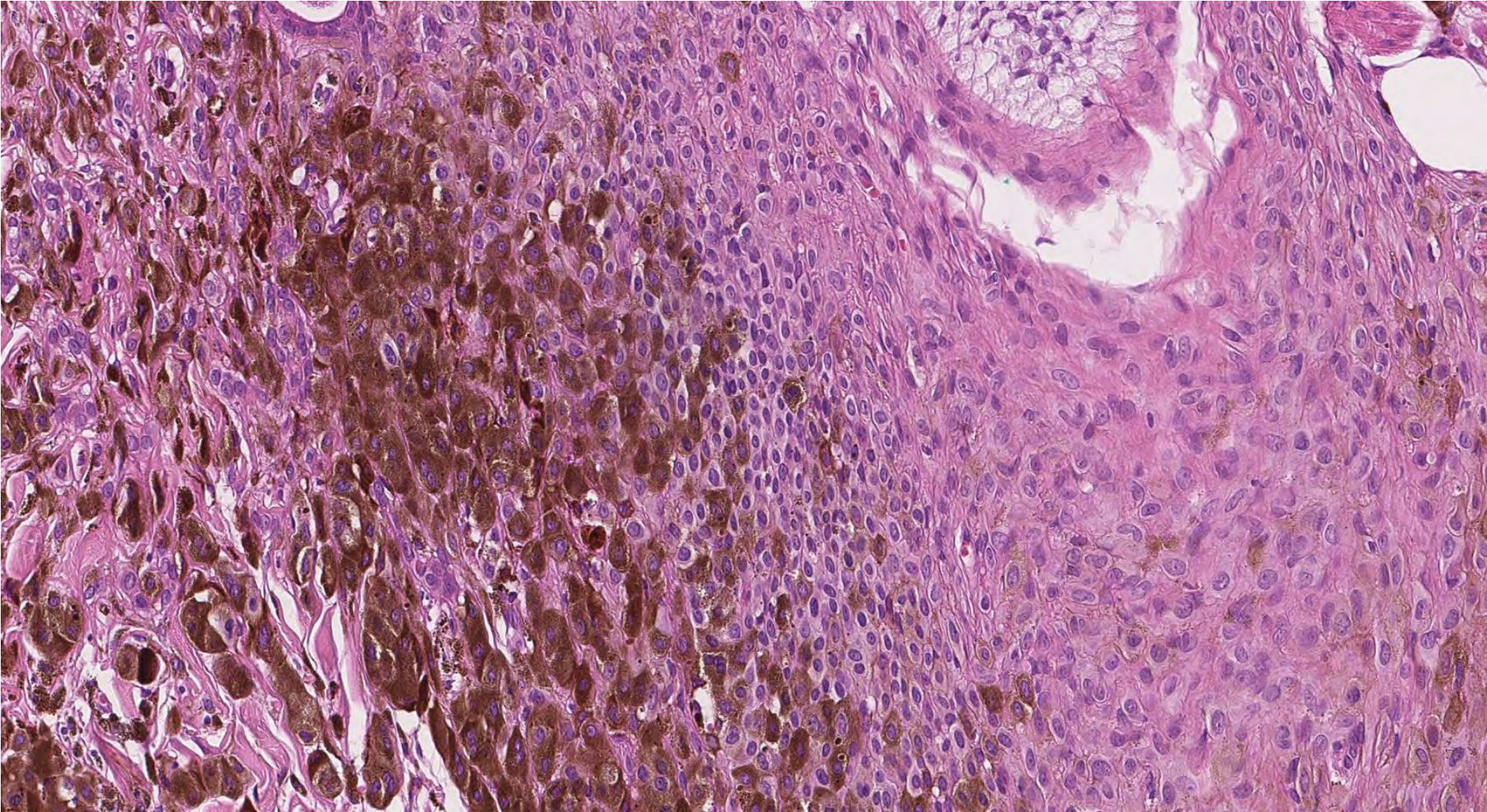


PKC gene fused melanocytic tumors
Cobblestone +/- pigmented (dermis)



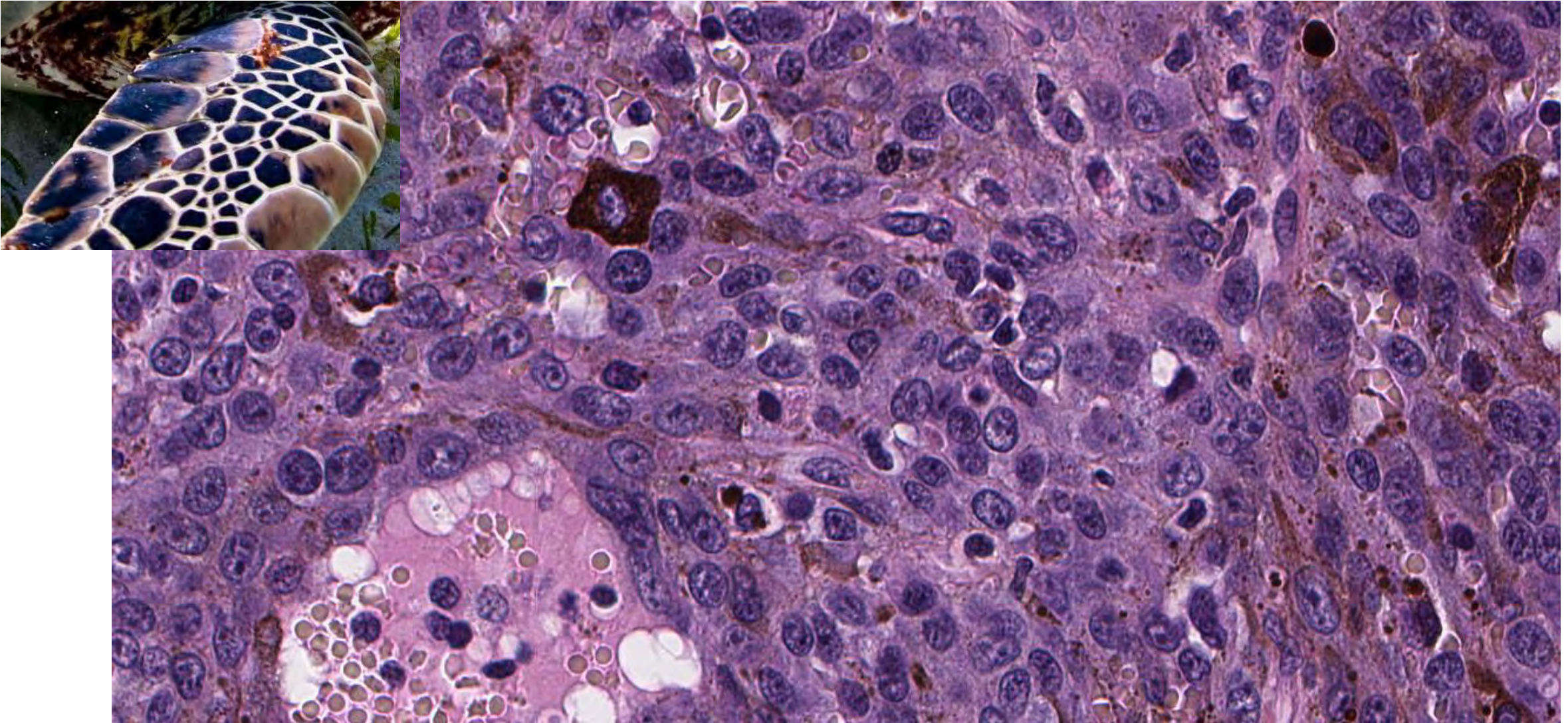
PKC gene fused melanocytic tumors

Cobblestone +/- pigmented (dermis)



