Practical Problems in Melanocytic Tumors

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General Rules for Melanocytic Tumors

- Low power examination
  - Symmetry
    - Junctional component
    - Dermal component
    - Pigmentation
    - Inflammation
- Medium Power examination
  - Circumscription
  - Growth pattern
    - Epidermis: nested vs. single cell
    - Dermis: regular nests vs. irregular nests or confluent
    - Maturation: do the melnocytes get smaller deeper in the dermis?

General Rules for Melanocytic Tumors

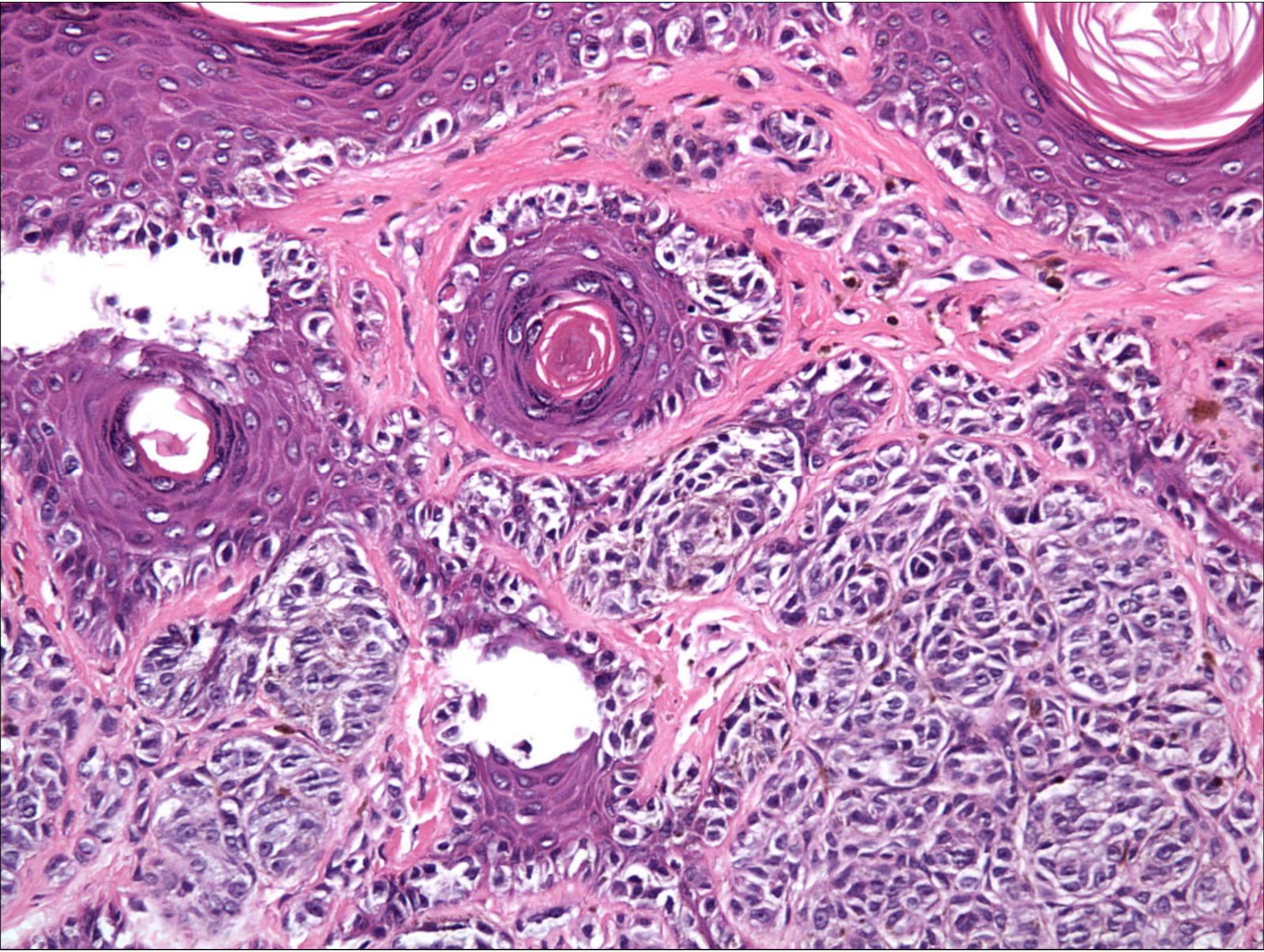
- High power examination
  - Upward (pagetoid) spread of melanocytes
  - Cytology
    - Nevoid
    - Epithelioid
    - Spindled
    - Pleomorphic
  - Dermal mitotic activity

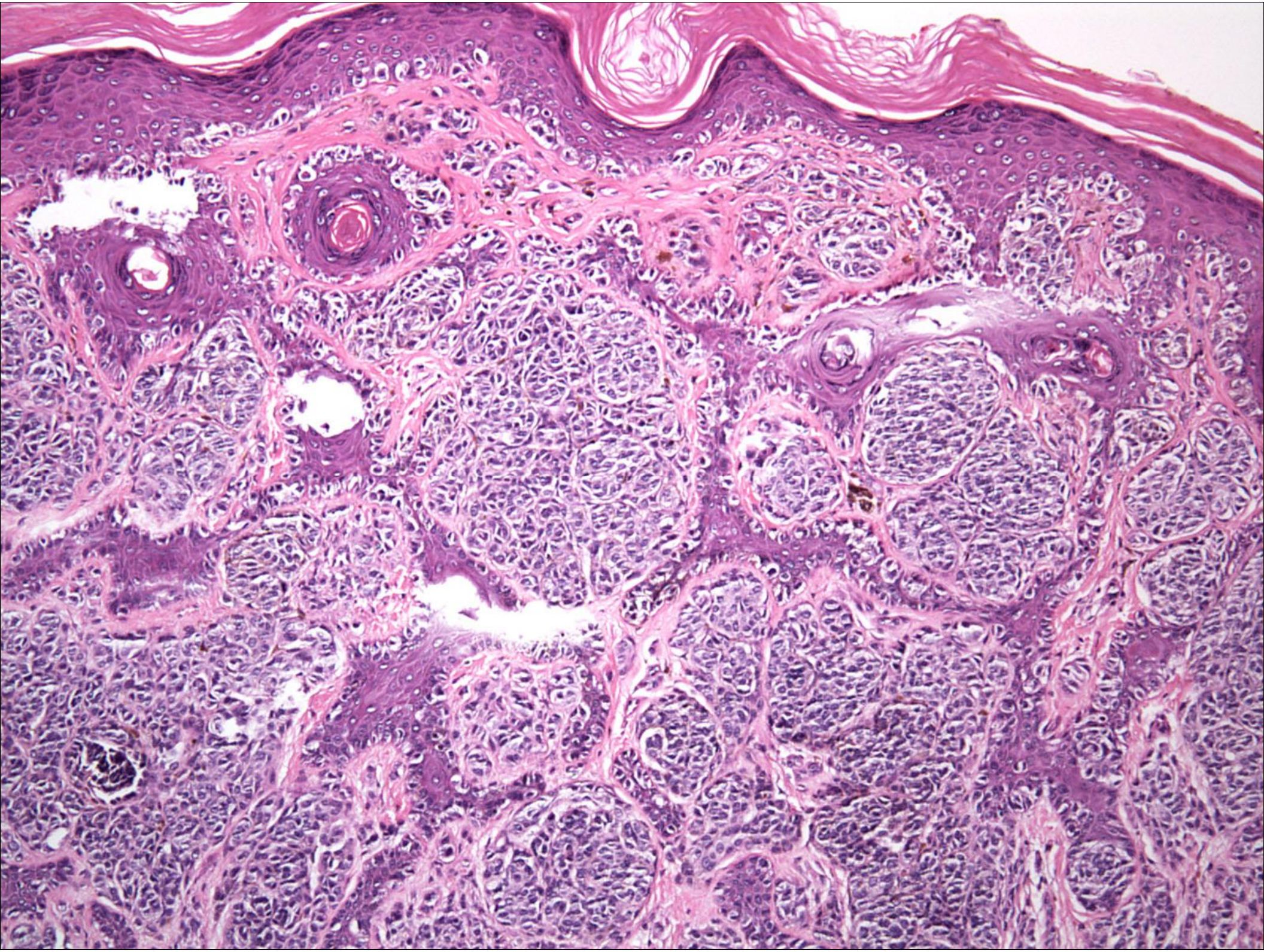
General Rules for Melanocytic Tumors

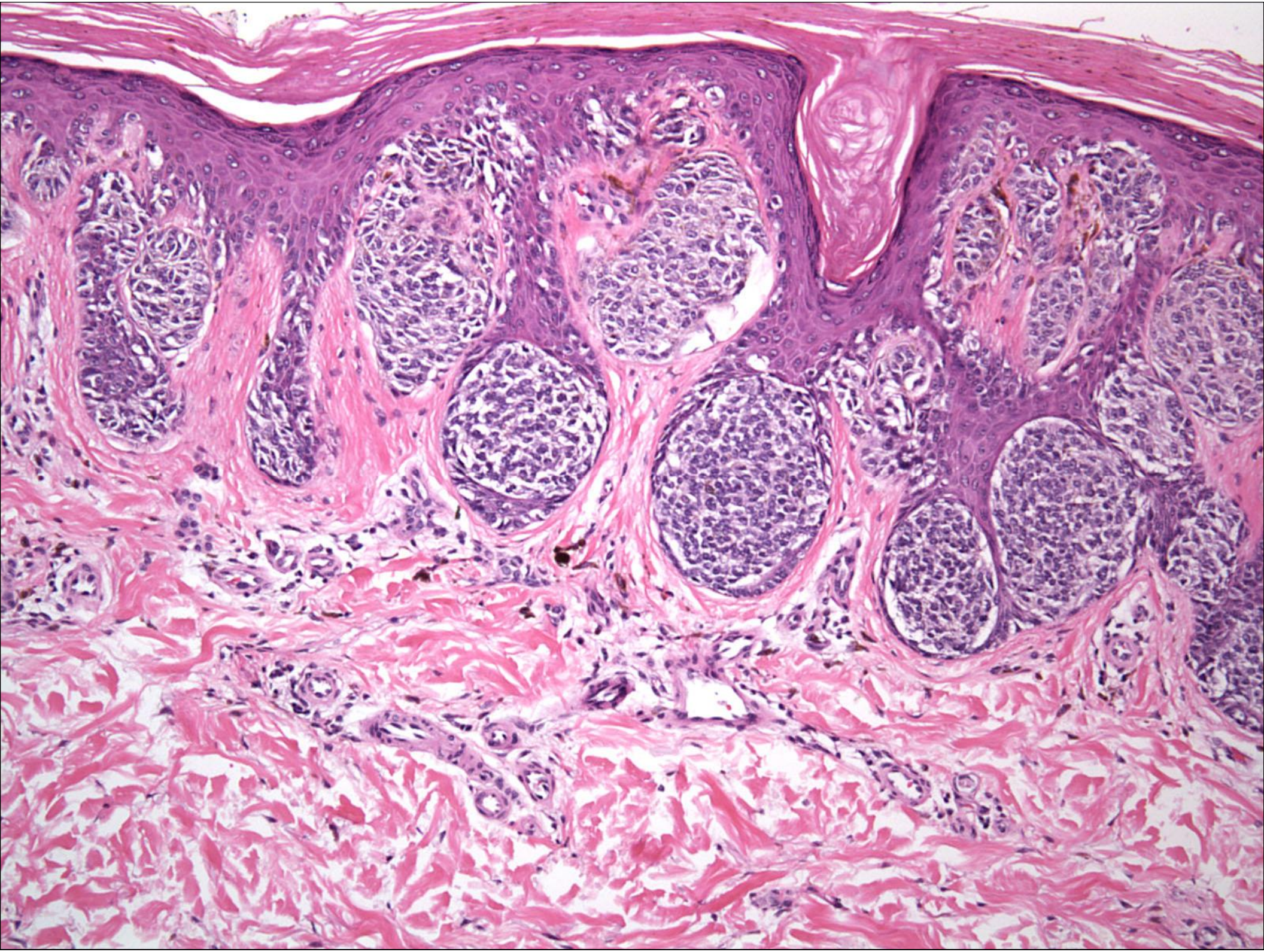
- The best special stain is H&E
  - Levels often helpful
- Do not sign out difficult cases when you are tired
  - Friday afternoon rule
- Do not be a hero
  - Show cases to colleagues
  - Get consults when necessary

Histology Issues

- Orientation important for accurate diagnosis
- Embedding is more important than cutting
- Beware of fixation artifacts

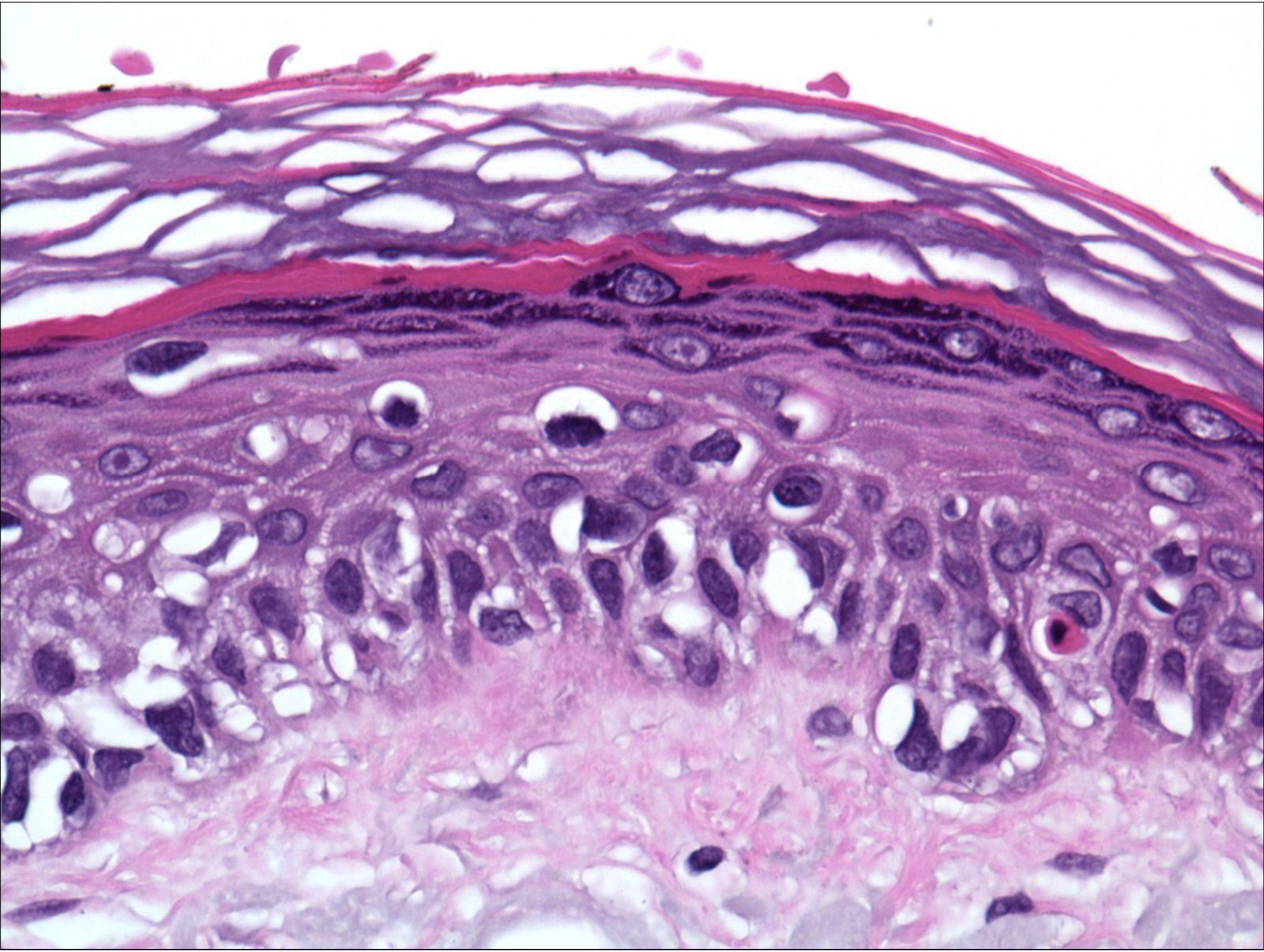


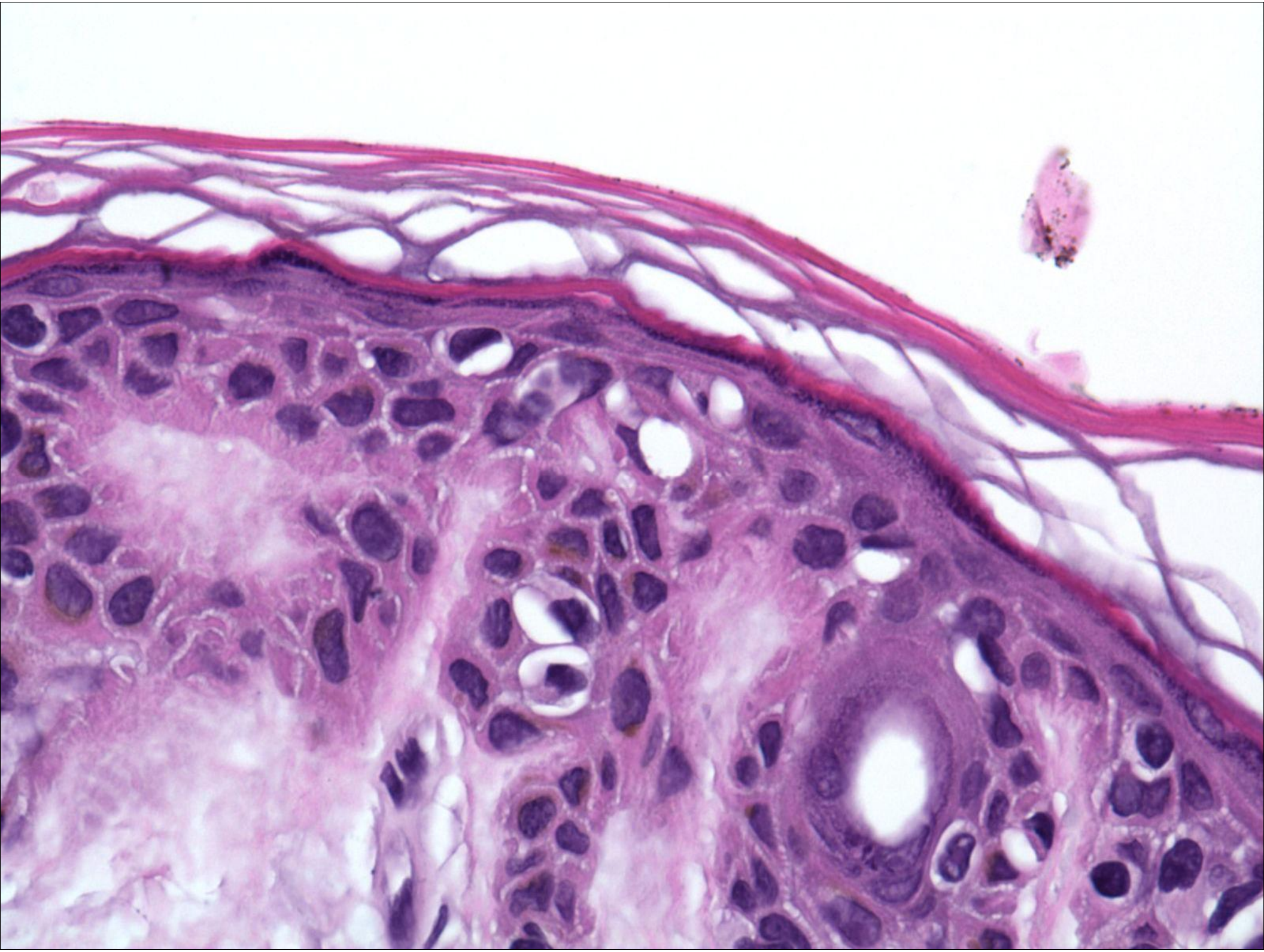




Histology

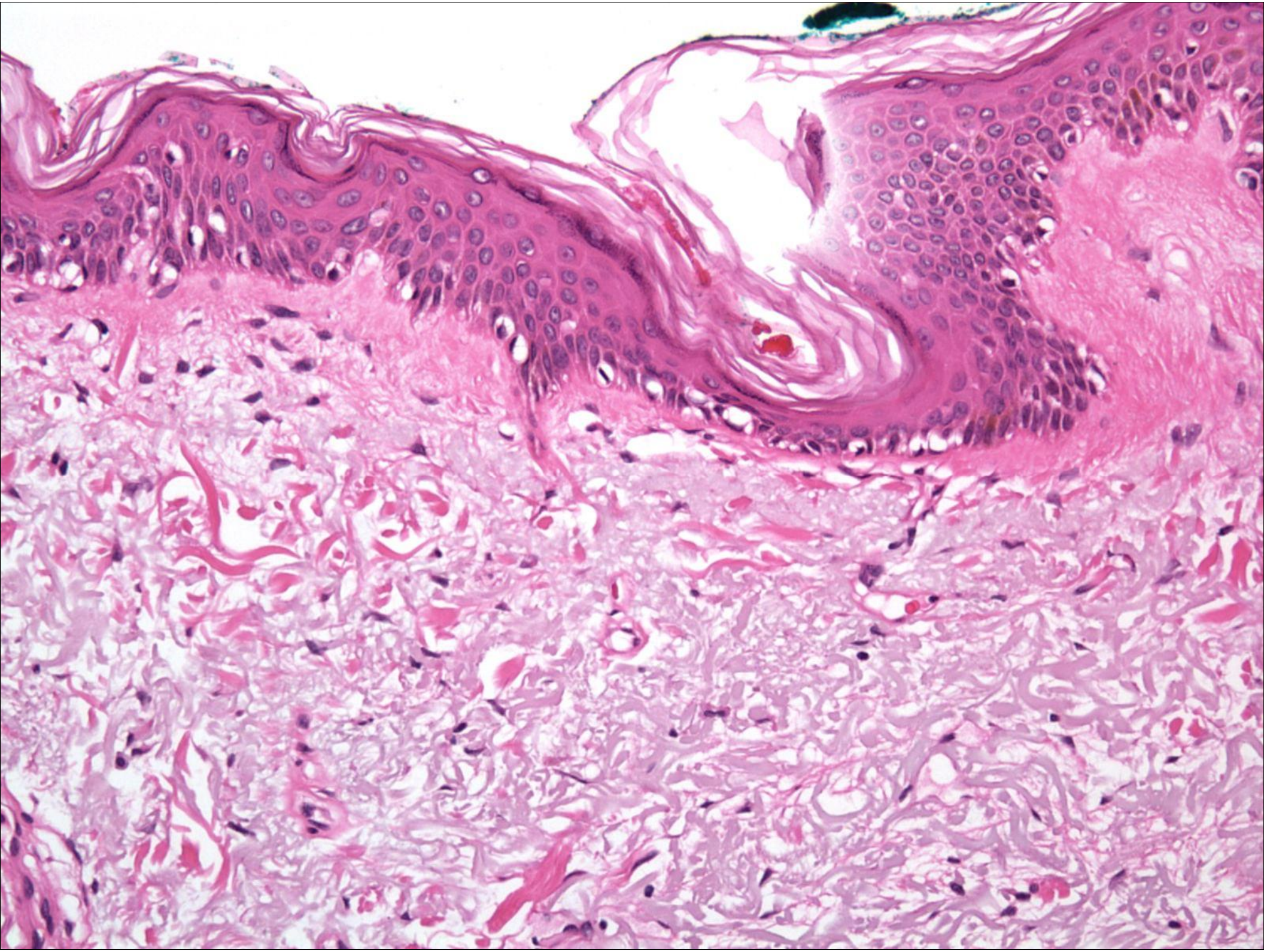
- Beware of keratinocytes with haloes
  - Fixation artifact
  - Resemble pagetoid melanocytes
  - Key: where is the cytoplasm?
    - Halo around nucleus without cytoplasm = keratinocyte
    - Halo around nucleus with attached cytoplasm = melanocyte





Margin Assessment

- Reactive melanocytic hyperplasia common
- Increased number of melanocytes ≠ positive margin
- Positive margin:
  - Contiguous proliferation of melanocytes
  - Nests
  - Extension far down adnexal structures
  - Prominent pagetoid spread



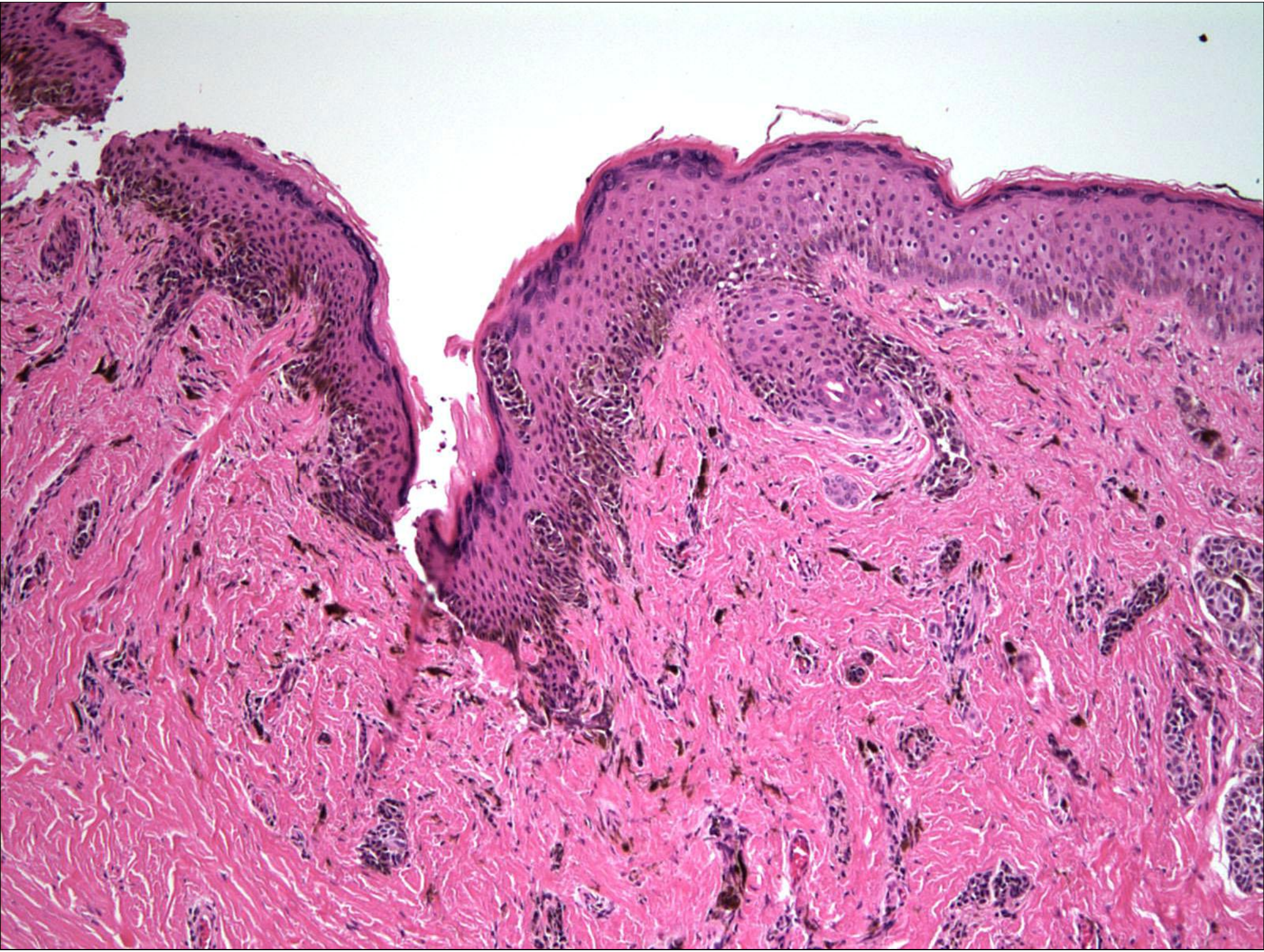
Margin Assessment

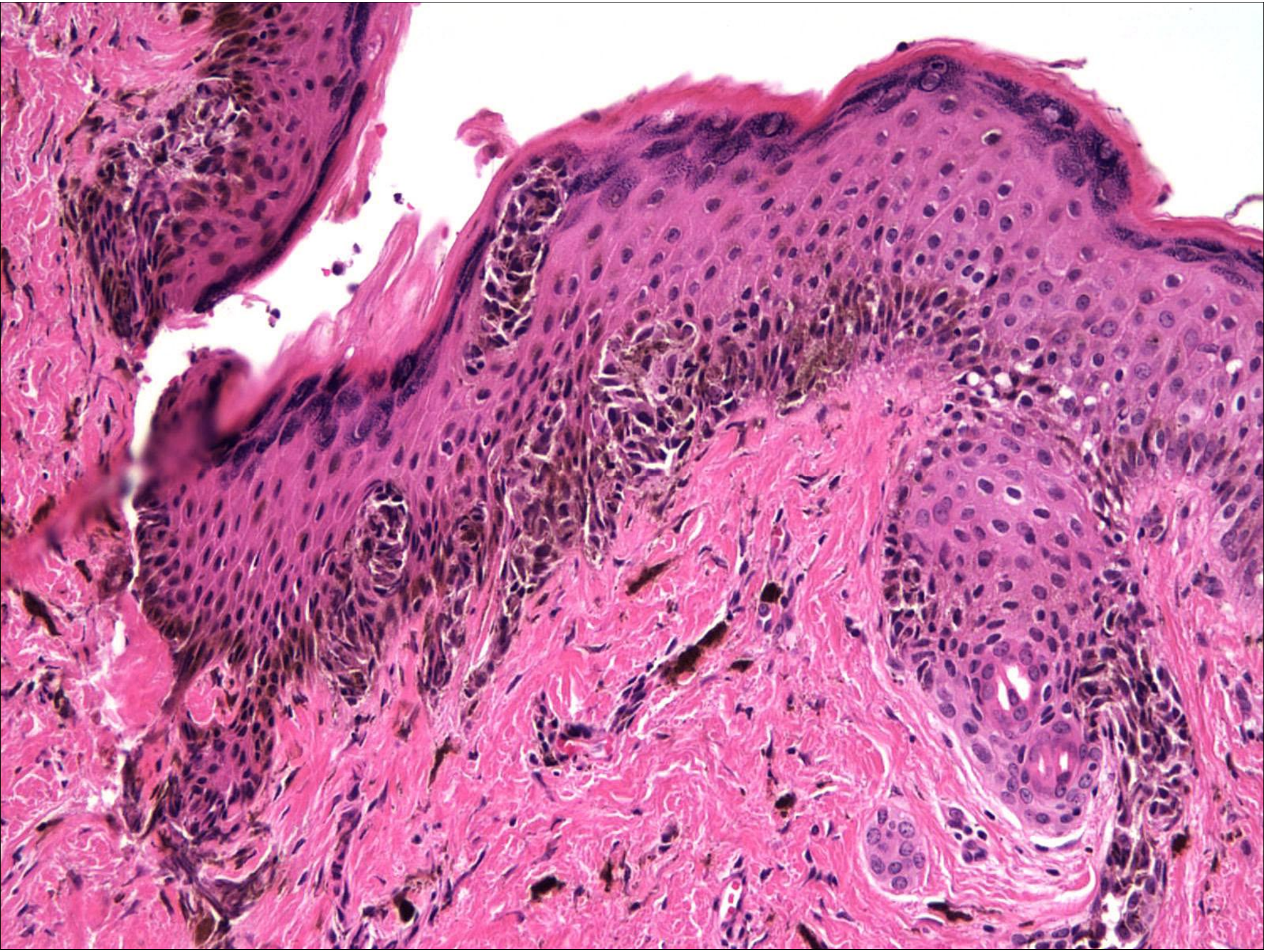
- Melanocytic hyperplasia does not increase risk of local recurrence
- Do not overcall

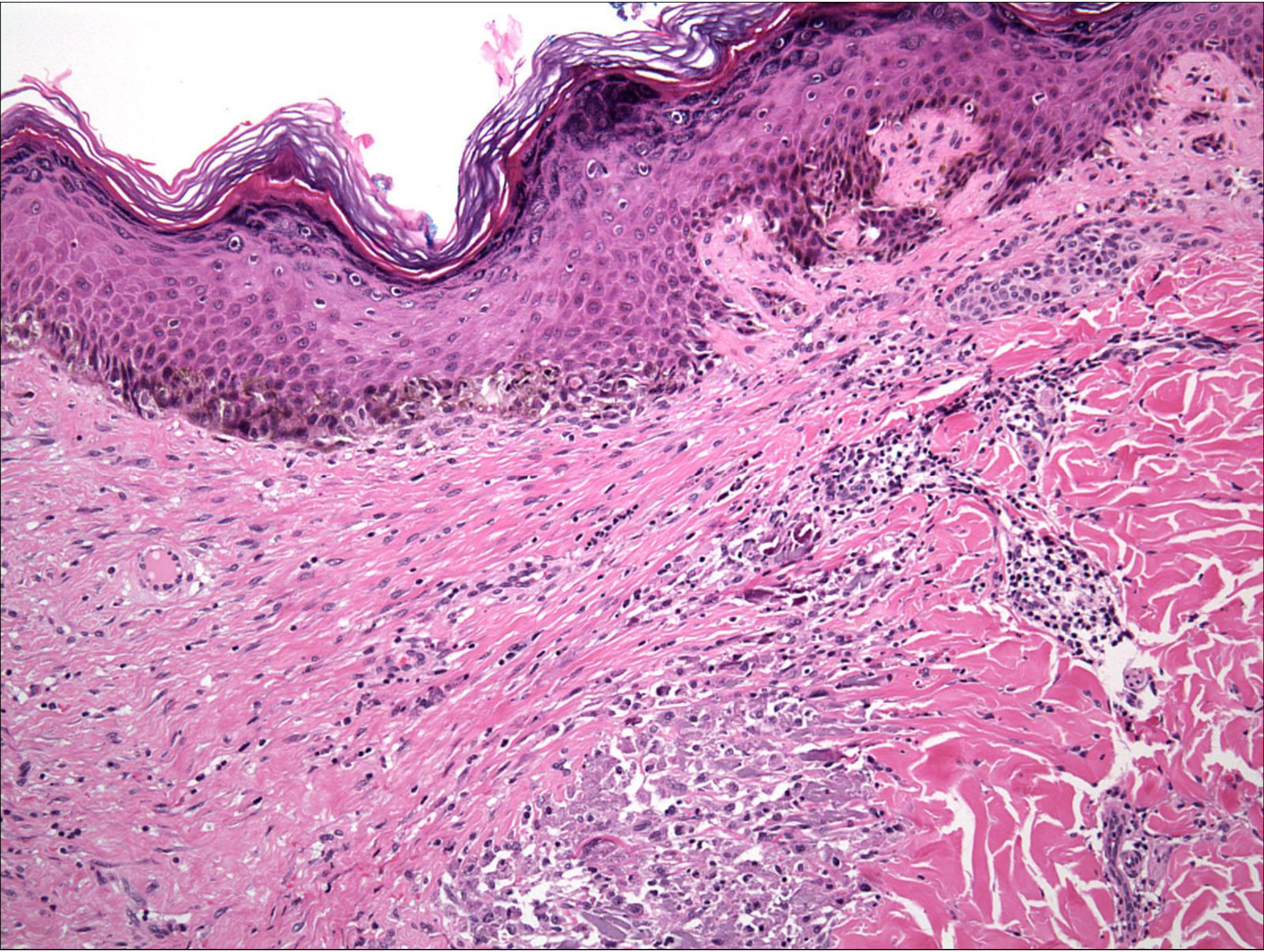
Tricky Melanocytic Lesions

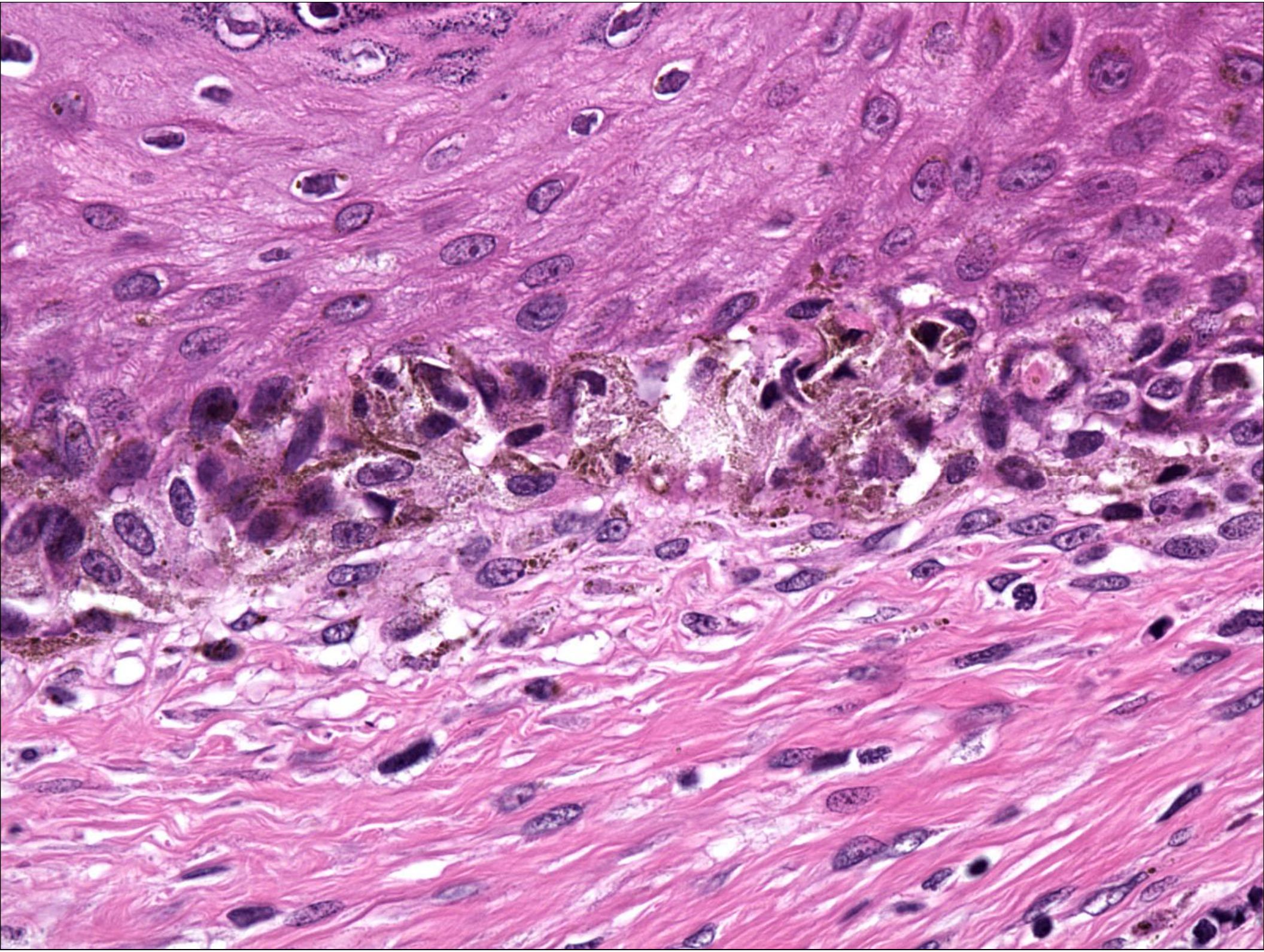
Recurrent (Persistent) Nevi

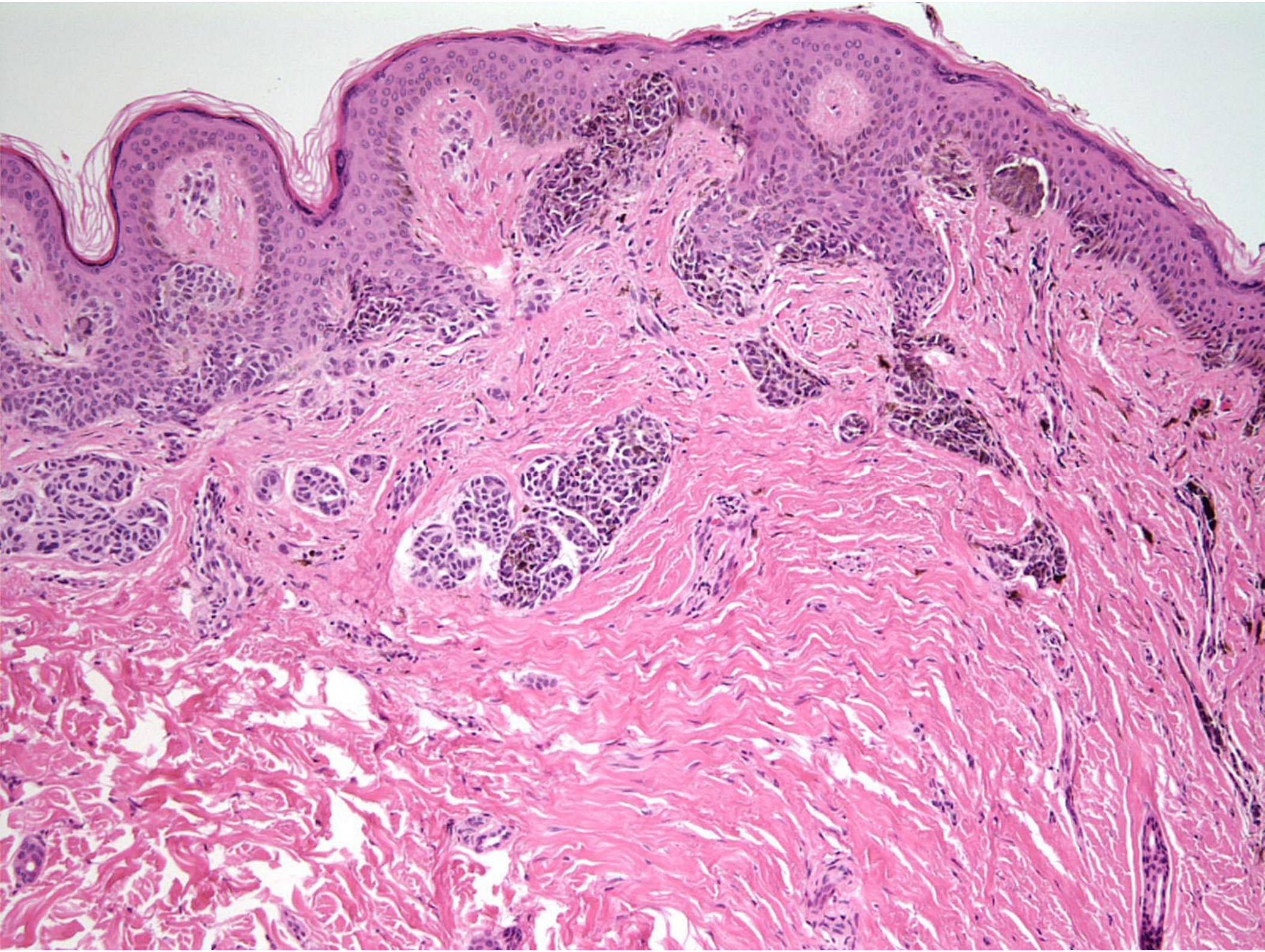
- Present as recurrent pigmented lesion or change in incompletely excised nevus
- Usually in setting of previous shave biopsy or trauma
  - Original biopsy may show incomplete or apparently complete removal
- Trauma prone areas
  - Lower legs
  - Where clothes rub
  - Face

