31. Basiskurs für Dermatohistopathololologie der ARGE

Salzburg, 2.-3.3.2023

Fälle 85-100

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Approach to microscopic examination of skin tumors

- Tumor vs. "pseudotumor" *(e.g., pseudoepitheliomatous hyperplasia in lichen simplex chronicus)*
- Differentiation *(e.g., epithelial, melanocytic, etc.)*
- Benign vs. malignant *(vs. "intermediate", hyperplasia, malformation, hamartoma)*
- Need (or not) of immunohistochemistry or other ancillary methods *(e.g., molecular studies for soft tissue tumors)*
- Diagnosis *(or differential diagnoses)*
- For malignant tumors: prognostic features, if applicable
- Assessment of surgical margins and other information relevant to further management of the patient

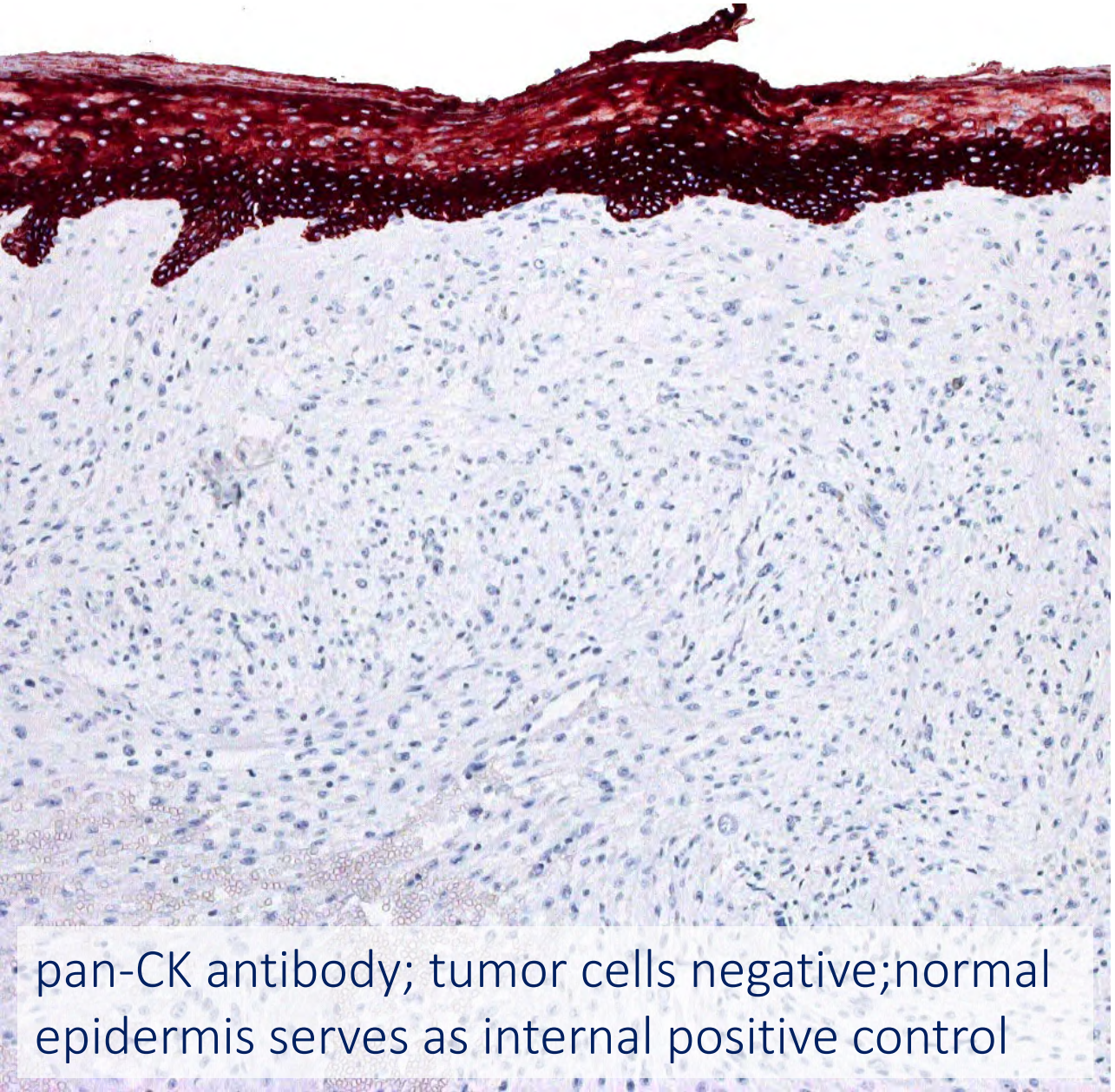
Microscopic diagnosis is the synthesis of many aspects

- Overall architecture (i.e., scanning magnification) including orientation and pattern of growth
- Presence of specific structures / features *(e.g., nests in melanocytic tumors, ghost cells in pilomatrical differentiation, etc.)*
- Cell morphology *(including mitoses, necrotic cells)*
- If needed: immunohistochemical features *(never rely on a single antibody, judge a phenotypic pattern)*
- Rarely: molecular analyses *(several methods depending on the question that should be answered)*
- **A single histopathological feature is never diagnostic *(e.g., a malignant tumor can be symmetrical and well circumscribed)***

Immunohistochemistry

- Thousands of monoclonal (and some polyclonal) antibodies
- In skin biopsies internal positive controls for most antibodies
- Only a (relatively) limited panel necessary for routine histopathological examination of skin specimens
- Choice of which antibodies should be used depends on morphological diagnosis and differential diagnoses
- Applied mostly for tumors, but several antibodies useful also for inflammatory disorders (e.g., *Treponema pallidum* for syphilis, CD123 for lupus erythematosus, MPO and MNDA for histiocytoid Sweet syndrome)

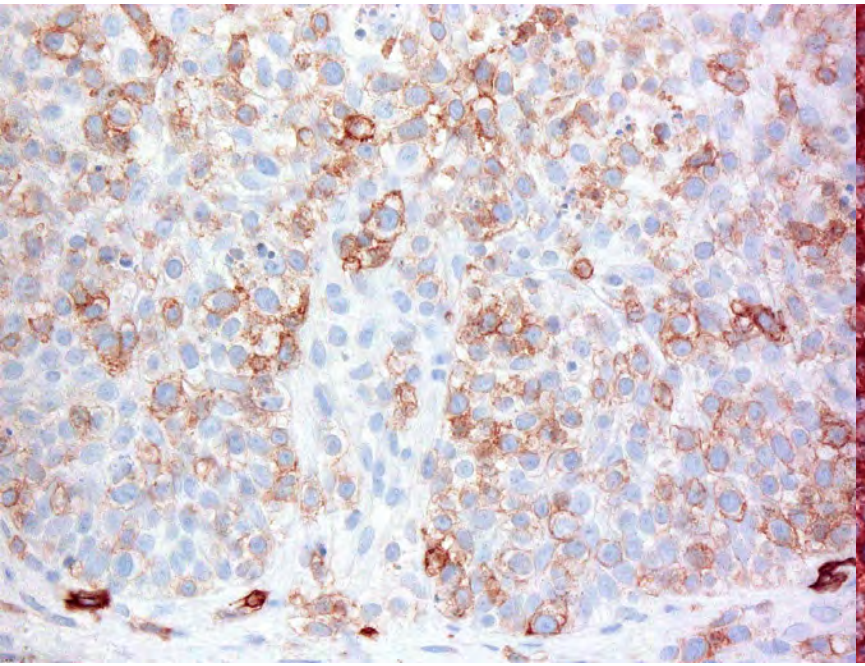
Immunohistochemistry – Controls



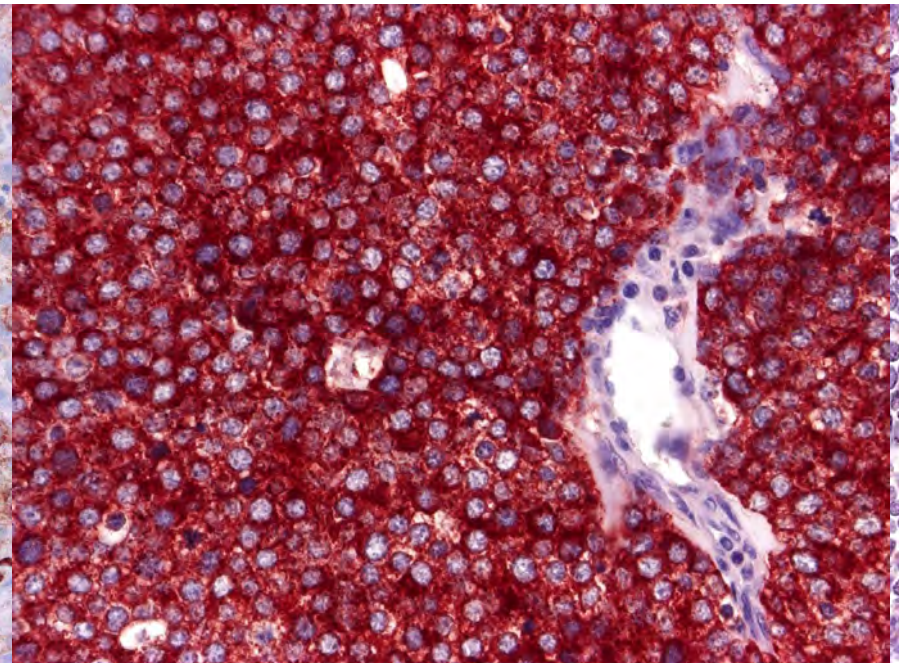
pan-CK antibody; tumor cells negative;normal epidermis serves as internal positive control

- Internal positive controls are available for the vast majority of antibodies used in routine immunohistochemistry
- Some antibodies need external controls to confirm negative results (e.g., BRAF)
- Repeat staining in negative cases if internal cells and/or structures serving as control are negative or not present on that particular section of tissue (e.g., normal sebaceous glands positive for PRAME)
- If several cases are stained at the same time, one positive case can serve as "external" control for negative ones

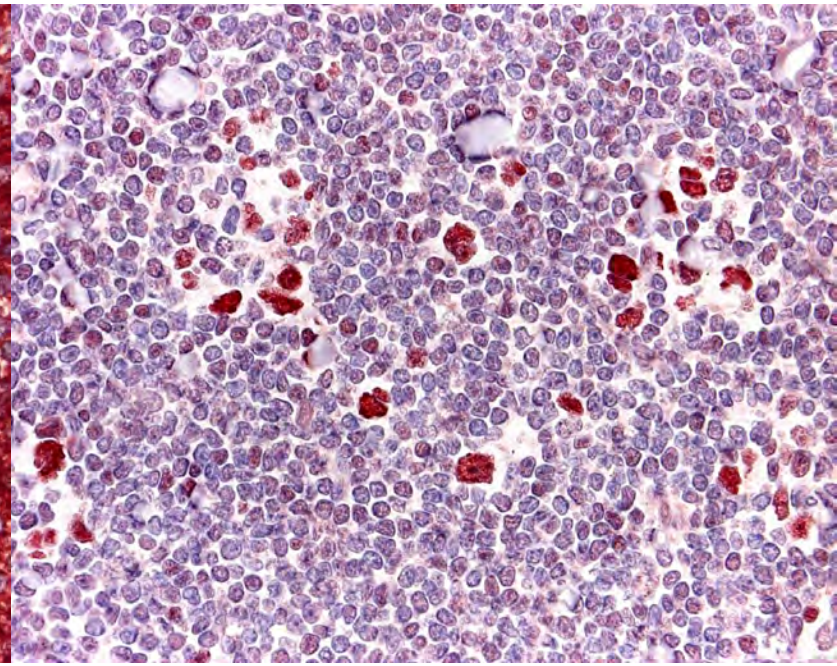
Immunohistochemistry – Pattern of positivity



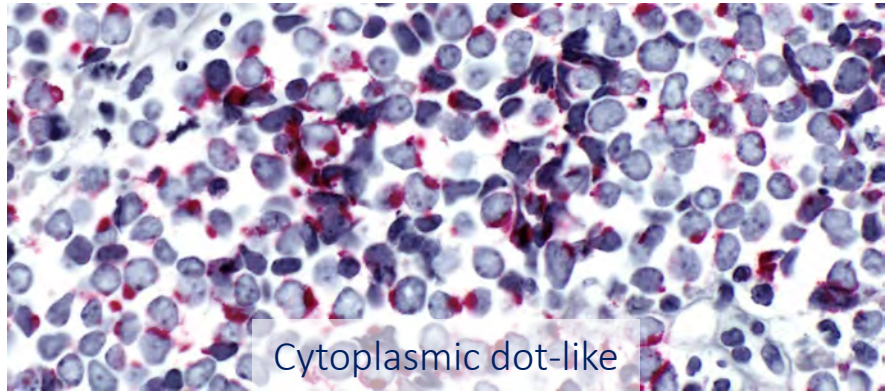
Membranous



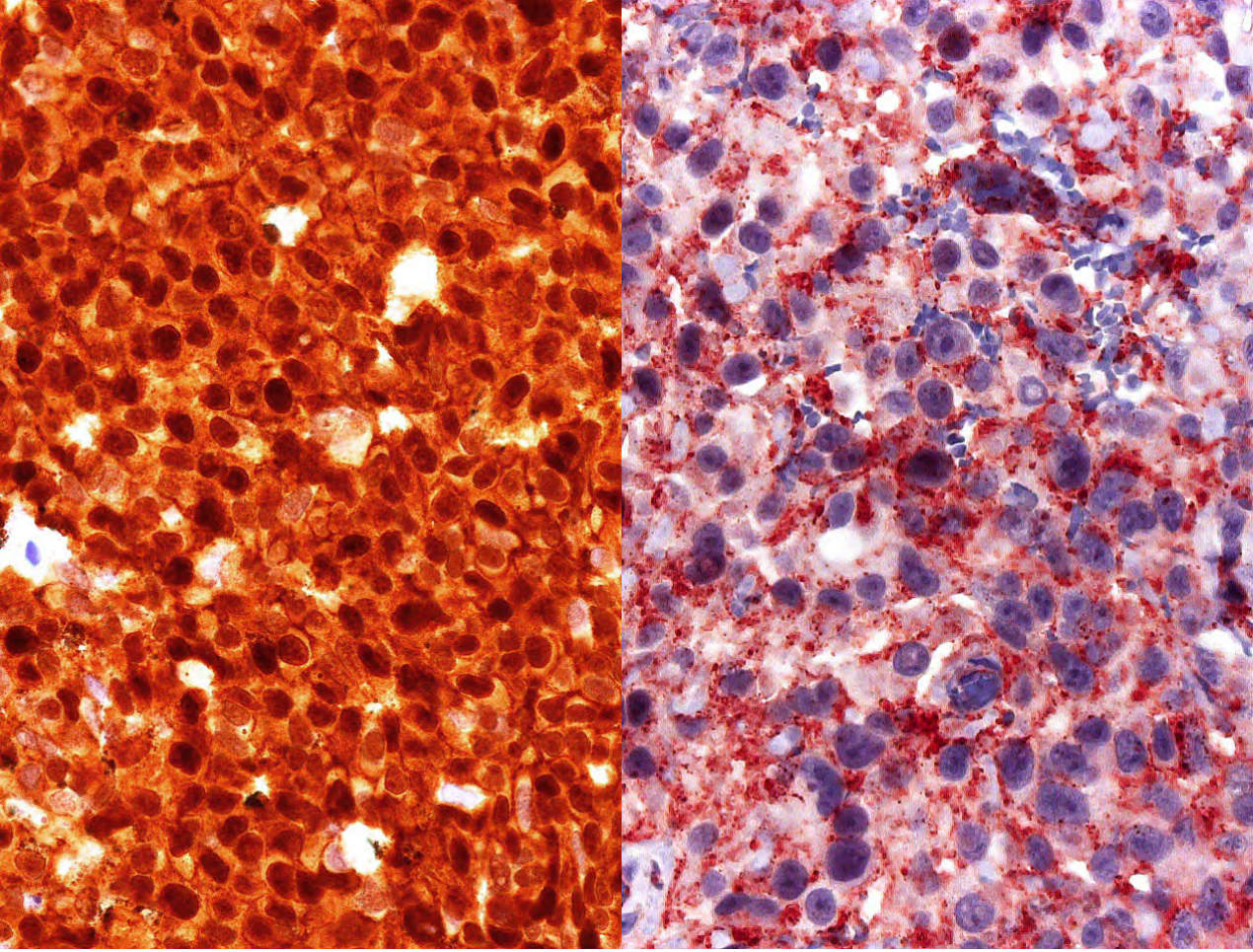
Cytoplasmic

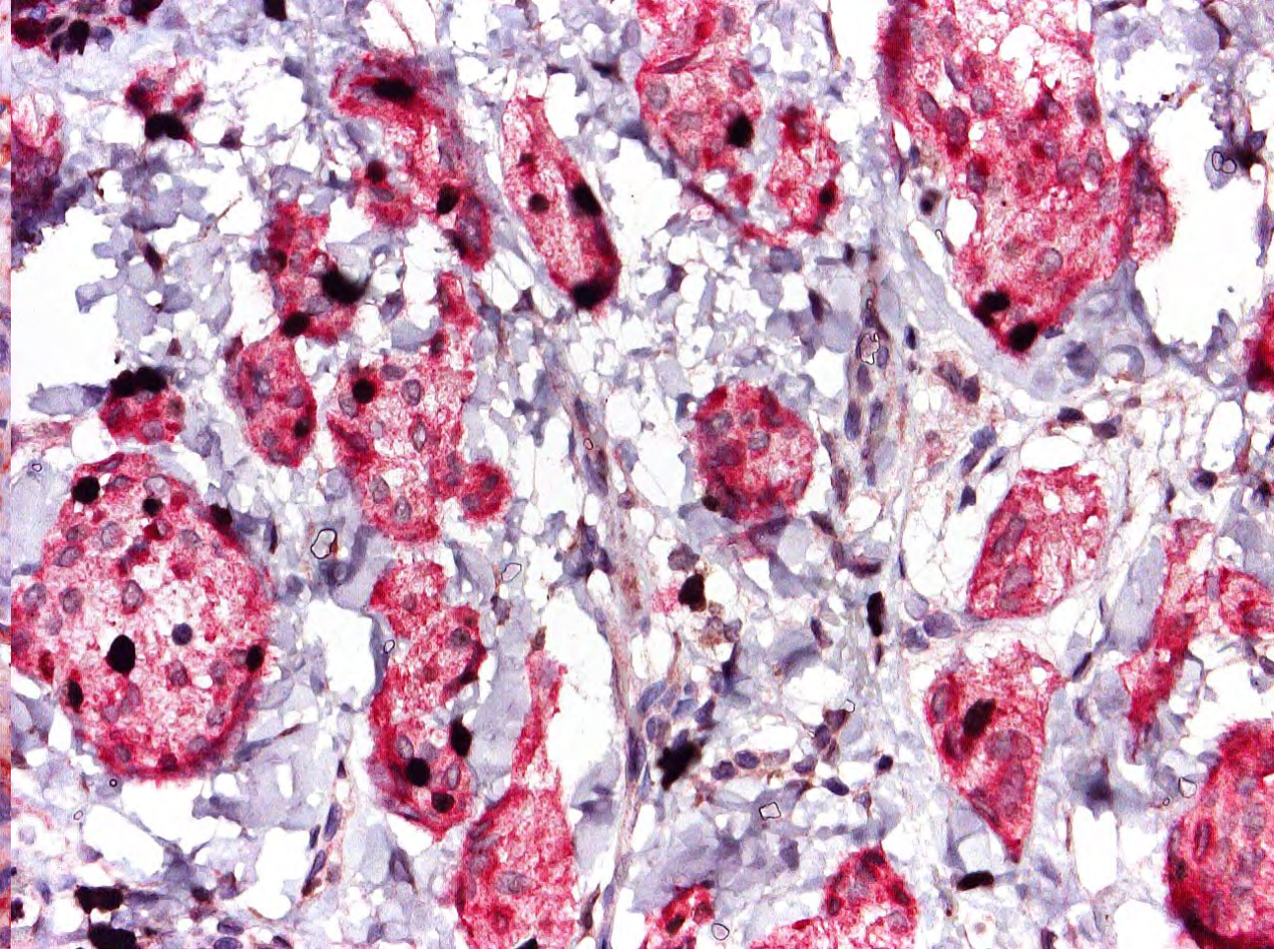


Nuclear



Cytoplasmic dot-like



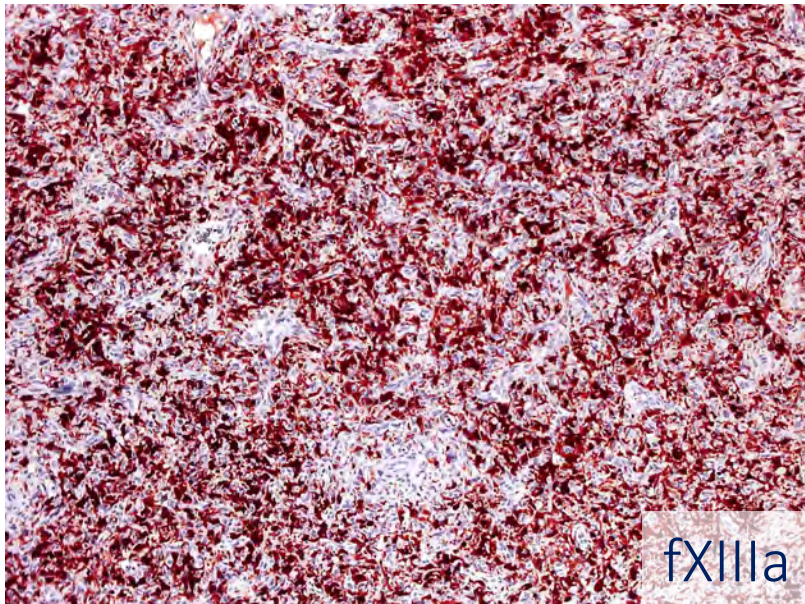


The staining pattern matters: for some antibodies only one type of staining is specific (in this example: ß-catenin, positive if nuclear; cytoplasmatic staining does not count)

"Double stainings" can be (rarely) helpful (here melan-A in red, cytoplasmatic to recognize melanocytes, and Ki-67 in brown, nuclear to highlight proliferating cells)

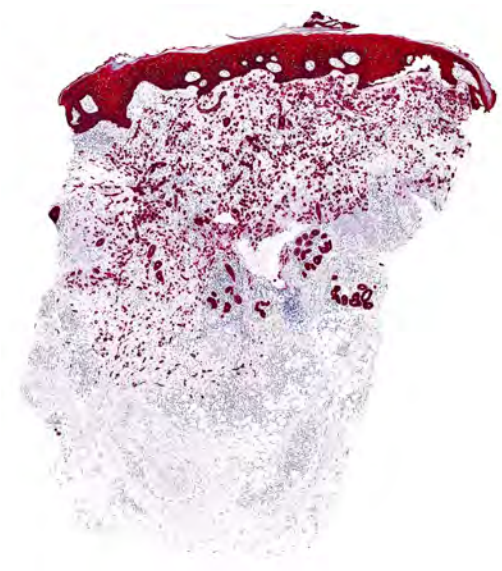
Immunohistochemistry
in most common benign cutaneous tumors

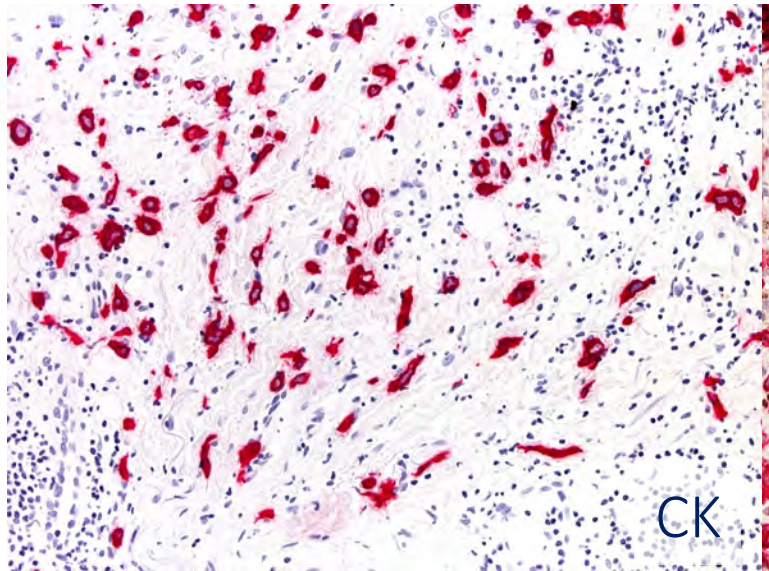
- Seborrheic keratosis: *not needed*
- Cherry hemangioma: *not needed*
- Pyogenic granuloma: *not needed*
- Melanocytic nevi (some cases): *Melan-A, S100, SOX10, PRAME, Ki67, others*
- Achrocordon / Skin tag: *not needed*
- Dermatofibroma (some cases): *CD34, fXIIIa*
- Lipoma: *not needed*
- Viral warts & Condyloma: *not needed*
- Cysts (infundibular, tricholemmal): *not needed*

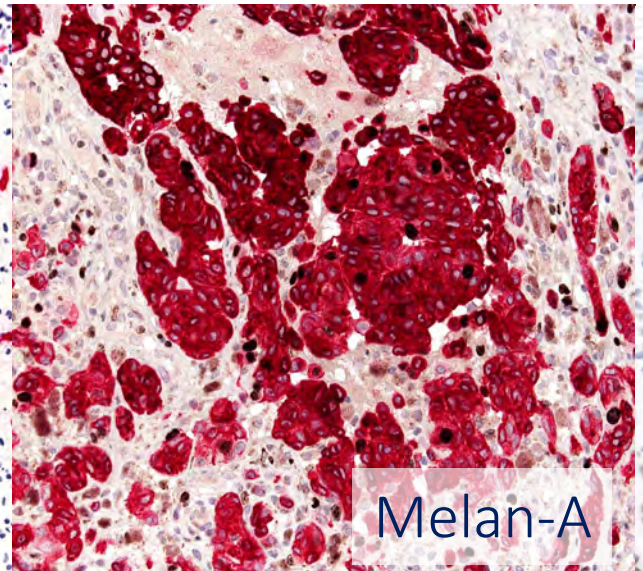


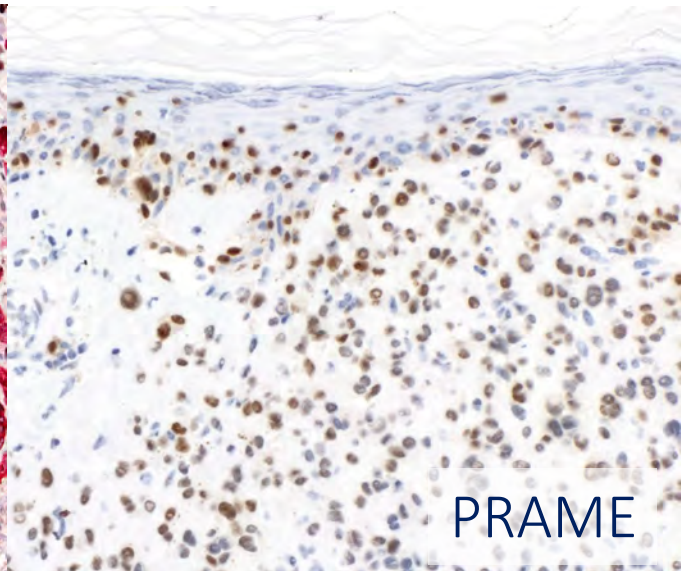
Immunohistochemistry
in most common malignant cutaneous tumors

- Basal cell carcinoma: *in most cases not needed; rarely BerEP4, PHLDA1*
- Actinic keratosis: *not needed*
- Squamous cell carcinoma: *in most cases not needed; rarely CK (various)*
- Melanoma (some cases): *Melan-A, S100, SOX10, PRAME, Ki67, others*





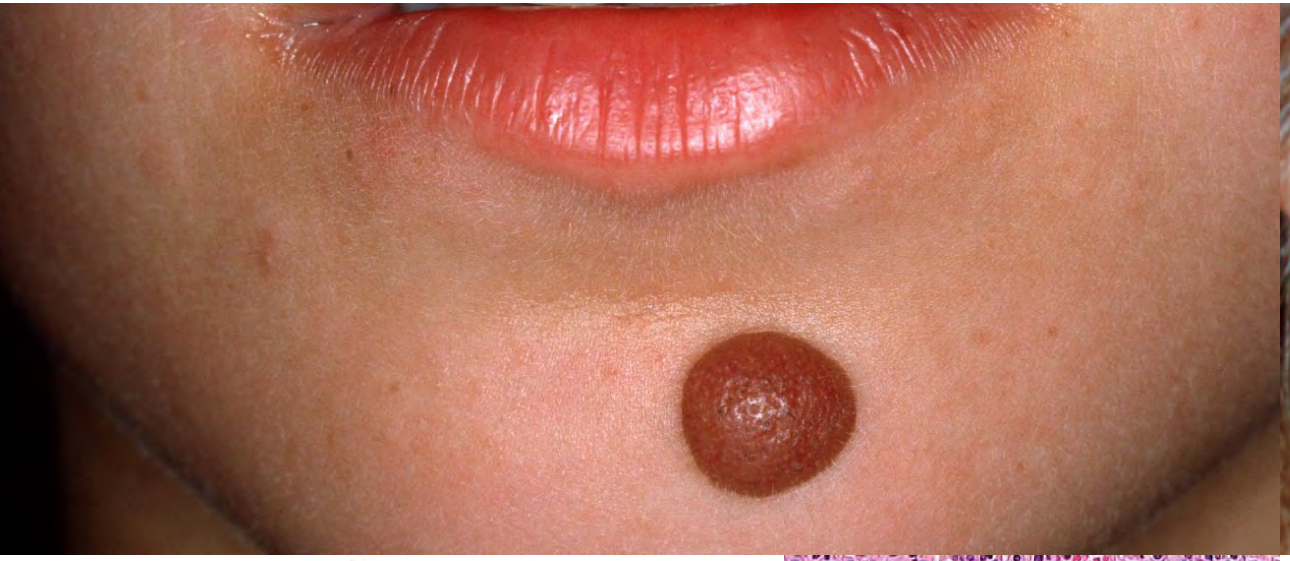


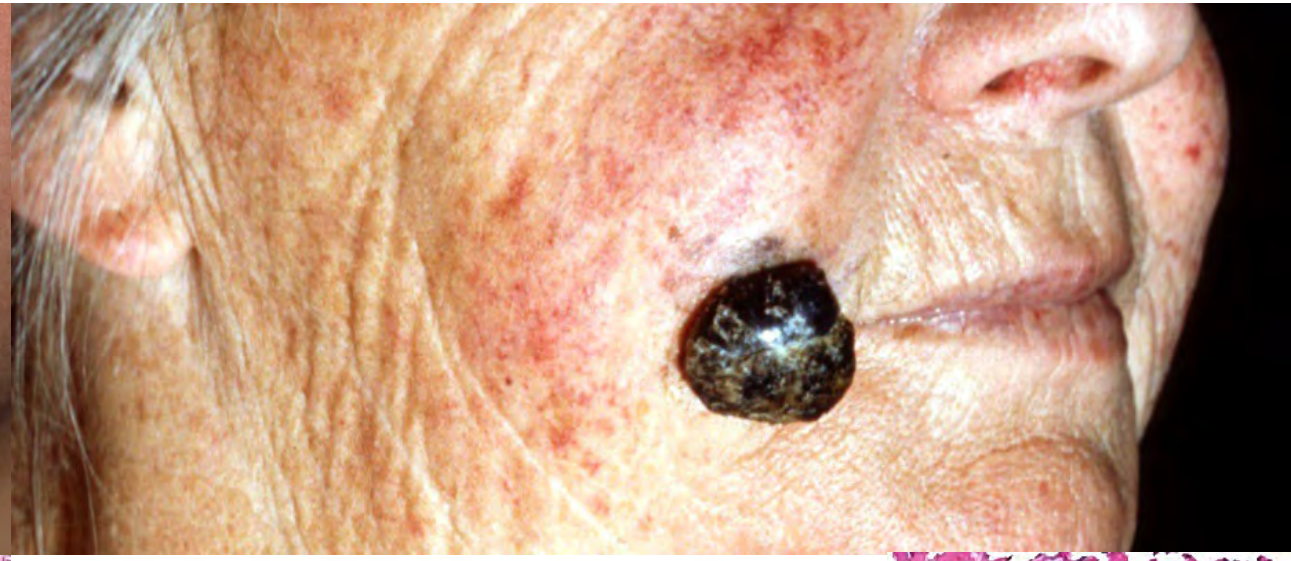


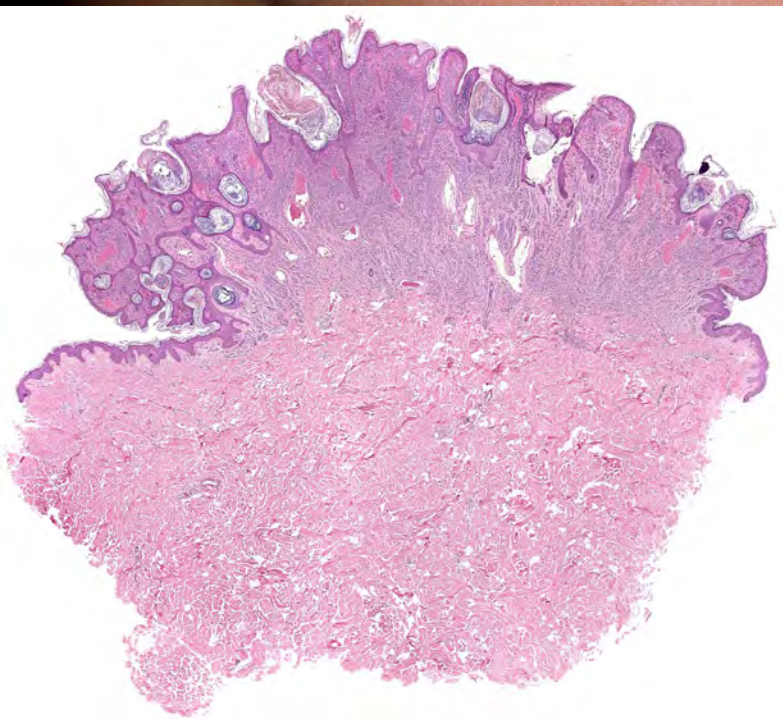
Immunohistochemical panels (selected antibodies)

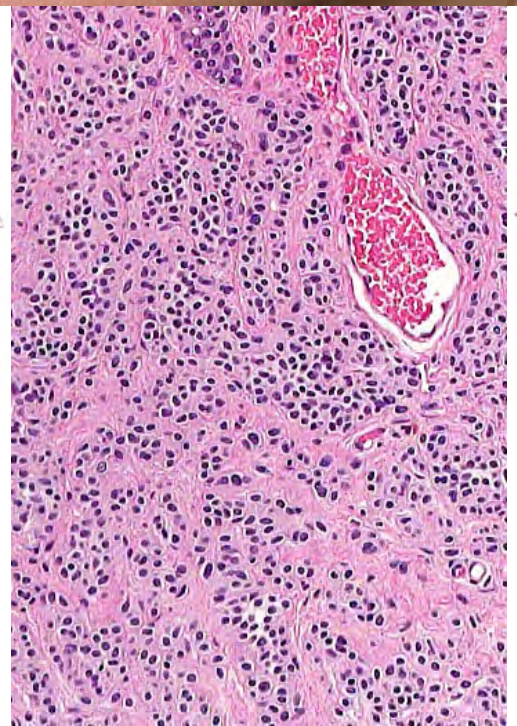
- **Epithelial tumors:** CK (various types), EMA, CEA, Ber-EP4, PHLDA1, p53, p63, ß-catenin
- **Melanocytic tumors:** Melan-A, S100, SOX10, HMB45, tyrosinase, PRAME, Ki-67, others (e.g., ALK, BAP1, BRAF, p16, ß-catenin, etc.)
- **Fibro-histiocytic tumors:** CD34, f.XIIIa
- **Vascular tumors:** ERG, CD31, CD34, D2-40, Ki-67, c-myc, HHV8
- **Neural tumors:** S100, SOX10, EMA, NF
- **Muscular tumors:** SMA, desmin, caldesmon
- **Lipomatous tumors:** S100, CD34, MDM2, CDK4
- **Histiocytic tumors:** CD1a, CD14, CD68, CD123, CD163, CD207, S100, MNDA
- **Mast cell tumors:** CD117, NASDCl, CD4, CD25, CD30
- **Lymphoproliferative lesions:** T-cell (CD3, CD4, CD5, CD8, TCR-ß, TCR-δ) and B-cell markers (CD20, CD79a, PAX5), others (e.g., CD21, CD30, Bcl-6, Bcl-2, MUM1, kappa, lambda, EBER-1)
- **Other tumors:** CK20, MCPyV, chromogranin-A, synaptophysin, CD10, NKIC3, others
- **Cutaneous metastases:** CK7, CK20, TTF1, CDX2, PSA, others

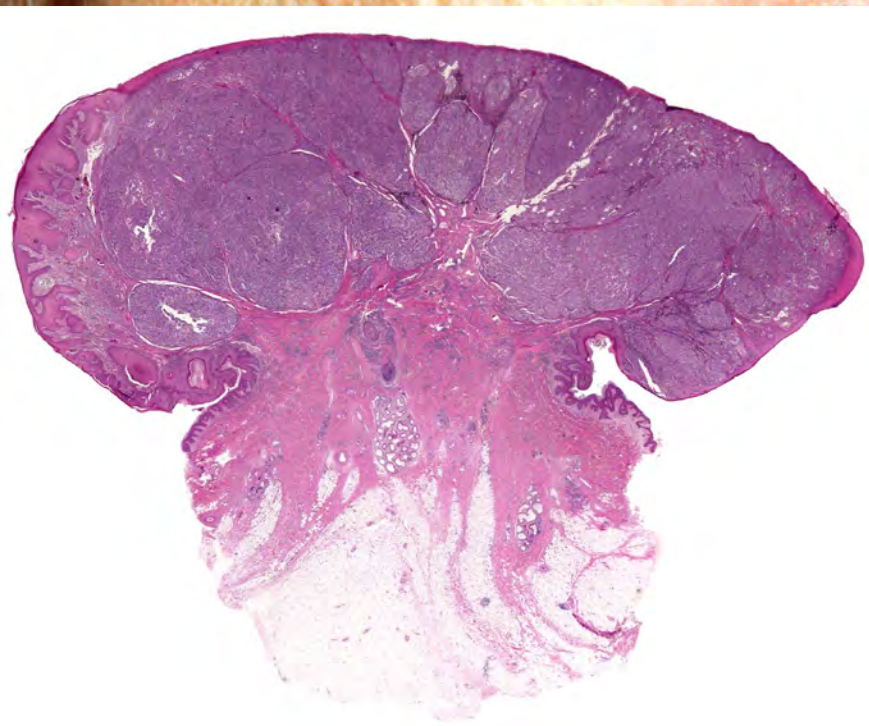
Melanocytic nevi & Melanoma(s)

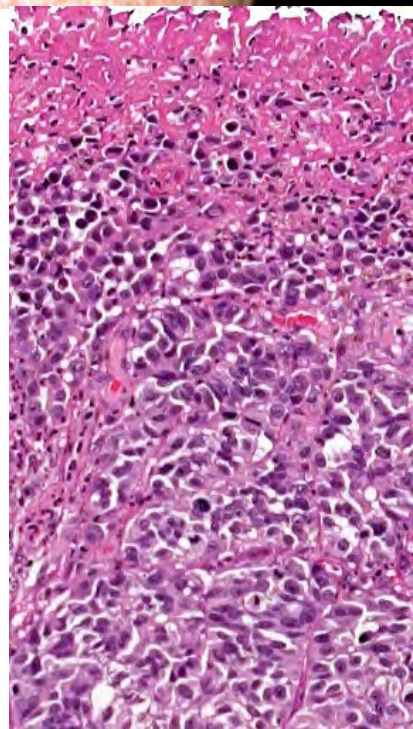












Main variants of melanocytic nevi & melanomas

- "Common" melanocytic nevus (junctional, compound, dermal)
- "Dysplastic" (Atypical / Clark) nevus
- Congenital melanocytic nevus
- Blue nevus & variants
- Spitz nevus & spitzoid tumors
- Acral melanocytic nevus
- Mucosal melanocytic nevus
- "Combined" melanocytic nevus
- Halo nevus
- Recurrent (persistent) nevus

- Lentigo maligna melanoma
- Superficial spreading melanoma
- Nodular melanoma
- Acral melanoma
- Mucosal melanoma
- Desmoplastic melanoma
- Melanoma arising in a nevus

The field of melanocytic tumors represents possibly the most problematic area in dermatopathology, comprising the largest number of variants, subvariants and problematic lesions; diagnosis, yet, is straightforward in >90% of cases.