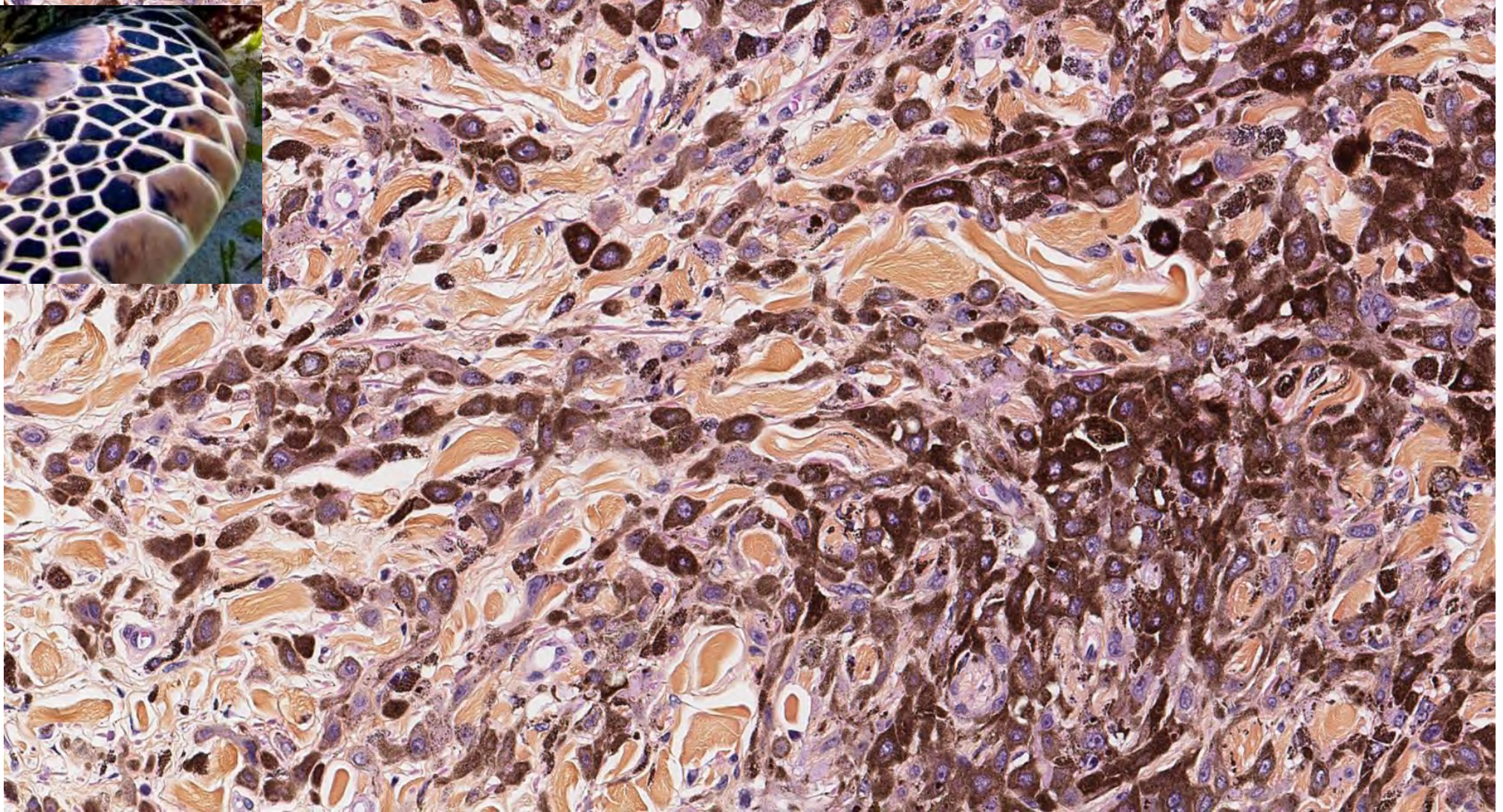
PKC gene fused melanocytic tumors

Green sea Turtle/Dragonscale cells



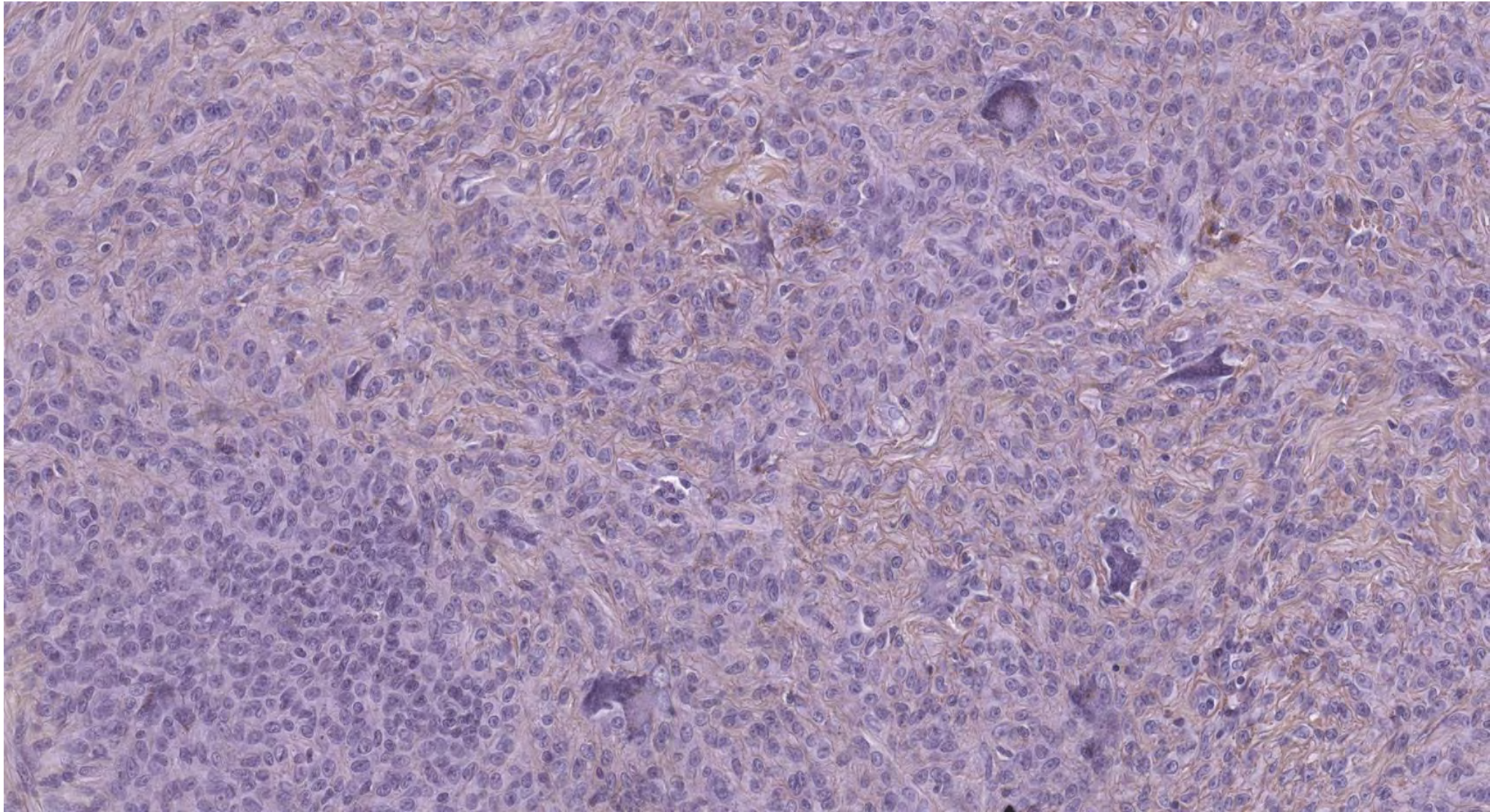
PKC gene fused melanocytic tumors

Green sea Turtle/Dragonscale cells



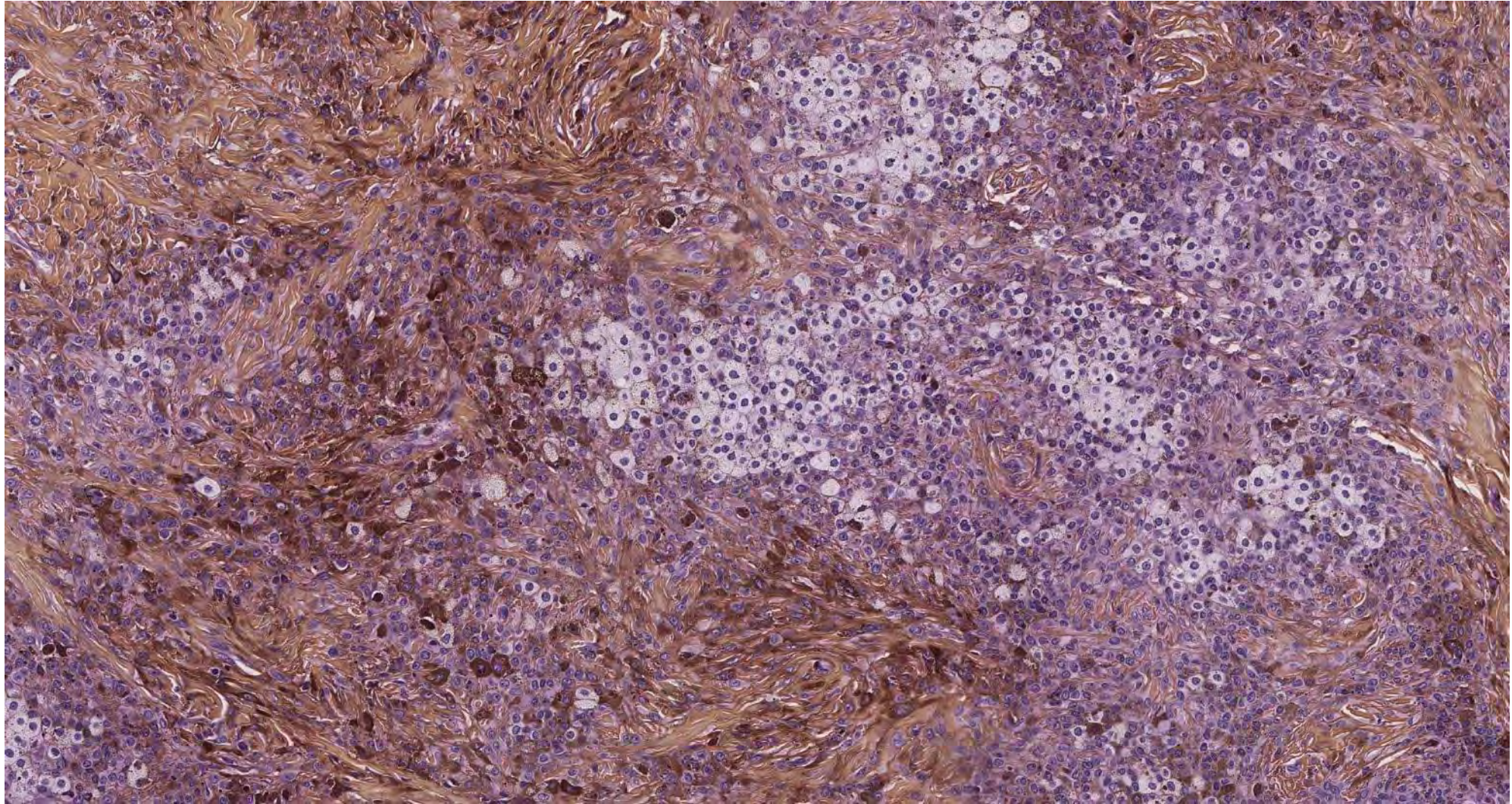
PKC gene fused melanocytic tumors

Multinucleated cells



PKC gene fused melanocytic tumors

Clear cells



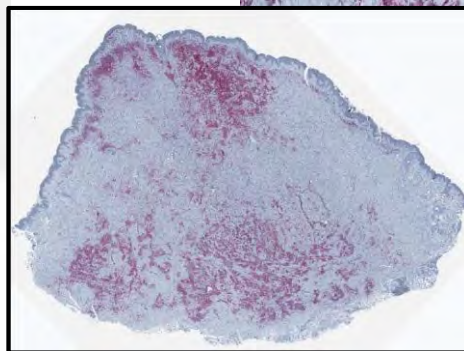
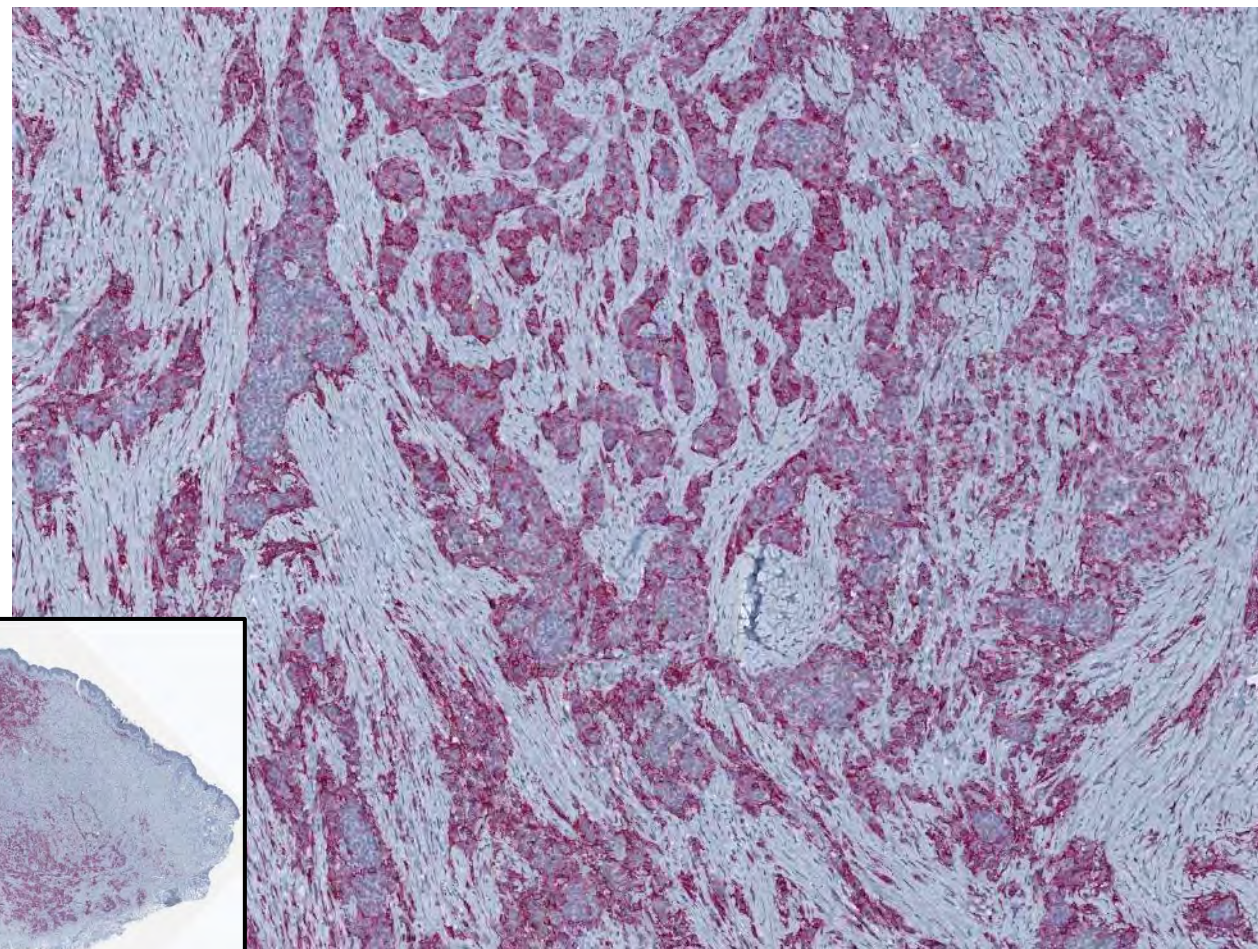
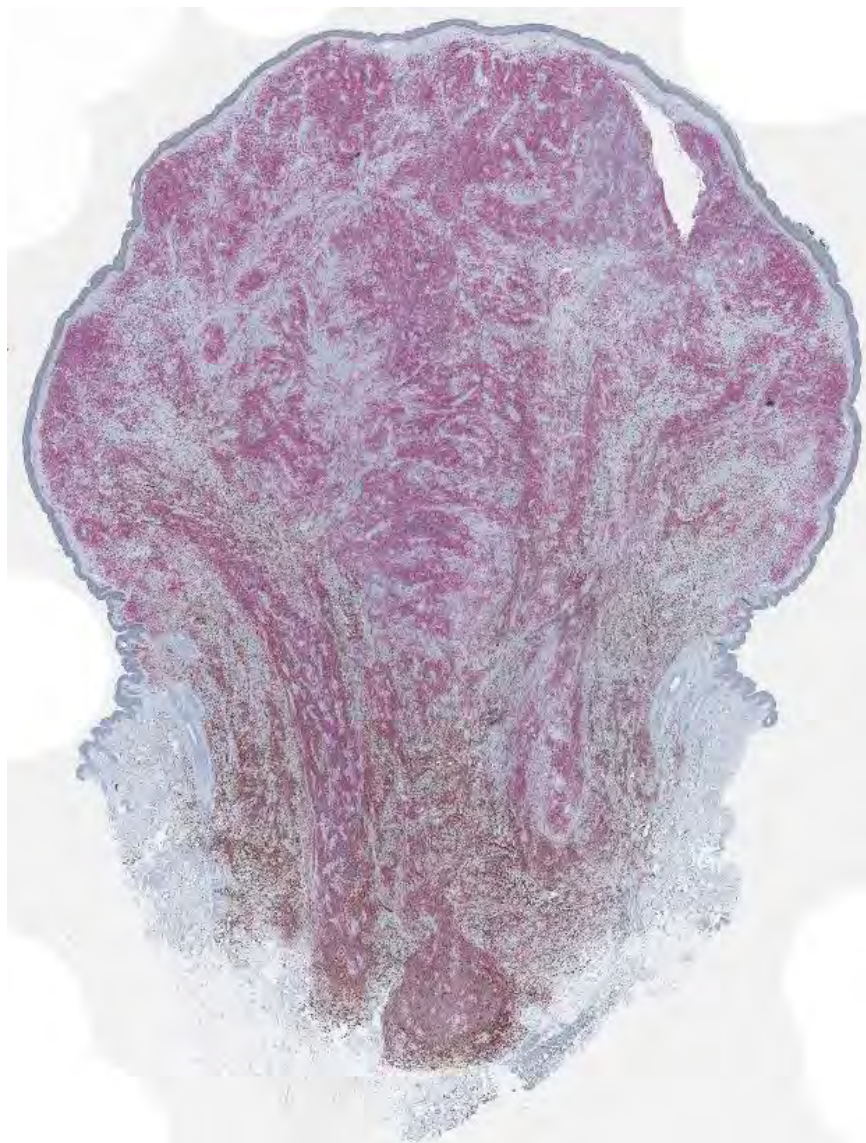
PKC gene fused melanocytic tumors

highly variable morphology

- Junctional PEM-like features
 - Upper dermis horizontal band
 - Dermal combined blue nevus features
 - Smooth muscle hyperplasia
 - Variable pigment load
 - Variable but constant fibrosis
-
- « PEM + Common + Blue » mixture suggests PKC gene fused tumour
 - Can have partial features and/or extreme ends of the spectrums

PKC gene fused melanocytic tumors

HMB45



S100 nuclear expression loss in upper dermis band



PRKCA/B-fused «Blue» melanocytic tumors

Take home messages

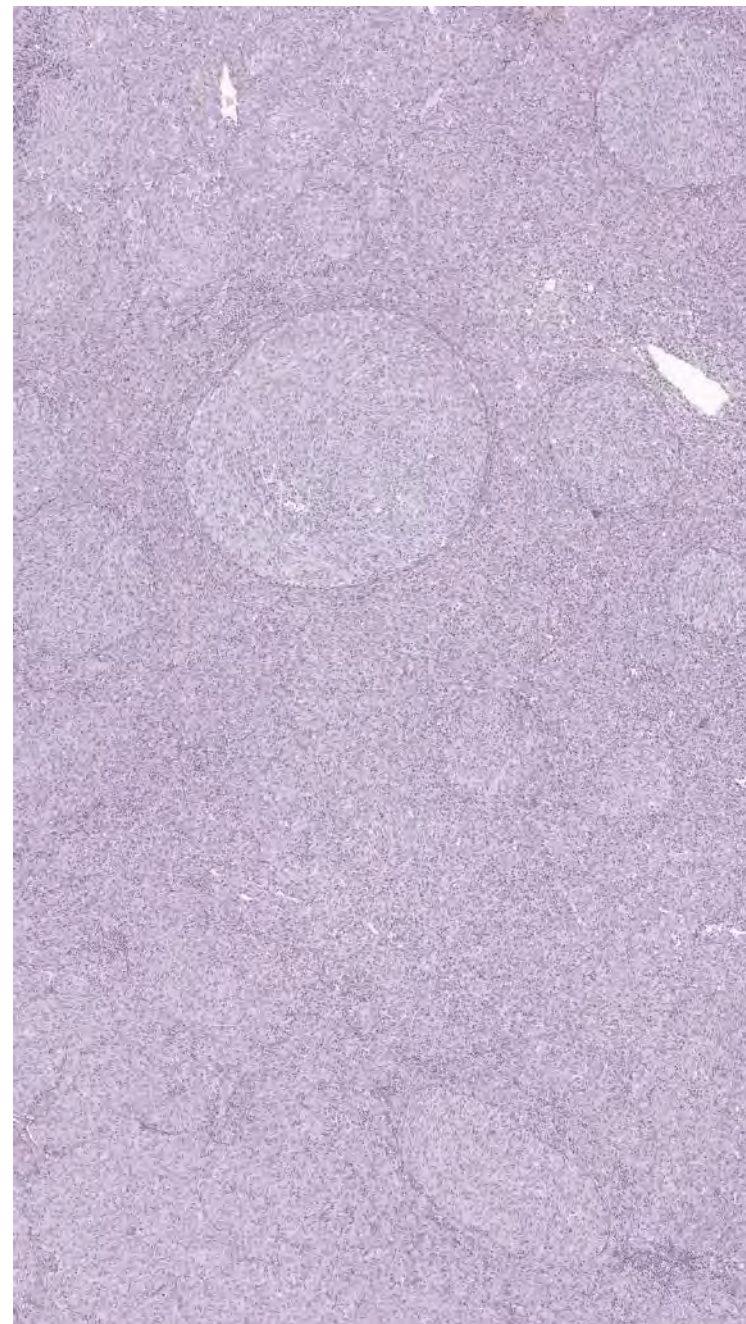
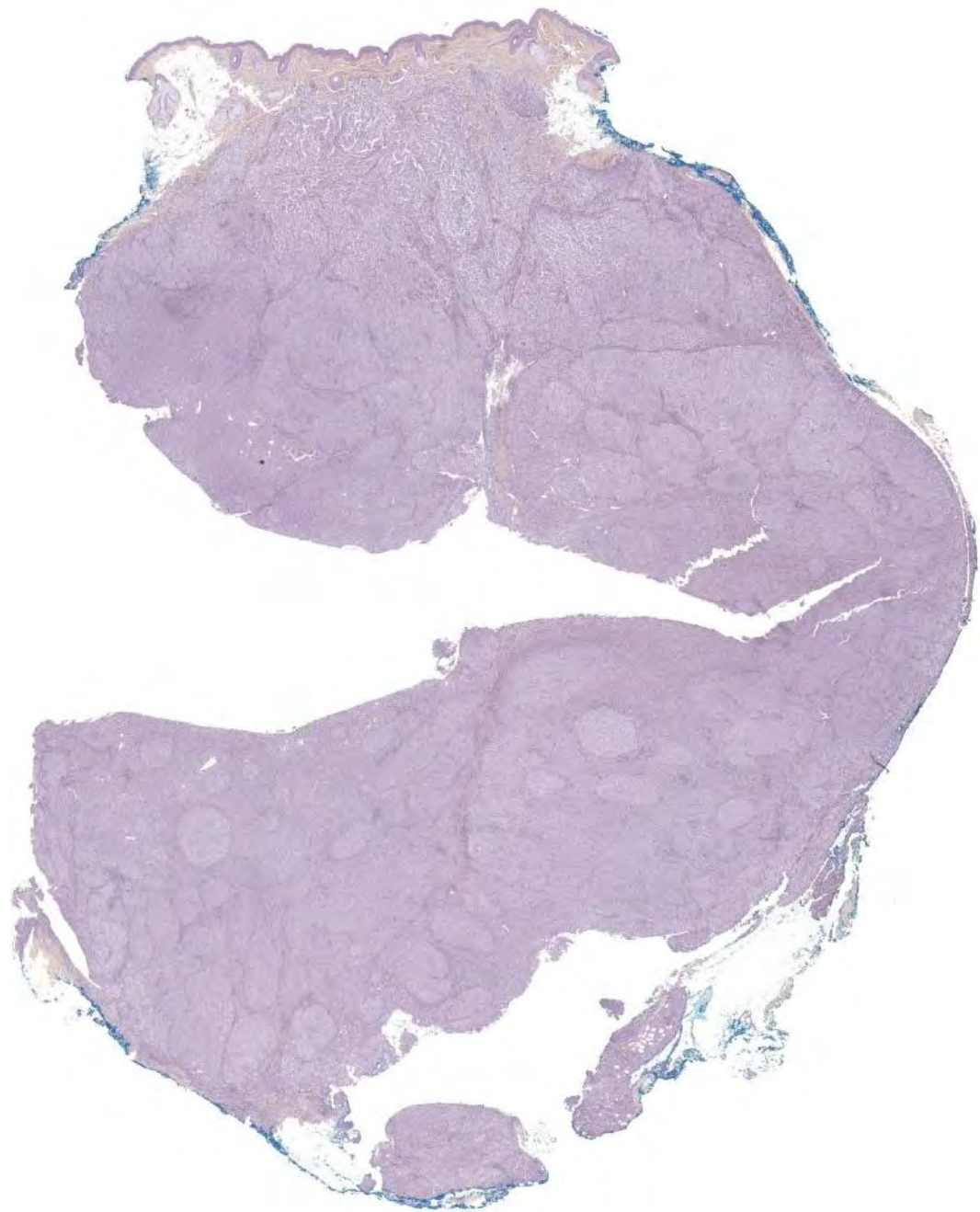
- Frequent tumour with **complex morphologic features**
Fibrosis +/- biphasic blue-common +/- dermal band +/- PEM-like
- Most cases are **benign**
- Clonal evolution can lead to rare malignant/potentially fatal cases even in children +/- BAP1-inactivation

