Clues for the diagnosis of melanocytic tumours

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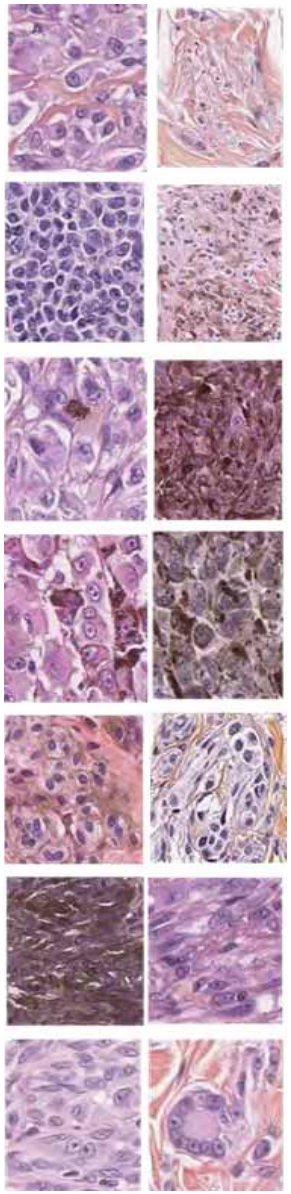
CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD
Chercher et soigner jusqu'à la guérison

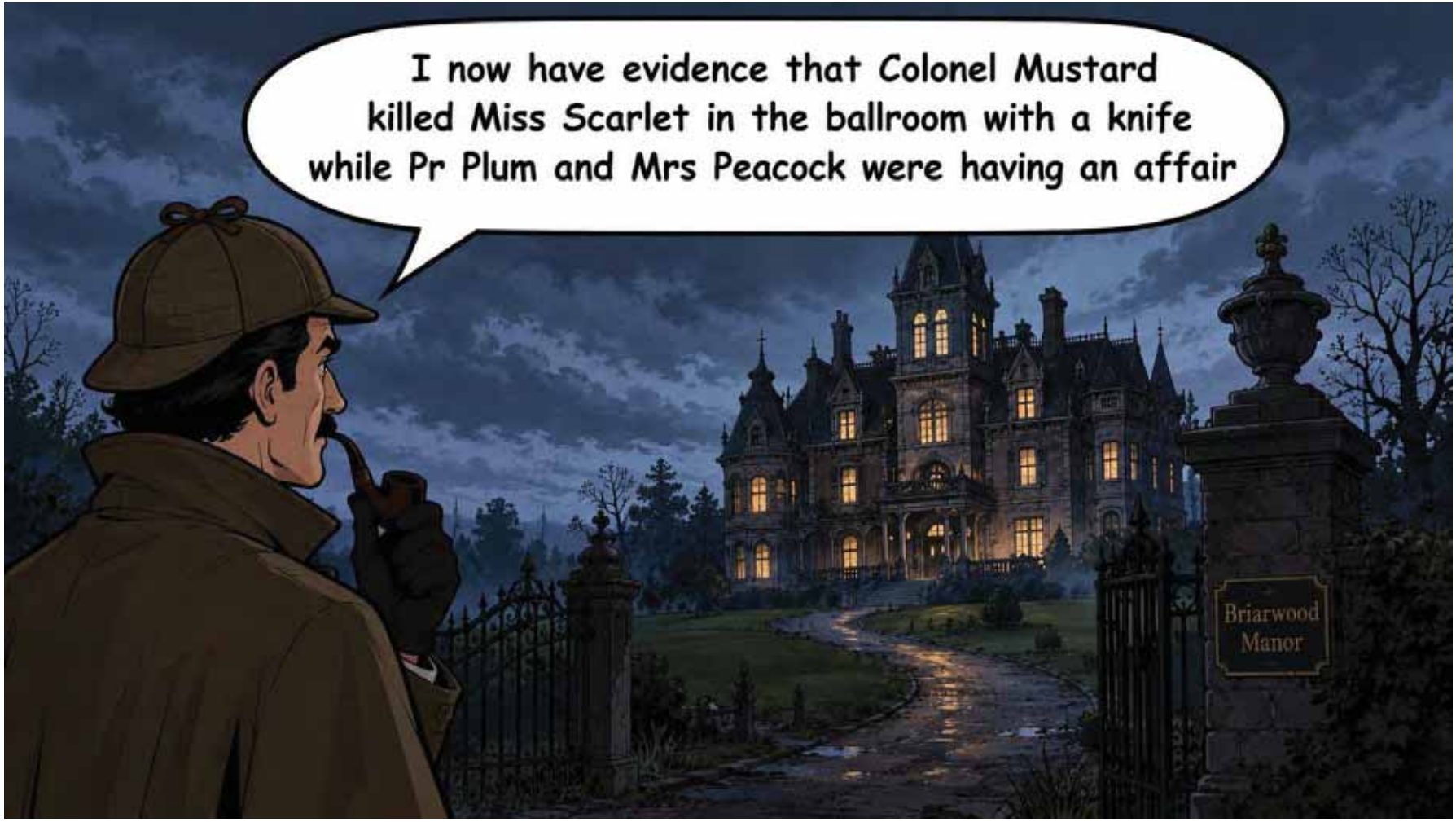


Financial disclosures: none

Teaching points

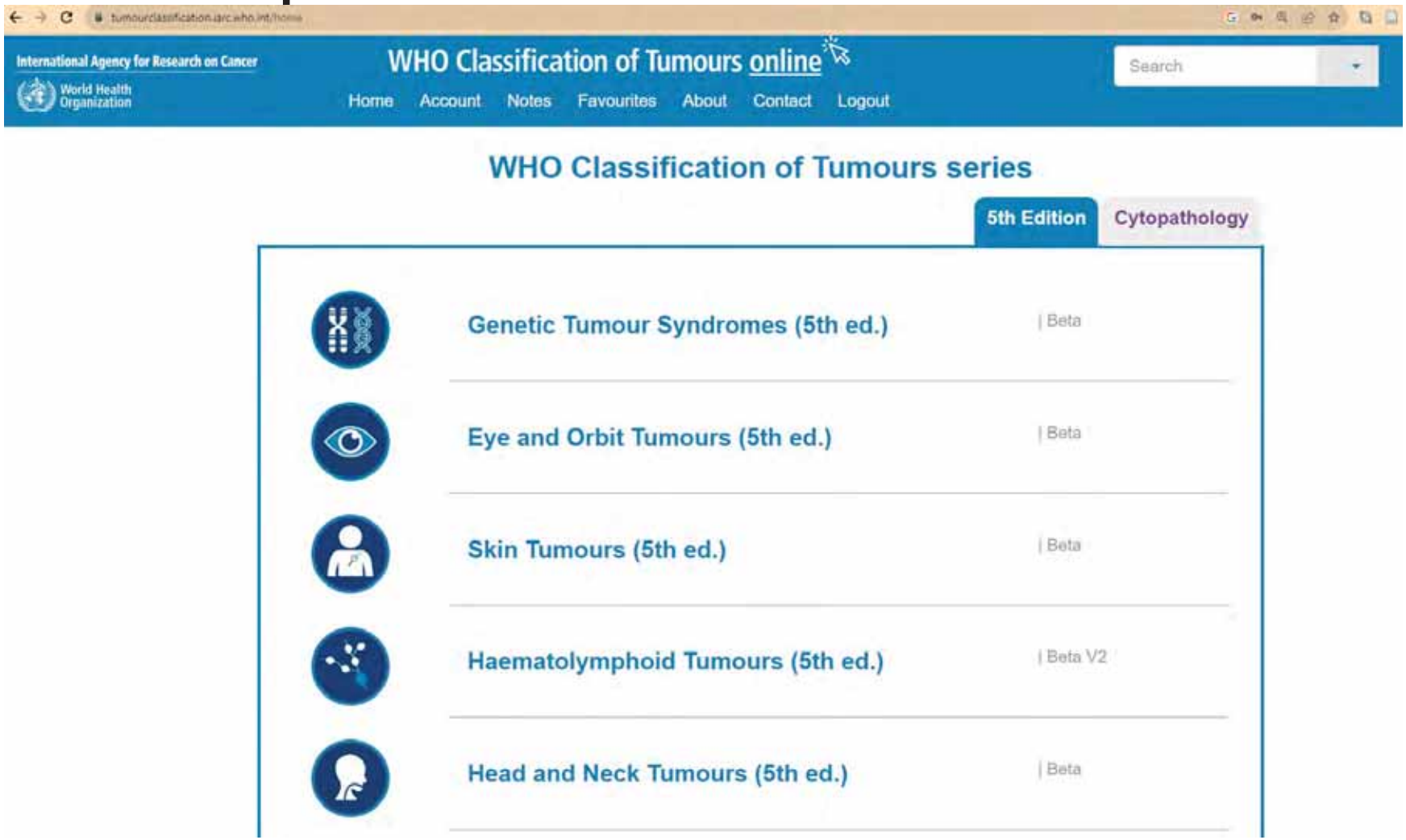
- Melanocytic proliferations represent different diseases (WHO 5th)
- Low and high power clues are found in all types/subtypes
- Usual and maybe less known clues

Low power clues are the best as they save time



Clues guide your next step (High power, IHC etc) not a «smoking gun»

WHO permanent online Classification



8 classes of cutaneous melanocytic tumours WHO 5th ed

	Sun-exposed skin with low or moderate CSD				Sun-exposed skin with high CSD		Tumours not caused by UV radiation					
Pathway	I				II	III	IV	V	VI	VII	VIII	IX
Endpoint of pathway	Low-CSD melanoma (including SSM)				High-CSD melanoma/LMM	Desmoplastic melanoma	Spitz melanoma	Acral lentiginous melanoma	Mucosal melanoma	Melanoma in CN	Melanoma in blue naevus	Uveal melanoma
Benign neoplasms (naevi)	Naevus				?[a] IMP	?[a] IMP	Spitz naevus	Field cells (field effect)[d]	?[a] Melanosis	CN	Blue naevus	Uveal naevus
Intermediate/low-grade dysplasias and melanocytomas	Low-grade dysplasia	BIM	WNT-activated DPMN		?[a] IAMP/dysplasia	?[a] IAMP/dysplasia	Spitz melanocytoma (atypical Spitz tumour)	IAMP/dysplasia	Atypical melanosis / dysplasia / IAMPUS	Nodule in CN (melanocytoma)	(Atypical) CBN (melanocytoma)	
Intermediate/high-grade dysplasias and melanocytomas	High-grade dysplasia / MIS	BIM/MELTUMP	WNT-activated DPMN / MELTUMP	PEM/MELTUMP	Lentigo maligna (MIS)	MIS	STUMP/MELTUMP	Acral lentiginous MIS	Mucosal MIS	MIS in CN	Atypical CBN	
Malignant neoplasms	Low-CSD melanoma (including SSM)	Melanoma in BIM	Melanoma in WNT-activated DPMN	Melanoma in PEM	High-CSD melanoma/LMM	Desmoplastic melanoma	Spitz melanoma (tumorigenic)	Acral lentiginous melanoma (VGP)	Mucosal lentiginous melanoma (VGP)	Melanoma in CN (tumorigenic)	Melanoma in blue naevus (tumorigenic)	Uveal melanoma
Common mutations[b,c] in addition to multiple DNA copy-number changes found in the malignant stages of all melanoma subtypes	*BRAF* p.V600E or *NRAS*	*BRAF* or *NRAS* + *BAP1*	*BRAF*, *MAP2K1*, or *NRAS* + *CTNNB1* or *APC*	*BRAF* + *PRKAR1A*	*NRAS*, *BRAF* (non-p.V600E), *KIT* or *NF1*	*NF1* *ERBB2*, *MAP2K1*, *MAP3K1*, *BRAF*, *EGFR*, *MET*	*HRAS* *ALK*, *ROS1*, *RET*, *NTRK1*, *NTRK3*, *BRAF*, *RASGRF1*, *RASGRF2*, *MAP3K8*, or *MET*	*KIT*, *NRAS*, *BRAF*, *HRAS*, *KRAS* *NTRK3*, *ALK* or *NF1*, *SPRED1*	*KIT*, *NRAS*, *KRAS* or *BRAF* *NF1*, *SPRED1*	*NRAS* *BRAF* p.V600E (small lesions) or *BRAF*	*GNAQ*, *GNA11*, *CYSLTR2*, *PLCB4* or *PRKCA*	*GNAQ*, *GNA11*, *CYSLTR2*, or *PLCB4*
	TERT *CDKN2A*, *TP53*, *PTEN*		*TERT* *CDKN2A*, *TP53*		*TERT* *CDKN2A*, *TP53*, *PTEN* *RAC1*	*TERT* *NRAS*, *PIK3CA*, *PTPN11*	*TERT*, *CDKN2A*	*CDKN2A* *TERT*, *TERT*, *TERT* *CCND1*, *GAB2*	*CDKN2A* *SF3B1*, *TERT*, *TERT*, *ATRX* *CCND1*, *CDK4*, *MDM2*		*BAP1* *EIF1AX*, *SF3B1*	*BAP1* *SF3B1*, *EIF1AX* *CENPE*, *TP53*, *RPL5*

8 classes of cutaneous melanocytic tumours

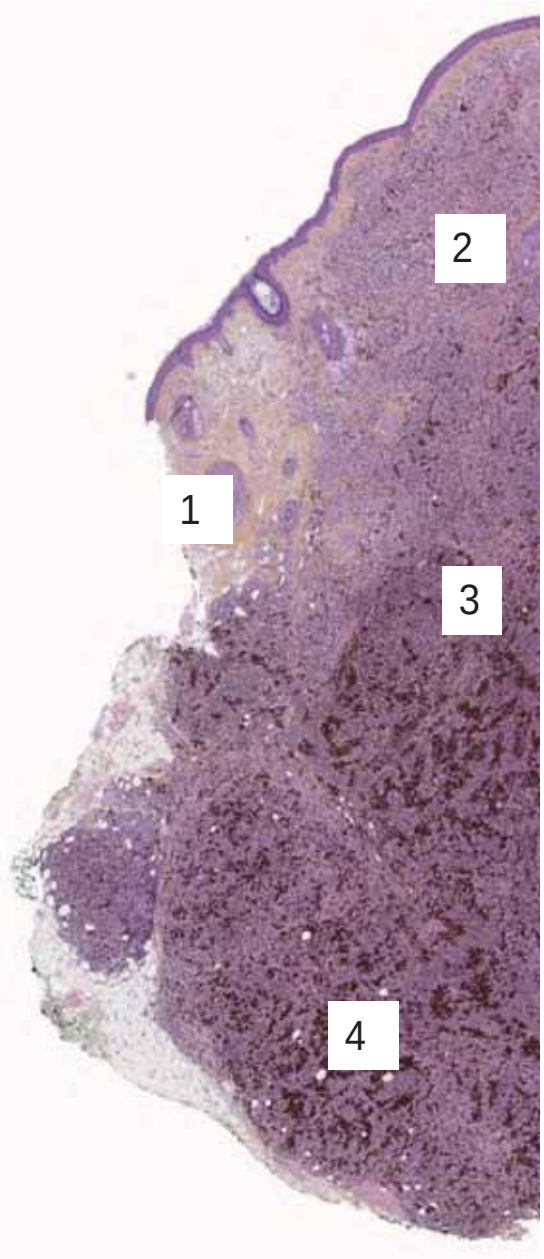
Pathway n°

	Sun-exposed skin with low or moderate CSD				Sun-exposed skin with high CSD			Tumours not caused by UV radiation				
Pathway	**I**				**II**	**III**	**IV**	**V**	**VI**	**VII**	**VIII**	**IX**
Endpoint of pathway	Low-CSD melanoma (including SSM)				High-CSD melanoma/LMM	Desmoplastic melanoma	Spitz melanoma	Acral lentiginous melanoma	Mucosal melanoma	Melanoma in CN	Melanoma in blue naevus	Uveal melanoma
Benign neoplasms (naevi)	Naevus				?[a] IMP	?[a] IMP	Spitz naevus	Field cells (field effect)[d]	?[a] Melanosis	CN	Blue naevus	Uveal naevus
Intermediate/low-grade dysplasias and melanocytomas	Low-grade dysplasia	BIM	WNT-activated DPMN		?[a] IAMP/dysplasia	?[a] IAMP/dysplasia	Spitz melanocytoma (atypical Spitz tumour)	IAMP/dysplasia	Atypical melanosis / dysplasia / IAMPUS	Nodule in CN (melanocytoma)	(Atypical) CBN (melanocytoma)	
Intermediate/high-grade dysplasias and melanocytomas	High-grade dysplasia / MIS	BIM/MELTUMP	WNT-activated DPMN / MELTUMP	PEM/MELTUMP	Lentigo maligna (MIS)	MIS	STUMP/MELTUMP	Acral lentiginous MIS	Mucosal MIS	MIS in CN	Atypical CBN	
Malignant neoplasms	Low-CSD melanoma (including SSM)	Melanoma in BIM	Melanoma in WNT-activated DPMN	Melanoma in PEM	High-CSD melanoma/LMM	Desmoplastic melanoma	Spitz melanoma (tumorigenic)	Acral lentiginous melanoma (VGP)	Mucosal lentiginous melanoma (VGP)	Melanoma in CN (tumorigenic)	Melanoma in blue naevus (tumorigenic)	Uveal melanoma
Common mutations[b,c] in addition to multiple DNA copy-number changes found in the malignant stages of all melanoma subtypes	*BRAF* p.V600E or *NRAS*	*BRAF* or *NRAS* + *BAP1*	*BRAF*, *MAP2K1*, or *NRAS* + *CTNNB1* or *APC*	*BRAF* + *PRKAR1A*	*NRAS*, *BRAF* (non-p.V600E), *KIT* or *NF1*	*NF1* *ERBB2*, *MAP2K1*, *MAP3K1*, *BRAF*, *EGFR*, *MET*	*HRAS* *ALK*, *ROS1*, *RET*, *NTRK1*, *NTRK3*, *BRAF*, *RASGRF1*, *RASGRF2*, *MAP3K8*, or *MET*	*KIT*, *NRAS*, *BRAF*, *HRAS*, *KRAS* *NTRK3*, *ALK* or *NF1*, *SPRED1*	*KIT*, *NRAS*, *KRAS* or *BRAF* *NF1*, *SPRED1*	*NRAS* *BRAF* p.V600E (small lesions) or *BRAF*	*GNAQ*, *GNA11*, *CYSLTR2*, *PLCB4* or *PRKCA*	*GNAQ*, *GNA11*, *CYSLTR2*, or *PLCB4*
	TERT *CDKN2A*, *TP53*, *PTEN*		*TERT* *CDKN2A*, *TP53*		*TERT* *CDKN2A*, *TP53*, *PTEN* *RAC1*	*TERT* *NRAS*, *PIK3CA*, *PTPN11*	*TERT*, *CDKN2A*	*CDKN2A* *TERT*, *TERT*, *TERT* *CCND1*, *GAB2*	*CDKN2A* *SF3B1*, *TERT*, *TERT*, *ATRX* *CCND1*, *CDK4*, *MDM2*		*BAP1* *EIF1AX*, *SF3B1*	*BAP1* *SF3B1*, *EIF1AX* *CENPE*, *TP53*, *RPL5*

8 classes of cutaneous melanocytic tumours

Melanoma type

	Sun-exposed skin with low or moderate CSD				Sun-exposed skin with high CSD		Tumours not caused by UV radiation					
Pathway	I				II	III	IV	V	VI	VII	VIII	IX
Endpoint of pathway	Low-CSD melanoma (including SSM)				High-CSD melanoma/LMM	Desmoplastic melanoma	Spitz melanoma	Acral lentiginous melanoma	Mucosal melanoma	Melanoma in CN	Melanoma in blue naevus	Uveal melanoma
Benign neoplasms (naevi)	Naevus				?[a] IMP	?[a] IMP	Spitz naevus	Field cells (field effect)[d]	?[a] Melanosis	CN	Blue naevus	Uveal naevus
Intermediate/low-grade dysplasias and melanocytomas	Low-grade dysplasia	BIM	WNT-activated DPMN		?[a] IAMP/dysplasia	?[a] IAMP/dysplasia	Spitz melanocytoma (atypical Spitz tumour)	IAMP/dysplasia	Atypical melanosis / dysplasia / IAMPUS	Nodule in CN (melanocytoma)	(Atypical) CBN (melanocytoma)	
Intermediate/high-grade dysplasias and melanocytomas	High-grade dysplasia / MIS	BIM/MELTUMP	WNT-activated DPMN / MELTUMP	PEM/MELTUMP	Lentigo maligna (MIS)	MIS	STUMP/MELTUMP	Acral lentiginous MIS	Mucosal MIS	MIS in CN	Atypical CBN	
Malignant neoplasms	Low-CSD melanoma (including SSM)	Melanoma in BIM	Melanoma in WNT-activated DPMN	Melanoma in PEM	High-CSD melanoma/LMM	Desmoplastic melanoma	Spitz melanoma (tumorigenic)	Acral lentiginous melanoma (VGP)	Mucosal lentiginous melanoma (VGP)	Melanoma in CN (tumorigenic)	Melanoma in blue naevus (tumorigenic)	Uveal melanoma
Common mutations[b,c] in addition to multiple DNA copy-number changes found in the malignant stages of all melanoma subtypes	*BRAF* p.V600E or *NRAS*	*BRAF* or *NRAS* + *BAP1*	*BRAF*, *MAP2K1*, or *NRAS* + *CTNNB1* or *APC*	*BRAF* + *PRKAR1A*	*NRAS*, *BRAF* (non-p.V600E), *KIT* or *NF1*	*NF1* *ERBB2*, *MAP2K1*, *MAP3K1*, *BRAF*, *EGFR*, *MET*	*HRAS* *ALK*, *ROS1*, *RET*, *NTRK1*, *NTRK3*, *BRAF*, *RASGRF1*, *RASGRF2*, *MAP3K8*, or *MET*	*KIT*, *NRAS*, *BRAF*, *HRAS*, *KRAS* *NTRK3*, *ALK* or *NF1*, *SPRED1*	*KIT*, *NRAS*, *KRAS* or *BRAF* *NF1*, *SPRED1*	*NRAS* *BRAF* p.V600E (small lesions) or *BRAF*	*GNAQ*, *GNA11*, *CYSLTR2*, *PLCB4* or *PRKCA*	*GNAQ*, *GNA11*, *CYSLTR2*, or *PLCB4*
	TERT *CDKN2A*, *TP53*, *PTEN*		*TERT* *CDKN2A*, *TP53*		*TERT* *CDKN2A*, *TP53*, *PTEN* *RAC1*	*TERT* *NRAS*, *PIK3CA*, *PTPN11*	*TERT*, *CDKN2A*	*CDKN2A* *TERT*, *TERT*, *TERT* *CCND1*, *GAB2*	*CDKN2A* *SF3B1*, *TERT*, *TERT*, *ATRX* *CCND1*, *CDK4*, *MDM2*		*BAP1* *EIF1AX*, *SF3B1*	*BAP1* *SF3B1*, *EIF1AX* *CENPE*, *TP53*, *RPL5*



4 step progression scheme of melanocytic tumors

Nevus

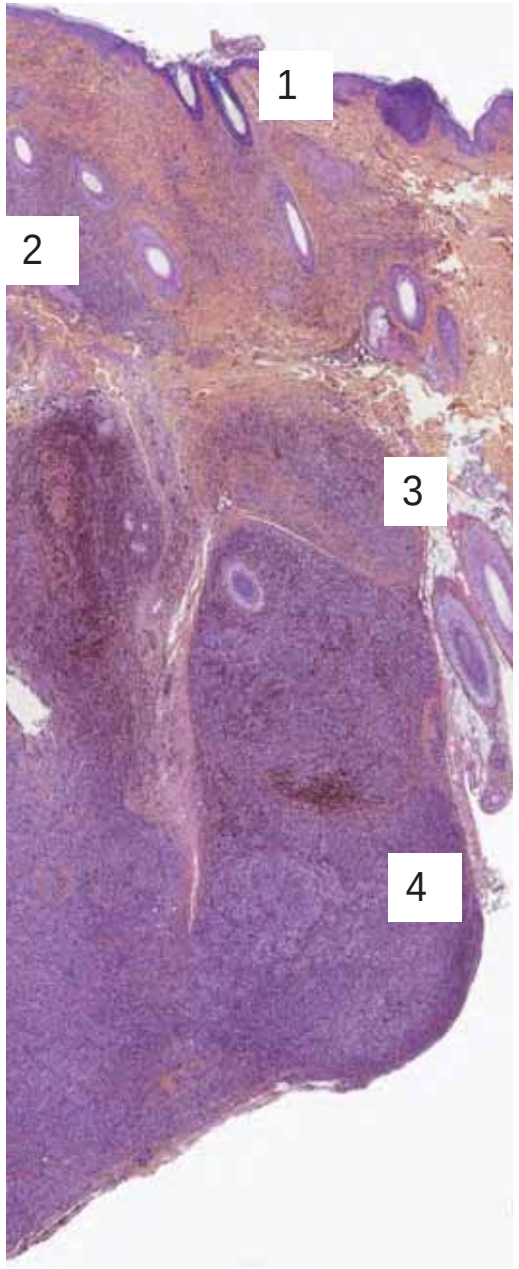
Single driver anomaly

Low grade dysplasia «melanocytoma»

High grade dysplasia «melanocytoma»

Melanoma

Multiple genomic alterations



8 classes of cutaneous melanocytic tumours

Nevus to melanoma progression model

	Sun-exposed skin with low or moderate CSD				Sun-exposed skin with high CSD		Tumours not caused by UV radiation				
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Endpoint of pathway	Low-CSD melanoma (including SSM)				High-CSD melanoma/LMM	Desmoplastic melanoma	Spitz melanoma	Acral lentiginous melanoma	Mucosal melanoma	Melanoma in CN	Melanoma in blue naevus	Uveal melanoma
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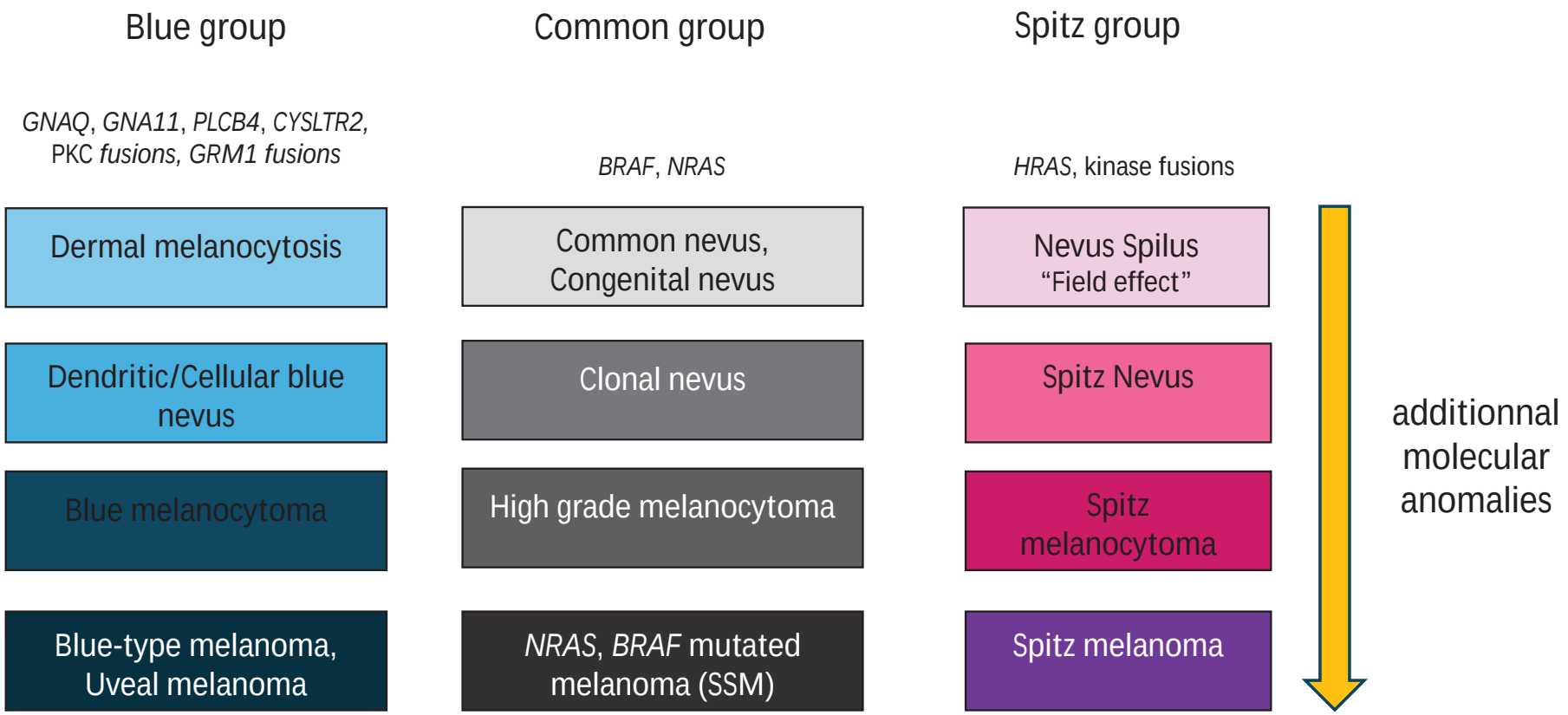
Integrative classification of melanocytic tumors
Nevus to melanoma groups



8 classes of cutaneous melanocytic tumours

Genetic anomalies (driver/passenger)

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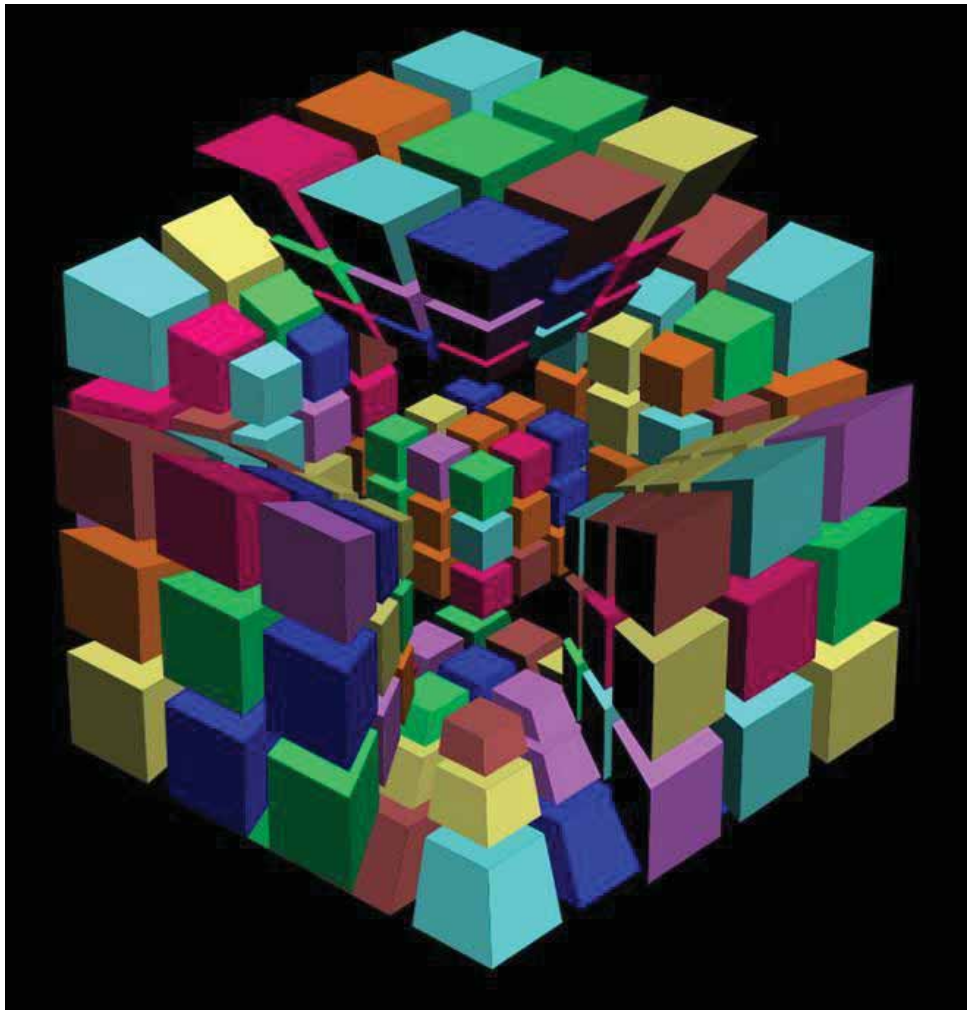
8 classes of cutaneous melanocytic tumours WHO 5th ed

- Different diseases
- Different causalities
- Different patients
- Different genetics
- Different treatment
- Different outcomes
- Different clues to diagnosis

Multi-dimensional classification



UV Exposure

Non-chronic sun damage

Chronic sun damage

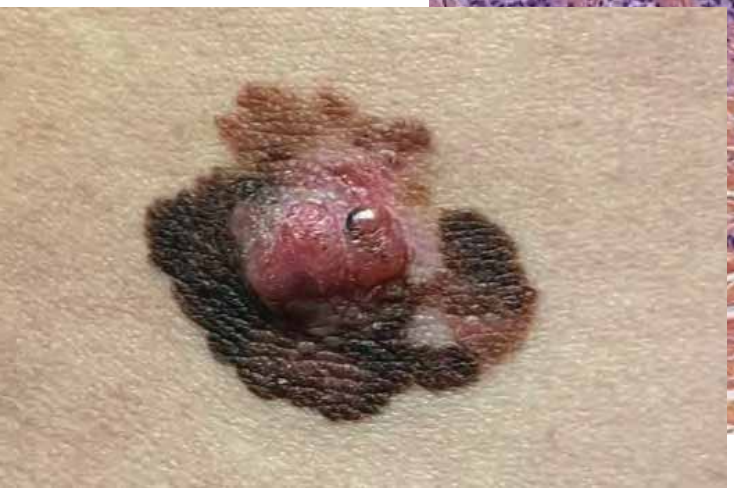
Sun sheltered areas

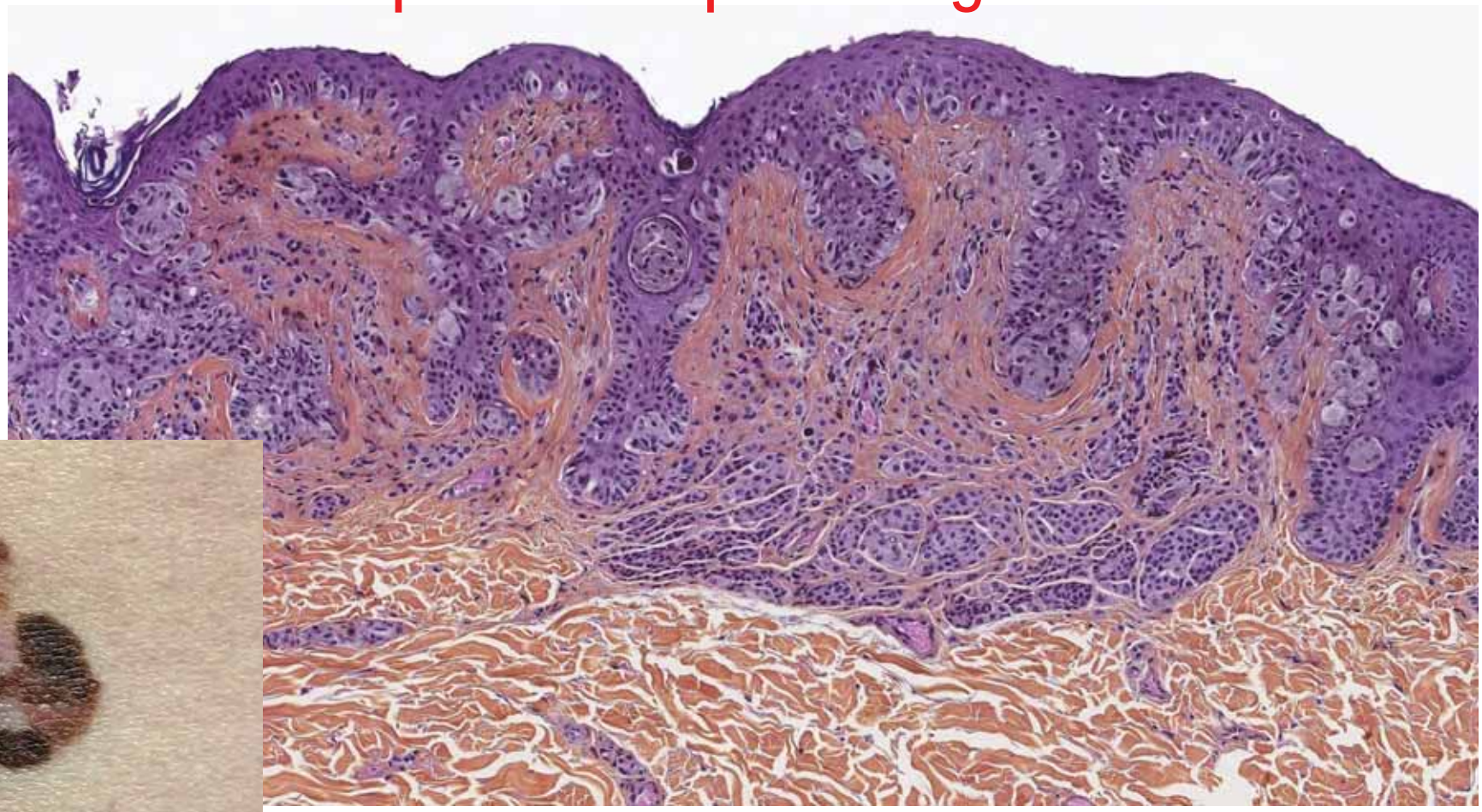
Non-chronic sun damage melanoma (*ie* sunburns)

Class I : 90%> Superficial Spreading Melanoma

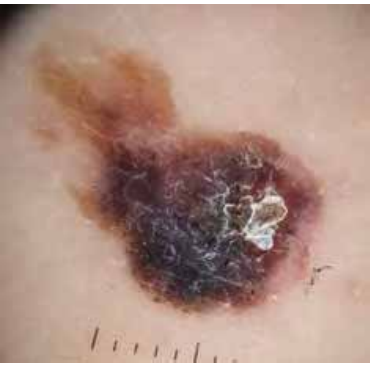
SSM ex-nevus

BRAF V600E

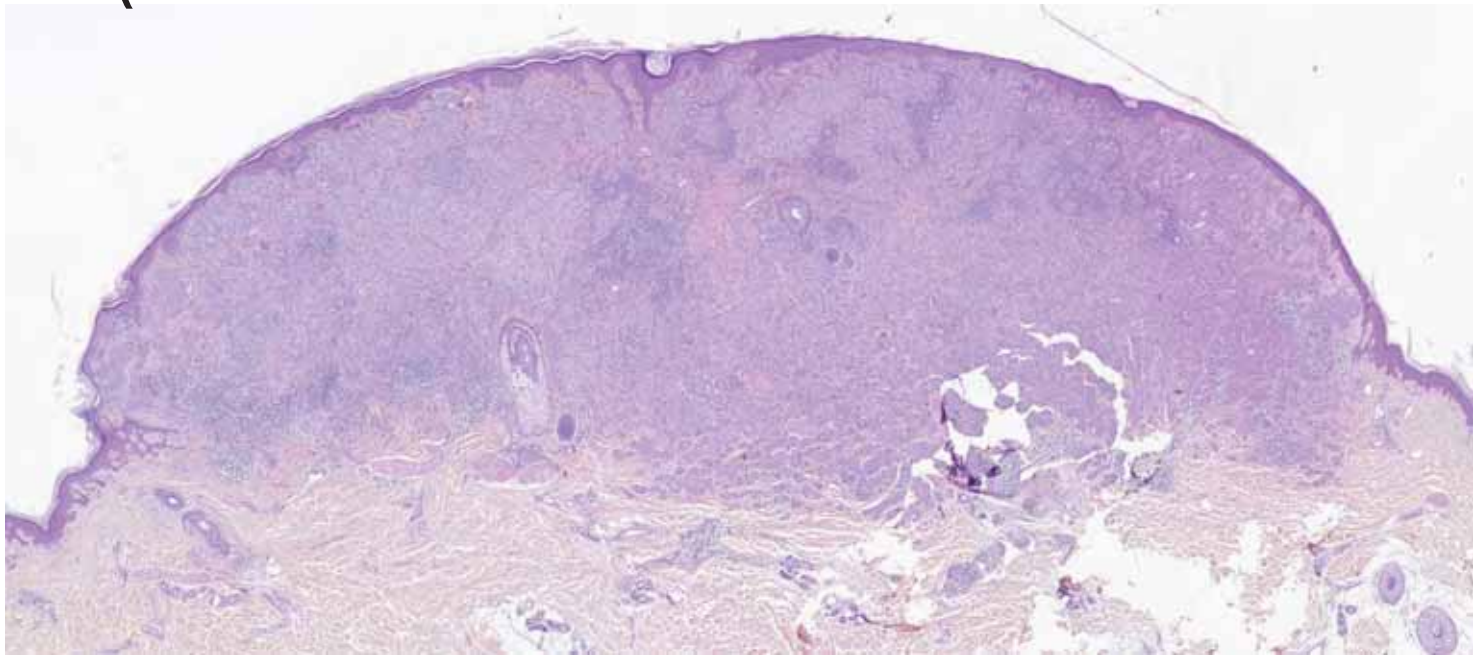




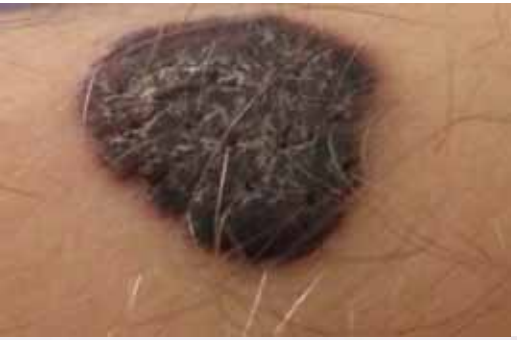
Non-chronic sun damage melanoma (*ie* sunburns)
Class I : <5% Nevoid Melanoma

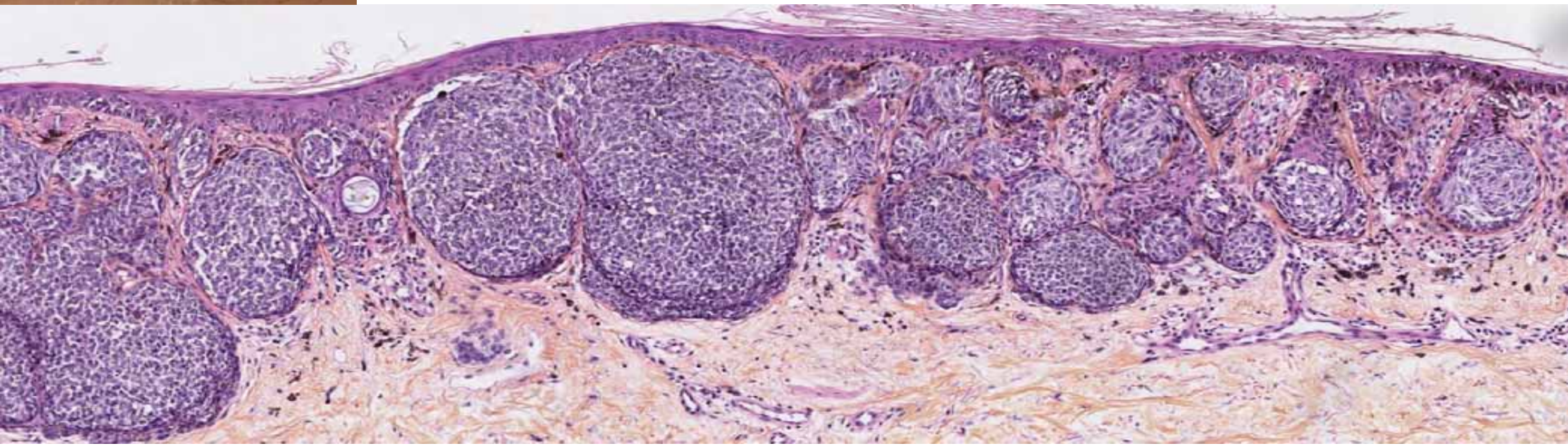


(NRAS mutations > BRAF V600E mutations)



Non-chronic sun damage melanoma (*ie* sunburns)
Class I : <5% Nested Melanoma



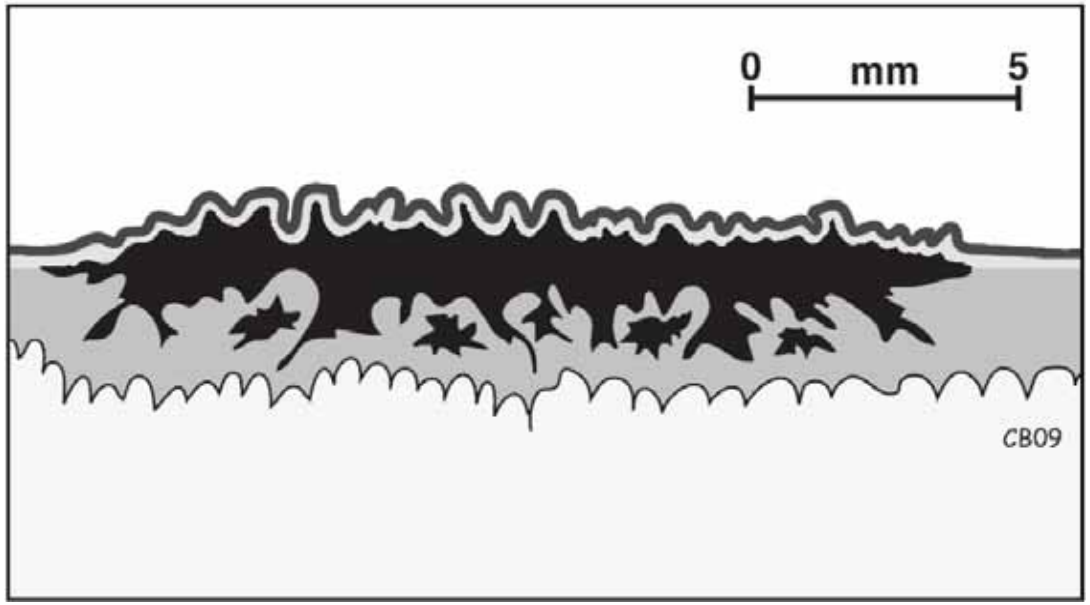


Clues in Class I melanocytic tumours
Small *BRAF*-mutated congenital-like nevus

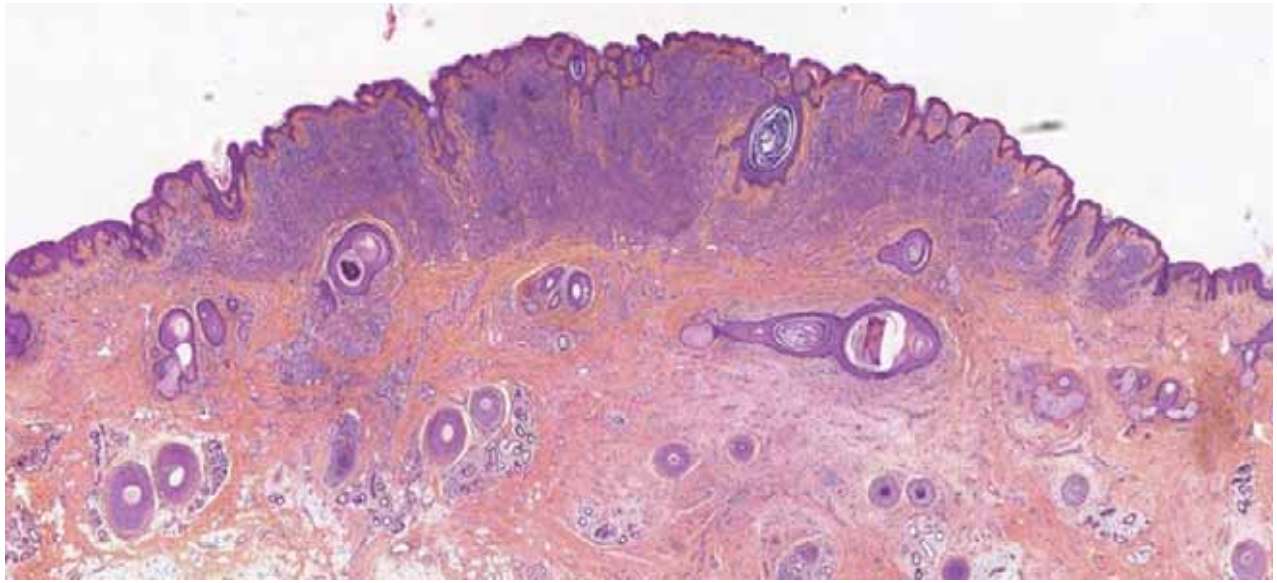
Common group

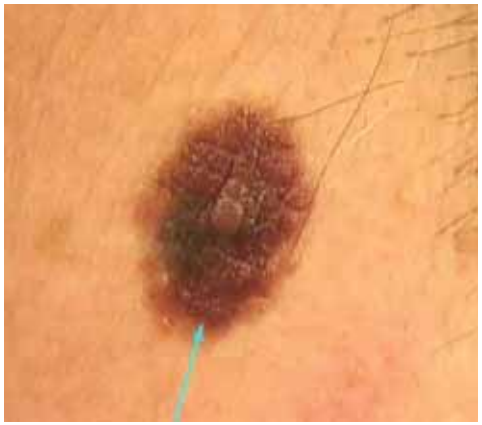
BRAF, *NRAS*

Common nevus,
Congenital nevus



Compound congenital-like nevus



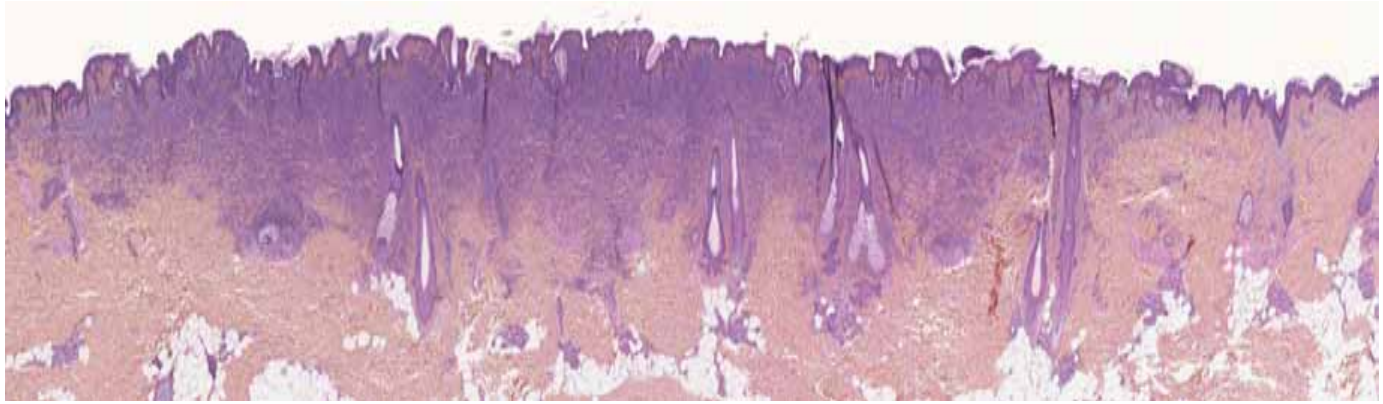


Dr Longueville

Compound congenital-like nevus
Low power clues

Verrucous surface

Dermal horizontal band of bland nevocytes between superficial and mid dermis

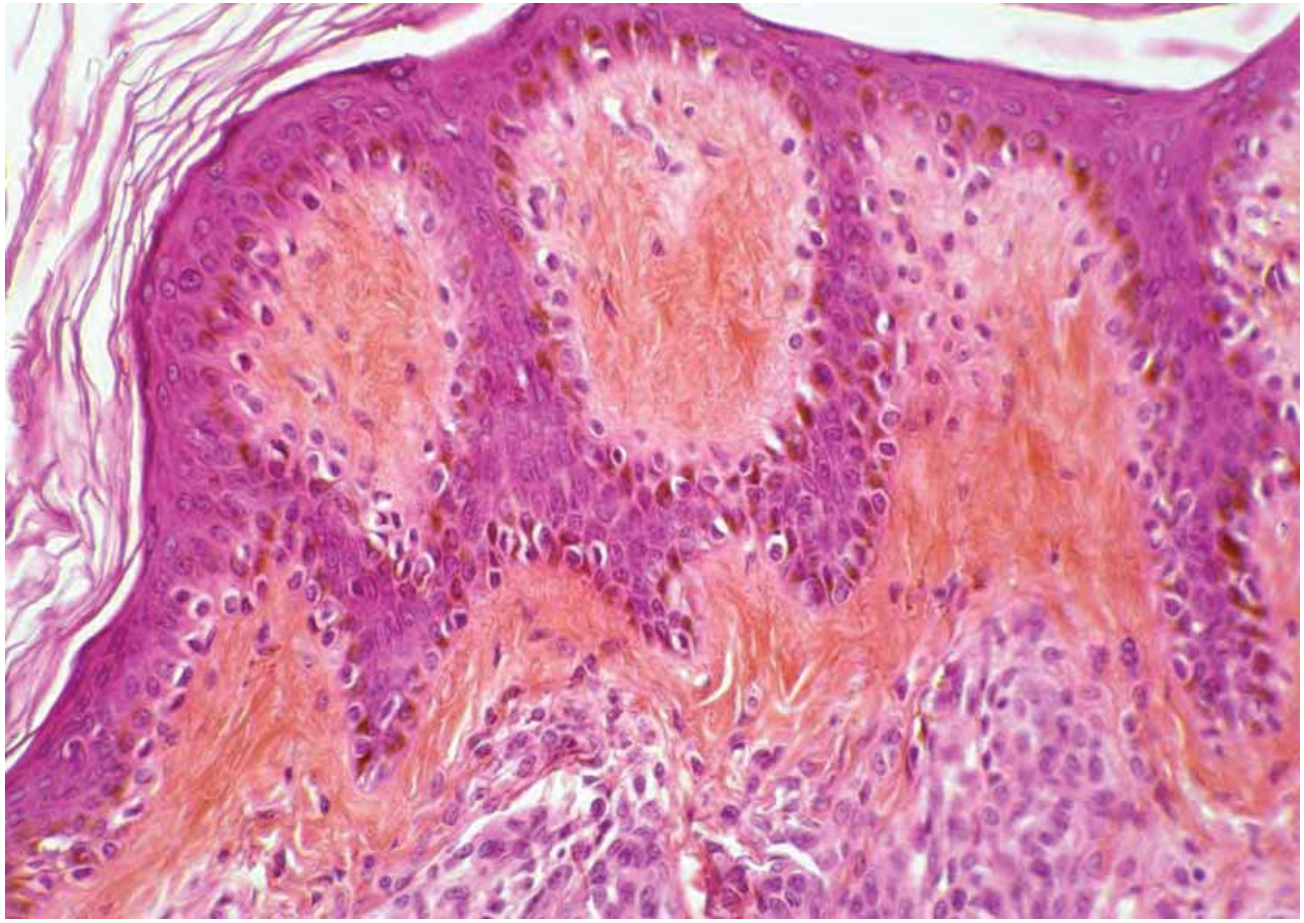


Deep flammeche extension

Perifollicular vertical extension

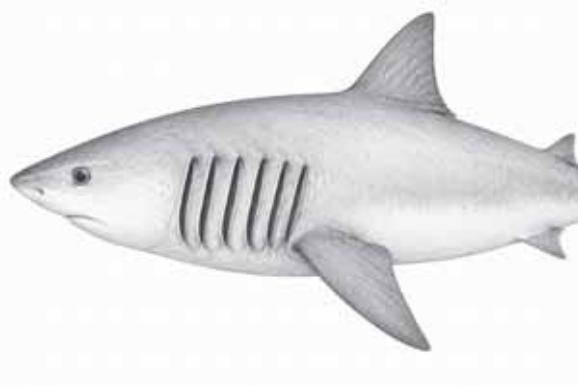
Hyperplasia of pilar structures more prone to folliculitis/osteonevus

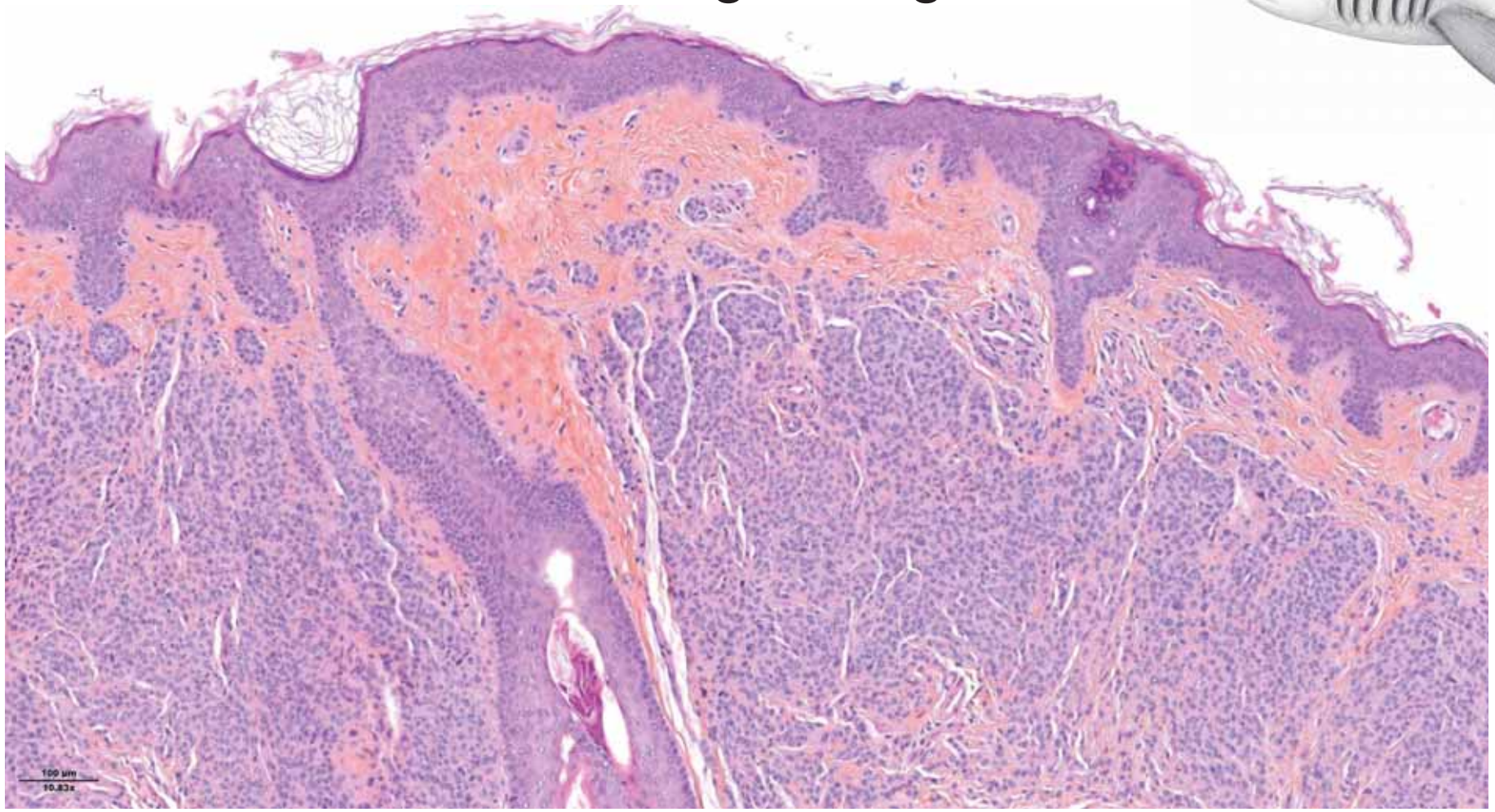
Lentiginous atypical junction



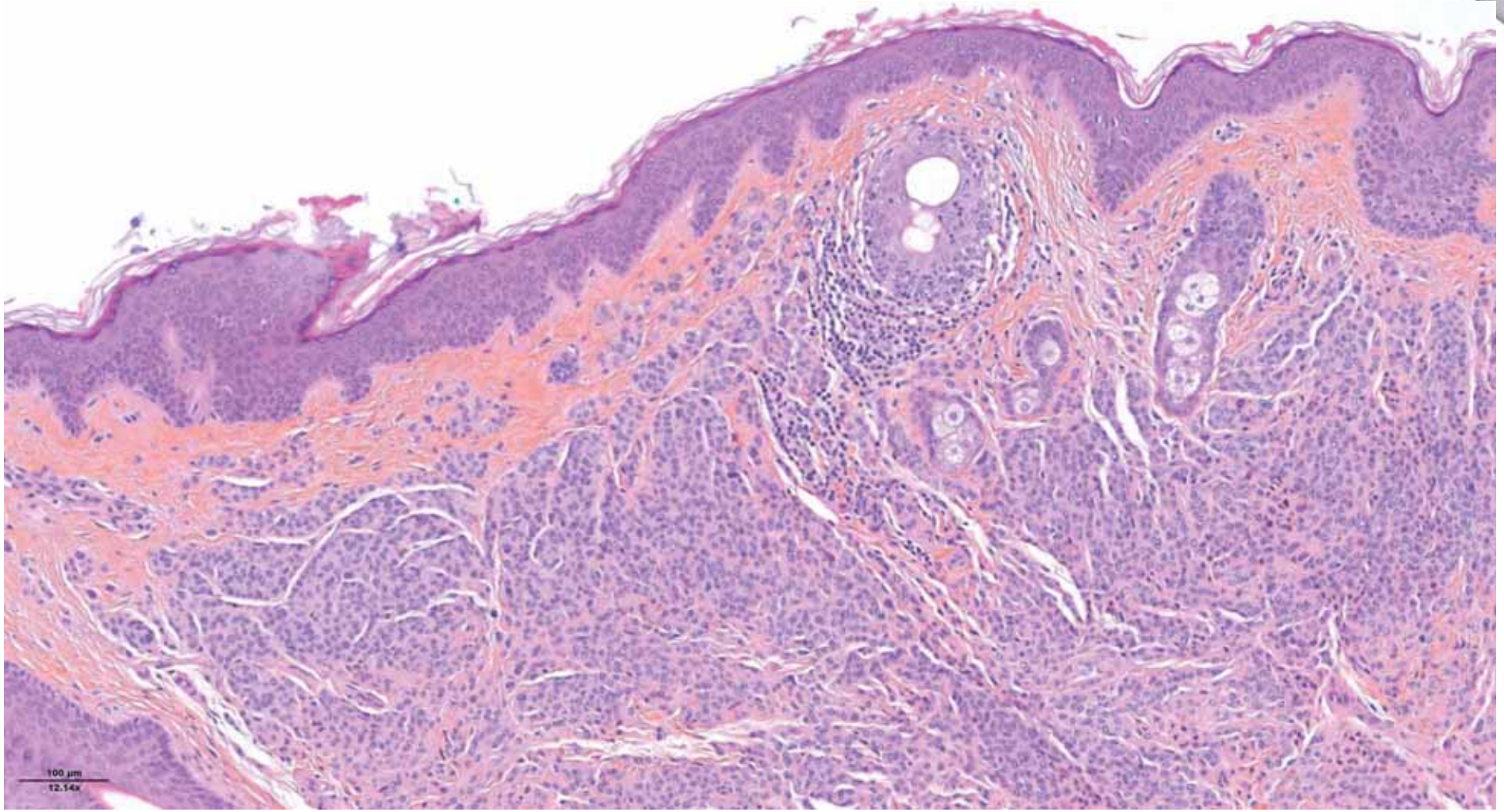
Lentiginous atypical junction

Shark gills sign

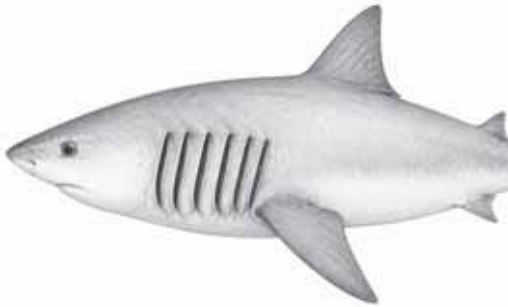


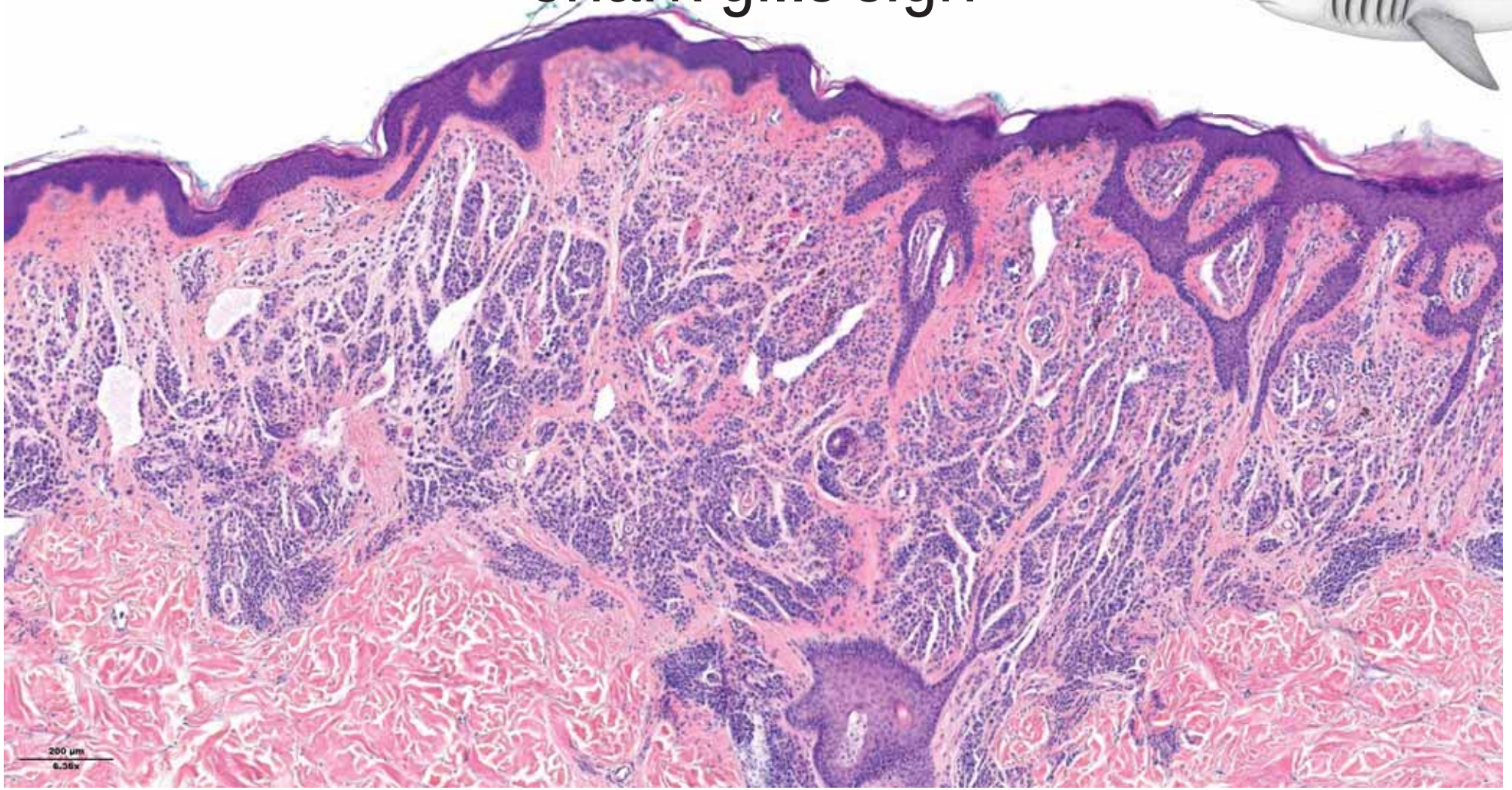


Shark gills sign

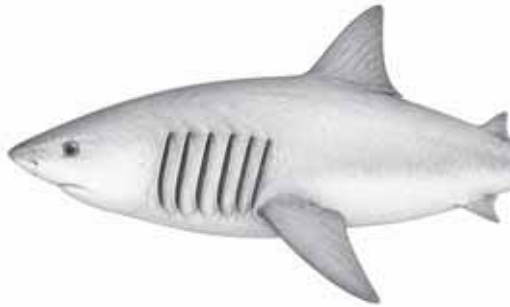


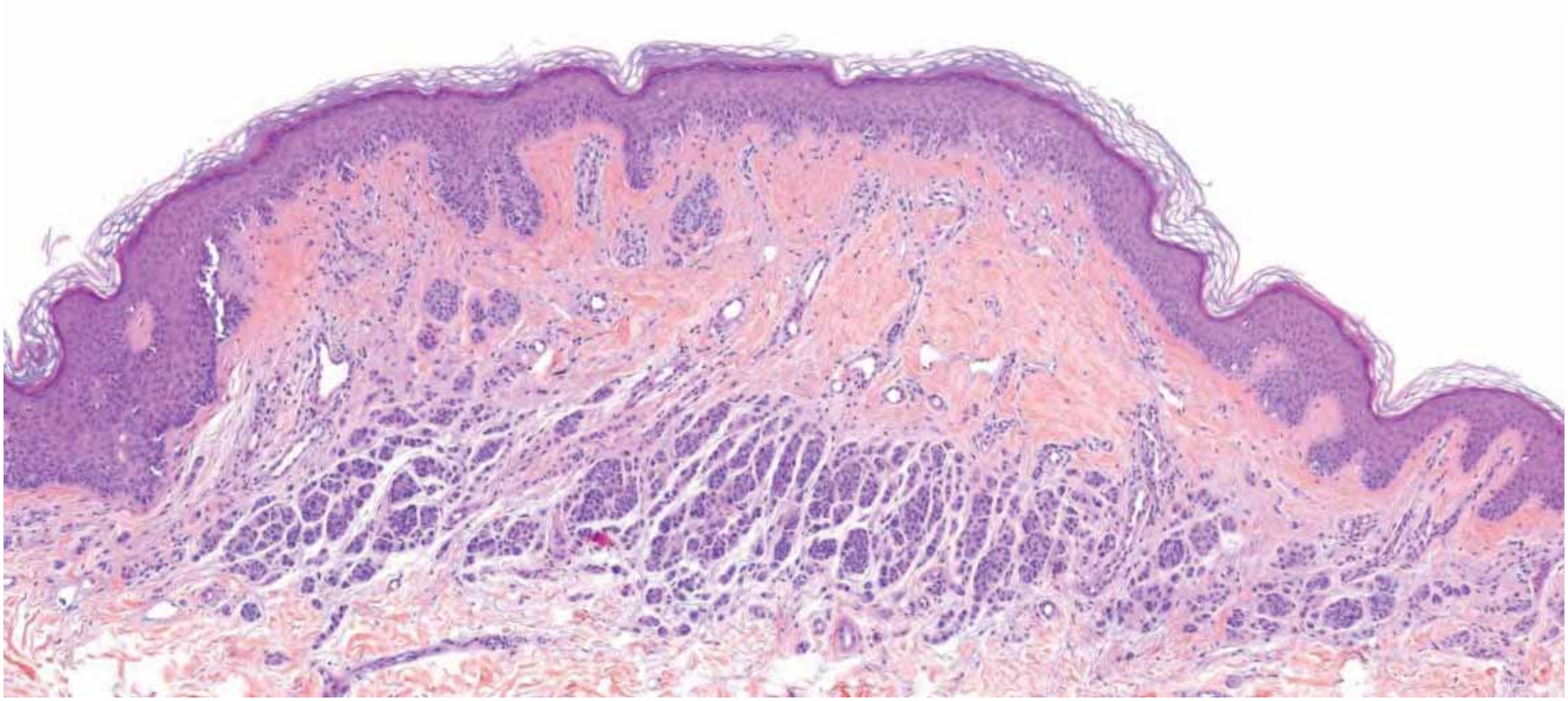
Shark gills sign



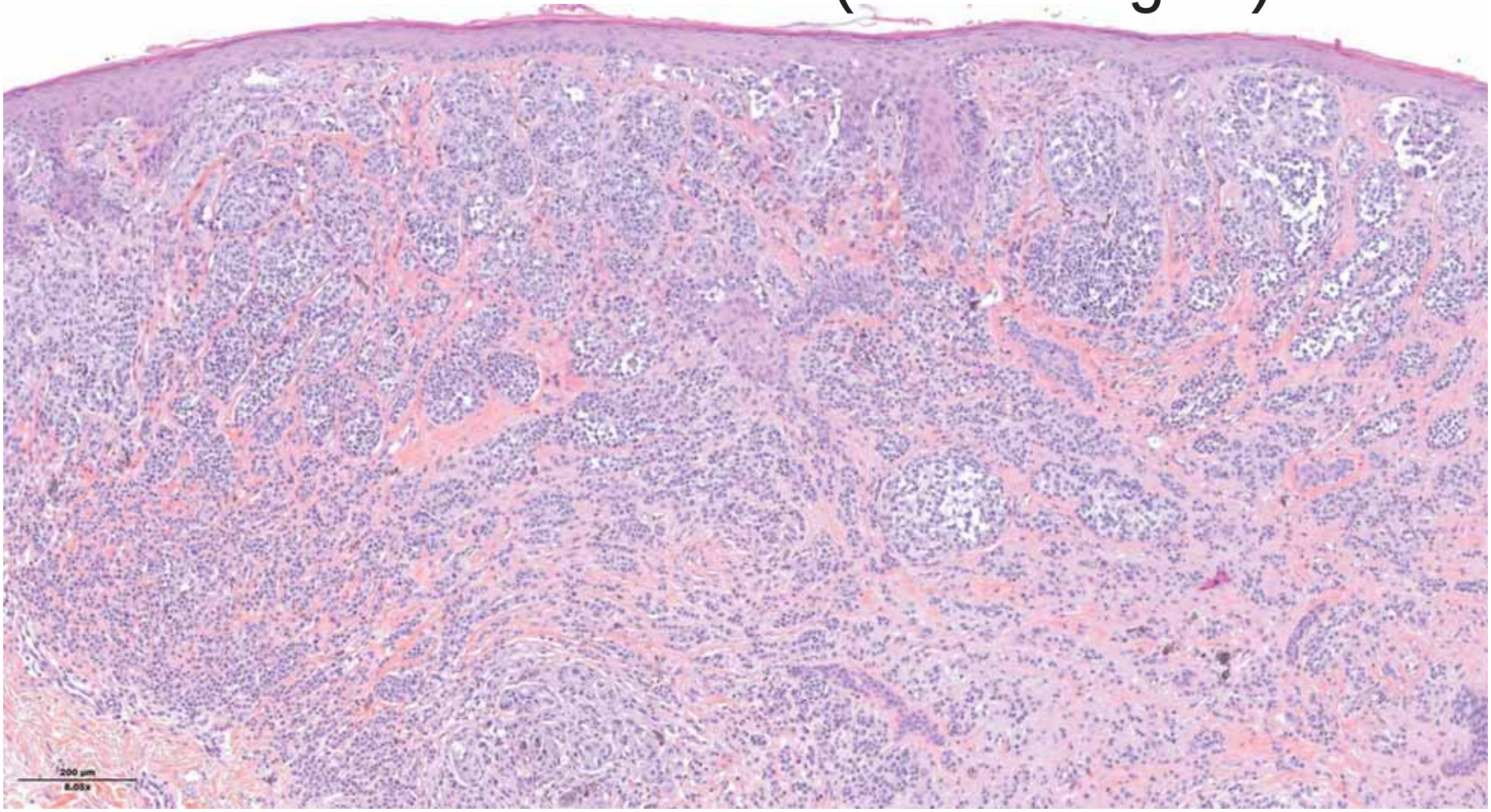


Shark gills sign

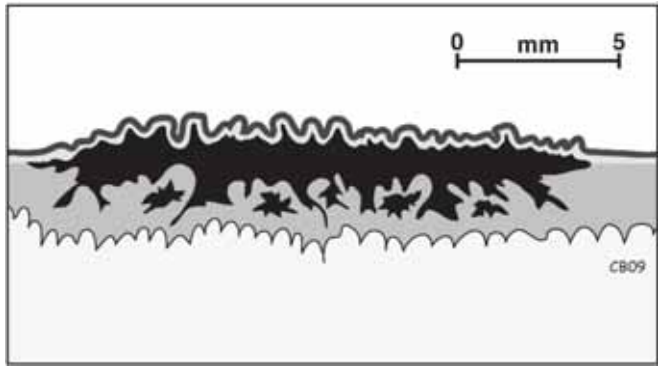


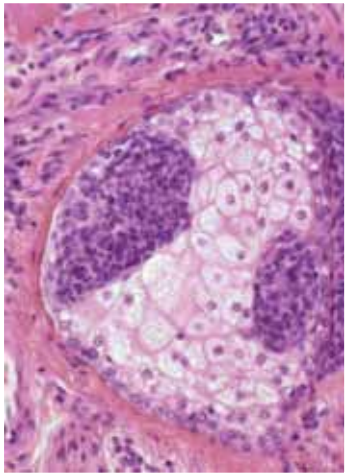


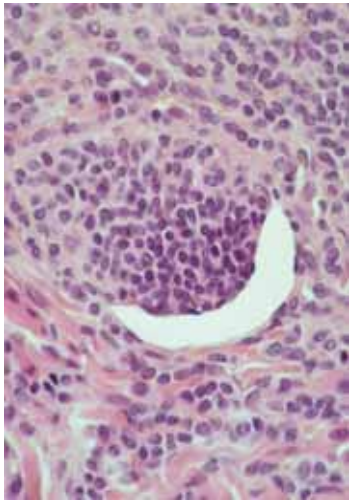
Nevoid melanoma (without gills)

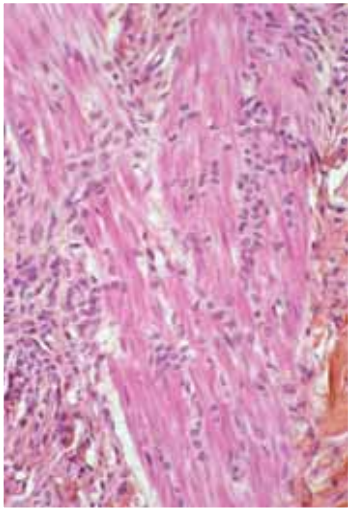


Compound congenital-like nevus high power clues

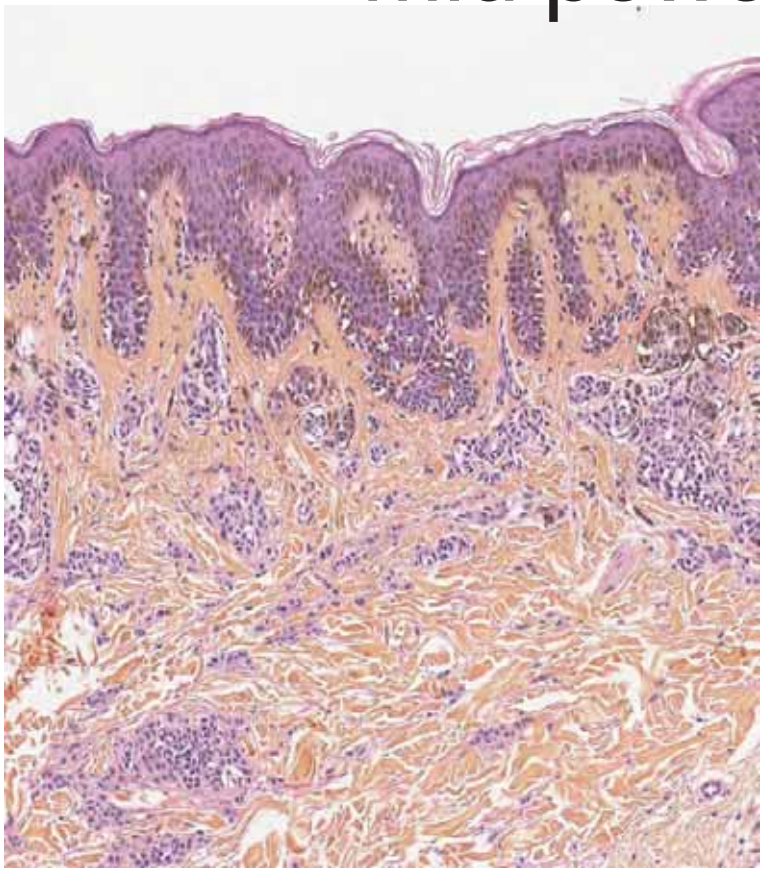


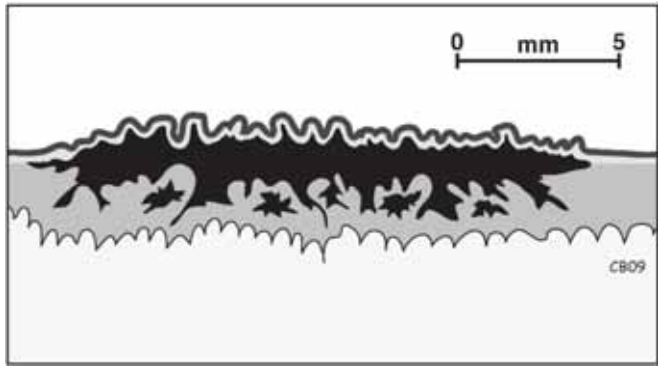


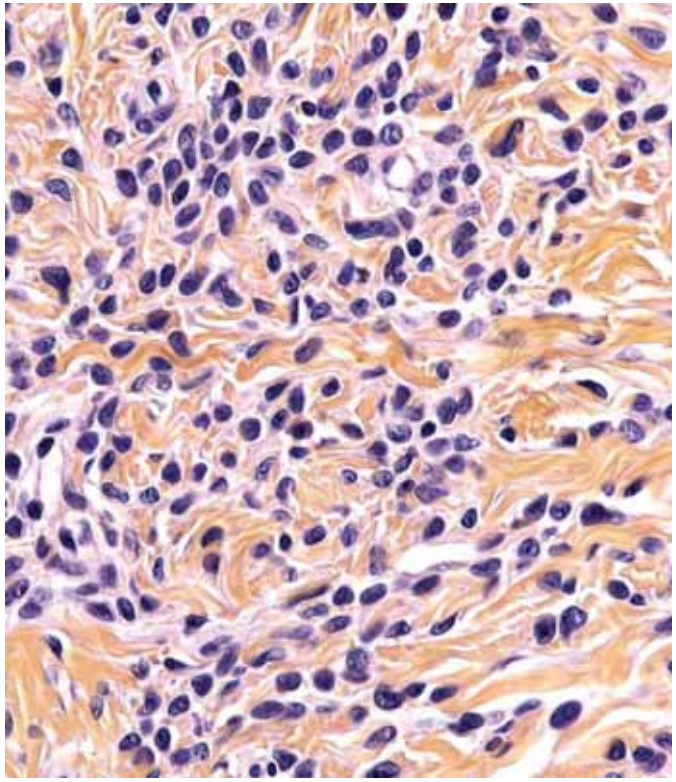




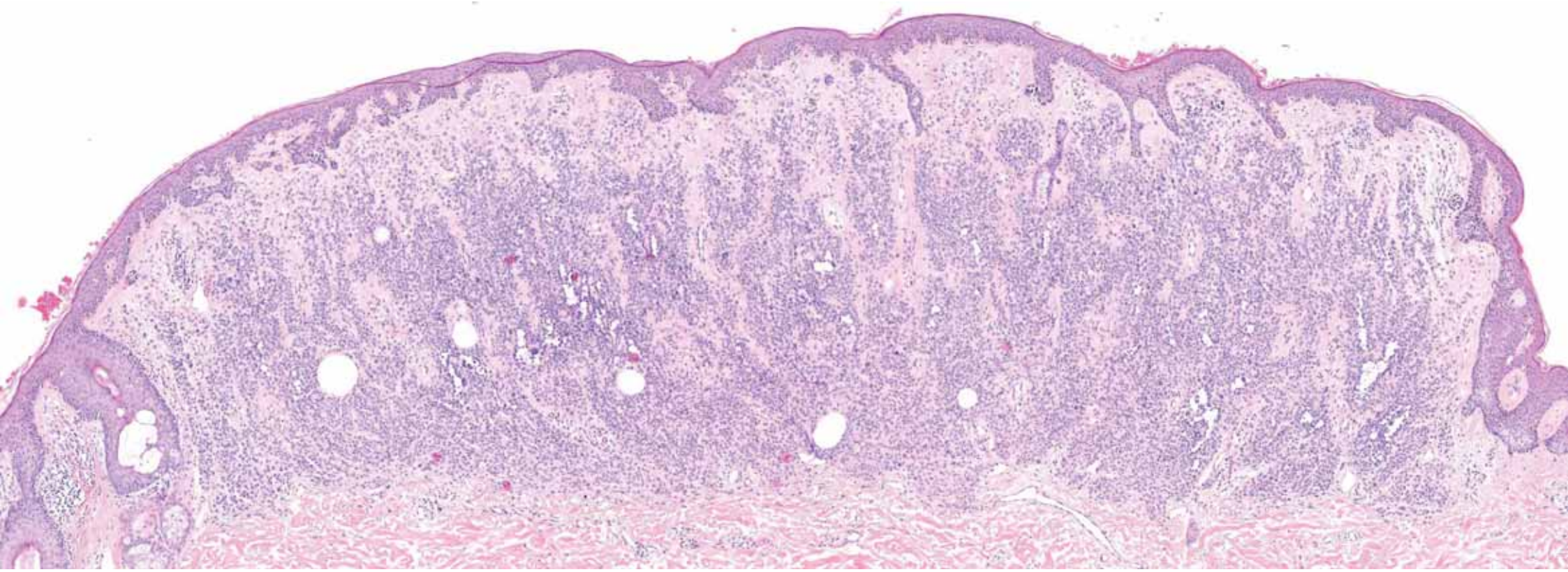
Compound congenital-like navus
mid power clues: dermal flammeche