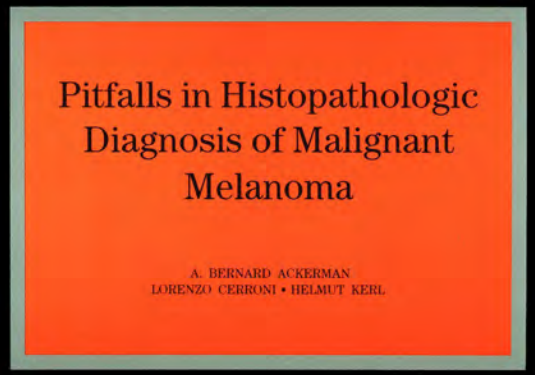


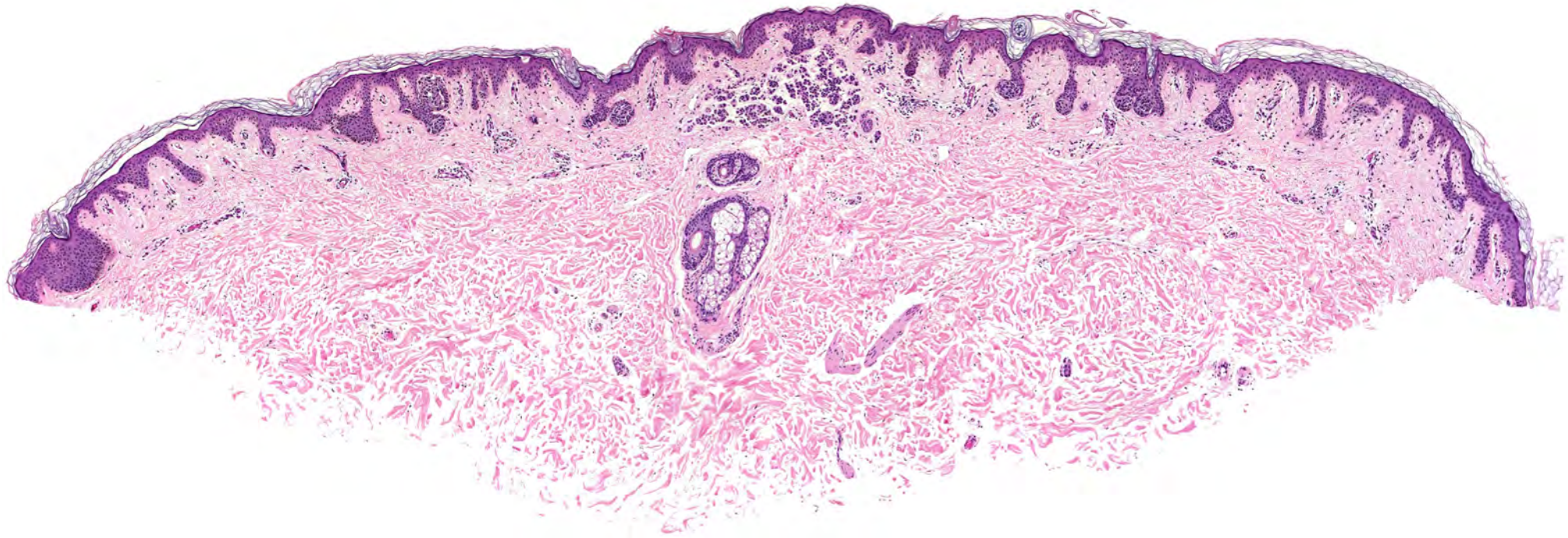
TABLE 4. Criteria for Histopathologic Diagnosis of Malignant Melanoma

Architectural pattern

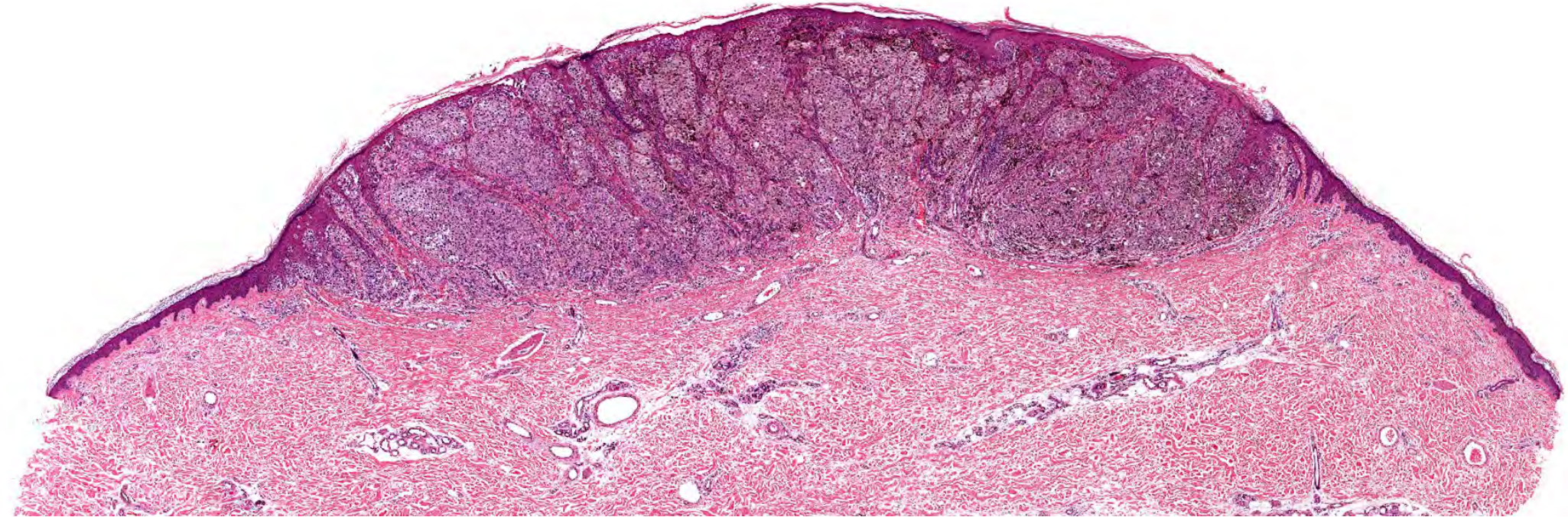
1. Asymmetric
2. Poorly circumscribed
3. No maturation of melanocytes with progressive descent into the dermis
4. Nests of melanocytes within the epidermis are not equidistant from one another
5. Nests of melanocytes vary markedly in sizes and shapes
6. Some nests of melanocytes become confluent
7. Melanocytes in some "nests" are not cohesive
8. Scatter of melanocytes above the dermo-epidermal junction
9. Melanocytes arranged as solitary units predominate over nests of melanocytes in some high-power fields
10. Melanocytes arranged as solitary units are not equidistant from one another
11. Melanocytes extend far down epithelial structures of adnexa in the same pattern as they are arrayed within the epidermis
12. Melanin is not distributed symmetrically within the epidermis, adnexa, and dermis

Cytologic features

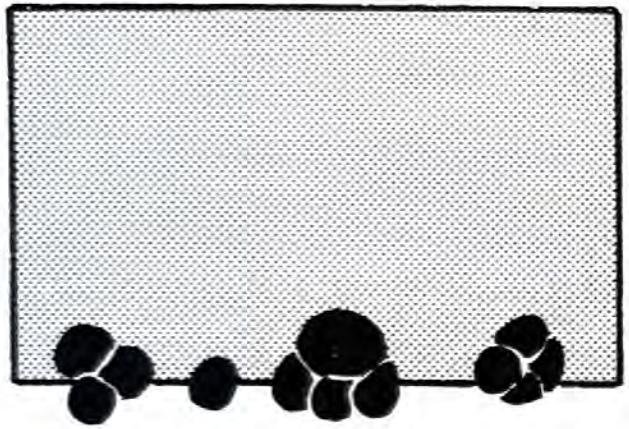
1. Melanocytes may be atypical
2. Melanocytes in mitosis
3. Melanocytes may be necrotic



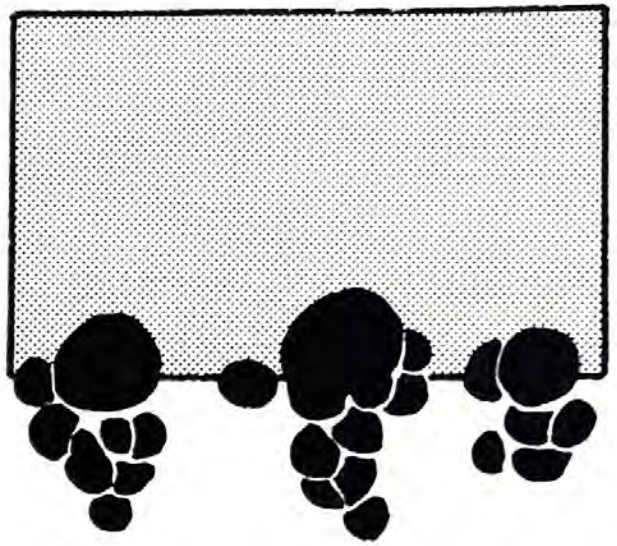
symmetrical
uniform nests
no pagetoid scatter
dermal maturation
no atypia



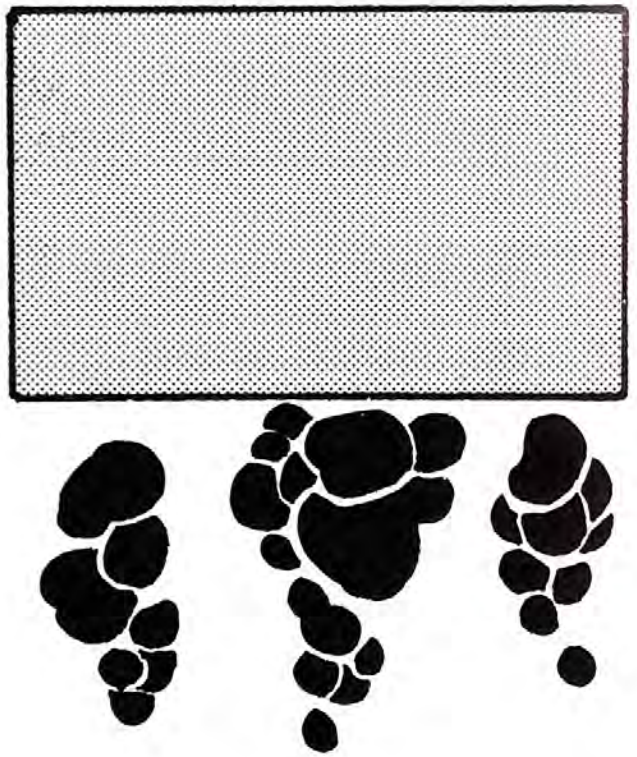
asymmetrical
variable nests
focal pagetoid scatter
no dermal maturation
atypical melanocytes



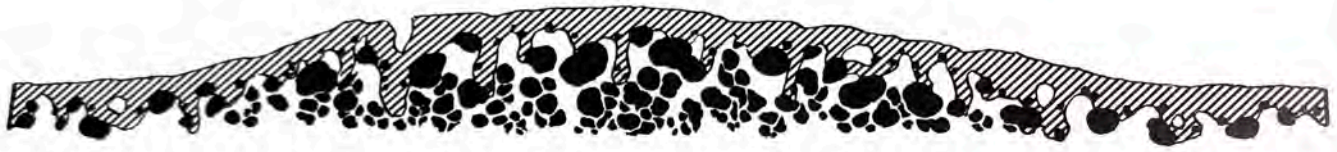
Junctional nevus



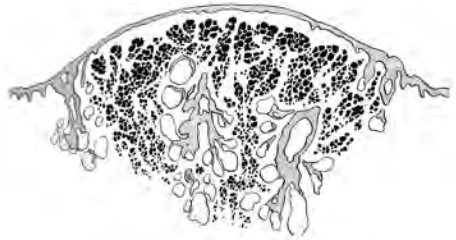
Compound nevus



Dermal nevus

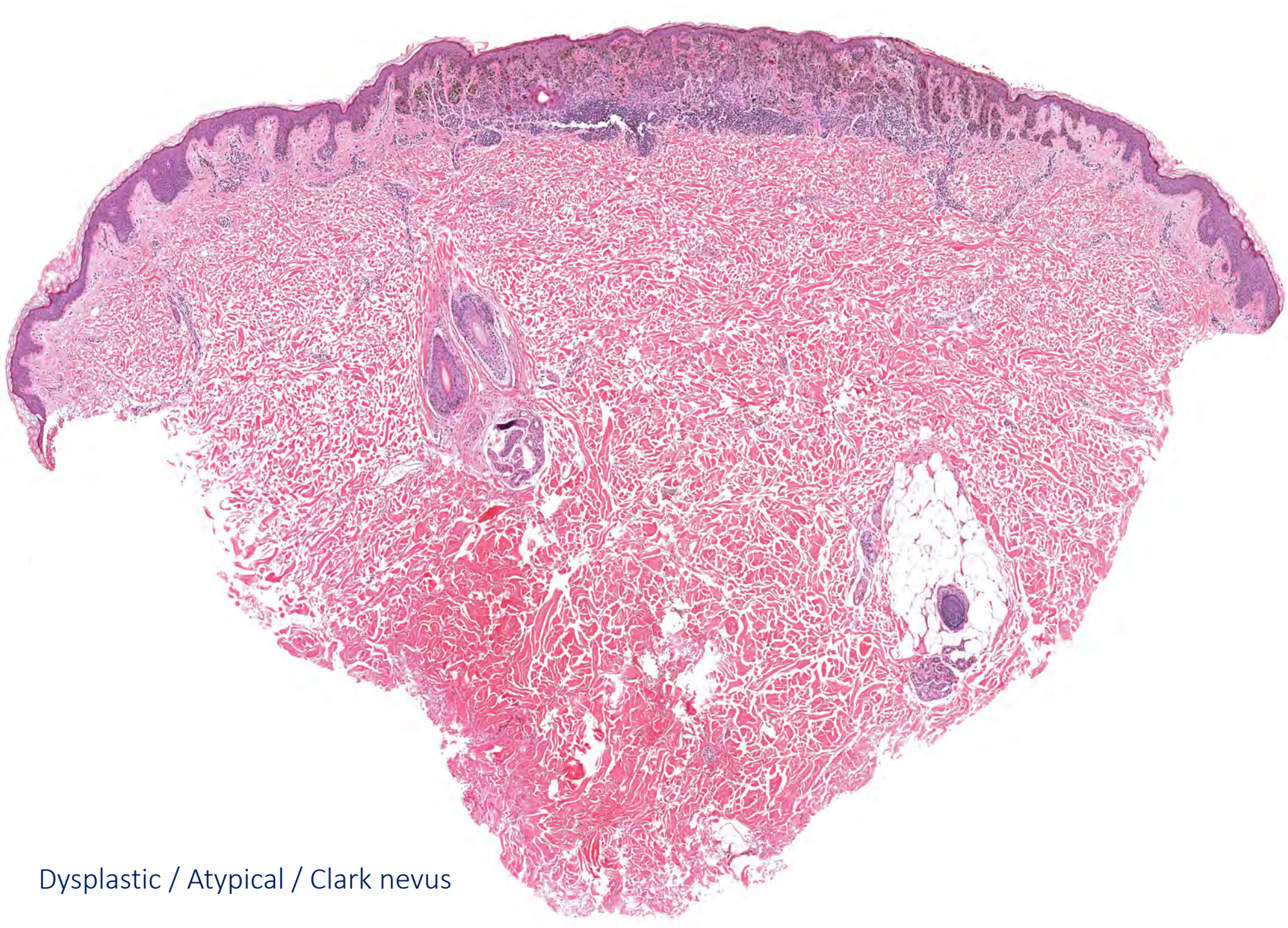


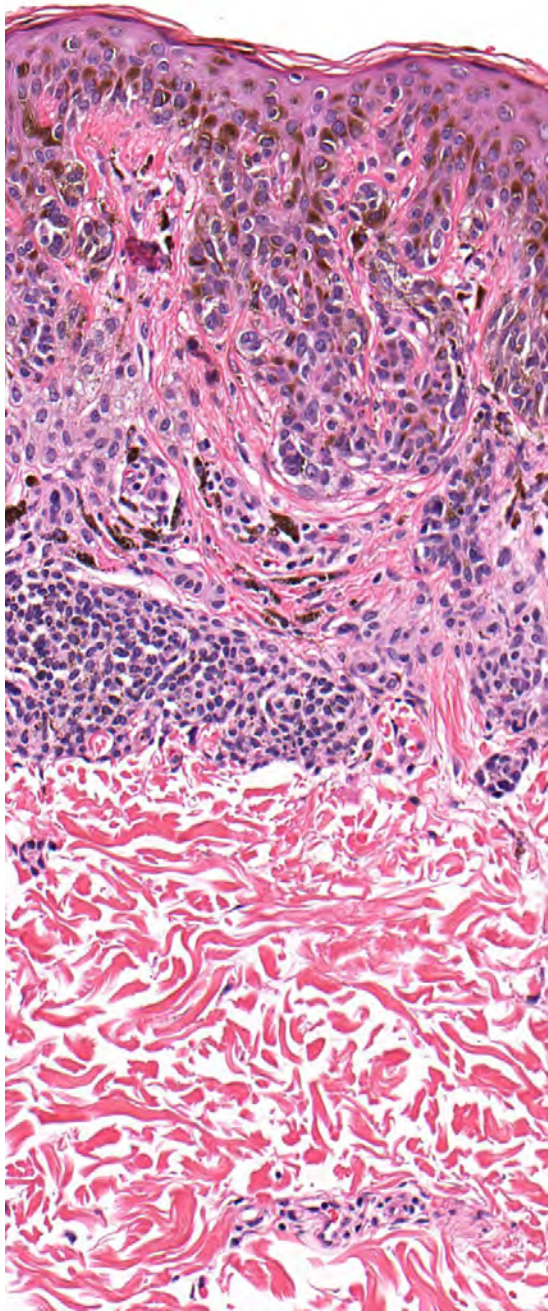
Dysplastic / Atypical / Clark nevus



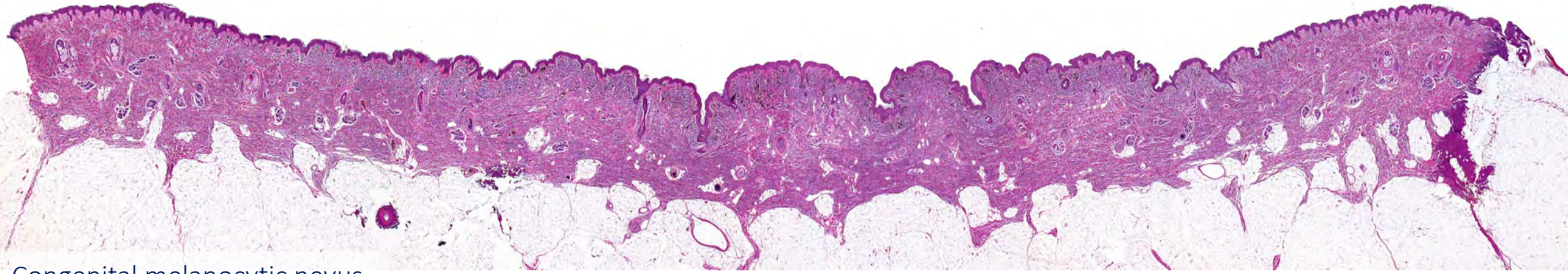
Dermal nevus, head & neck (Mischer nevus)

Dermal nevus, trunk & extremities (Unna nevus)

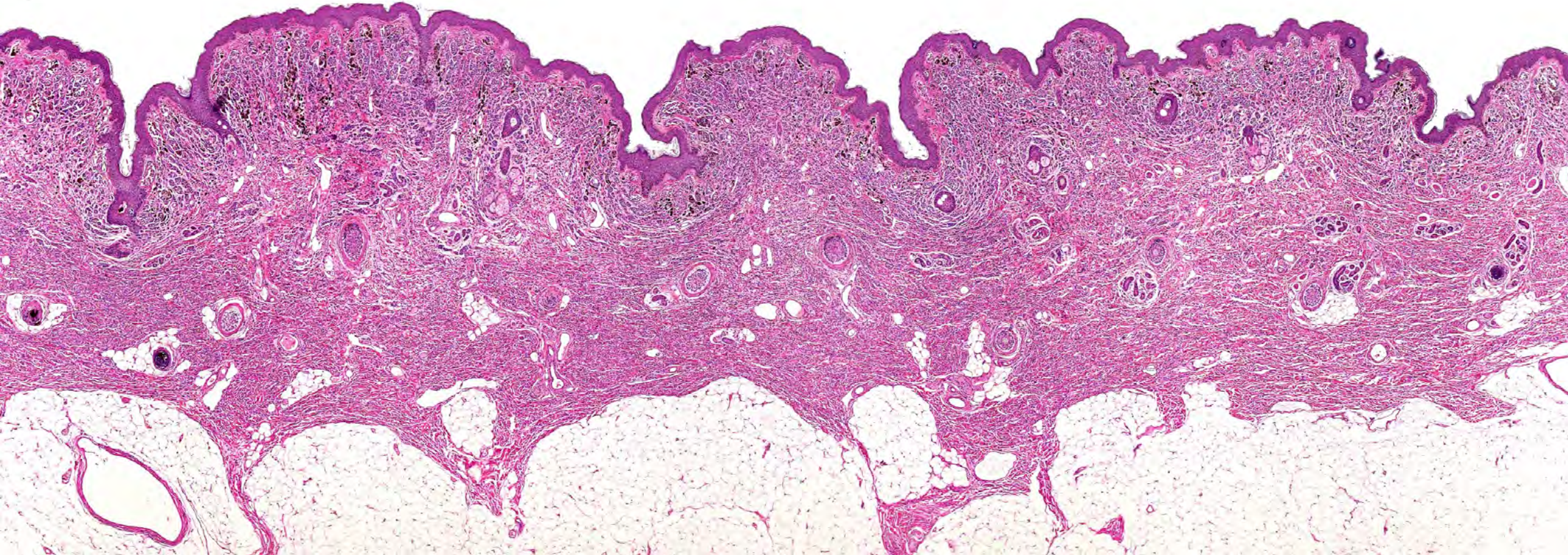




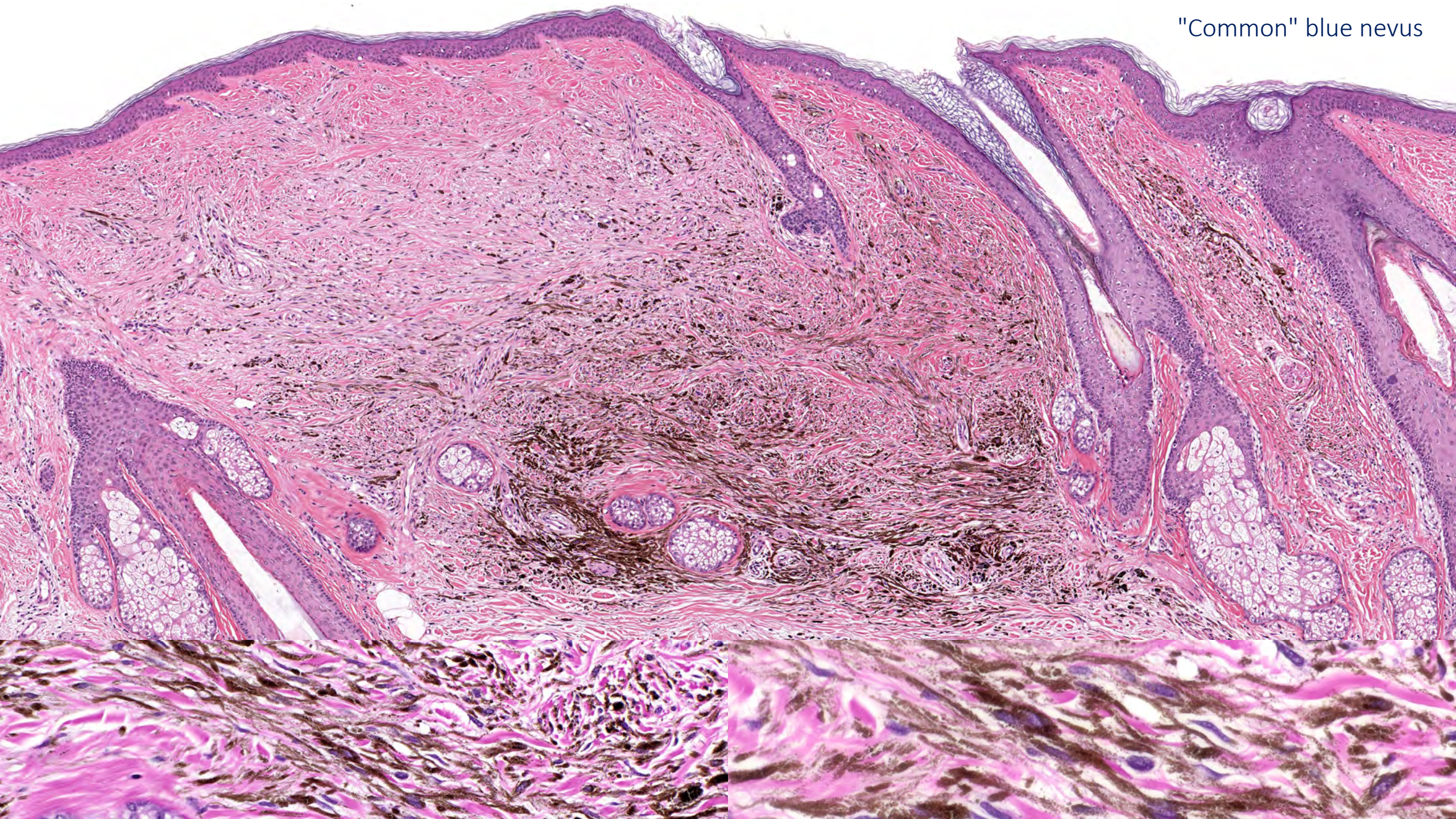
Dysplastic / Atypical / Clark nevus

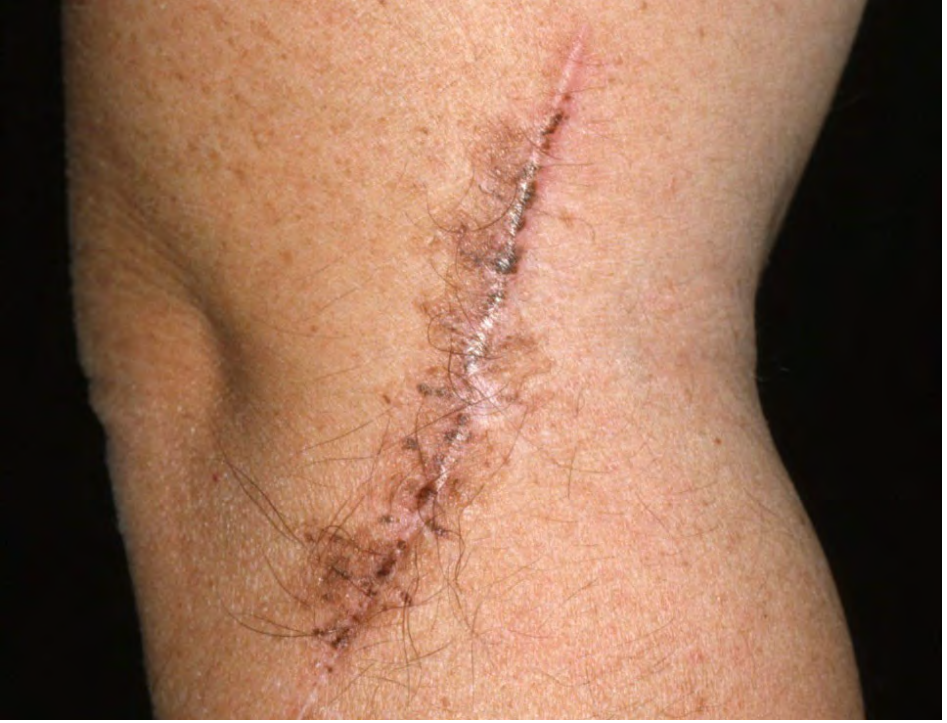


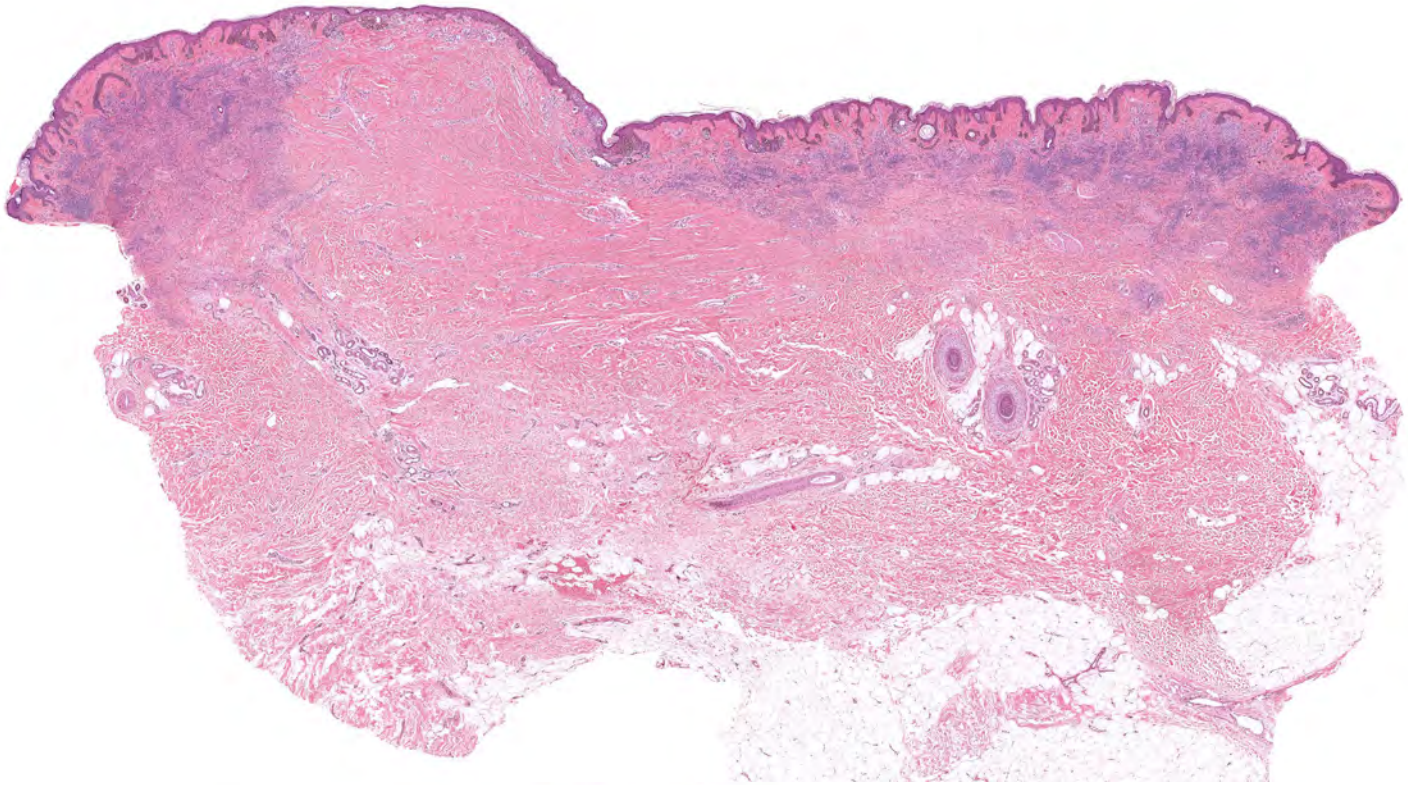
Congenital melanocytic nevus



"Common" blue nevus

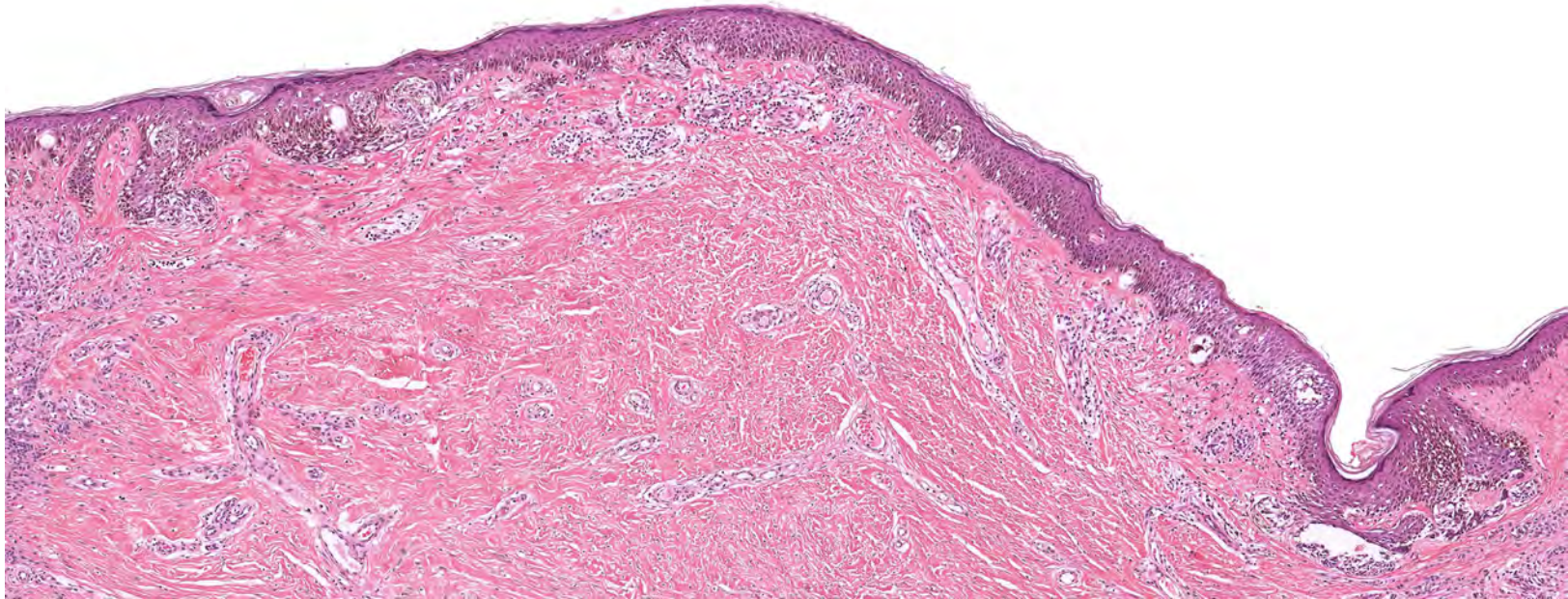


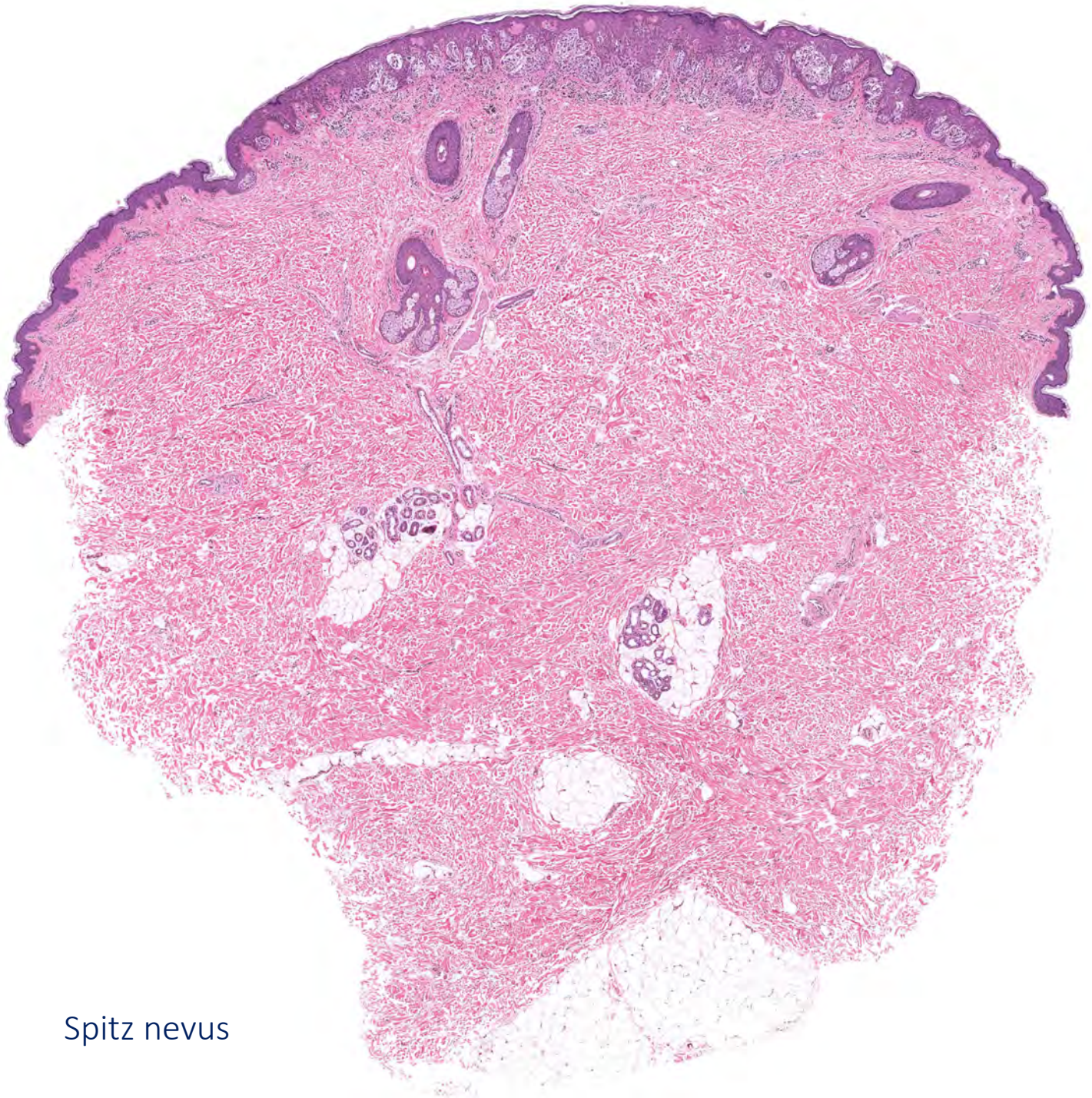


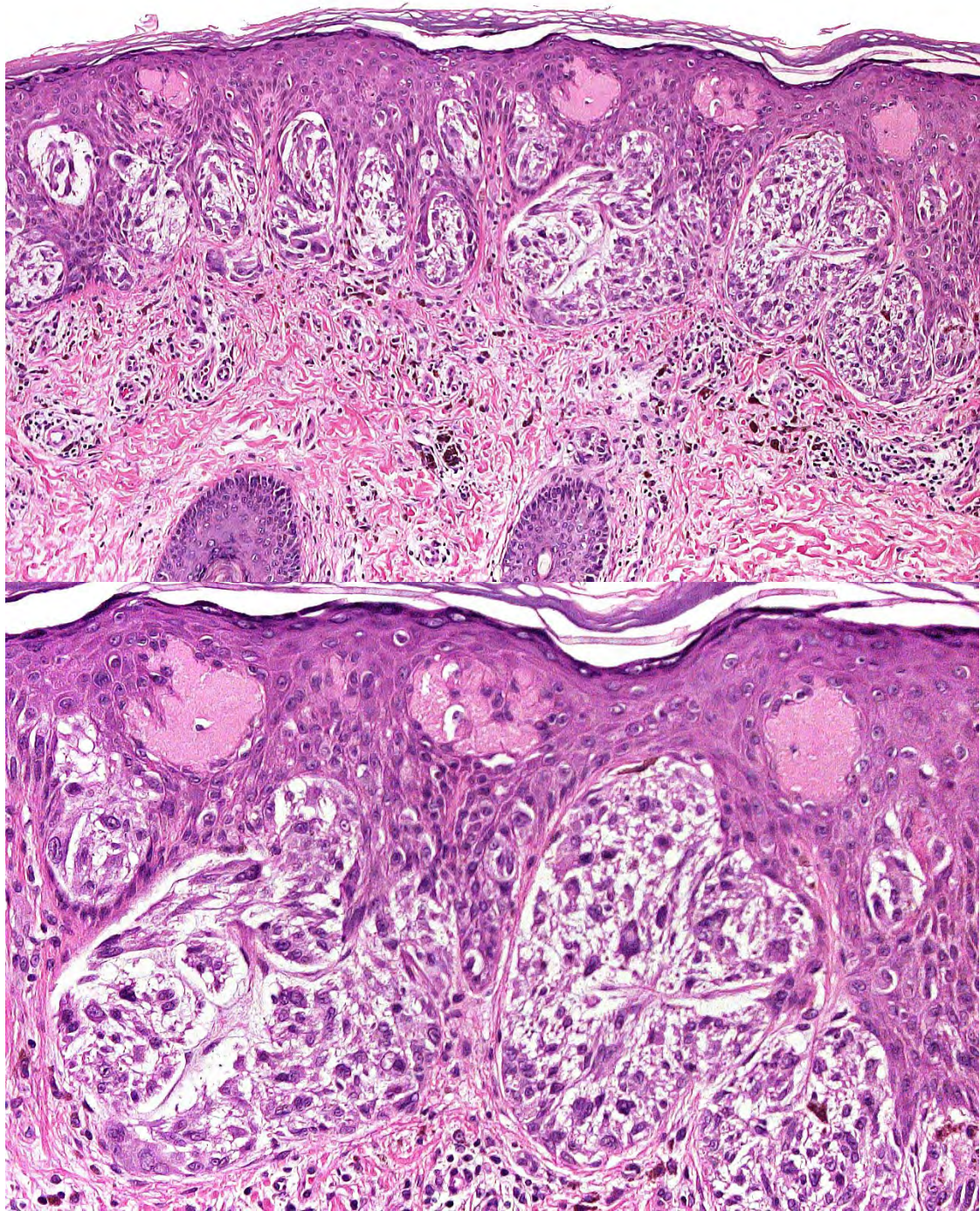


Recurrent (persistent) nevus

- Atypical distribution of melanocytes within the epidermis (melanoma-like) over the scar of a melanocytic nevus that has been incompletely excised
- The atypical features are restricted to the portion of the epidermis over the scar
- Onset usually <12 months from the primary excision (a lesion recurring after more than 12 months is suspicious for persistent melanoma rather than nevus)

