

Pediatric Melanocytic Lesions: An Update

Raymond Barnhill
Institut Curie
Paris, France

Mission of the Pathologist

Re: Pediatric Melanocytic Lesions

- Avoid overdiagnosis and underdiagnosis melanoma
- Due diligence

Due Diligence

- Need clinical information
 - ✓ Age
 - ✓ Anatomic site

Due Diligence

- Knowledge about mimics of melanoma
 - ✓ Congenital nevi
 - ✓ Spitz tumors
 - ✓ Site-specific nevi

Pediatric Melanoma: Perspectives

- Because of the rarity of true biologic melanoma and the occurrence of mimics of melanoma, both over and under diagnosis of melanoma occur
- Specific knowledge is essential for final interpretation



Due Diligence

- Consider referral to consultants and institutions with expertise

Pediatric Melanoma

Clinical Criteria

Age	<ul style="list-style-type: none"> • <u>Melanoma is rare < 10 – 12 years of age</u>, especially near birth and < 1 year of age 	
Anatomic site	<ul style="list-style-type: none"> • <u>High risk: Scalp, particularly in prepuberty</u> • Mimics of melanoma: scalp (but melanoma occurs) and vulvar nevi 	
Clinical history	<ul style="list-style-type: none"> • Changing or new lesion, itching, pain, bleeding, ulceration suggest melanoma 	
Gross morphological features suggesting melanoma	<ul style="list-style-type: none"> • Polypoid lesion resembling hemangioma or pyogenic granuloma • >5 mm, especially >10 mm • Irregular shape/color; black; amelanotic • Ulceration 	<ul style="list-style-type: none"> • Amelanotic • Bleeding/bump • Color uniformity • De novo, any diameter

Fatal Pediatric Melanoma: Anatomic Site $n = 10$ cases

- ❖ 10/10 cases: Scalp, neck, back (< 15 years of age)
 - 6/10 cases: Scalp
 - 4/10 cases < 10 years of age



Pediatric Melanoma: Gold Standard

- The most rigorous criterion is:
 - Metastases and death

I. Melanocytic nevi

- Congenital nevi
- [Spitz tumors]
- Site-specific nevi

I. Melanocytic nevi

Congenital nevi
(CMN)

Biological Significance of Congenital Nevi

- Clinical and histological mimics of melanoma
- Precursors to highly aggressive central nervous system and skin pediatric melanomas:
 - CNS melanoma 100% fatal

Biological Significance of Congenital Nevi (CMN)

- Greatest risk factor for pediatric melanoma (both CNS and skin)!
 - Abnormal screening Magnetic Resonance Imaging (MRI) of brain and spine in early life

Biological Significance of Congenital Nevi (CMN)

- Greatest risk factor for pediatric melanoma (after CNS disease):
 - Severity of CMN phenotype: large size (> 40 or 60 cm) and multiple smaller CMN (often 80% of cutaneous surface)
 - congenital melanocytic nevus syndrome



Congenital Nevi Mimics of Melanoma

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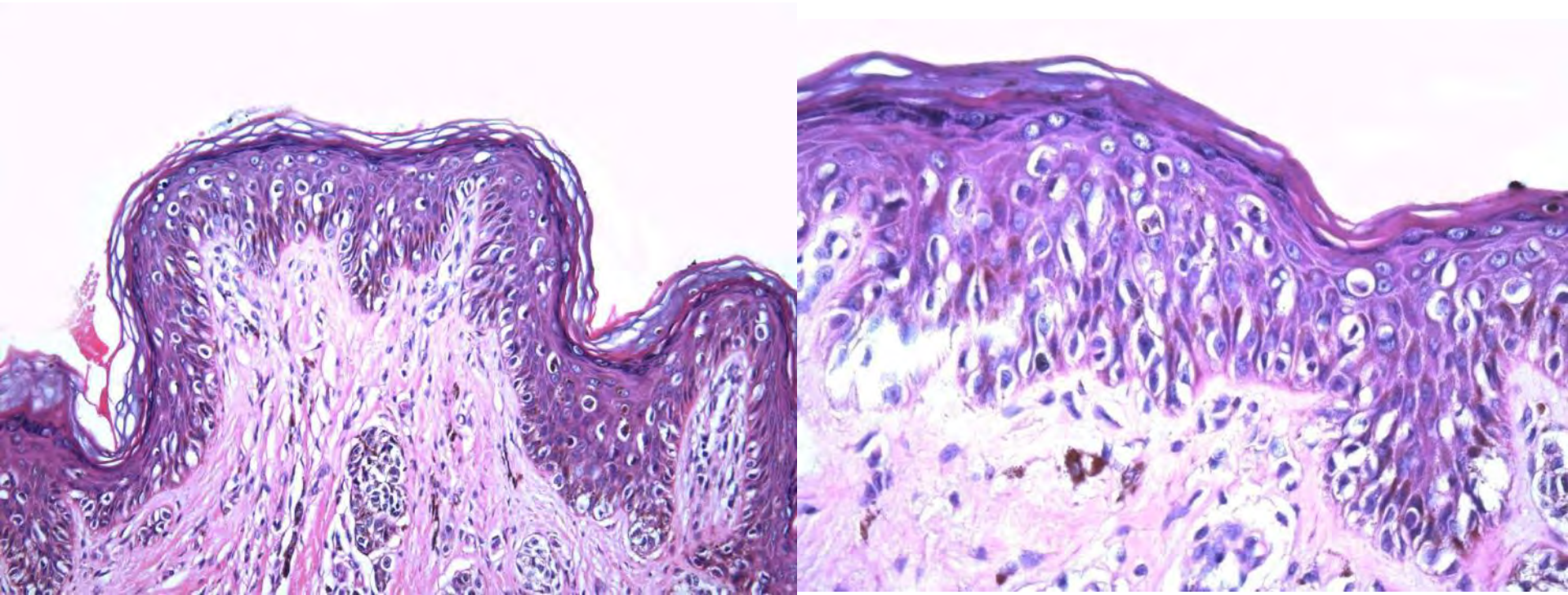
Congenital Nevi Mimics of Melanoma



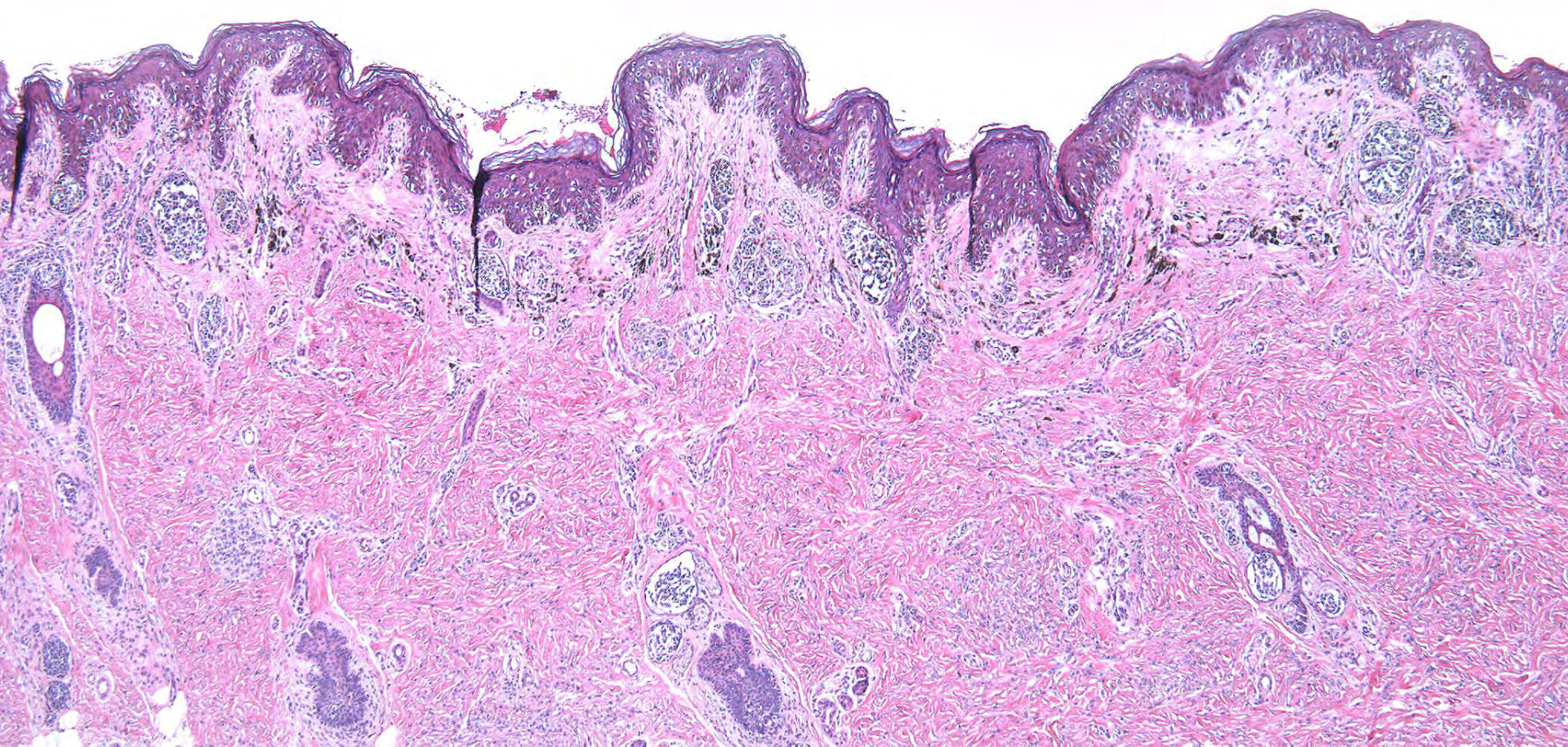
- Pagetoid melanocytosis
- Proliferative nodules

Congenital Nevi

Mimics of Melanoma



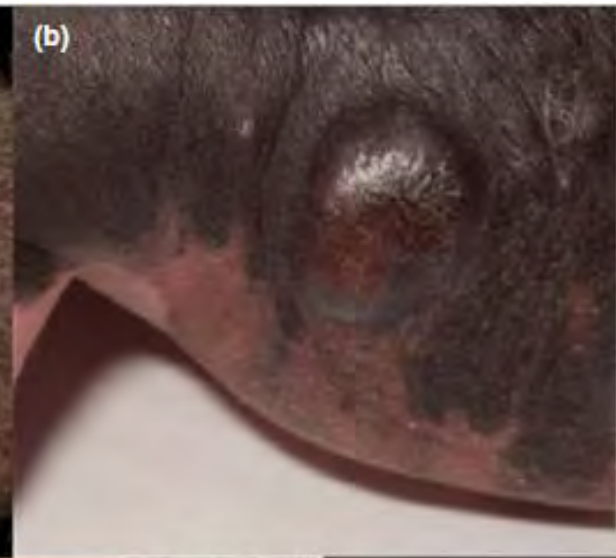
- Pagetoid Melanocytosis



Congenital Nevi

Mimics of Melanoma

- Proliferative nodules

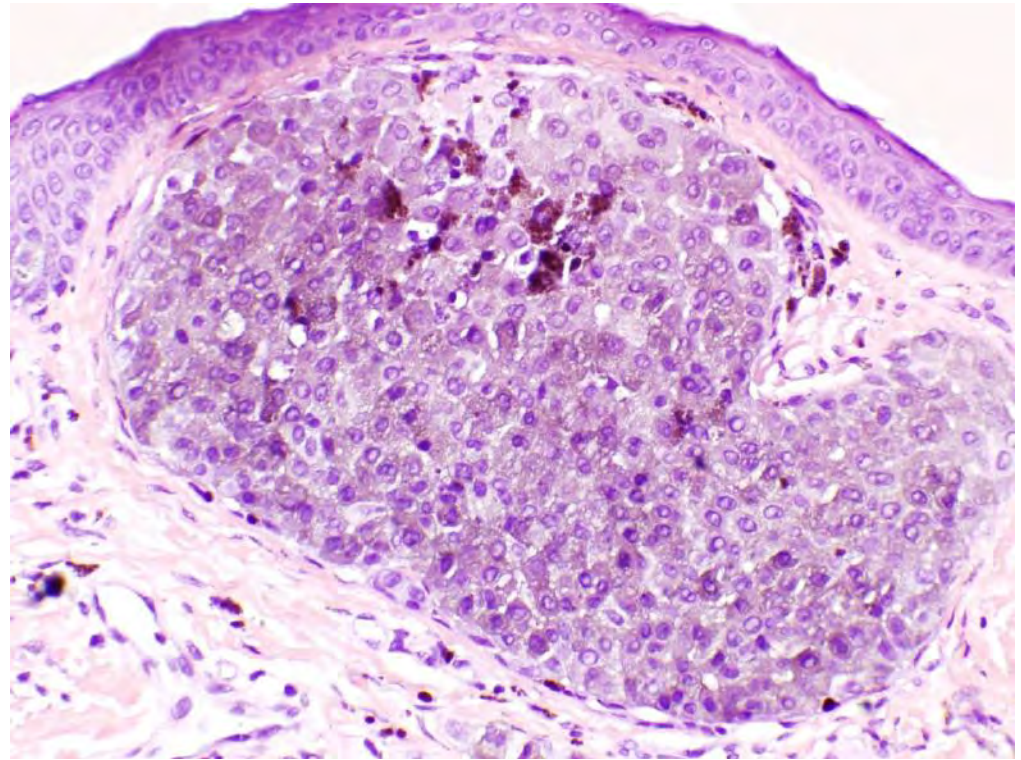


Proliferative Nodules in CMN

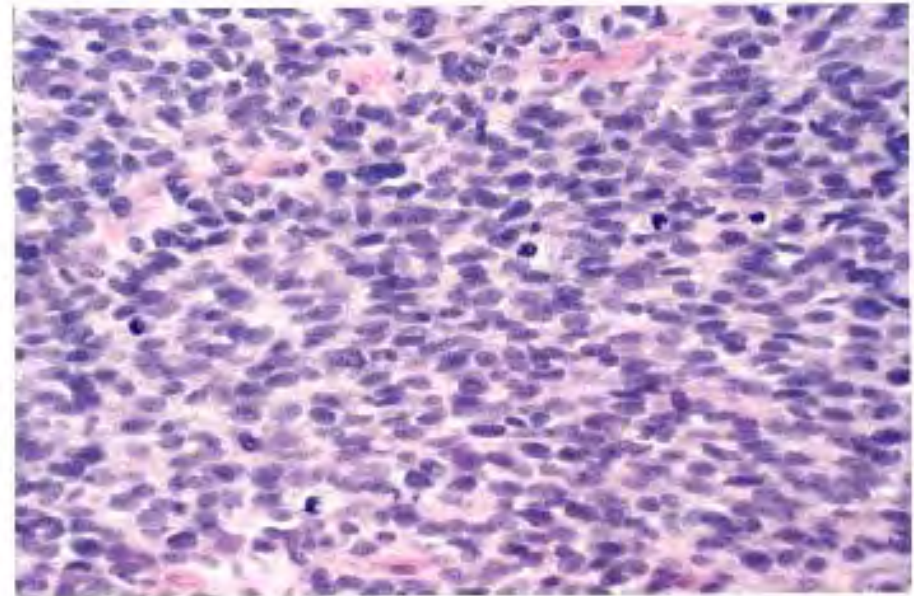
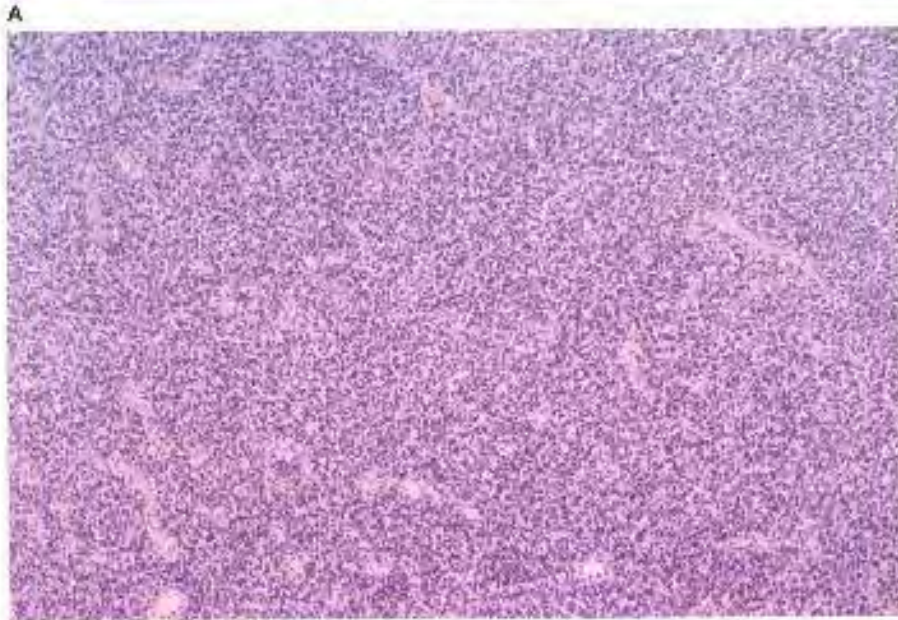
Criterion	Benign	Melanoma
Age	Birth, < 1 y, < 10 y	Increasing age
Anatomic site	Any site, often <u>multiple</u>	Scalp/neck/back, Solitary
Size	< 1 mm to > 1 cm	<u>≥</u> 1 cm
Cell type	Ovoid/nevoid, epithelioid, spindle, small cell	Epithelioid, small, spindle, undifferentiated
Architecture	Symmetrical, no ulceration, <u>blends with nevus</u> , maturation, no necrosis	<u>Ulceration</u> , abrupt border, no maturation, necrosis
Cytological atypia	Usually low grade	<u>High grade</u>
Mitotic rate	0 to 1-2 mitoses/mm ²	<u>> 5 to 6 to 25</u> <u>mitoses/mm²</u>
Molecular	None to whole chromosomal losses or gains, <u>exceptions</u>	DNA copy number gains and losses

Congenital Proliferative Nodule

- Newborn patient
- Site: Back
- Diameter 2 mm*
- Thickness 0.9 mm*
- Abrupt interface
- Slight asymmetry
- No ulceration*
- 0 mitoses/mm²*
- Low-grade atypia*



Congenital Proliferative Nodule: An Uncertain Lesion



- Ulceration
- Hypercellular nodule
- Monomorph ovoid cells
- Mitotic rate - 26 per mm²

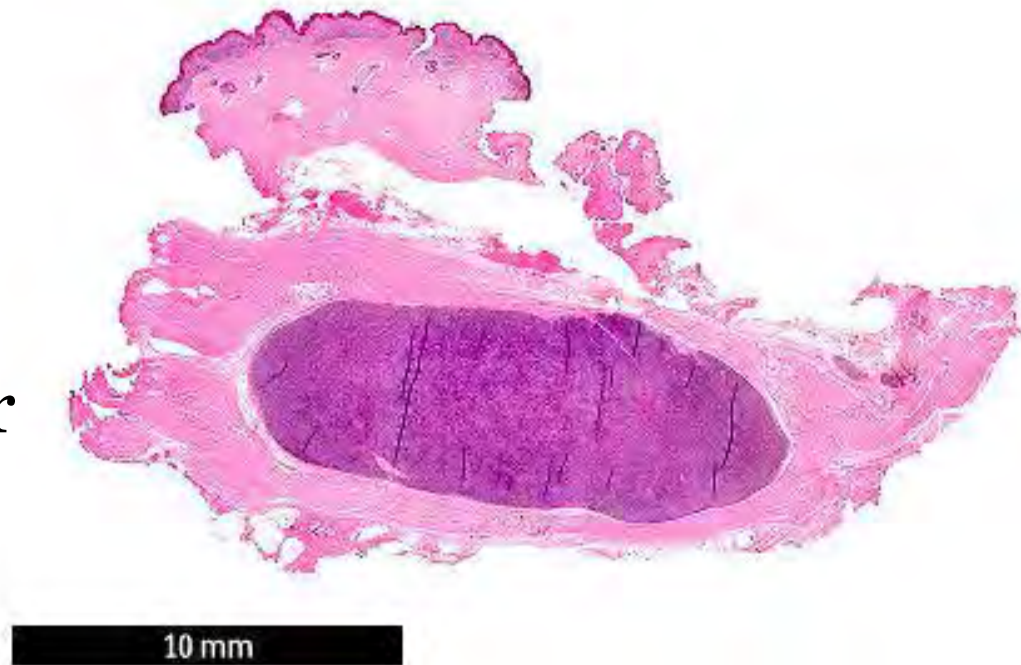
Congenital Proliferative Nodule Uncertain Malignant Potential