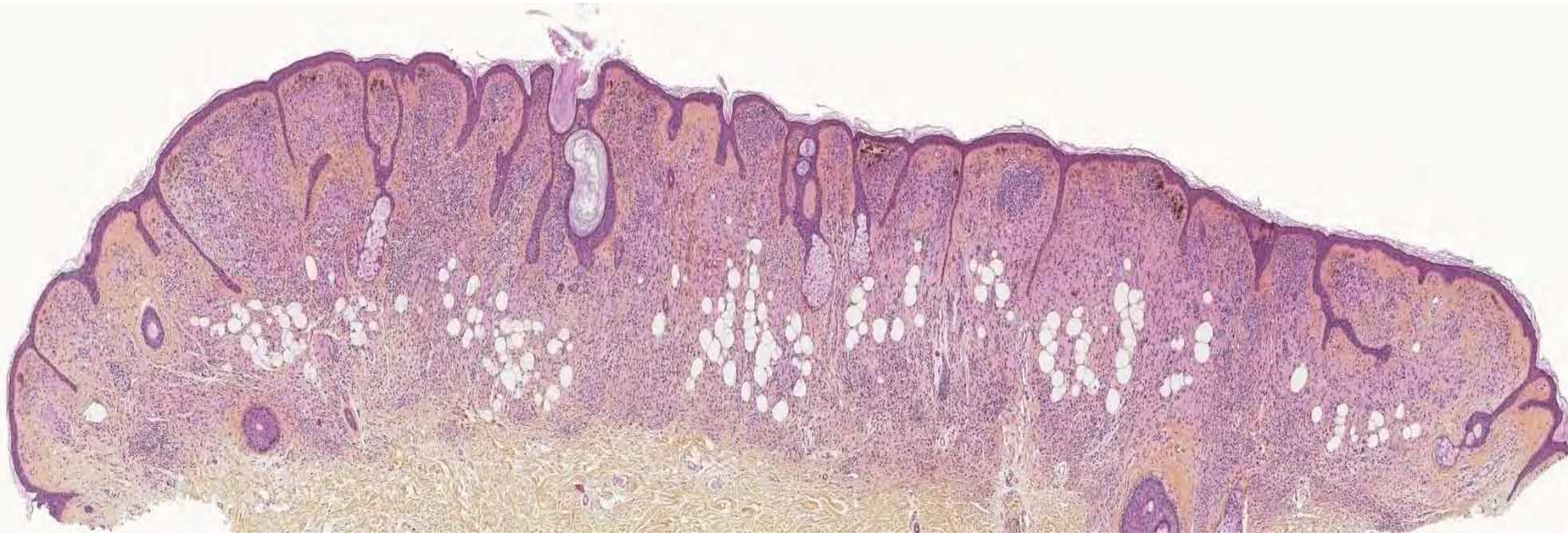


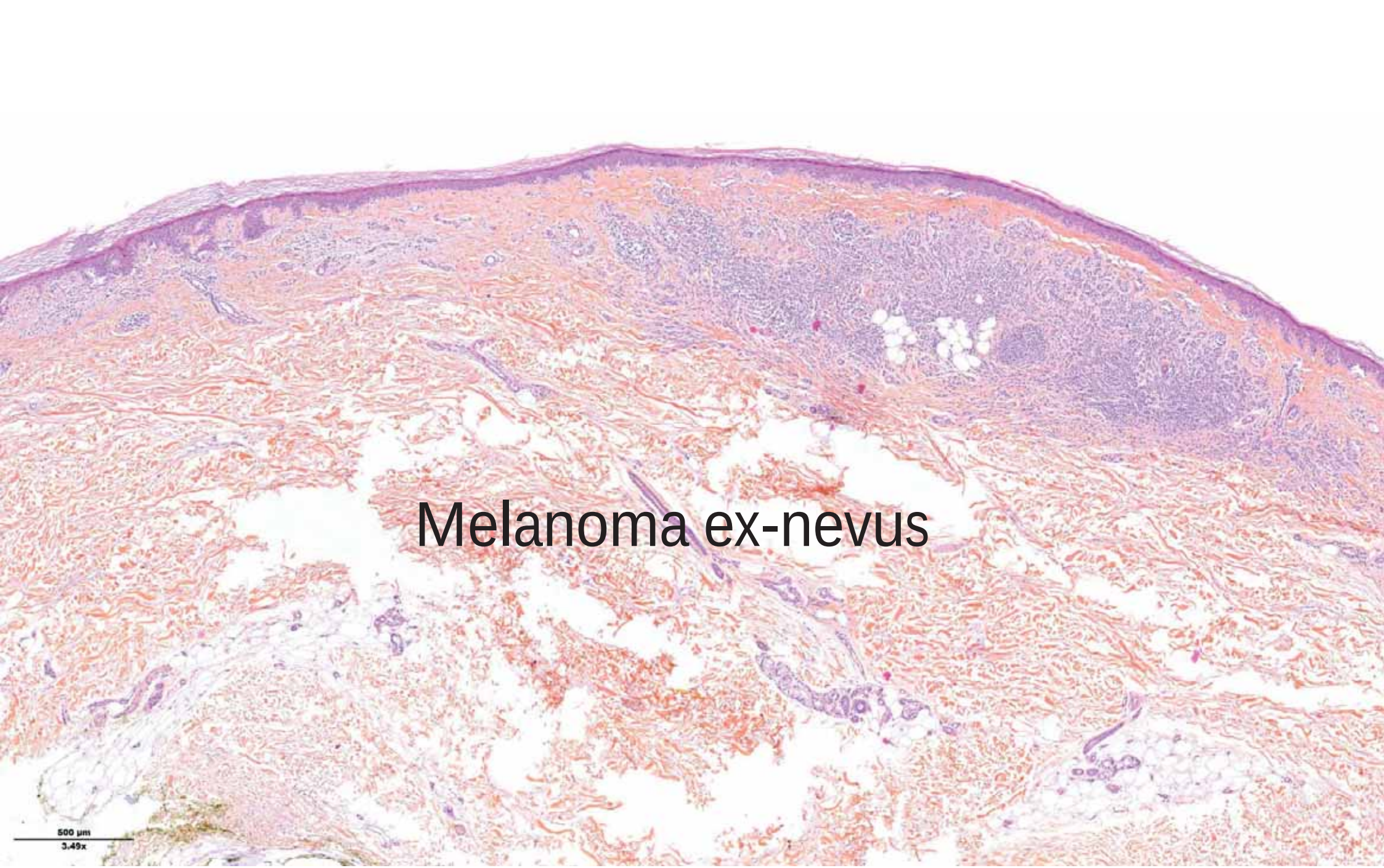


Adipocytic involution in nevus



Adipocytic involution in nevus

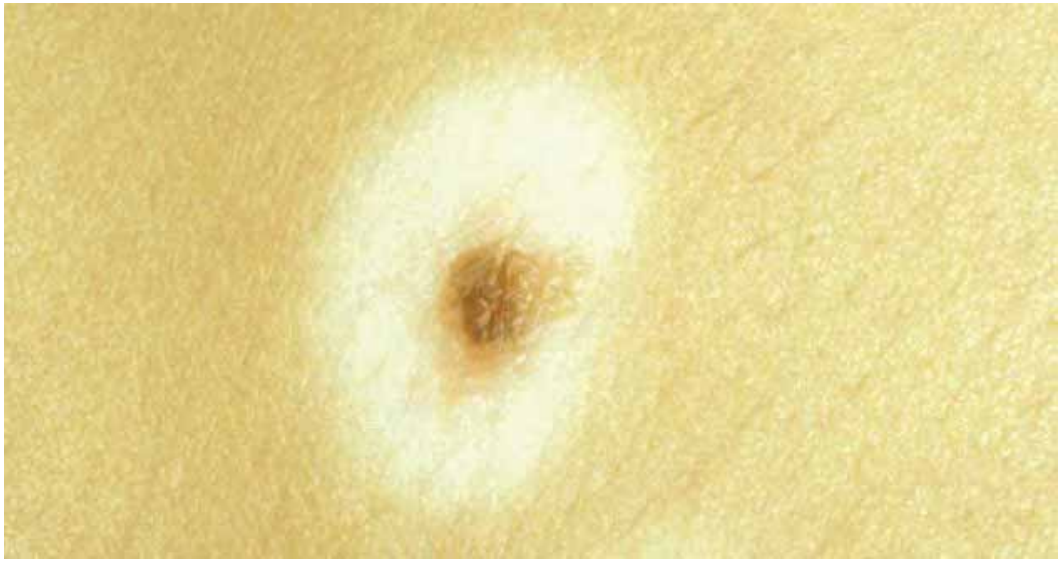




Melanoma ex-nevus

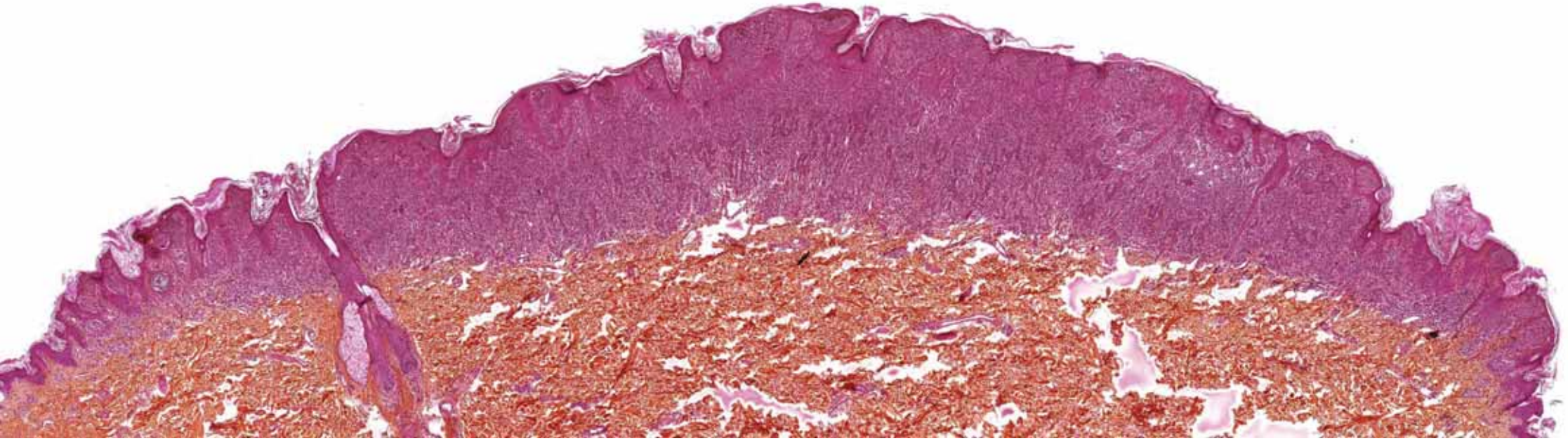
Sutton nevus
Clinical clues:

- Always question a Dg of Sutton nevus outside the trunk of a teenager
- Weak correlations between clinical and histological presentations
- A standard clinically recognized Sutton nevus is usually not removed

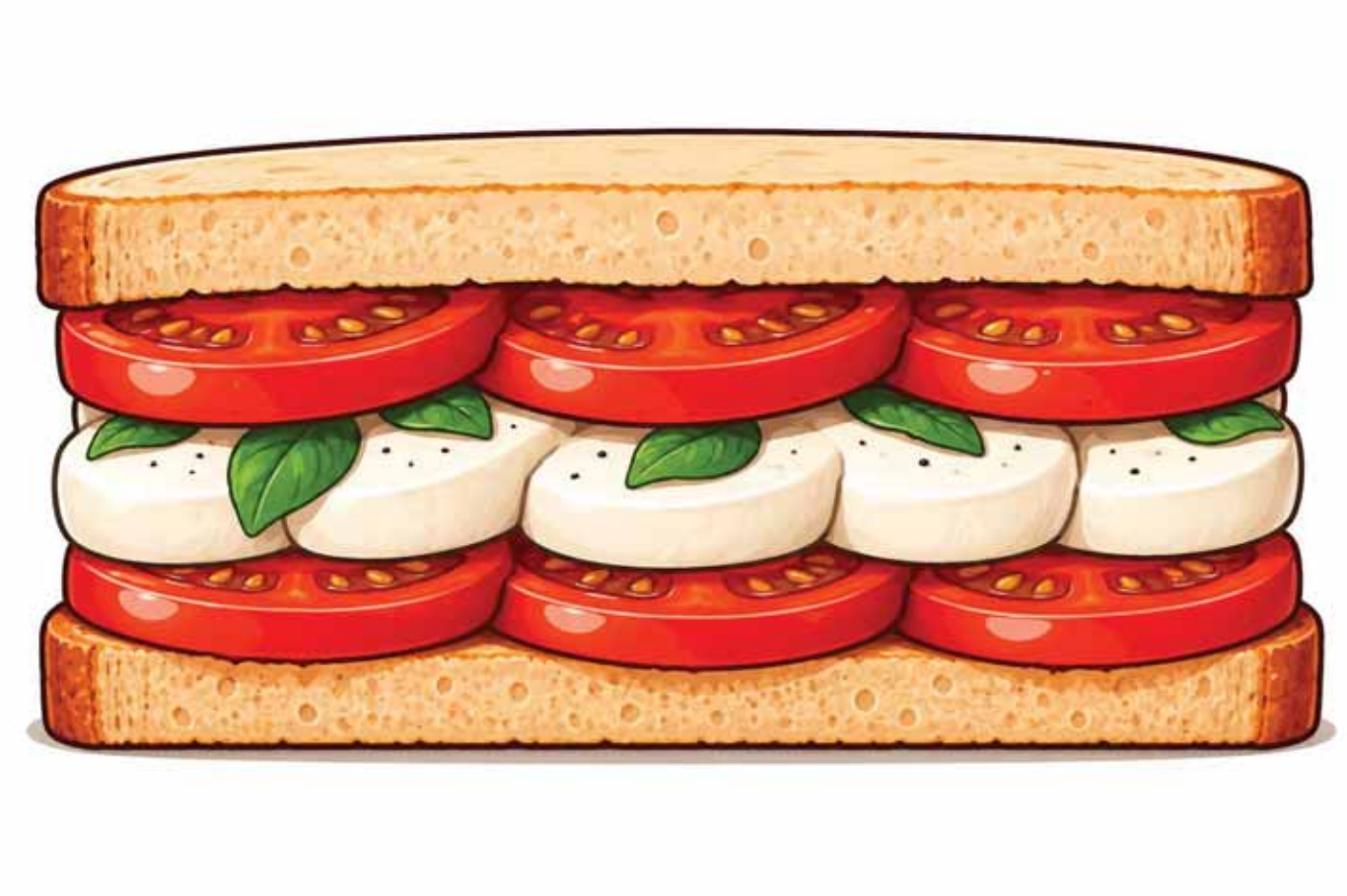


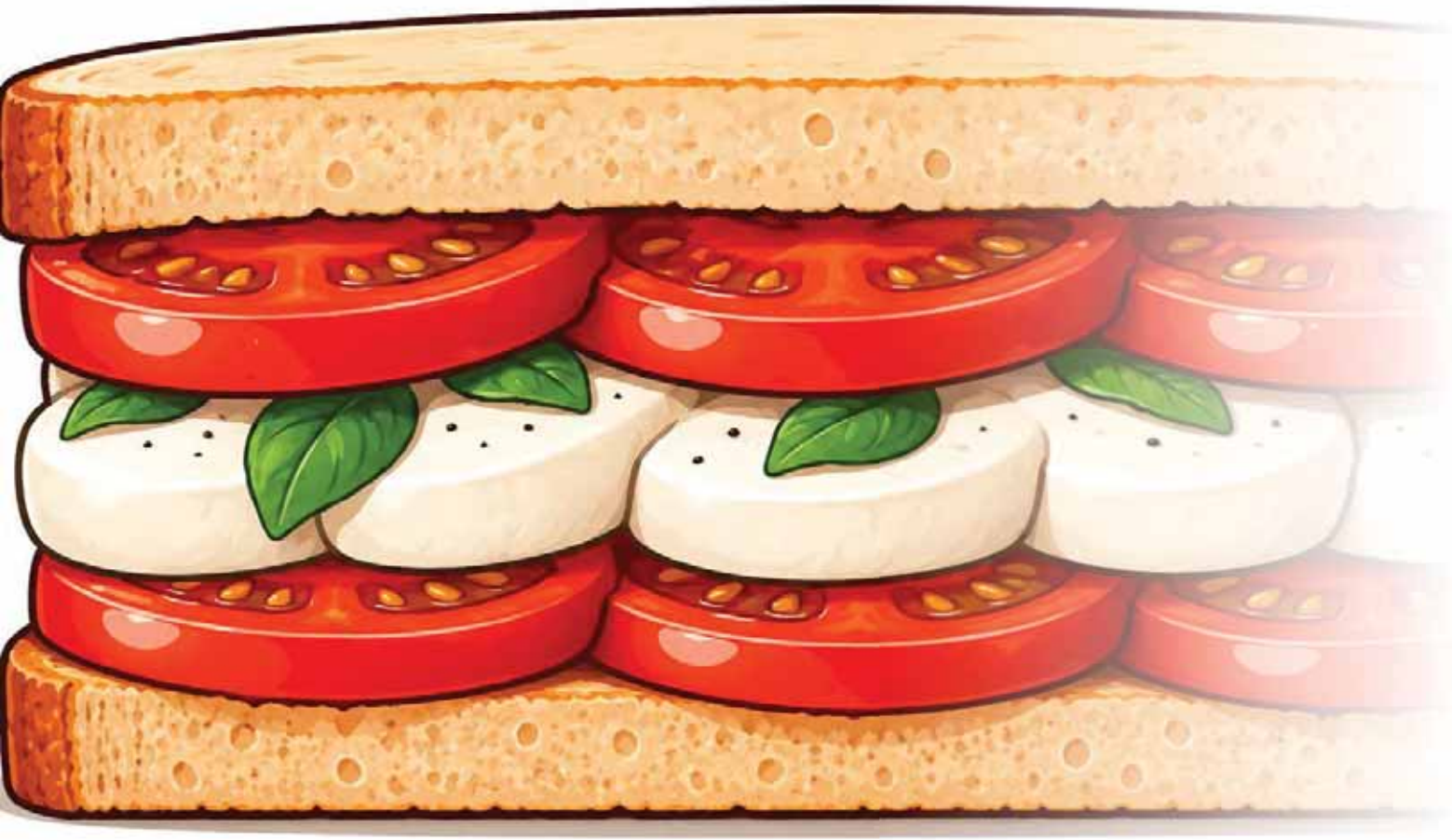
Sutton nevus
Usual histological clues:

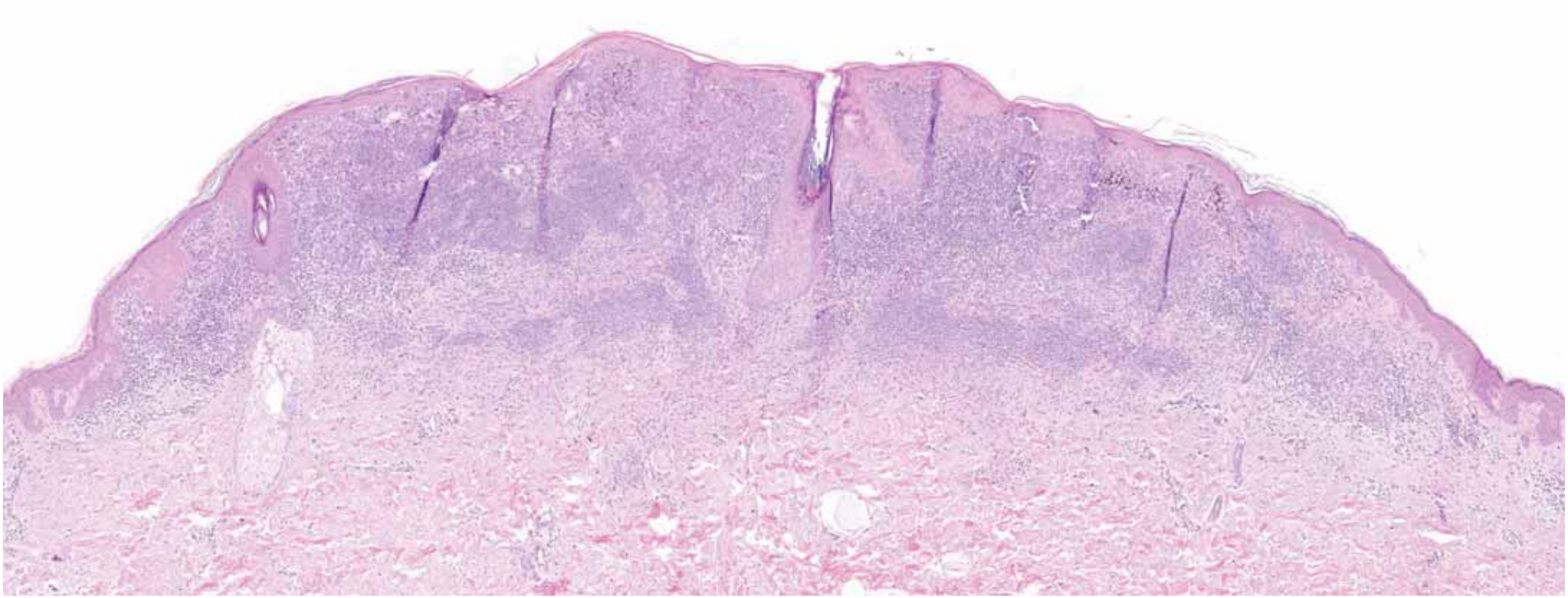
- Nevus with lateral inflammation/edema without melanophages
- Horizontal filling of lymphocytes «boxed» in the papillary dermis

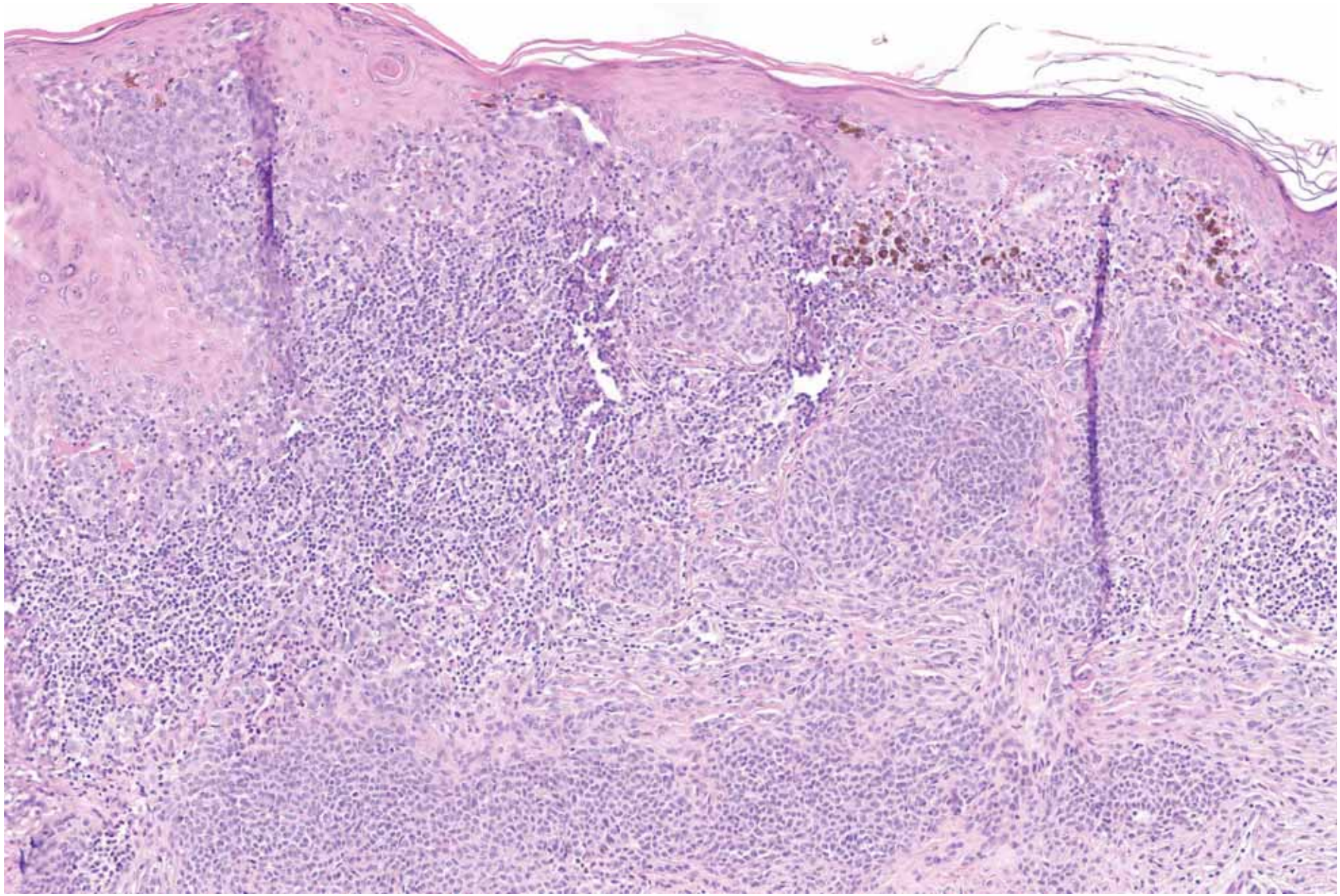


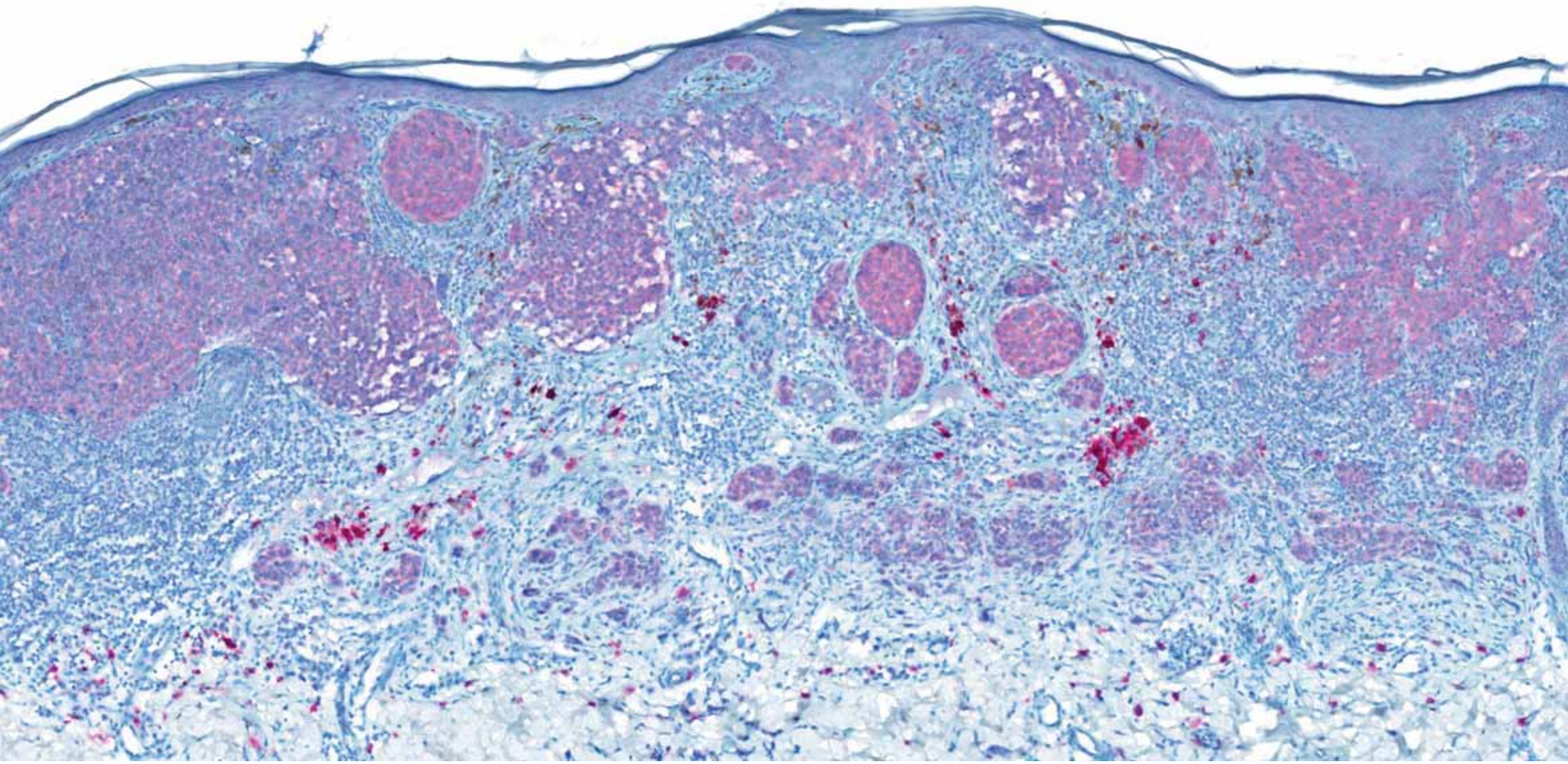
«Sandwich sign» for Sutton nevus

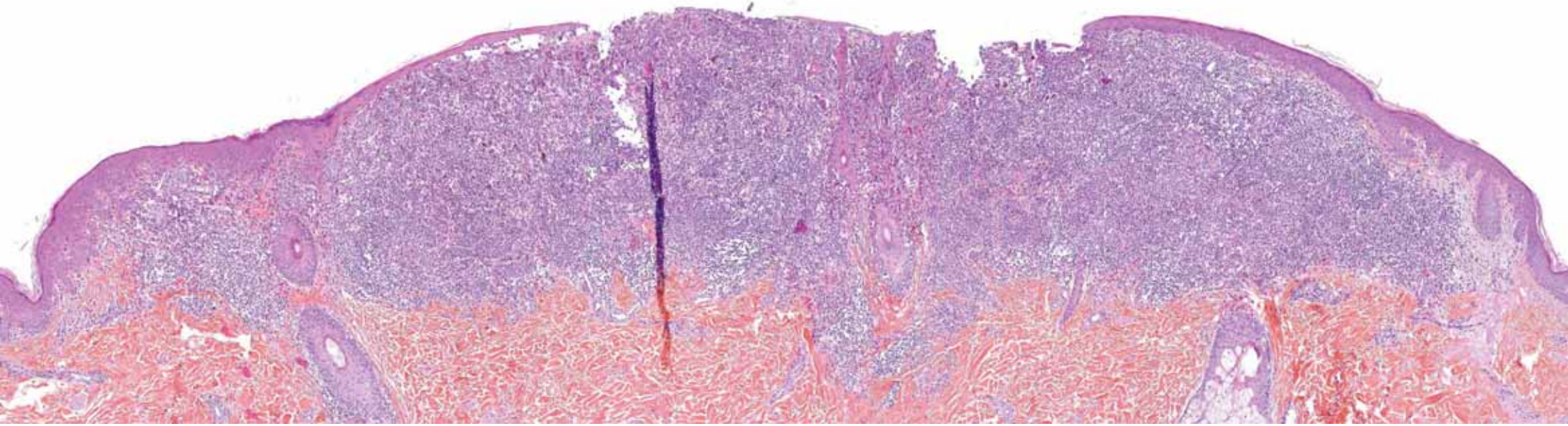


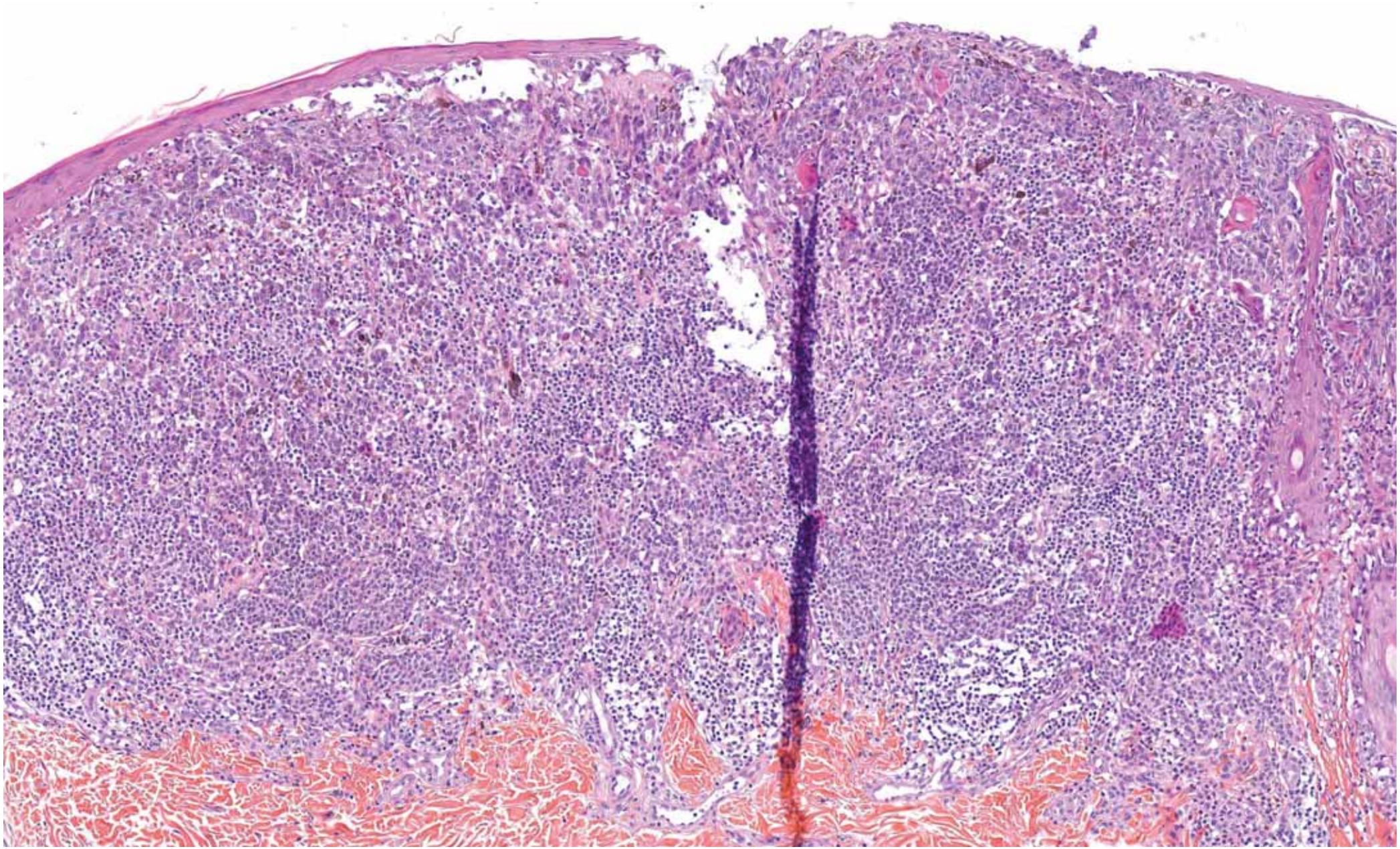

Epidermis
Superficial nests of melanocytes
Lymphocytic infiltrate
Deep nests of melanocytes
Dermis

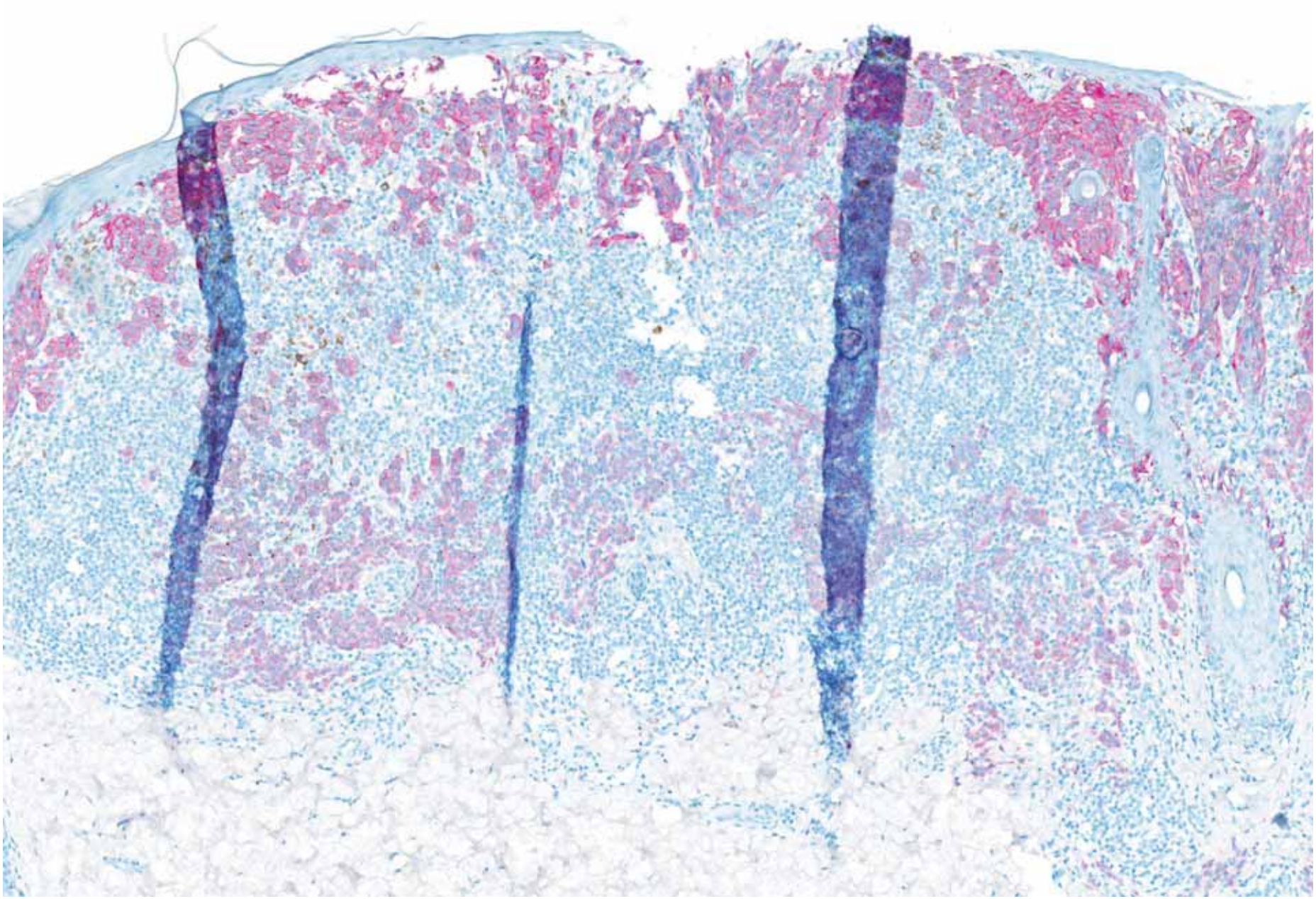












Clues for class I melanocytomas

- BAP1-inactivated melanocytoma
- WNT-activated melanocytoma
- PRKAR1A-inactivated melanocytoma

Secondary genetic alteration biphenotypic/clonal morphology

BRAF, *NRAS*, *MAP2K1*

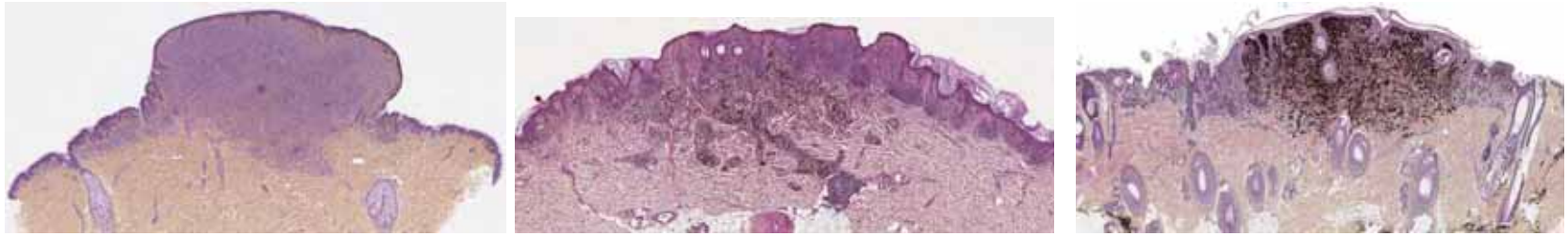
Common nevus,
Congenital nevus

additionnal molecular anomalies

BAP1 inactivated melanocytoma (BIM)

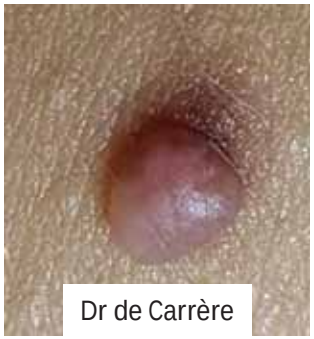
WNT activated melanocytoma (WAM)

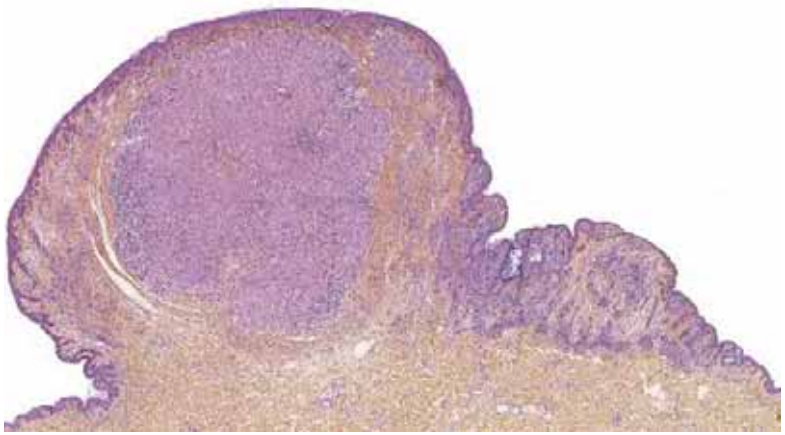
PRKAR1A inactivated melanocytoma (PEM)



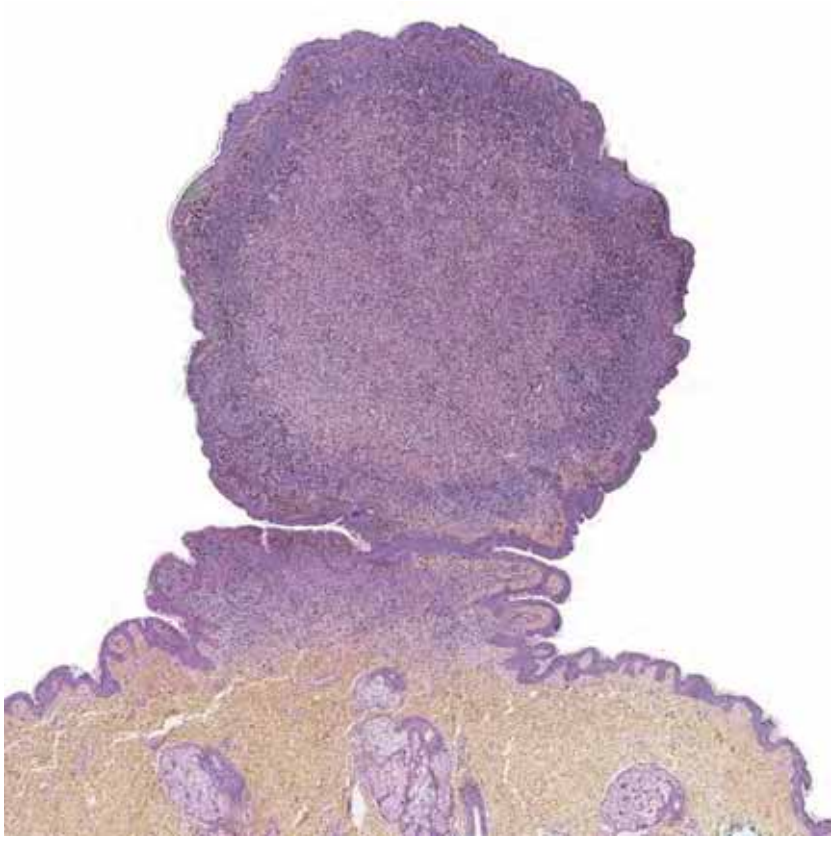
BAP1-inactivated melanocytic tumors
Somatic > germline mutation of BAP1

- Children or young adults
- Female>Male
- Sun-exposed areas
- Modification of a nevus
- Growing unpigmented nodule <1cm
- Inflammatory features
- Multiple lesions: germline

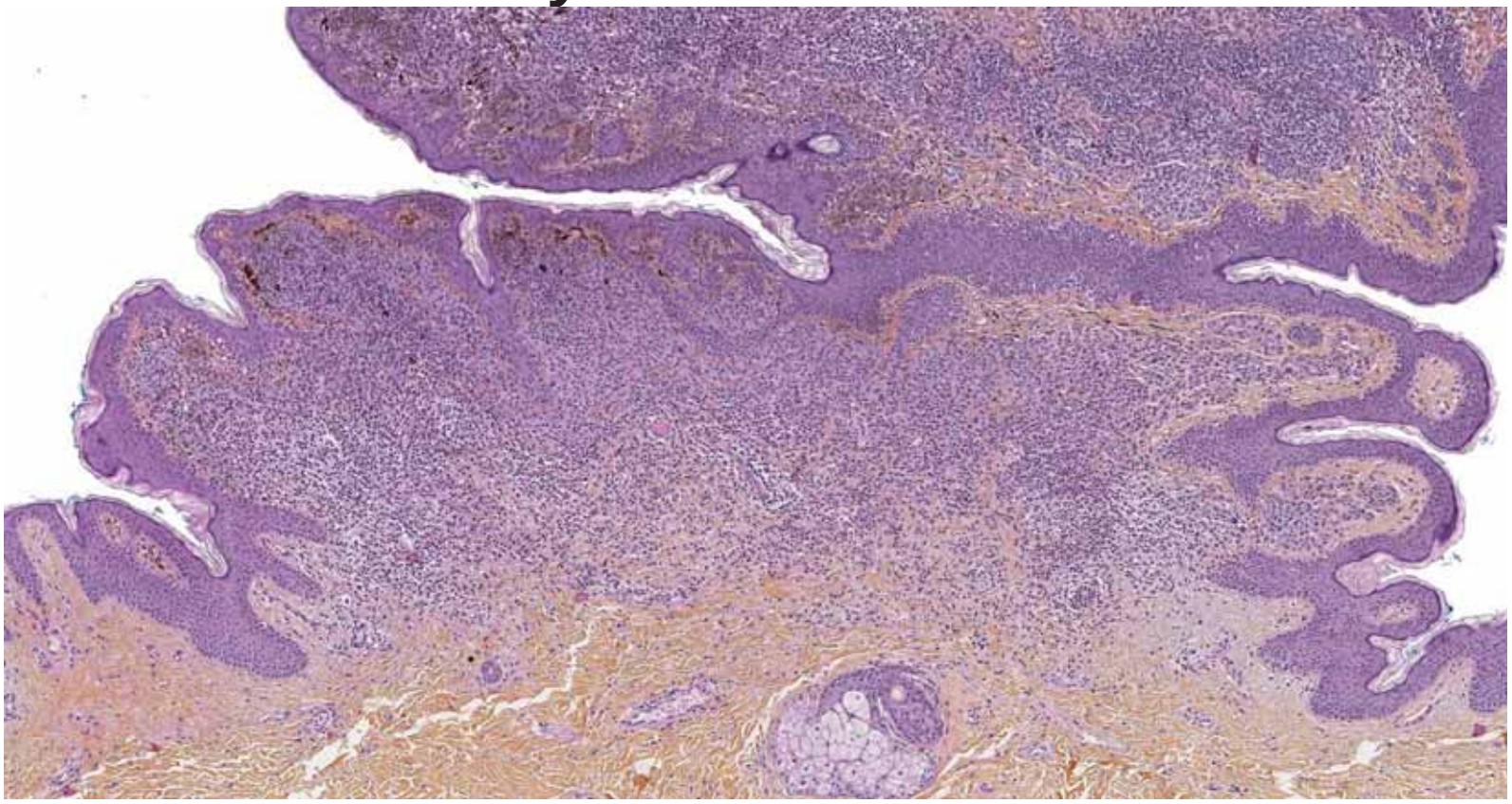




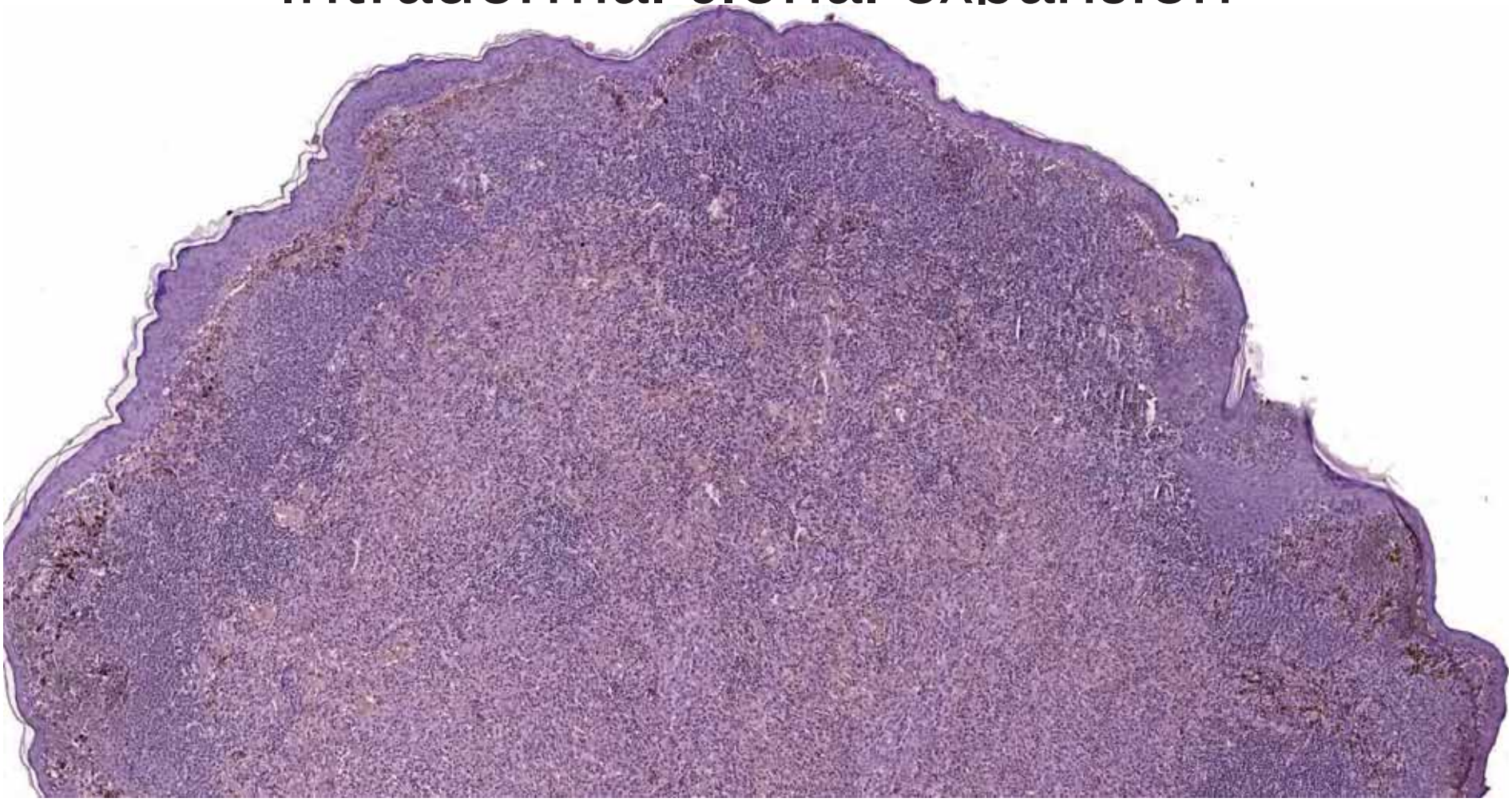
BIM classical clues



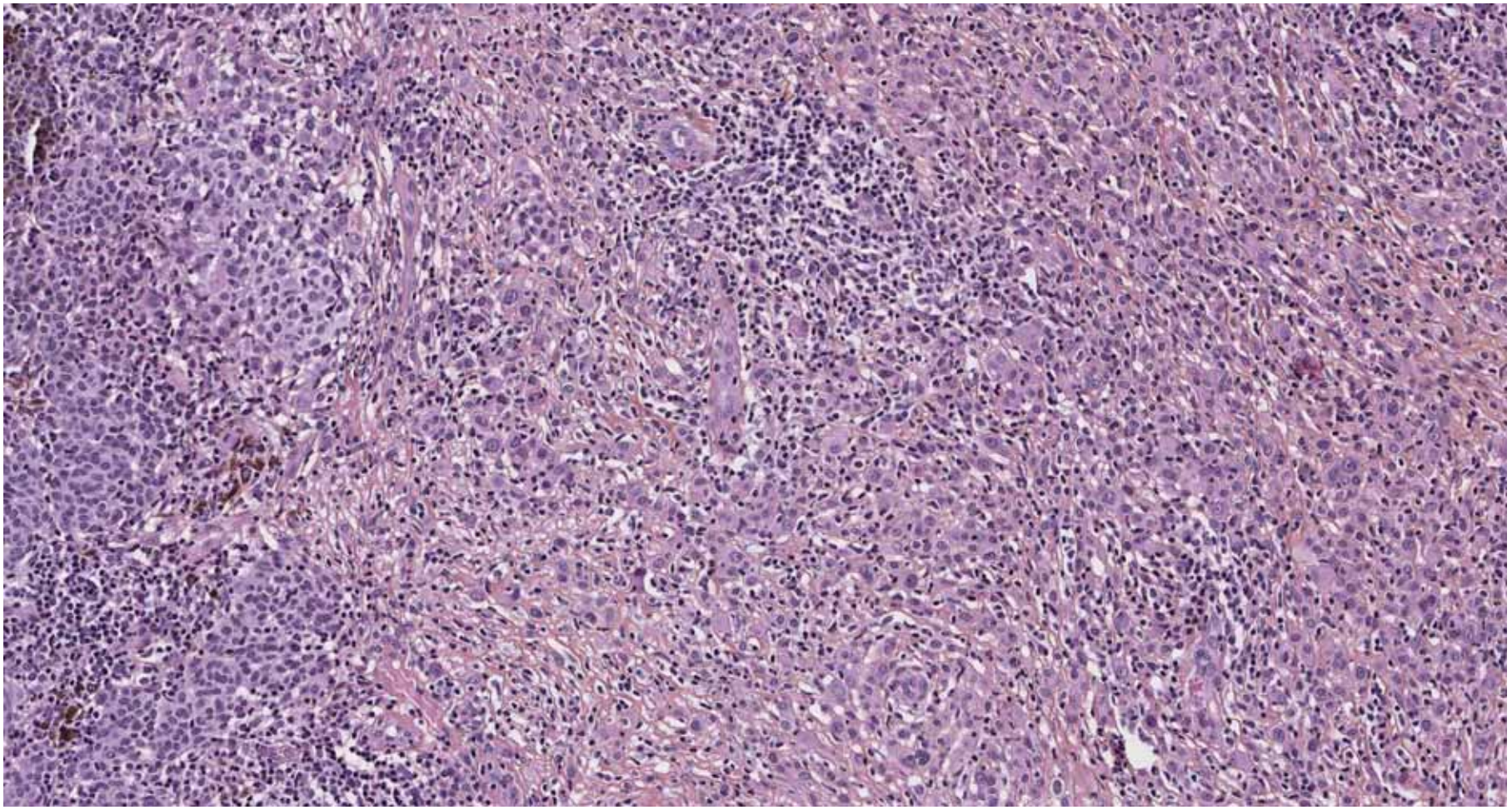
Combined lesion: lateral compound common nevus usually BRAF V600E mutated



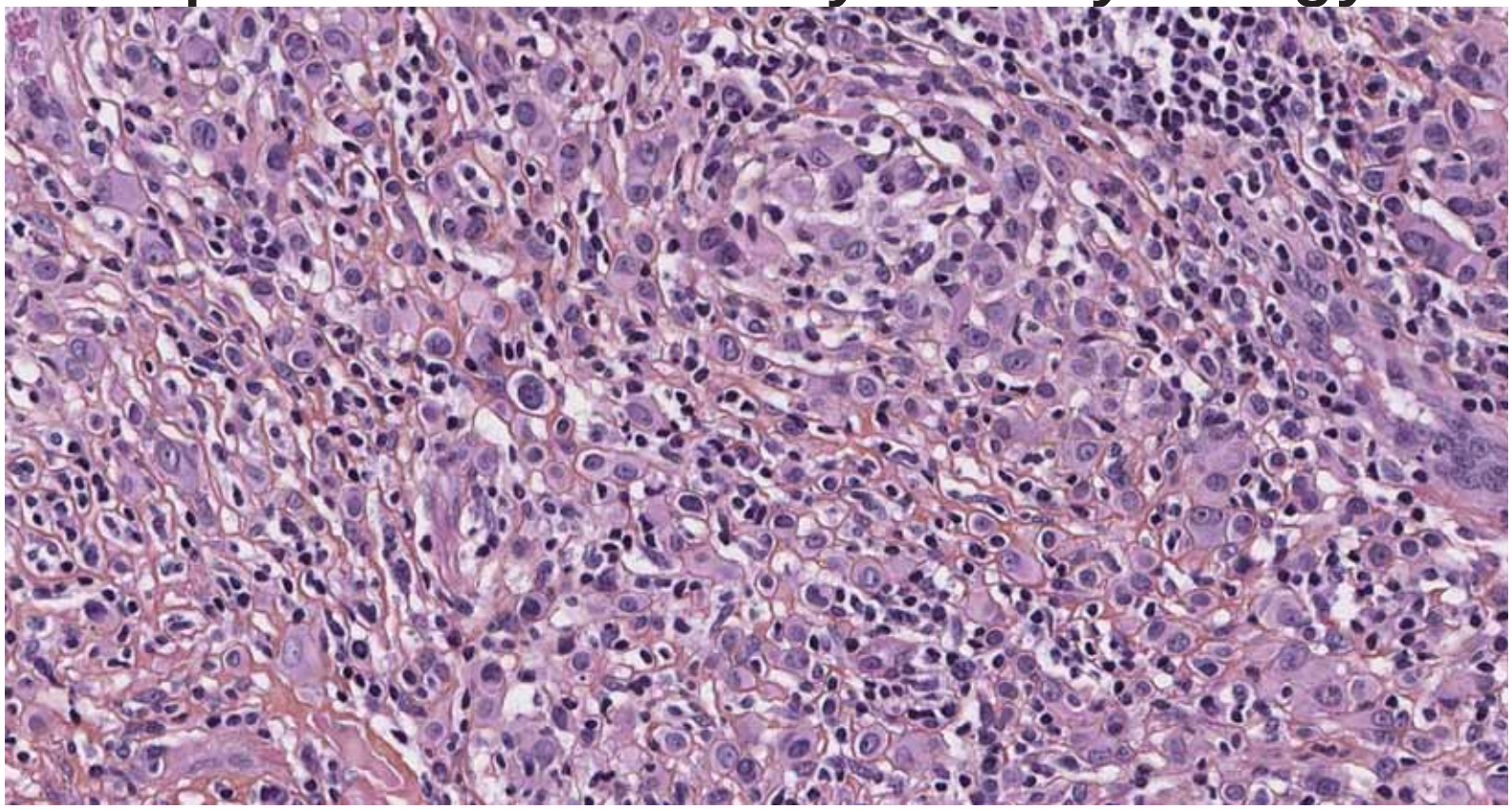
Intradermal clonal expansion



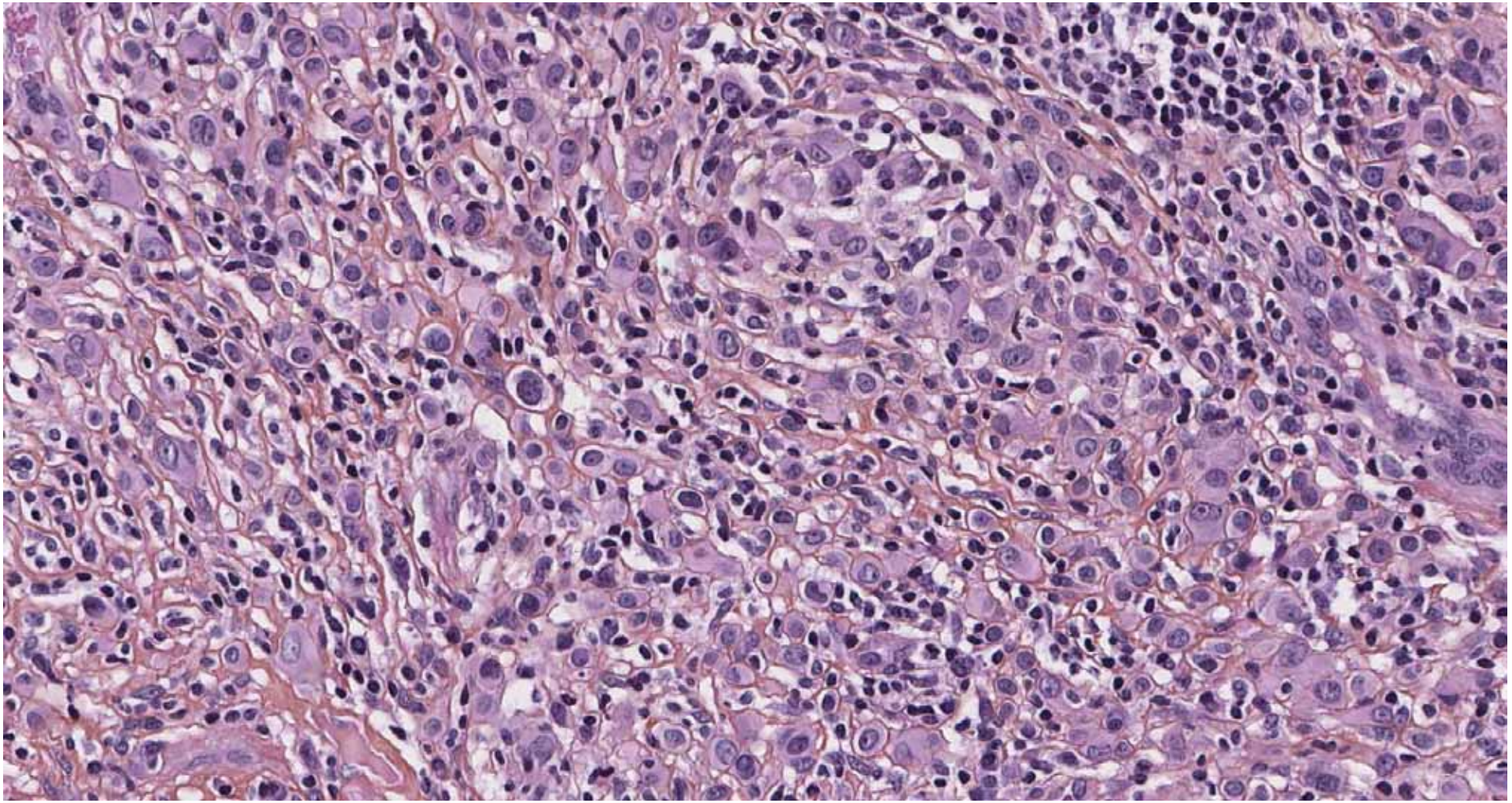
Unpigmented clone with « loose » density



Low proliferative, epithelioid/nevocytoid cytology



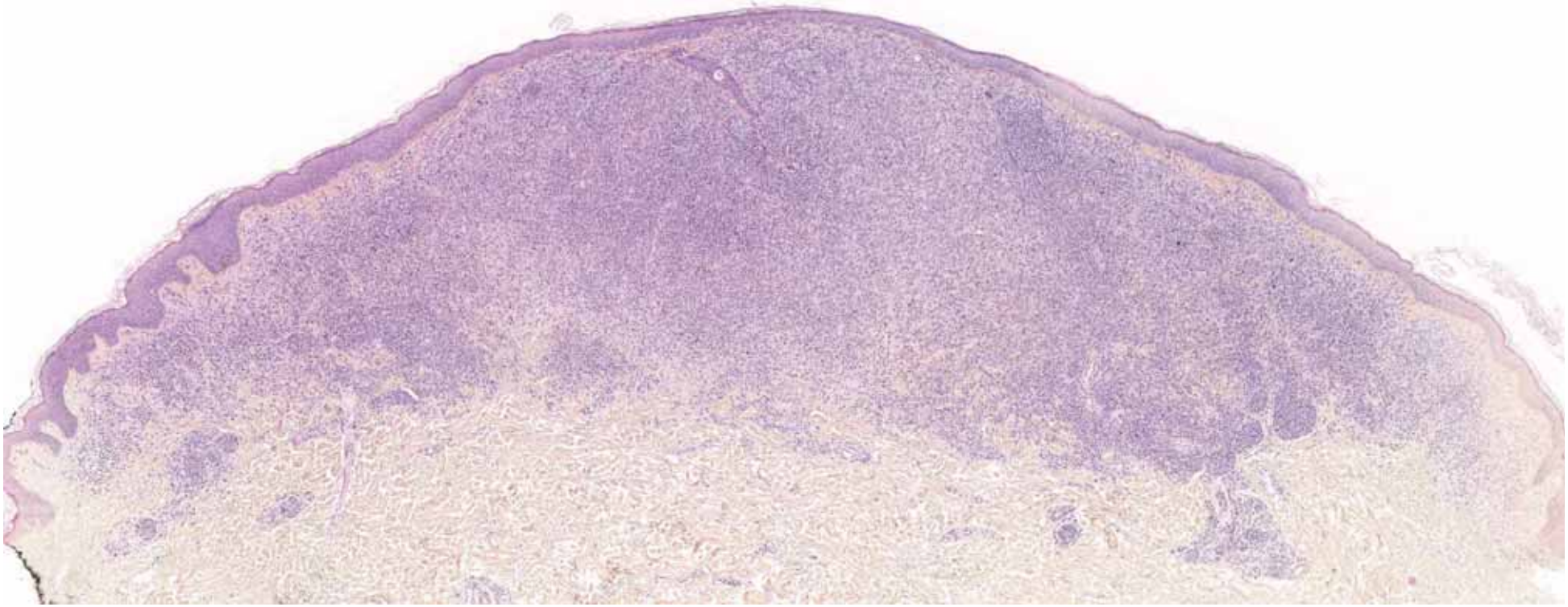
Lymphoid infiltrate with «kissing figures»



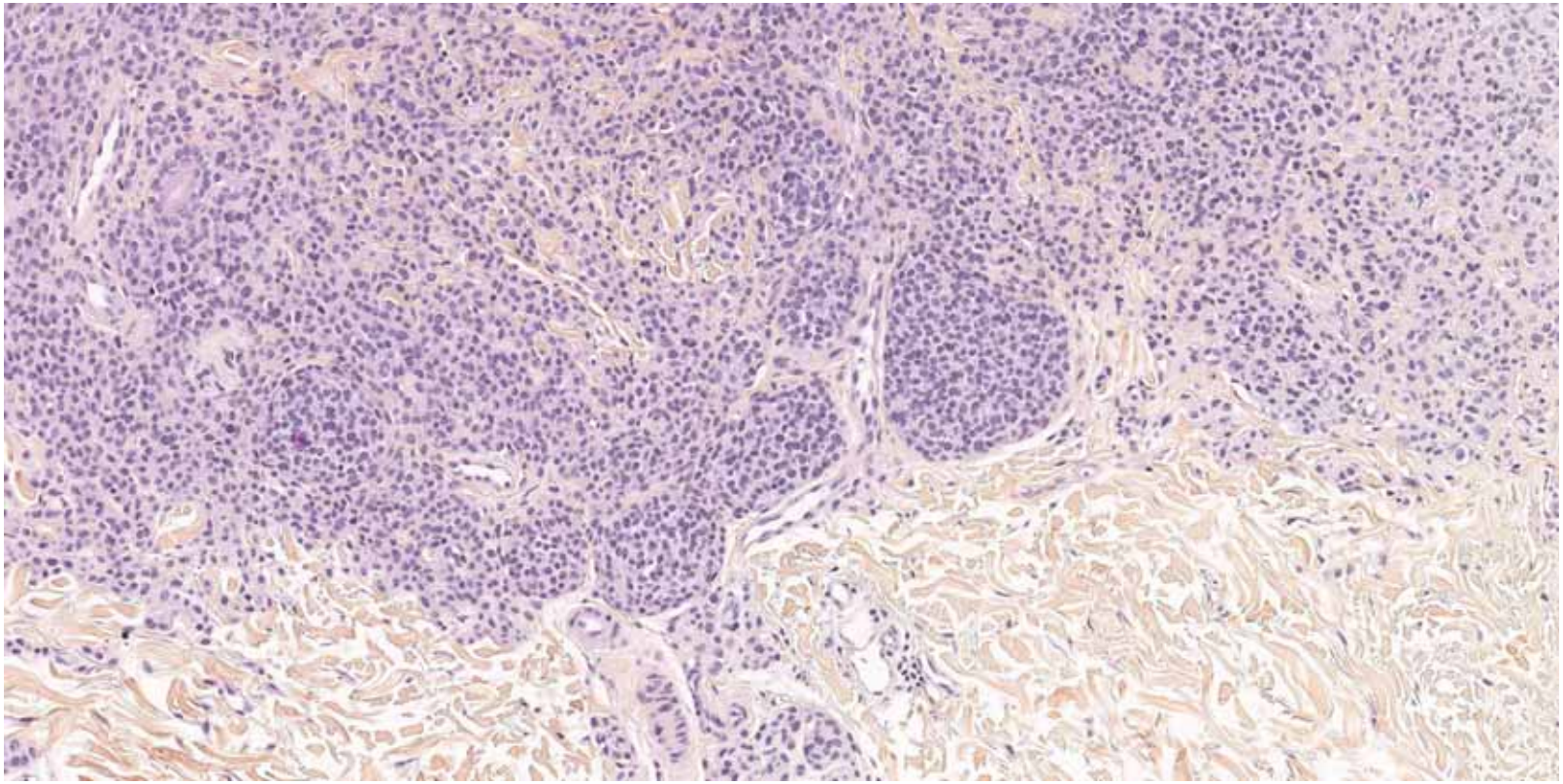
Inconstant clues
BAP1-inactivated melanocytoma

- Dermal nests of nevoid melanocytes
- Chondroid matrix

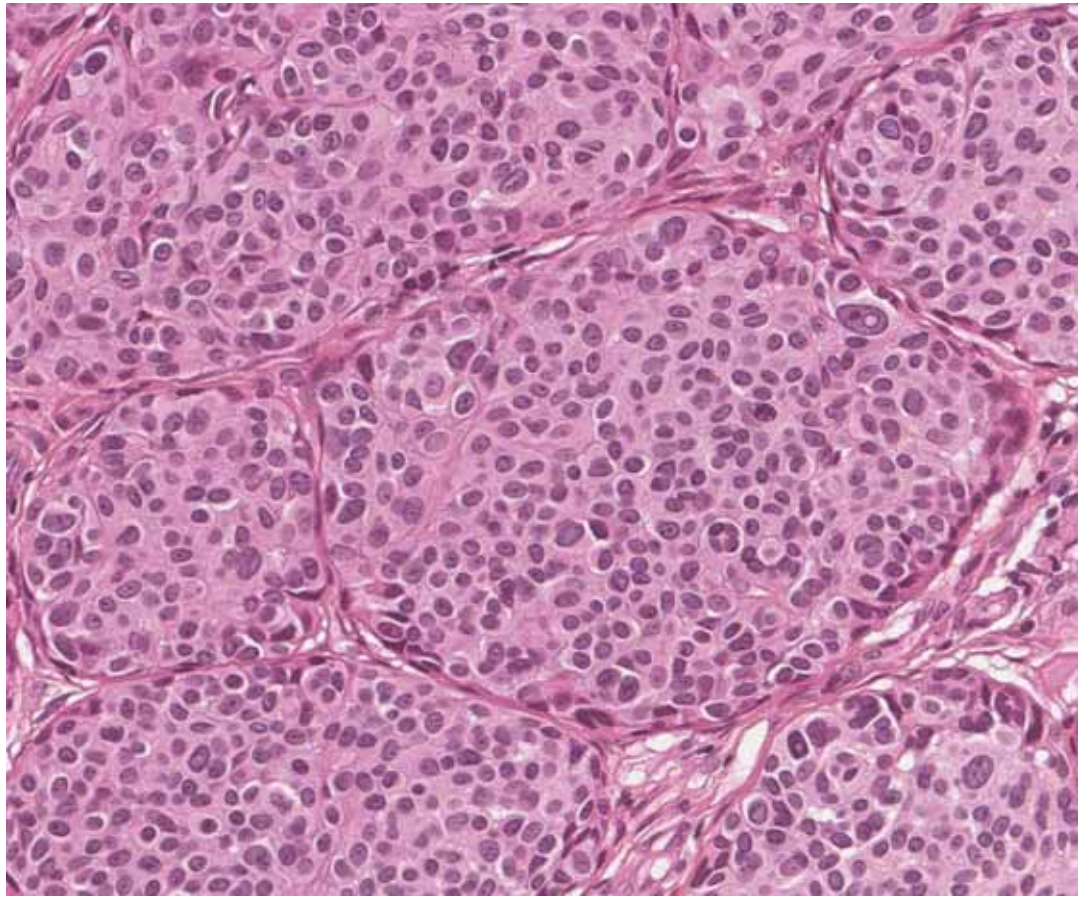
Nests of nevoid cells should always question for BAP1 loss



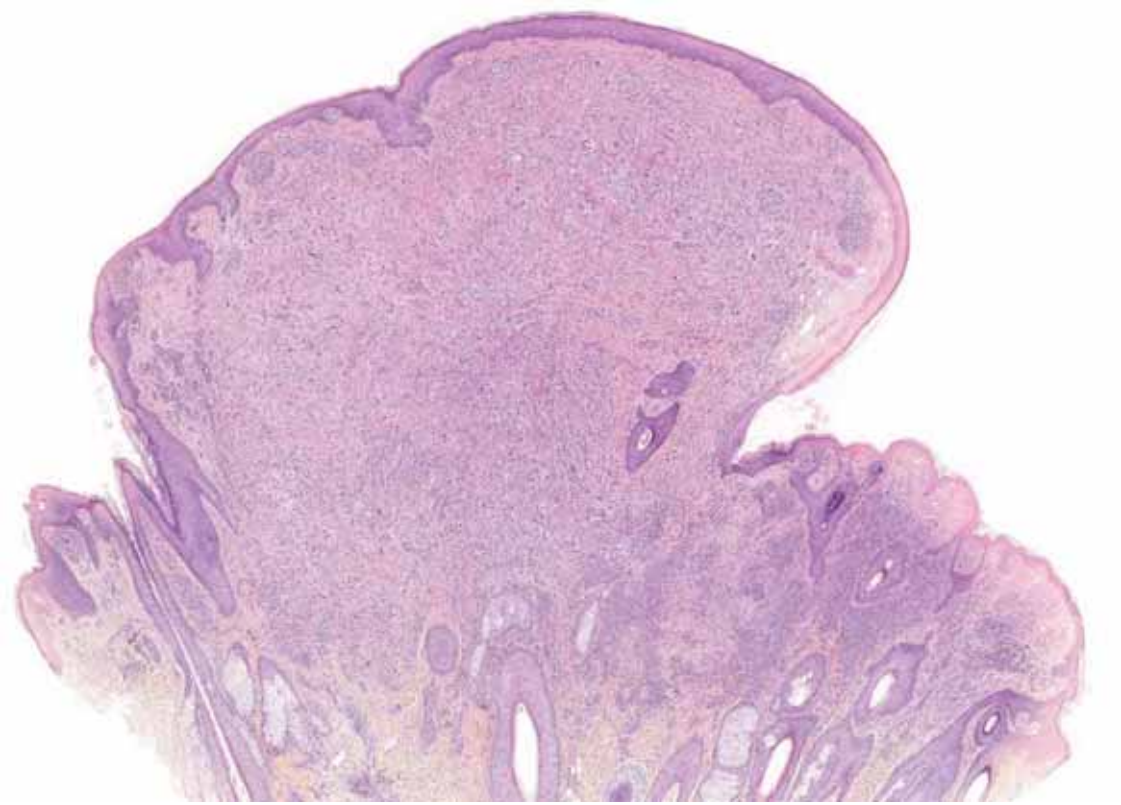
Nests of nevoid cells should always question for BAP1 loss



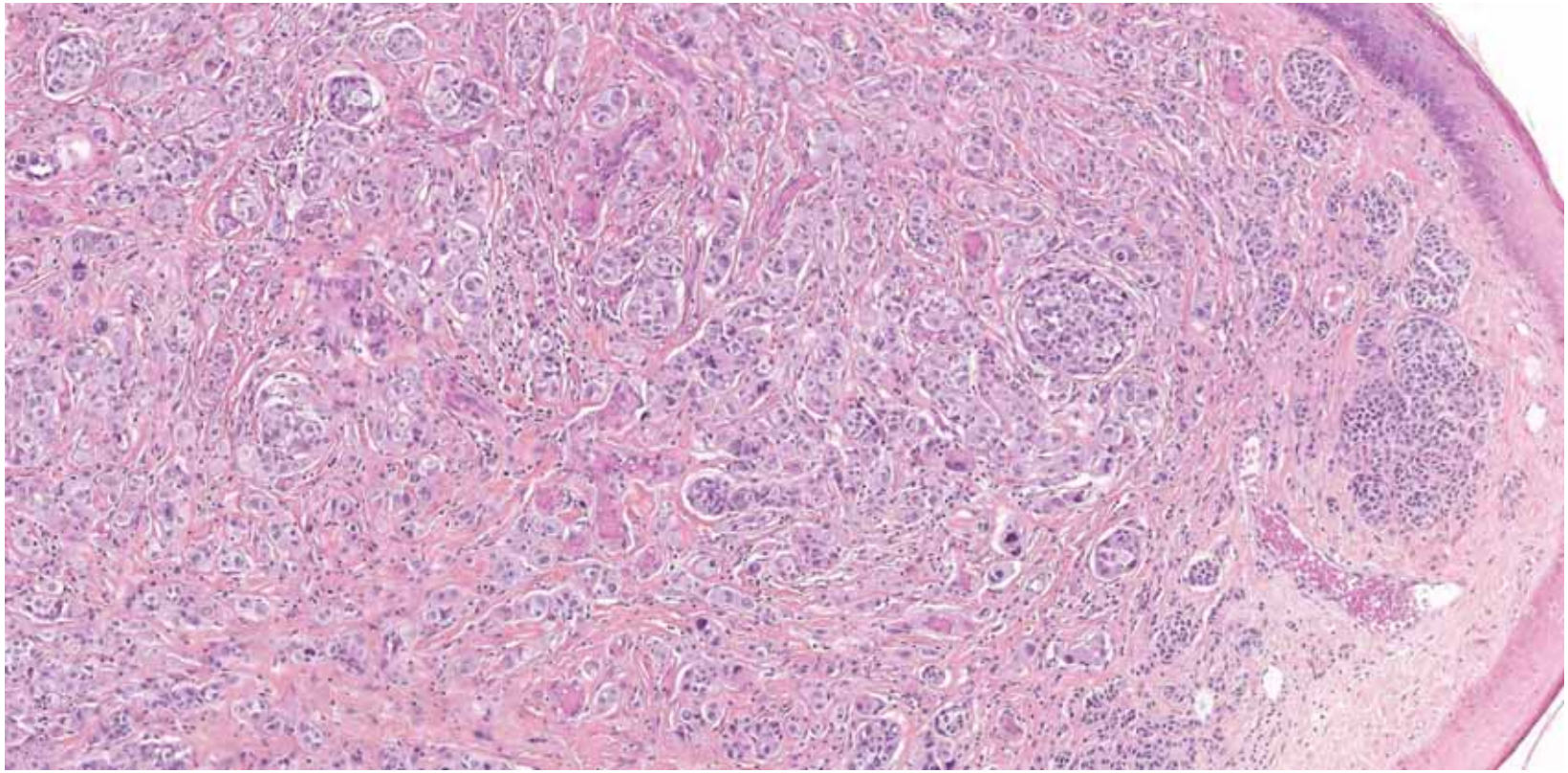
Nests of nevoid cells should always question for BAP1 loss



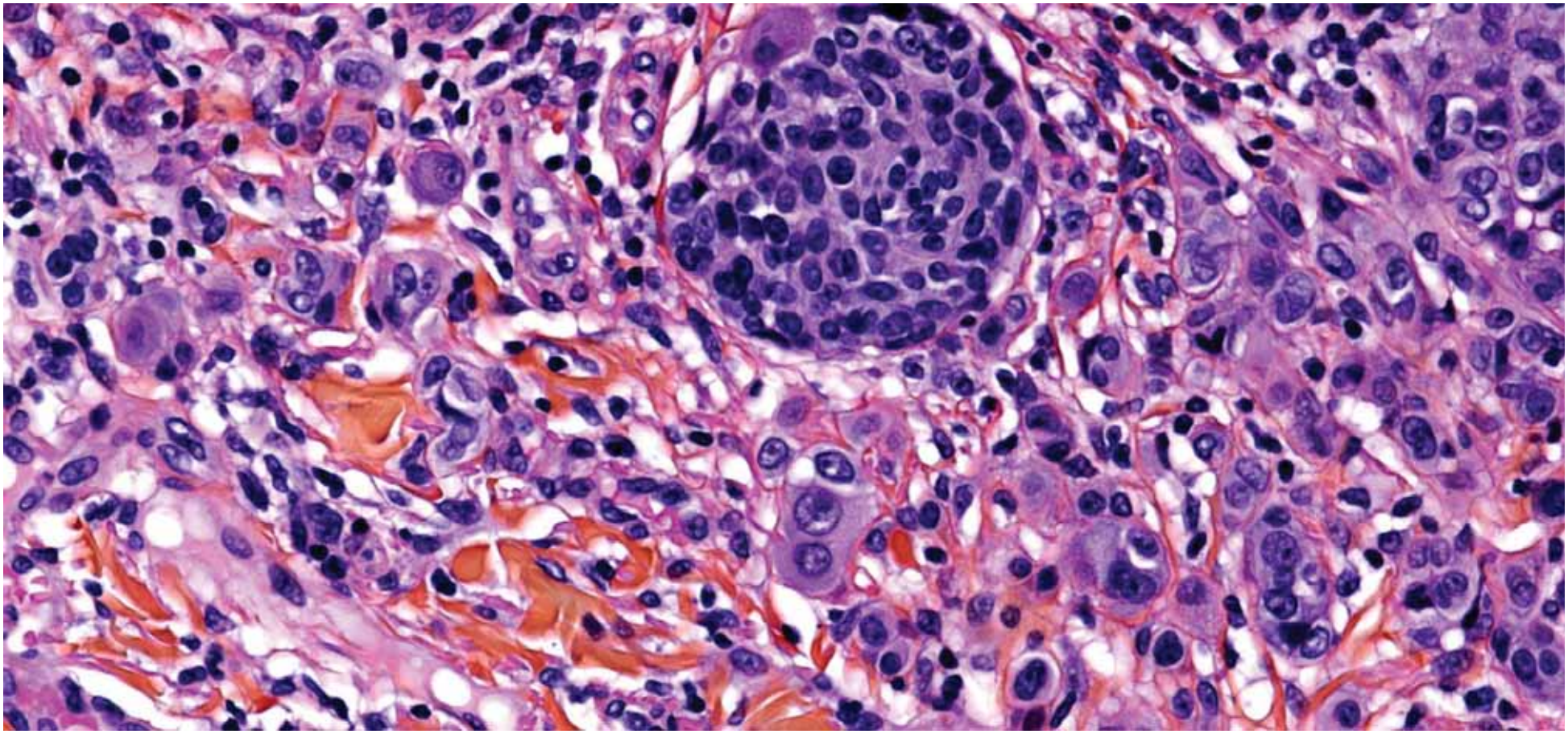
Nests of nevoid cells should always question for BAP1 loss



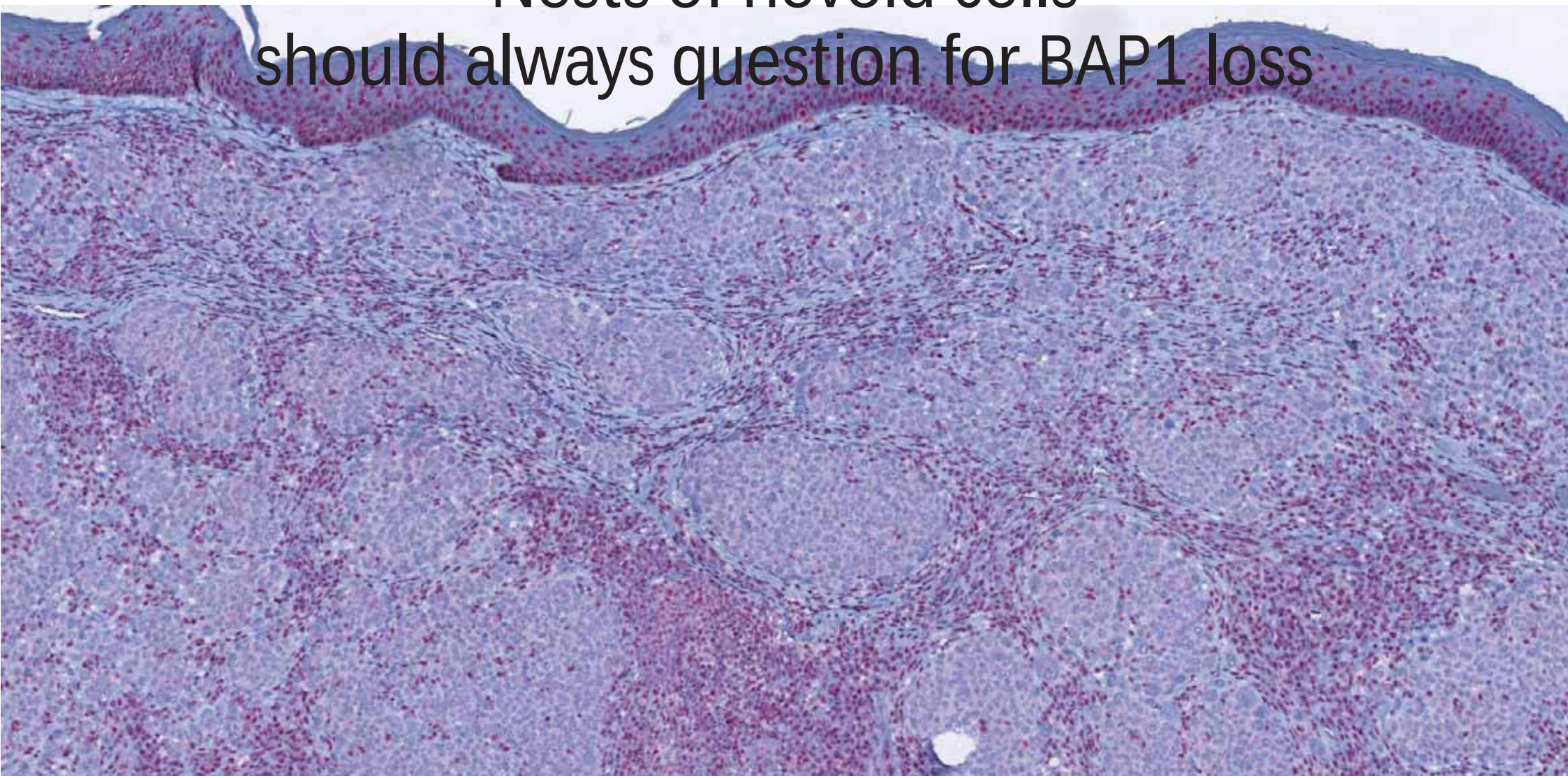
Nests of nevoid cells should always question for BAP1 loss



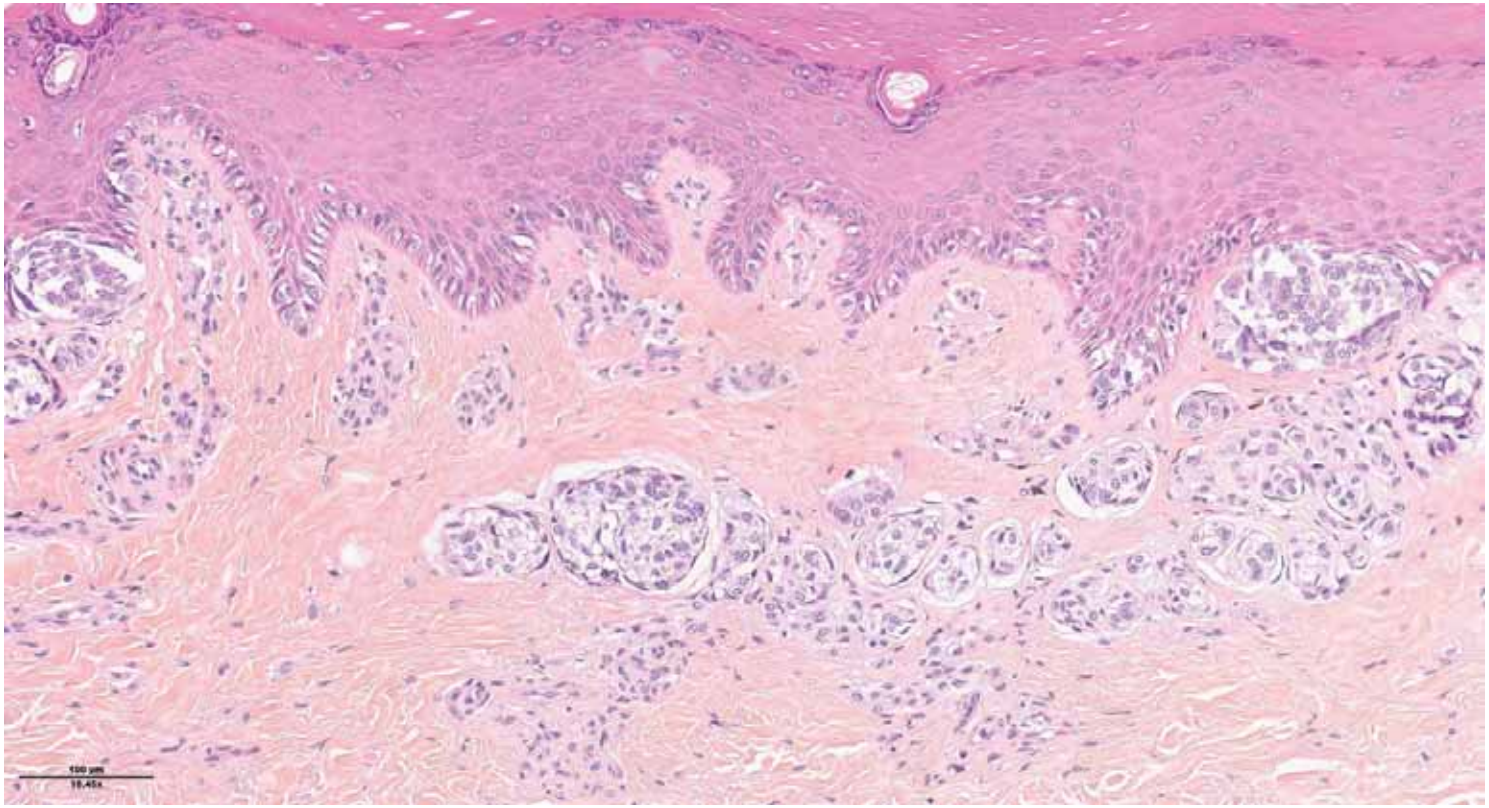
Nests of nevoid cells should always question for BAP1 loss



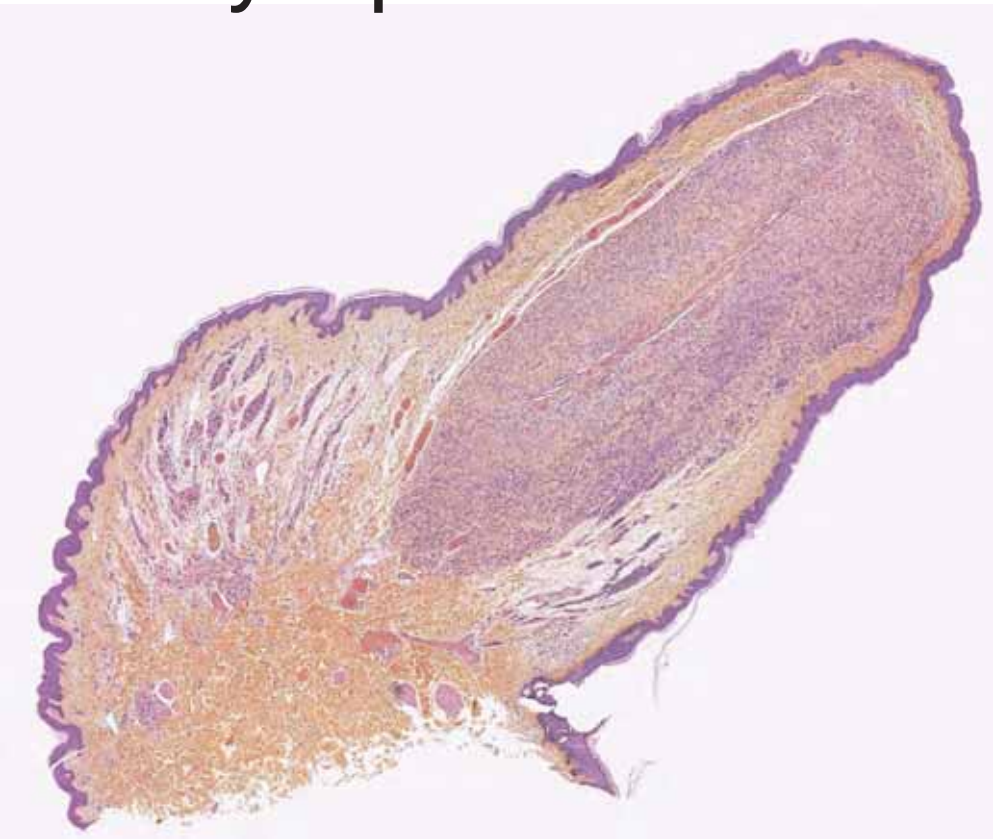
Nests of nevoid cells
should always question for BAP1 loss