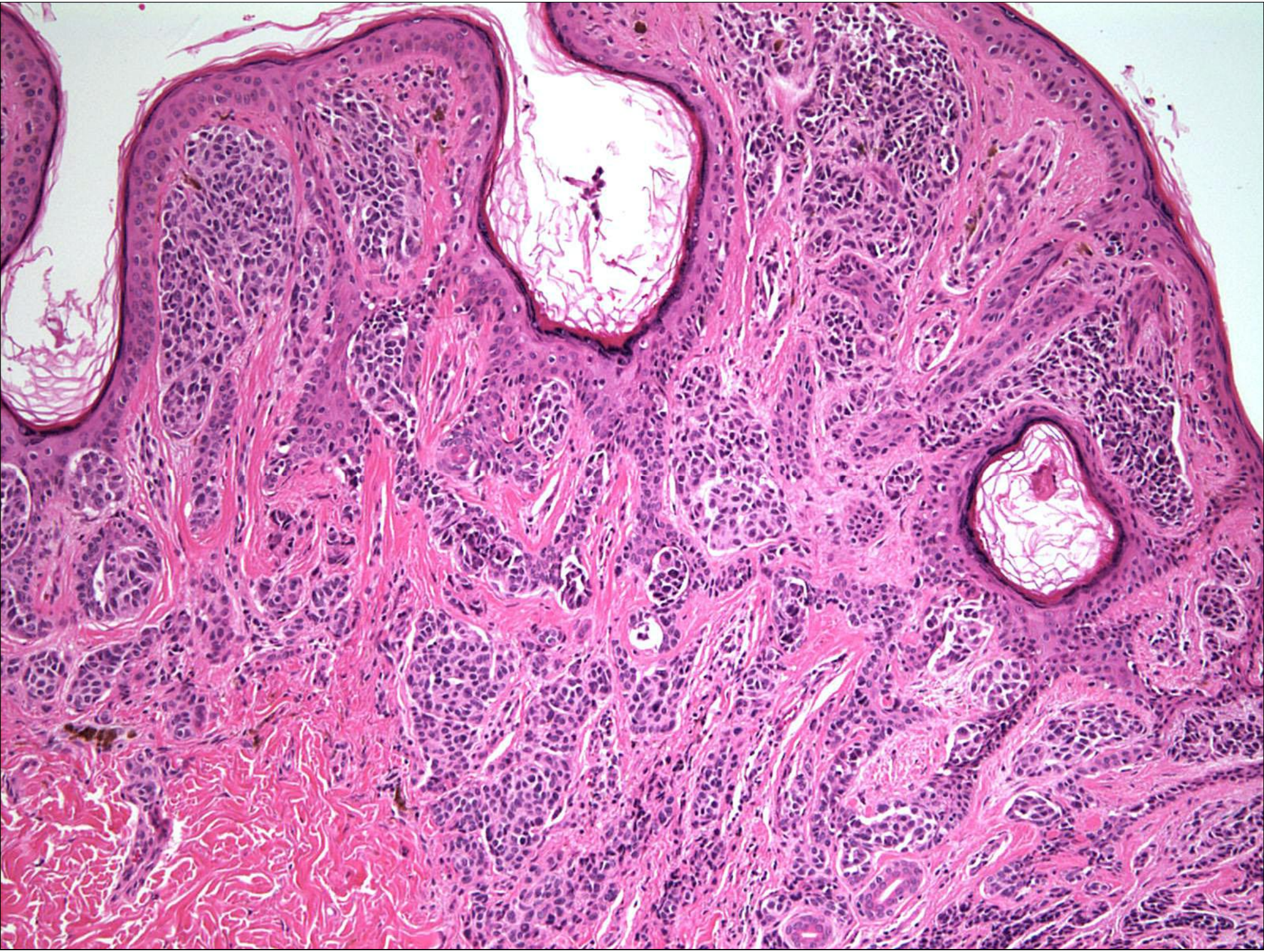












Recurrent Nevi

Microscopic features

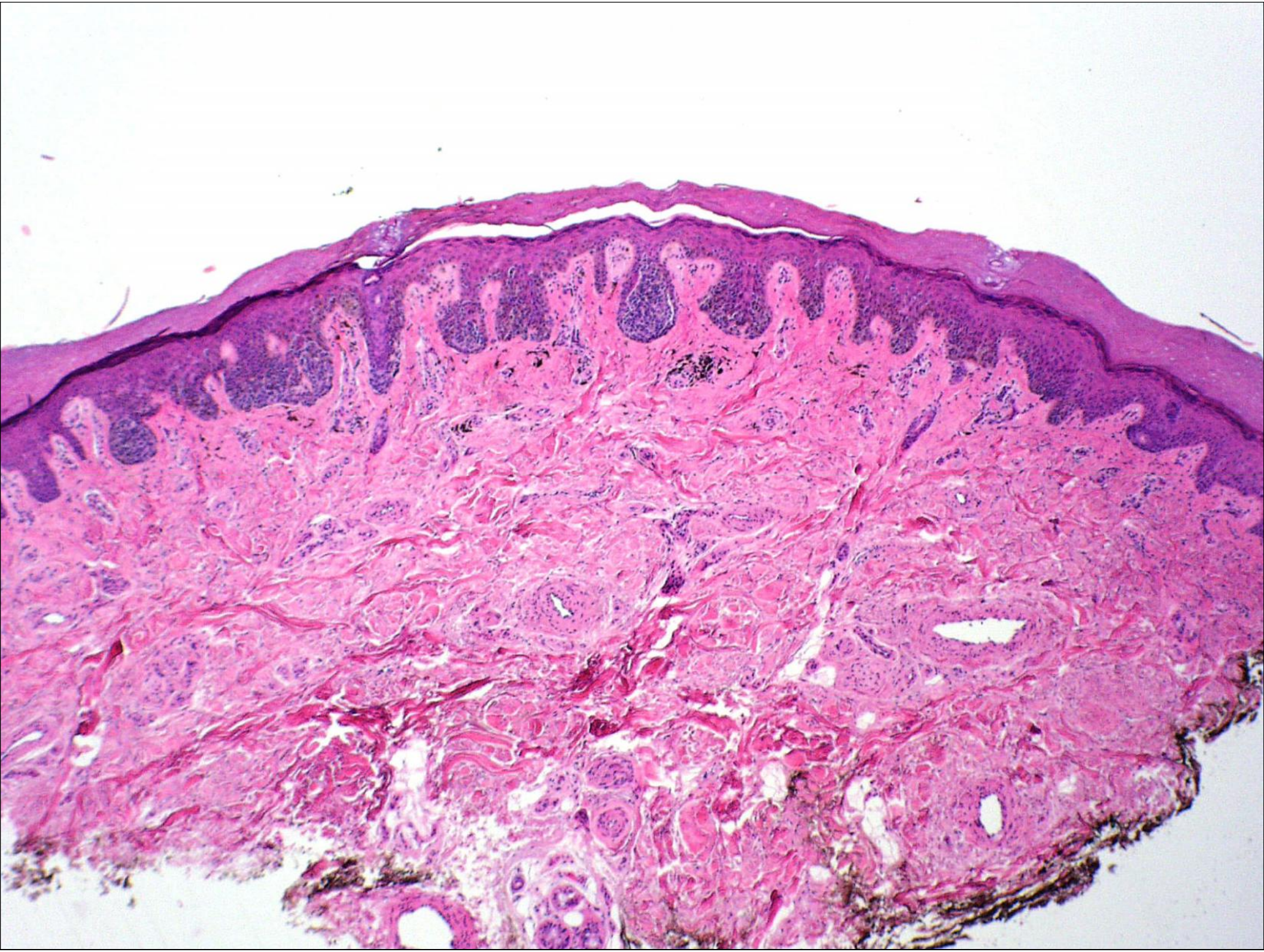
- Effacement of normal rete peg pattern
- Dermal scar
- Irregular junctional melanocytic proliferation
  - Asymmetric
  - Single cells
  - Pagetoid spread
  - Cytologically bland
  - Limited to area over scar

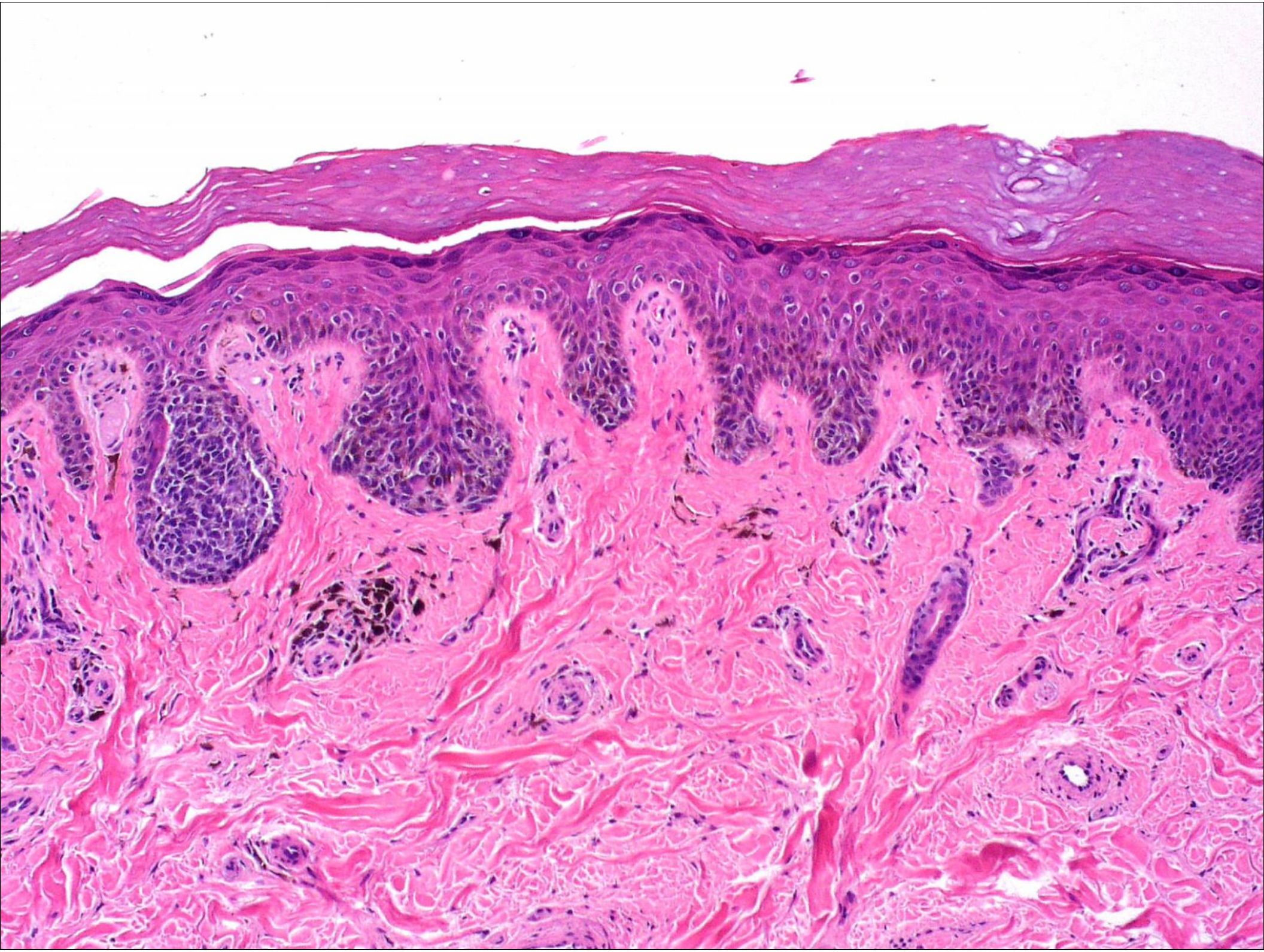
Recurrent Nevi

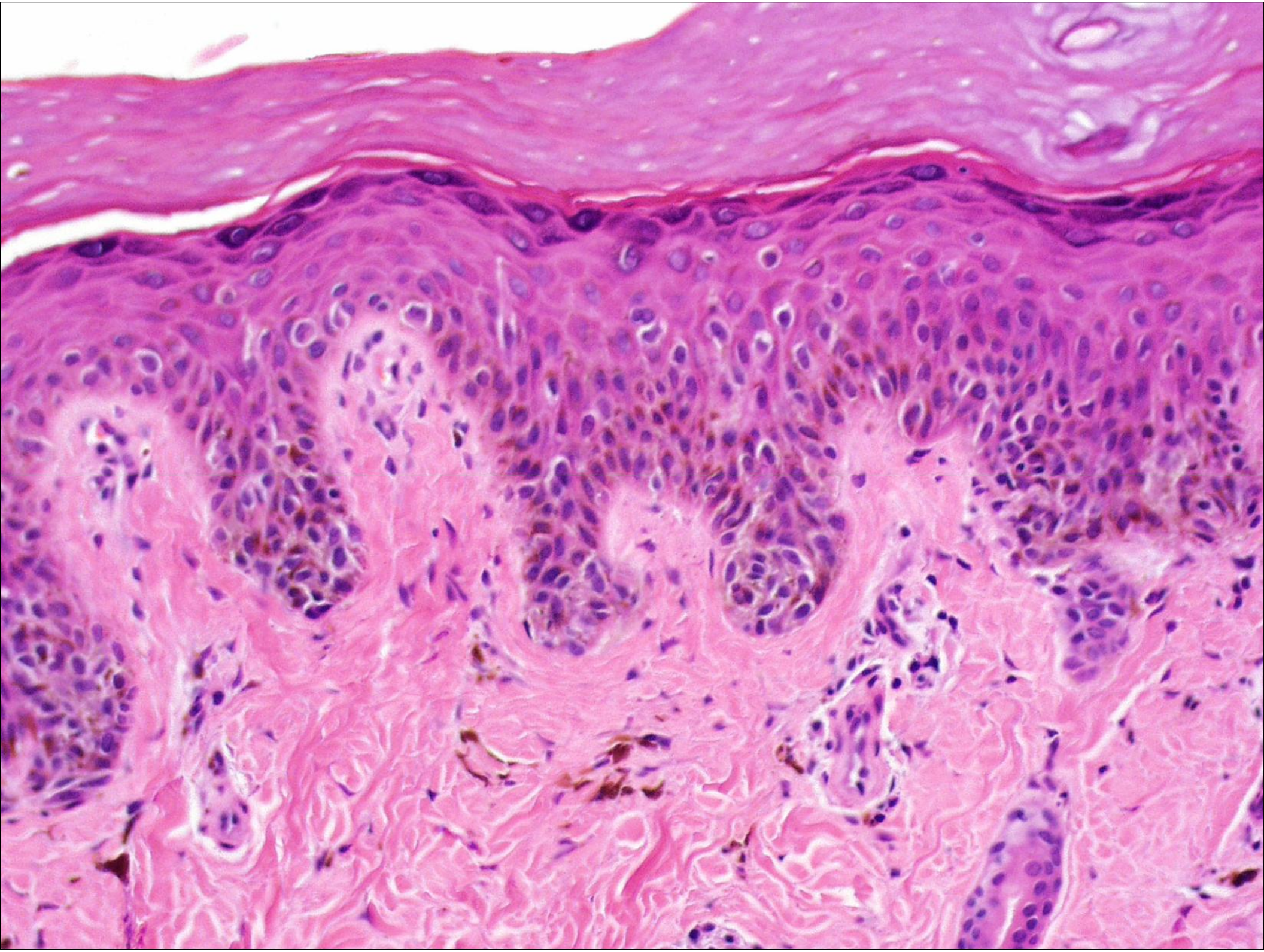
- Practical Tips
  - Architecturally worrisome only over scar
  - Bland nuclei
  - Dermal component bland
  - History/location
  - Absence of history or benign nevus, be careful:
    - Consider descriptive diagnosis of ‘atypical melanocytic proliferation over scar, see note’
    - Note: In the appropriate clinical context this could represent a recurrent nevus, but a regressed melanocytic lesion or regressed melanoma could be considered.

Nevi of “special sites”

- Scalp, including hairline
- Ear
- Intertriginous areas
- Genital skin
- Ankles
- Acral skin







Acral Lentiginous Melanoma

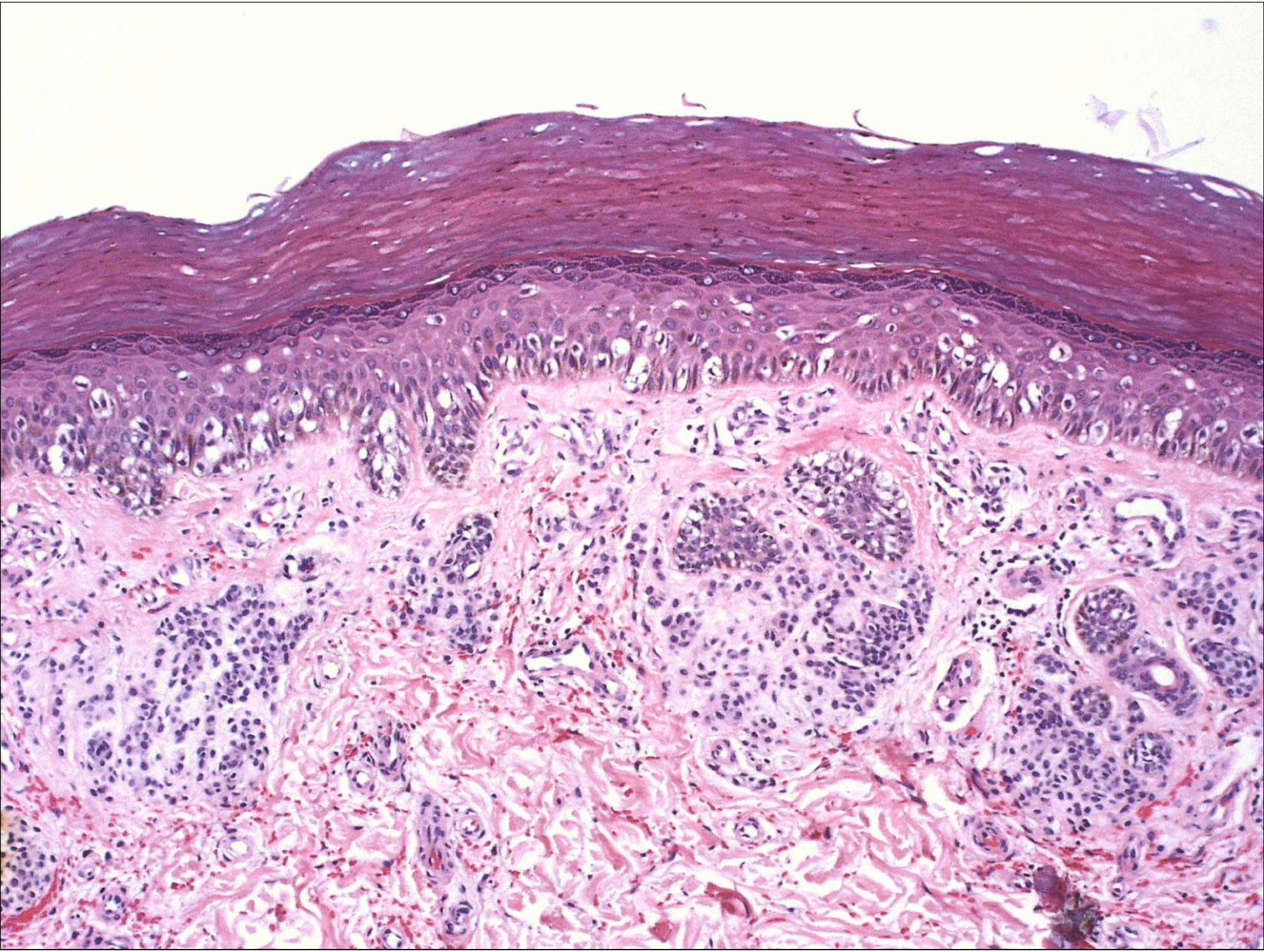
- Clinical Features
  - Older patients 7th and 8th decades
  - Rare <30 years of age
  - Usually large (1-3 cm)
  - Irregularly pigmented
  - Foot > hand
  - Most common form of melanoma in darker pigmented people

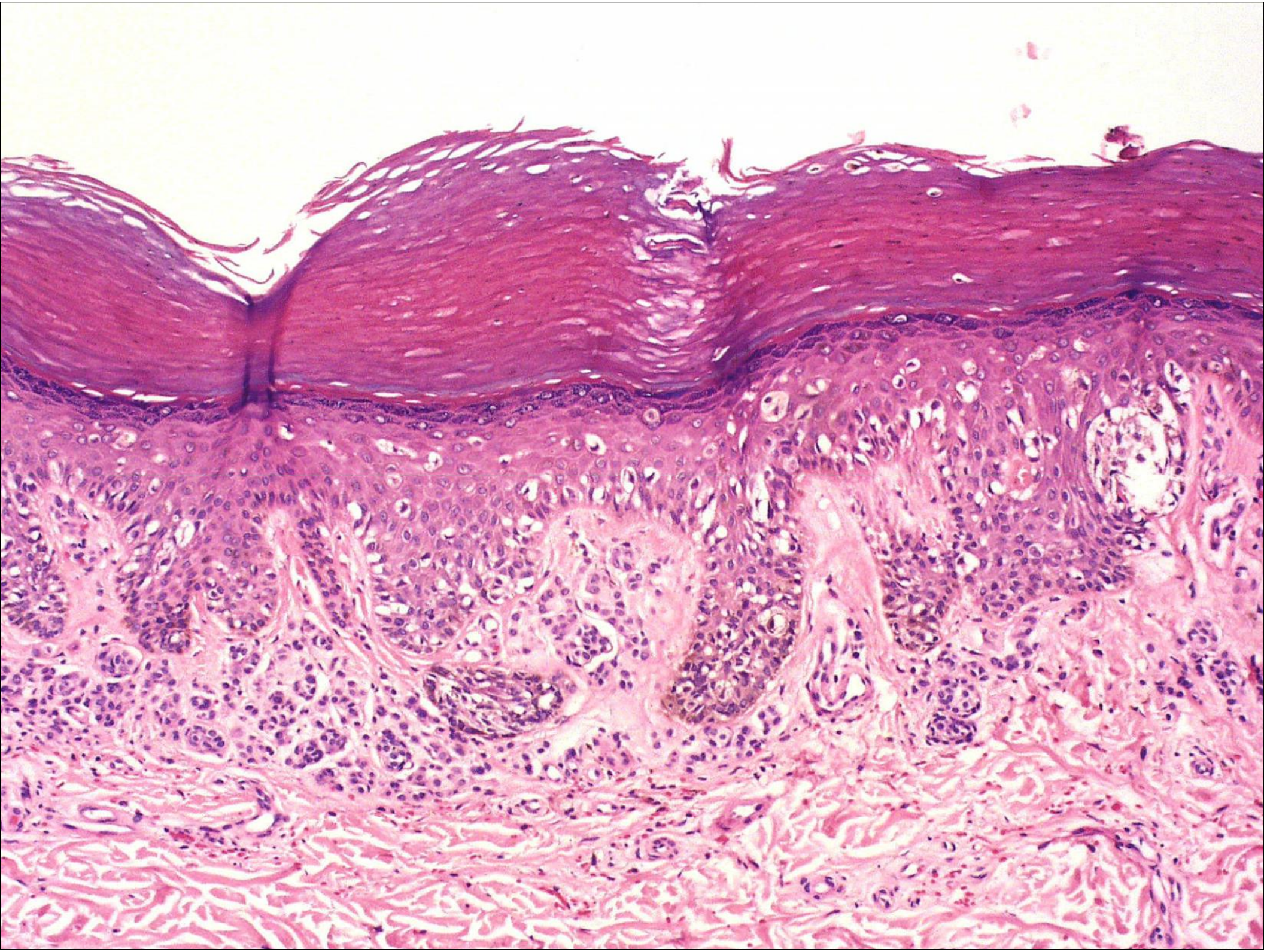
Acral Lentiginous Melanoma

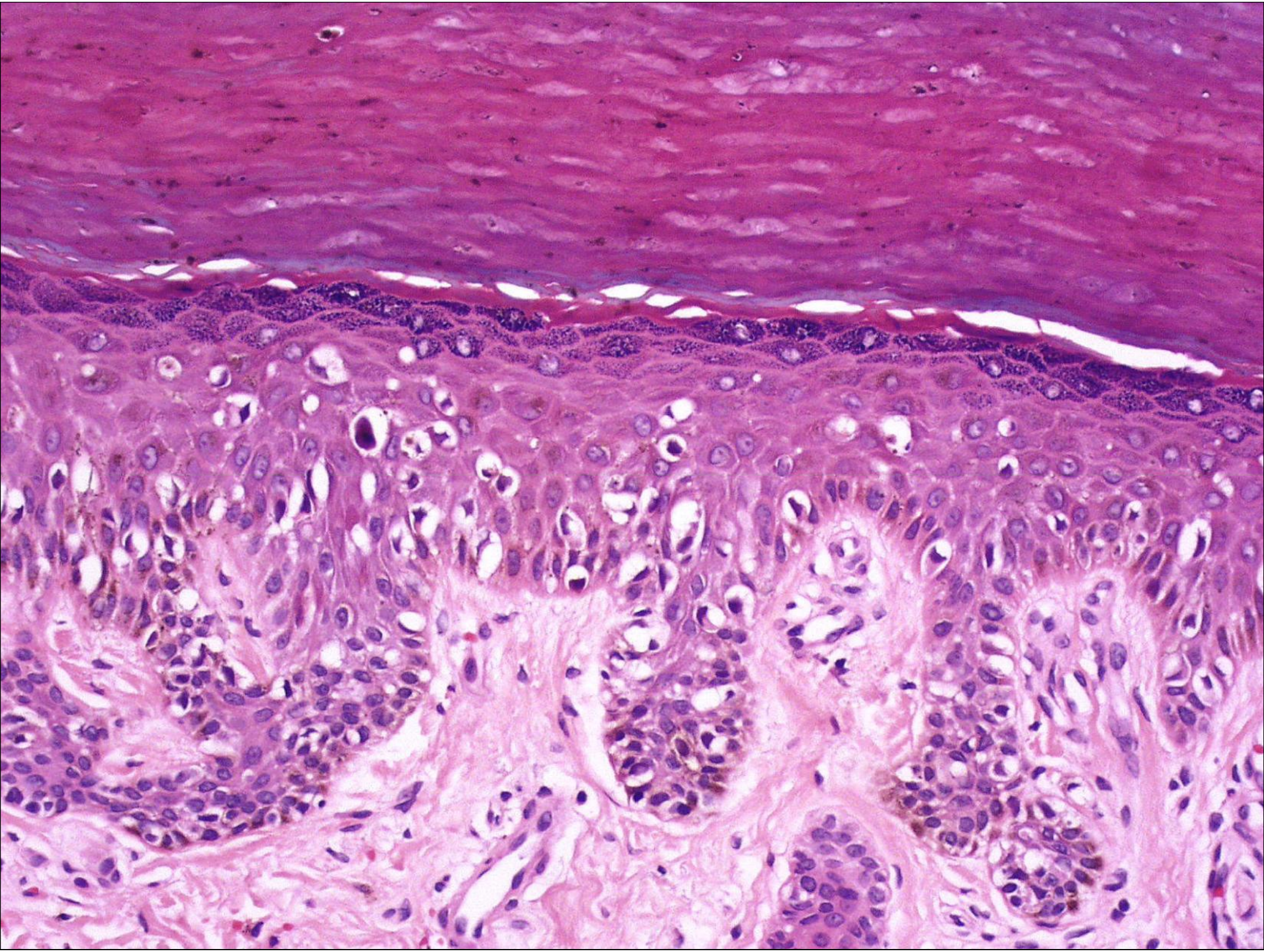
- Microscopic features
  - Asymmetric
  - Single cell growth pattern
  - Irregular nests
  - Variable upward migration (more prominent in older lesions)
  - Pagetoid spread > than acral nevi
  - Hyperchromatic nuclei with haloes

Acral Lentiginous Melanoma

- Microscopic features
  - Skip areas frequent
  - Biopsies not always diagnostic (especially from lesion edge)
    - Consider re-biopsy if clinically suspicious
  - Nests often absent in early lesions
  - Dermal component can be relatively bland
  - Mixed types common (superficial spreading) (especially dorsal surface)







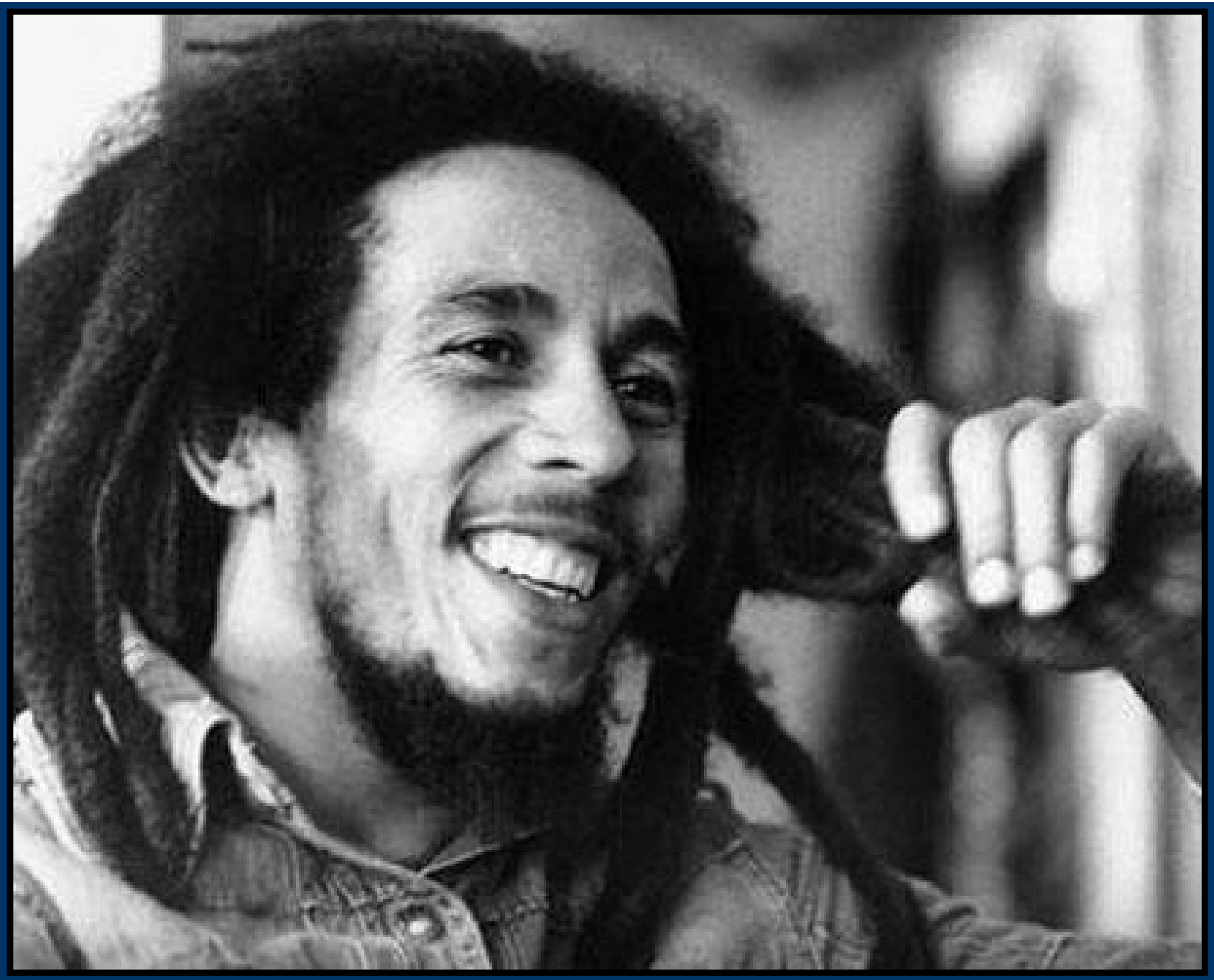
Acral nevus vs. Acral melanoma

Nevus

- Younger patients
- Small (<1 cm)
- Nuclei less hyperchromatic
- Single cell pattern on rete tips
- Pagetoid spread more central
- Dermal component bland

Melanoma

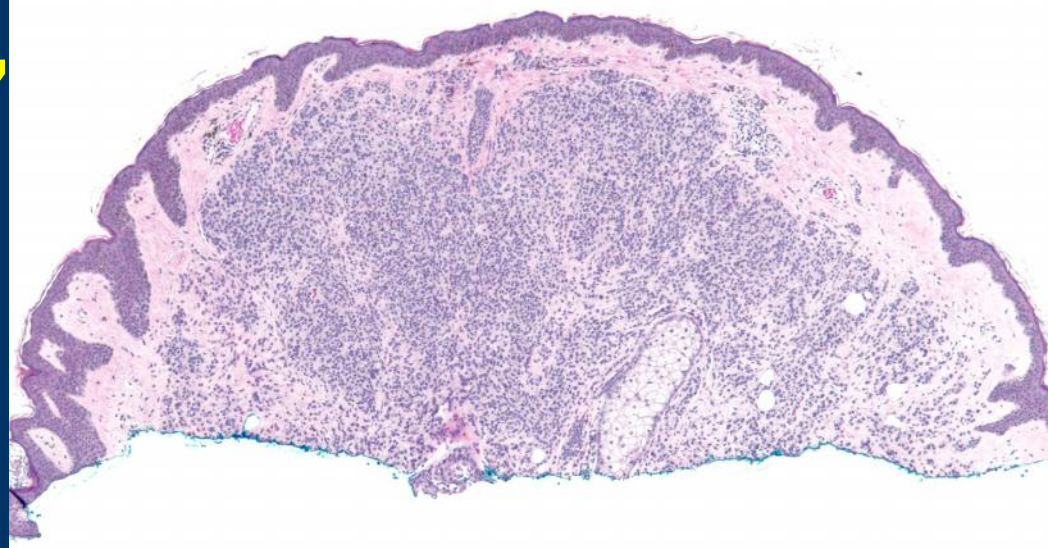
- Older patients
- Larger (>1 cm)
- Angulated hyperchromatic nuclei
- Single cell pattern contiguous
- Pagetoid spread throughout
- Dermal component with atypia

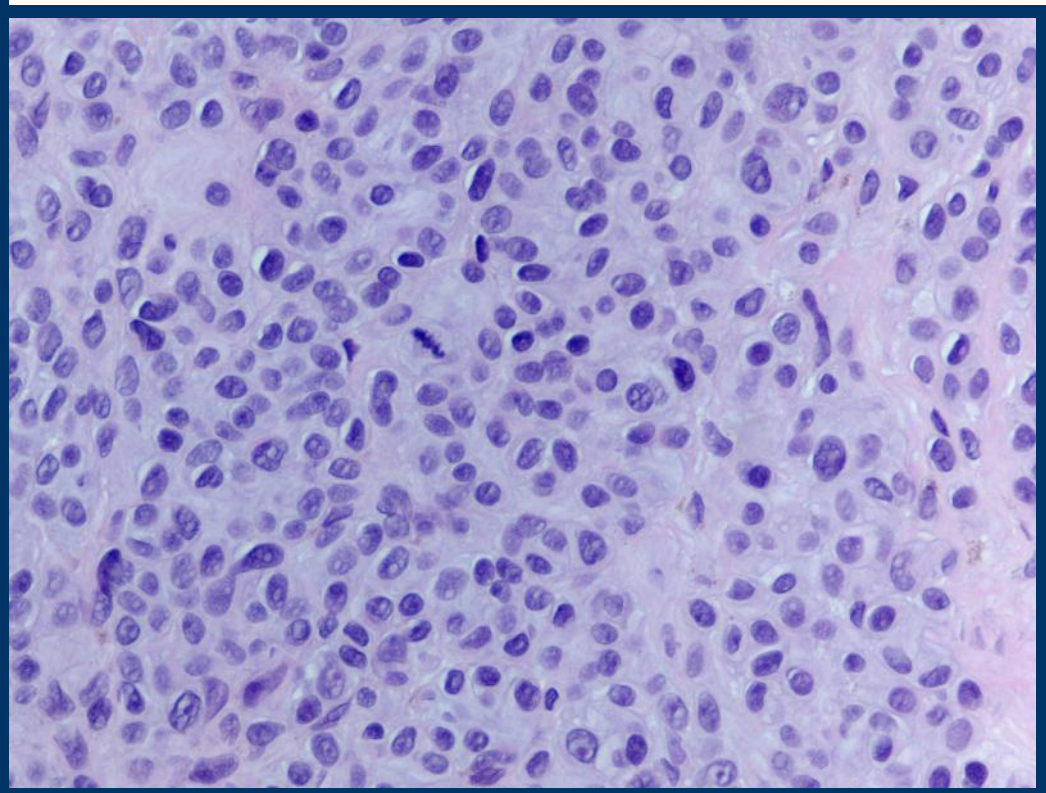


Rasta no abide amputation. I don’t allow a man to be dismantled.