- No evidence of recurrence or metastasis on long-term follow up > 6 years

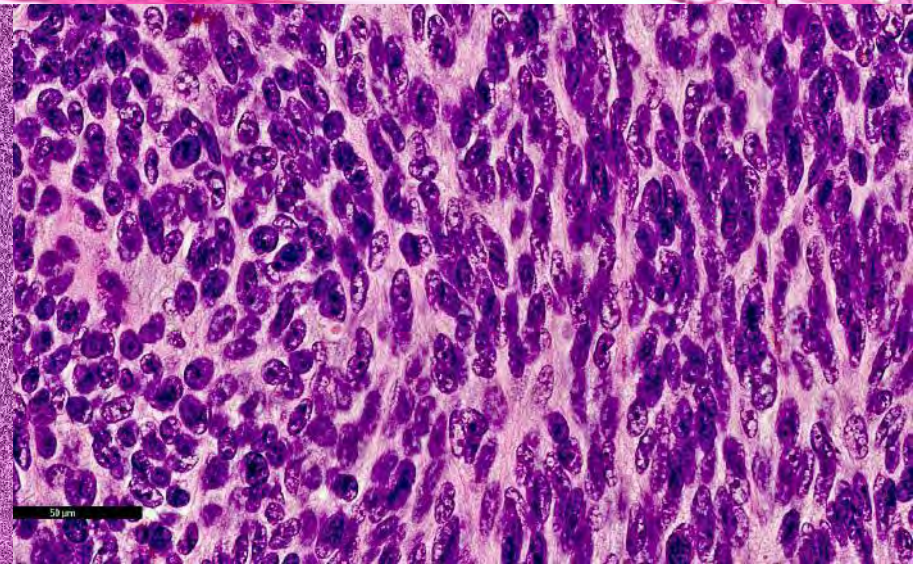
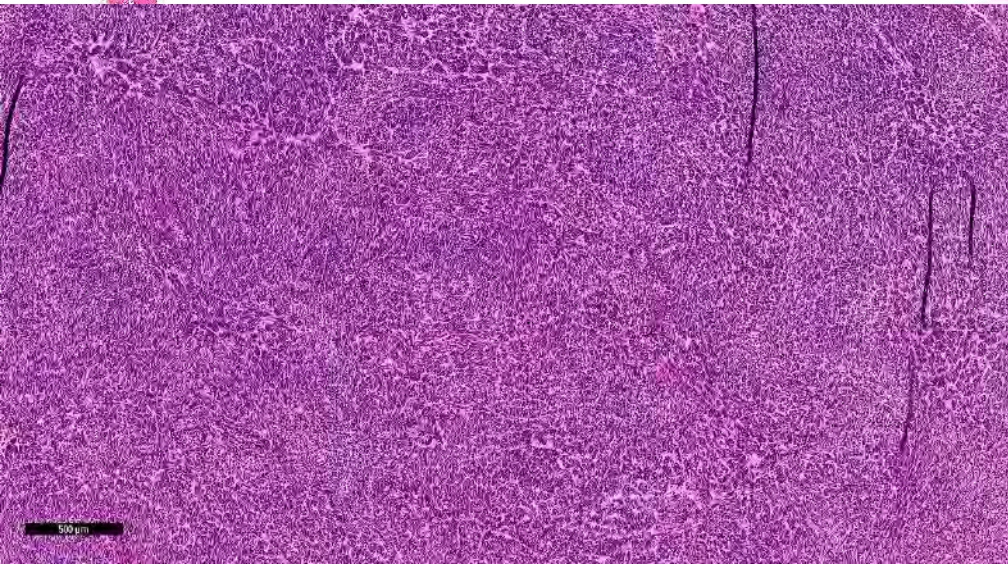
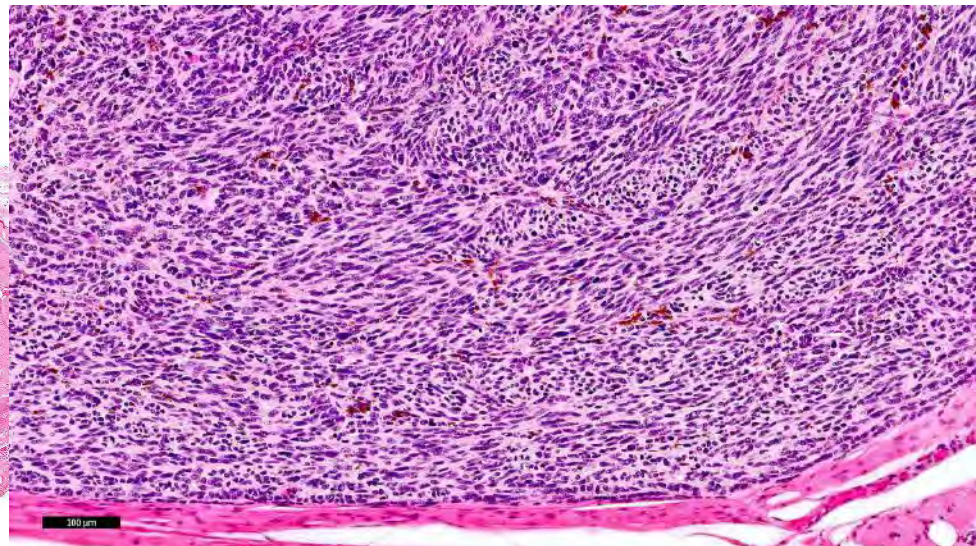


Nodule in Giant Congenital Nevus

- 5 year-old female
- New intramuscular nodule – 12 x 4 mm
- On back
- Well-circumscribed
- Symmetrical
- Smooth abrupt border
- Hypercellular
- Cytological atypia
- 13 mitoses per mm²
- No necrosis



Nodule in Giant Congenital Nevus



Nodule in Congenital Nevus

- Array comparative genomic hybridization:
 - Gains in whole chromosomes: 6, 8, 9, 15, 17, 19, 22
 - Losses in whole chromosomes: 2, 4, 14, 21

Clinical Course and Outcome

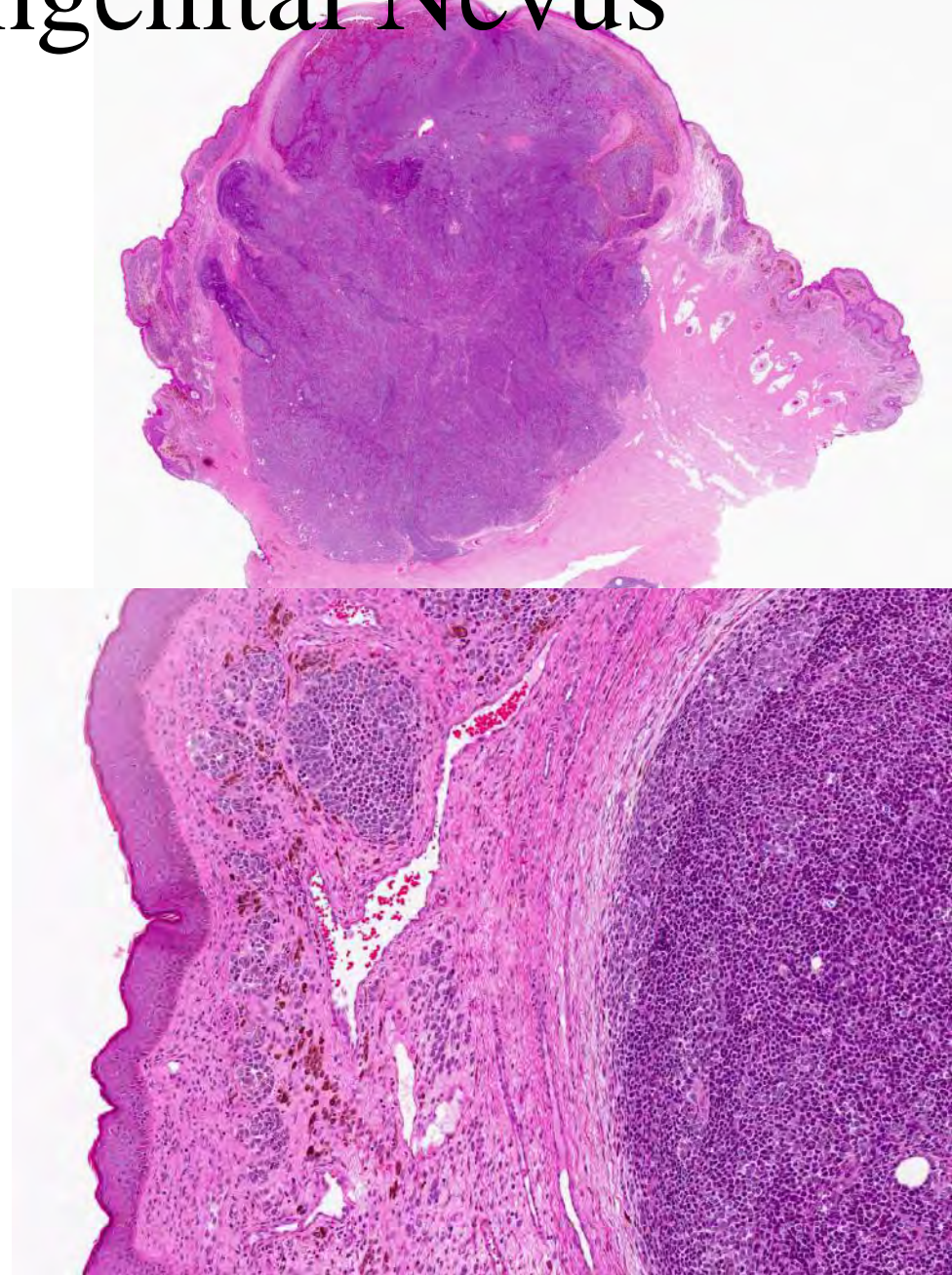
- Re-excision: No evidence of any residual lesion
- Past history of multiple nodules
- No evidence of disease at five years follow-up: no evidence of recurrence, metastasis, or development of new nodules.
- No excision of any lesions

Clinical Course and Outcome

Final diagnosis: Atypical nodule
with uncertain malignant
potential

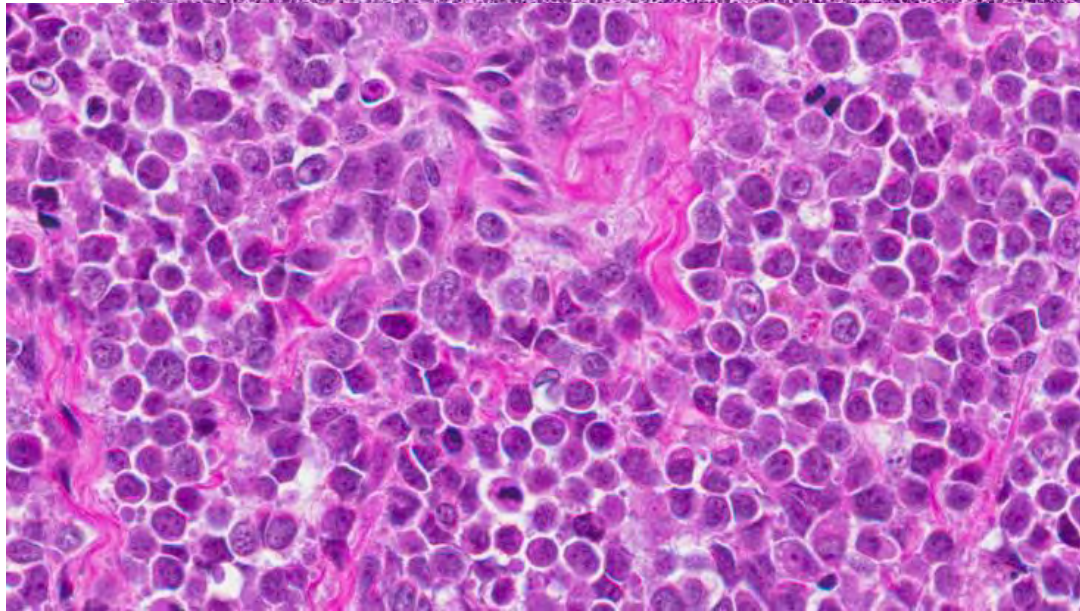
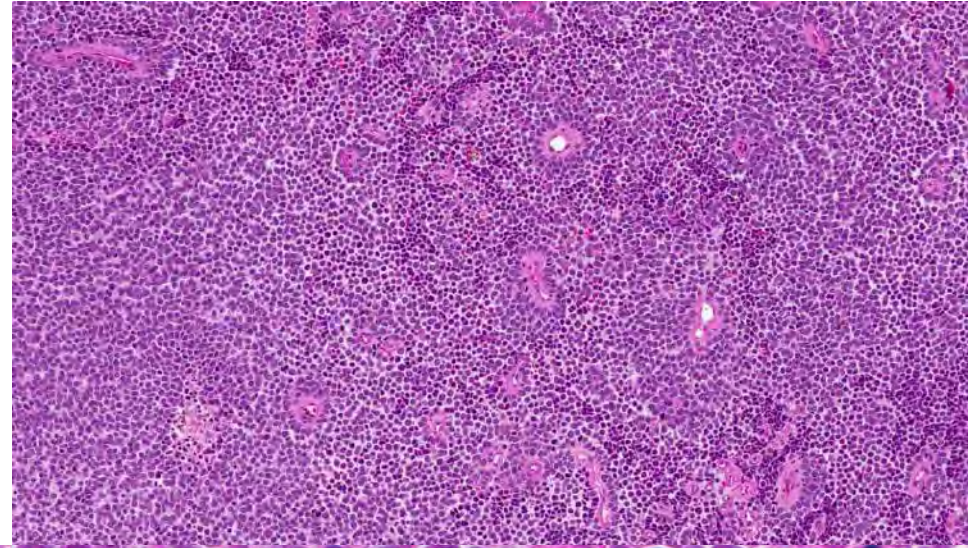
Nodule in Congenital Nevus

- 7 year-old male with nodule of neck/shoulder in giant congenital nevus
- Discreet nodule with irregular borders in dermis and subcutis
- Absence of « blending » with surrounding nevus or maturation



Nodule in Congenital Nevus

- Comprised of monomorphous atypical polygonal melanocytes
- Conspicuous mitotic activity



Nodule in Congenital Nevus

- Array comparative genomic hybridization
 - Gains in whole chromosomes: 2, 4, 6, 8, 10, 13, 19, 20, 21
 - Gain in chromosome: 1q
 - Loss in whole chromosome: 14

Nodule in Congenital Nevus

- Based on array CGH findings, an atypical/benign neoplasm was favored at first institution
- At second institution, MELTUMP was favored with therapy for melanoma

Clinical Course and Outcome

- Patient developed metastatic melanoma and died two years later
- Final diagnosis: melanoma arising in a congenital nevus

Take Home Message

- There are exceptions to all criteria, even molecular!
- All clinical, histopathological, and ancillary information must be utilized on a case-by-case basis for optimal patient care.

Melanocytic nevi

Site Specific Nevi



Nevi of Special Site Mimics of Melanoma

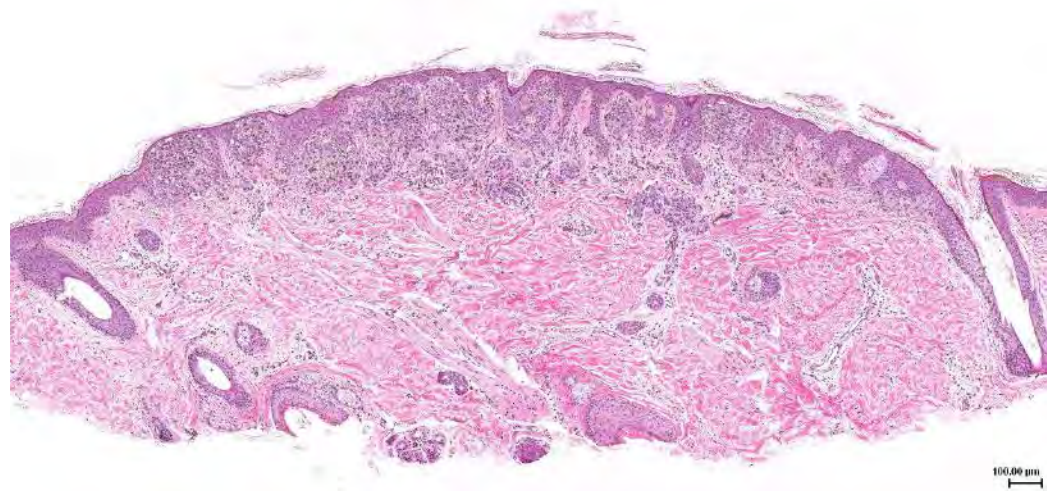
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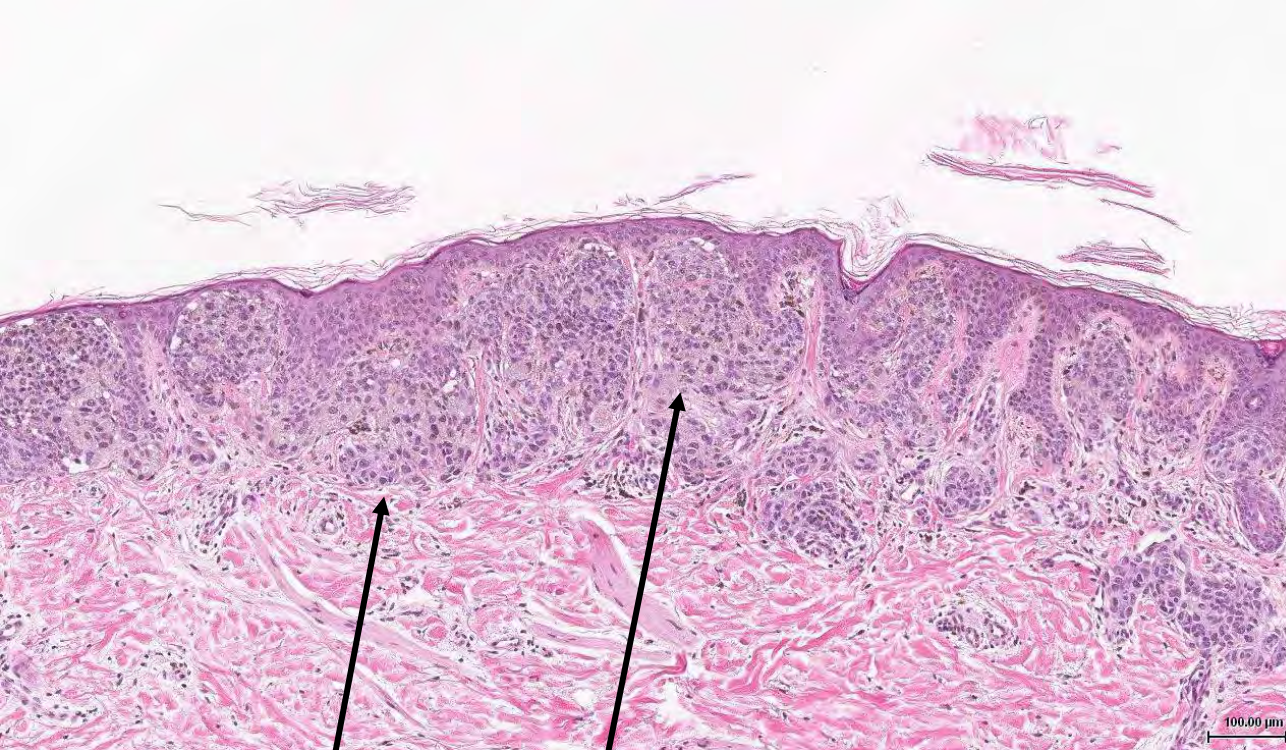


Atypical Compound Nevus, Scalp

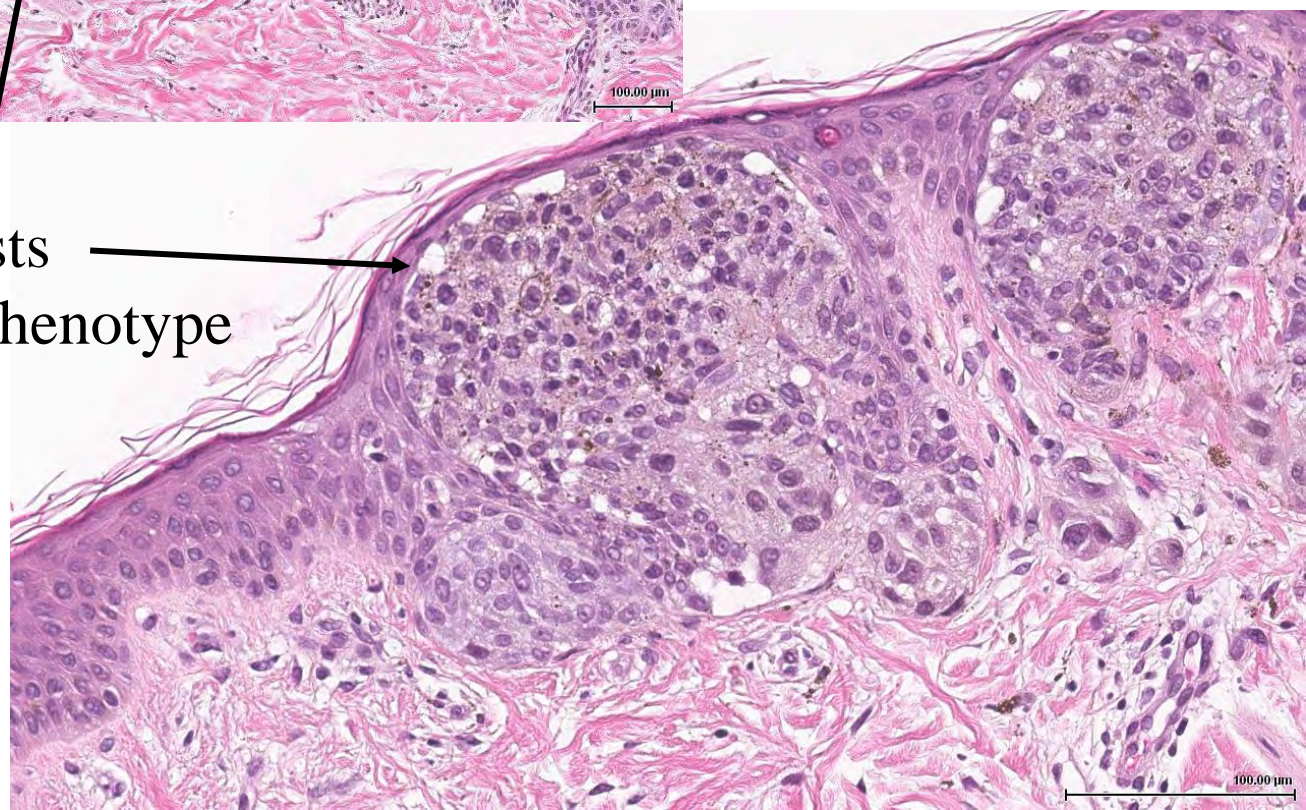


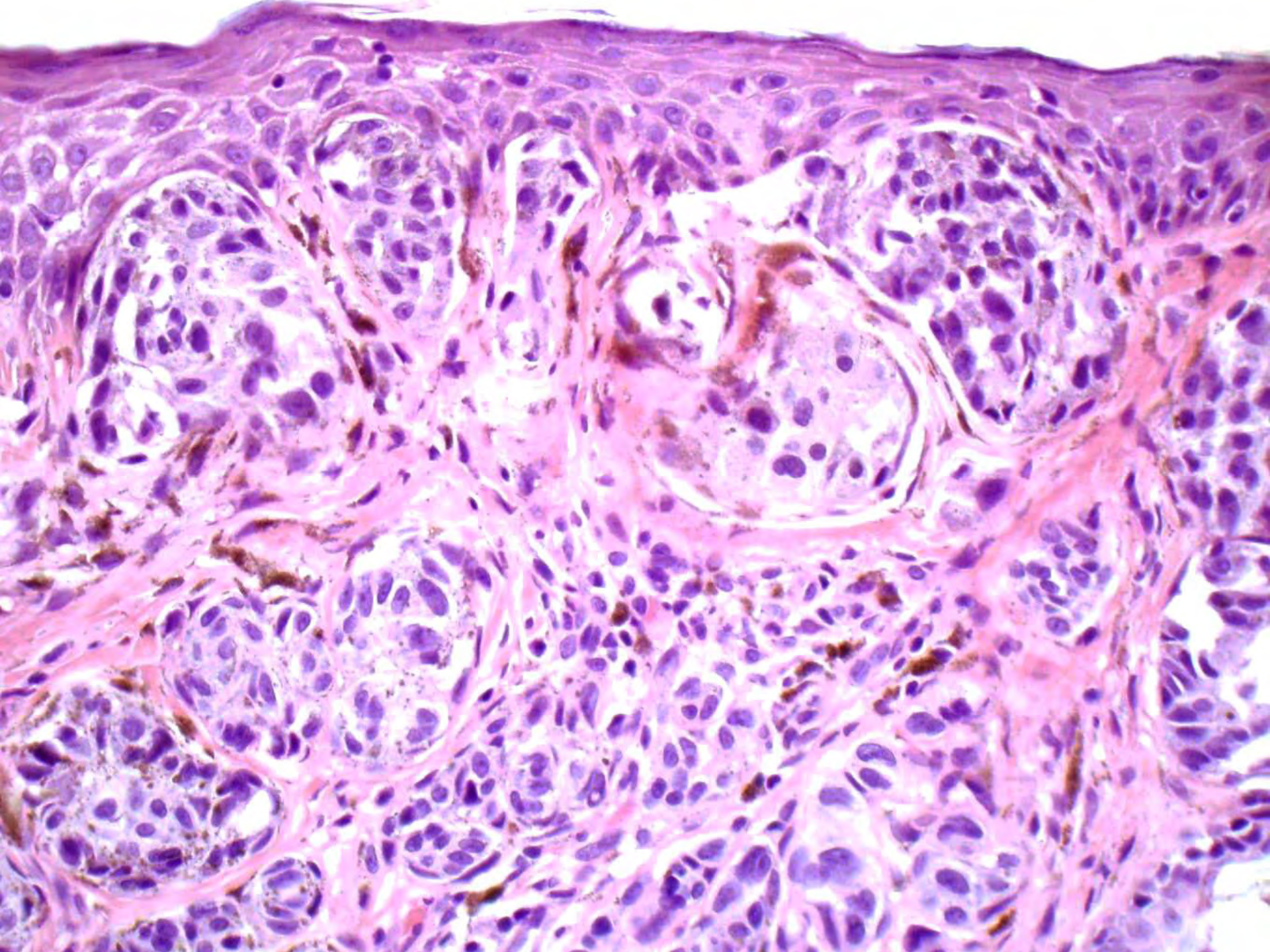
- Age: 8 years
- Diameter: 6 mm
- Well circumscribed
- Symmetrical
- Mitotic rate: 1 per mm^2