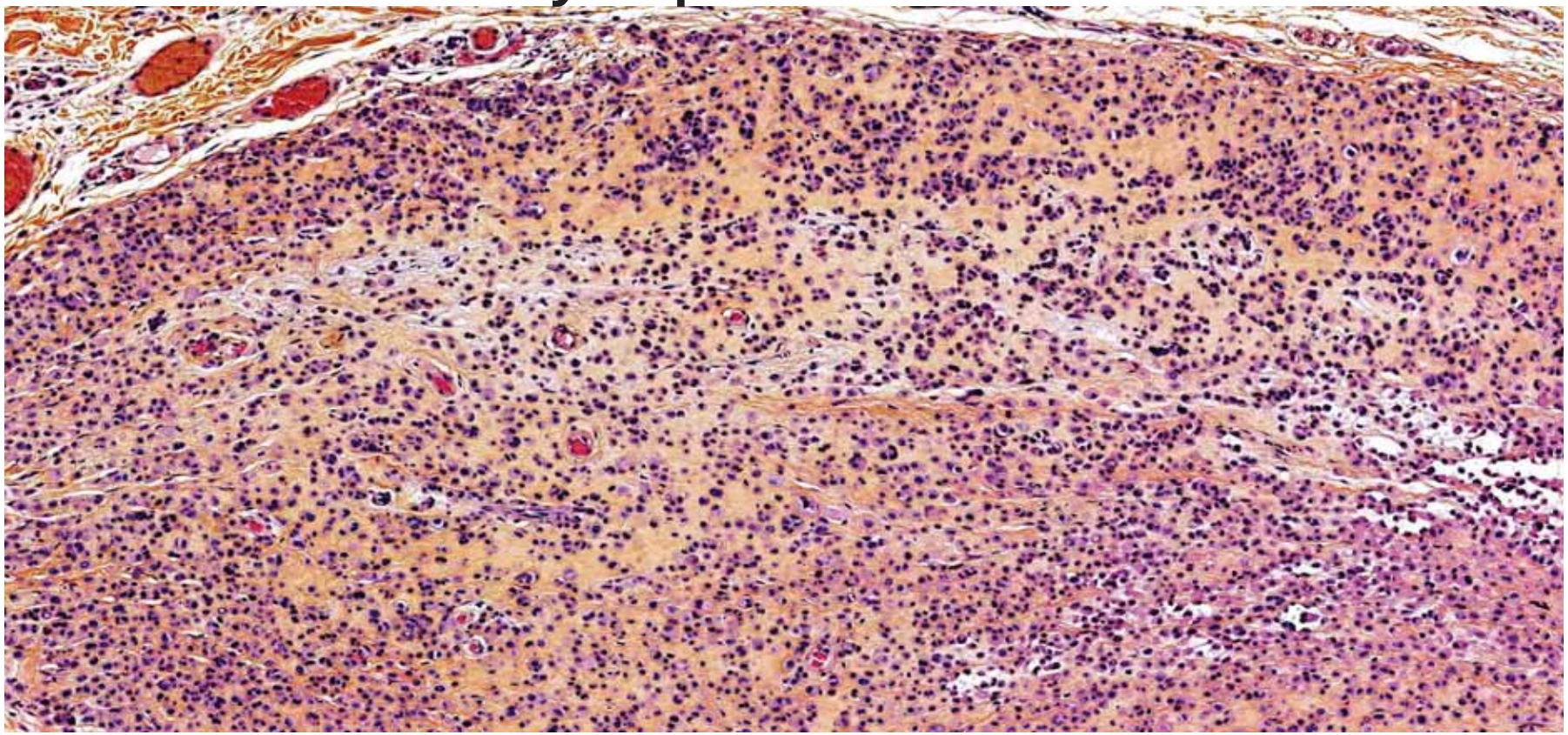
Nests are a common finding in compound nevi



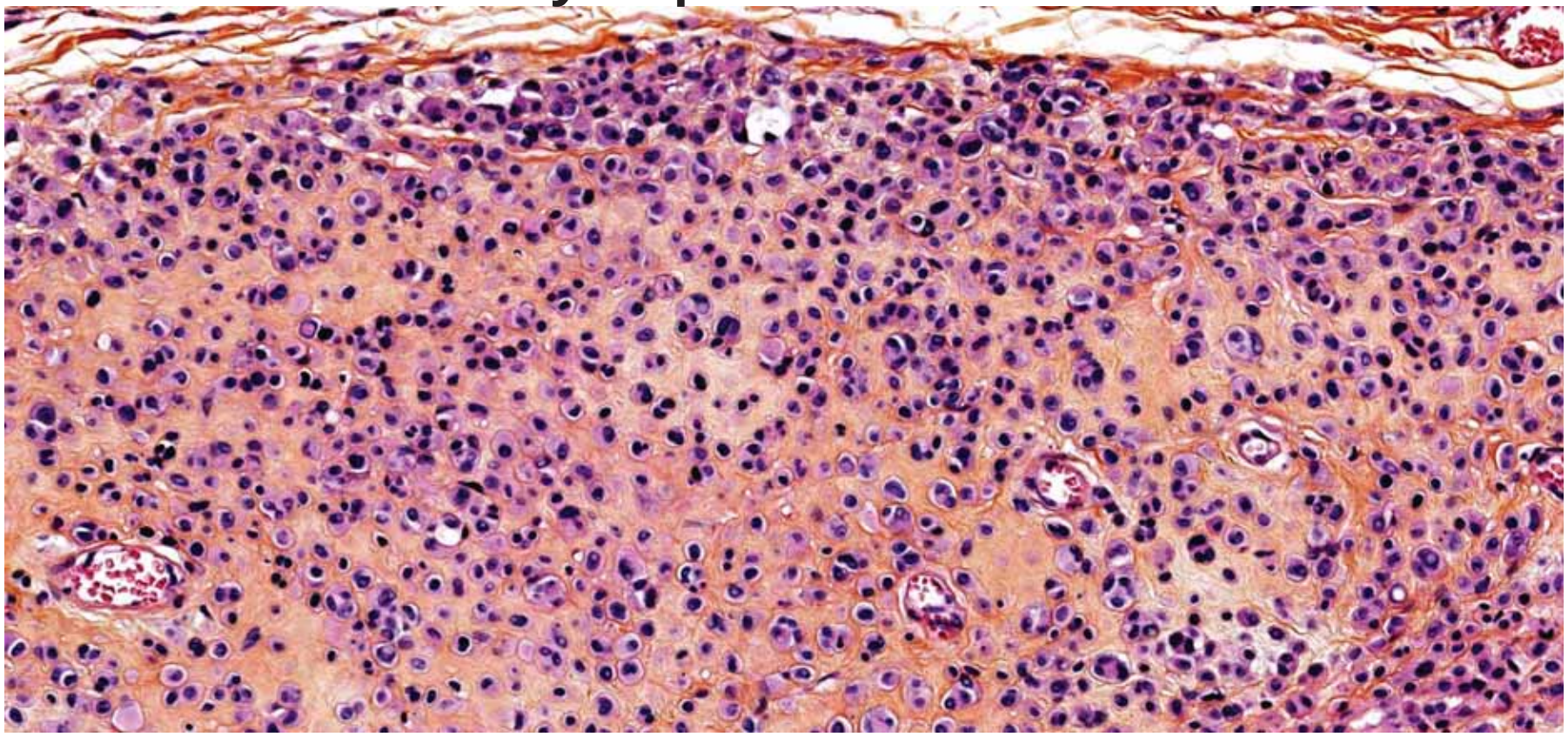
Chondroid differentiation should always question for BAP1 loss



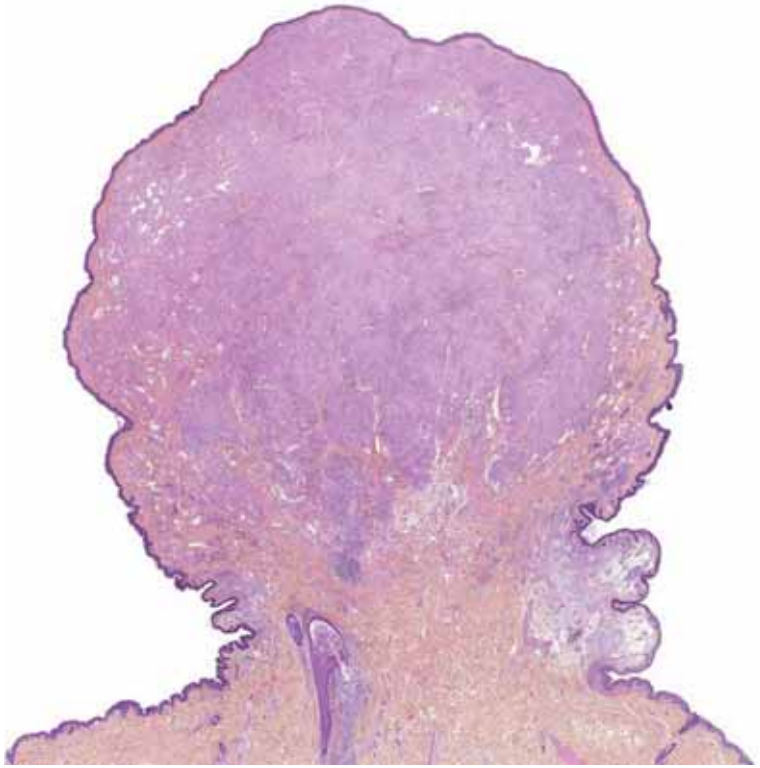
Chondroid differentiation should always question for BAP1 loss



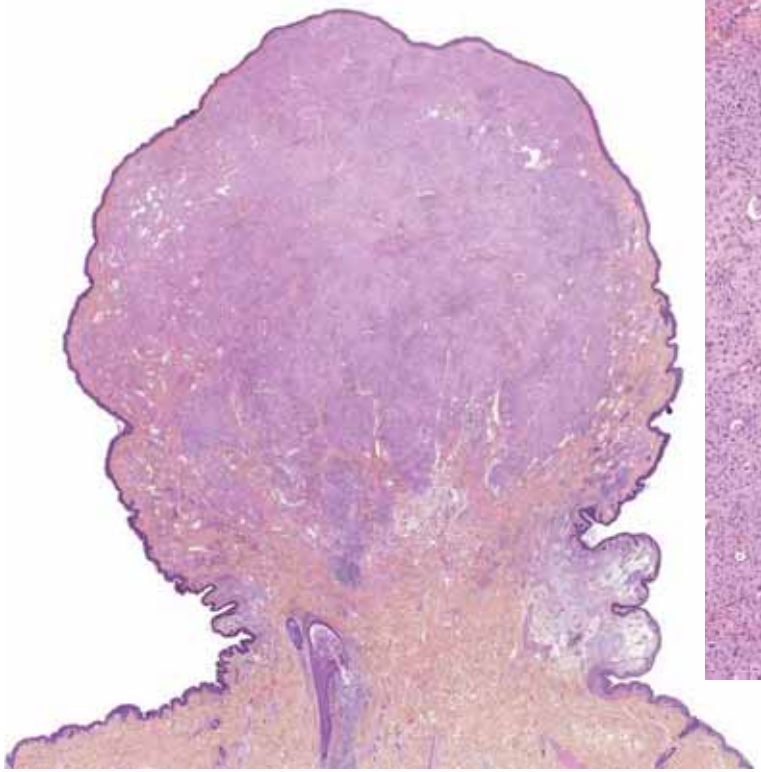
Chondroid differentiation should always question for BAP1 loss

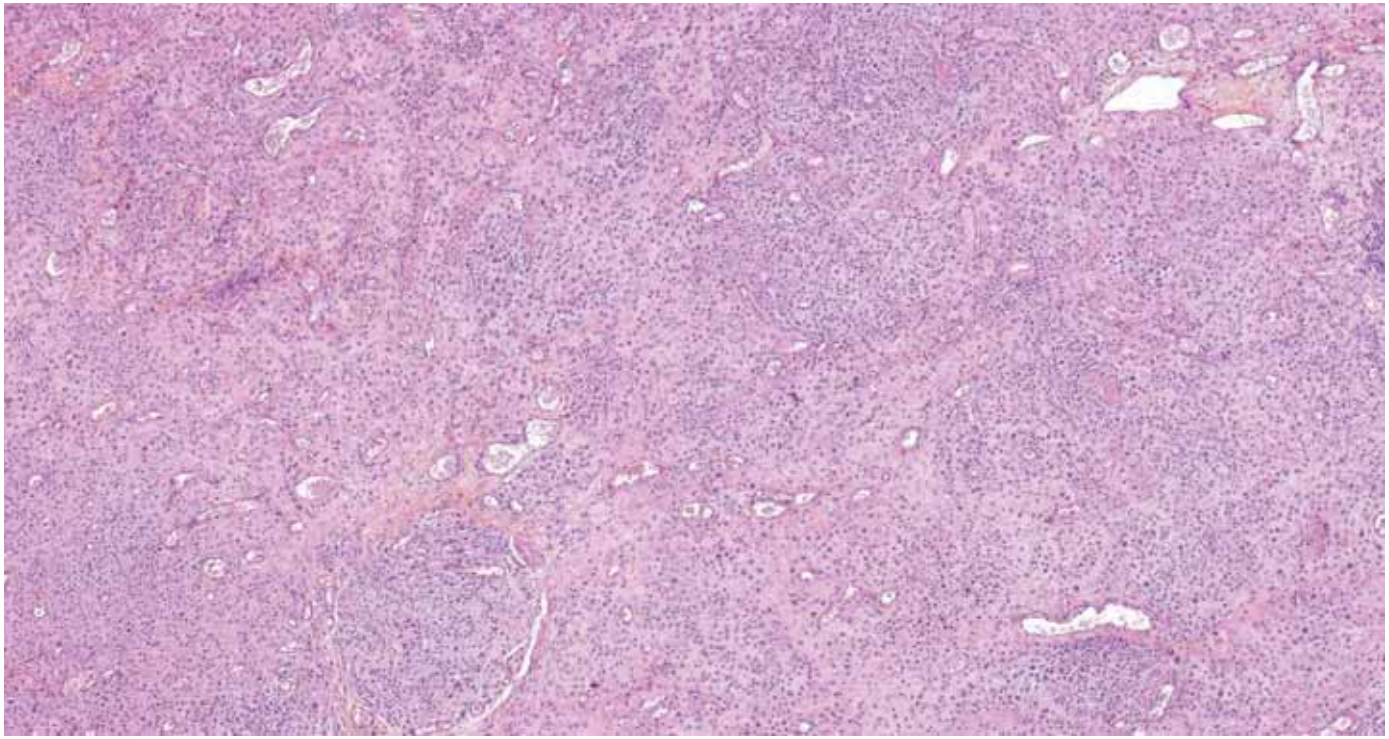


Chondroid differentiation should always question for BAP1 loss

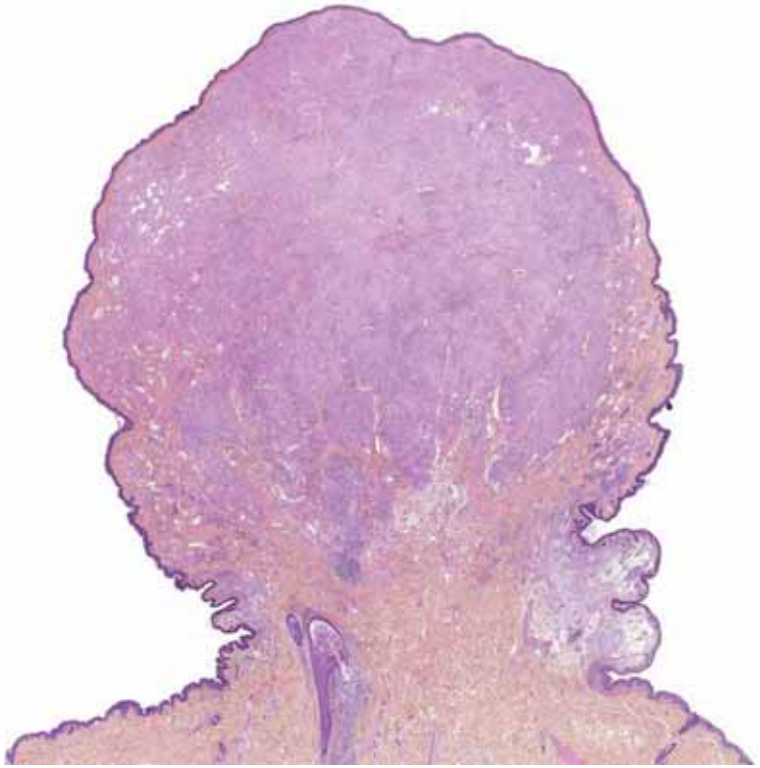


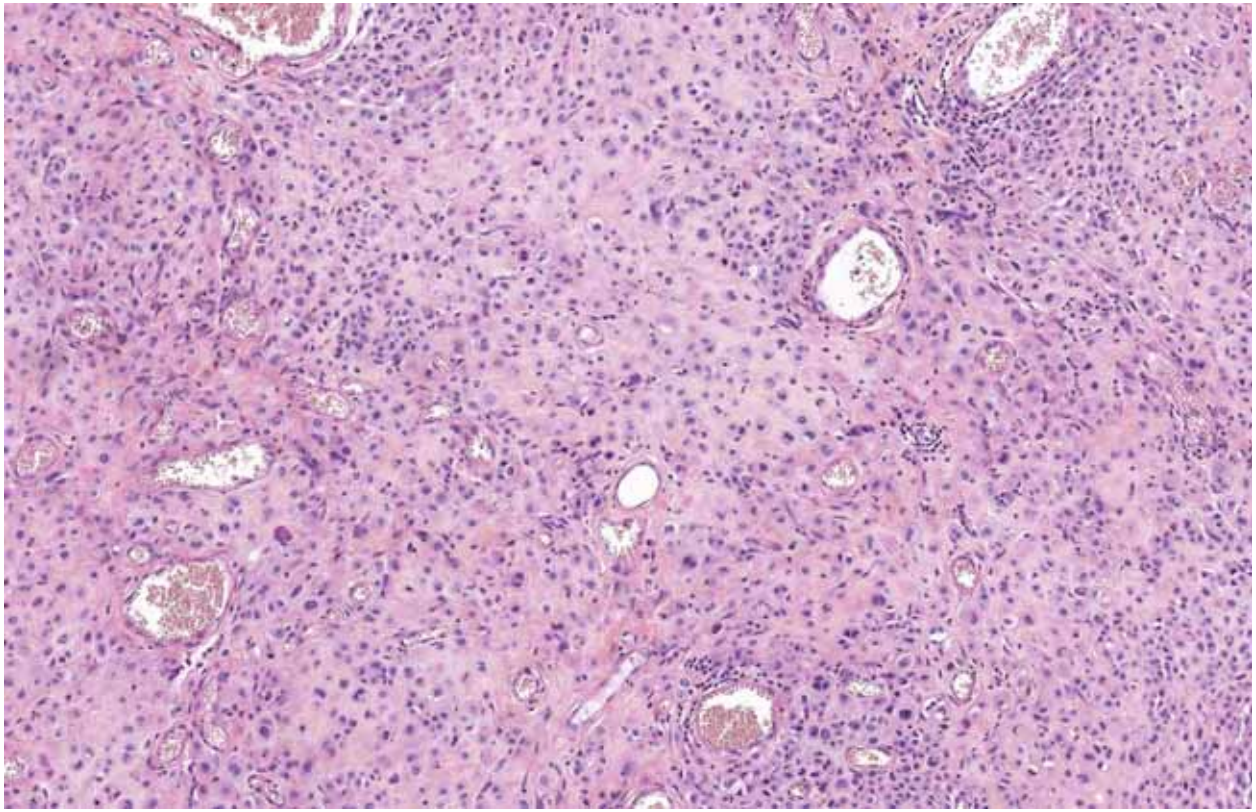
Chondroid differentiation should always question for BAP1 loss



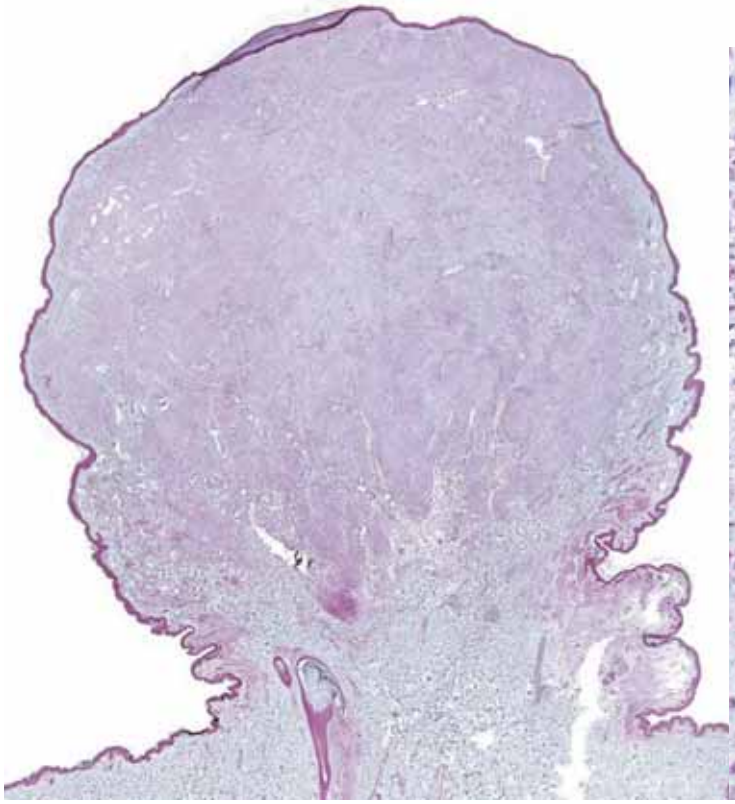


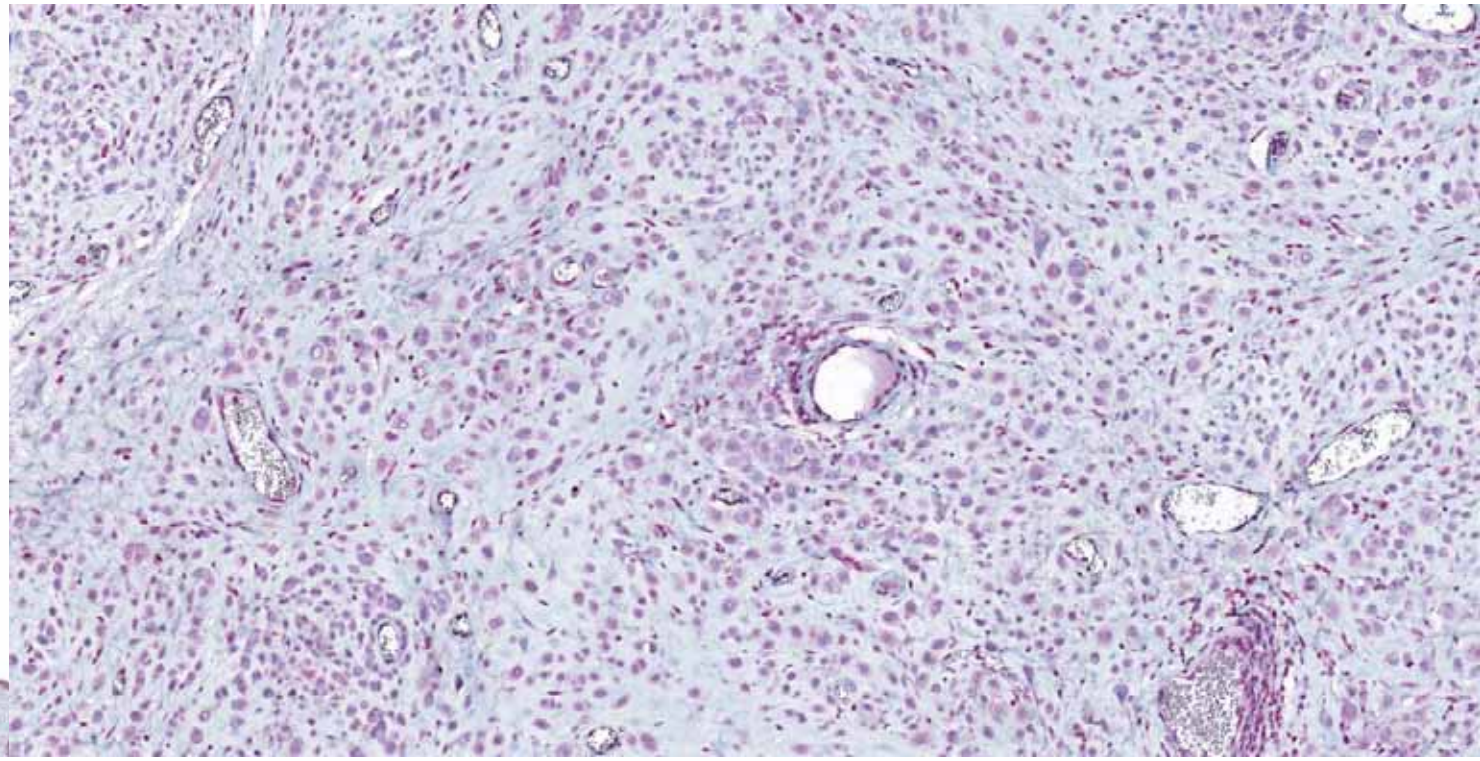
Chondroid differentiation should always question for BAP1 loss



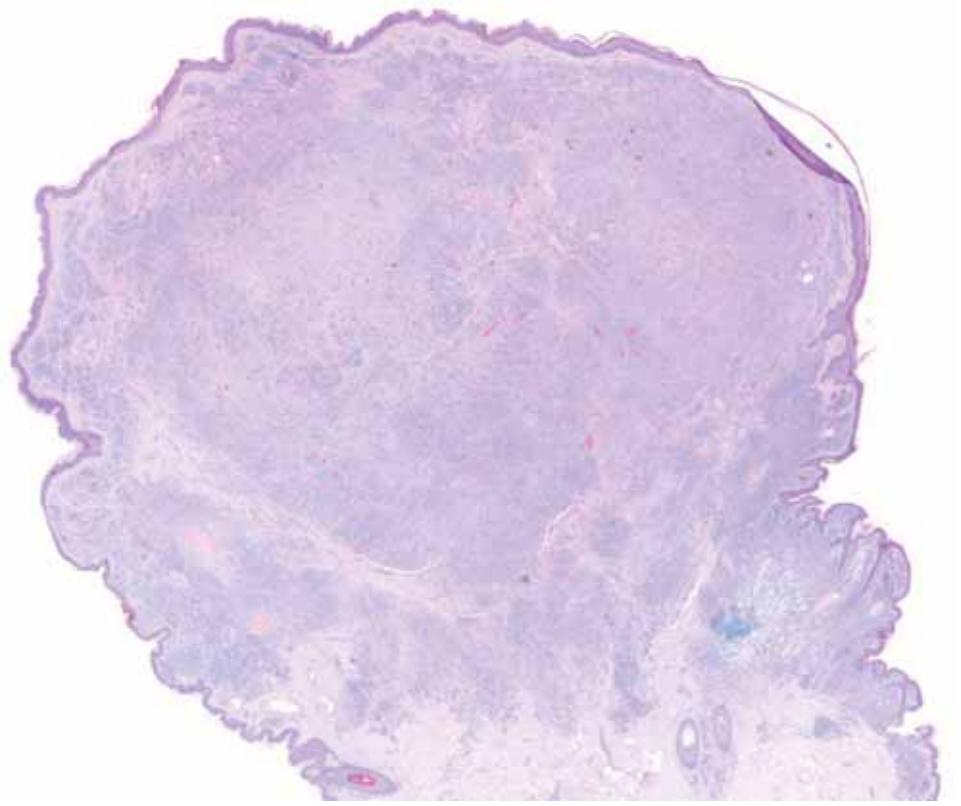


Chondroid differentiation should always question for BAP1 loss

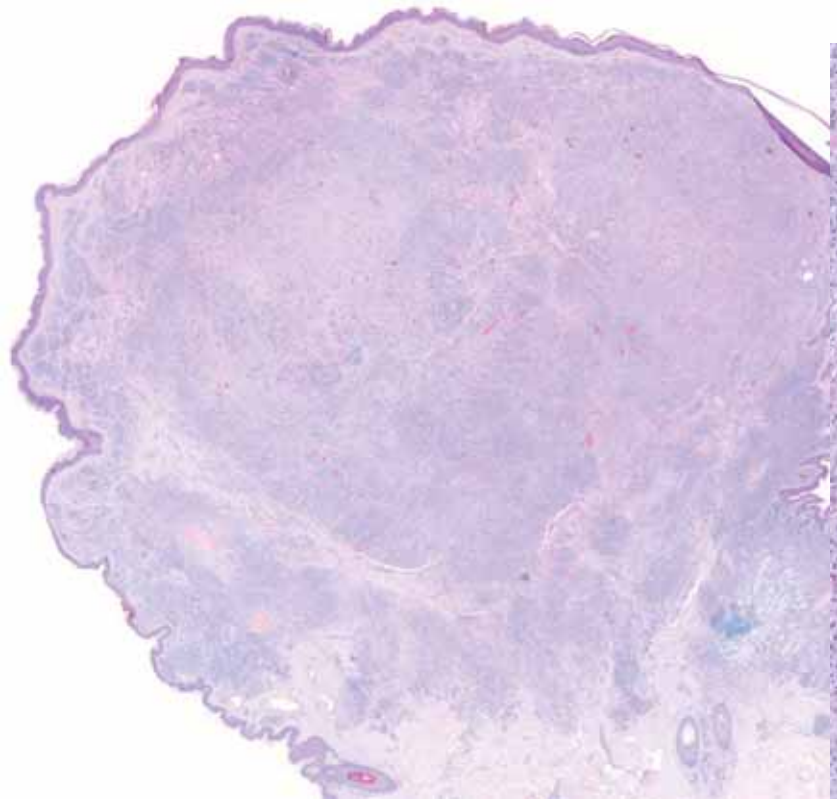


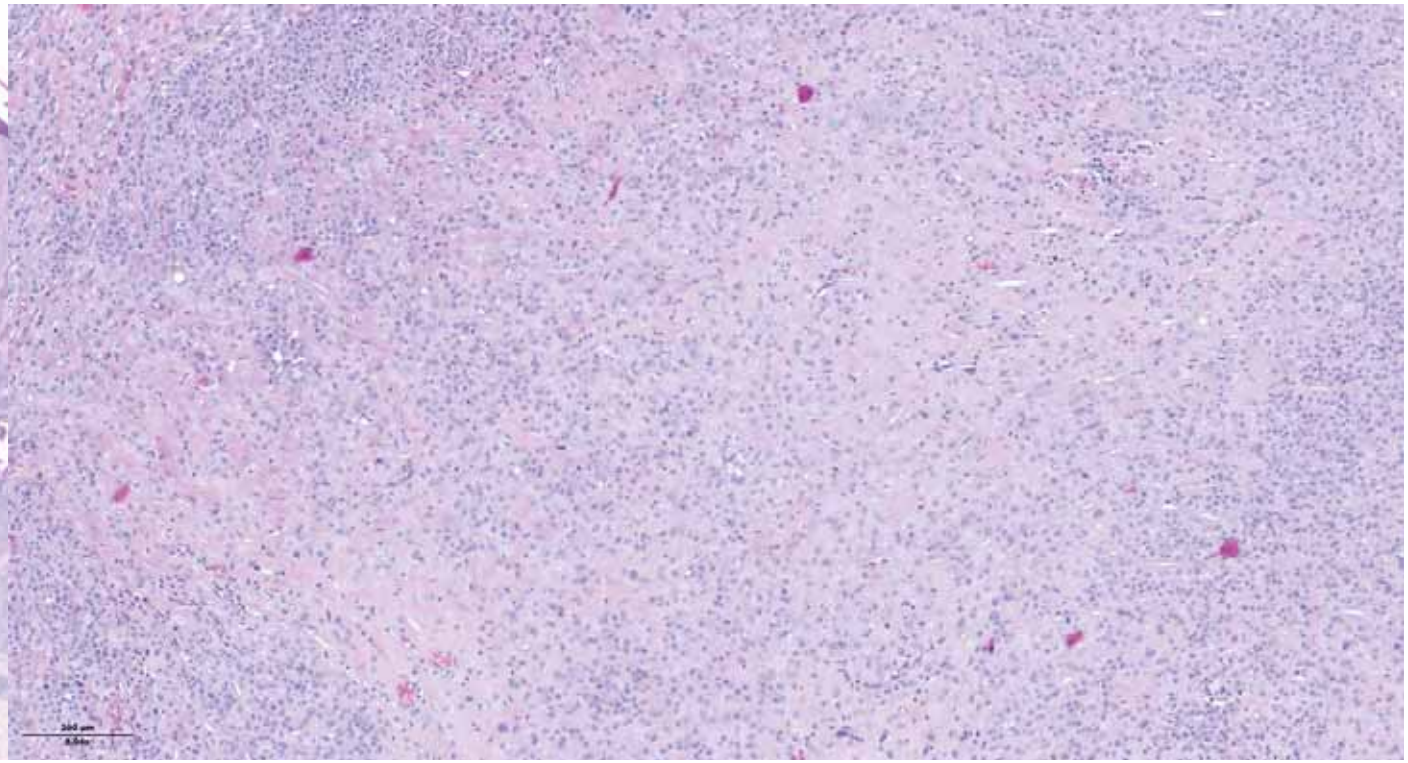


Chondroid differentiation should always question for BAP1 loss



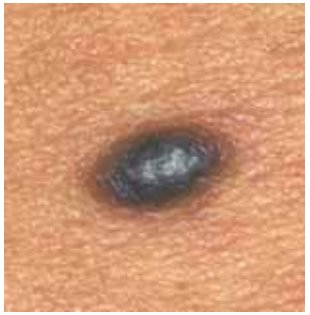
Chondroid differentiation should always question for BAP1 loss





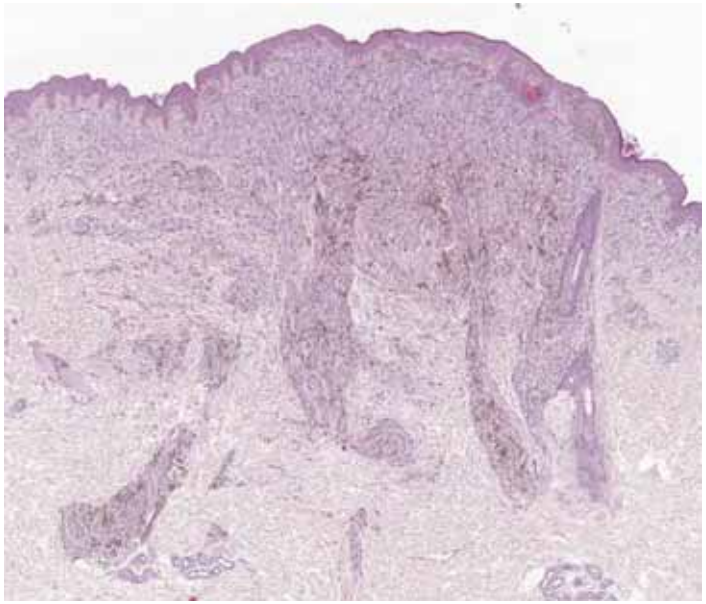
WNT-activated melanocytoma

- Young adults
- Upper body
- Small pigmented lesion
- Combined lesion

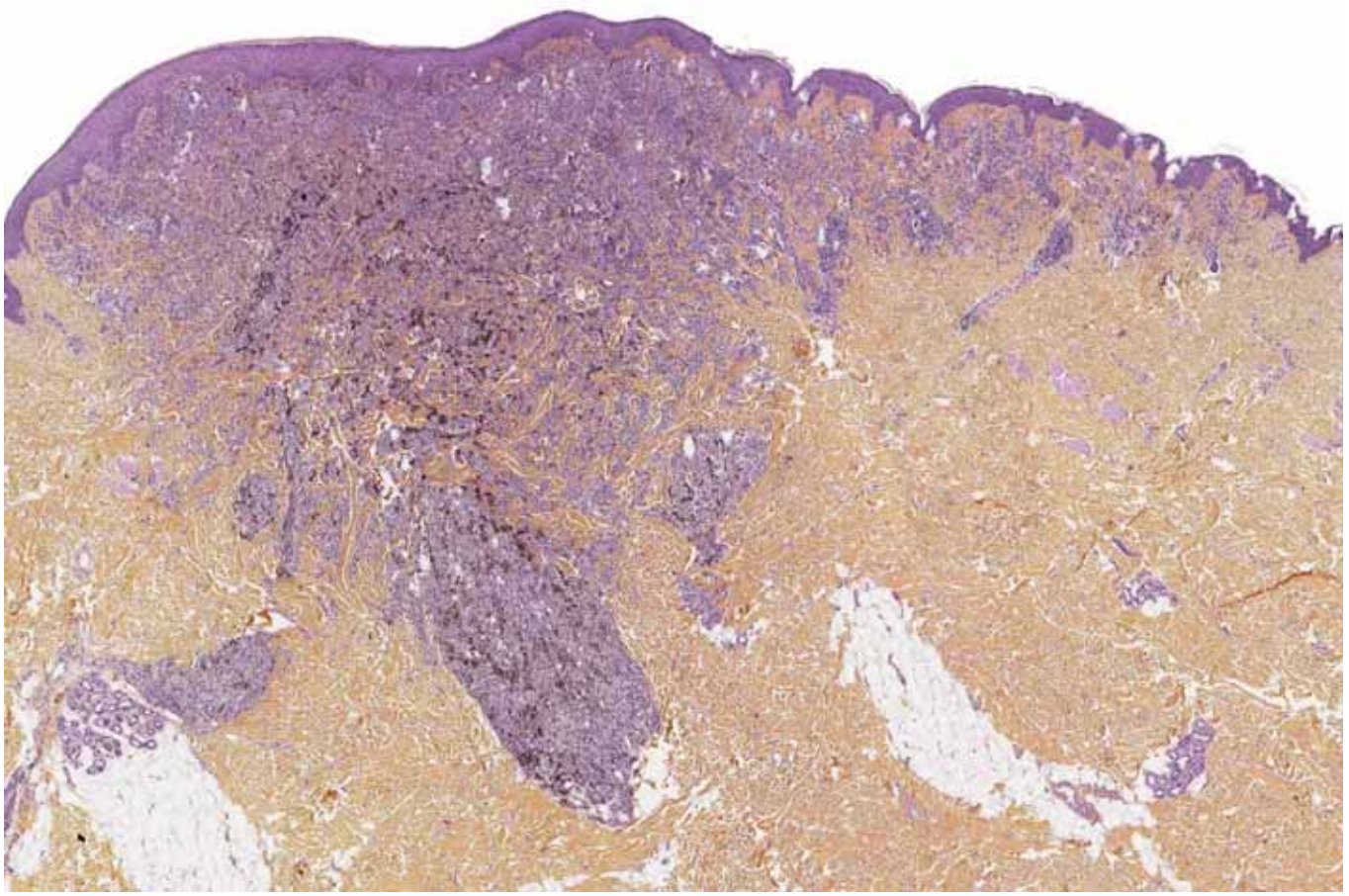


WAM classical clues

- Vertical expansion with peri-vascular expansions
- Absence of vertical maturation
- Peaceful transition with nevus component



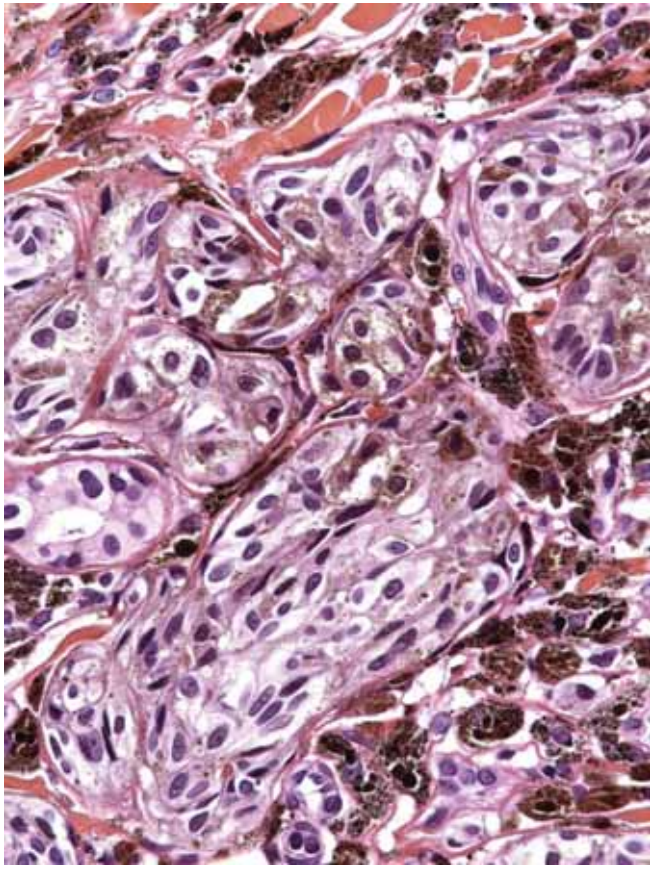
Deep vertical expansions into the subcutis



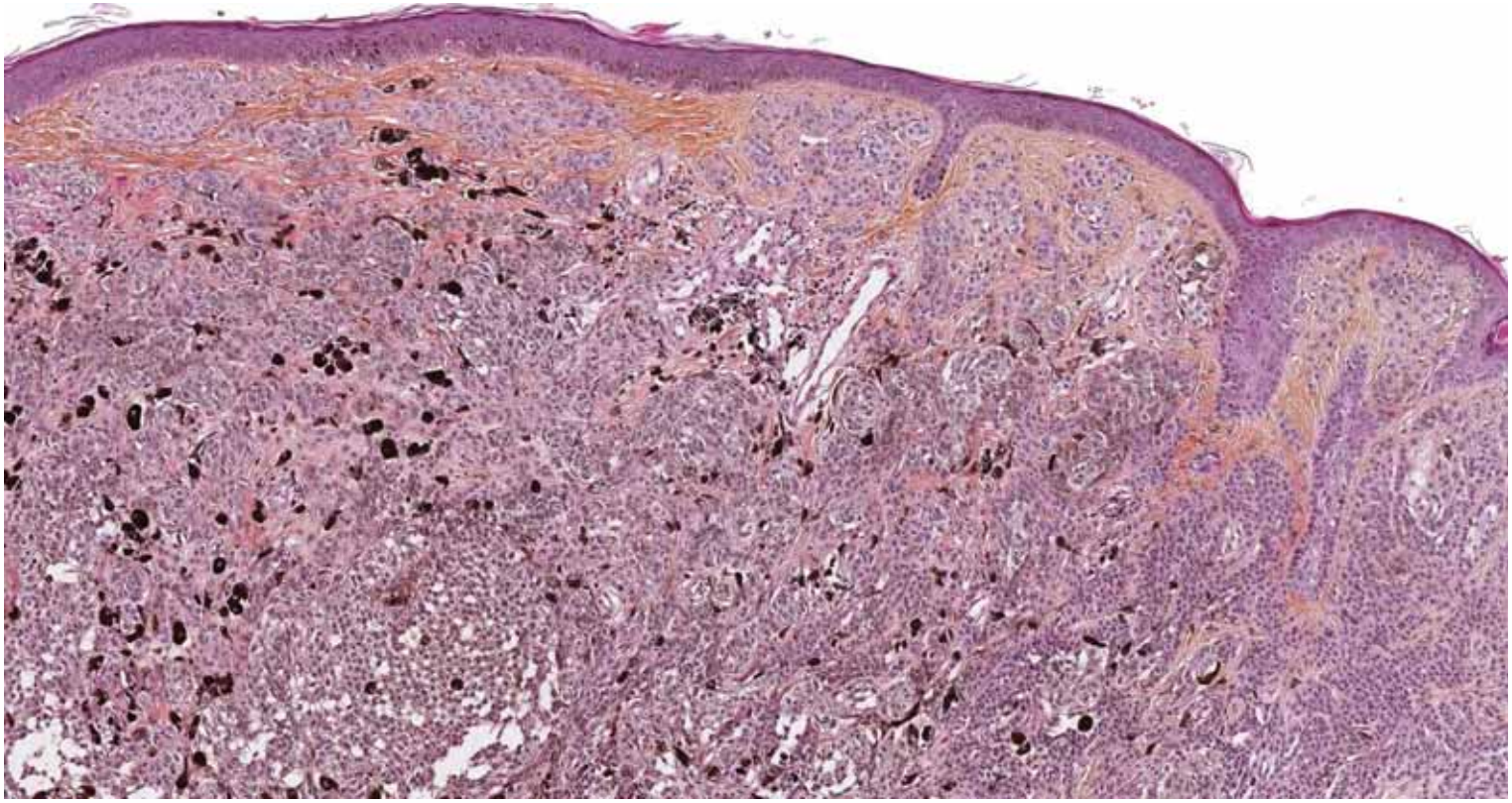
Spatula

WAM classical clues

- Vertical expansion with peri-vascular expansions
- Absence of vertical maturation
- Peaceful transition with nevus component
- Typical cytology



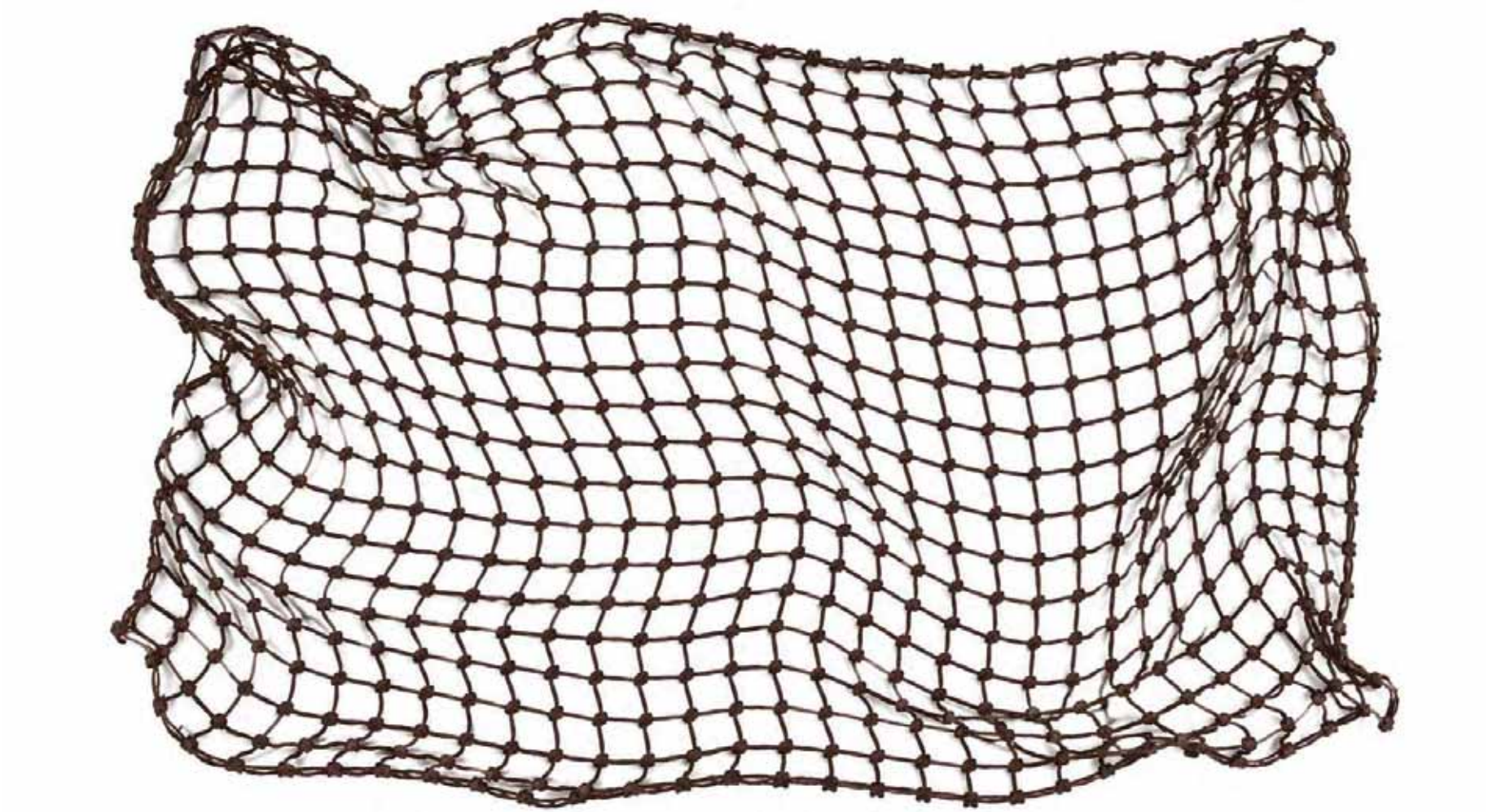
Peaceful transition between common and pigmented clones



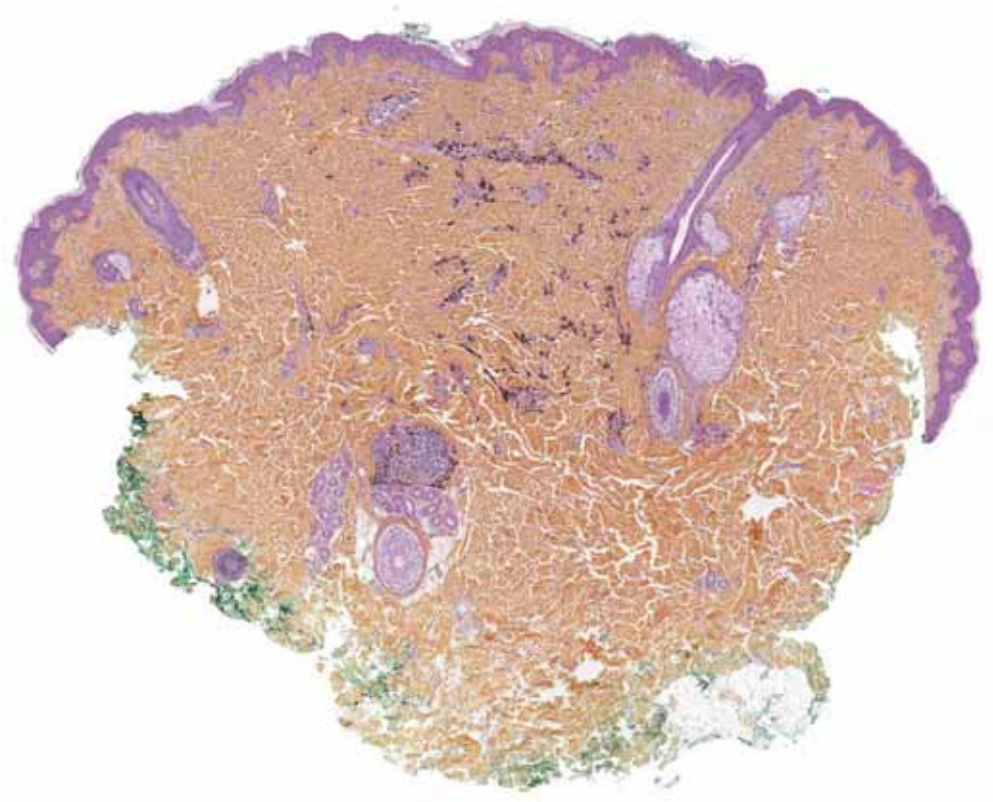
Other clues suggestive of WNT-activated melanocytoma

- Low power dermal grid of melanophages
- Beta catenin immunohistochemistry showing «alien letters»

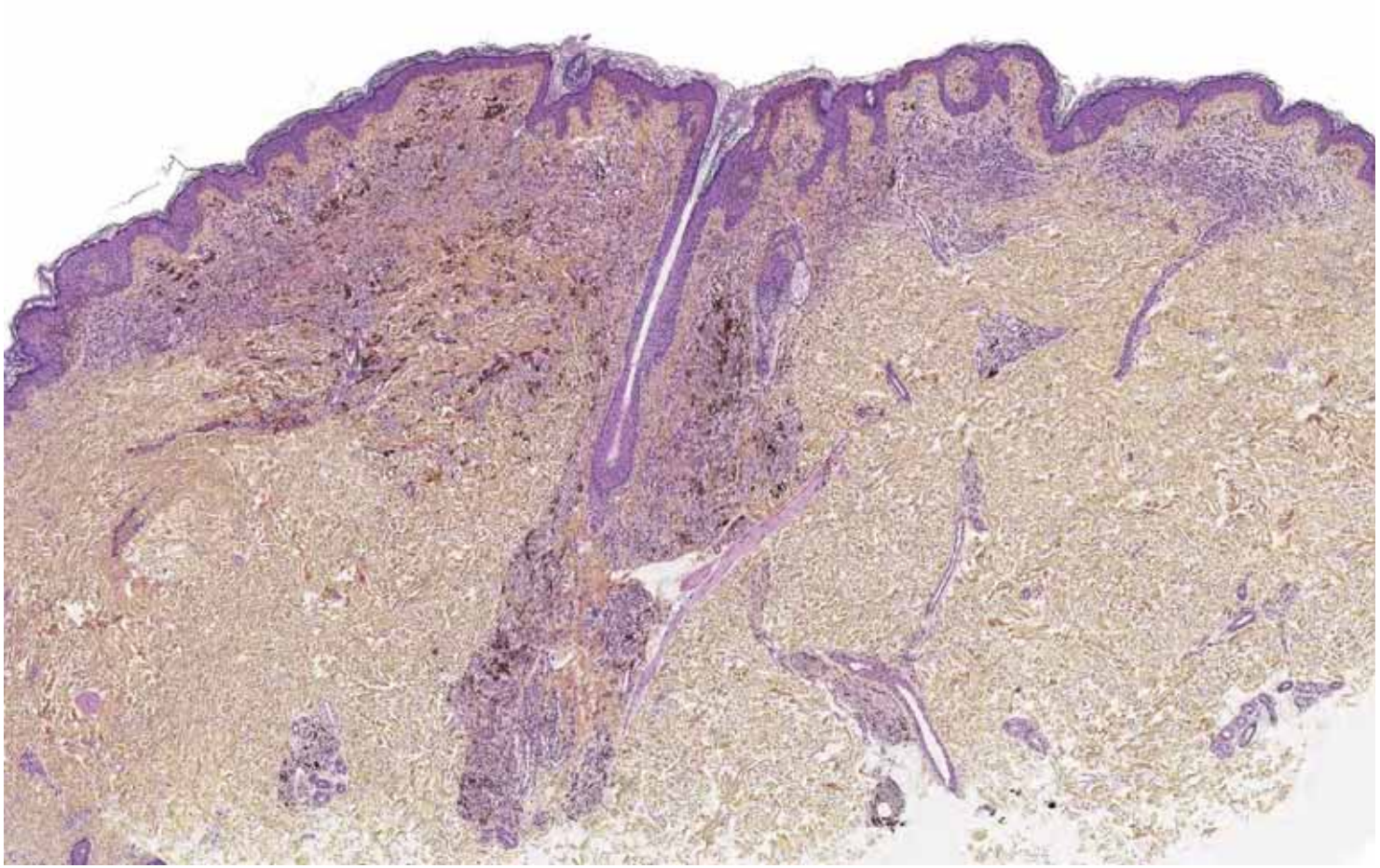
Grid/Mesh of melanophages



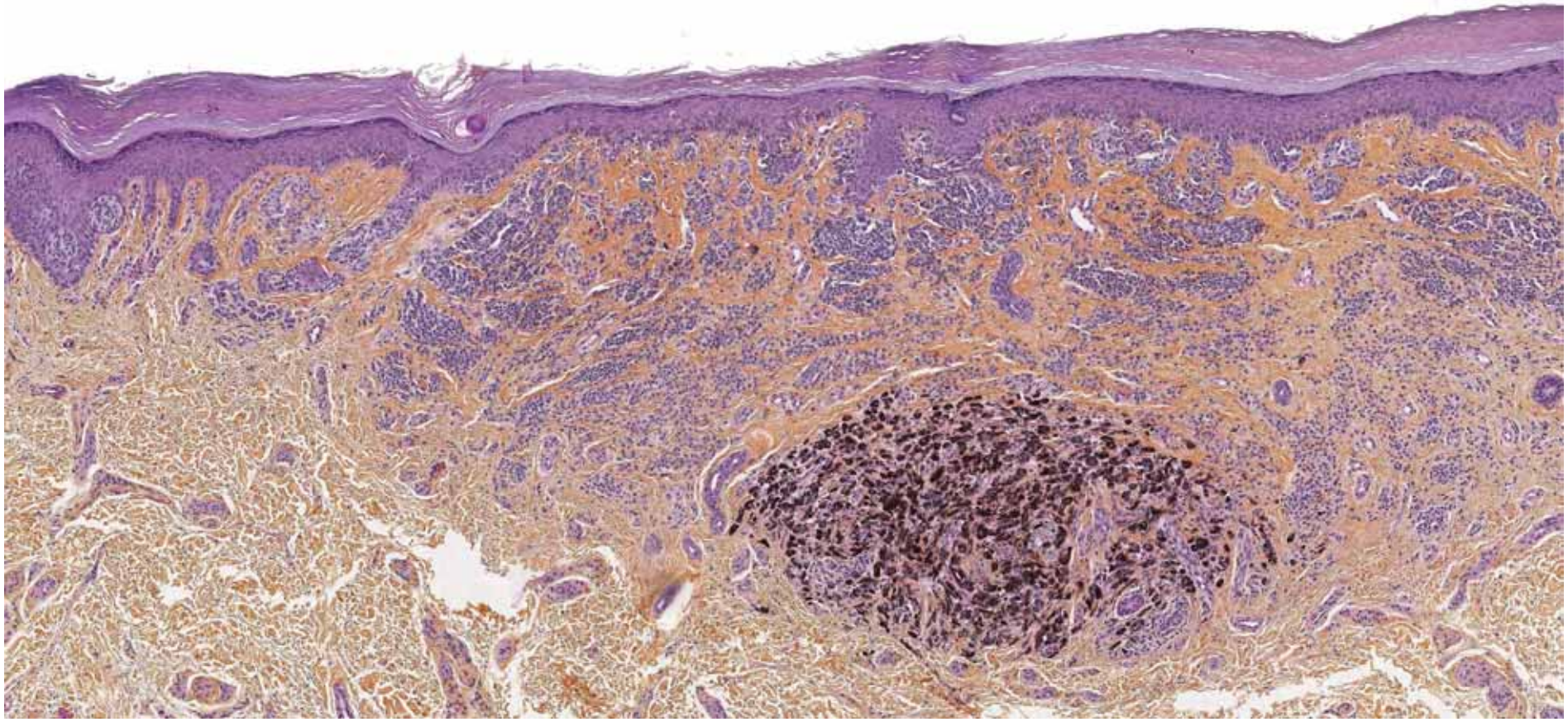
Grid/Mesh of melanophages



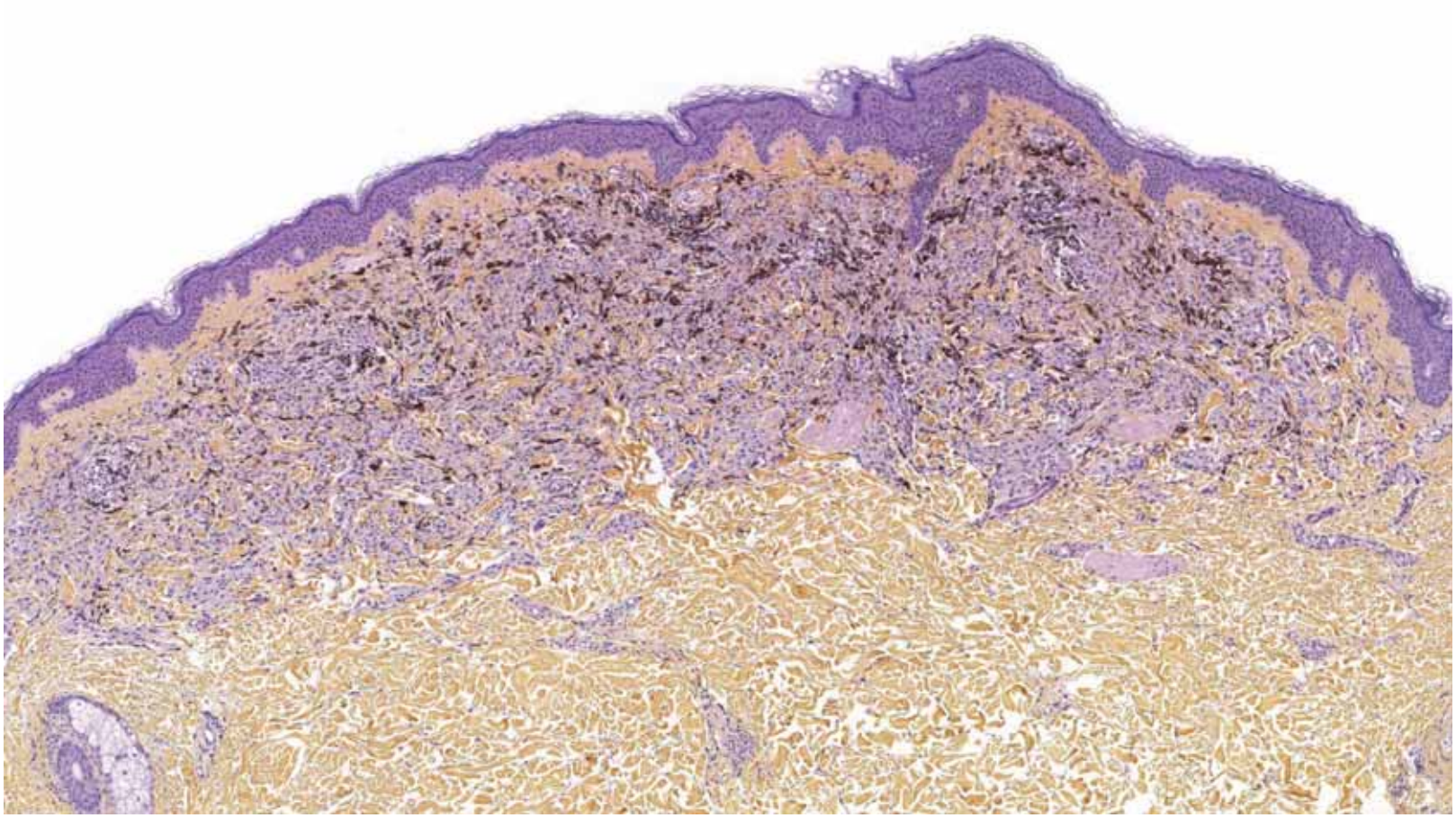
Combined WAM
Grid/Mesh of melanophages



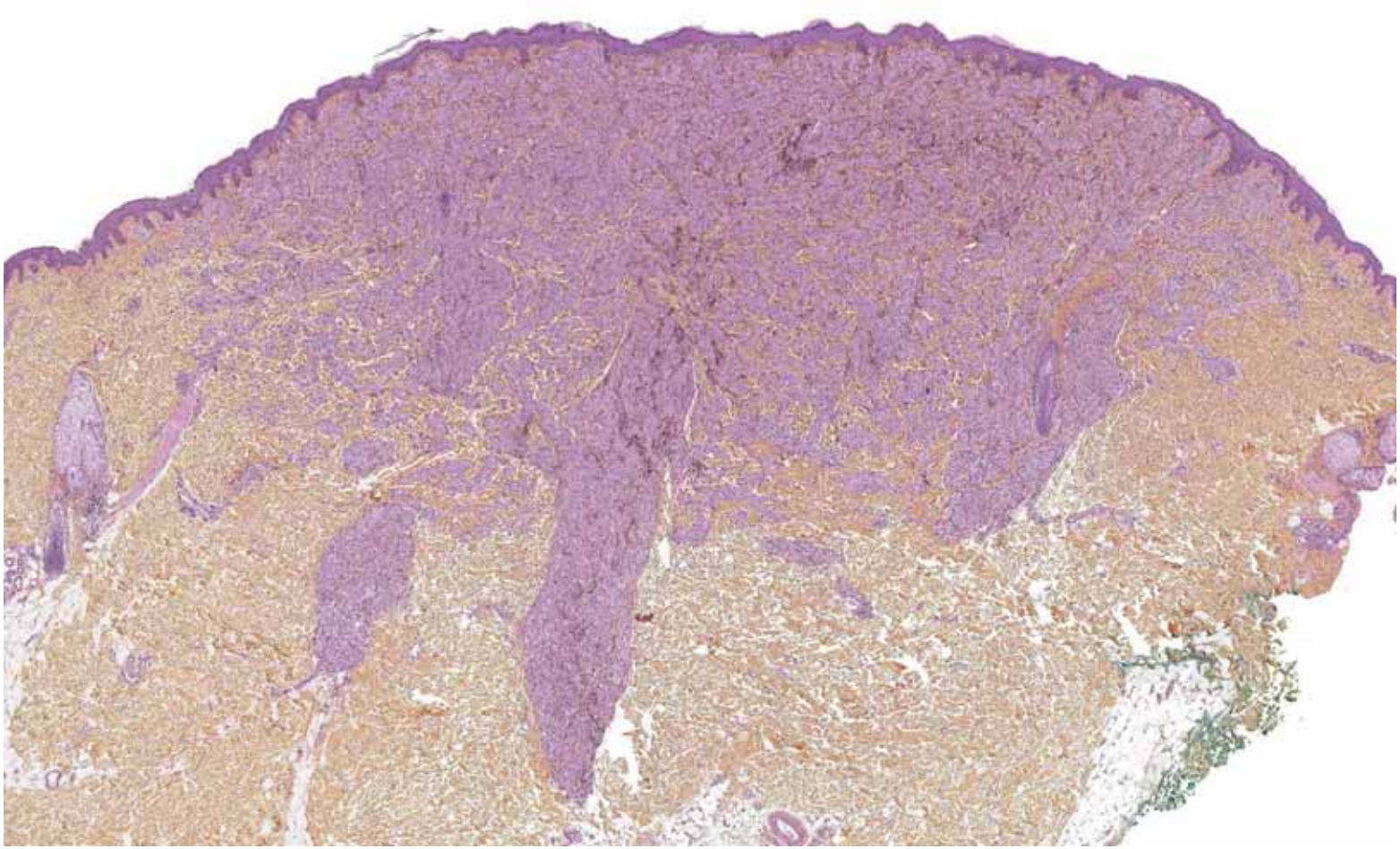
Combined WAM
Grid/Mesh of melanophages



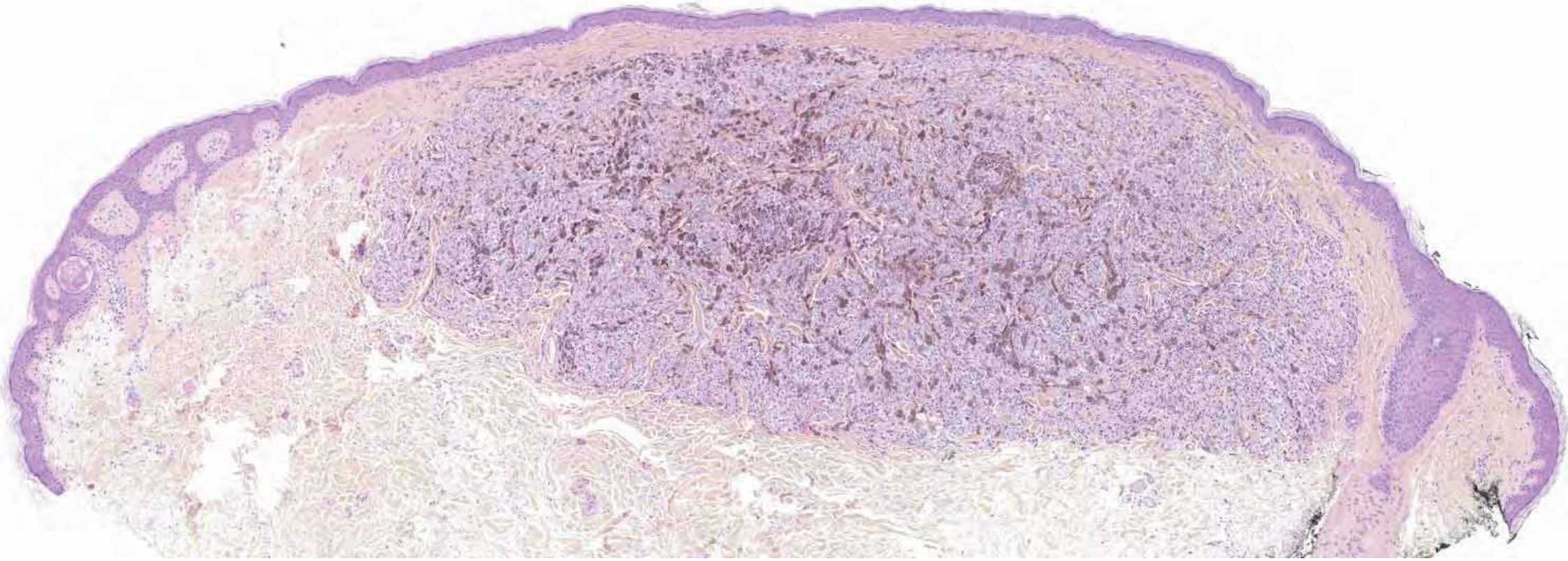
Plexiform WAM
Grid/Mesh of melanophages

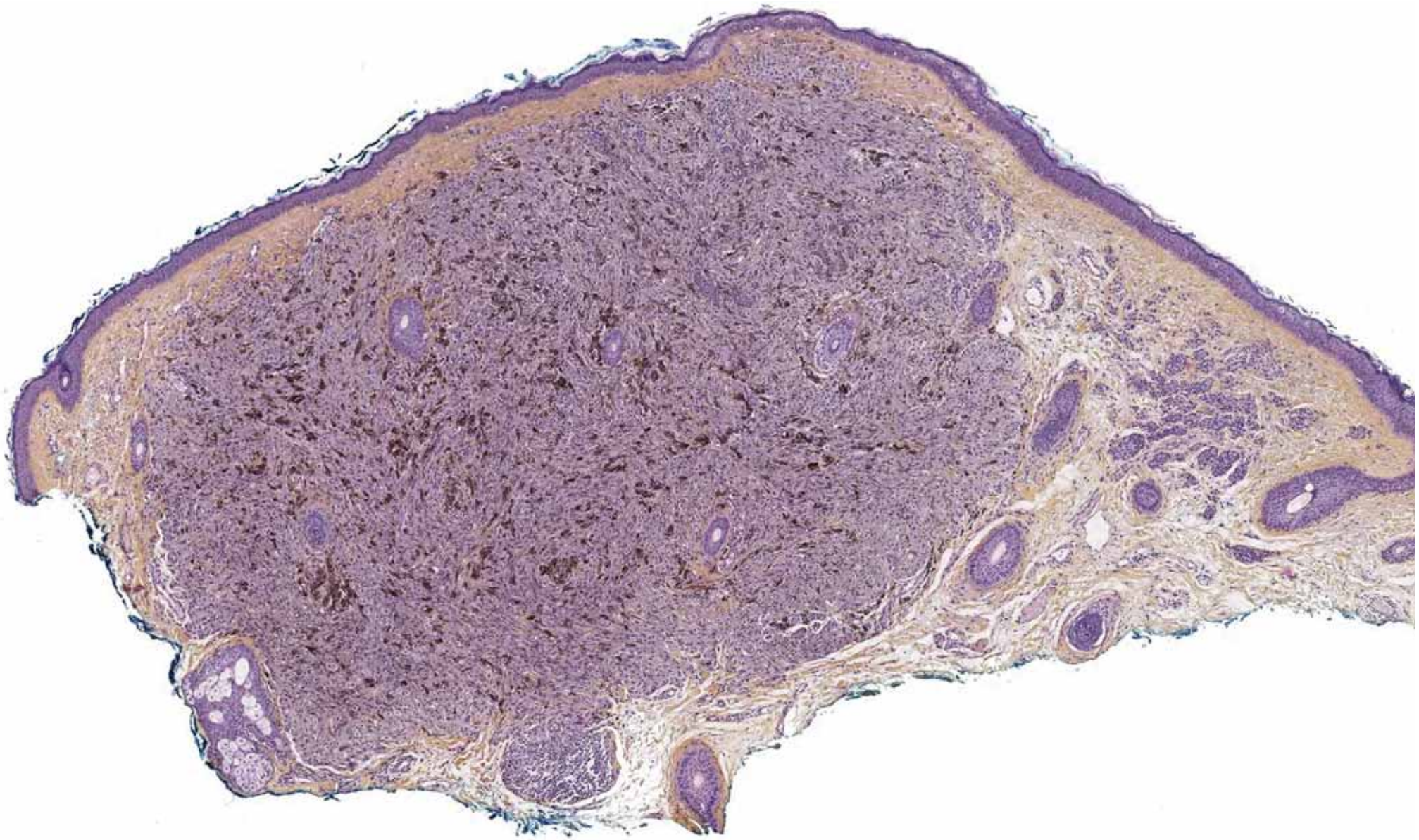


WAM
Grid/Mesh of melanophages



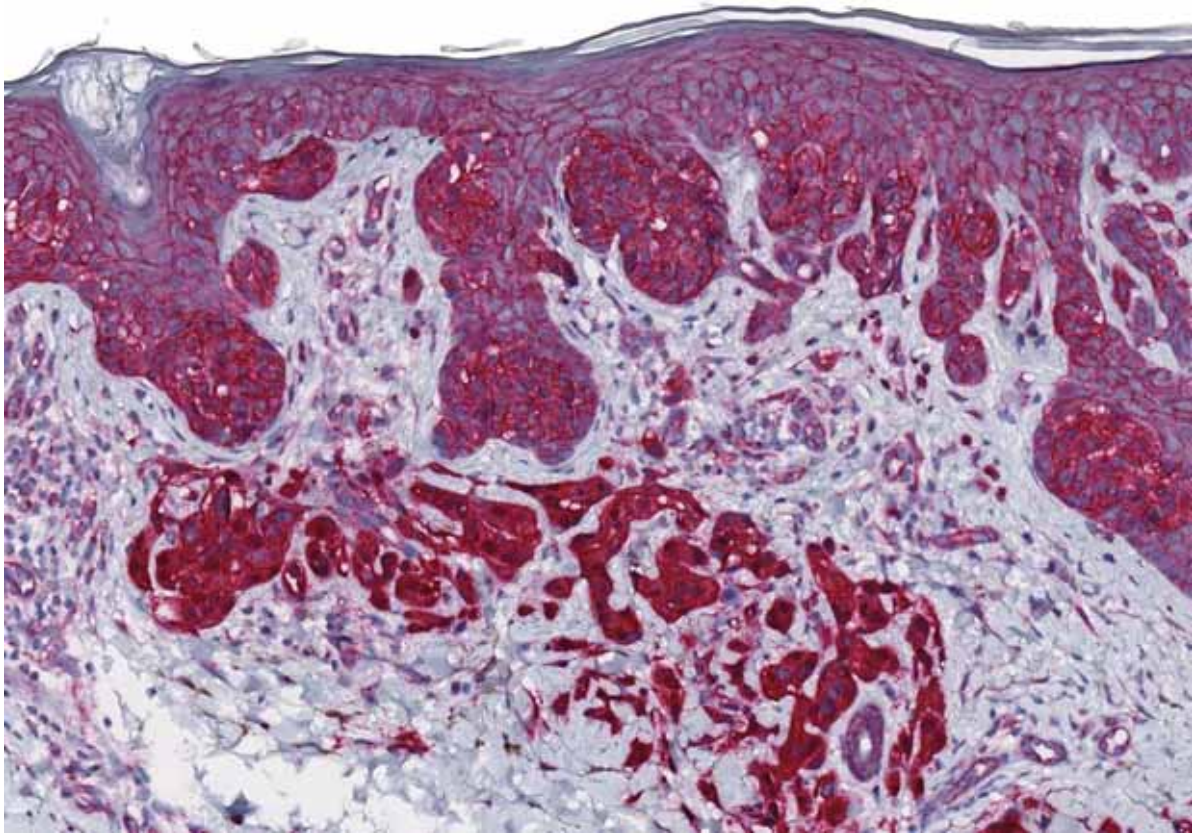
Grid/Mesh of melanophages





Beta-catenin IHC draws « Alien letters »

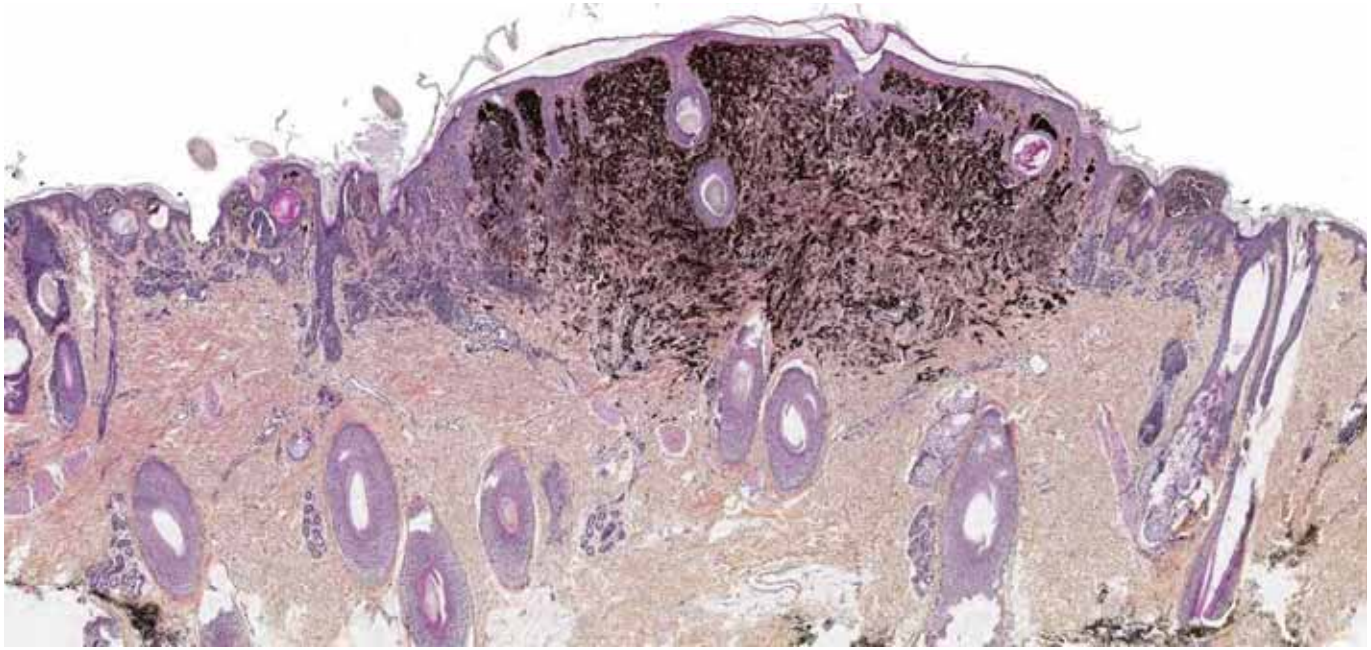
Beta-catenin IHC draws « Alien letters »



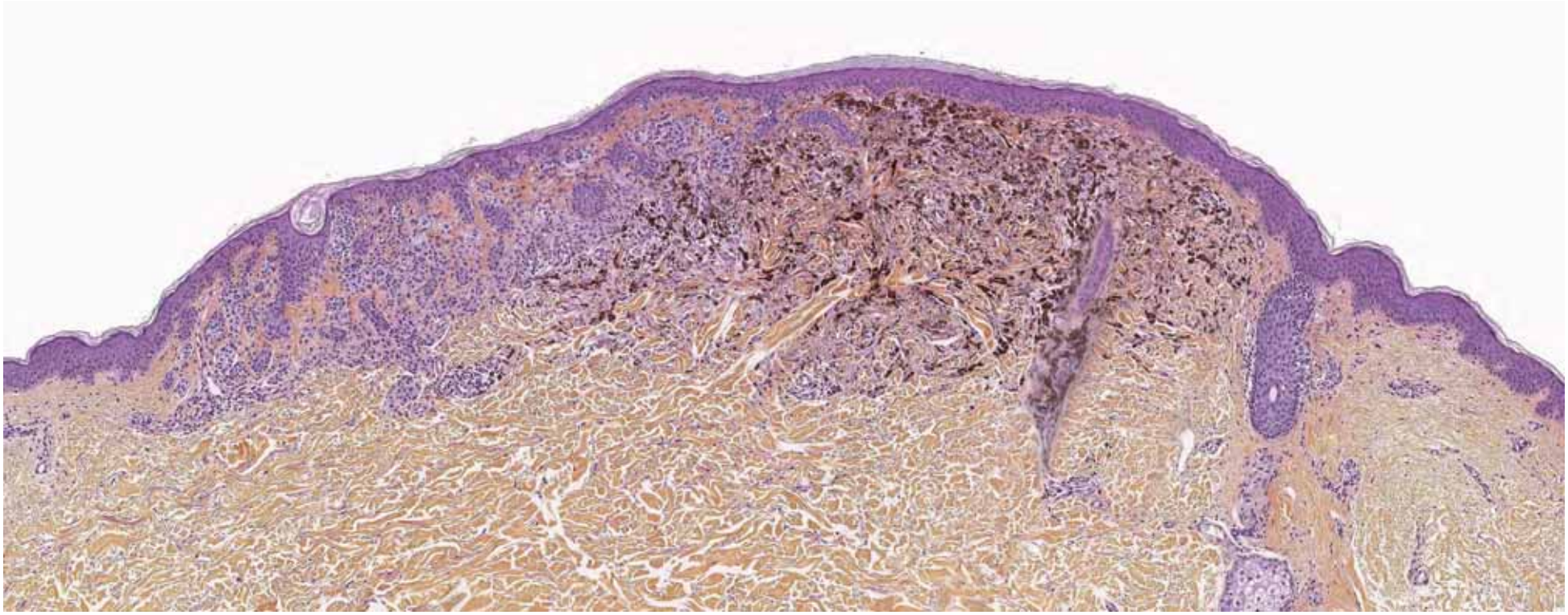
Combined Pigmented Epitheliod Melanocytoma
Usual clues

- Low cellularity
- Predominance of melanophages
- Fried egg nuclei
- Vacuolated cytoplasm
- Hyperplasia is associated with junctional component

Combined Pigmented Epithelioid Melanocytoma (*BRAF* V600E+ *PRKAR1A* mutations)

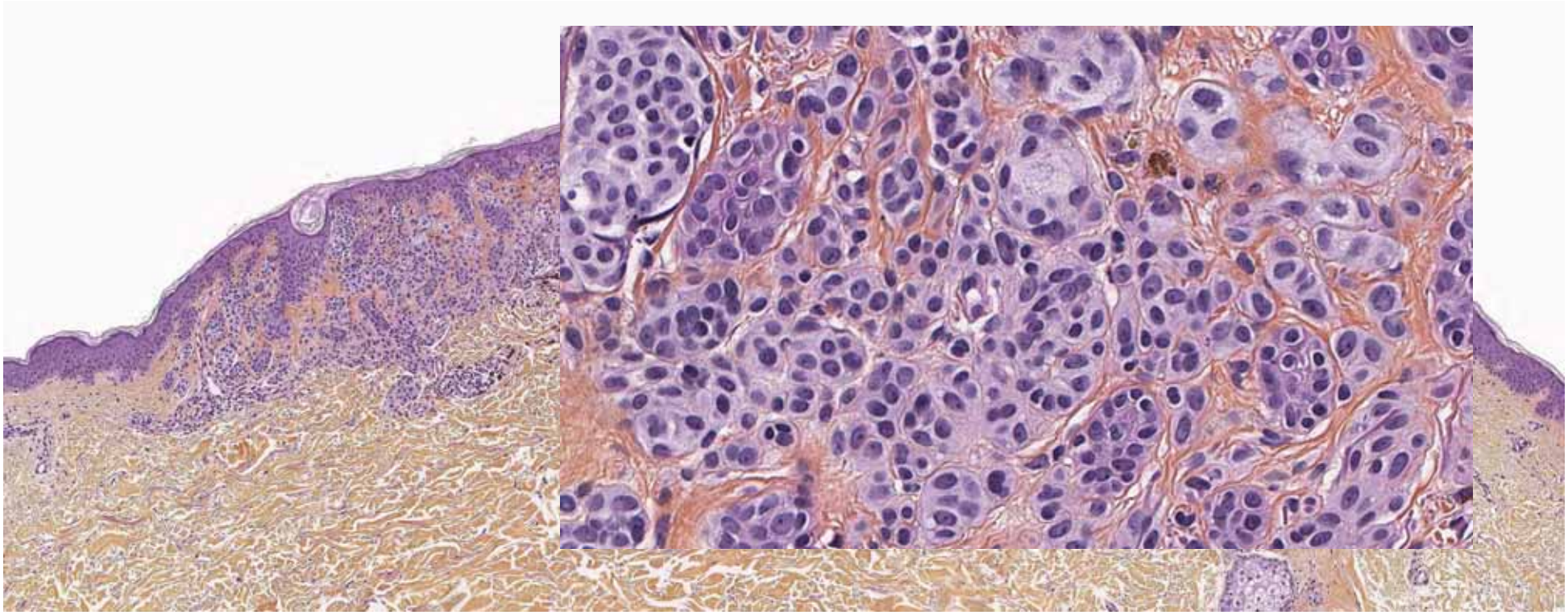


PRKAR1A-inactivated melanocytic tumor with a *BRAF* V600E background

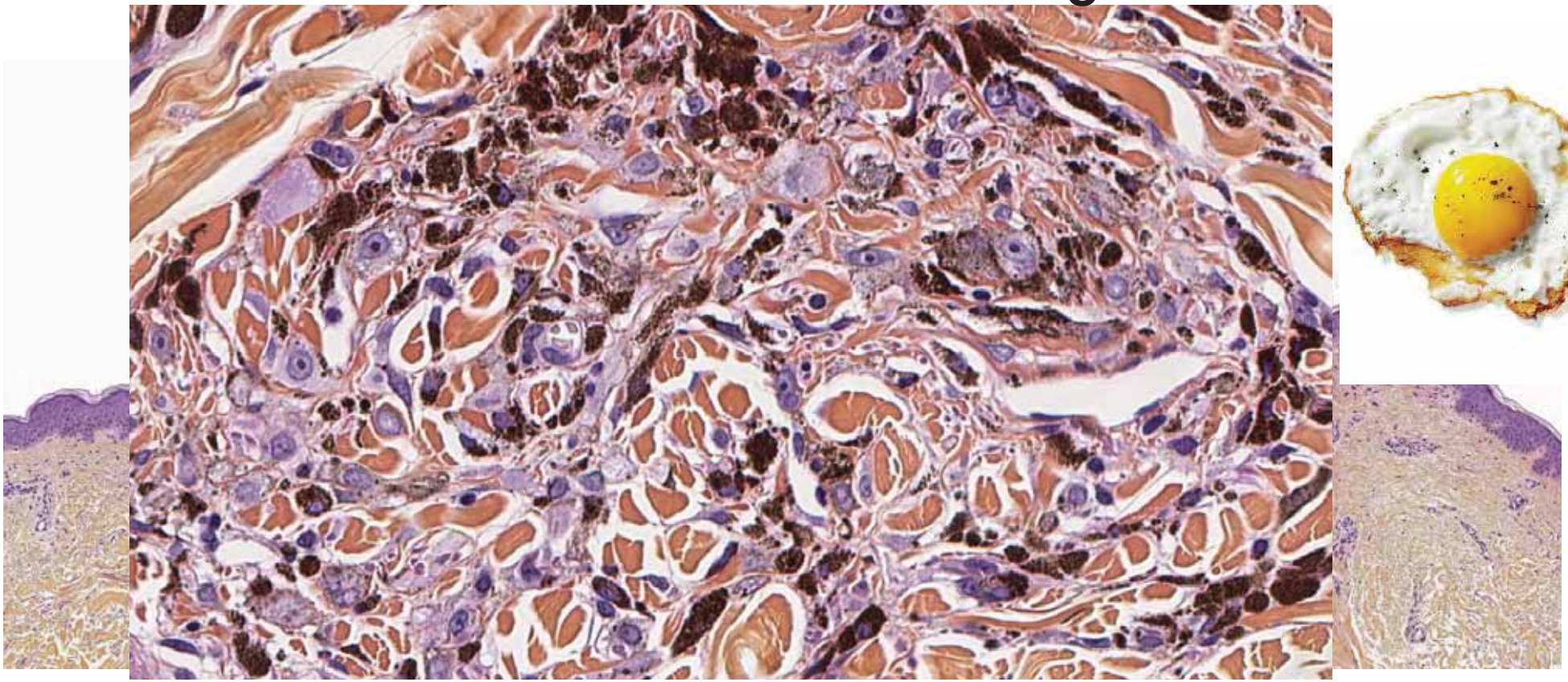


F50 Shoulder

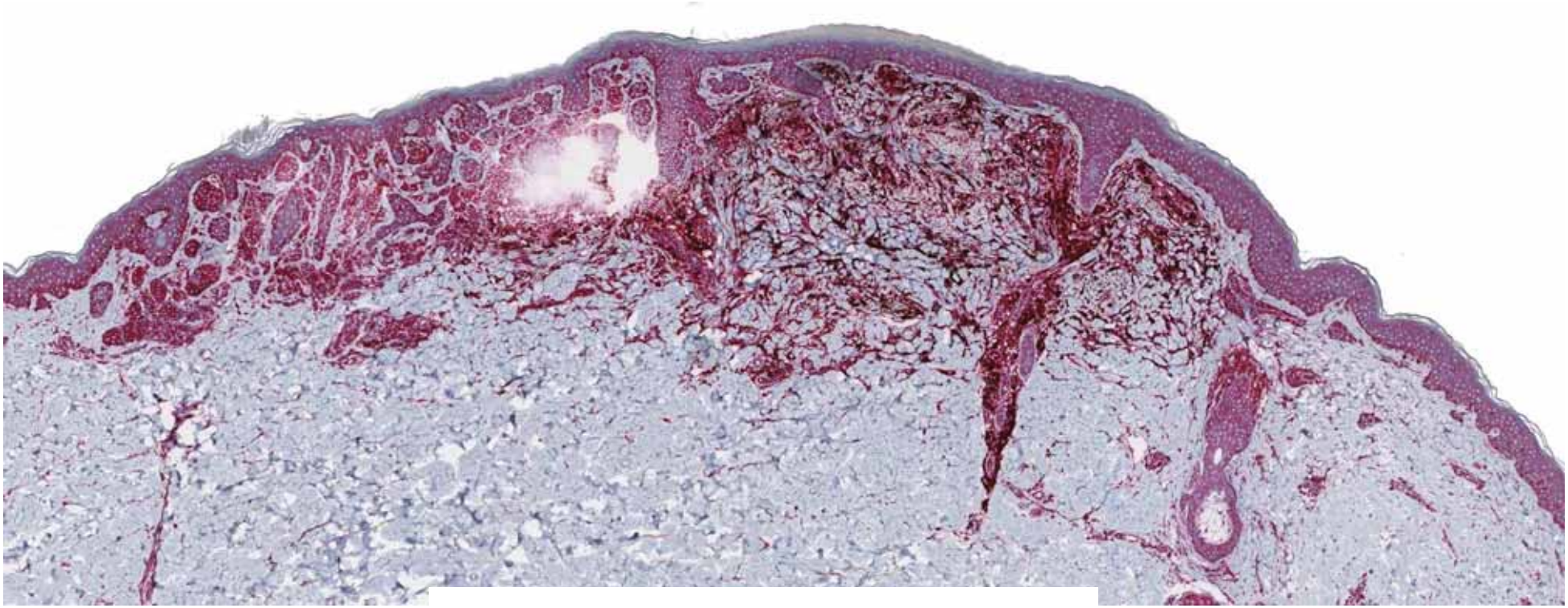
PRKAR1A-inactivated melanocytic tumor with a *BRAF* V600E background



