Pediatric Melanocytic Lesions: An Update

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Mission of the Pathologist
Re: Pediatric Melanocytic Lesions

- Accurate and understandable diagnostic reports for clinicians and patients
  - Prognosis
  - Management, vis-à-vis, surgery, other therapies
- Do no harm and due diligence
  - Do not miss melanoma!
  - Do not over-diagnose melanoma!

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

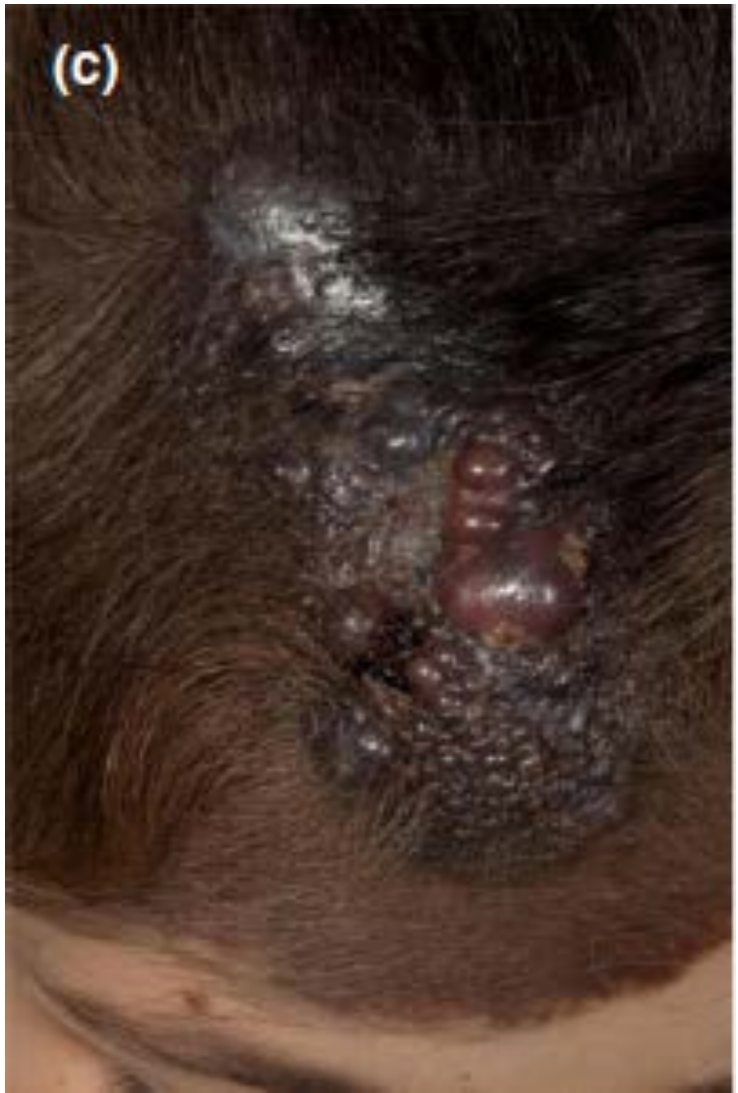
- Consider referral to consultants and institutions with expertise

Pediatric Melanoma Clinical Criteria

Age	• Melanoma is rare < 10 – 12 years of age, especially near birth and < 1 year of age	
Anatomic site	• High risk: Scalp, particularly in prepuberty • Mimics of melanoma: scalp, vulva	
Clinical history	• Changing or new lesion, itching, pain, bleeding, ulceration suggest melanoma	
Gross morphological features suggesting melanoma	• Polypoid lesion resembling hemangioma or pyogenic granuloma • >5 mm, especially >10 mm • Irregular shape/color; black; amelanotic • Ulceration	• **A**melanotic • **B**leeding/bump • **C**olor uniformity • **D**e 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 only (< 15 years of age)
- 4/10 cases: Scalp (< 10 years of age)



Pediatric Melanoma: Certainty of Diagnosis

- The most rigorous criterion is:
  - Distant metastases**
  - Death from melanoma***

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)!

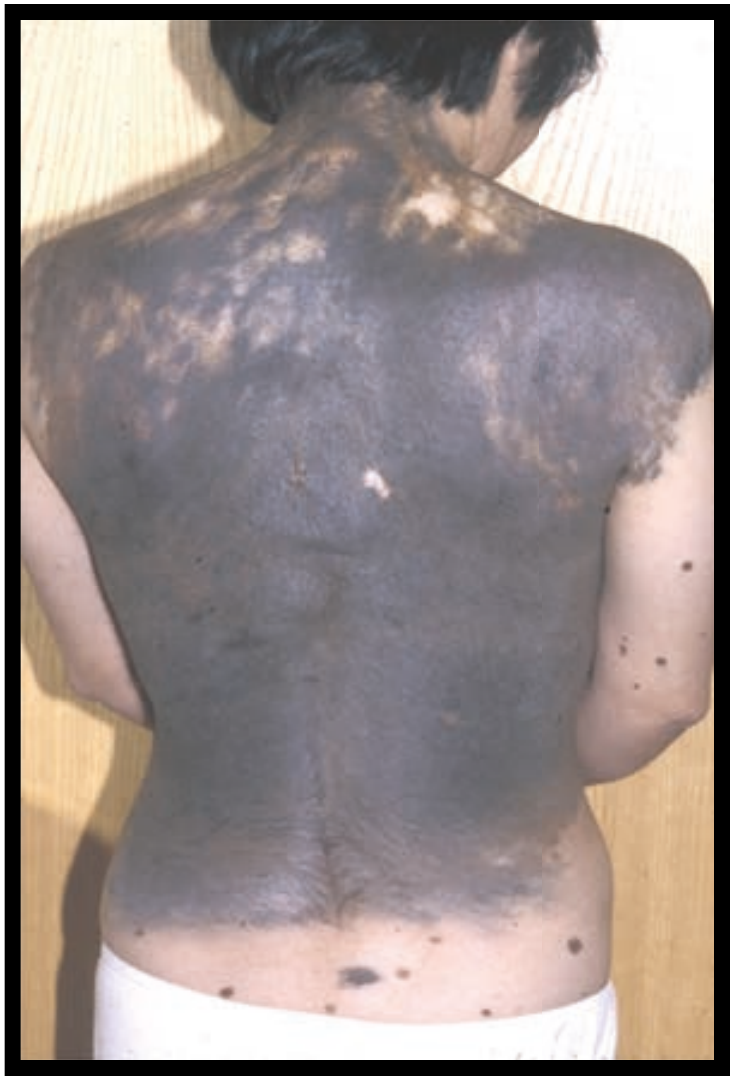
  -Abnormal screening Magnetic Resonance Imaging (MRI) of brain and spine in early life