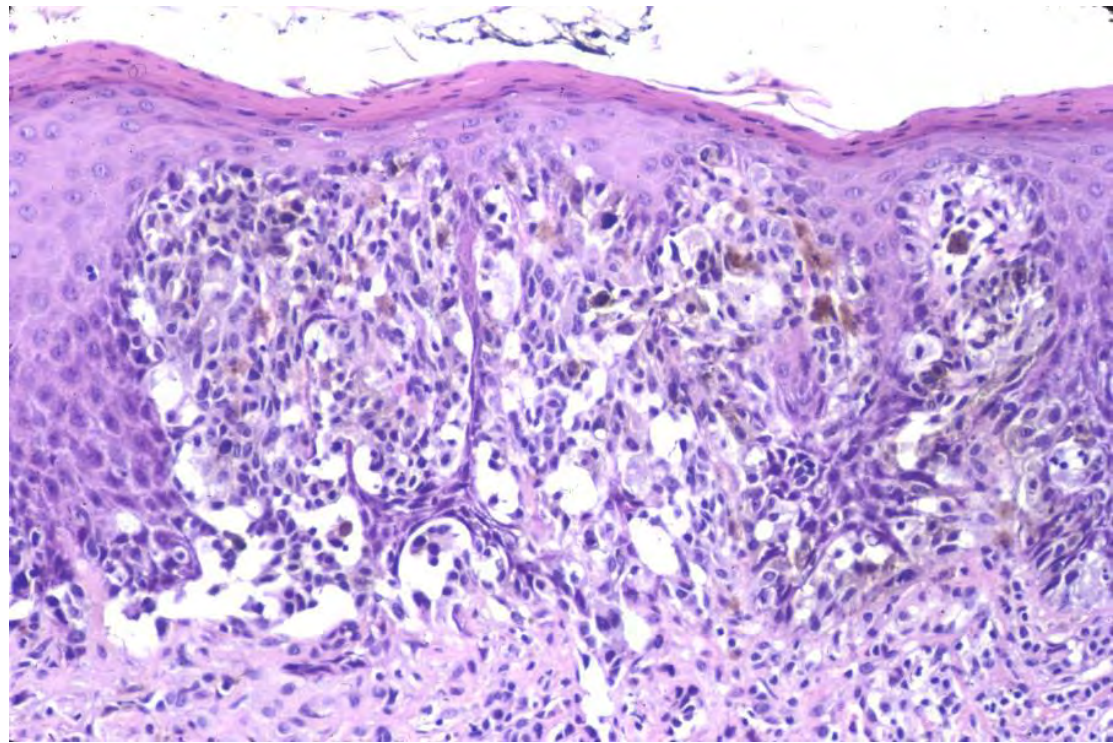
- Large confluent nests
- Epithelioid nevus phenotype
- Cytological atypia





Atypical compound nevus of vulva

- 8 year old female
- Confluent junctional nesting
- Enlarged spindled and epithelioid melanocytes
- Mimic of melanoma



Scalp Nevus

- Mimic of melanoma
- Rare precursor of melanoma

II. Melanoma

Pediatric Melanoma

- Congenital
- Childhood – birth to puberty, about 10 years
- Adolescence – puberty (about 10 years) to 18 years of age
- Adulthood – >18 years

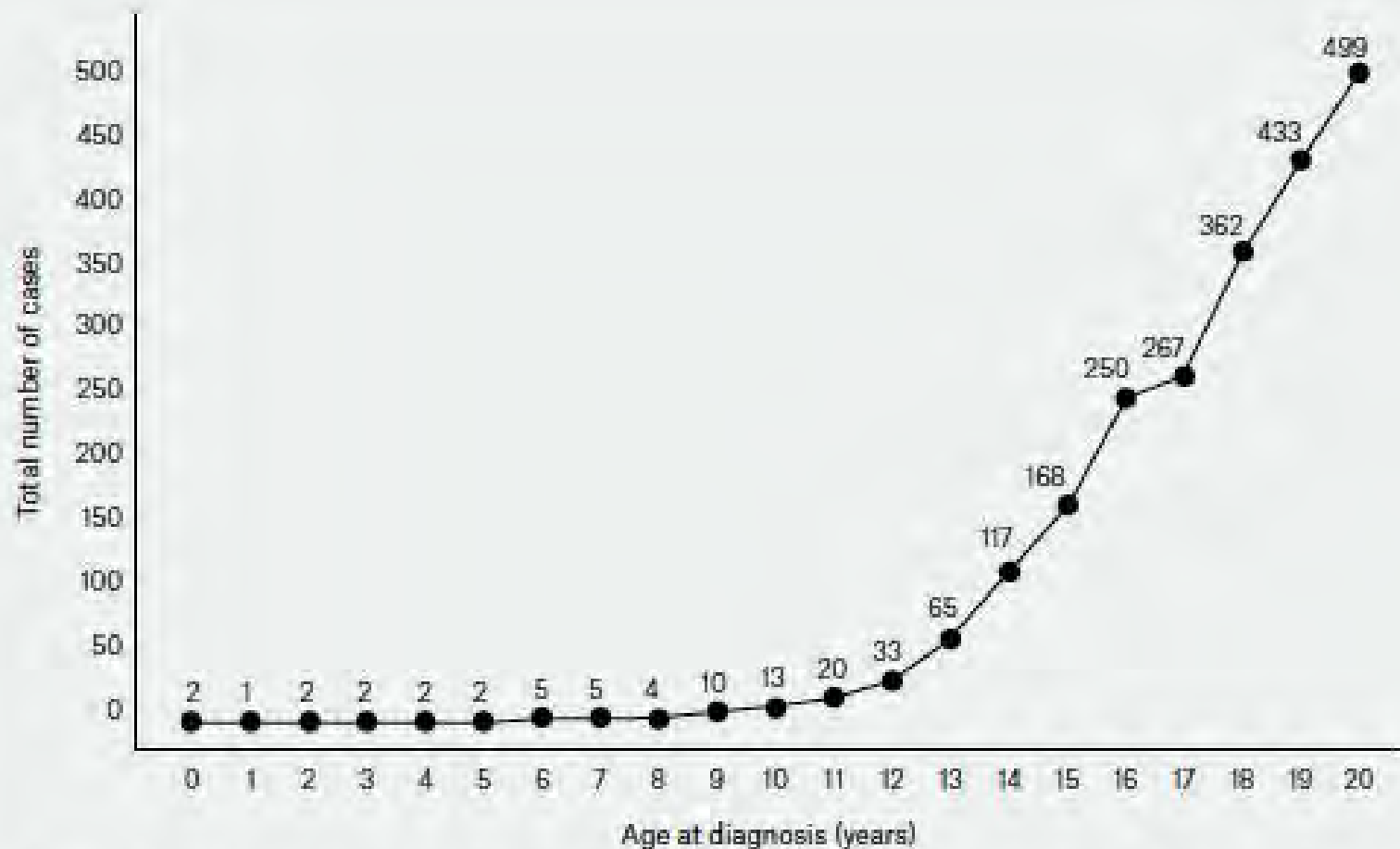


Figure 4. Number of childhood and adolescent melanoma cases in Australia, excluding NSW, from 1982-2014, based on data from the Australian Institute of Health and Welfare

Figure courtesy of Dr Serigne Lo

Two Different Diseases

- Prepubertal melanoma
- Postpubertal melanoma

Prepubertal Melanoma

- De novo melanoma (developmental basis poorly understood)
 - “Nodular” (rapidly evolving)
 - ✓ Nevoid cell
 - ✓ Epithelioid cell
 - ✓ Spindle cell
 - Conventional melanoma

Lifetime Melanoma Risk Associated with Congenital Nevi

- For all CMN: 1 to 2%
- Small and medium CMN: $< 1\%$
- Large/giant CMN: about 2.5%
- Most severe CMN syndrome ~
80% of skin surface (multiple
CMN): 10 to 15%

Congenital Melanoma

Congenital Melanoma

- Maternal melanoma metastatic to fetus
- De novo congenital melanoma
- Melanoma arising in congenital nevus

De Novo Congenital Melanoma: Analysis of 2 Cases With Array Comparative Genomic Hybridization

Albert Su, MD, Lawrence Low, MD, PhD,* Xinmin Li, PhD,* Shengmei Zhou, MD,†
Leo Mascarenhas, MD, MS,‡ and Raymond L. Barnhill, MSc, MD**

Abstract: Congenital melanoma is extraordinarily rare, and 3 types have been described: transplacental metastases from the mother, de novo congenital melanoma, and melanoma occurring in association with a congenital melanocytic nevus. We describe 2 reports of array comparative genomic hybridization analysis of de novo congenital melanoma. The first patient was male, and the second was female; both had a scalp lesion present at birth, which grew quickly. The scalp mass from patient 1 showed a heterogeneous, anaplastic melanocytic neoplasm with large size and depth, high mitotic rate,

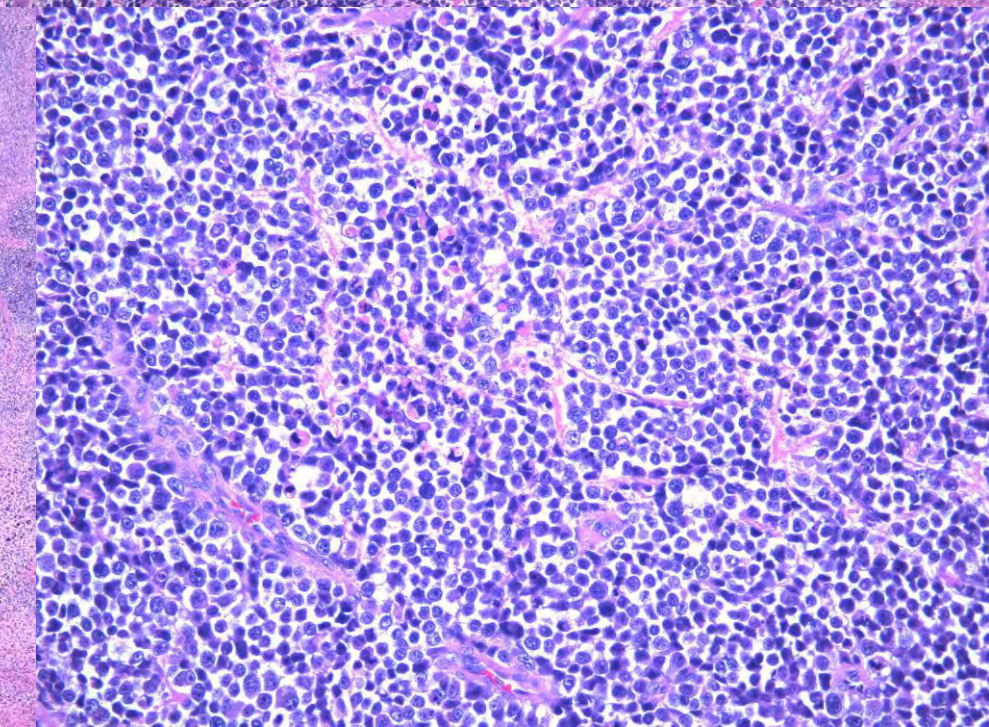
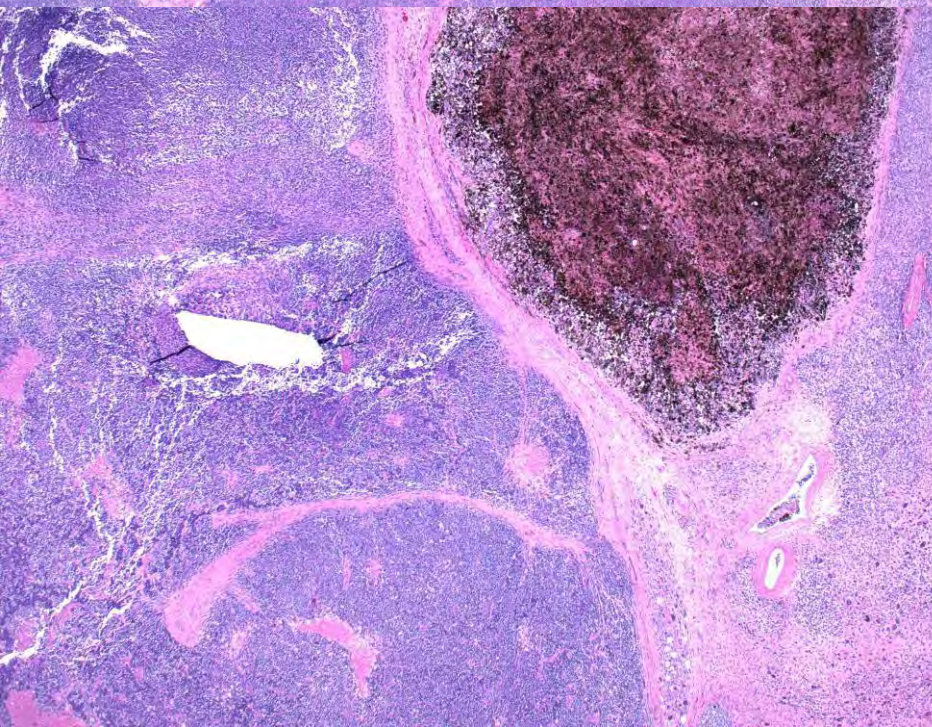
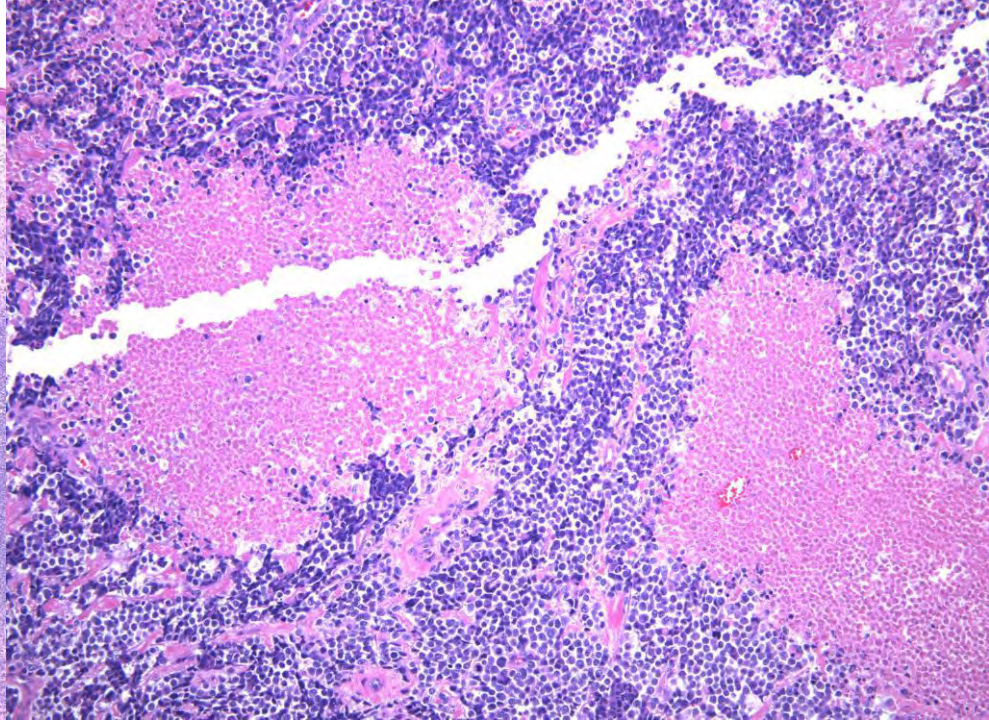
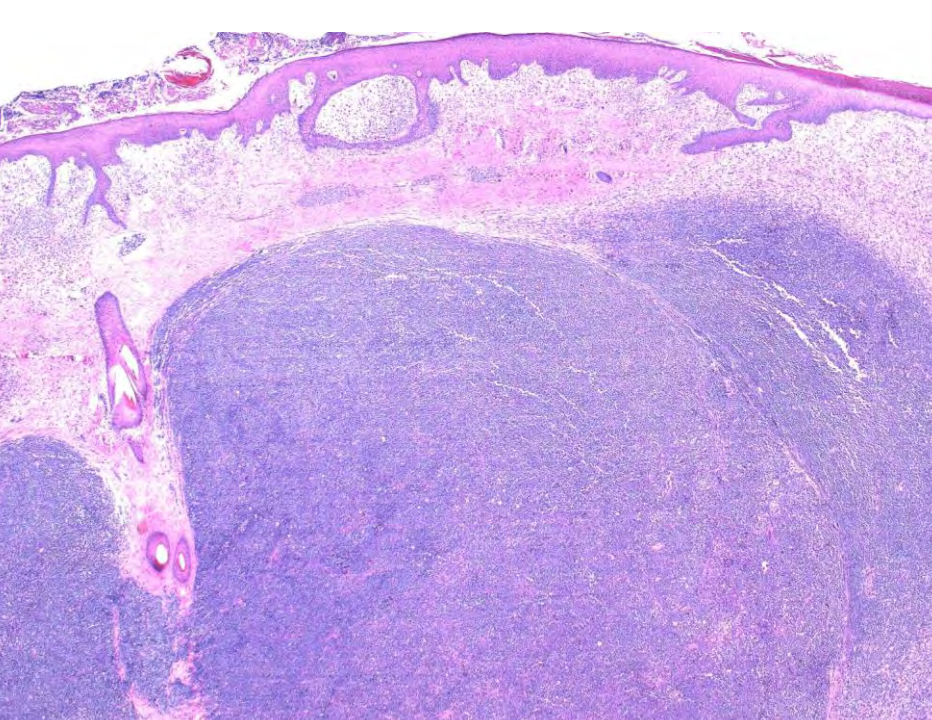
INTRODUCTION

Congenital or infantile melanoma is extraordinarily rare; according to a recent review of the literature, 27 cases have been reported.¹ Three types of congenital melanoma have been described: transplacental metastases from the mother,²⁻⁴ de novo congenital melanoma,^{1,5,6} and melanoma occurring in association with a congenital melanocytic nevus.⁷⁻¹¹ Because of the rarity of the disease, a diagnosis of congenital melanoma must be made with caution. Although traditional histopatho-

Congenital Melanoma: De Novo

- Extremely rare
- Scalp
- Dermal nodular proliferation
- Small, intermediate, or large cells
- Usually fatal





Course and Outcome

- Array CGH:
 - Multiple segmental chromosomal losses
- Evolution: Distant metastases and death at 5 months

Childhood Melanoma

Nevoid Melanoma [formerly “small cell” melanoma]

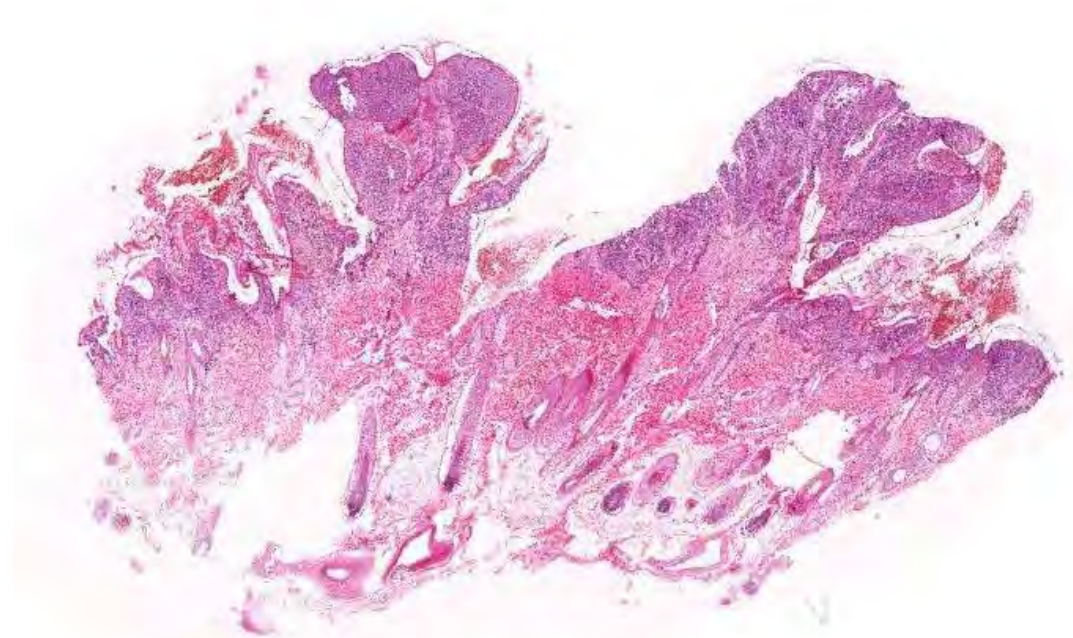
- De novo
- Melanoma arising in congenital nevus