PRKAR1A-inactivated melanocytic tumor with a *BRAF* V600E background

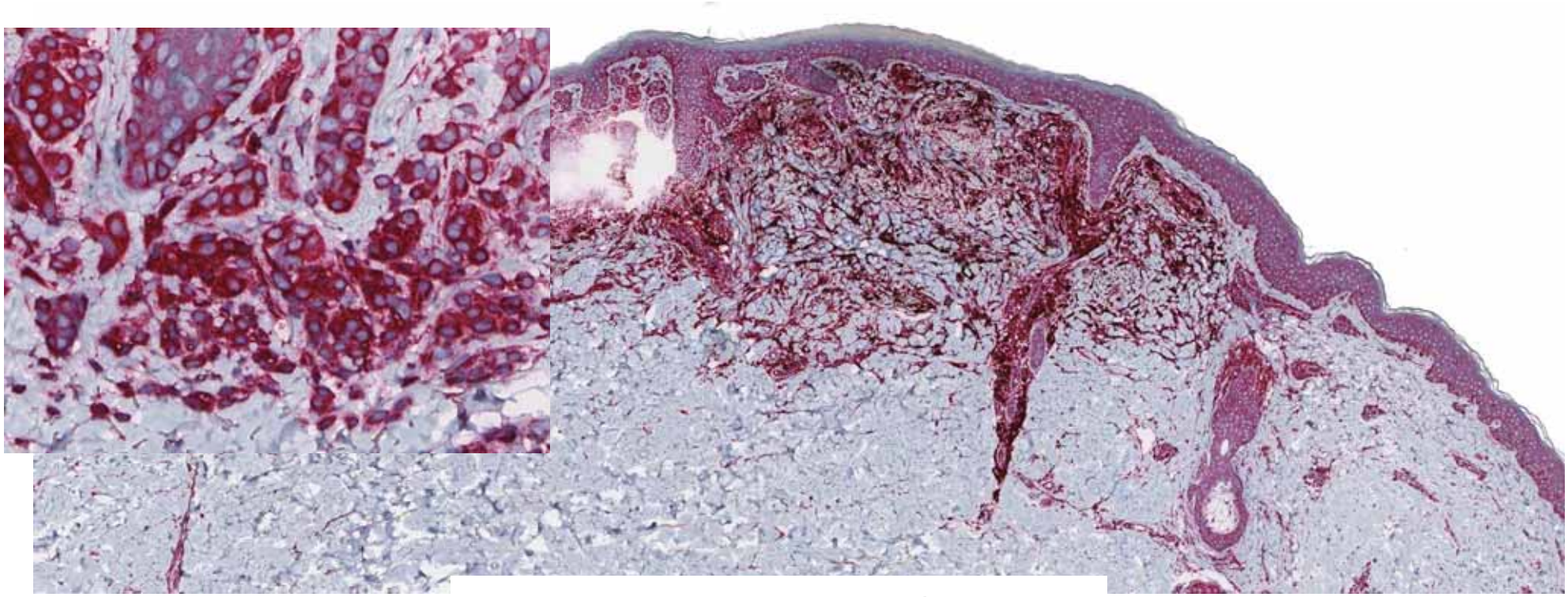


PRKAR1A-inactivated melanocytic tumor with a *BRAF* V600E background



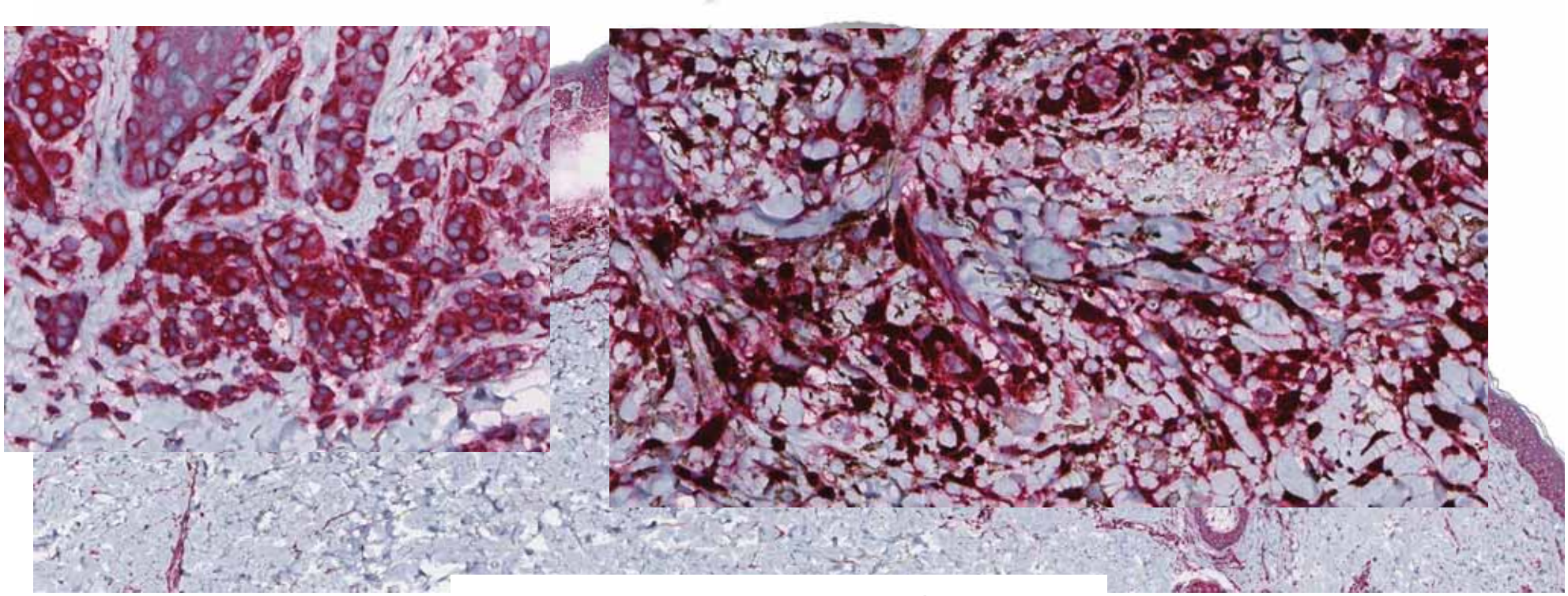
PRKAR1A IHC

PRKAR1A-inactivated melanocytic tumor with a *BRAF* V600E background



PRKAR1A IHC

PRKAR1A-inactivated melanocytic tumor with a *BRAF* V600E background

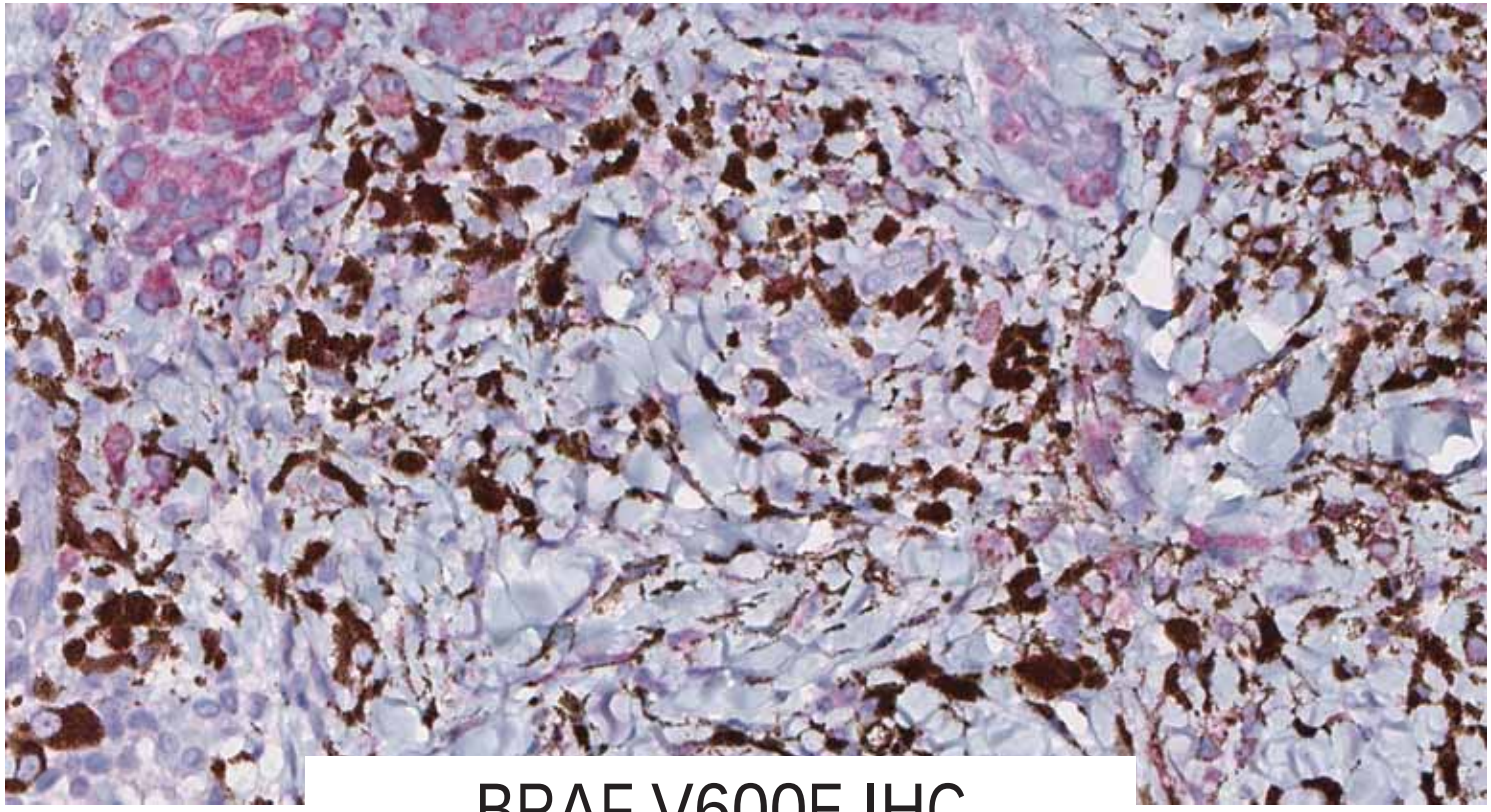


PRKAR1A IHC

PRKAR1A-inactivated melanocytic tumor with a *BRAF* V600E background

BRAF V600E IHC

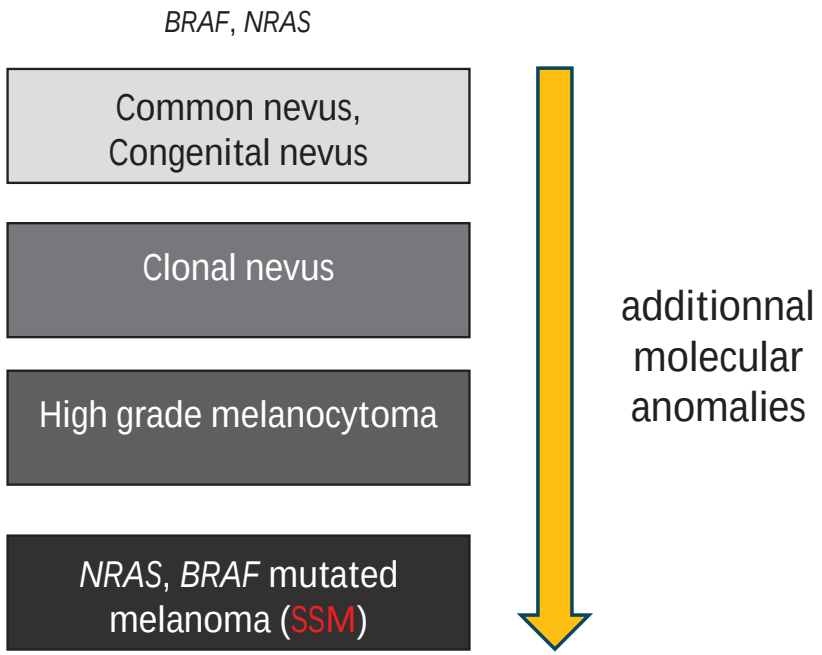
PRKAR1A-inactivated melanocytic tumor with a *BRAF* V600E background



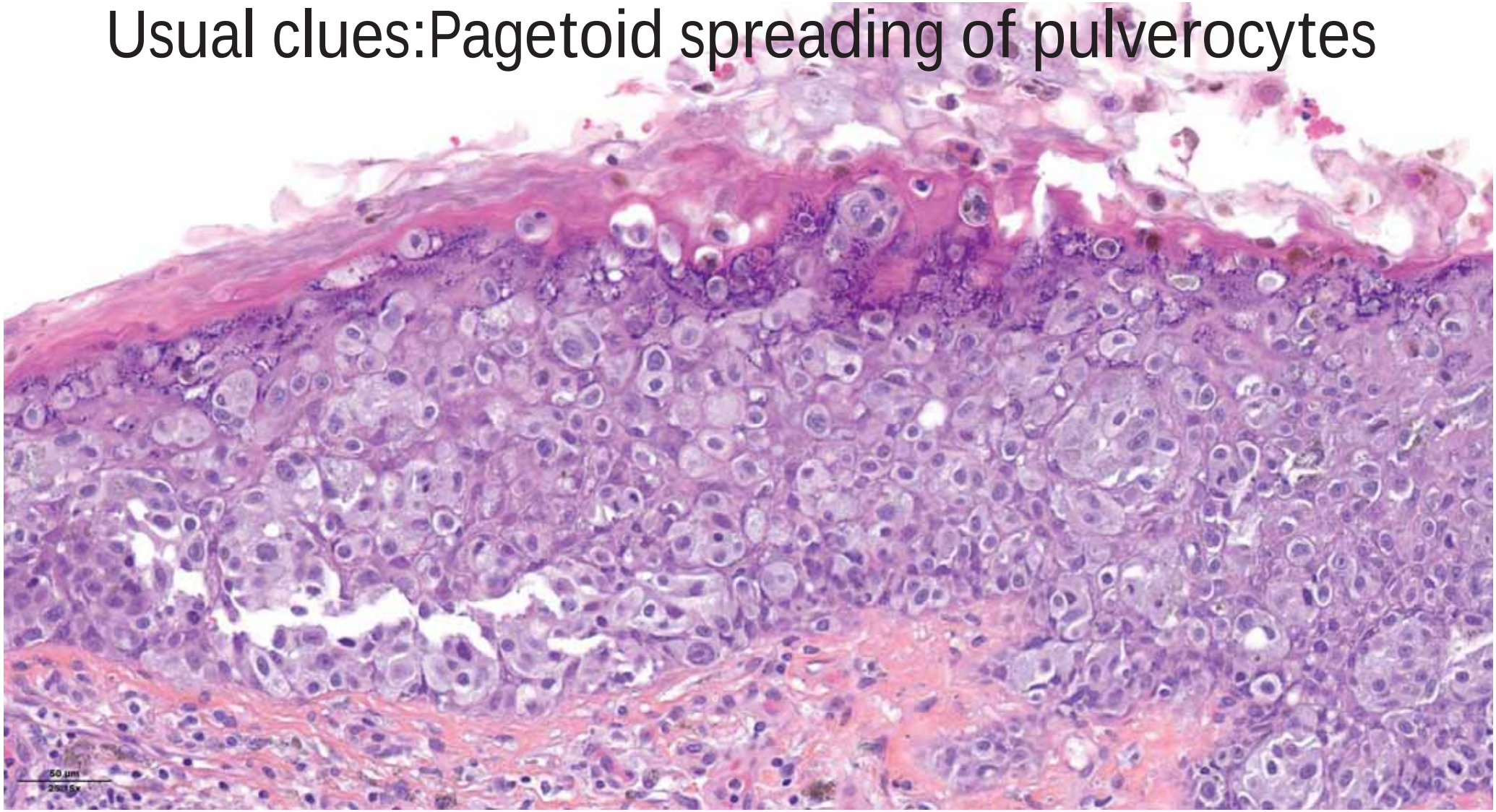
BRAF V600E IHC

Superficial spreading melanoma (SSM)
Usual clues

Common group



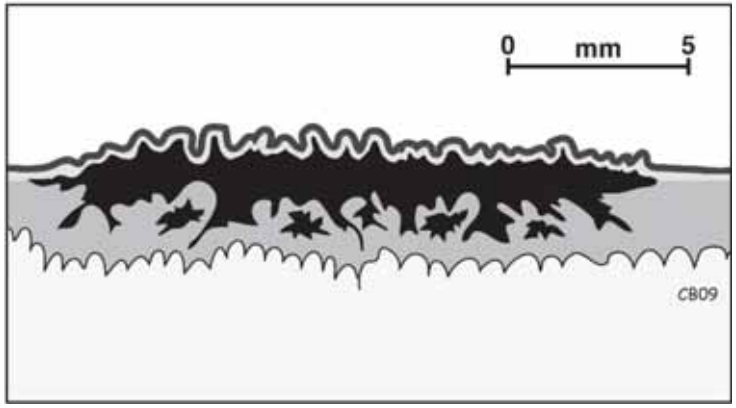
Superficial spreading melanoma (SSM)
Usual clues:Pagetoid spreading of pulverocytes

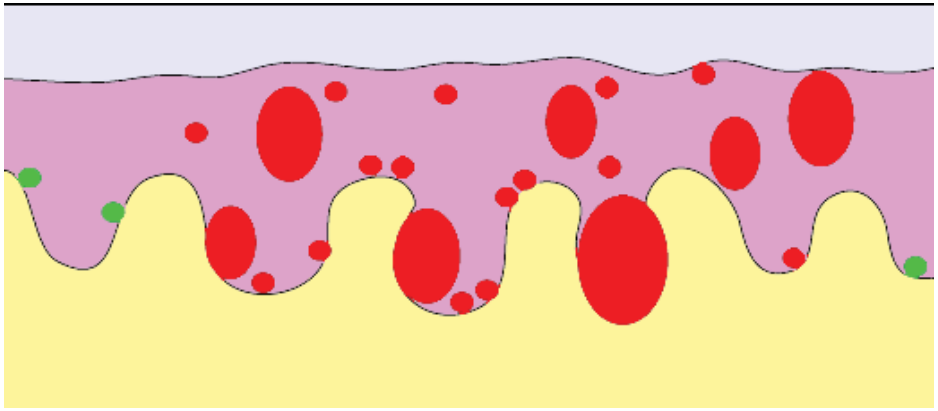


SSM ex-nevus
Chicane/Zig-Zag transition clue

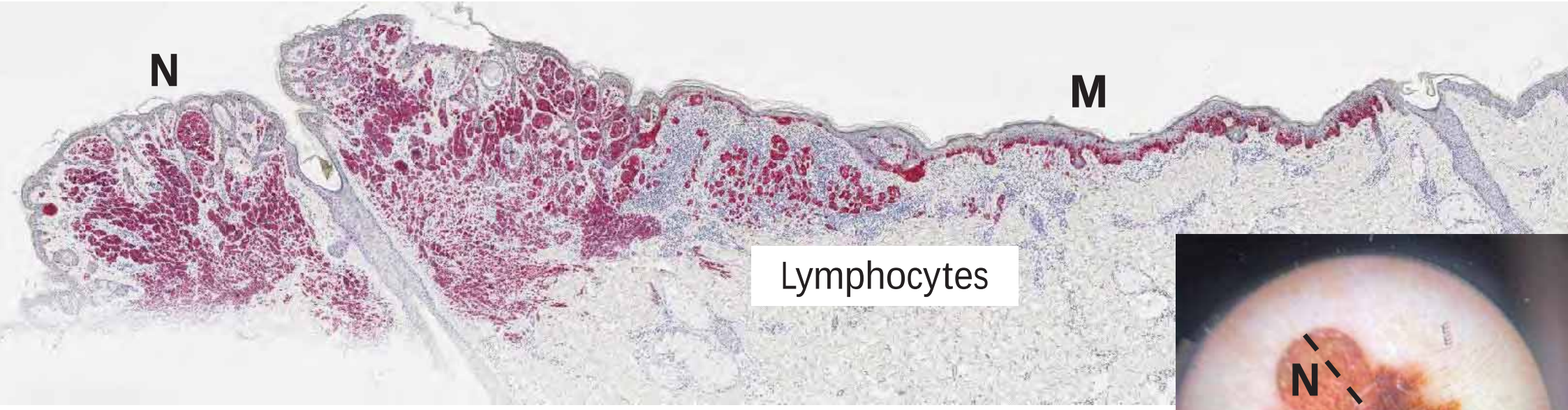
Malignant progression pattern

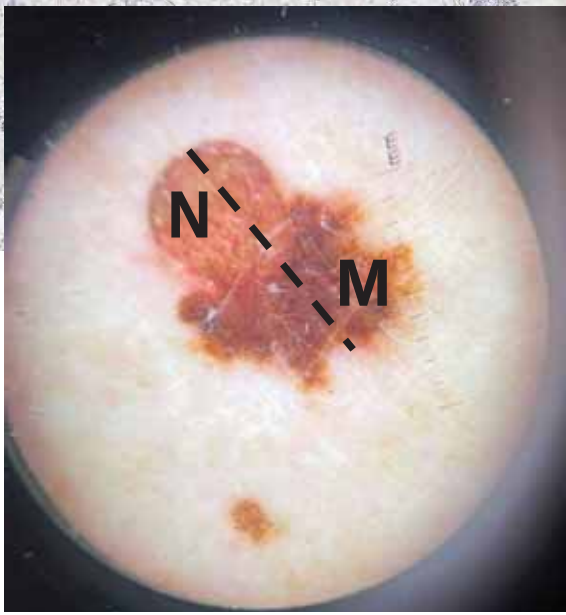
- Intricating a congenital nevus pattern and a pagetoid pattern





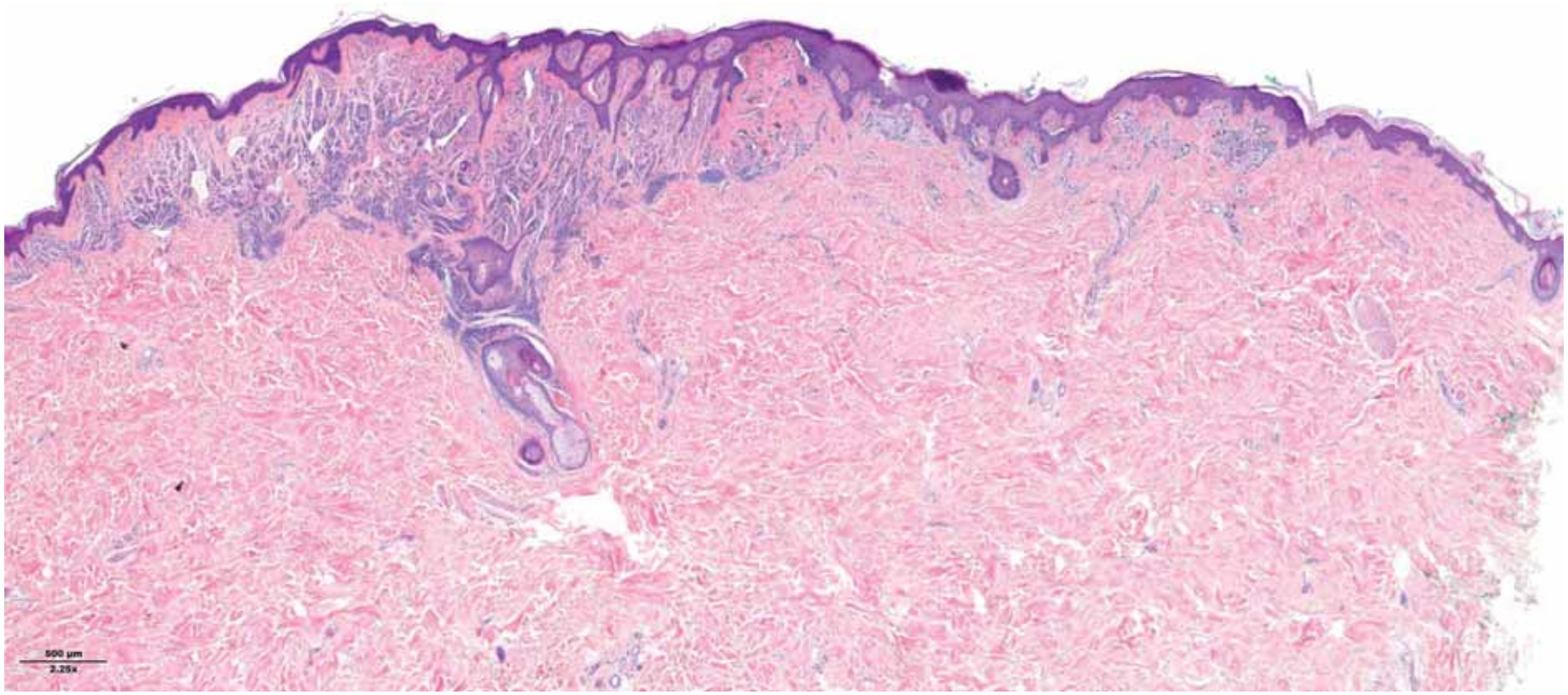
Nevus to SSM melanoma lateral transformation model «chicane/zig-zag» architecture



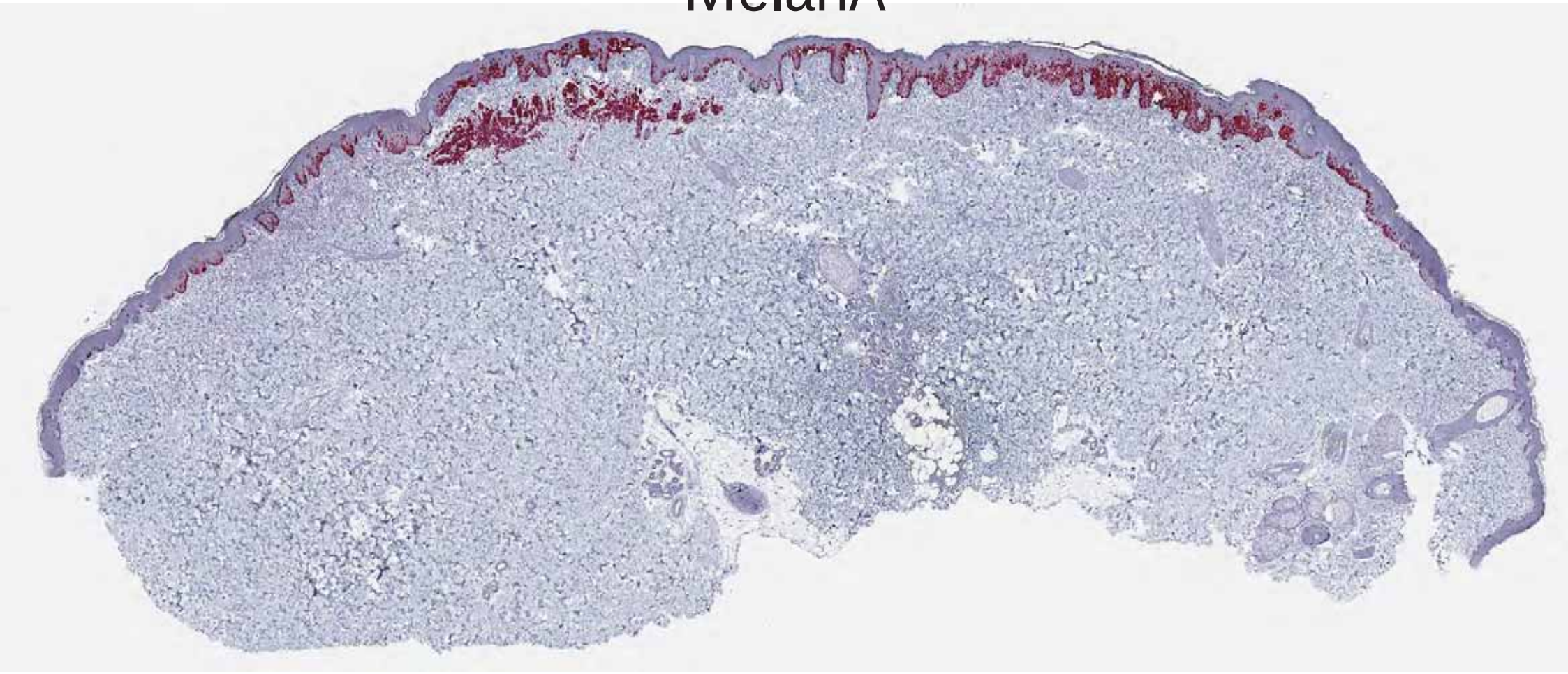


MelanA

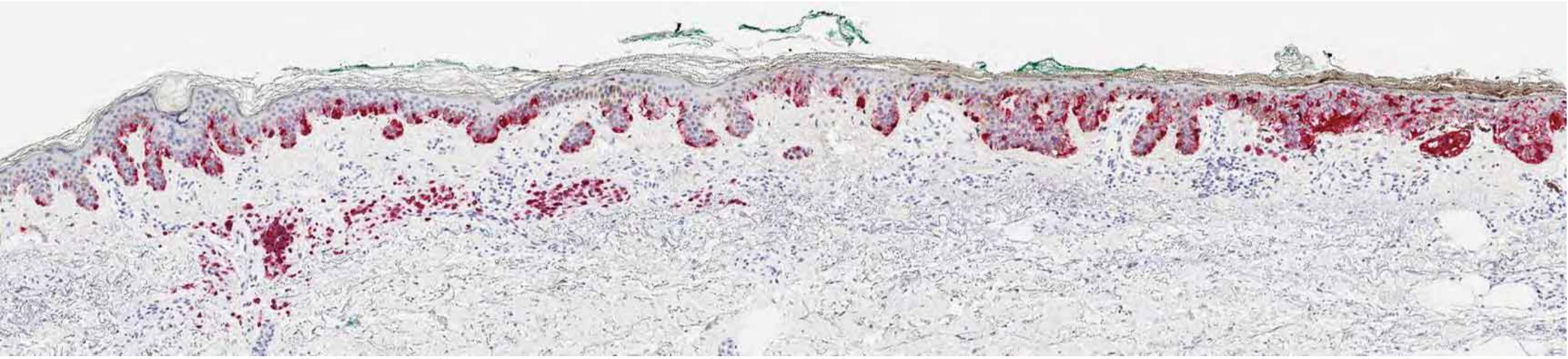
Nevus to SSM melanoma lateral transformation model «chicane/zig-zag» architecture



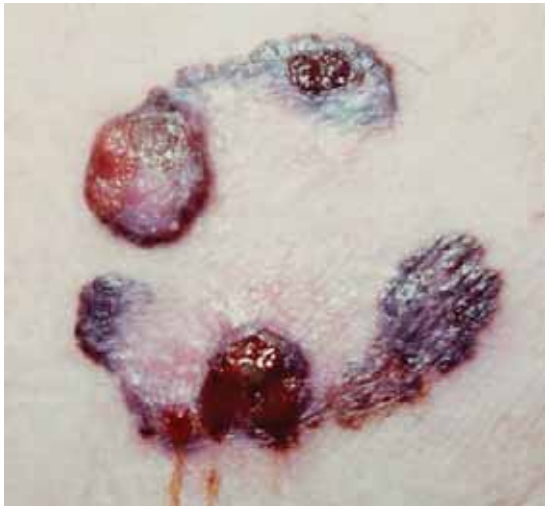
Asymetrical melanocytic distribution
«chicane/zig-zag» architecture
MelanA

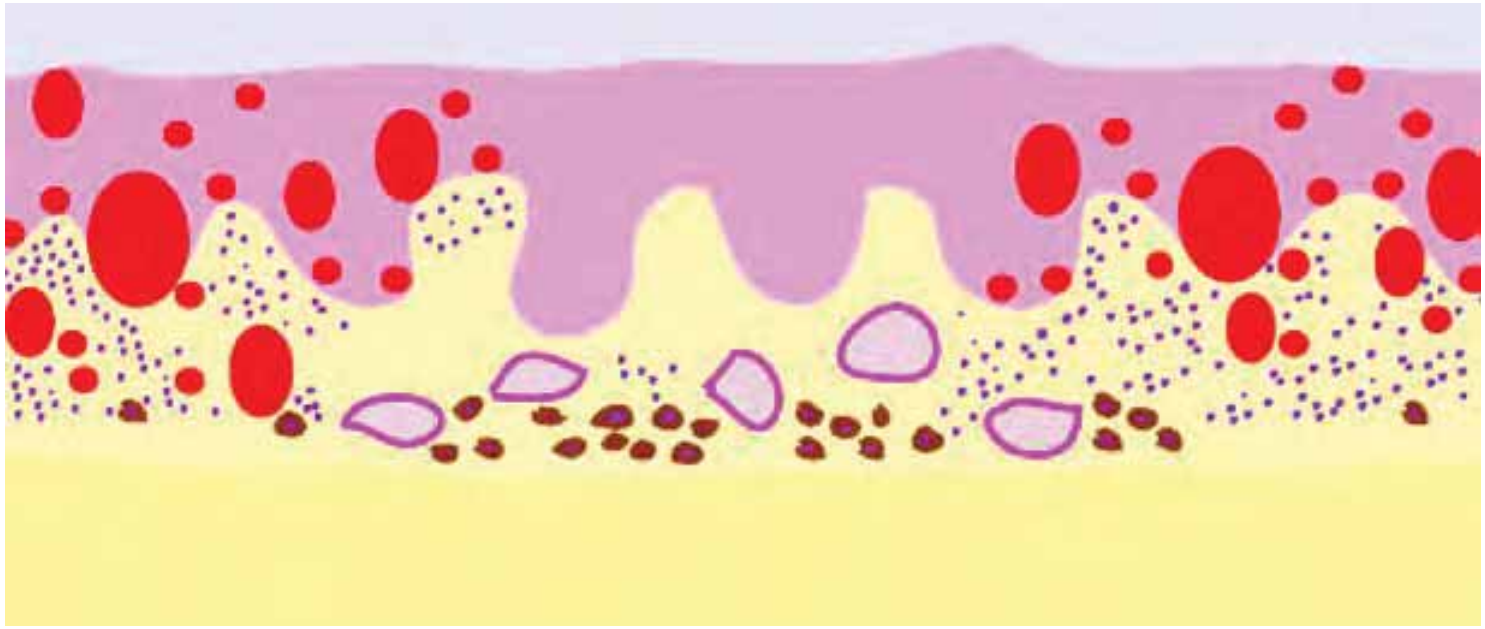


Asymetrical melanocytic distribution «chicane/zig-zag» architecture MelanA

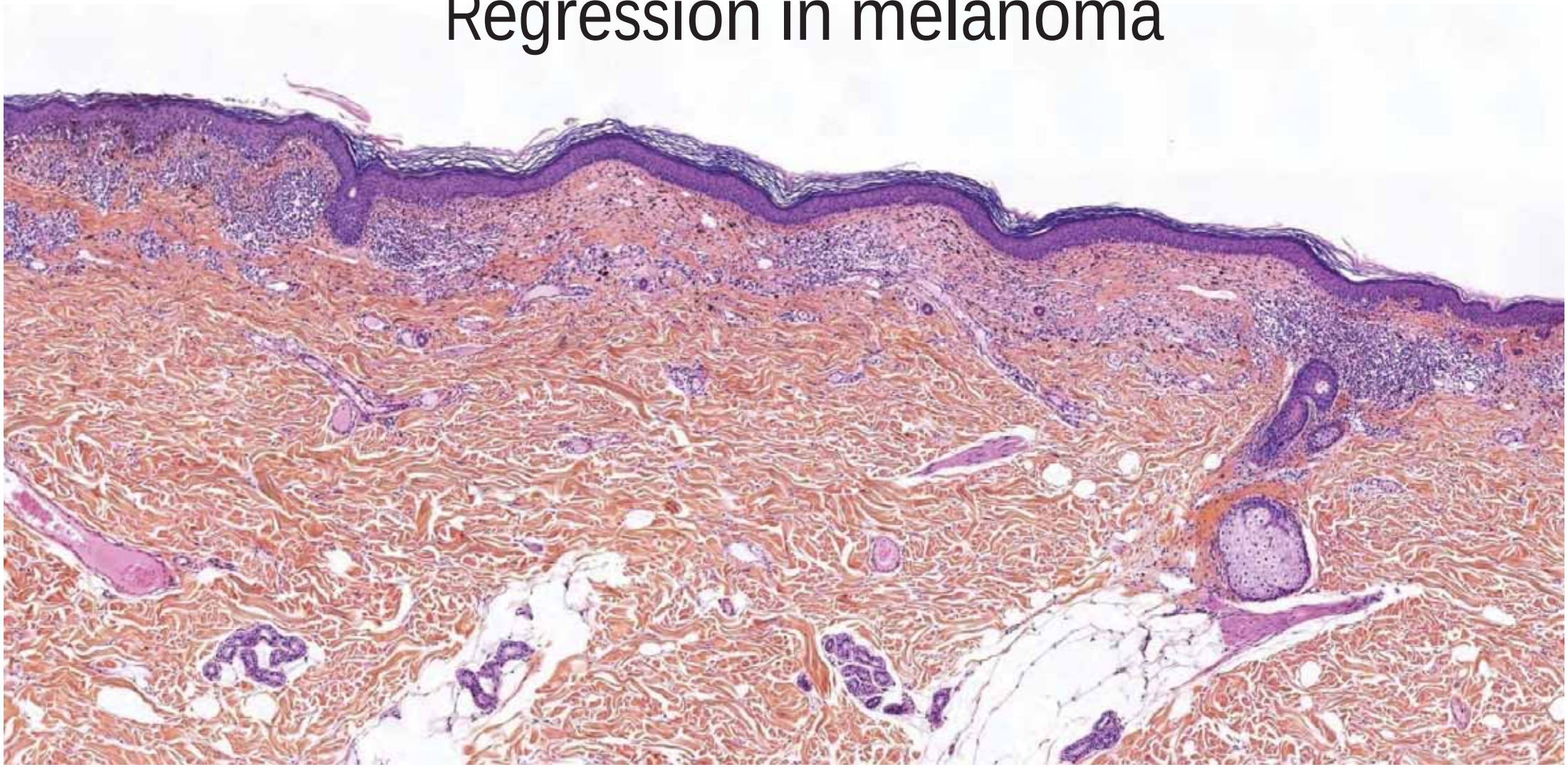


Regression in melanoma (SSM+++)

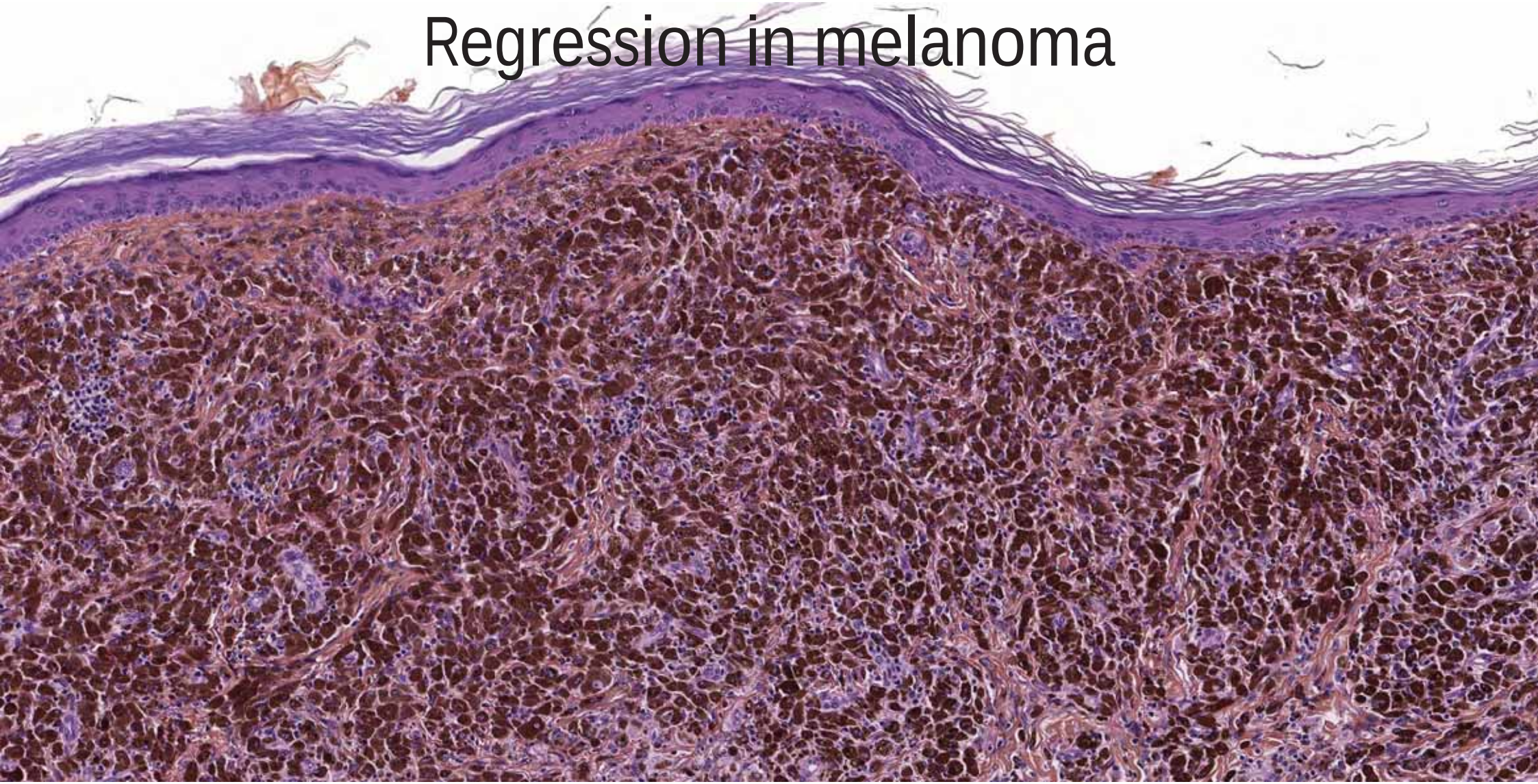




Regression in melanoma

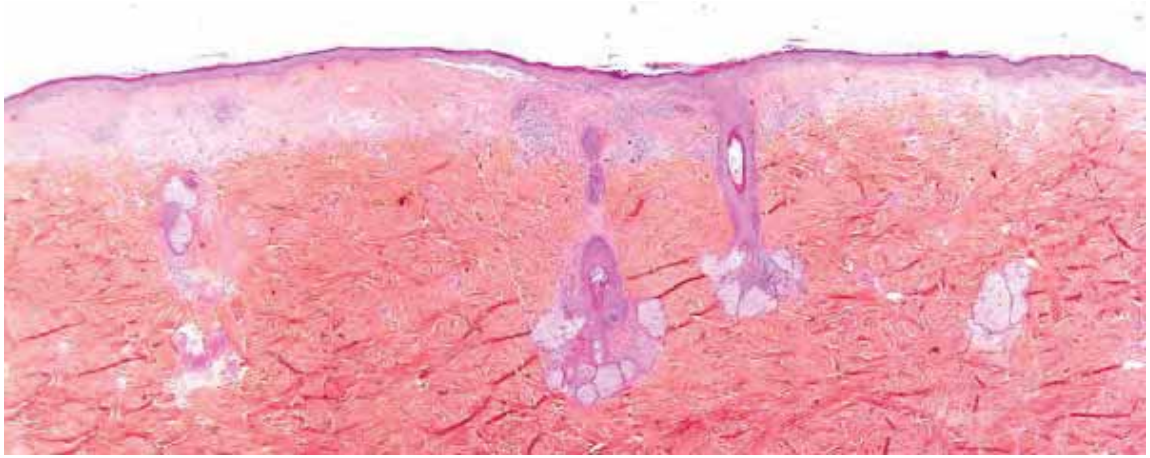


Regression in melanoma

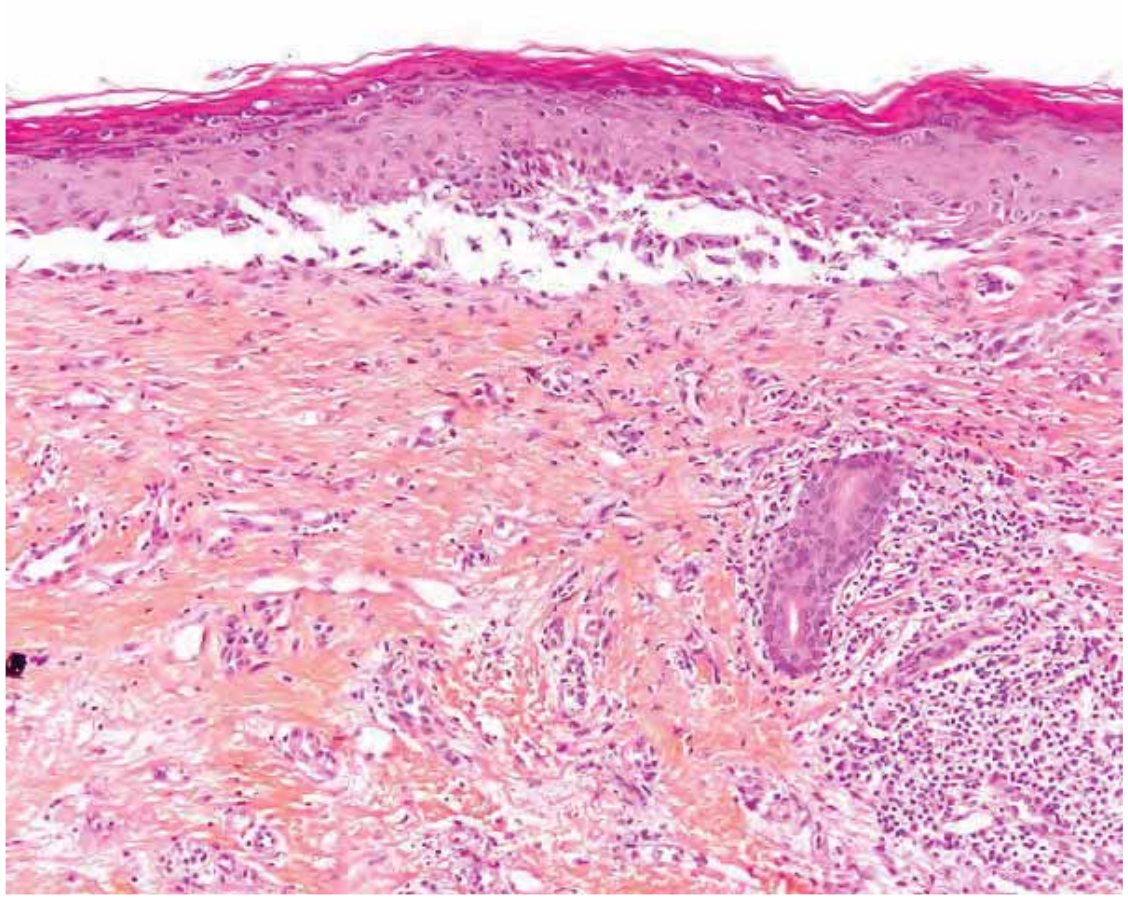


Regression : Slit throat sign

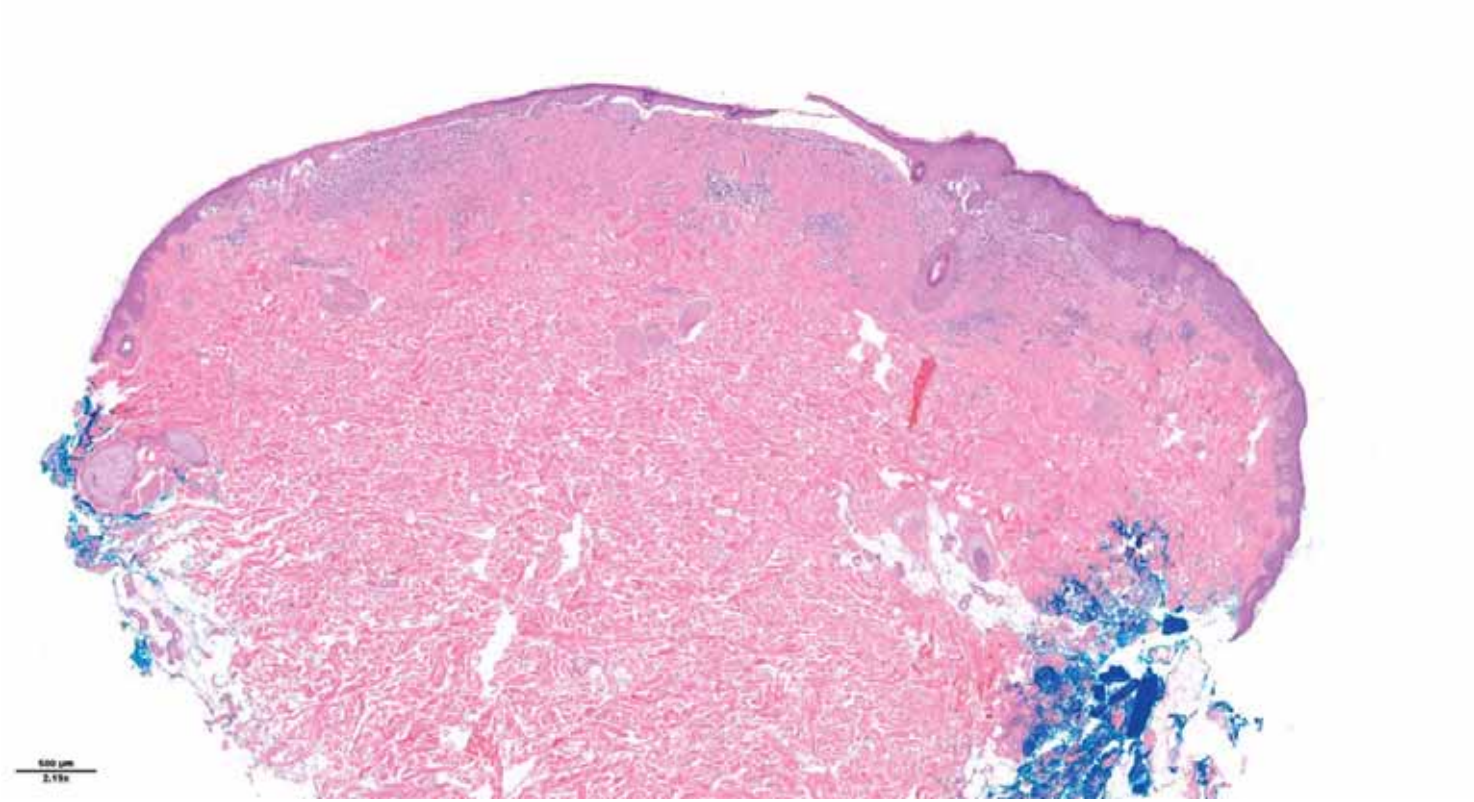
Slit throat sign suggests regression
Junctional clefting in a flat epidermis with underlying horizontal fibrosis



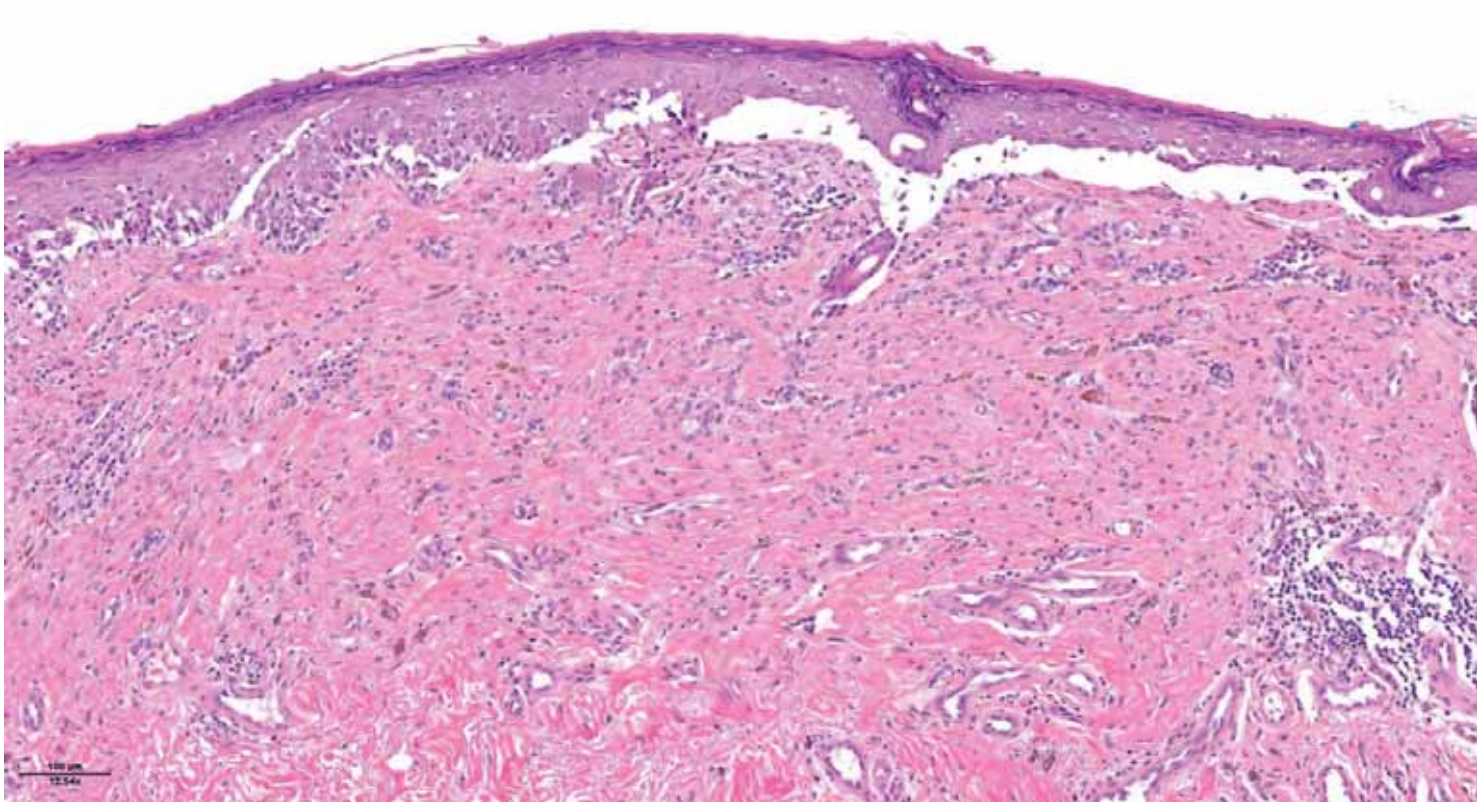
Slit throat sign suggests regression
Junctional clefting in a flat epidermis with underlying horizontal fibrosis



Slit throat sign suggests regression
Junctional clefting in a flat epidermis with underlying horizontal fibrosis

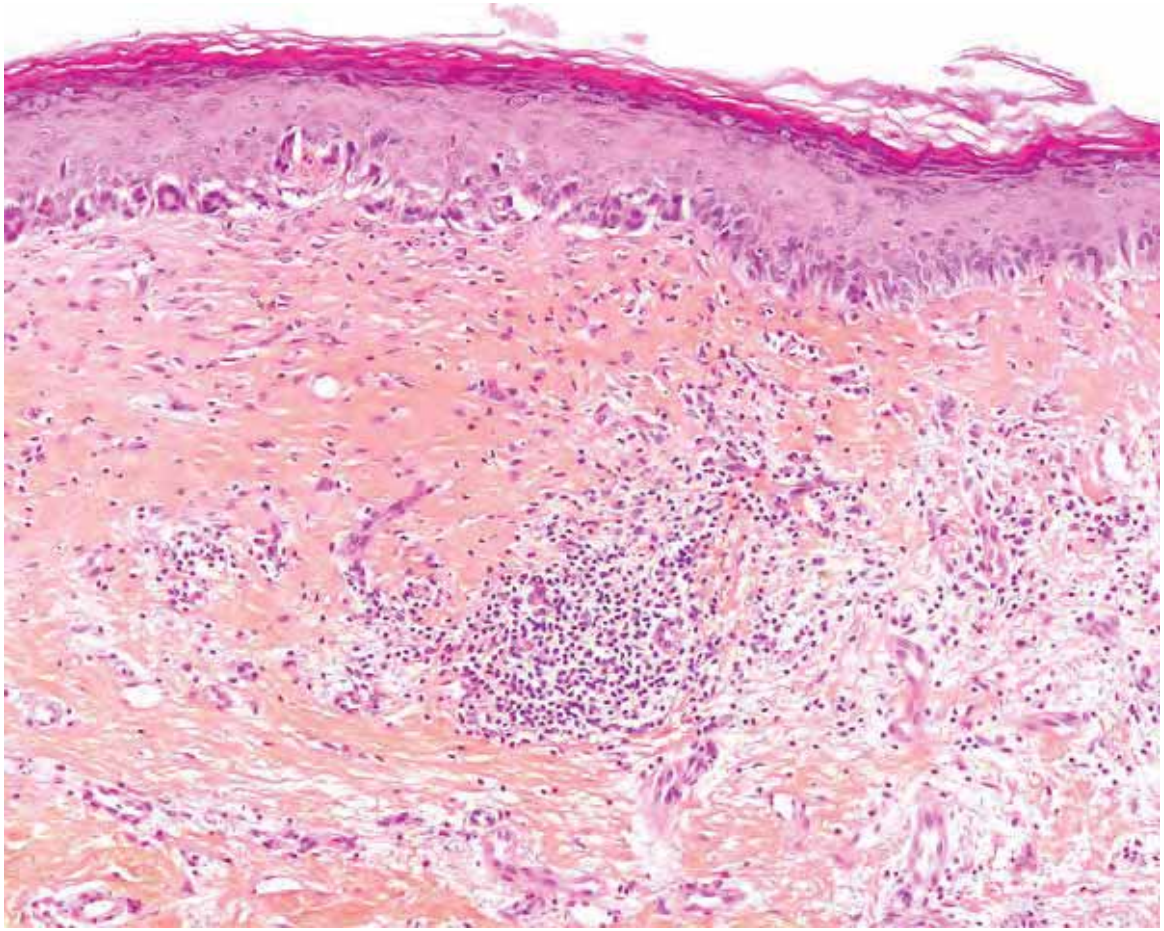


Slit throat sign suggests regression
Junctional clefting in a flat epidermis with underlying horizontal fibrosis

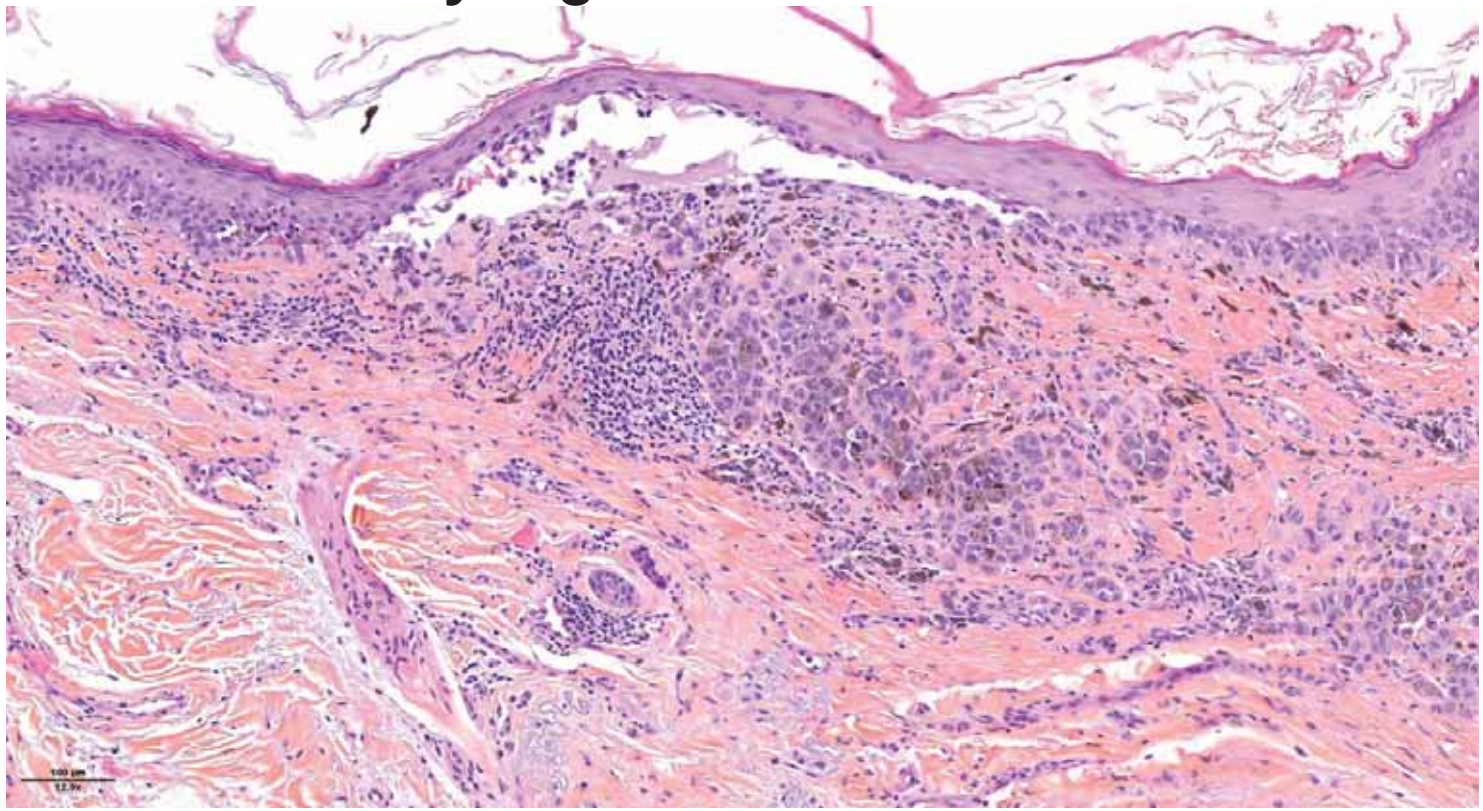


Slit throat sign suggests regression
Junctional clefting in a flat epidermis with underlying horizontal fibrosis

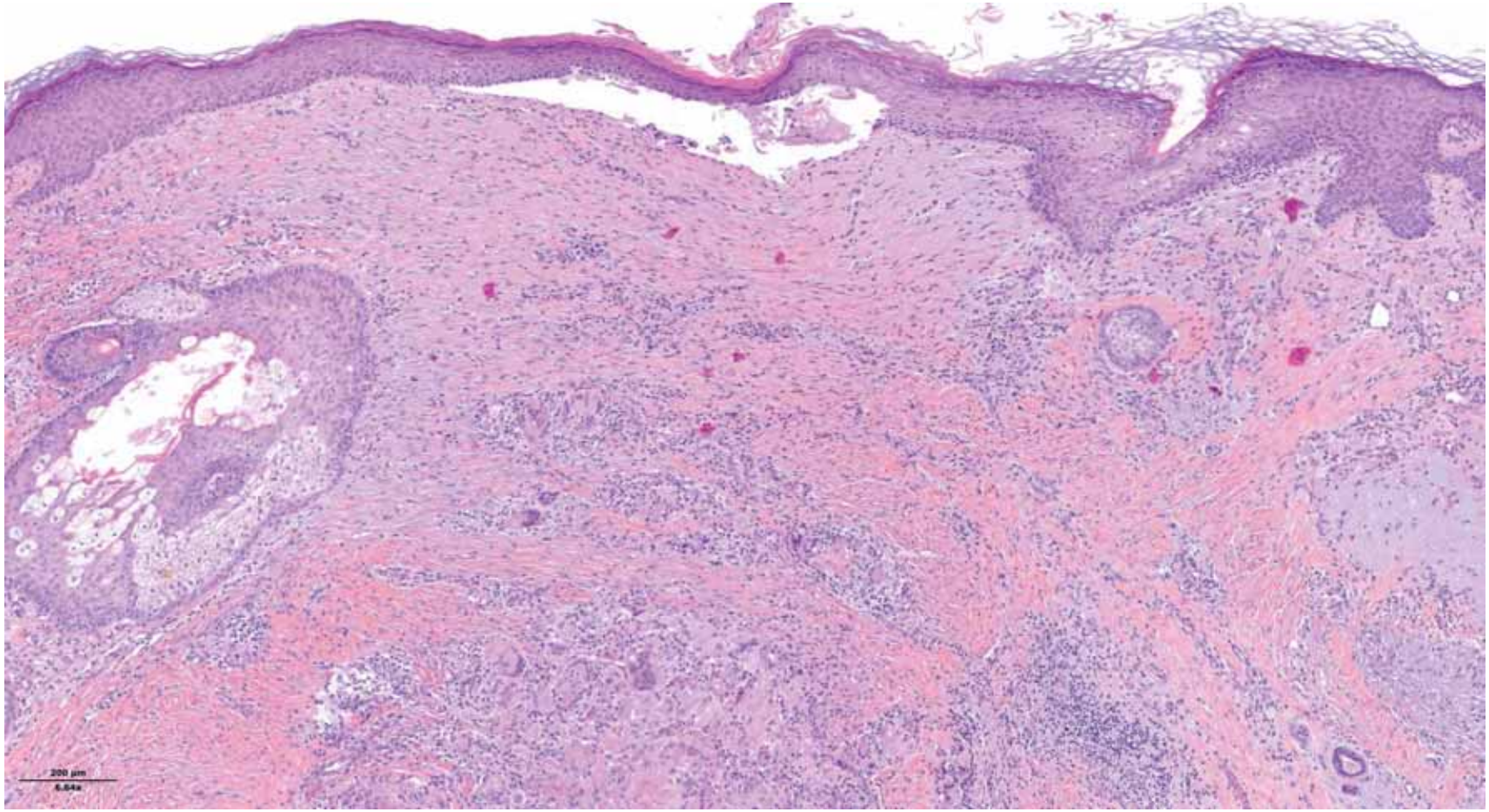
Melanocytes lack intercellular connections



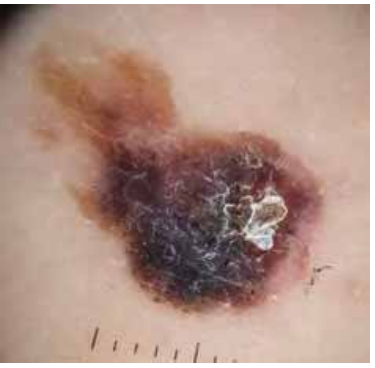
Slit throat sign suggests regression
Junctional clefting in a flat epidermis with underlying horizontal fibrosis



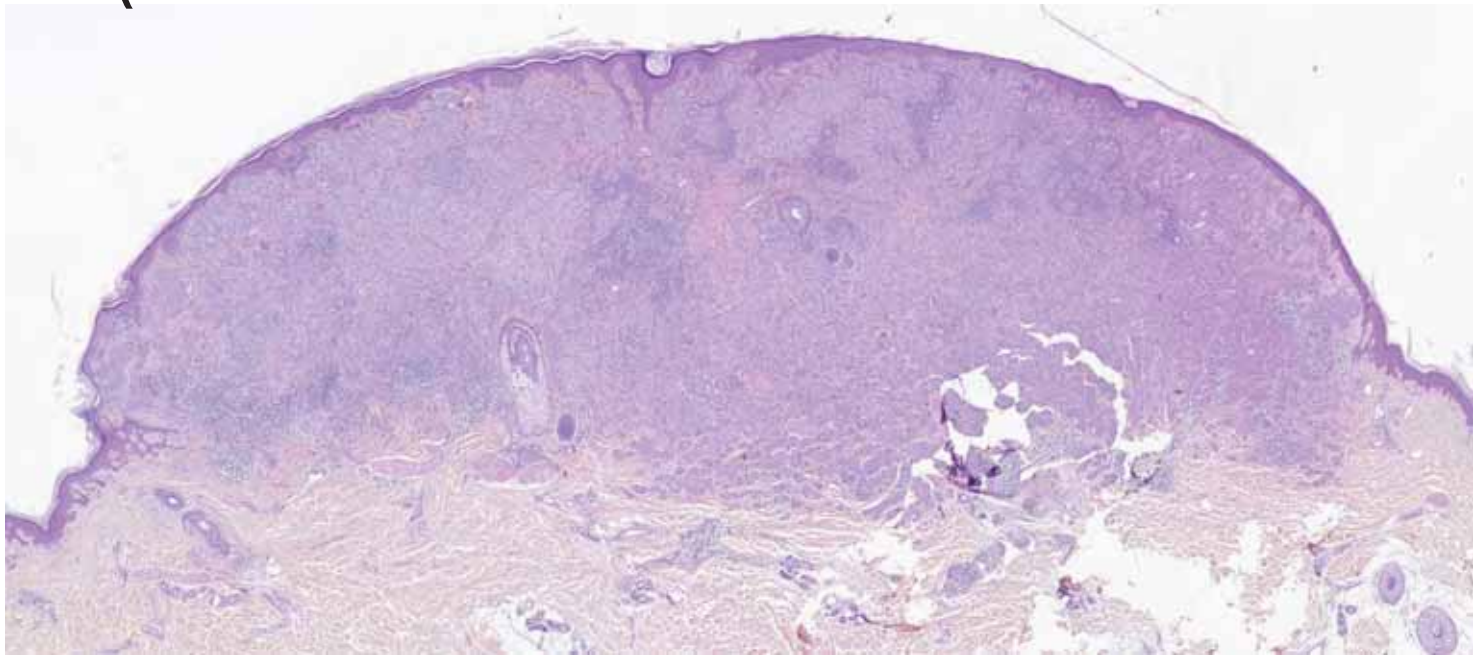
Slit throat sign
can also be found underneath a scar

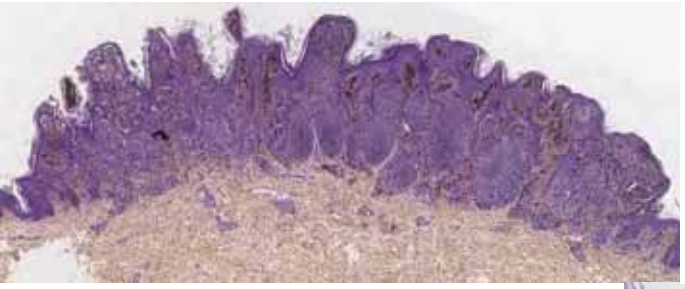


Non-chronic sun damage melanoma (*ie* sunburns)
Class I : <5% Nevoid Melanoma



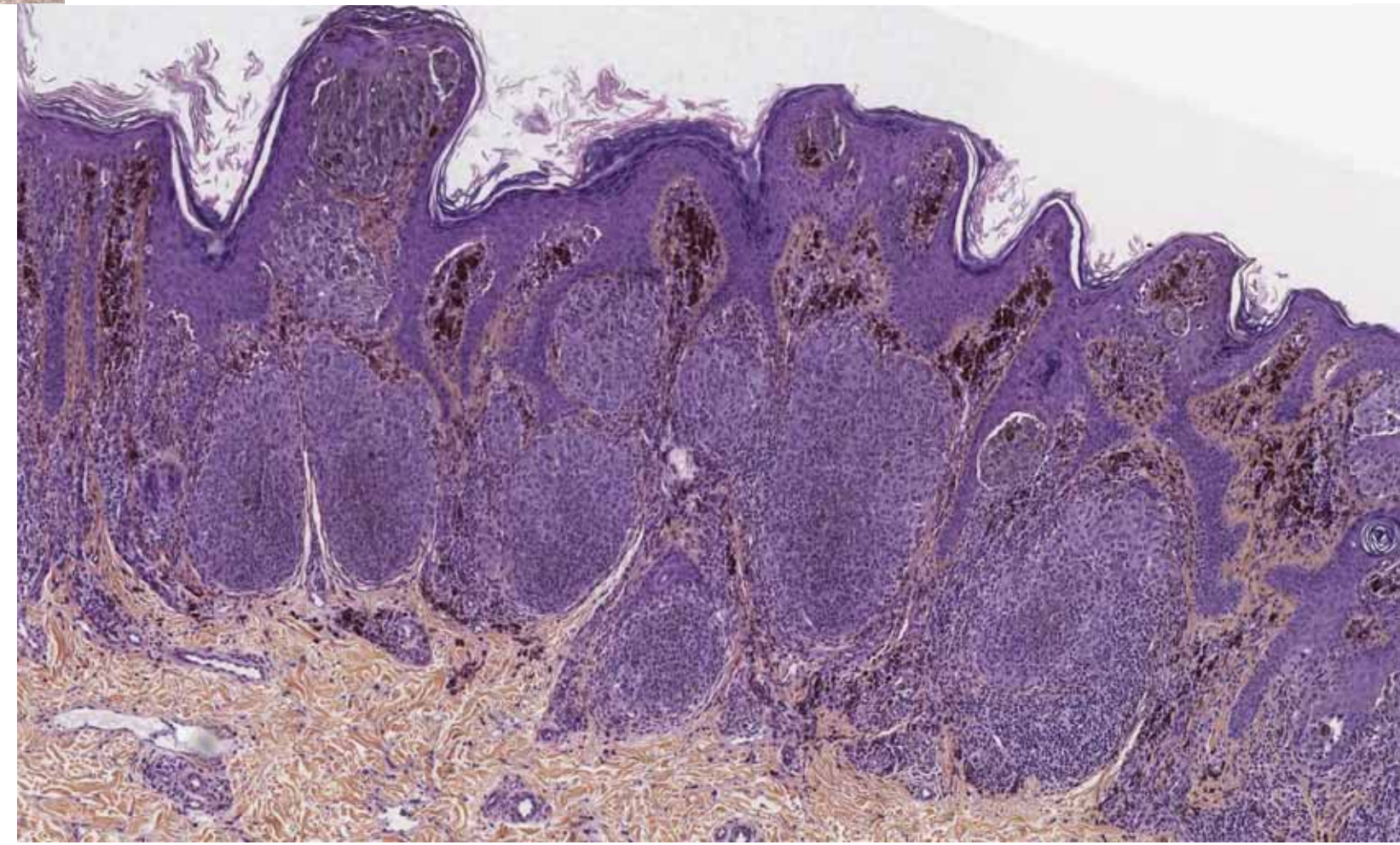
(NRAS mutations > BRAF V600E mutations)



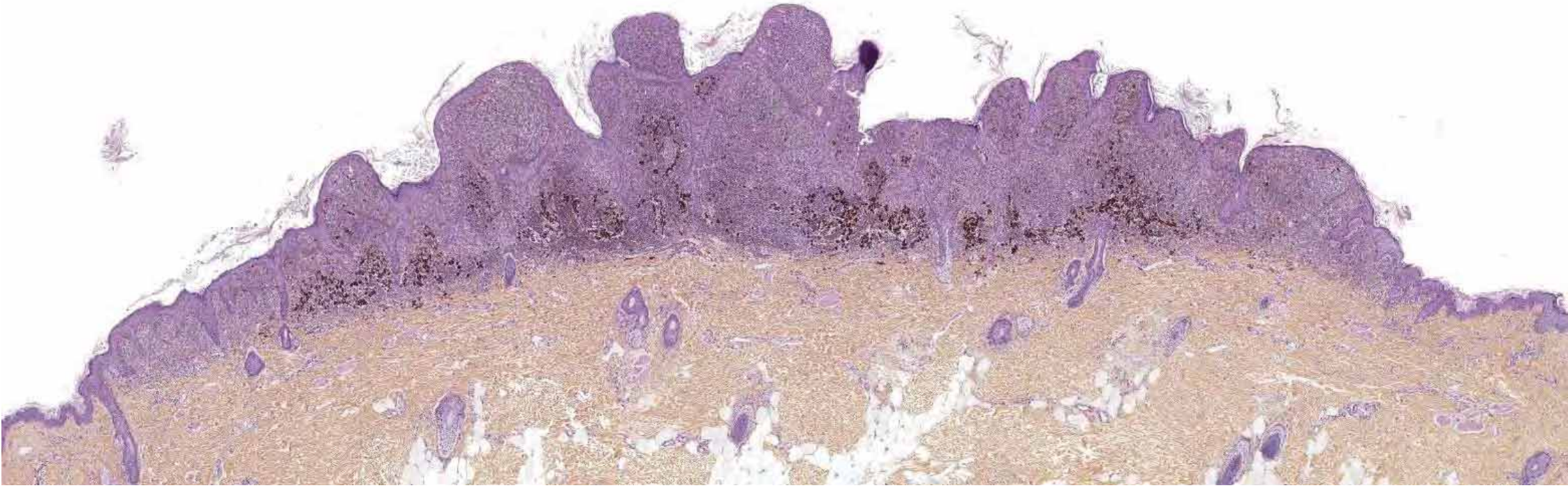


Exophytic (papillomatous)
&
Large nested

«puffy-shirt appearance»
PMID 31237702

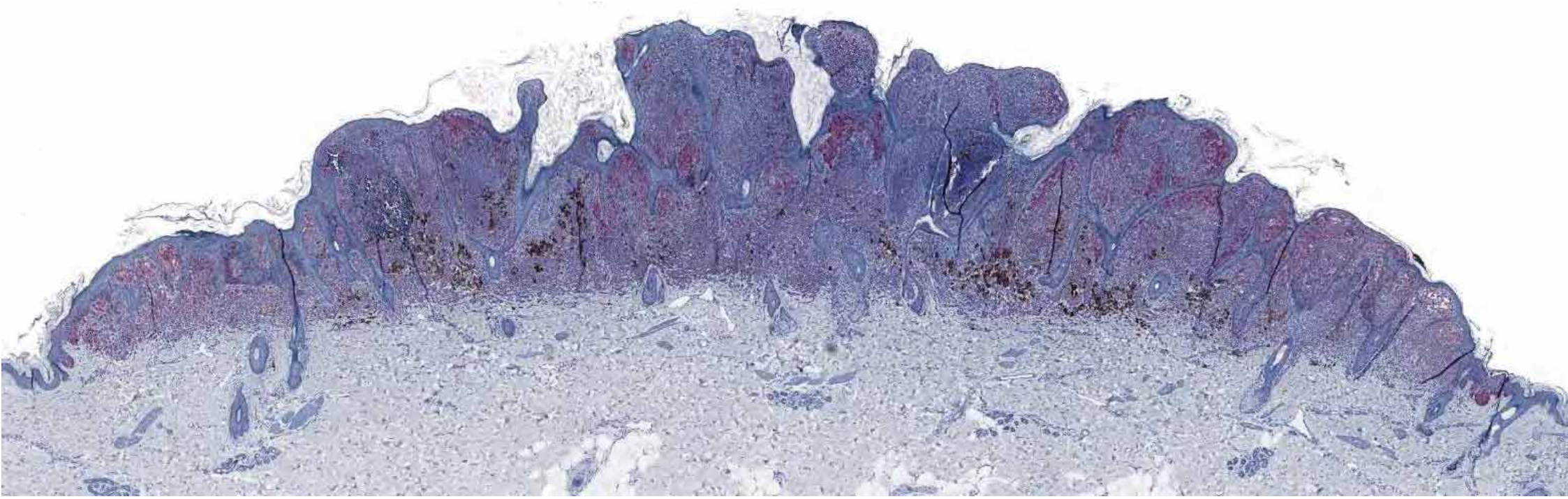


Nevoid melanoma (ImmunoHistoChemistry)

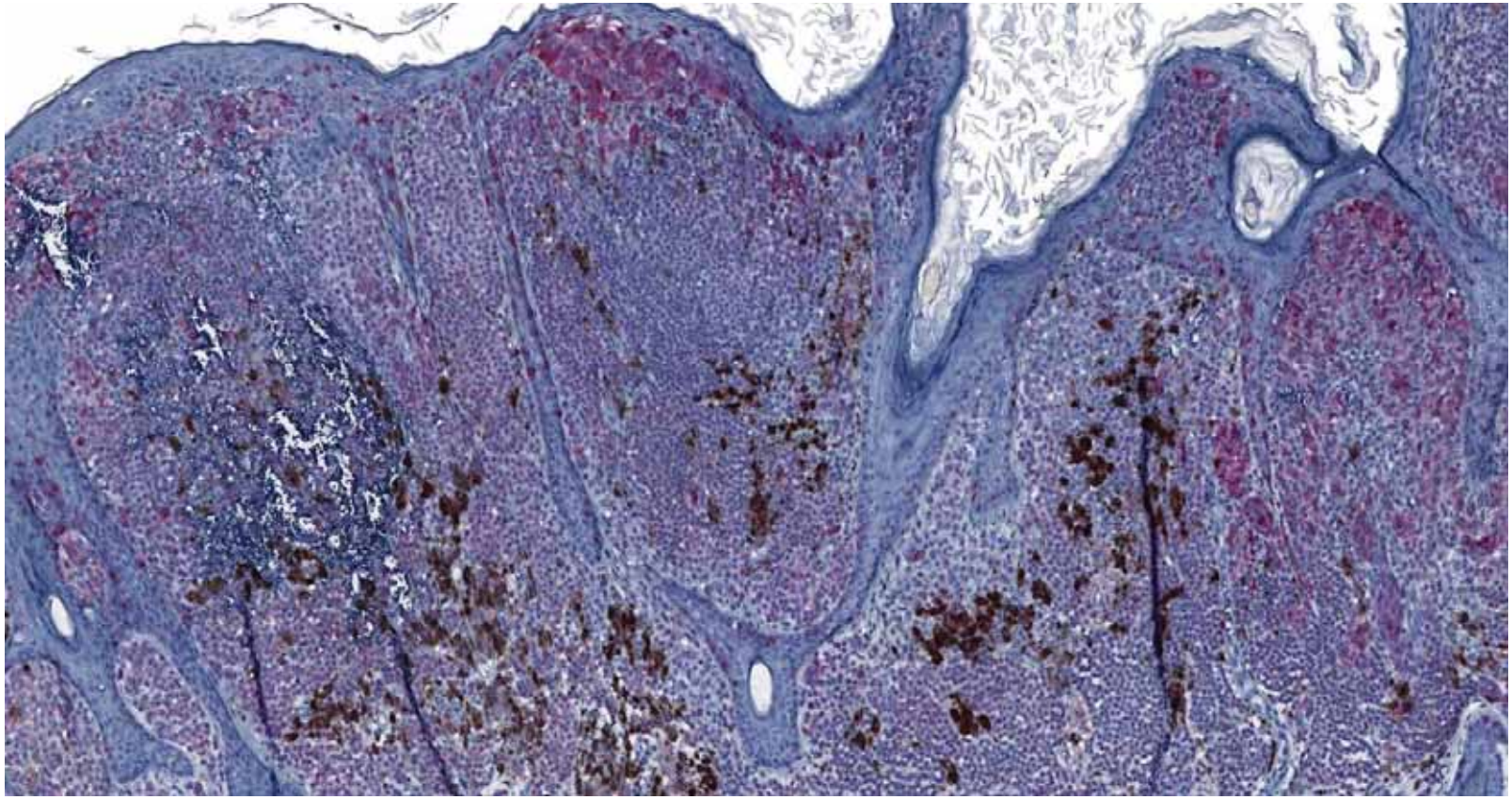


Puffy shirt appearance PMID: 31237702

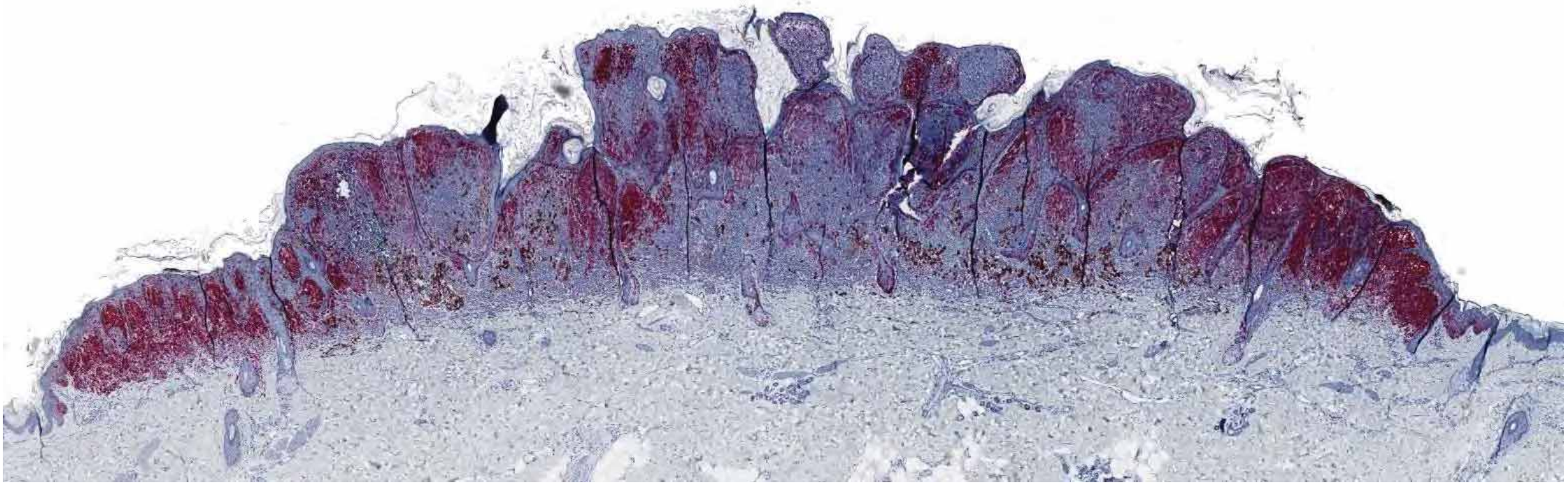
MelanA heterogeneous



MelanA heterogeneous



HMB45 heterogeneous



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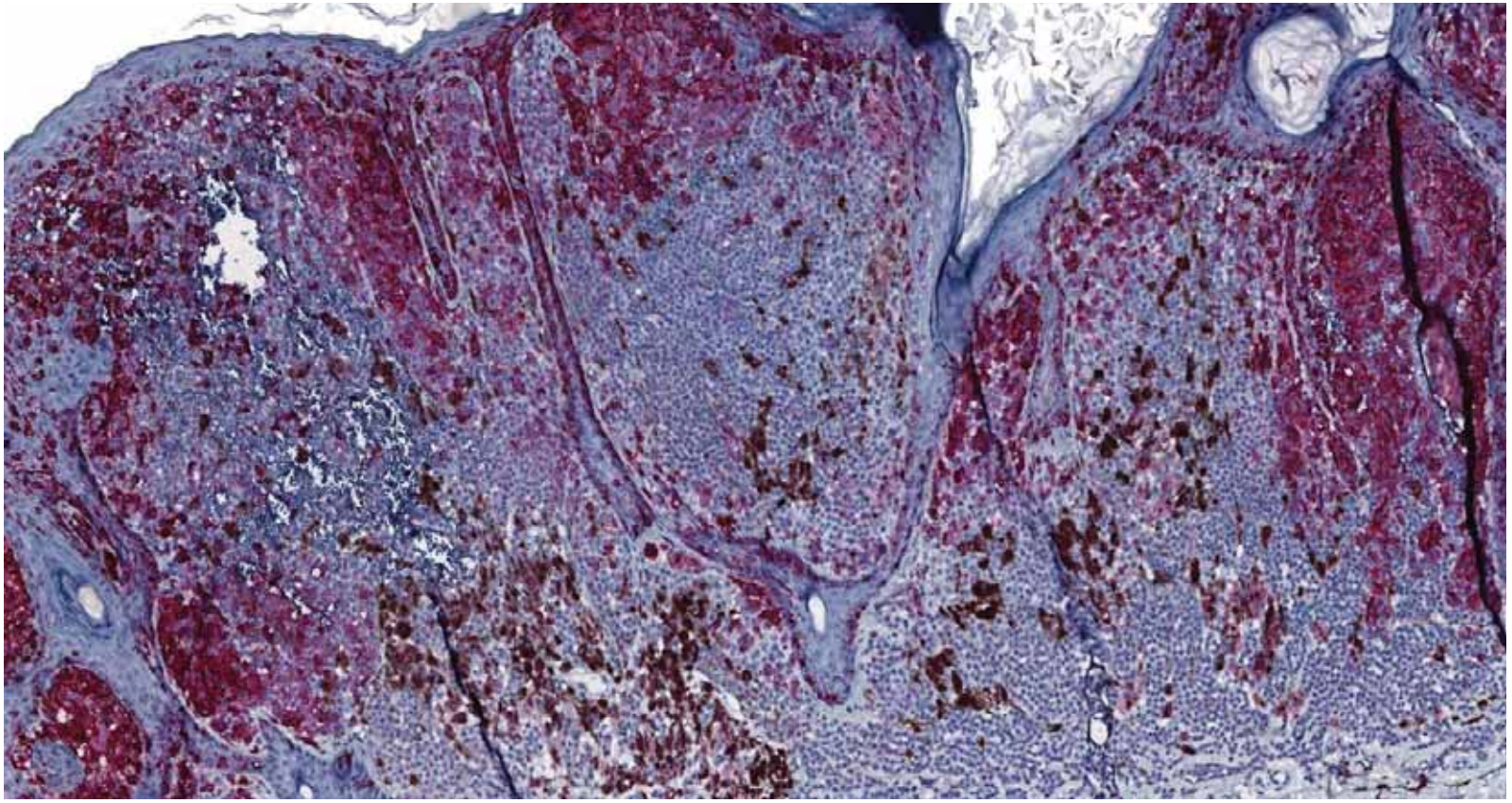
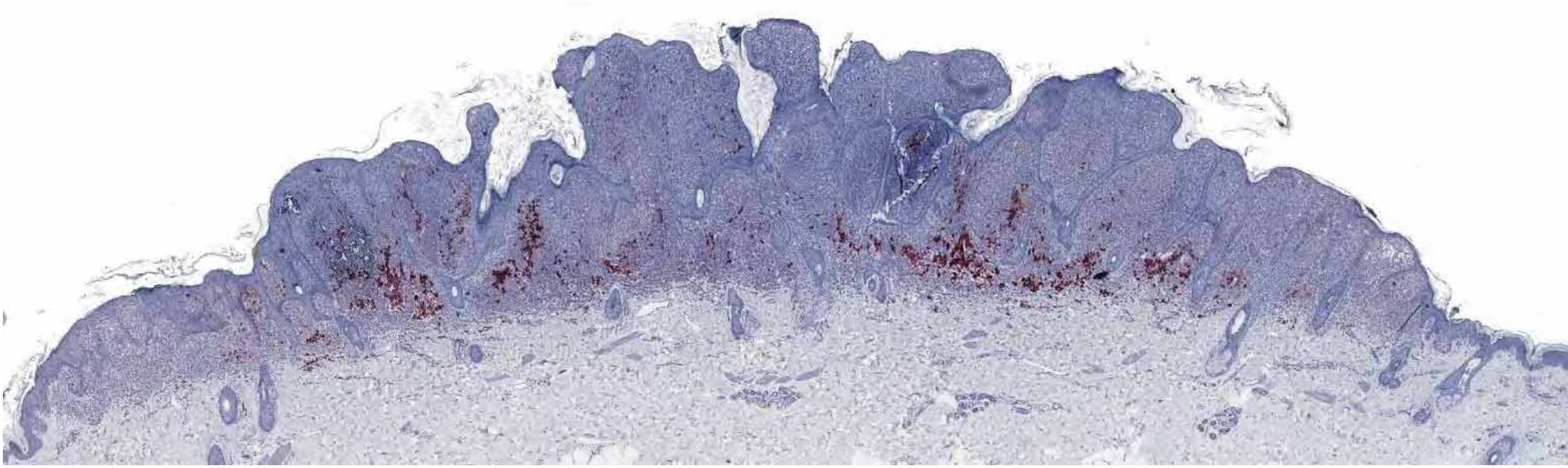
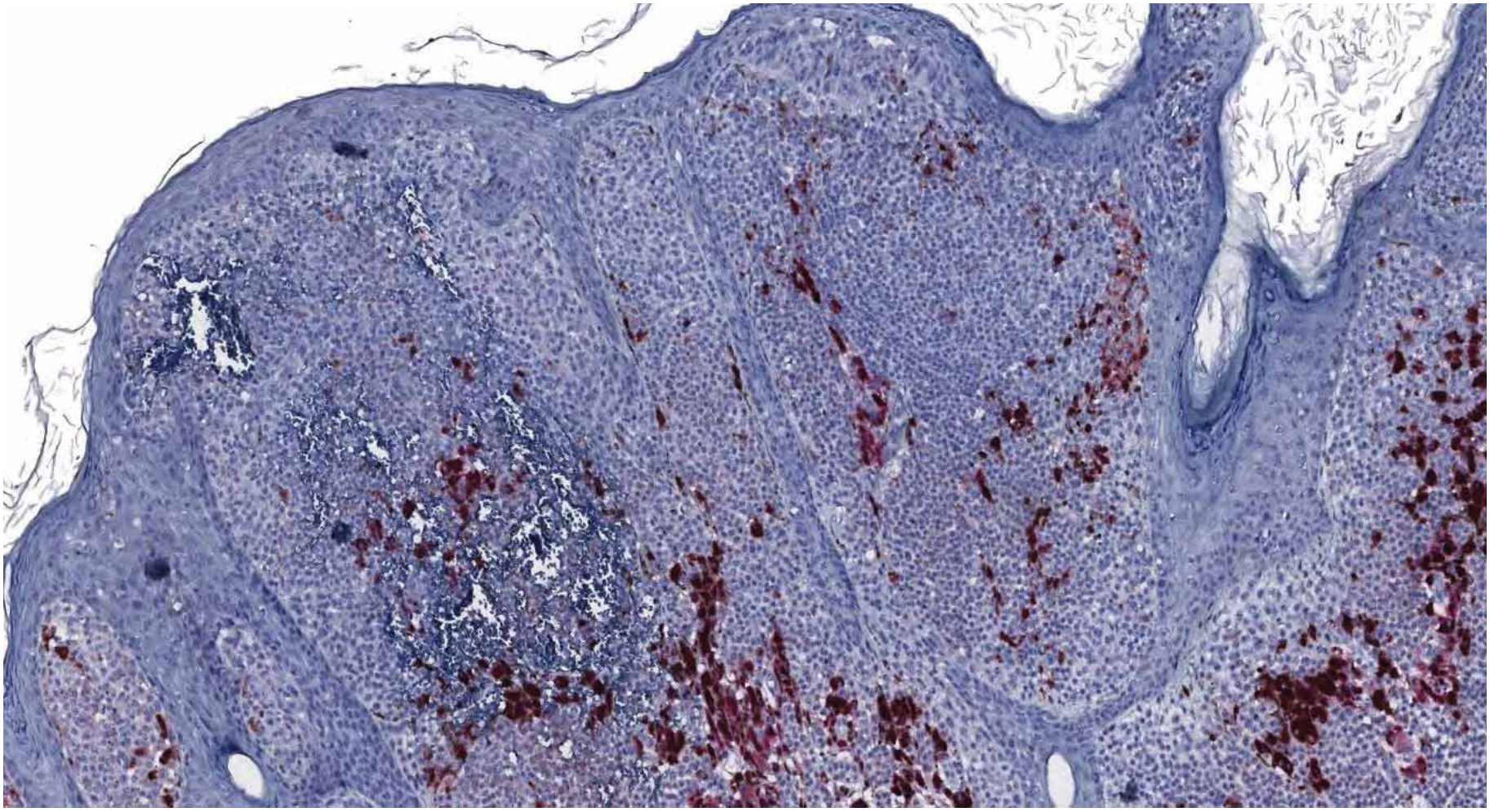