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



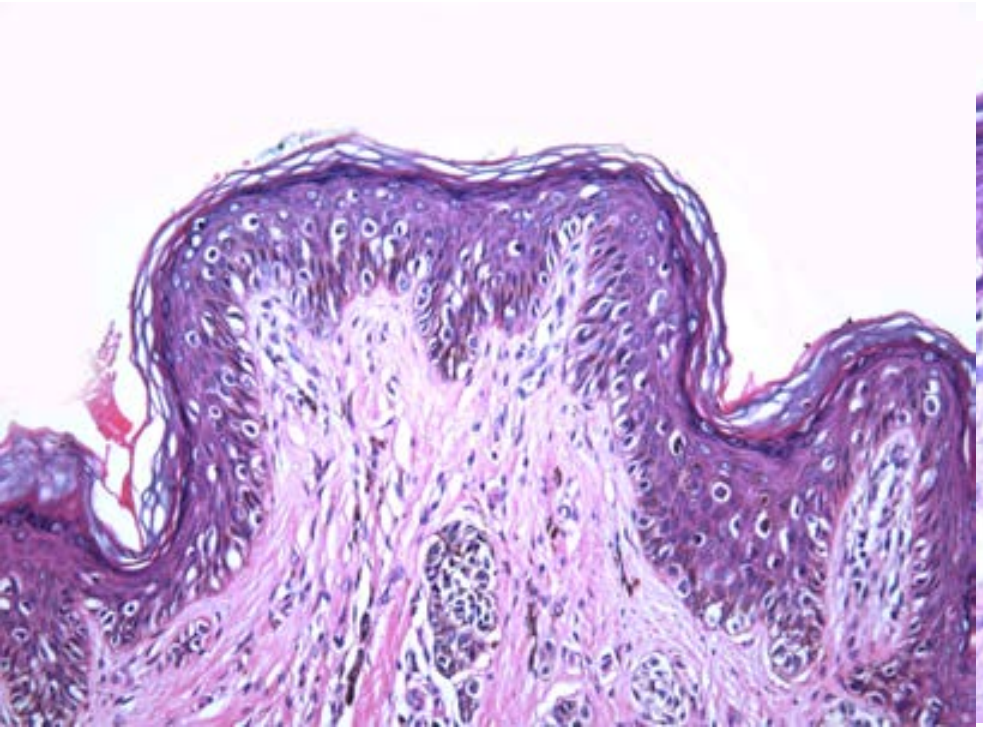
Congenital Nevi
Mimics of Melanoma

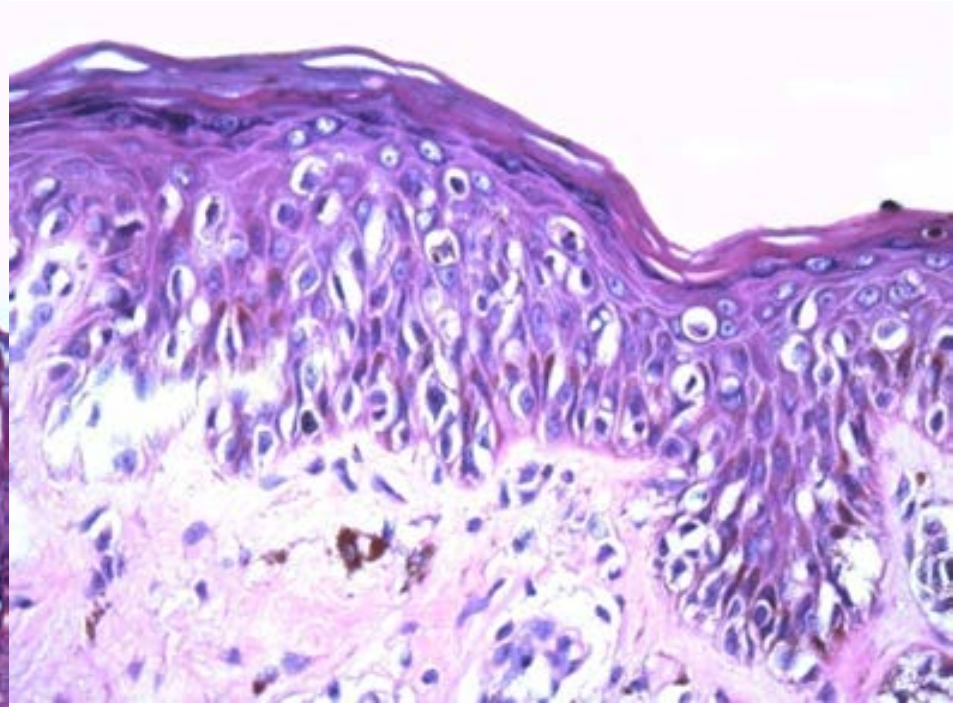
Congenital Nevi
Mimics of Melanoma

- Pagetoid melanocytosis
- Proliferative nodules

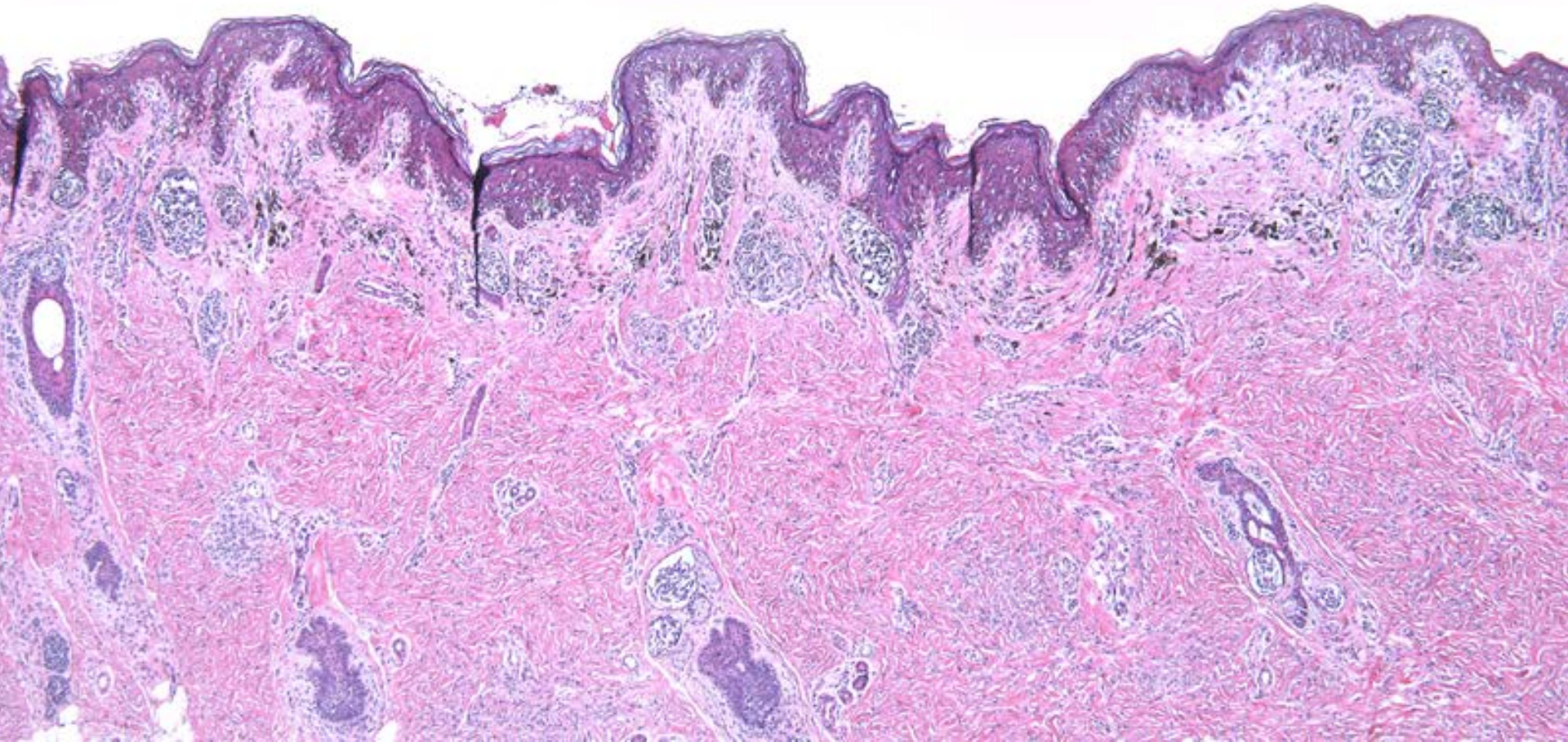
Congenital Nevi

Mimics of Melanoma



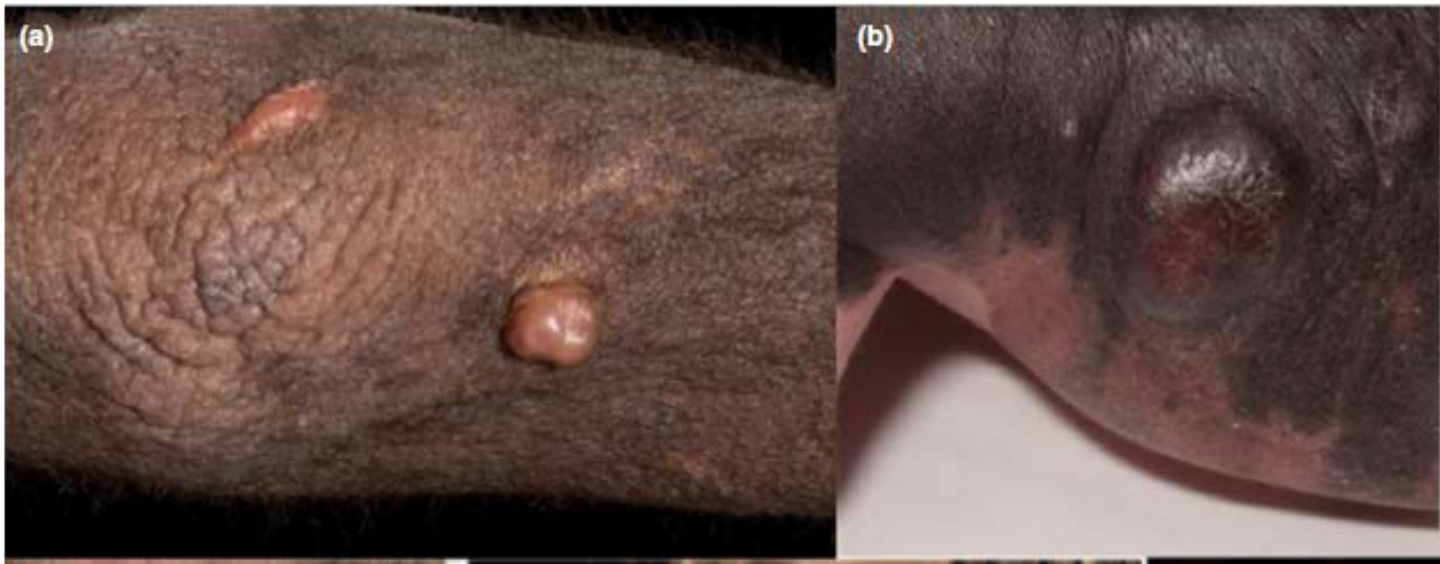


- Pagetoid Melanocytosis