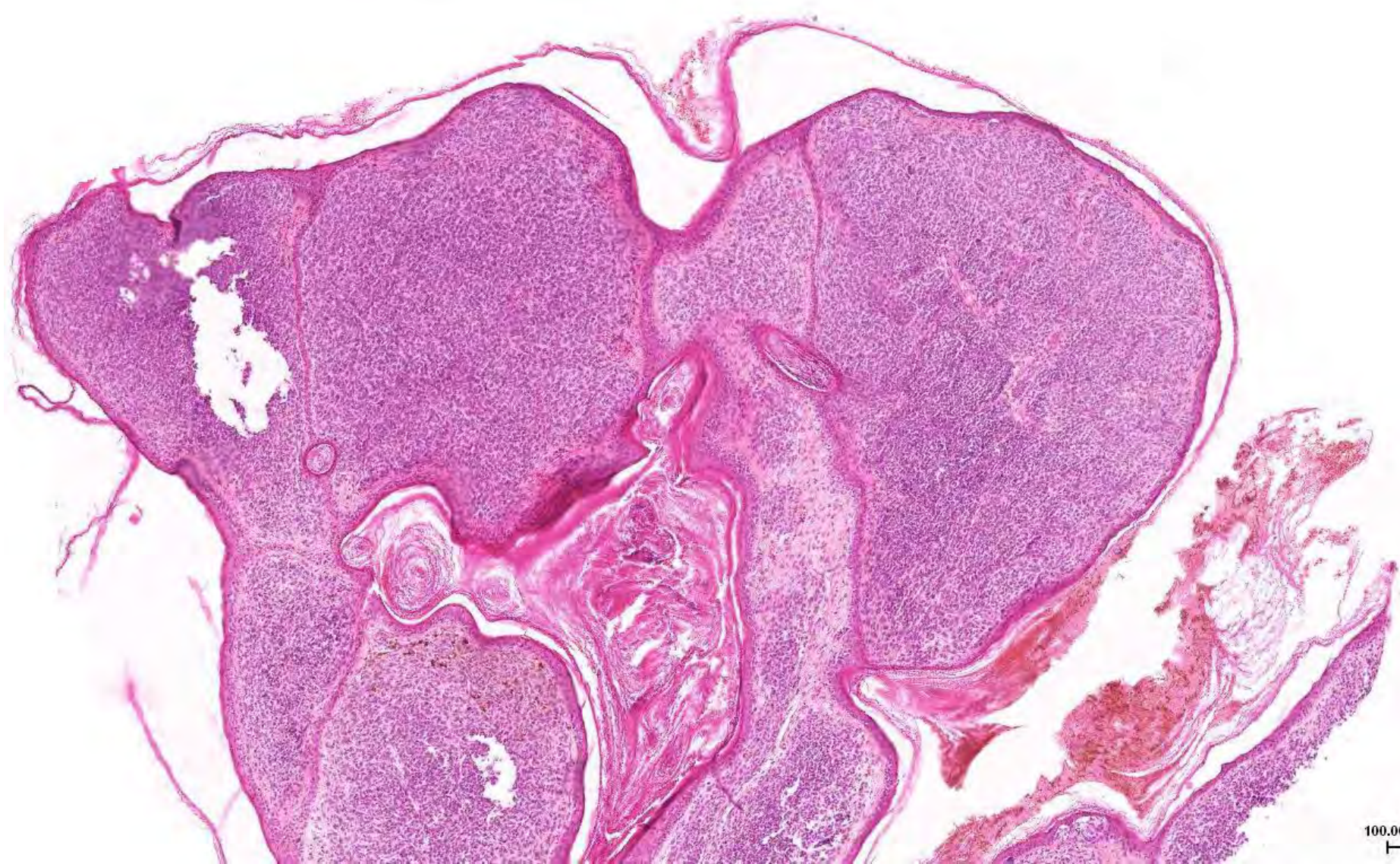
De Novo Nevroid Melanoma

- Extremely rare
- Scalp
- Resemblance to nevus
- Nevroid cells
- Usually fatal

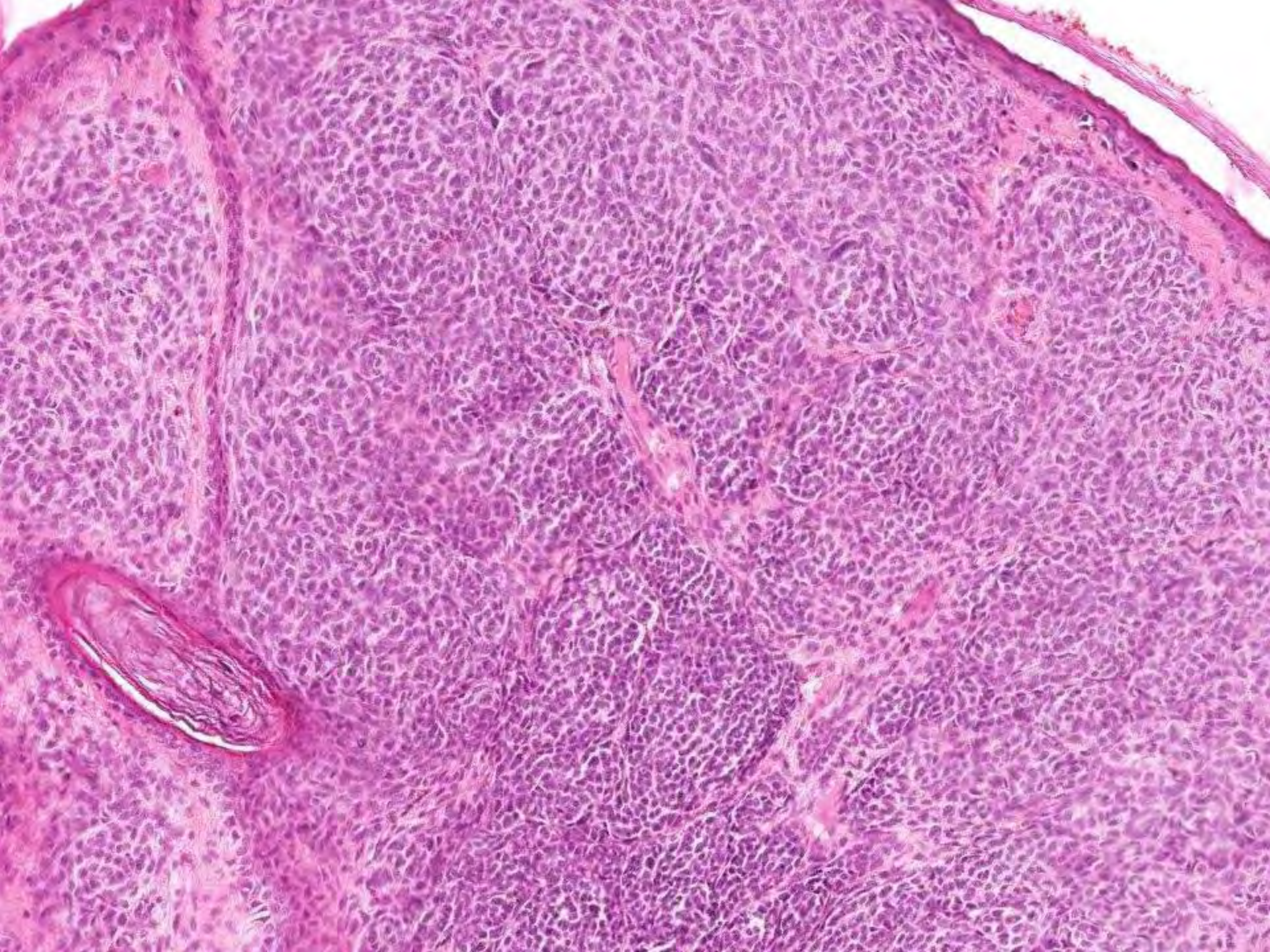
Nevoid Melanoma

- 4 year-old male
- Scalp
- Resemblance to verrucous nevus
- Breslow 5.4 mm
- Level IV
- Nevoid cell

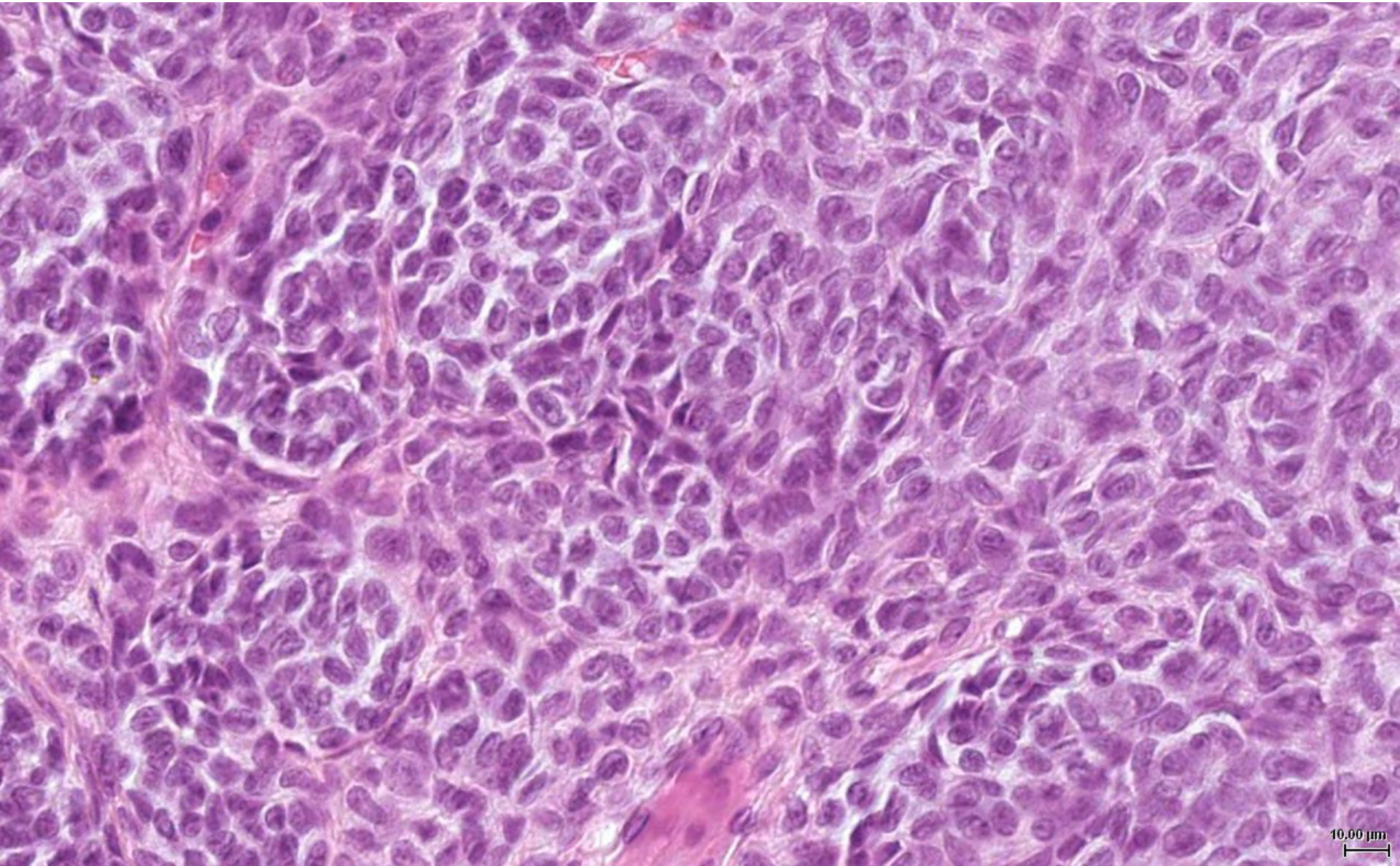




100.00 μ m



- Metastases
- Death in 12 months



Nevoid Melanoma

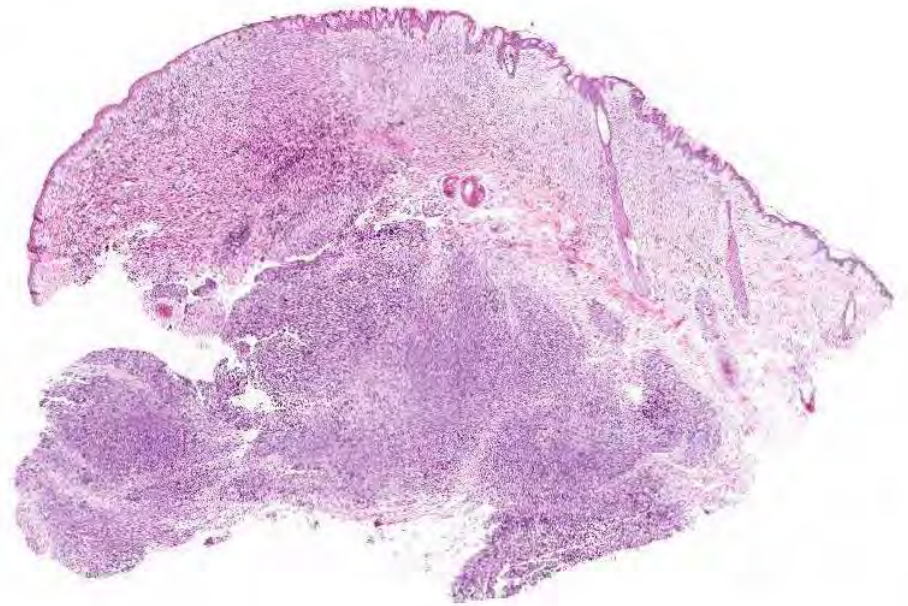
- Nevoid melanoma in congenital nevus

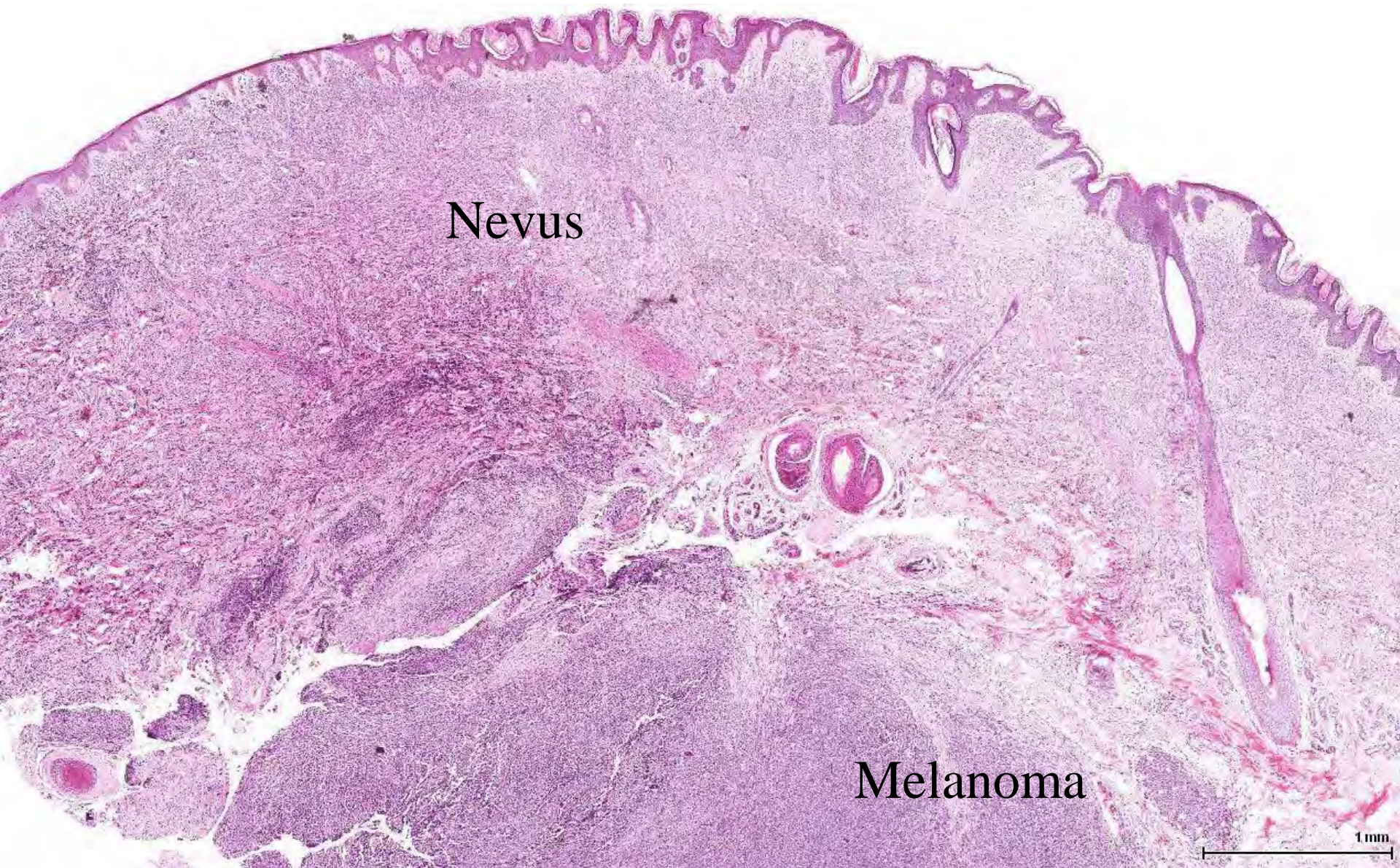
Nevoid Melanoma

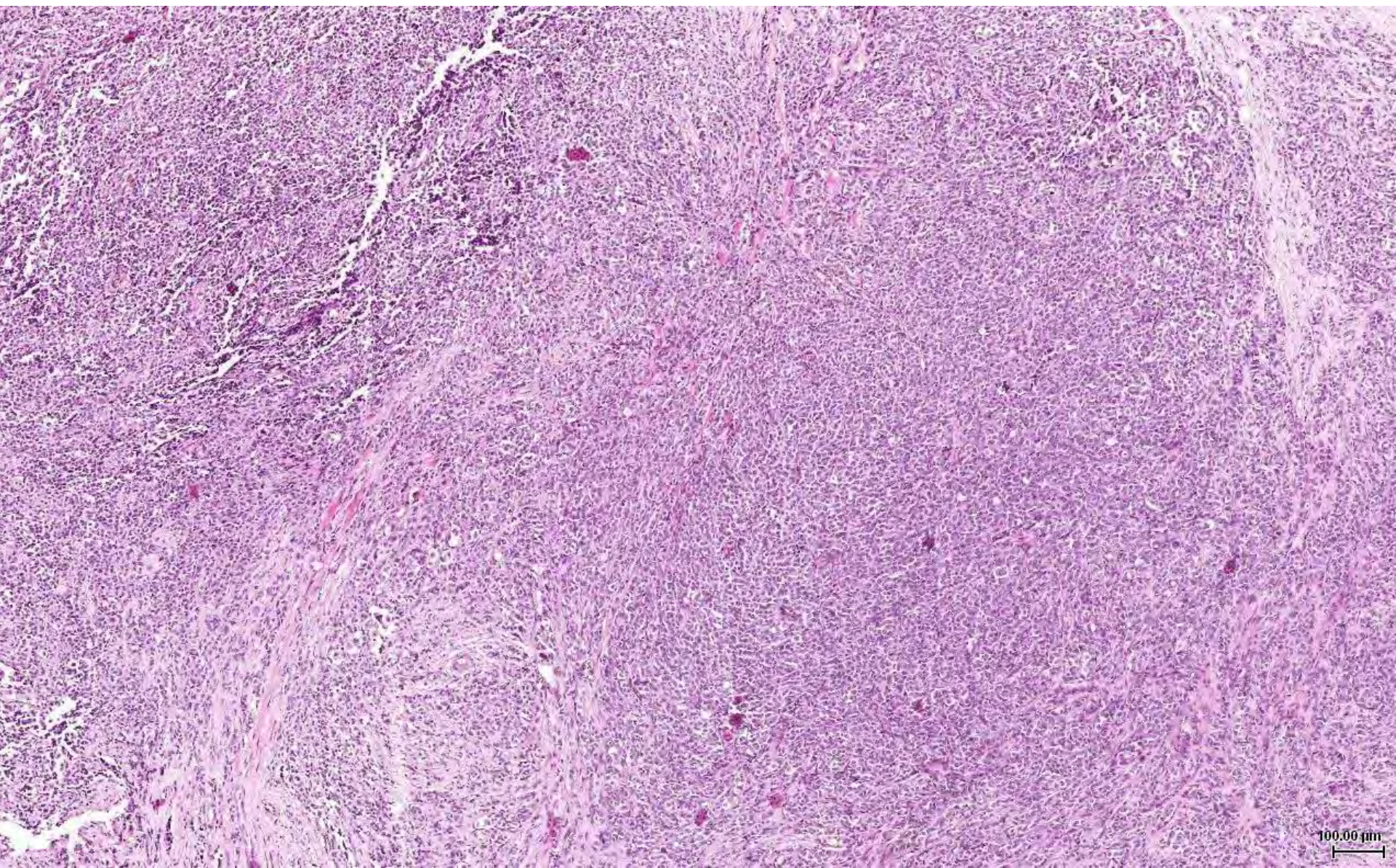
- Nevoid melanoma in congenital nevus

Nevoid Melanoma

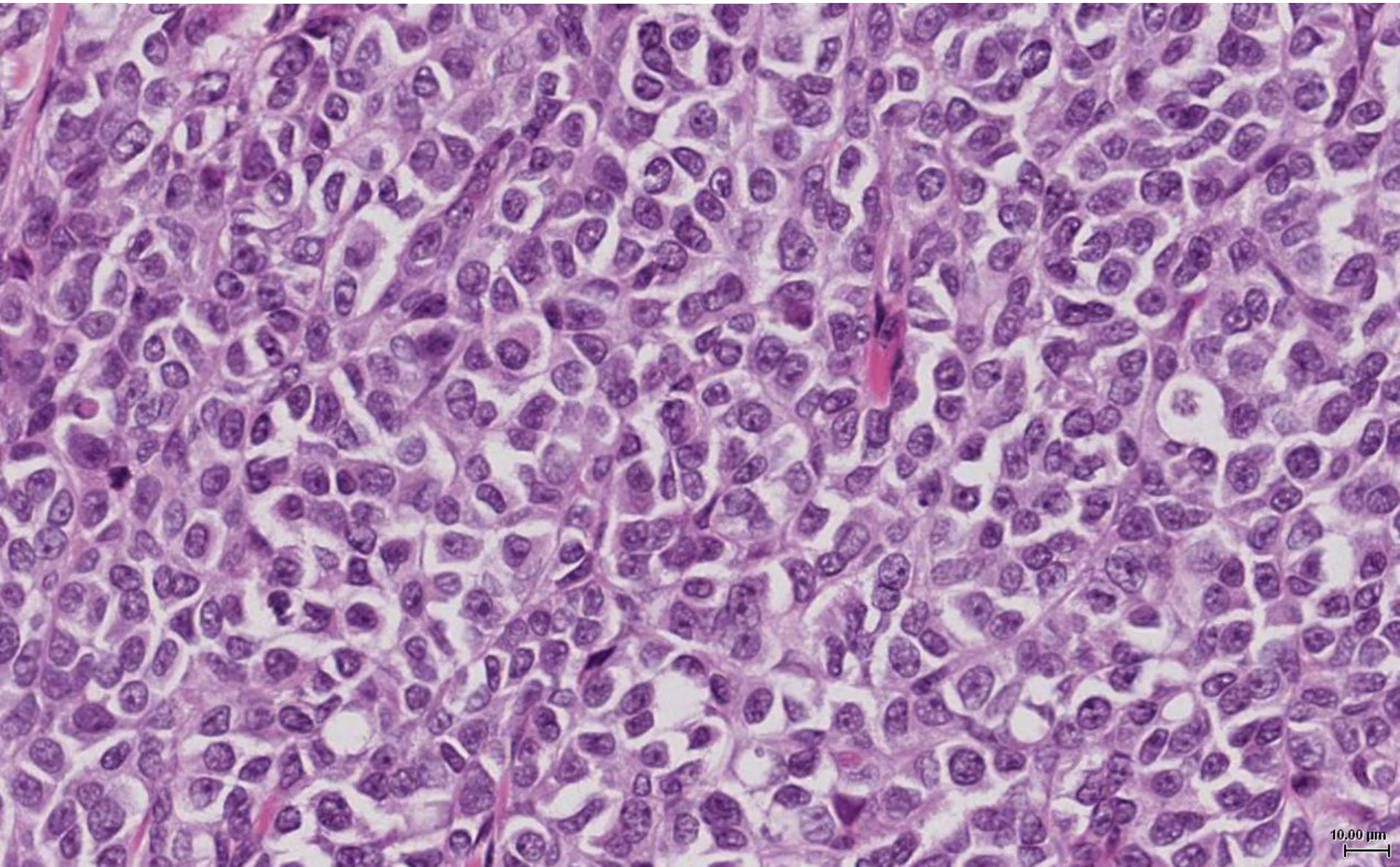
- 12 year old male
- Scalp
- Nevoid cell phenotype
- Arising in congenital nevus