Nevi during “hormonal states”

- Common nevi in pregnant patients or teenagers may have some atypia and rare mitotic figures
- Low power features resemble conventional nevus





Mitotic Activity Within Dermal Melanocytes of Benign Melanocytic Nevi: A Study of 100 Cases With Clinical Follow-up

Steven M. Ruhoy, MD, Steven E. Kolker, MD,† and Todd C. Murry, MD, PhD‡*

- Incidence ~1%
- More common in young patients
- Head and neck and extremities
- 80% one MF
- 89% upper dermis
- Congenital or Spitz features

(*Am J Dermatopathol* 2011;33:167–172)

Frequent Mitotic Activity in Banal Melanocytic Nevi Uncovered by Immunohistochemical Analysis

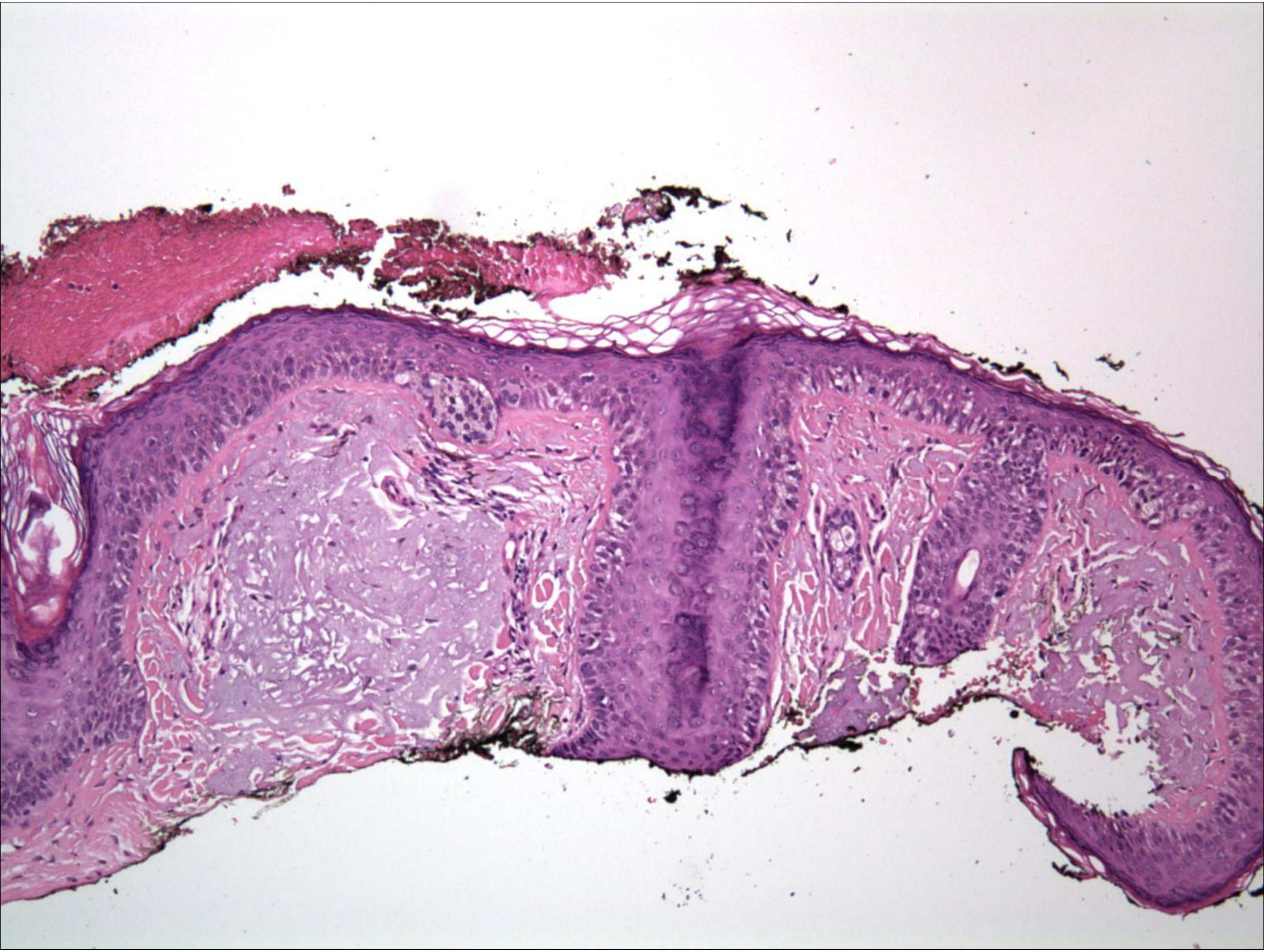
Katharina Glatz, MD, Christoph Hartmann, MD,* Milos Antic, MD,* and Heinz Kutzner, MD†*

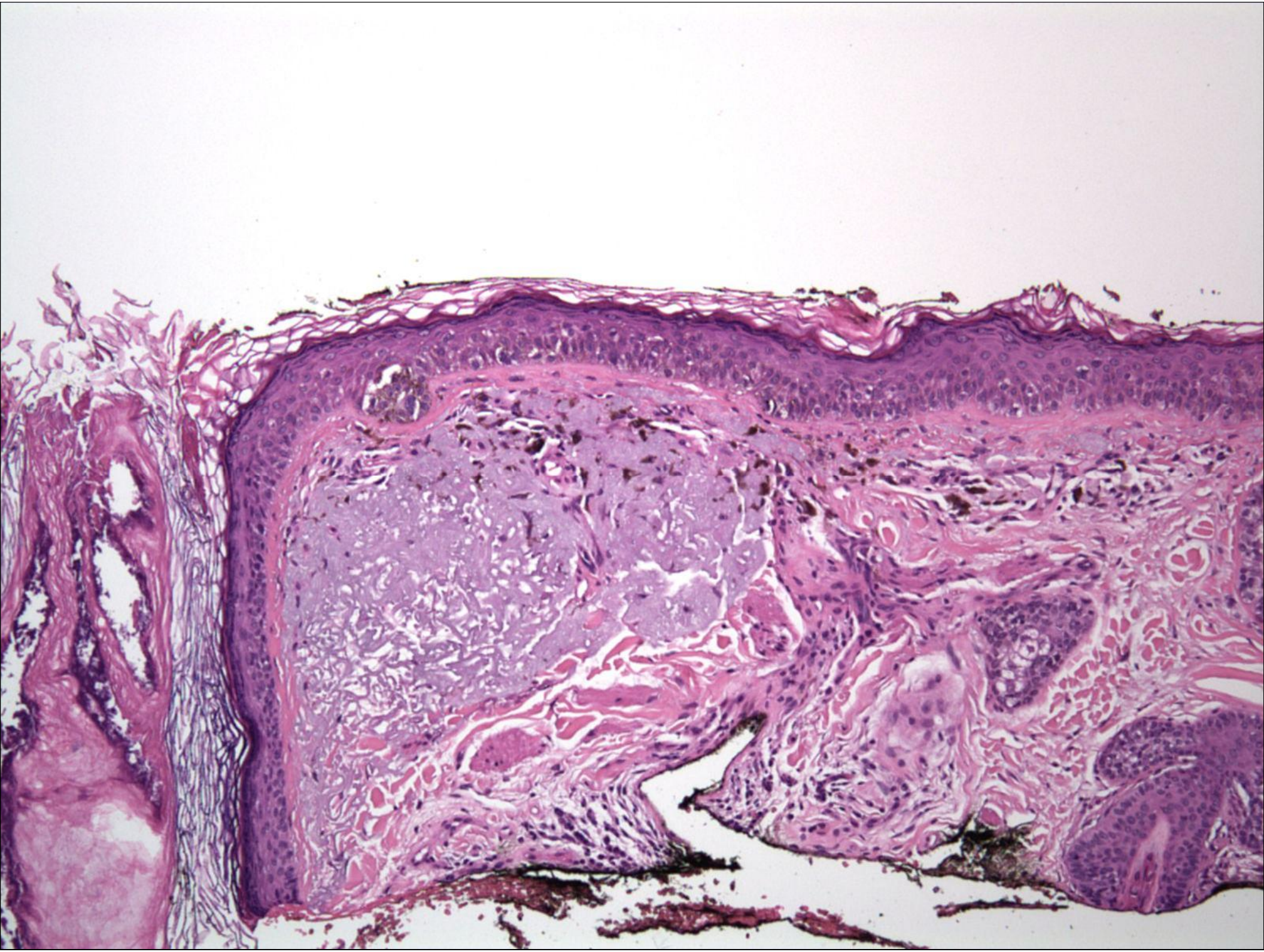
- PHH3 and MPM2 stains
- Young patients
- 0.24 MF/mm2
- Upper dermis 3:1
- Traumatized and inflamed nevi more likely to have MFs

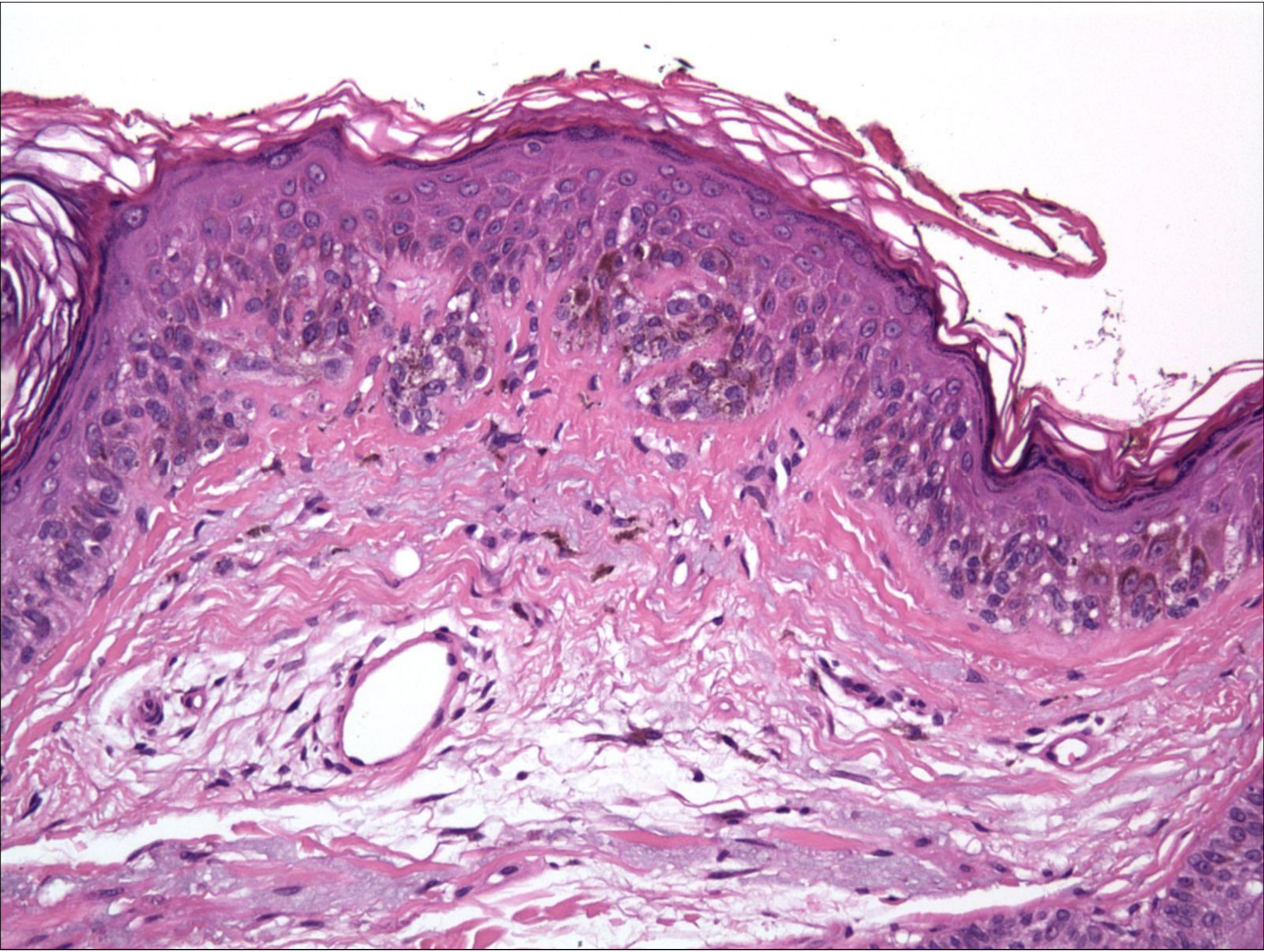
(*Am J Dermatopathol* 2010;32:643–649)

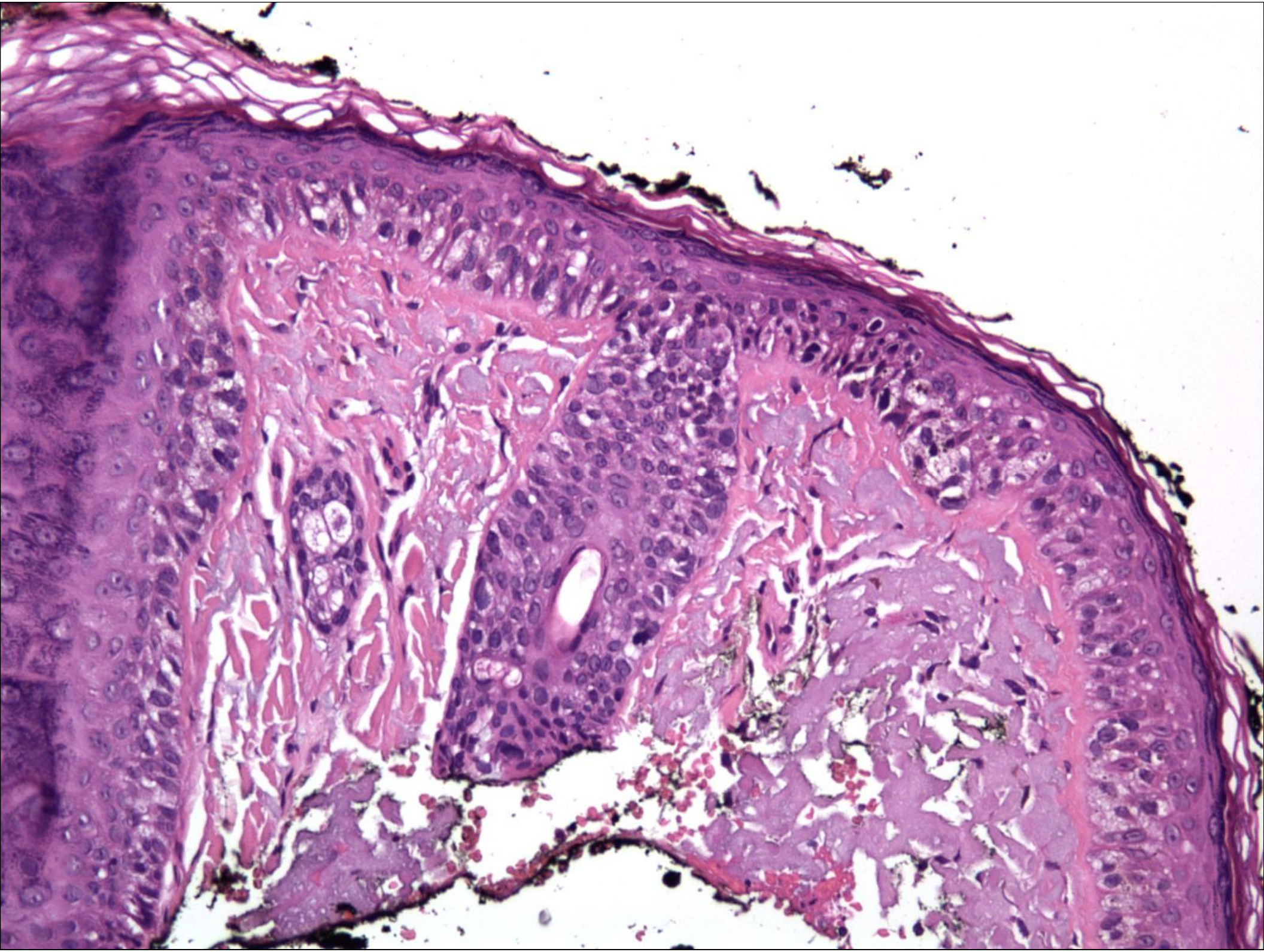
Melanoma In Situ on Sun-damaged Skin (Lentigo Maligna)

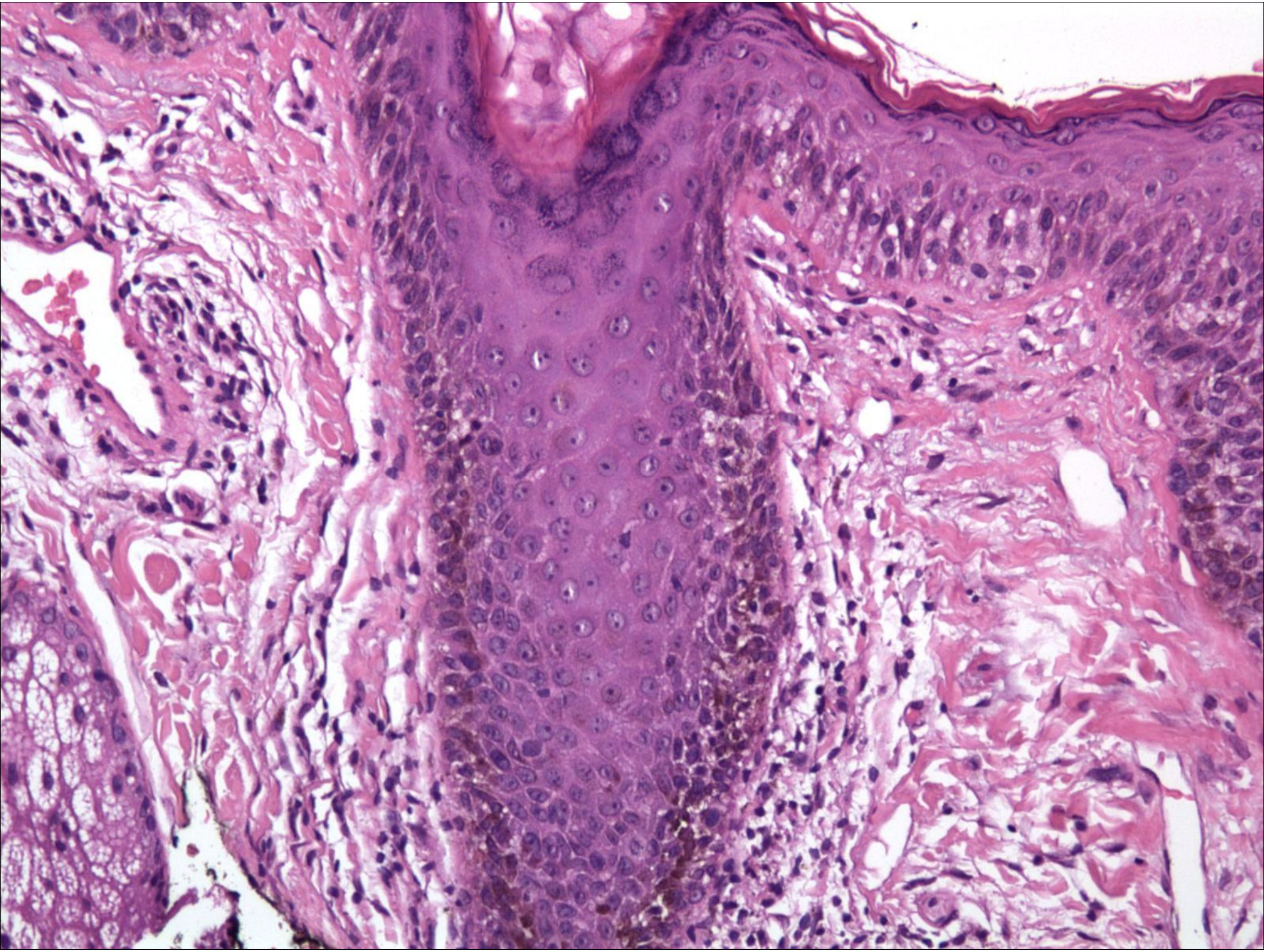
- Subtle on heavily sun damaged skin of head and neck (lentigo maligna type)
- Contiguous proliferation of melanocytes
- Focal nests
- Upward migration usually not prominent
- Atypia usually mild





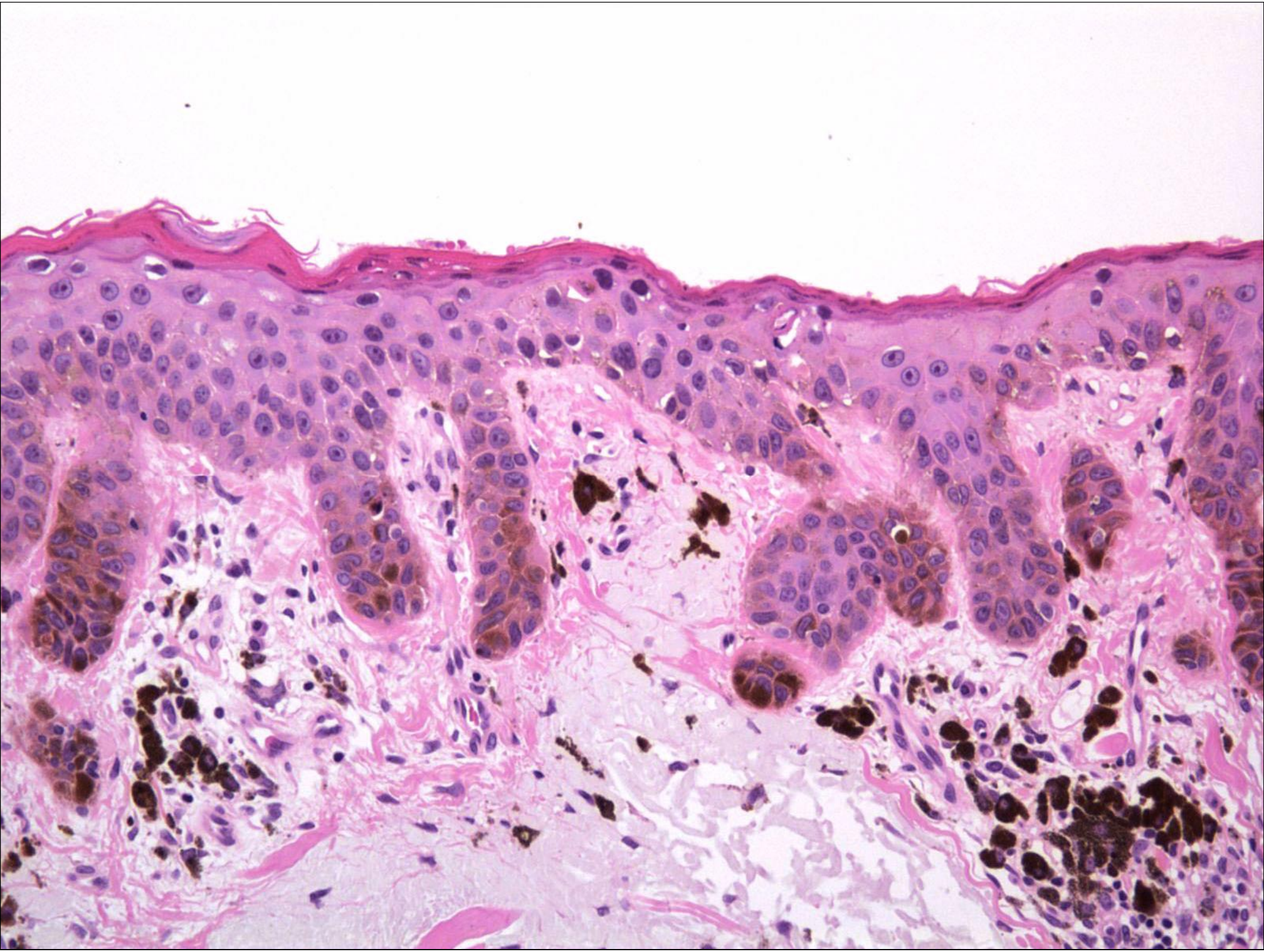






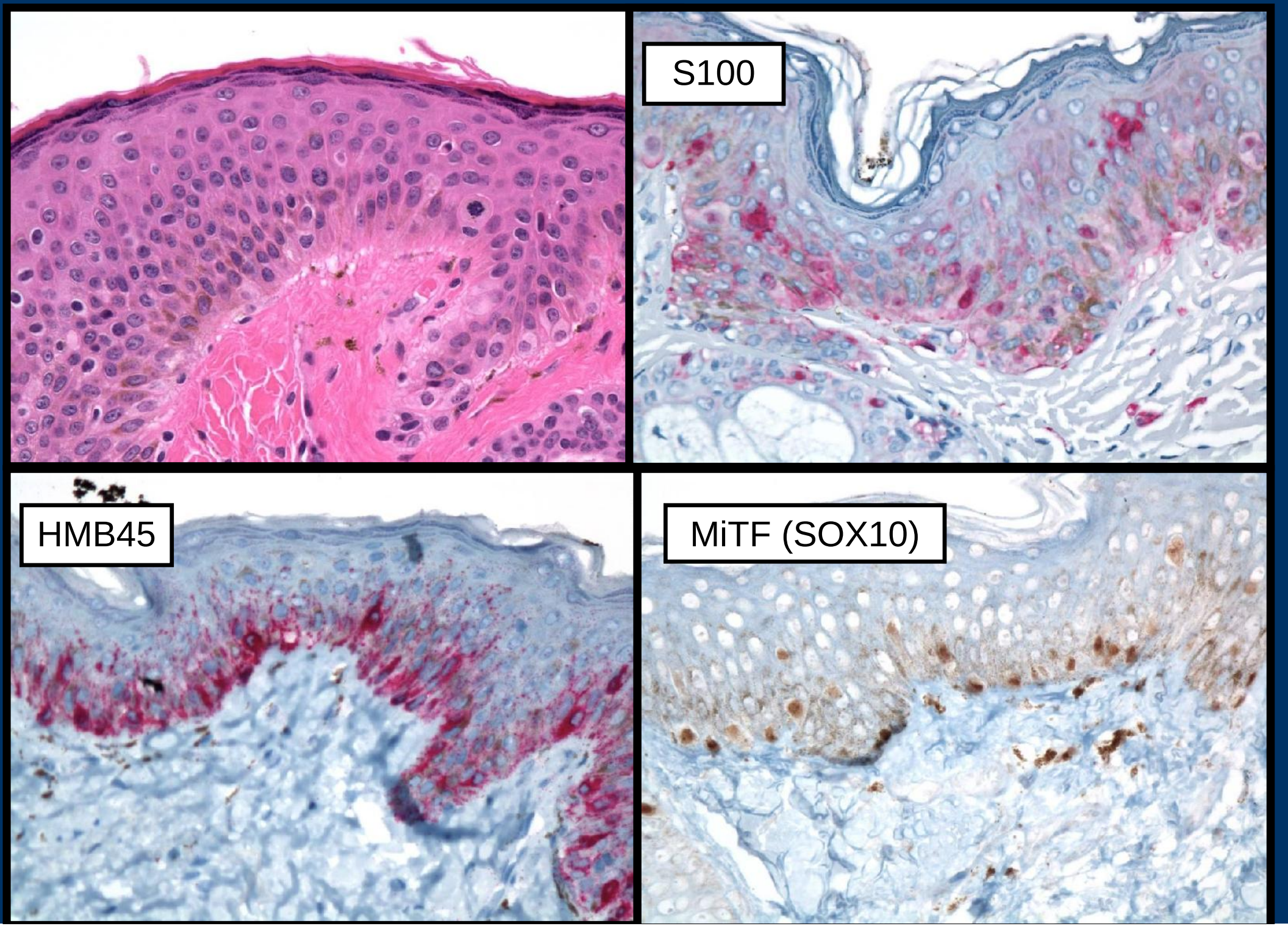
Melanoma in Situ

- Differential diagnosis
  - Pigmented actinic keratosis
  - Solar lentigo



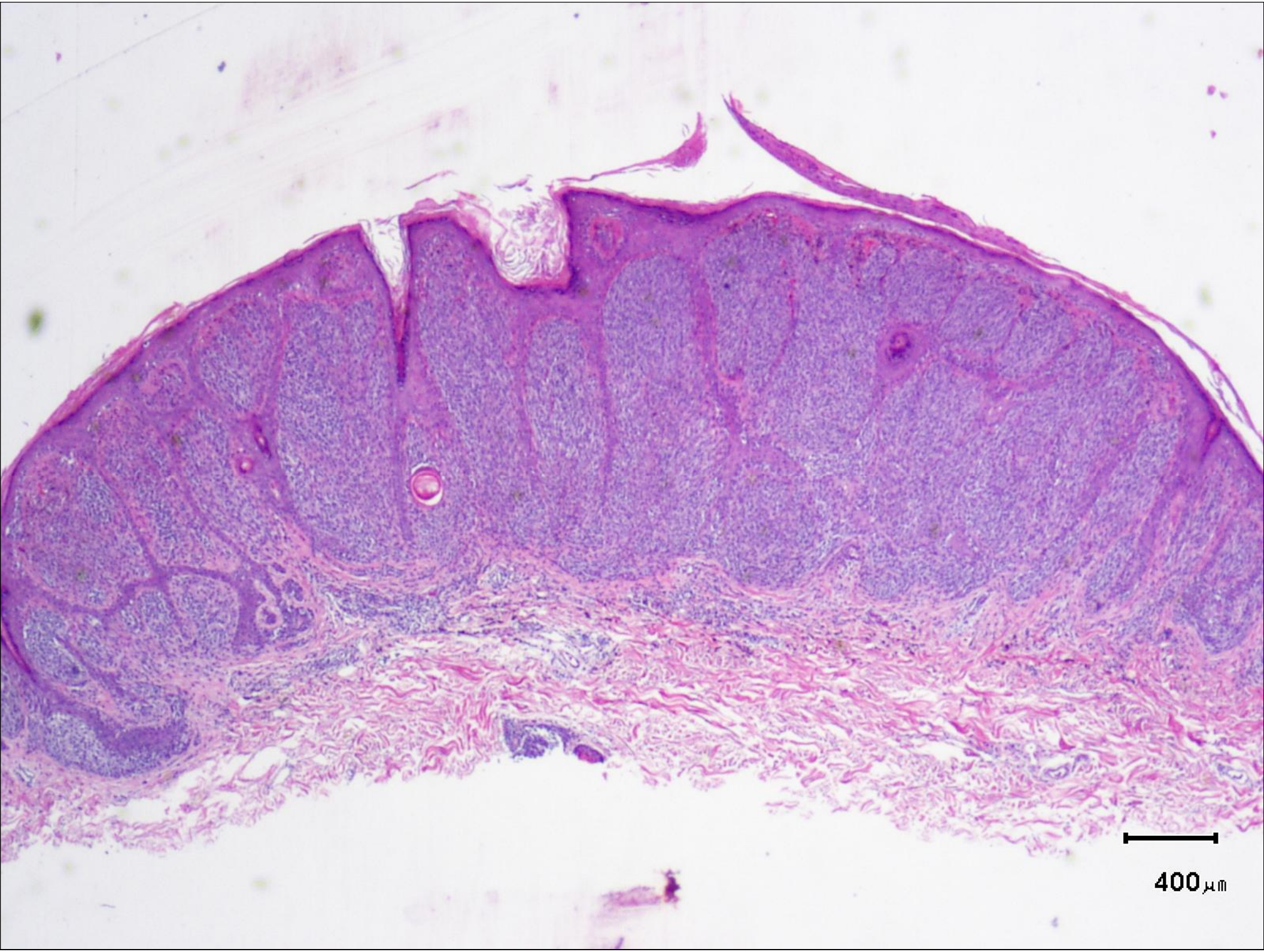
Melanoma In Situ on Sun-damaged Skin

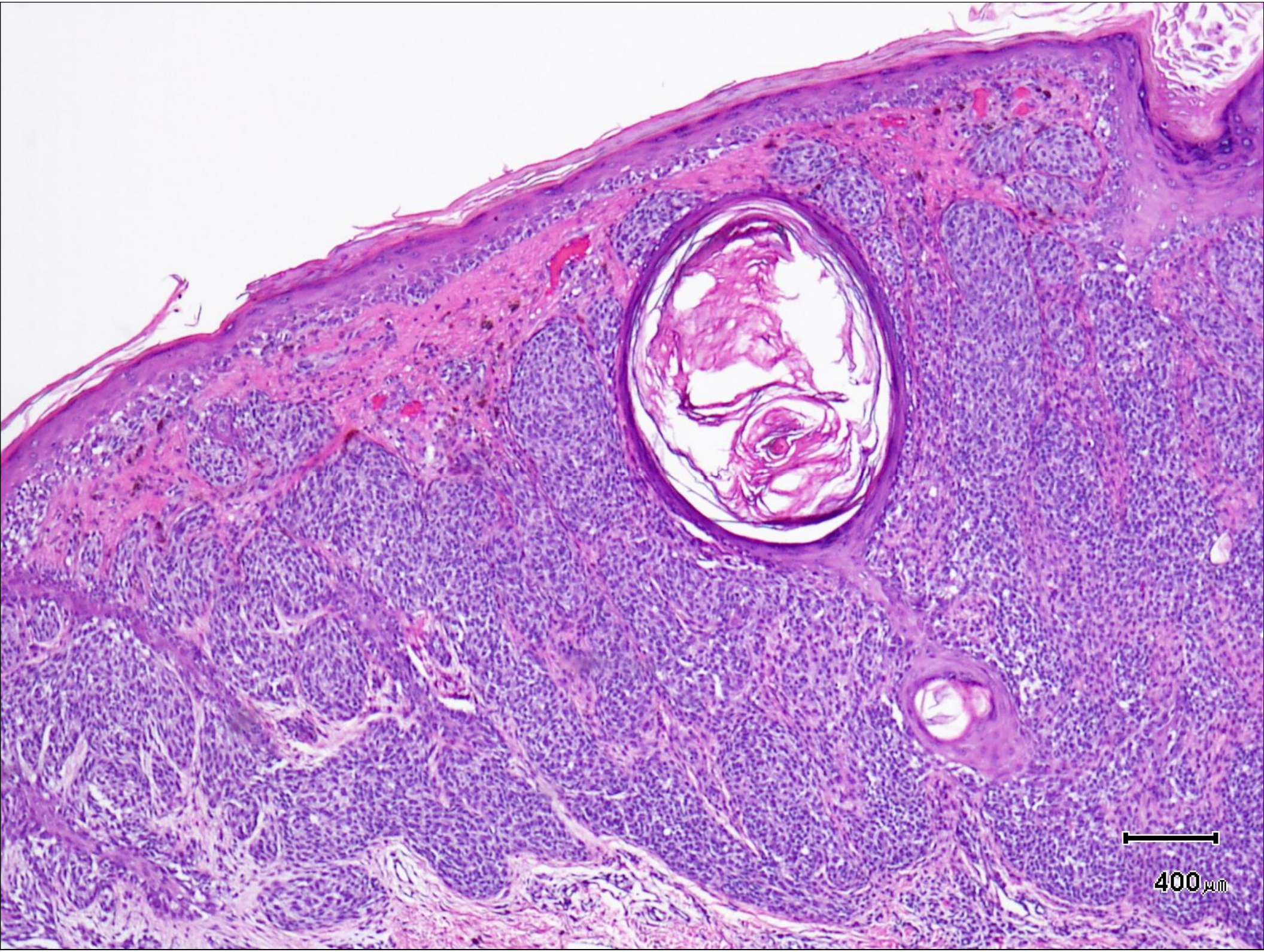
- Practical tips
  - Any contiguous proliferation of melanocytes or nests worrisome for melanoma in situ
  - Extension down follicles
  - Junctional dysplastic nevi uncommon in heavily sun-damaged skin of elderly patients
  - Immunostains can help distinguish pigmented AK from MIS (red chromogen can be helpful)
    - HMB45, S100, MiTF, SOX-10 (beware of pitfalls)
    - Beware Melan-A in inflamed skin


S100
HMB45
MiTF (SOX10)

Nevoid Melanoma

- Clinical features
  - May be innocuous
  - Verrucous to dome shaped
- Microscopic features
  - Resembles nevus on scanning magnification
  - Small epithelioid melanocytes
  - Subtle atypia
  - Mitotic activity
  - Ki-67 labeling throughout


400 µm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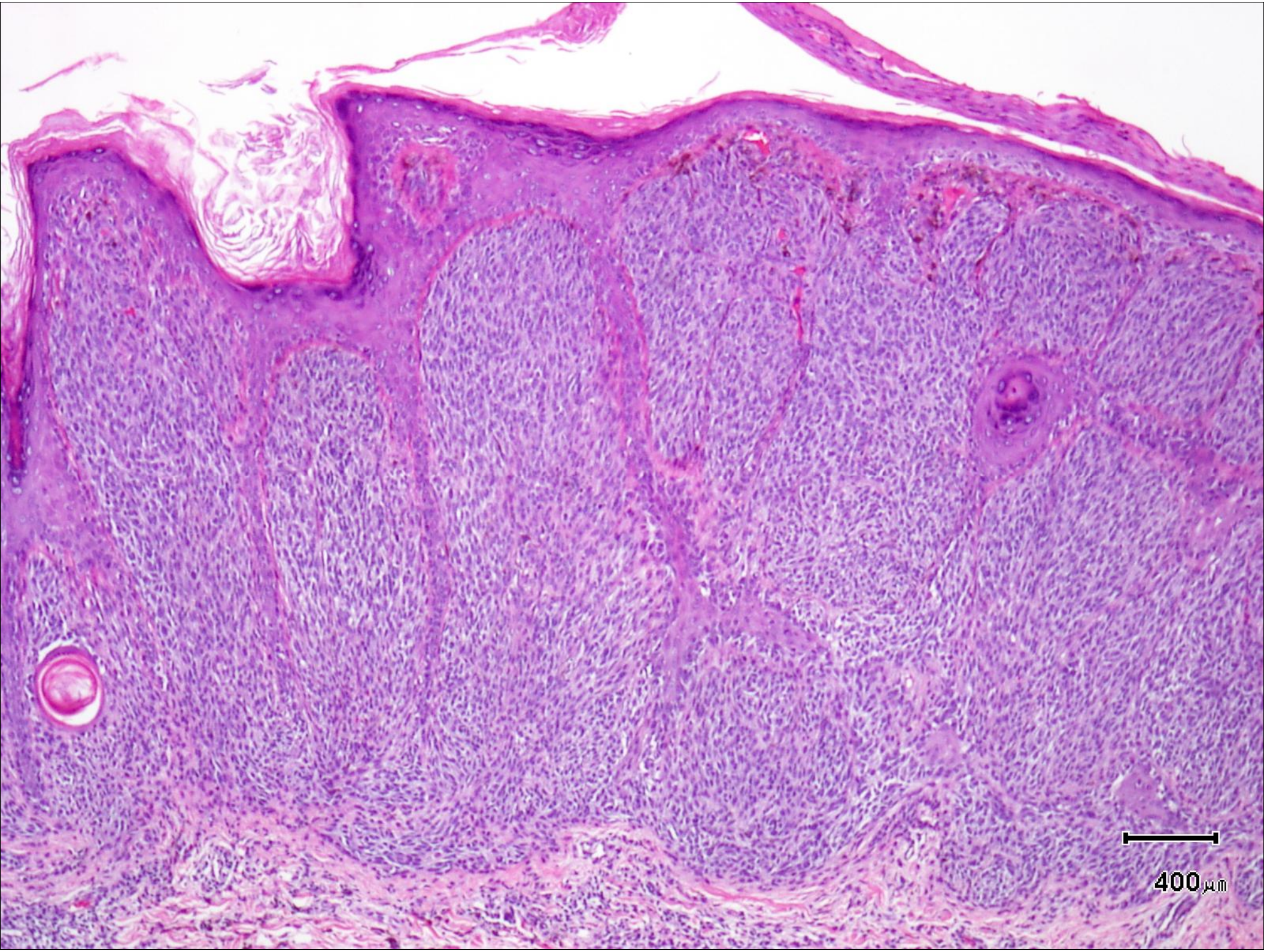
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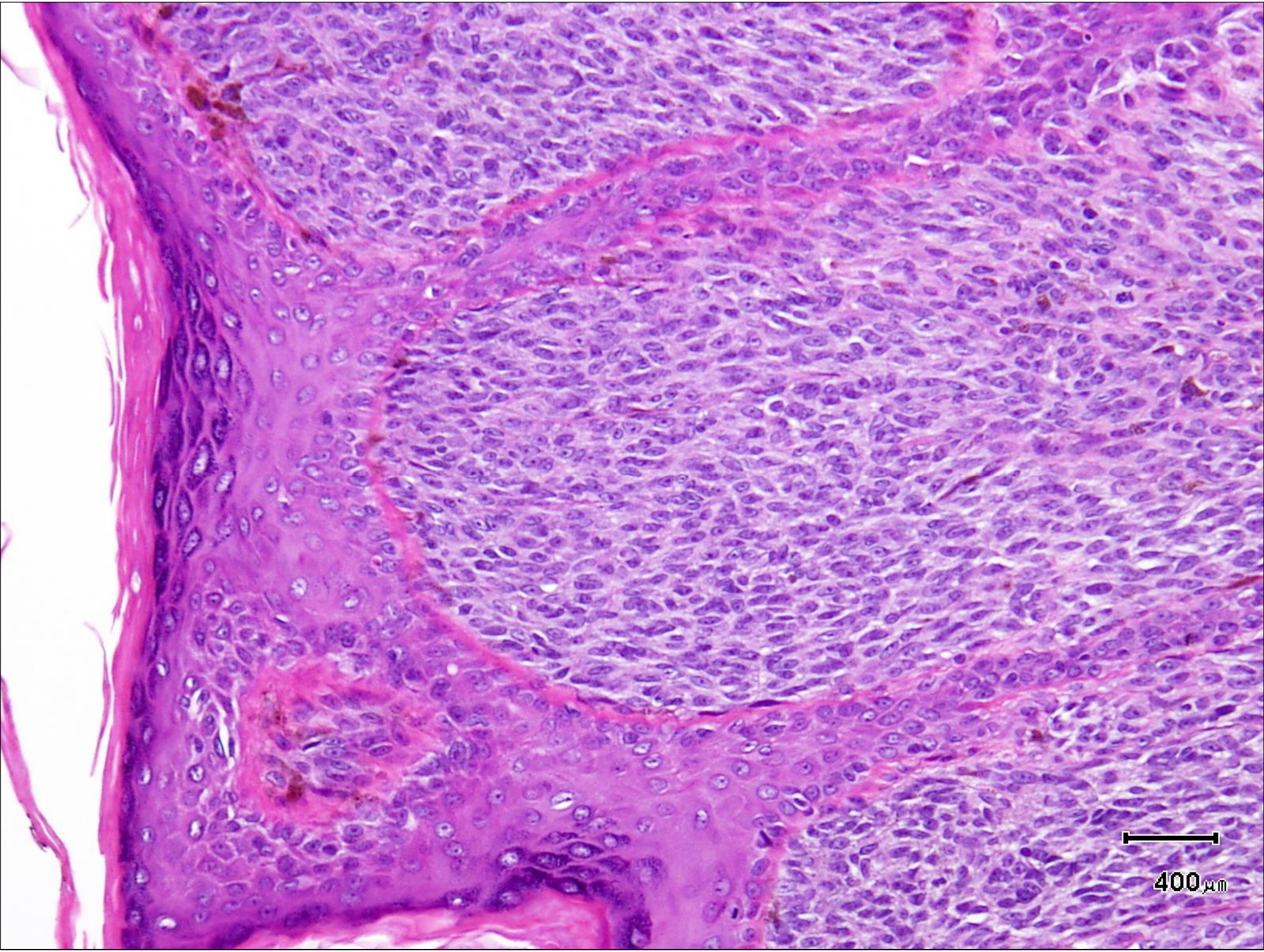
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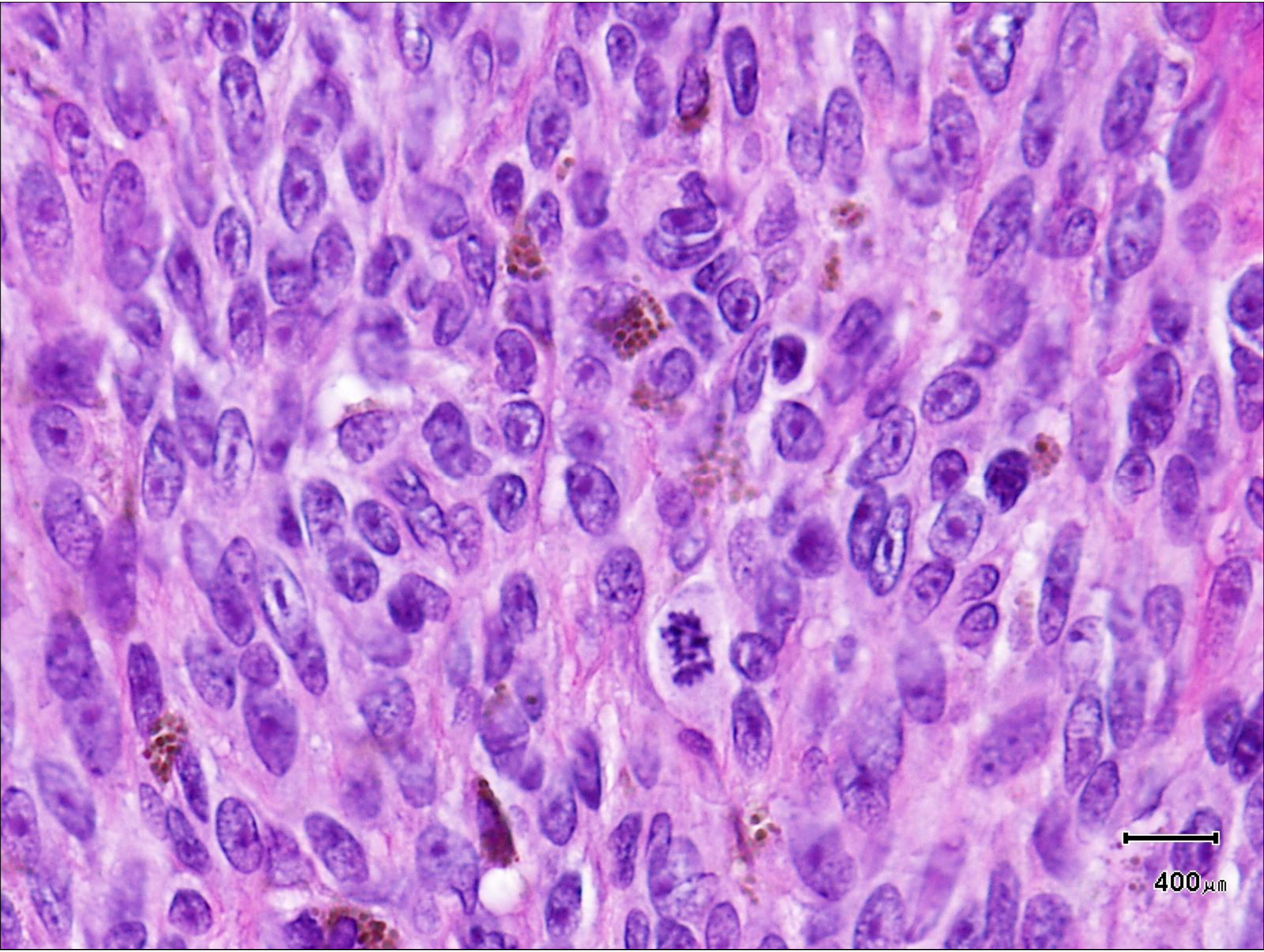