Congenital Nevi
Mimics of Melanoma

- Proliferative nodules

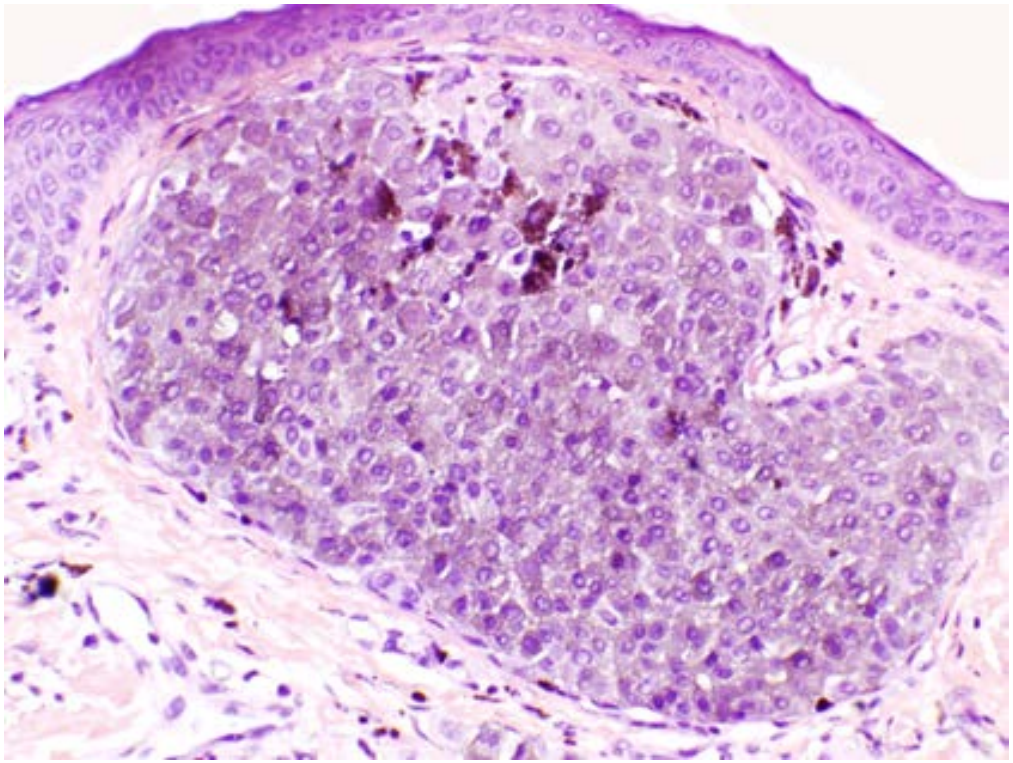


Proliferative Nodule in CMN

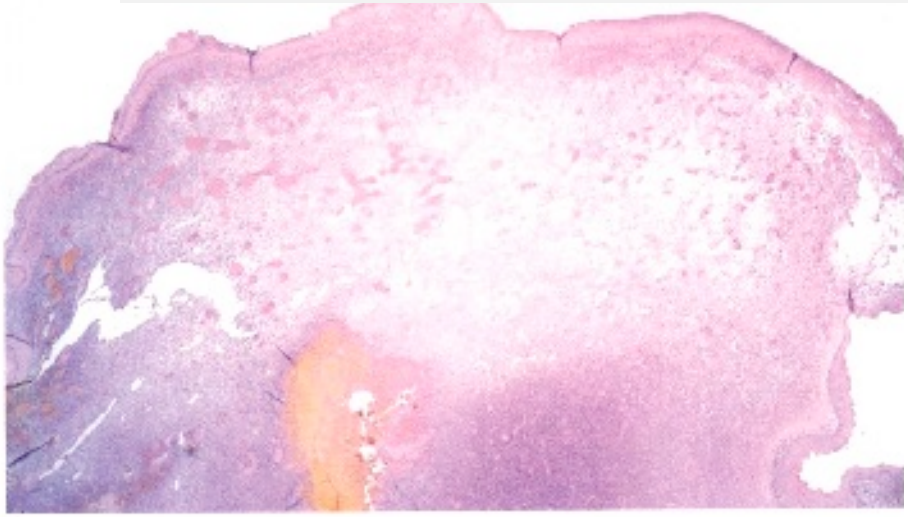
Criterion	Benign	Melanoma
Age	Birth, < 1 y, < 10 y	Increasing age
Anatomic site	Any site, often Multiple	Scalp/neck/back, Solitary
Size	< 1 mm to > 1 cm	Larger
Cell type	Ovoid/nevoid, epithelioid, spindle, small cell,	Epithelioid, small, spindle, undifferentiated
Architecture	Symmetrical, no ulceration, blends with nevus, maturation, no necrosis	Asymmetrical, ulcerated, abrupt border, no maturation, necrosis
Cytological atypia	Usually low grade	Usually high grade
Mitotic rate	0 to 1-2 mitoses/mm^2	> 2 to 25 mitoses/mm^2
Molecular	None to whole chromosomal losses or gains	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/mm^2