- Distant metastases
- Death in 6 months



Postpubertal Melanoma

Postpubertal Melanoma

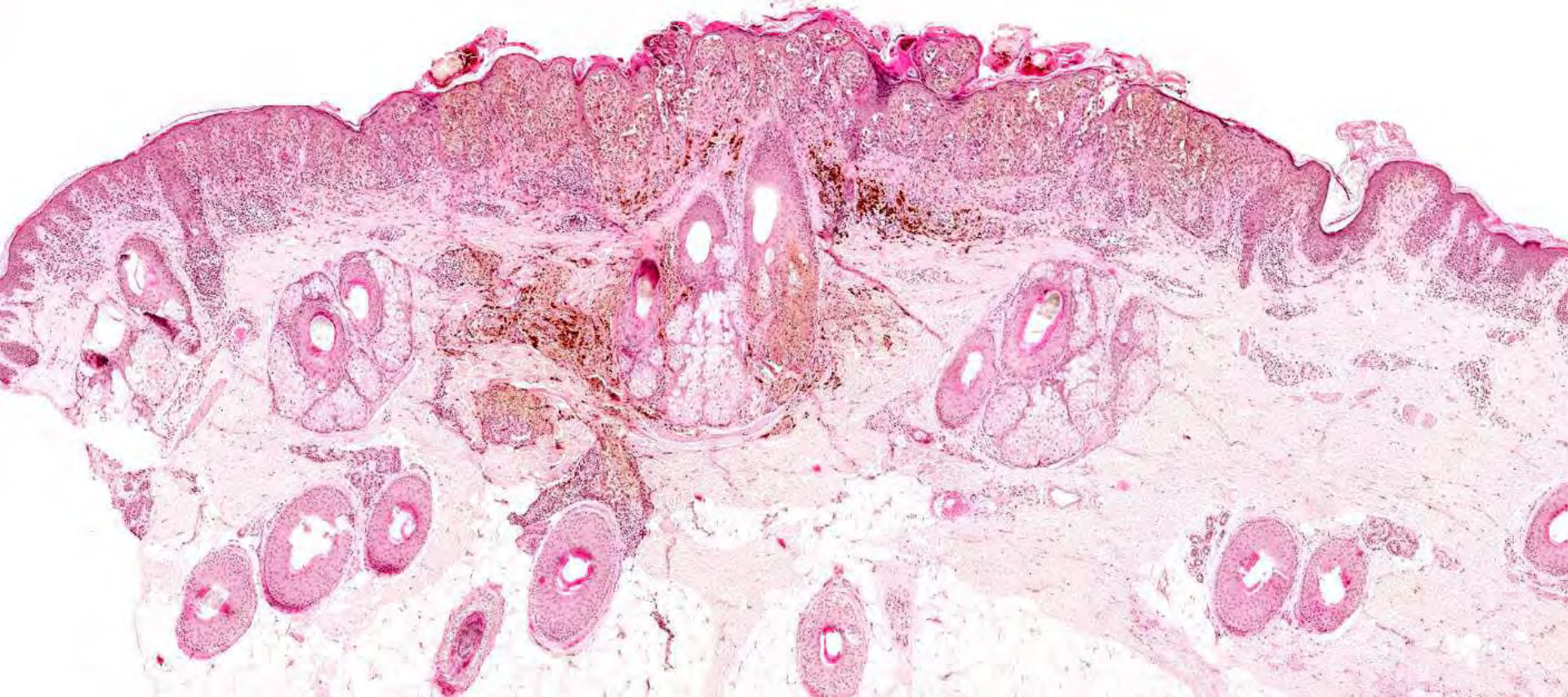
- Melanoma arising in congenital melanocytic nevi
- De Novo melanoma
- Conventional adult melanomas
- Spitz melanoma

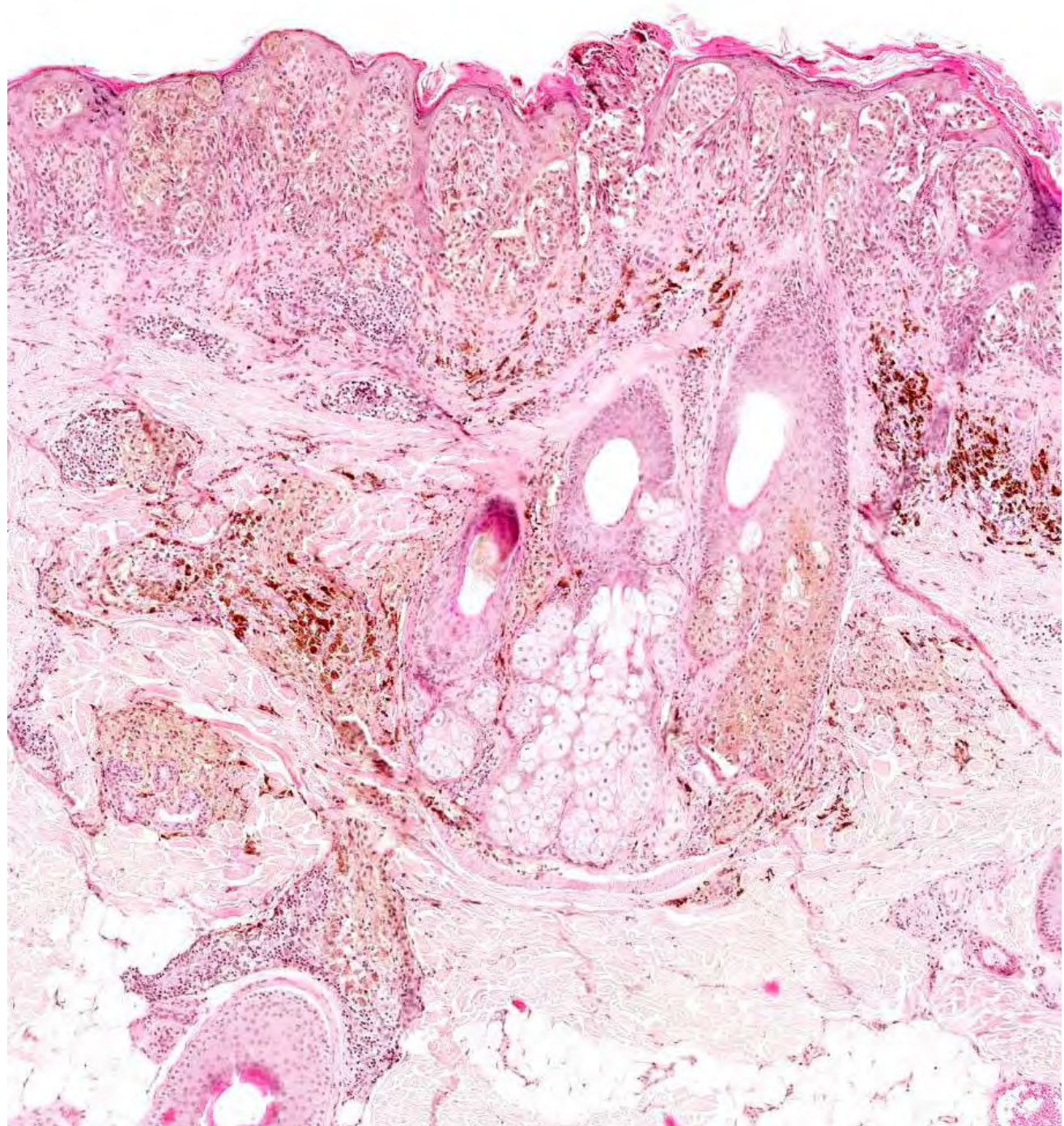
Adolescent Melanoma

- 15 year-old female
- Right temple melanocytic lesion
- Clinical information:
 - New lesion present for 6 months,
 - “Different” from other nevi
 - A changing lesion