400 µm

Nevoid Melanoma

- Outcome
  - Recurrence rate 50%
  - Metastasis 25-50%
  - Mortality ≥ 25%
  - Likely due to more advanced stage at presentation
- Practical tips
  - Examine all nevi at least briefly at high power
  - Beware of nevi with sheet-like growth pattern

Desmoplastic (Neurotropic) Melanoma

Clinical Features

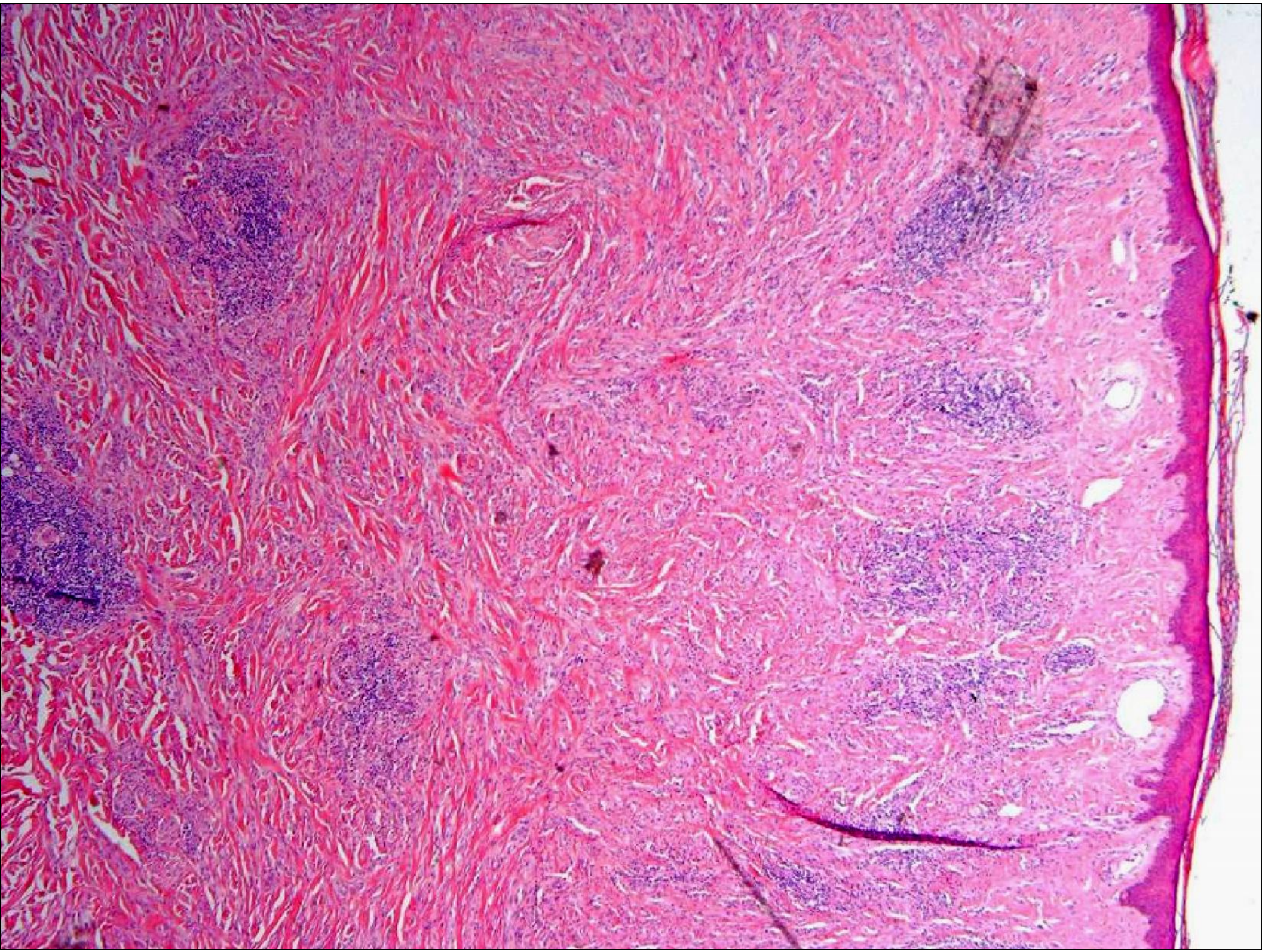
- Approximately 4% of all melanomas
- Present in 6th to 7th decades
- Most commonly involve head and neck
- Lower extremity tumors more common in women
- More than half clinically amelanotic
  - Potential for delayed diagnosis
  - Clinically suspected in minority of cases

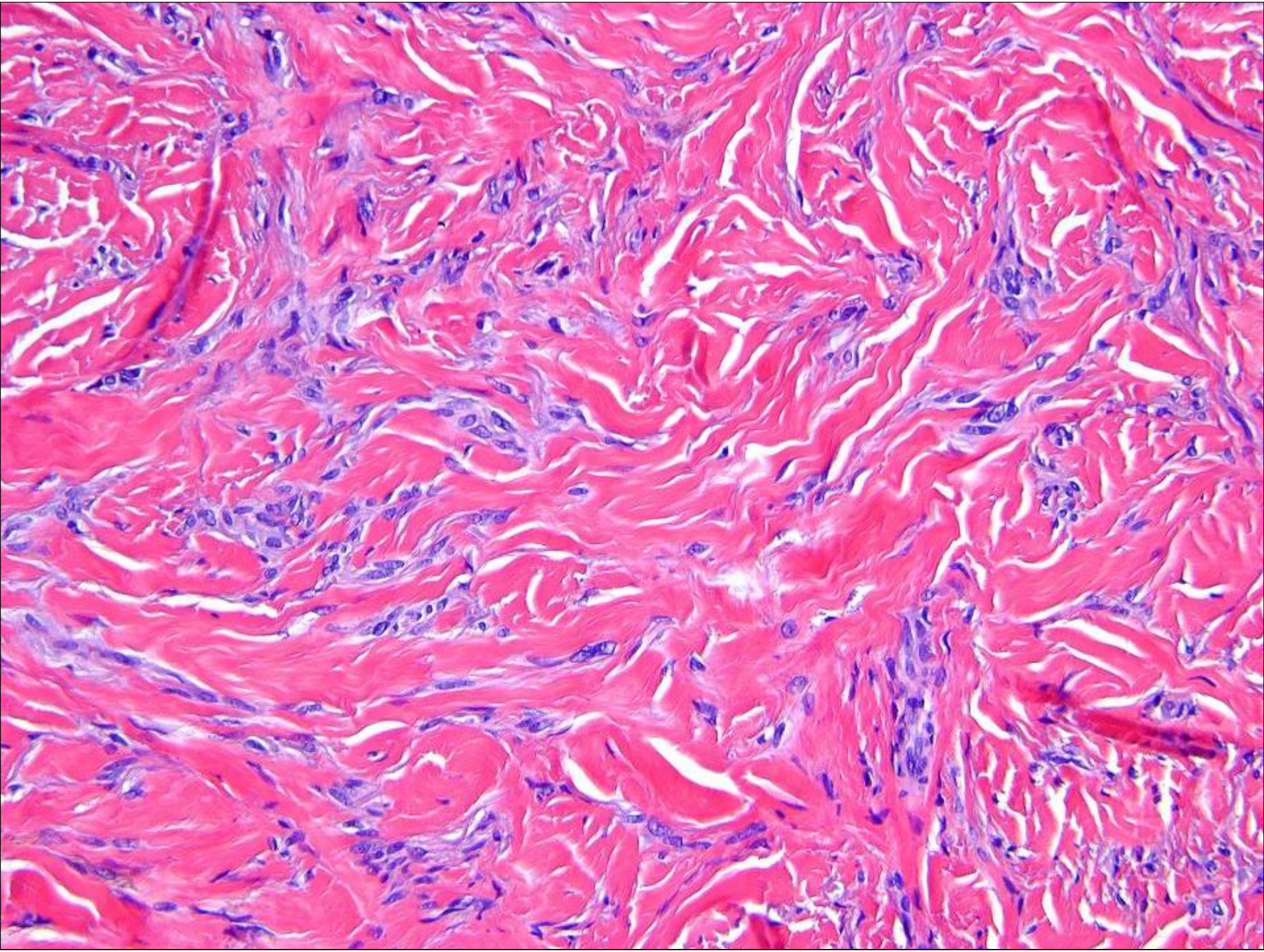
Histopathology

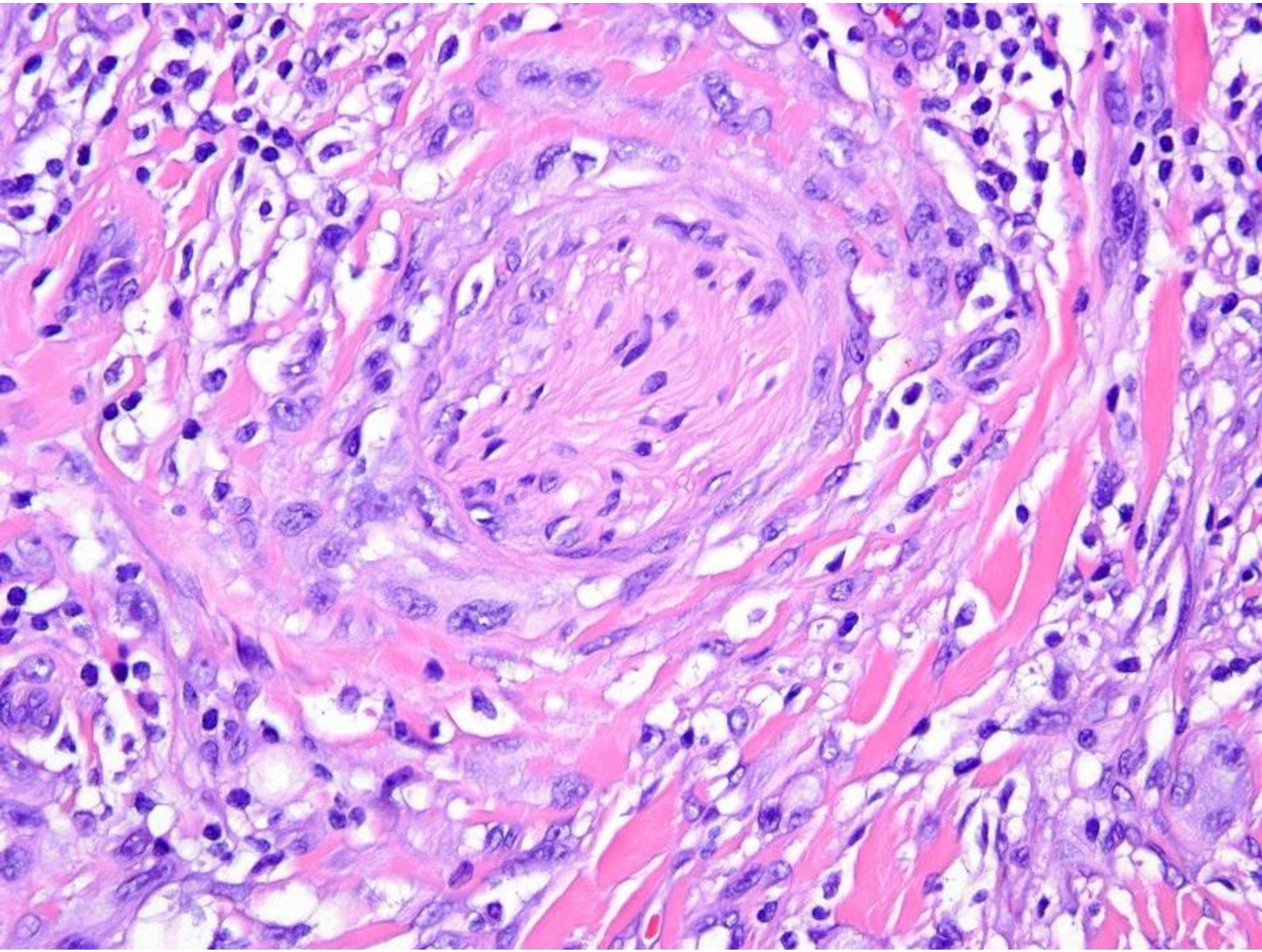
- Majority involve reticular dermis (Clark's level IV) or subcutis (Clark's level V)
- Breslow level: 2.5->4 mm
- Epidermal ulceration up to 25%
  - Potential confusion with scar
- Hyperchromatic spindle cells
  - Rare cases with deceptively bland nuclei
- Packeted arrangement

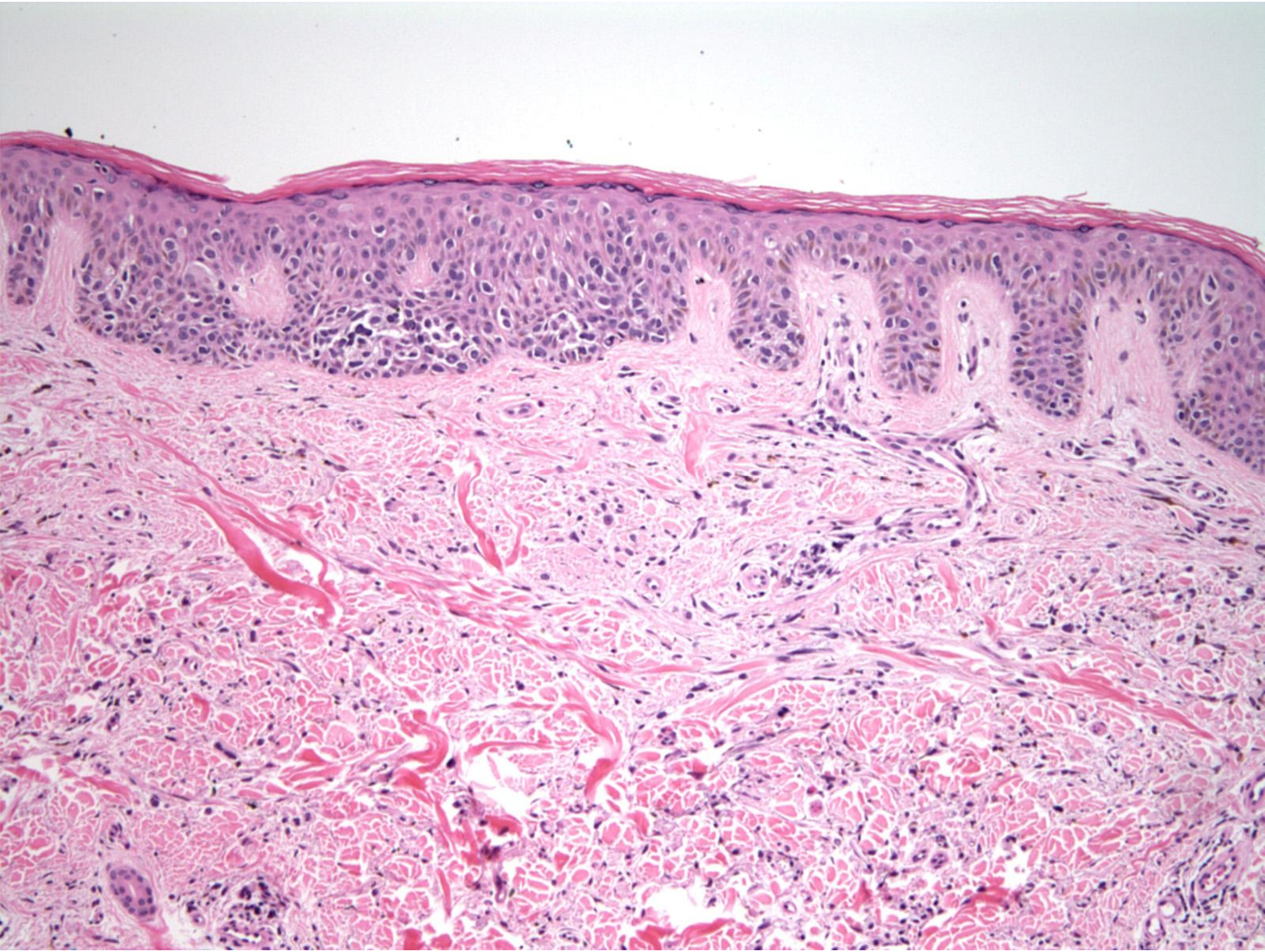
Histopathology

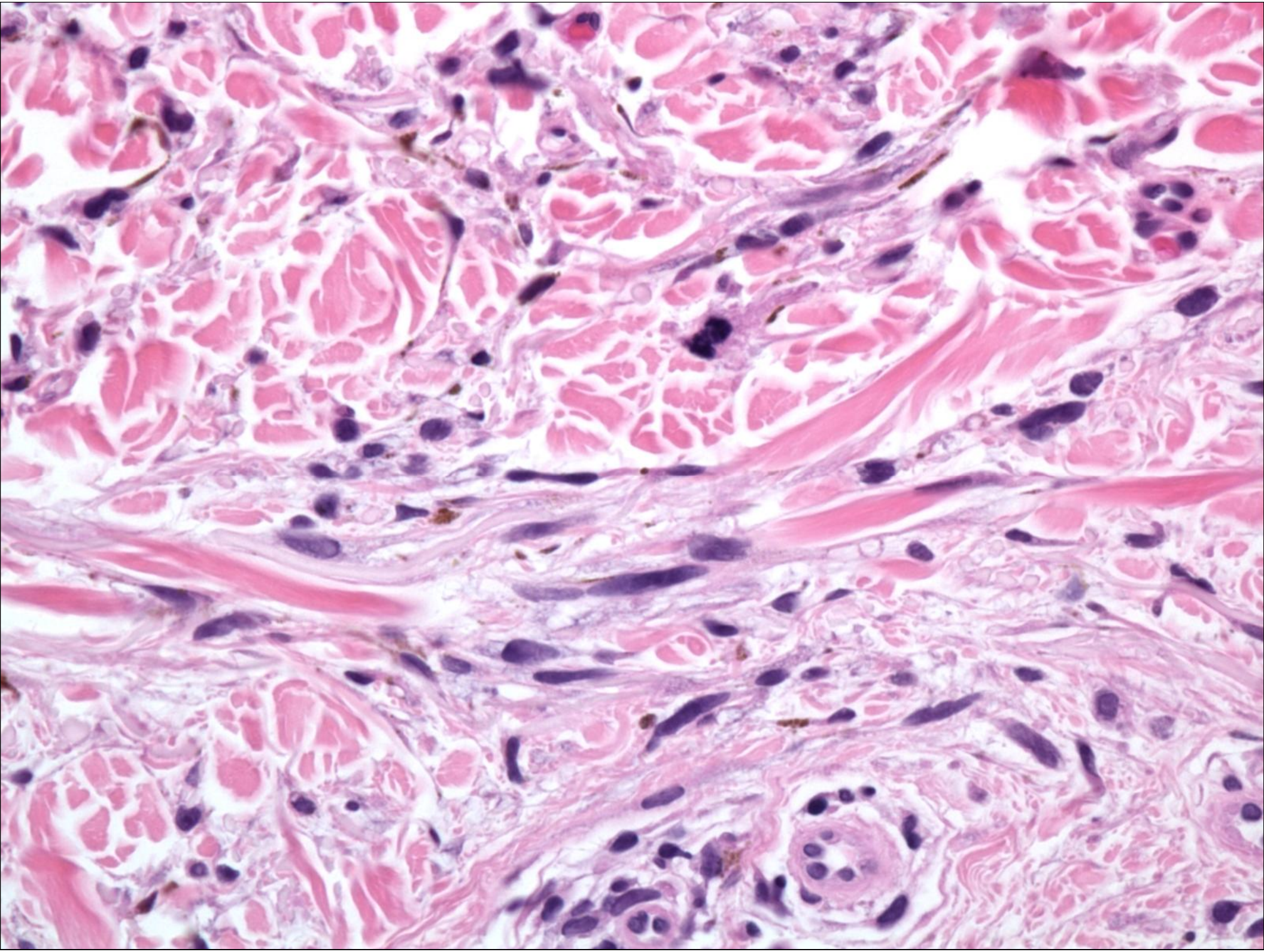
- Perineural invasion in 1/3 of cases
  - Breslow depth >1.5mm
- Mitotic figures usually conspicuous
- Melanin pigment absent to sparse
- Admixed lymphocytic infiltrate
- Overlying junctional atypical melanocytic proliferation (40-90%)
- May have admixed conventional melanoma

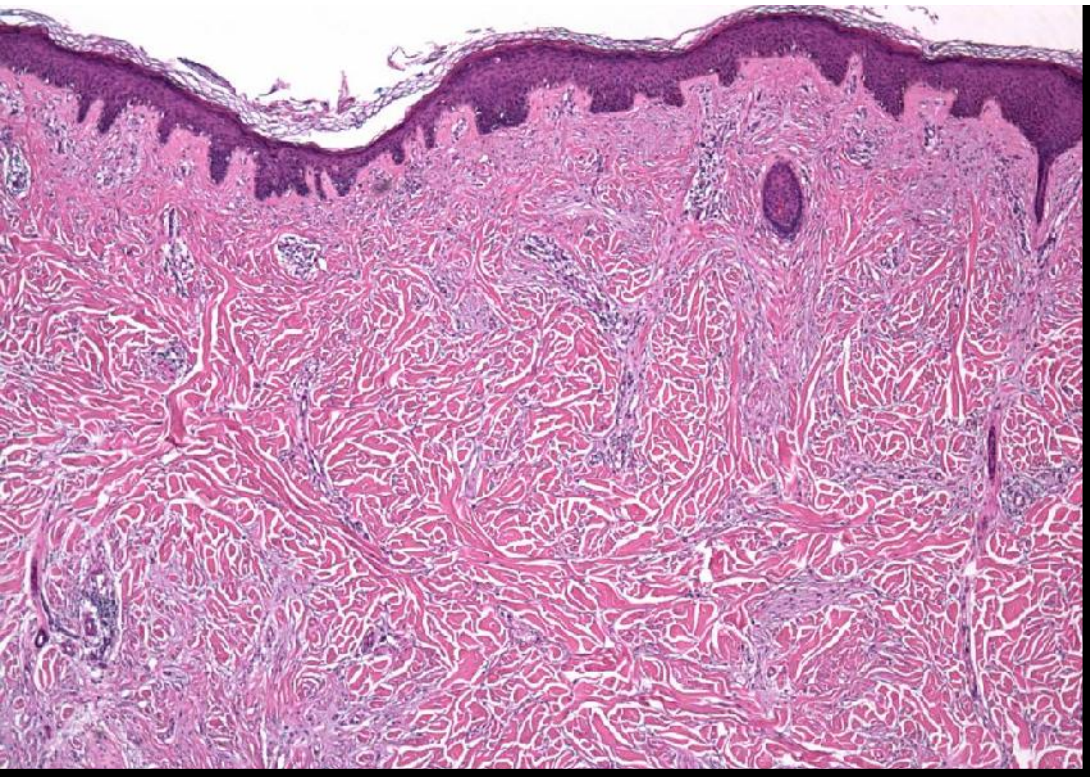
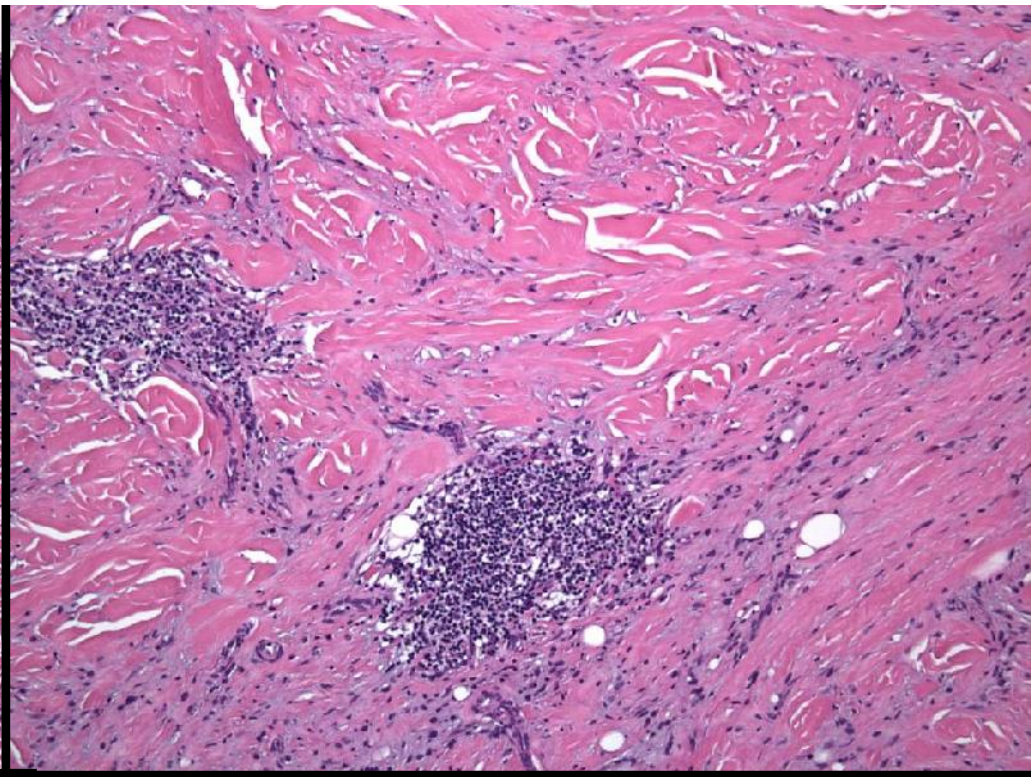
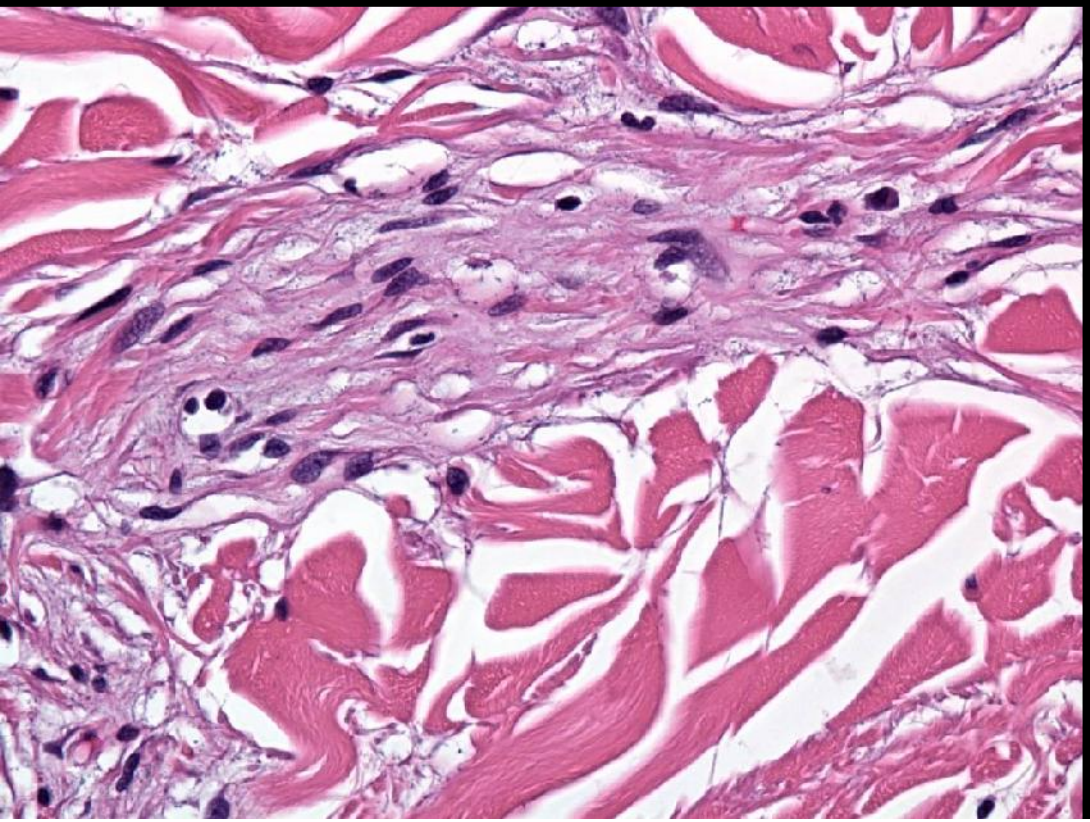
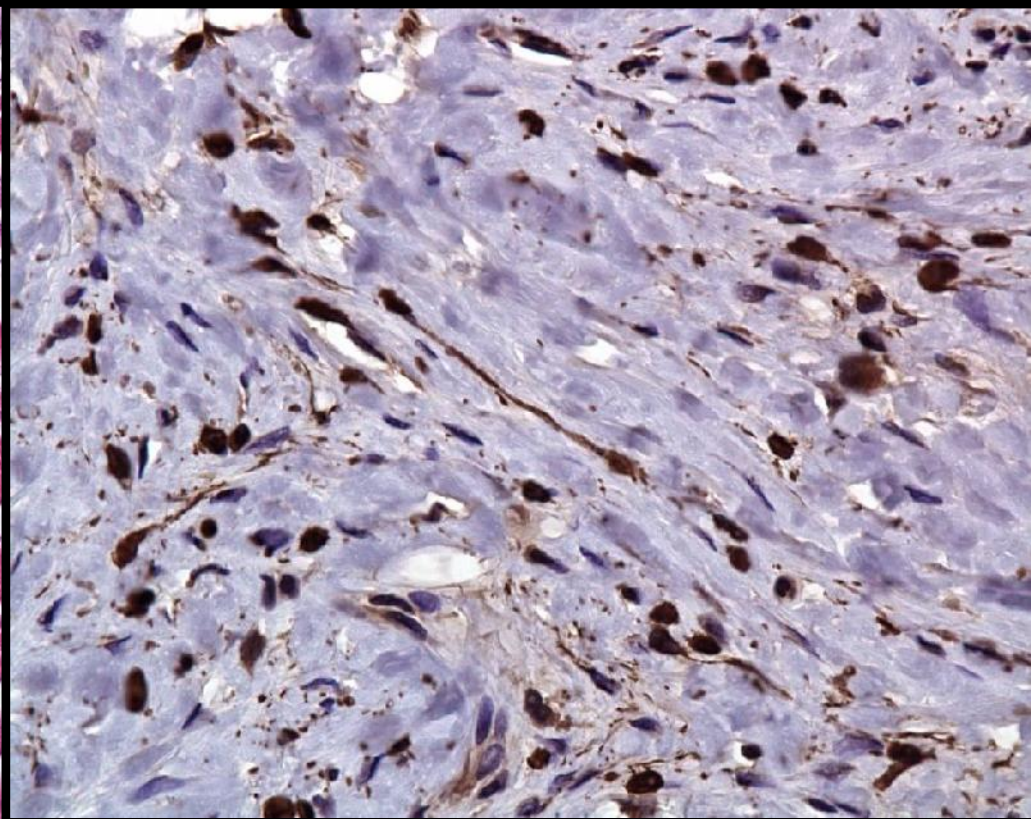


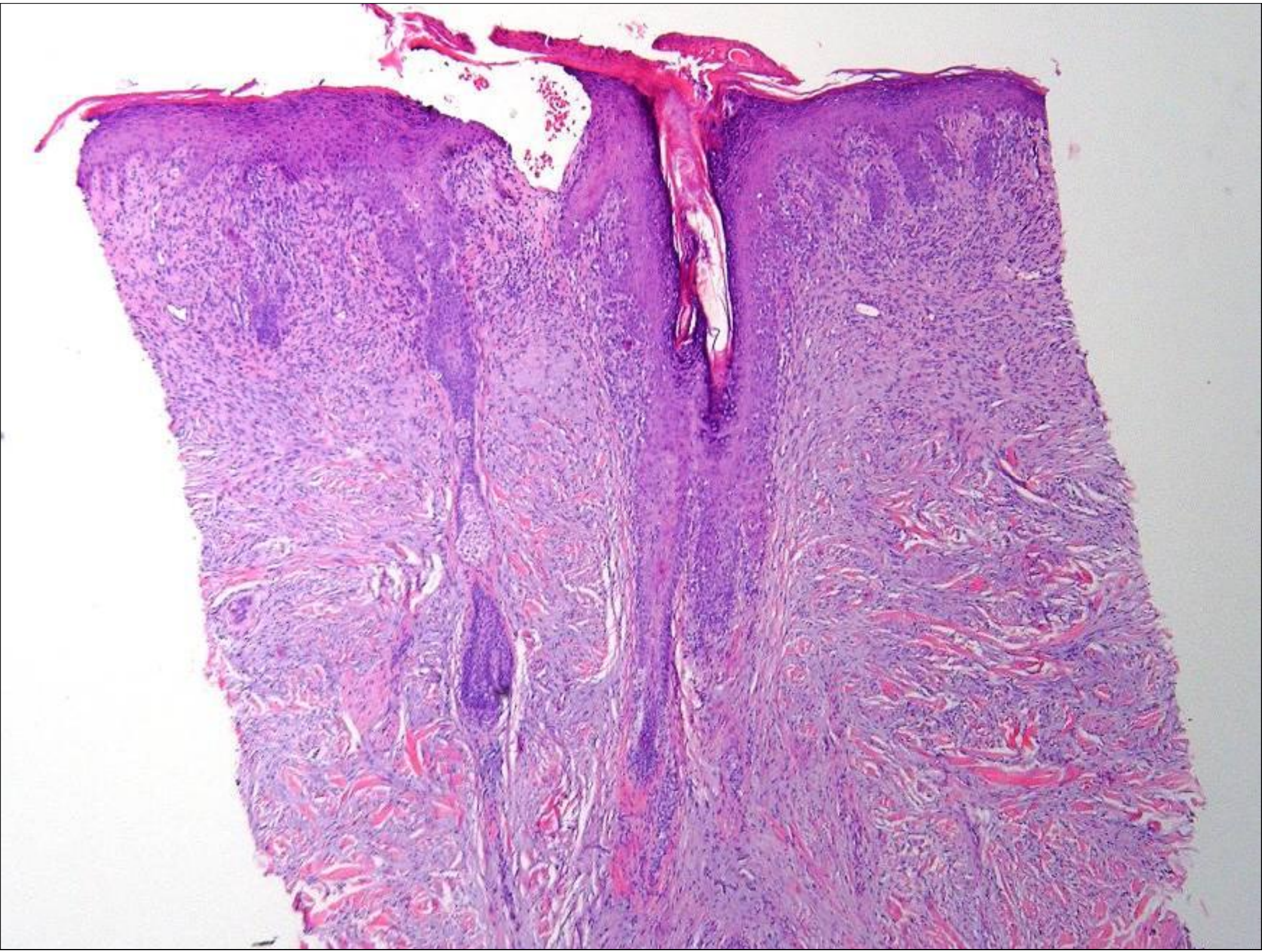


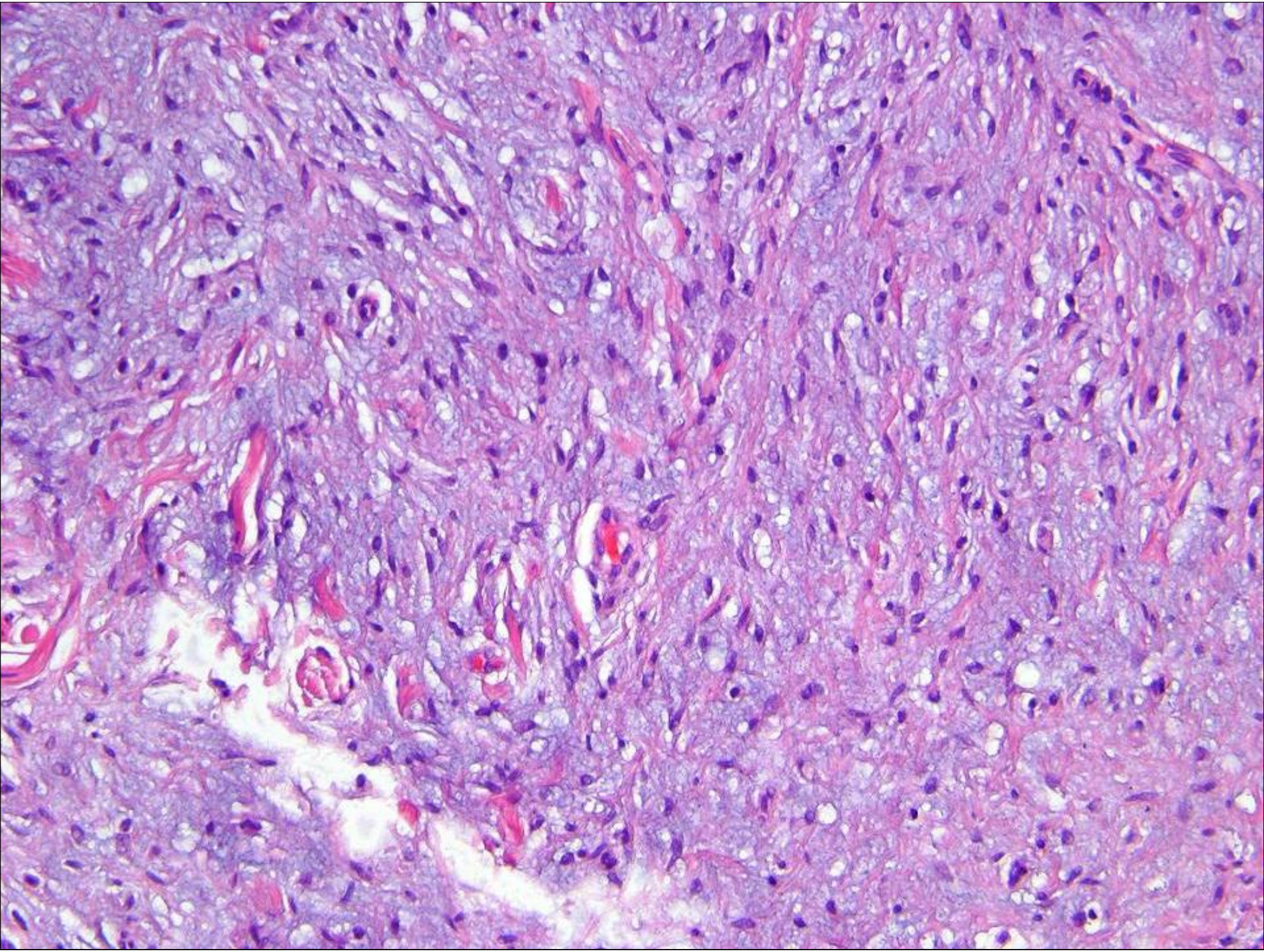










Immunohistochemistry

- S100 and SOX-10 strongly positive
- Melanocyte specific markers (e.g. HMB45) of limited utility (<5% positive)
- Smooth muscle actin negative
  - Fibroblasts in stromal response positive
- Usually cytokeratin and desmin negative
  - Rare cases with anomalous expression

Behavior Compared with Conventional Melanoma

- Higher rate of local recurrence (10-50%)
  - Secondary to infiltrative growth pattern
  - Neurotropism increases risk
- Lower rate of lymph node metastasis
- Comparable rate of visceral metastasis
- Overall survival similar to or better than conventional melanoma

Differential Diagnosis

- Malignant cutaneous spindle cell tumors
  - Sarcomatoid squamous cell carcinoma (CK+, S100-)
  - Atypical fibroxanthoma (CK-, S100-)
- Desmoplastic Spitz
- Hypo-pigmented blue nevus
- MPNST

Dermal Pleomorphic Spindle Cell Tumor Differential Diagnosis

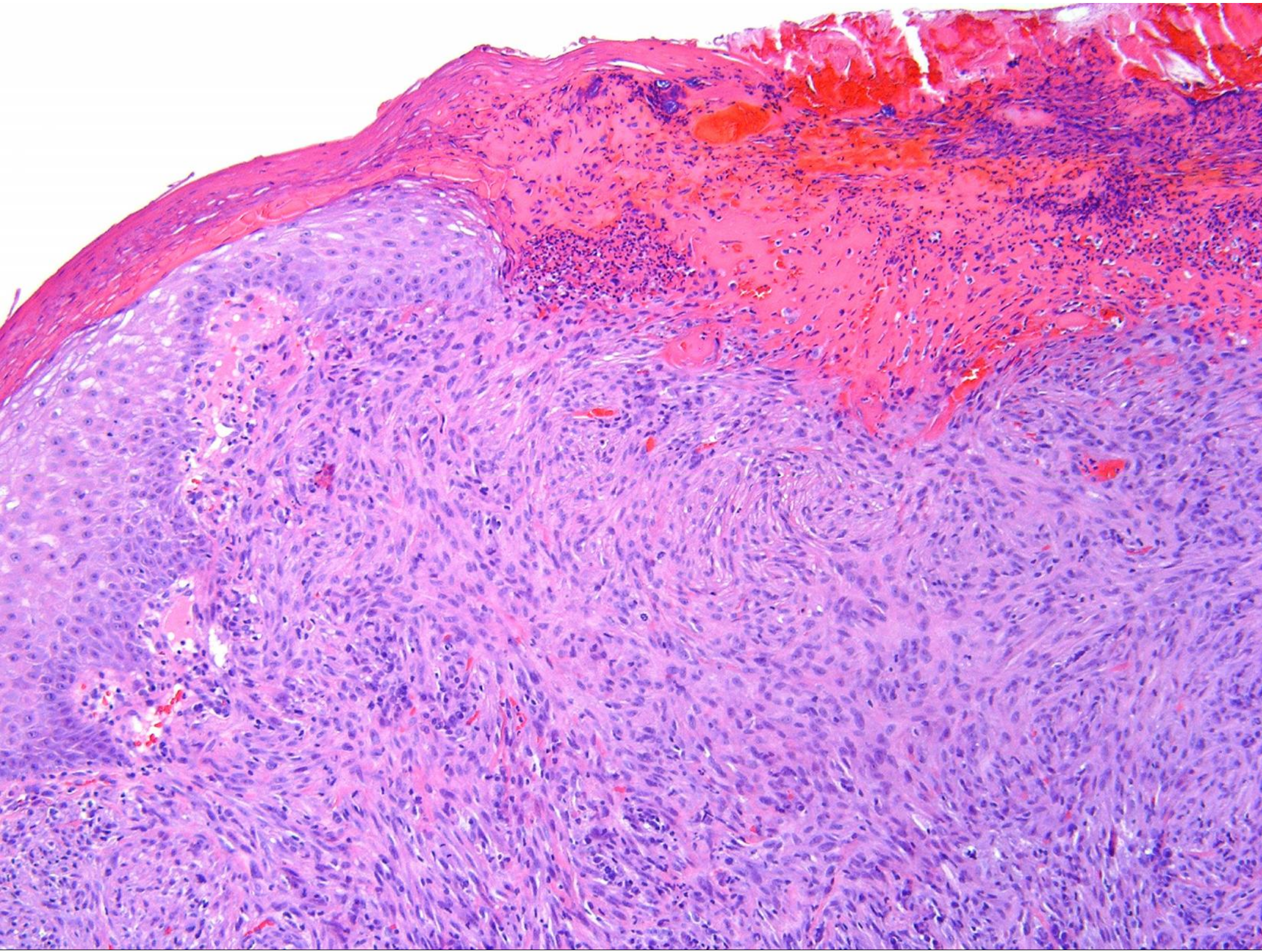
- The (un)Holy Trinity
  - Sarcomatoid (spindle cell) squamous cell carcinoma
  - Desmoplastic/spindle cell melanoma
  - Atypical fibroxanthoma/superficial undifferentiated pleomorphic sarcoma (pleomorphic dermal sarcoma)