Congenital Proliferative Nodule: An Uncertain Lesion



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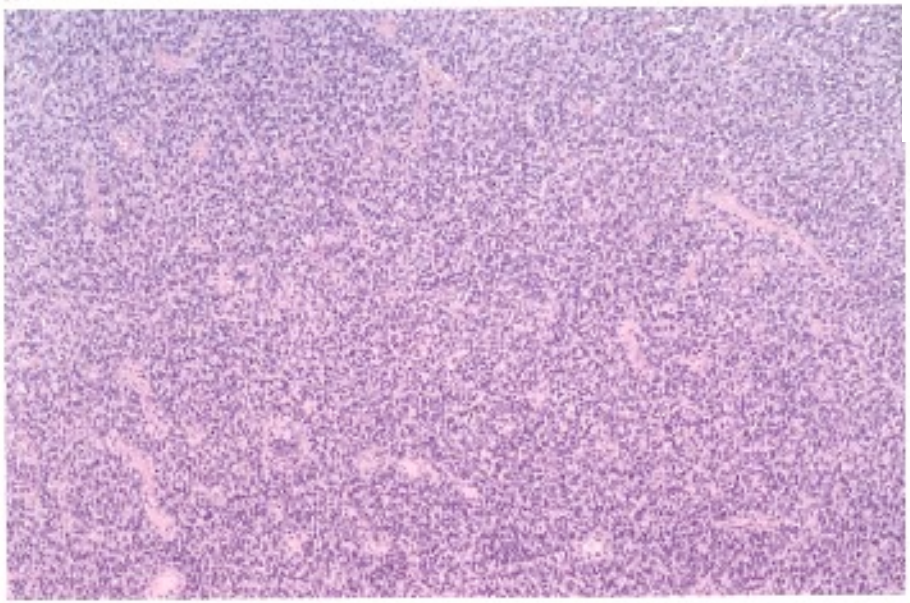
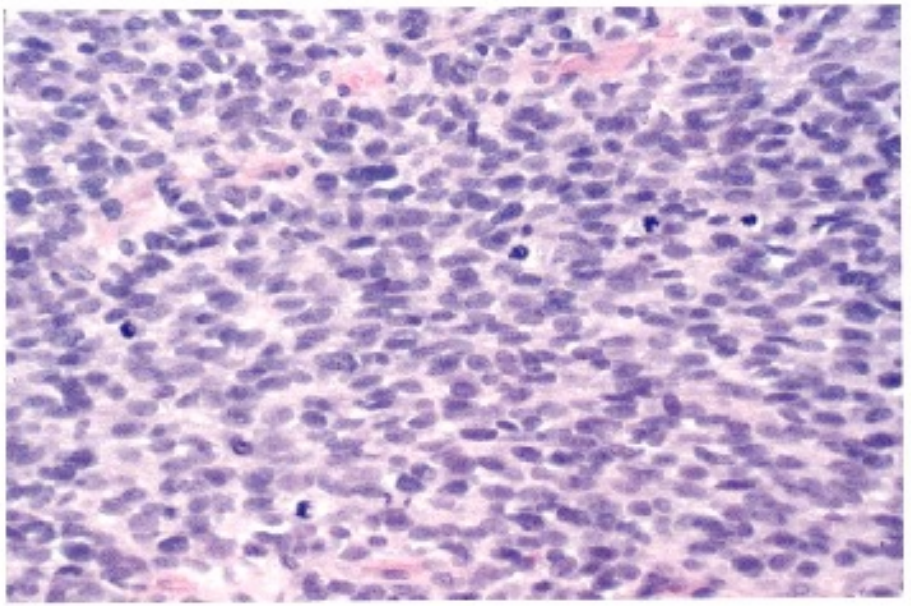




C

- Ulceration
- Hypercellular nodule
- Monomorph ovoid cells
- Mitotic rate - 26 per mm^2

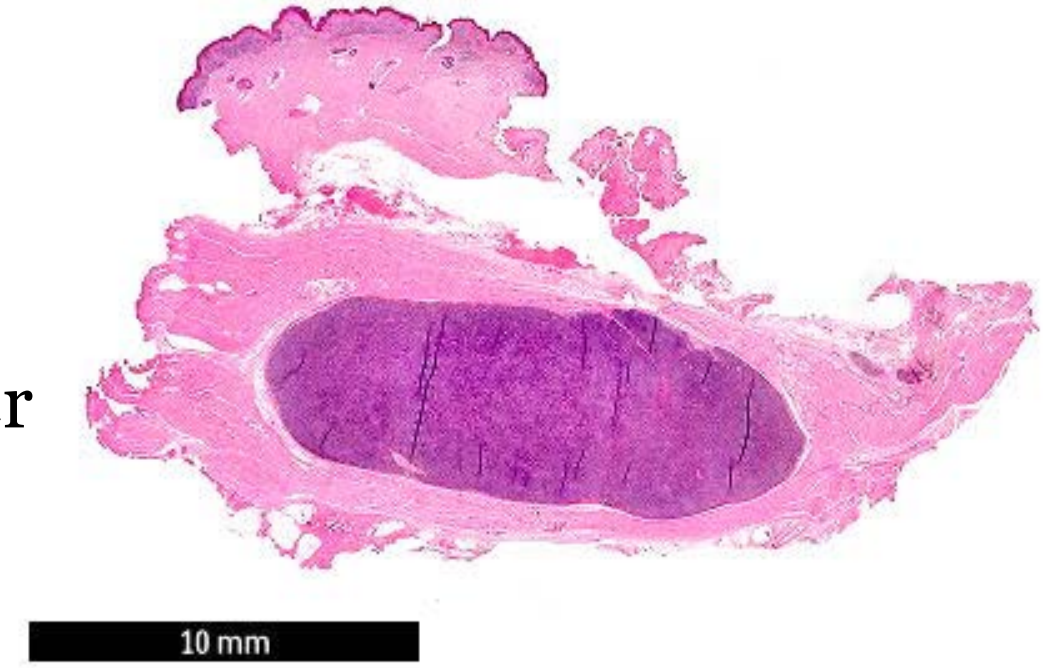
Barnhill RL, Pathology of melanocytic nevi and malignant melanoma. Second Edition. New York: Springer, 2004, 130-131.