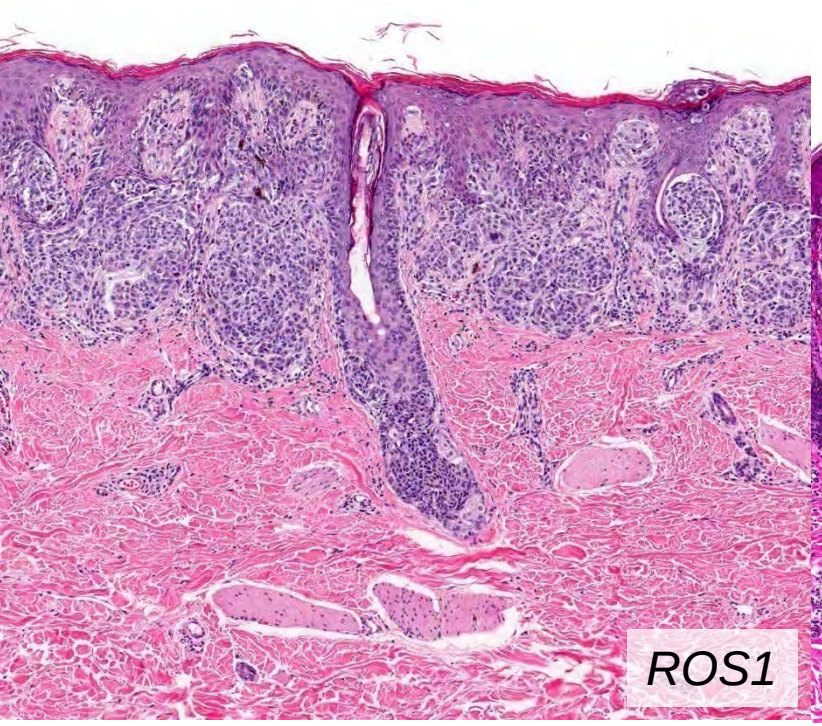


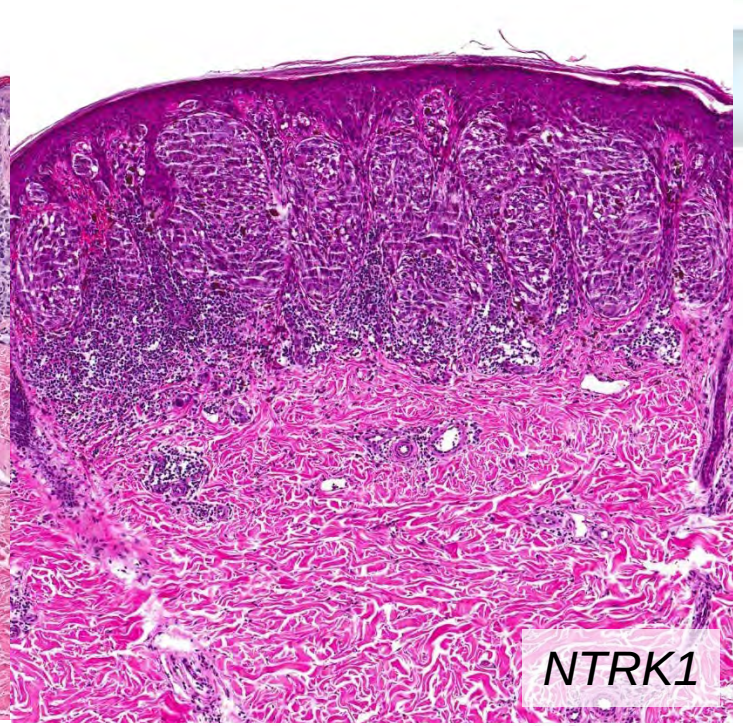


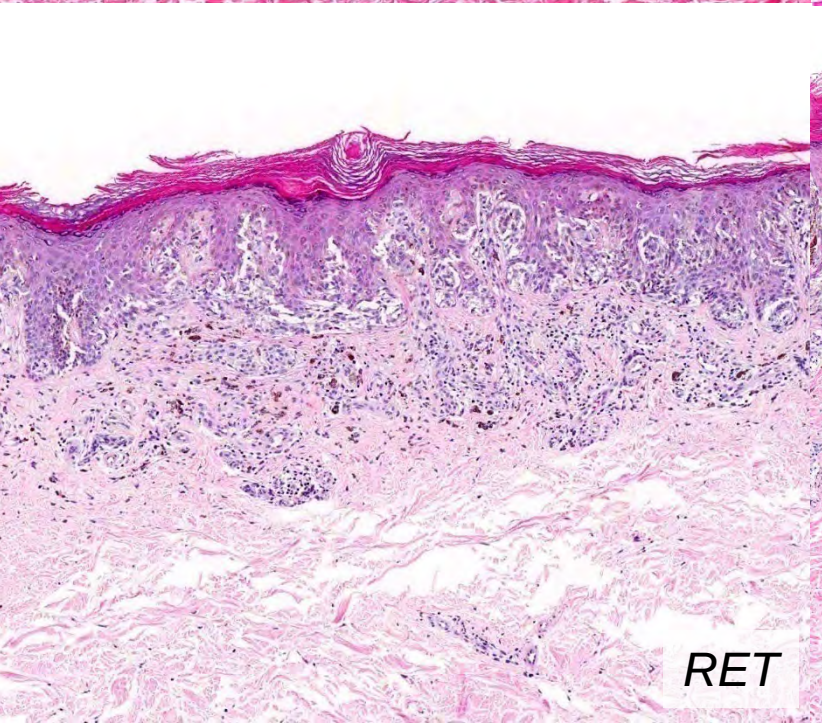


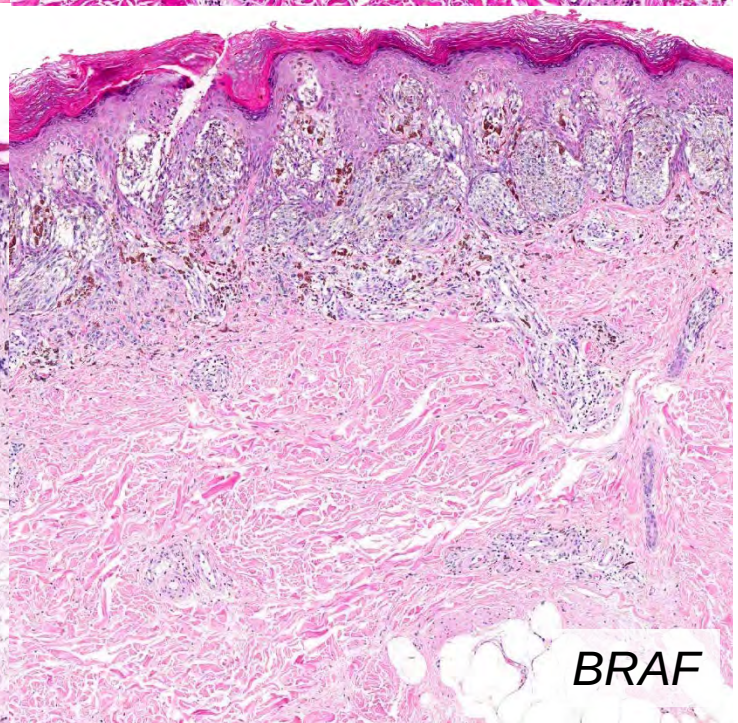
Spitz nevus

The exploding galaxy of "Spitz nevus"









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Kinase fusions are frequent in Spitz tumours and spitzoid melanomas

Thomas Wiesner[1,2,*], Jie He[3,*], Roman Yelensky[3,*], Rosaura Esteve-Puig[4], Thomas Botton[4], Iwei Yeh[4], Doron Lipson[3], Geoff Otto[3], Kristina Brennan[3], Rajmohan Murali[5,6], Maria Garrido[4], Vincent A. Miller[3], Jeffrey S. Ross[3], Michael F. Berger[1], Alyssa Sparatta[4], Gabriele Palmedo[7], Lorenzo Cerroni[2], Klaus J. Busam[5], Heinz Kutzner[7], Maureen T. Cronin[3], Philip J. Stephens[3] & Boris C. Bastian[1,4,5]

Spitzoid neoplasms are a group of melanocytic tumours with distinctive histopathological features. They include benign tumours (Spitz naevi), malignant tumours (spitzoid melanomas) and tumours with borderline histopathological features and uncertain clinical outcome (atypical Spitz tumours). Their genetic underpinnings are poorly understood, and alterations in common melanoma-associated oncogenes are typically absent. Here we show that spitzoid neoplasms harbour kinase fusions of *ROS1* (17%), *NTRK1* (16%), *ALK* (10%), *BRAF* (5%) and *RET* (3%) in a mutually exclusive pattern. The chimeric proteins are constitutively active, stimulate oncogenic signalling pathways, are tumourigenic and are found in the entire biologic spectrum of spitzoid neoplasms, including 55% of Spitz naevi, 56% of atypical Spitz tumours and 39% of spitzoid melanomas. Kinase inhibitors suppress the oncogenic signalling of the fusion proteins *in vitro*. In summary, kinase fusions account for the majority of oncogenic aberrations in spitzoid neoplasms and may serve as therapeutic targets for metastatic spitzoid melanomas.

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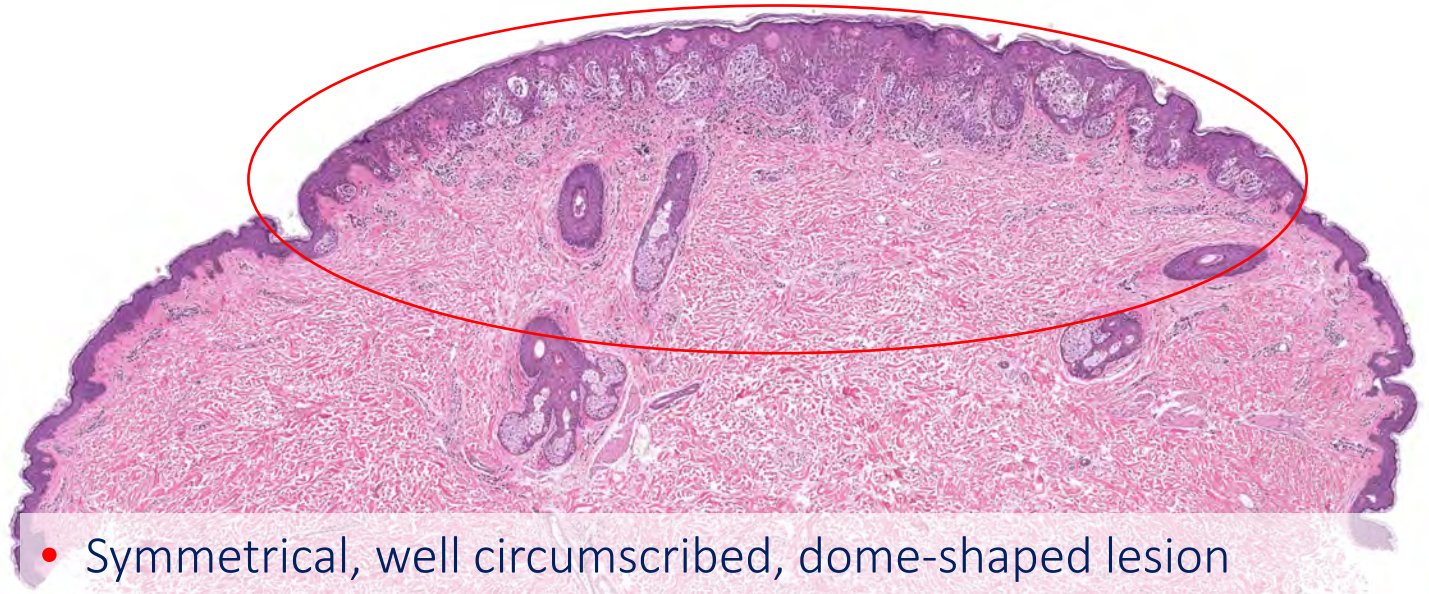
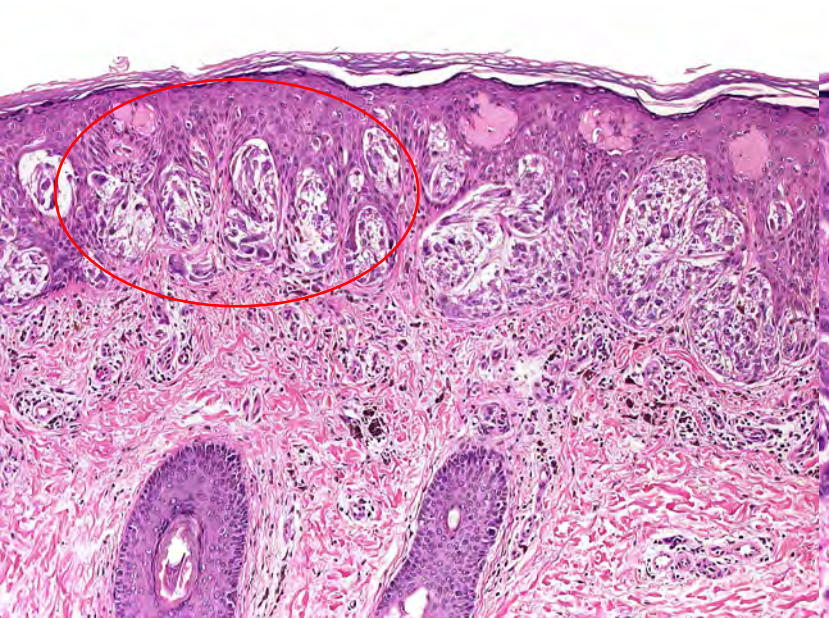
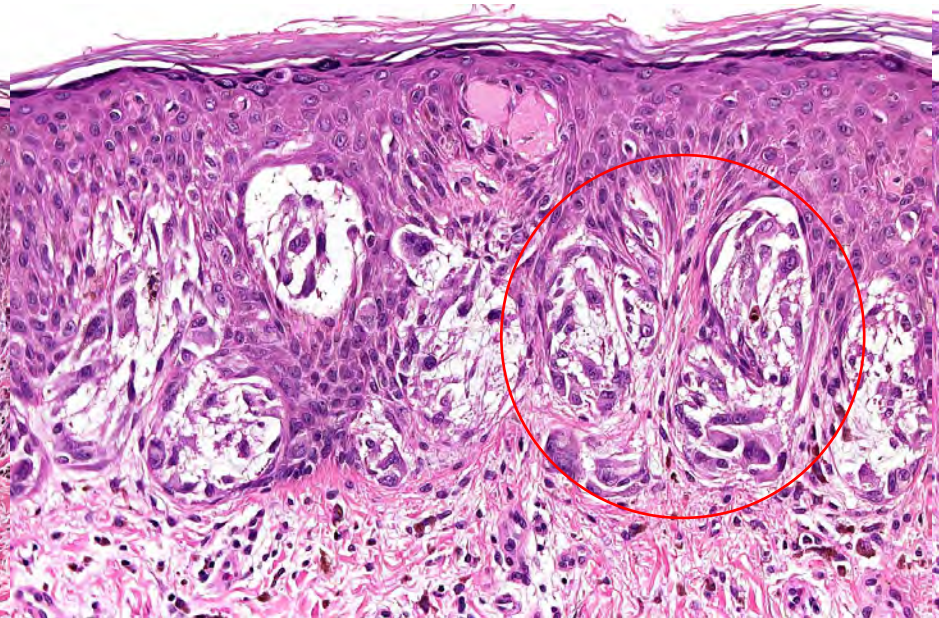
Does a "Spitz nevus" exist?

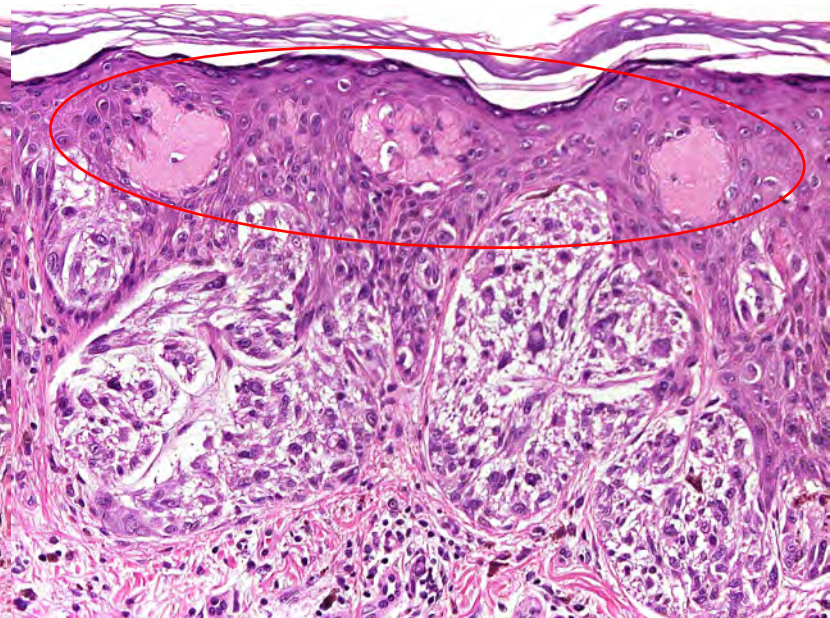
- Sophie Spitz did not describe a nevus
- "Spitzoid" melanocytes *(large epithelioid cells with abundant eosinophilic or amphophilic cytoplasm and large vesicular nuclei that contain prominent nucleoli)* are not restricted to "Spitz nevi"
- Molecular studies revealed many different genetic alterations related to benign and malignant "spitzoid tumors"
- Diagnosis of "Spitz nevus" should be restricted to (rare) prototypic examples of that melanocytic tumor



- Symmetrical, well circumscribed, dome-shaped lesion
- Vertical nests; sometimes focal "perforation" of the epidermis
- Spindle and epithelioid cells
- "Kamino bodies"







nature genetics

Germline mutations in *BAP1* predispose to melanocytic tumors

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Common acquired melanocytic nevi are benign neoplasms that are composed of small, uniform melanocytes and are typically present as flat or slightly elevated pigmented lesions on the skin. We describe two families with a new autosomal dominant syndrome characterized by multiple, skin-colored, elevated melanocytic tumors. In contrast to common acquired nevi, the melanocytic neoplasms in affected family members ranged histopathologically from epithelioid nevi to atypical melanocytic proliferations that showed overlapping features with melanoma. Some affected individuals developed uveal or cutaneous melanomas. Segregating with this phenotype, we found inactivating germline mutations of *BAP1*, which encodes a ubiquitin carboxy-terminal hydrolase. The majority of melanocytic neoplasms lost the remaining wild-type allele of *BAP1* by various somatic alterations. In addition, we found *BAP1* mutations in a subset of sporadic melanocytic neoplasms showing histological similarities to the familial tumors. These findings suggest that loss of *BAP1* is associated with a clinically and morphologically distinct type of melanocytic neoplasm.

We report a type of melanocytic neoplasm that was inherited in an autosomal dominant pattern in two unrelated families and that was clinically, histopathologically and genetically distinct from common acquired nevi (**Fig. 1a**). Beginning in the second decade of life, affected family members progressively developed skin-colored to reddish-brown, dome-shaped to pedunculated, well-circumscribed papules with an average size of 5 mm (**Fig. 1b** and **Supplementary Figs. 1–4**). The number of tumors per individual varied markedly, ranging from 5 to over 50. No intellectual disabilities or dysmorphic features were identified in affected individuals.

Histopathological examination identified primarily dermal tumors composed entirely or predominantly of epithelioid melanocytes with abundant amphophilic cytoplasm and prominent nucleoli. The melanocytes often contained large, vesicular nuclei that varied substantially in size and shape (**Fig. 1c** and **Supplementary Figs. 5–7**). The cytological features of some of the cells were reminiscent of Spitz nevi; however, characteristic features (such as epidermal hyperplasia, hypergranulosis, Kamino bodies, clefting around junctional melanocytic nests and spindle-shaped melanocytes) frequently seen in Spitz nevi were consistently absent. In addition, 37 of 42 (88%) tumors in the families showed mutations in the *BRAF* proto-oncogene, which are typically absent in Spitz nevi[1].

Some of the neoplasms showed one or more atypical features such as high cellularity, considerable nuclear pleomorphism and several chromosomal aberrations. These tumors were classified as 'neoplasms of uncertain malignant potential', and the affected individuals were managed as if they had melanoma (**Supplementary Fig. 8**). Both families were identified because of the occurrence of multiple epithelioid melanocytic tumors, but, in each family, one affected individual had uveal melanoma, and three members of family 2 had been diagnosed with cutaneous melanoma (**Fig. 1a** and **Supplementary Table 1**).

We analyzed 22 melanocytic neoplasms from three affected individuals (II-1, II-4 and II-7) in family 1 by array-based comparative genomic hybridization (aCGH). We found losses affecting the entire chromosome 3 or portions of the short arm of chromosome 3 in 50% of tumors. The smallest overlap of the deleted regions encompassed 5.8 Mb, extending from position 47,976,758 to 53,848,761 (hg 18 assembly) and encoded at least 150 known genes (**Fig. 2a**).

The frequent loss of the 3p21 region suggested a second hit[2] resulting in the elimination of the remaining wild-type allele of a mutated tumor suppressor gene in this region. To support this hypothesis,

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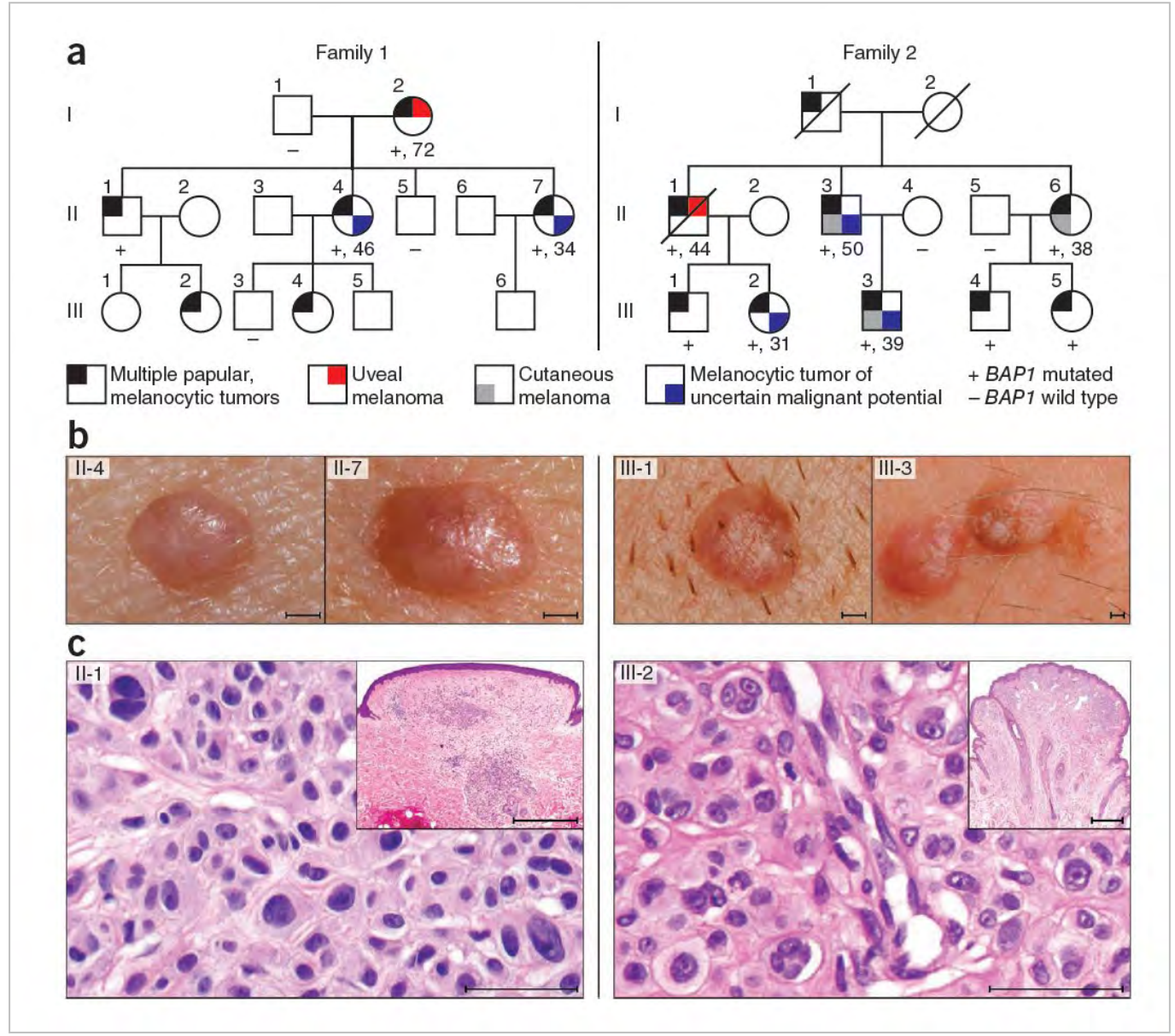
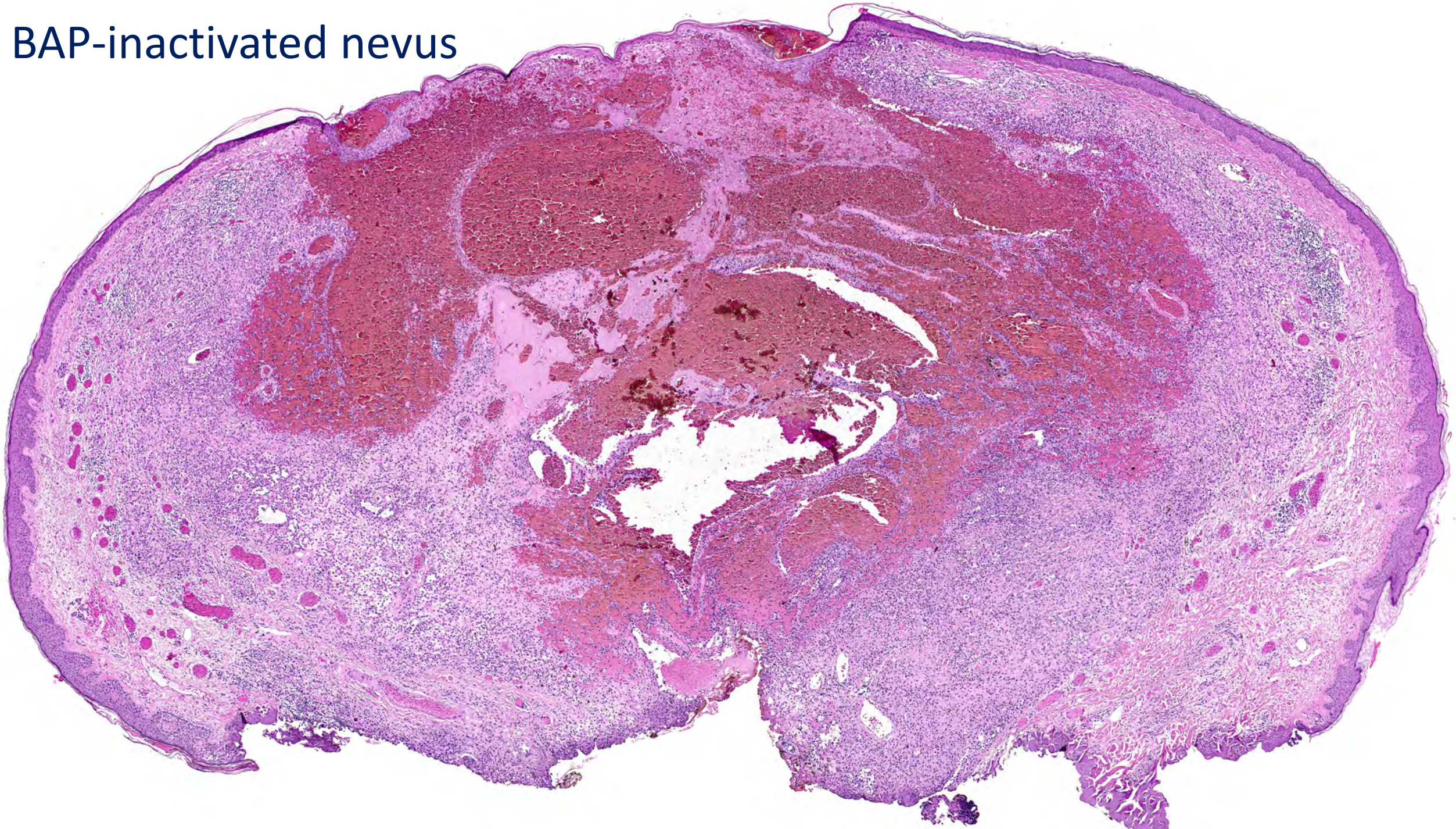
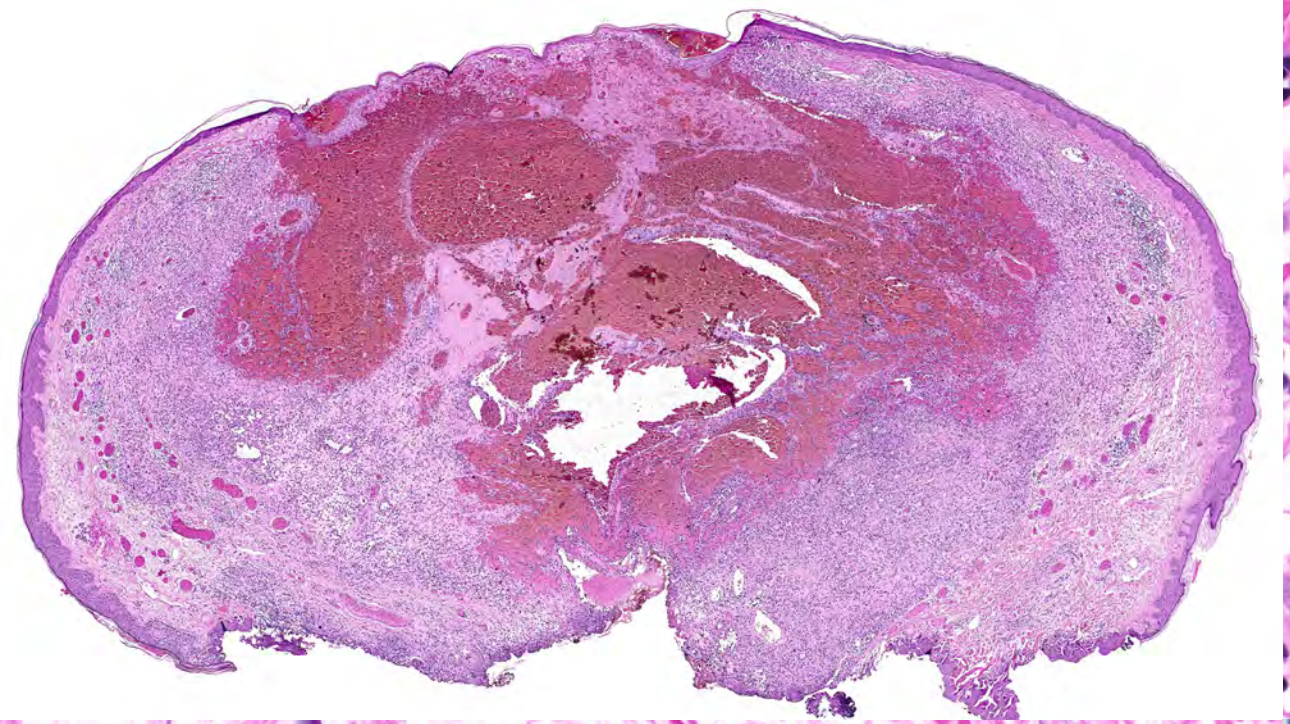
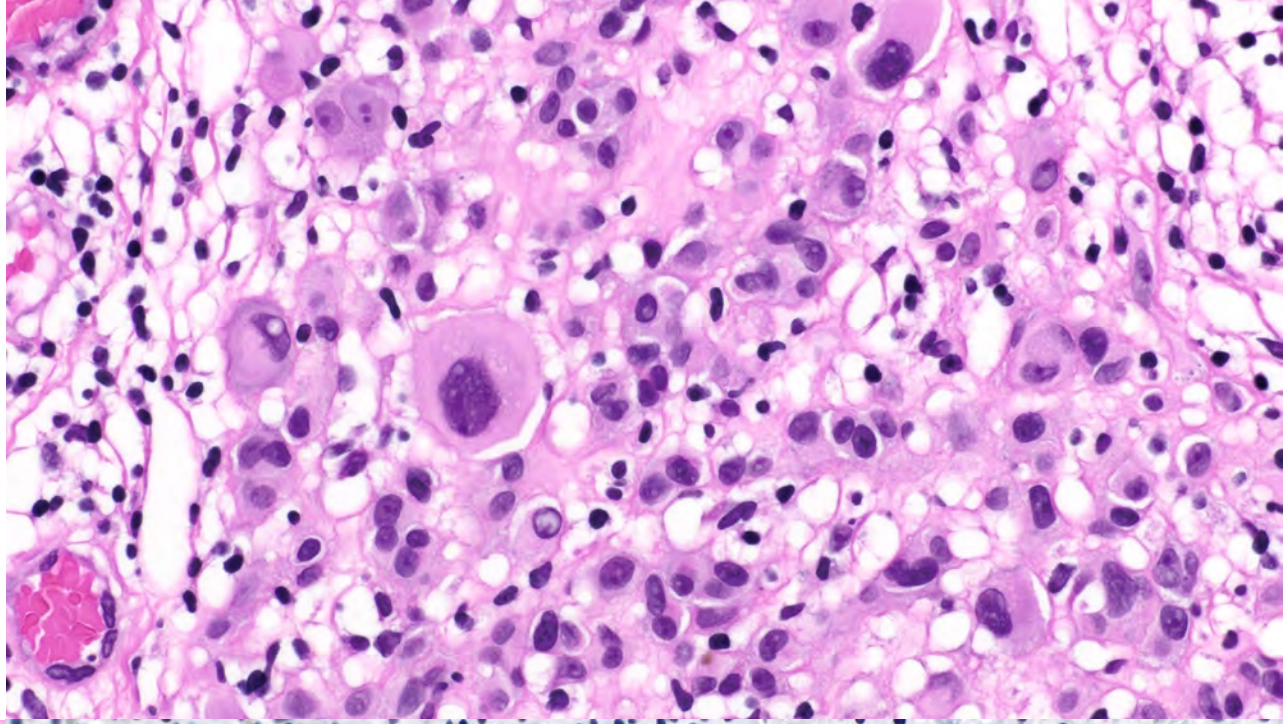
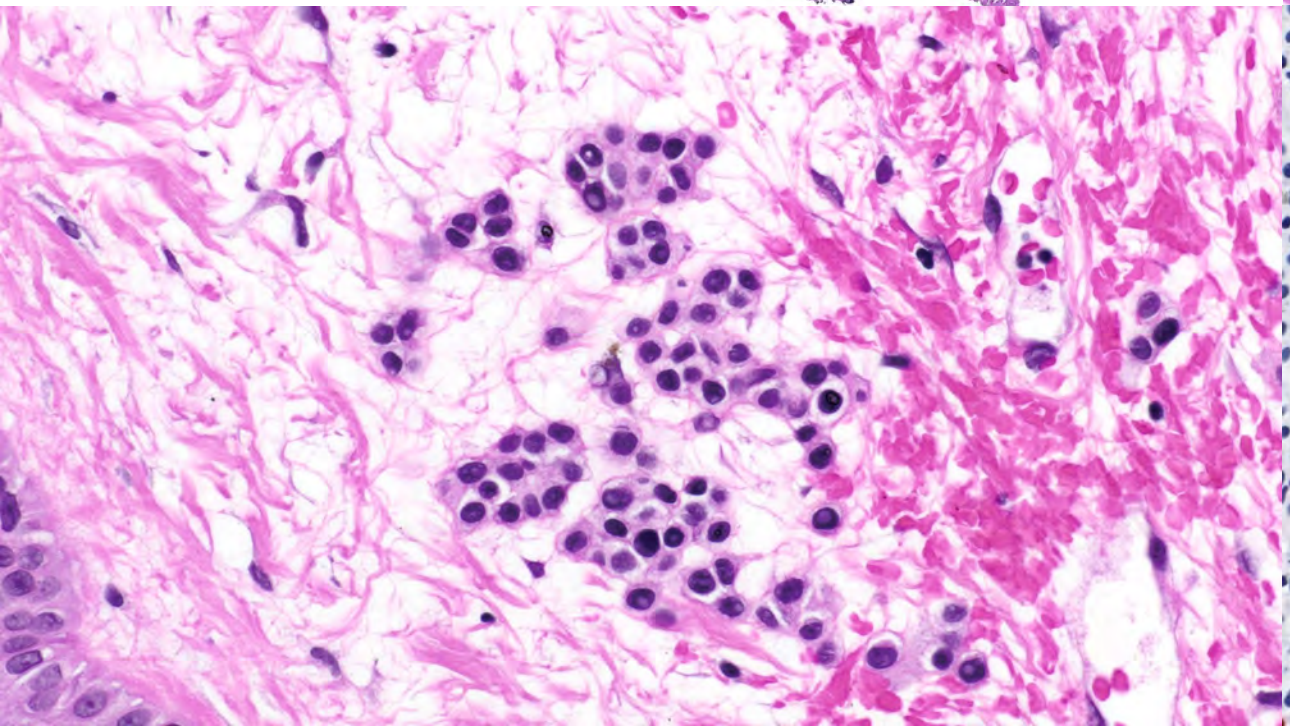