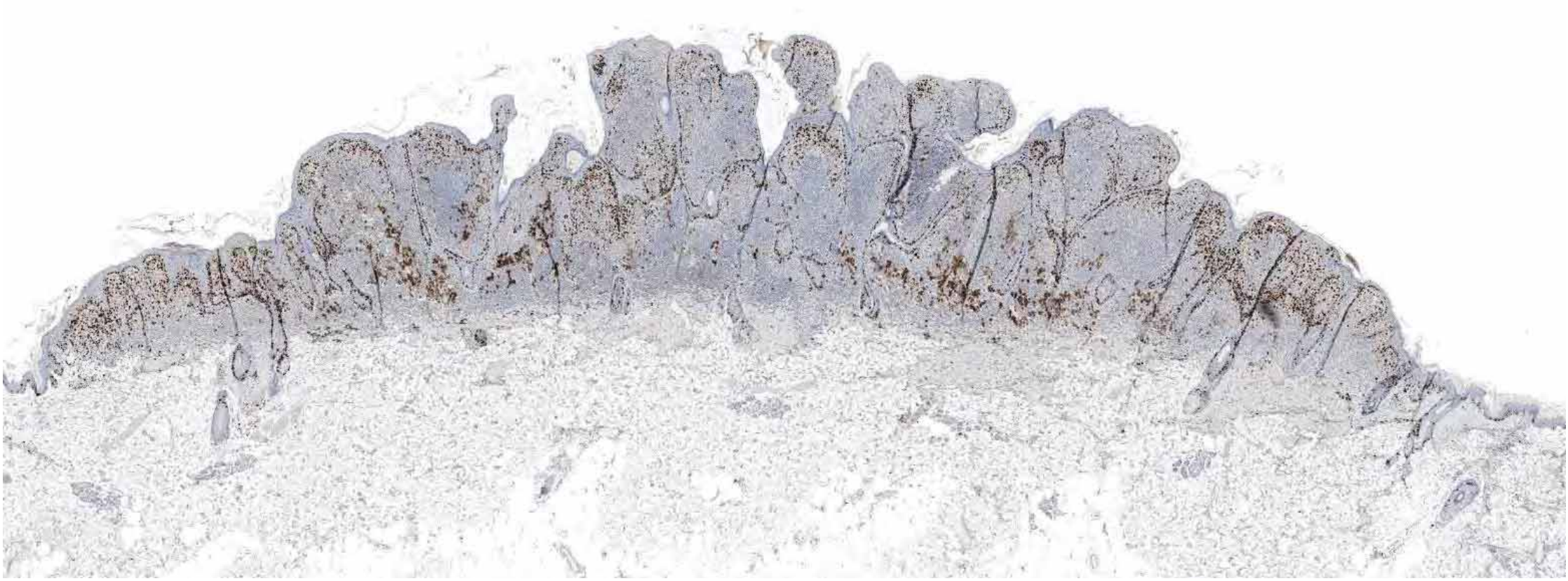
Complete loss of p16



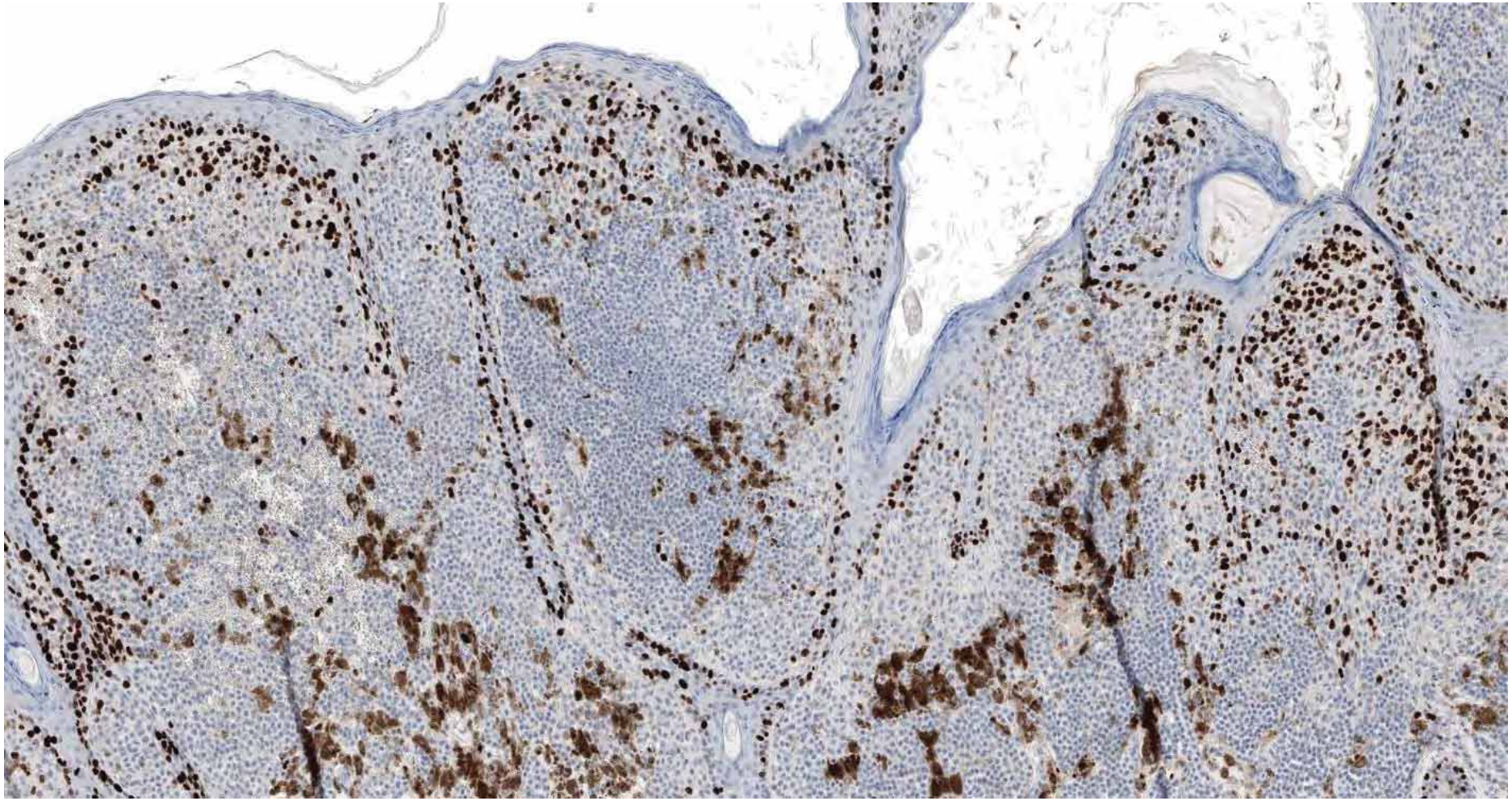
Complete loss of p16



Ki-67 top heavy gradient

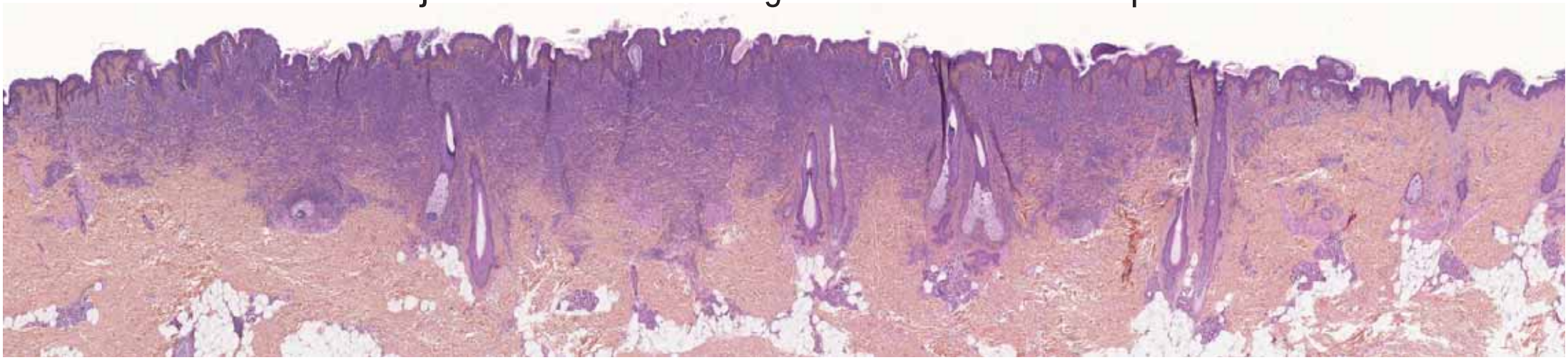


Ki-67 top heavy gradient



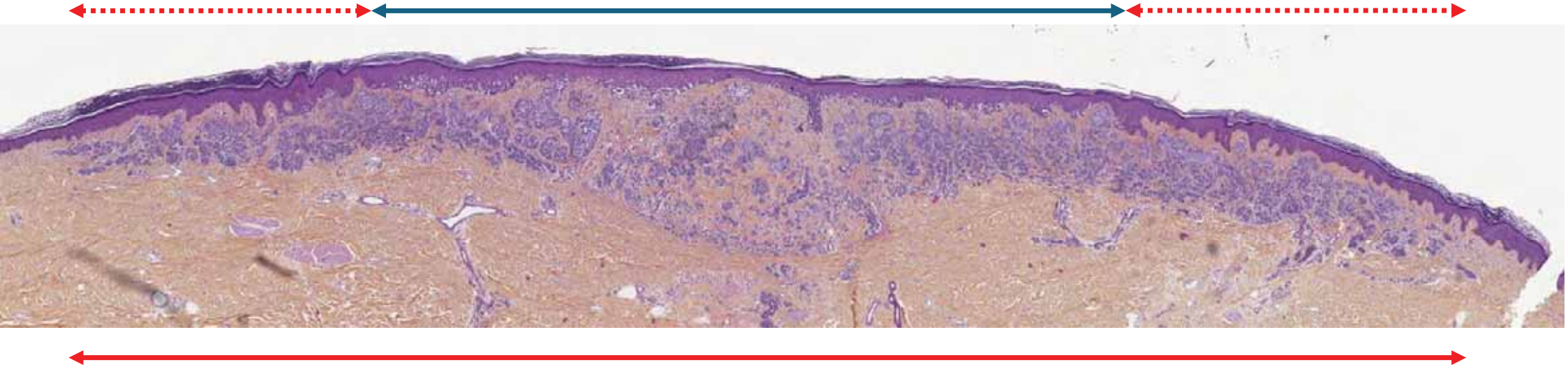
Inverted shouldering or coathanger sign

Usual junctional shouldering over the dermal component



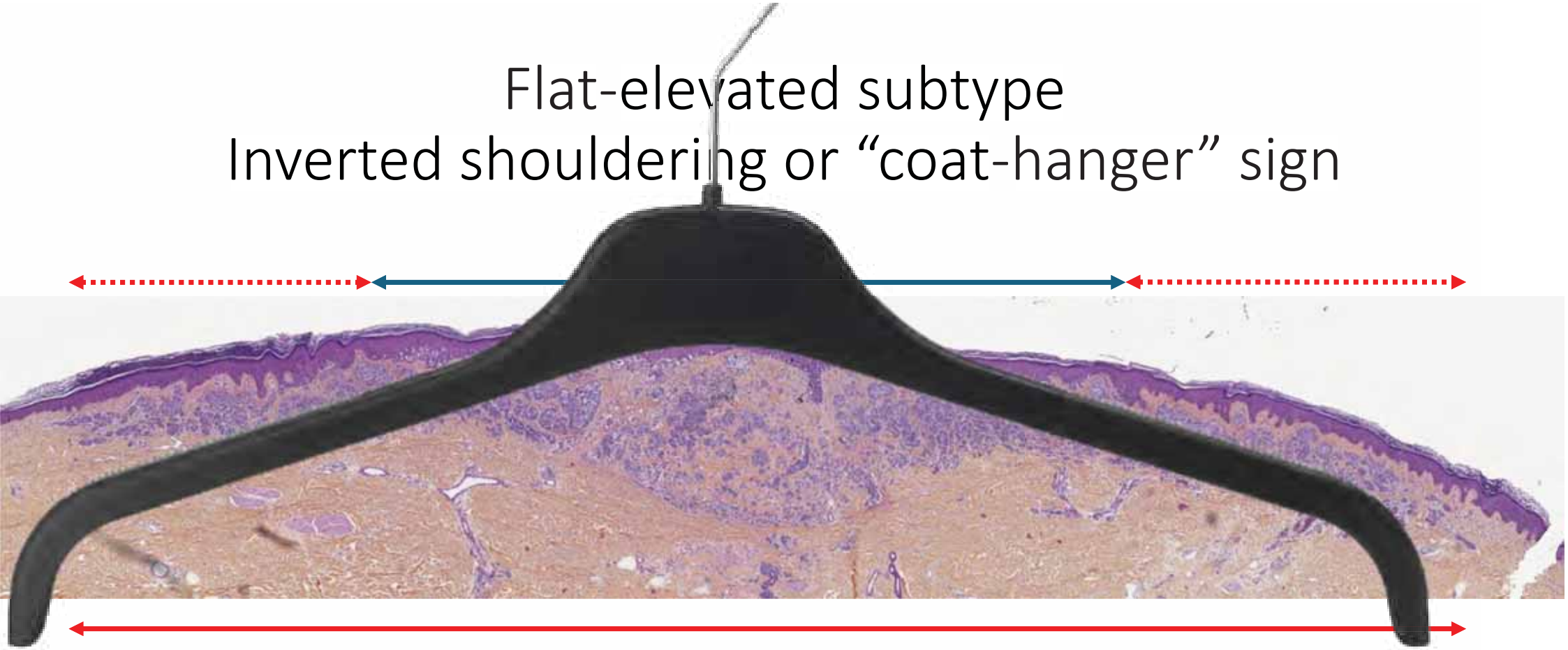
Small *BRAF*-mutated congenital-like nevus

Flat-elevated subtype
Inverted shouldering or “coat-hanger” sign



Occasionally, superficial dermal horizontal band is much longer than junctional lesion

Flat-elevated subtype
Inverted shouldering or “coat-hanger” sign



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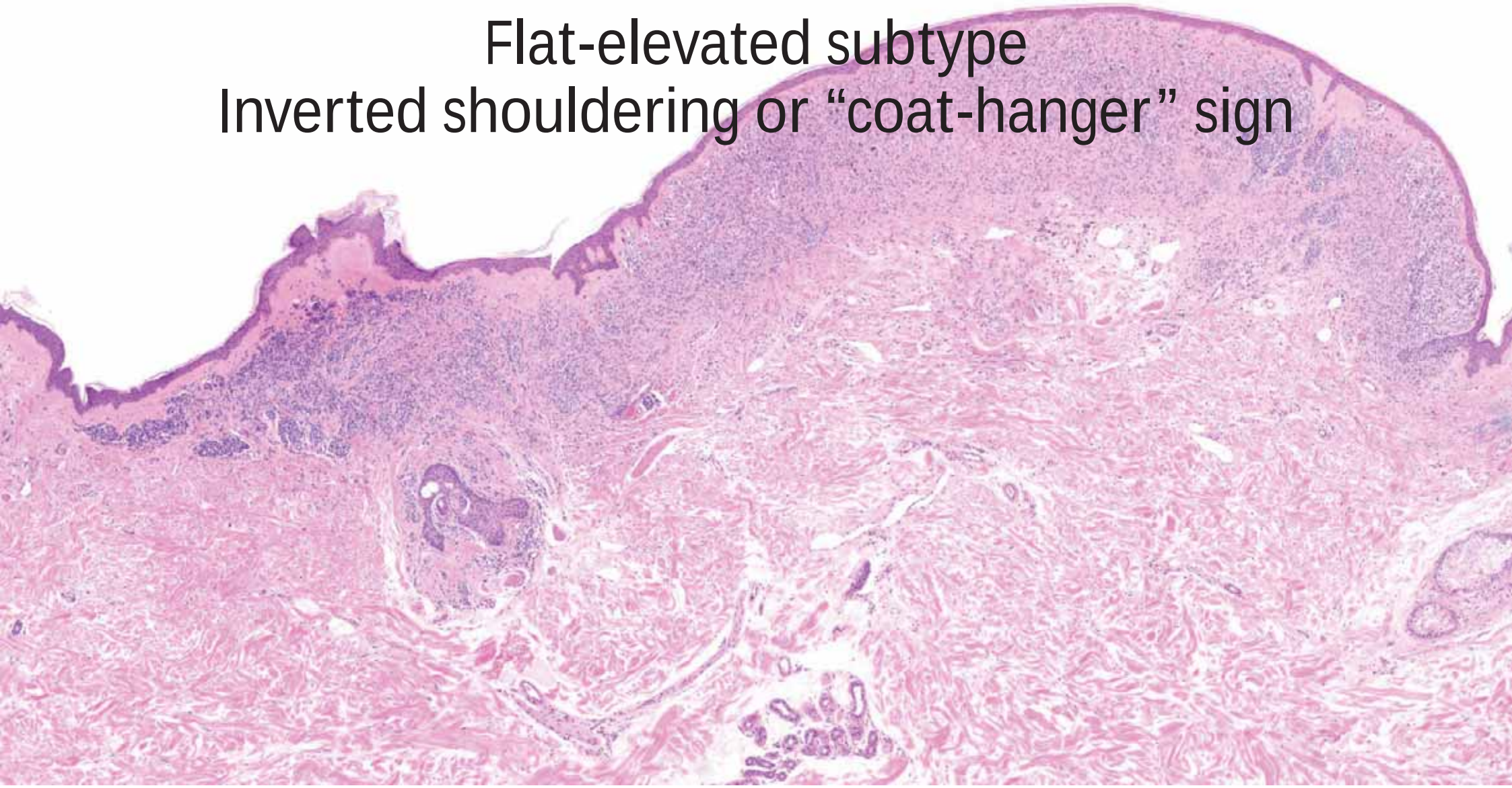
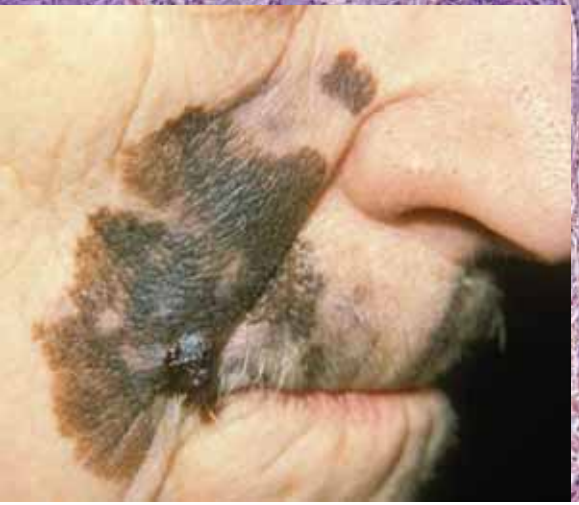
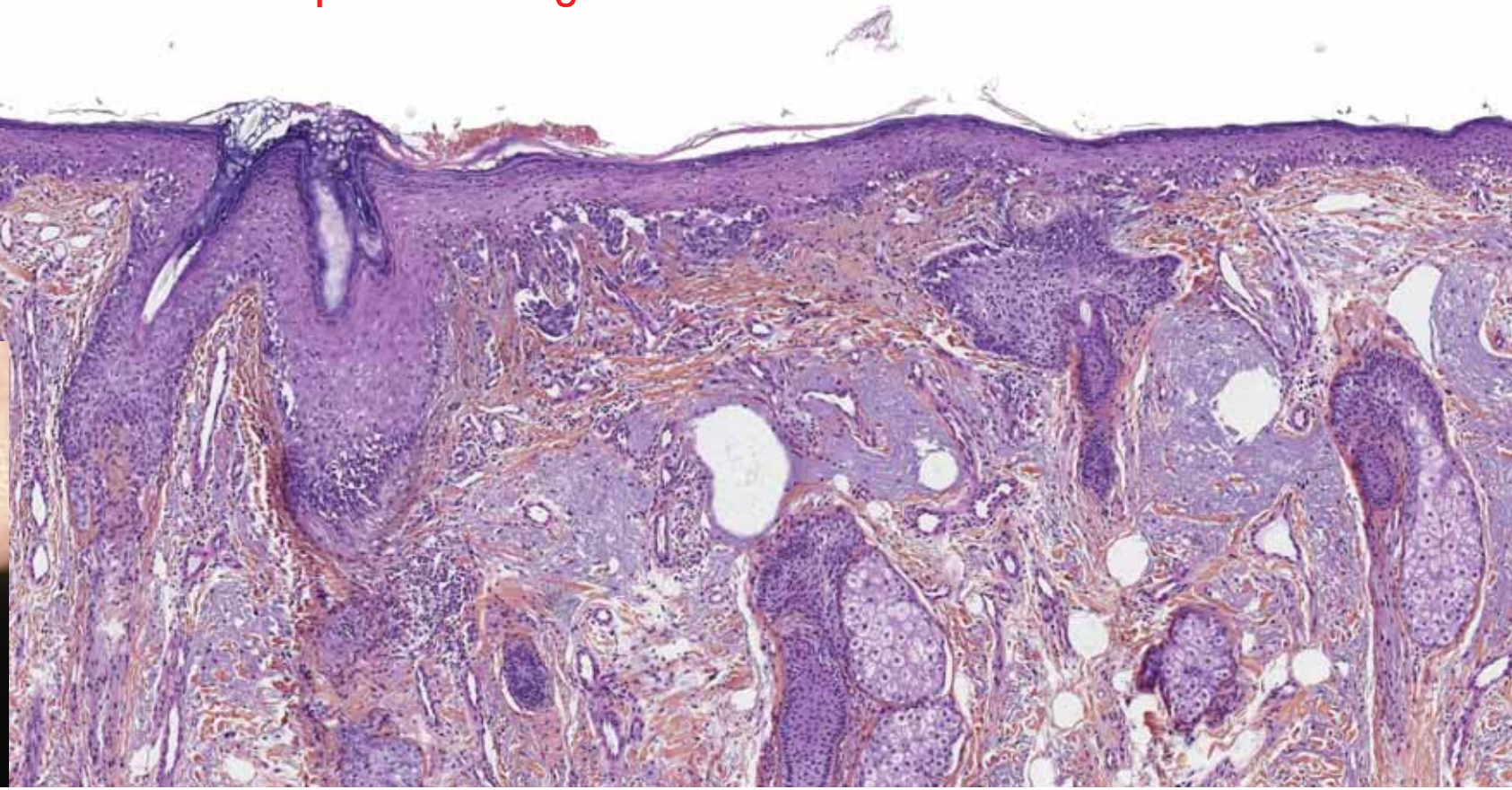


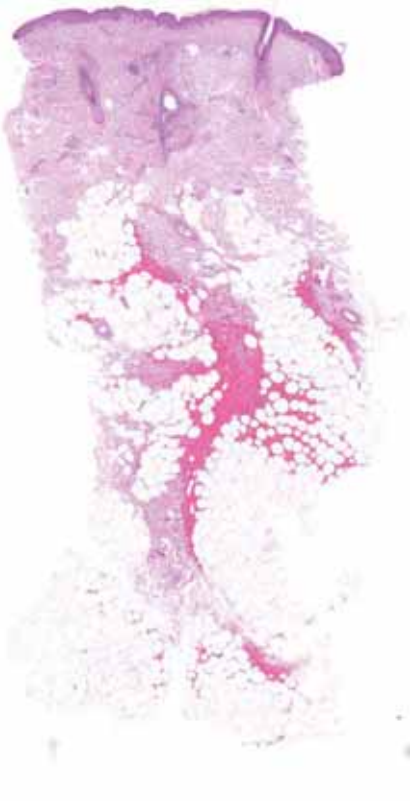
Chronic sun damage melanoma (TMB high)
Class II: Lentigo Maligna Melanoma (LMM)

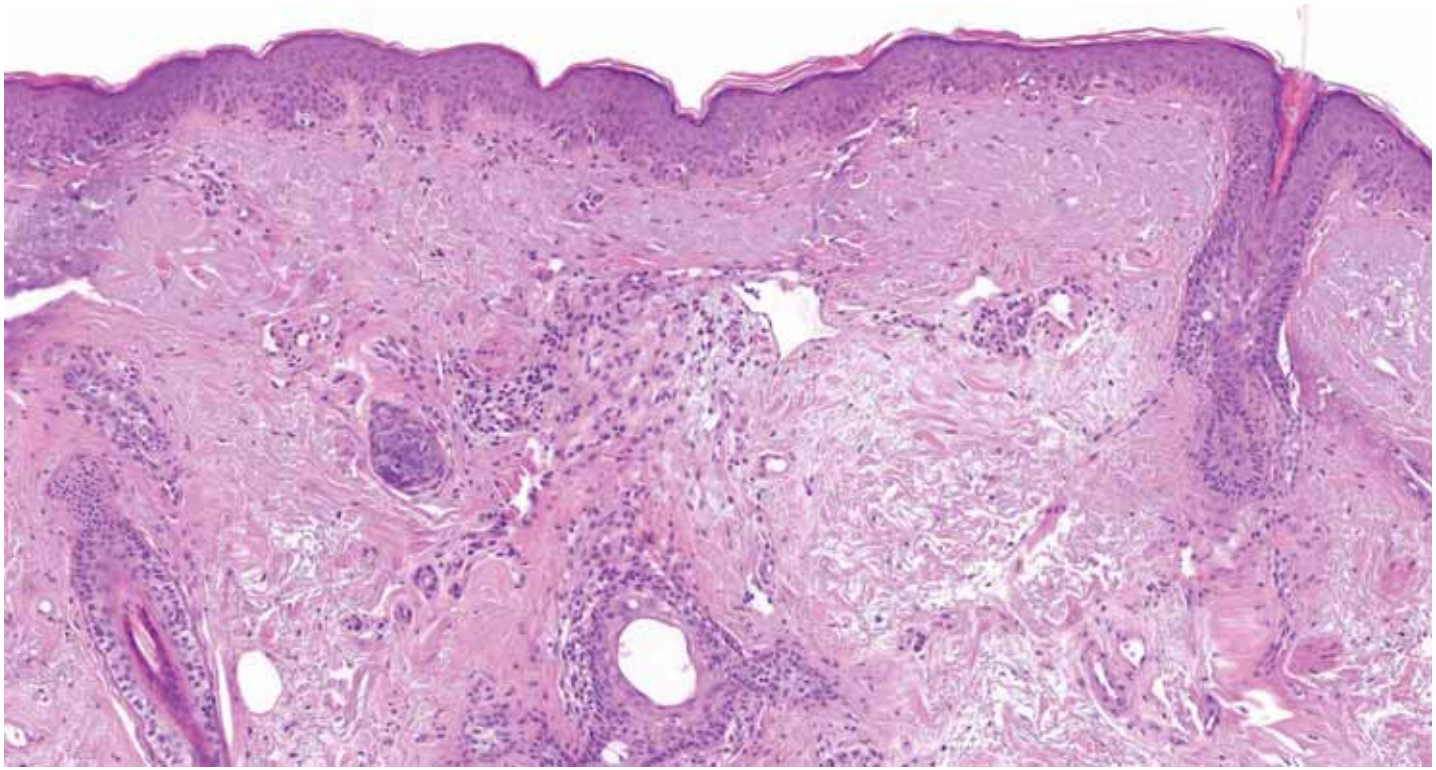
No pre-existing nevus



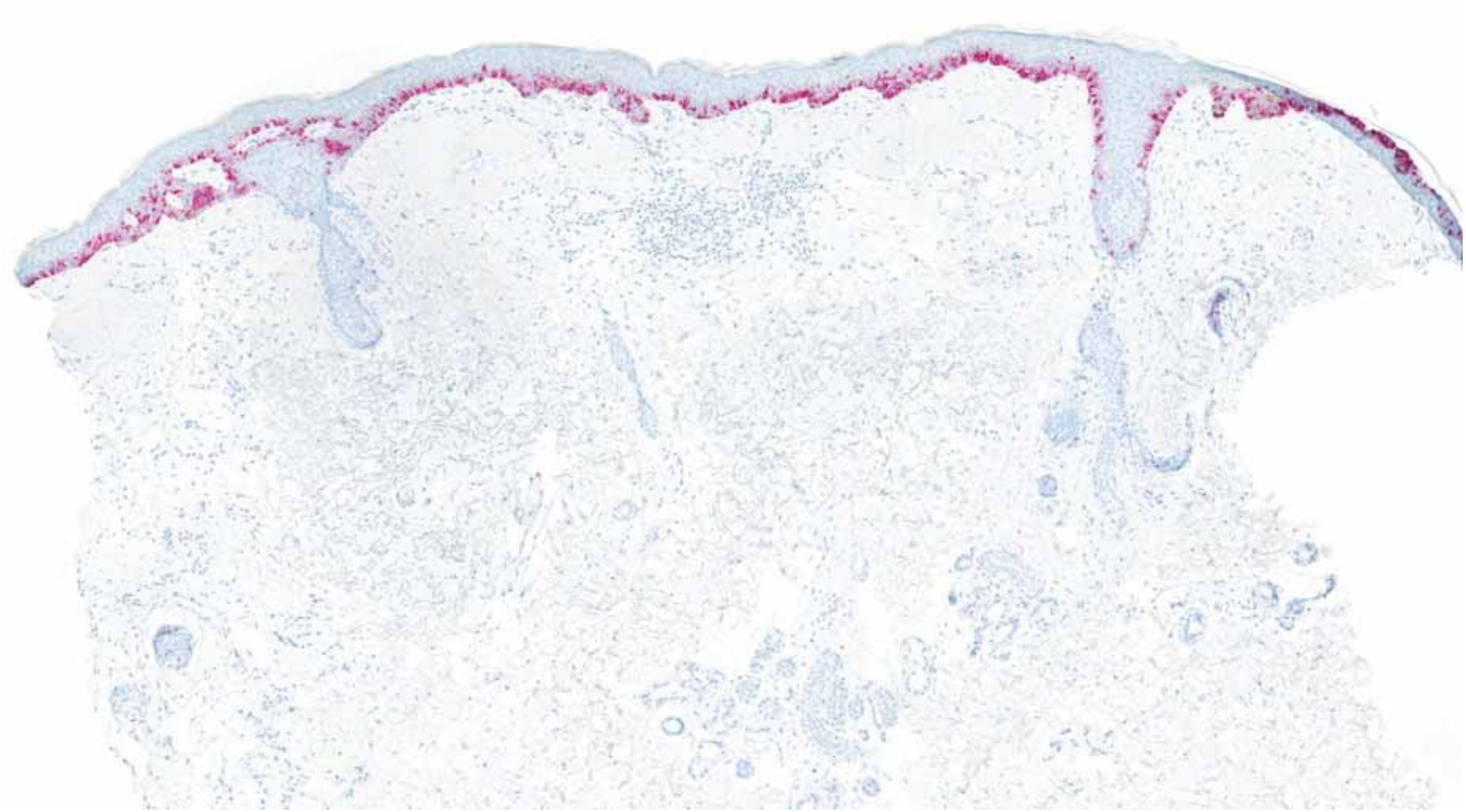


Clues in Class II (LM *in situ*)
MelanA/SOX10/PRAME > HE

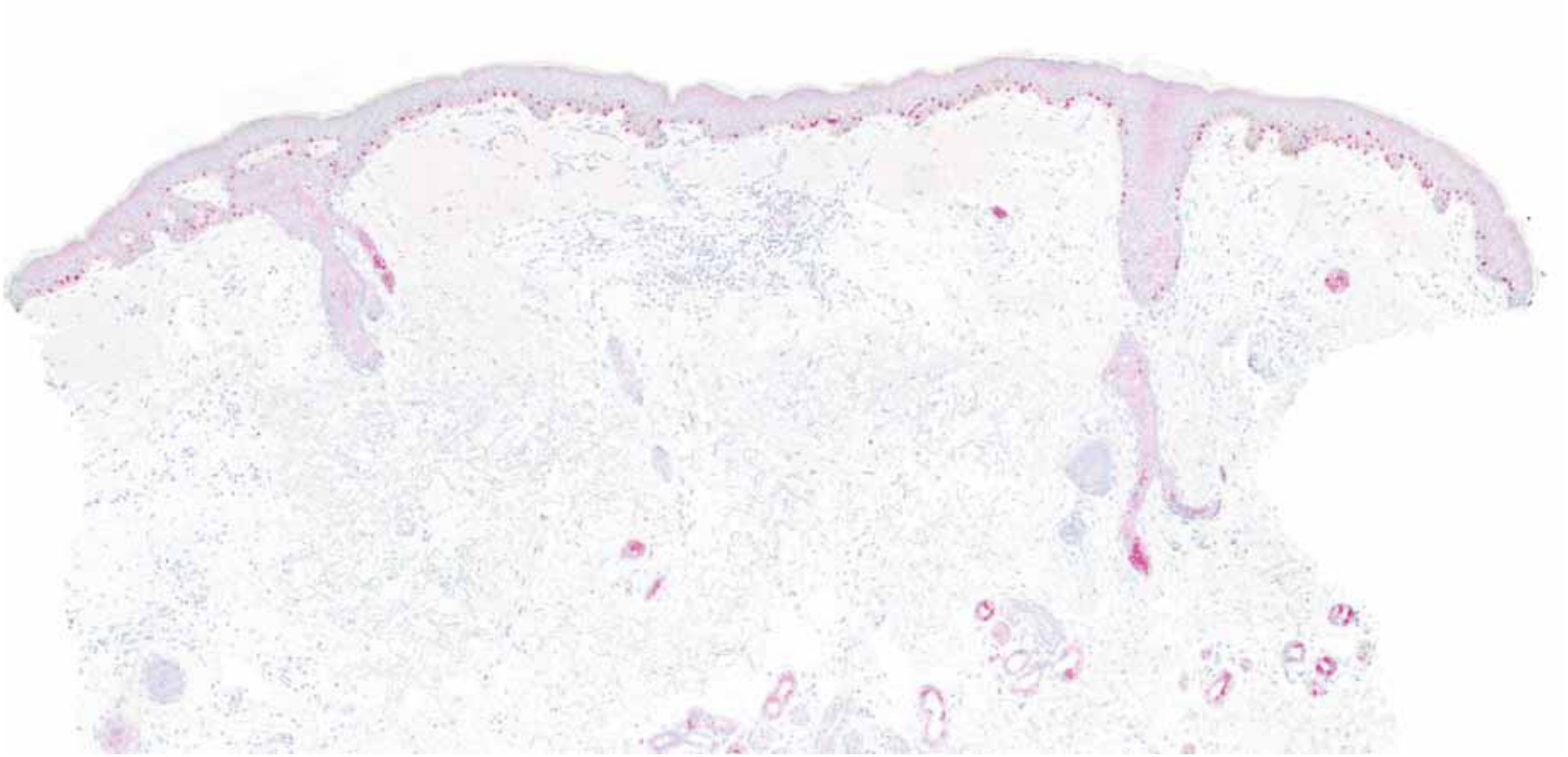




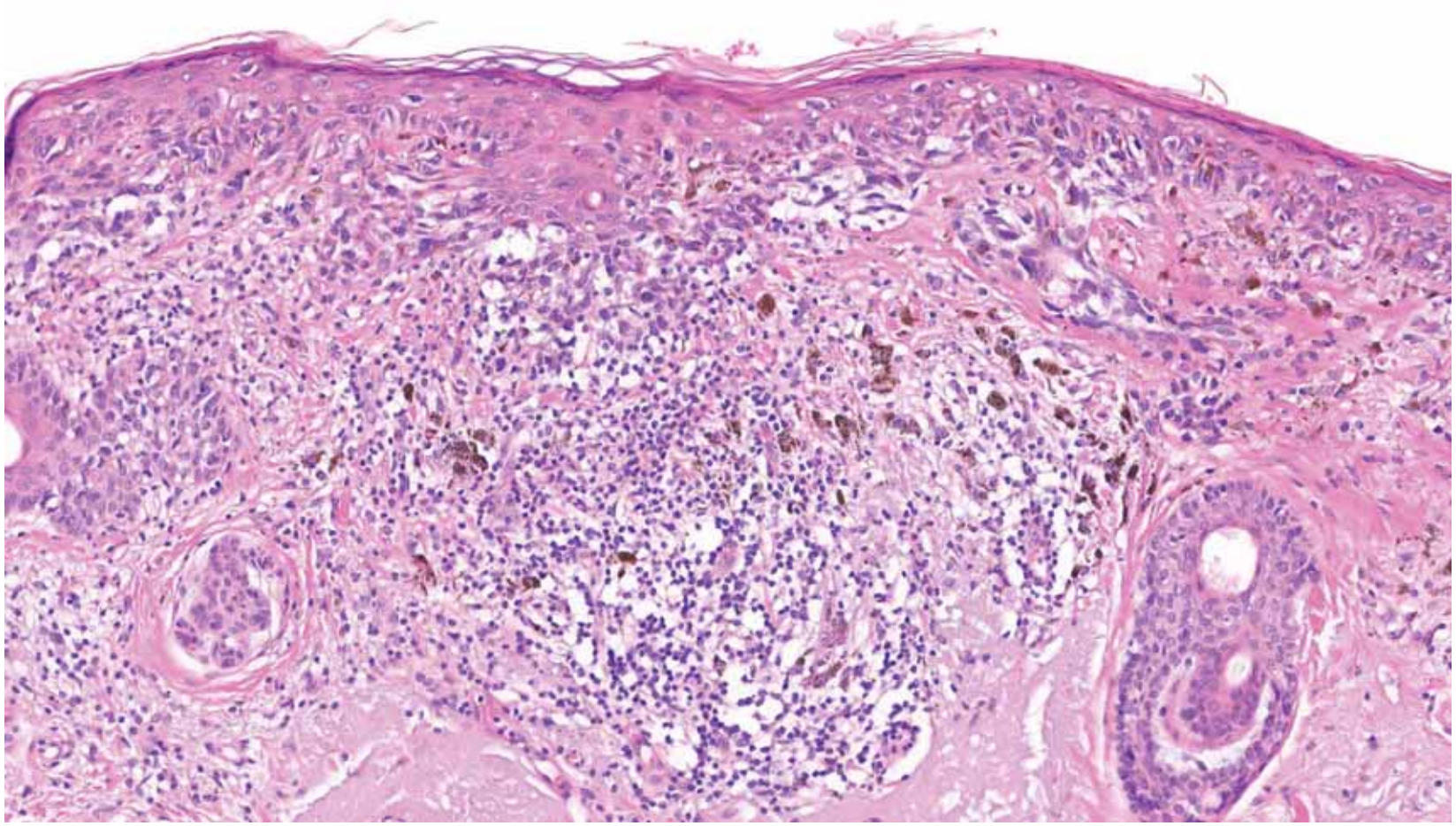
Clues in Class II (LM)
MelanA/SOX10/PRAME > HE



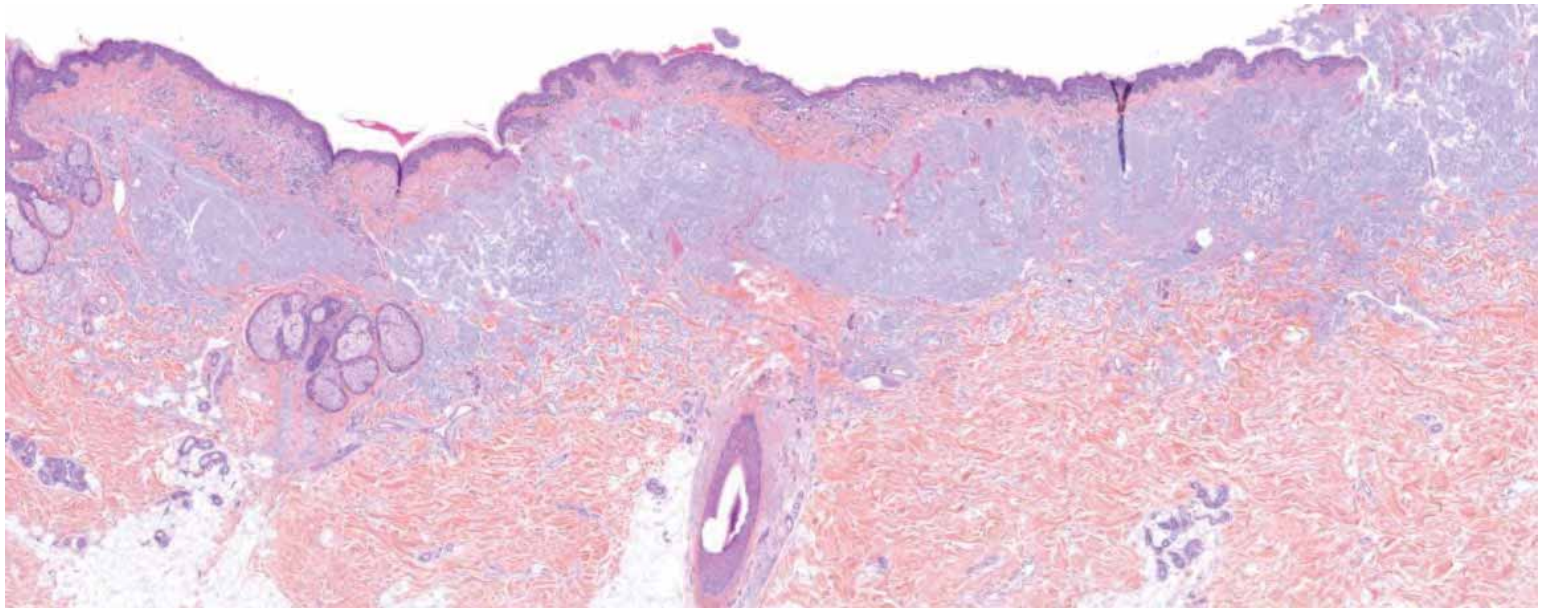
Clues in Class II (LM)
MelanA/SOX10/PRAME > HE



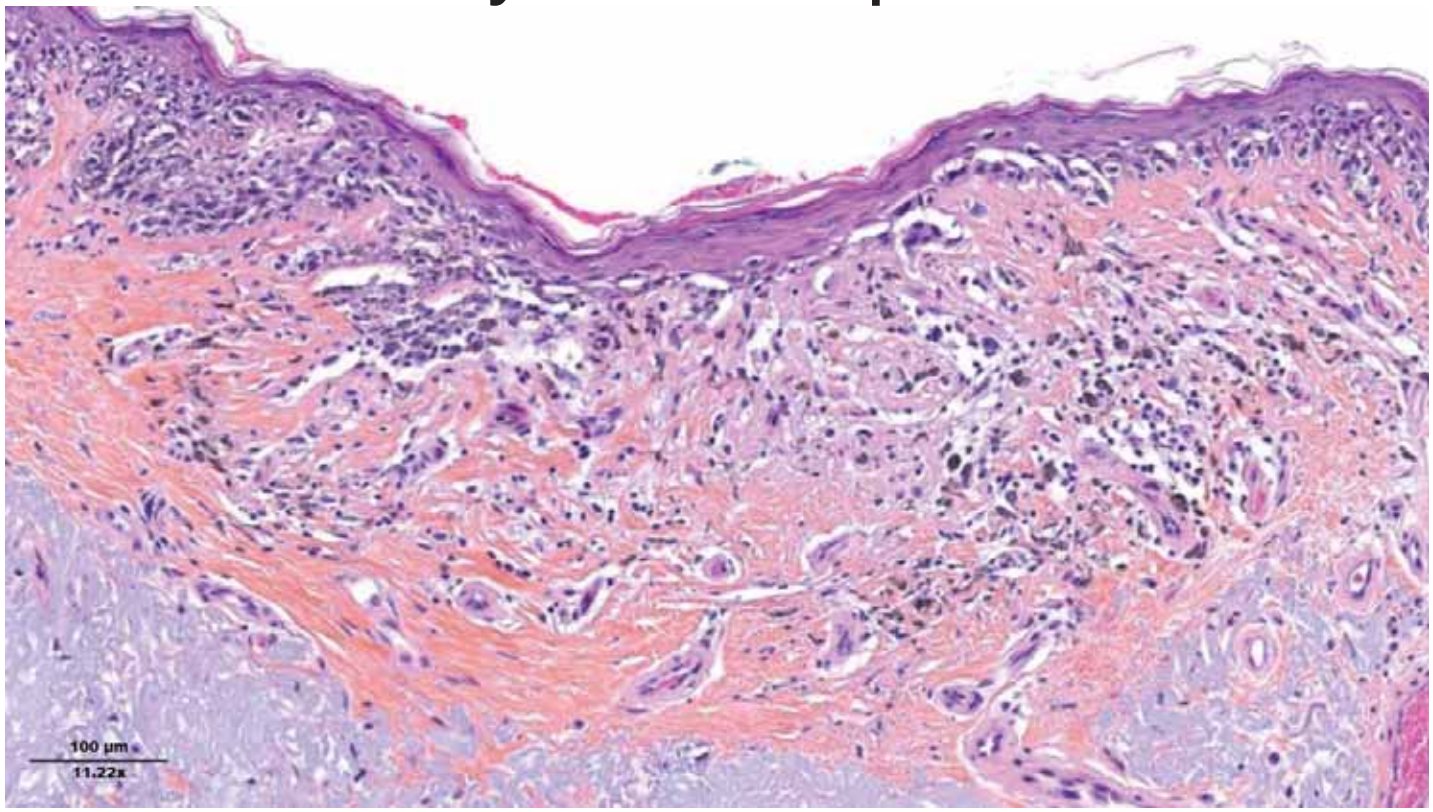
Clues in Class II (LMM)
Junctional nesting underscored by lymphocytes = early invasive phase



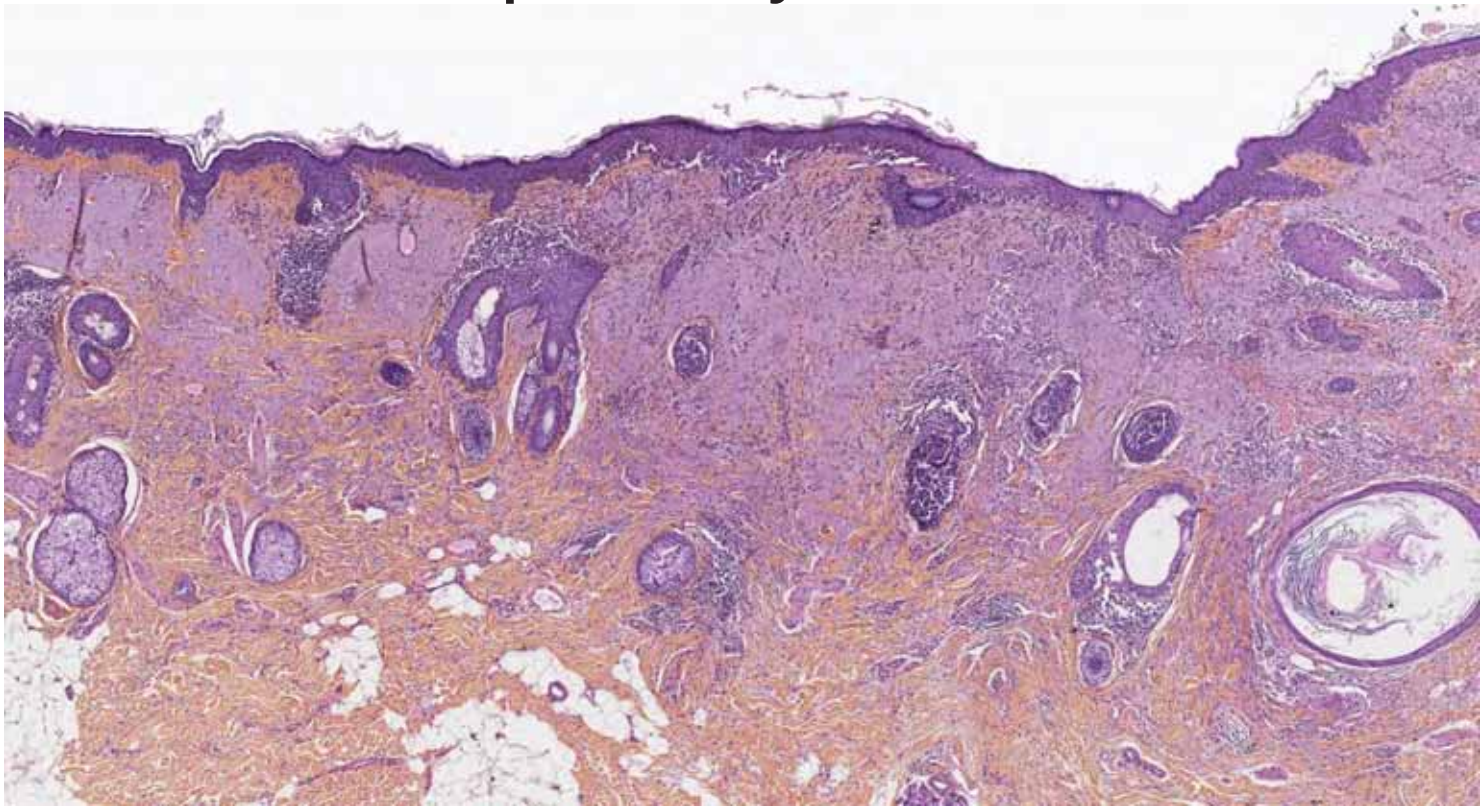
Clues in Class II (LMM)
Inflammation pushing down elastosis= early invasive phase



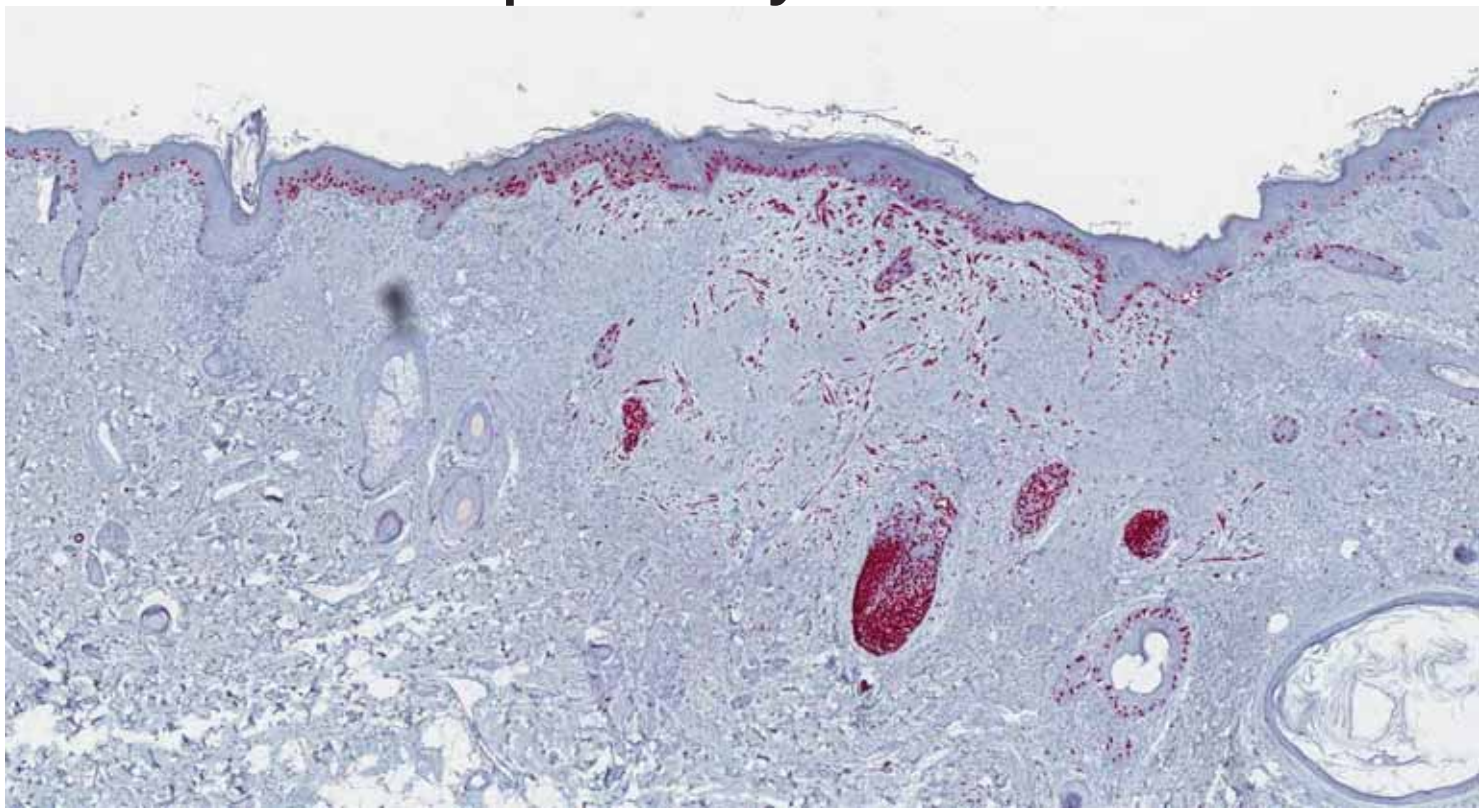
Clues in Class II (LMM)
Inflammation pushing down elastosis= early invasive phase



Clues in Class II (LMM)
Ruling out early desmoplastic invasive component must be put on your check-list



Clues in Class II (LMM)
Ruling out early desmoplastic invasive component must be put on your check-list

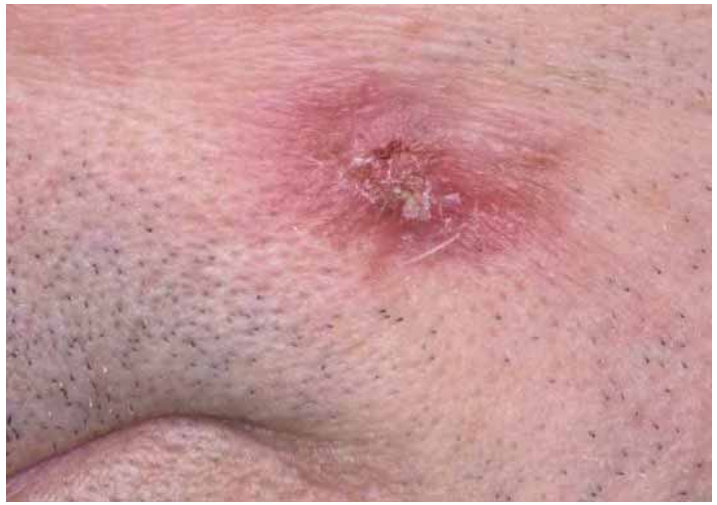


Sox10 IHC

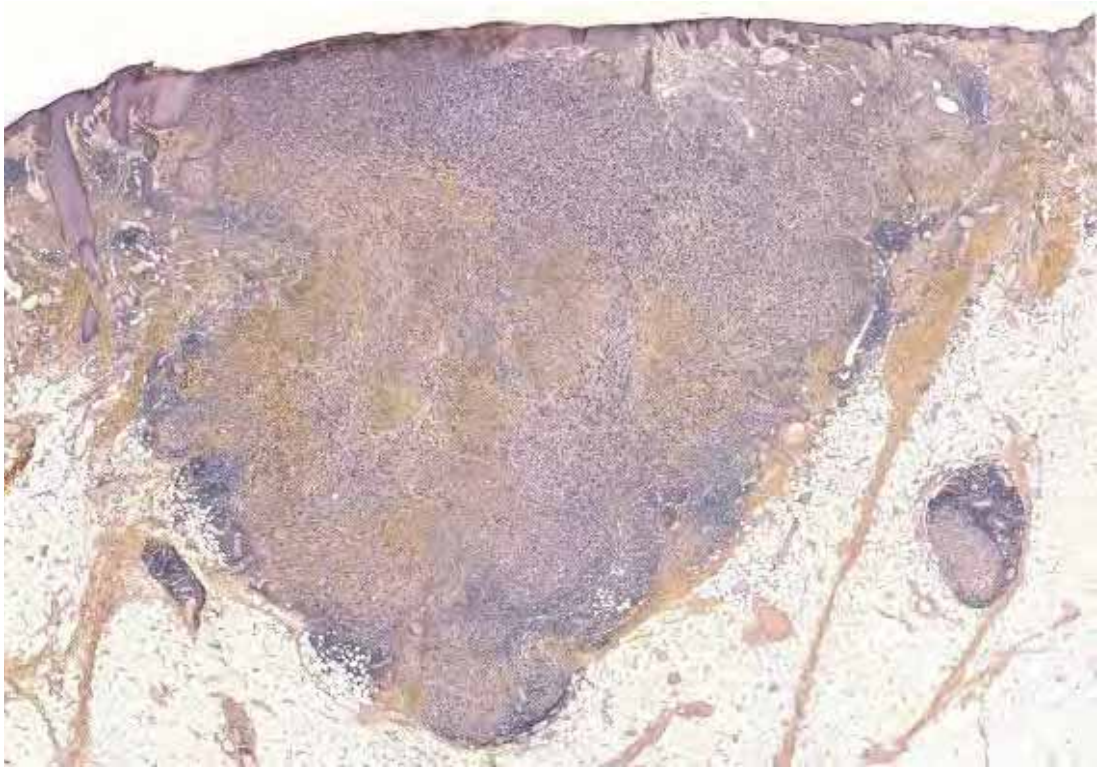
Chronic sun damage melanoma (TMB high)
Class II: Lentigo Maligna Melanoma (LMM)

- No nevus
- More melanA/sox than HE
- Nesting before invasion
- Search for Desmoplatic Melanoma

Chronic sun damage melanoma (TMB high)
Class III: Desmoplastic Melanoma

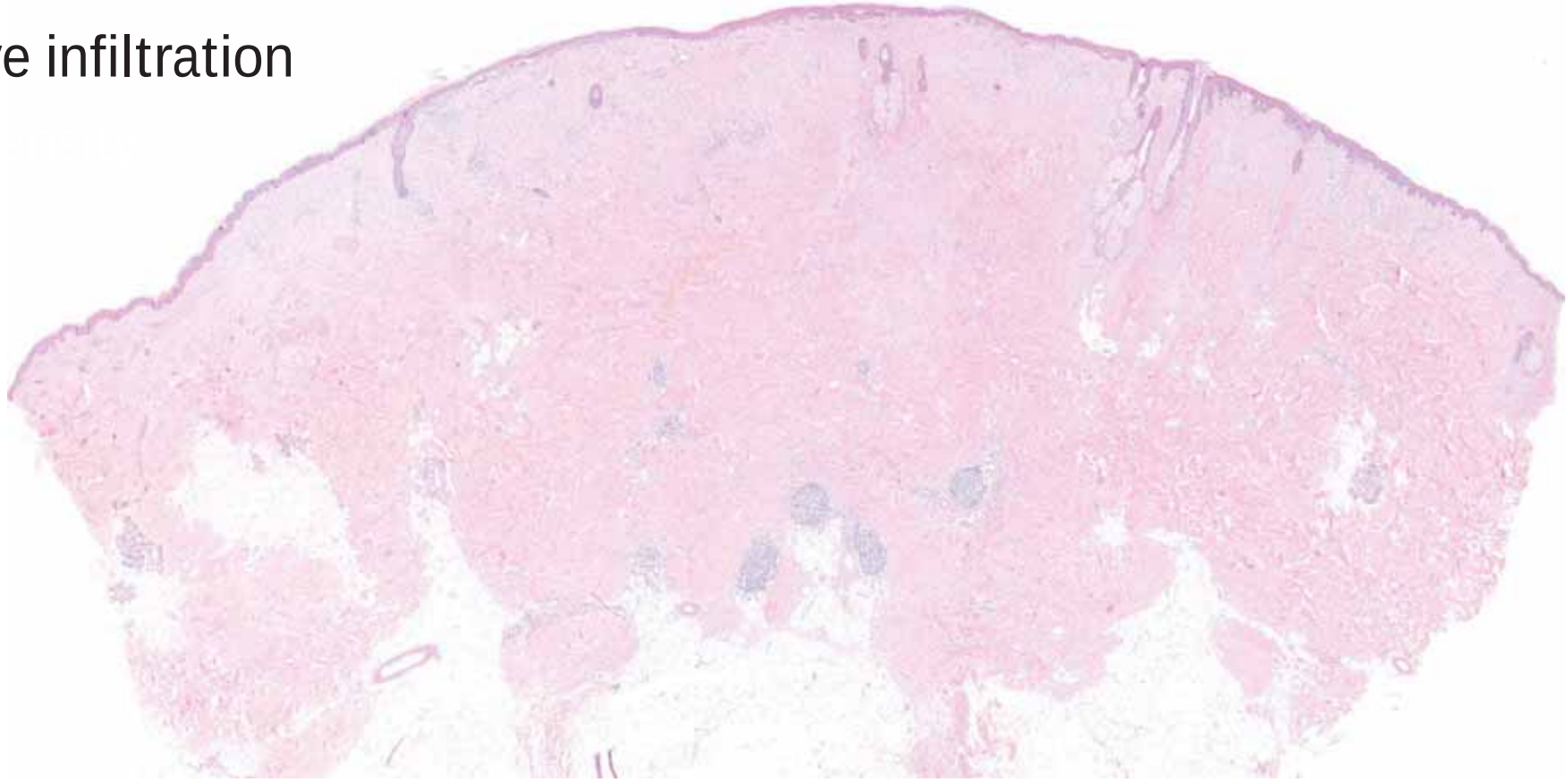


Unpigmented
No pre-existing nevus
NF1 mutations>



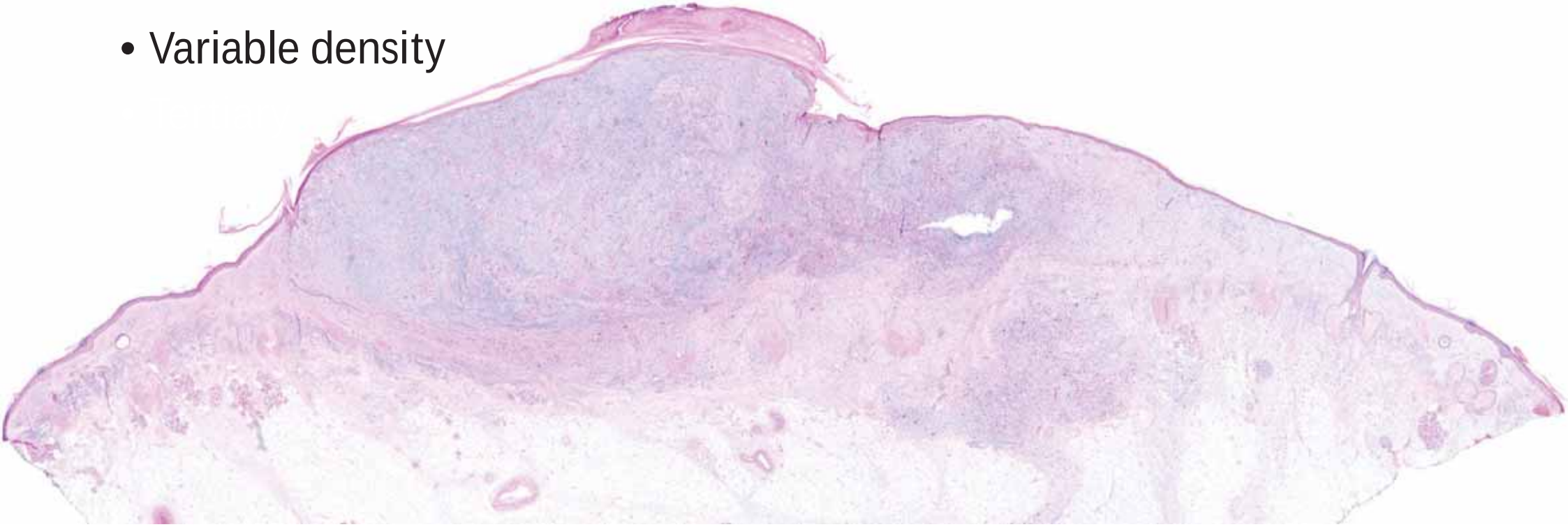
Chronic sun damage melanoma (TMB high)
Class III: Desmoplastic Melanoma

- Destructive infiltration



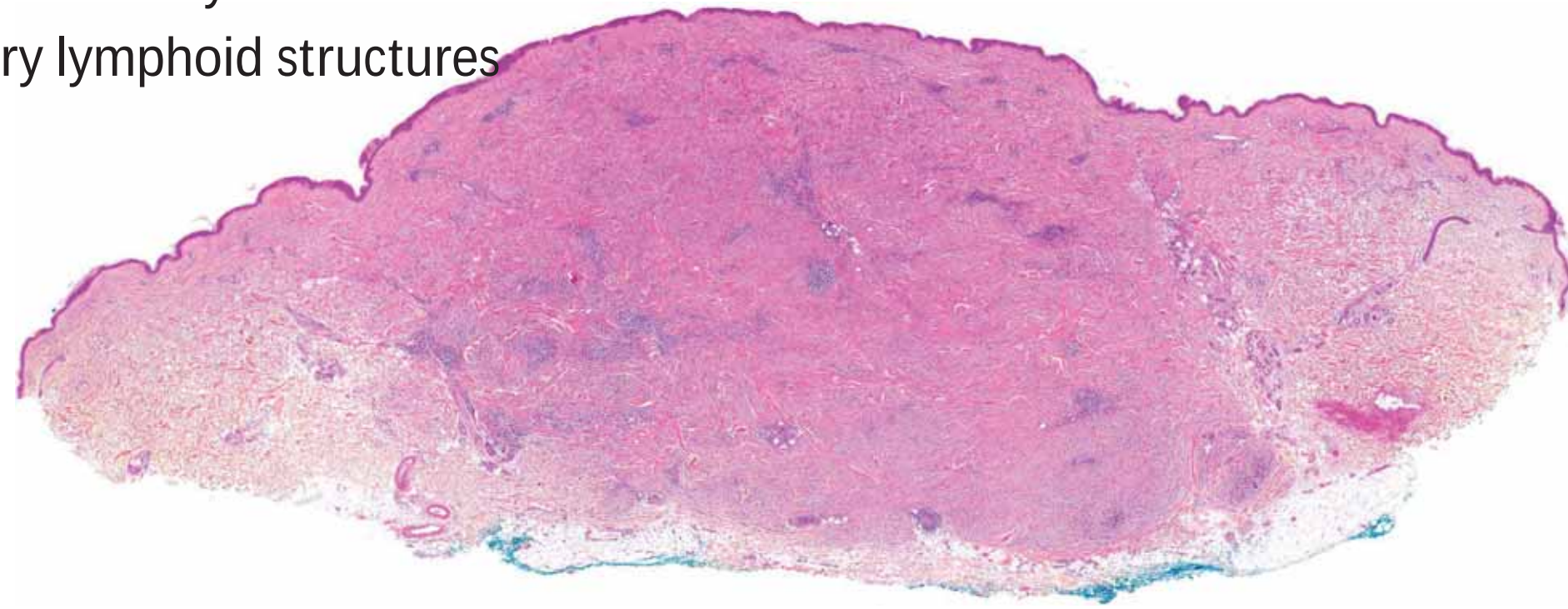
Chronic sun damage melanoma (TMB high)
Class III: Desmoplastic Melanoma

- Destructive infiltration
- Variable density



Chronic sun damage melanoma (TMB high)
Class III: Desmoplastic Melanoma

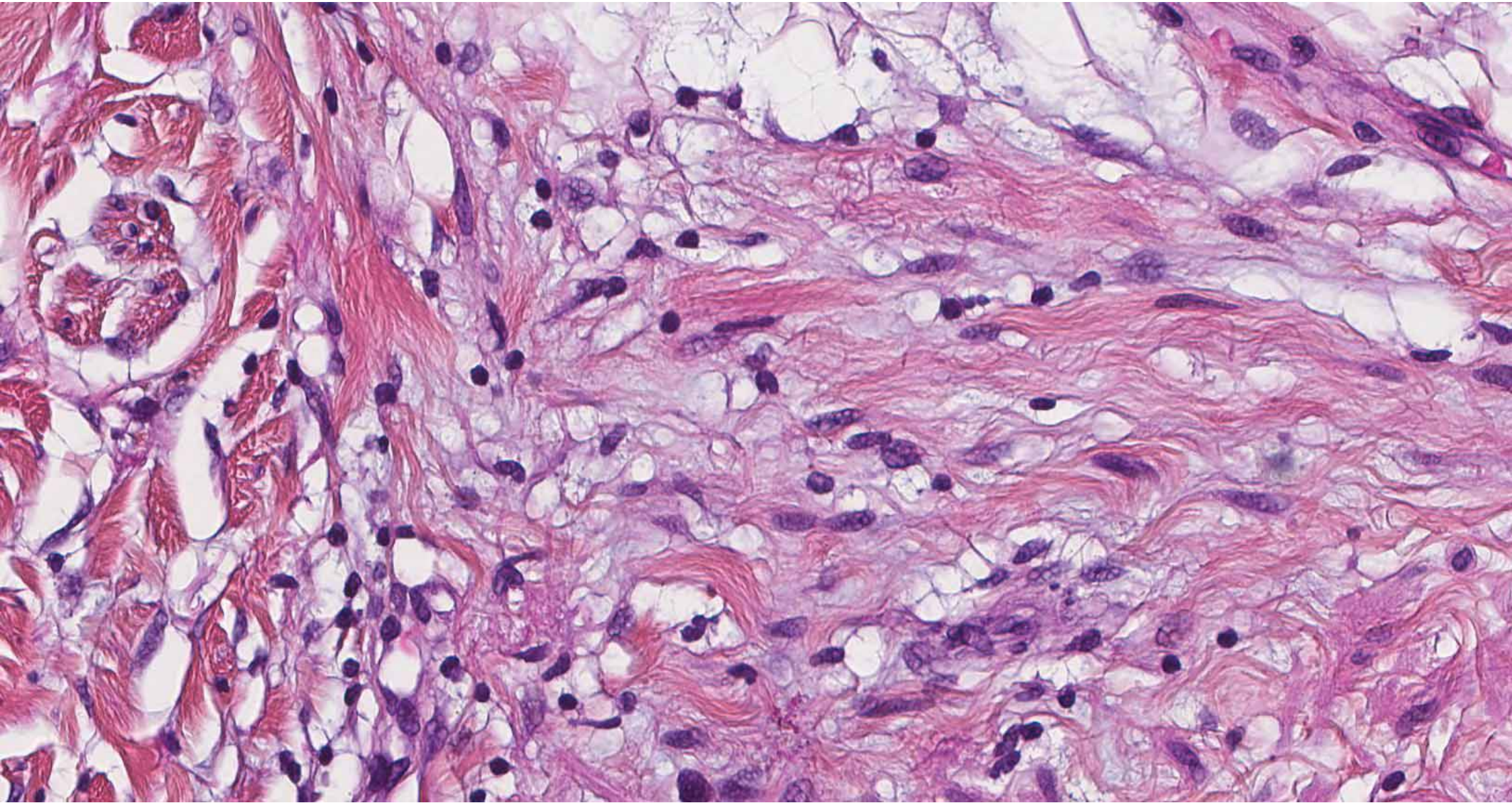
- Destructive infiltration
- Variable density
- Tertiary lymphoid structures

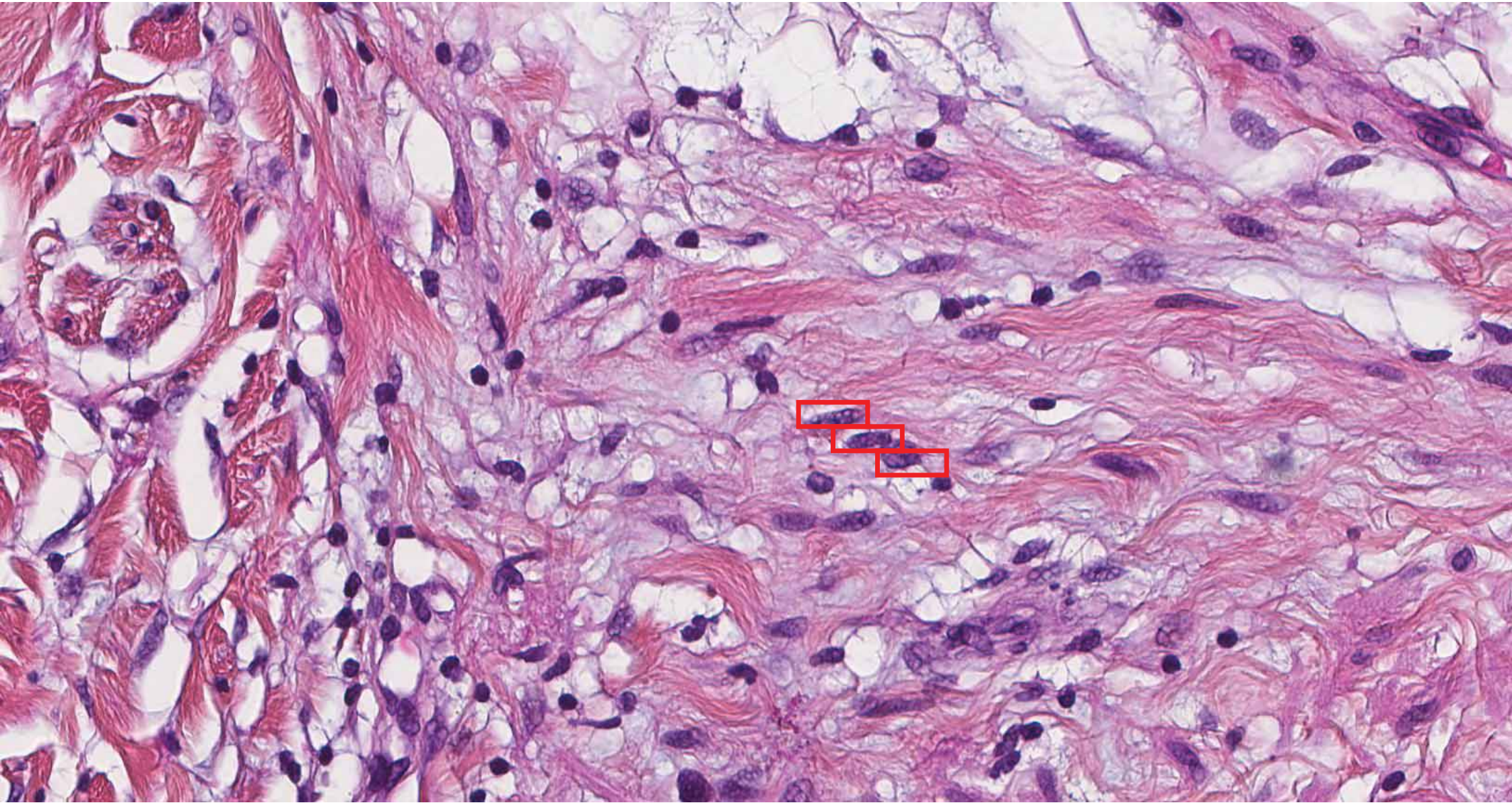


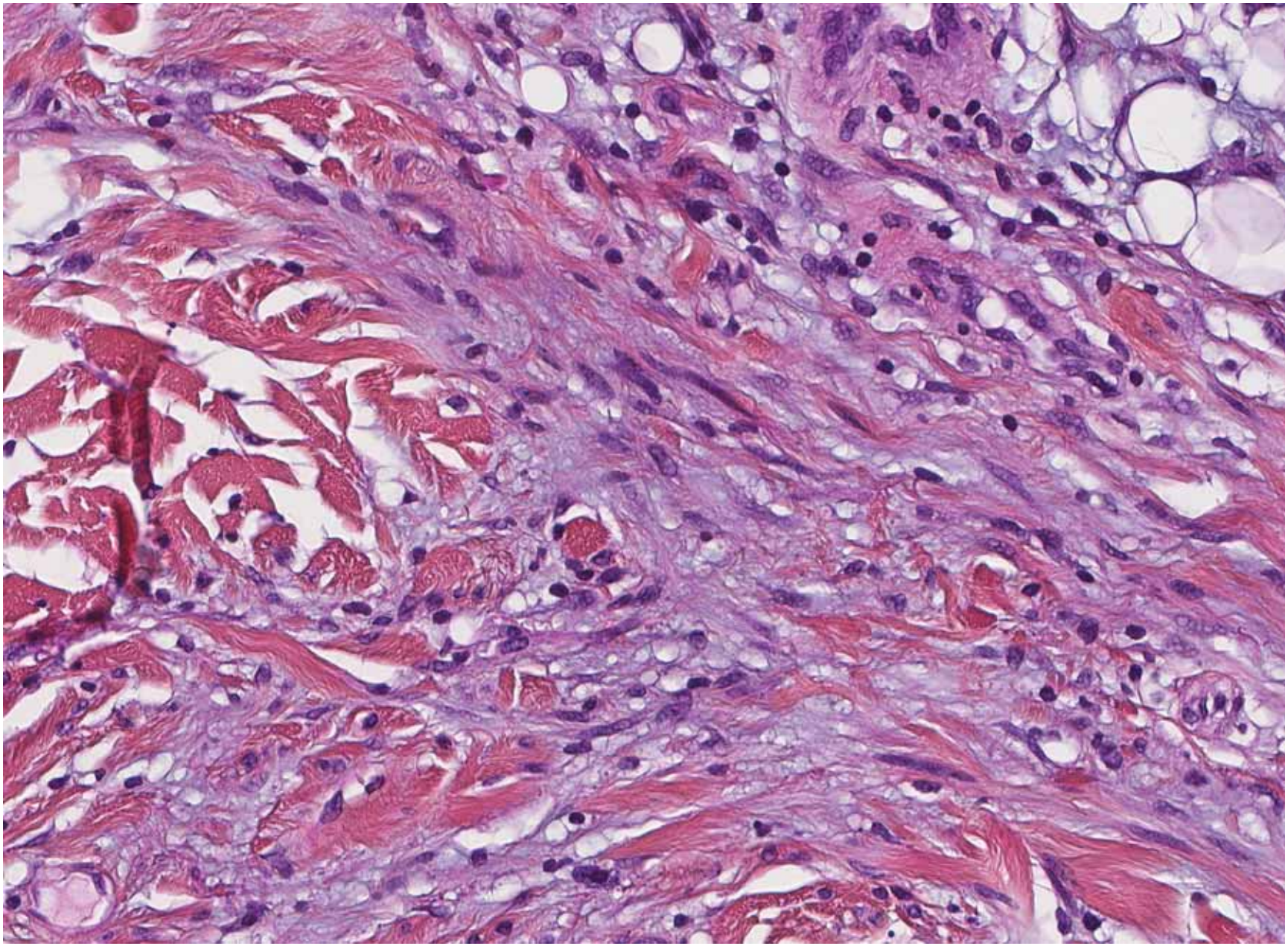
Chronic sun damage melanoma (TMB high)
Class III: Desmoplastic Melanoma

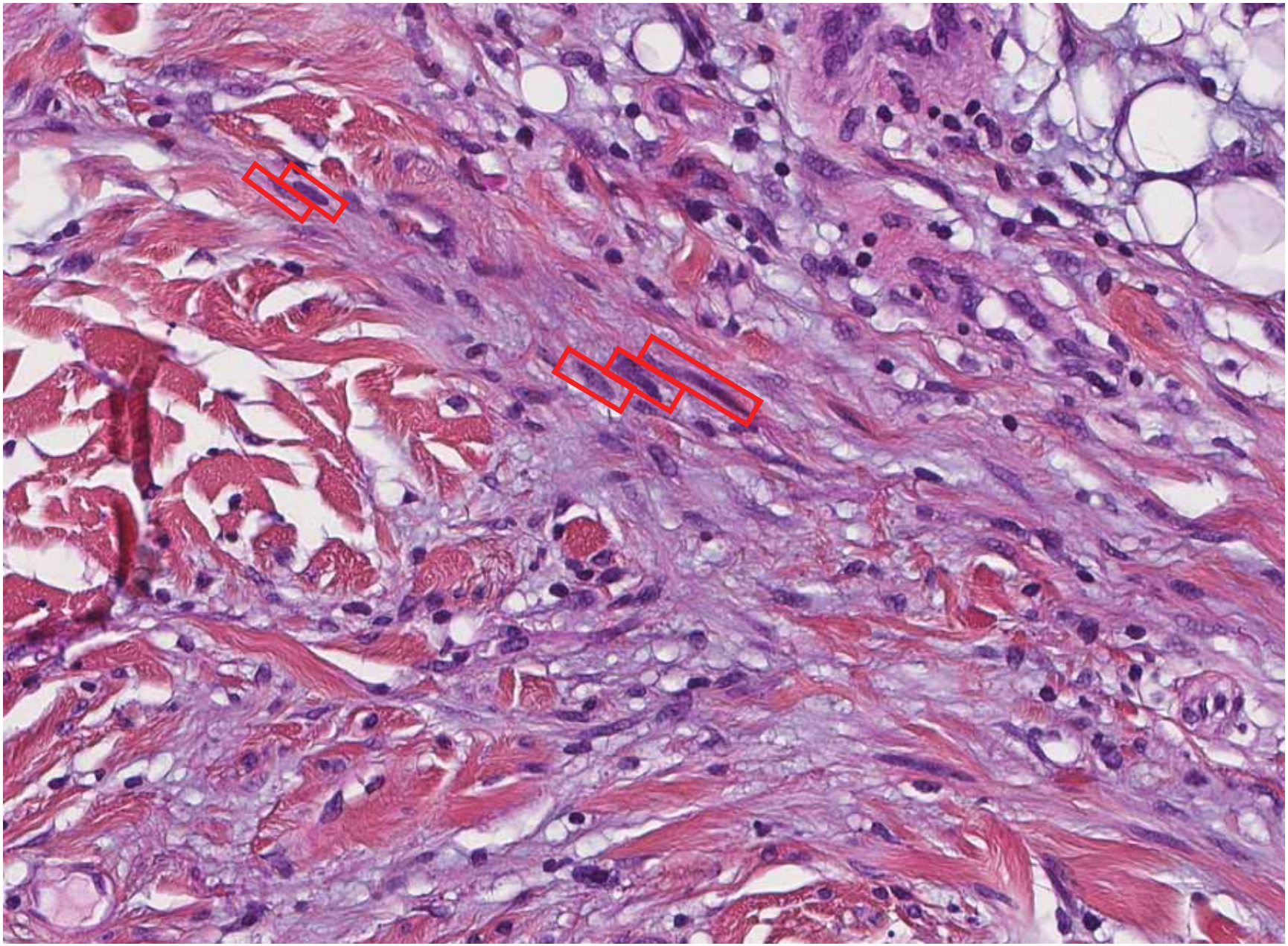
- Short stair sign
- Myxoid background
- MelanA for LM