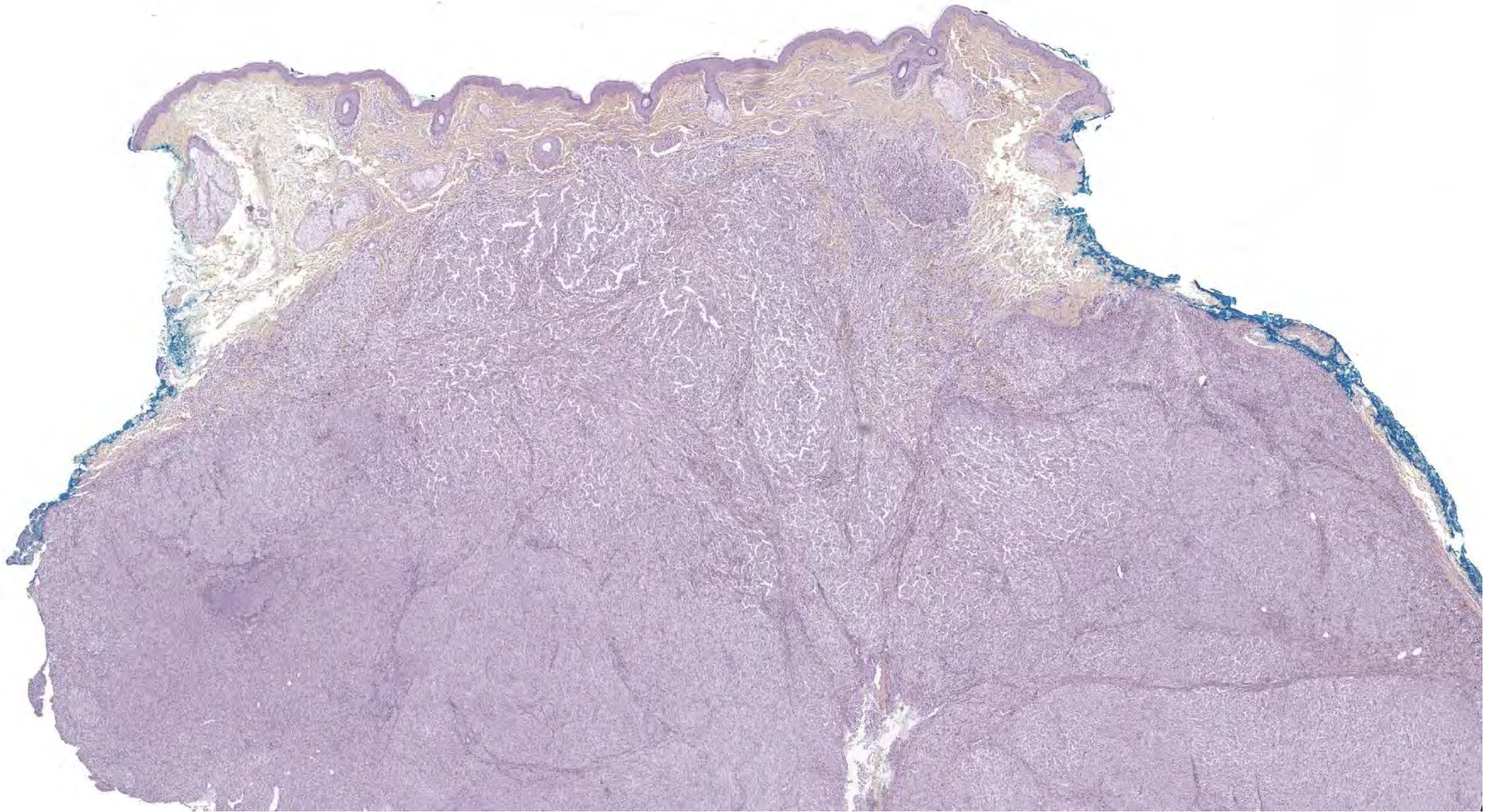
Case 18

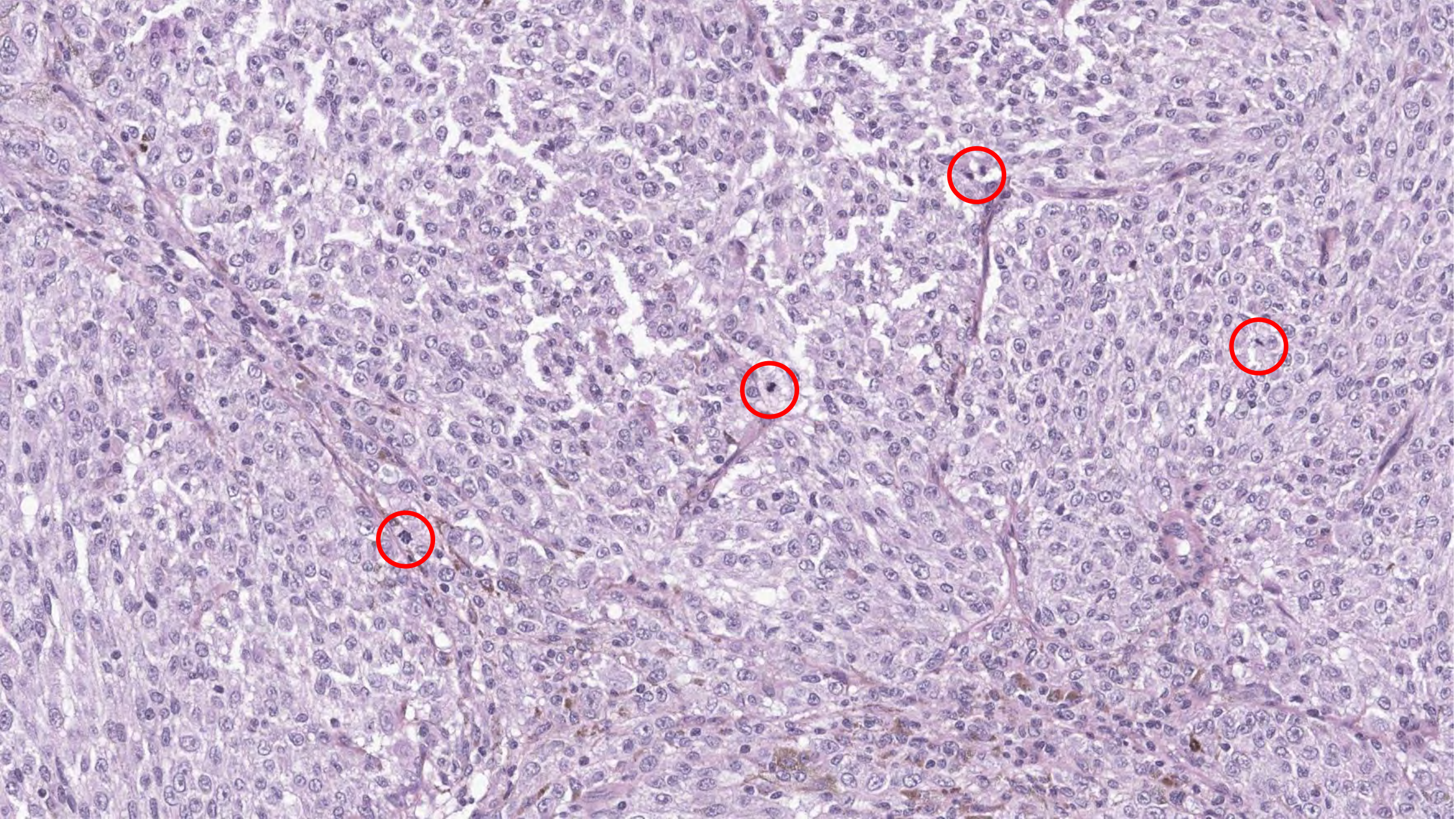
Arnaud de la Fouchardière

Teenager (F16) with a slowly growing nodule on the left temporal area (several years between 2 pictures)









What is your diagnosis?

A metastatic uveal melanoma

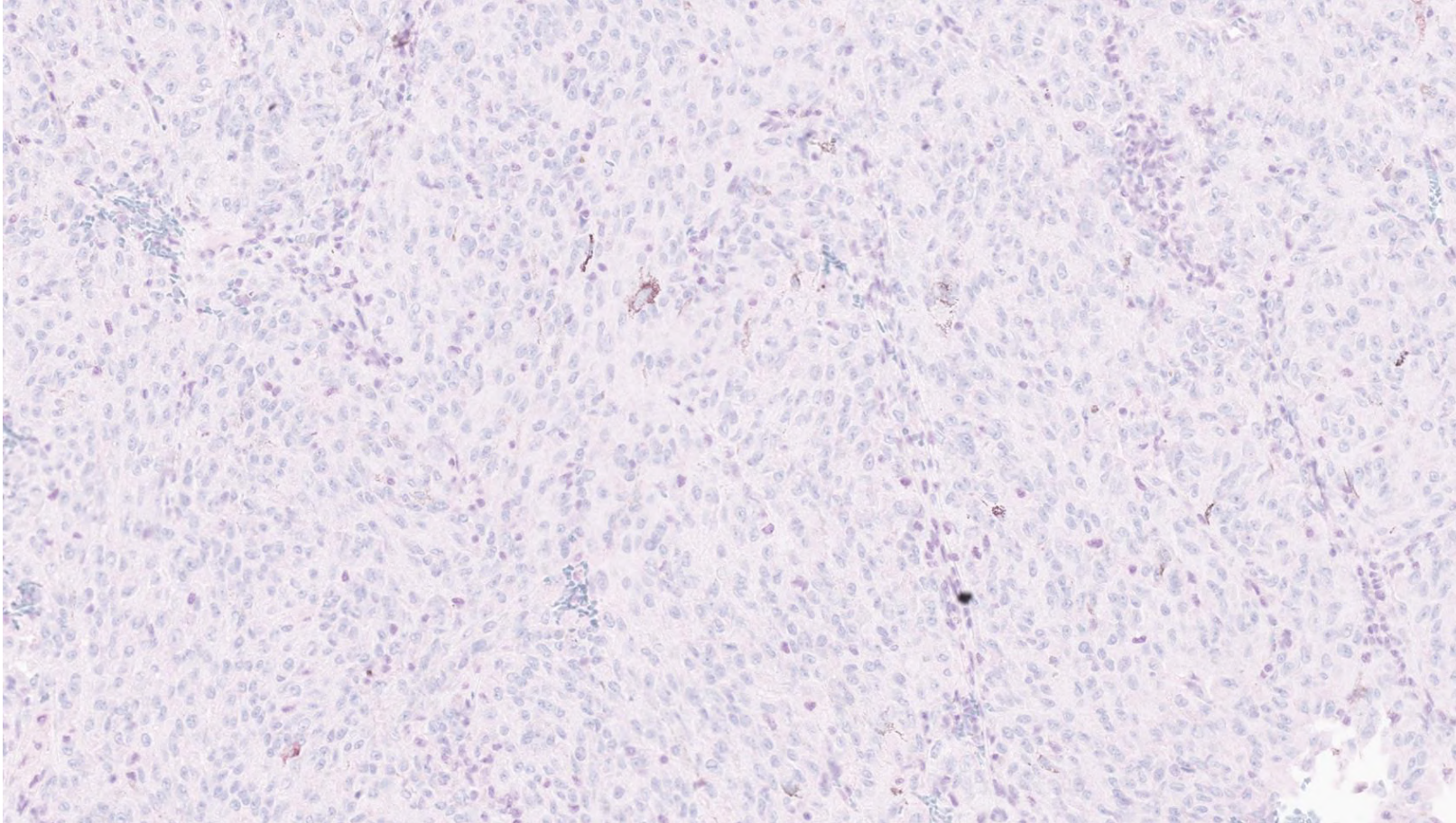
B Malignant BAP1-inactivated melanoma (WHO Class I)

C Spitzoid melanoma

D Malignant Blue melanoma ex blue nevus

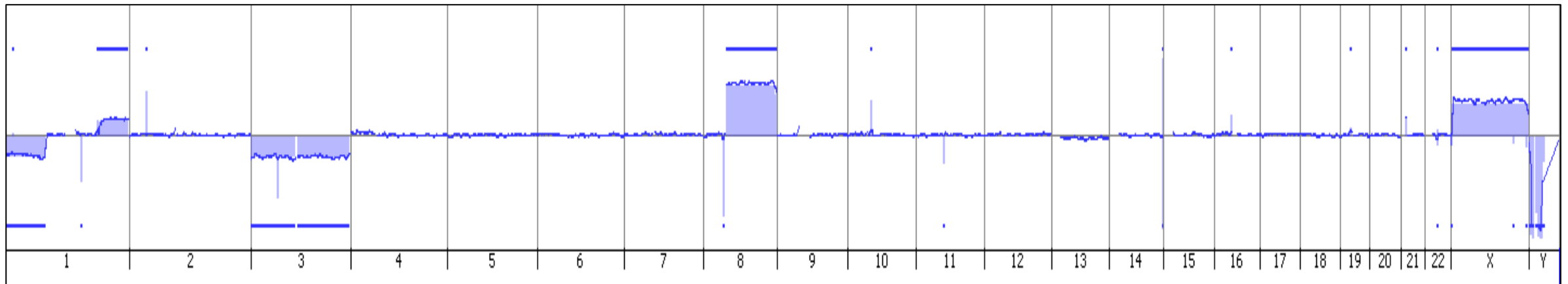
E Nevoid melanoma

BAP1 nuclear expression lost:
malignant transformation of a BIM?