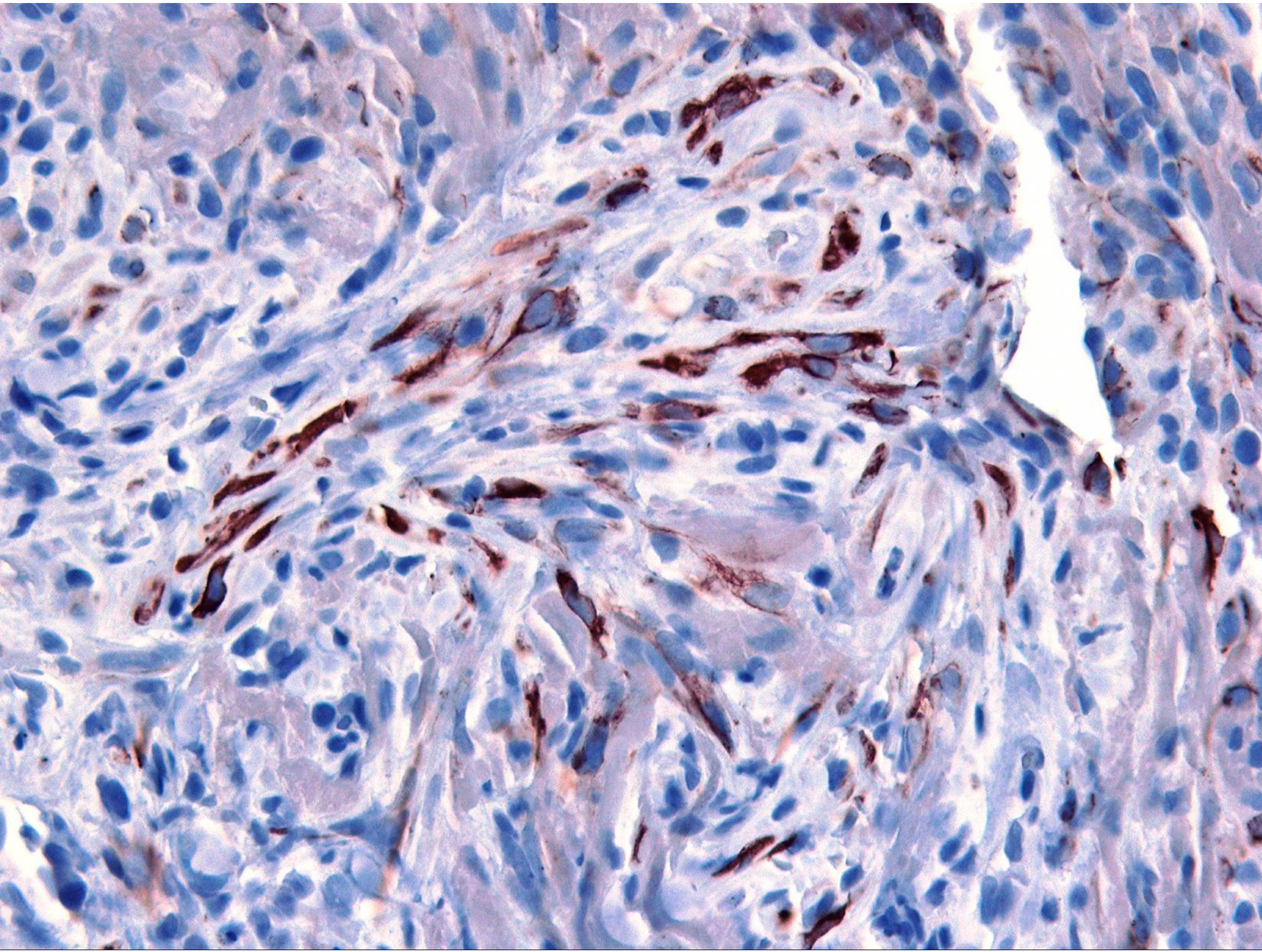
Dermal Pleomorphic Spindle Cell Tumor Differential Diagnosis

- Immunohistochemistry
  - Crucial for accurate diagnosis
  - Must be selected carefully
  - Must be interpreted carefully
  - Many stains commonly used of questionable value

Sarcomatoid Squamous cell carcinoma

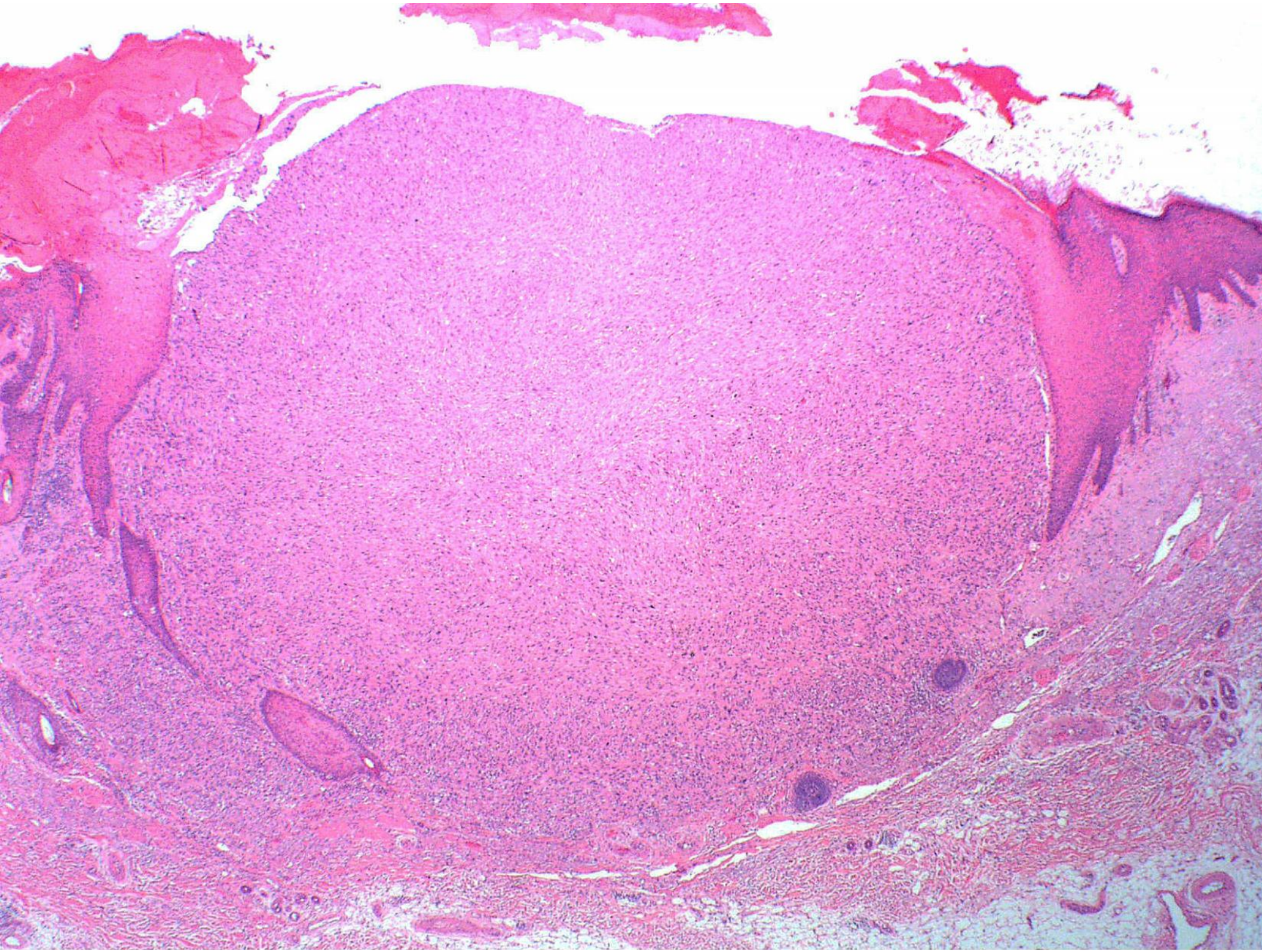
- Sun damaged skin, head and neck, extremities
- May have overlying actinic keratosis or SCC in situ
- More densely cellular
- Atypical spindled cells

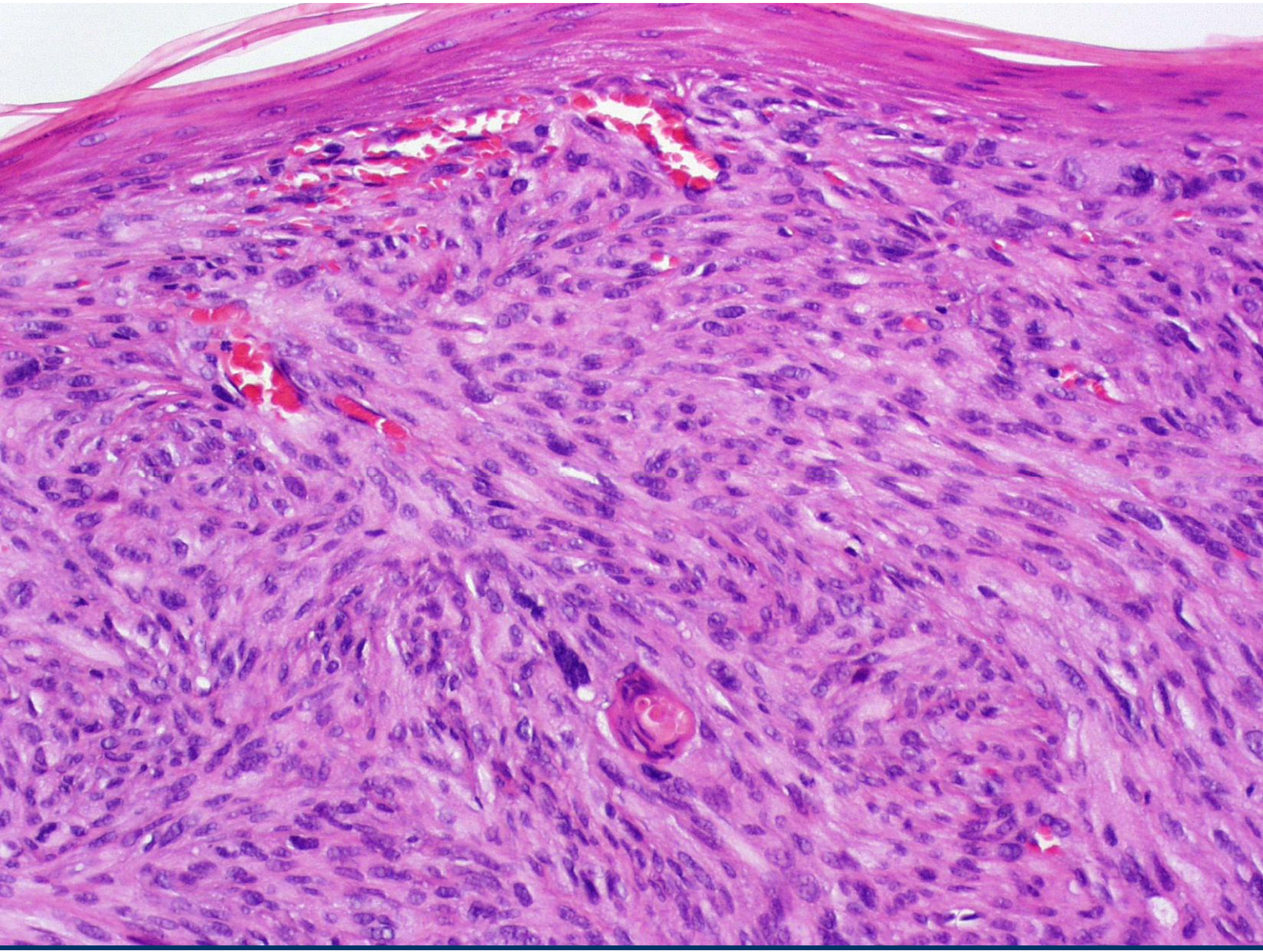


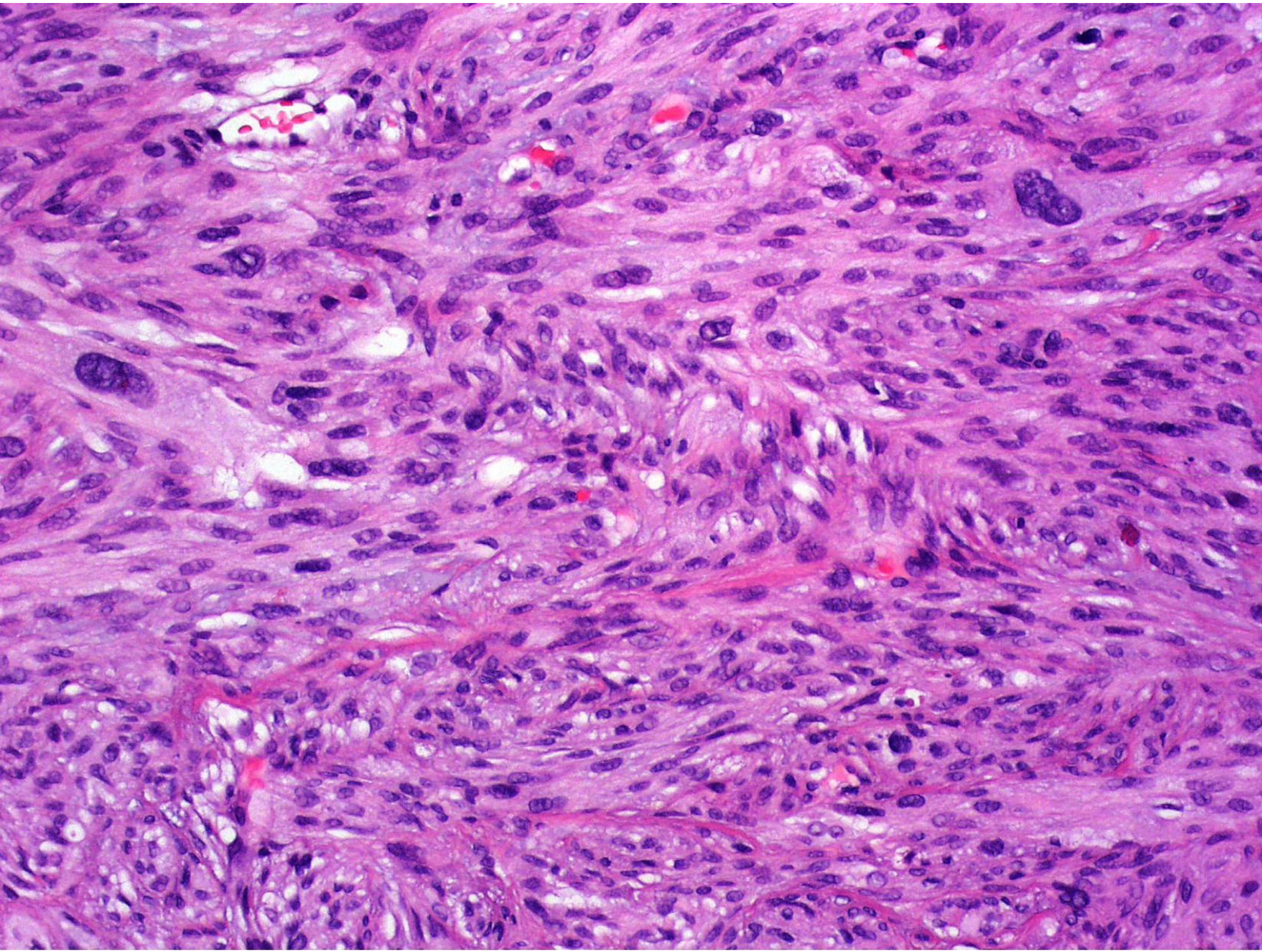


Atypical Fibroxanthoma (AFX)

- Histologically identical to MFH, but with largely benign behavior
- Almost always occurs in sun damaged skin
- Must be small (<1-1.5 cm), confined to dermis/subcutis, circumscribed and completely visualized
- Diagnosis of exclusion (







Immunostains

Sarcomatoid SCC

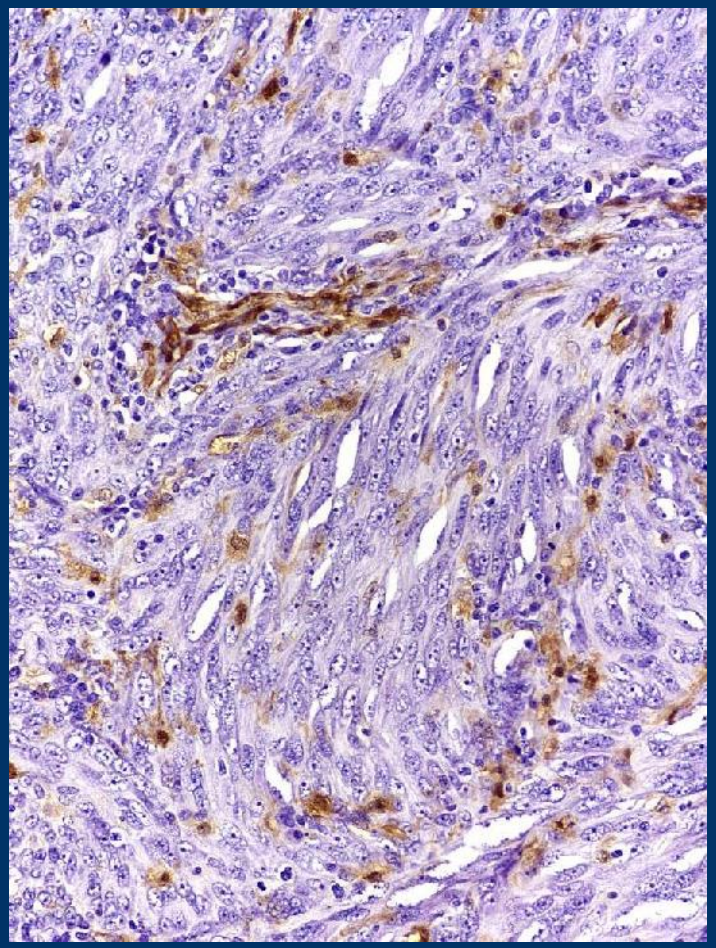
- Cytokeratin expression may be very focal or absent
- Often express only HMWCK
  - 34ßE12 and CK 5/6 are most sensitive markers
- p63
  - Transcription factor essential for maintaining proliferative capacity of epidermal stem cells
  - Nuclear stain
  - Useful in discriminating sarcomatoid squamous cell carcinoma from atypical fibroxanthoma

Vimentin

- Expressed by essentially all sarcomas, all melanomas, and almost all sarcomatoid SCC
- Little to no role in diagnosis of cutaneous soft tissue tumors
- Worthless in this differential diagnosis
  - All three are positive

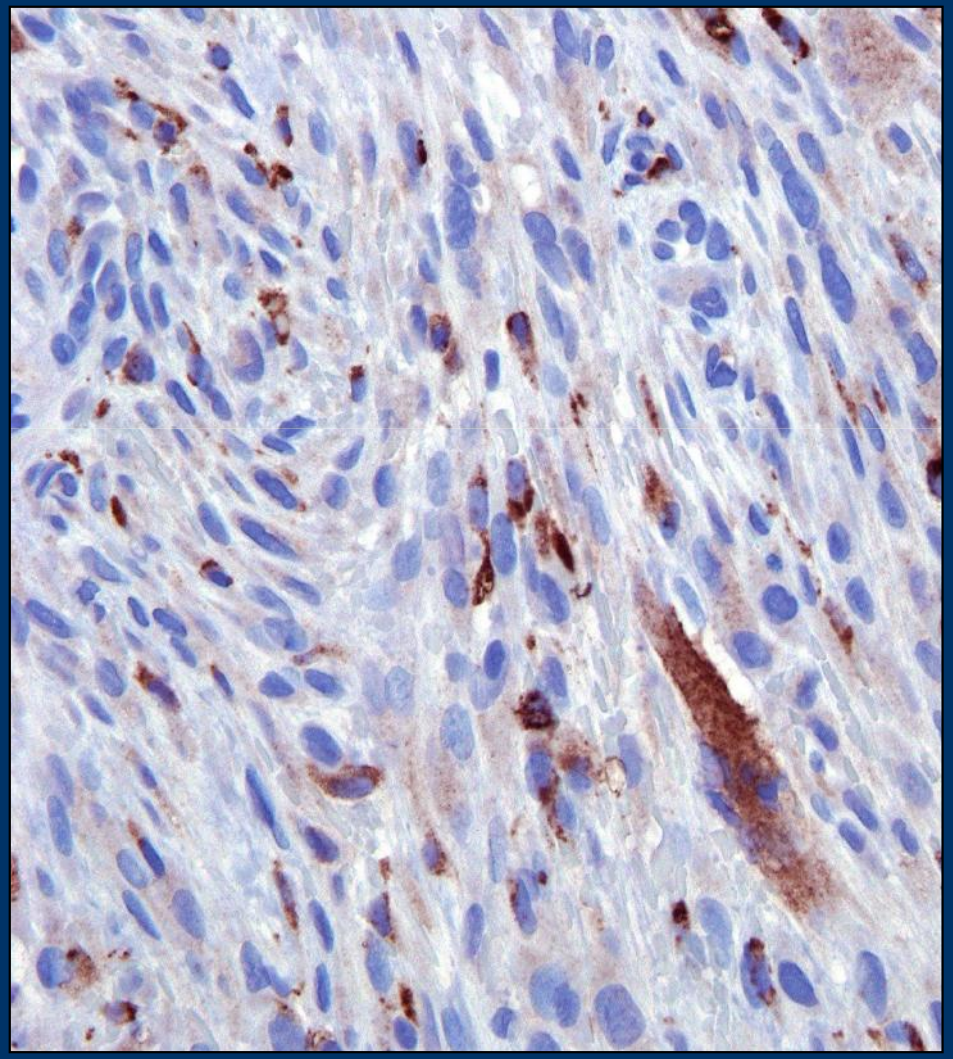
S100 protein

- Nearly 100% positive in normal melanocytes and nevi
- Negative in 2-3% of melanoma
- May be positive in LMS, some CA (but not SCC), MPNST, others
- Pitfall: highlights entrapped dendritic cells



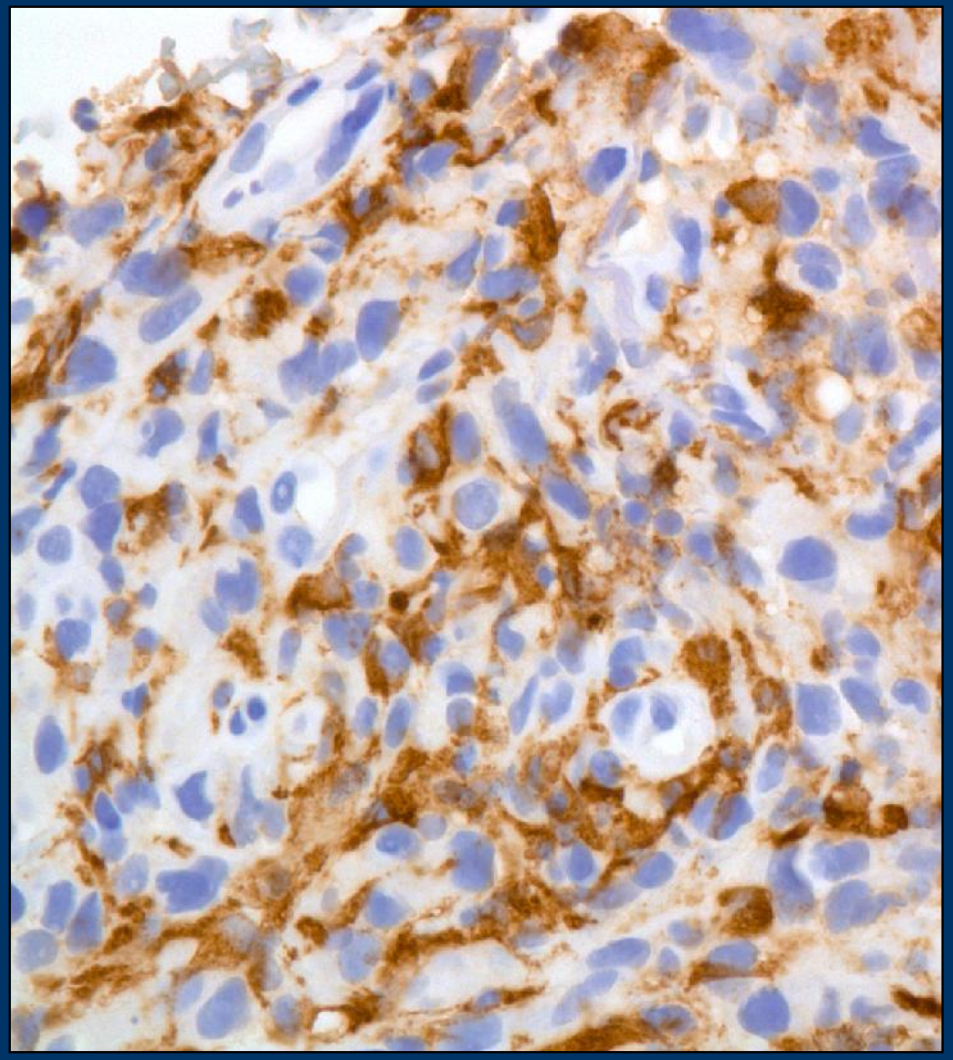
CD68

- 110 kd transmembrane glycoprotein expressed in lysosomes
- Organelle specific
- Sensitive but not specific for histiocytes
- Can be expressed by carcinomas, melanomas, leiomyosarcomas, angiosarcomas, others
- CD68 expression in a spindle cell tumor does not make it “fibrohistiocytic”



CD163

- Hemoglobin scavenger molecule
- Theoretically histiocyte specific
- More sensitive than CD68
- Highlights histiocytes not apparent on H&E sections



CD10

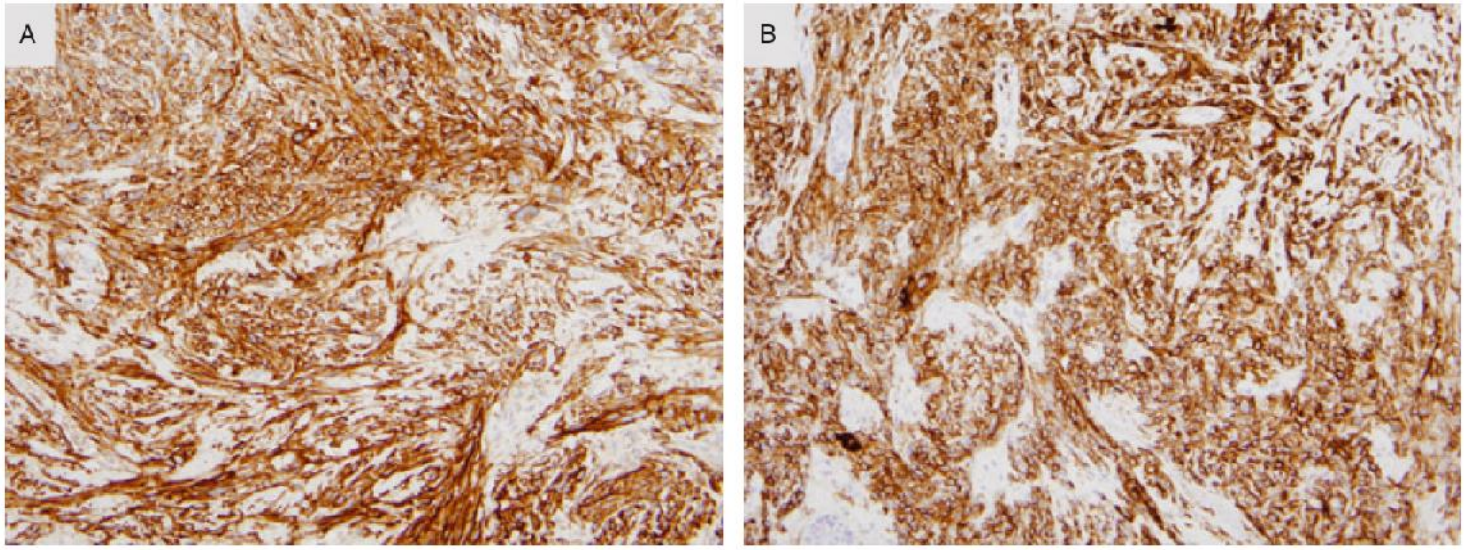


Fig. 3. Direct comparison of atypical fibroxanthoma with squamous cell carcinoma. A) Atypical fibroxanthoma (CD10, original magnification: ×200). B) Spindle cell variant of squamous cell carcinoma (CD10, original magnification: ×200).

J Cutan Pathol 2011; 38: 884–888. © 2011

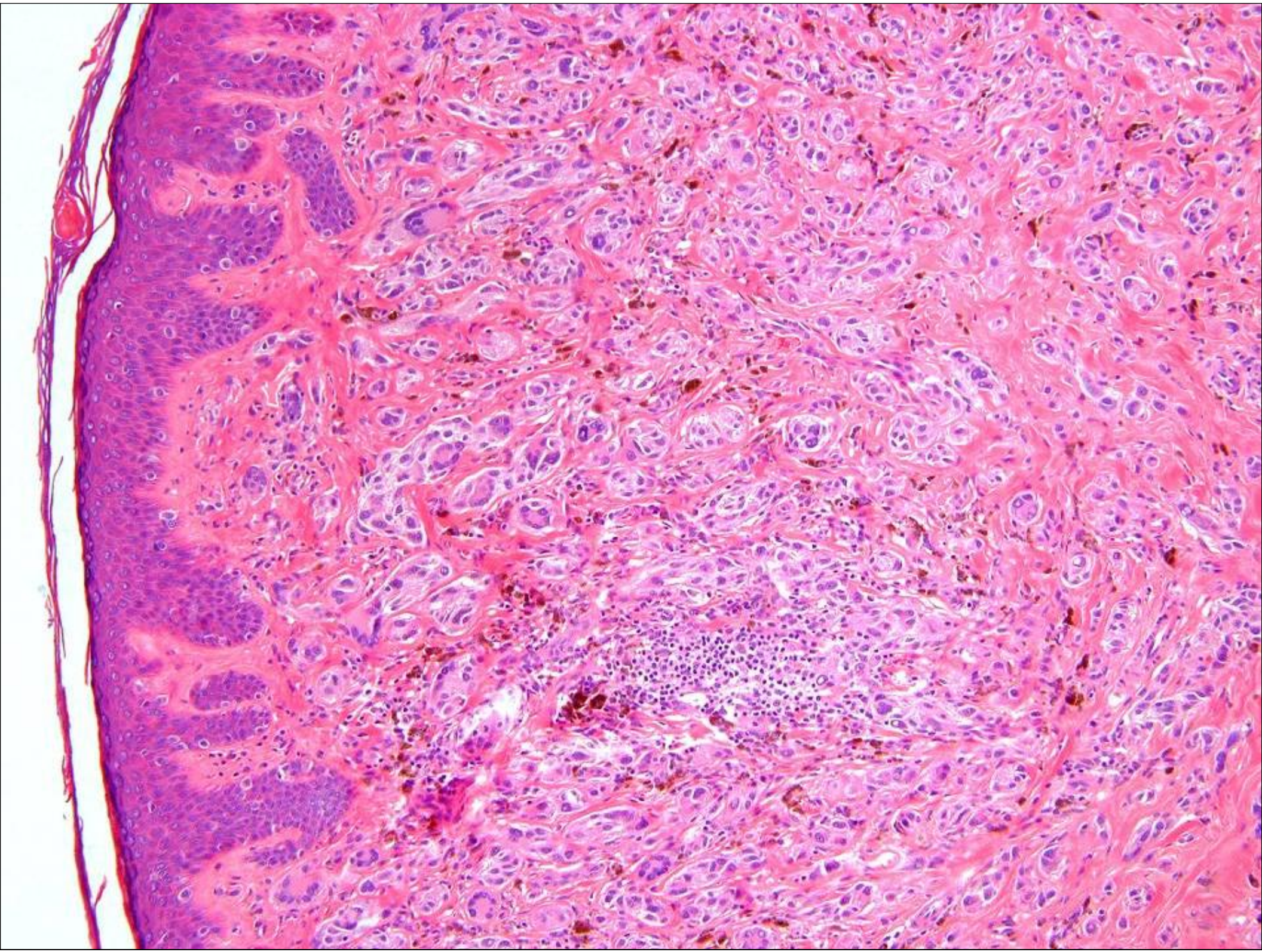
- Neutral endopeptidase
- Also known as acute lymphoblastic leukemia antigen (CALLA)
- Frequently positive in AFX
- Positive in sarcomatoid SCC in 50-60% of cases
- Only reliably useful stains in AFX are negative keratin, p63 and S100

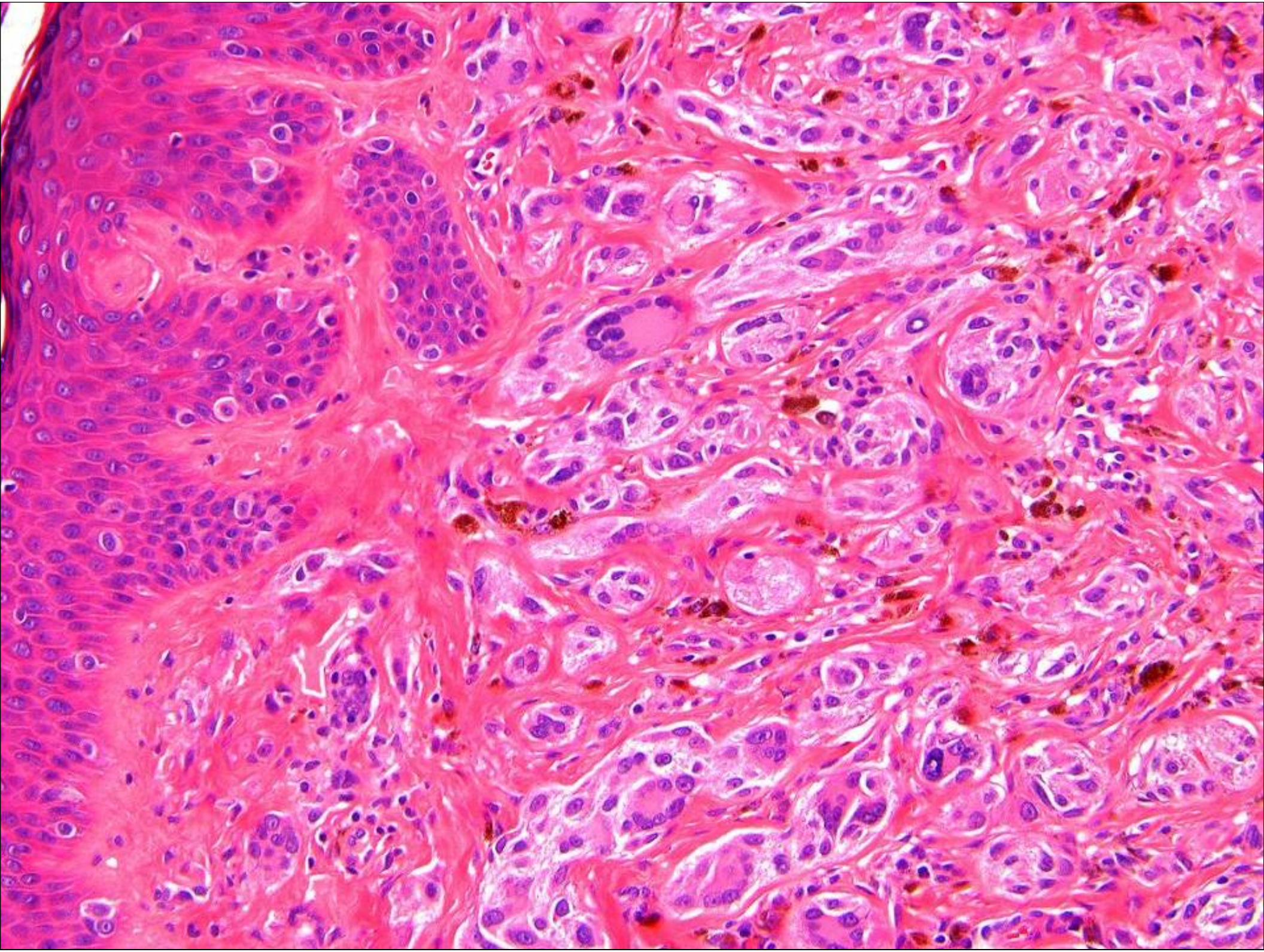
DM vs. AFX vs. SSCC

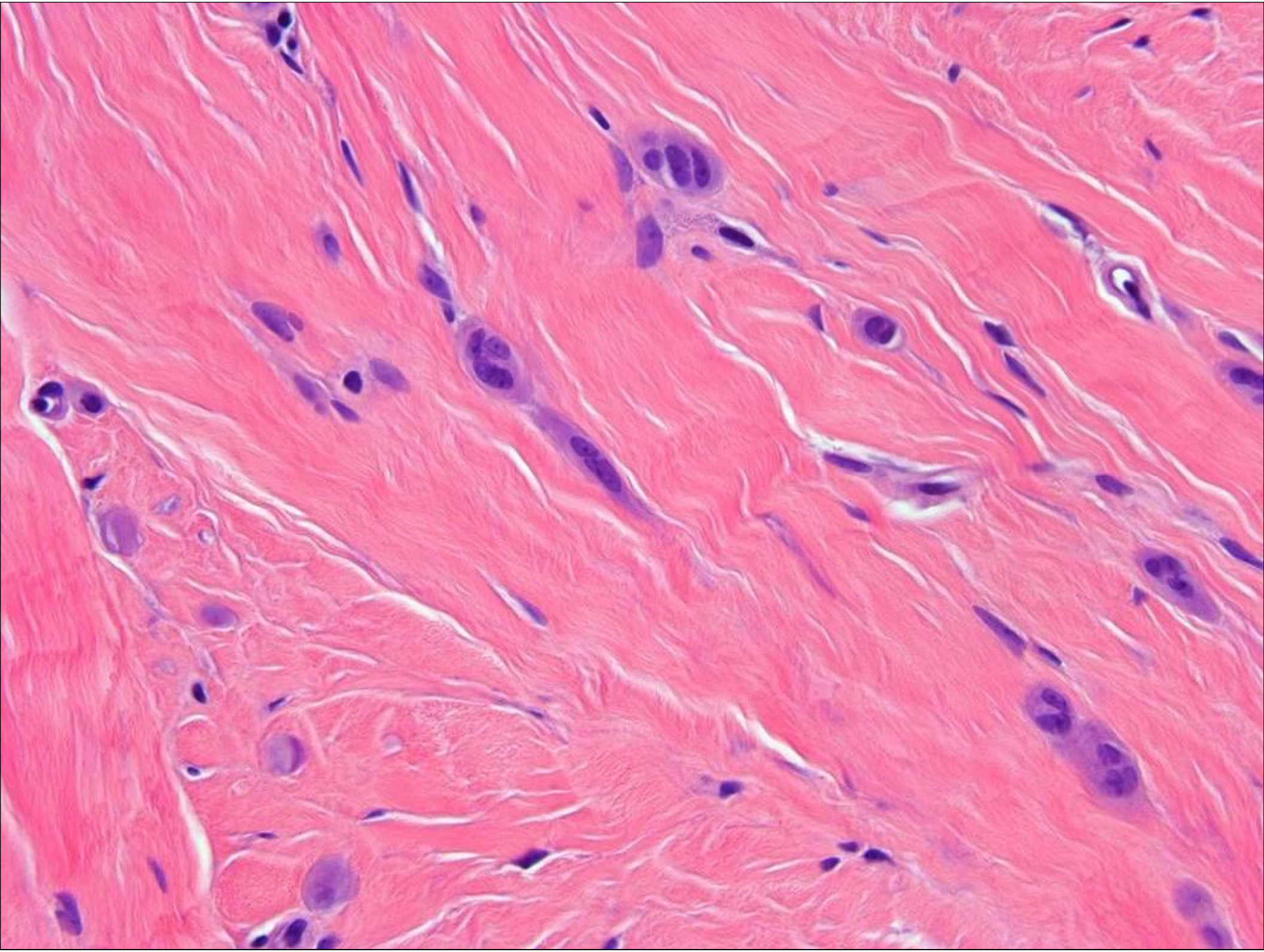
	DM	AFX	SSCC
Clinical	H&N	H&N	Variable
Pattern	Packeted, Short fasc.	Storiform	Storifom, fascicles
Cytology	Spindled	Pleo-morphic	Pleo to spindled
Immuno	S100+, CK-	S100-, CK-, SMA -/+	S100-, CK+, SMA -/+
Clues	Atypical junctional melanocytes. Lymphoid aggregates	No epidermal component	AK or SCC