Congenital Proliferative Nodule Uncertain Malignant Potential

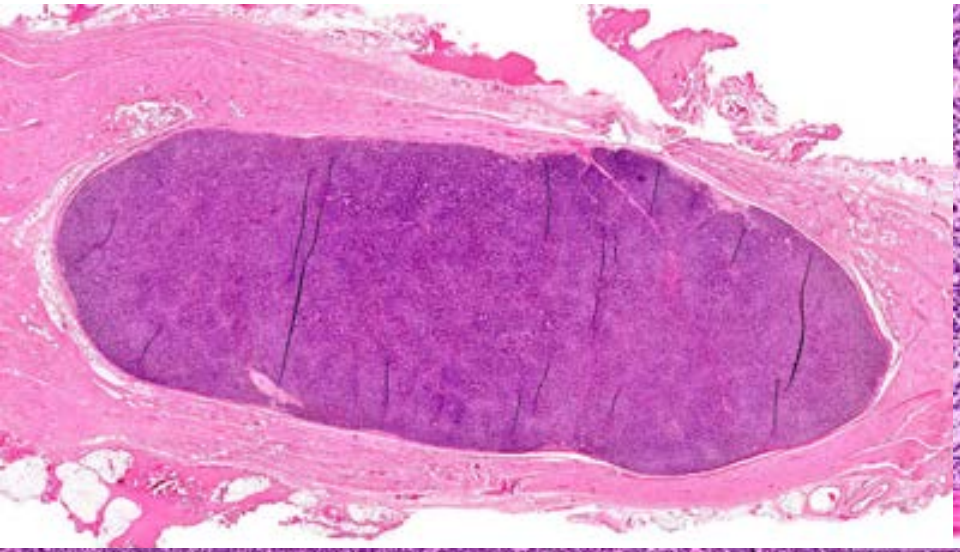
- No evidence of recurrence or metastasis on long-term follow up > 6 years

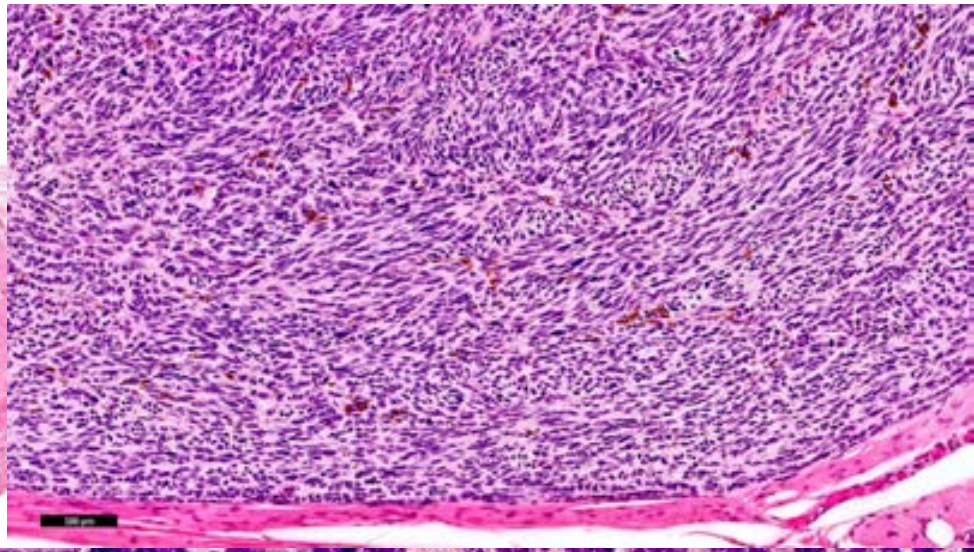
Nodule in Giant Congenital Nevus

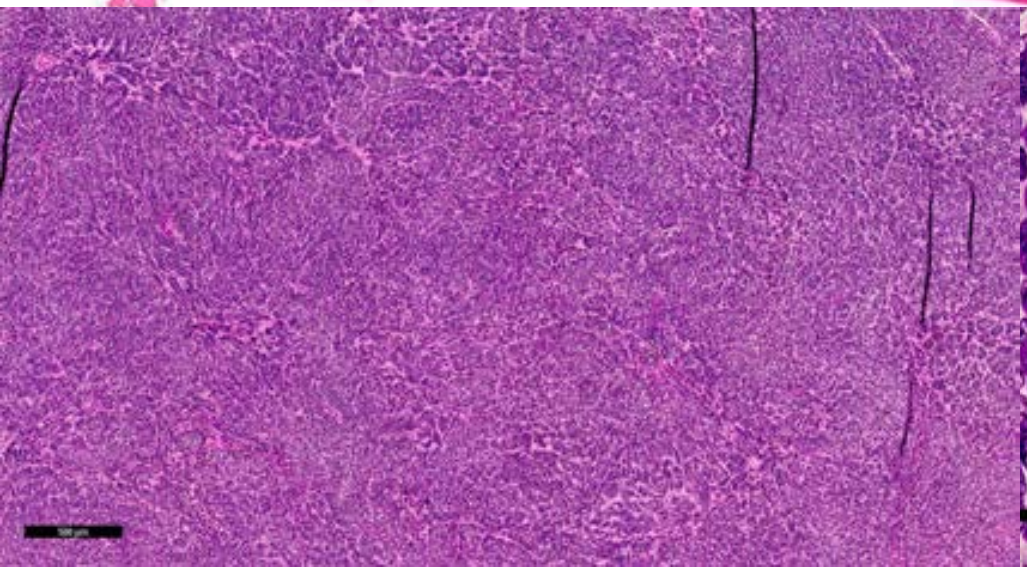
- 5 year-old female
- New intramuscular nodule – 12 x 4 mm
- On back
- Well-circumscribed
- Symmetrical
- Smooth abrupt border
- Hypercellular
- Cytological atypia
- 13 mitoses per mm^2
- No necrosis