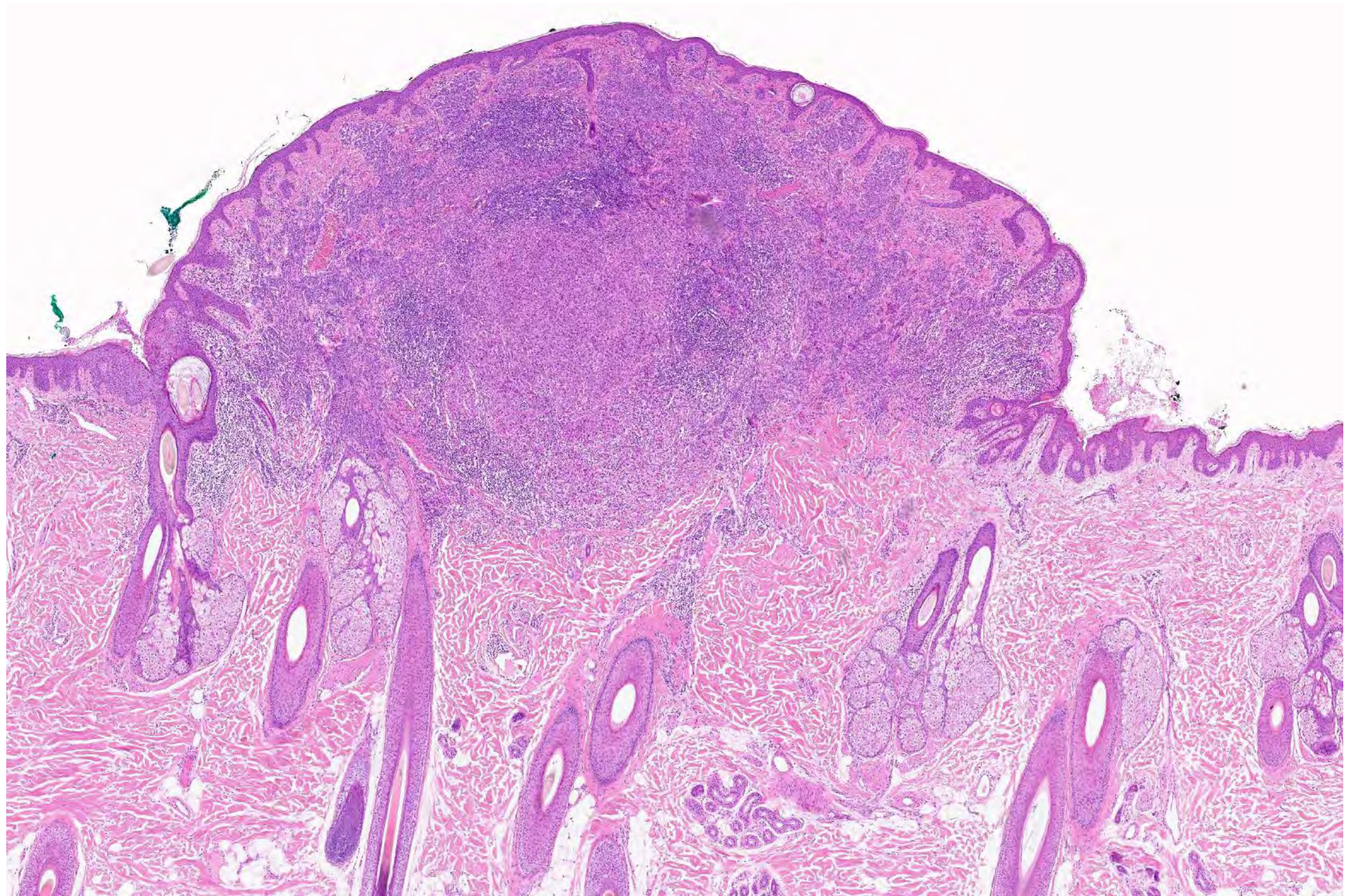
Molecular results

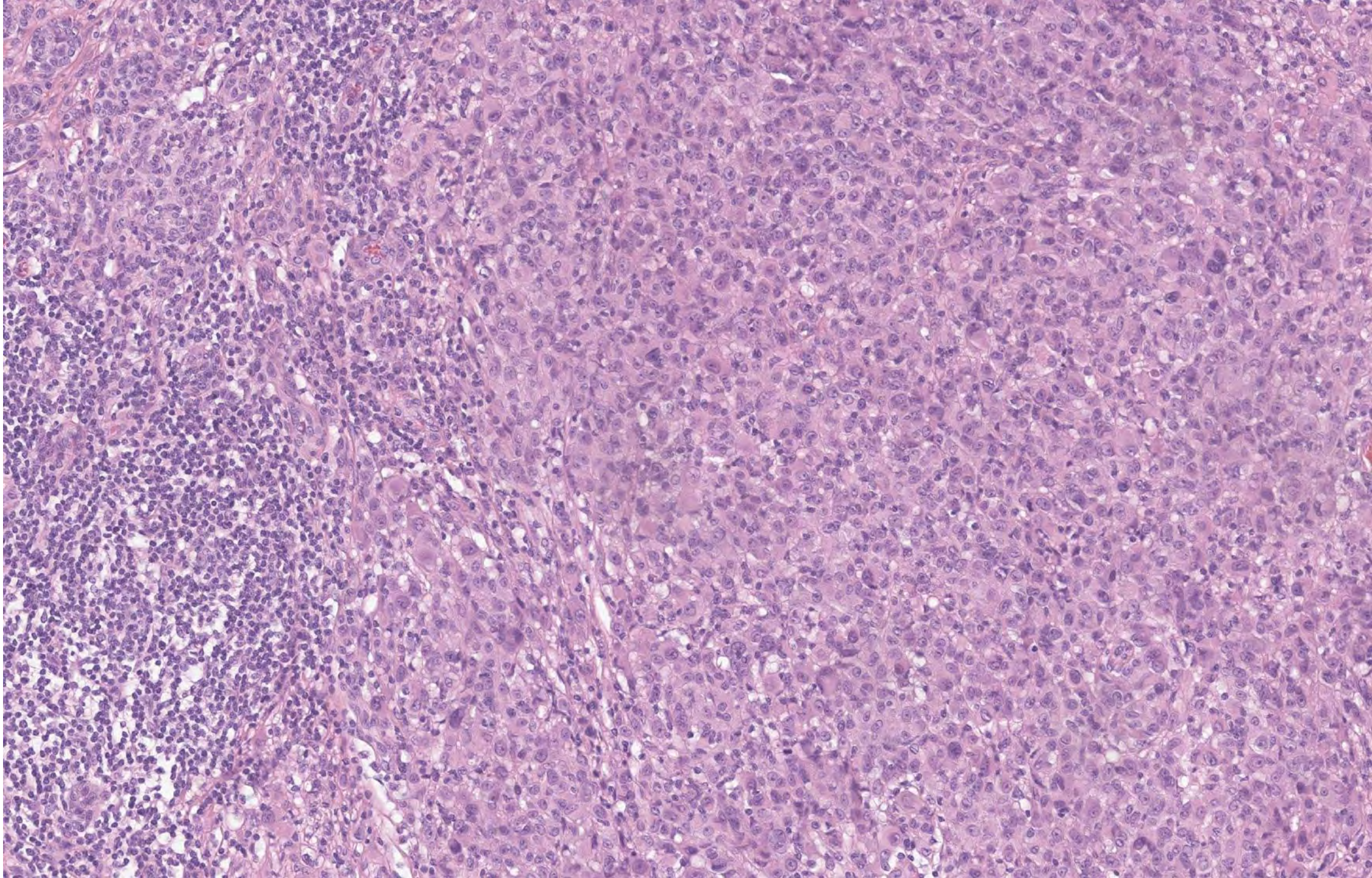
- RNA-seq : **GNA11** p.Q209P Mutation
- Underexpression of BAP1
- TMB low
- Array-CGH