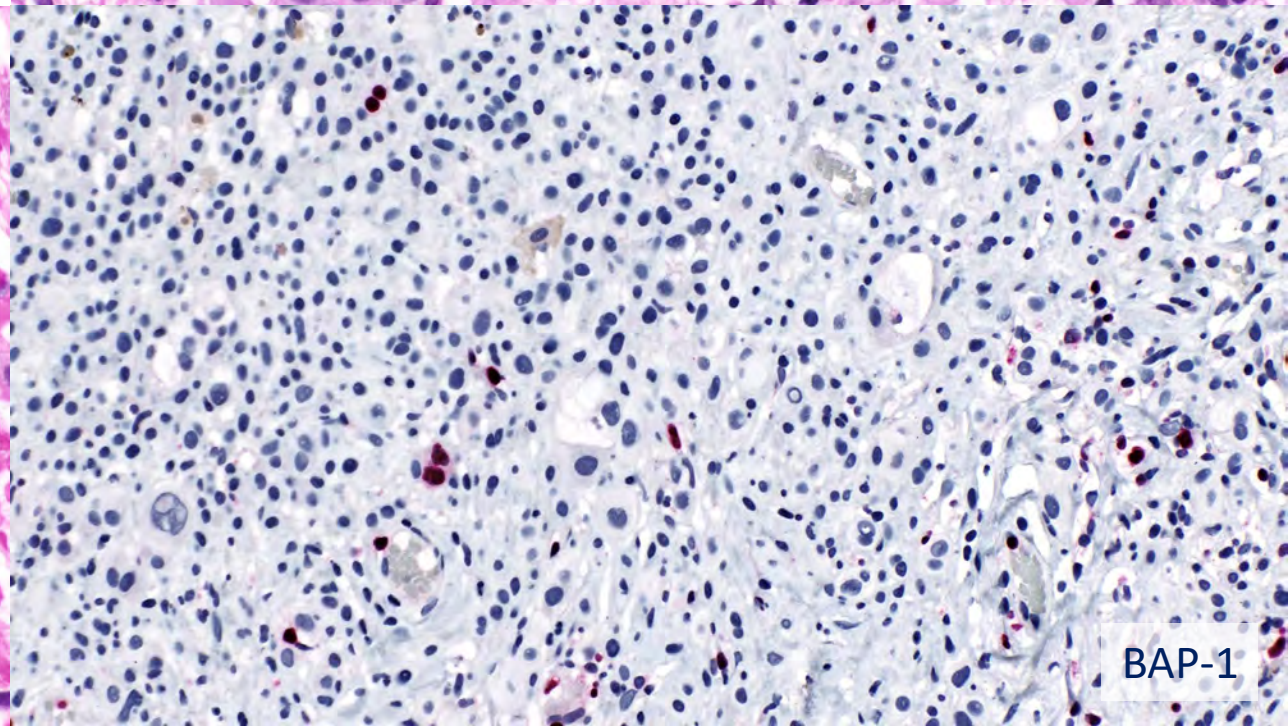
BAP-inactivated nevus










BAP-1

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Kinase fusions are frequent in Spitz tumours and spitzoid melanomas

Thomas Wiesner[1,2,*], Jie He[3,*], Roman Yelensky[3,*], Rosaura Esteve-Puig[4], Thomas Botton[4], Iwei Yeh[4], Doron Lipson[3], Geoff Otto[3], Kristina Brennan[3], Rajmohan Murali[5,6], Maria Garrido[4], Vincent A. Miller[3], Jeffrey S. Ross[3], Michael F. Berger[1], Alyssa Sparatta[4], Gabriele Palmedo[7], Lorenzo Cerroni[2], Klaus J. Busam[5], Heinz Kutzner[7], Maureen T. Cronin[3], Philip J. Stephens[3] & Boris C. Bastian[1,4,5]

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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)

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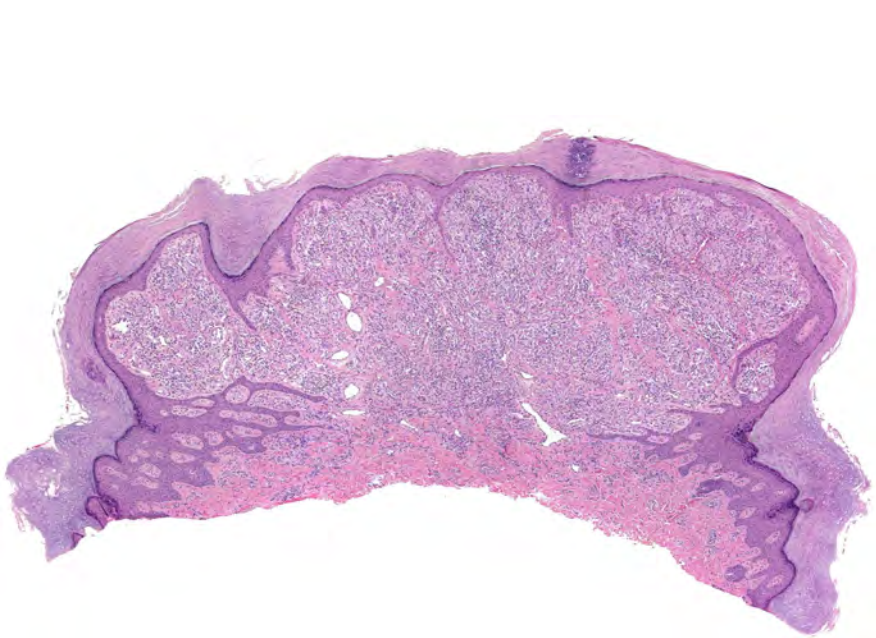

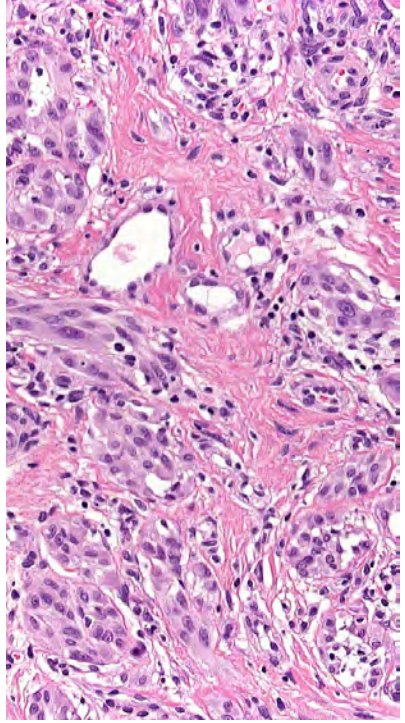

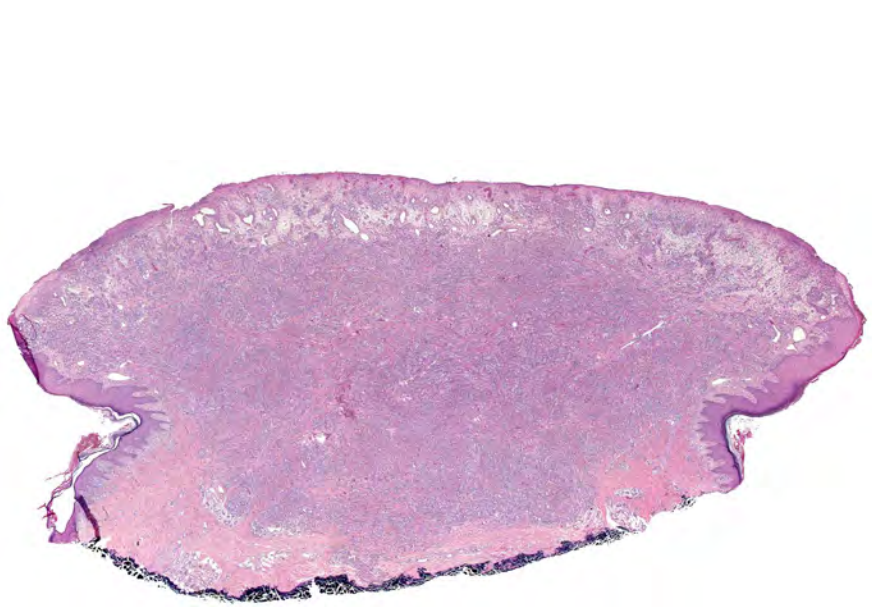

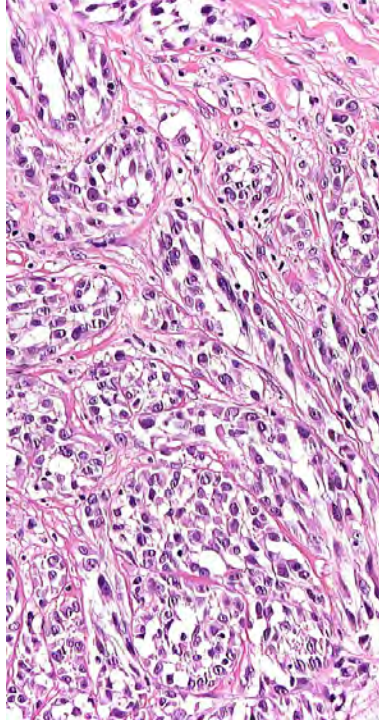

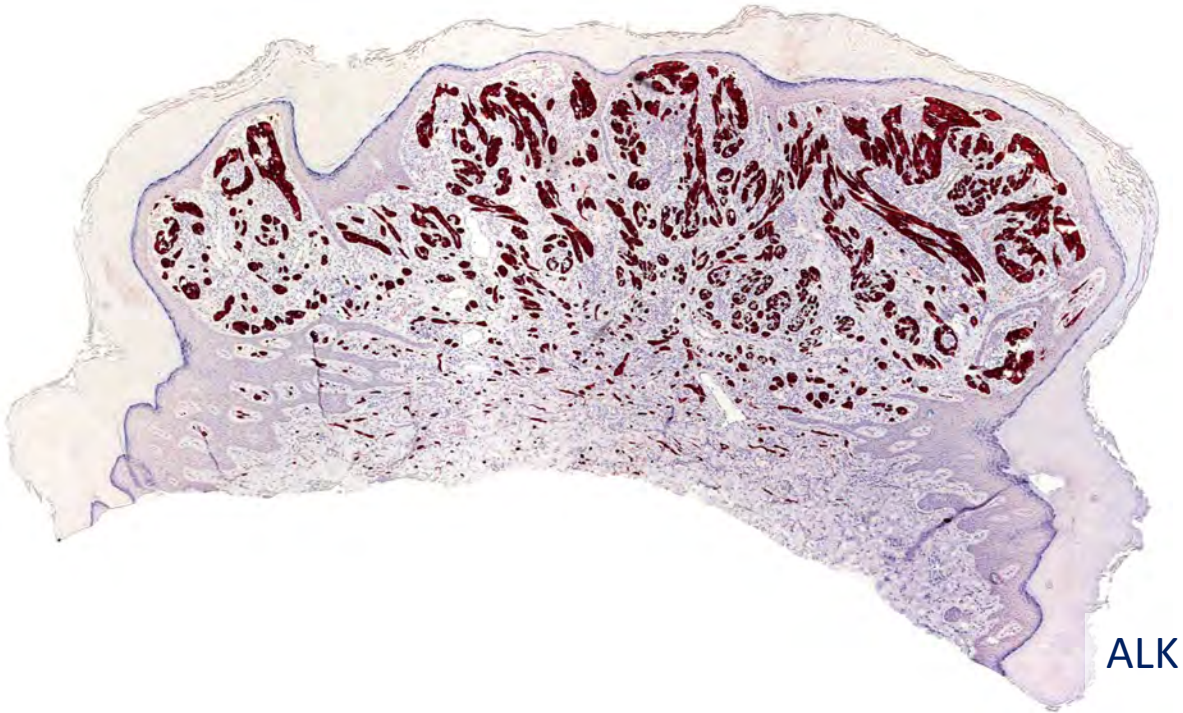

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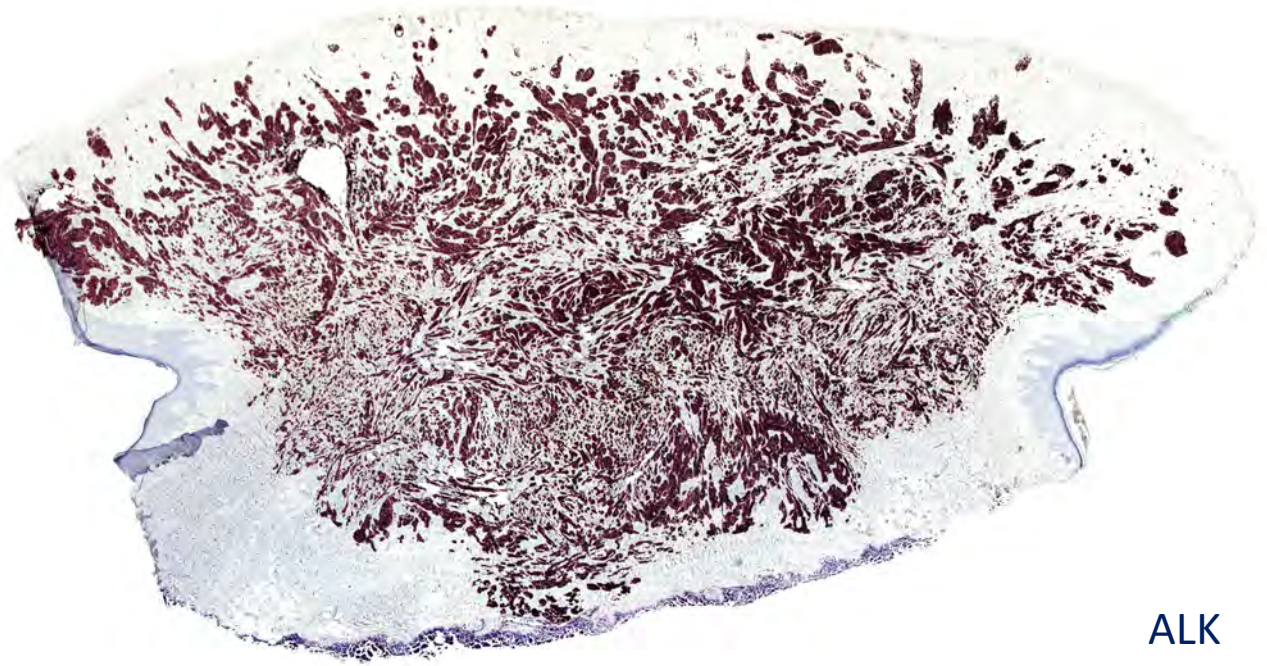

ALK

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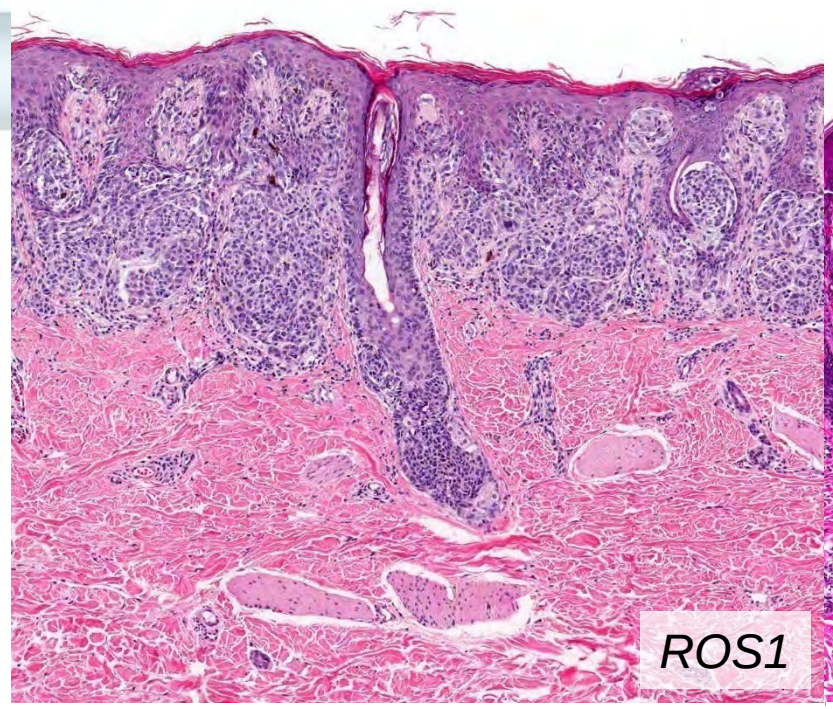

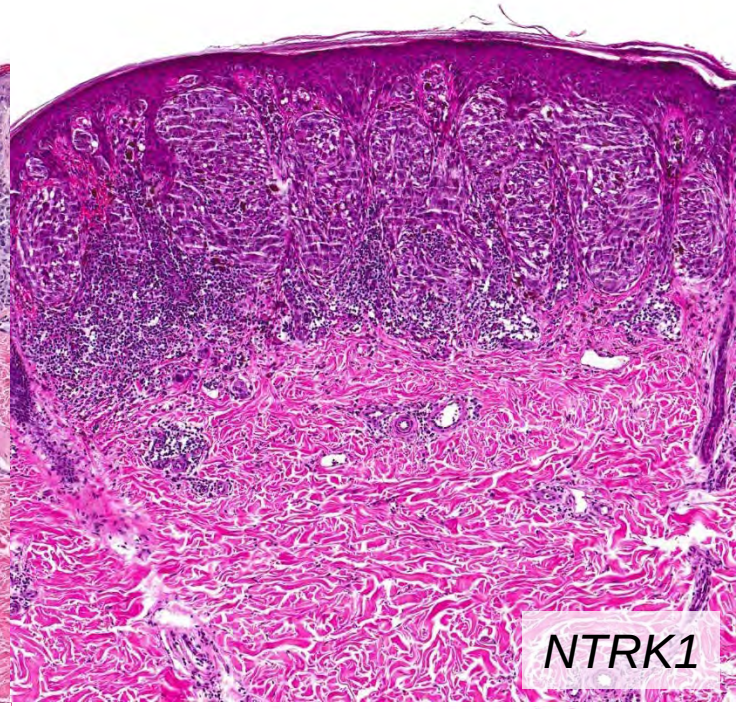

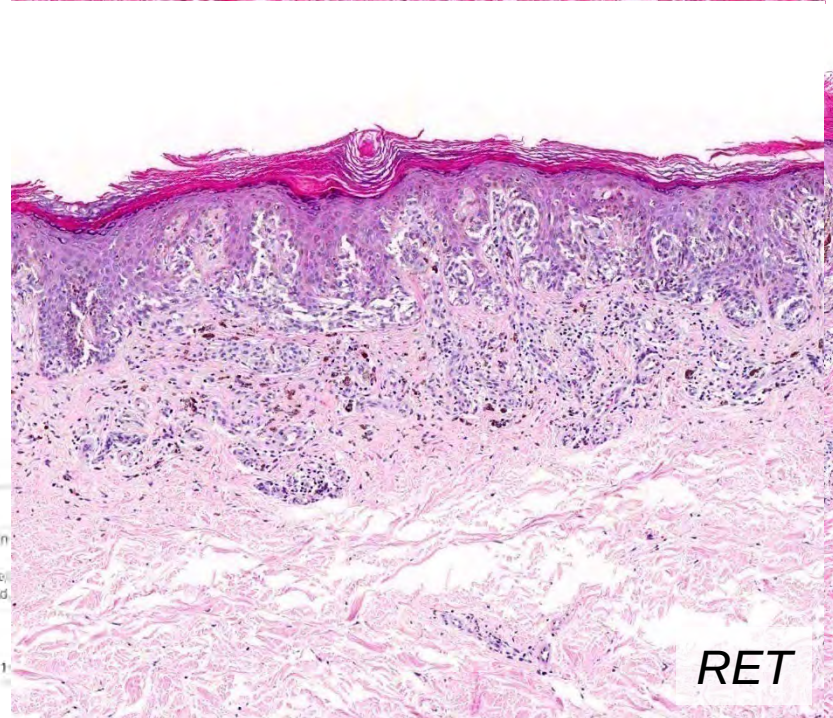

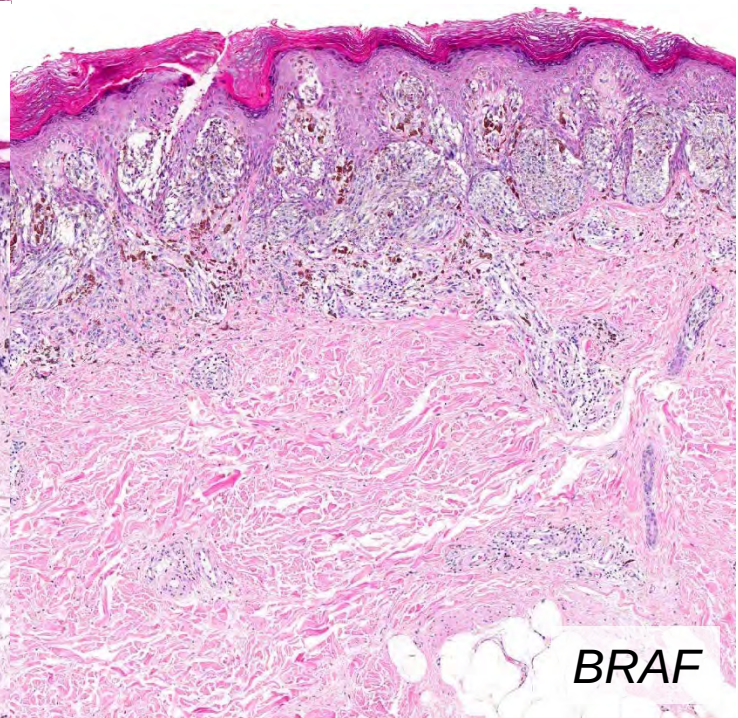

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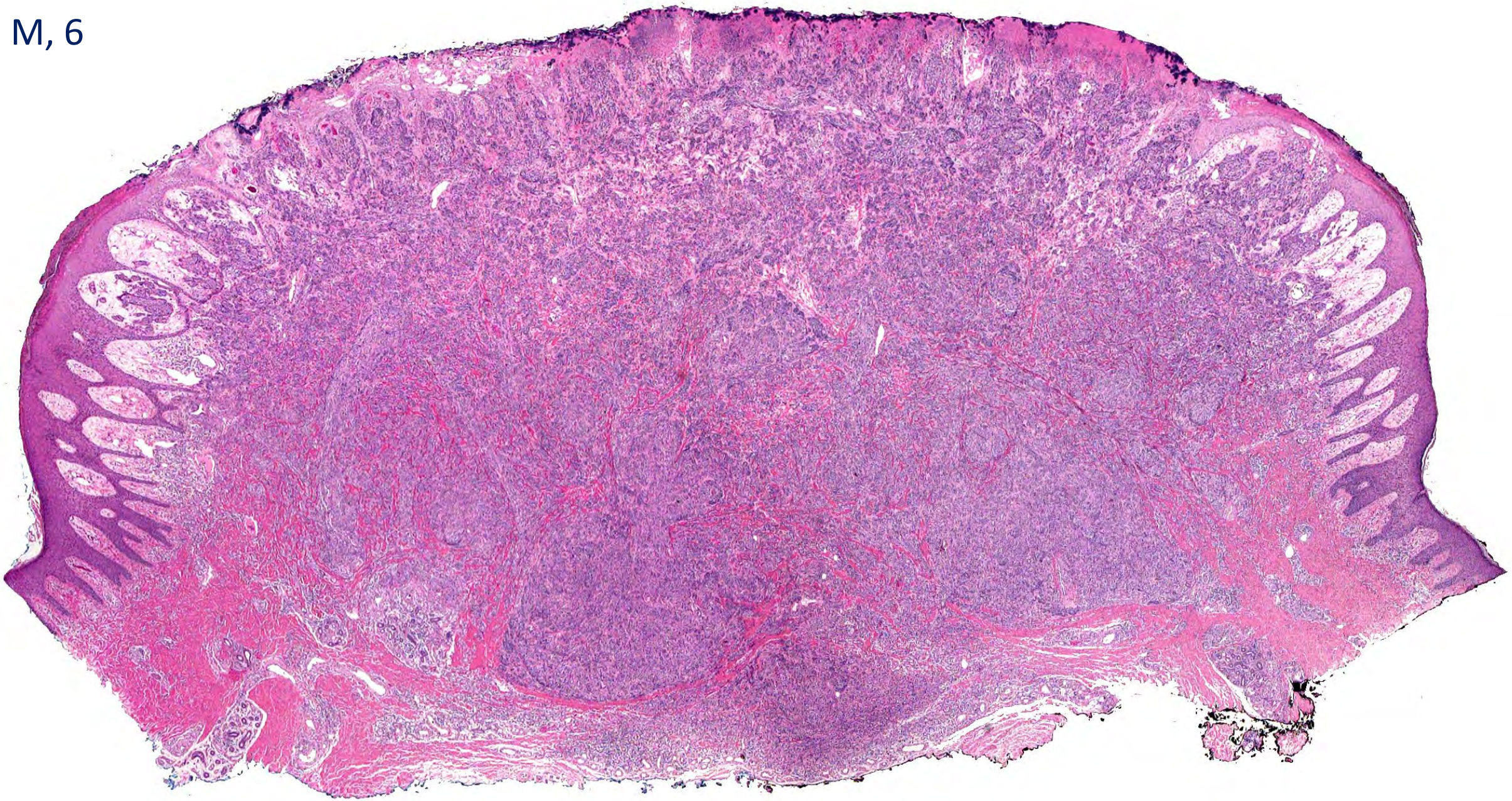
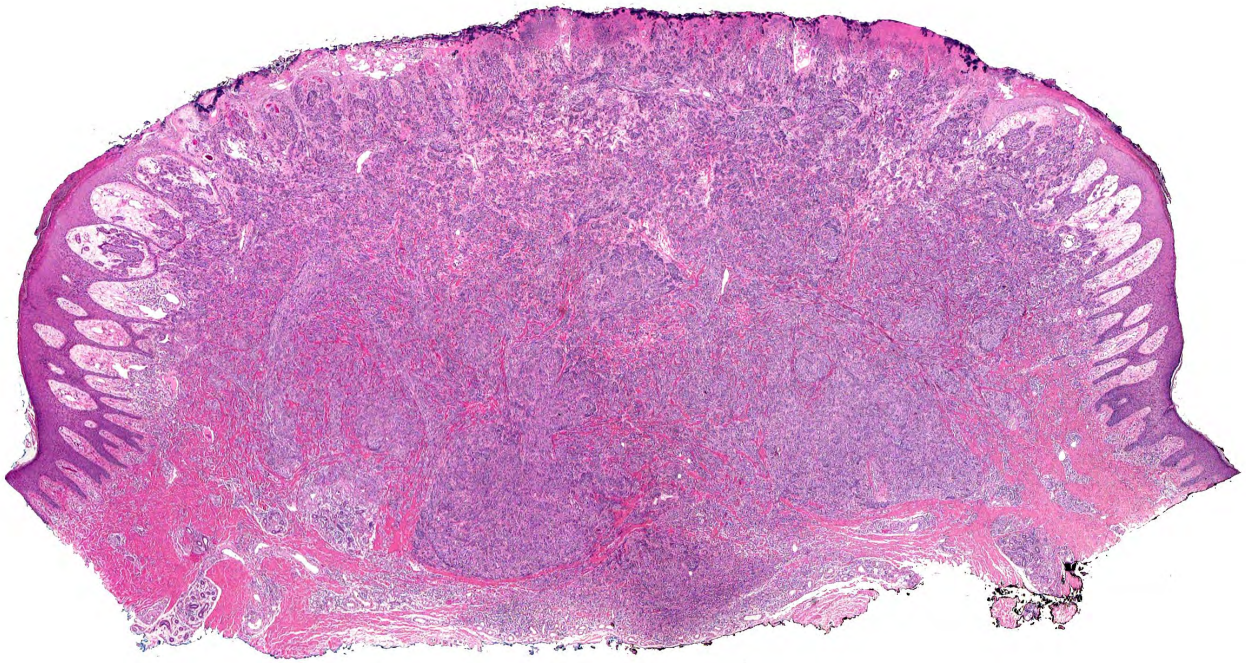
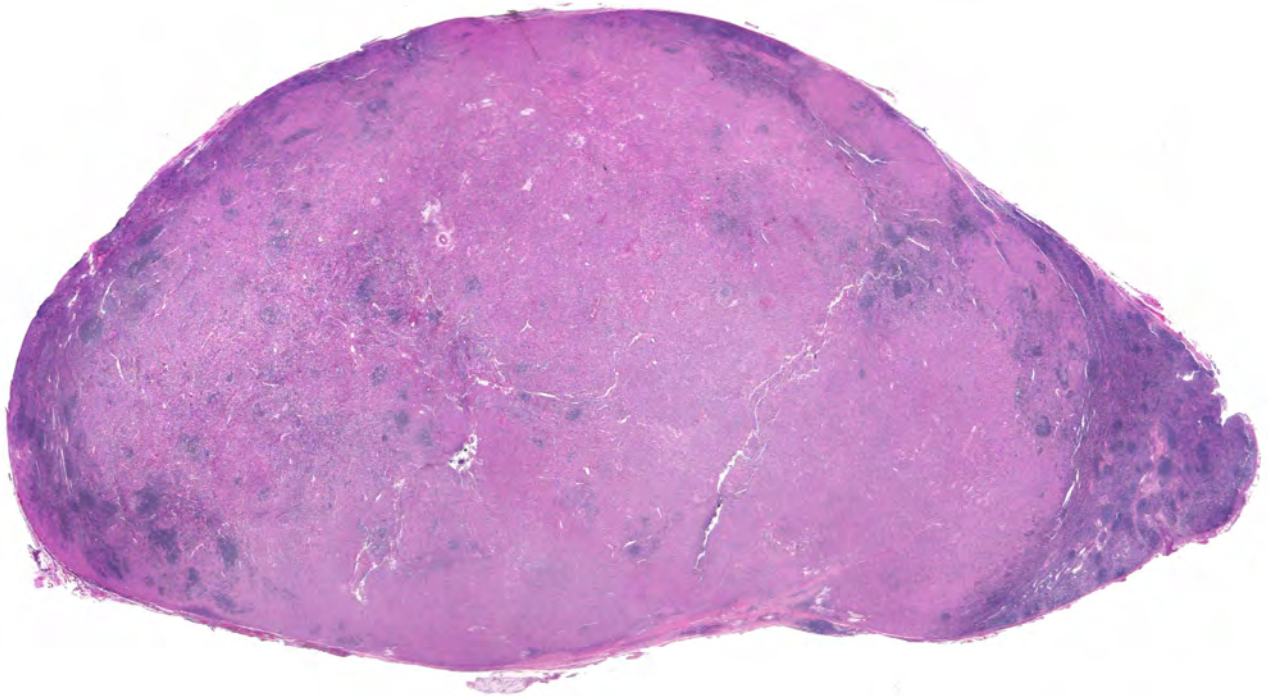
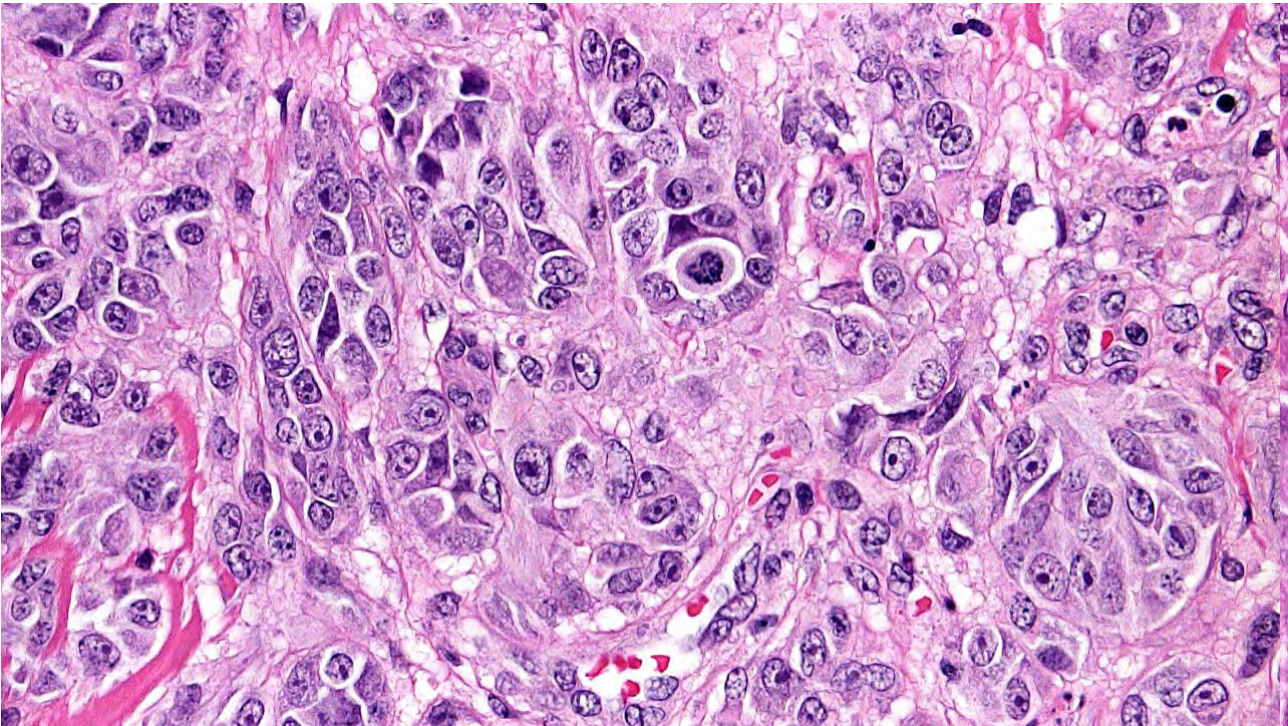
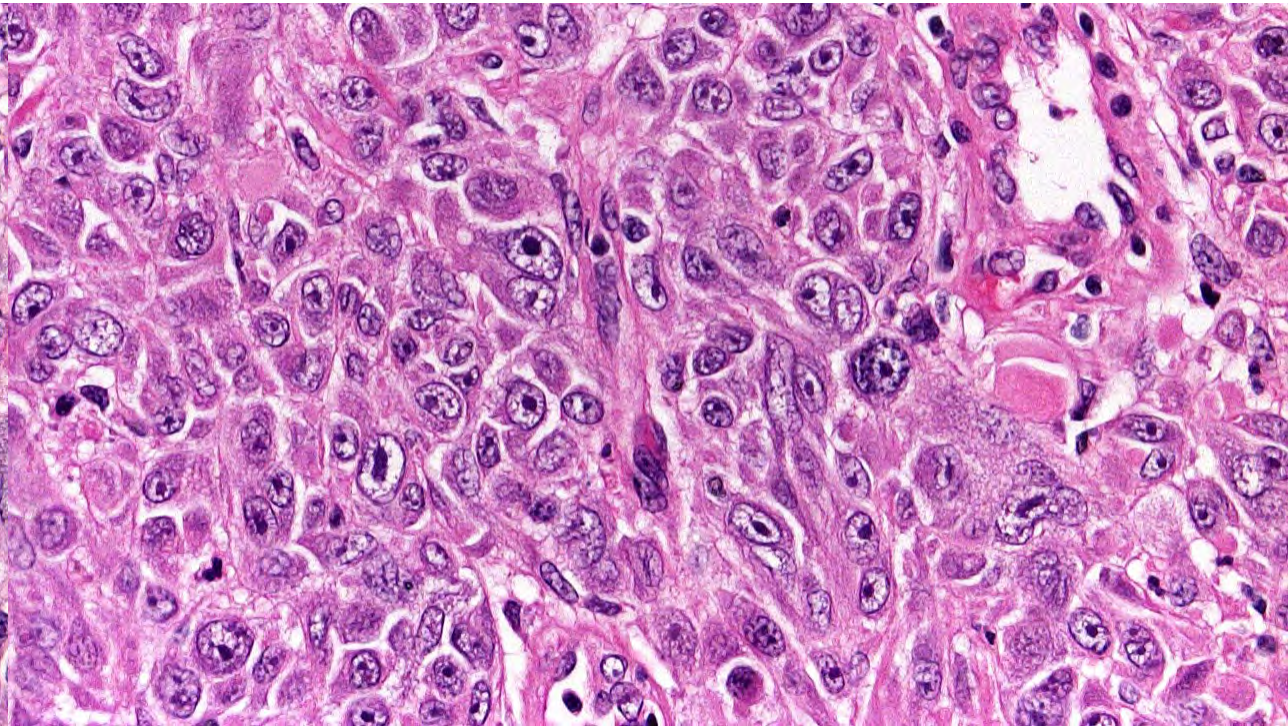


Spitz melanoma of childhood









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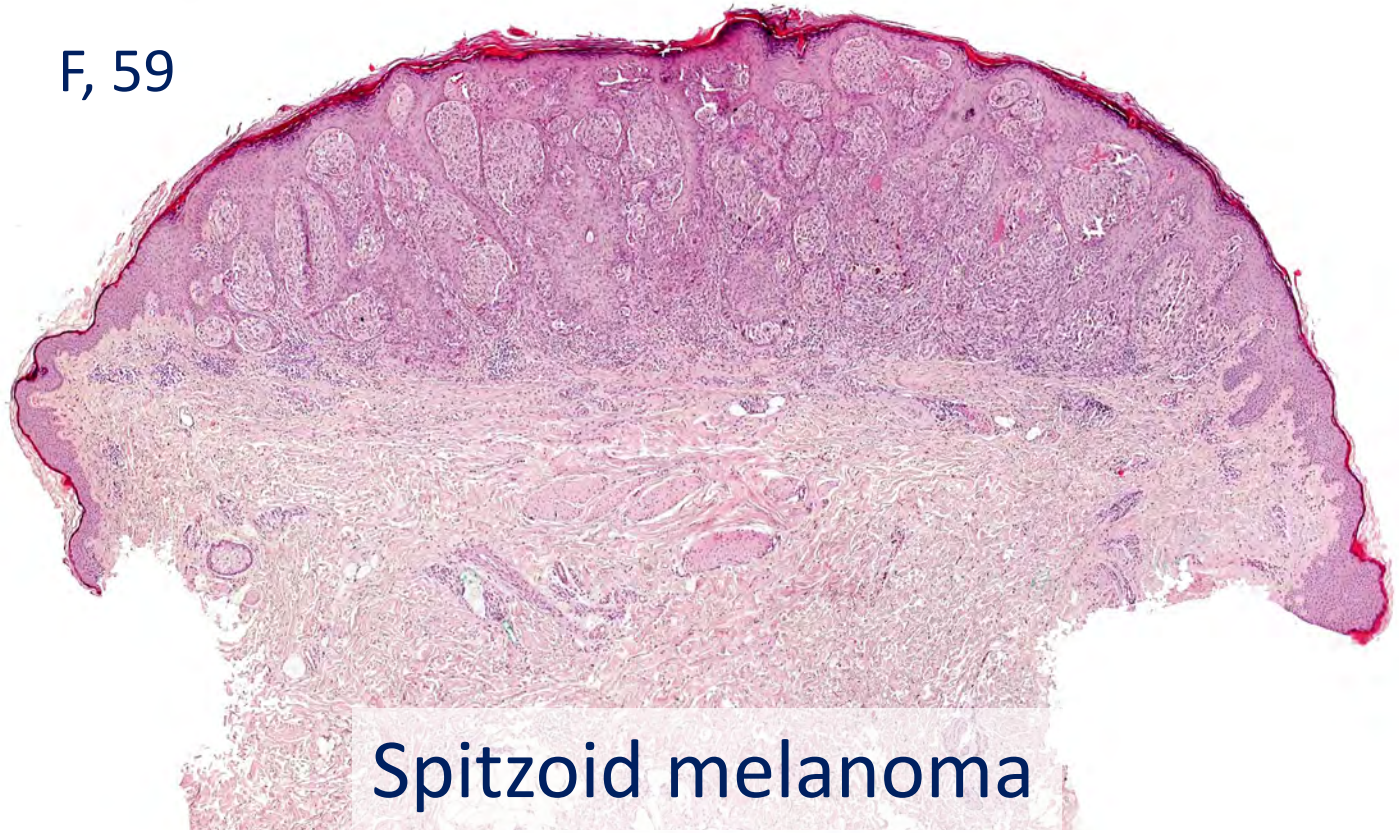
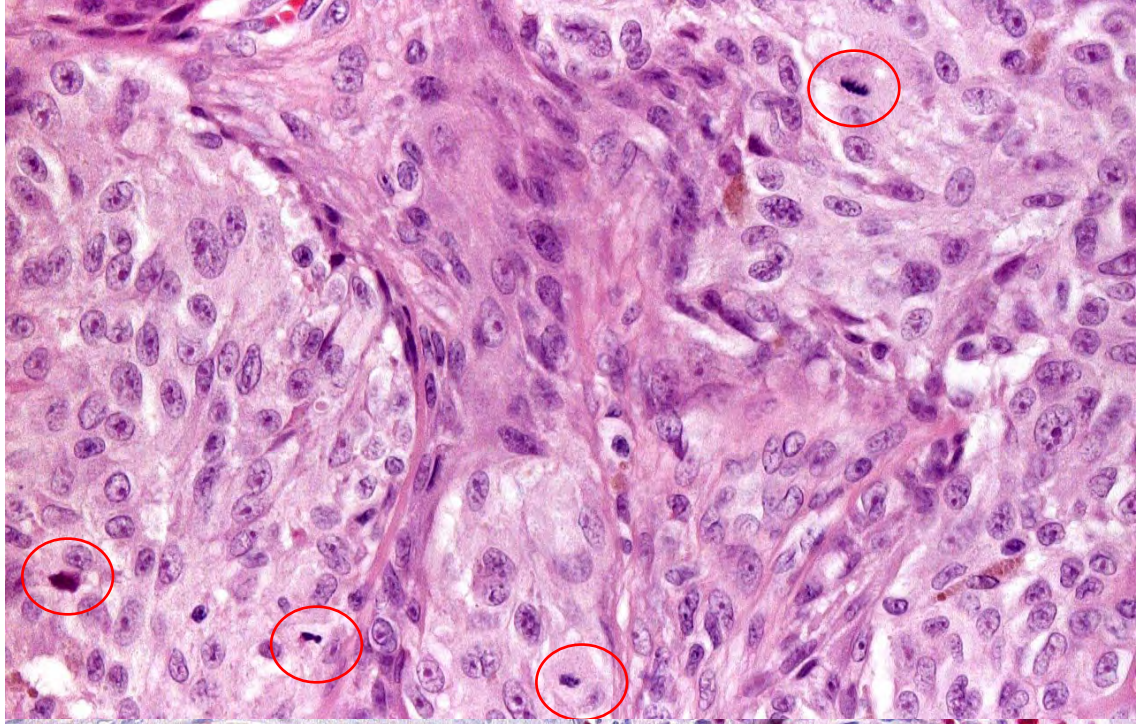
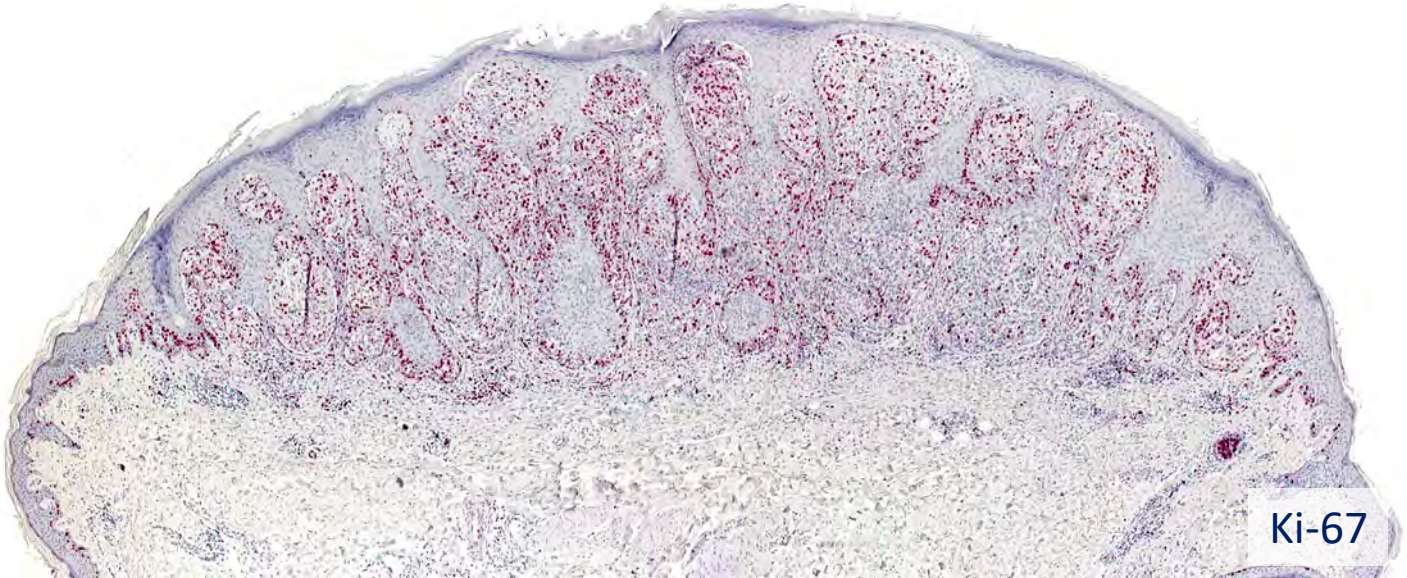