Short stair sign

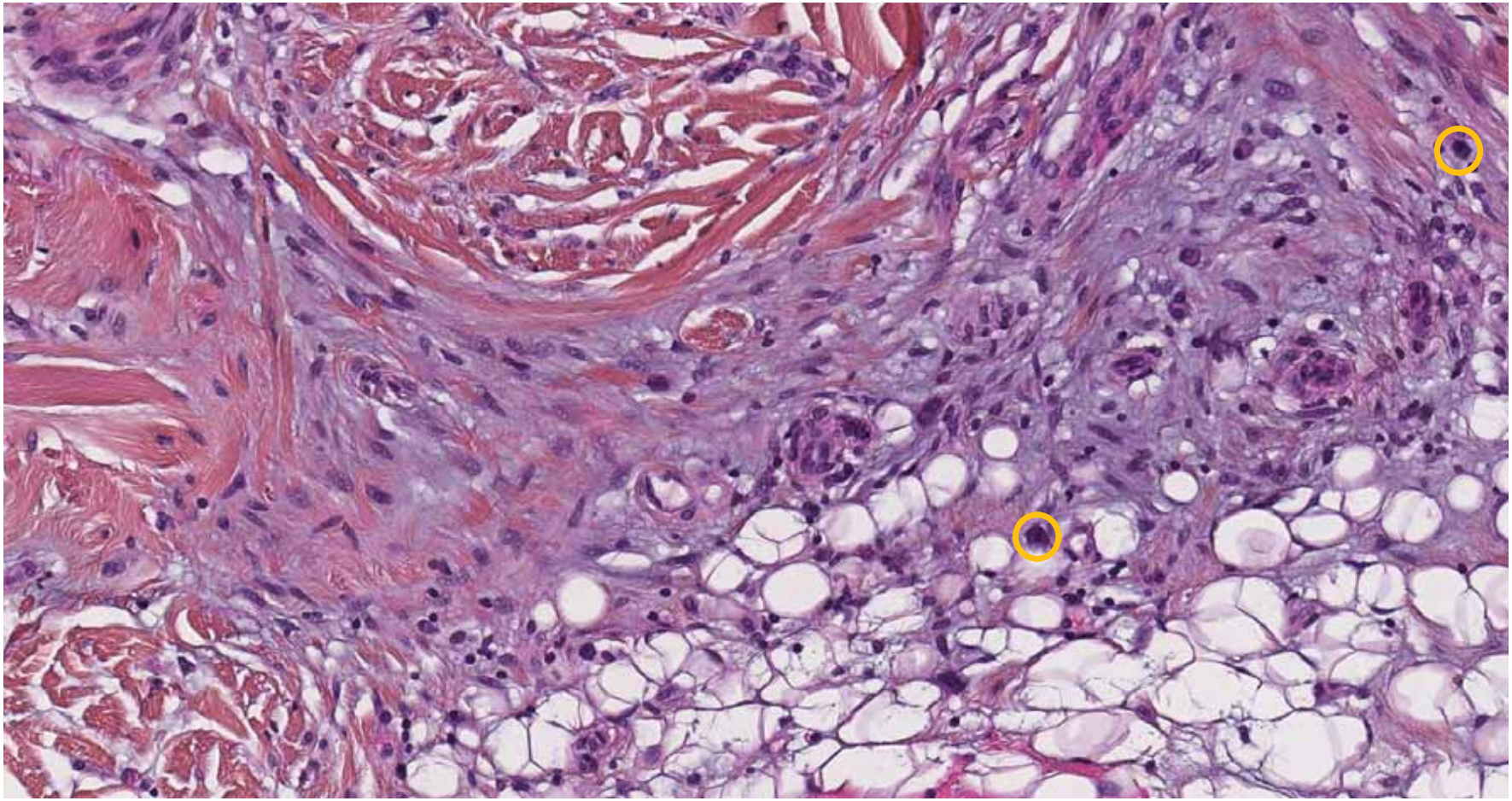




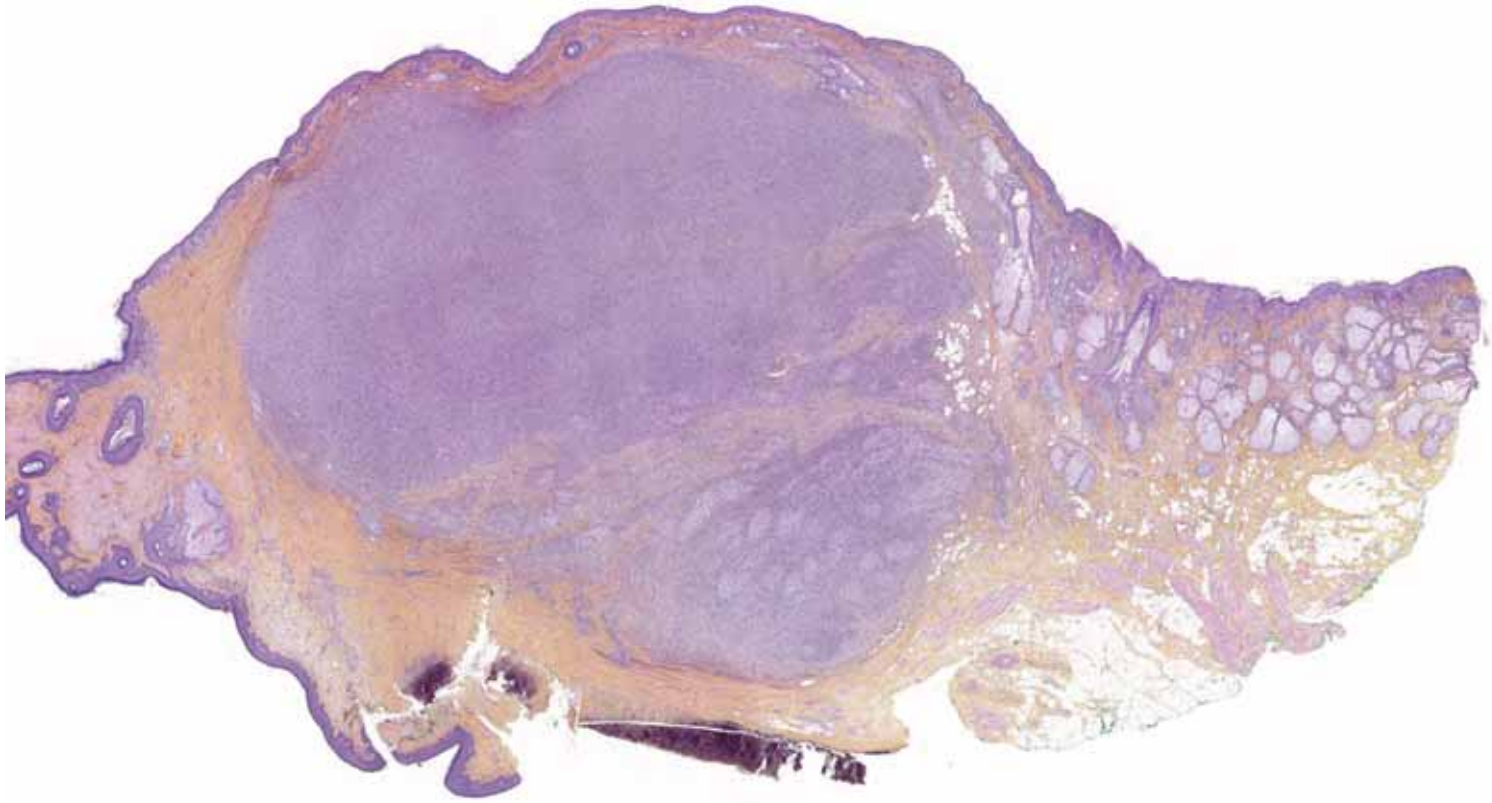




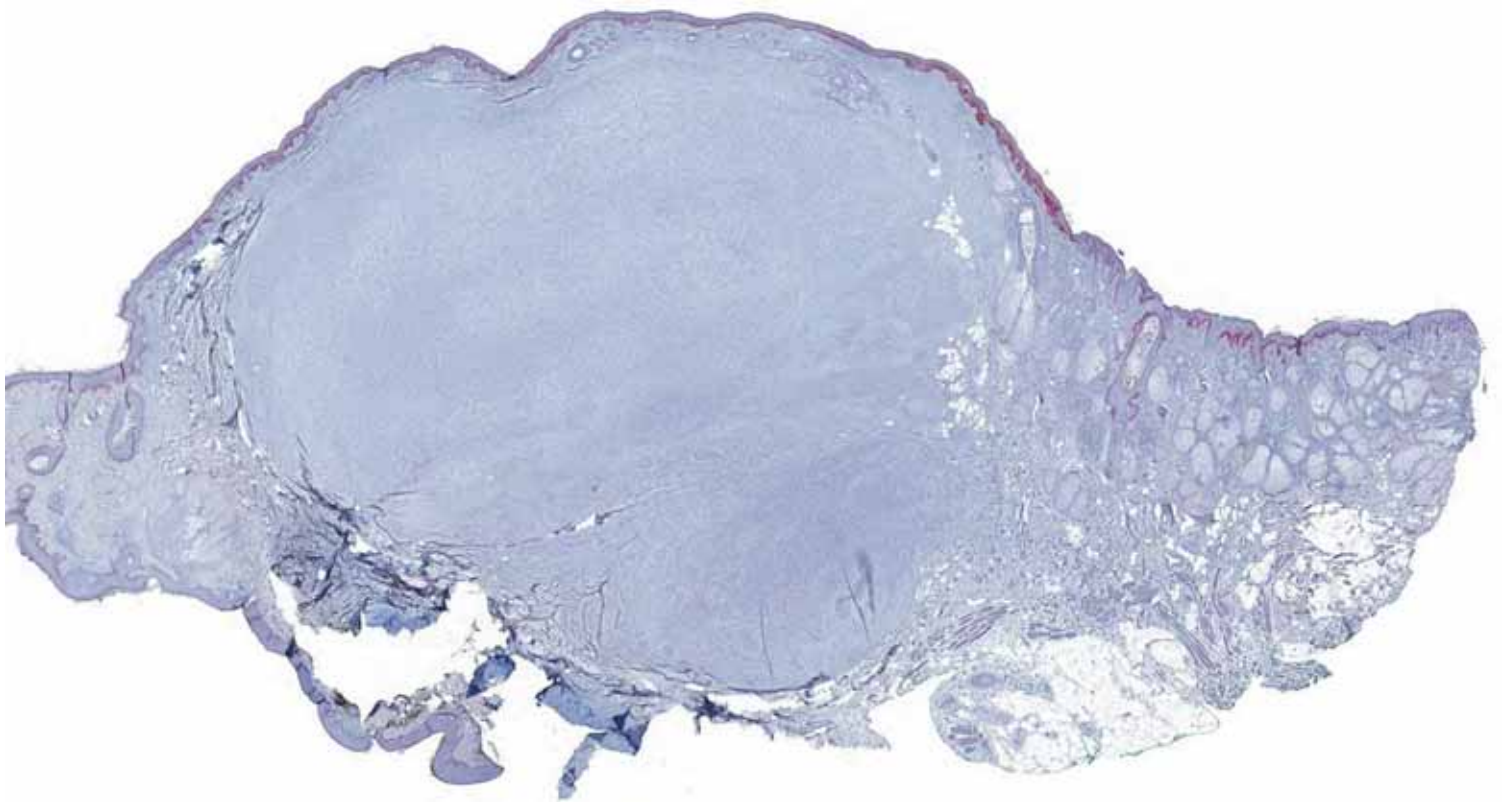
Mastocytes in DM underscore the myxoid background



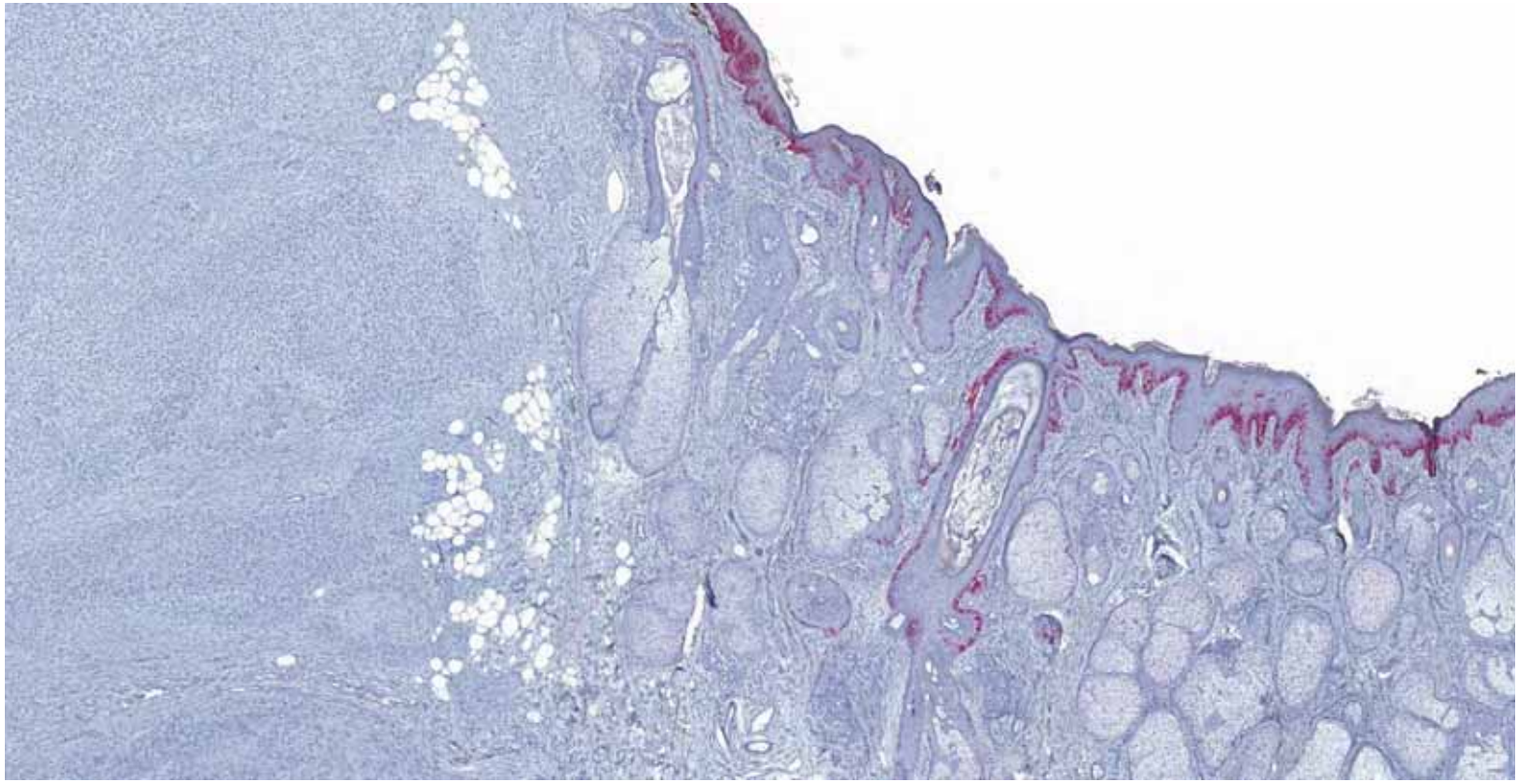
MelanA in DM is negative in dermis but highlights LM on top



MelanA in DM is negative in dermis but highlights LM on top

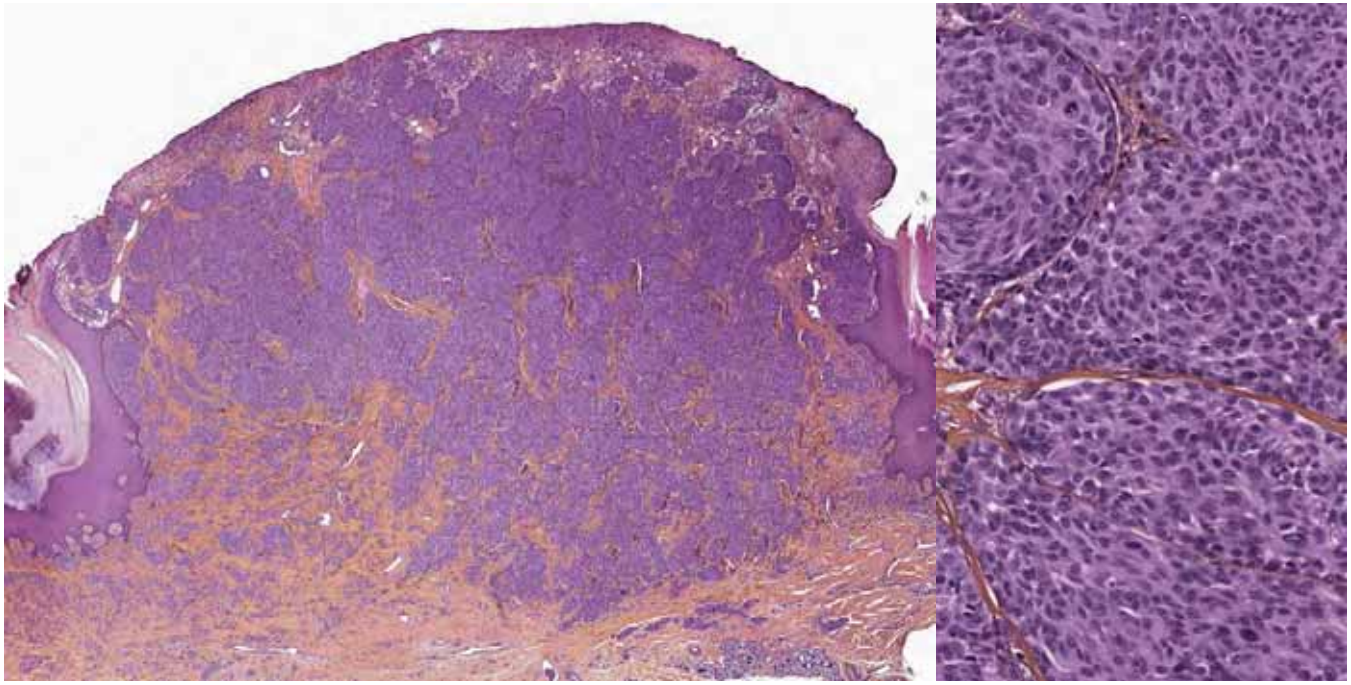


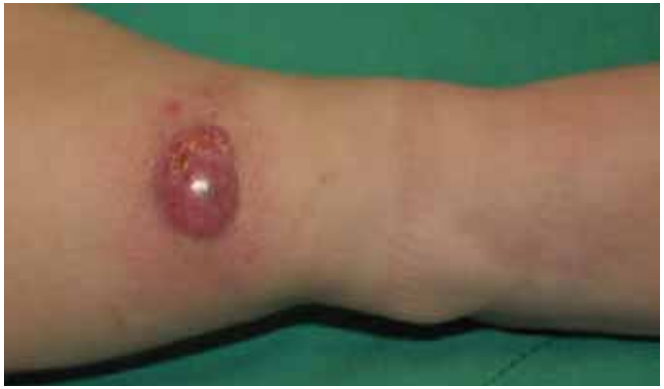
MelanA in DM is negative in dermis but highlights LM on top



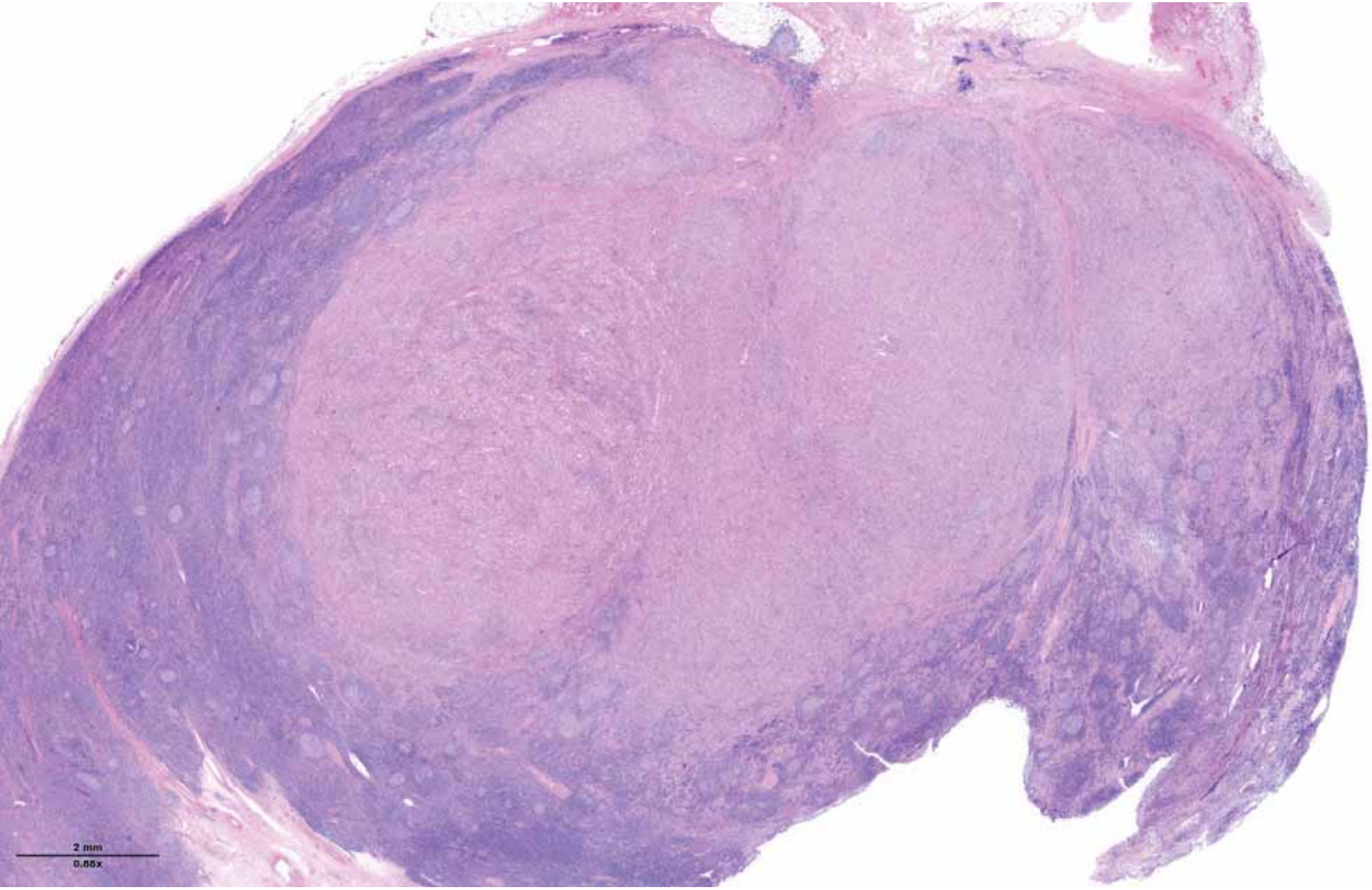
Class IV: Spitz melanoma

Children / young adults
UV-independant
Specific genomic features
Nevus to melanoma progression model

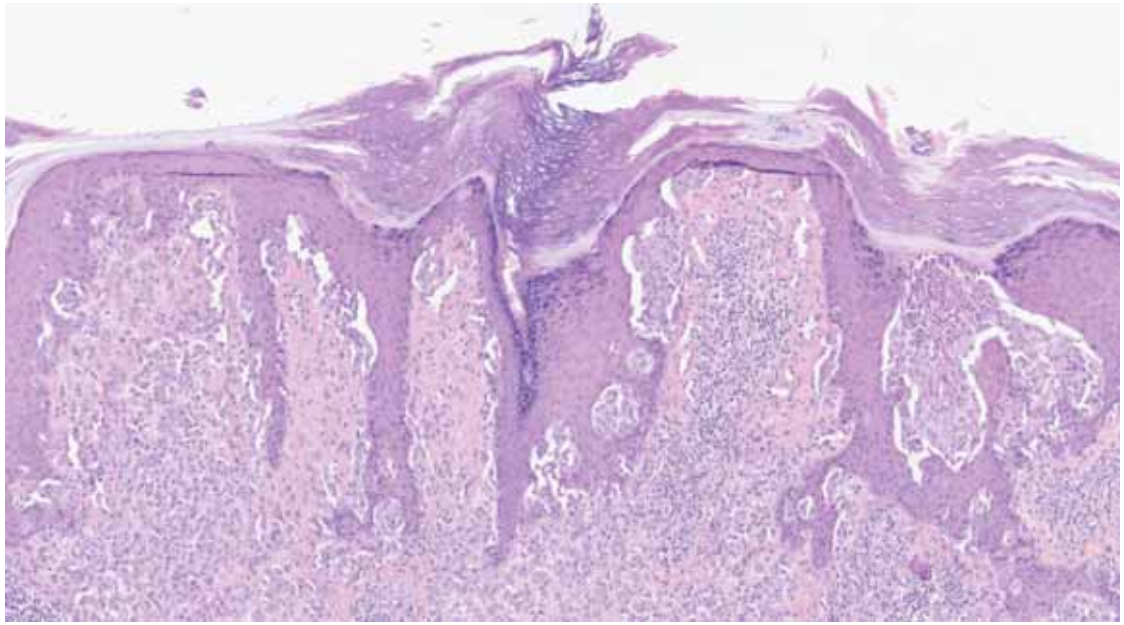


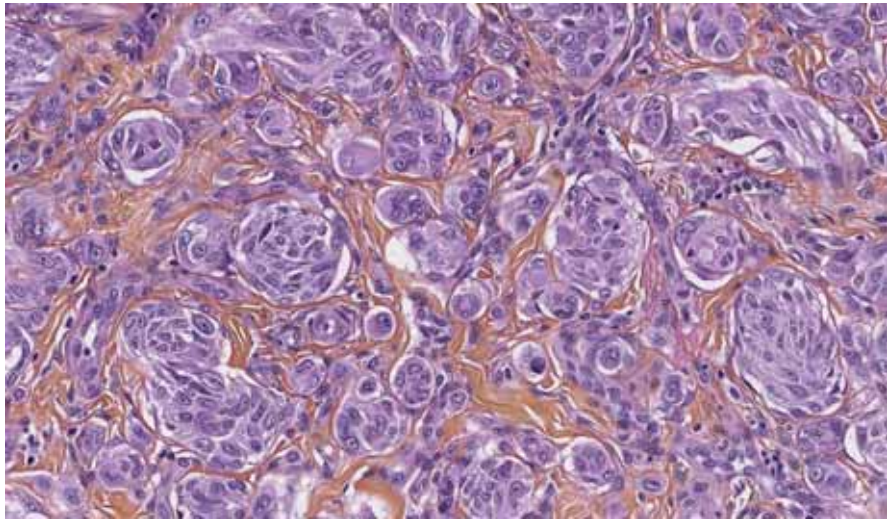


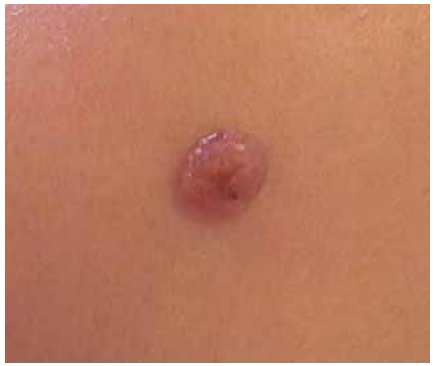
Dr Captier

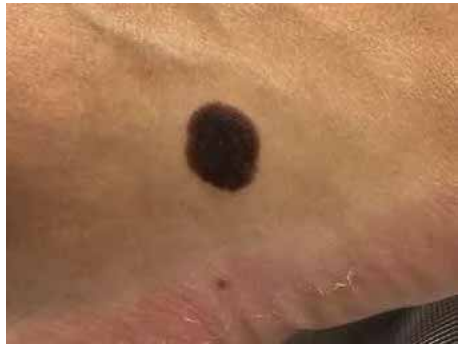

2 mm
0.55x

Class IV: Spitz nevus cytomorphology



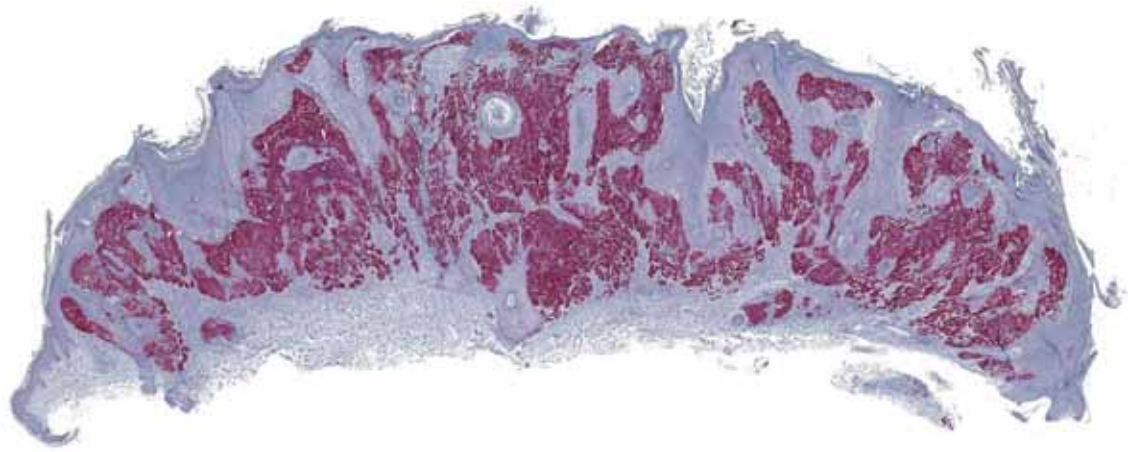






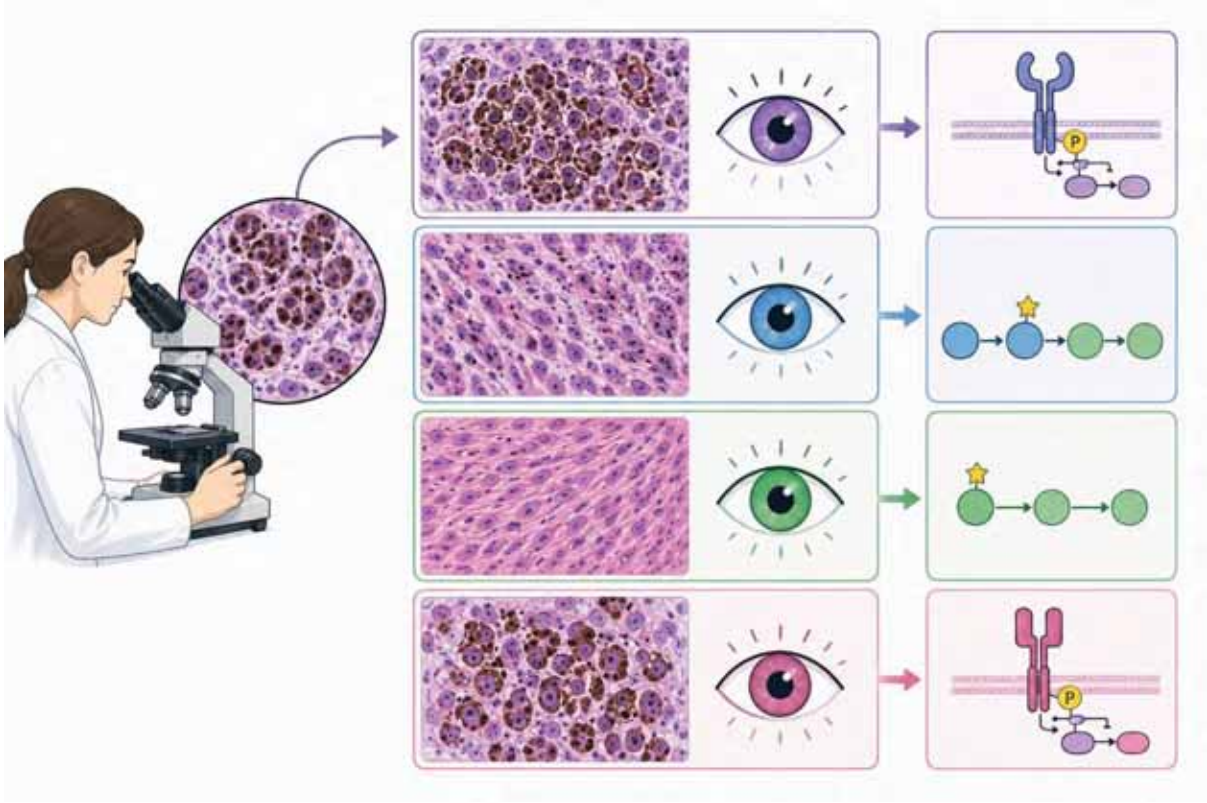
Molecular anomalies of Spitz tumours

- *HRAS* mutations (11p)
- Tyrosine kinase fusions
  - ***ALK***
  - ***ROS1***
  - ***NTRK1***
  - *NTRK2*
  - ***NTRK3***
  - *RET*
  - *MET*
  - *MERTK*
  - *LCK*
  - *FGFR1*
- Serine-threonine kinase fusions
  - ***BRAF***
  - ***MAP3K8***
  - *MAP3K3*



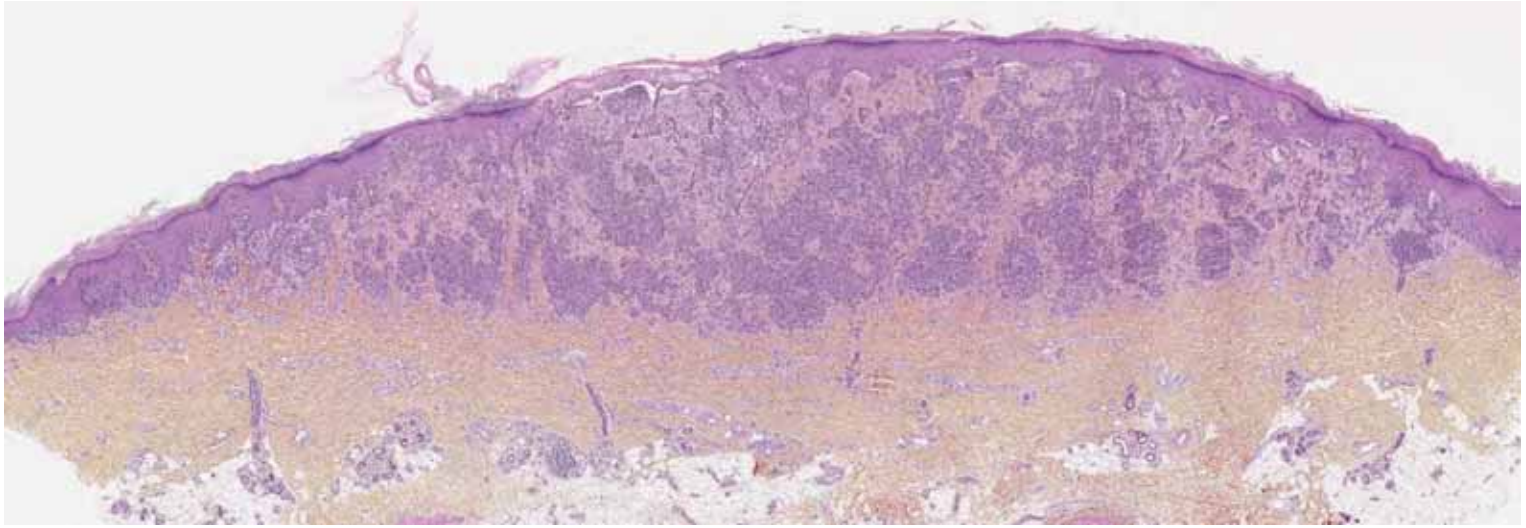
NTRK1 IHC

“Molecular eyes” clues
How to guess underlying molecular anomalies



NTRK1-fused Spitz tumours

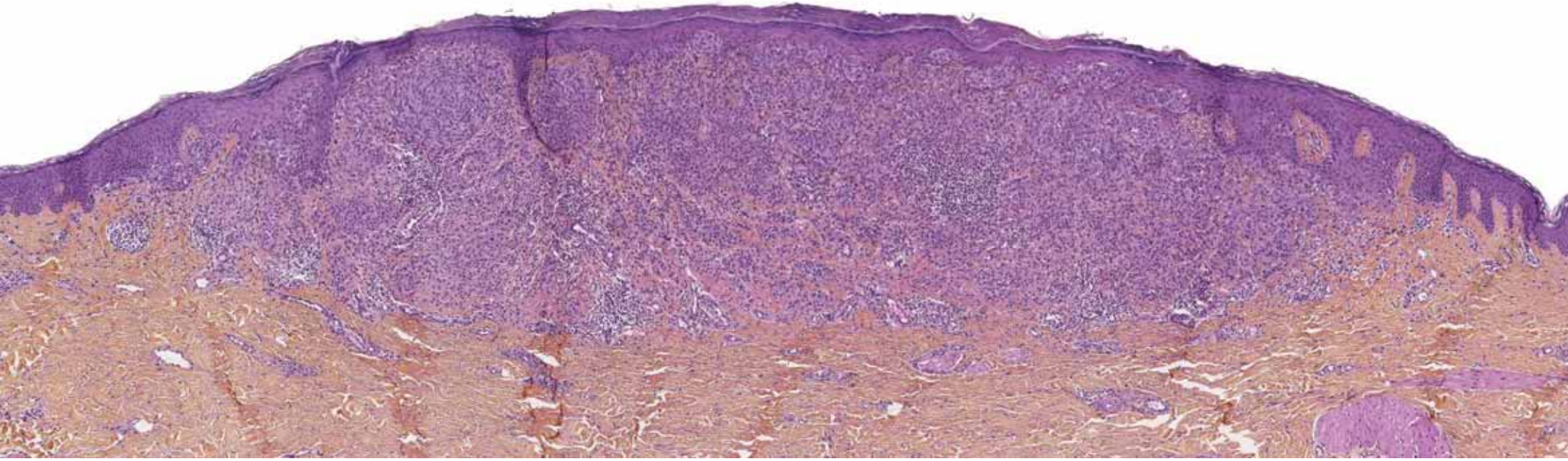
"Flat base" silhouette



F35; 25mm acral lesion

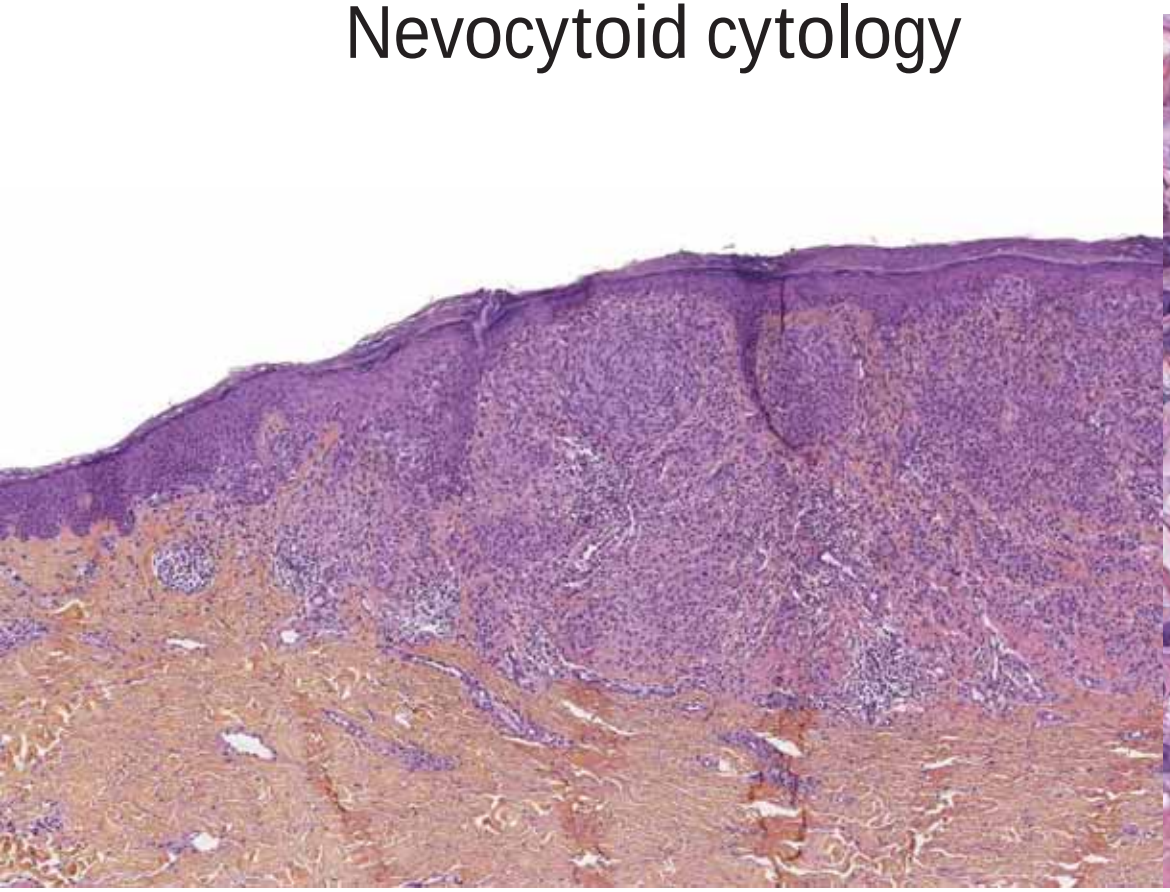
NTRK1-fused Spitz tumours

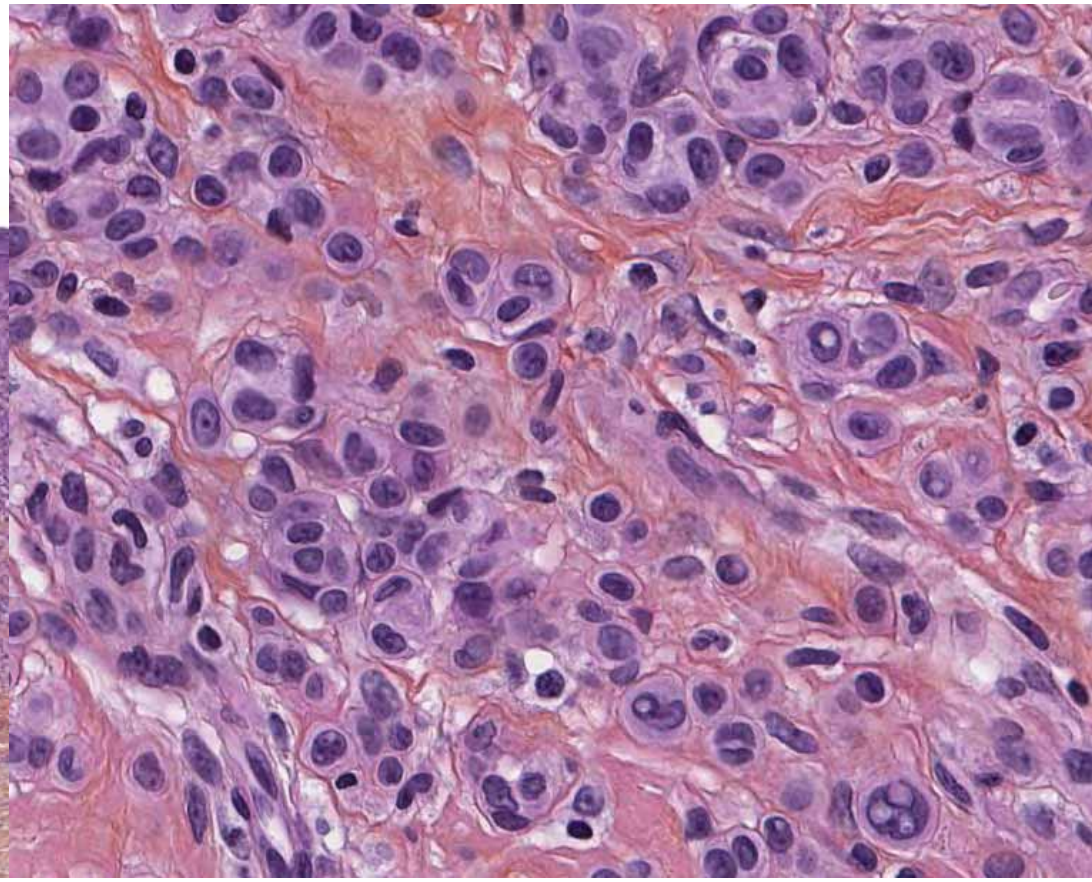
“Flat base” silhouette

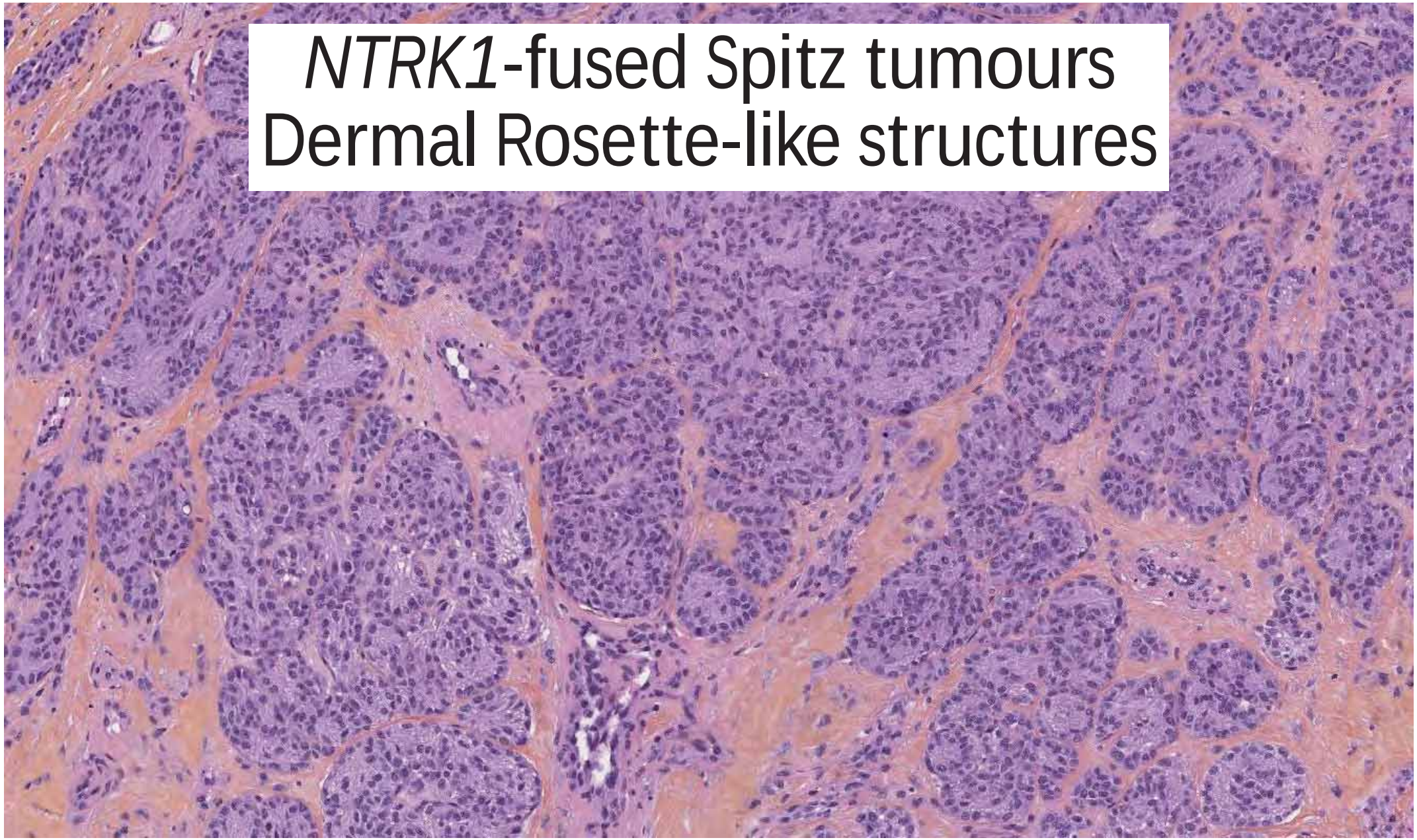


NTRK1-fused Spitz tumours

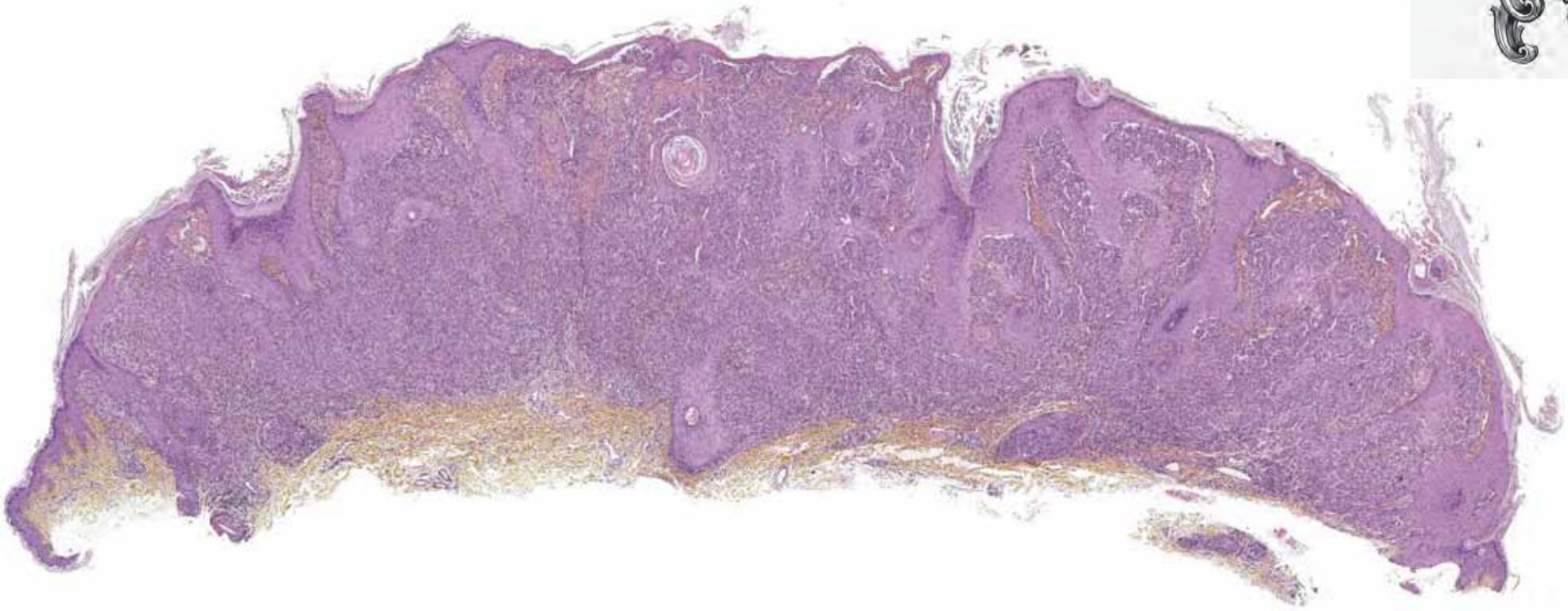
Nevocytoid cytology



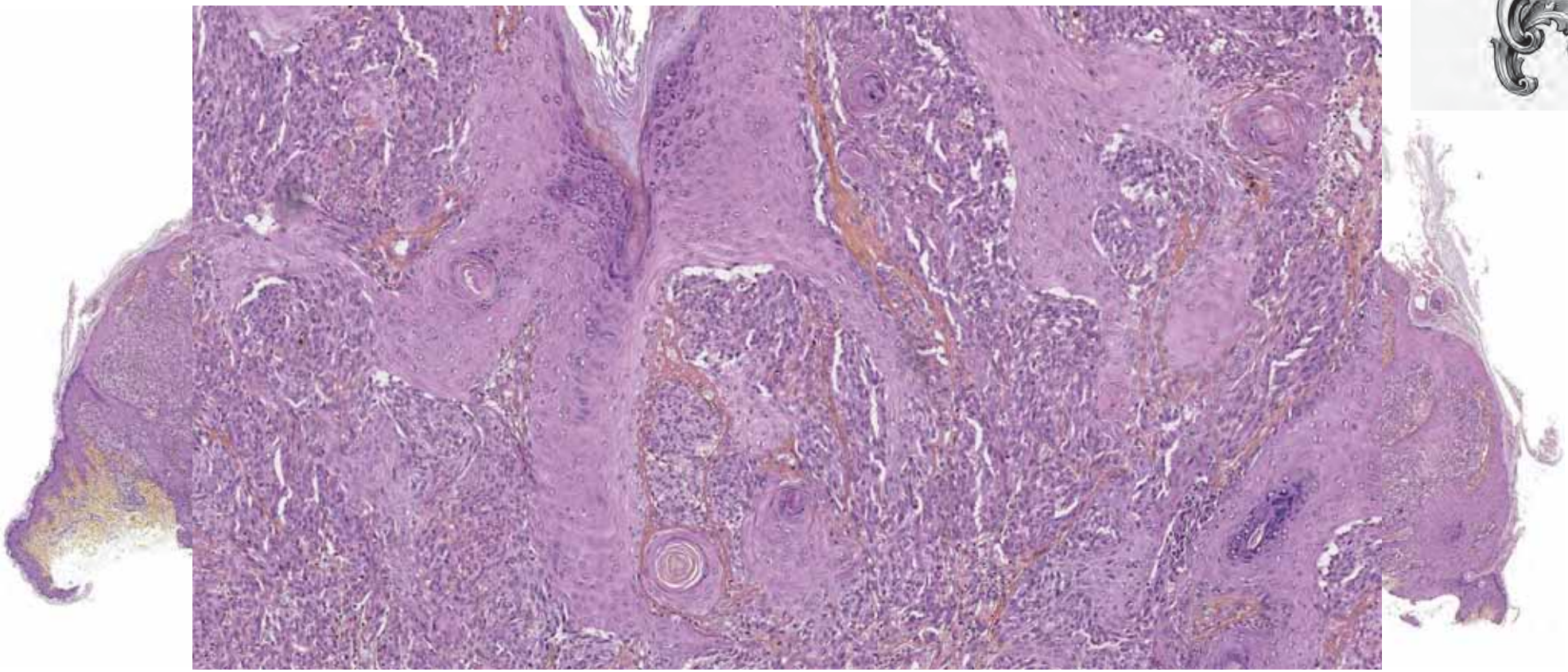



NTRK1-fused Spitz tumours
Dermal Rosette-like structures

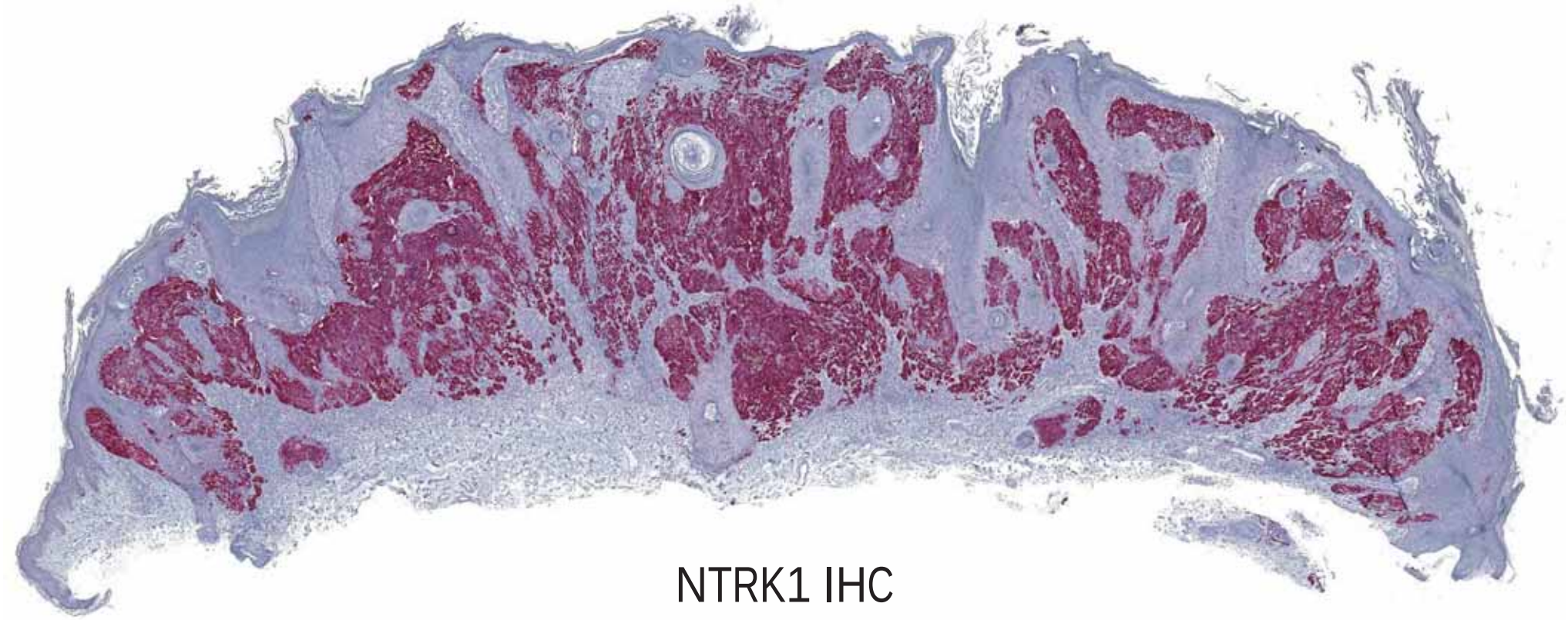
NTRK1-fused Spitz tumours
Fillagree-like rete Ridges



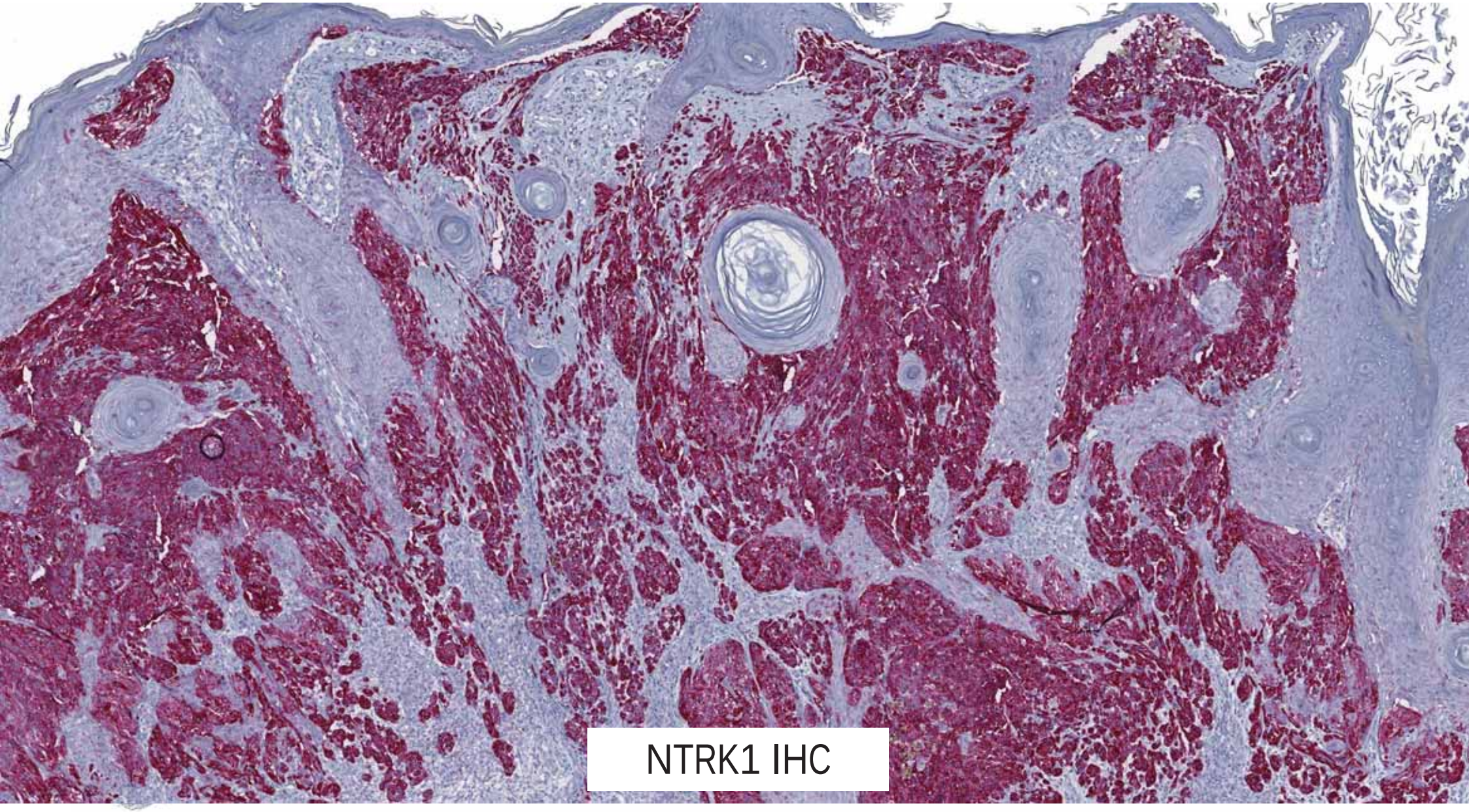
NTRK1-fused Spitz tumours
Fillagree-like rete Ridges



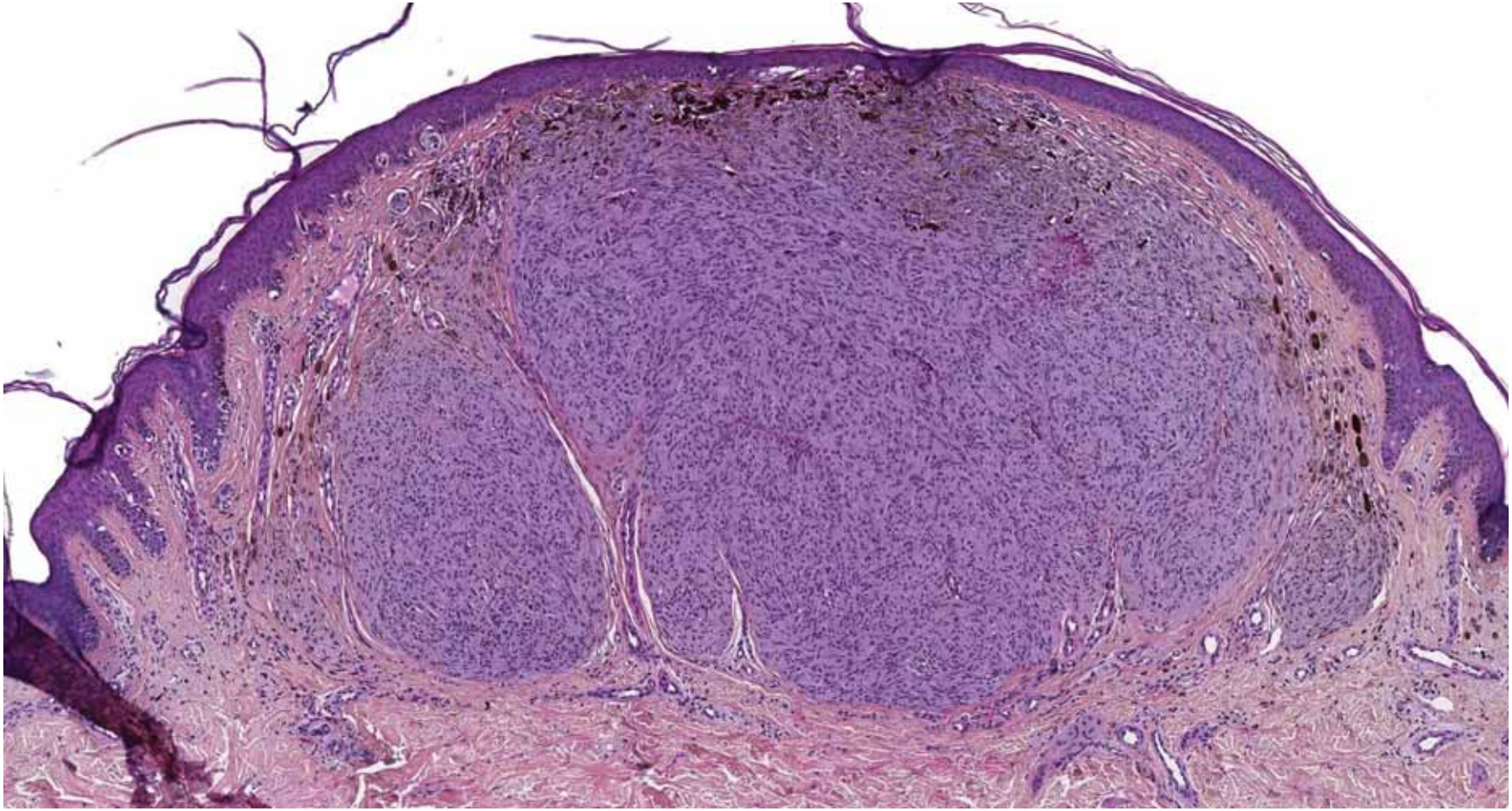
NTRK1-fused Spitz tumours
Fillagree-like rete Ridges



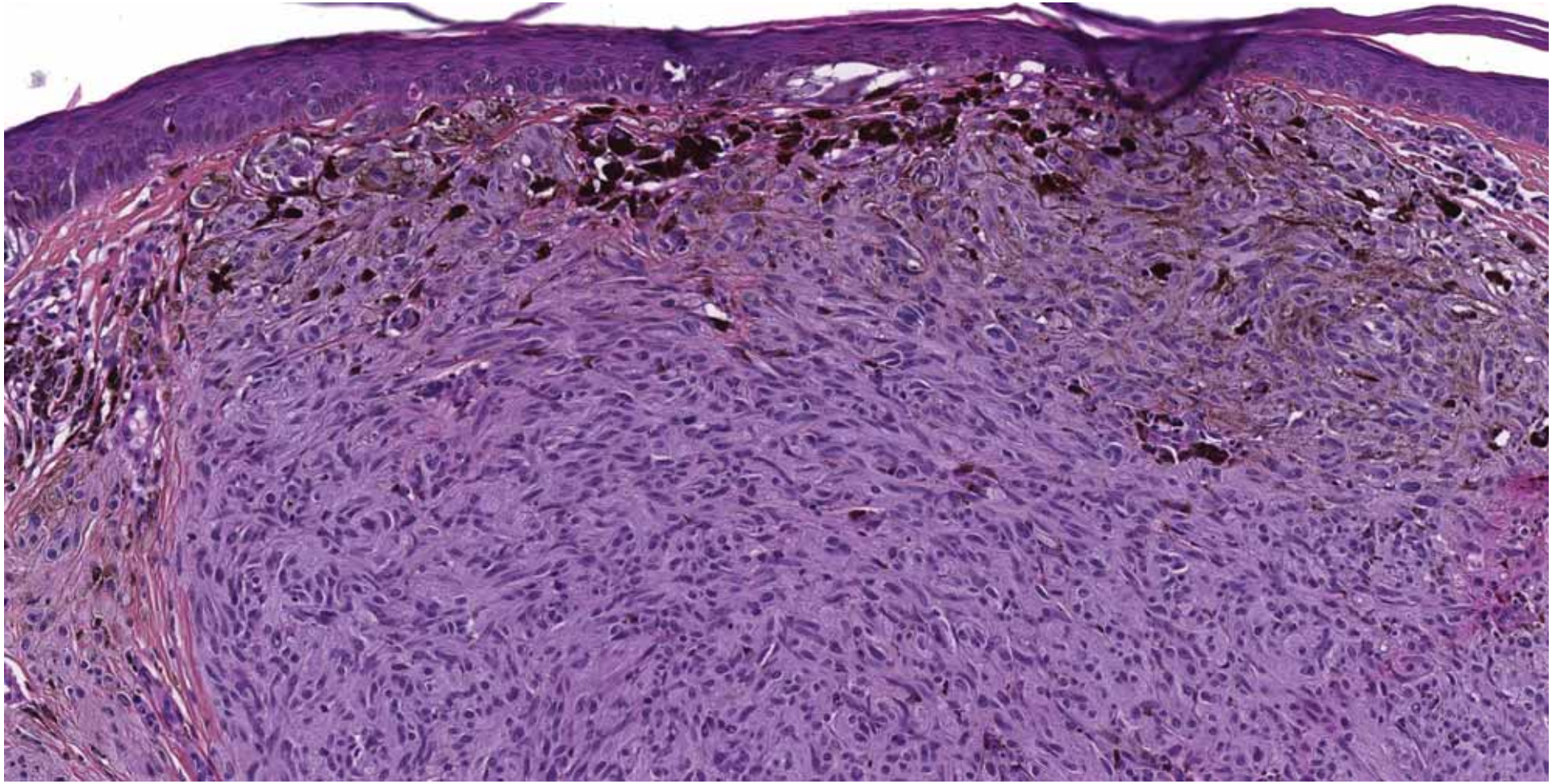
NTRK1 IHC


NTRK1 IHC

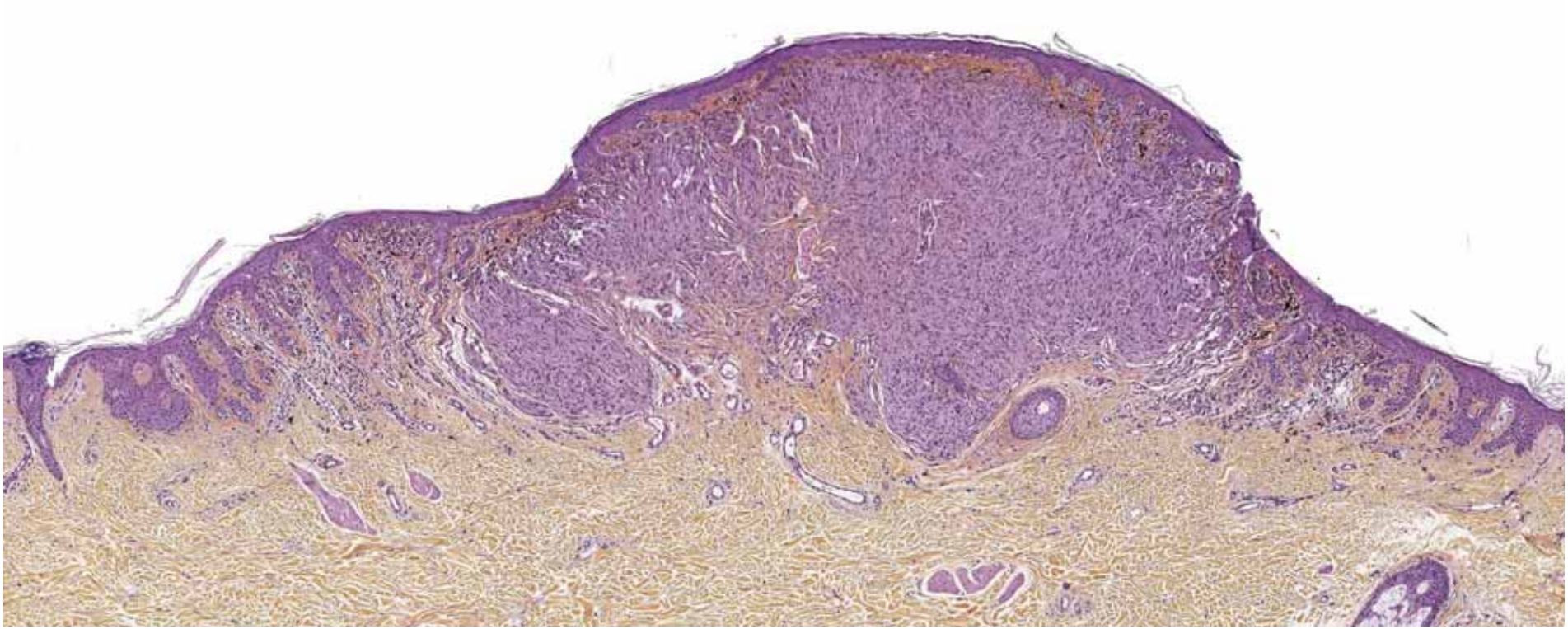
MYO5A-NTRK3: pseudoschwannomatous morphology



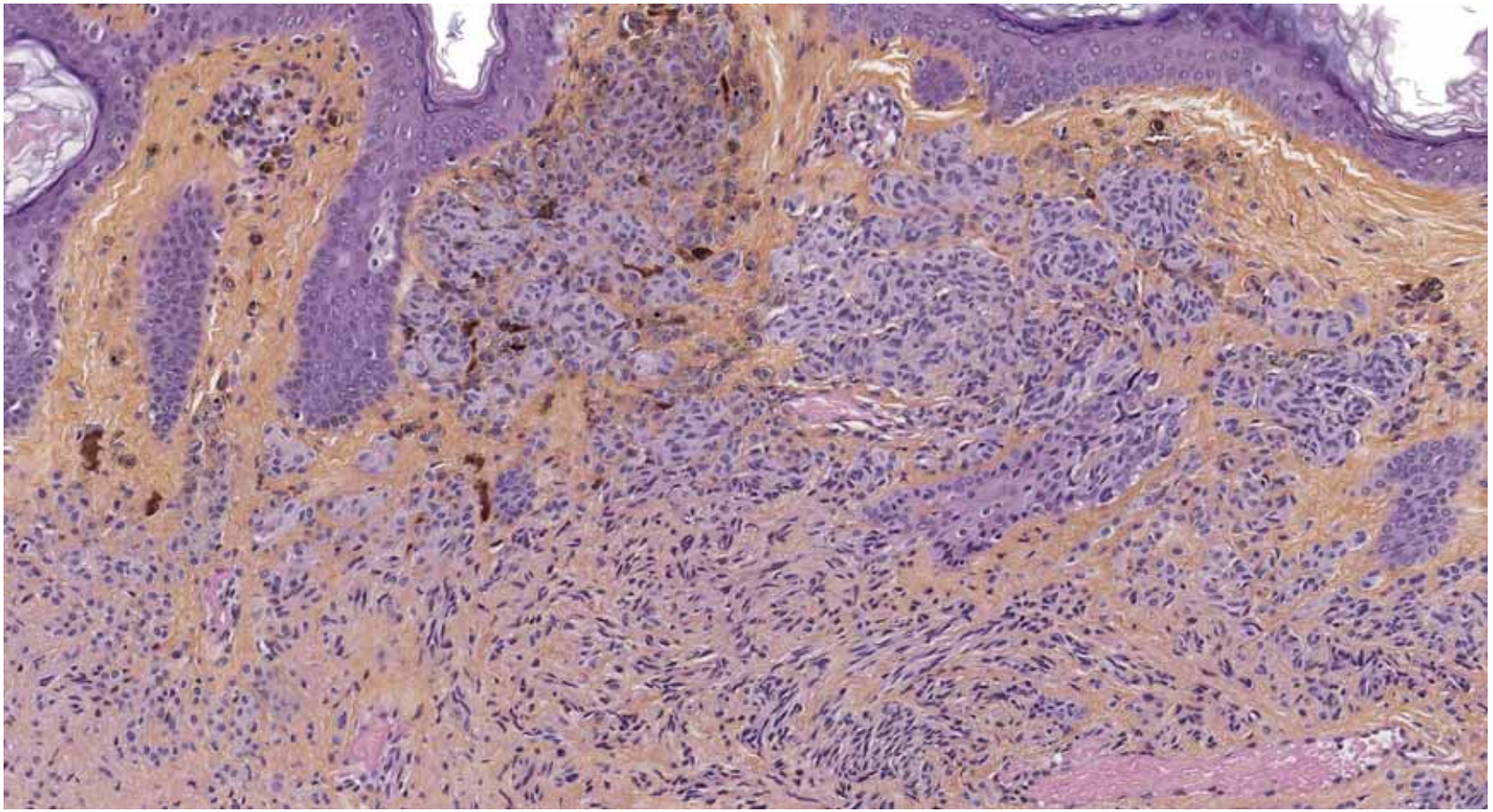
MYO5A-NTRK3: pseudoschwannomatous morphology



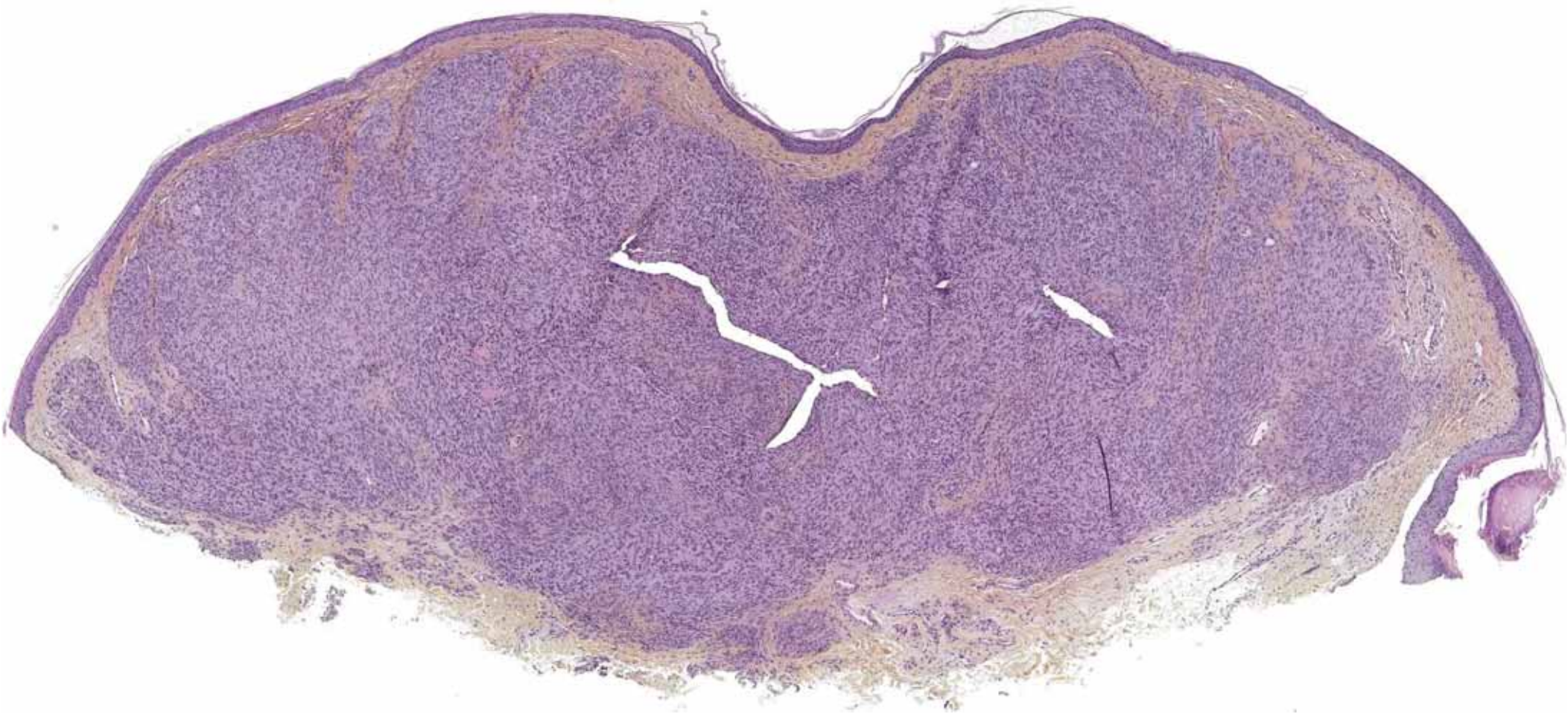
Abrupt transition in dermal architecture and cytology

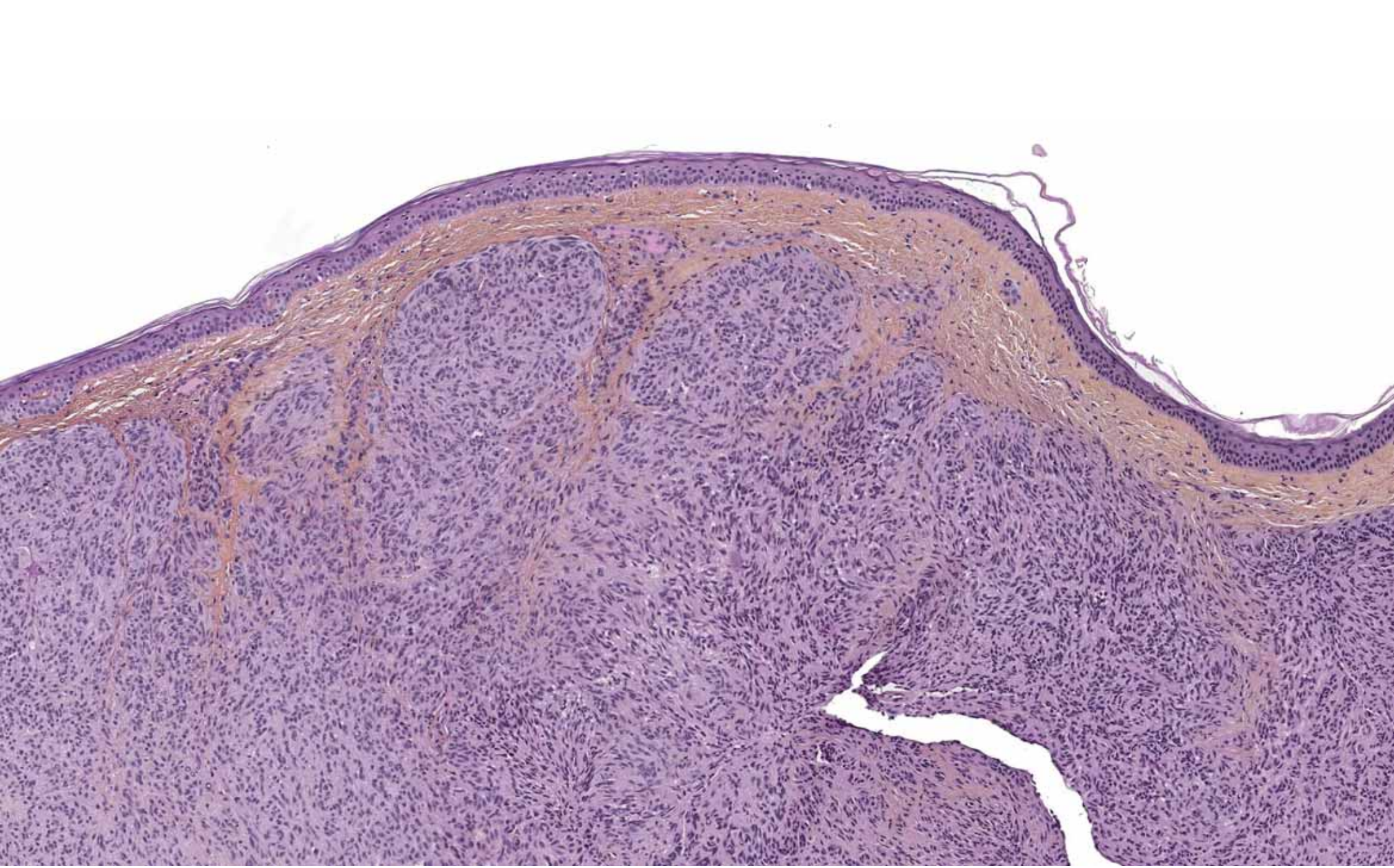


Small pigmented nests in the upper dermis transitionning into sheets of spindled bland melanocytes

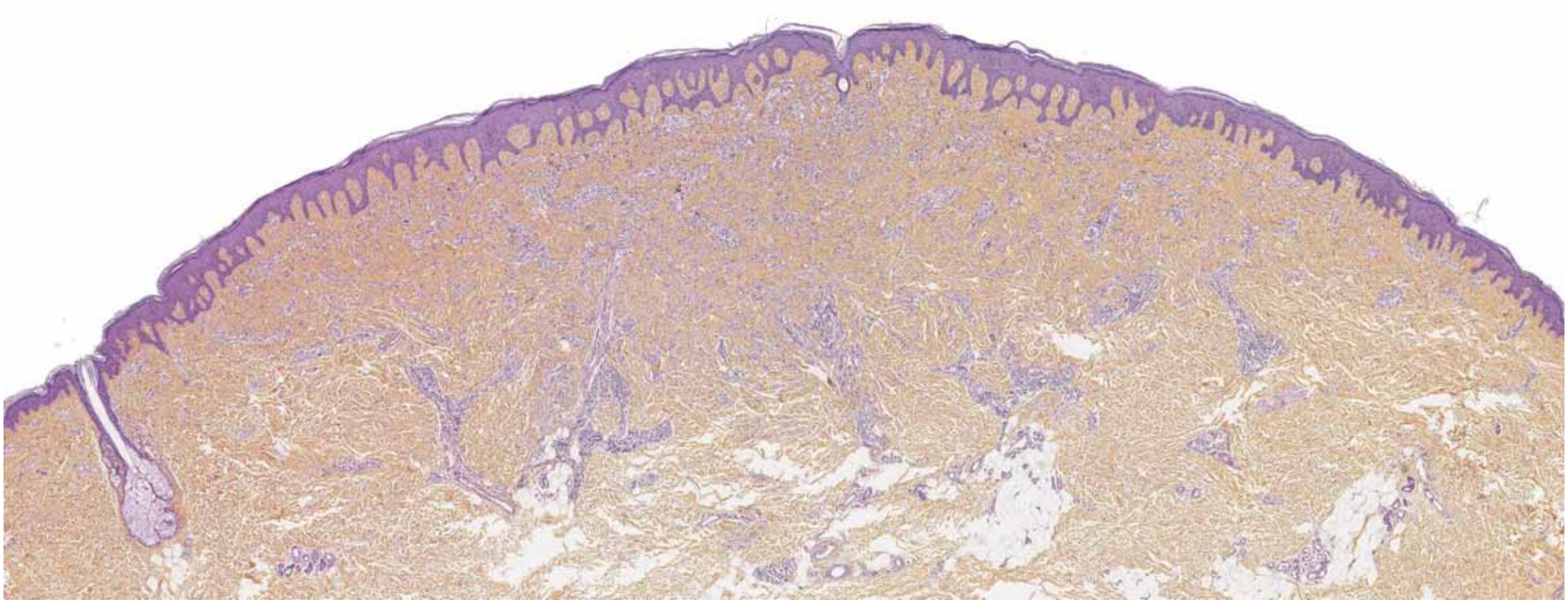


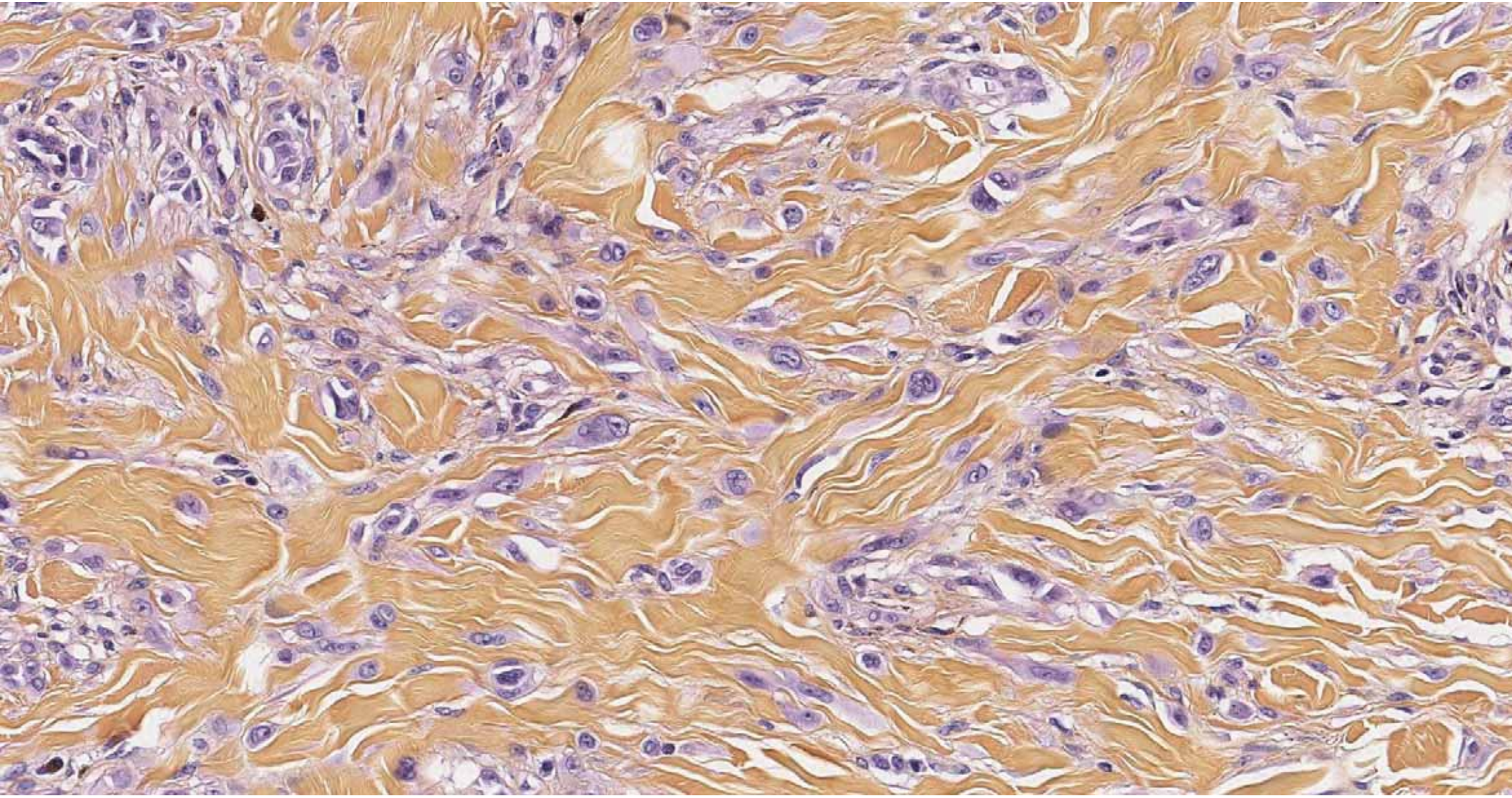
MYO5A-NTRK3: pseudoschwannomatous morphology