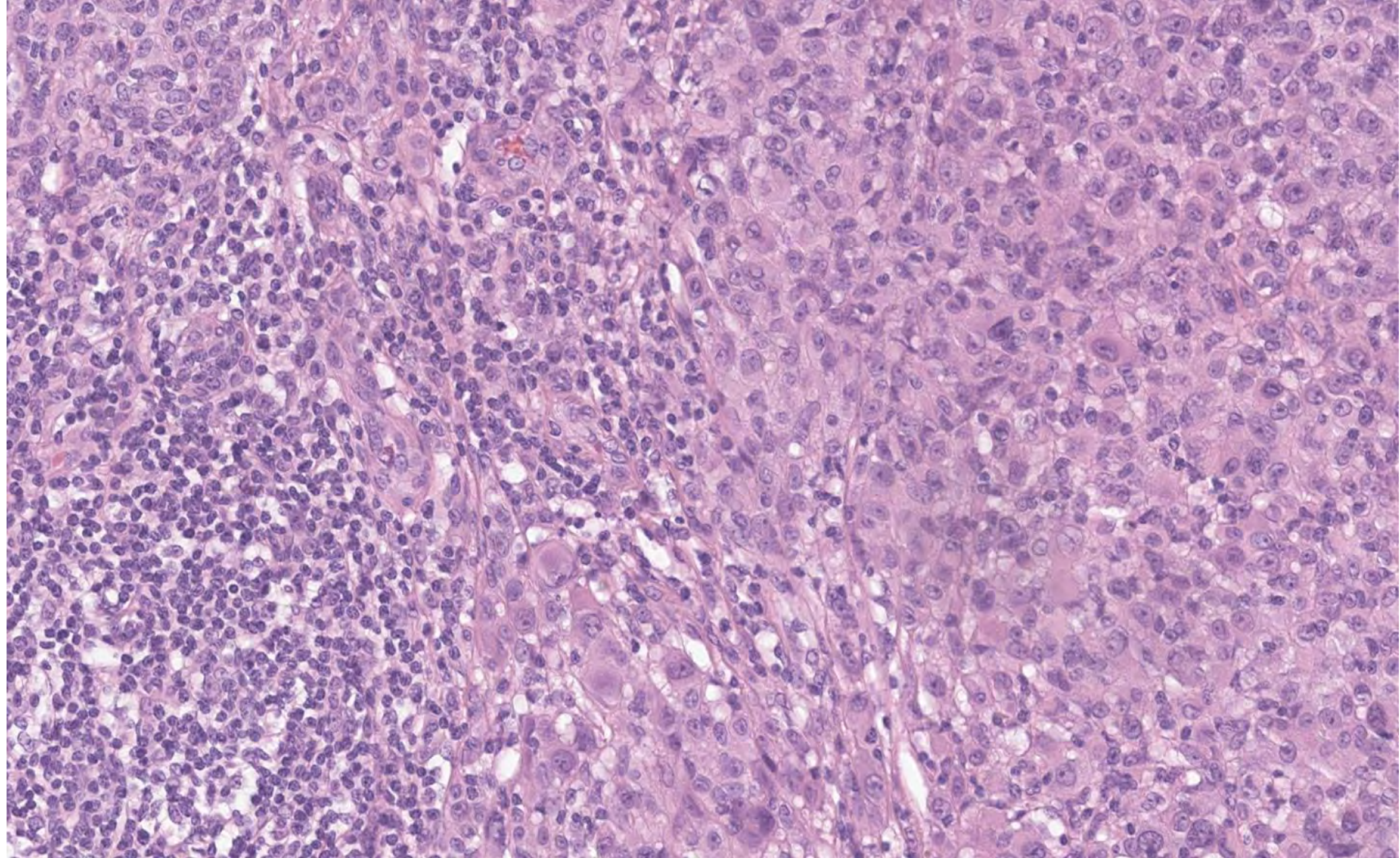


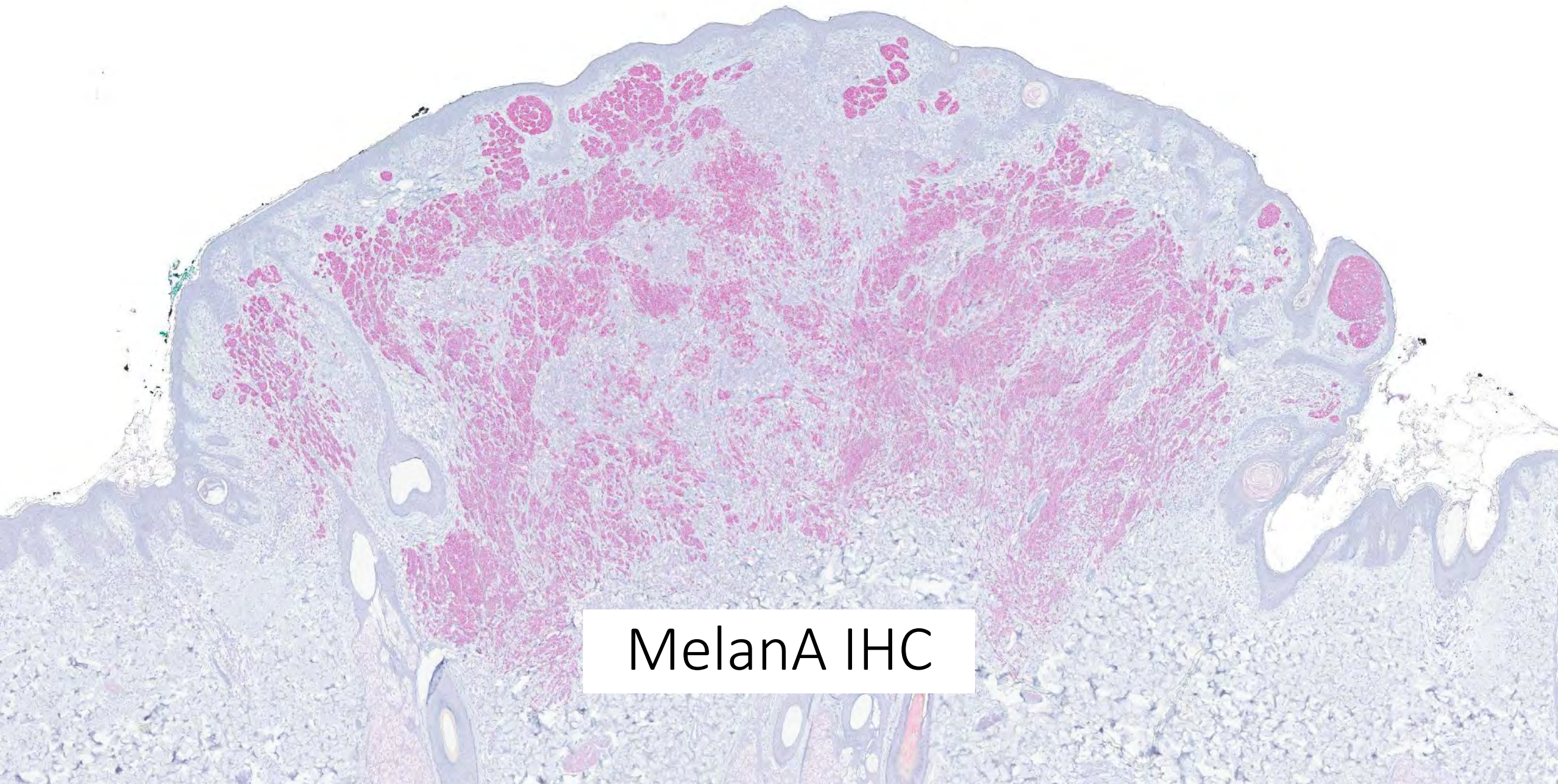
6 months later

- Two growing nodules on scalp and back

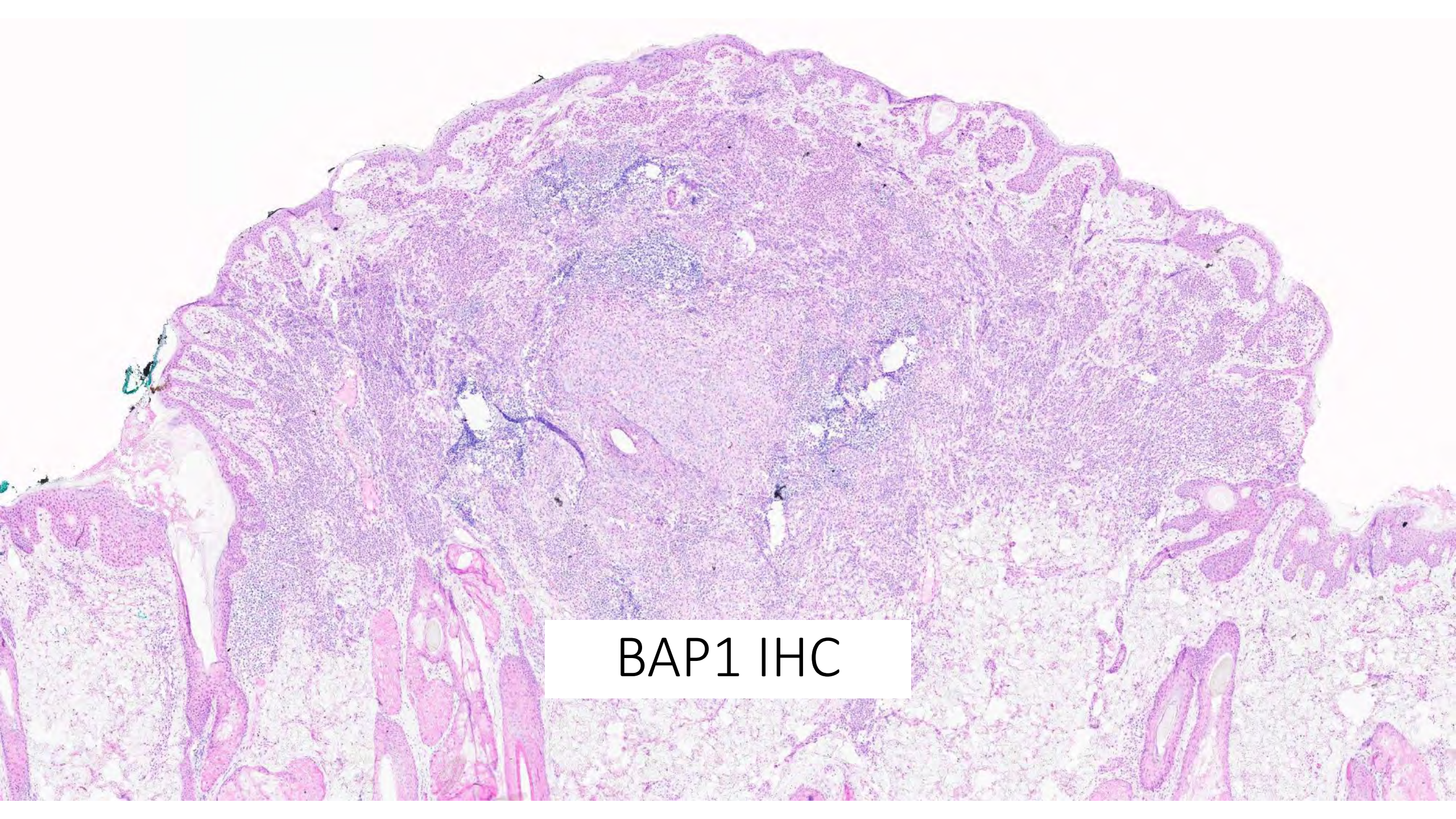




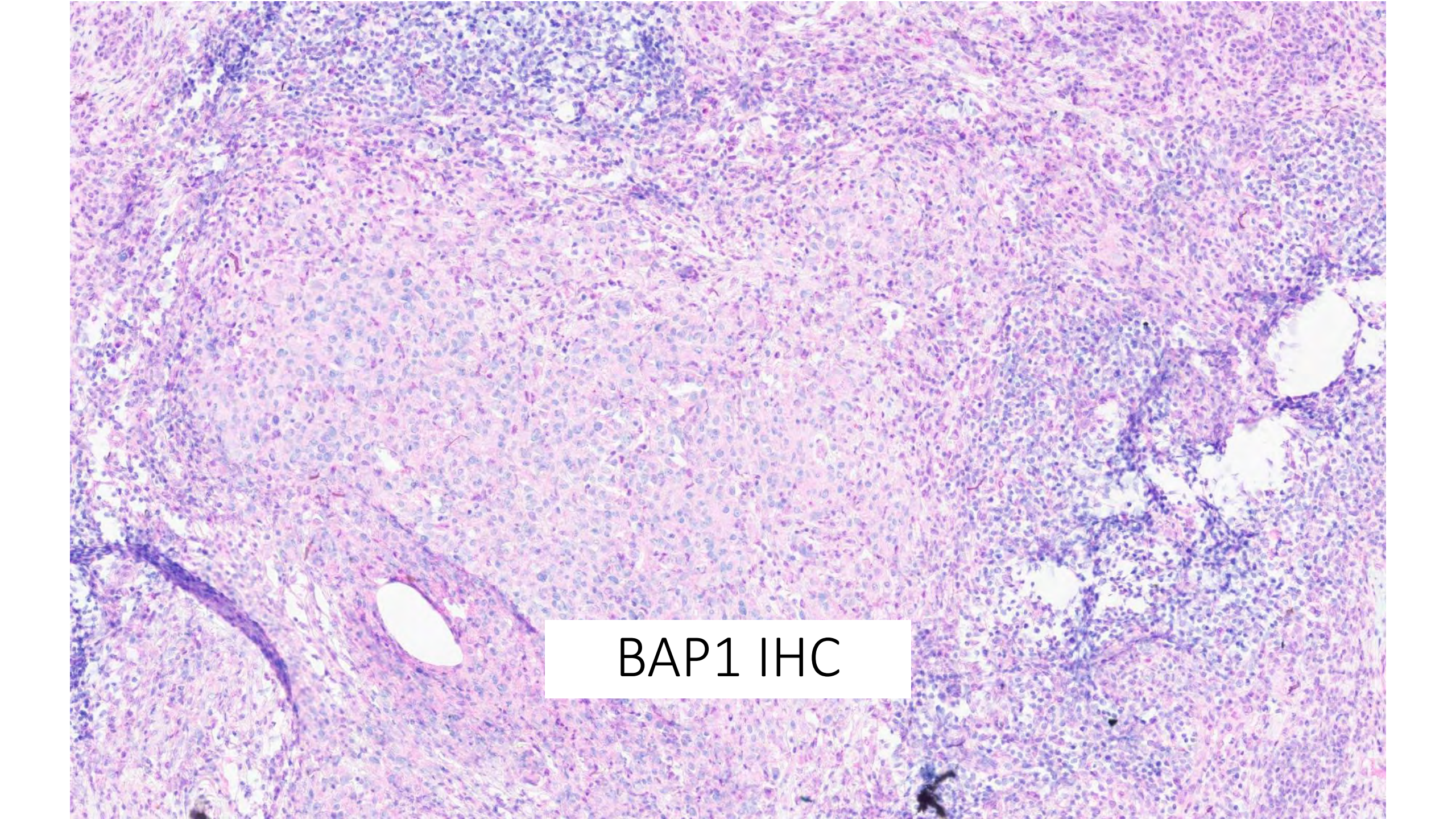




MelanA IHC



BAP1 IHC



A histological section of tissue, likely from a glandular organ, stained with hematoxylin and eosin (H&E). The tissue shows a dense population of cells with prominent nuclei (stained blue/purple) and pink-stained cytoplasm and extracellular matrix. There are several large, clear, oval spaces (cysts or dilated ducts) scattered throughout the tissue. The overall architecture suggests a complex, possibly neoplastic, process.

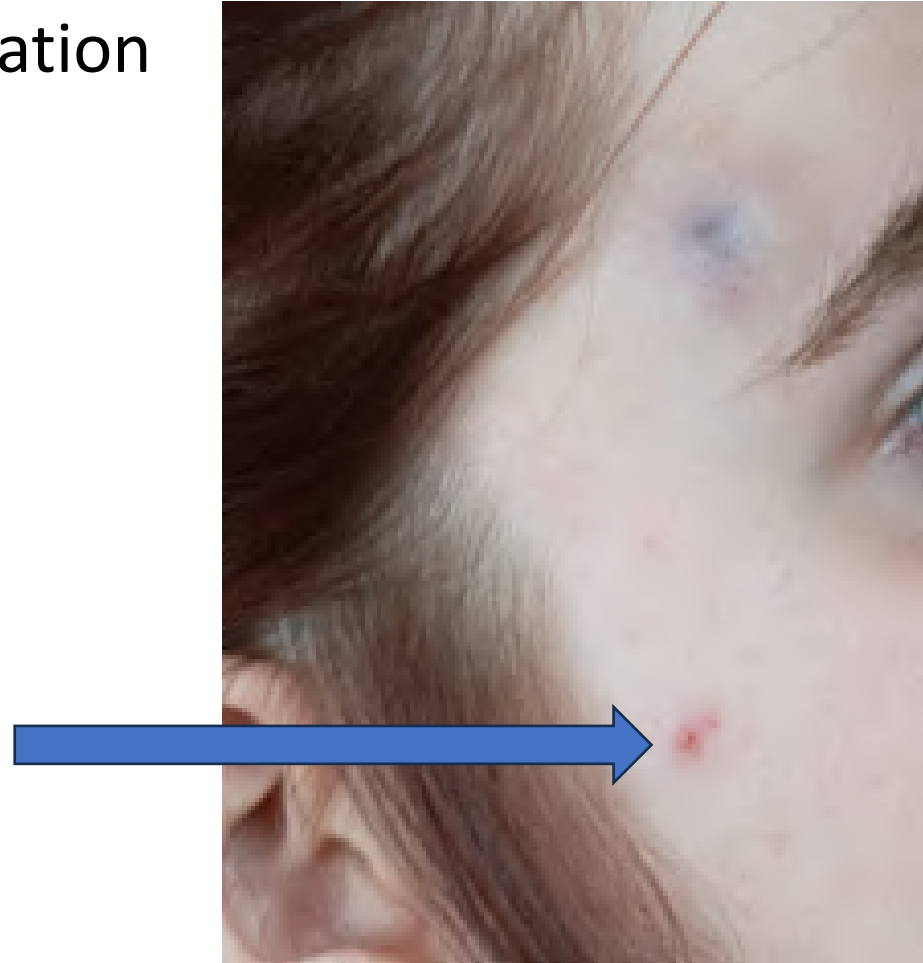
BAP1 IHC

Final diagnosis lesion n°2

- BAP1-inactivated Melanocytoma

Final diagnosis lesion n°2

- Melanocytoma with BAP1 inactivation



Clinical complementary information

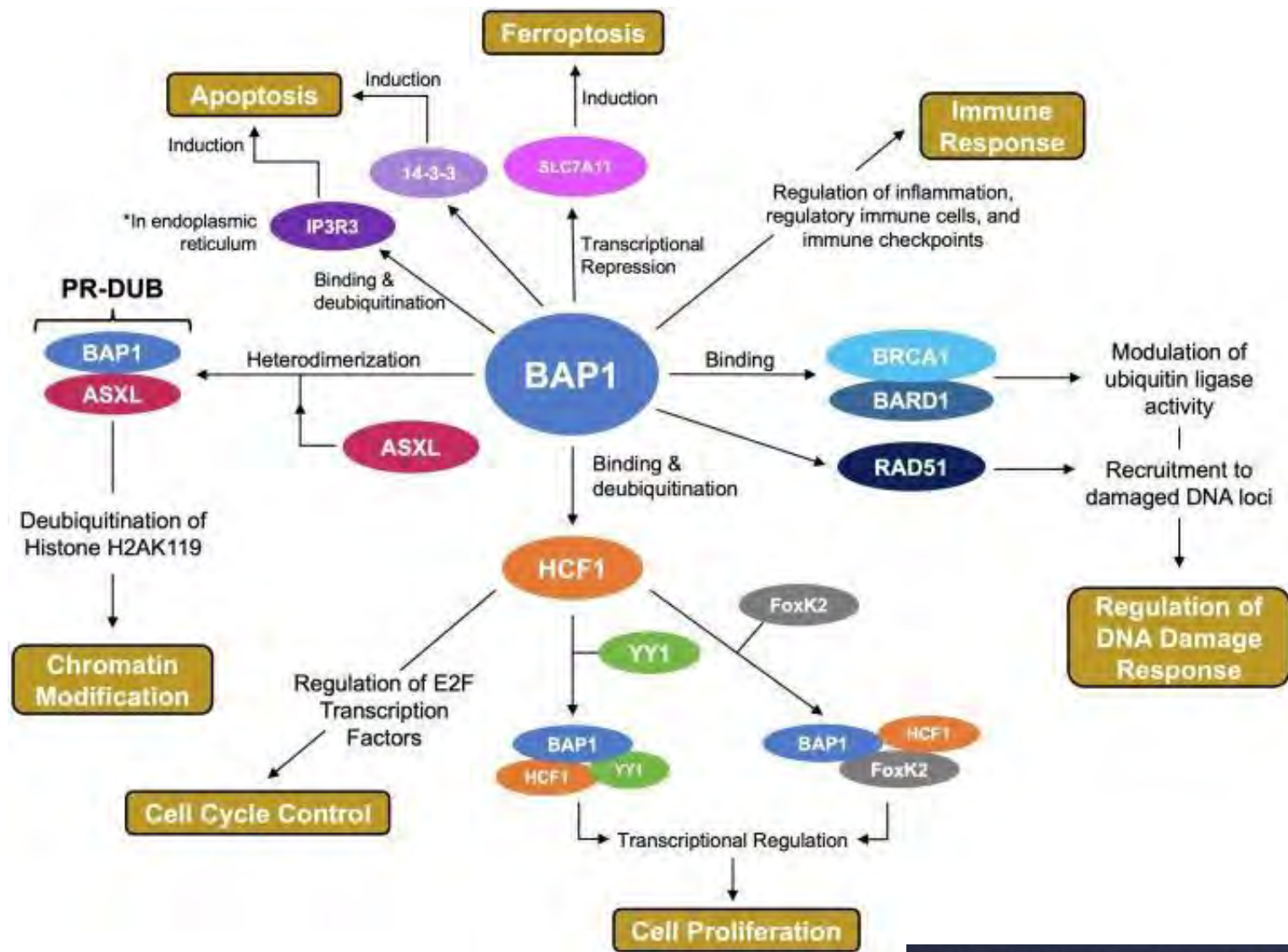
Familial history enriched:

- Lethal ocular melanoma (grandmother on mother side)
- Multiple cancer at young age (uncle mother side)
 - Mother tested for BAP1 TPS

Final diagnosis

- BAP1 tumor predisposition syndrome revealed by a melanoma ex-blue nevus in an adolescent

BAP1-related tumour predisposition syndrome

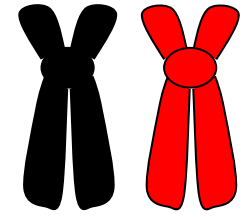


BAP1: Not just a BRCA1-associated protein

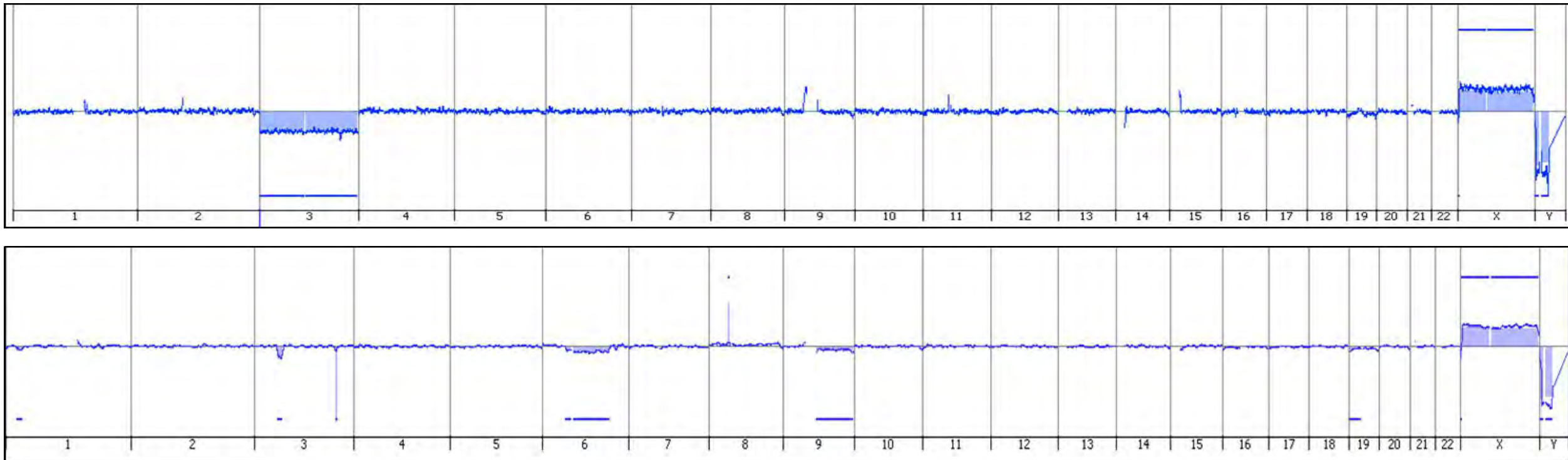
Bryan H. Louie • Razelle Kurzrock

Open Access • Published: August 19, 2020 • DOI: <https://doi.org/10.1016/j.ctrv.2020.102091> •