Spitzoid melanoma





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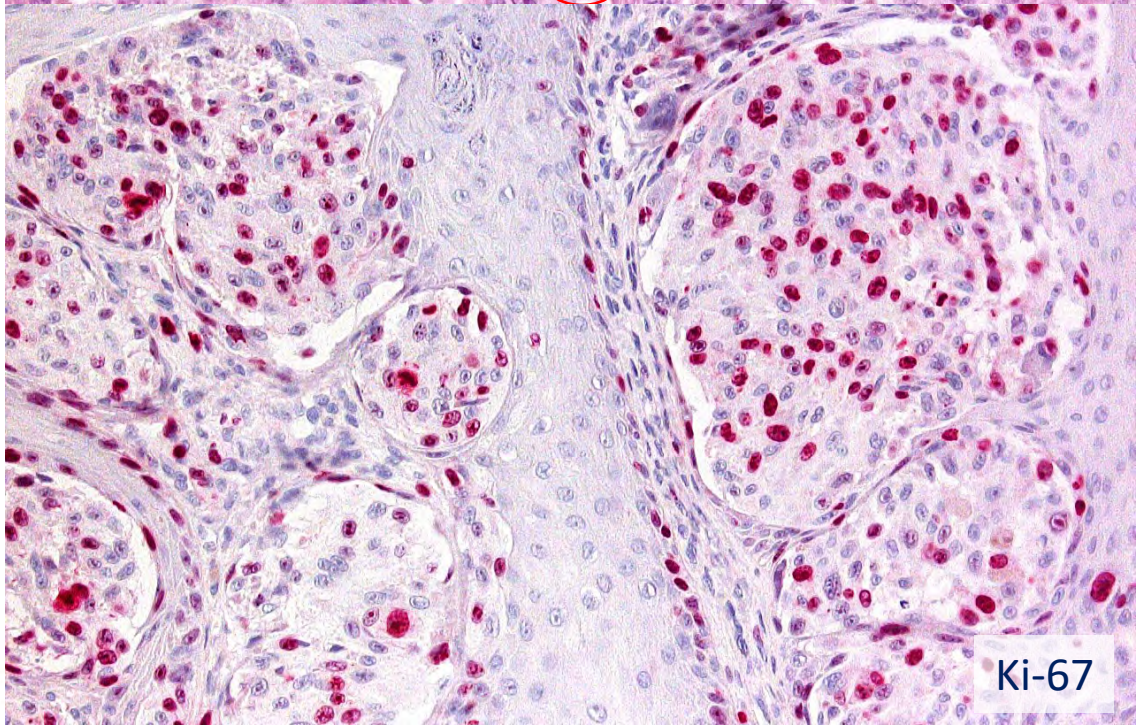

Ki-67

Uncommon Histopathological Variants of Malignant Melanoma: Part 1

Carlo Cota, MD,† Andrea Saggini, MD,*‡ Viviana Lora, MD,† Heinz Kutzner, MD,§ Arno Rütten, MD,§ Omar Sangüeza, MD,¶ Luis Requena, MD,‖ and Lorenzo Cerroni, MD**

Abstract: Despite new horizons opened by recent advances in molecular pathology, histological evaluation still remains the diagnostic gold standard regarding cutaneous melanocytic neoplasms. Several histological variants of melanoma have been described, and their knowledge is crucial for accurate diagnosis and classification of cases with unusual clinicopathological features. Uncommon histological variants of melanoma have been described based on a broad constellation of features, including architectural pattern, stromal alterations, cytological attributes, and other morphological properties. This review is aimed at providing an extensive discussion of unusual but distinctive histopathological variants of melanoma.

Key Words: melanoma, pigmented epithelioid melanocytoma, animal-type melanoma, plexiform melanoma, spitzoid melanoma, balloon cell melanoma

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LEARNING OBJECTIVES

After participating in this activity, the physician should be better able to:

1. Analyze different types of melanocytic tumors regarding architectural, cytomorphological, and immunohistochemical features.
2. Assess the histopathological pattern of different types of melanoma with particular regard to specific variants characterized either by the presence of peculiar cell types (eg, balloon cells, multinucleated cells, signet-ring cells, etc.), by unconventional morphology (eg, follicular melanoma, bullous melanoma, small melanoma, etc.), or by stromal changes (eg, desmoplasia).
3. Distinguish between several melanoma variants with peculiar structural features and recognize challenges related to measurement of tumor thickness.

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All authors and staff in a position to control the content of this CME activity and their spouses/life partners (if any) have disclosed that they have no financial relationships with, or financial interests in, any commercial organizations relevant to this educational activity.

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Despite new horizons opened by recent advances in molecular pathology, histological evaluation still remains the diagnostic gold standard regarding cutaneous melanocytic neoplasms.[1–3] In addition to main melanoma categories listed in the WHO classification of tumors (Table 1),[4] several other histological variants have been described, and their knowledge is crucial for accurate diagnosis and classification of cases with unusual clinicopathological features.[5,6] Uncommon histological variants of melanoma have been described based on a broad constellation of features, including architectural pattern, stromal alterations, cytological attributes, and other morphological properties.[7,8]

This is the first part of a review aimed at providing an extensive discussion of unusual but distinctive histopathological variants of melanoma, as described in the available literature. For practical purposes, histological entities are listed according to alphabetical order.

ANGIOMATOID MELANOMA

The term "angiomatoid melanoma" has been coined for tumors of malignant melanocytes characterized by a low-power silhouette distorted by the presence of variably large spaces filled with erythrocytes (Fig. 1).[8,9] First reported in metastatic lesions of melanoma,[9] the angiomatoid pattern may also be found in primary tumors.[10,11] Histopathologic evidence of hemorrhagic spaces in angiomatoid melanomas may be associated with clinical features suggestive of a vascular neoplasm/malformation.[8] Of note, most primary angiomatoid tumors reported in the literature to date have been thick melanomas with dismal prognosis.[10]

Histopathologically, irregular hemorrhagic, pseudovascular, cavernous-like spaces seem to separate melanocytic complexes, with single cells and/or small cellular aggregates apparently floating within hemorrhagic areas.[8,10] These spaces are not true vessels, being rather lined by neoplastic melanocytes, as proved by immunohistochemical staining for melanocytic and endothelial markers[8]; indeed, the term "pseudovascular" has also been used to describe cases with an analogous histologic picture.[8,10] In this context, it should be reminded that focal positivity for podoplanin in neoplastic melanocytes may be observed in otherwise conventional melanoma.[10] Expression of additional vascular antigens (such as CD31, ERG, and FLI-1) should be investigated in dubious cases to avoid potential pitfalls. Although the pseudovascular

Uncommon Histopathological Variants of Malignant Melanoma. Part 2

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Abstract: Despite new horizons opened by recent advances in molecular pathology, histological evaluation still remains the diagnostic gold standard regarding cutaneous melanocytic neoplasms. Several histological variants of melanoma have been described, and their knowledge is crucial for accurate diagnosis and classification of cases with unusual clinico-pathological features. Uncommon histological variants of melanoma have been described based on a broad constellation of features, including architectural pattern, stromal alterations, cytological attributes, and other morphological properties. This review is aimed at providing an extensive discussion of unusual but distinctive histopathological variants of melanoma.

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(*Am J Dermatopathol* 2019;41:321–342)

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This is the second part of a review aimed at providing an extensive discussion of unusual but distinctive histopathological variants of melanoma, as described in the available literature. For practical purposes, histological entities are listed according to alphabetical order.

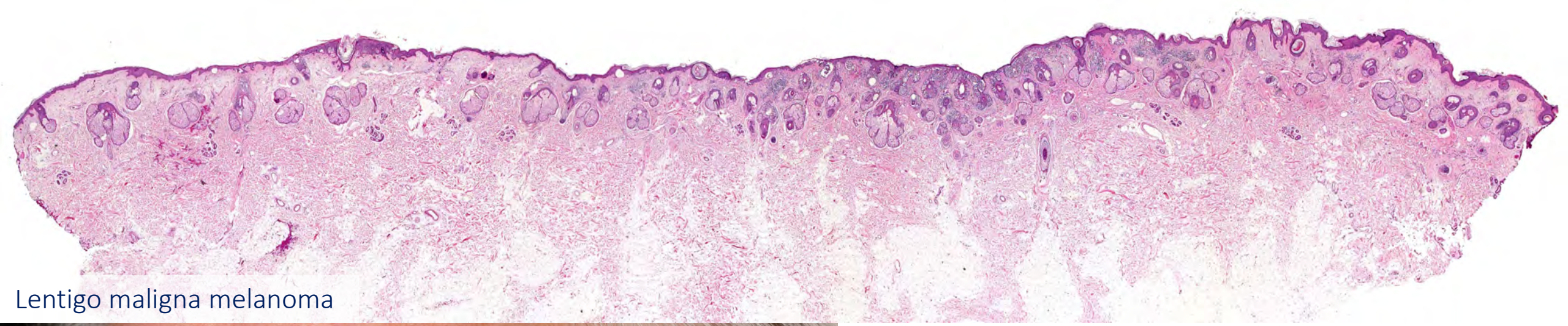
MYXOID MELANOMA

Variable amounts of extracellular mucin may be focally observed in conventional melanoma (Fig. 1).[8,9] According to the definition by Hitchcock et al,[10] the term "myxoid melanoma" should apply to cases with myxoid changes exceeding 15% of the stroma. Prominent myxoid changes in melanoma seem to be related to desmoplastic melanoma and melanoma with neuroid differentiation.[8] Although melanocytes have been demonstrated to be able to induce glycosaminoglycan synthesis, reactive mesenchymal cells seem to be the likely culprit of acid mucopolysaccharides production in myxoid melanoma.[11,12] Prominent extracellular deposition of mucin may be also observed in melanoma metastases, with primary lesions usually exhibiting a nonmyxoid appearance.[13,14] In one case of myxoid melanoma, stromal changes were thought to be related to the effects of prolonged phototherapy applied for over 30 months on an undiagnosed melanocytic neoplasm.[15] Of note, a mucinous-like appearance may be the result of marked intratumoral edema, a phenomenon referred to as "pseudo-myxoid" changes.[16] The mucinous quality of extracellular material should be confirmed by means of histochemical staining for alcian blue at pH 2.5 and/or colloidal iron.[8]

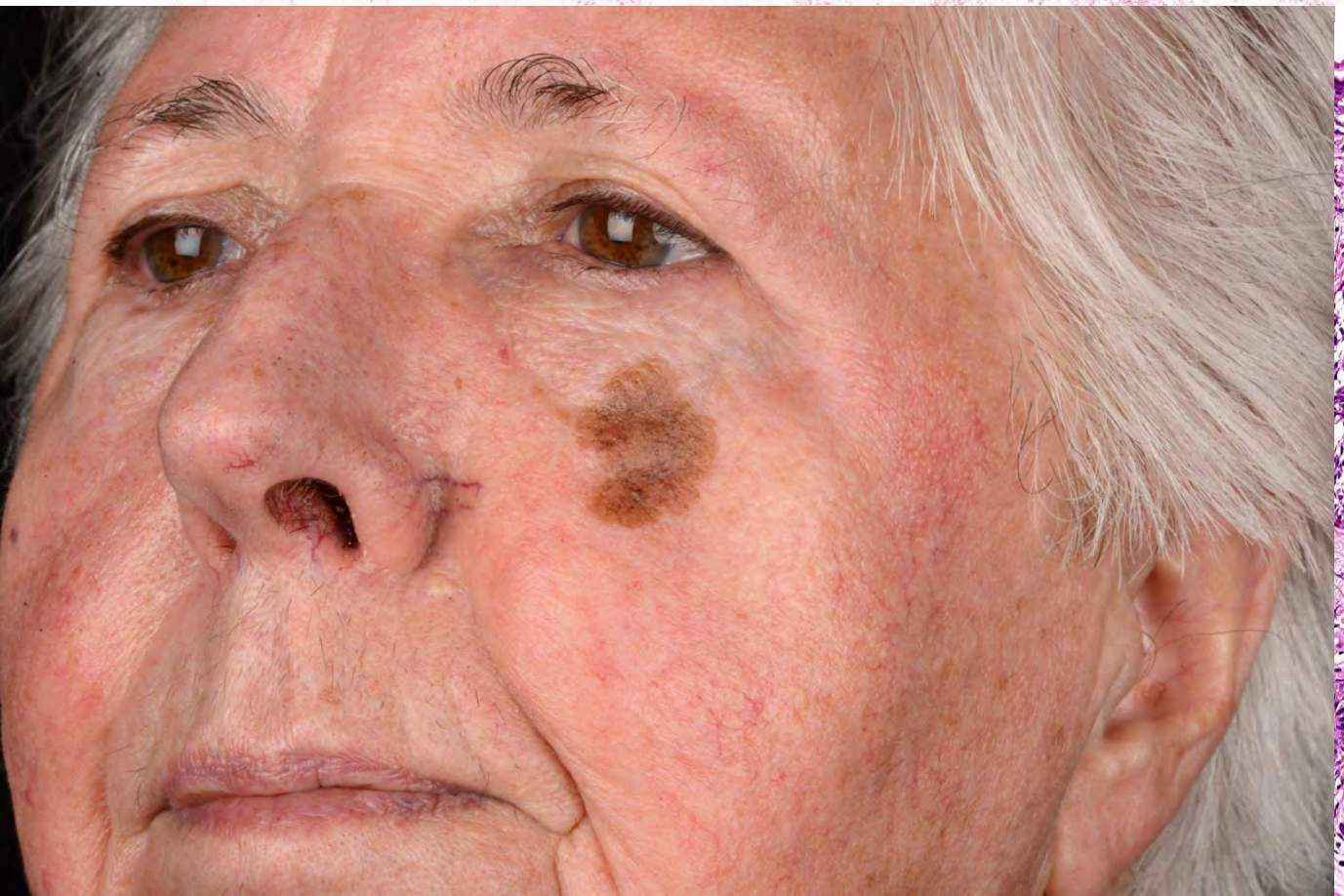
Extensive mucin deposition in melanoma results in a diagnostic challenge, especially in tumors lacking evidence

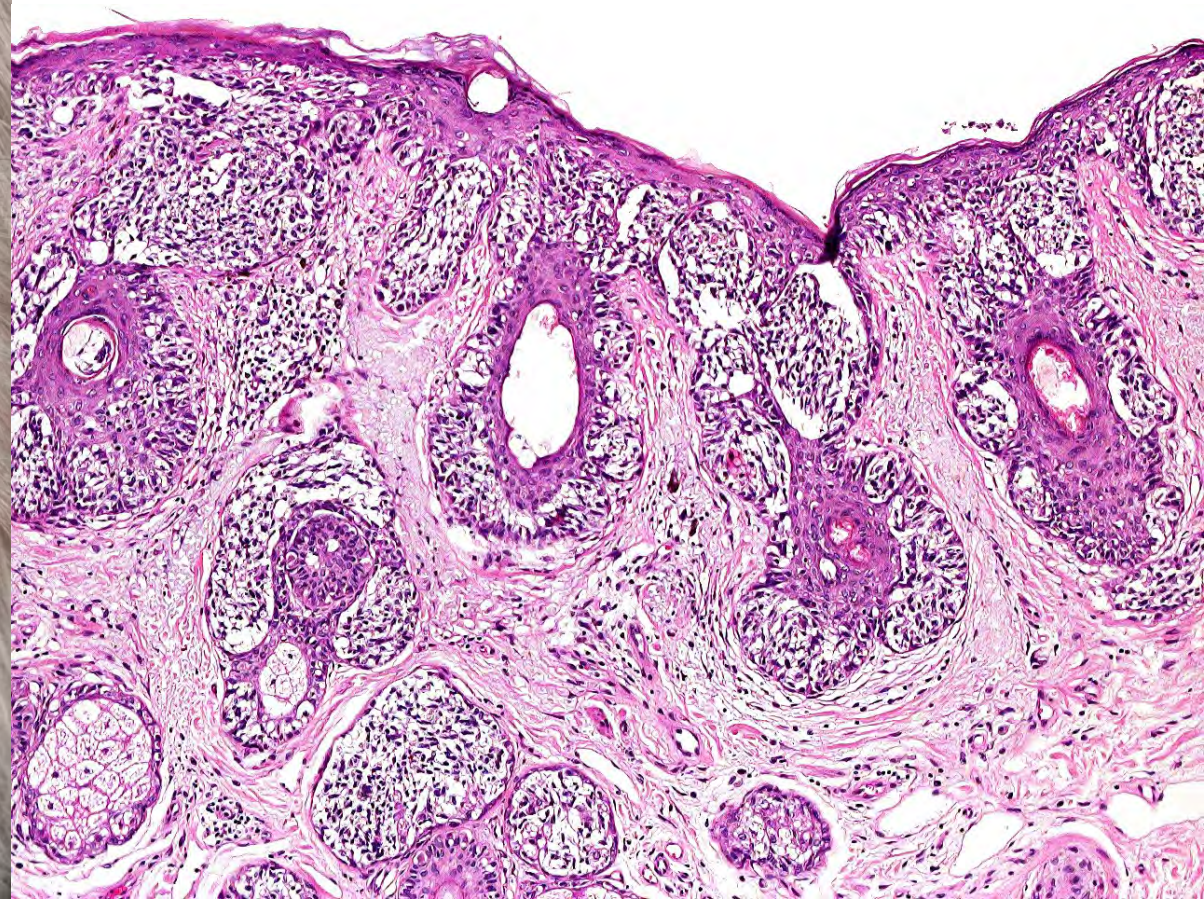
Working classification of "spitzoid" lesions

- **"Conventional" Spitz nevus:** *HRAS* mutations
- **Spitz "lineages":** *MAP2K1* fusion, *MAP3K8* fusion, *BRAF* fusion, *ALK* fusion, *ROS1* fusion, *NTRK1* fusion, *NTRK3* fusions, *RET* fusion, and probably other molecular aberrations; within each lineage, "Spitz nevus", atypical Spitz tumor, Spitz melanoma
- **Spitz melanoma (of childhood):** Spitz lineage initiating event; additional progression events (homozygous loss of *CDKN2A*, mutations in *TERT*, *CDK4*, *p53*, etc.); spread beyond local lymph nodes, but prognosis seems better than classic melanoma
- **Spitzoid melanoma:** "conventional" melanoma that histopathologically resembles a Spitz nevus; initiating mutations in *BRAF*, *NRAS*; other mutations related to tumor progression

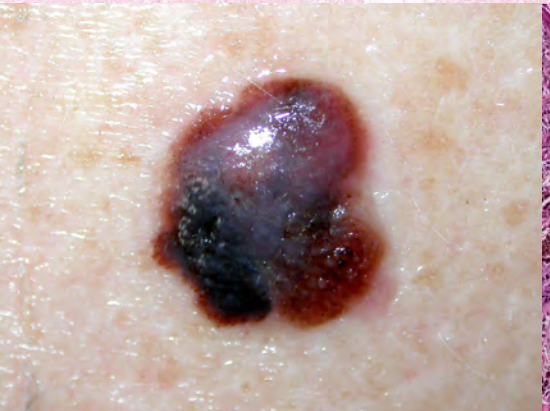


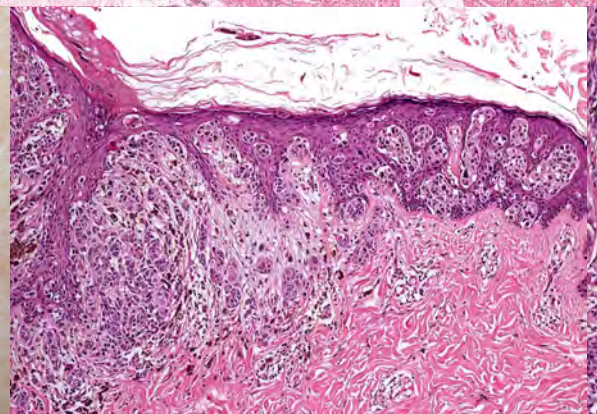
Lentigo maligna melanoma

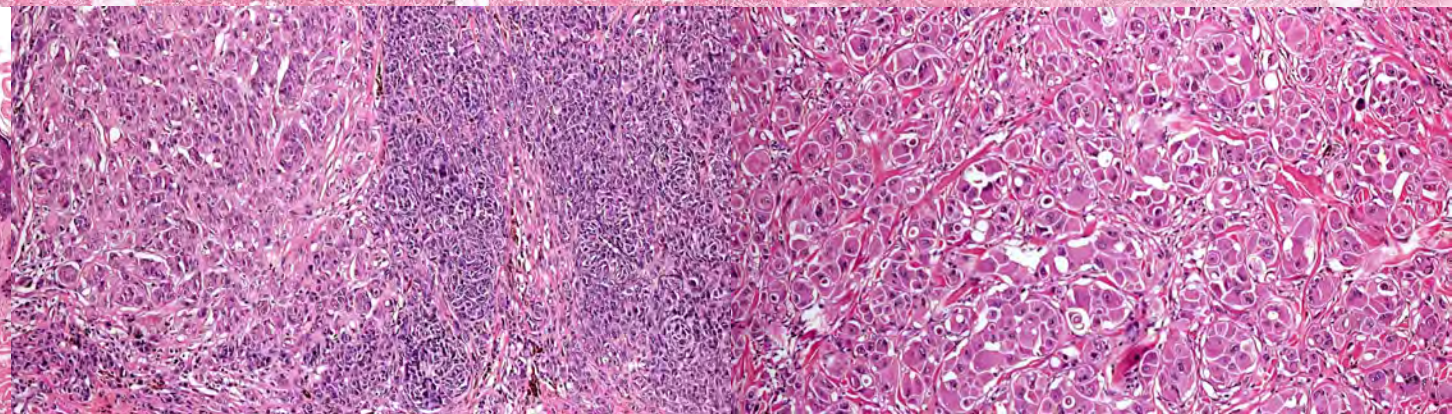


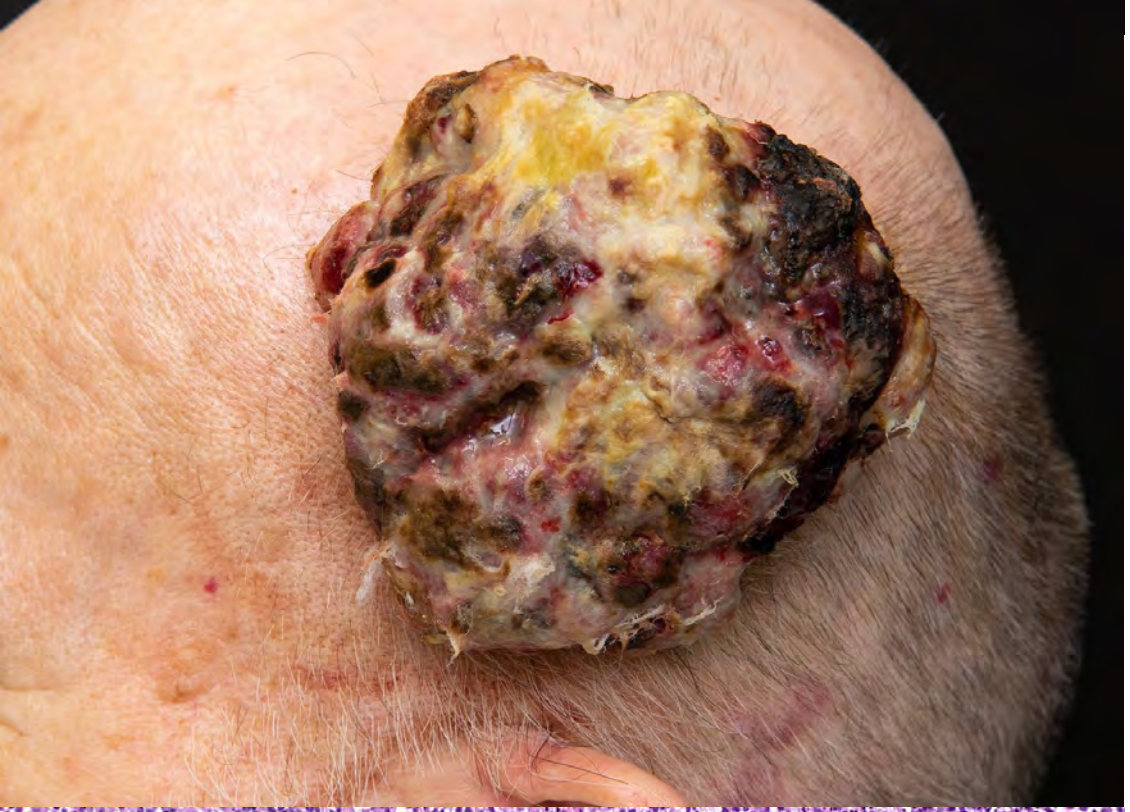


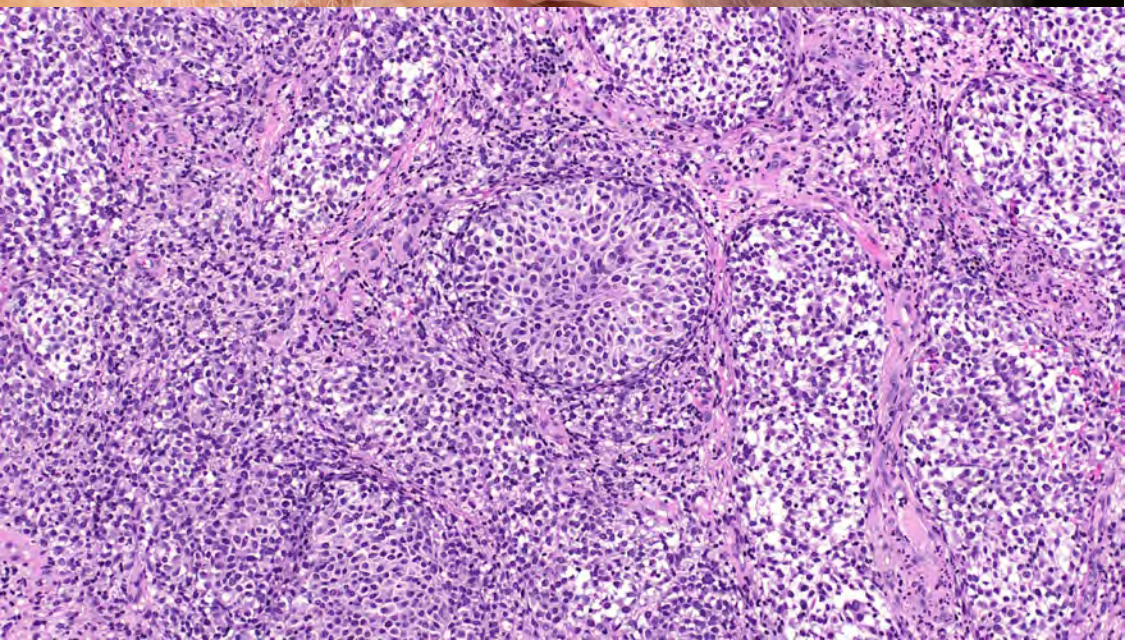
"Superficial spreading" melanoma

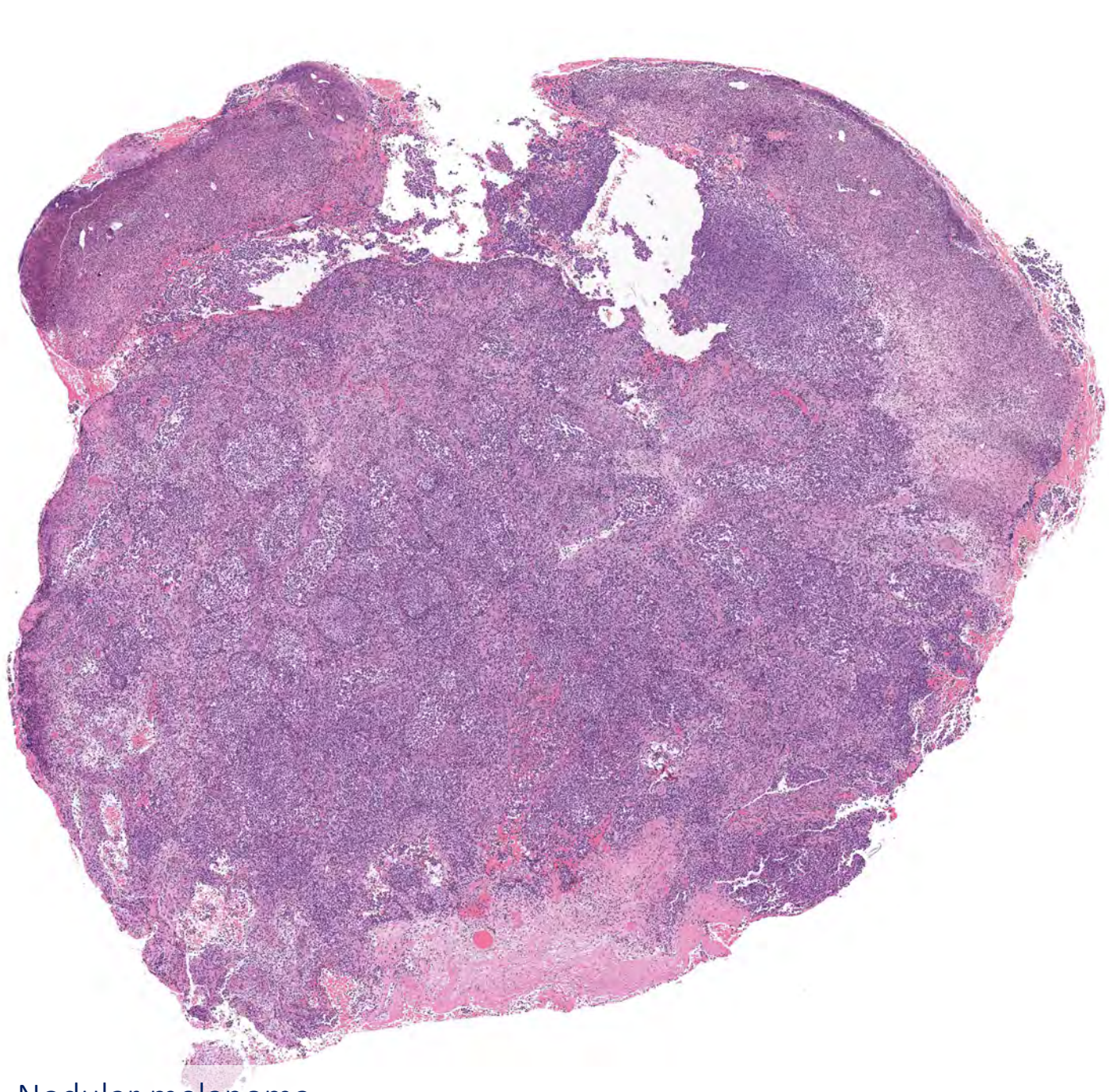




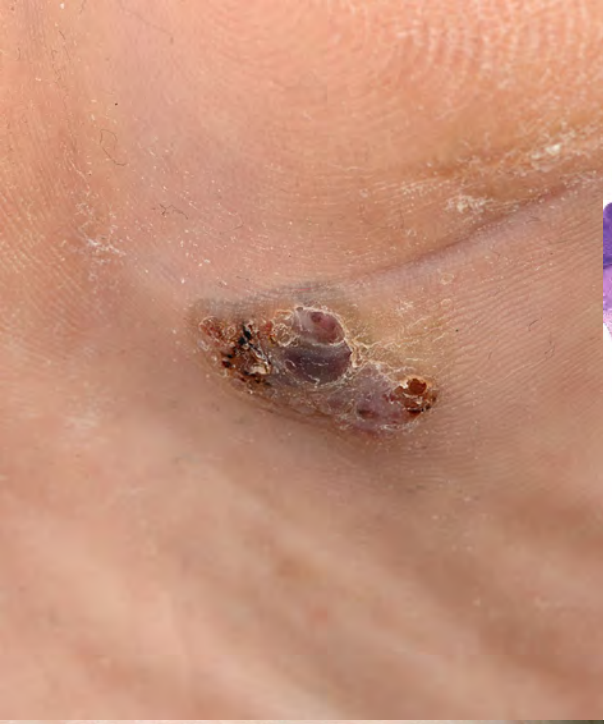


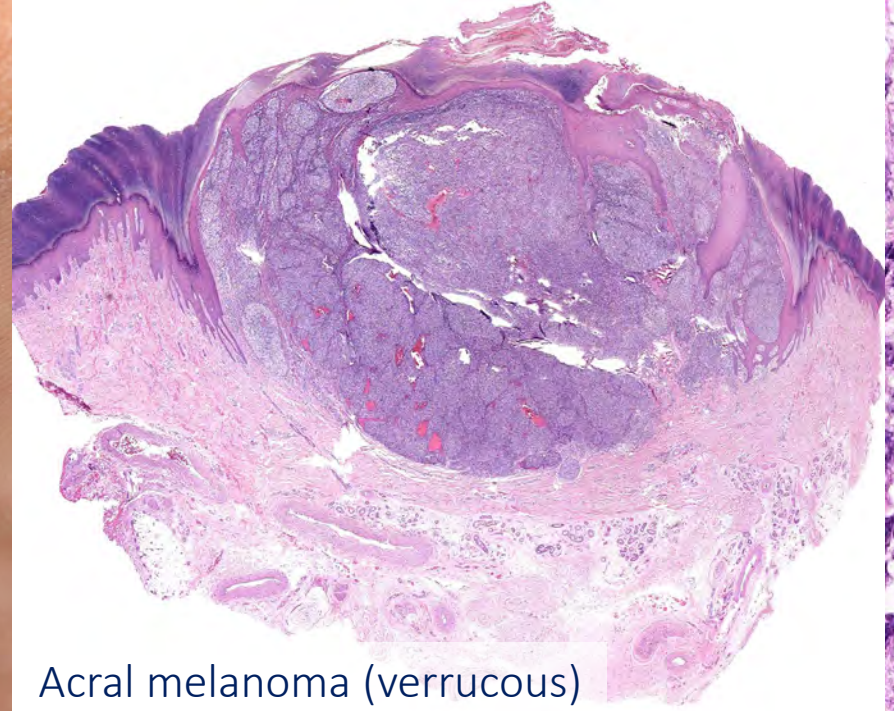




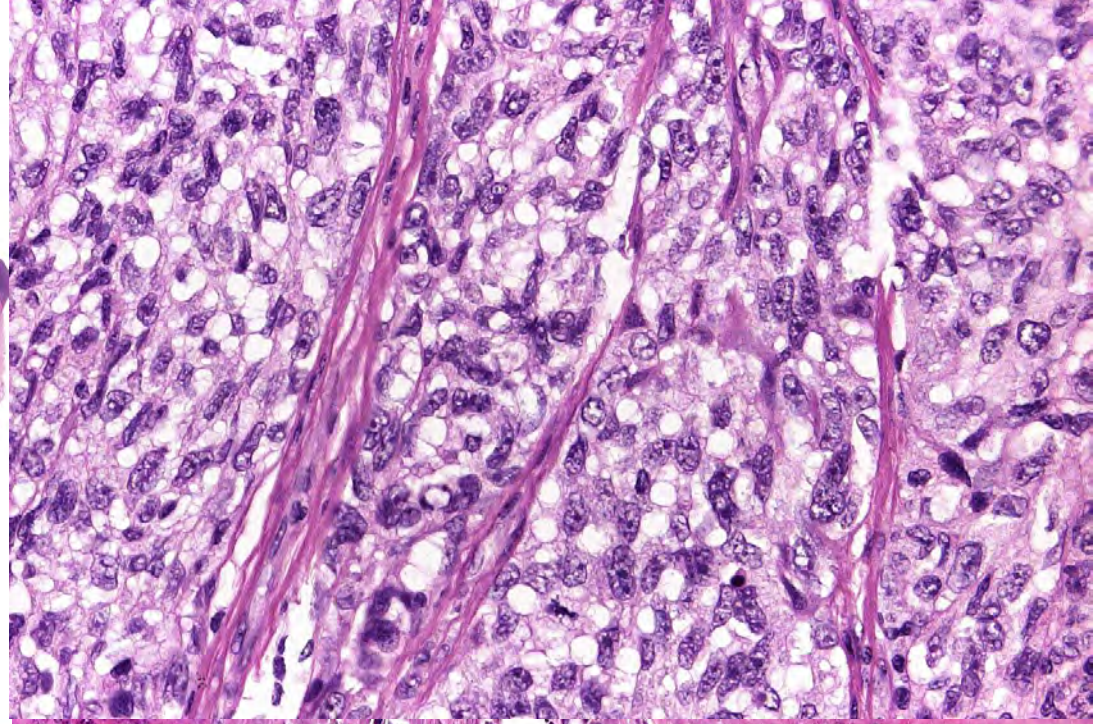


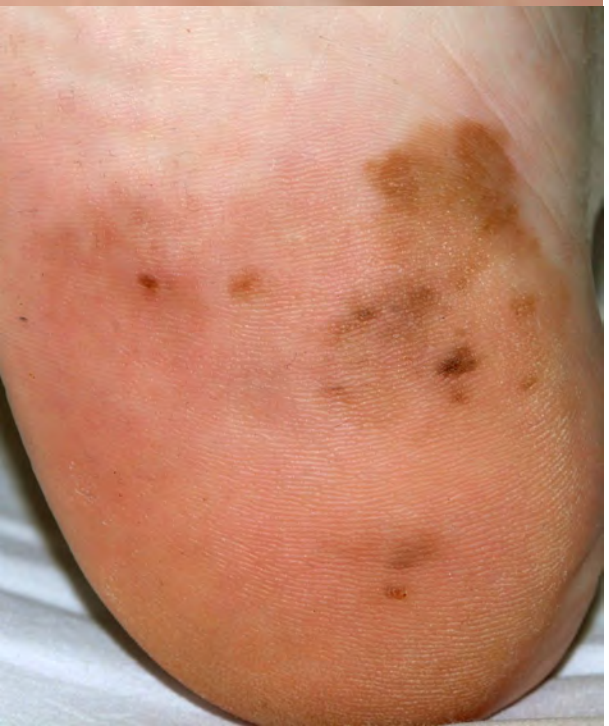
Nodular melanoma

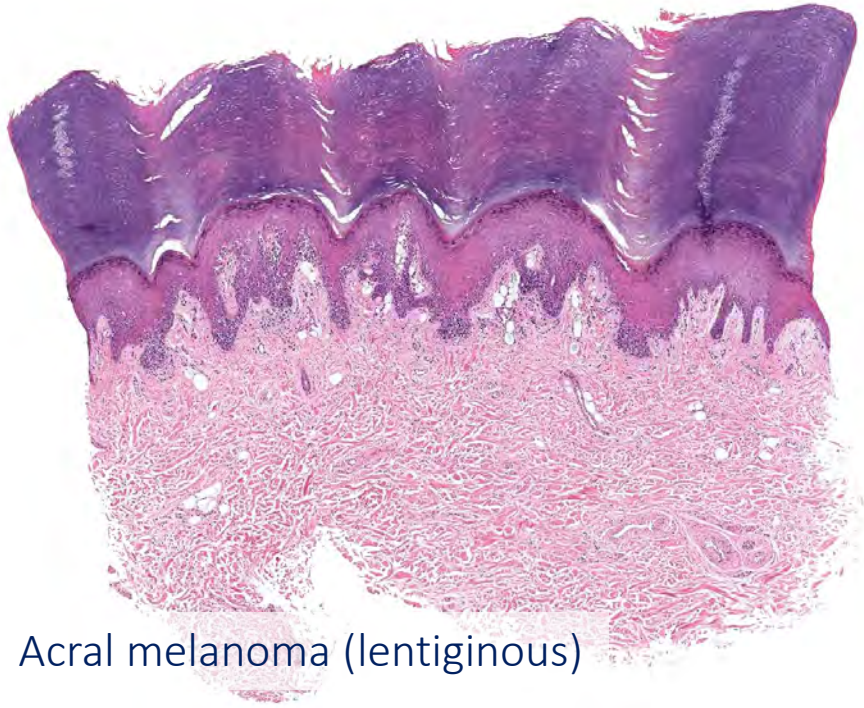




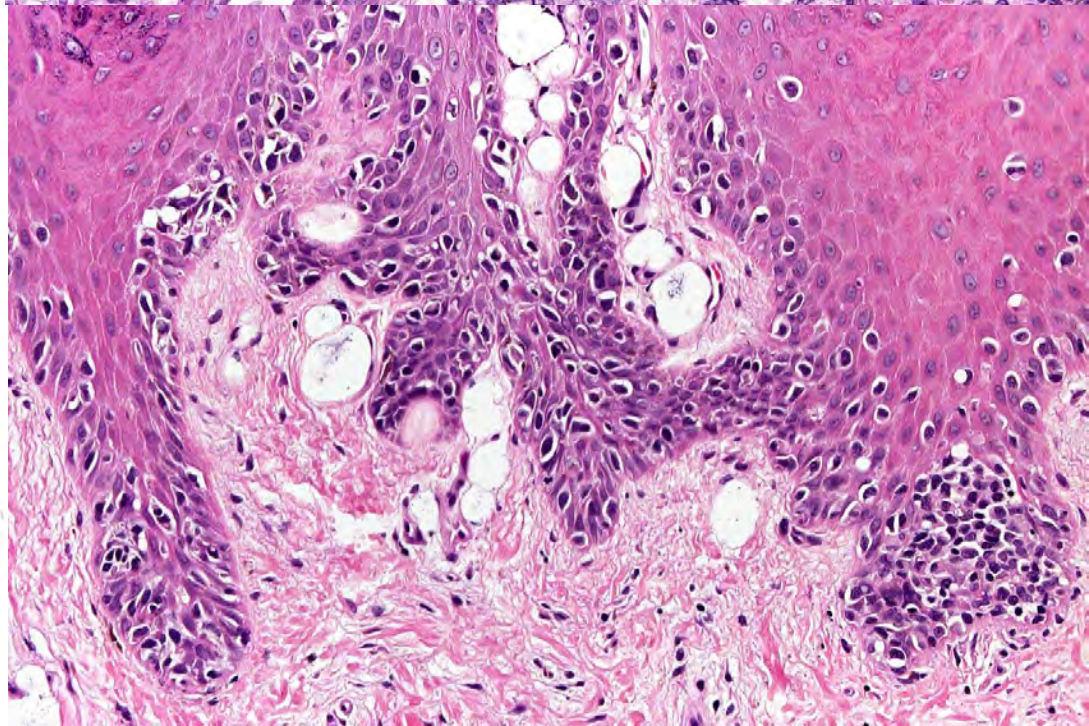
Acral melanoma (verrucous)