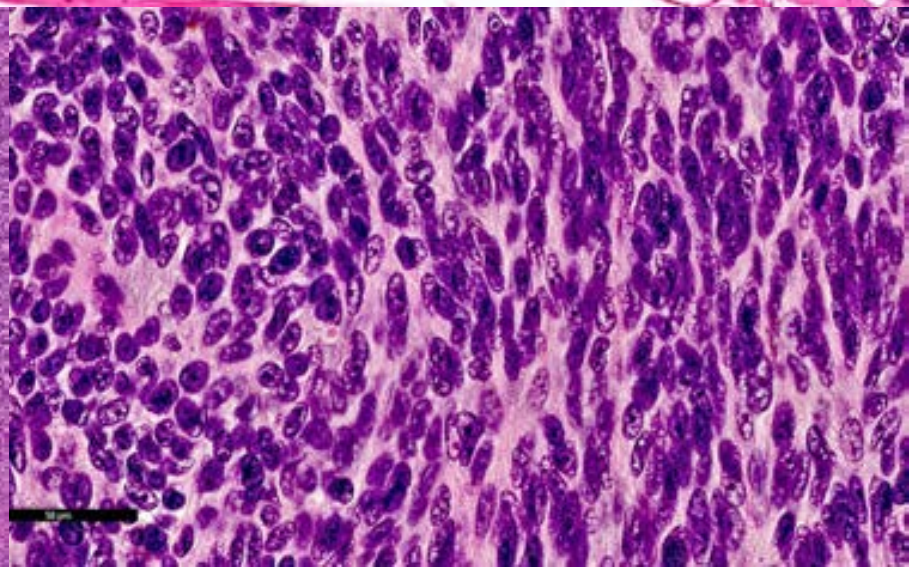


Nodule in Giant Congenital Nevus









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

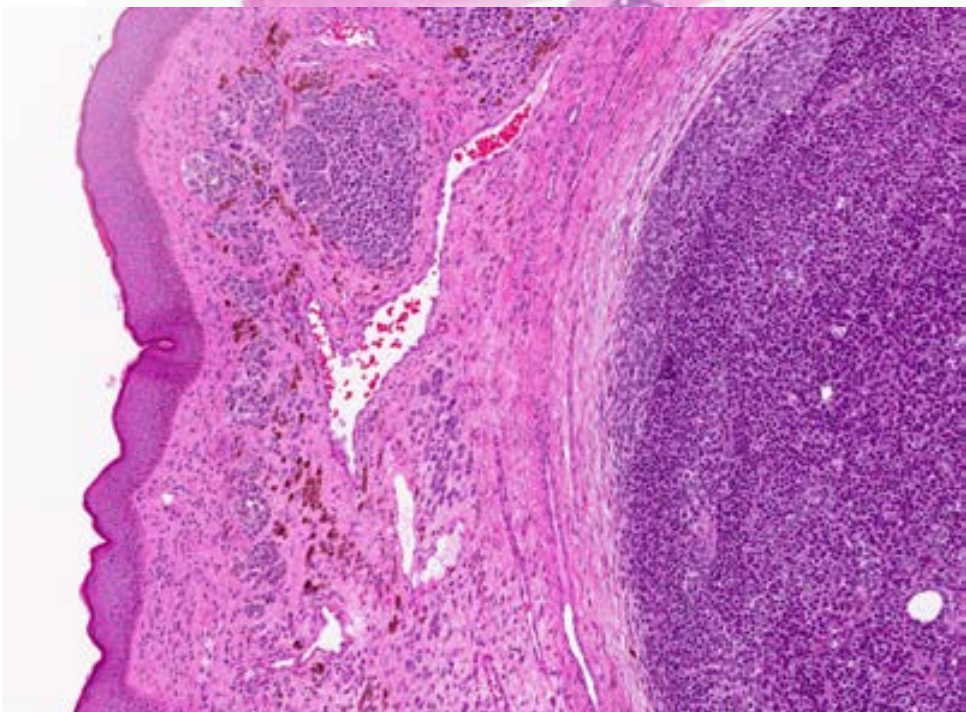
- Re-excision: No evidence of any residual lesion
- Past history of multiple nodules
- No evidence of disease at five years follow-up: no evidence of recurrence, metastasis, or development of new nodules.
- No excision of any lesions

Clinical Course and Outcome

Final diagnosis: Atypical nodule with uncertain malignant potential

Nodule in Congenital Nevus

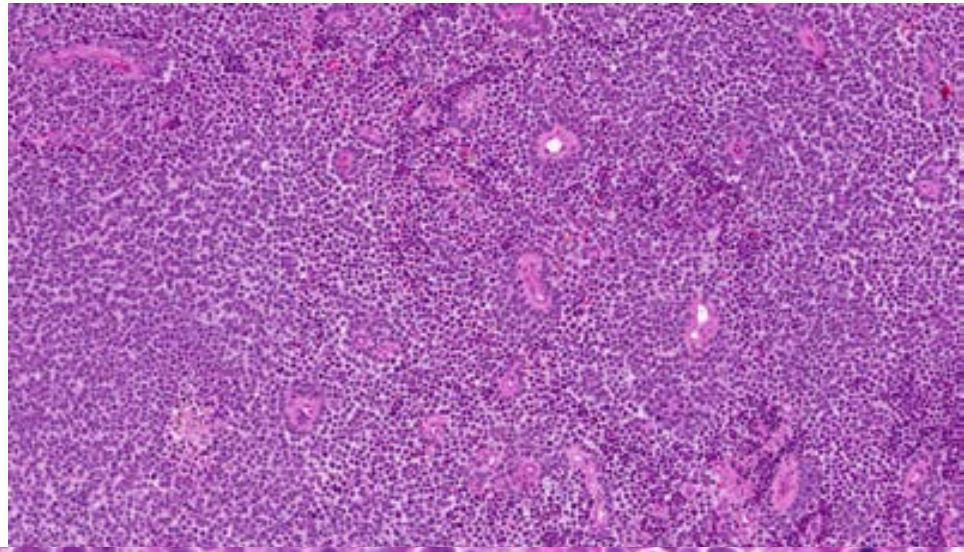
- 7 year-old male with nodule of neck/shoulder in giant congenital nevus
- Discreet nodule with irregular borders in dermis and subcutis
- Absence of « blending » with surrounding nevus or maturation