«Knudson-type» 2 hit model



- Germline mutation of one *BAP1* allele
- Loss of the second allele (Monosomy 3 or segmental 3p21 loss)



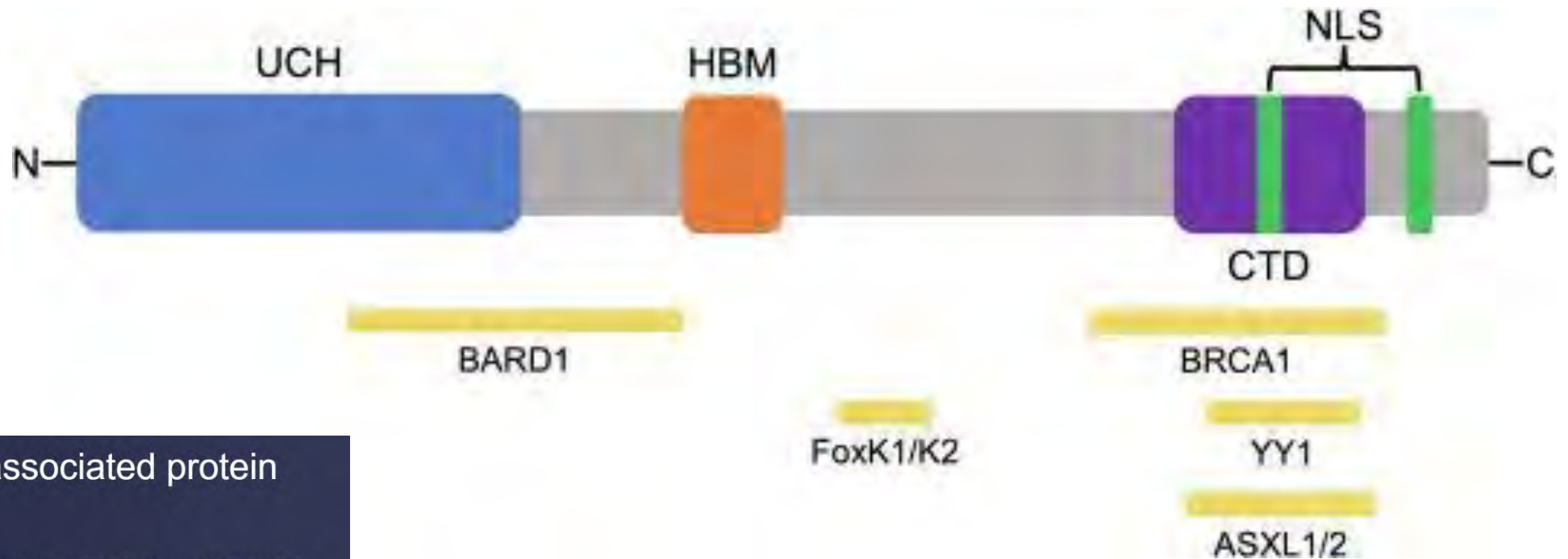
BAP1 protein structure

UCH: ubiquitin carboxy-terminal hydrolase

HBM: HCF1-binding domain

NLS: nuclear localization signal x2

CTD: C-terminal protein interaction domain

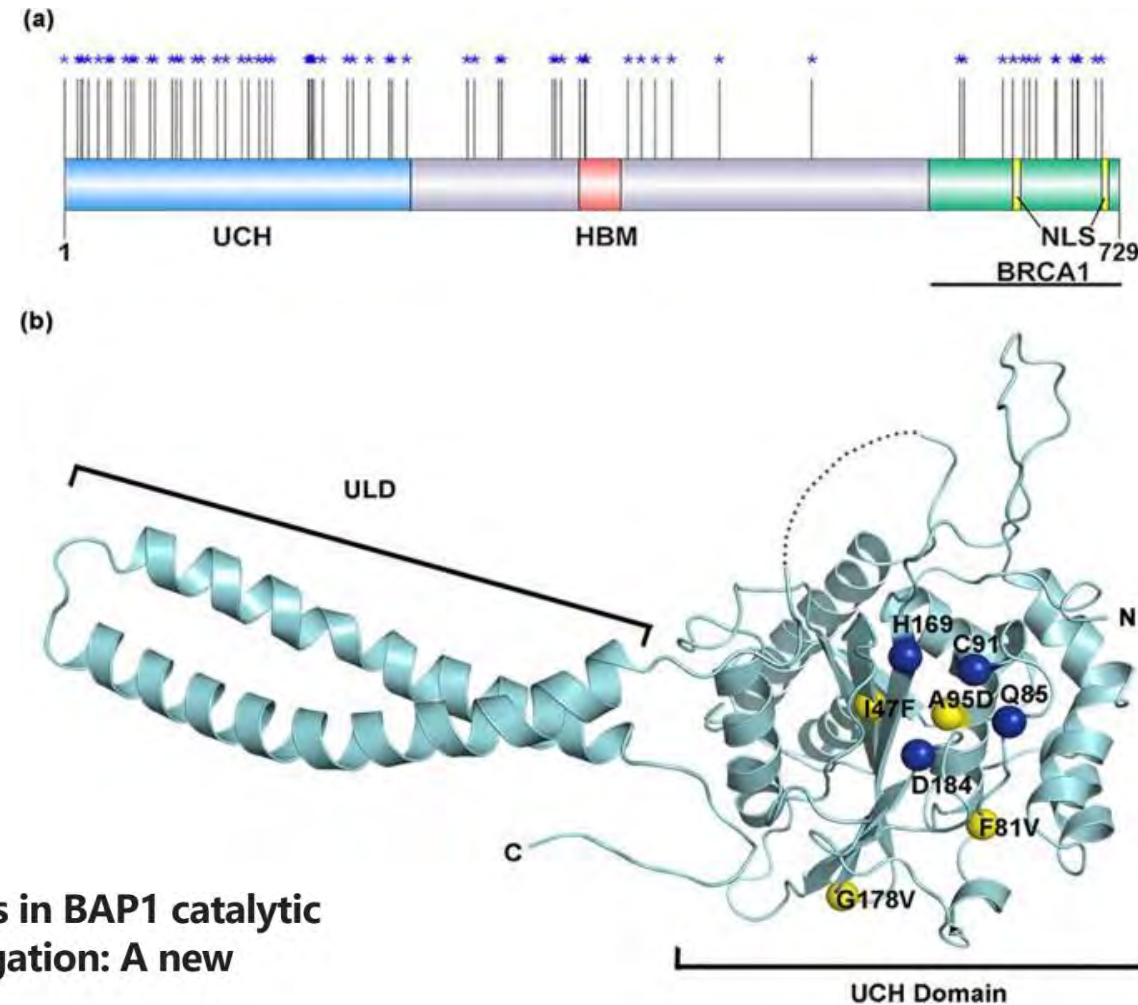


BAP1: Not just a BRCA1-associated protein

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Open Access • Published: August 19, 2020 • DOI: <https://doi.org/10.1016/j.ctrv.2020.102091>

Site of germline mutations



Cancer associated missense mutations in BAP1 catalytic domain induce amyloidogenic aggregation: A new insight in enzymatic inactivation

[Sushmita Bhattacharya](#), [Pranita Hanpude](#) & [Tushar Kanti Maiti](#)

[Scientific Reports](#) 5, Article number: 18462 (2016) | [Cite this article](#)

Main tumours associated with a *BAP1*-TPDS

- Mesothelioma (pleural and peritoneal)
- Uveal melanoma
- Clear cell renal cancer
- Atypical cutaneous melanocytic tumors (BAP1-IMT)
- Cutaneous melanoma ex-BIMT

Arise at a younger age

Less frequent tumours associated with a *BAP1*-TPDS

- Mesothelioma (pleural and peritoneal)
- Uveal melanoma
- Clear cell renal cancer
- Atypical cutaneous melanocytic tumors (BAP1-IMT)
- Cutaneous melanoma *ex-BIMT*
- Meningiomas
- Multiple basal cell carcinomas
- Hepatocellular carcinoma
- Cholangiocarcinoma

Arise at a younger age

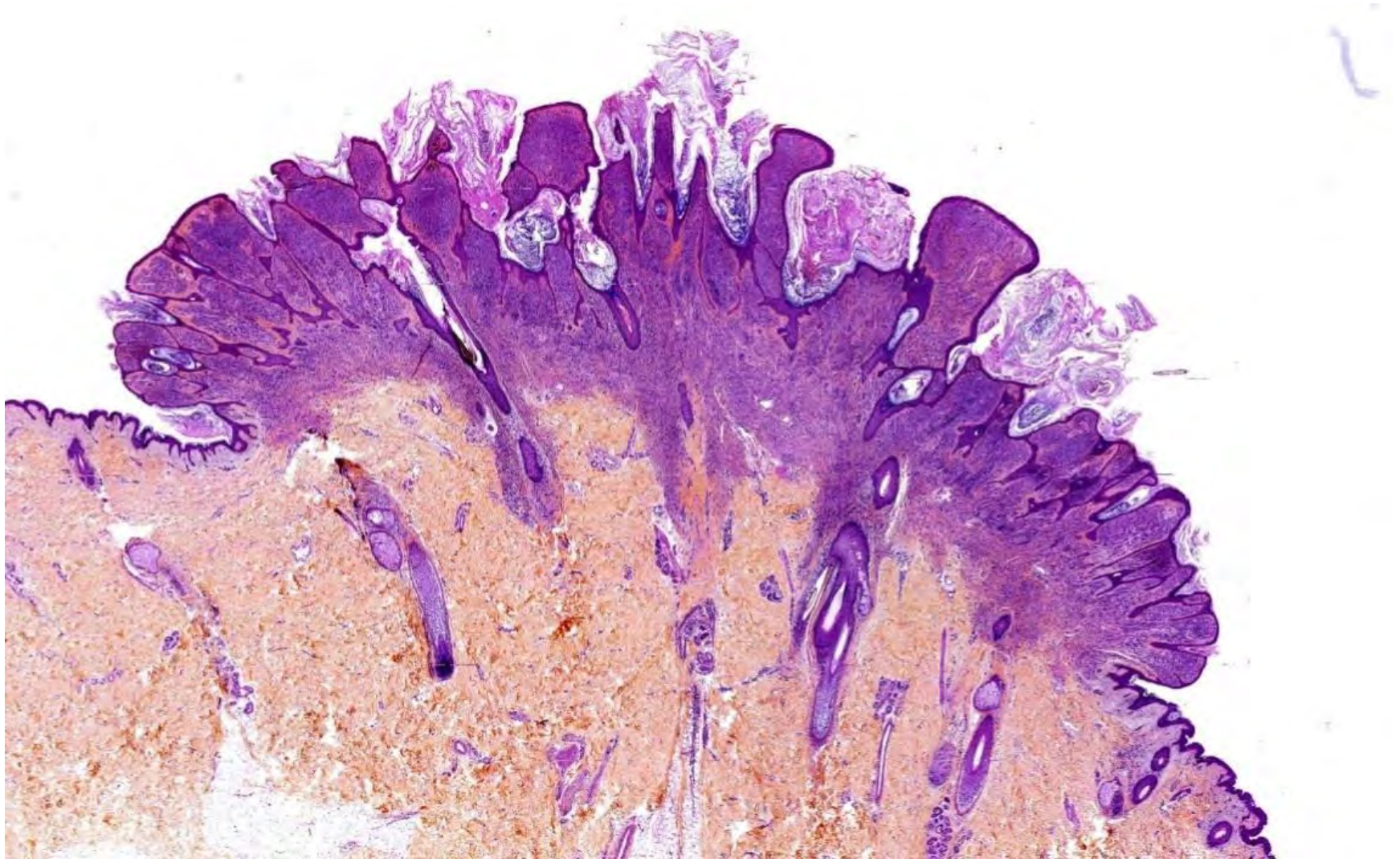
BAP1-TPDS frequency from 1 case

- Uveal melanoma <4%
- Clear cell Renal cancer <4%
- Mesothelioma 8-10%
- BAP1-inactivated melanocytoma <12%
- Basal cell carcinoma 100%

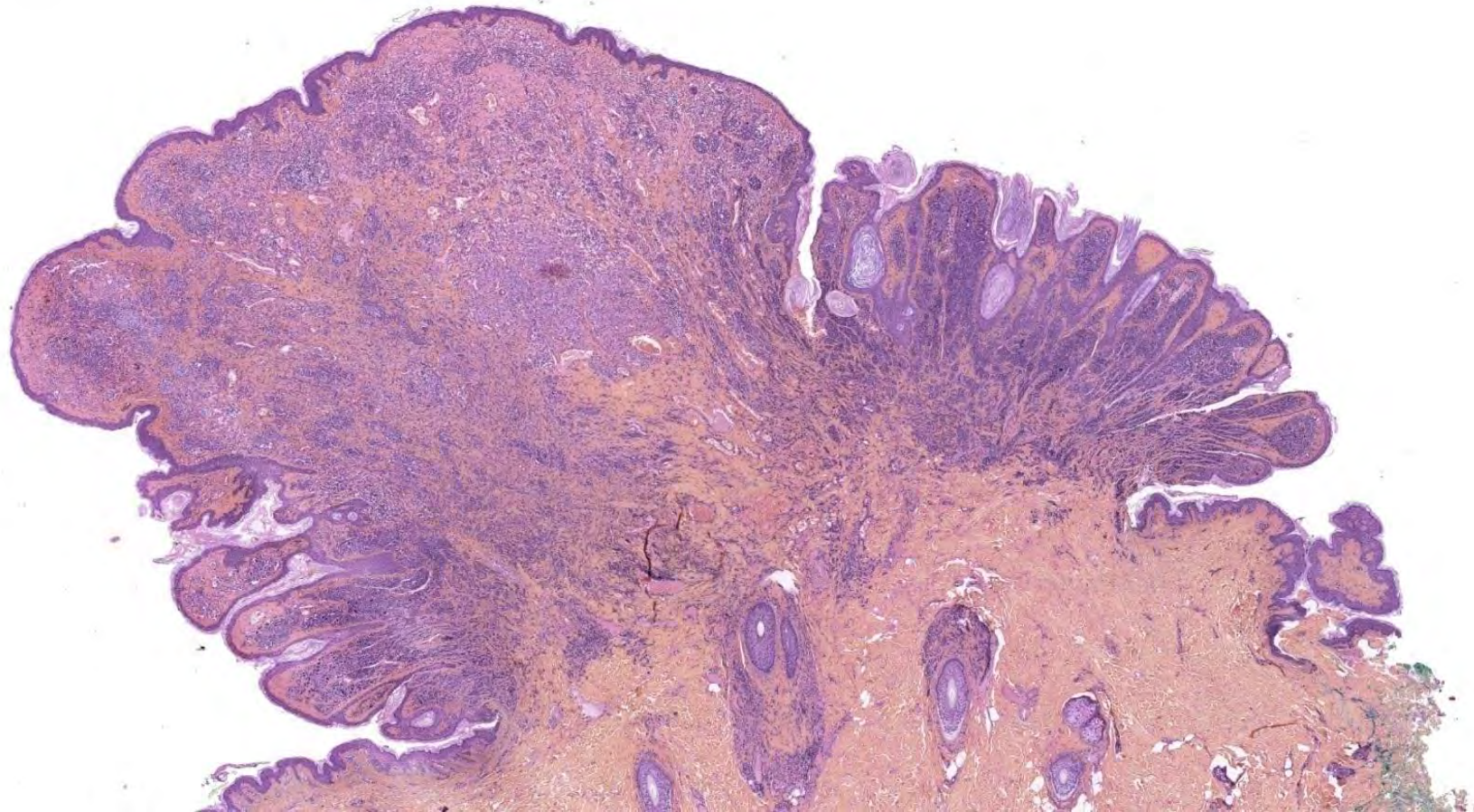
BAP1-IMT skin phenotype

- BAP1-IMT do not arise from normal skin melanocytes
- An individual with X nevi can only develop X BAP1-IMT at most
- Coherent with the mice model