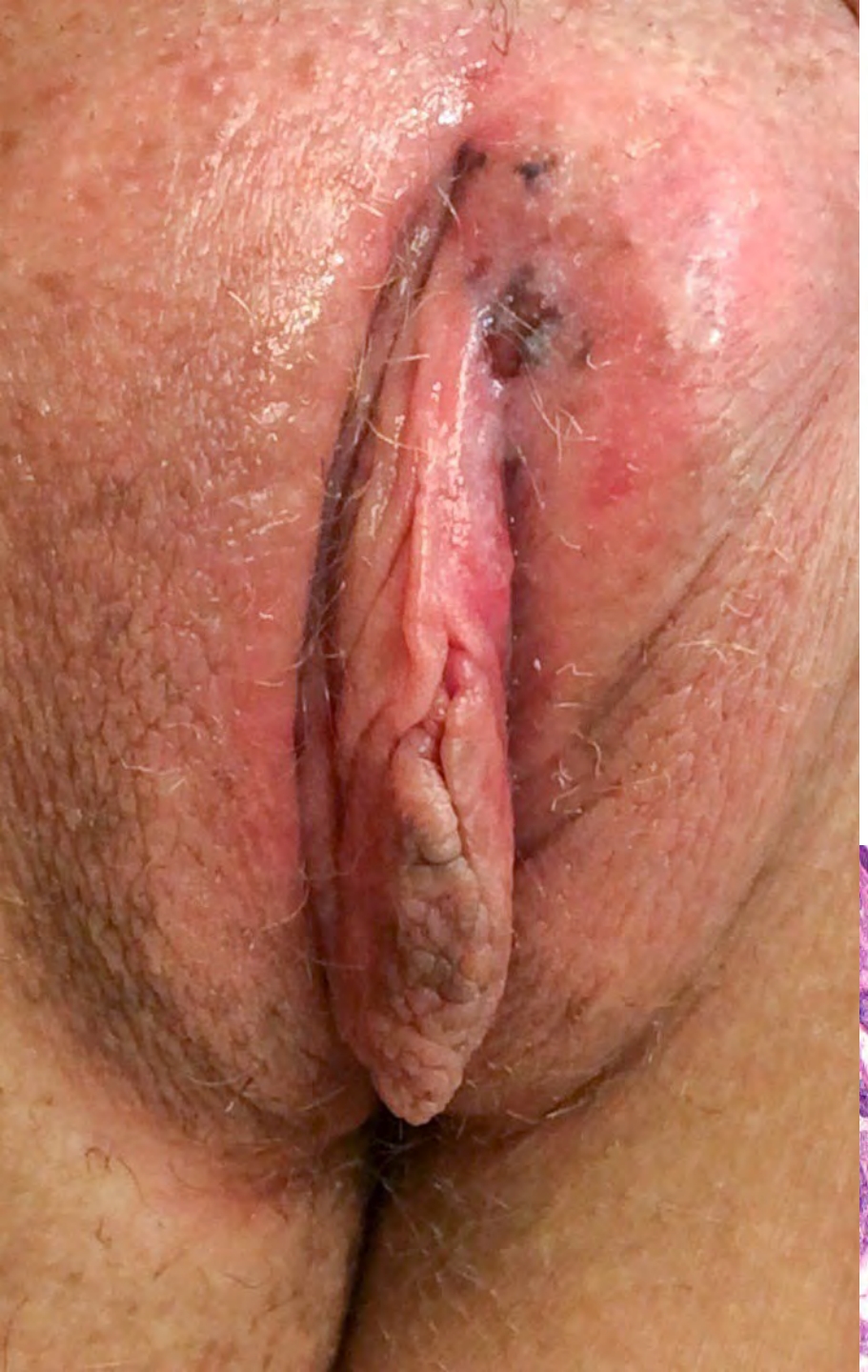


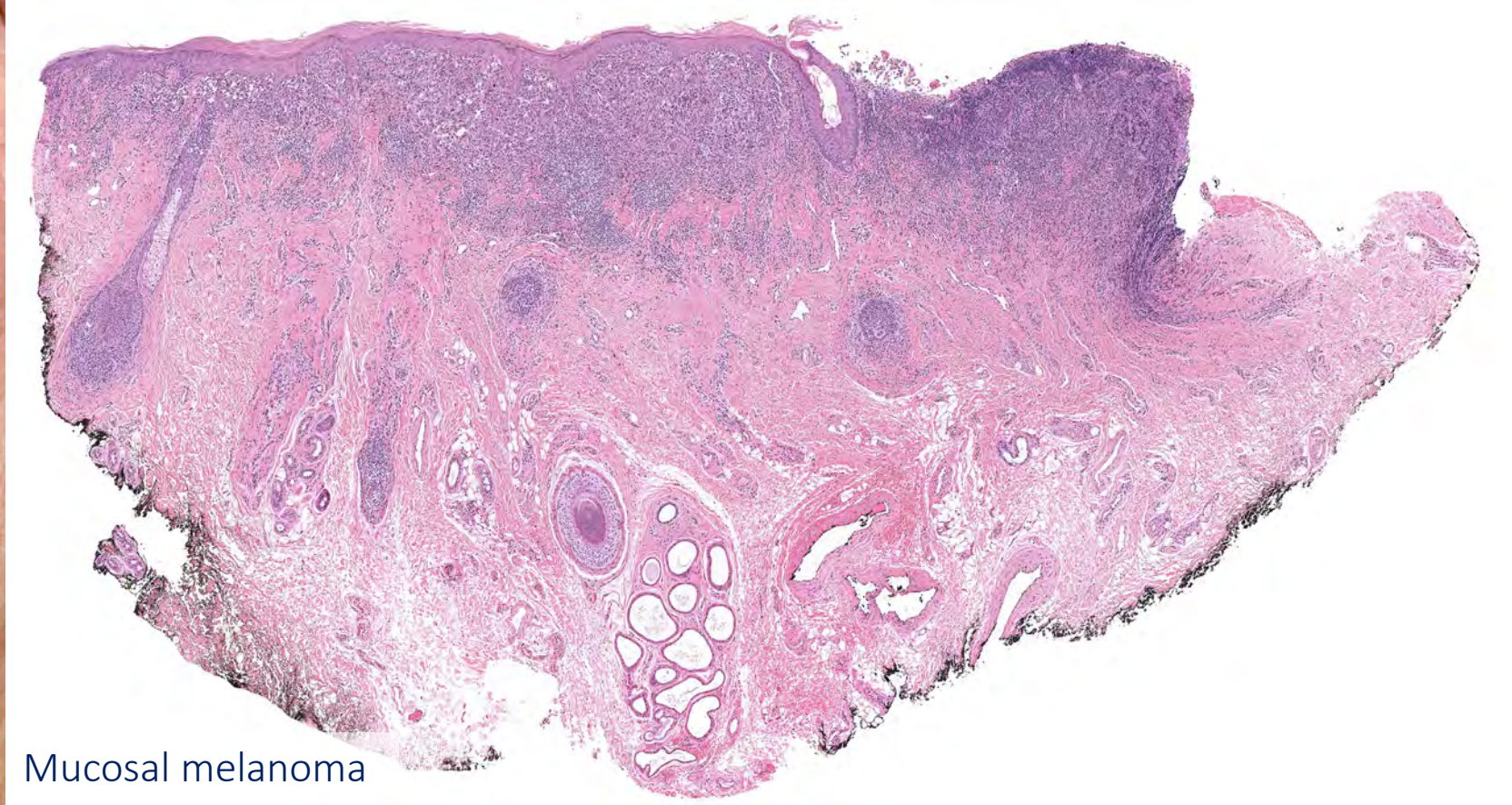




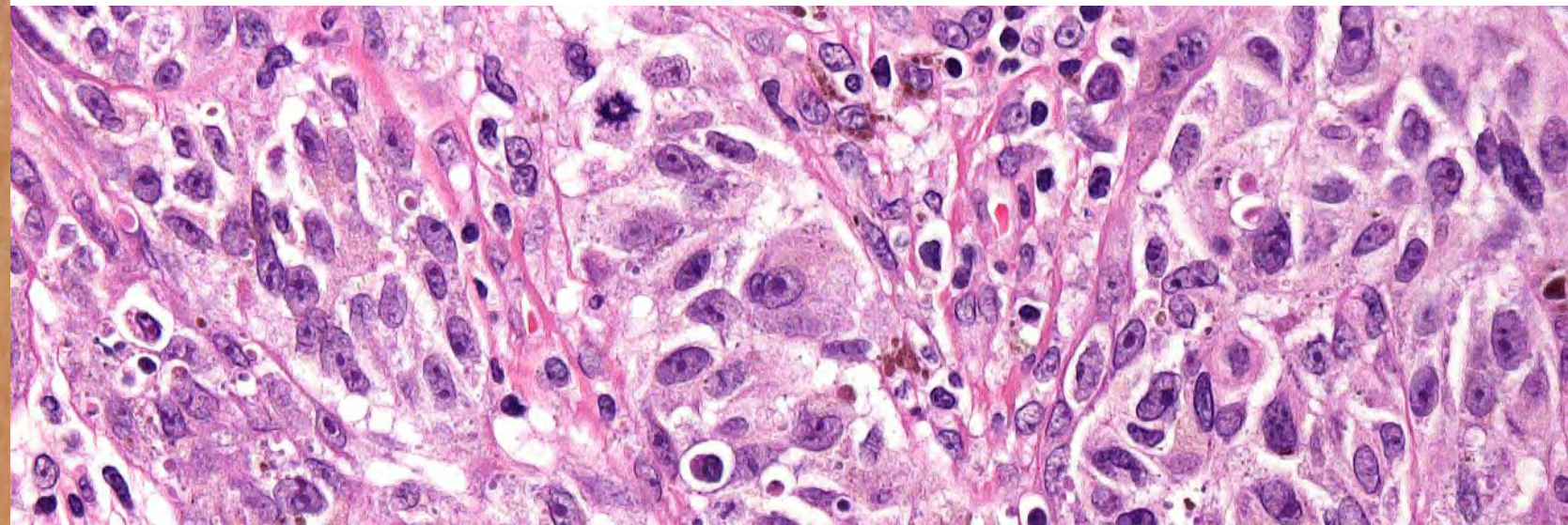
Acral melanoma (lentiginous)

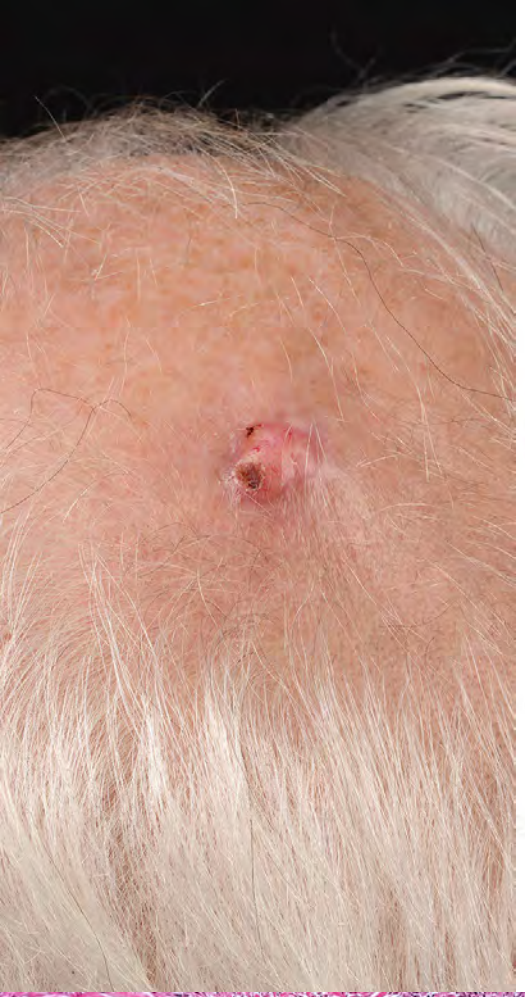


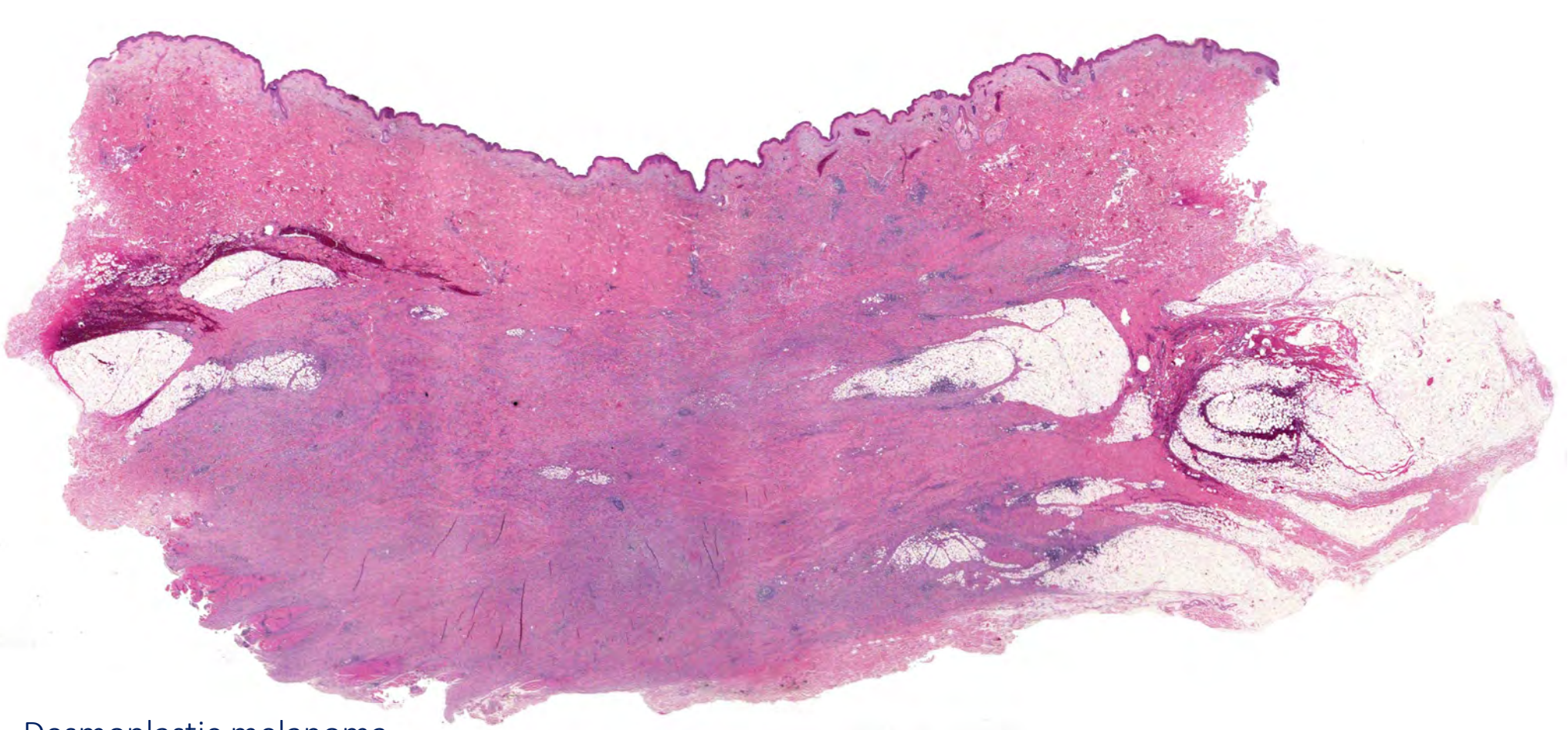




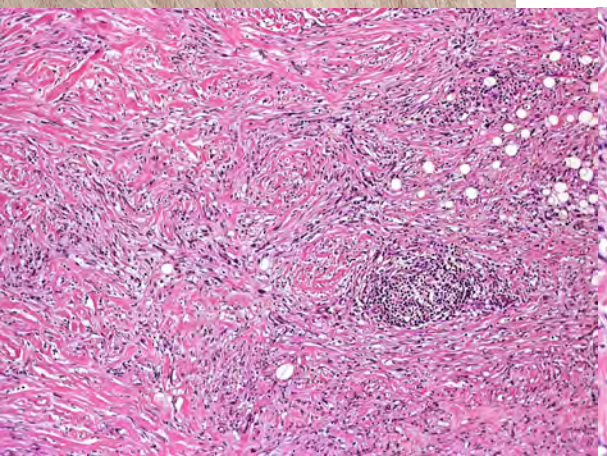
Mucosal melanoma

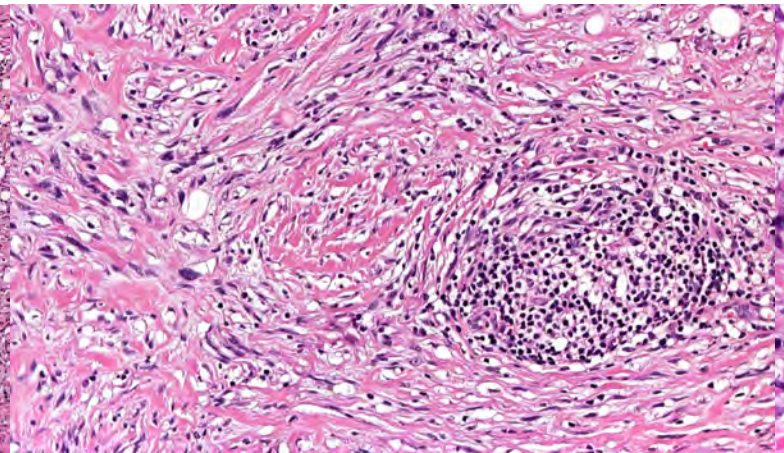


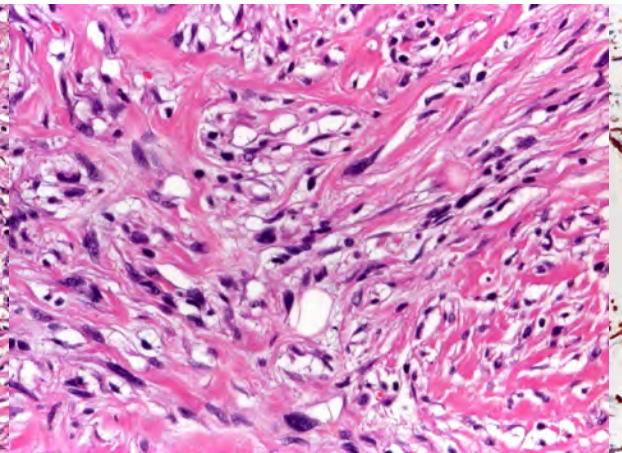


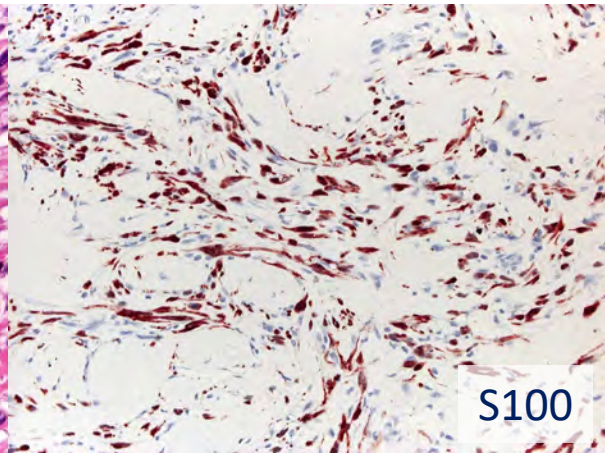


Desmoplastic melanoma









S100

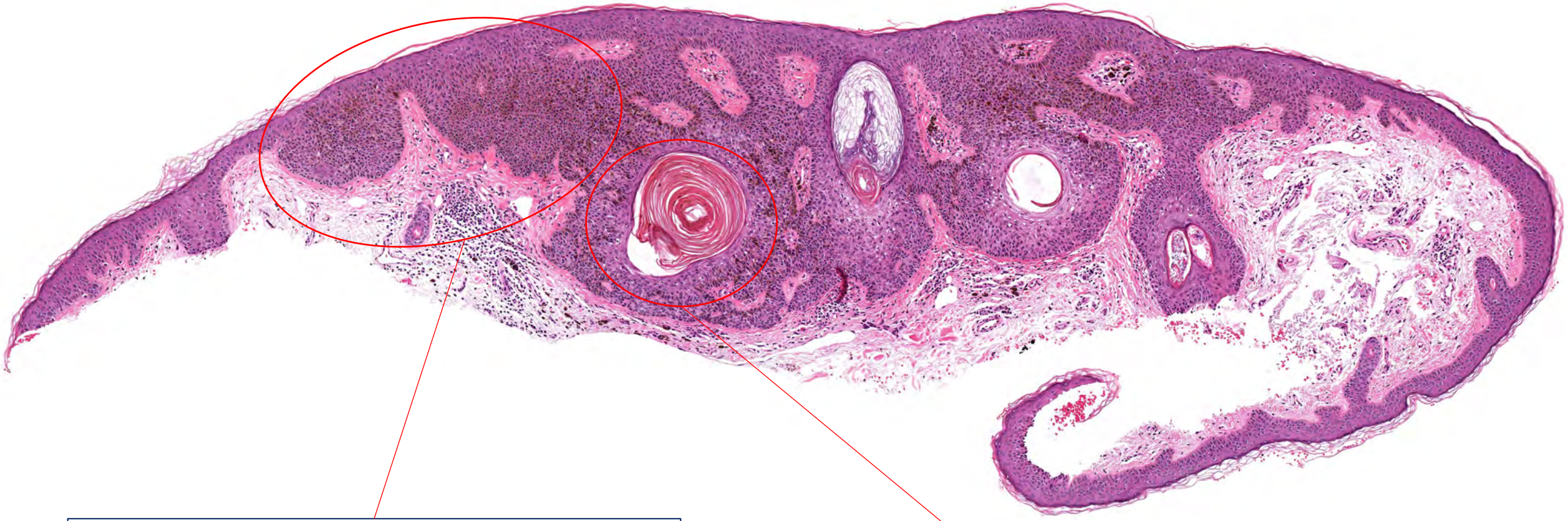
Immunohistology for melanocytic tumors

- **Differential diagnosis (undifferentiated malignant tumors):** *confirm melanocytic lineage by immunohistochemical stainings*
- **Differential diagnosis (melanocytic nevus vs. melanoma):** *the architecture of the lesion (symmetry, circumscription) may be better appreciated with immunostainings; PRAME, Ki-67 may provide useful diagnostic information; some Spitz tumors show specific staining according to the molecular pathway (yet no differentiation benign / malignant); some other stainings helpful in specific contexts*
- **Minimal invasion ("microinvasion"):** *a staining for melanocytes should be performed before rendering a diagnosis of MM "in situ"*
- **Depth of invasion:** *in some cases immunohistochemistry may be helpful in determining the depth of invasion (e.g., desmoplastic MM)*
- **Margins of excision:** *evaluation of the surgical margins may be easier with immunohistochemical stainings*

FÄLLE 85 – 100

CASE 85
M, 75. Face.

Seborrheic keratosis

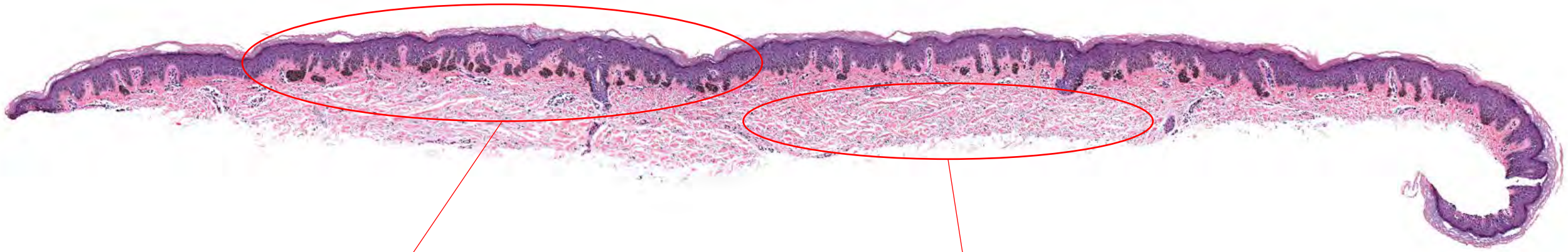


Irregular acanthosis of the epidermis with partly pigmented basaloid cells without atypia

"Pseudo" horn cyst

CASE 86
M, 57. Hand.

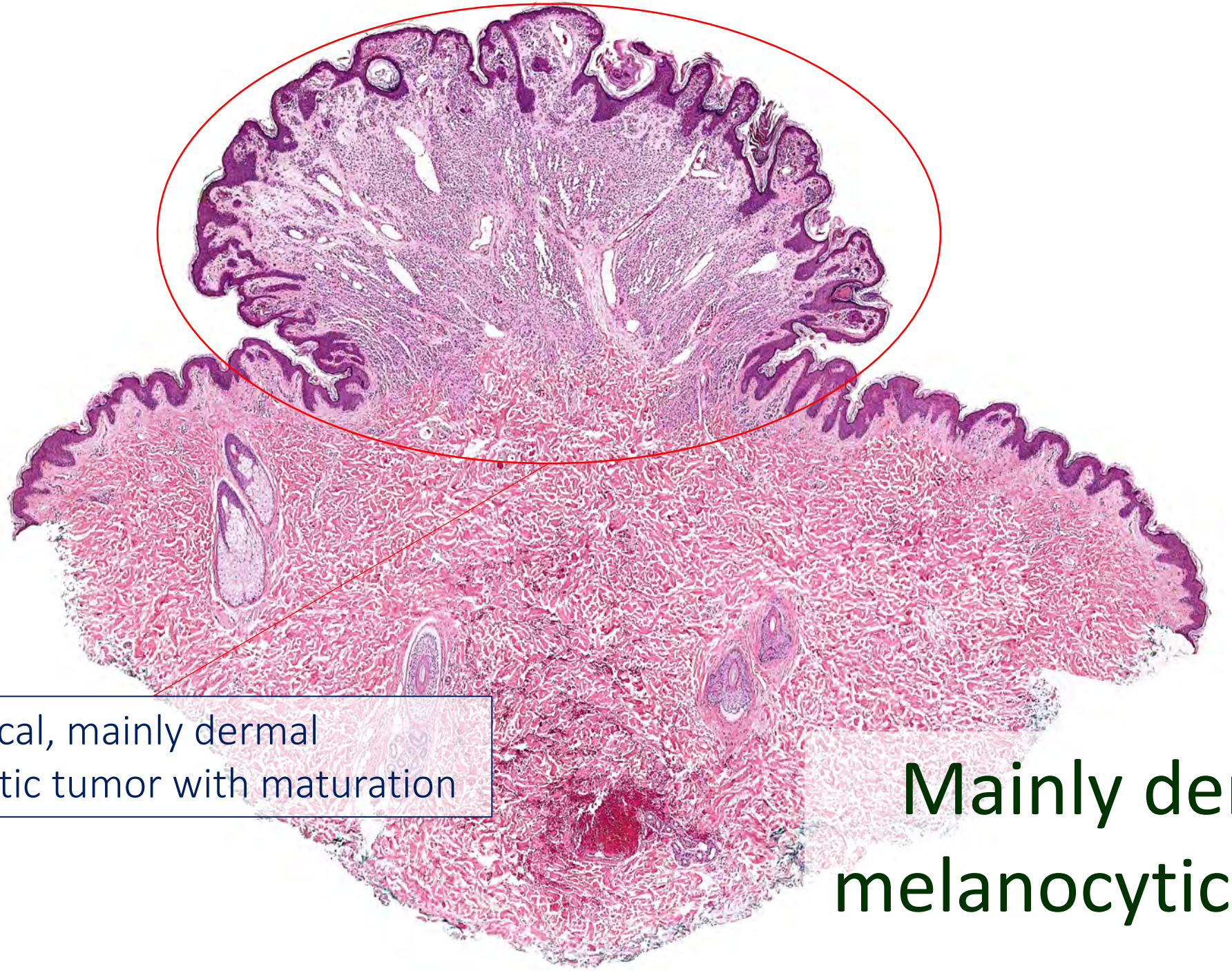
Lentigo actinica



Elongated, pigmented rete ridges without increase in the number of melanocytes

Actinic elastosis

CASE 87
M, 32. Back.

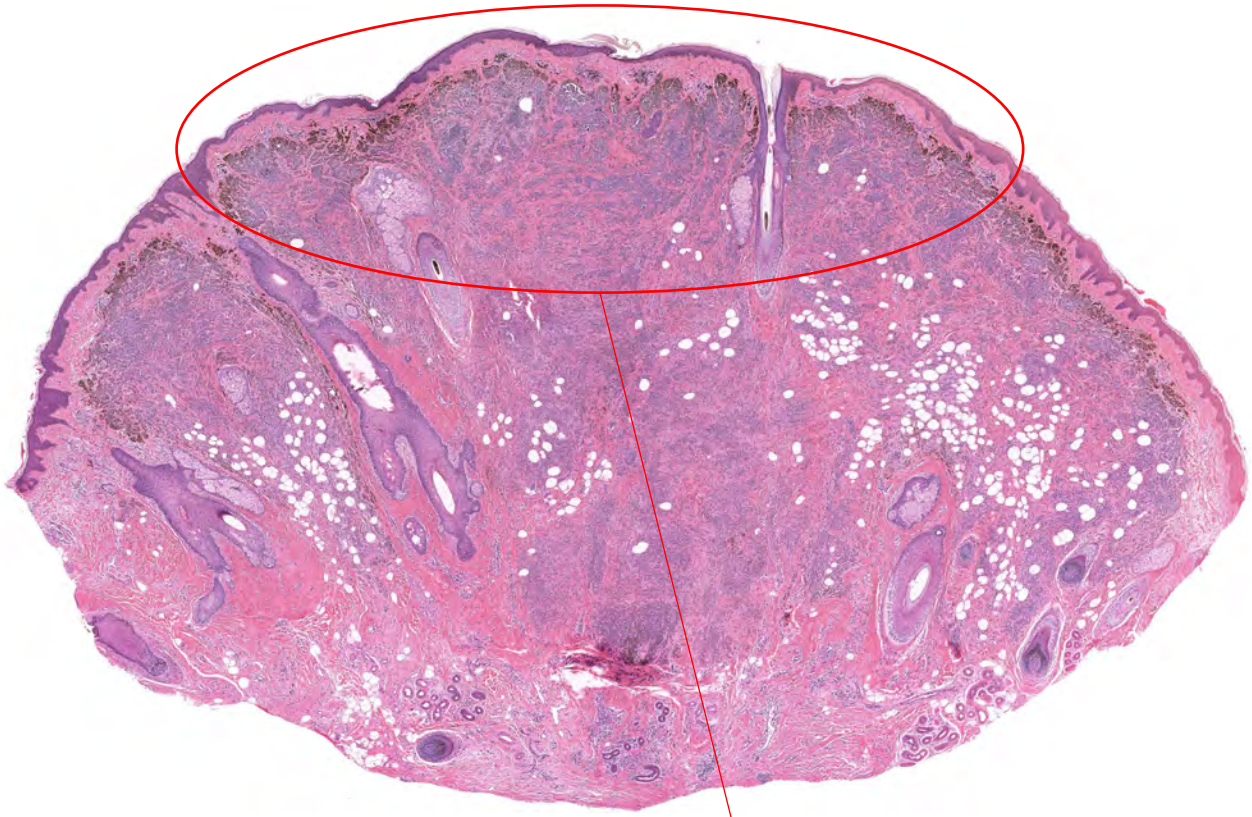


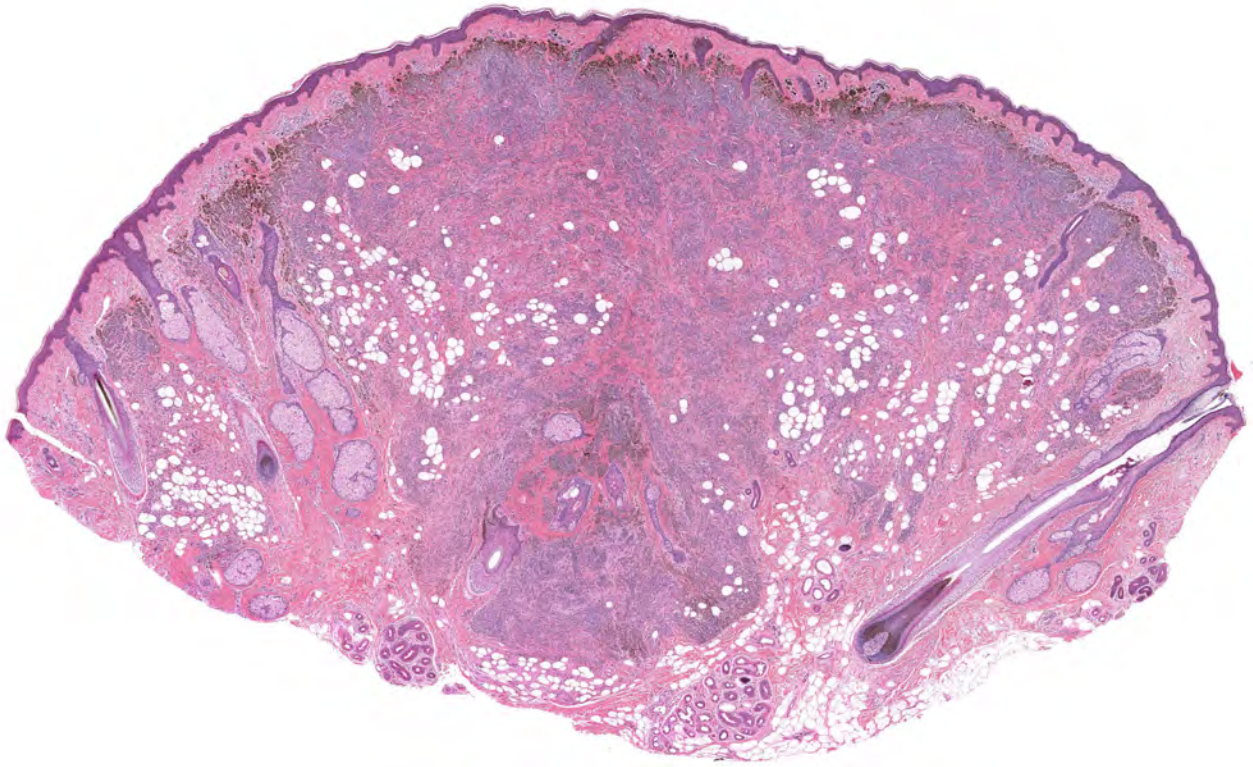
Symmetrical, mainly dermal melanocytic tumor with maturation

Mainly dermal melanocytic nevus

CASE 88
F, 38. Chin.