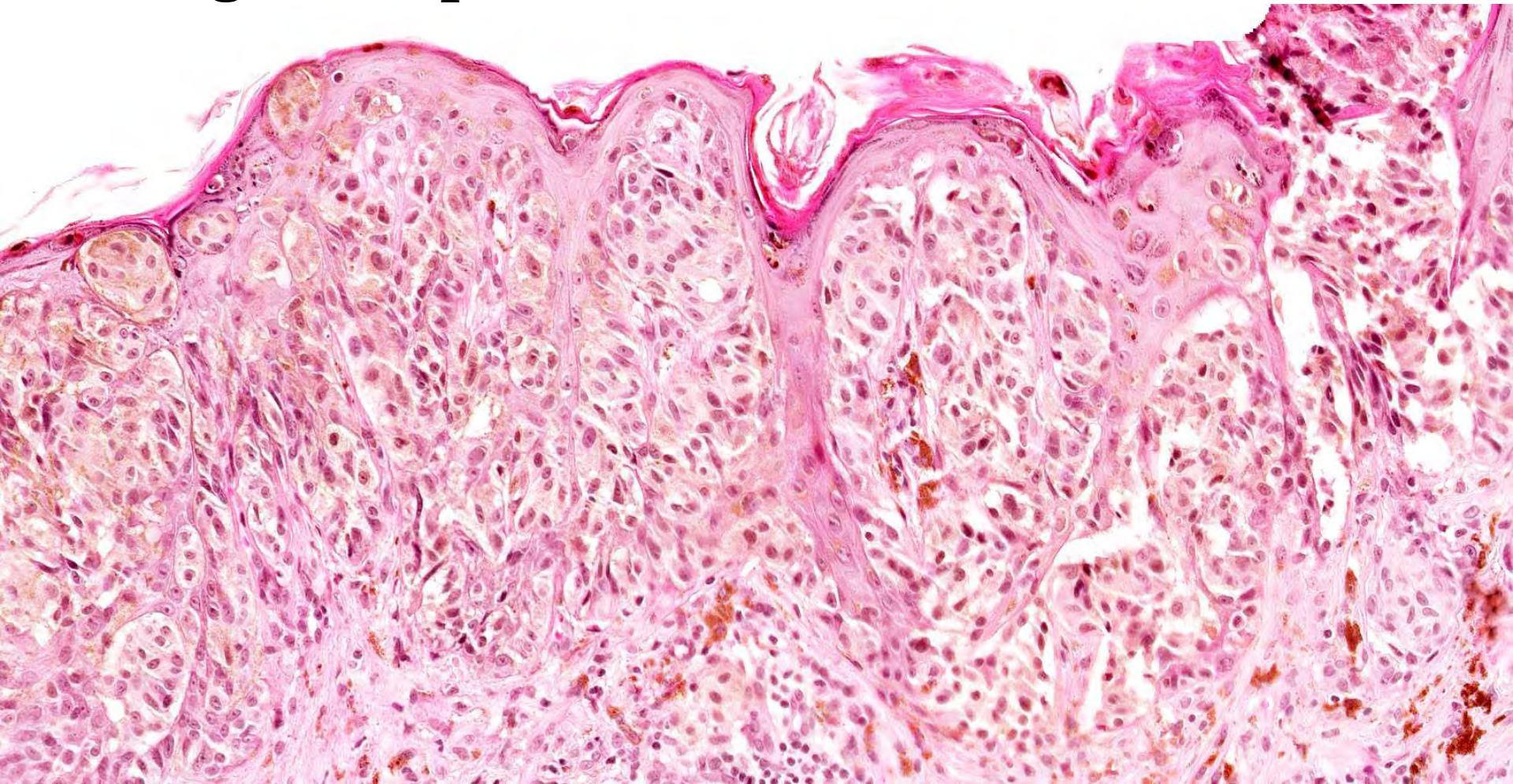
Adolescent Melanoma

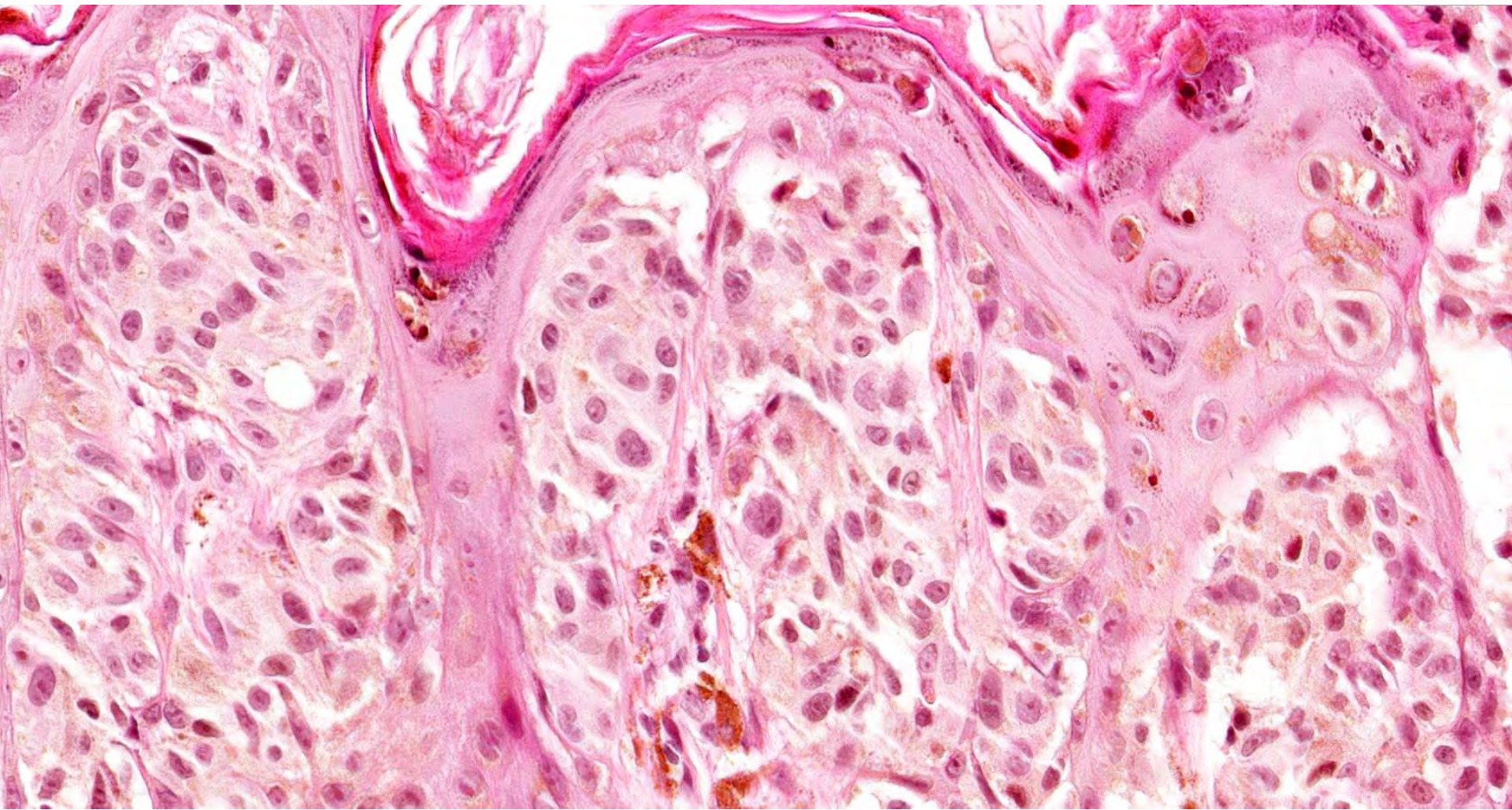
- Asymmetry
- Poor circumscription



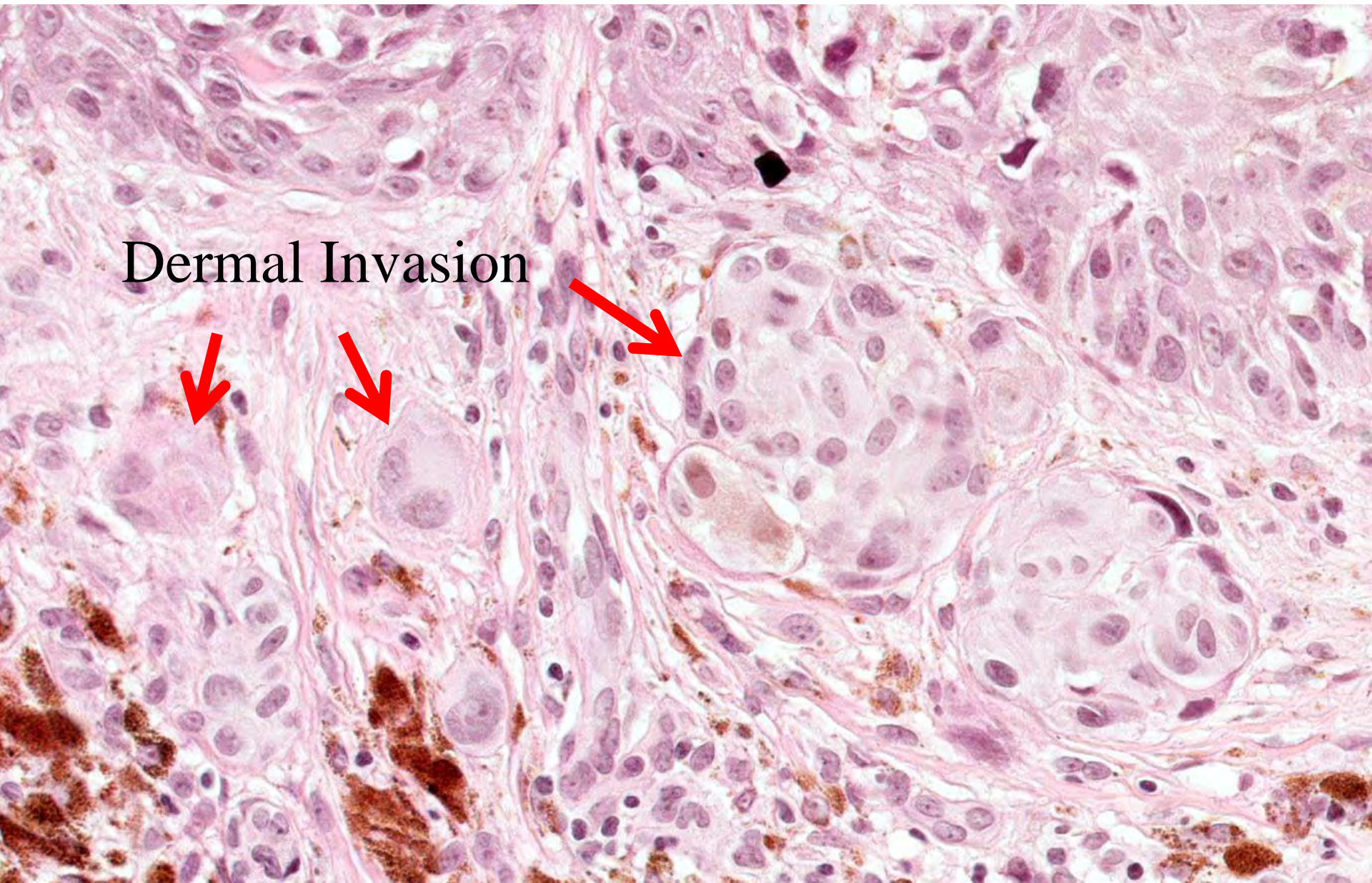


- Replacement of epidermis
- Pagetoid spread



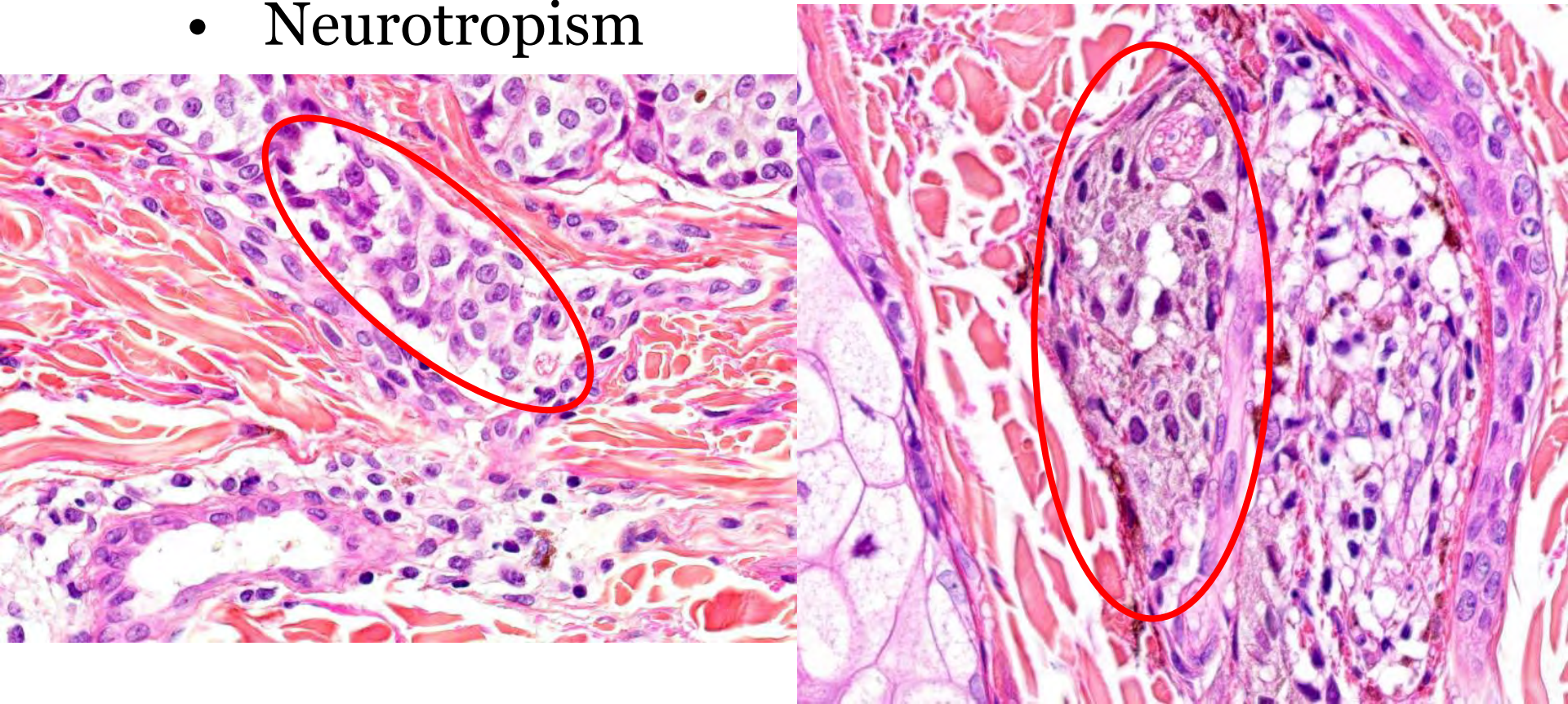


Dermal Invasion



Adolescent Melanoma

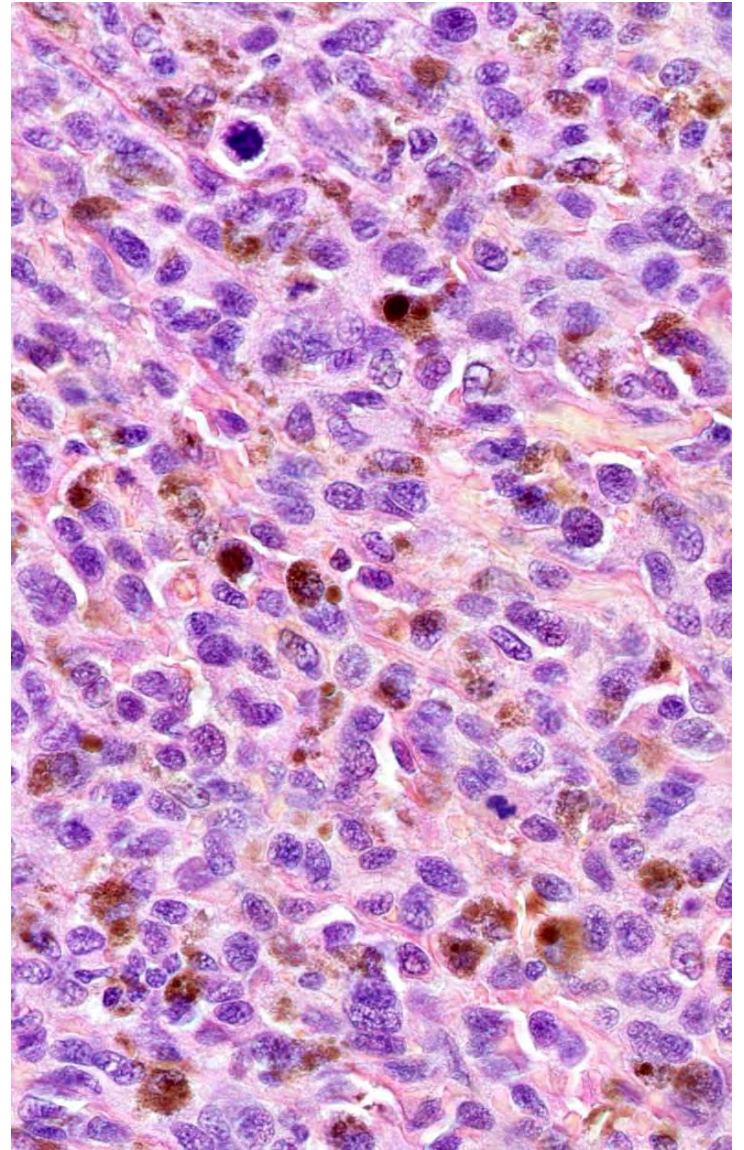
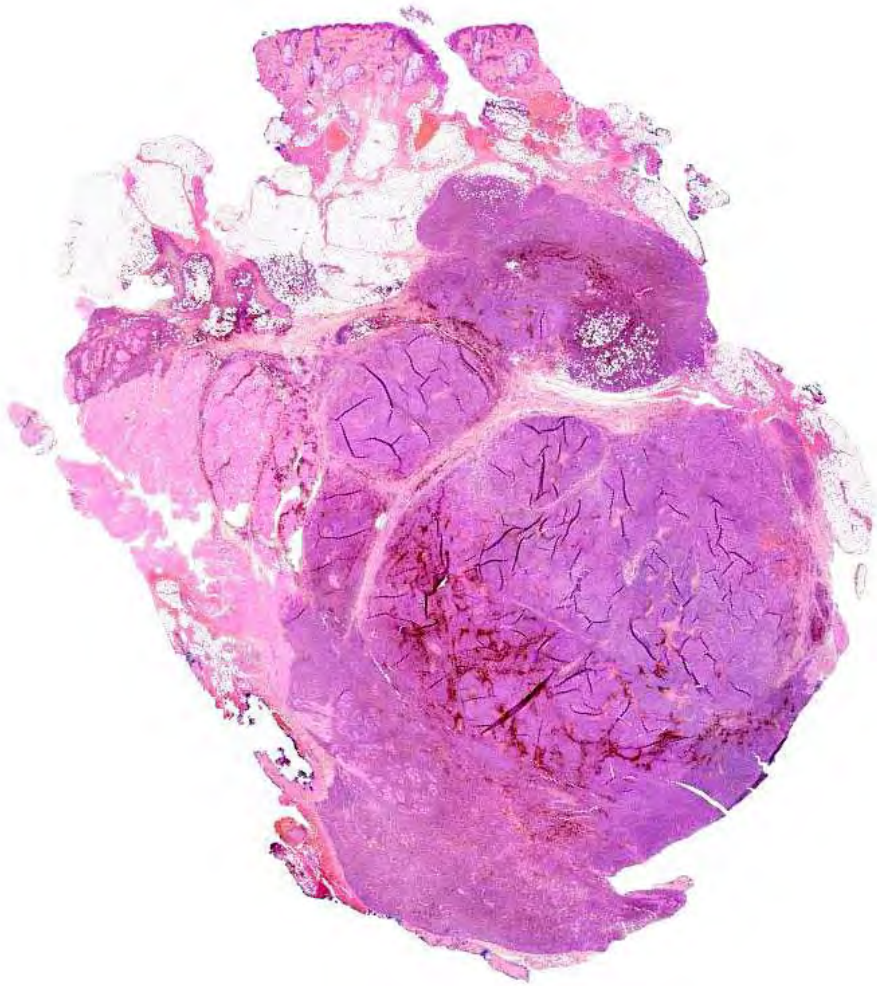
- Angiotropism
- Neurotropism



Low-CSD Melanoma

- Breslow: 1.6 mm
- Level V
- Ulceration: absent
- Mitotic rate: 1 per mm²
- Neurotropism
- Angiotropism
- p16 – complete loss of expression

- Development of Metastasis, Lower Lip Area, 4 Years Later

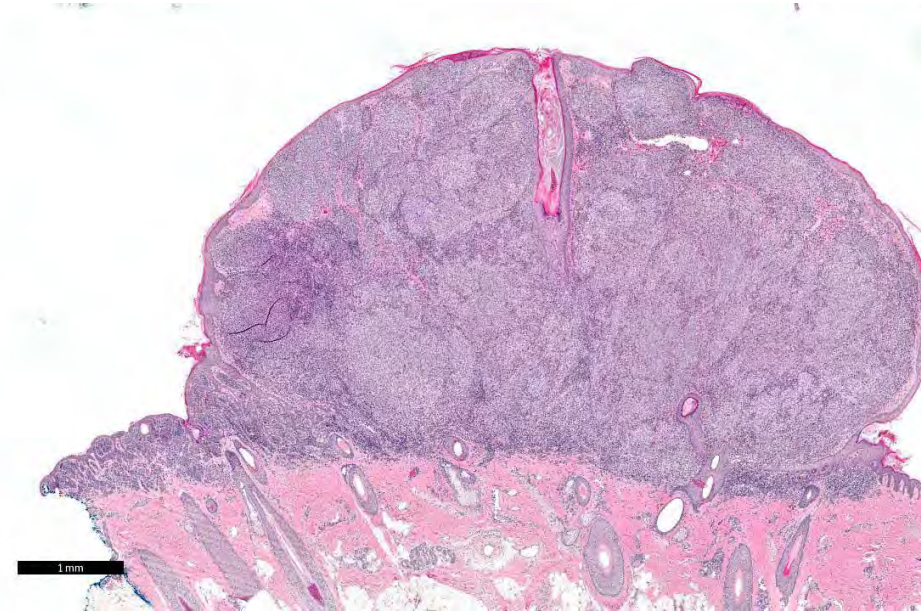


Adolescent Melanoma

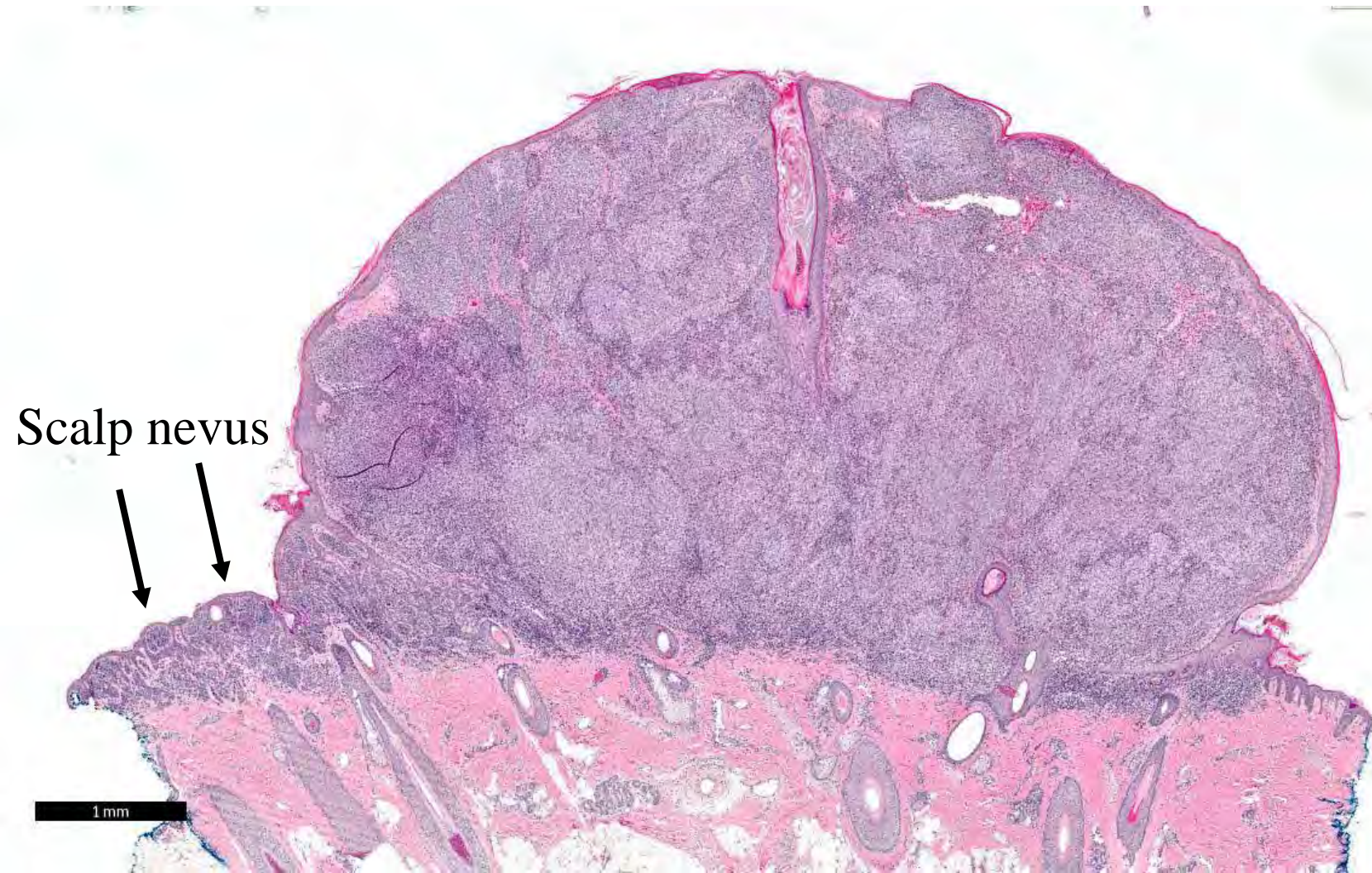
- Simultaneous multiple regional lymph nodes involved
- BRAF mutation
- No follow-up available

Melanoma arising in scalp nevus

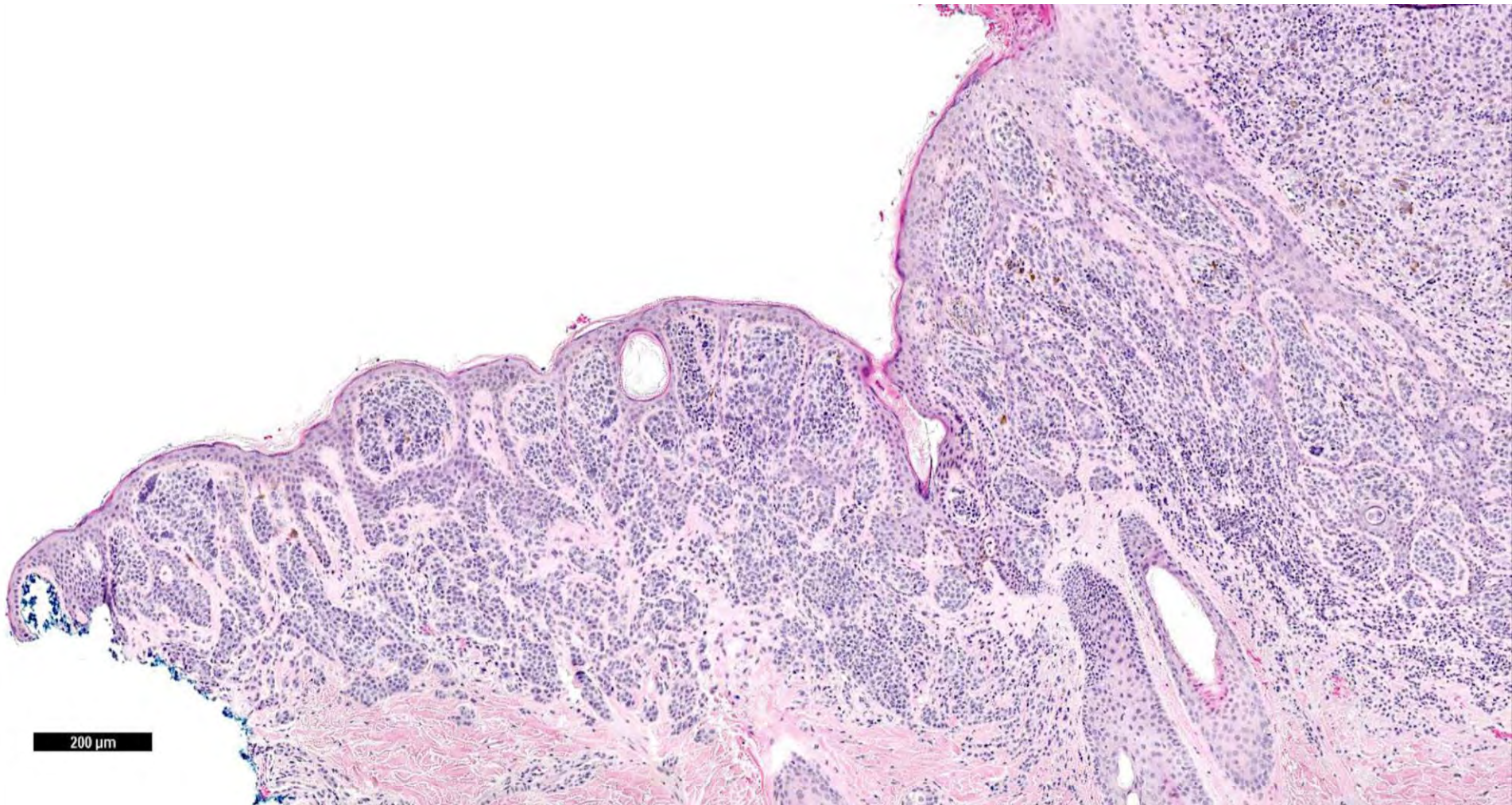
- 12 year-old female
- Frontal scalp
- Enlarging lesion, change in color, bleeding
- Diameter 8 mm
- Breslow 4.7 mm
- Level IV
- Ulceration
- Mitotic rate: 13 per mm²
- Vertical growth phase
- Angiotropism