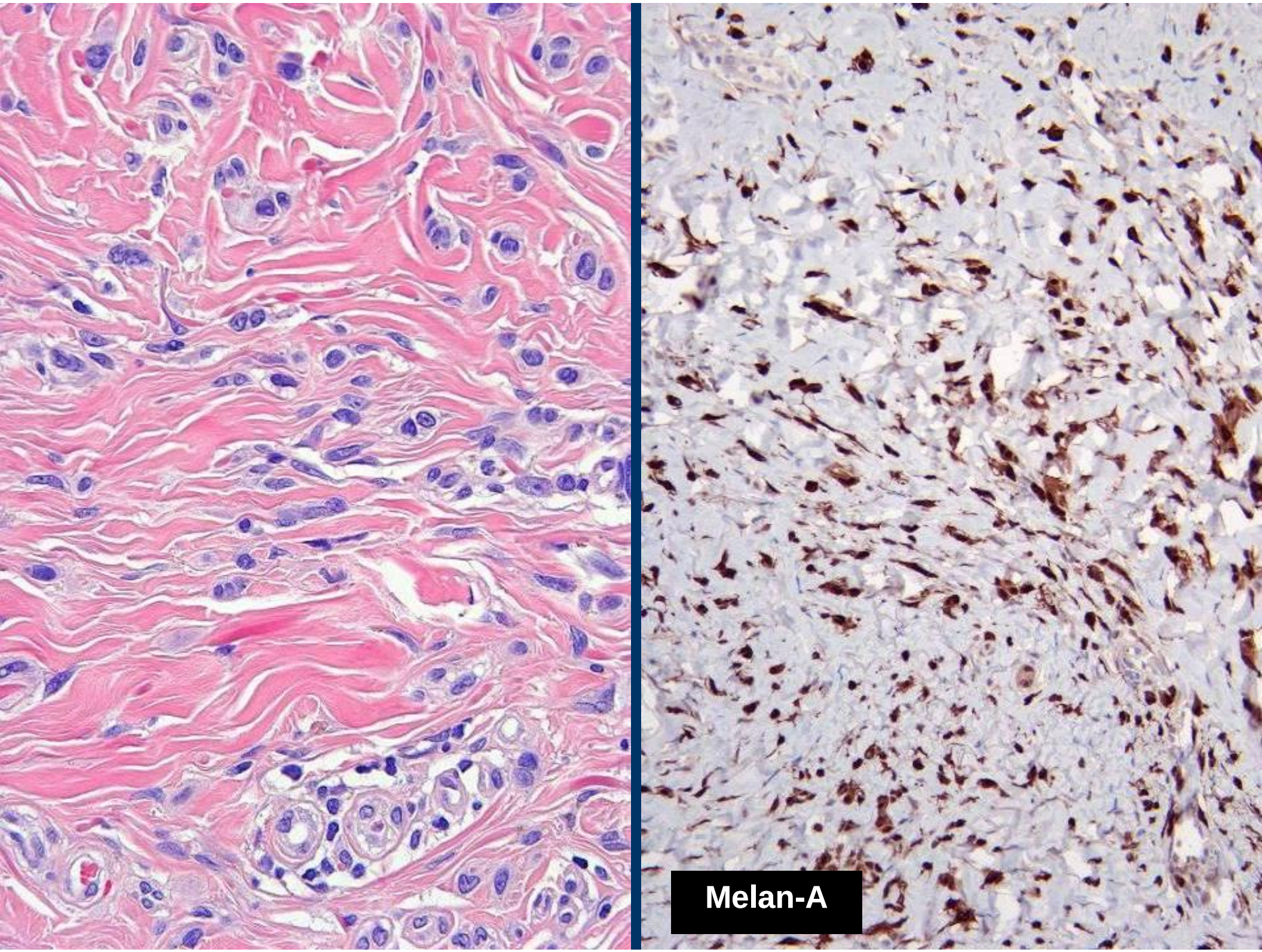
Desmoplastic (Spitz) Nevus

- Clinical features
  - Young adults
  - Extremities
- Microscopic Features
  - Wedge-shaped
  - Junctional component uncommon
  - Small nests and multinucleated cells in superficial aspects
  - Spindled to epithelioid, mild to moderate cytologic atypia
  - Absent mitotic figures (<1/20 HPF)
  - Absent inflammatory infiltrate
  - Immunoreactive for specific melanocytic markers







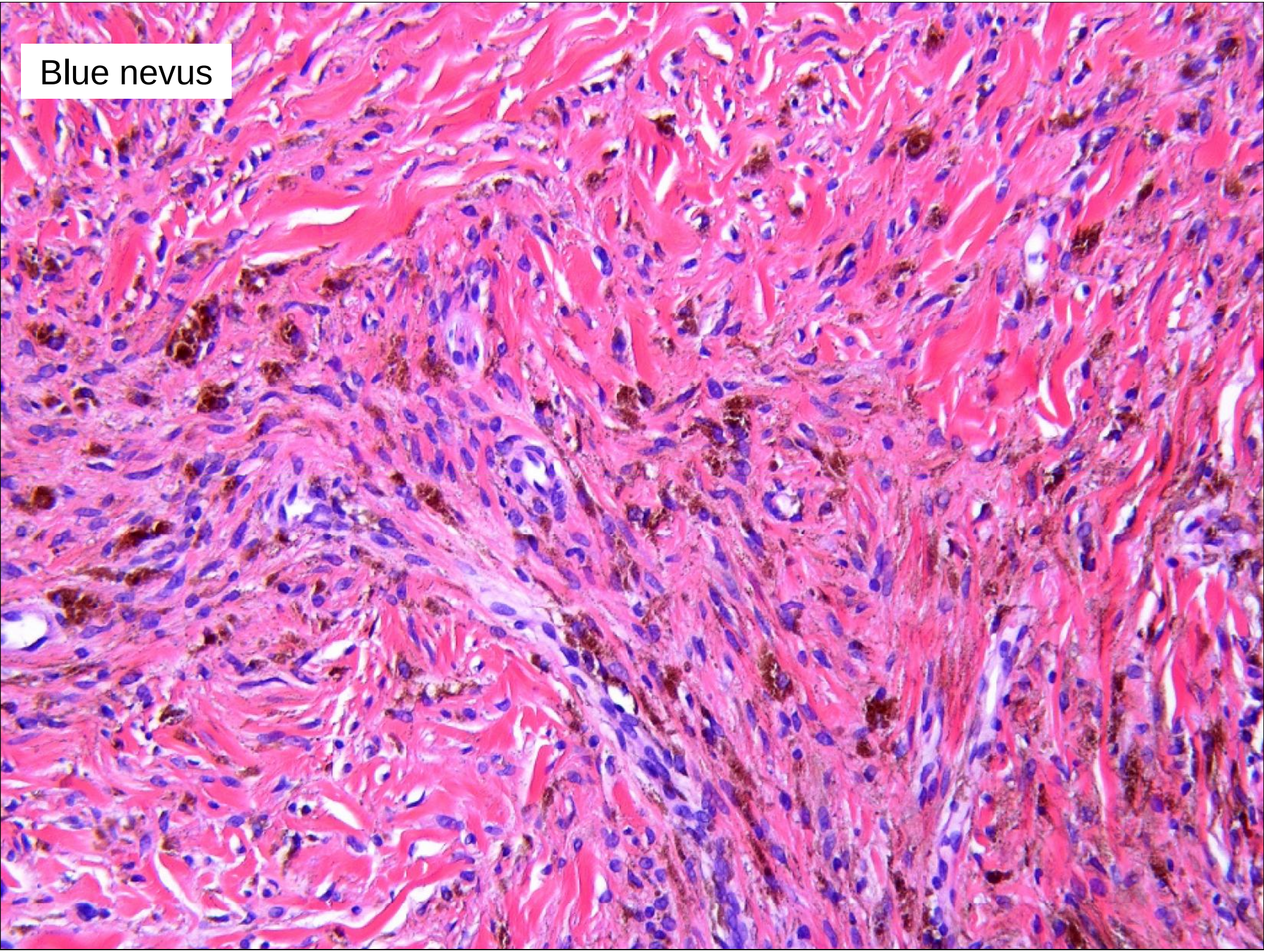

Melan-A

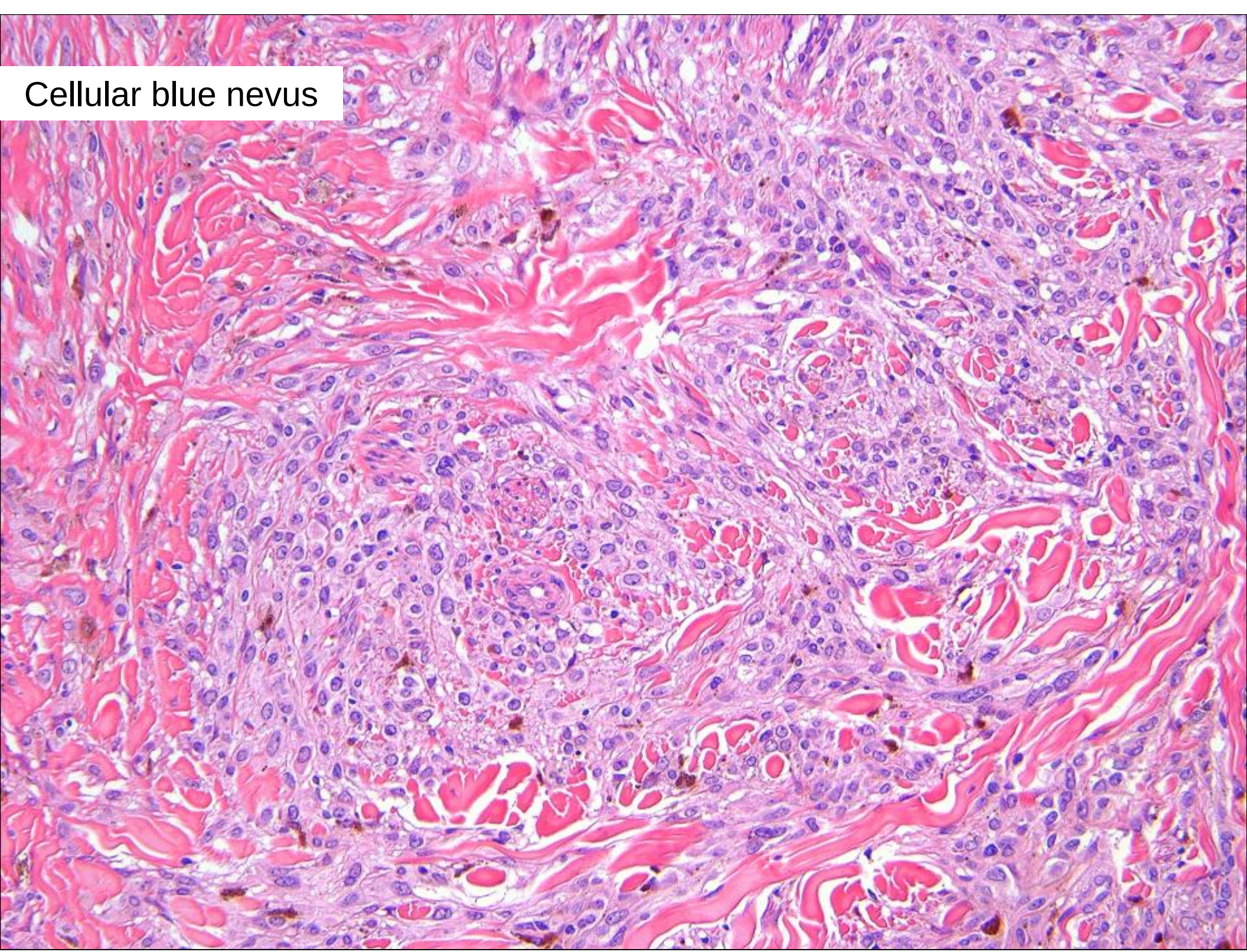
Blue Nevus Family

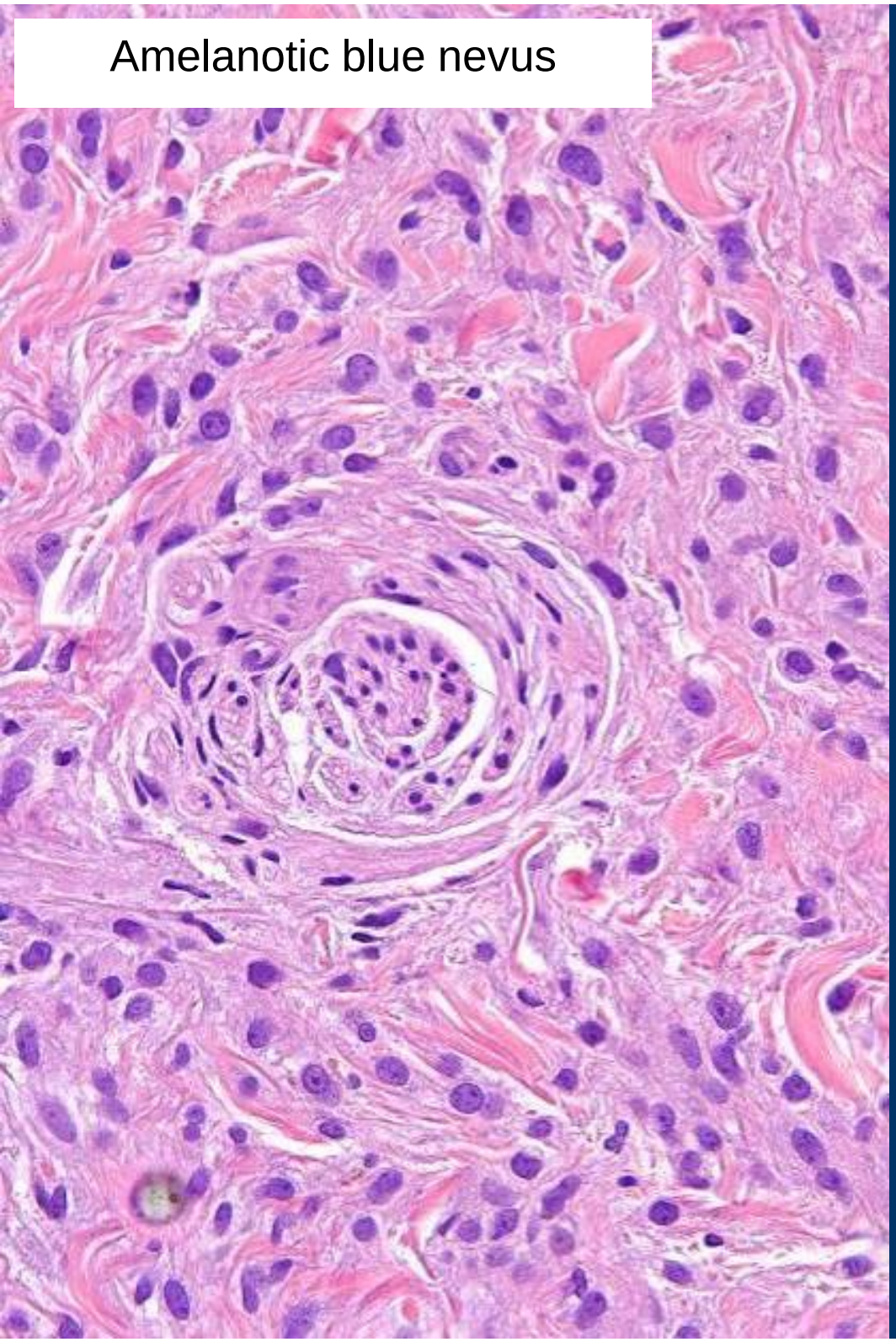
- Clinical features
  - Present in childhood to middle aged
  - Pigmented lesions with blue-black color
  - Flesh-colored papules (amelanotic blue nevus)

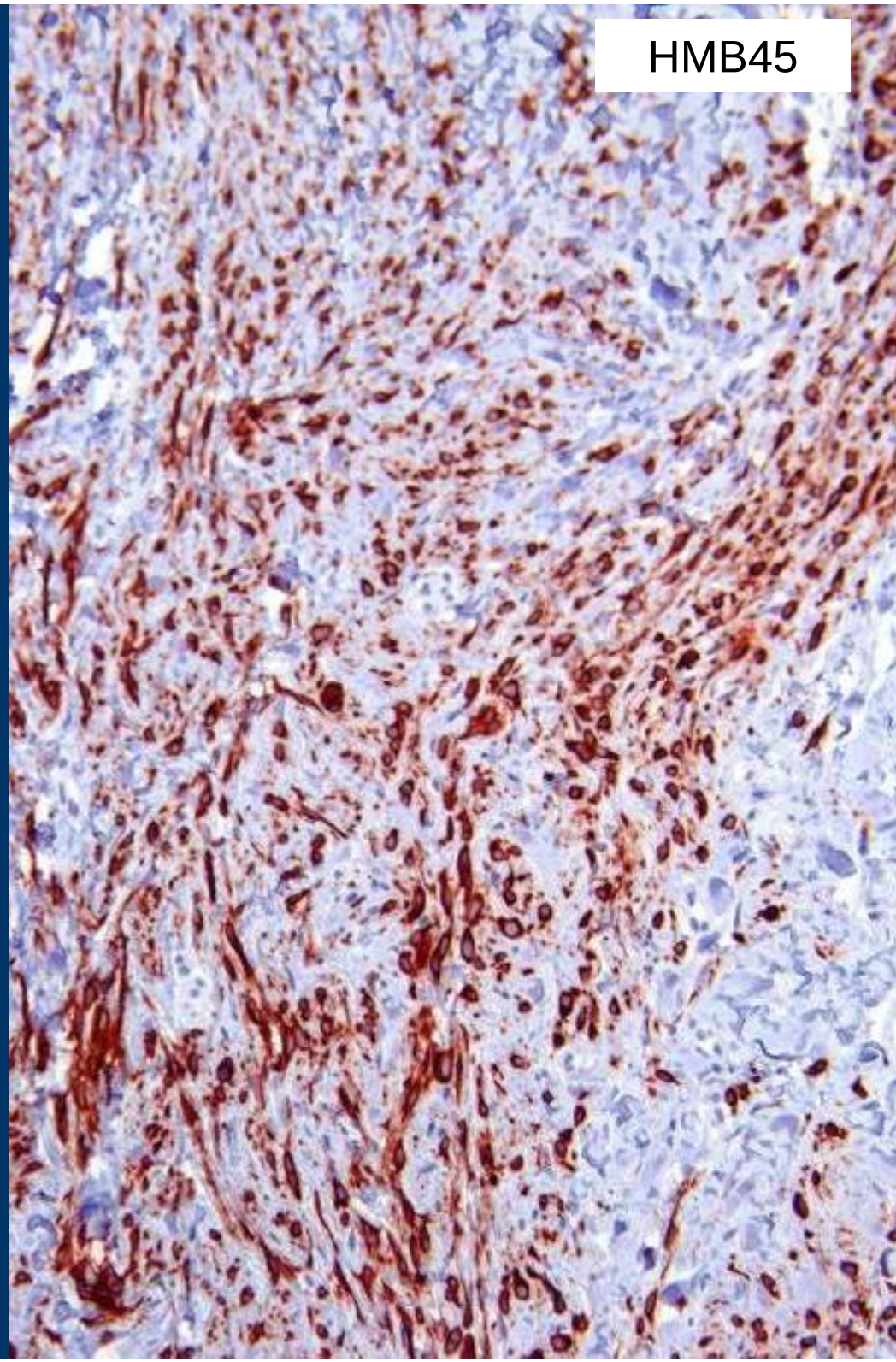
Blue Nevus Family: Histopathology

- Oval to spindled melanocytes
- Mitotic figures absent
- No nuclear hyperchromasia
- Absence of lymphocytic infiltrate
- Absence of junctional component
- May have perineural involvement
- Positive for melanocytic specific markers


Blue nevus

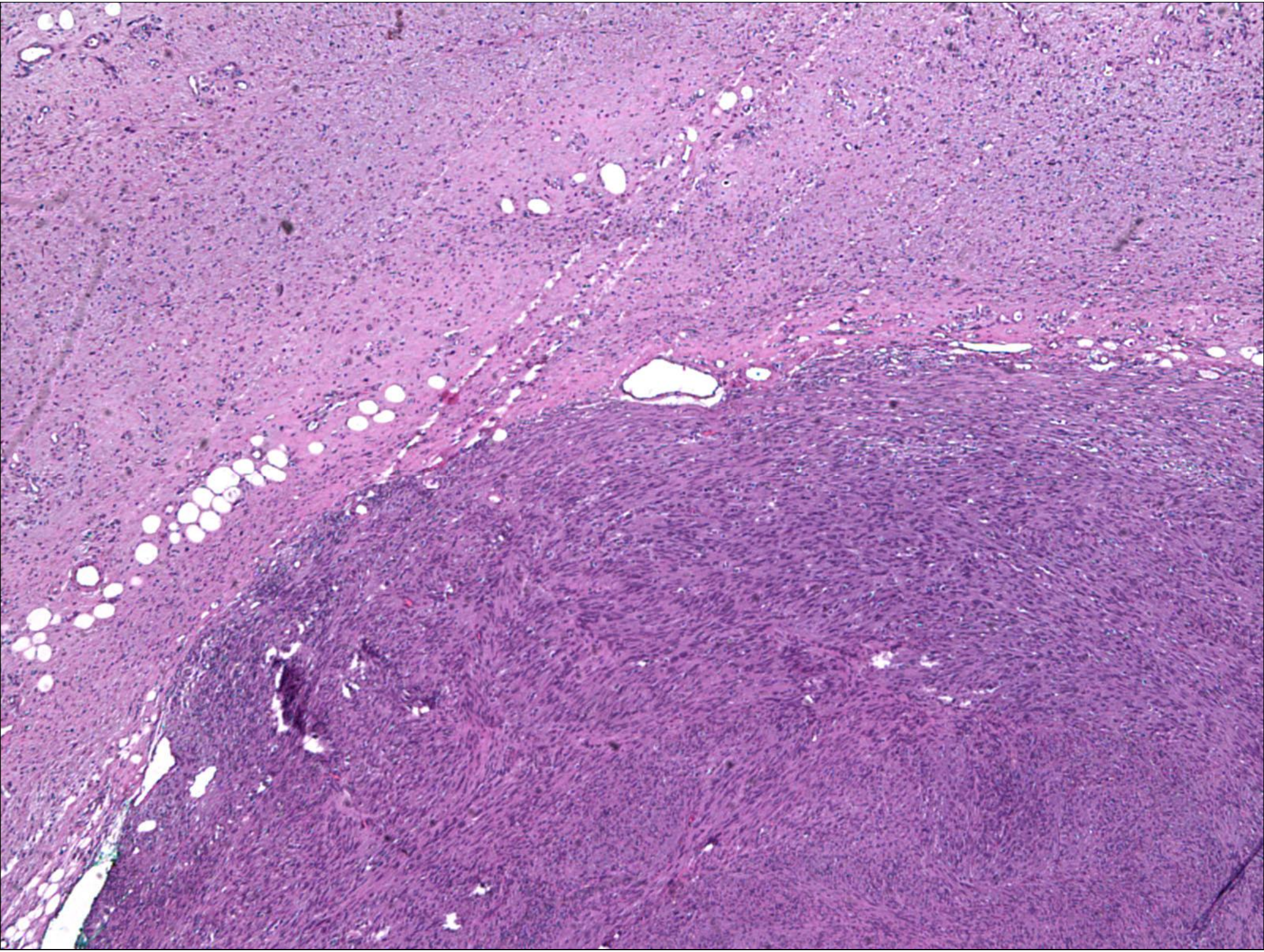

Cellular blue nevus

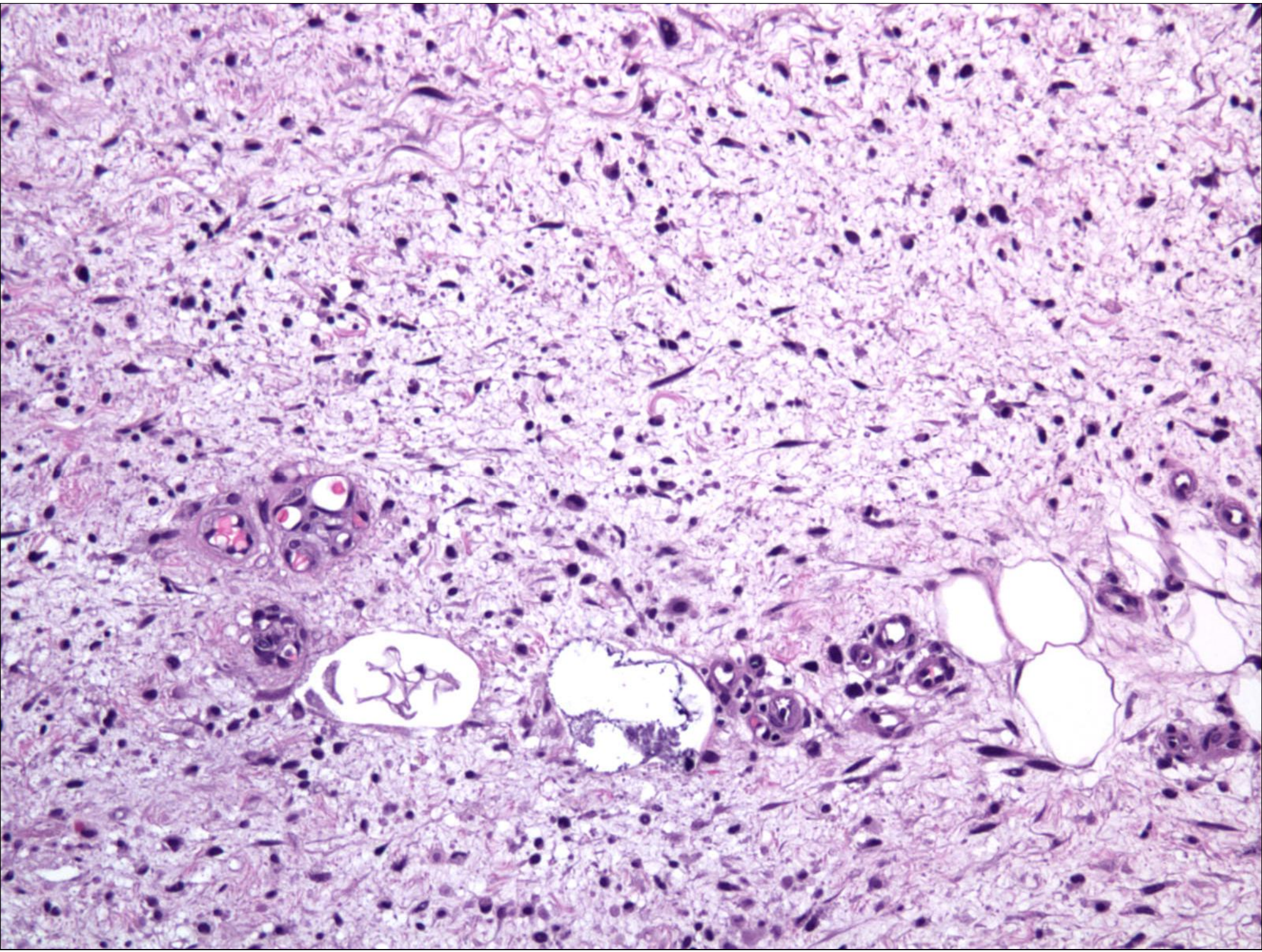

Amelanotic blue nevus

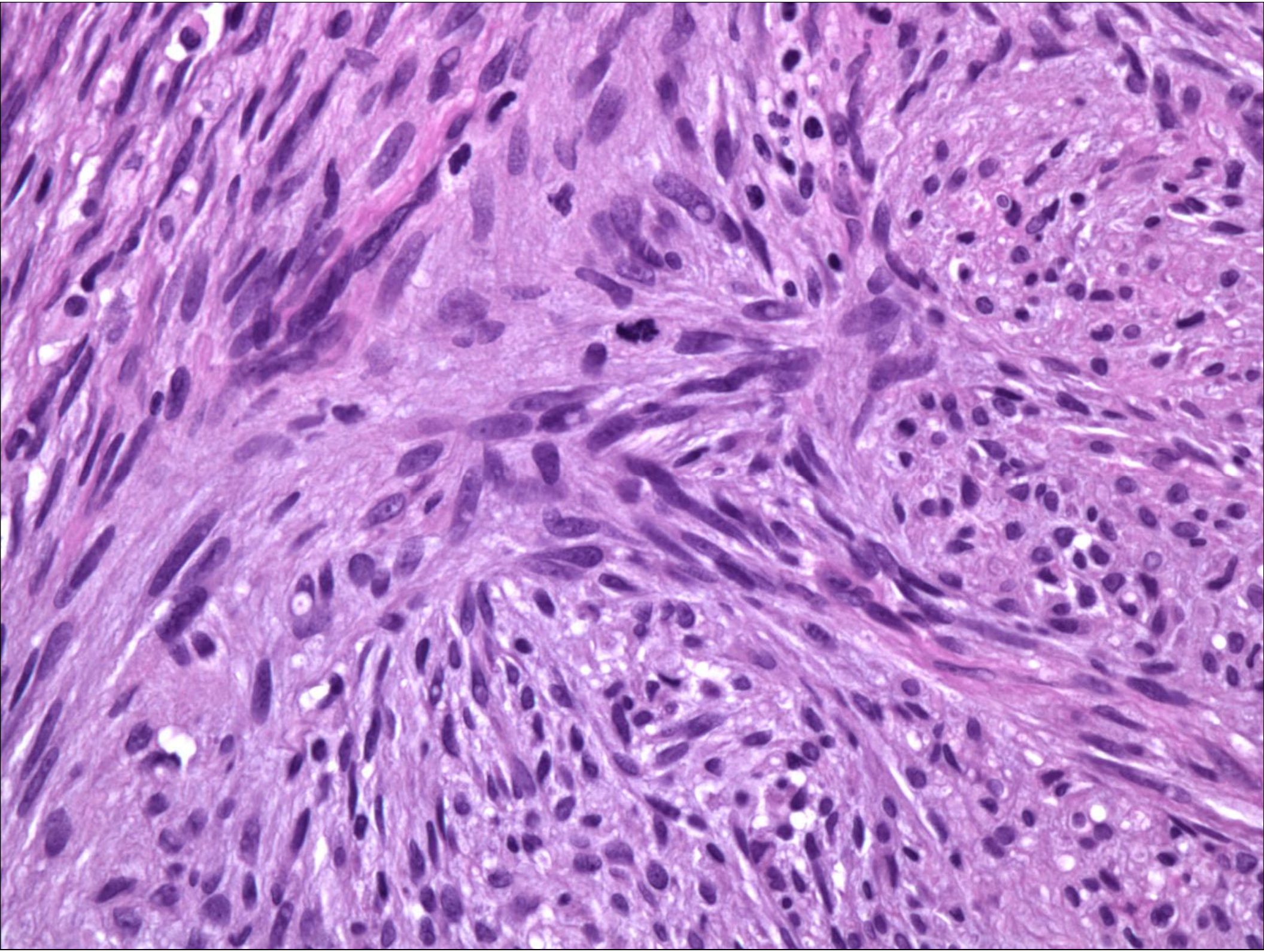

HMB45

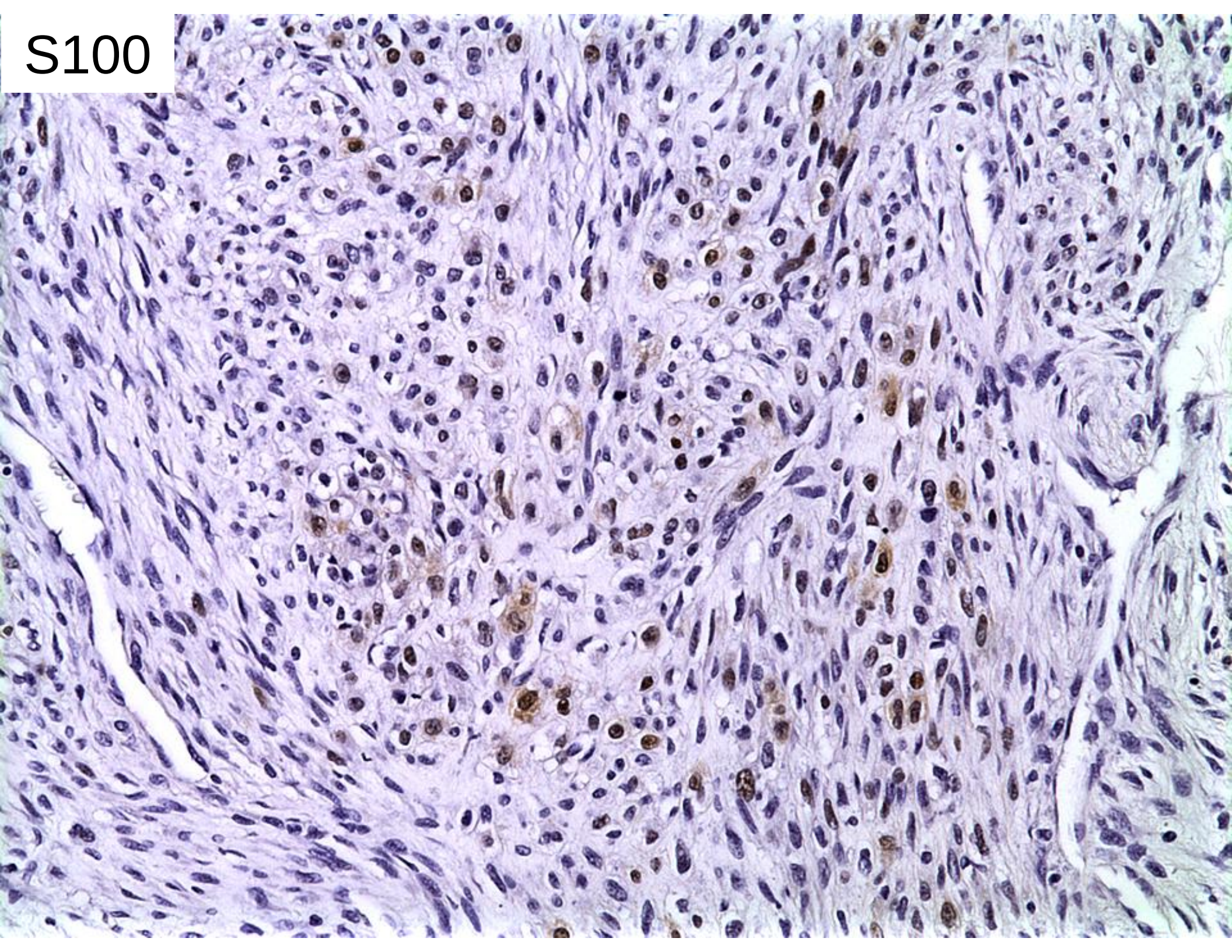
Cutaneous Malignant Peripheral Nerve Sheath Tumor

- Rare
- Frequent association with documented neurofibromatosis (40%)
- Associated neurofibroma in majority of cutaneous MPNST
- More cellular tumor than desmoplastic melanoma
- S100 may be weaker than desmoplastic melanoma (not always)
- May be epithelioid








S100

Back to Spitz tumors

Spitz Nevus

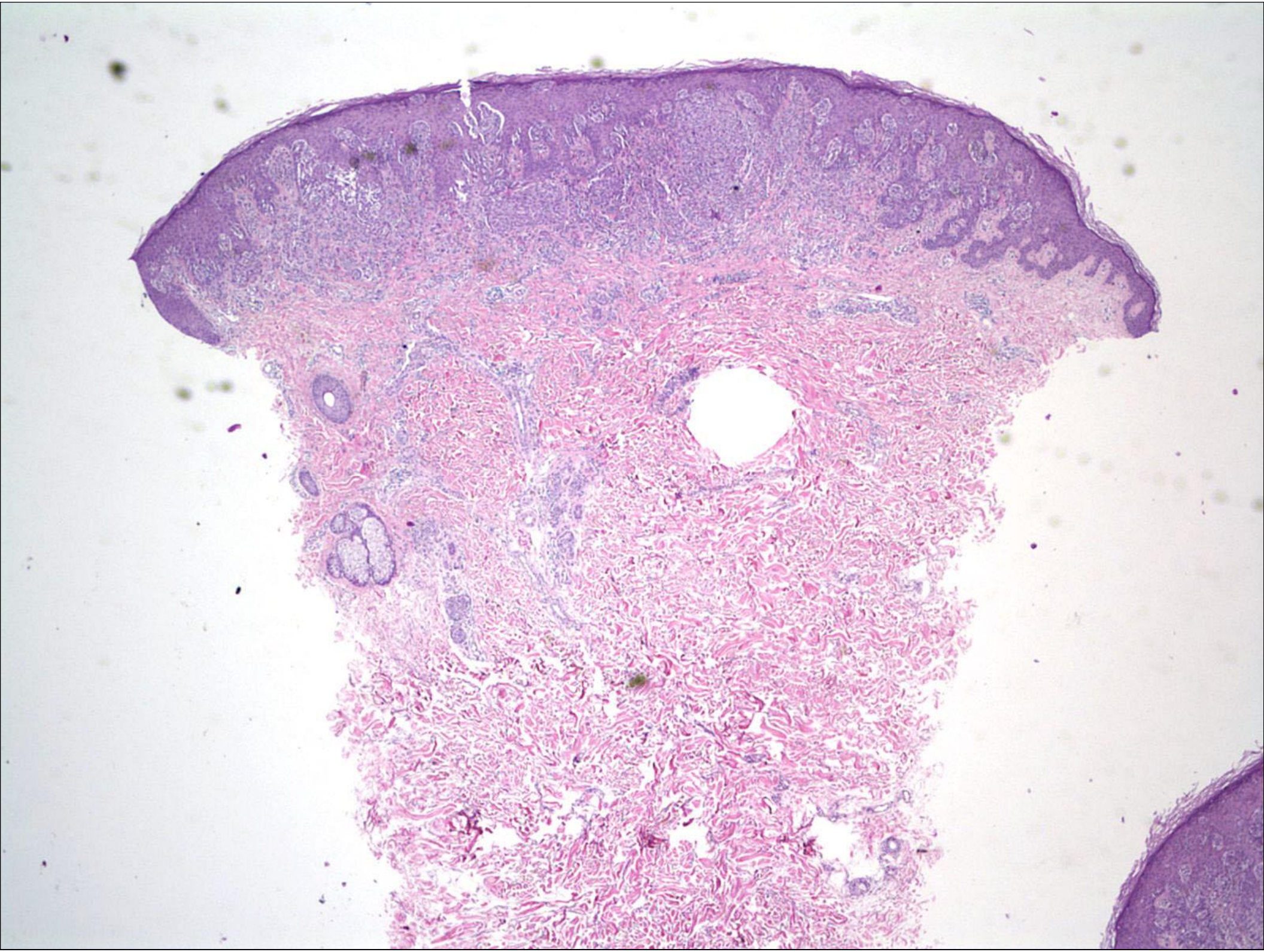
- Clinical features
  - Young age (<20 years)
    - <20 think Spitz, >40 think melanoma
  - Usually <0.6 cm
  - Rapid growth followed by stable phase
  - Red to red-brown to dark brown
  - Head and neck, proximal extremities (in women esp. legs)