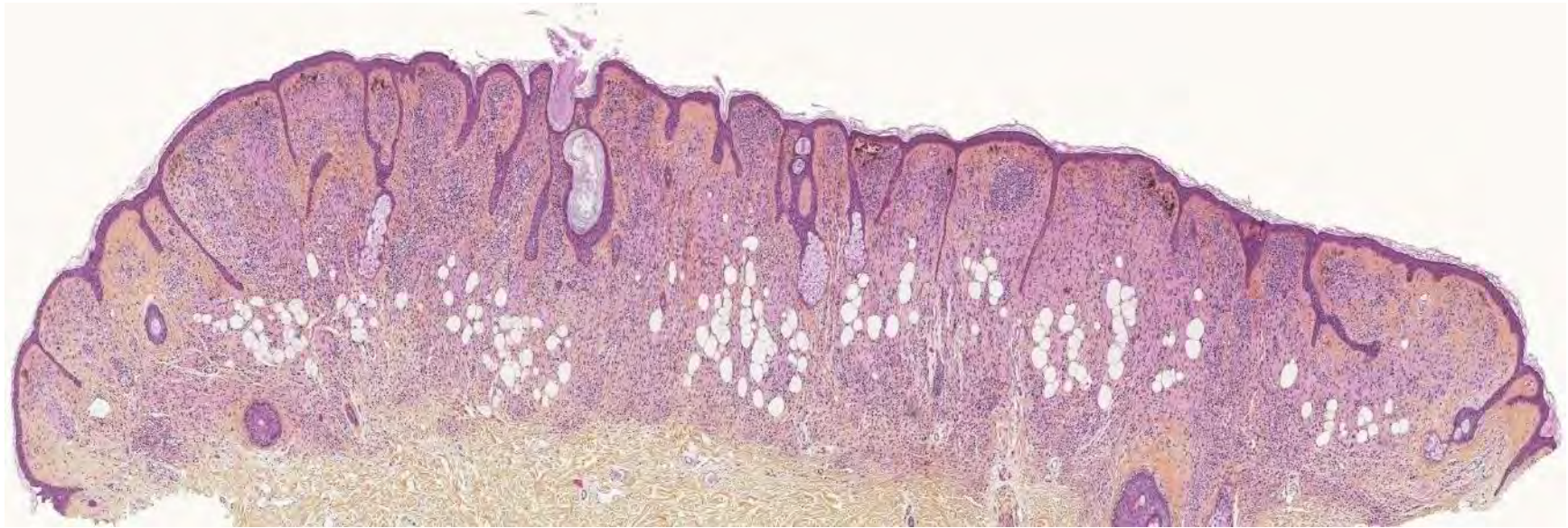
BAP1-imts keep the morphologic features of the nevi they arise from