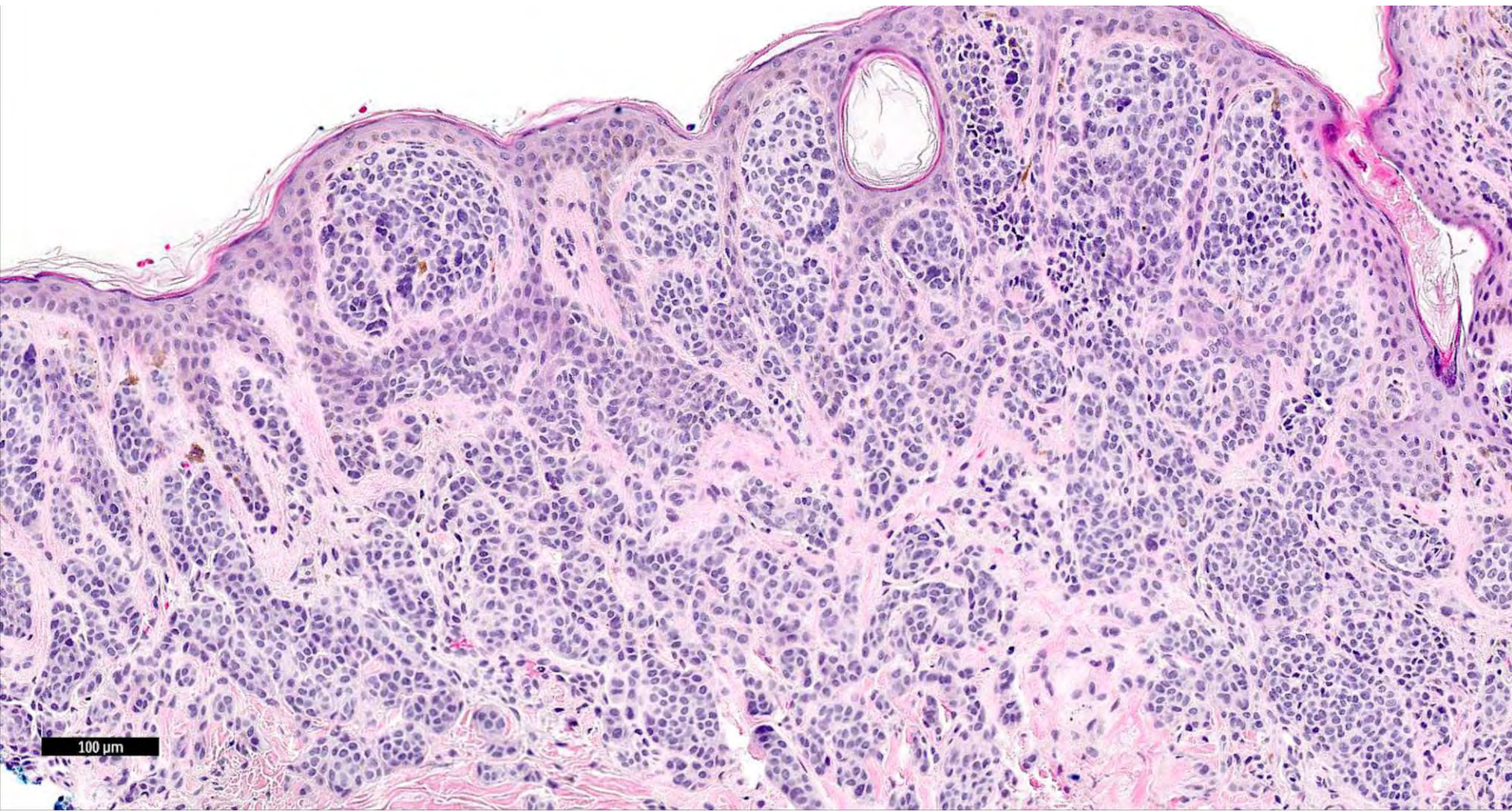
Melanoma arising in scalp nevus



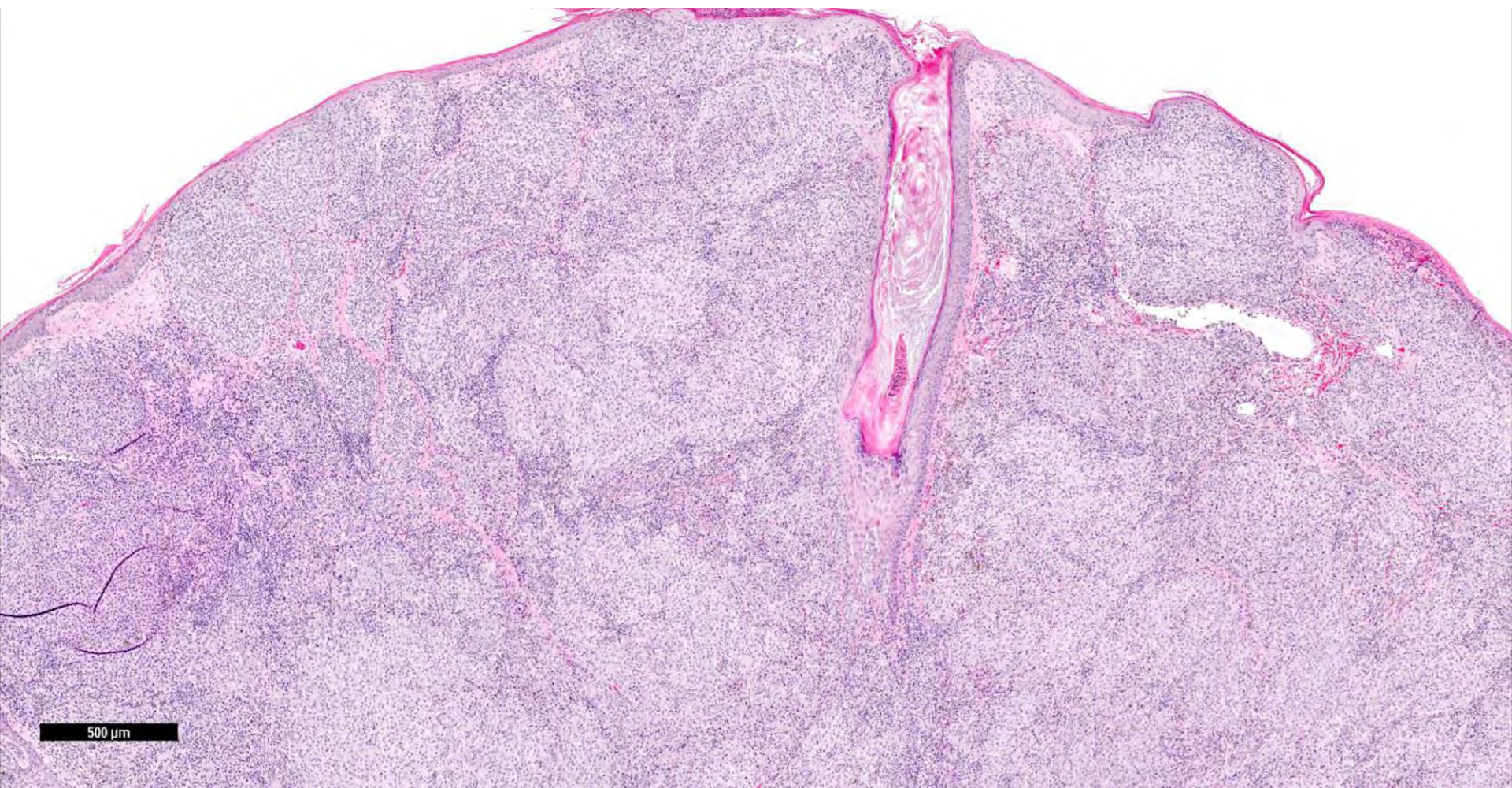
Melanoma arising in scalp nevus



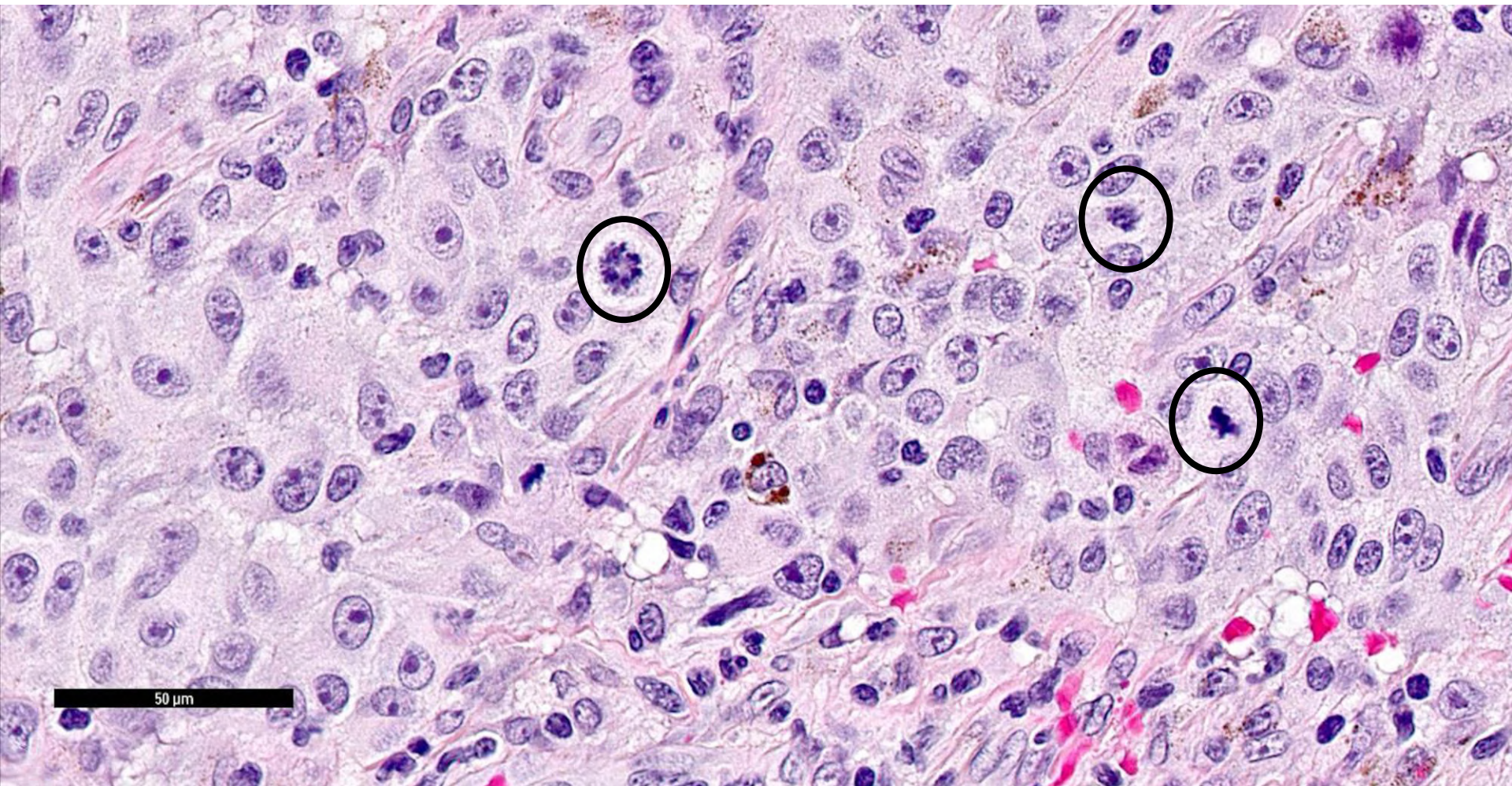
Melanoma arising in scalp nevus



Melanoma arising in scalp nevus



Melanoma arising in scalp nevus





Take Home Messages

1. Clinical information, especially age, anatomic site, must always be considered
2. Mimics of melanoma – congenital nevi, Spitz tumors, site-specific nevi
3. Utilize due diligence and obtain comprehensive information

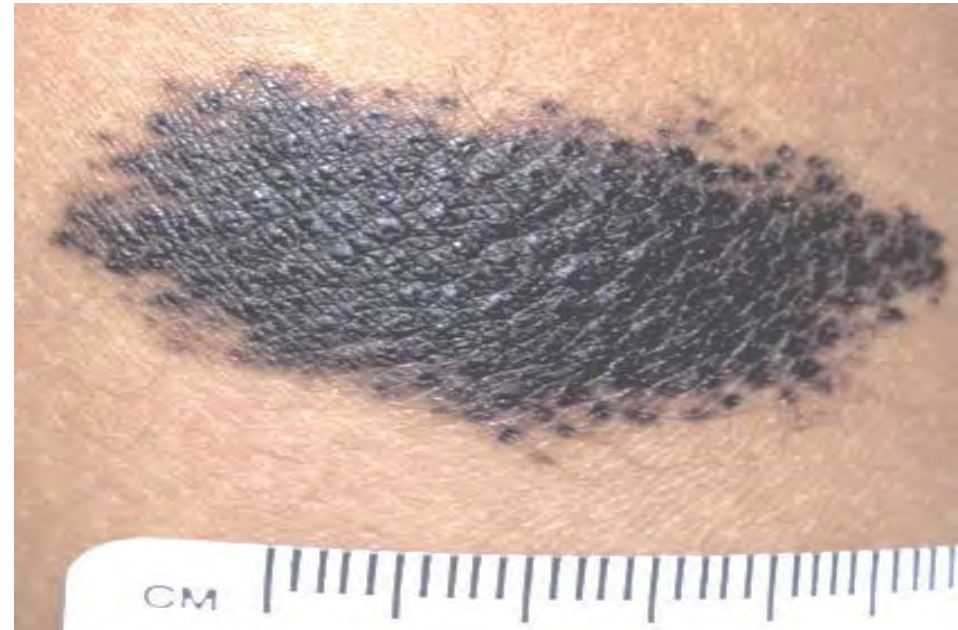
Take Home Messages

- 3. Melanomas arising in congenital nevi are highly aggressive
- 4. Consider referral to consultants and institutions with expertise

Congenital Nevi

Clinical Features

- Prevalence 1:2,000 to 1:20,000
- 1.5 to 20 cm
- Well-defined
- Uniform brown to brown-black color
- Rugose, or pebbled surface



Large/Giant Congenital Nevi

Clinical Features

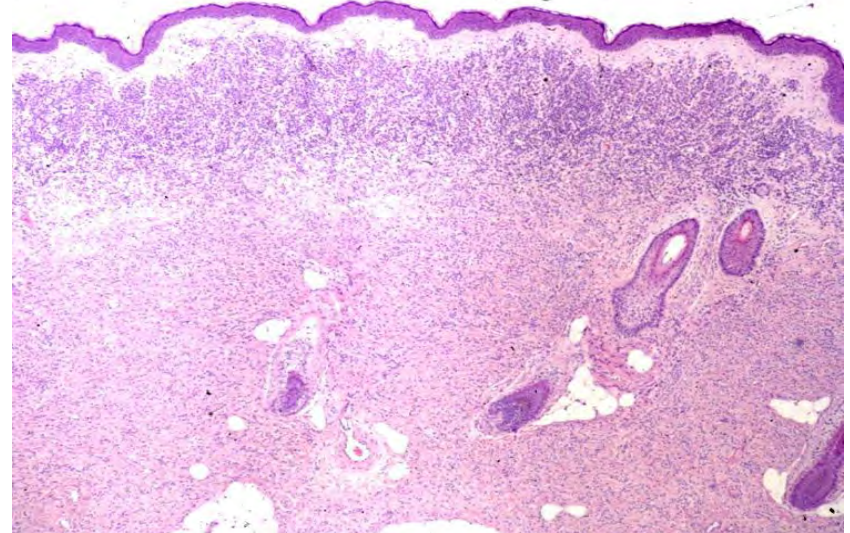
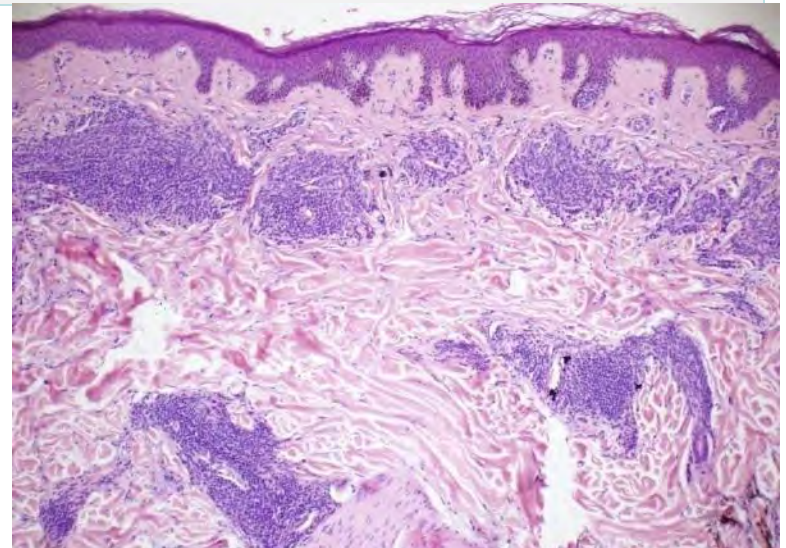
- Prevalence about 1:500,000
- > 20 cm
- > 40 cm
- Major surface area
- Brown-black color
- Rugose, doughy
- Satellite nevi

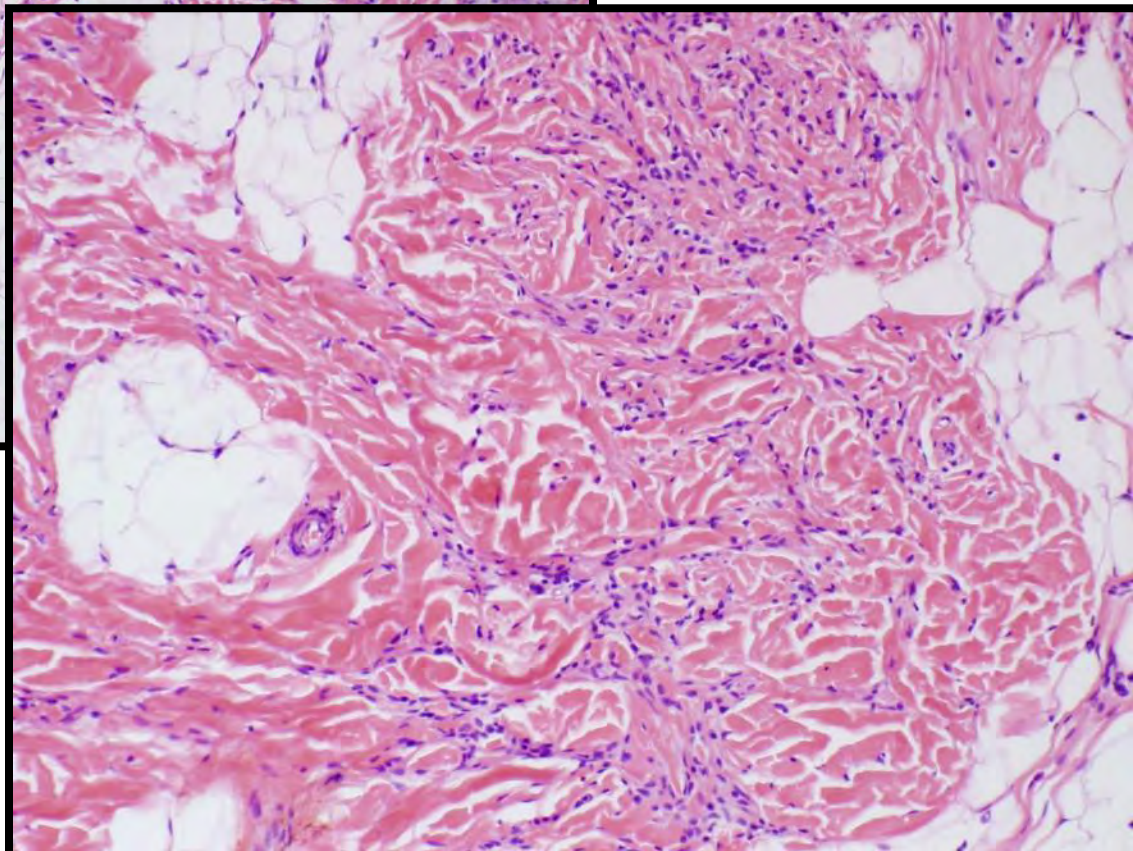
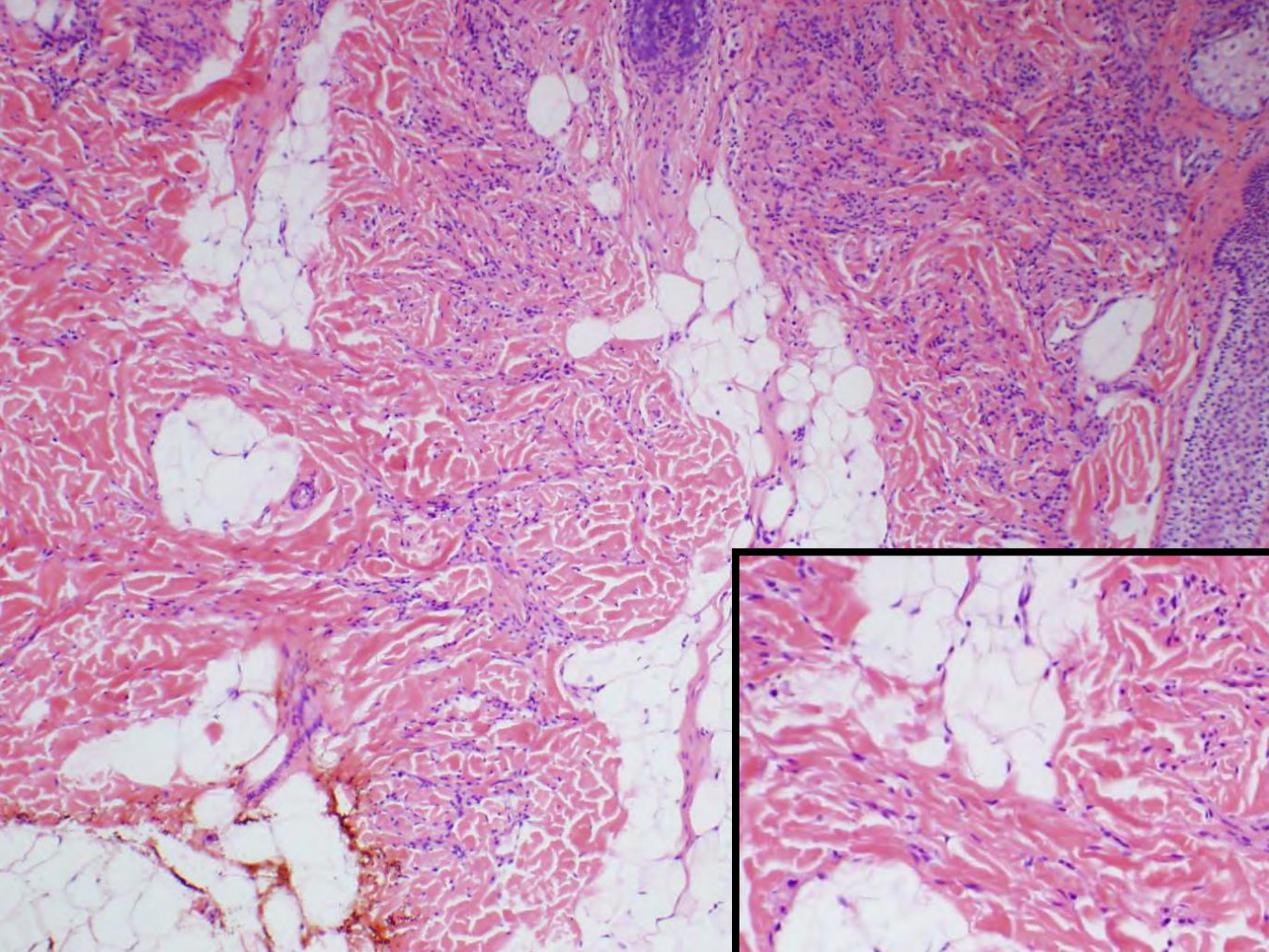


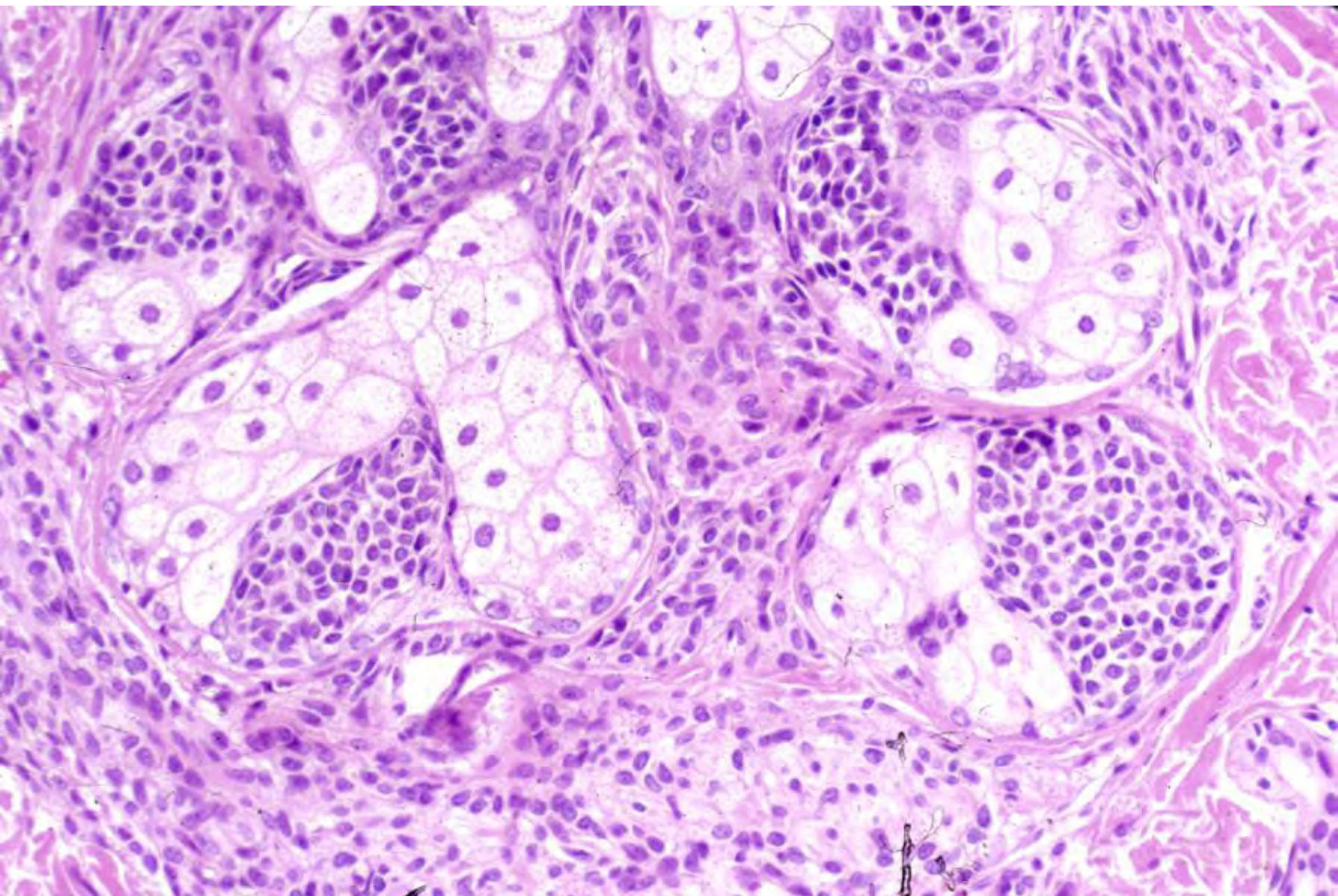
Congenital Nevi

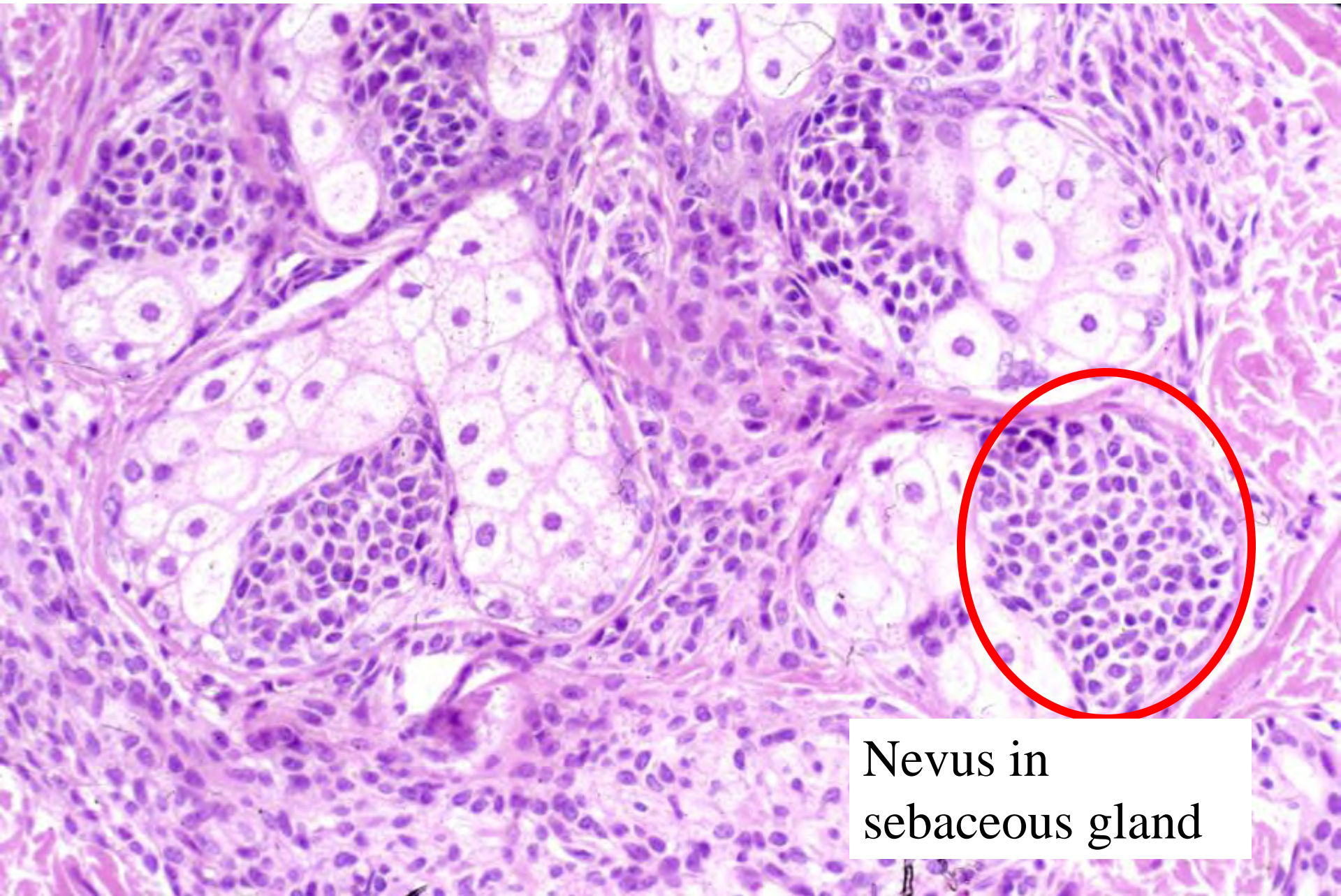
Histological Features

- Nevus cells in discrete aggregates assoc with blood vessels, nerves or appendages
- Nevus cells in diffuse pattern with maturation