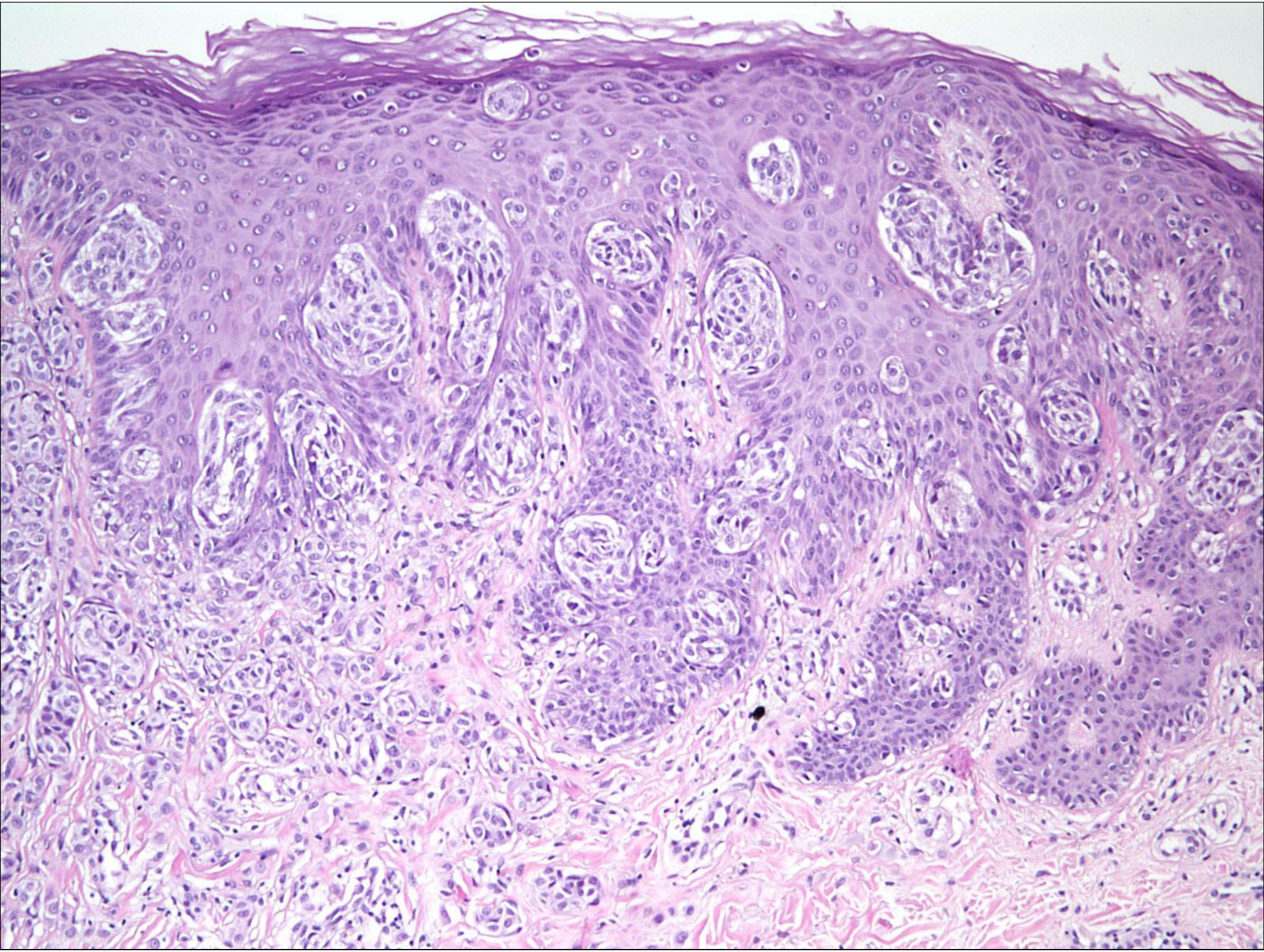
Spitz Nevus

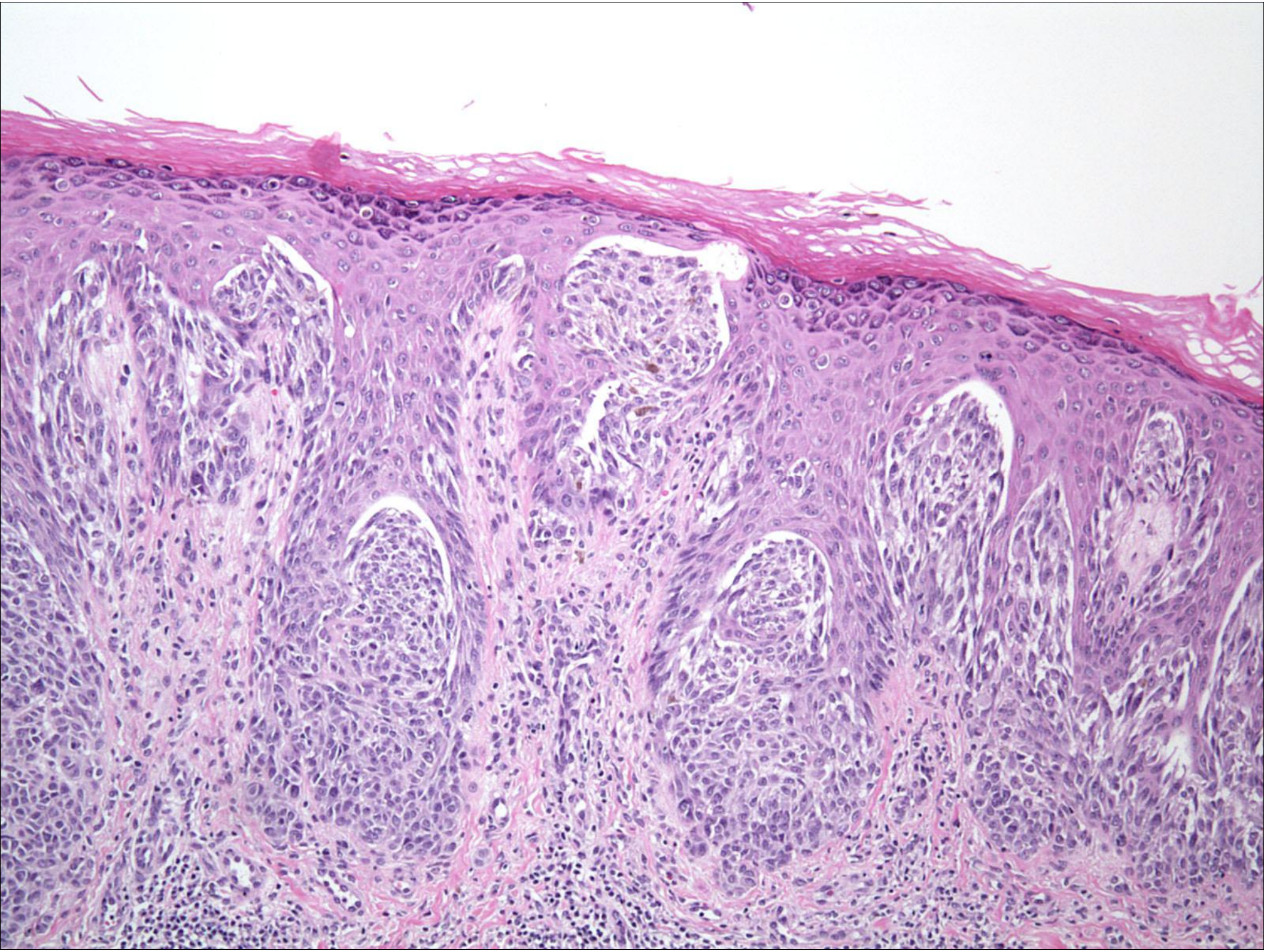
- Variants
  - Typical
    - Junctional
    - Compound
    - Intradermal
  - Pigmented spindle cell nevus (of Reed)
  - Desmoplastic Spitz

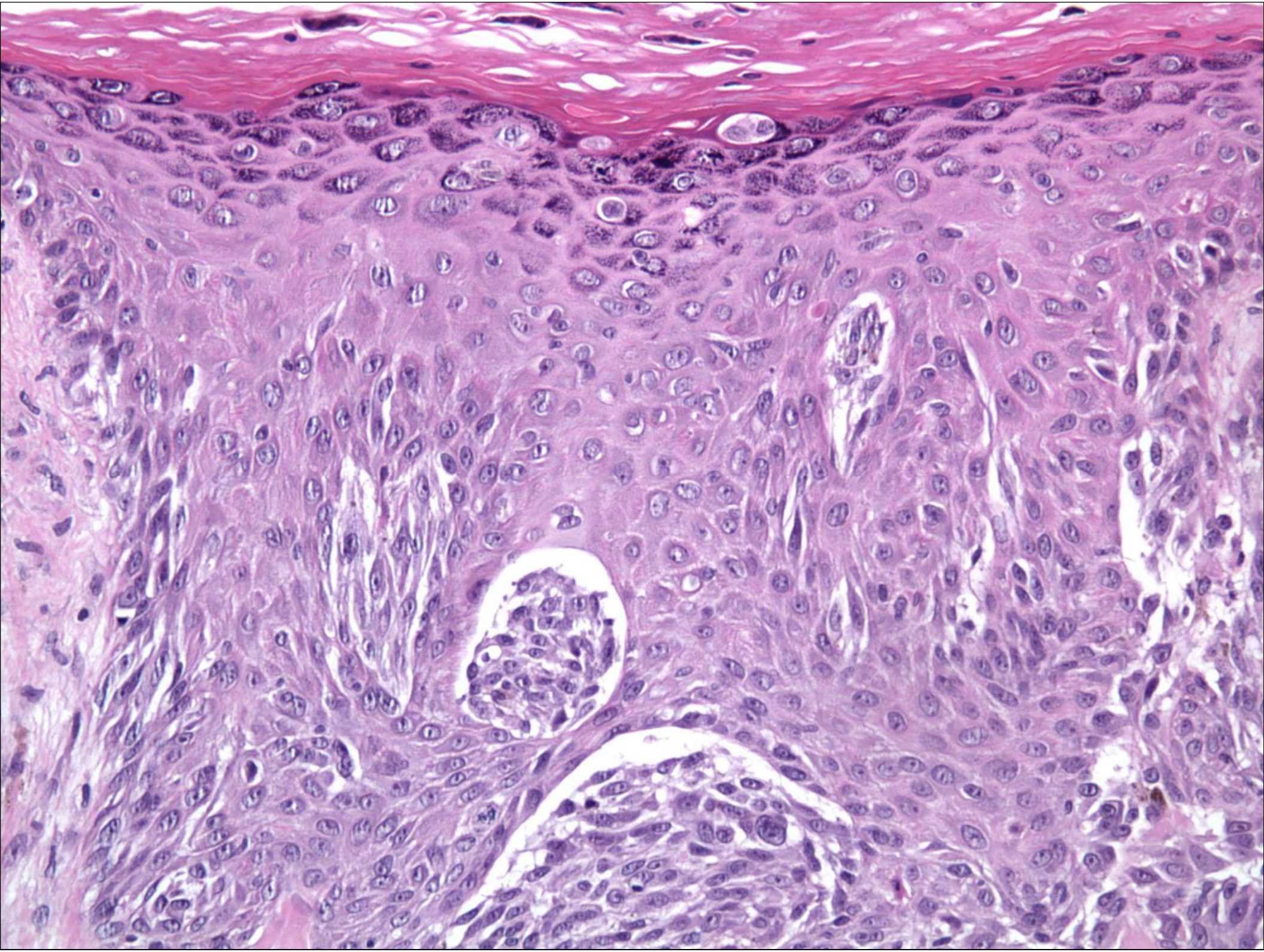
Typical Spitz Nevus

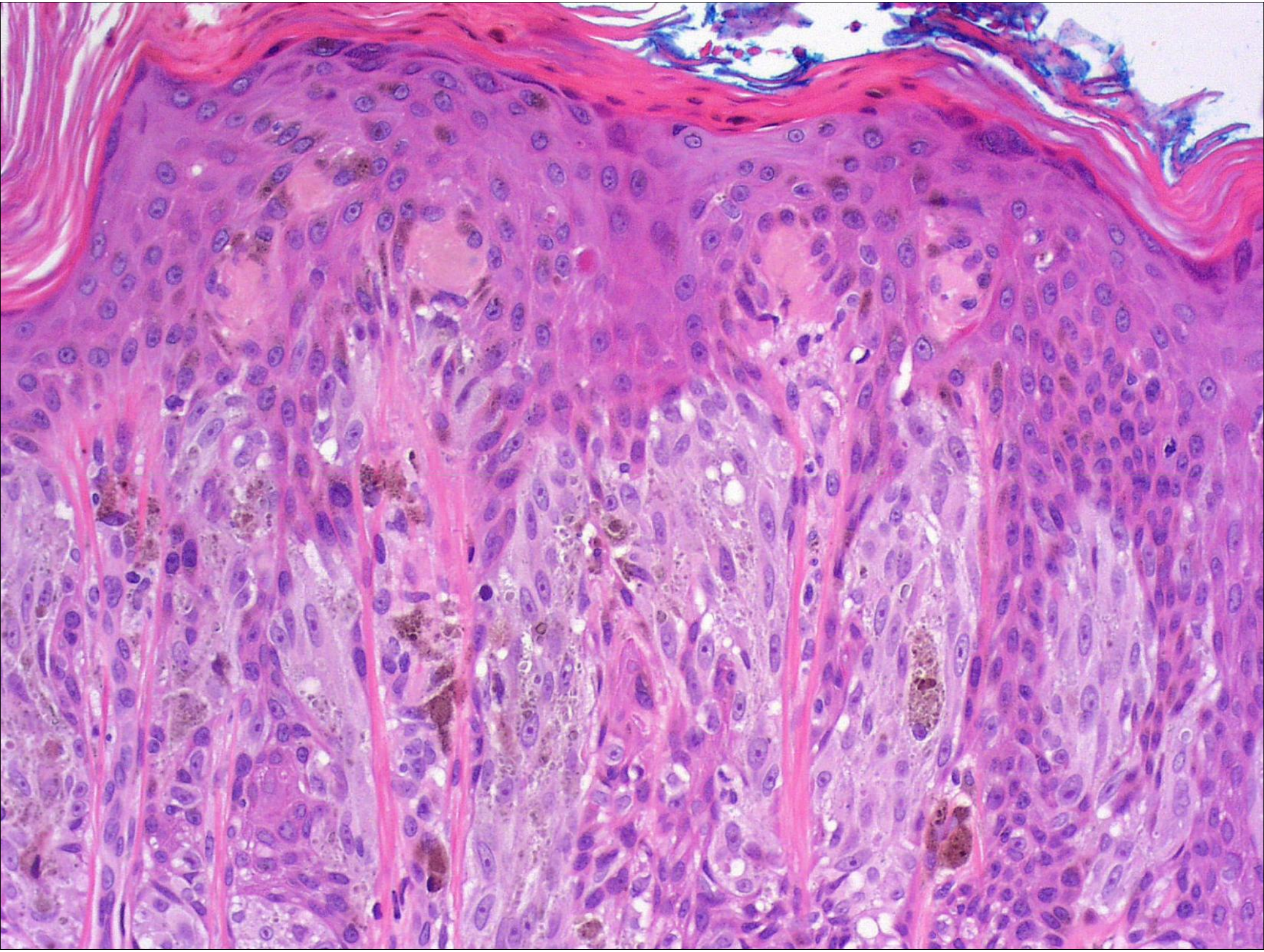
- Microscopic features
  - Symmetric
  - Predominantly nested
  - Clefts overlying junctional nests
  - Epithelioid and spindled melanocytes
  - Kamino bodies (often)
  - Maturation
  - Absence of dermal mitotic figures
    - Rare superficial MFs may be seen

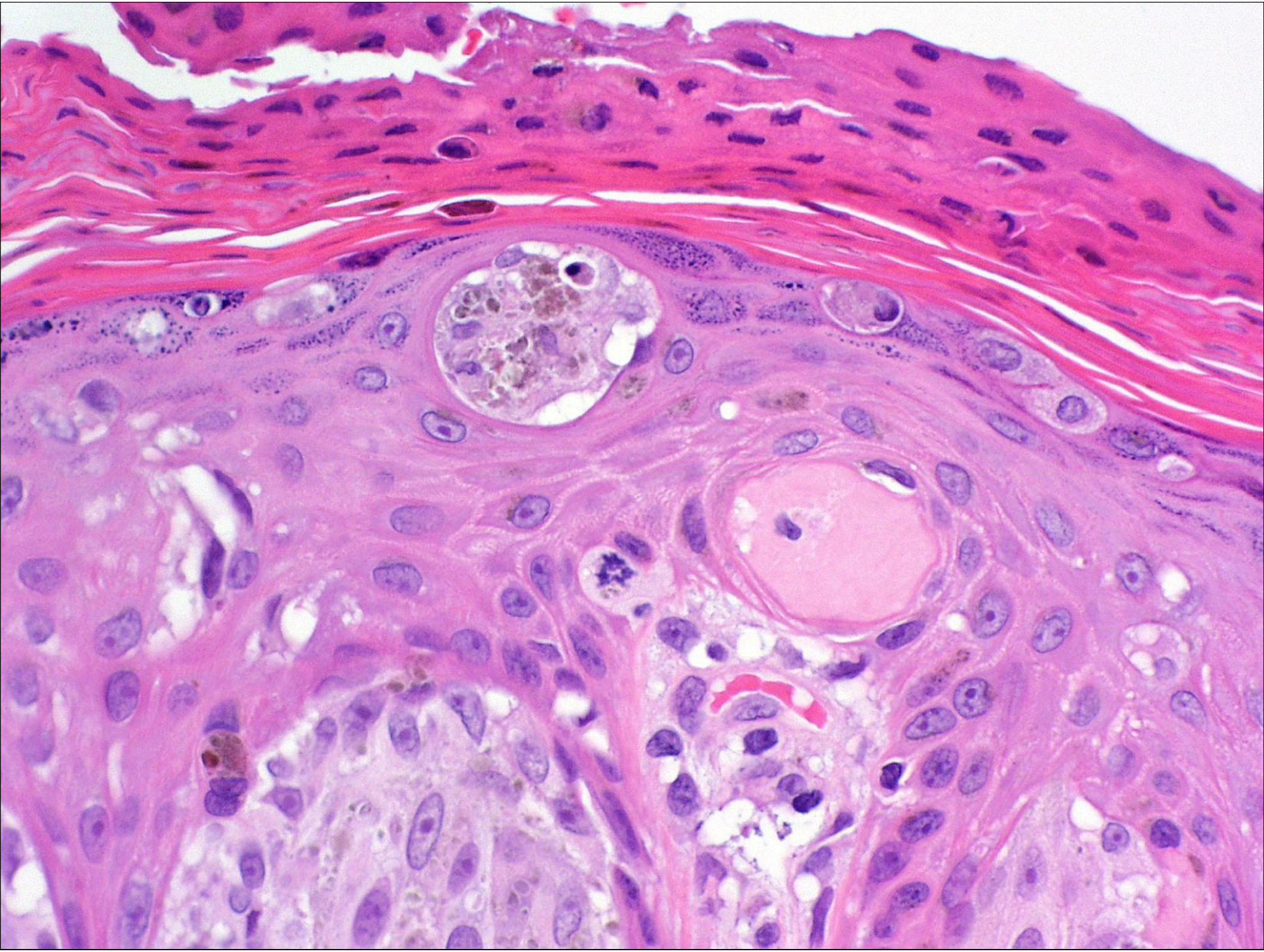


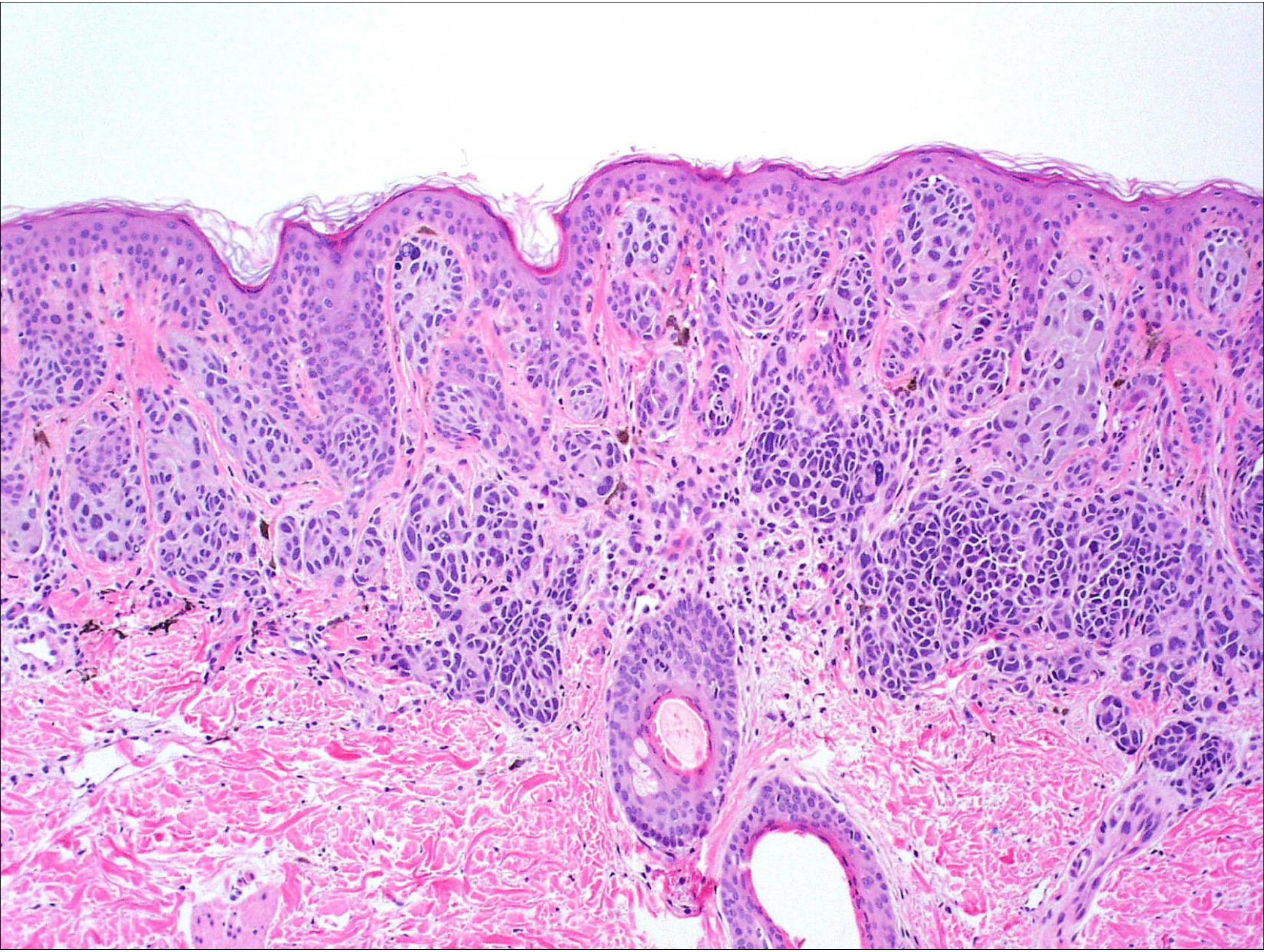






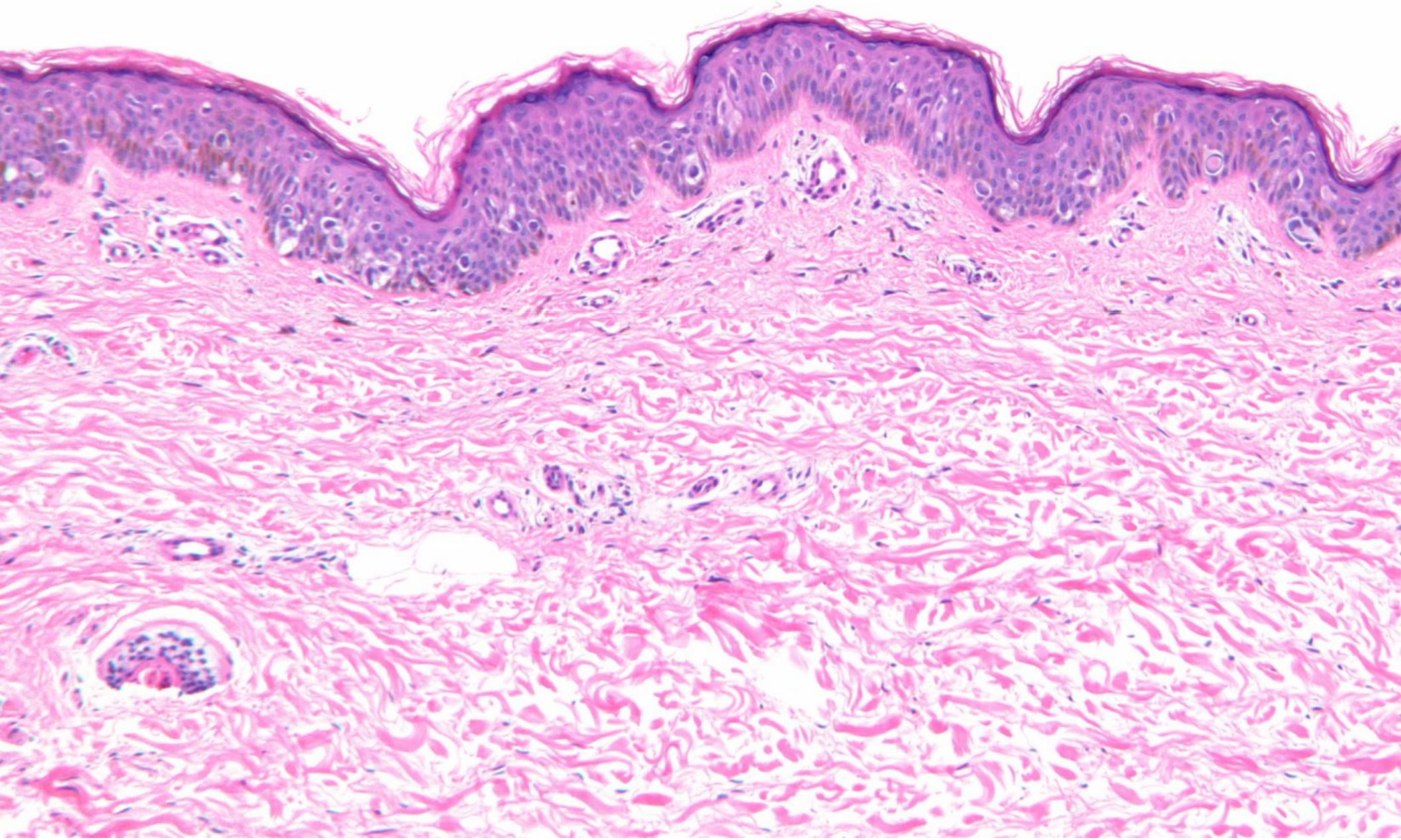


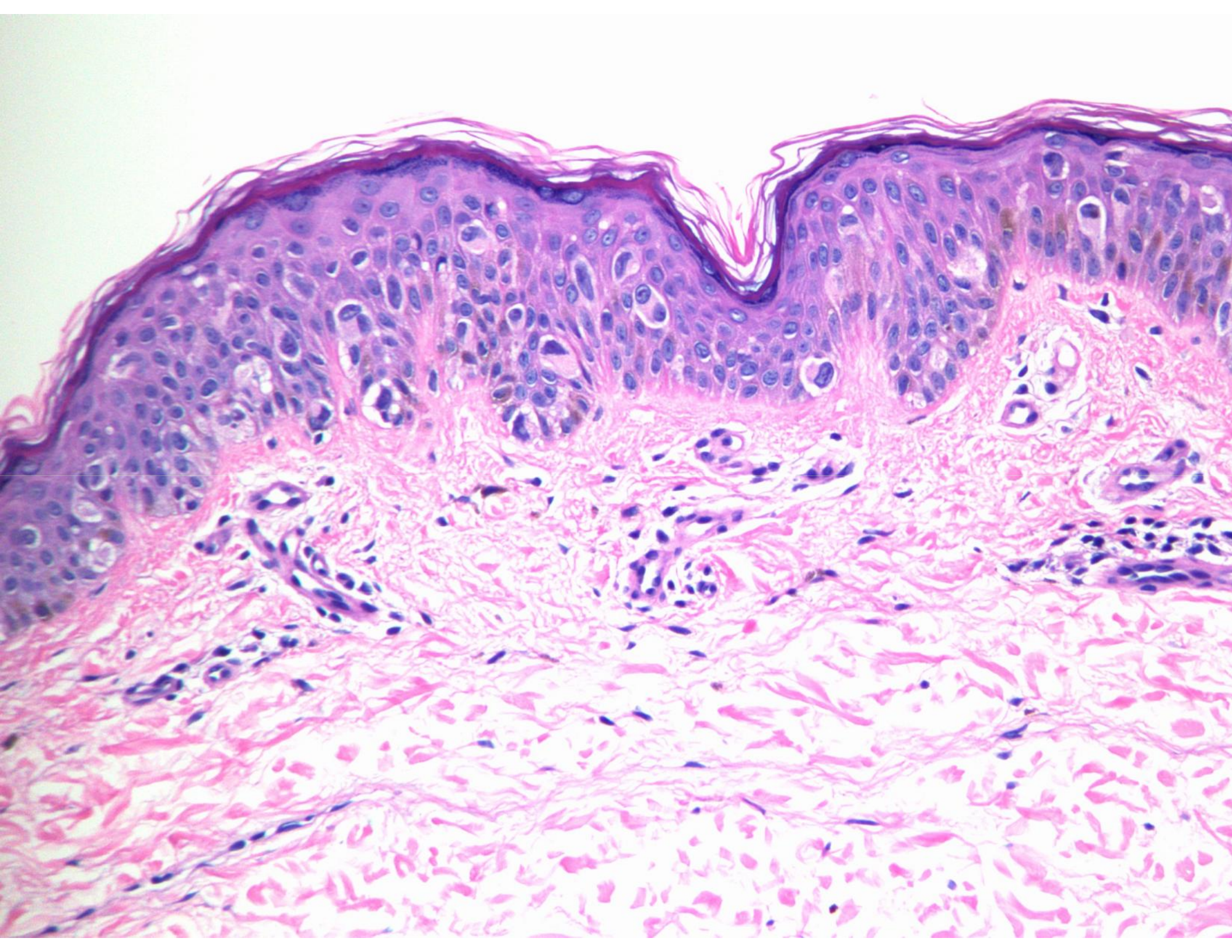


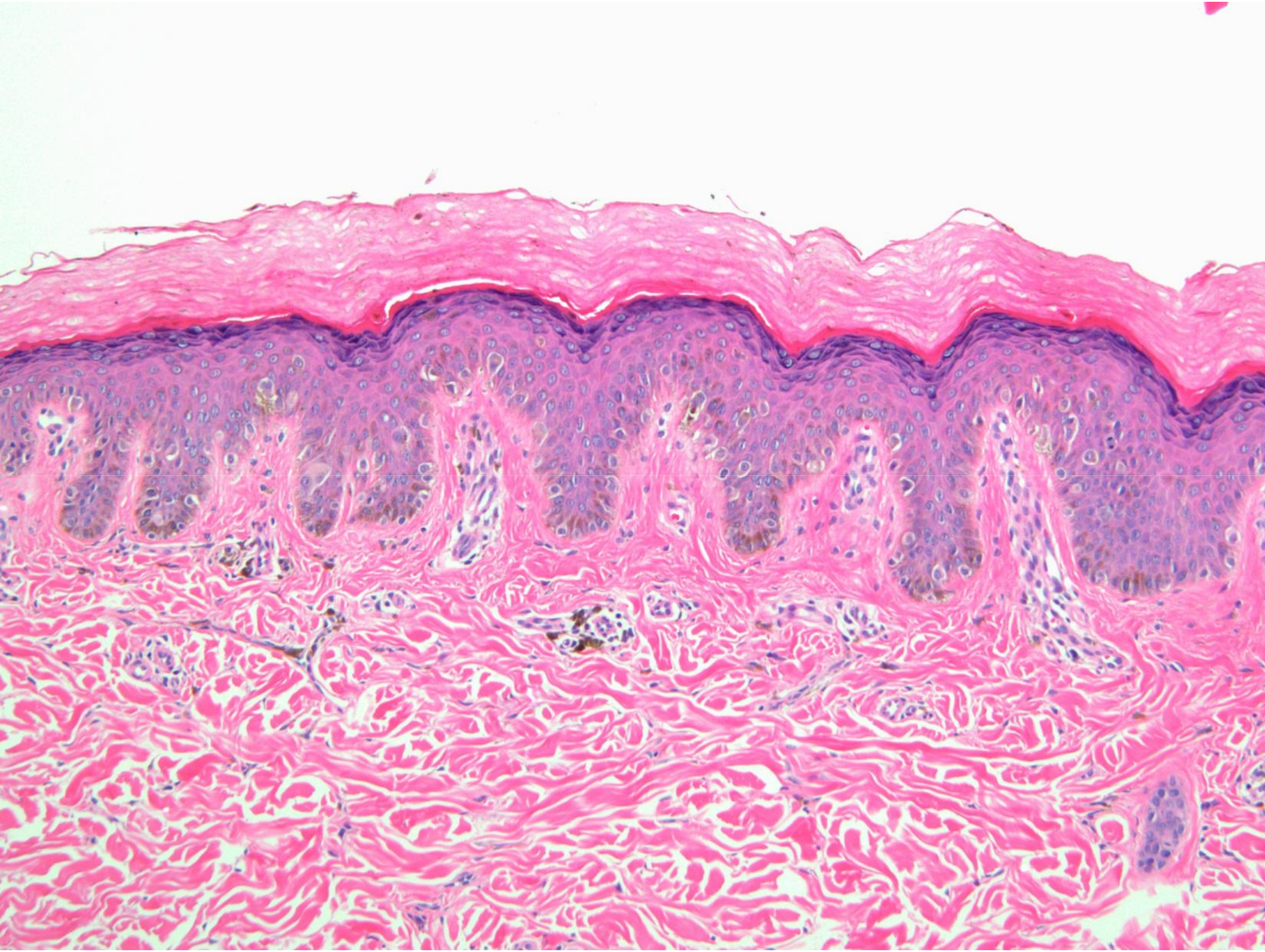


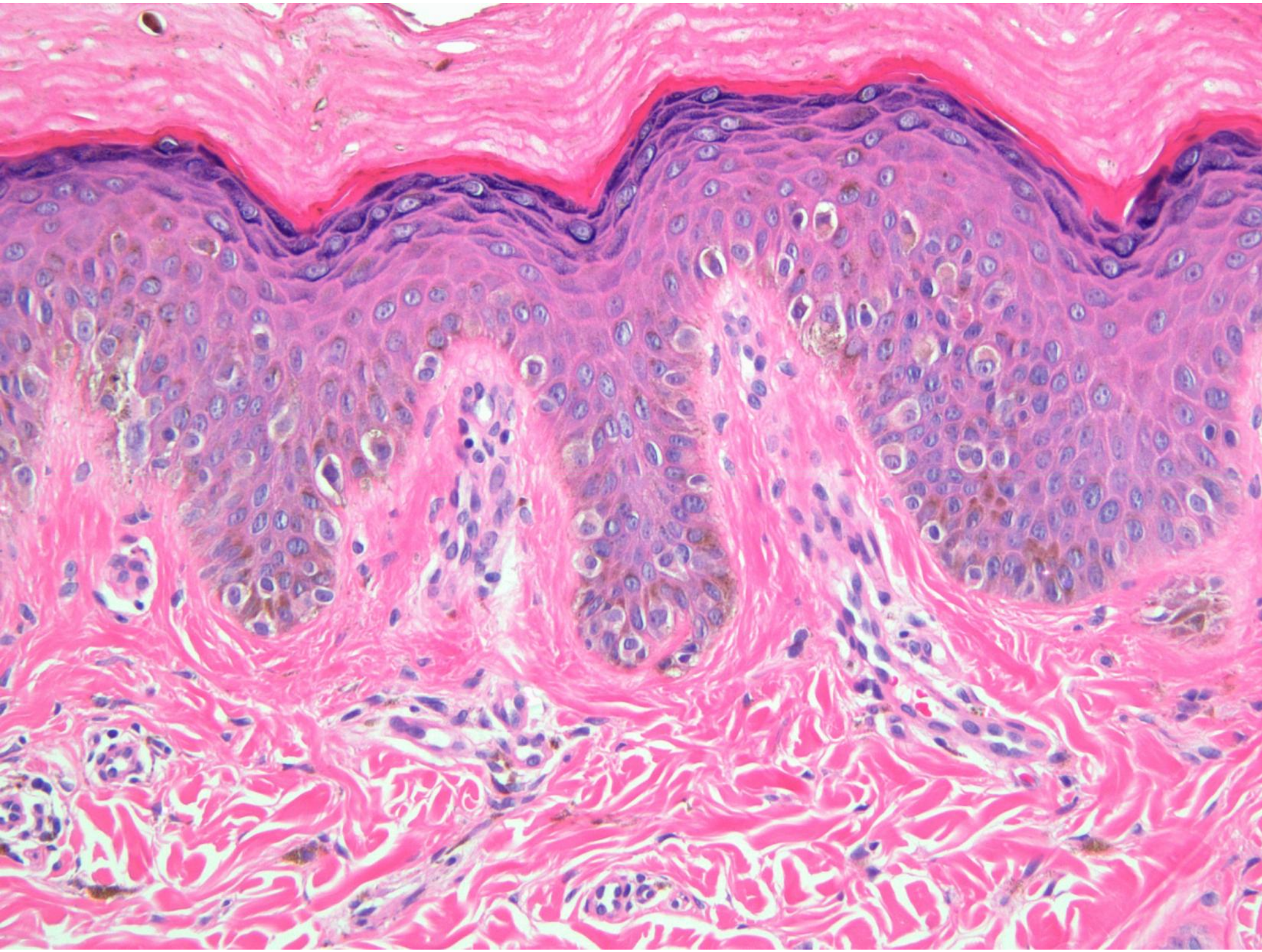
Pagetoid Spitz Nevus

- Young women
- Lower legs most common site
- Microscopic features
  - Relatively symmetric
  - Predominantly single cells
  - Prominent upward migration
  - Usually no dermal component (rare cases with focal superficial dermal involvement)









Pagetoid Spitz Nevus

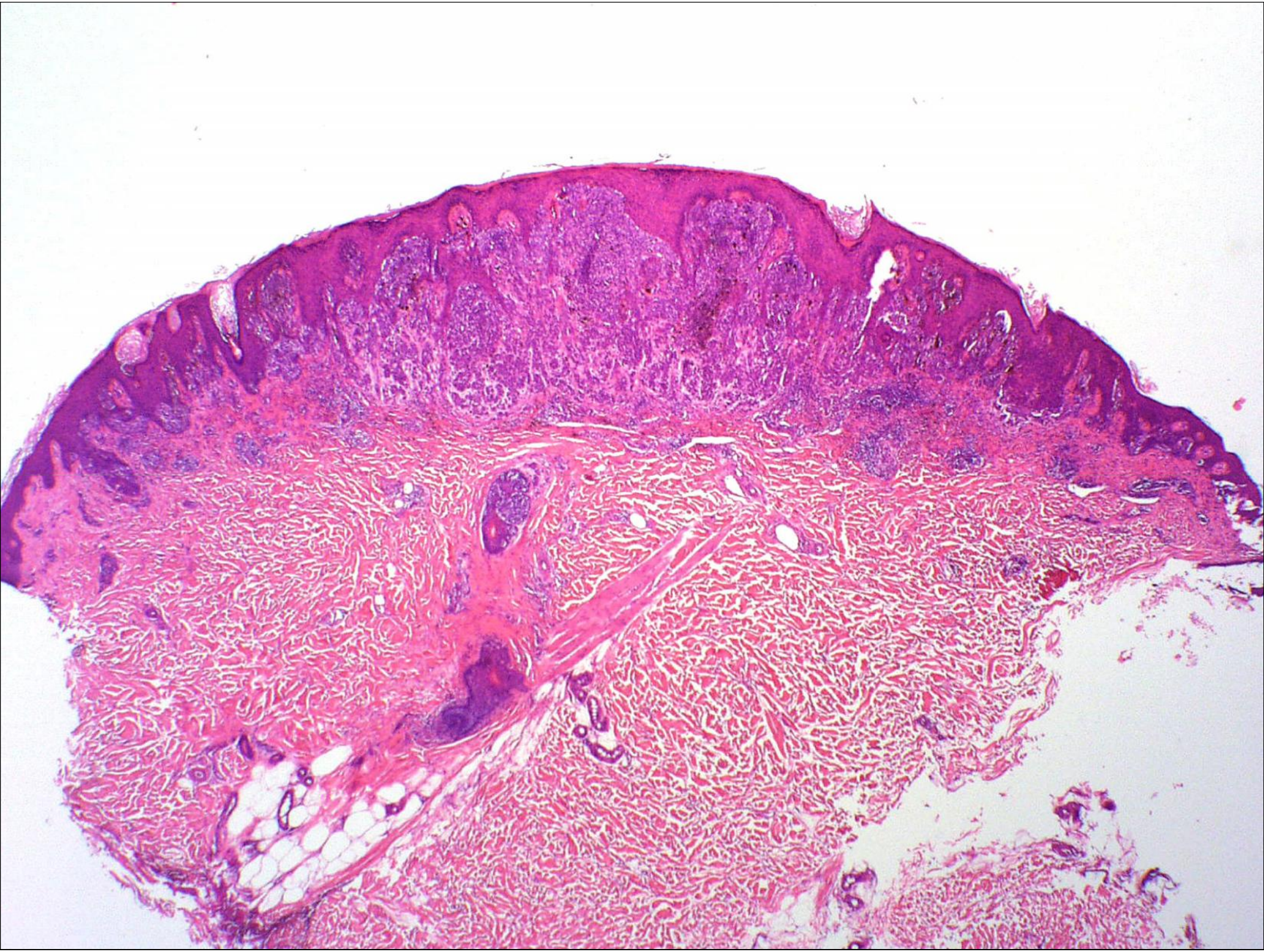
- Clinical presentation very important
- Small, symmetric
- Significant overlap with melanoma in situ
- Recommend conservative but complete excision