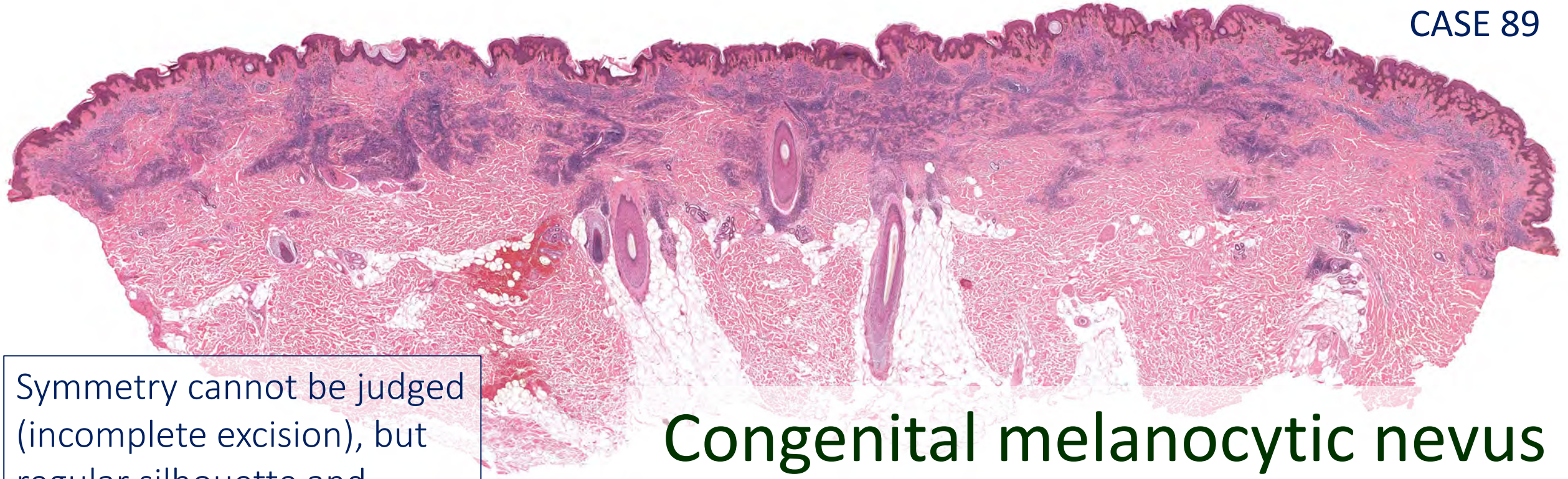
Dermal melanocytic nevus





Symmetrical, dermal melanocytic tumor with pigmentation located mostly within the upper portion of it

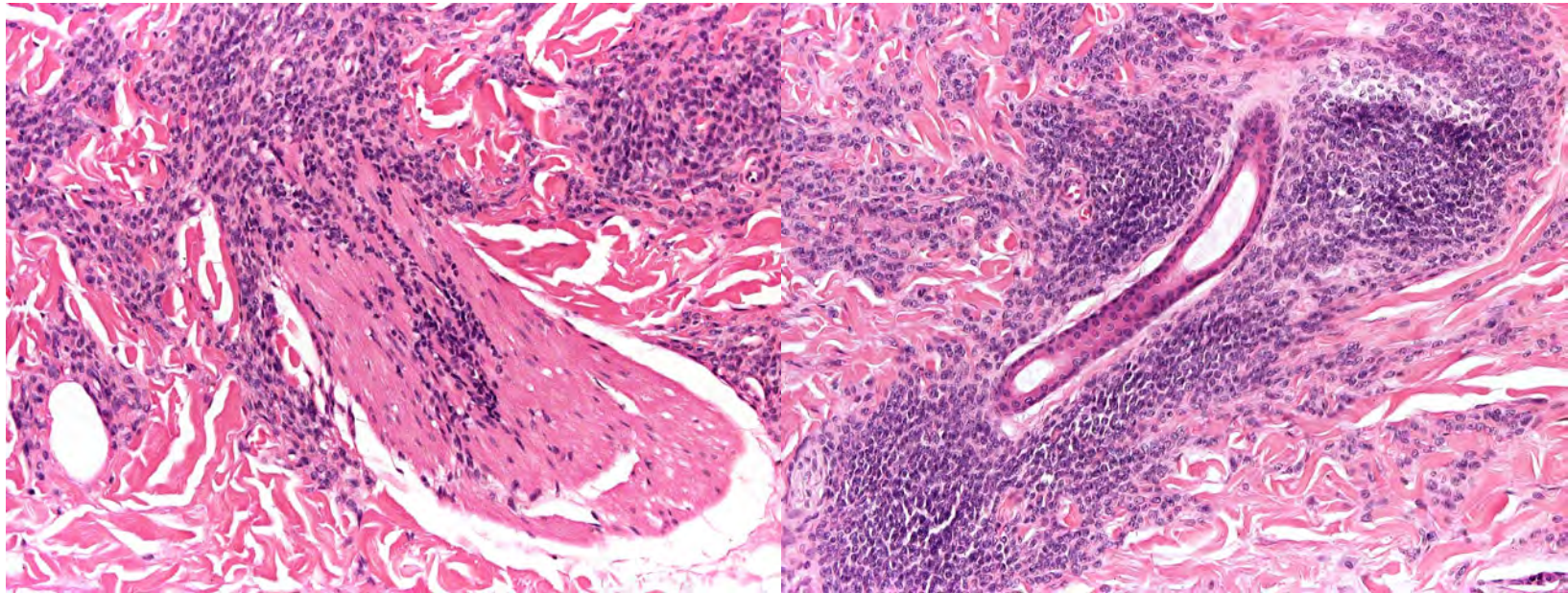
CASE 89



Congenital melanocytic nevus

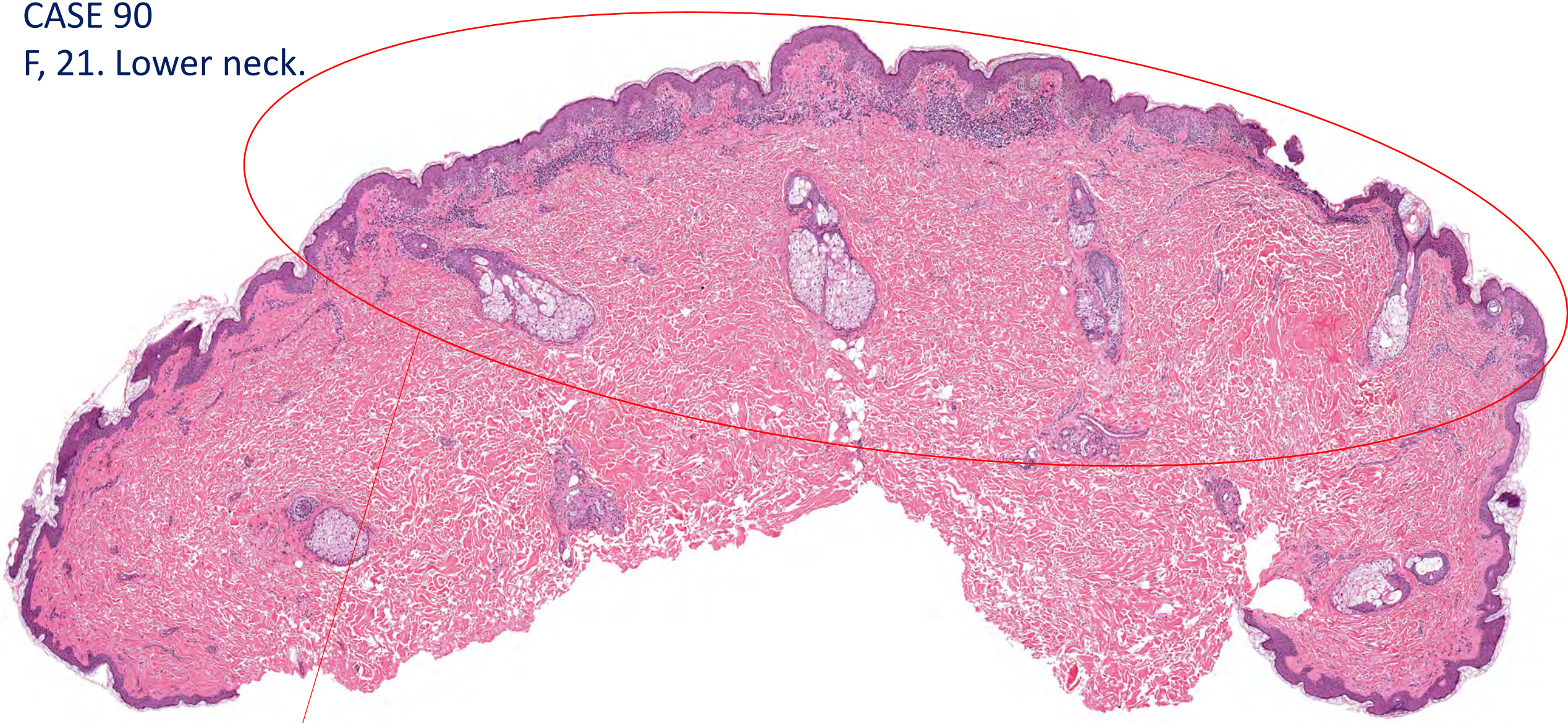
Symmetry cannot be judged (incomplete excision), but regular silhouette and regular distribution of pigment

Nevoid melanocytes without atypia growing along and focally within the adnexal structures

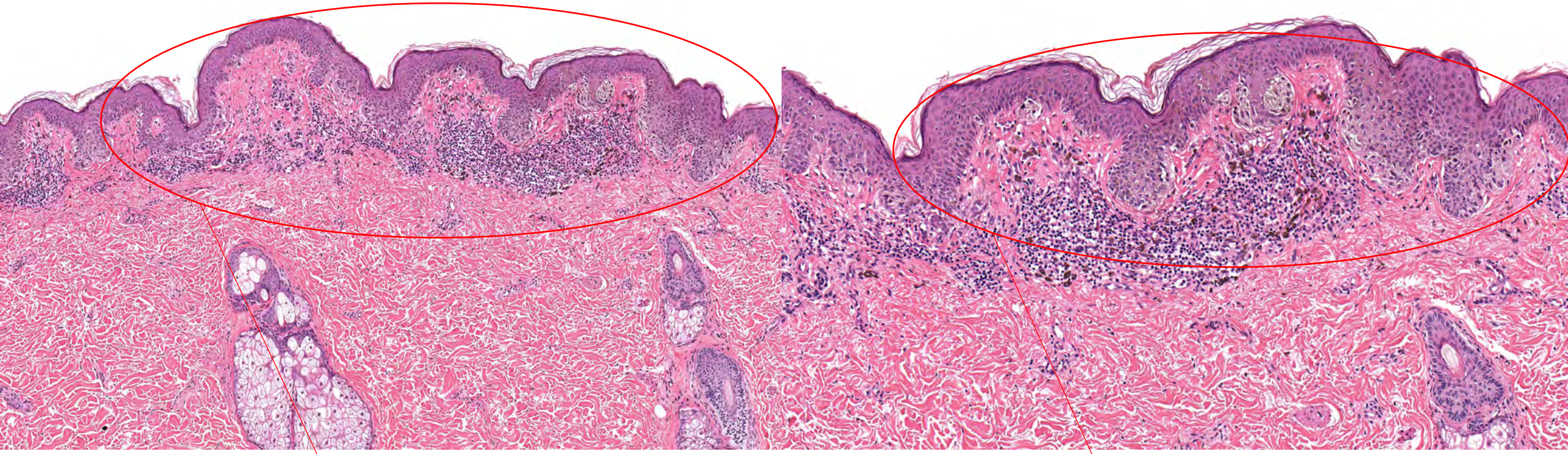


CASE 90

F, 21. Lower neck.



"Dysplastic" melanocytic nevus

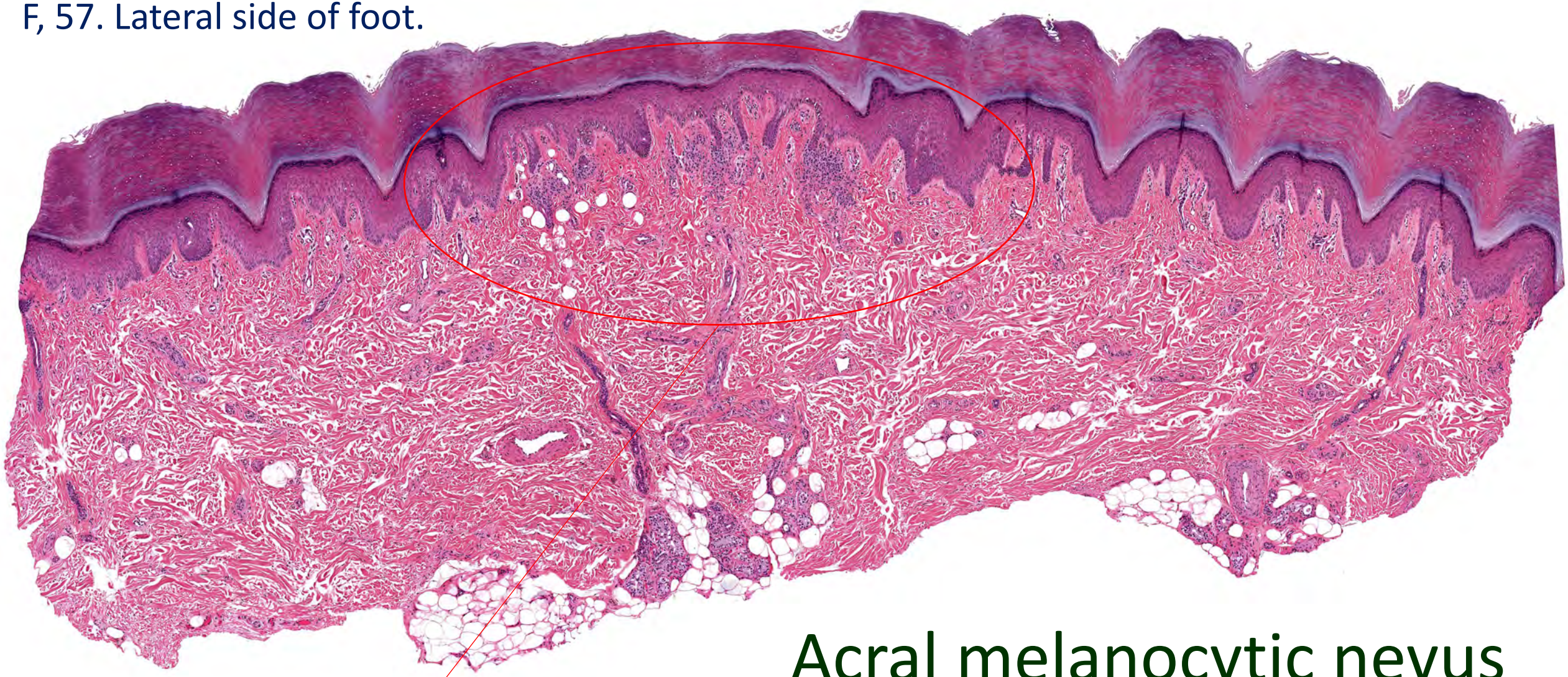


In the epidermis nests predominate over solitary melanocytes

Melanocytic complexes arranged mostly at the dermo-epidermal junction

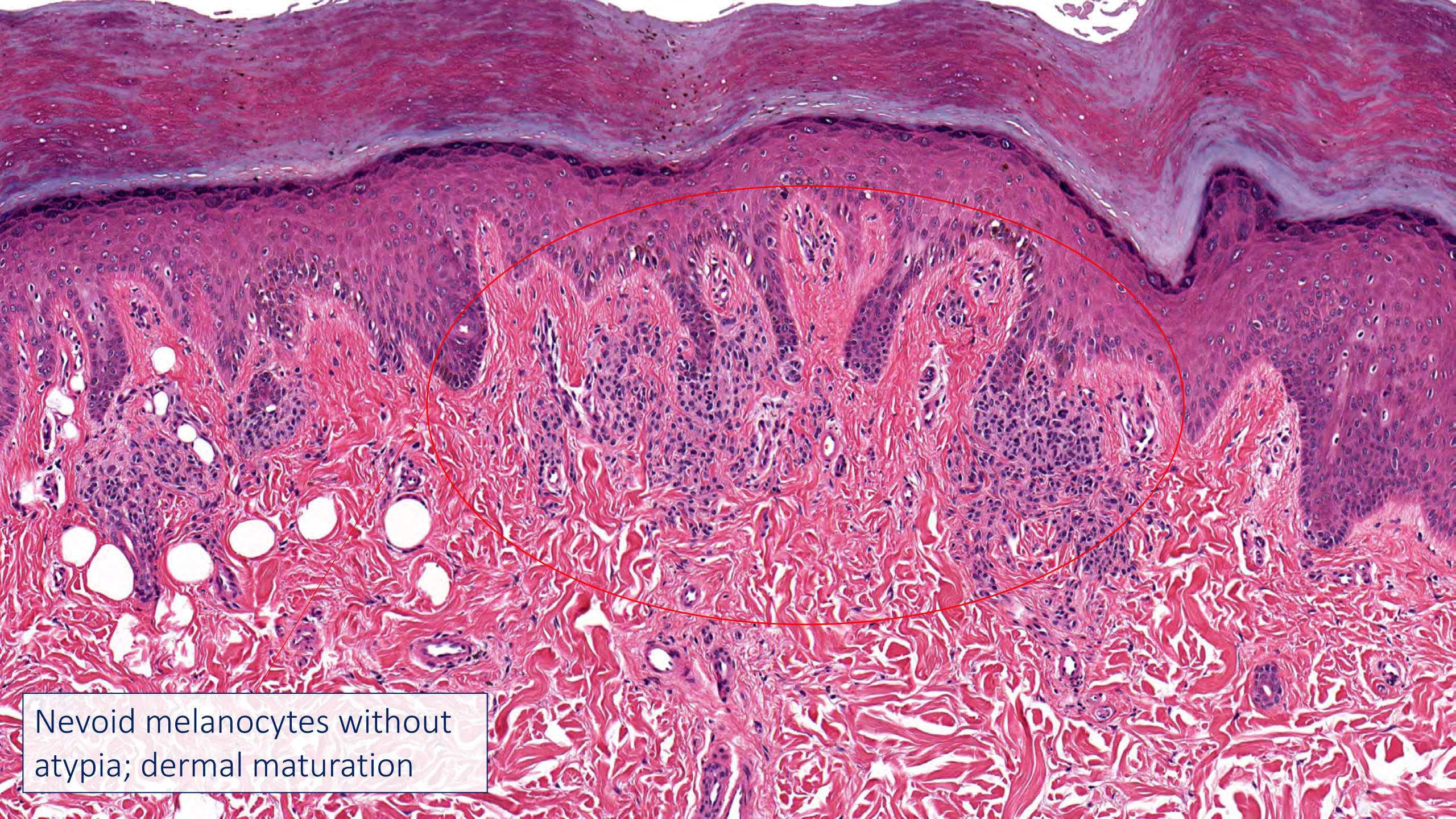
CASE 91

F, 57. Lateral side of foot.

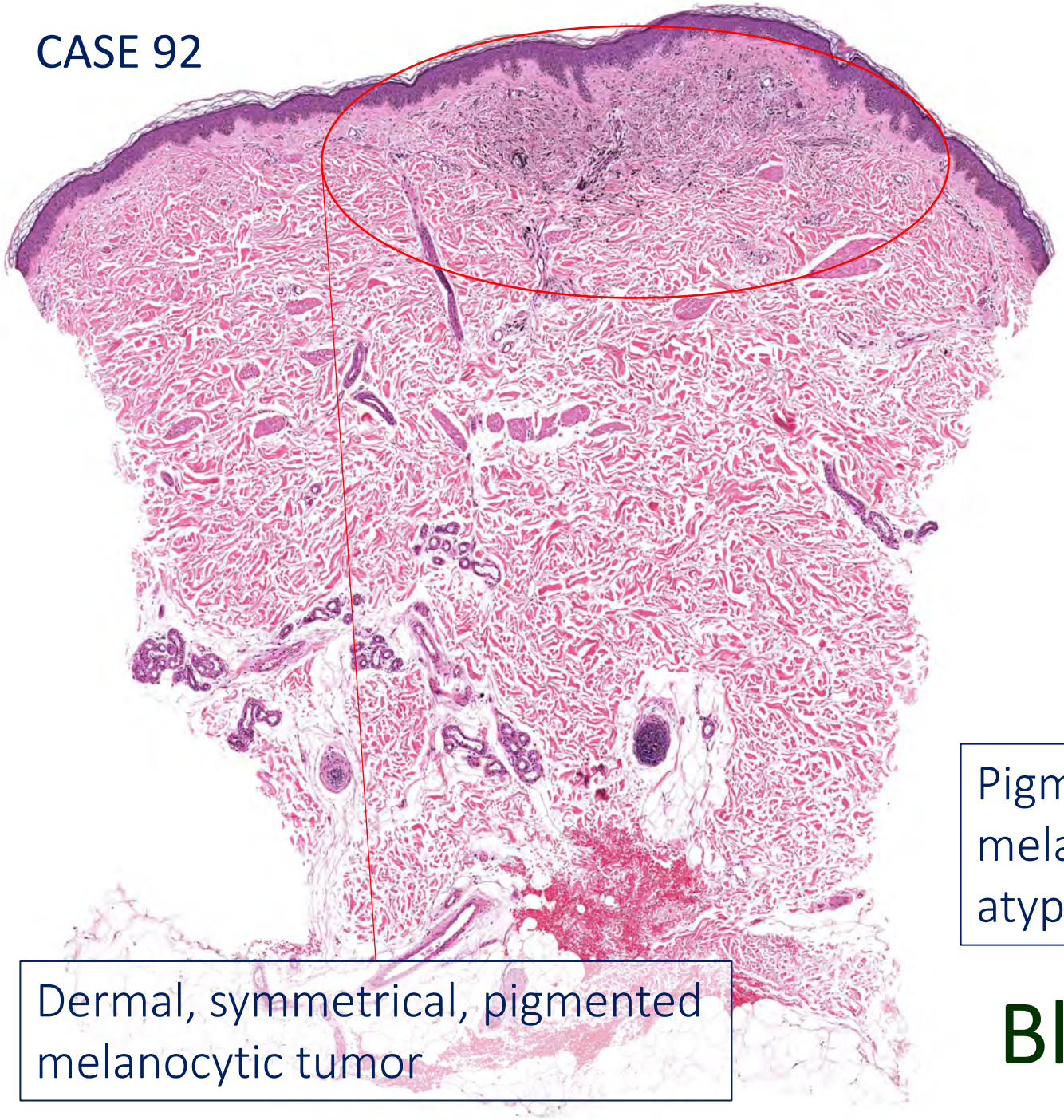


Acral melanocytic nevus

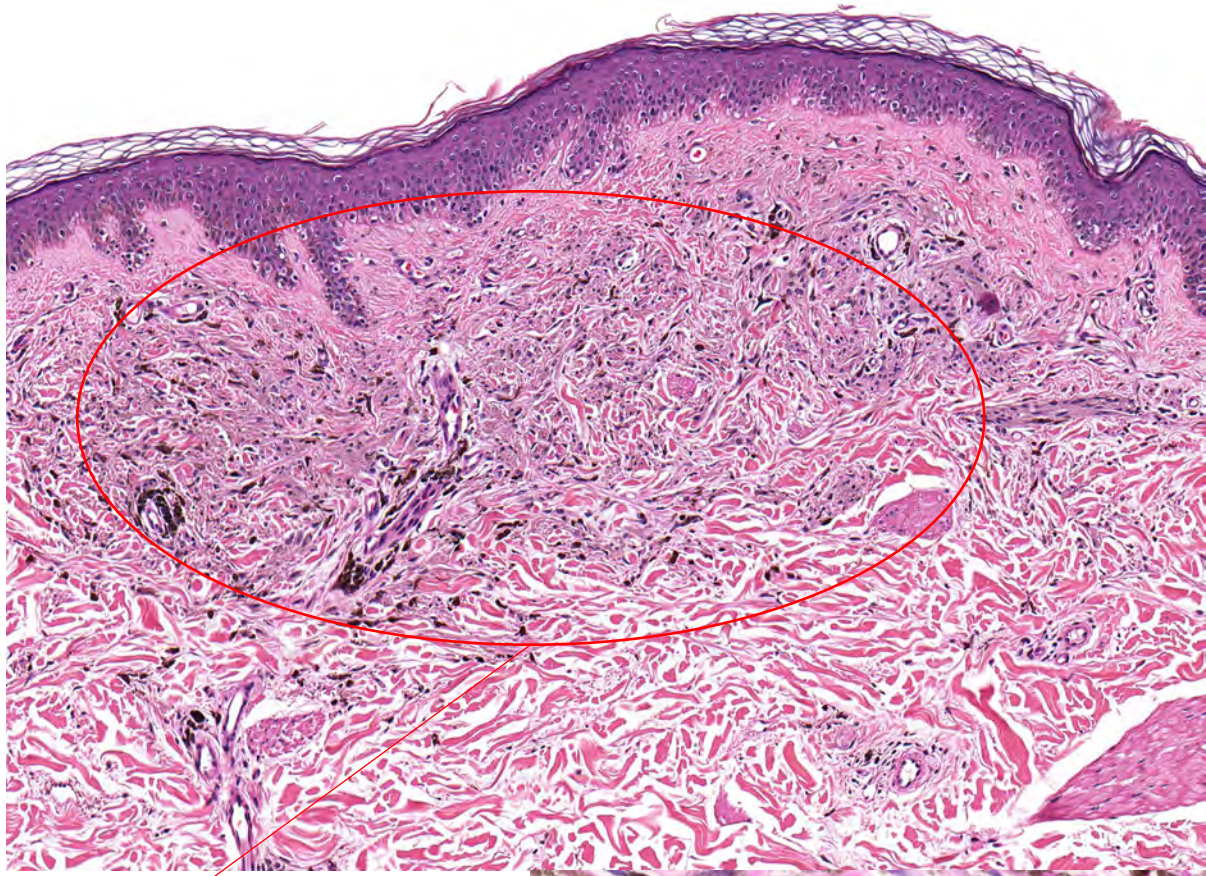
Symmetrical melanocytic tumor on acral skin


Nevoid melanocytes without atypia; dermal maturation

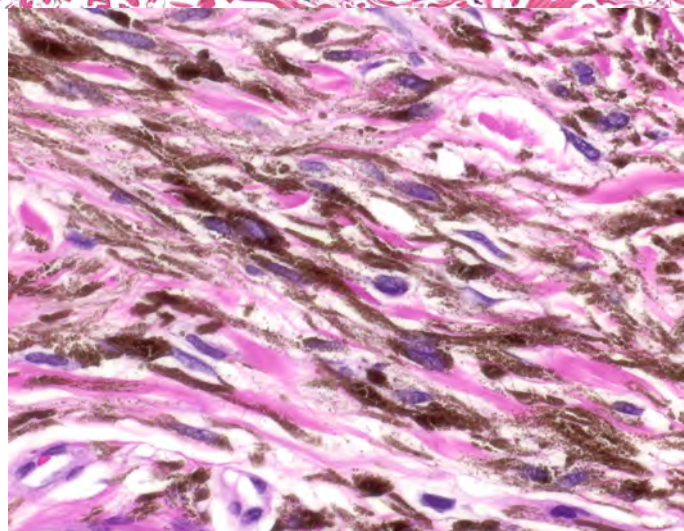
CASE 92



Dermal, symmetrical, pigmented melanocytic tumor

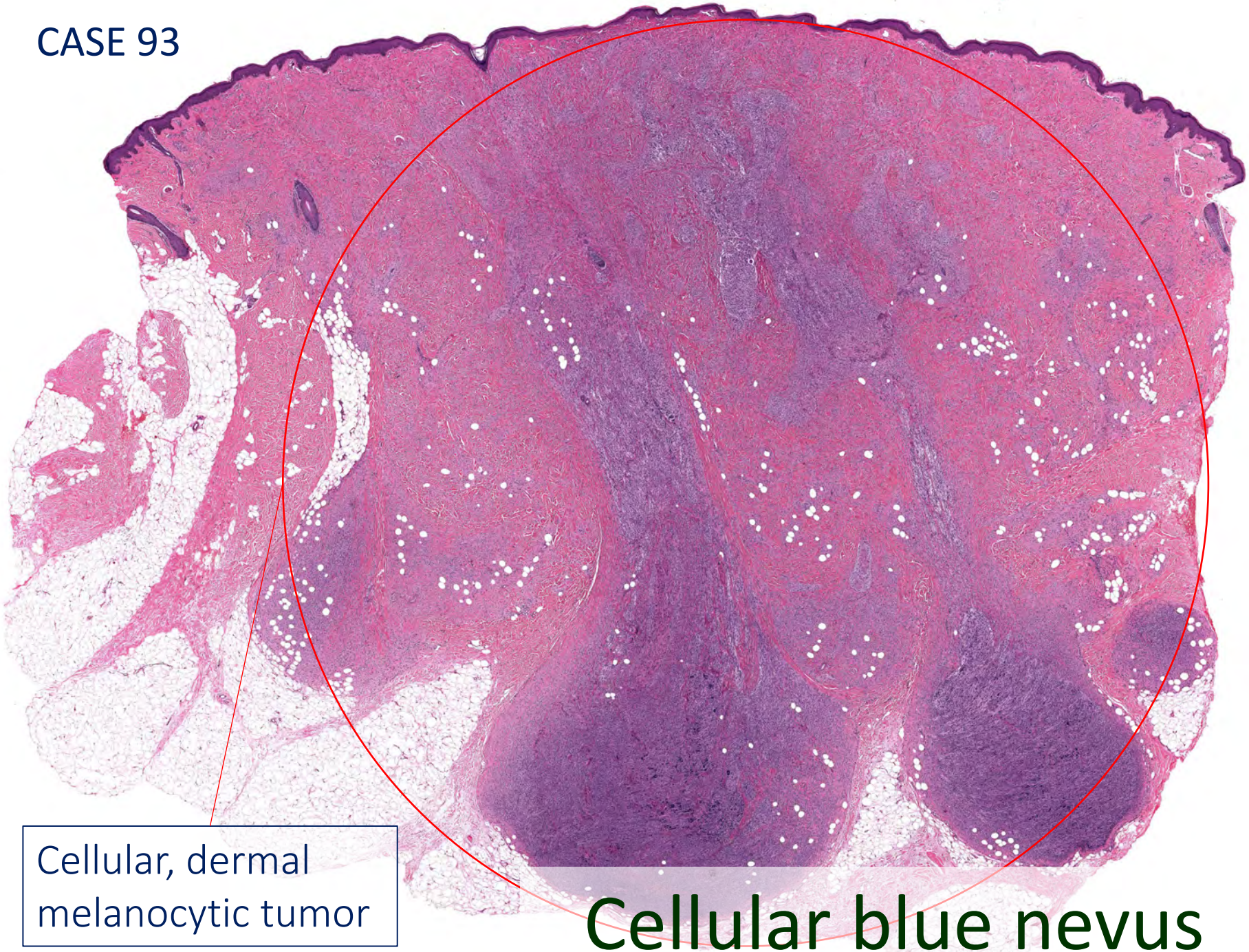


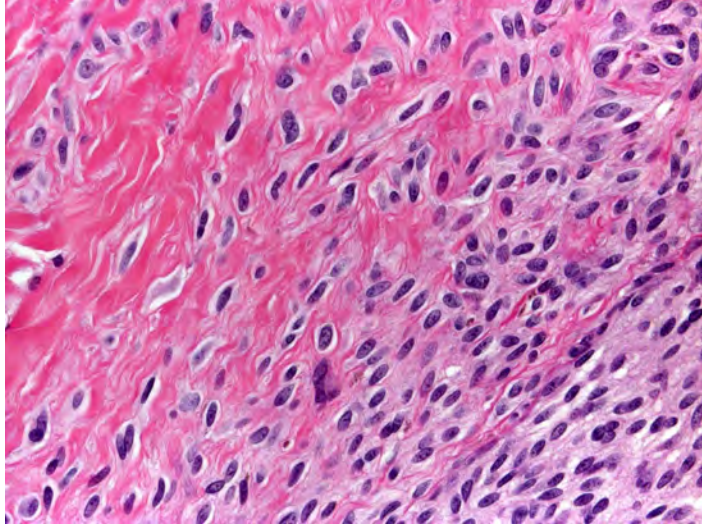
Pigmented, dendritic melanocytes without atypia



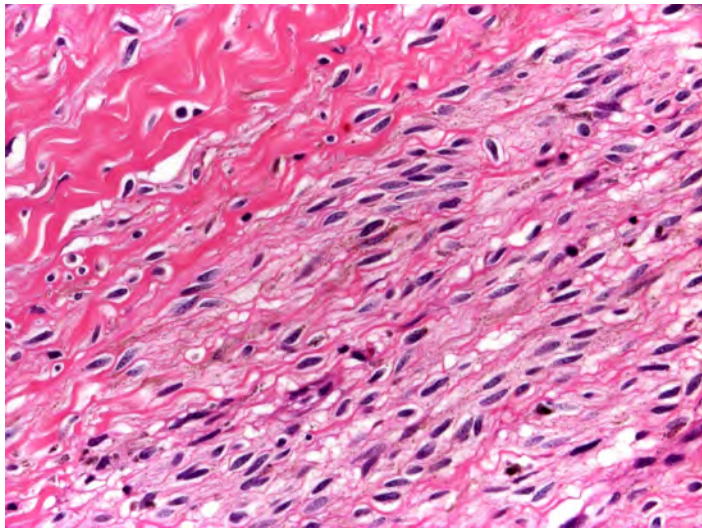
Blue nevus

CASE 93





Oval, spindled and a few dendritic melanocytes without atyipia

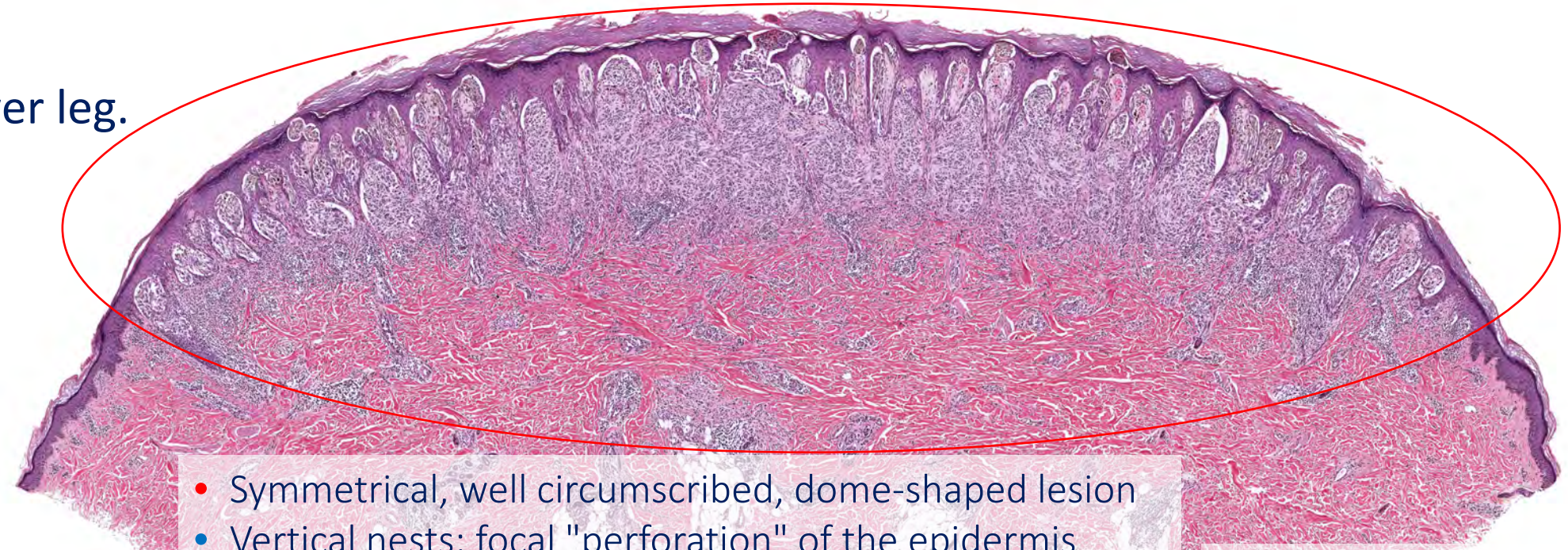


Cellular, dermal melanocytic tumor

Cellular blue nevus

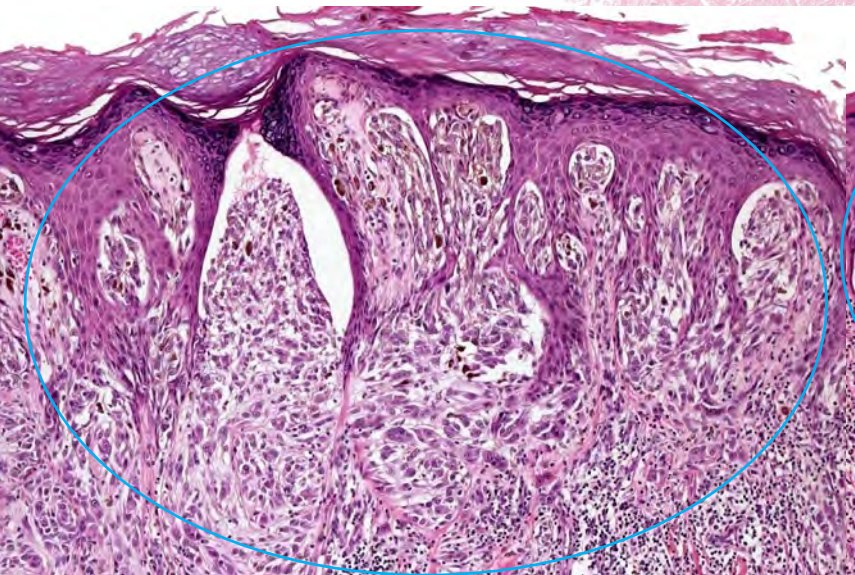
CASE 94

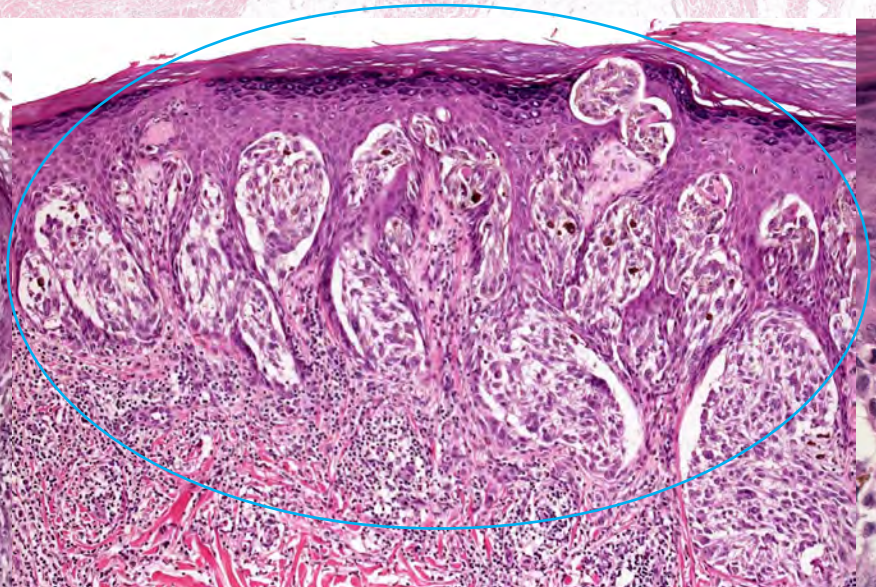
F, 6. Lower leg.