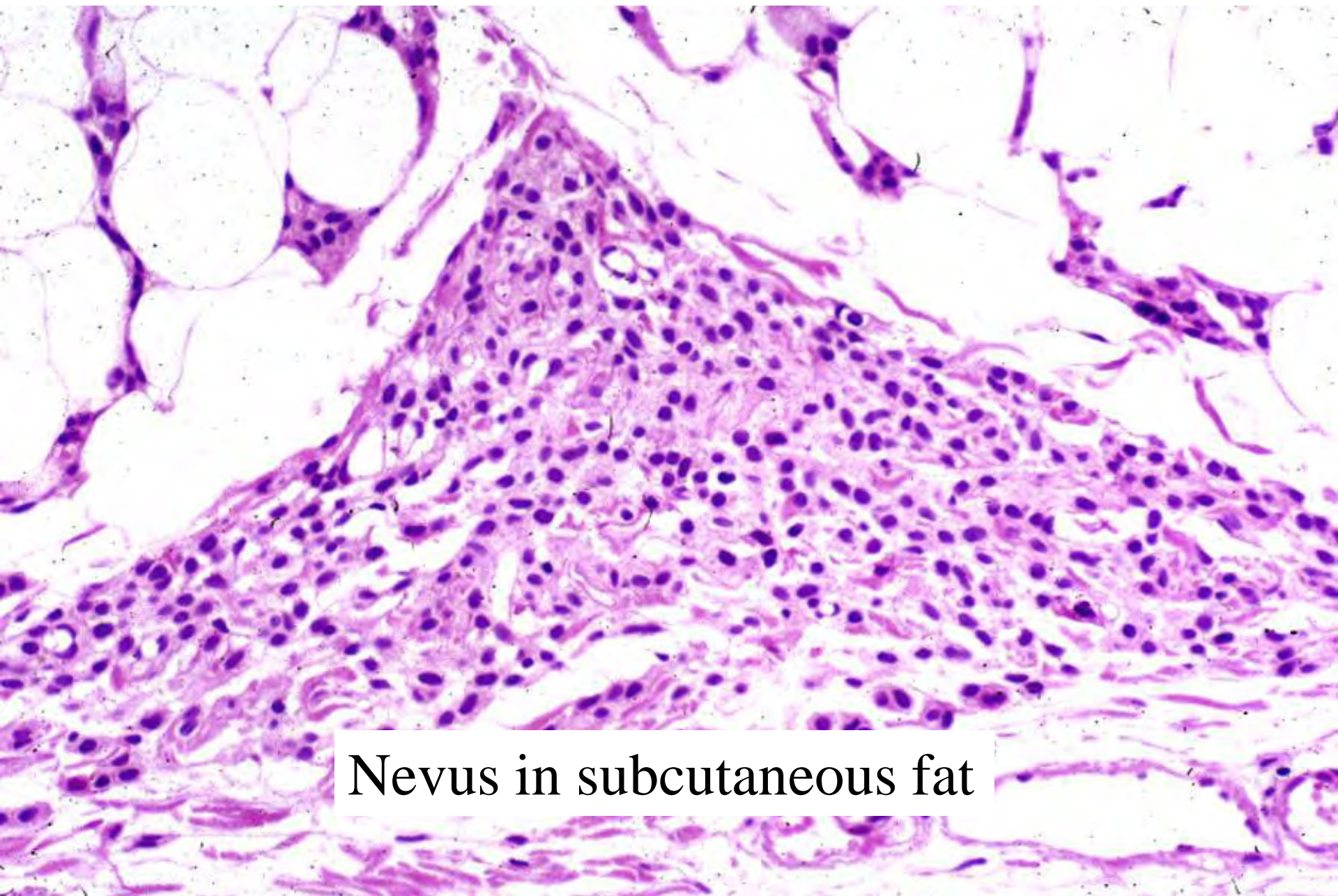






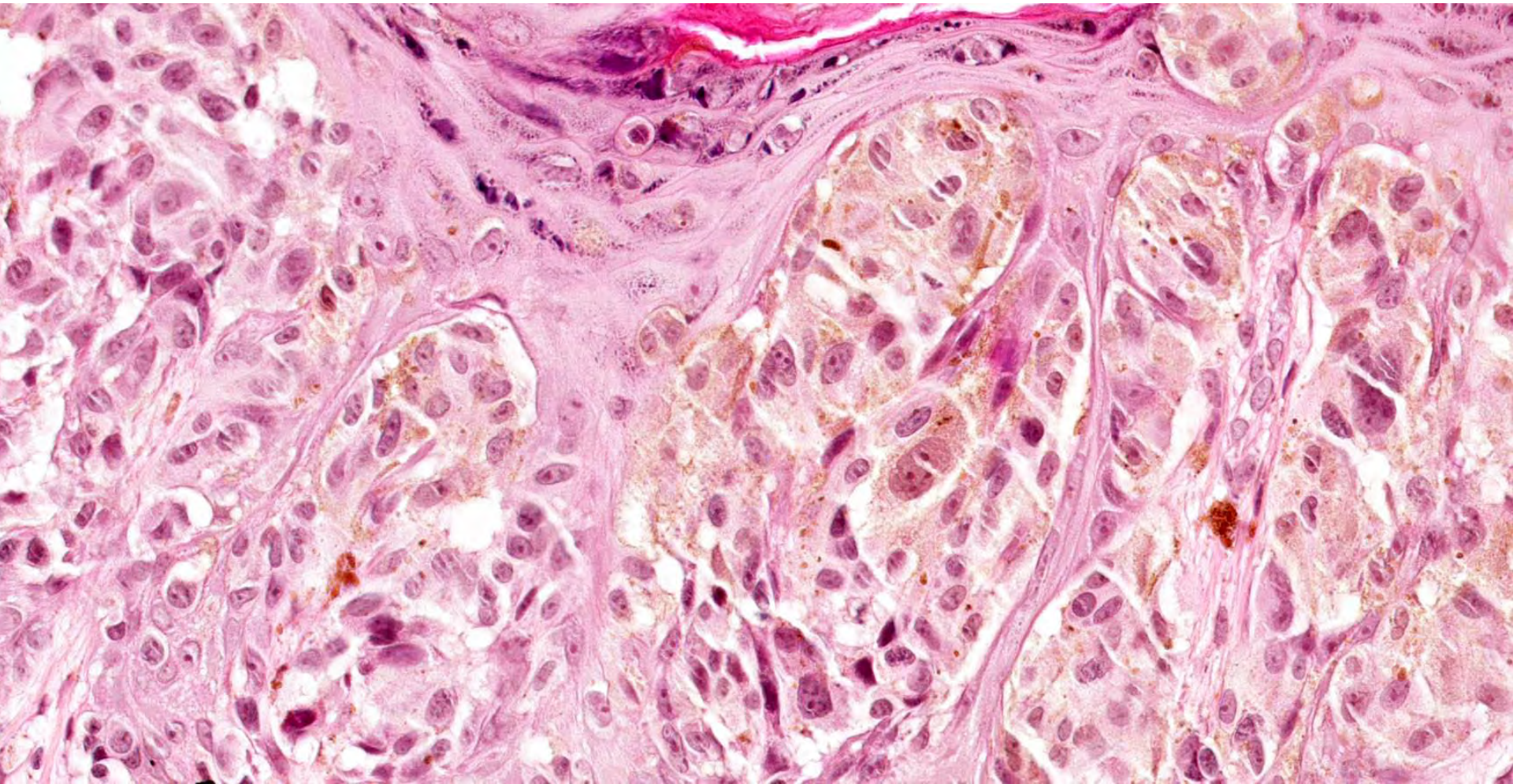


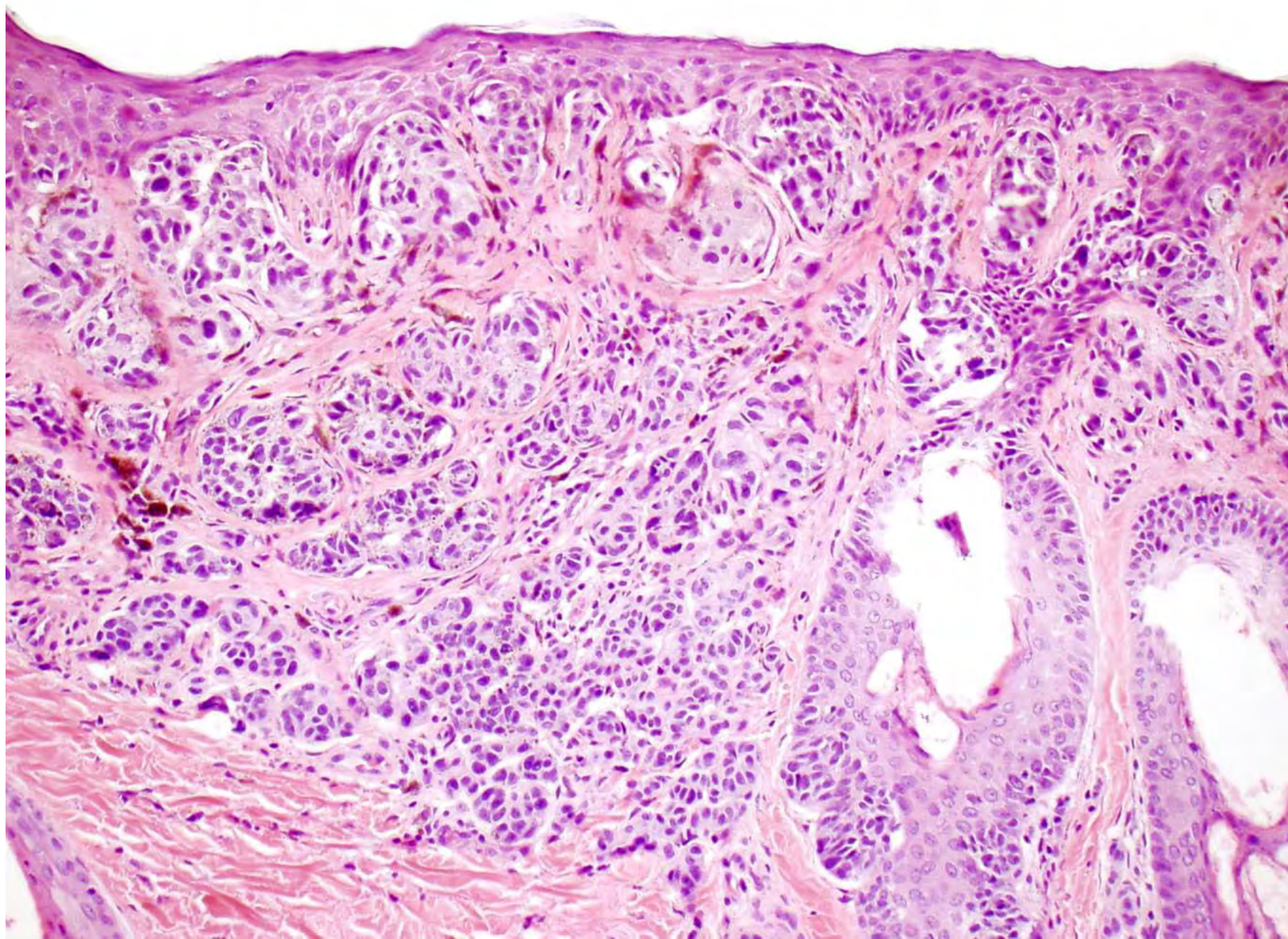
Nevus in
sebaceous gland

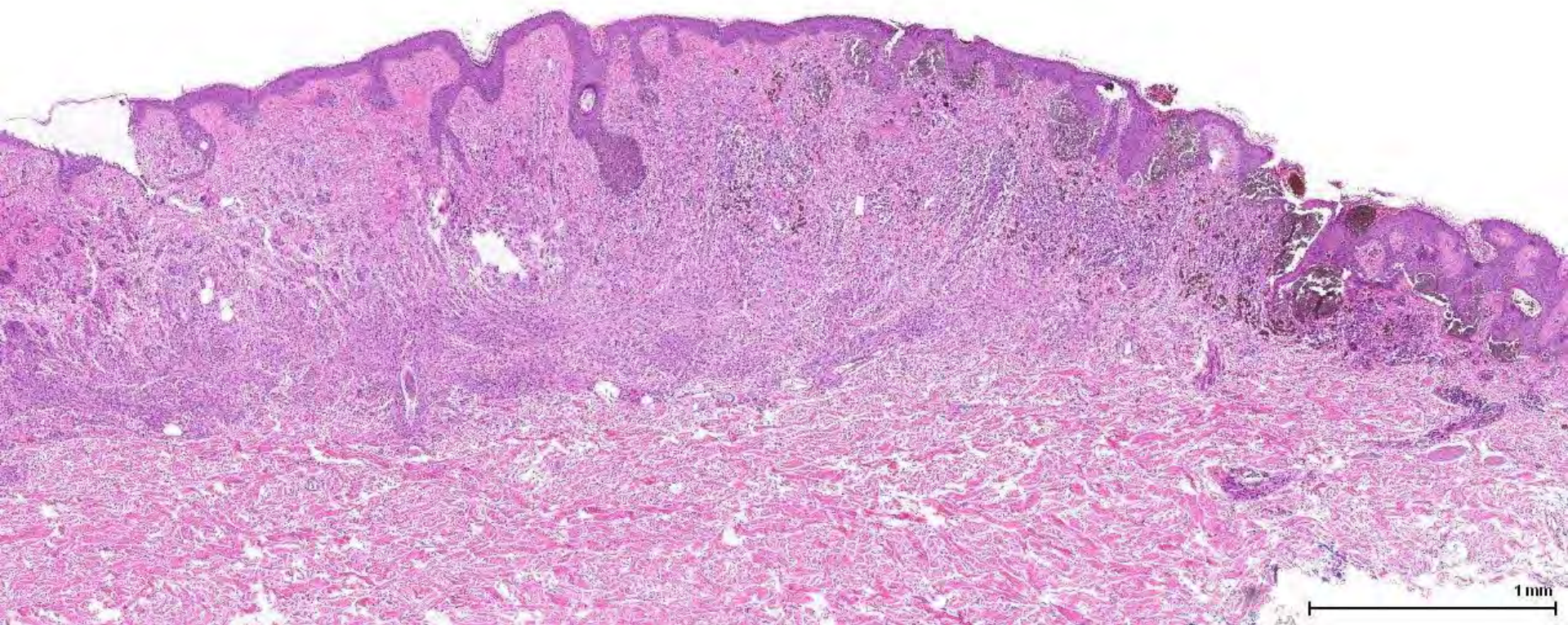


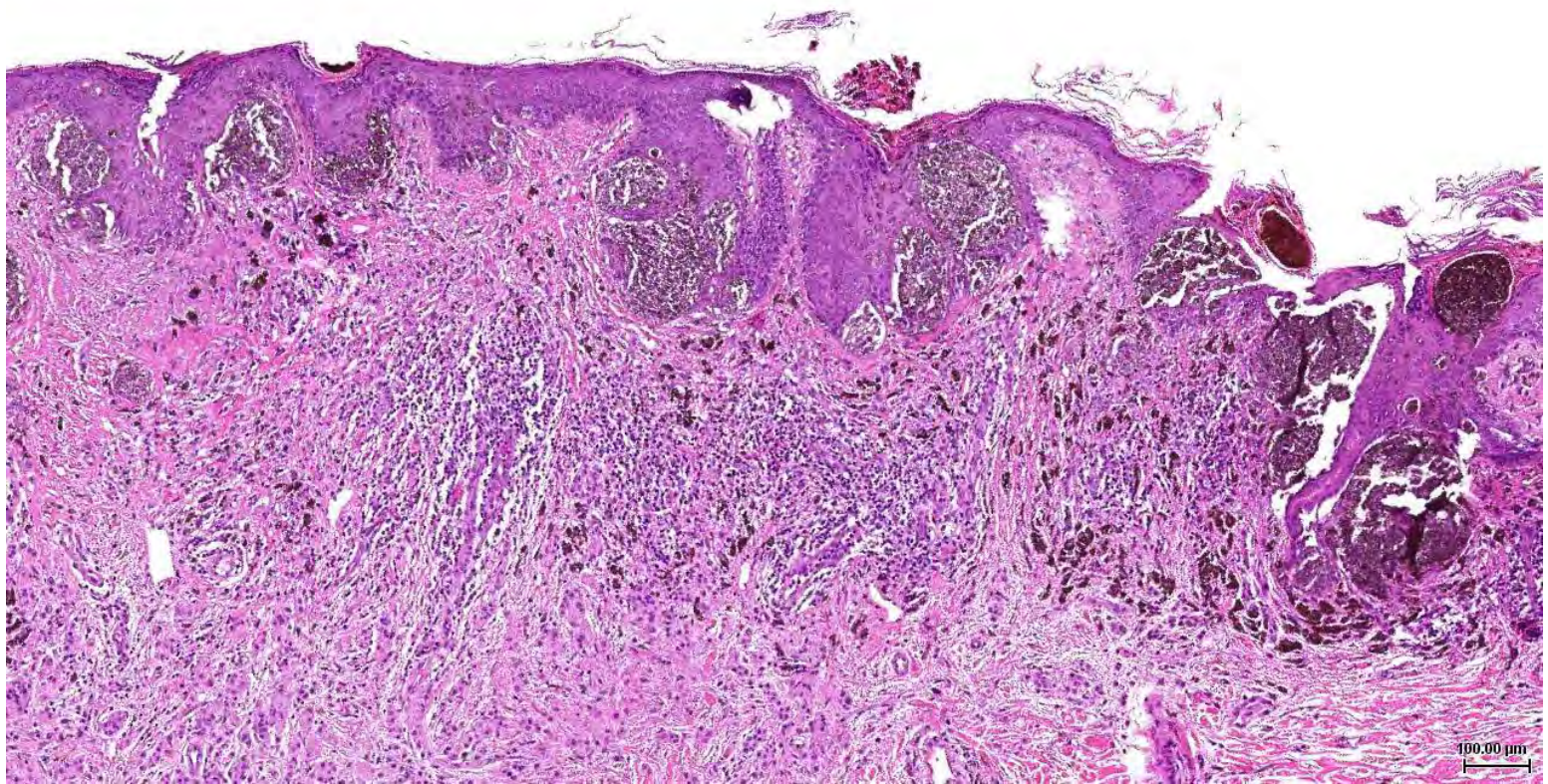
Nevus in subcutaneous fat

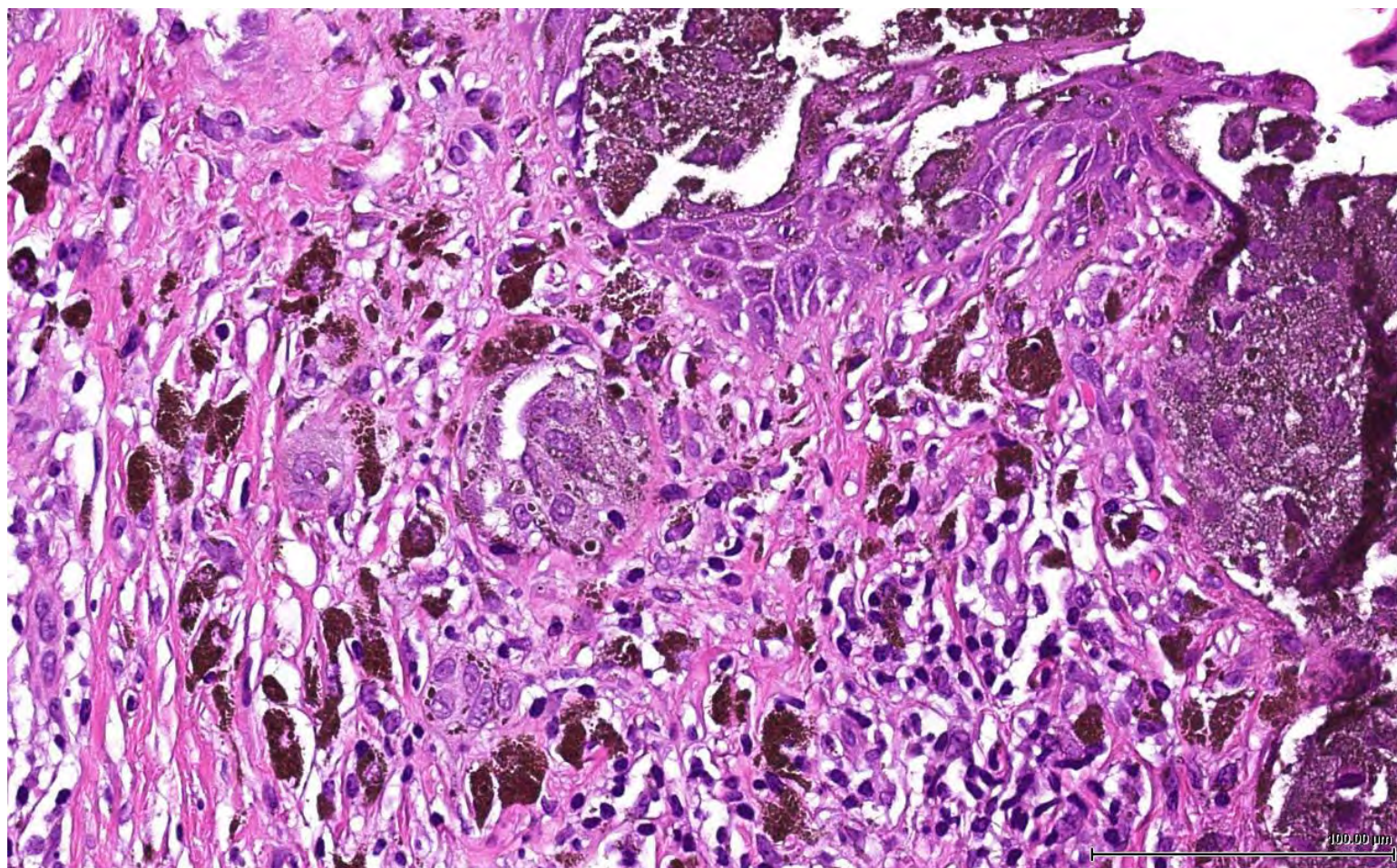












Xeroderma Pigmentosa

Lentiginous Melanoma

- 3 year-old male
- Face
- Breslow: 0.18 mm
- Level II
- Xeroderma pigmentosum, aggressive variant

Lentiginous Melanoma Resembling Lentigo Maligna