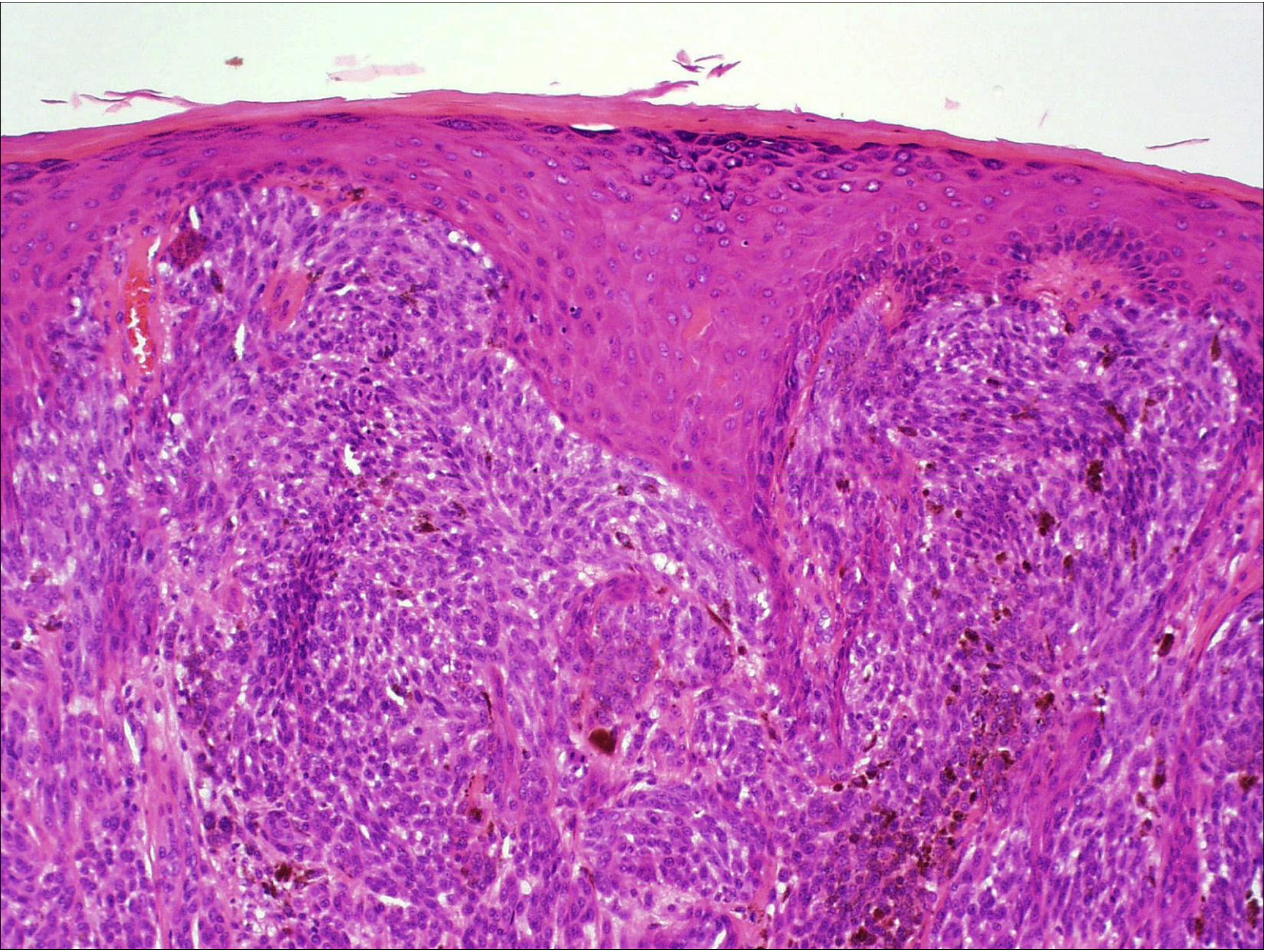
Spitzoid Melanoma

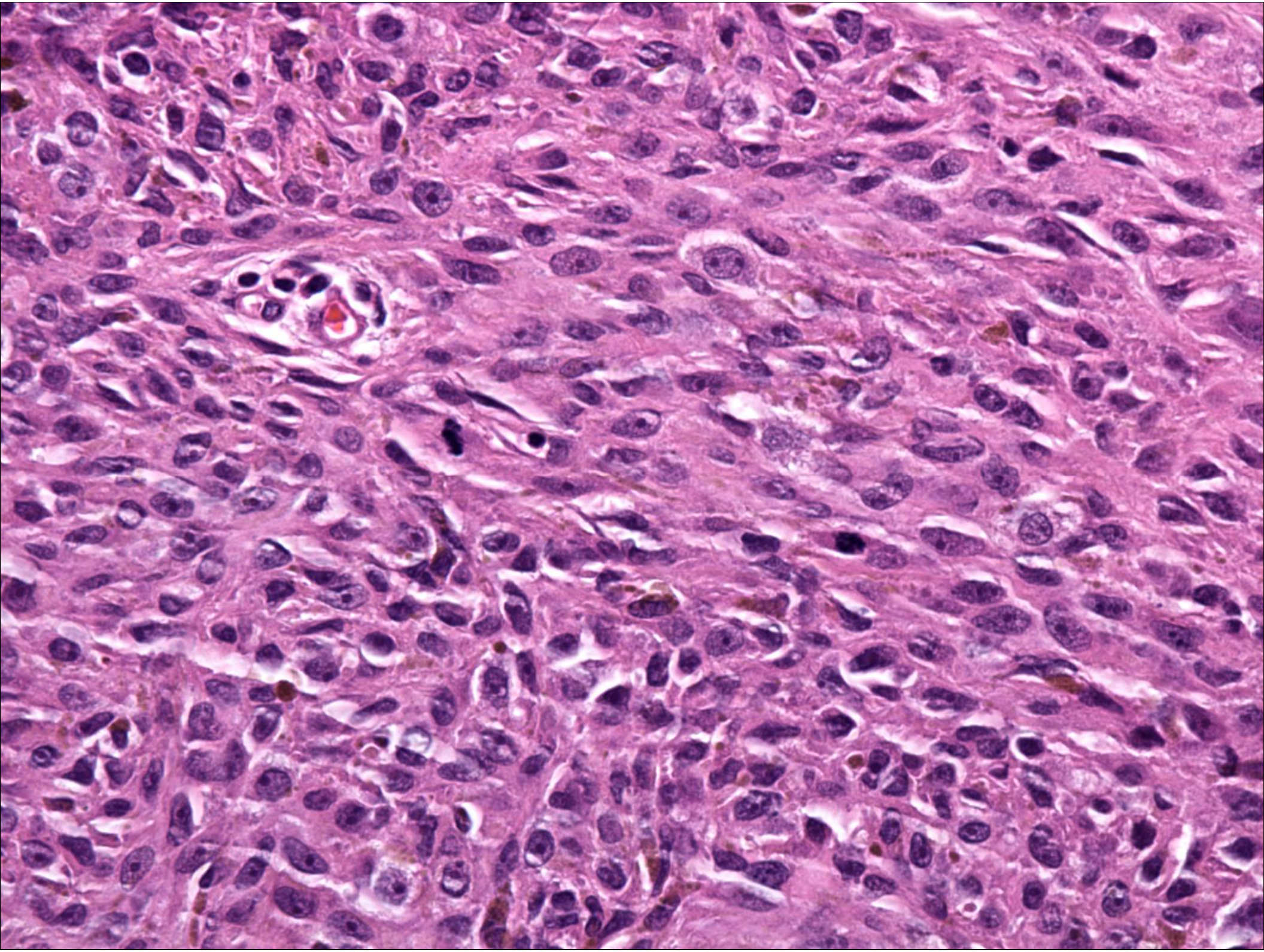
- Clinical Features
  - Adults (can occur in children)
  - Not clinically distinctive
- Microscopic features
  - Can be similar to Spitz nevus
    - Symmetric
    - Circumscribed
    - Epithelioid melanocytes
    - Clefts may be present
    - Rarely small Kamino bodies (not clusters)
    - Pagetoid may be absent

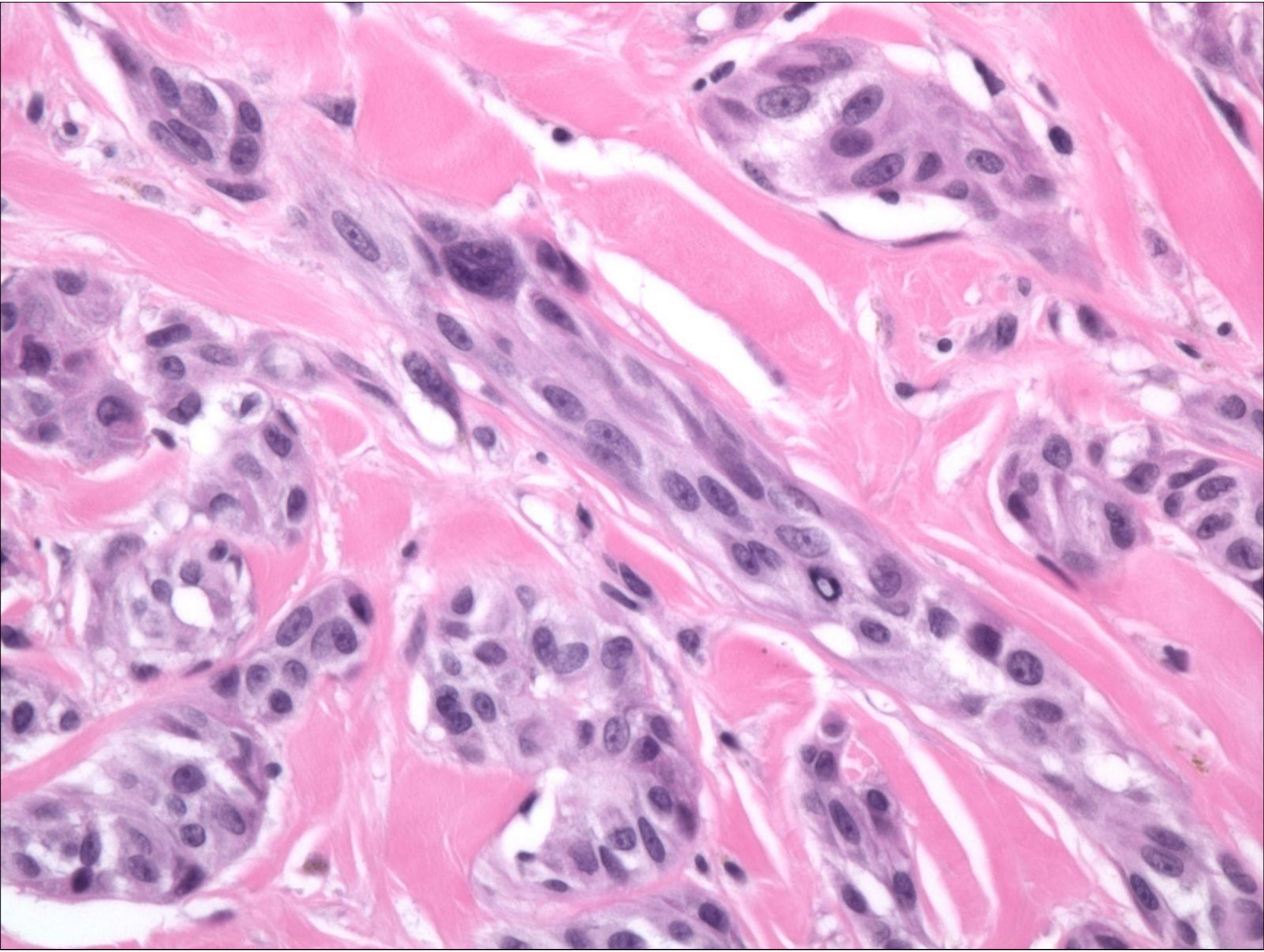
Spitzoid Melanoma

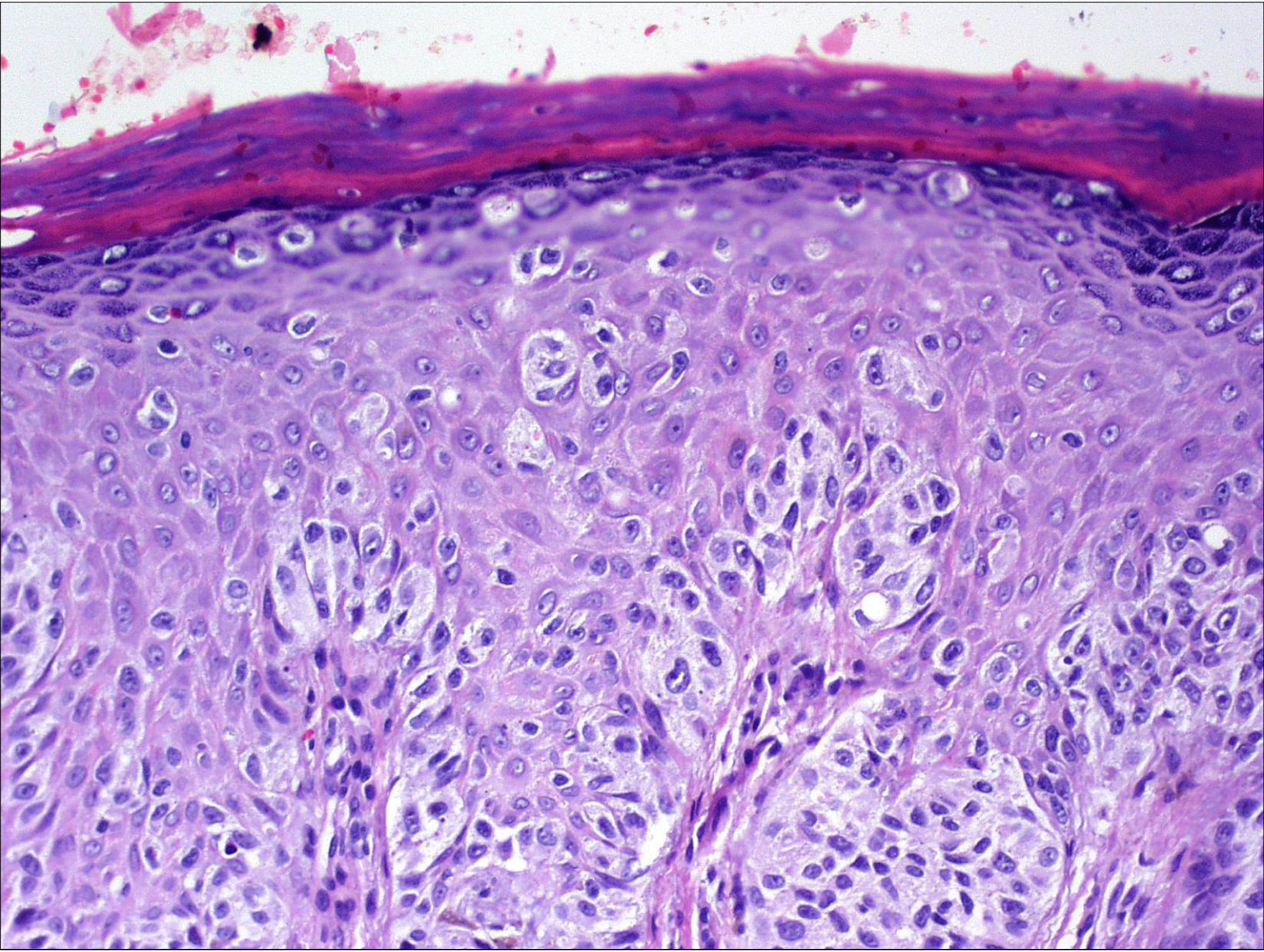
- Differences from Spitz nevi
  - Deep tumors: reticular dermis to subcutis
  - Solid sheets
  - Large nodules
  - Lack of maturation
  - Dermal mitotic figures
  - Increased pleomorphism at same latitude
  - Prominent nucleoli deep
  - Irregular pigment
  - Asymmetry and prominent pagetoid spread when present











Hantschke et al AJSP 2004;28: 1621-5

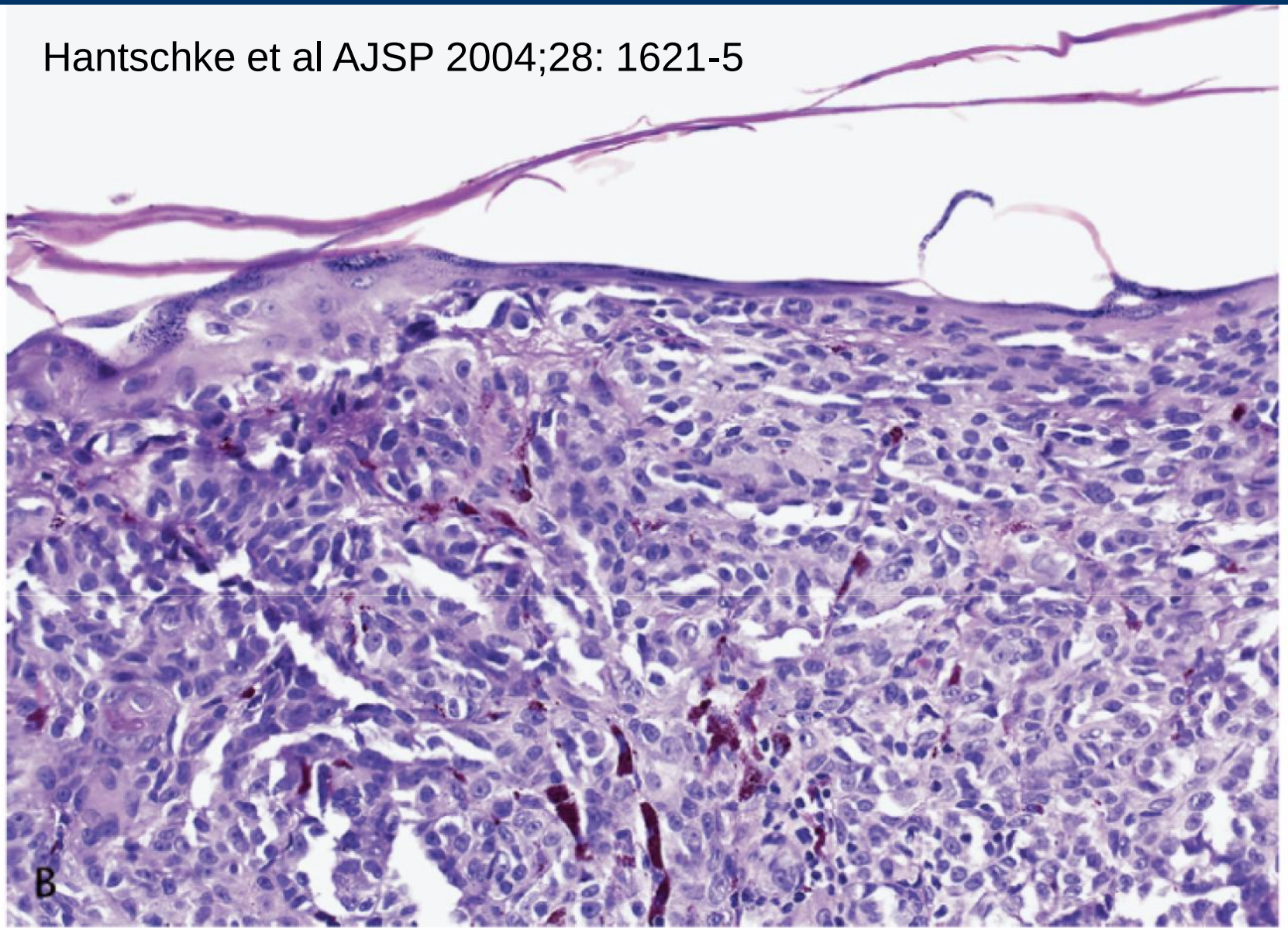


FIGURE 2. Melanoma with an epidermis that is very thin in some areas, with loss of the basal and some suprabasal layers and of rete ridges (A). Focally, small subepidermal cleft formation can be observed (B).

Spitz Nevus vs. Spitzoid Melanoma

Spitz

- Symmetric
- No consumption of epidermis
- Nested
- Pagetoid spread (nests, fewer single cells)
- Epithelioid/spindled
- No dermal MFs
- No individual cell necrosis
- Kamino bodies (clusters)

Spitzoid Melanoma

- Symmetric or asymmetric
- Consumption of epidermis
- Sheets
- Pagetoid spread (single cells > nests)
- Epithelioid/spindled
- Dermal MFs
- Individual cell necrosis
- No to rare Kamino bodies (no clusters)

Atypical Spitz Tumor

- Traditionally wastebasket term for when you can't decide
- Other choices:
  - Spitz tumor of uncertain malignant potential (STUMP)
  - Atypical Spitz nevus
  - Atypical spitzoid melanocytic proliferation
- Subjective

Ki-67

- Spitz
- Low proliferative rate
- 0-10%
- Zonal (upper portion of lesion)

- Melanoma
- High proliferative rate
- 5-40%
- Present at all levels

Caveats:

1. Overlap
2. Lymphocytes Ki-67 positive
3. Thin melanomas
4. Classic cases tested

p16

- Spitz
- Diffusely positive
  - 40-80% of cells
  - Positive at all levels
  - Nuclei and cytoplasm

- Melanoma
- Variably positive
  - 0-40% of cells
  - Less staining in dermis
  - Cytoplasm

Caveats:

1. Overlap
2. Thin melanomas
3. Classic cases tested

Cyclin D1

- Spitz
- 5-20%
- Zonal restricted to upper dermis

- Melanoma
- 5-25%
- Throughout

Caveats:

1. Overlap
2. Thin melanomas
3. Classic cases tested

Immunohistochemical Stains

- Approach with caution
- No magic bullet
- Beware of overlap
- Can be supportive in selected cases

Fluorescence In Situ Hybridization (FISH) as an Ancillary Diagnostic Tool in the Diagnosis of Melanoma

Pedram Gerami, MD, Susan S. Jewell, PhD,† Larry E. Morrison, PhD,†*
Beth Blondin, BSc,† John Schulz, BSc,† Teresa Ruffalo, BSc,† Paul Matushek, IV, MS,†
Mona Legator, BSc,† Kristine Jacobson, MS, MAJ,† Scott R. Dalton, MC,‡
*Susan Charzan, MS,§ Nicholas A. Kolaitis, BS,§ Joan Guitart, MD,**
Terakeith Lertsbarapa, MD, Susan Boone, MD,**
Philip E. LeBoit, MD,§ and Boris C. Bastian, MD§

- 4 probes: 6p25, 6 cent, 6q23, 11q13
- Criteria
  - >38% nuclei with > 2 signals for 11q13 or
  - >55% nuclei more 6p25 than 6 centromere or
  - >40% nuclei with less 6q23 than 6 cent. or
  - >29% nuclei with > 2 signals for 6p25
- Sensitivity 87%; specificity 95%

Gerami et al. Am J Surg Pathol 2009;33:1146–1156

FISH limits

- Technically challenging
- Expensive equipment
- Still difficult in thin melanomas
- Limited availability
- Less accurate in ambiguous tumors
  - Sensitivity 70% in spitzoid melanomas
  - Specificity ~80%

Update in Molecular Diagnostics in Melanocytic Neoplasms

Chelsea Cooper, BA, Jennifer Sorrell, MD,* and Pedram Gerami, MD*†*

(*Adv Anat Pathol* 2012;19:410–416)

TABLE 1. Criteria Used to Determine Whether a Sample Is FISH Positive[21,22]

FISH Probe	Criteria for a Positive FISH
6p25-RREB1	6p25 > 2 in > 29% of cells
Cep6	6p25 > Cep6 in > 55% of cells
6q23-MYB	6q23 < Cep6 in > 40% of cells
11q13-CCND1	11q13 > 2 in > 38% of cells
9p21-CDKN2A	7-9 cells equal to zero in 9p21
8q24-MYC	8q24 > 2 in > 20% of cells

FISH indicates fluorescence in situ hybridization.

Risk Assessment for Atypical Spitzoid Melanocytic Neoplasms Using FISH to Identify Chromosomal Copy Number Aberrations

Pedram Gerami, MD,† Richard A. Scolyer, MD,‡ Xiaowei Xu, MD, PhD,§ David E. Elder, MD,§ Ronnie M. Abraham, MD,§ Douglas Fullen, MD,‖¶ Victor G. Prieto, MD, PhD,#** Philip E. LeBoit, MD,†† Raymond L. Barnhill, MD,‡‡ Chelsea Cooper, BA,* Pedram Yazdan, MD,* Joan Guitart, MD,*† Ping Liu, PhD,§§ Ekaterina Pestova, PhD,§§ and Klaus Busam, MD‖‖*

- 64 atypical Spitz tumors with 5 years uneventful follow-up
- 11 atypical Spitz tumors with aggressive course
- Analyzed by FISH

Atypical Spitz

- Homozygous 9p21 deletion
  - 3/3 patients DOD
  - 6/8 with advanced locoregional disease
- Multivariate analysis: adverse outcome
  - Mitotic rate p = 0.03
  - Homozygous 9p21 deletion p = <0.0001
- Atypical Spitz with homozygous 9p21 deletion = form of spitzoid melanoma

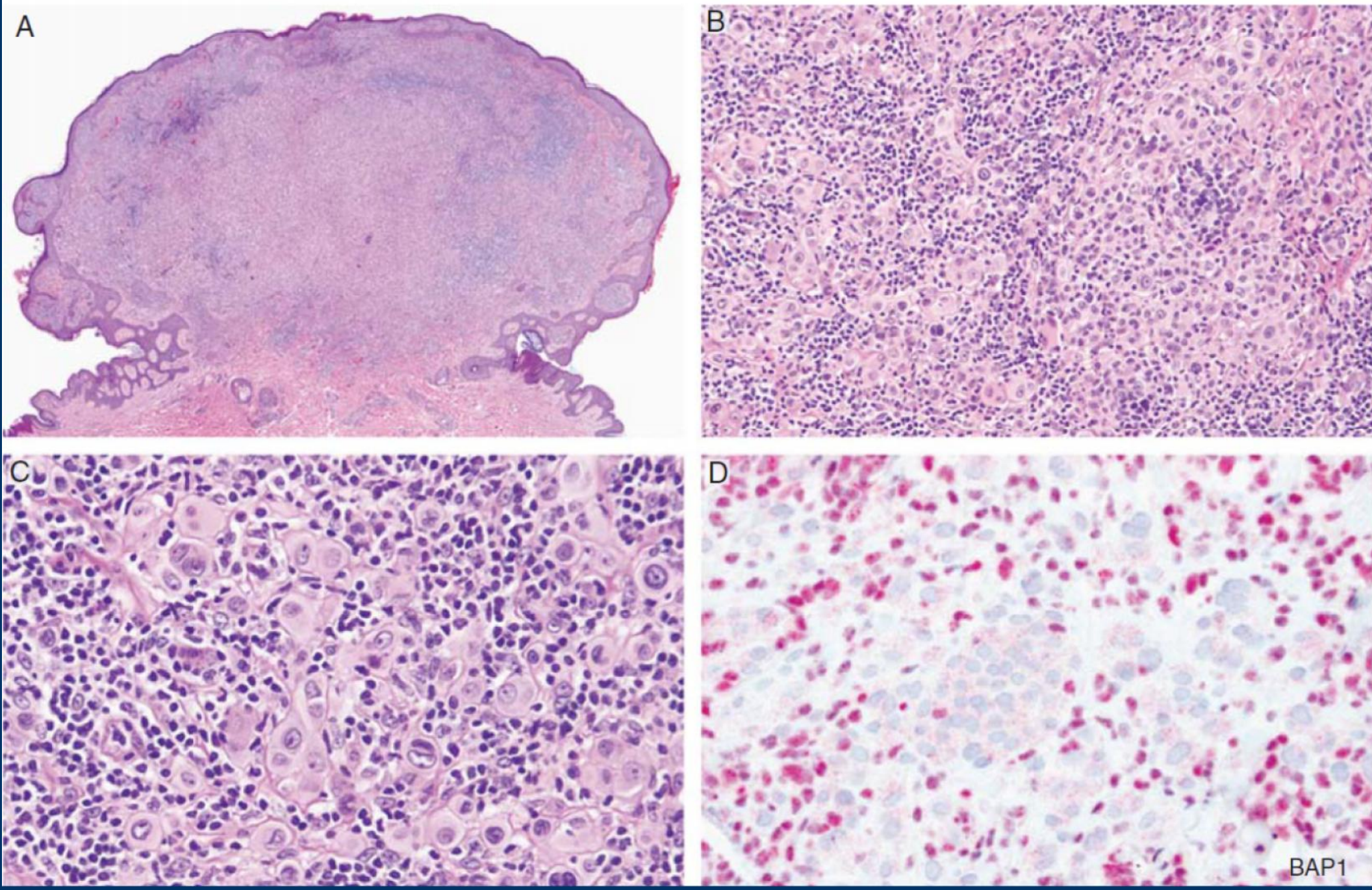
A Distinct Subset of Atypical Spitz Tumors is Characterized by *BRAF* Mutation and Loss of BAP1 Expression

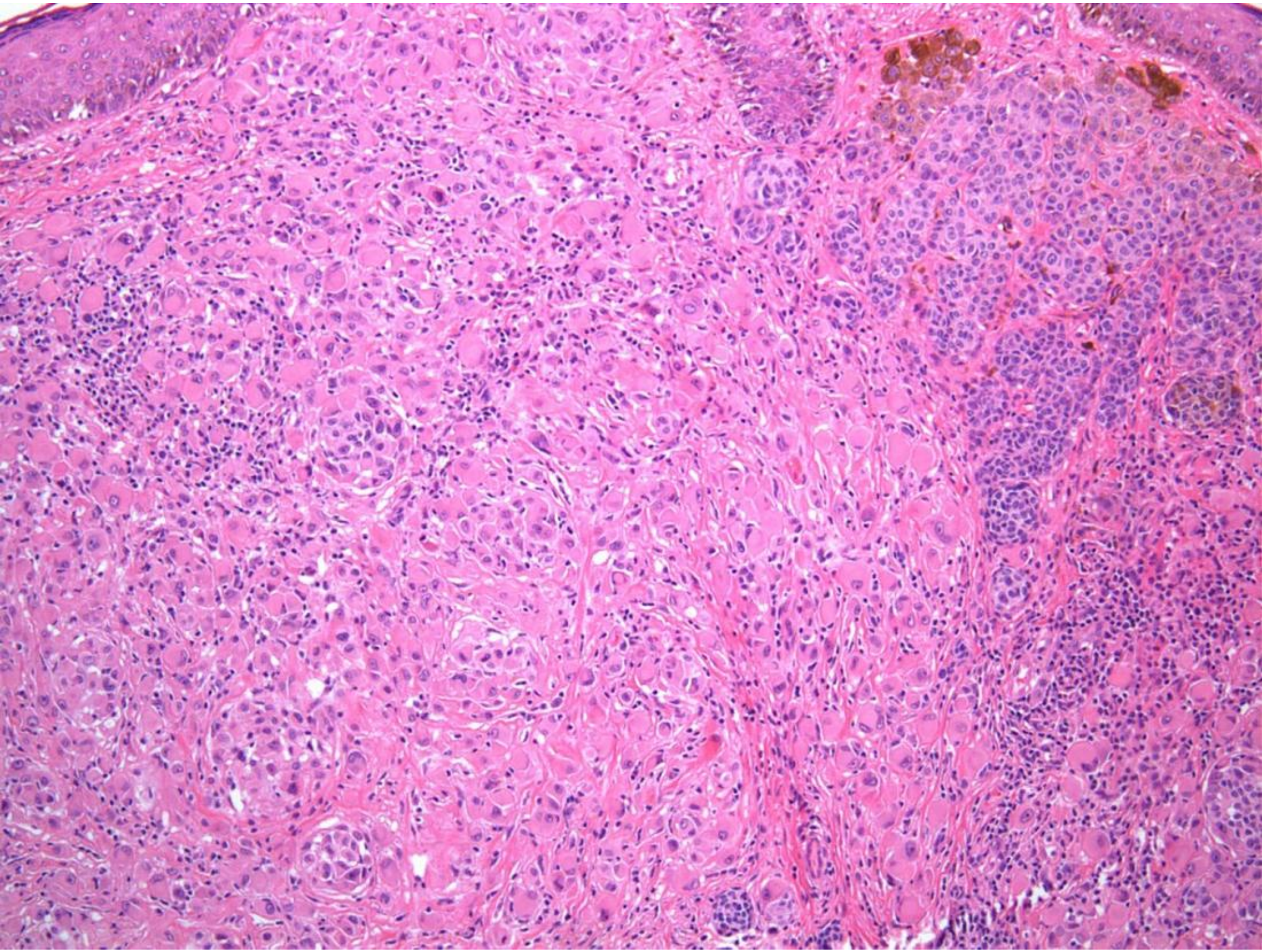
Thomas Wiesner, MD,† Rajmohan Murali, MBBS, MD,*‡ Isabella Fried, MD,† Lorenzo Cerroni, MD,† Klaus Busam, MD,‡ Heinz Kutzner, MD,†§ and Boris C. Bastian, MD*‡‖¶*

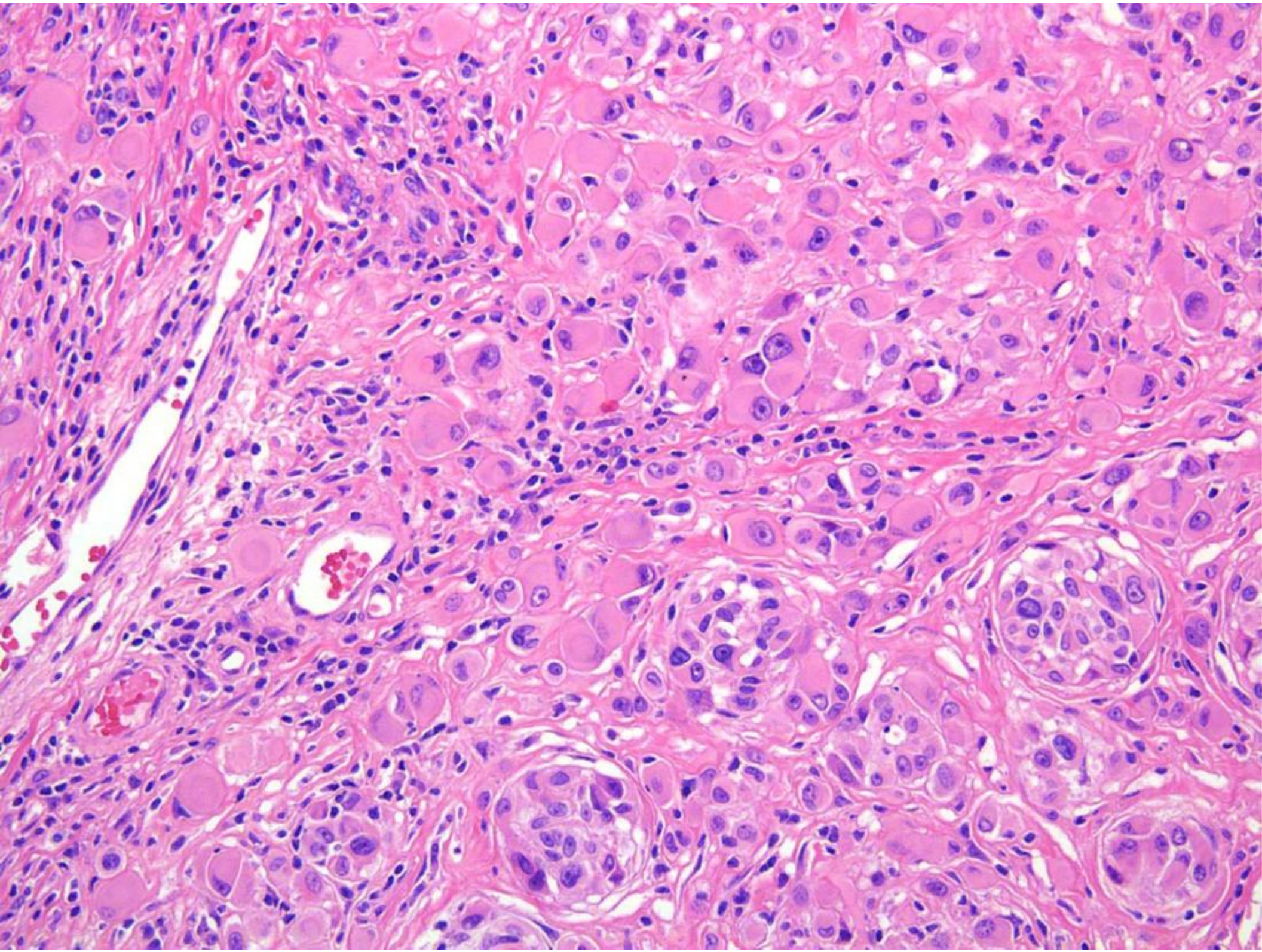
(*Am J Surg Pathol* 2012;36:818–830)

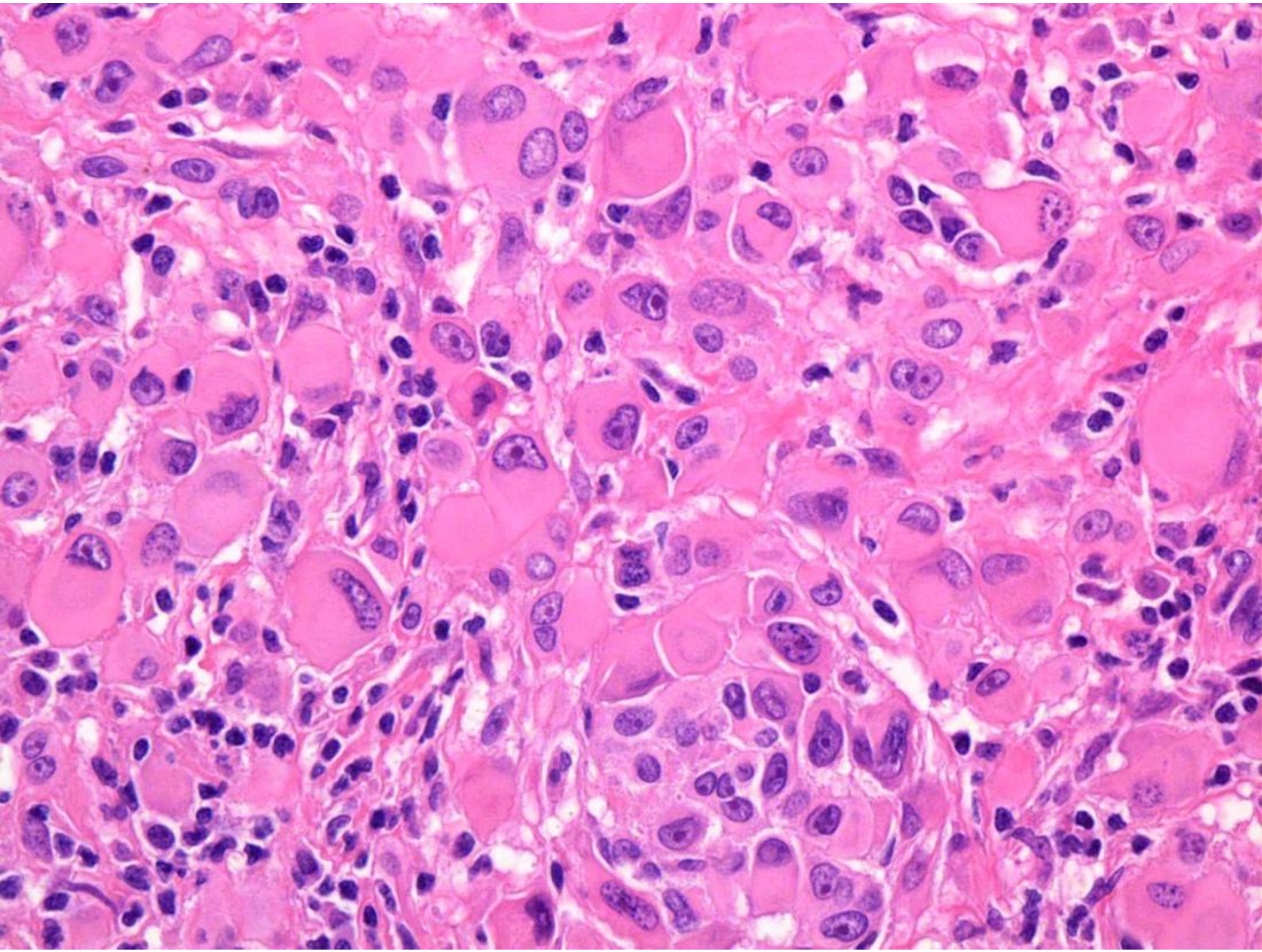
Examined 32 atypical Spitz nevi

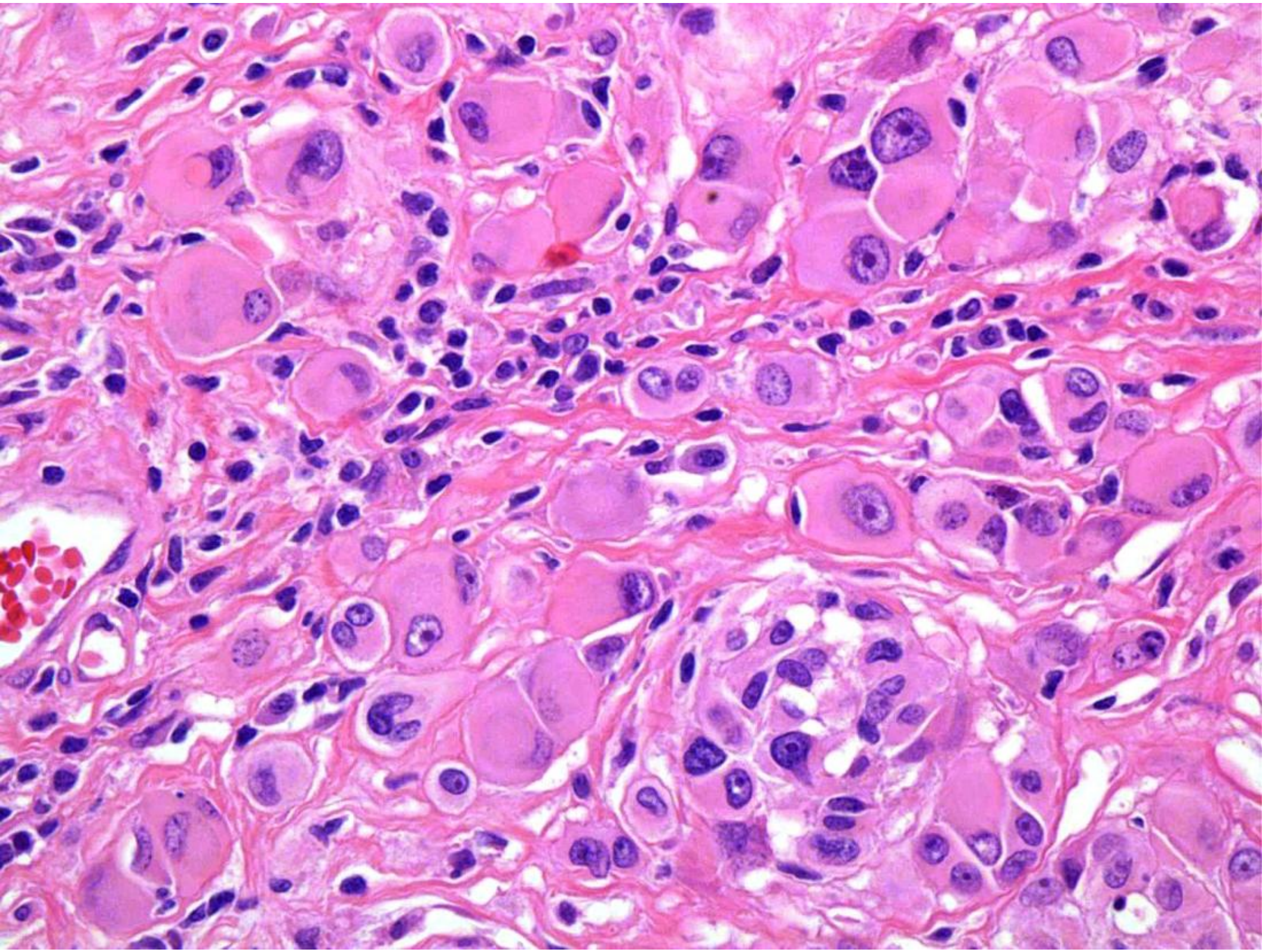
- 28% with loss of BAP1 expression
  - 8/9 *BRAF* V600E mutation
- Distinct histologic features
  - Polypoid, mostly intradermal
  - Sheets of epithelioid cells with defined cell borders
  - Numerous TILs


A
B
C
D
BAP1









Kinase fusions are frequent in Spitz tumours and spitzoid melanomas

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Table 1 | Frequency of kinase fusions in spitzoid neoplasms.

Fusion	Spitz naevus ($n=75$) % (number of cases)	Atypical Spitz tumour ($n=32$) % (number of cases)	Spitzoid melanoma ($n=33$) % (number of cases)	Total ($n=140$) % (number of cases)
ROS1	25.3 (19)	6.3 (2)	9.1 (3)	17.1 (24)
ALK	10.7 (8)	15.6 (5)	3 (1)	10 (14)
NTRK1	10.7 (8)	25 (8)	21.2 (7)	16.4 (23)
BRAF	5.3 (4)	6.3 (2)	3 (1)	5 (7)
RET	2.7 (2)	3.1 (1)	3 (1)	2.9 (4)
Total	54.7 (41)	56.3 (18)	39.4 (13)	51.4 (72)

Spitz tumors

- Molecularly diverse group
- Molecular findings refining diagnosis
- Wastebasket getting smaller

Molecular classification of melanoma

- Intermittently sun-exposed skin: ***BRAF***, *NRAS*
- Chronically sun-damaged skin: ***KIT***, *KIT* and *NRAS, NRAS, BRAF*
- Acral skin: ***KIT***, *BRAF, NRAS* and *BRAF*
- Mucosa: ***KIT***, *NRAS, BRAF*

Future

- “Melanoma” and “Spitz tumors”
  - Not just one disease
  - Collection of morphologically similar melanocytic tumors with varying genetic abnormalities
  - Genetic abnormalities will increasingly refine diagnosis, prognosis and treatment