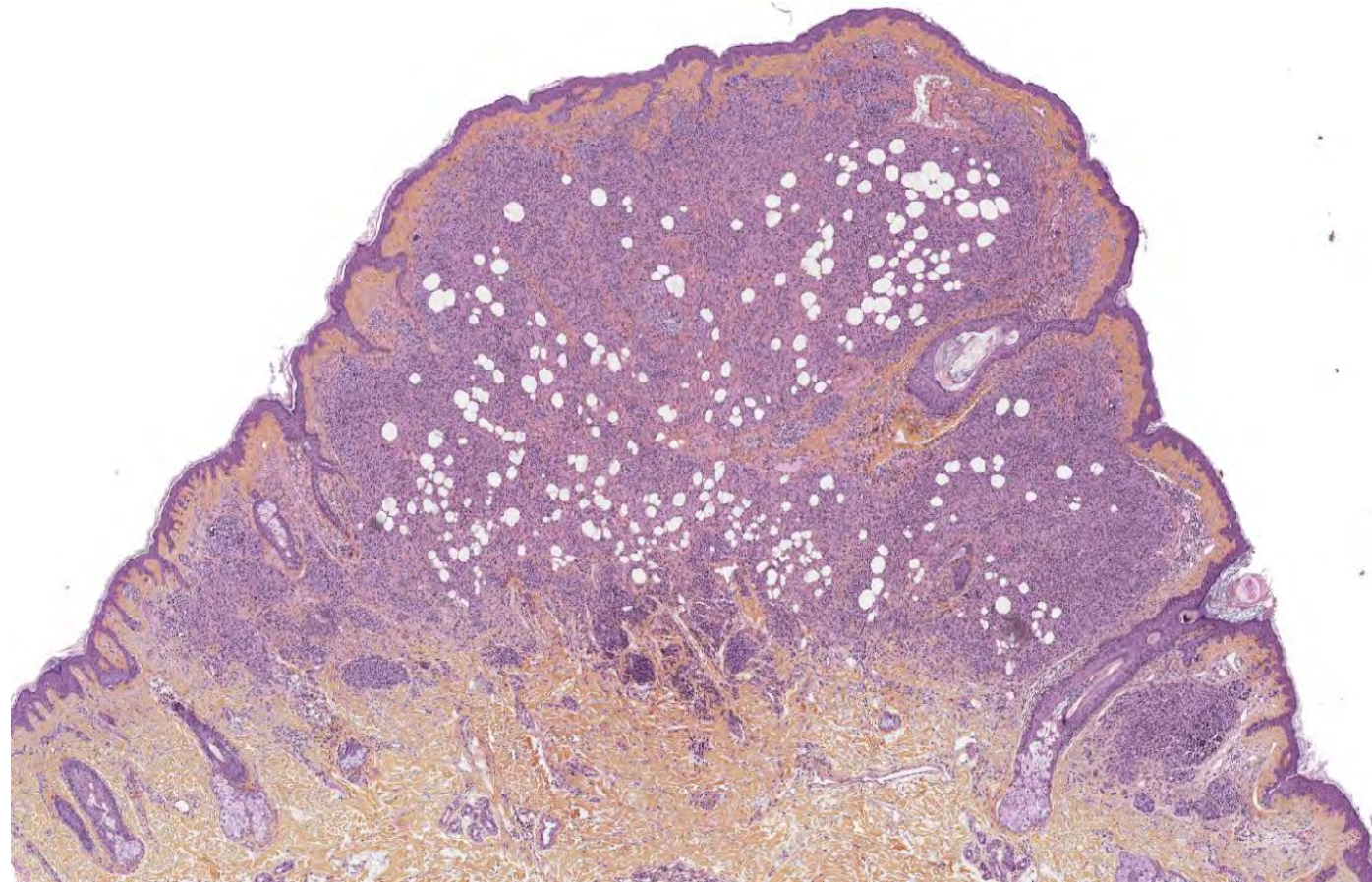
Verrucous BIMT



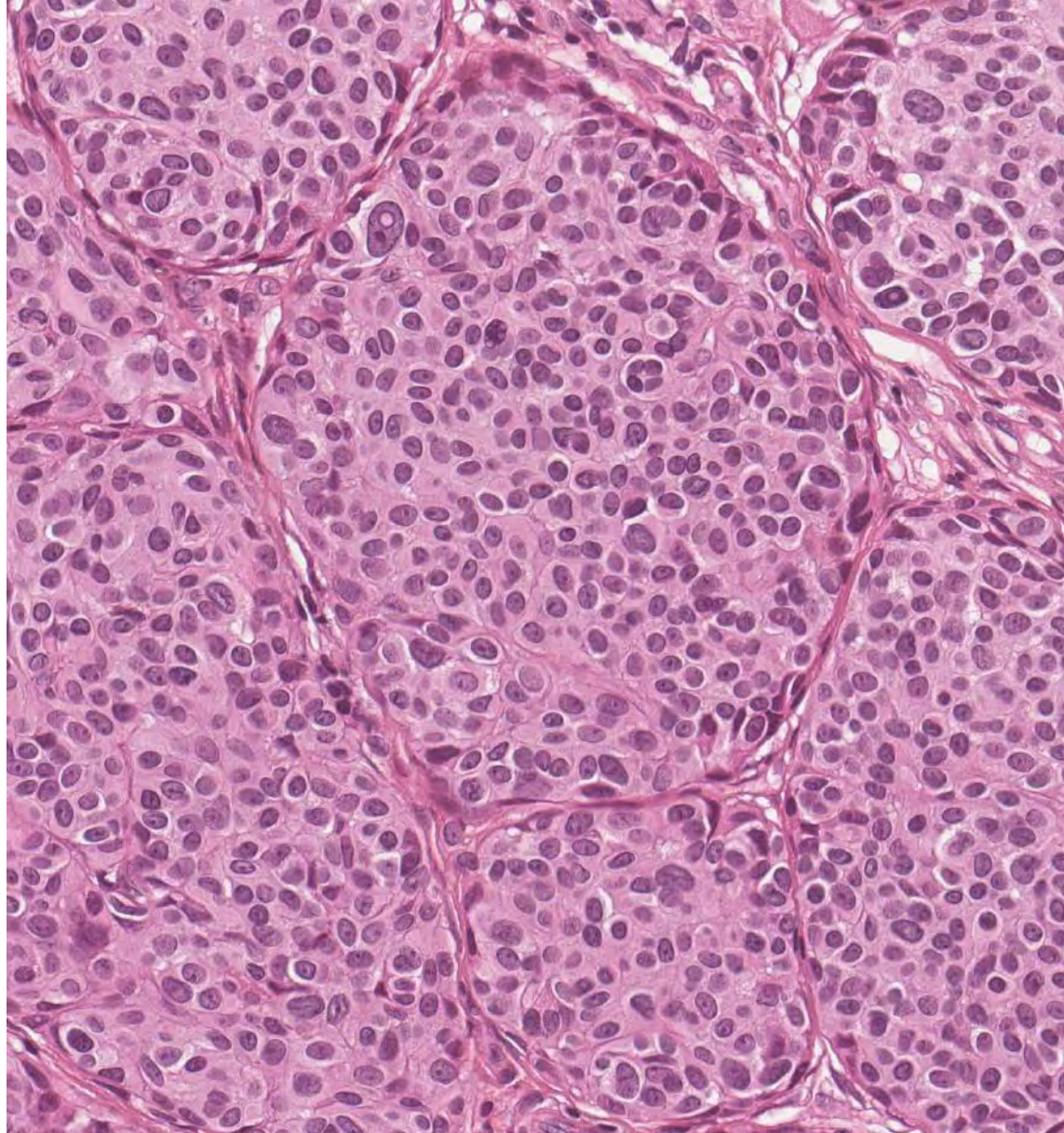
Nevus with lipidic inclusions



BIMT with lipidic inclusions

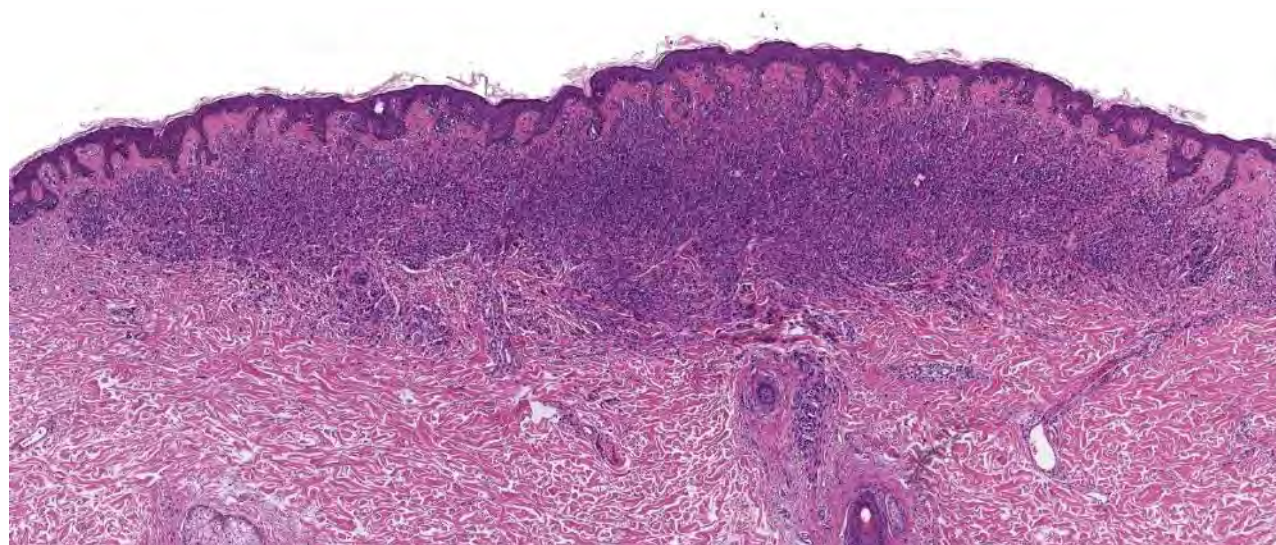


Packed dermal nests of nevoid cells

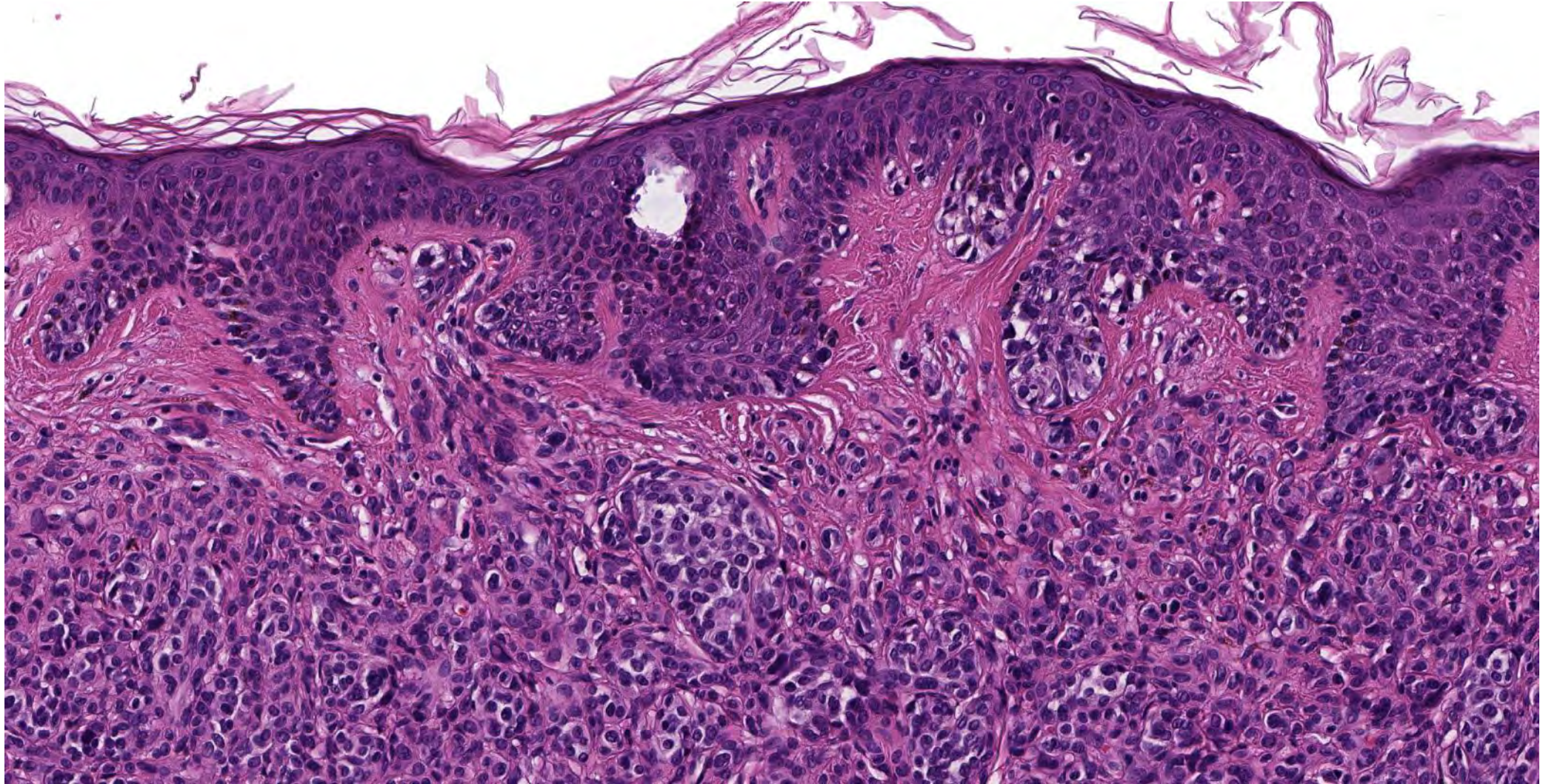


Estimated a <16% frequency of germline mutations following a *BAP1*-IMT

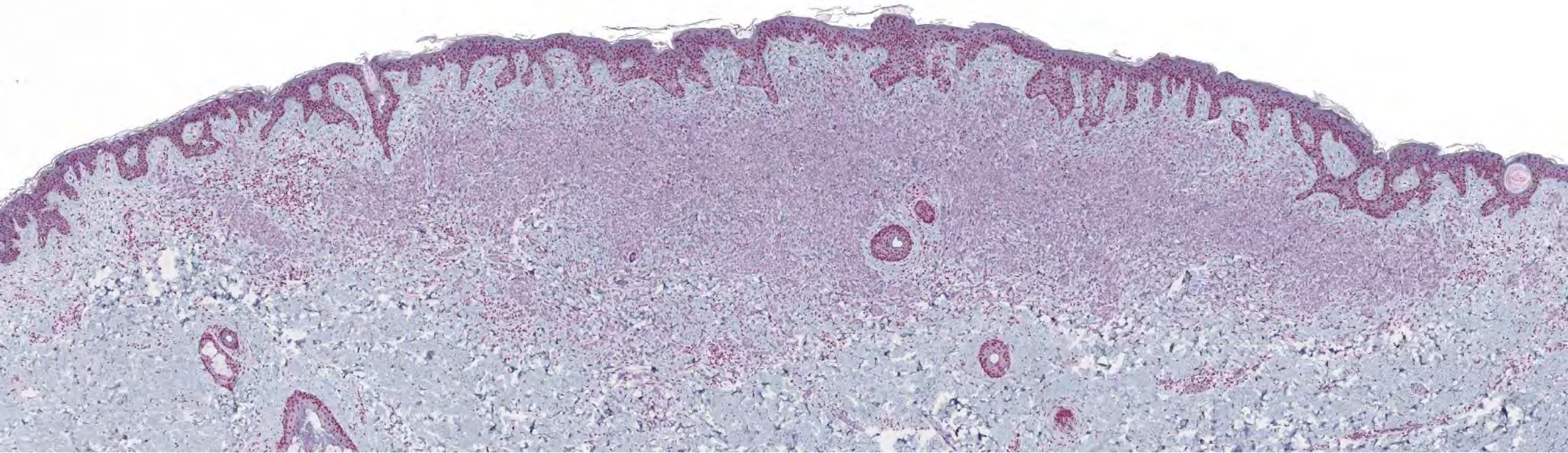
We recommend, following the diagnosis of a Melanocytic tumor with loss of BAP1 expression, performing a BAP1 immunohistochemistry in all other cutaneous melanocytic tumors removed previously or simultaneously and all skin melanomas.



Microscopic analysis and BAP1 immunohistochemistry of other compound nevi

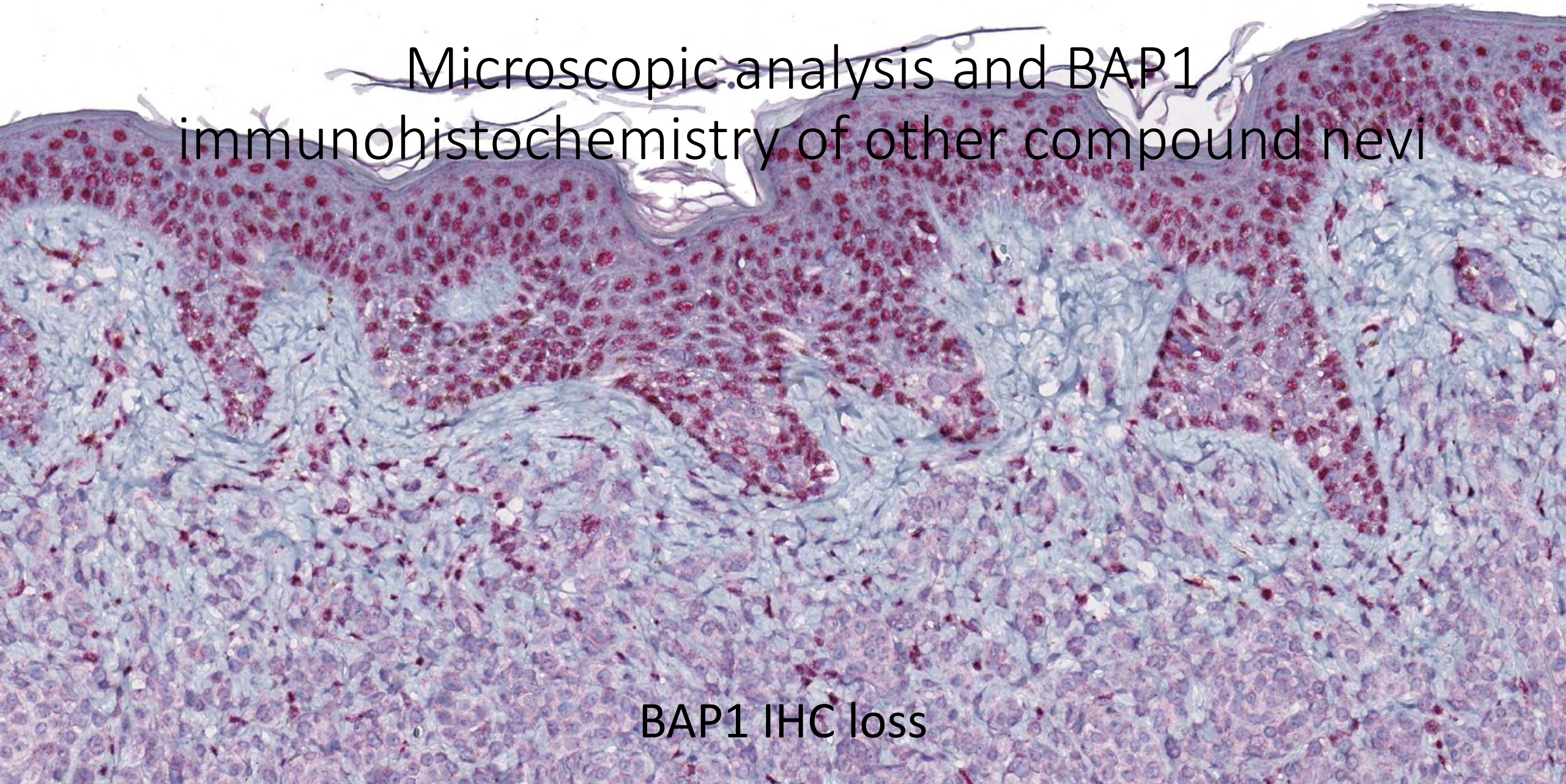


Microscopic analysis and BAP1 immunohistochemistry of other compound nevi



BAP1 IHC loss

Microscopic analysis and BAP1 immunohistochemistry of other compound nevi



BAP1 IHC loss

Estimated a <16% frequency of germline mutations following a *BAP1*-IMT

- We recommend, following the diagnosis of a Melanocytic tumor with loss of BAP1 expression, performing a BAP1 immunohistochemistry in all other cutaneous melanocytic tumors removed previously or simultaneously and all skin melanomas.
- 12% frequency confirmed by a recent study of 108 cases

J Am Acad Dermatol. 2018 Sep;79(3):525-534. doi: 10.1016/j.jaad.2018.05.005. Epub 2018 May 10.

Histomorphologic spectrum of germline-related and sporadic *BAP1*-inactivated melanocytic tumors.

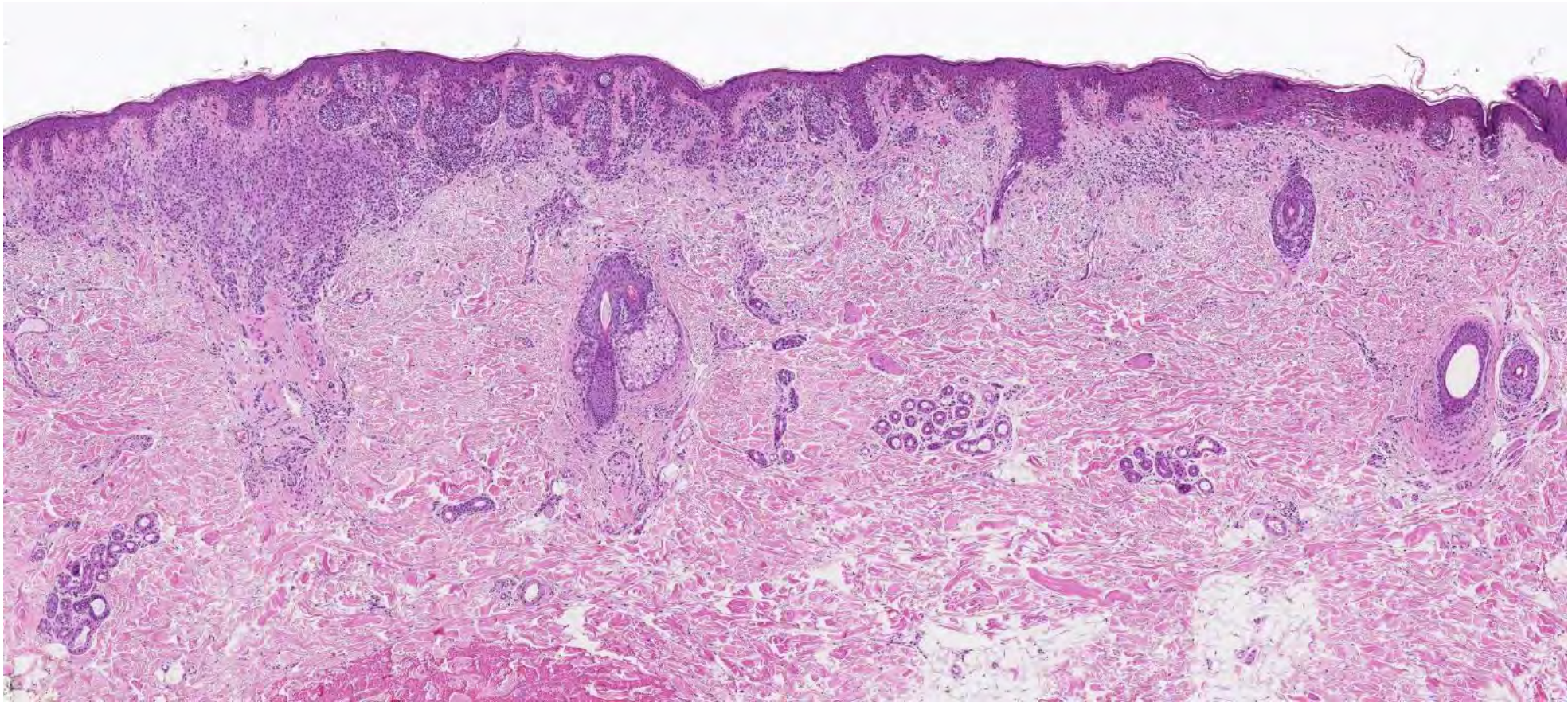
Garfield EM¹, Walton KE¹, Quan VL¹, VandenBoom T¹, Zhang B¹, Kong BY¹, Isales MC¹, Panah E¹, Kim G², Gerami P³.

Overestimation of cutaneous melanoma in *BAP1*-TPDS

- Malignant cutaneous melanoma is extremely rare in this setting.
- Most cases are just large *BAP1*-inactivated nevi
- Progression of a *BAP1*-IMT is the most frequent method of transformation

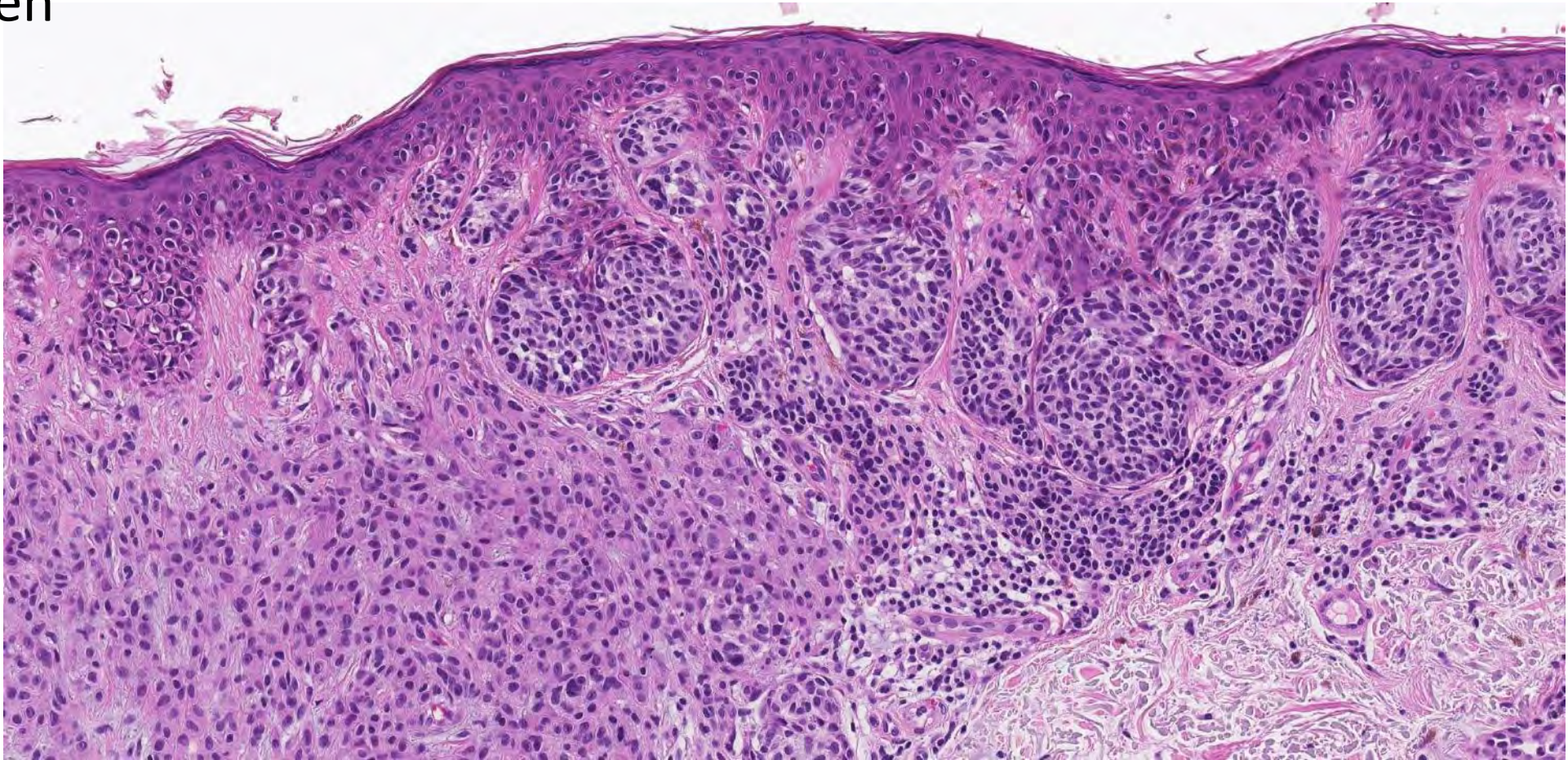
Overestimation of cutaneous melanoma in *BAP1*-TPDS

- Occasional Superficial Spreading Melanoma (SSM) ex-nevus can be seen



Overestimation of cutaneous melanoma in *BAP1*-TPDS

- Occasional Superficial Spreading Melanoma (SSM) ex-nevus can be seen



BAP1-TPDS

Take home messages

- Not exceptionnal
- Variable phenotype, early cancers
- Model for gene-environment interaction
- Positive screening in children can lead to lifetime surveillance
- Helps understand carcinogenesis outside of the syndrome
- Ongoing identification of rare tumour types

Follow me on social media

Molecular pathology of melanocytic tumors

- X/Twitter: @melanopath
- Instagram: melanopath
- Youtube Channels: Formations et enseignement Centre Léon Bérard
- The melanoledge channel