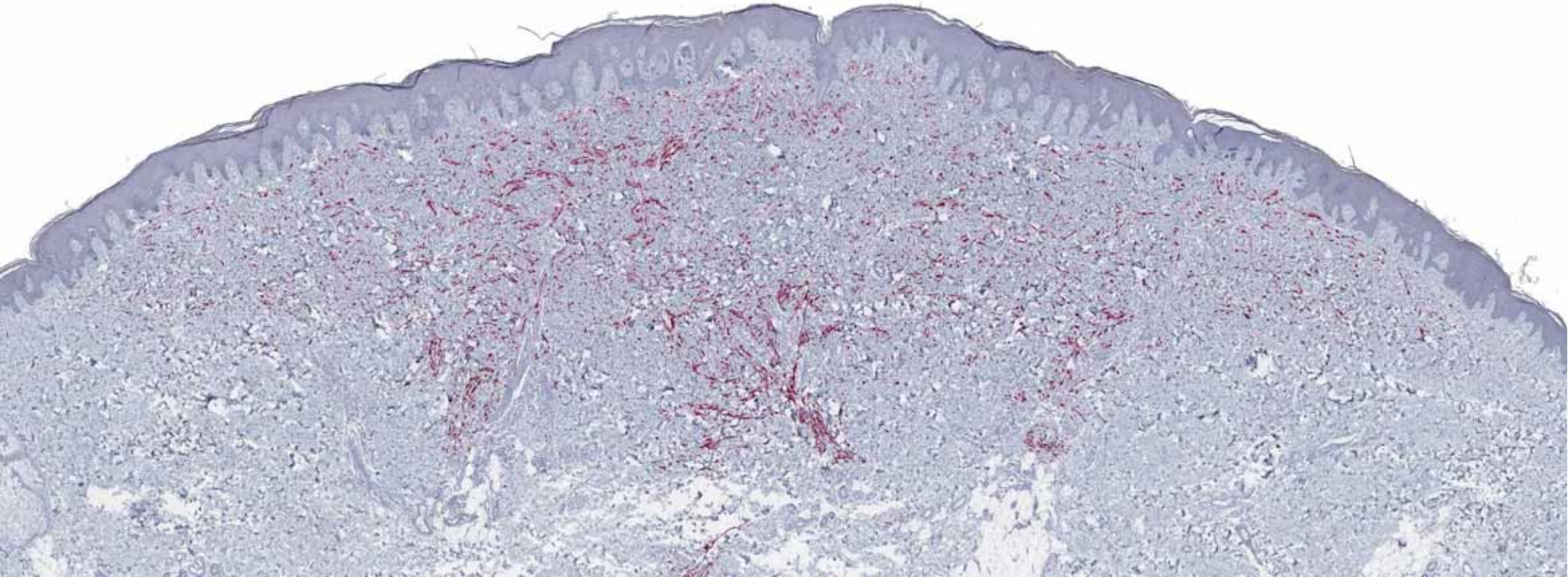


Desmoplastic Spitz Nevus



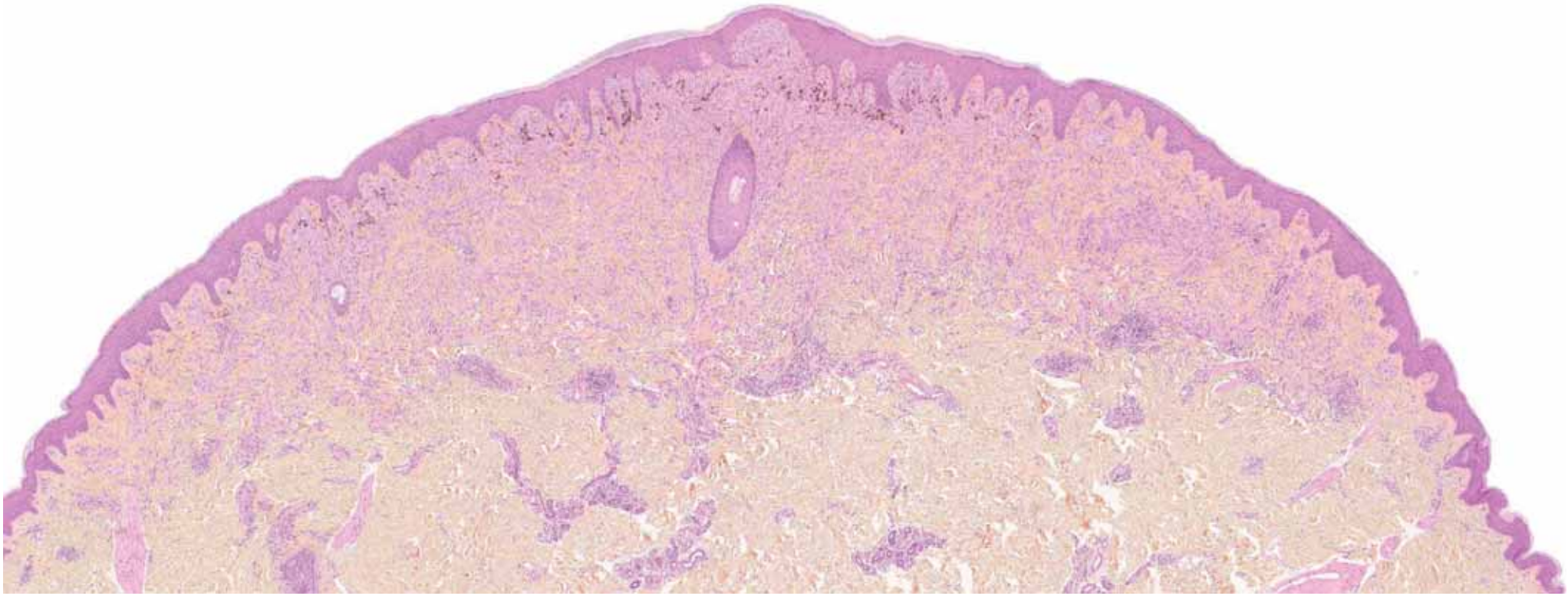


Desmoplastic Spitz Nevus
p16 > melanA

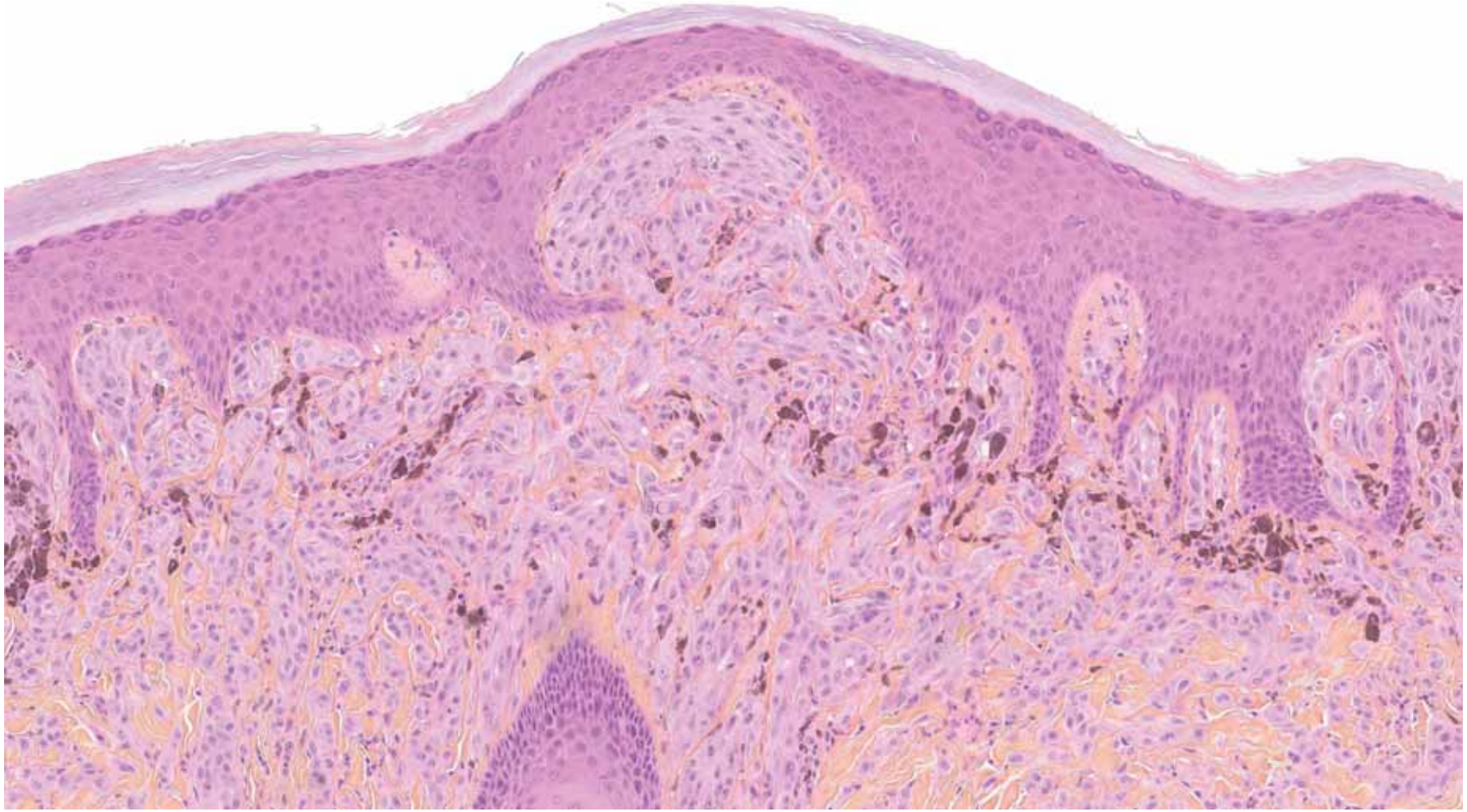


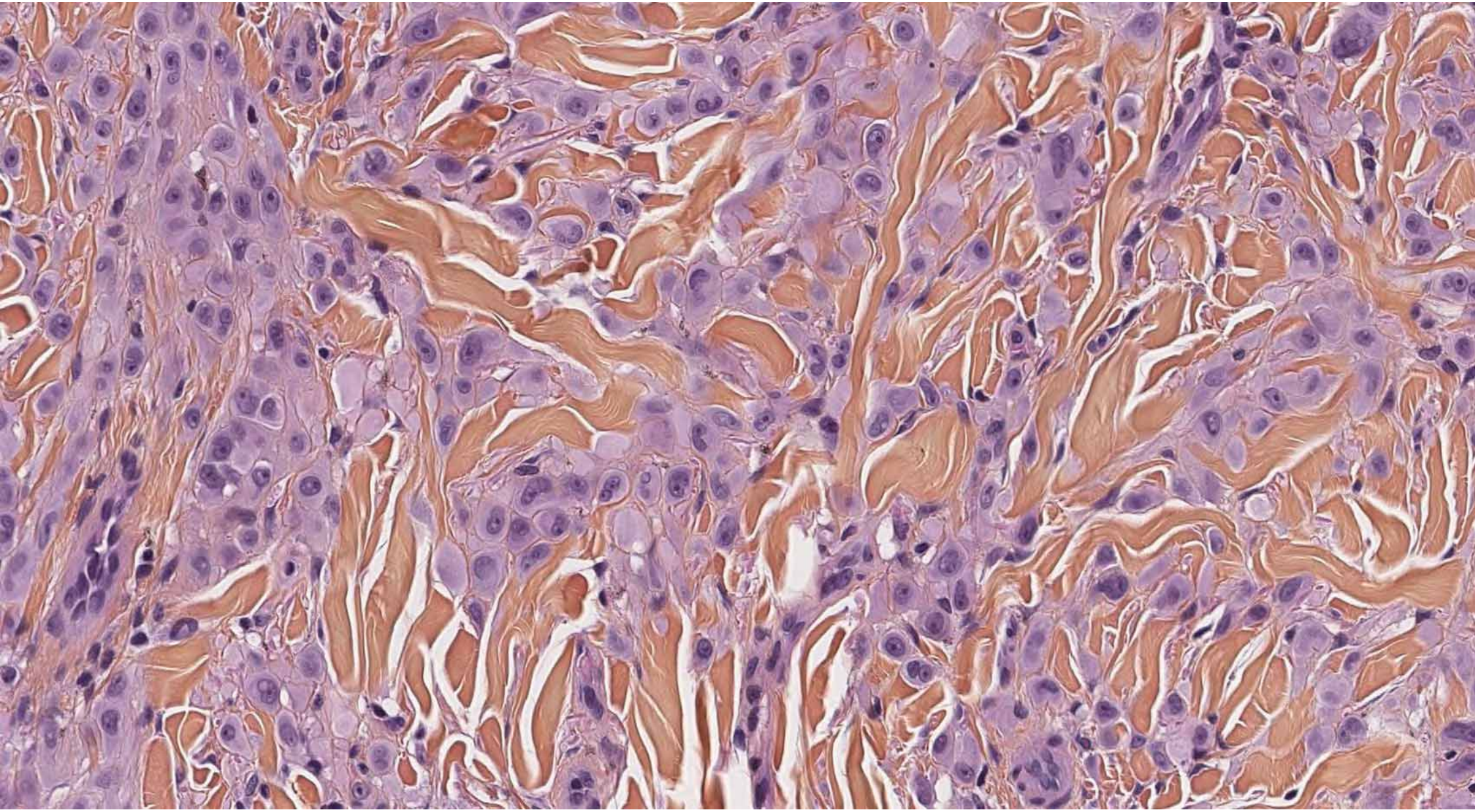
Spitz tumors with *HRAS* mutation

- Isolated lesions
- Desmoplastic morphology



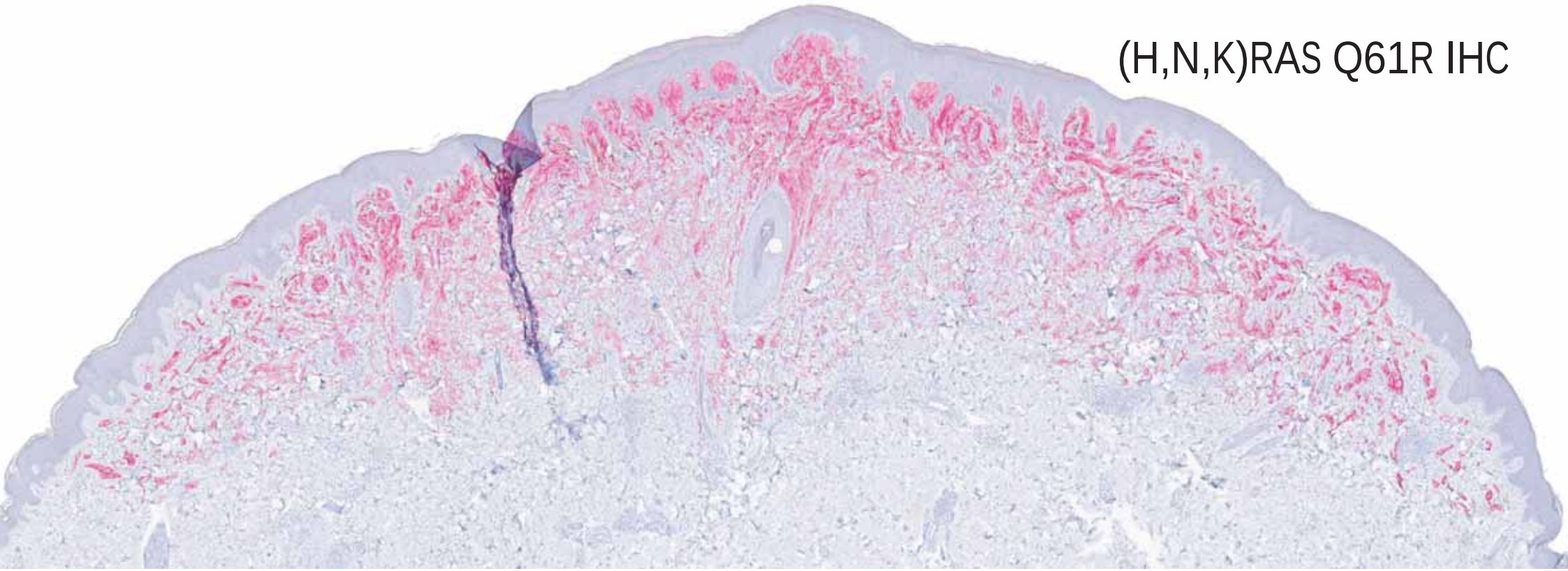
Spitz tumors with *HRAS* mutation





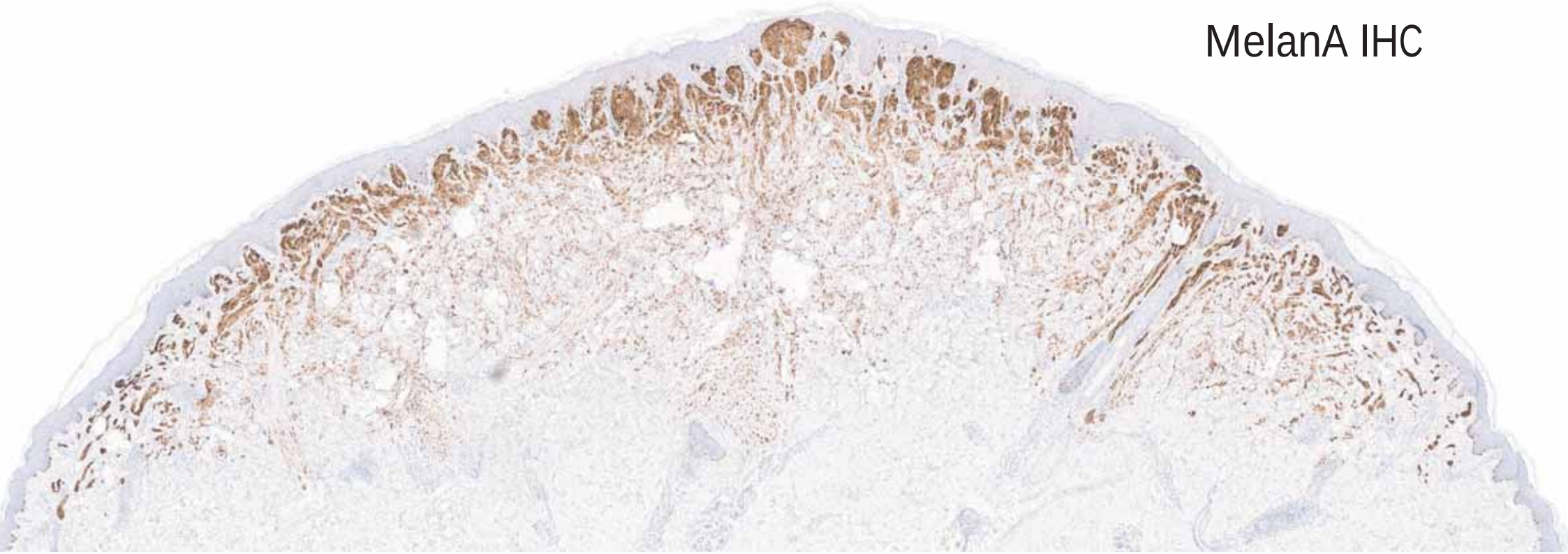
Spitz tumors with *HRAS* mutations

- Isolated lesions



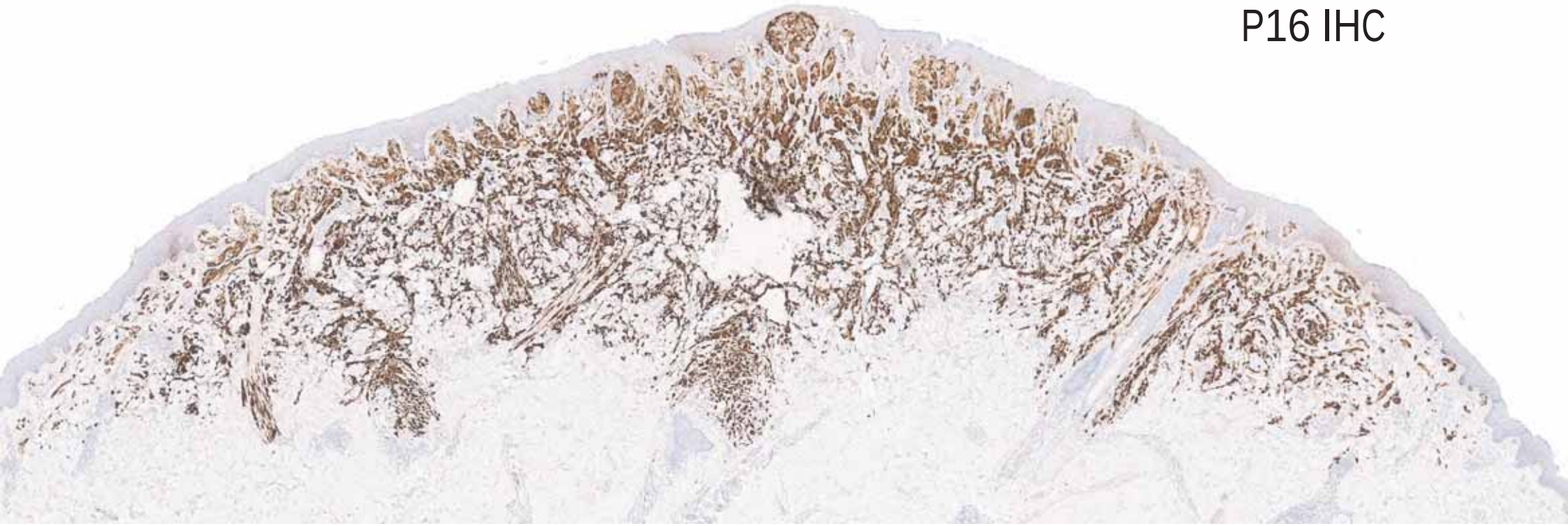
Spitz tumors with *HRAS* mutations

P16 > MelanA

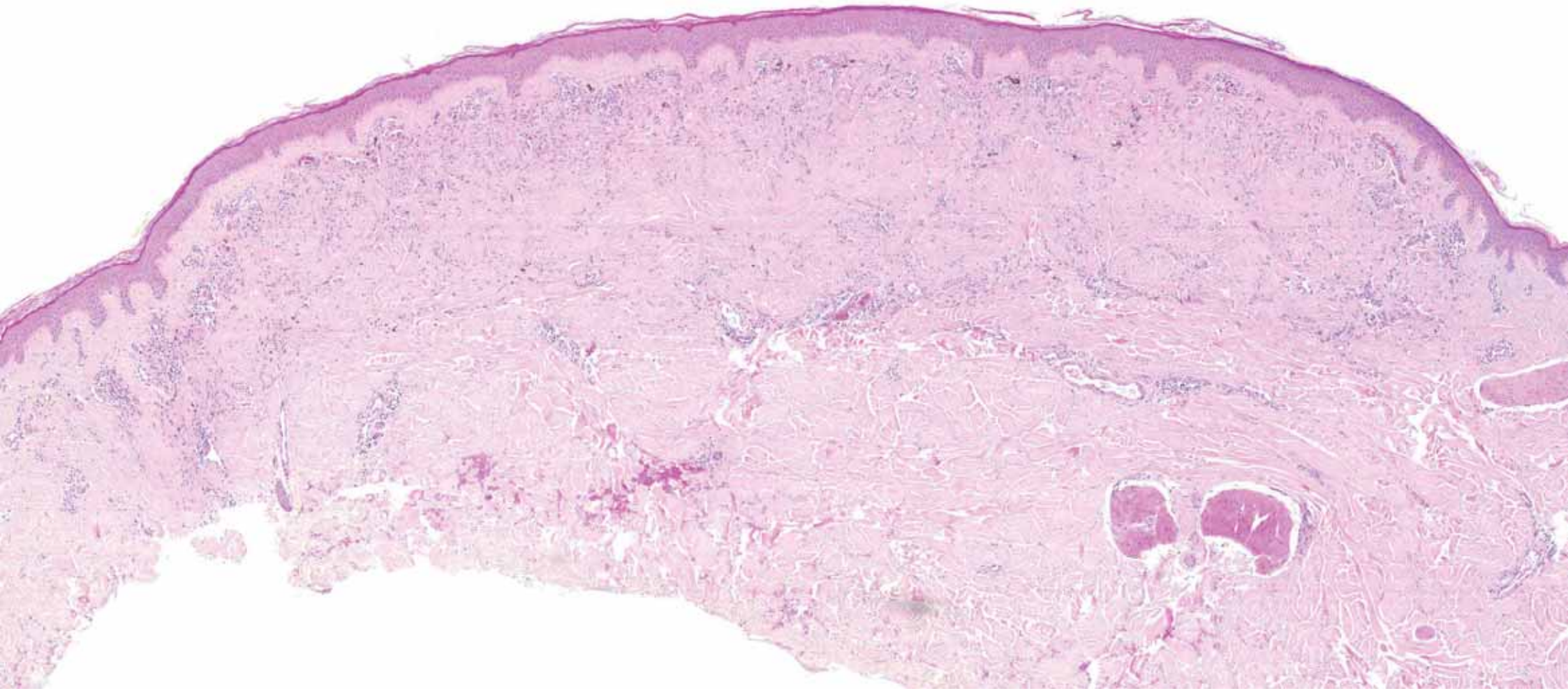


Spitz tumors with *HRAS* mutations

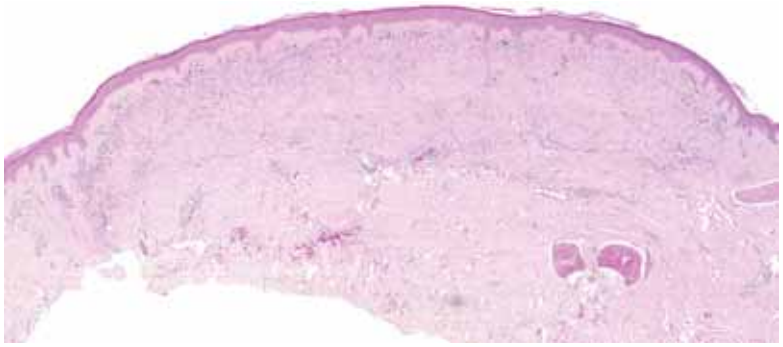
P16 > MelanA



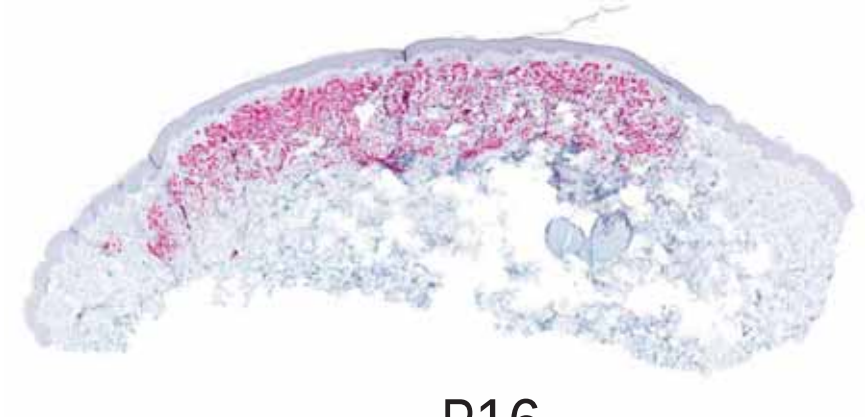
Desmoplastic Nevus (BRAF V600E background)



Desmoplastic Nevus (BRAF V600E background)

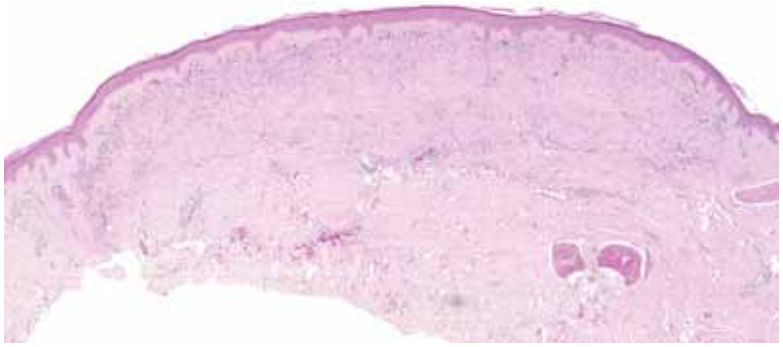


MelanA

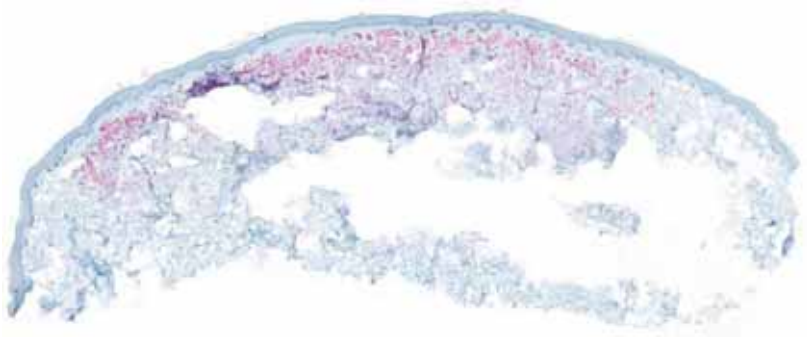


P16

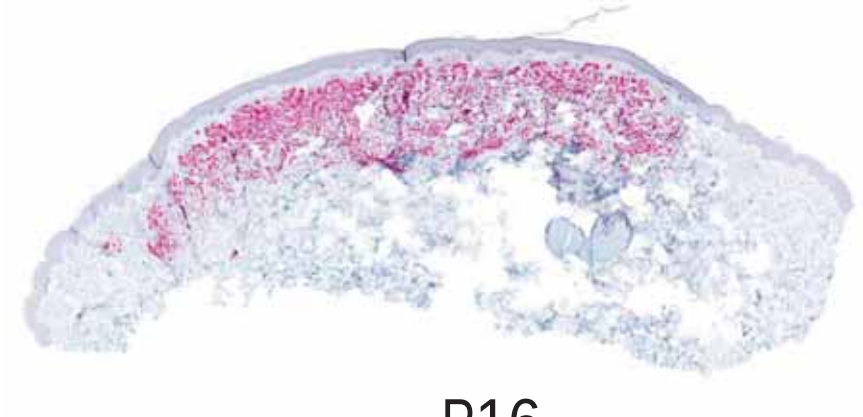
Desmoplastic Nevus (BRAF V600E background)



MelanA



BRAF V600E

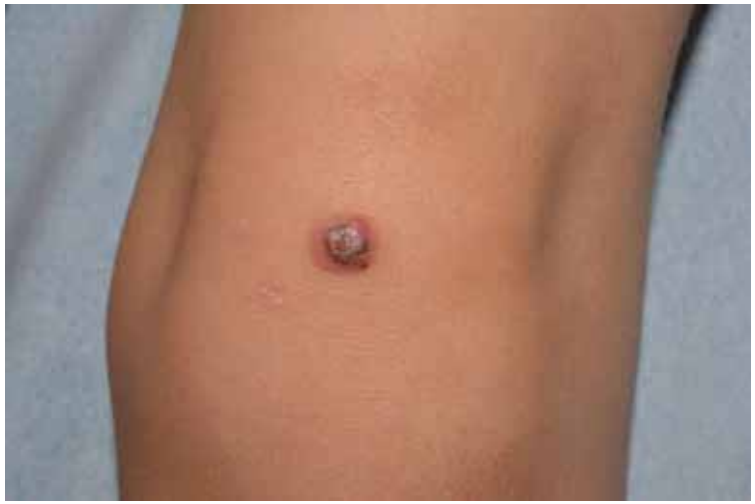


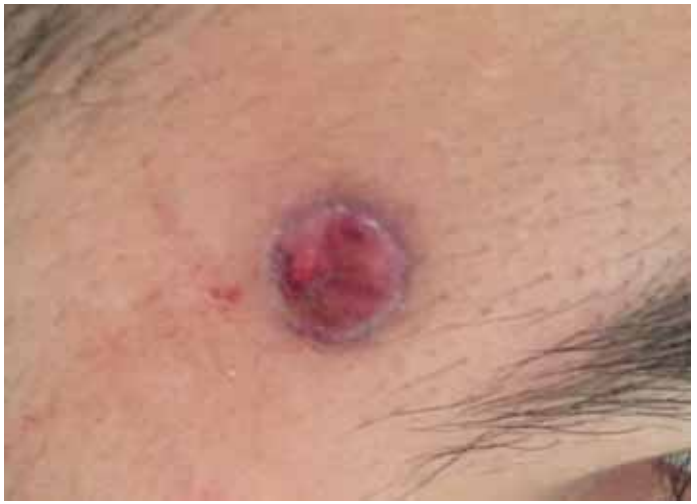
P16

MAP3K8-altered melanocytic tumors

- Young patients
- Lower limb
- Wide ulceration

MAP3K8 fusions
Clinical presentation

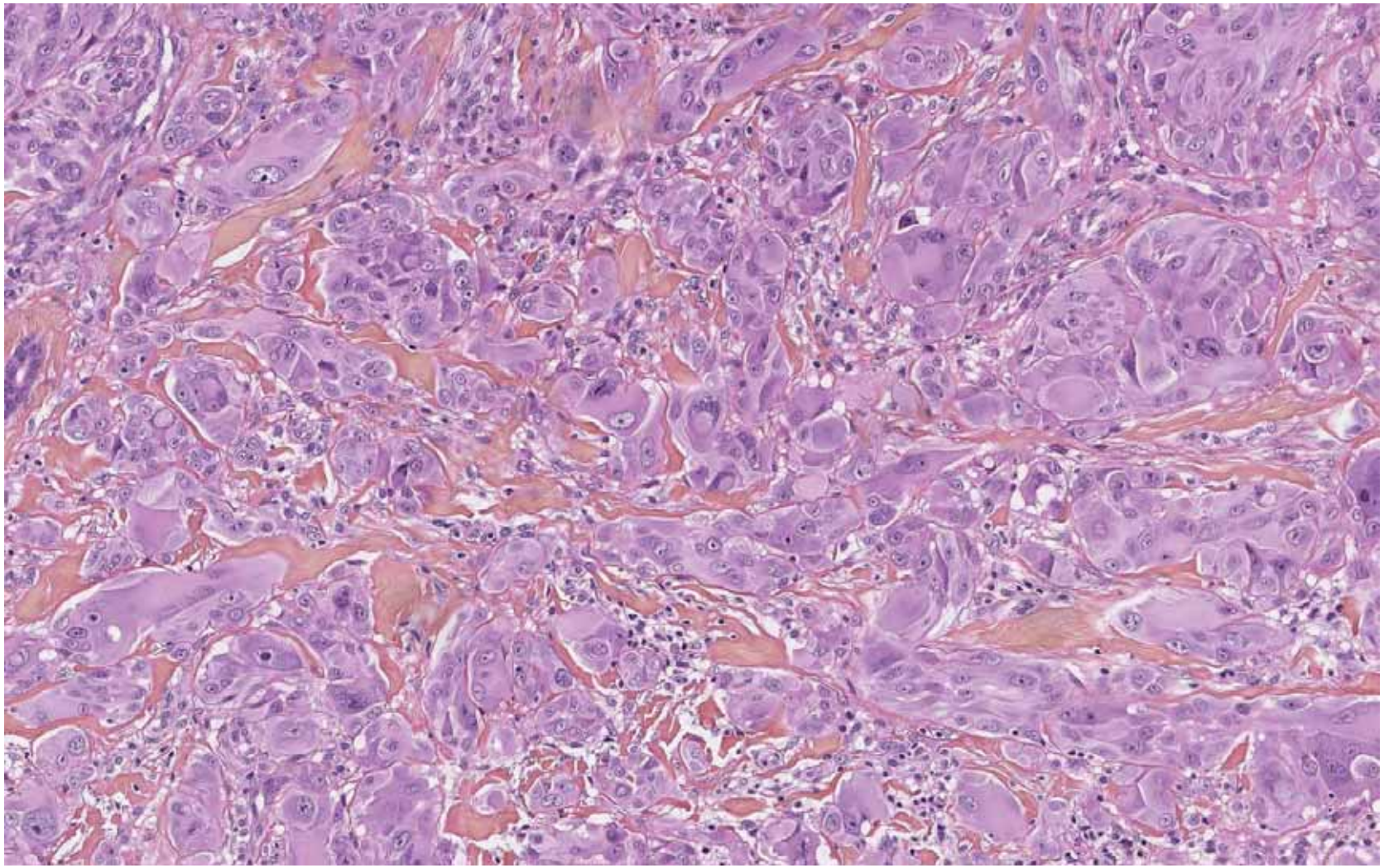


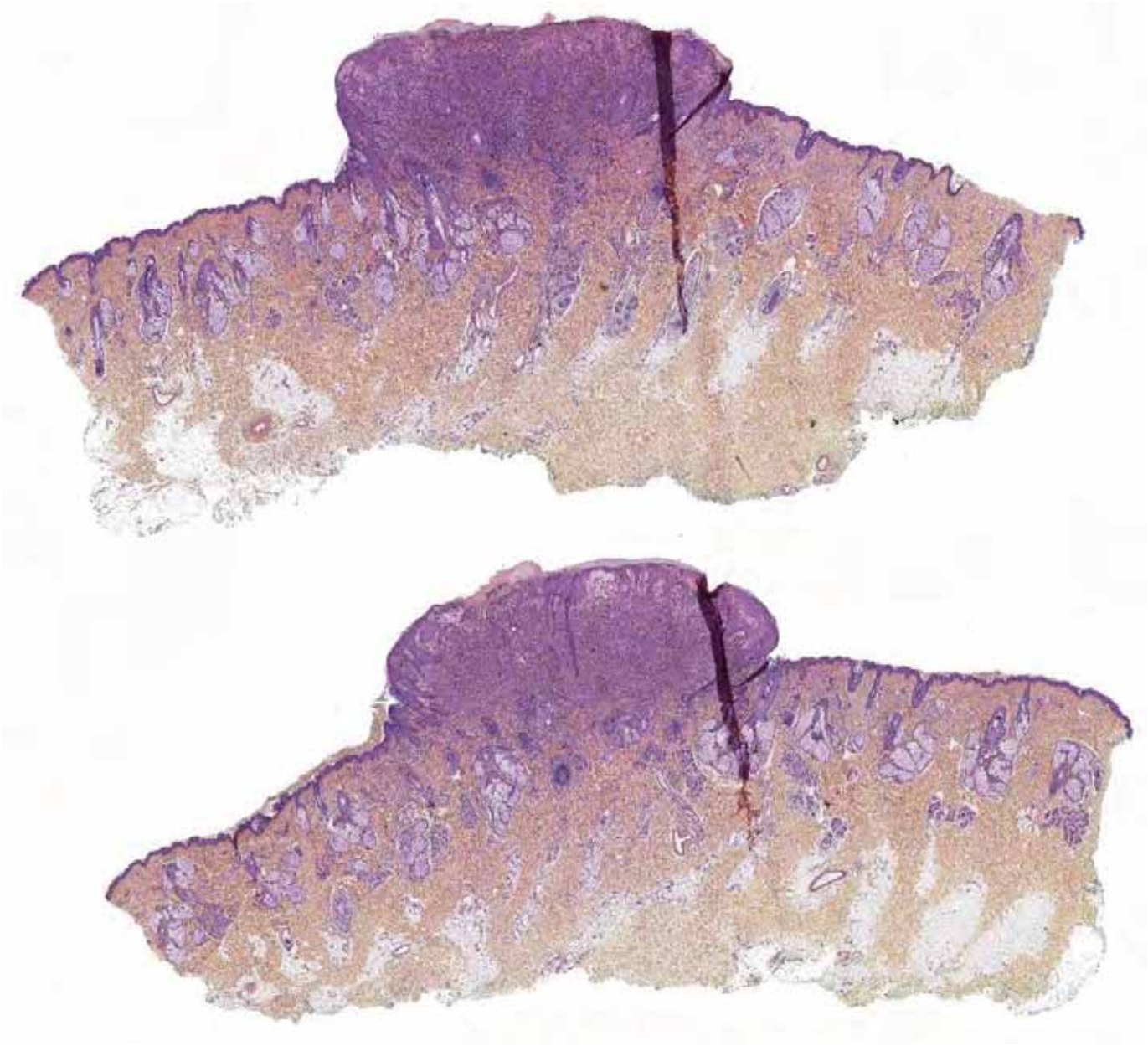


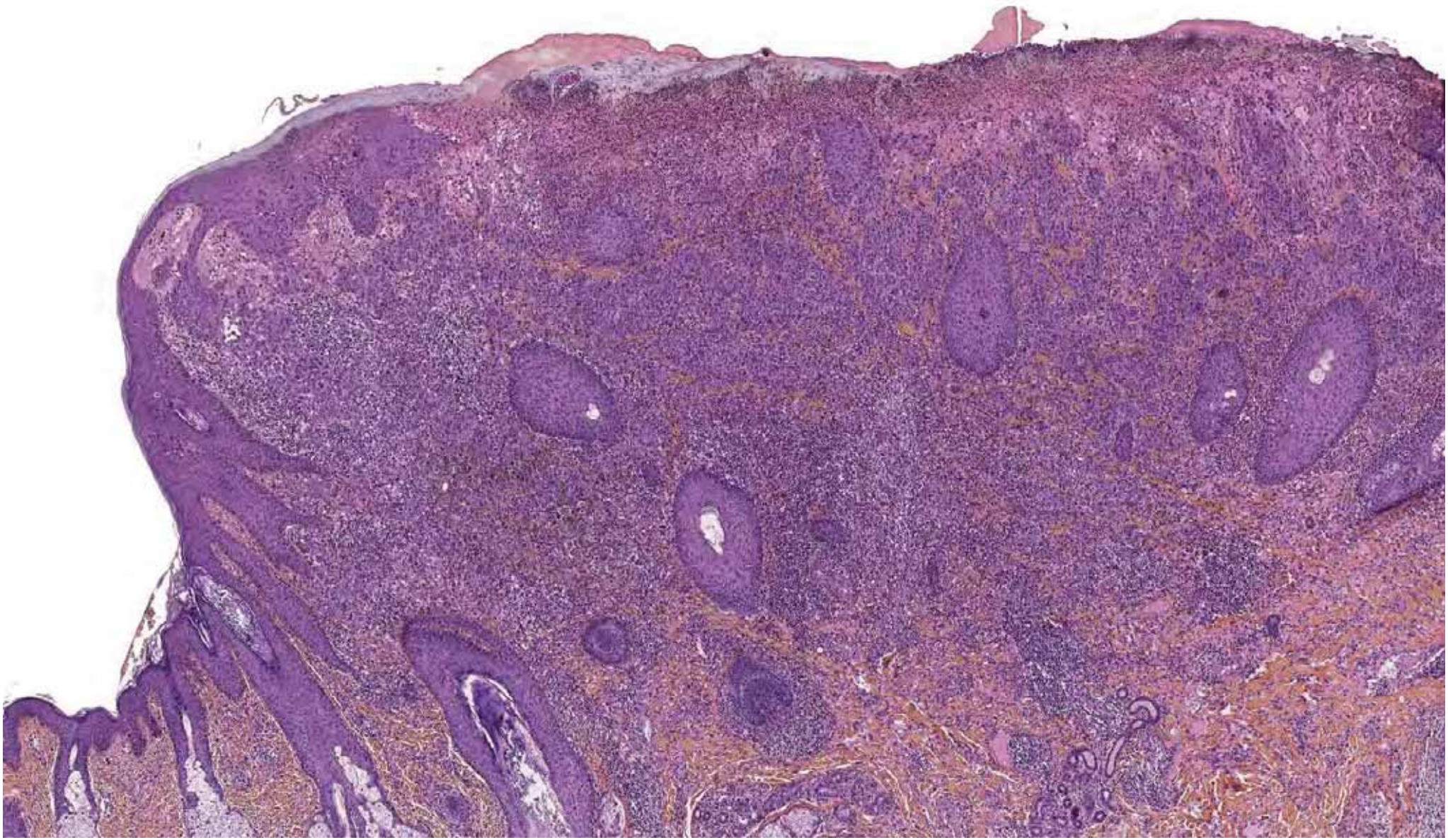
MAP3K8-altered melanocytic tumors

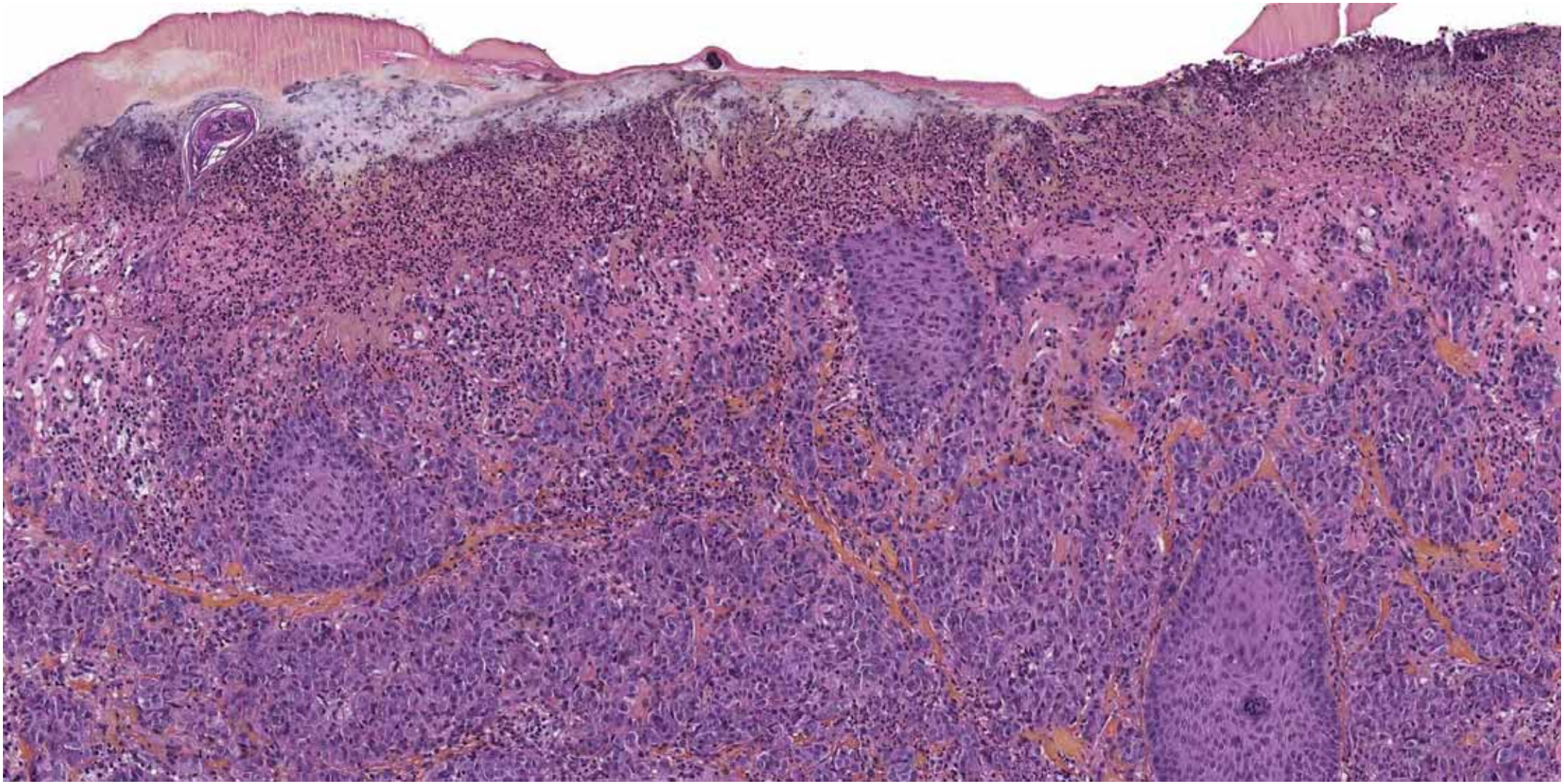
- Young patients
- Lower limb
- Wide ulceration
- Large dermal epithelioid melanocytes
- Multinucleated cells (pseudo-granulomatous morphology)
- Pigmented clones

MAP3K8 fusions

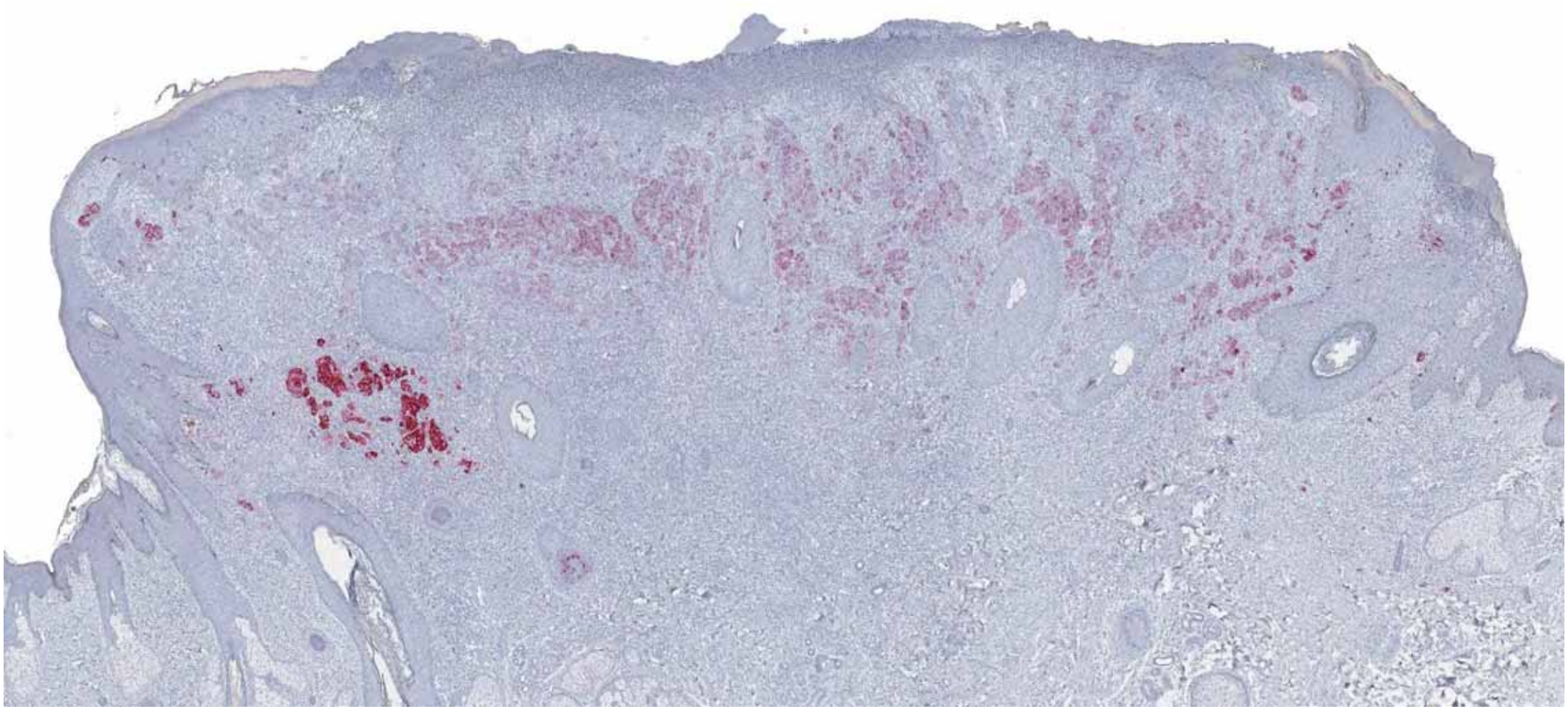




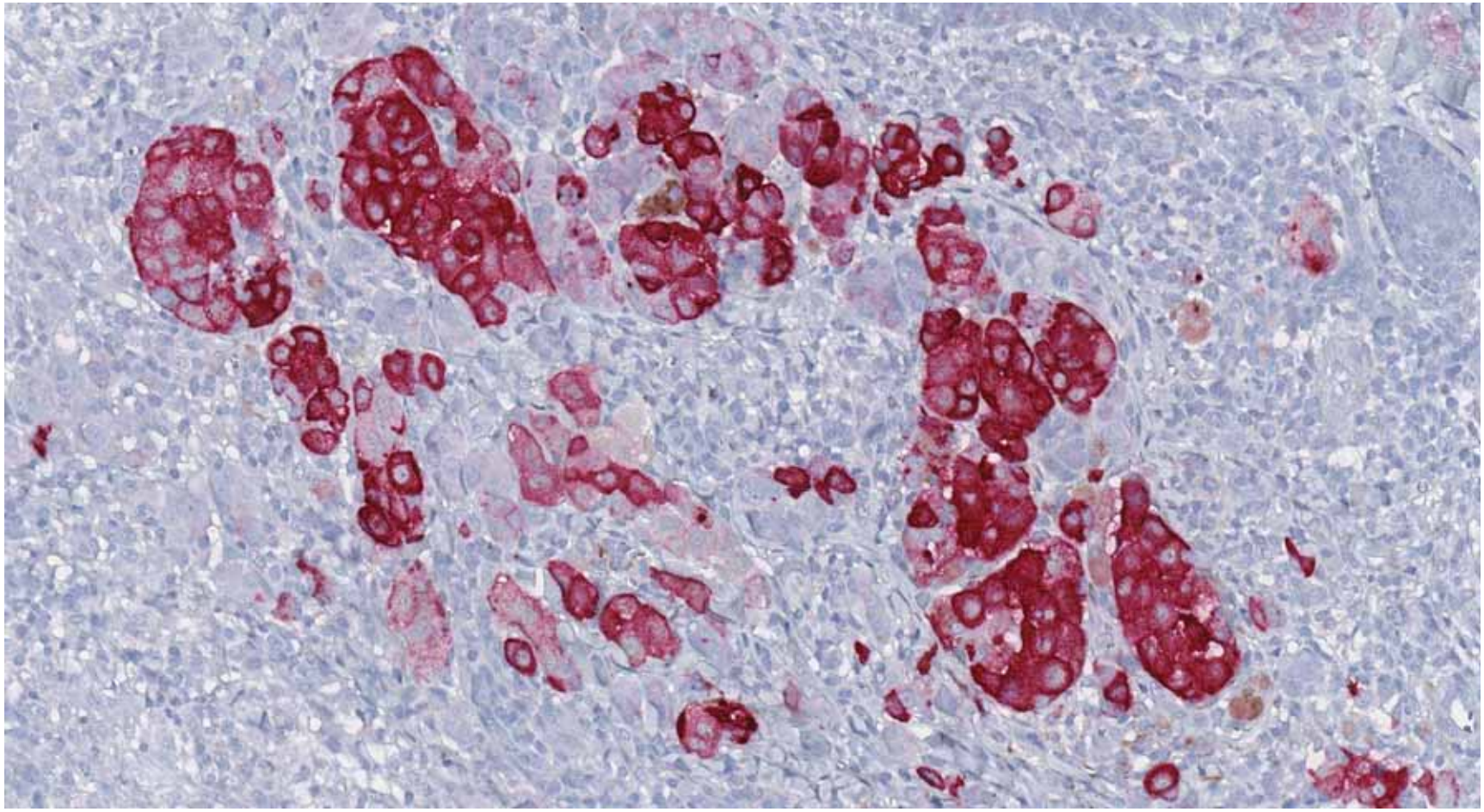


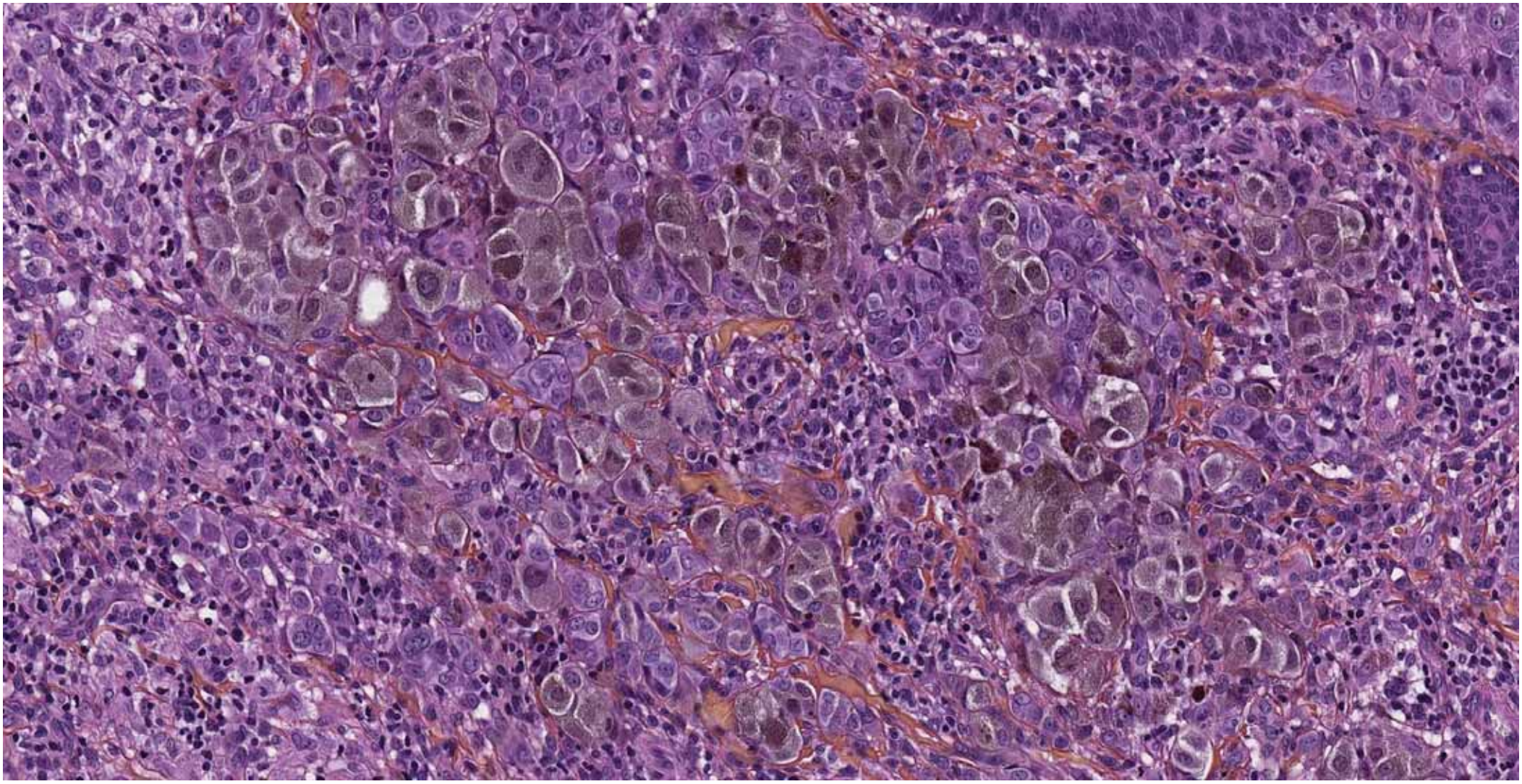


HMB45 IHC

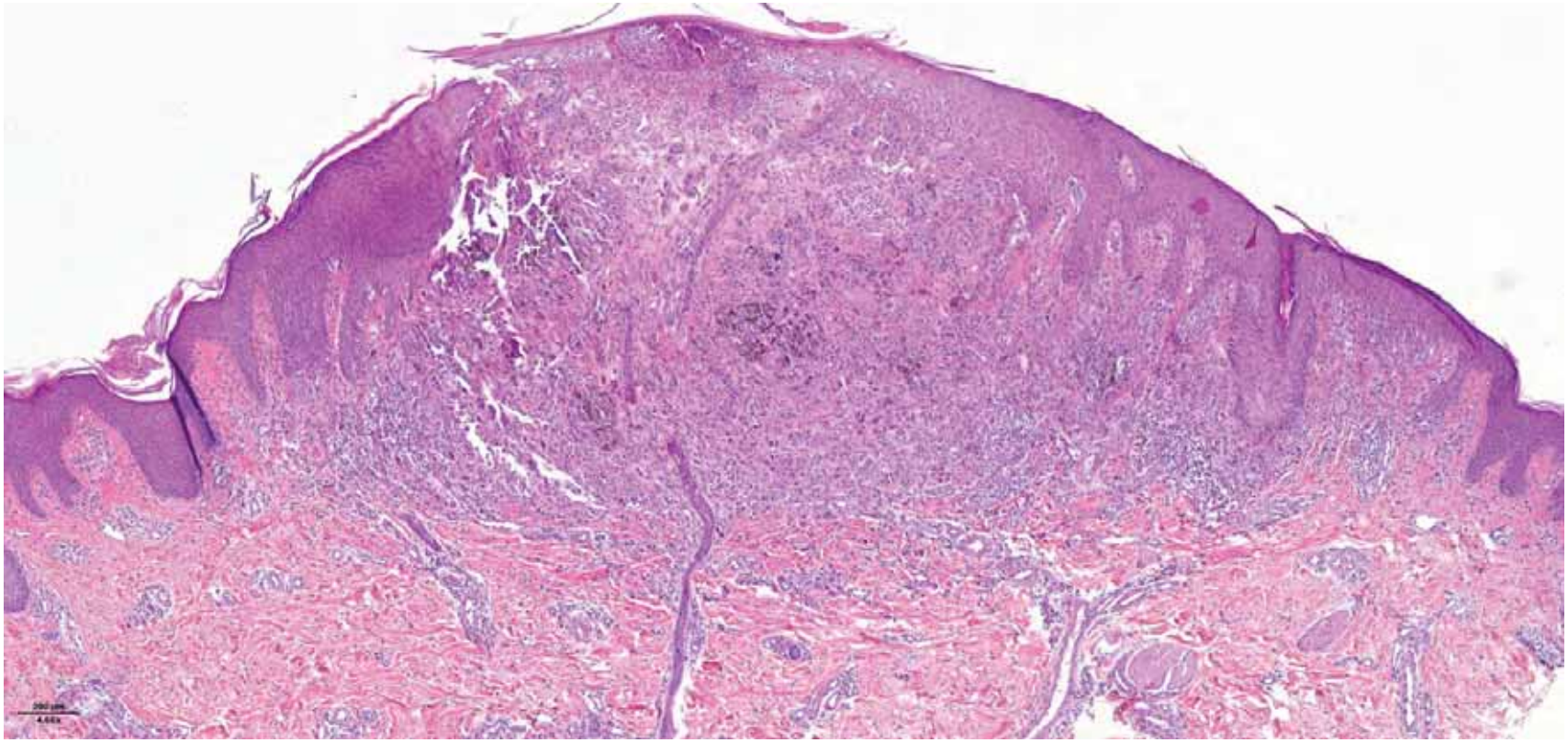


HMB45 IHC



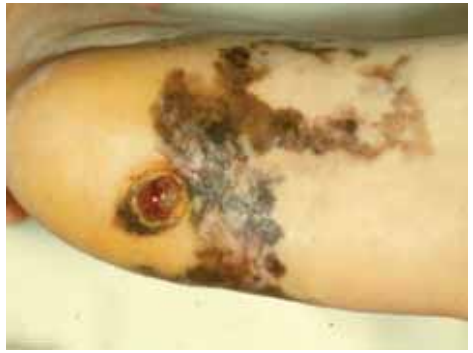


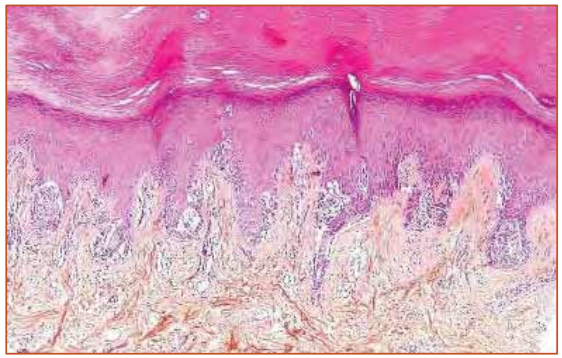
MAP3K8

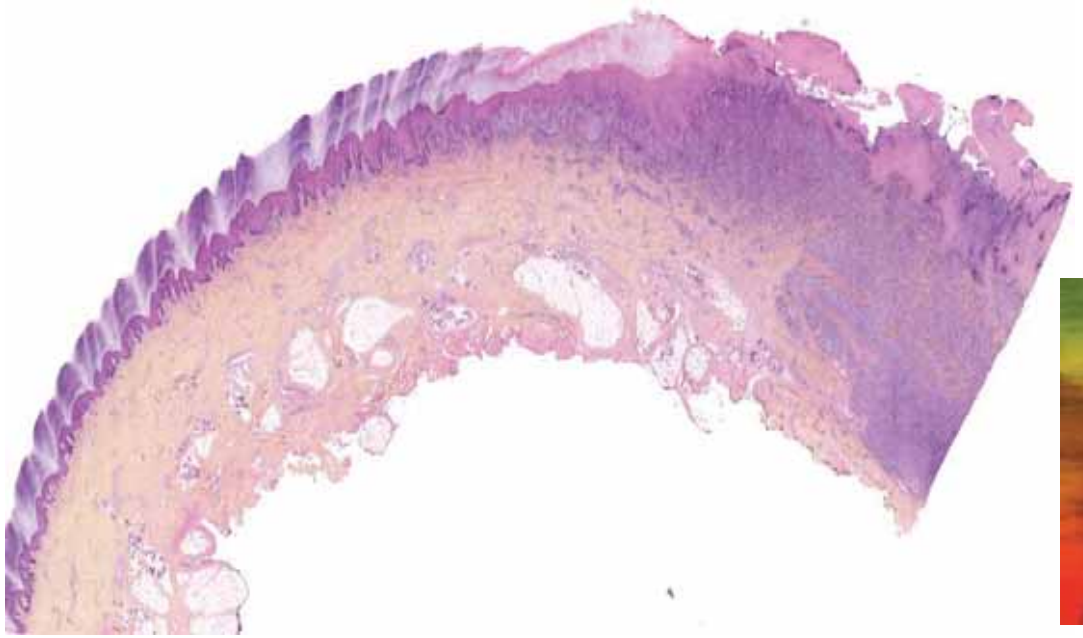


Class V Acral Lentiginous Melanoma

UV-independant (TMB low)
Identical frequency in all phototypes
No pre-existing nevus
Specific genomic model







Genomic hailstorm in ALM

- Non-random genomic hailstorm areas
- 5p : h-tert, RICTOR, SKP2
- 11q : CCND1, PAK1, GAB2, YAP1
- 12q: MDM2, CDK4
- 22q: CRKL, Sox10, EP300

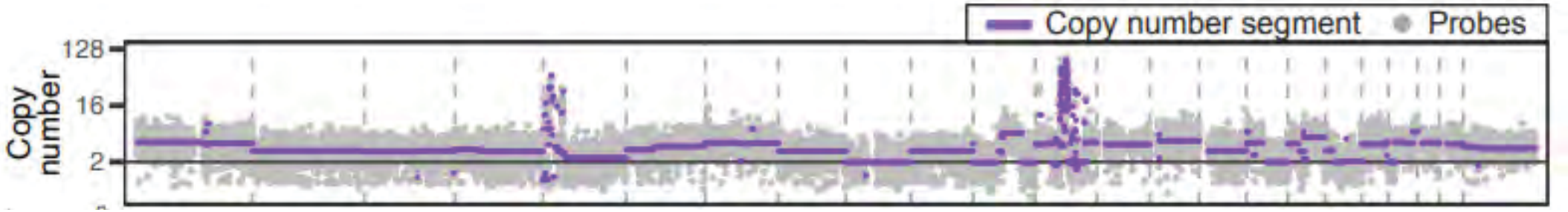
› Nat Commun. 2024 Jul 21;15(1):6146. doi: 10.1038/s41467-024-50233-z.

The genetic evolution of acral melanoma

Meng Wang [1 2], Satoshi Fukushima [3], Yi-Shuan Sheen [4], Egle Ramelyte [5], Noel Cruz-Pacheco [1 2], Chenxu Shi [1 2], Shanshan Liu [1 2], Ishani Banik [1 2], Jamie D Aquino [6], Martin Sangueza Acosta [7], Mitchell Levesque [5], Reinhard Dummer [5], Jau-Yu Liau [4], Chia-Yu Chu [4], A Hunter Shain [1 2], Iwei Yeh [1 2 6], Boris C Bastian [8 9 10]

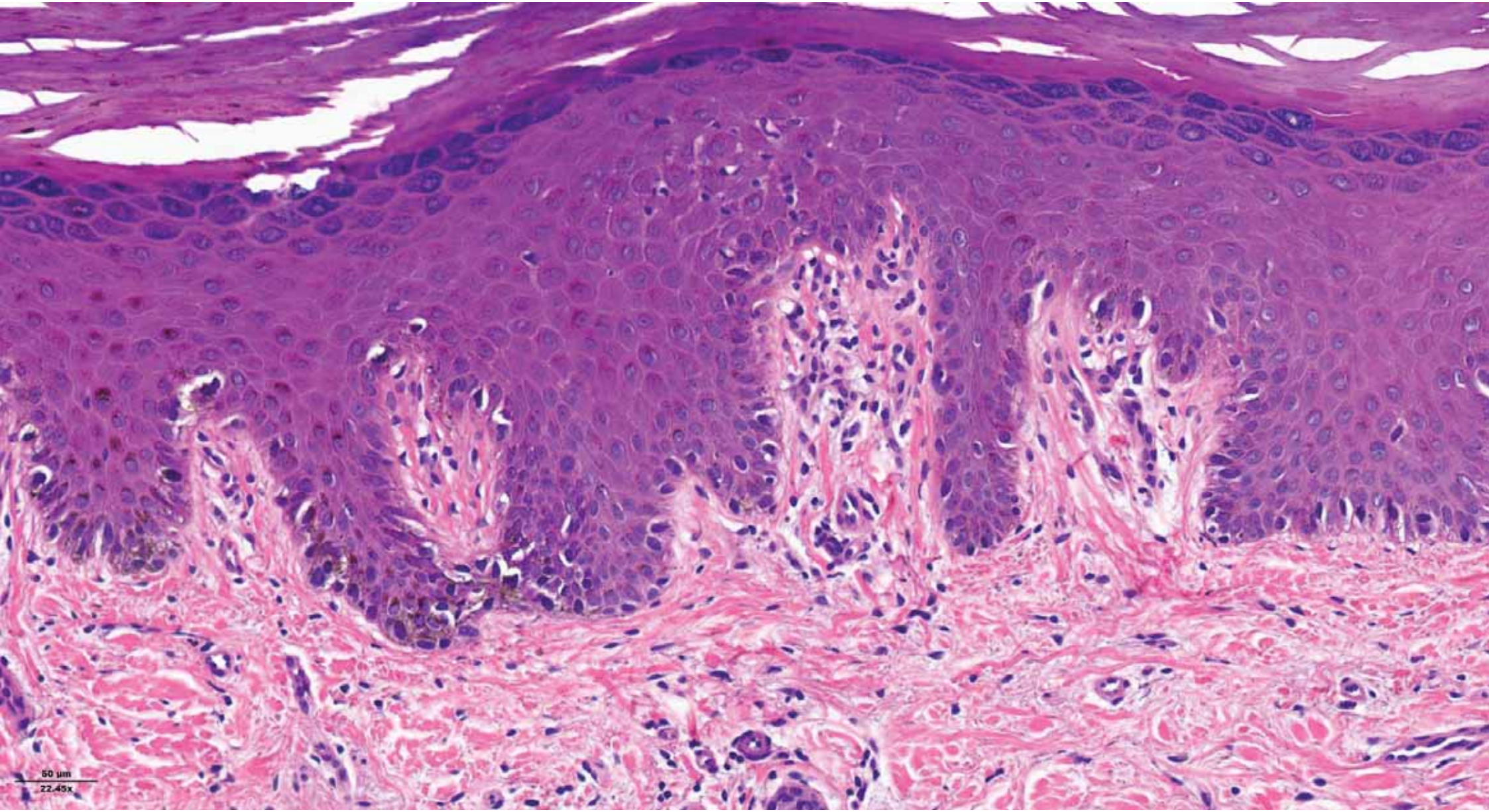
Affiliations + expand

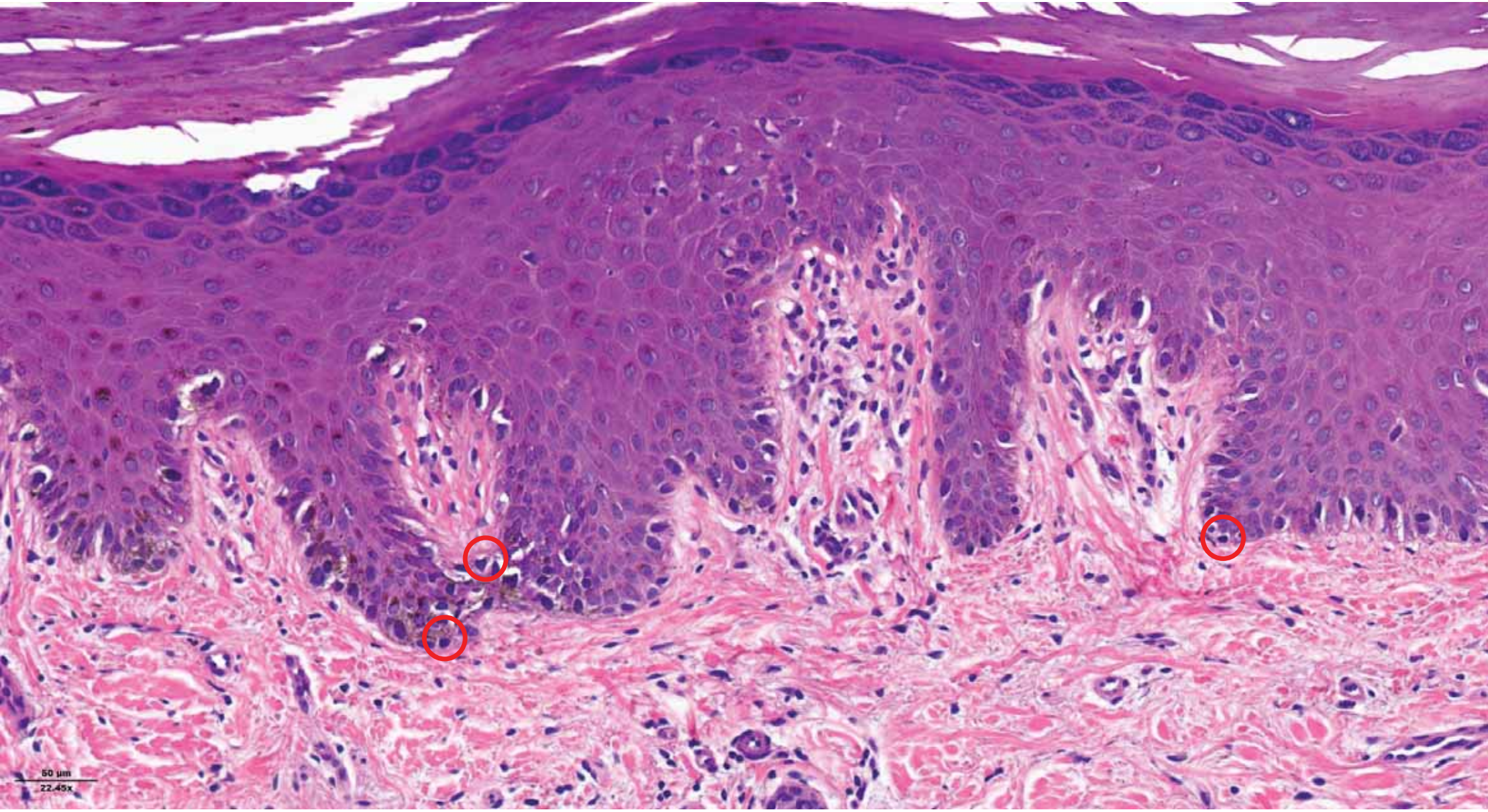
PMID: 39034322 PMCID: PMC11271482 DOI: 10.1038/s41467-024-50233-z

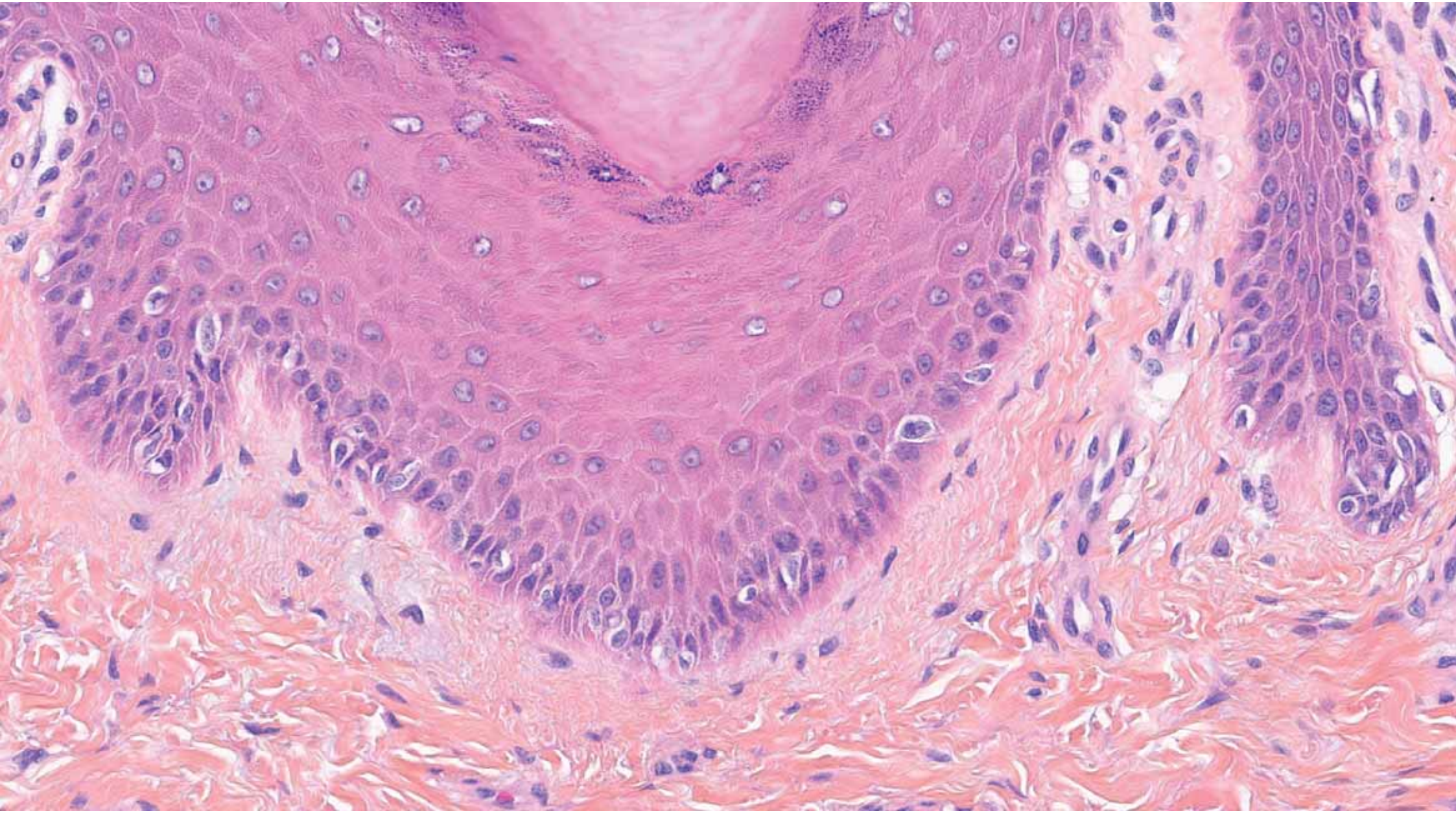


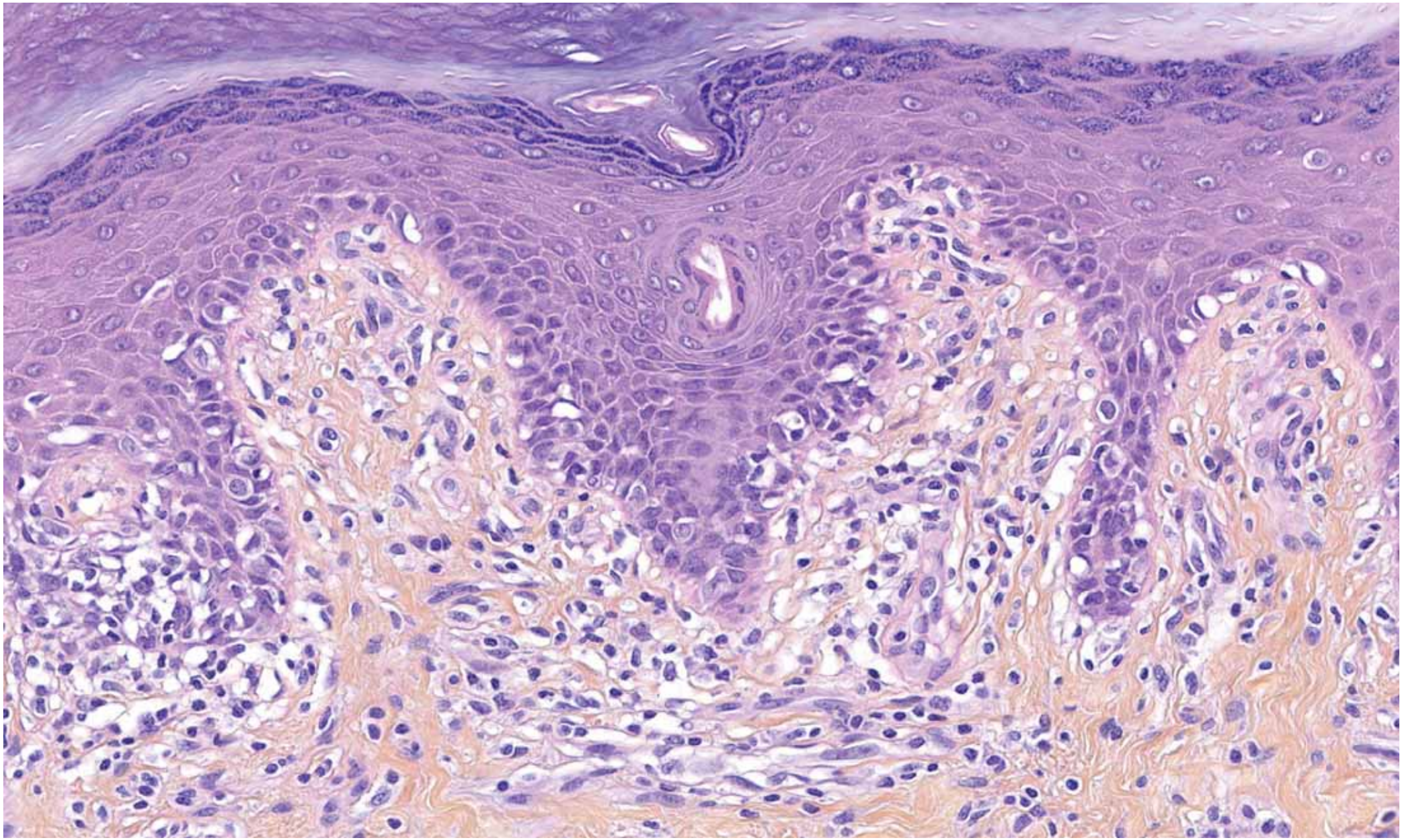
Lateral junctional lentiginous component

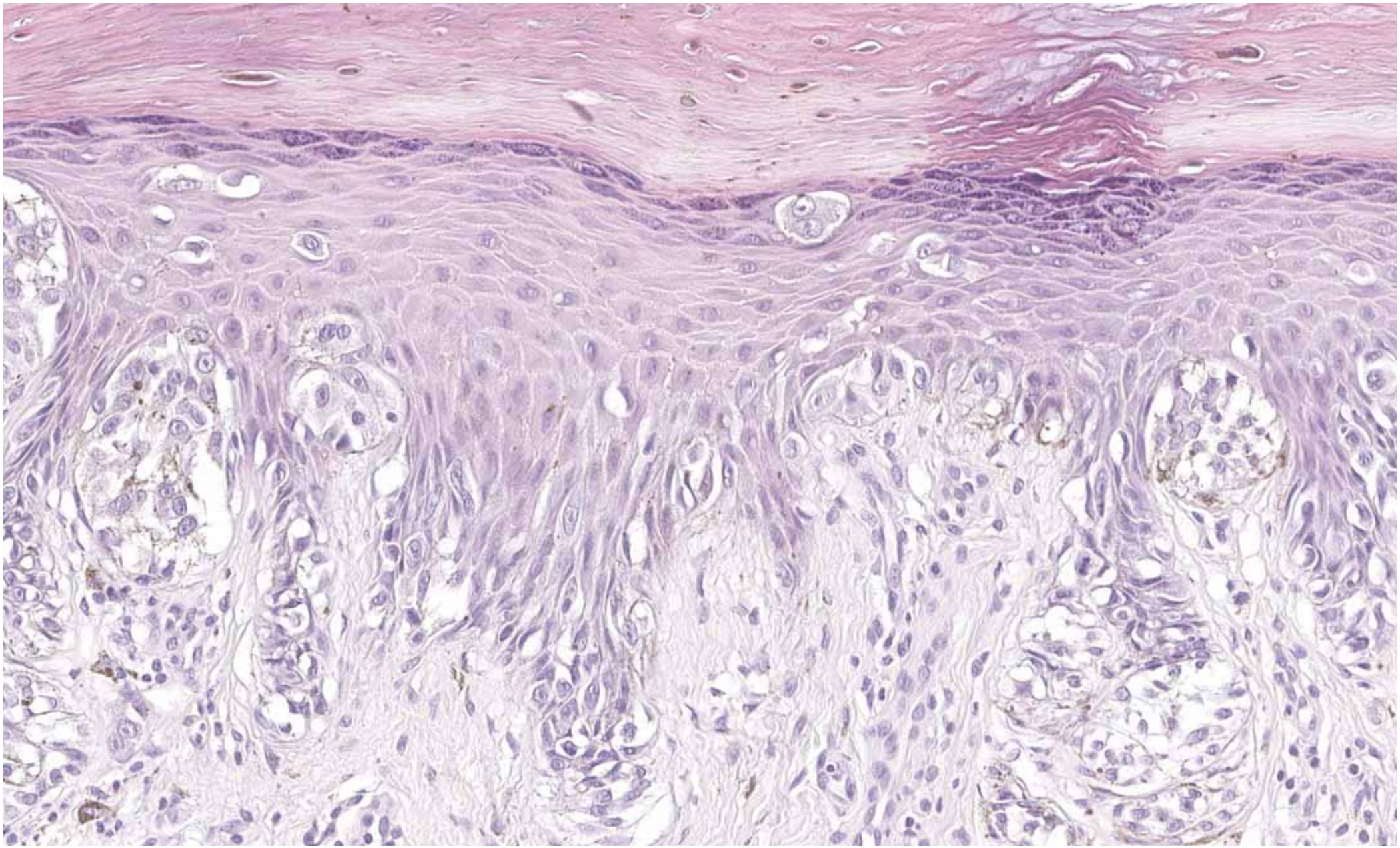
- Limited ascent of cells
- Quadrangular hyperchromatic nuclei