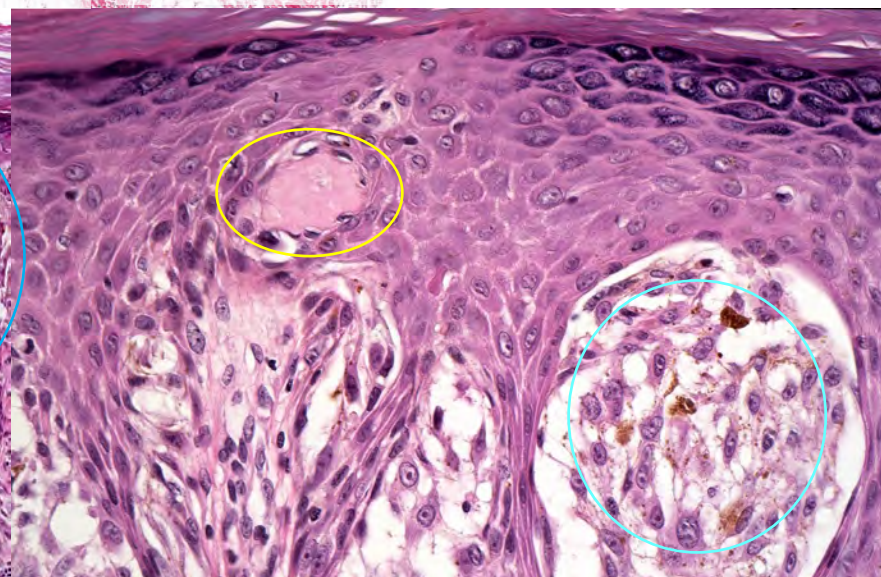


- Symmetrical, well circumscribed, dome-shaped lesion
- Vertical nests; focal "perforation" of the epidermis
- Spindle and epithelioid cells
- "Kamino bodies"

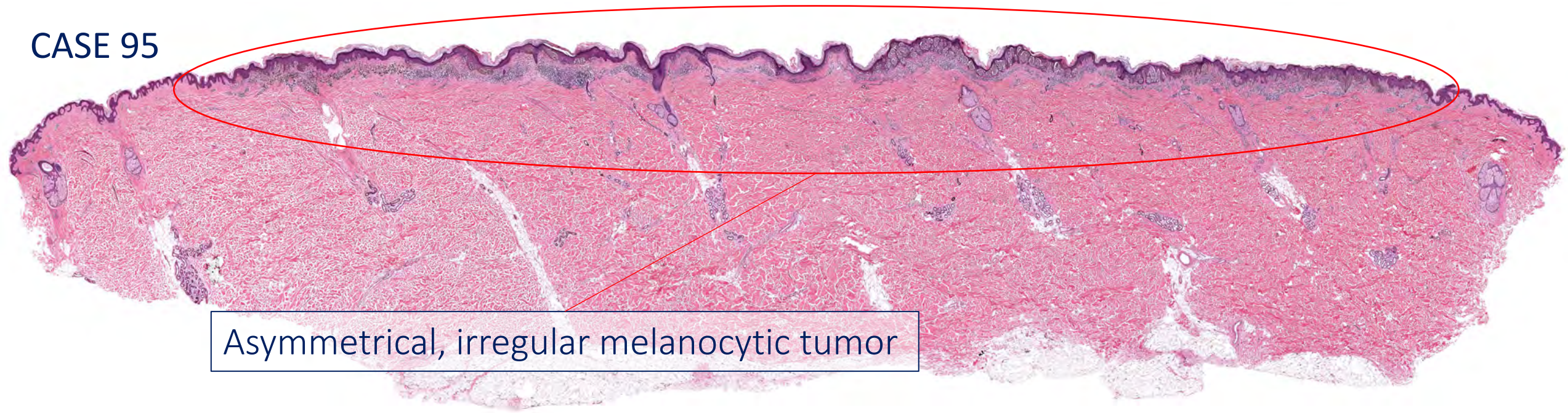
Spitz nevus



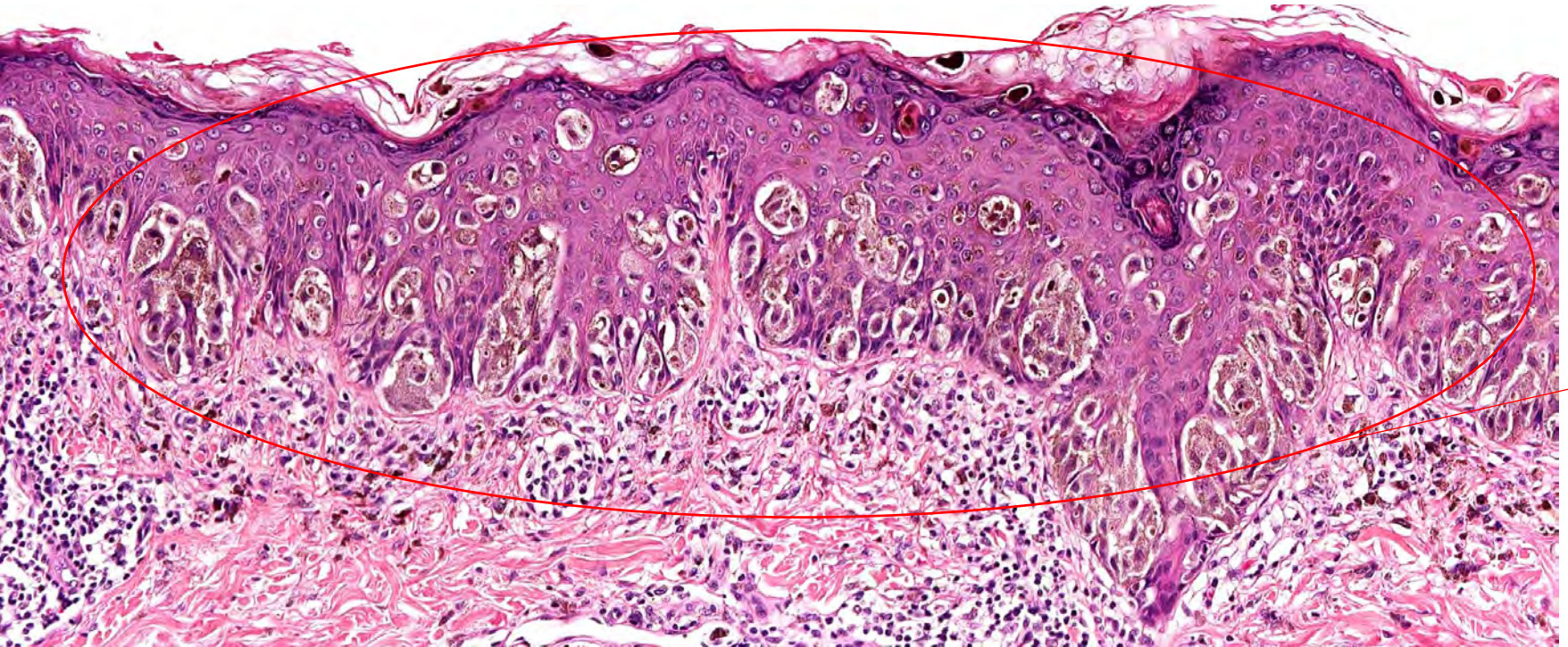




CASE 95



Asymmetrical, irregular melanocytic tumor

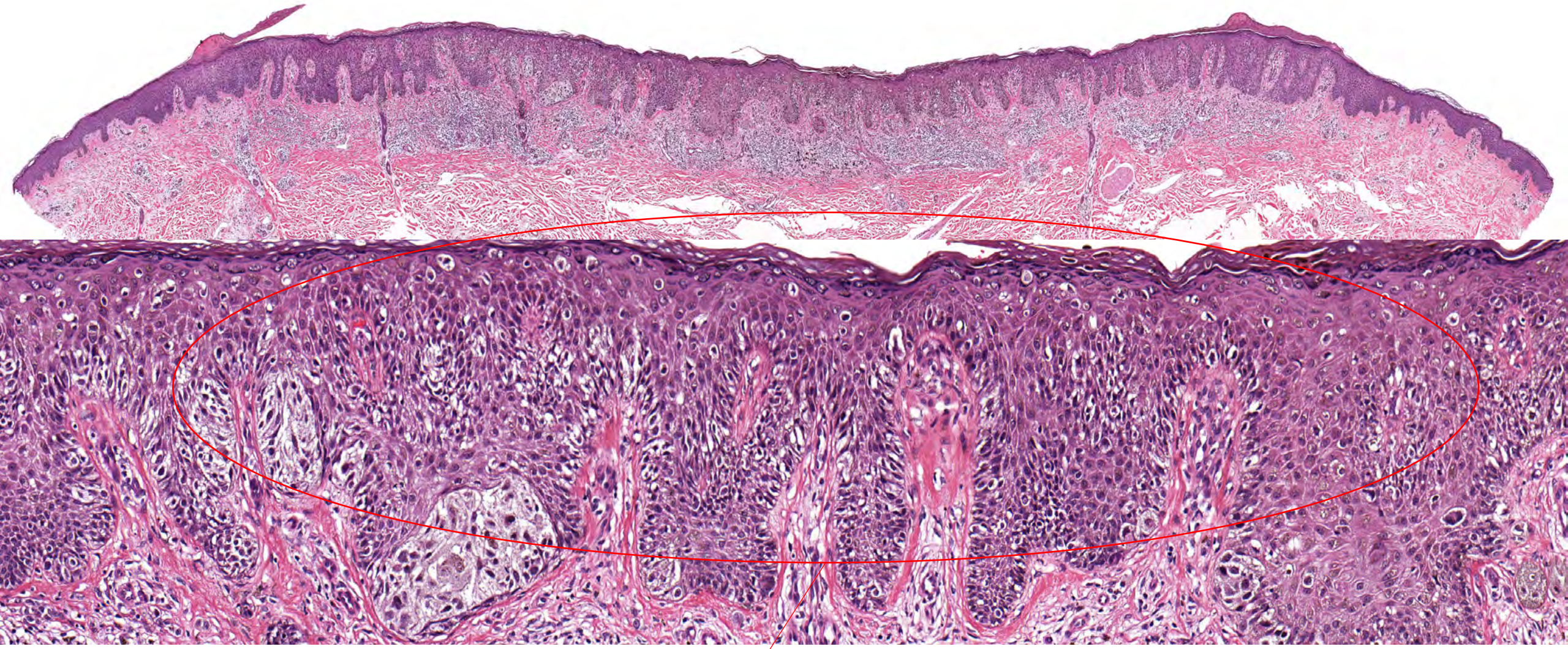


"Pagetoid" spread of intraepidermal melanocytes

Melanoma in situ

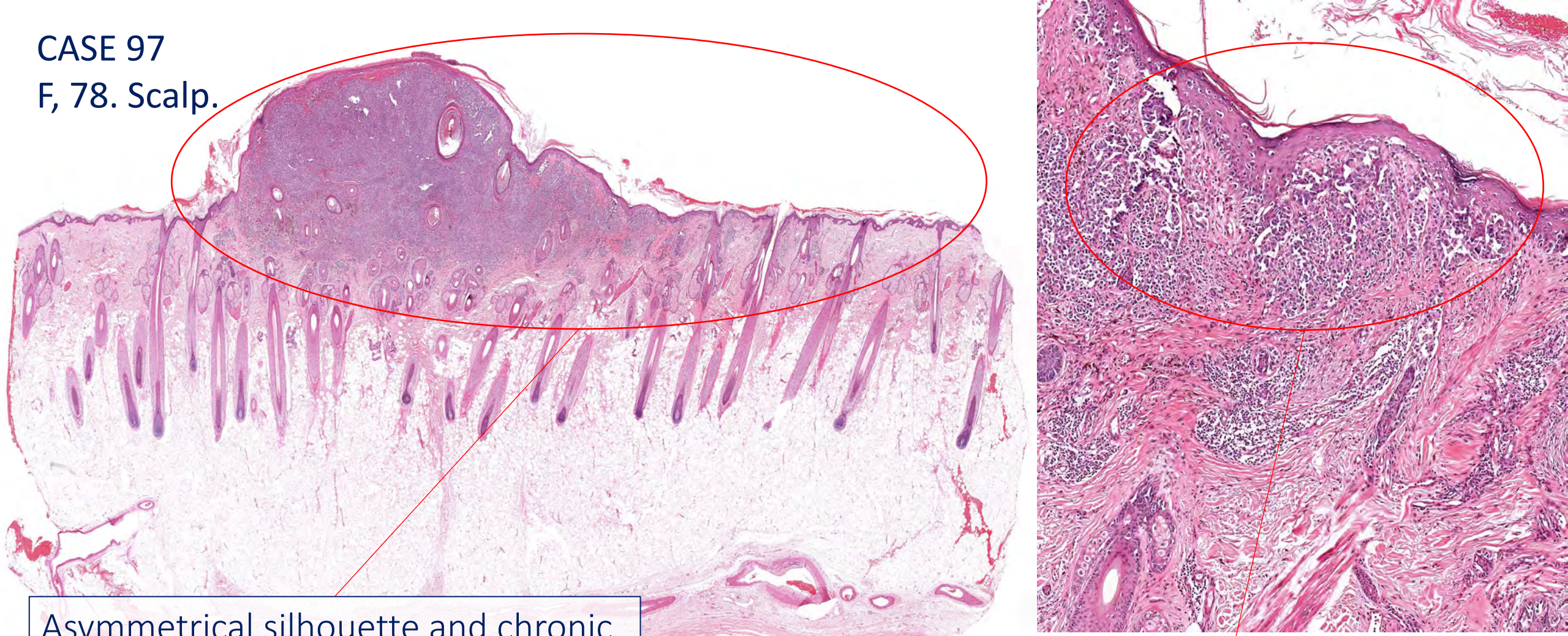
CASE 96
F, 31. Lower leg.

Melanoma *(superficial spreading)*



Pagetoid spread of pleomorphic melanocytes in all layers of the epidermis, including the horny layer

CASE 97
F, 78. Scalp.



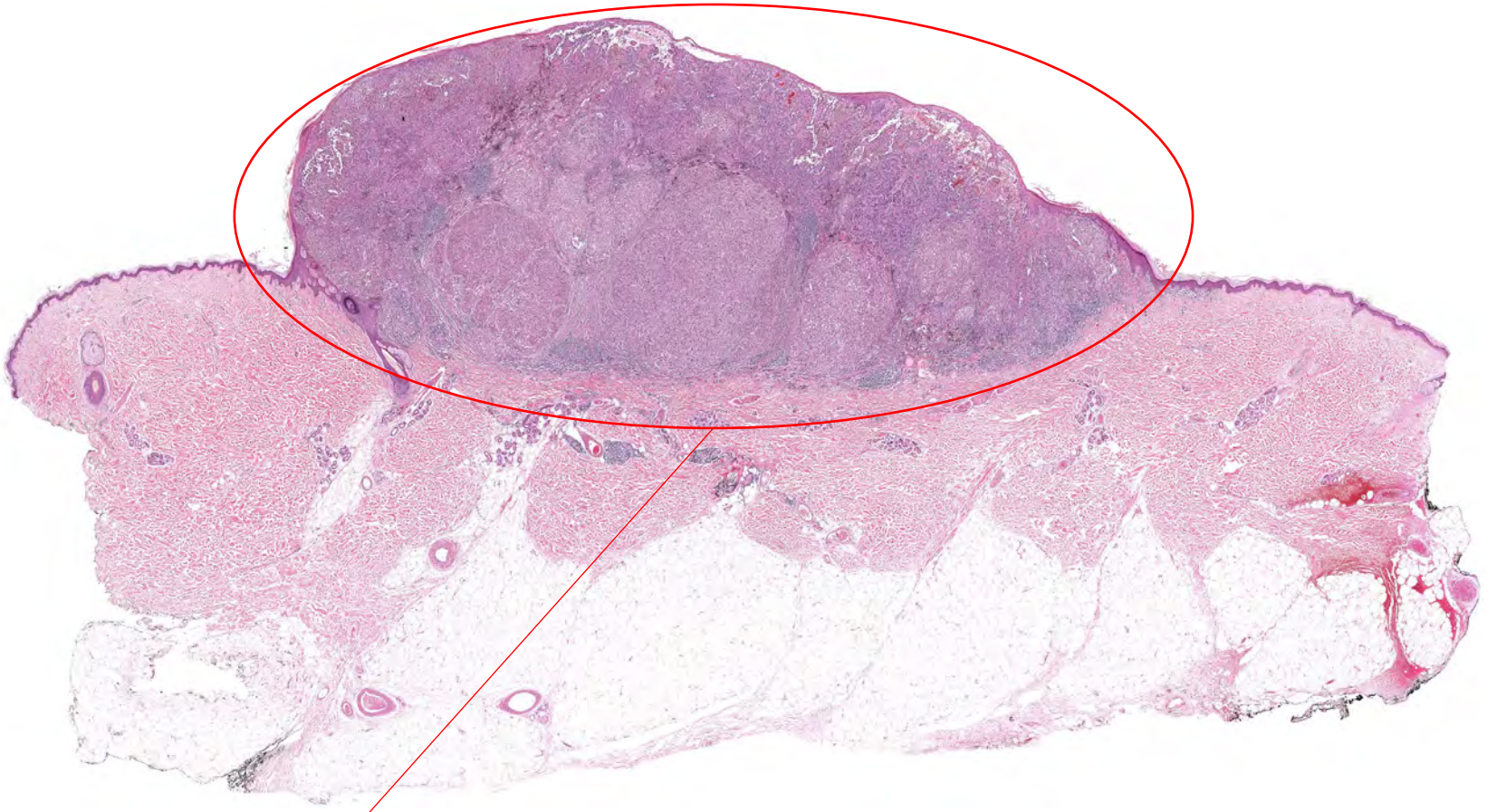
Asymmetrical silhouette and chronic sun-damage (actinic elastosis)

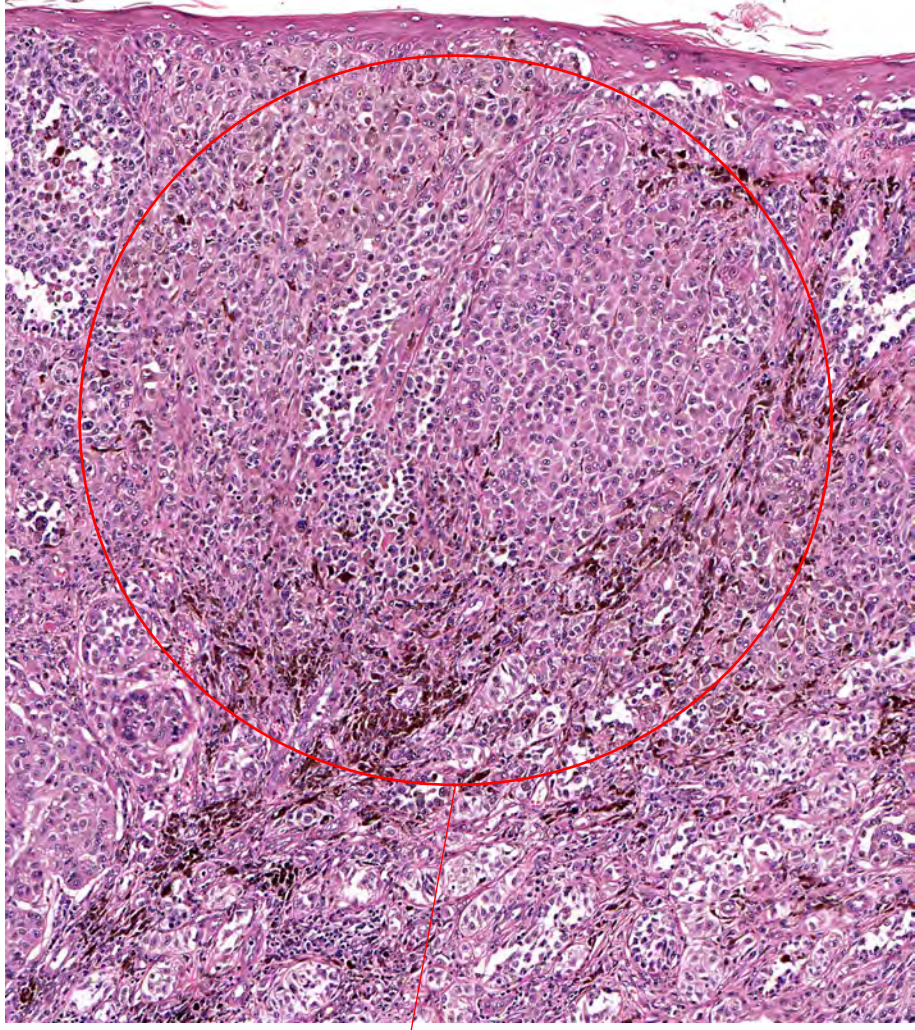
Pagetoid spread of melanocytes in all layers of the epidermis

Melanoma

(lentigo maligna melanoma)

CASE 98
M, 65. Thorax.





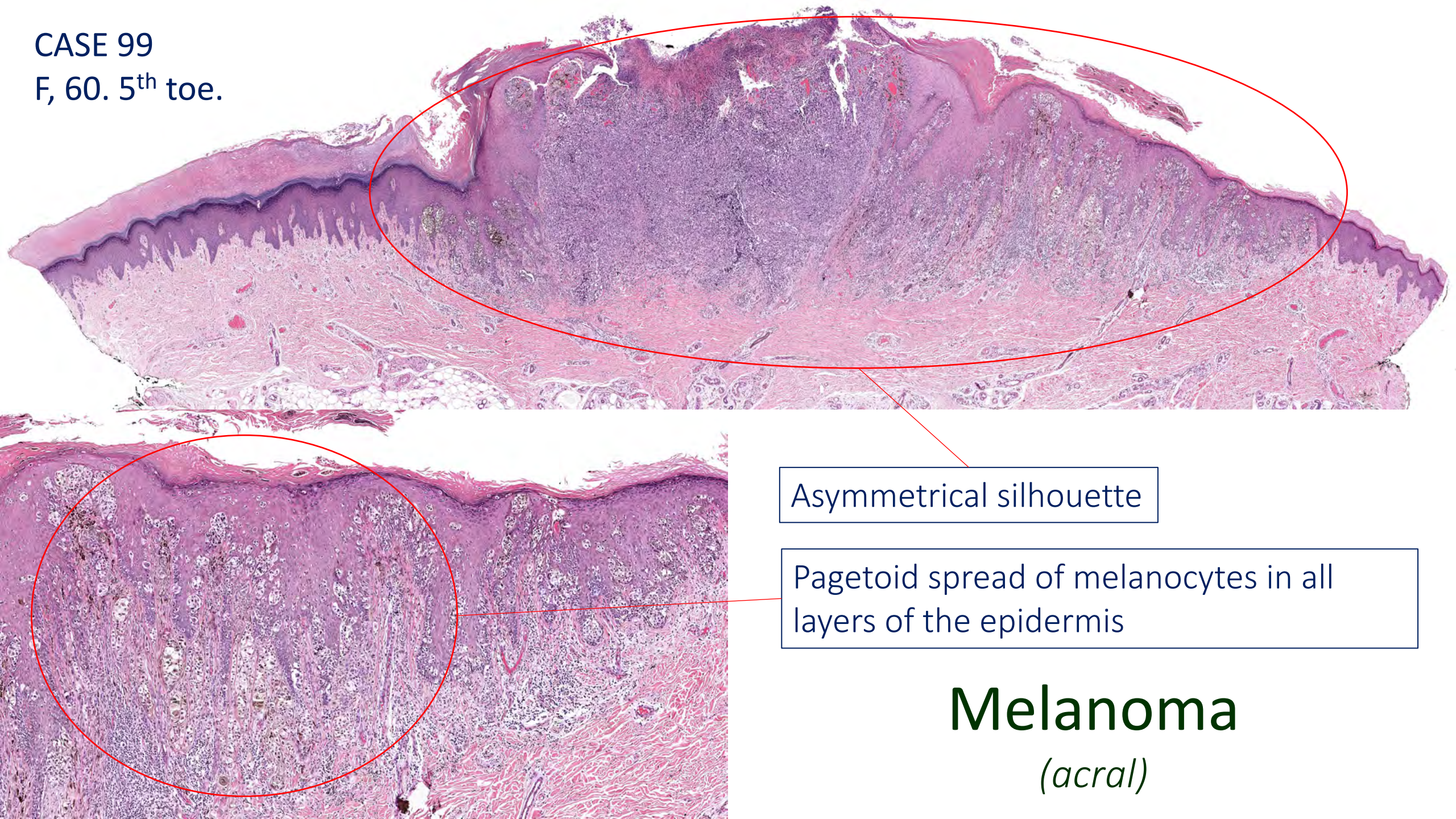
Asymmetrical silhouette

Melanoma

(nodular)

Atypical, pleomorphic melanocytes without maturation

CASE 99
F, 60. 5th toe.



Asymmetrical silhouette

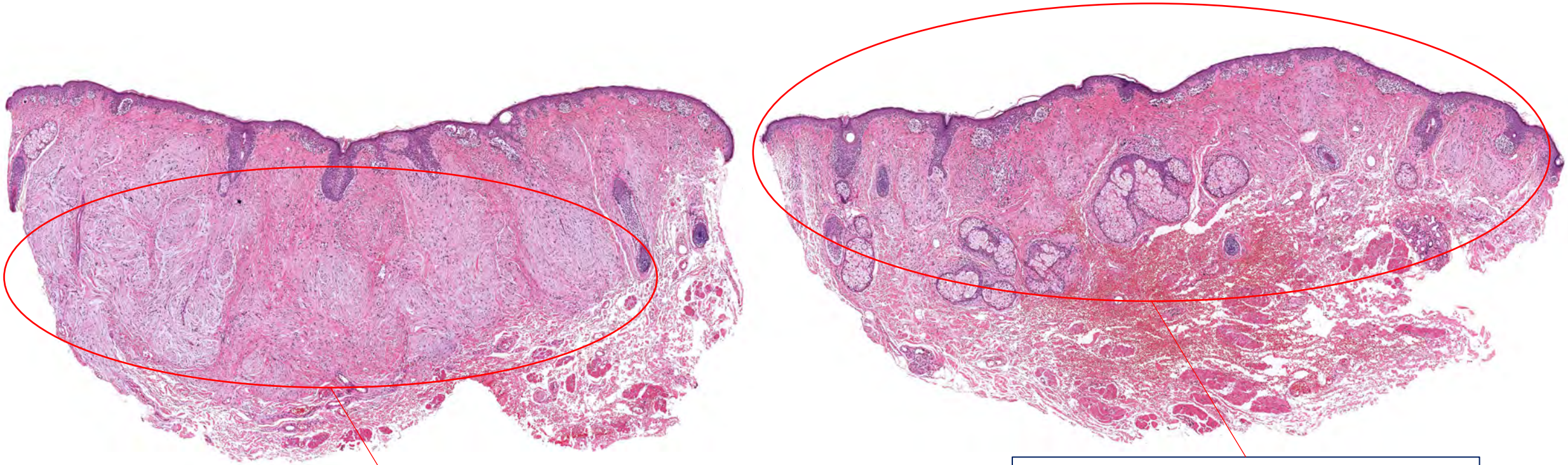
Pagetoid spread of melanocytes in all layers of the epidermis

Melanoma

(acral)

CASE 100

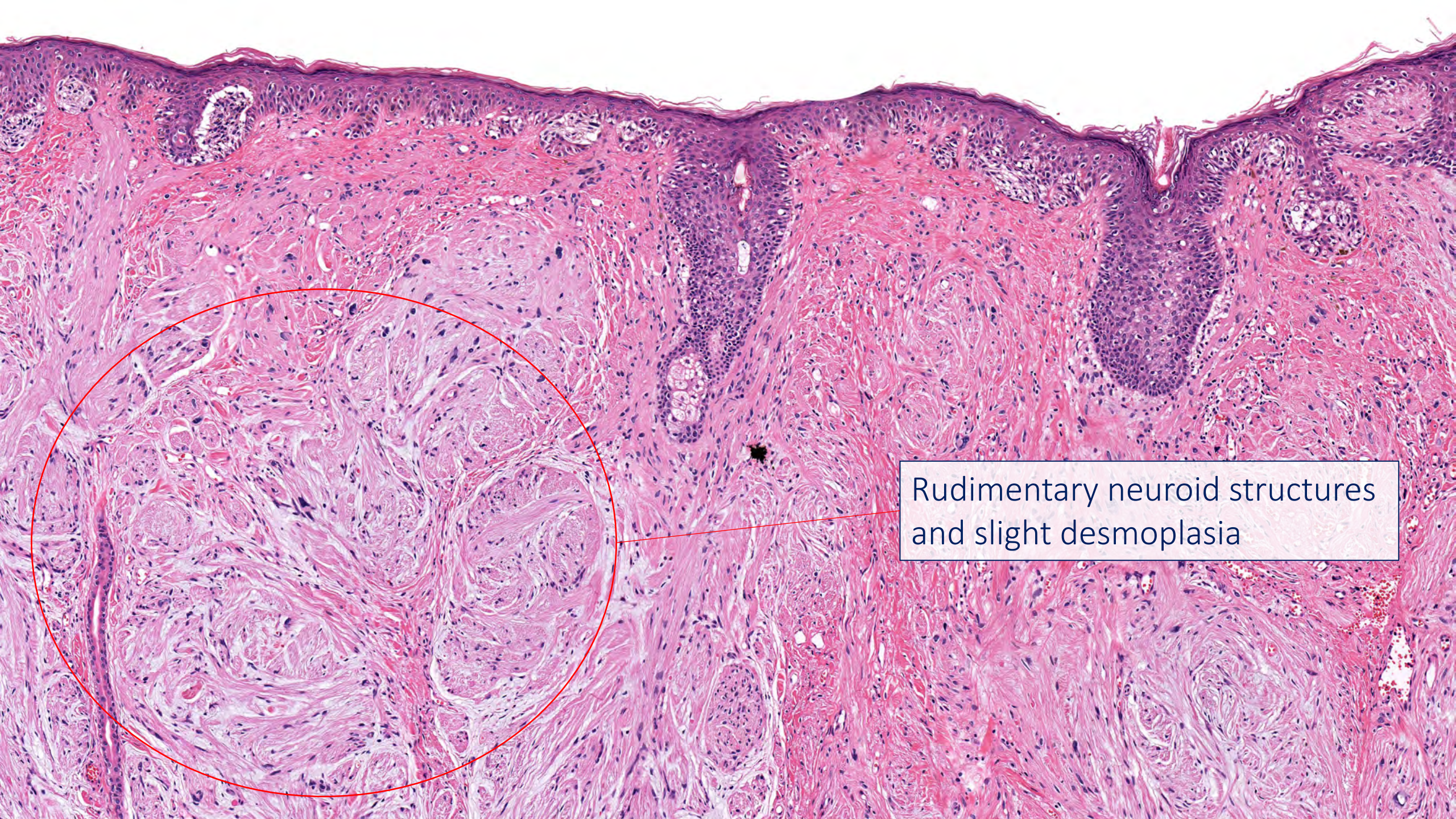
F, 56. Corner of the eye.

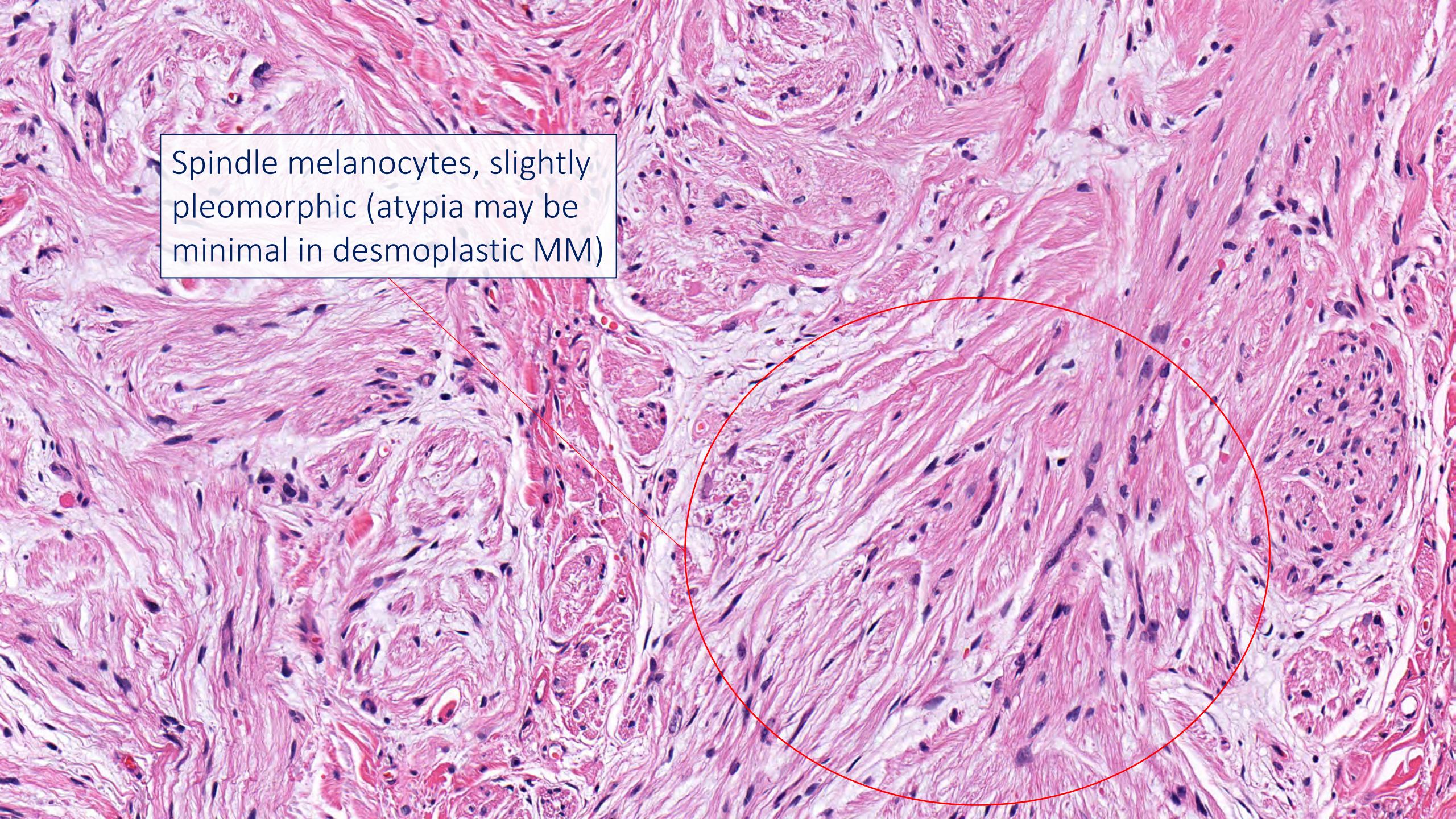


"Pink" dermis with high cellularity

Asymmetrical distribution of intraepidermal nests

Desmoplastic ("neuroid") melanoma


Rudimentary neuroid structures
and slight desmoplasia


Spindle melanocytes, slightly pleomorphic (atypia may be minimal in desmoplastic MM)

Cutaneous Desmoplastic Melanoma

Reappraisal of Morphologic Heterogeneity and Prognostic Factors

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Abstract: Desmoplastic melanoma (DM) is a variant of melanoma, which may be confused with nonmelanocytic benign or malignant spindle cell proliferations. The histologic hallmark of DM is the presence of fusiform melanocytes dispersed in a prominent collagenous stroma. Phenotypic heterogeneity of DM is underrecognized. Desmoplasia may be prominent throughout the entire tumor ("pure" DM) or represent a portion of an otherwise nondesmoplastic melanoma ("combined" DM). We reviewed melanomas with desmoplasia from 92 patients seen at a single institution between 1980 and 2002. Fifty-five of the tumors were pure DM. Thirty-seven were classified as combined. Mean follow-up of patients was 46 months for those alive at the last follow-up. Univariate analysis of clinical and pathologic parameters revealed four significant variables for disease-free survival: Clark level (IV vs. V; $P = 0.005$), DM subtype (pure vs. combined; $P = 0.01$), tumor mitotic rate (<1, 1–4, >4 mitoses/mm^2; $P = 0.01$), and tumor thickness (<1 mm, 1–4 mm, >4 mm; $P = 0.02$). Only histologic subtype ($P = 0.02$) and Clark level ($P = 0.05$) were independently significant by Cox regression analysis. Our results indicate that distinguishing pure from combined forms of DM is clinically relevant for prognosis (pure forms being associated with longer disease-specific survival). Failure to make this distinction may account for conflicting reports in the literature on the biologic behavior and prognosis of DM.

Key Words: desmoplastic, melanoma, prognostic factors

(*Am J Surg Pathol* 2004;28:1518–1525)

Desmoplastic melanoma (DM) is a histologic variant of melanoma, characterized by the presence of fusiform melanocytes dispersed in a prominent collagenous stroma. In the first report on DM by Conley et al in 1971, the tumor was characterized as "a very unusual variant of spindle cell melanoma which produces or elicits the production of abundant collagen."[8] Jain and Allen described DMs as "collagenizing fibrosarcoma-like tumors."[13] Reed and Leonard defined DMs as "fibrous tumors whose individual spindle cells are isolated in a dense fibrous matrix."[20] They termed a related variant of spindle cell melanoma with "neuroma-like" features "neurotropic melanoma."[20]

DM may be confused with a variety of benign or malignant nonmelanocytic spindle cell proliferations, such as dermal scar, dermatofibroma, sarcomas, especially fibrosarcoma, atypical fibroxanthoma, nerve sheath tumors, and even sarcomatoid carcinomas.[2,15,23,26] The misdiagnosis of DM is a recurring issue of malpractice claims related to melanoma.[27] The various types of misdiagnoses suggest a broad range in the histologic appearances of DM.

Heterogeneity among tumors classified as DM is apparent in the literature, which describes a spectrum of spindle cell neoplasm from fibrous to neural/schwannian features. Some DMs display a uniform appearance, while others are reported to have arisen in association with a "conventional" melanoma. Our review of tumors from patients referred to our institution with a diagnosis of DM is further testament to this heterogeneity. Some pathologists use the term "desmoplastic melanoma" quite liberally for any spindle cell melanoma with or without neurotropism, even if desmoplasia is only a focal and minor feature. Others reserve the term for melanomas with prominent fibrosis throughout the entire invasive tumor component. In this review, we describe our experience with 92 melanomas with desmoplasia. A number of clinical and histologic parameters are analyzed for potential prognostic significance. Emphasis is placed on the distinction of DM with prominent fibrosis (designated herein as "pure" DM) from melanomas, in which desmoplasia is only a partial, usually minor component (referred herein as "combined" DM).

METHODS

Cases of patients diagnosed with primary DM between 1980 and 2002 were retrieved from the archives of the Department of Pathology of Memorial Sloan-Kettering Cancer Center. The study was conducted with Institutional Review Board approval. Cases were only accepted when the slides of the excision of the entire invasive tumor were available for review. Cases of DM with only partial biopsies of the tumor were excluded. For an invasive spindle cell tumor to be accepted as

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TABLE 1. Clinical and Histologic Features of 92 Patients With Desmoplastic Melanoma

	Pure	Combined
	(N=55)	(N=37)
Age (yr) [mean (range)]	64.5 (11–92)	61.1 (22–87)
Tumor thickness (mm)		
Mean	5.3	7.4
Median	3.6	5.0
Clark level		
III	0	1
IV	20	13
V	35	23
Follow-up time (mo)		
Mean	42	52
Range	12–126	15–196
Sex		
Male	32 (58%)	26 (70%)
Female	23 (42%)	11 (30%)
Anatomic site		
Lower extremity	3 (5.5%)	3 (8%)
Upper extremity	11 (20%)	5 (13.5%)
Back	1 (2%)	0 (0%)
Face	16 (29%)	14 (38%)
Neck	3 (5.5%)	2 (5%)
Scalp	10 (18%)	8 (22%)
Trunk	11 (20%)	5 (13.5%)
Ulceration		
Absent	46 (84%)	28 (76%)
Present	9 (16%)	9 (24%)
TMR (mitoses/mm^2)		
0	18 (33%)	7 (19%)
1	22 (40%)	9 (24%)
2	5 (9%)	8 (22%)
3	4 (7%)	5 (13.5%)
4	3 (5.5%)	5 (13.5%)
5	1 (1.8%)	1 (2.7%)
10	1 (1.8%)	0 (0%)
12	1 (1.8%)	2 (5.4%)
In situ		
No	15 (27%)	10 (27%)
Yes	40 (73%)	27 (73%)
Nerve involvement		
No	23 (42%)	17 (46%)
Yes	32 (58%)	20 (54%)
Status		
AWD	3 (5.5%)	2 (5%)
DOC	0 (0%)	3 (8%)
DOD	2 (3.5%)	14 (38%)
NED	50 (91%)	18 (49%)

AWD, alive with disease; DOC, dead of other cause; DOD, dead of disease; NED, no evidence of disease.

DMs were classified as "pure" if the overwhelming majority (90% of the invasive melanoma) of the invasive tumor was associated with prominent stromal fibrosis. Melanomas, in which densely cellular tumor foci without stromal fibrosis constituted more than 10% of the entire tumor, were classified as "combined" DM. Spindle cell melanomas, including spindle cell neurotropic melanomas without any intratumoral desmoplasia or desmoplasia involving less than 10% of the invasive tumor, were excluded from this study.

Desmoplastic melanoma & variants

- "Pure" or "mixed" variants depending on the amount of desmoplastic stroma; pure variants have a better prognosis (mixed variants should probably be referred to as "melanoma with desmoplasia")
- Overlapping features with spindle cell melanoma, neuroid melanoma, neurotropic melanoma, myxoid melanoma (variants of the same type?)
- Common on face in elderly persons, but may be encountered on any area of the body and also in children
- In-situ component helpful for diagnosis if present, but may be missing (particularly in partial biopsies)
- Patchy lymphoid infiltrates within a desmoplastic spindle cell neoplasm represent an important clue
- Melan-A, HMB-45, MiTF oft negative; S-100, SOX-10, p75 NGFR positive
- Margins may be difficult to assess, particularly in re-excision specimens (beware of S-100 positivity in scars)

Melanomas and melanocytic nevi – not only H&E

- Several molecular pathways have been identified in melanomas arising at different cutaneous sites (e.g., chronic sun-damaged skin, intermittently sun-exposed skin, oral mucosa, genital mucosa, palmo-plantar sites)
- Several molecular pathways identified also for melanocytic nevi at different sites; numerous fusions and mutations described for Spitz nevi and tumors (and melanomas related to these lesions)
- Some "combined" nevi show presence of more molecular alterations in the different parts of the tumor, thus representing "evolving" (and more concerning) lesions
- Integration of all data helpful in controversial cases