50 µm
22.45x

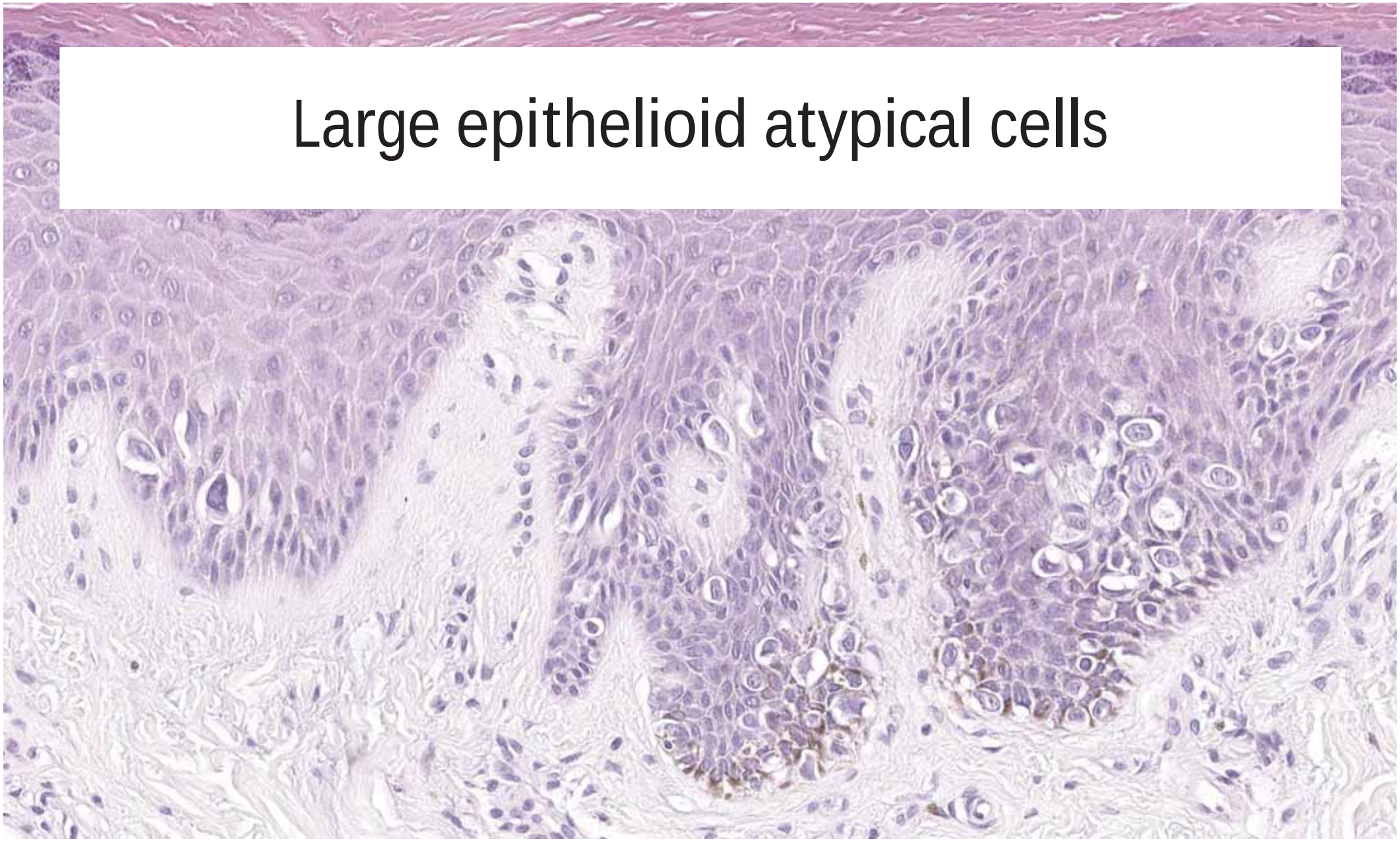

50 µm
22.45x





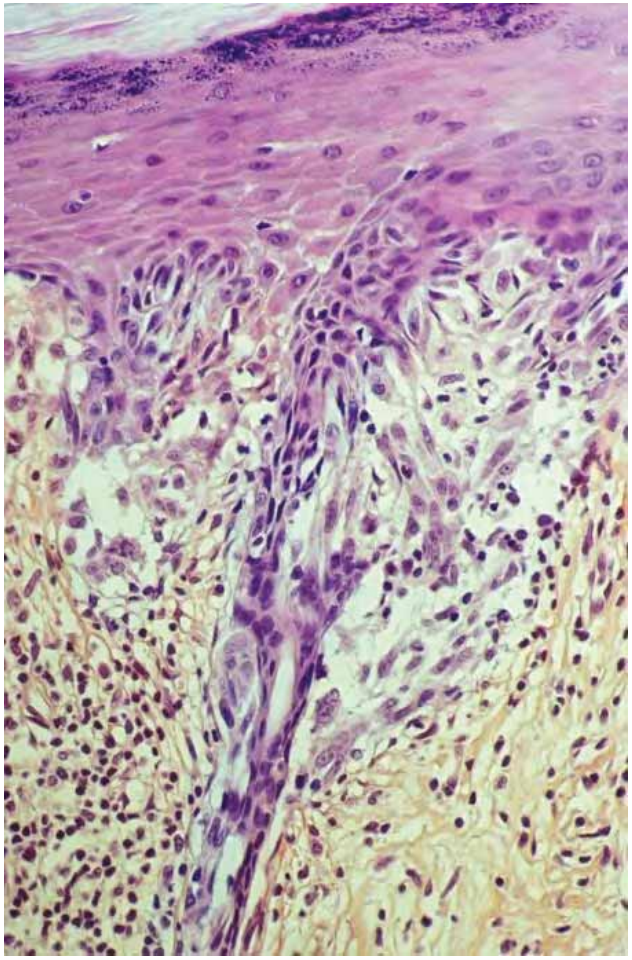


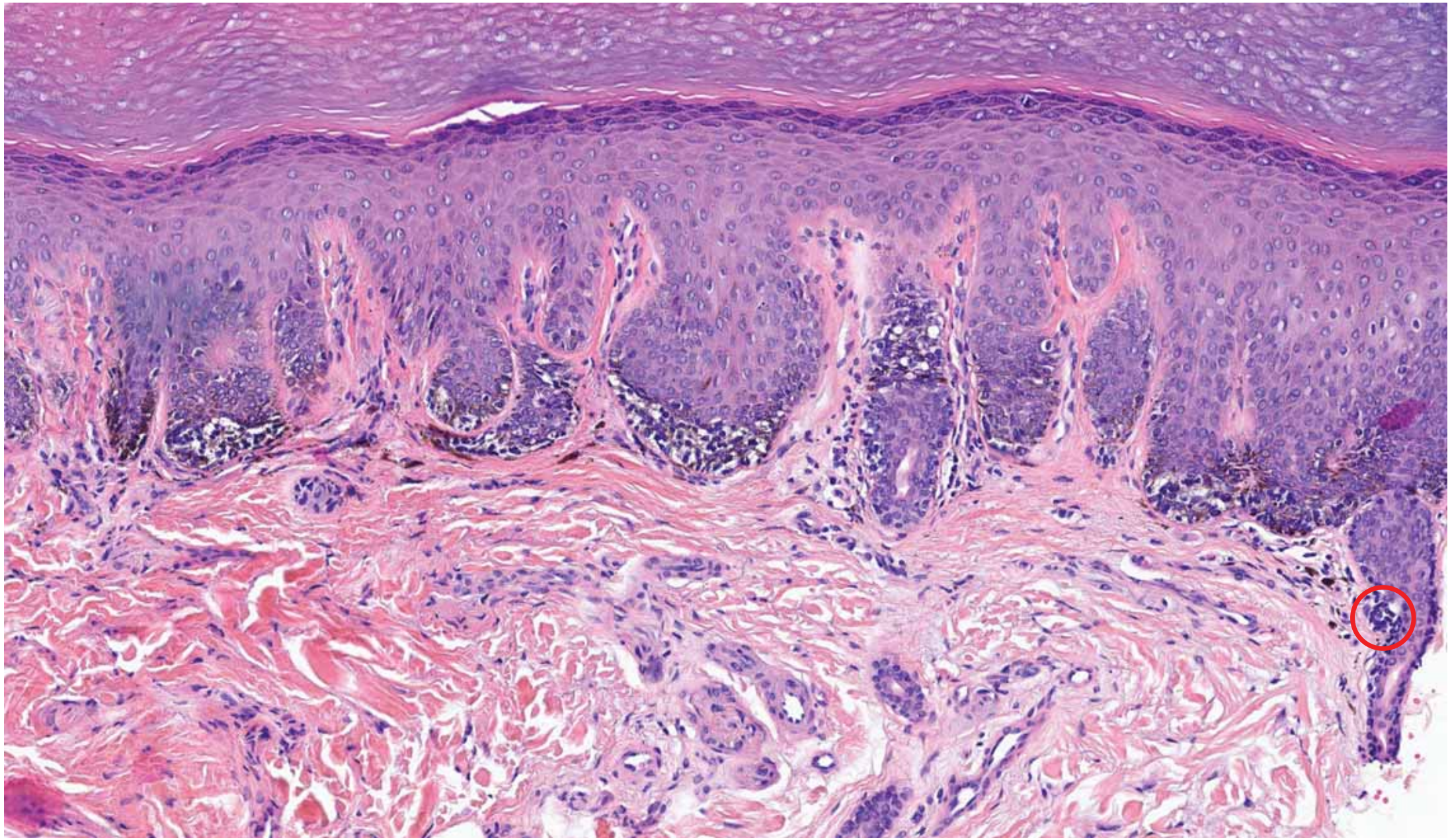
Large epithelioid atypical cells

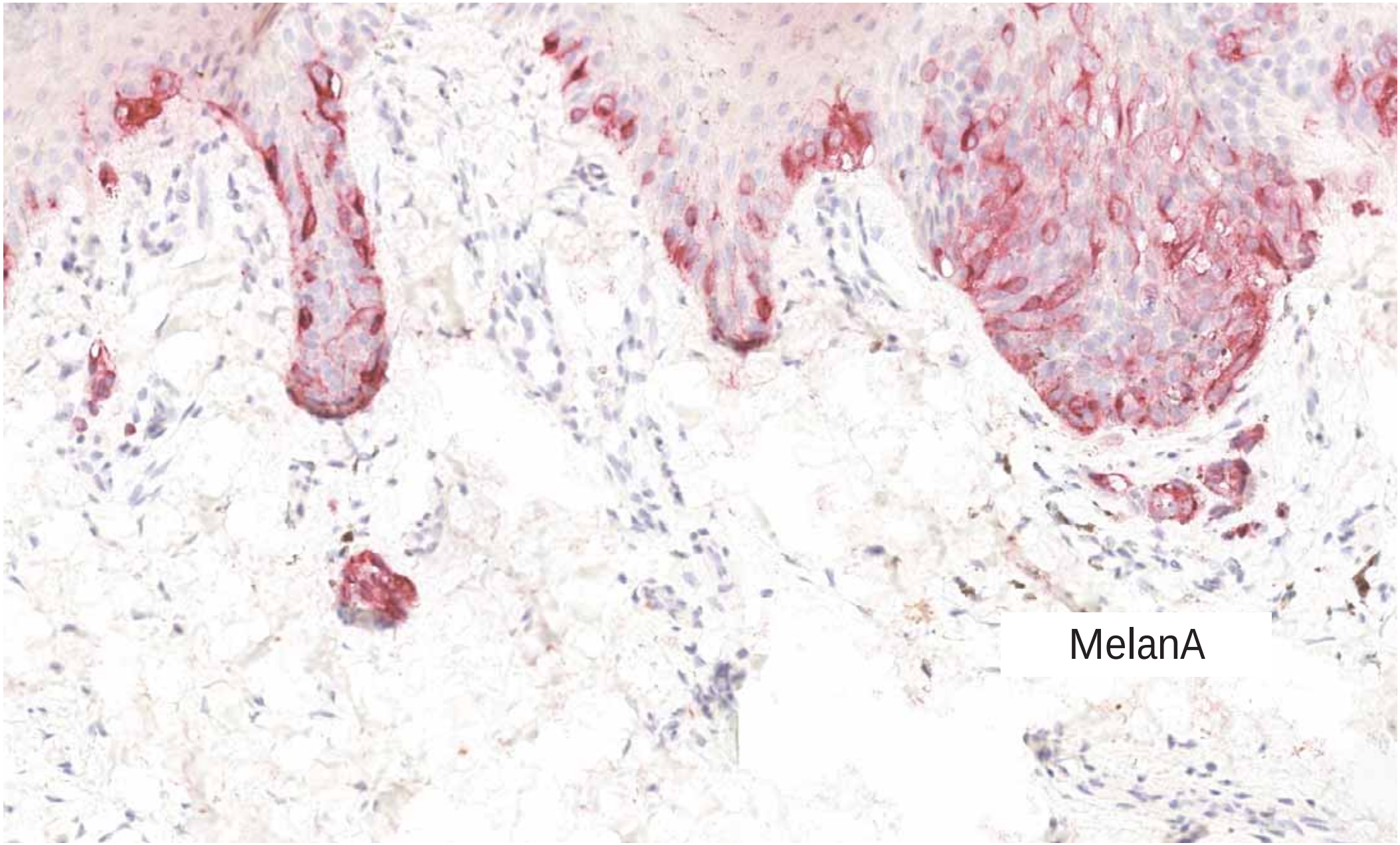


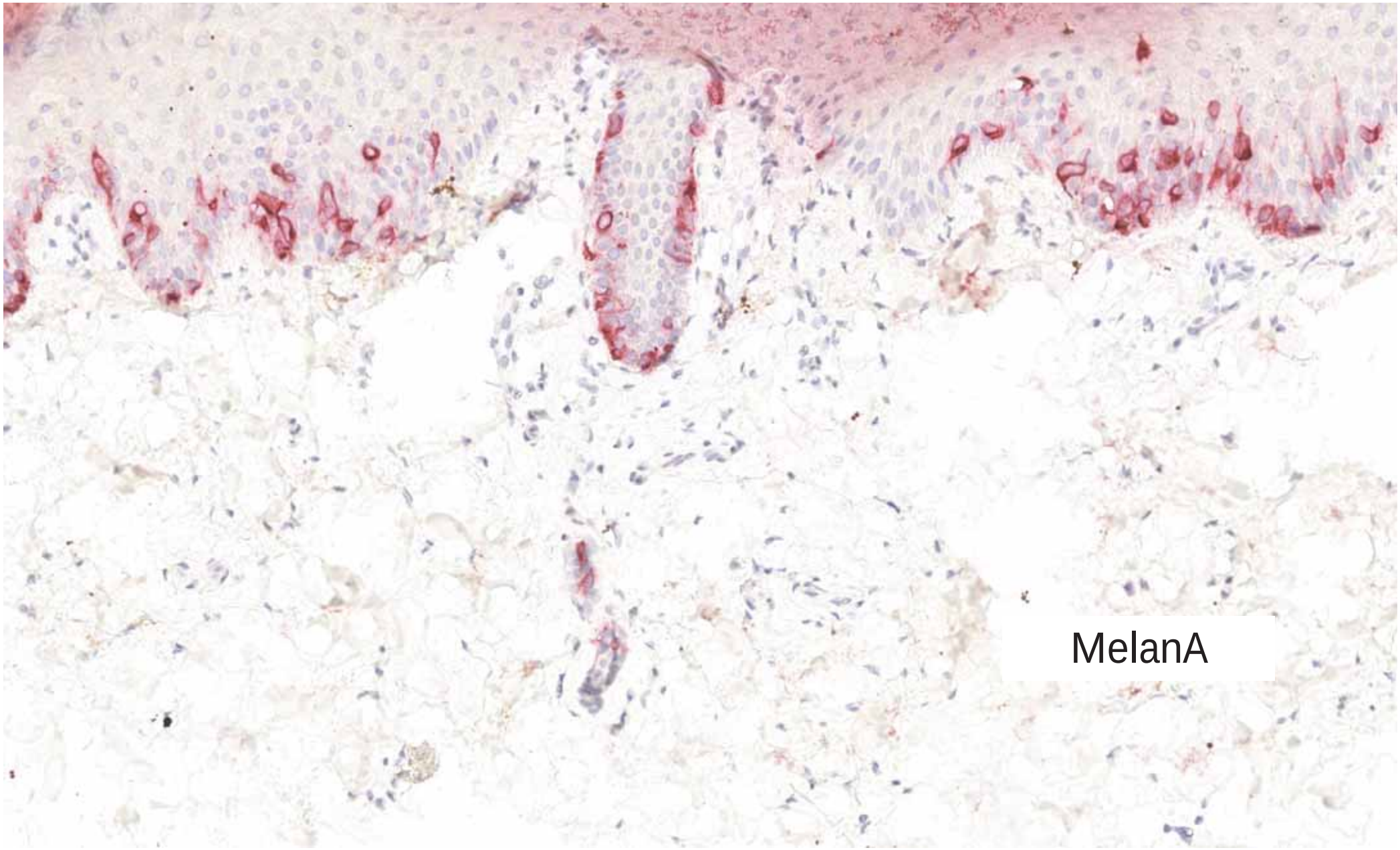
Lateral junctional lentiginous component

- Peri-sudoral invasion



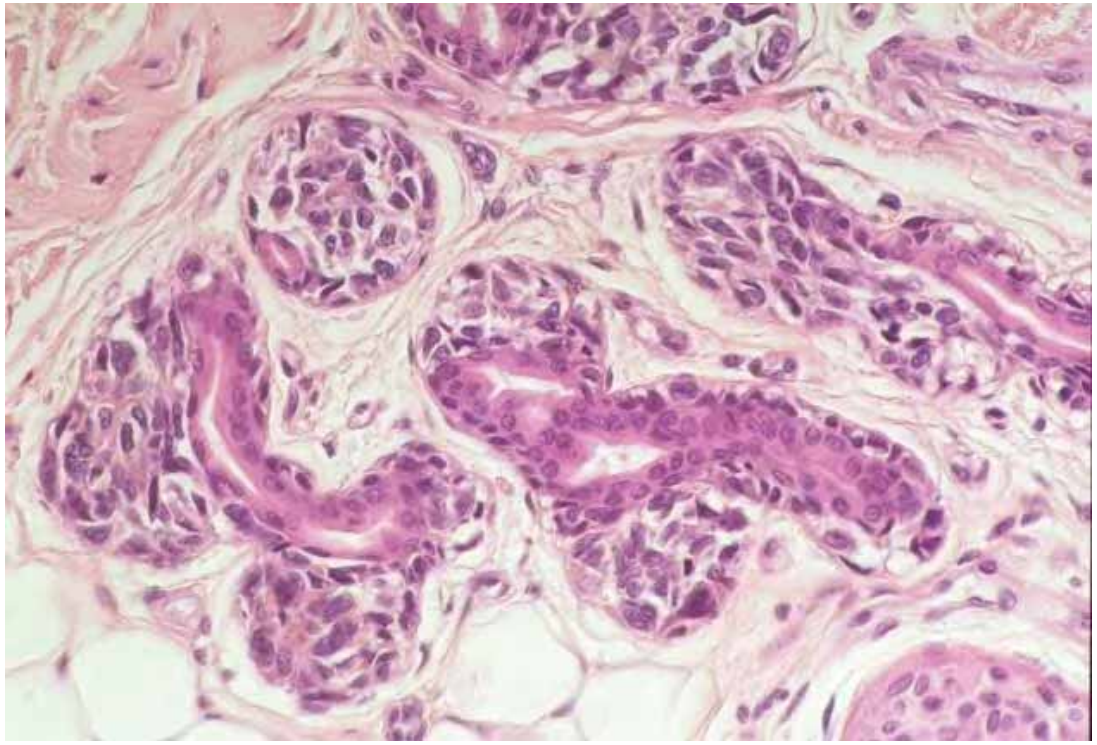



MelanA


MelanA

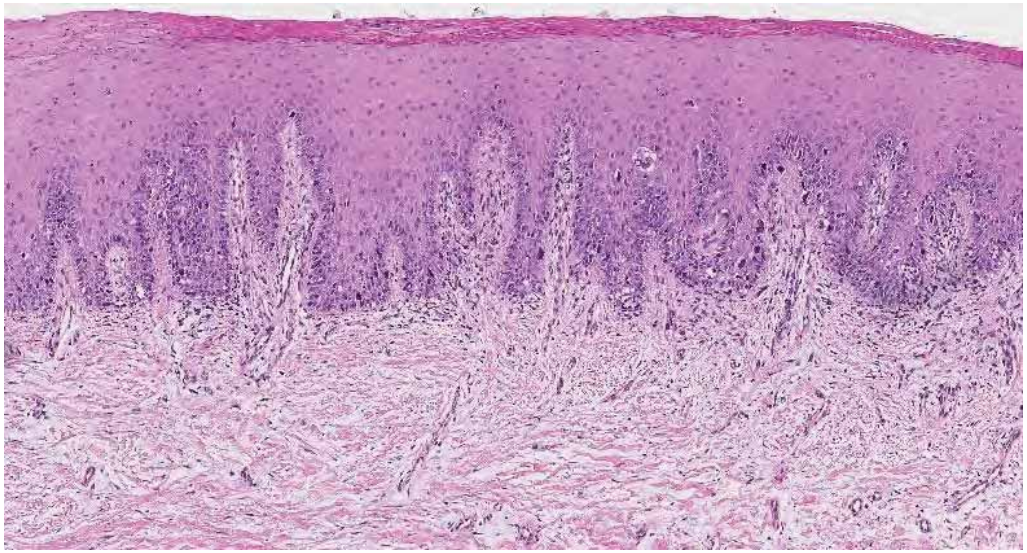
Lateral junctional lentiginous component

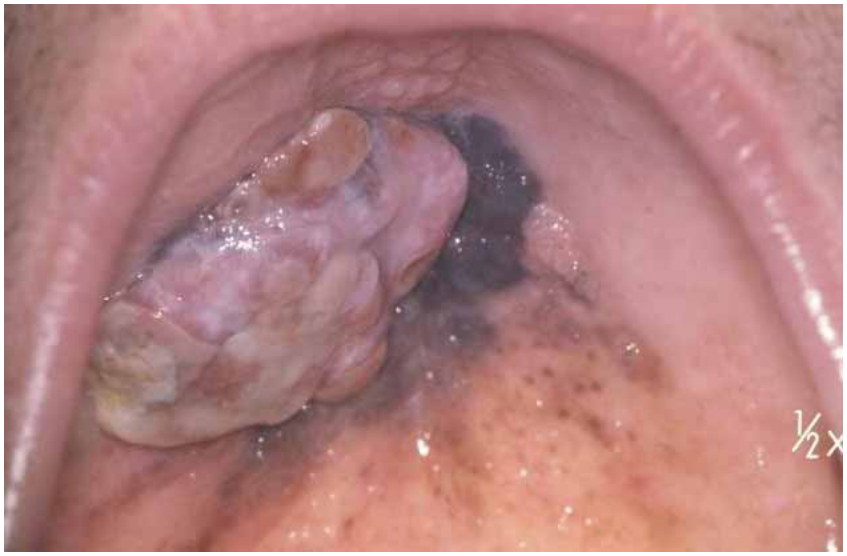
- Peri-sudoral invasion



Class VI Mucosal Lentiginous Melanoma

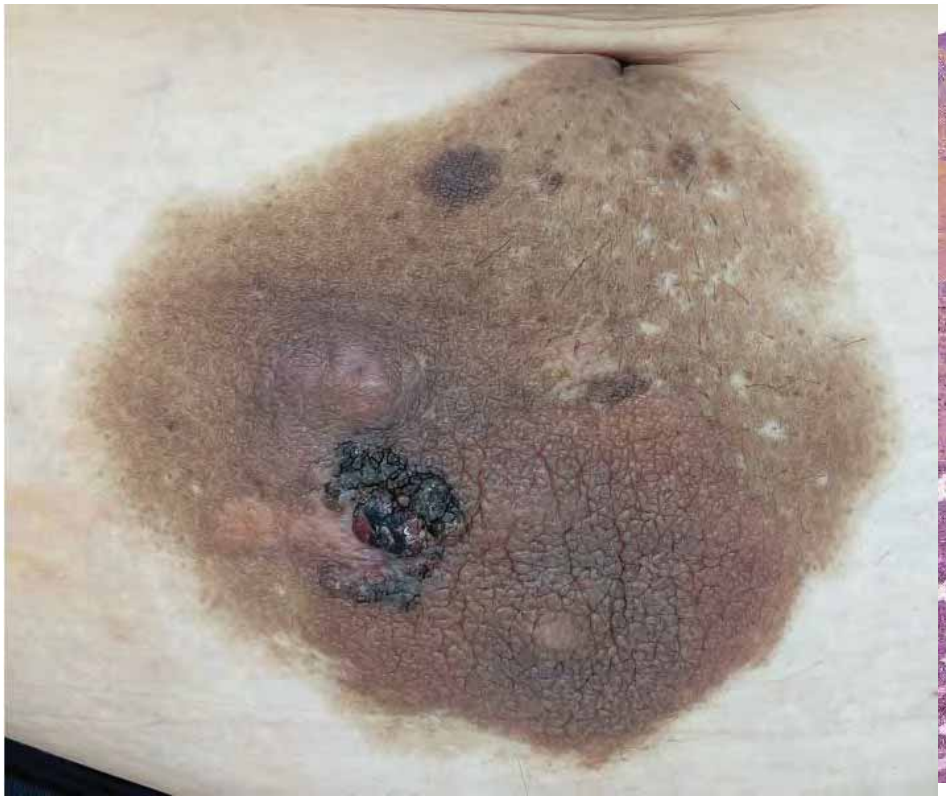
UV-independant (TMB low)
Identical frequency in all phototypes
No pre-existing nevus
Specific genomic model

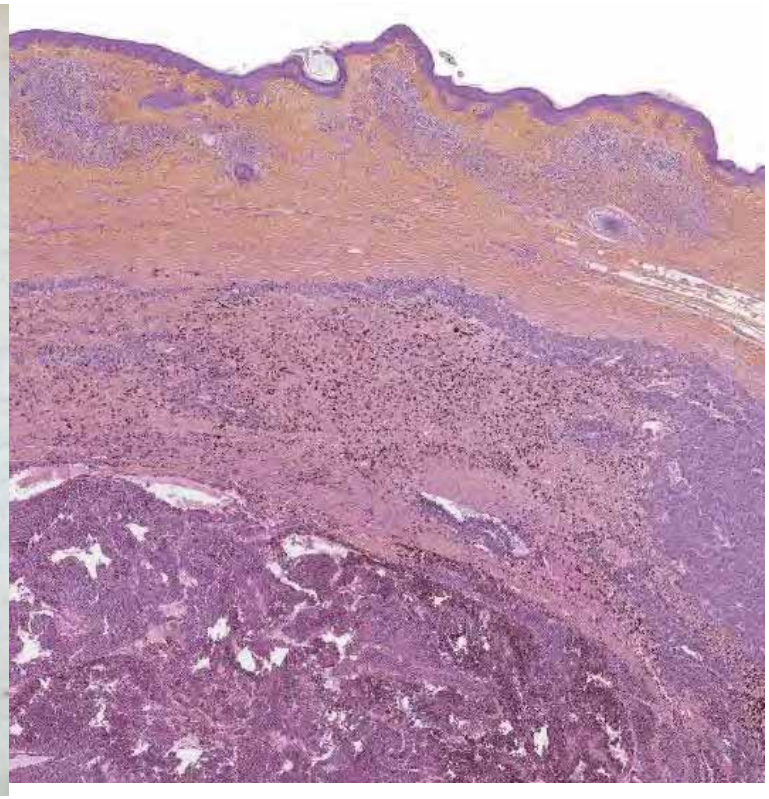


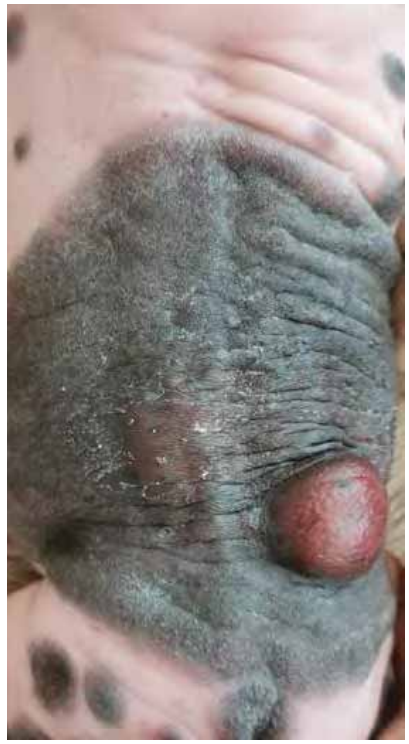


Class VII Melanoma ex-giant Congenital nevus

NRAS exon 3 mutations
Fatal risk in early life







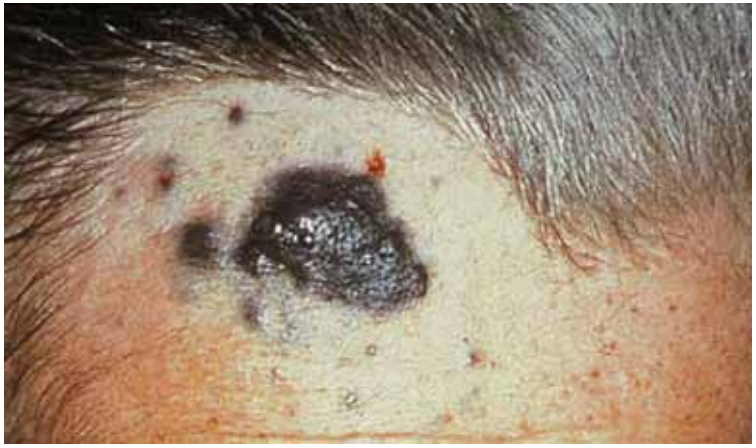
Class VIII

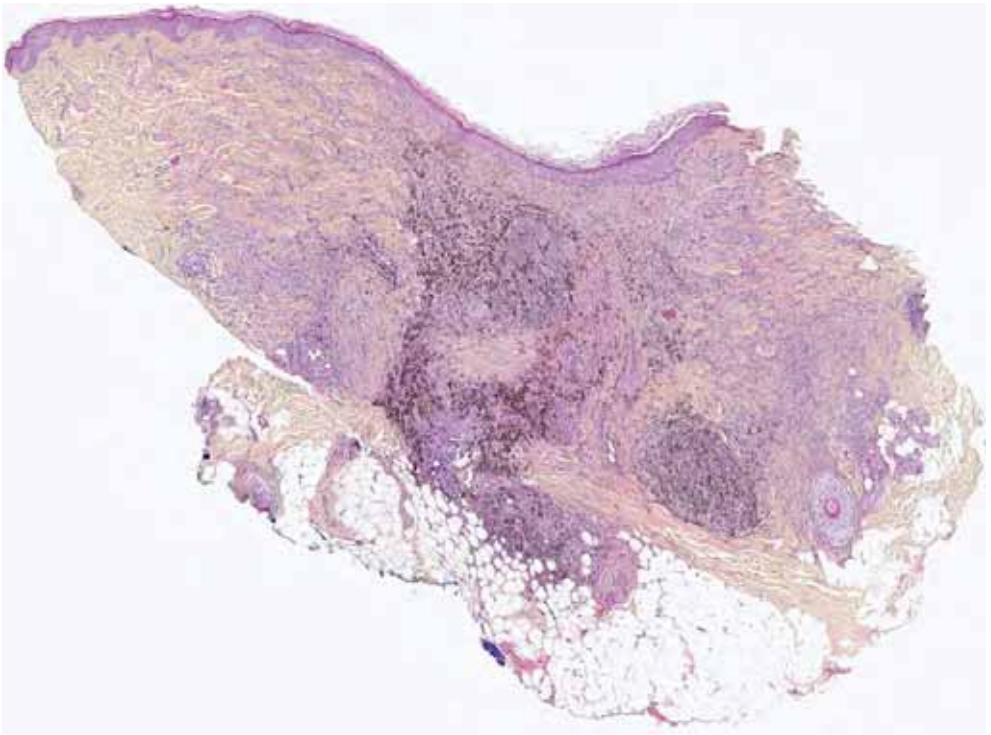
Melanoma ex-Blue Nevus

UV-independant (TMB low)

Nevus to melanoma progression model

Specific genetic anomalies





Specific hotspot «blue» melanocytic»mutations

Some are also found in pigmented uveal and leptomeningeal lesions/angiomas

CYSLTR2

p.L129Q

GRM1 *gene fusion*

MYO10::GRM1

GNAQ

exon5 (p.Q209) >exon4 (p.R183)

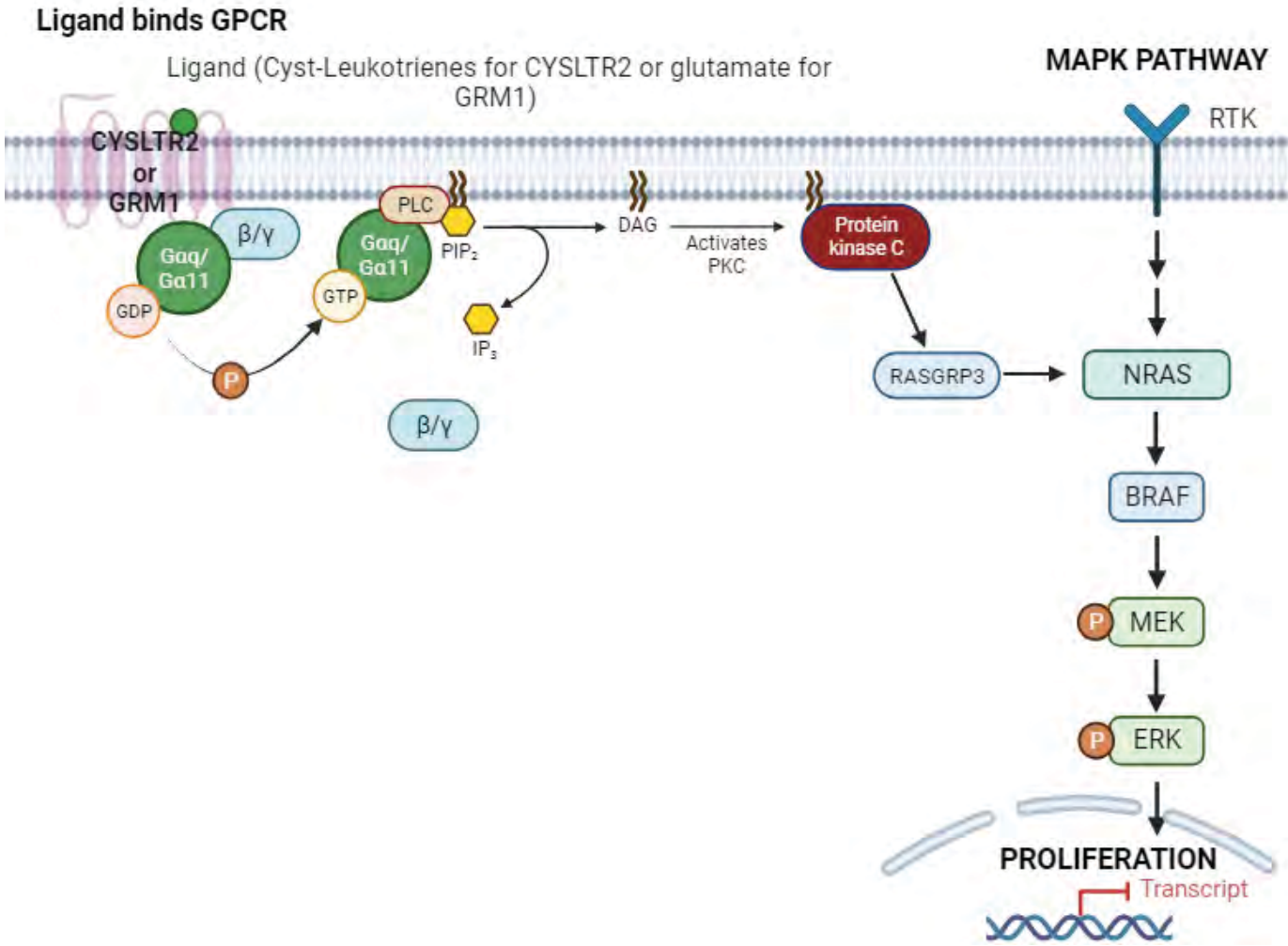
GNA11

exon5 (p.Q209) >exon4 (p.R183)

PLCB4

p.D630

PRKCA PRKCB PRKCG *gene fusions*



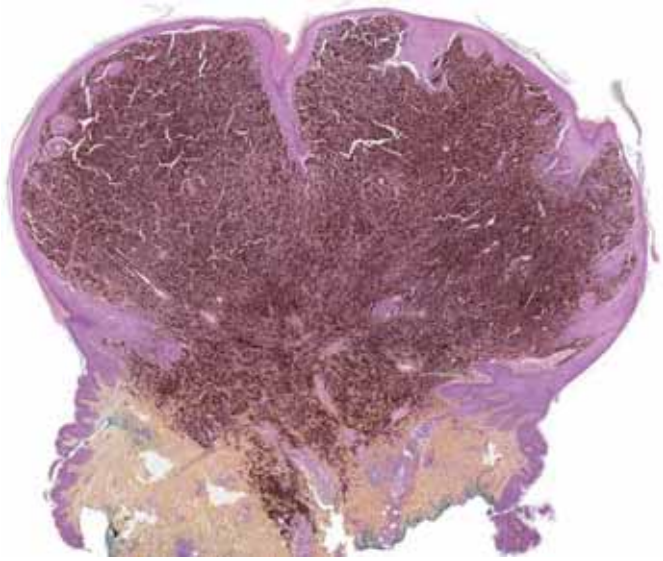
PKC gene fused melanocytic tumors highly variable morphology

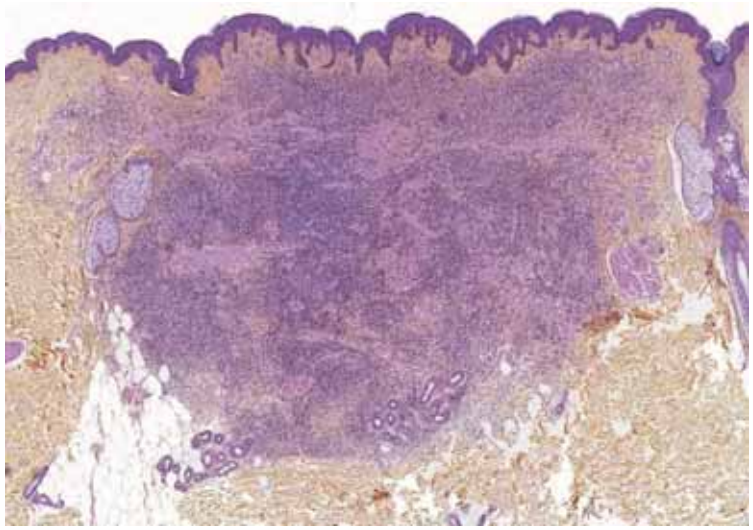
- Junctional PEM-like features
- Upper dermis horizontal band
- Dermal combined blue nevus features
- Variable pigment load
- Variable but constant fibrosis

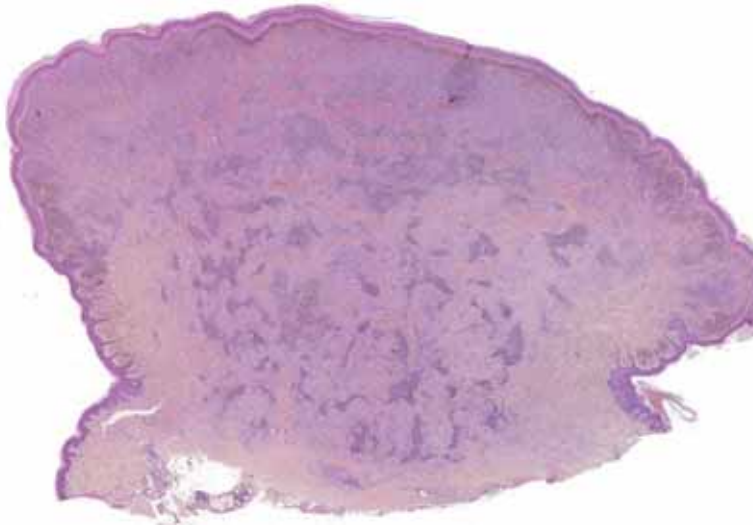
- « PEM + Common + Blue» mixture suggests PKC gene fused tumour
- Can have partial features and/or extreme ends of the spectrums

PKC gene fused blue nevus
highly variable morphology

«PEM-like + Common nevus + blue» mixture suggests PKC gene fused tumour

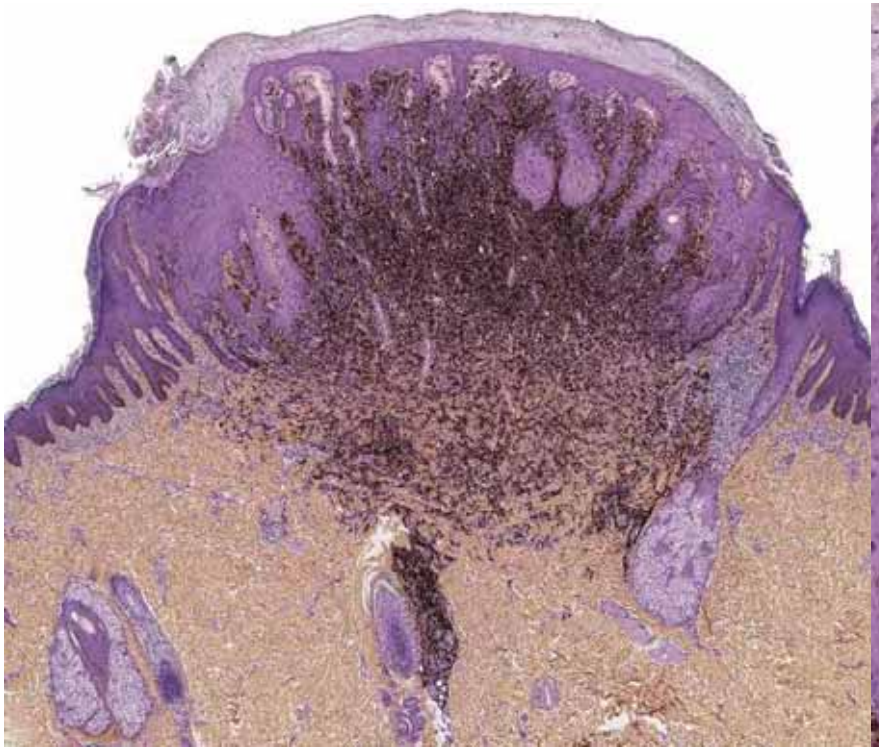


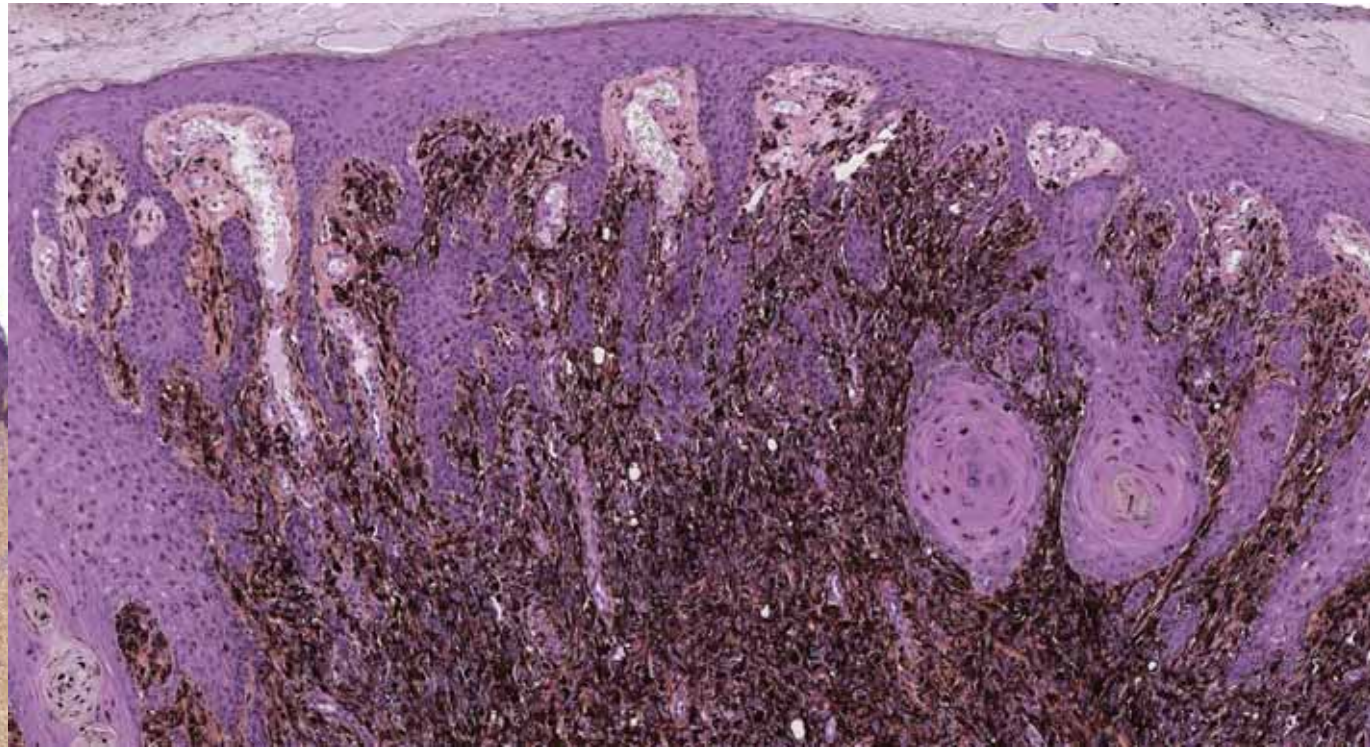




PKC gene fused melanocytic tumors

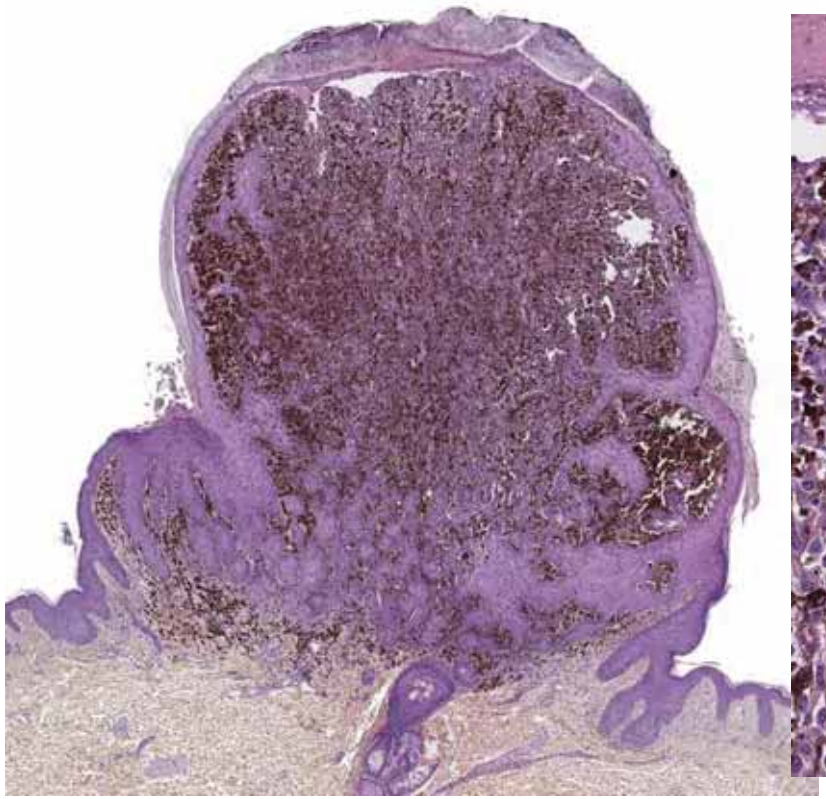
Junctional PEM-like features

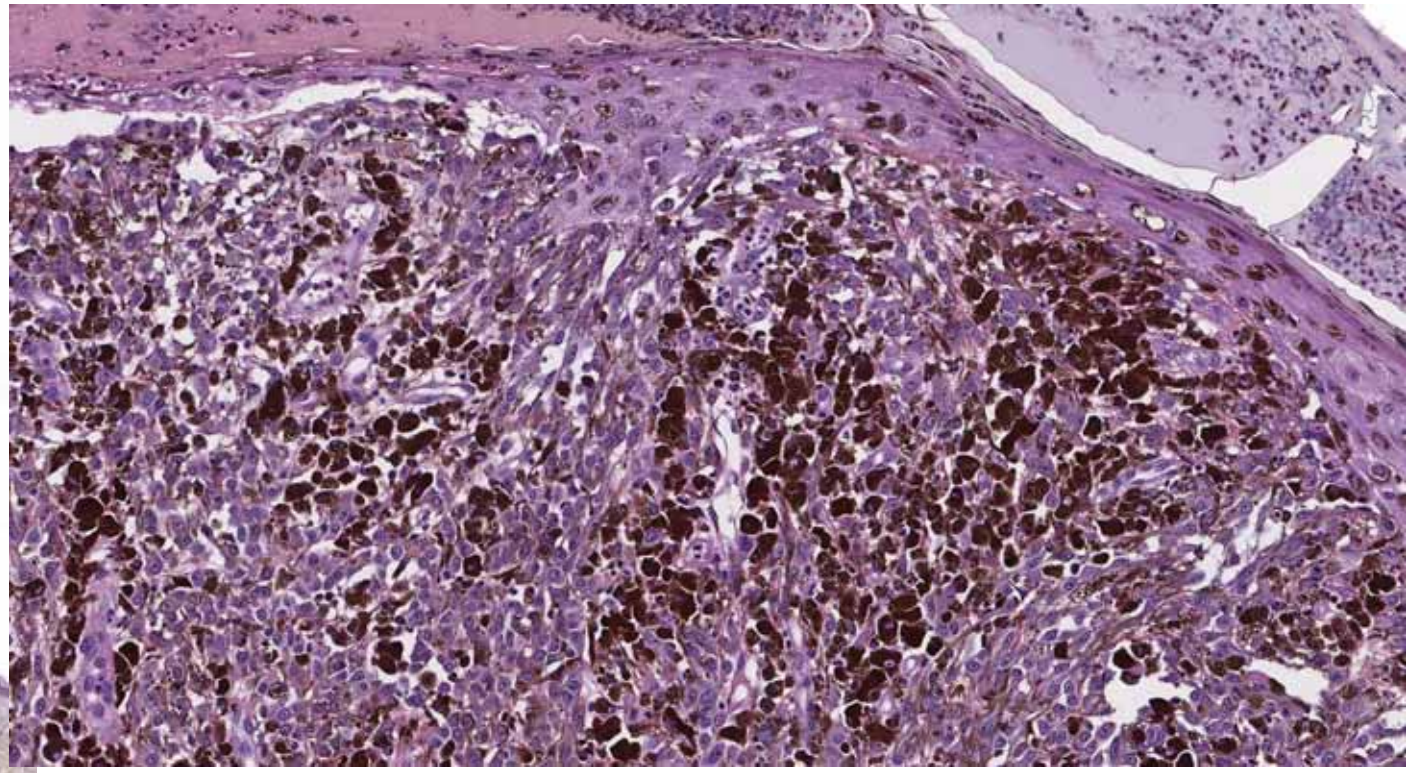




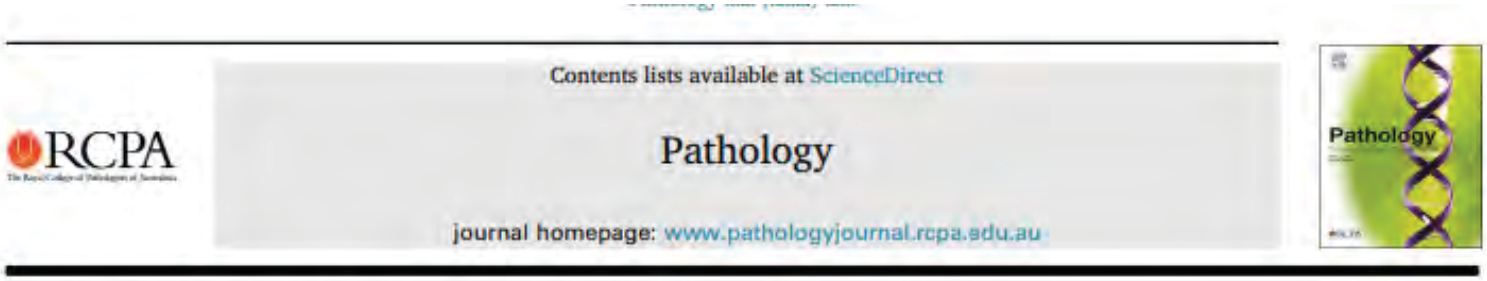
PKC gene fused melanocytic tumors

Junctional PEM-like features





Loss of S100 expression in the superficial band is a good diagnostic sign of PKC-fused blue nevus



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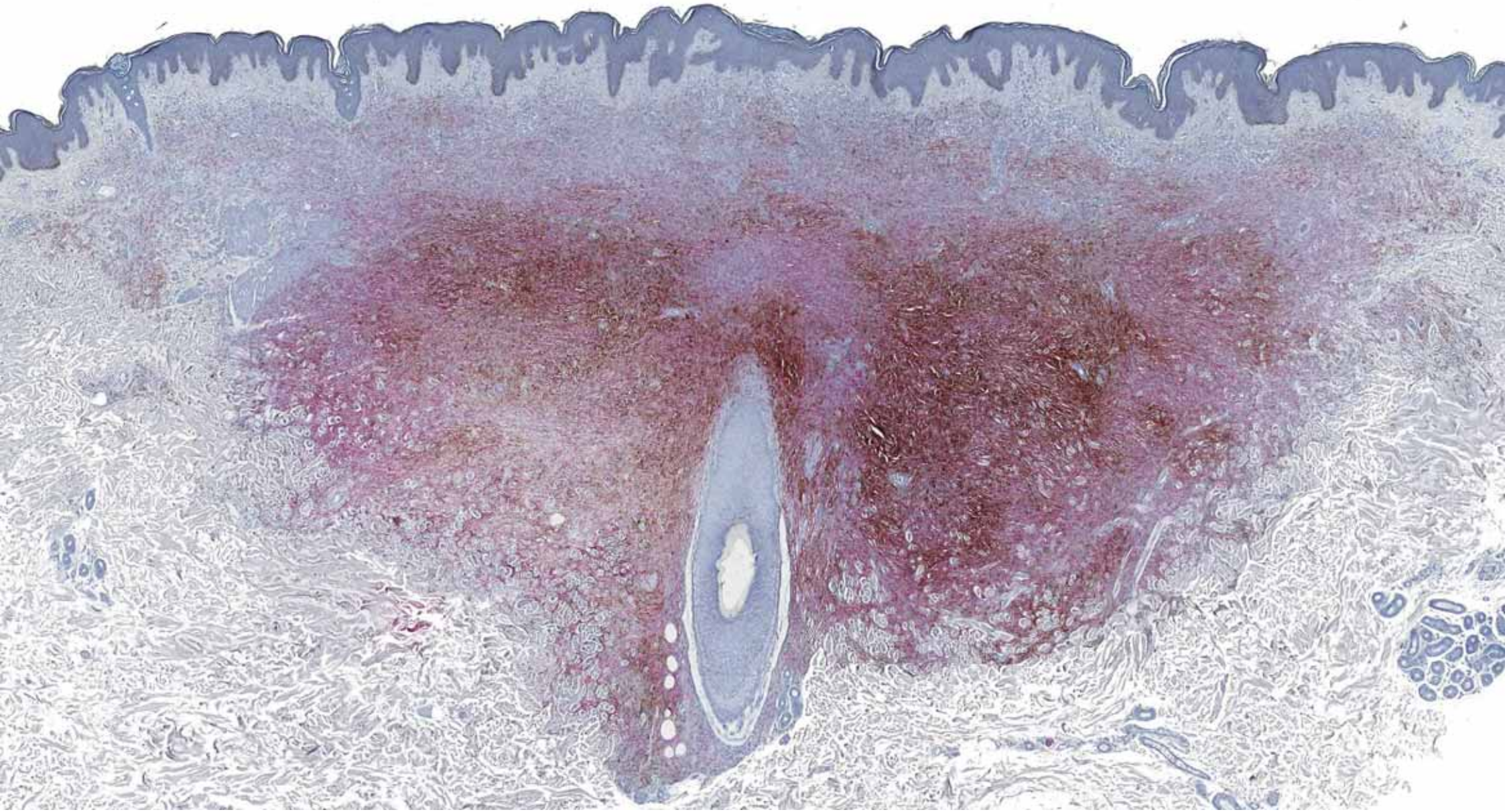
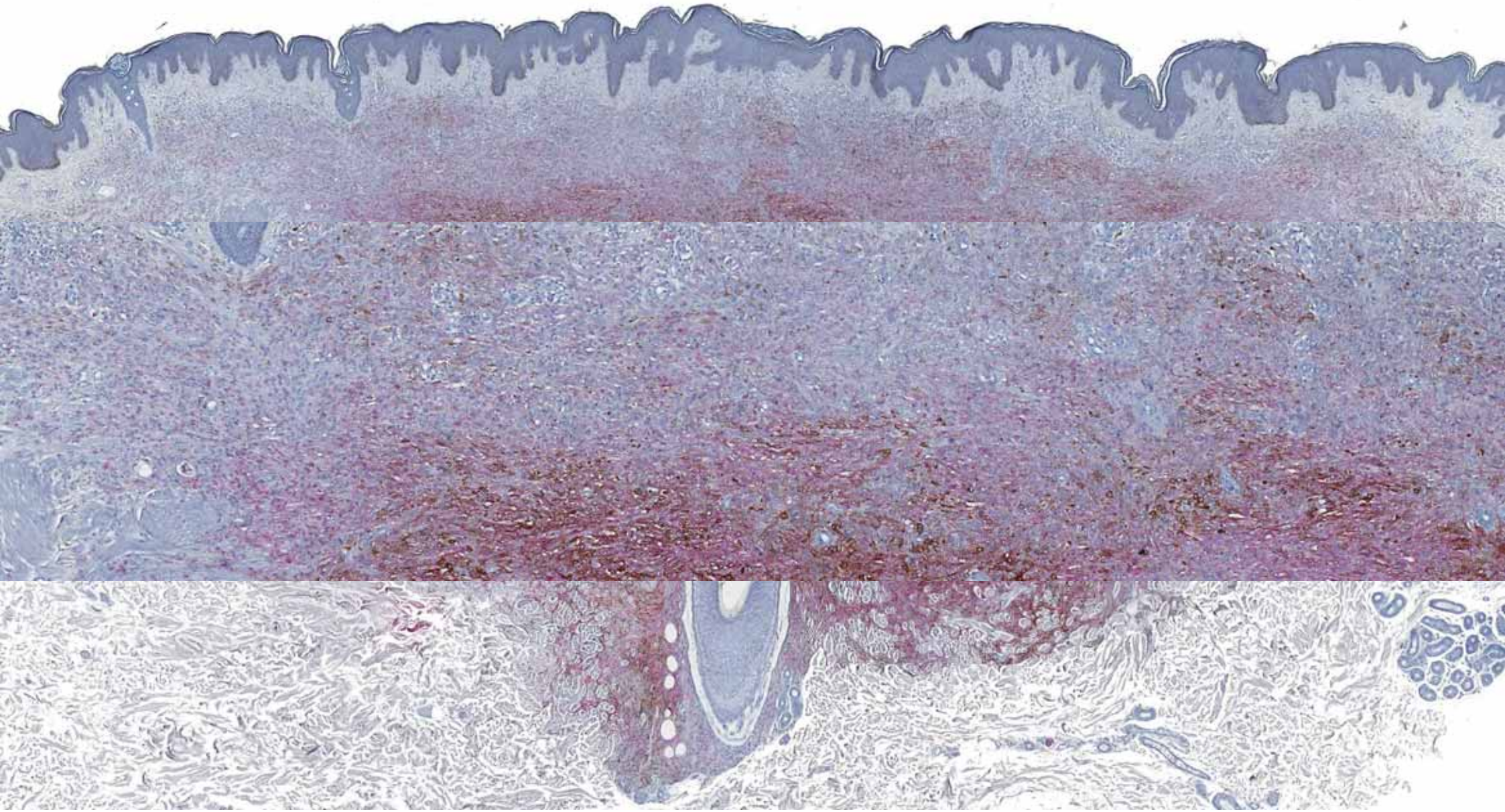
ANATOMICAL PATHOLOGY

S100 protein expression in PKC-fused blue naevi, cellular blue naevi and PRKAR1A-inactivated pigmented epithelioid melanocytomas

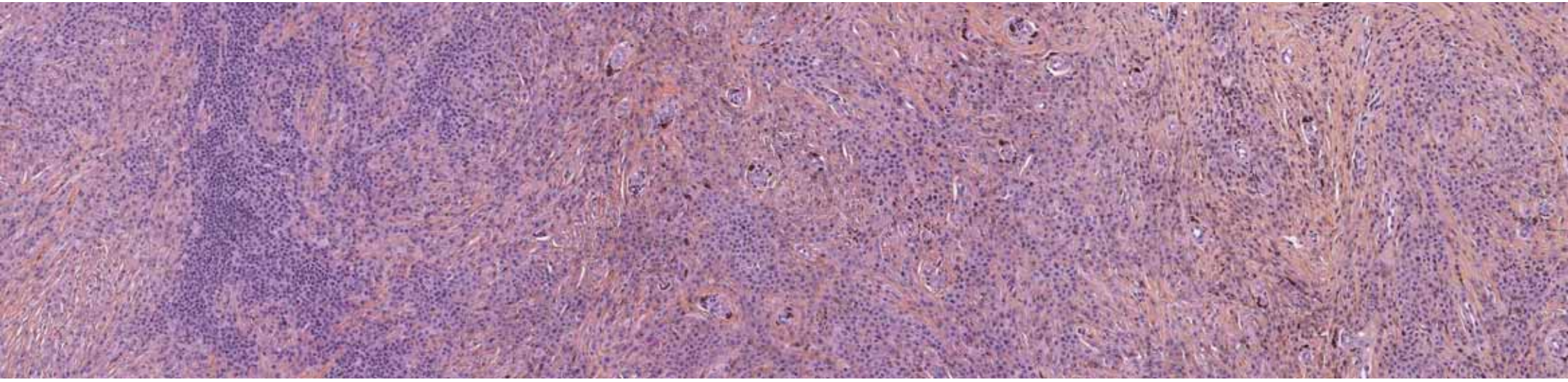
Pauline Hayenne [1], Daniel Pissaloux [1,2], Franck Tirode [1,2], Arnaud de la Fouchardiere [1,2,*]

[1] *Department de Biopathologie, Centre Léon Bérard, Lyon, France*
[2] *Université de Lyon, Université Claude Bernard Lyon 1, INSERM 1052, CNRS 5286, Centre Léon Bérard, Cancer Research Center of Lyon, Equipe Labellisée Ligue contre le Cancer, Lyon, France*



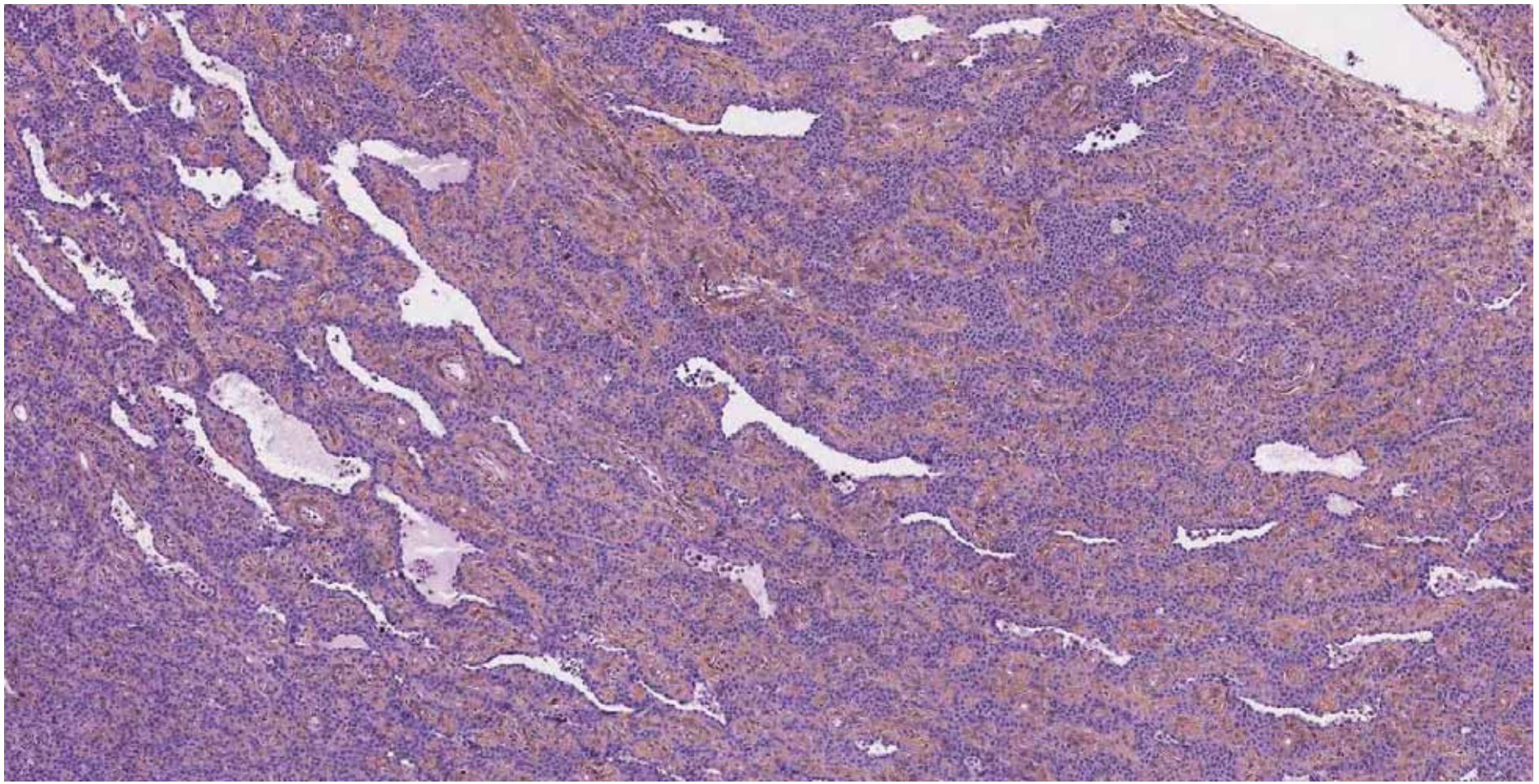


PKC gene fused blue nevus
highly variable morphology
Biphasic architecture (dermis)
«Combined common nevus + blue» morphology



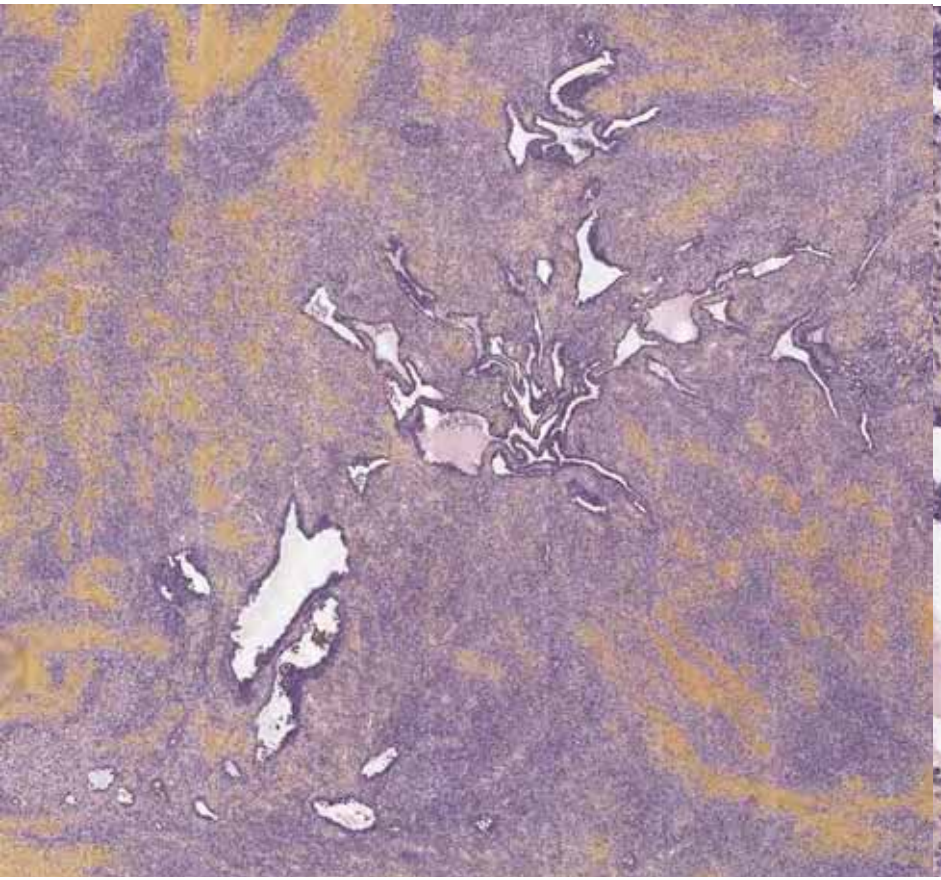
PKC gene fused melanocytic tumors

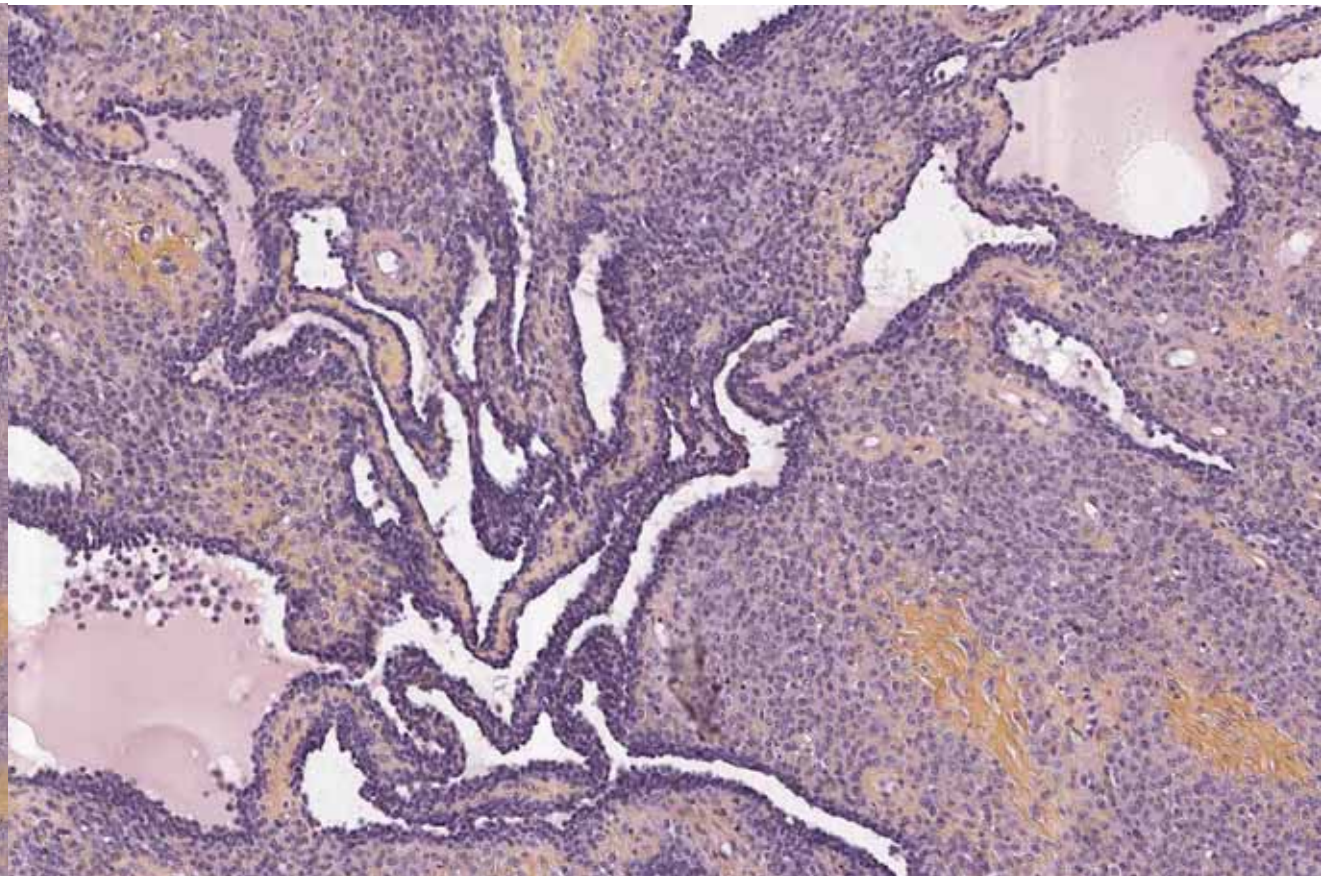
Pseudo-vascular clefting in cellular areas



PKC gene fused melanocytic tumors

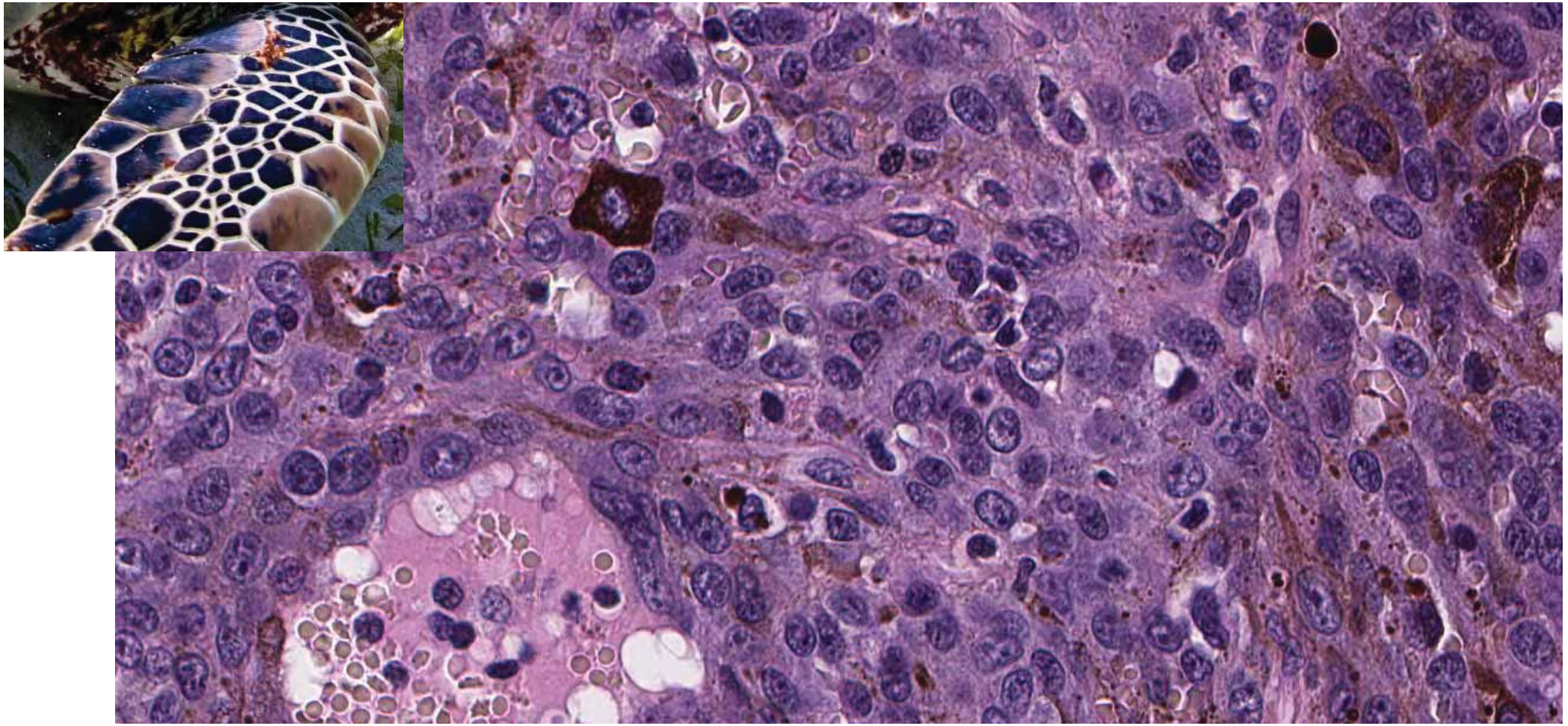
Pseudo-vascular clefting in cellular areas





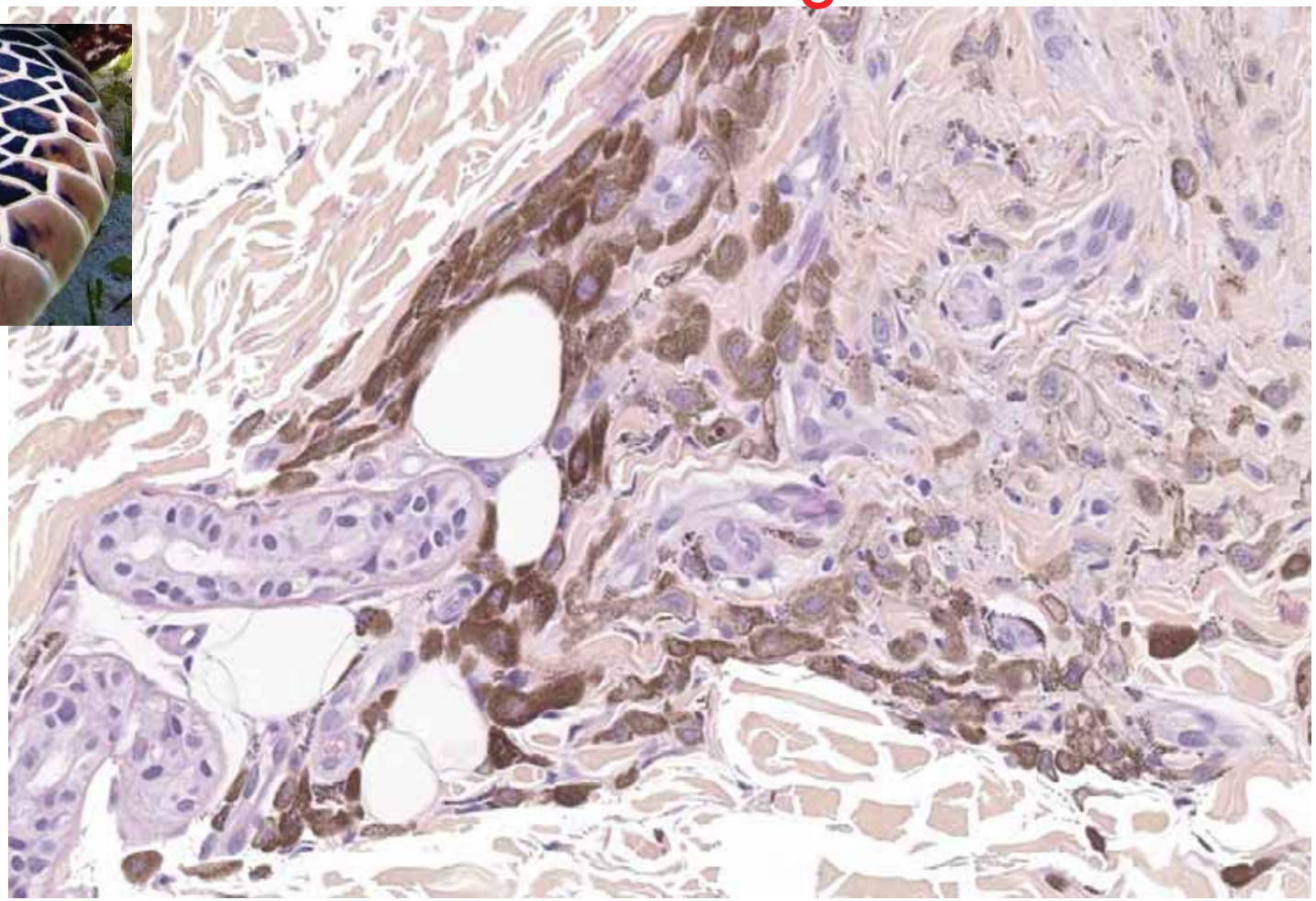
PKC gene fused melanocytic tumors

Green sea Turtle/Dragonscale cells

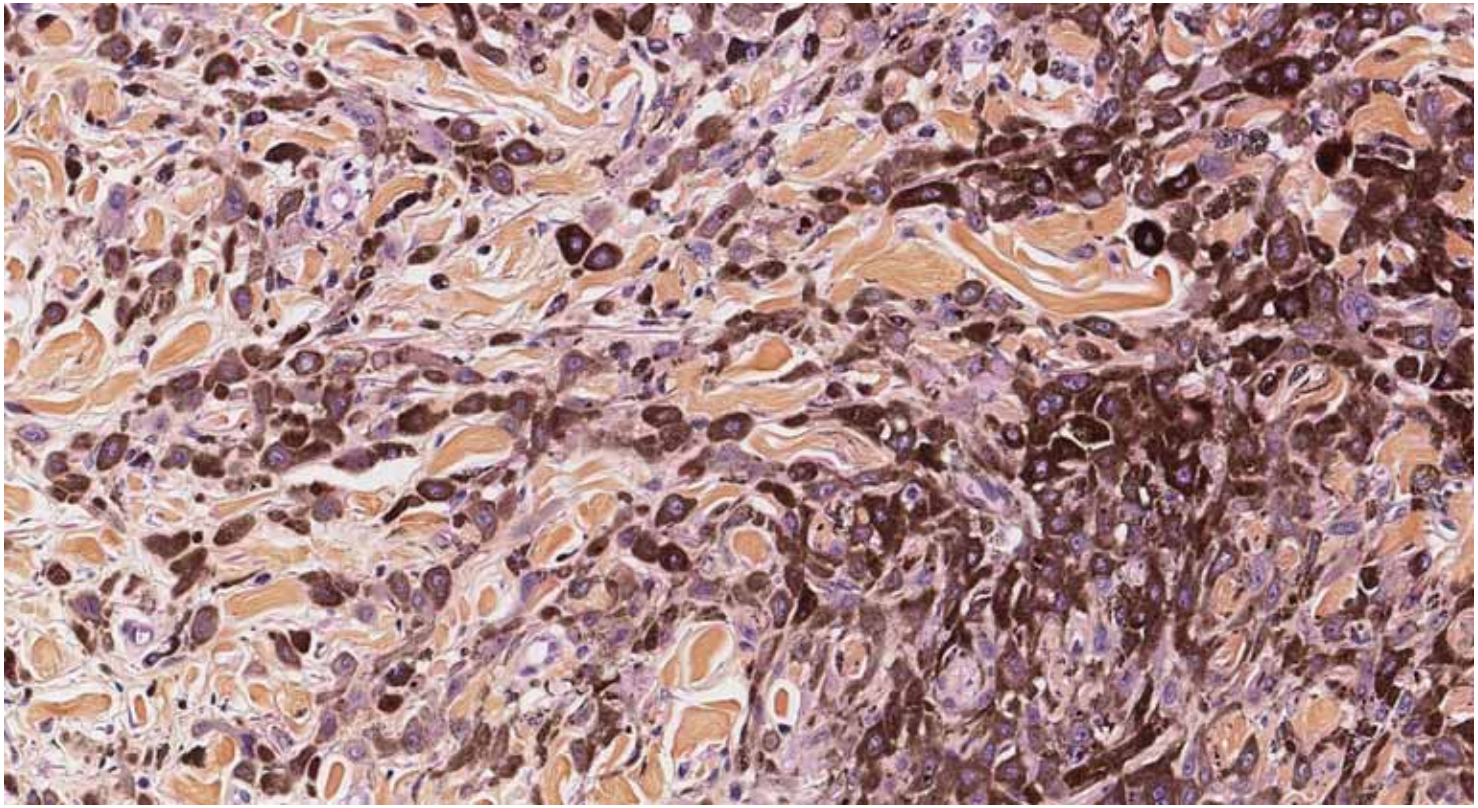


PKC gene fused melanocytic tumors

Green sea Turtle/Dragonscale cells



Dragonscale cells



Histopathology

Original Article

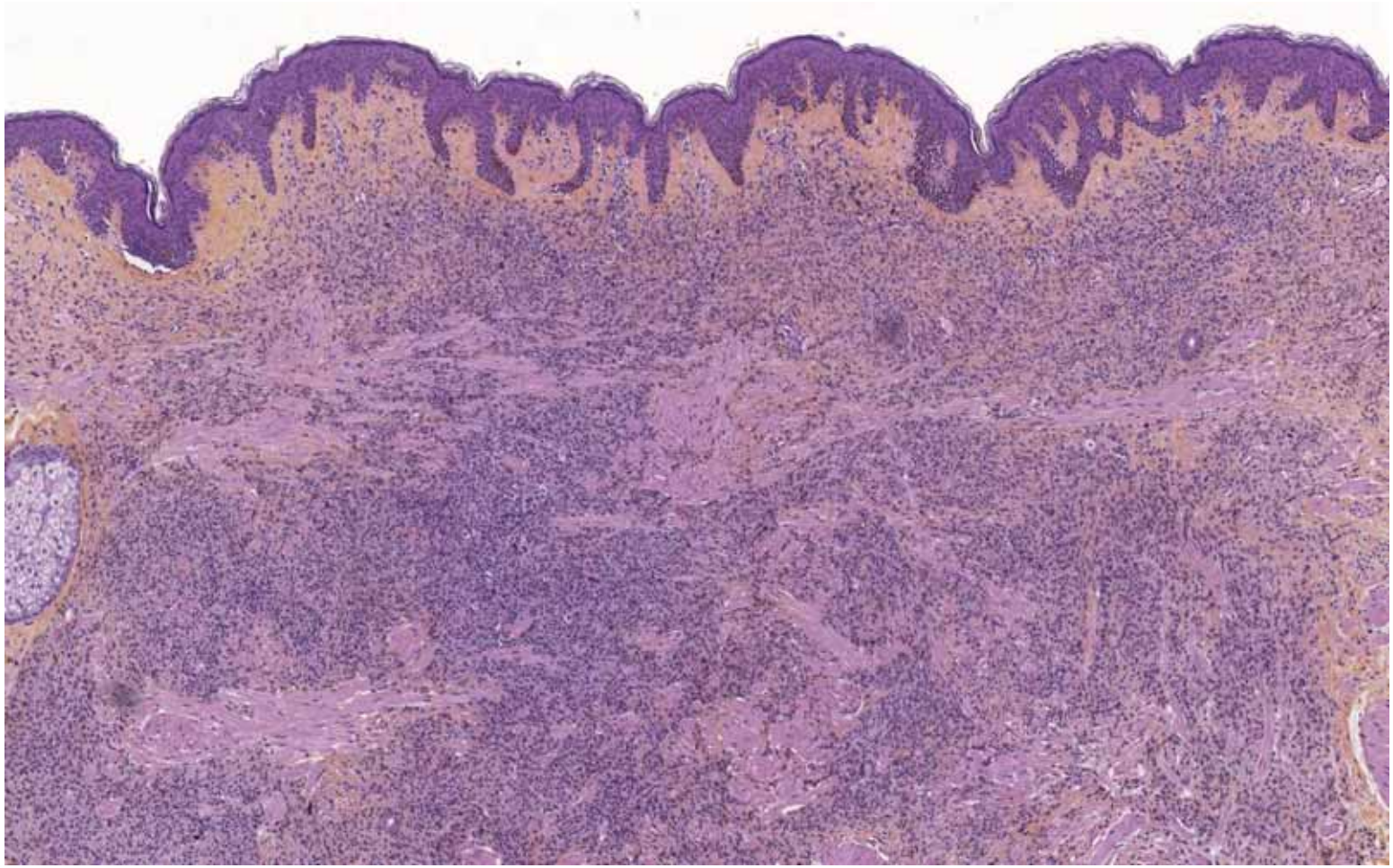
Smooth muscle hyperplasia in protein kinase C-fused blue naevi: Report of 12 cases

Dimitrios Goutas, Pauline Hayenne, Franck Tirode, Daniel Pissaloux, Iwei Yeh, Arnaud de la Fouchardiere

First published: 15 May 2024 | https://doi.org/10.1111/his.15211

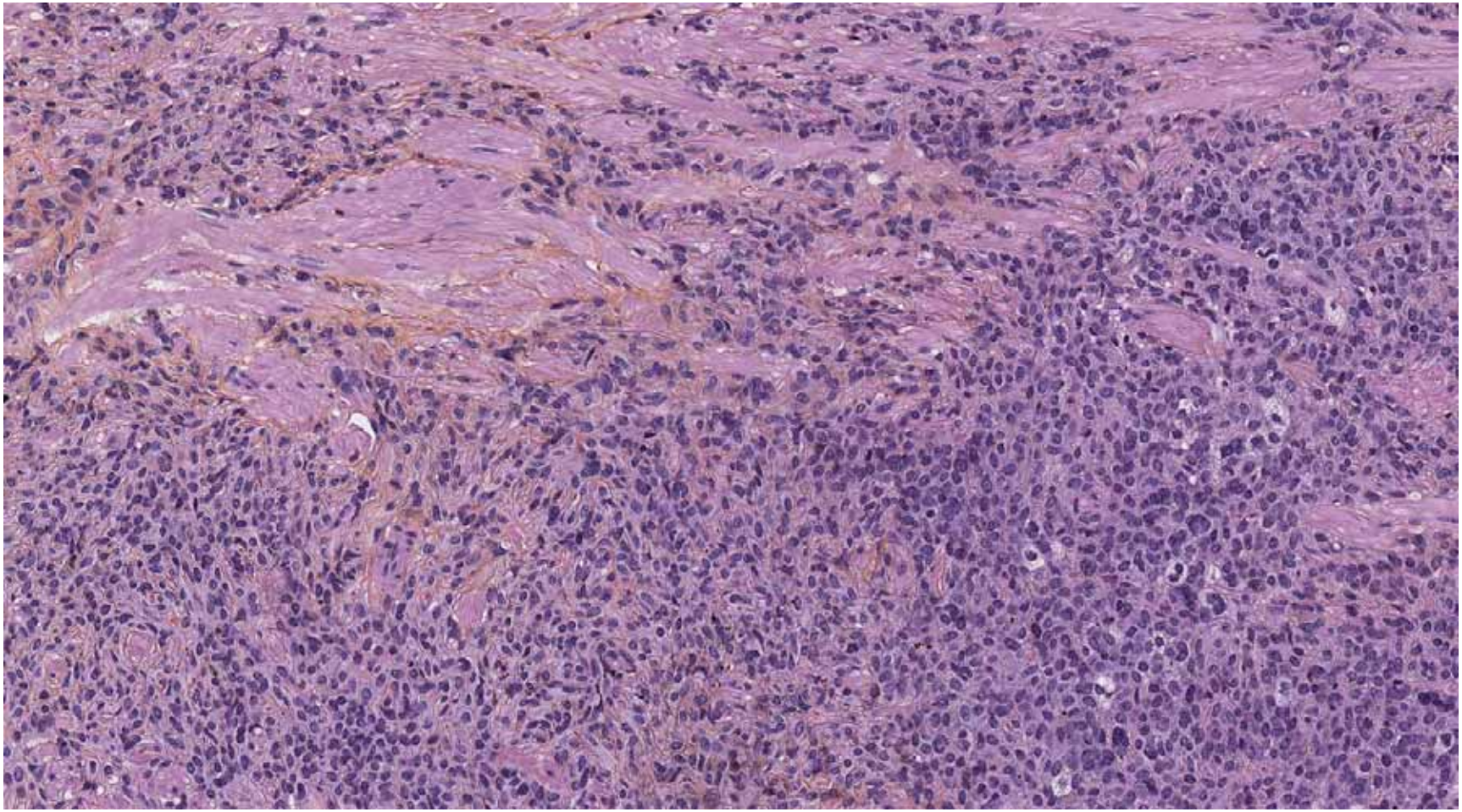
PKC gene fused melanocytic tumors

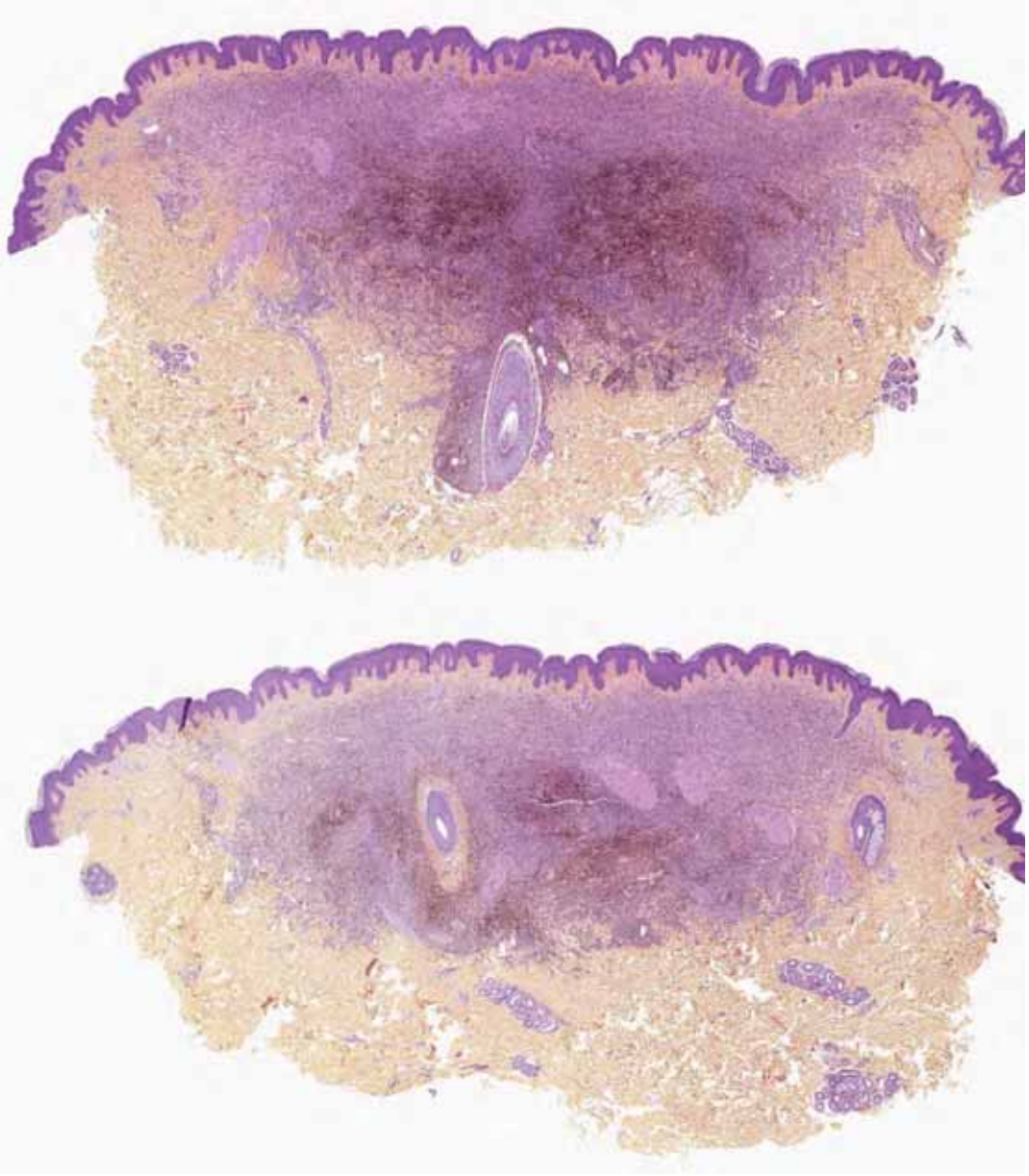
Smooth muscle hyperplasia



PKC gene fused melanocytic tumors

Smooth muscle hyperplasia





Clues in melanocytic tumours

- Very useful at low power to screen cases
- Must be confirmed by smoking gun in some instances
- Are fun to learn and use

Follow me on social media
Molecular pathology of melanocytic tumors

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Youtube : Formations et enseignement Centre Léon Bérard

The melanoledge channel (PKC-fused, dendritic and cellular blue nevus)