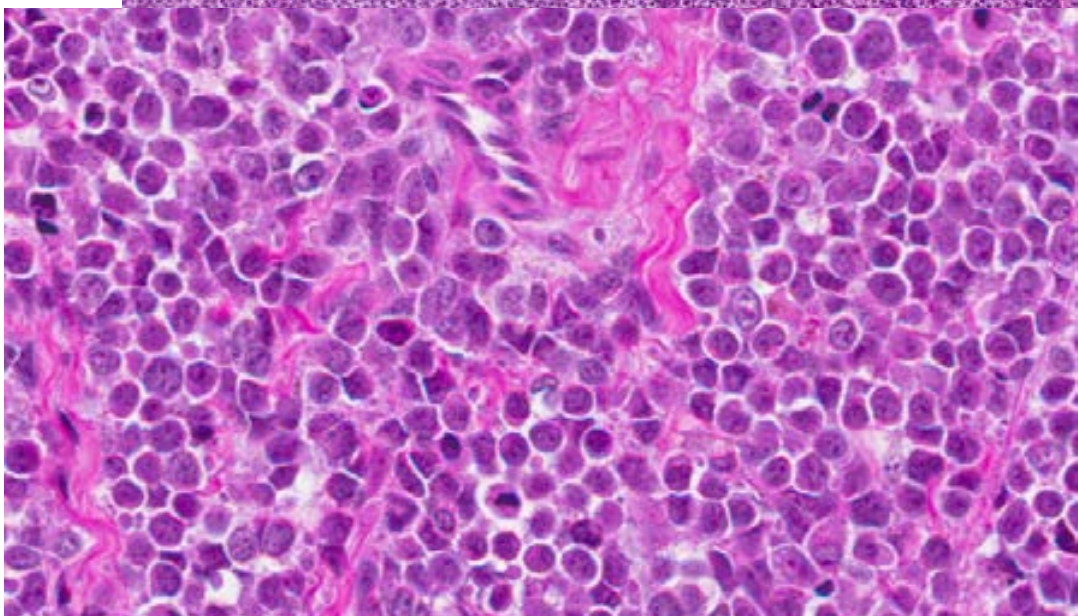


Courtesy David Elder

Nodule in Congenital Nevus

- Comprised of monomorphous atypical polygonal melanocytes
- Conspicuous mitotic activity





Courtesy David Elder

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

Courtesy David Elder

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

Courtesy David Elder

Clinical Course and Outcome

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

Courtesy David Elder

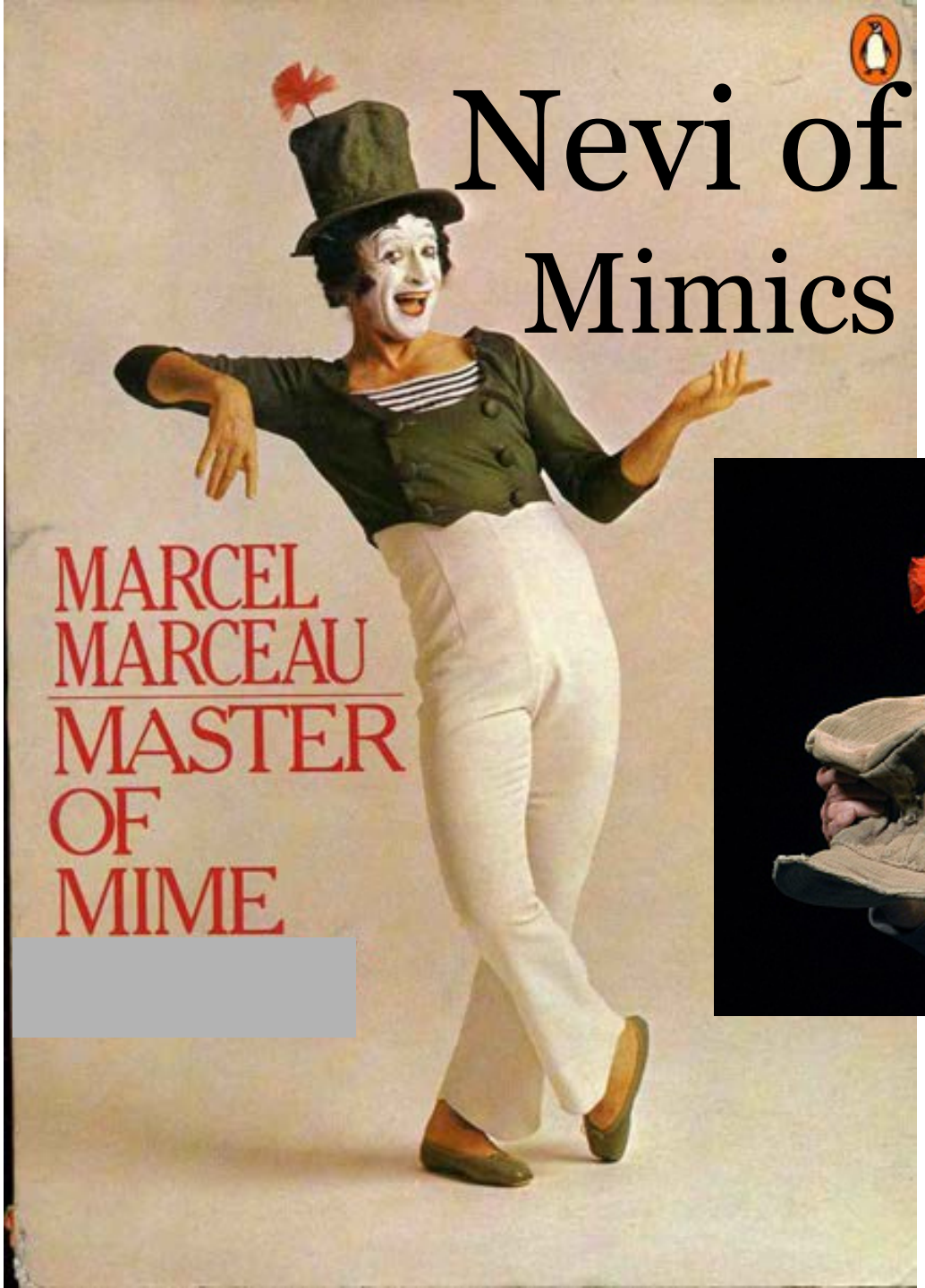
Take Home Message

- 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

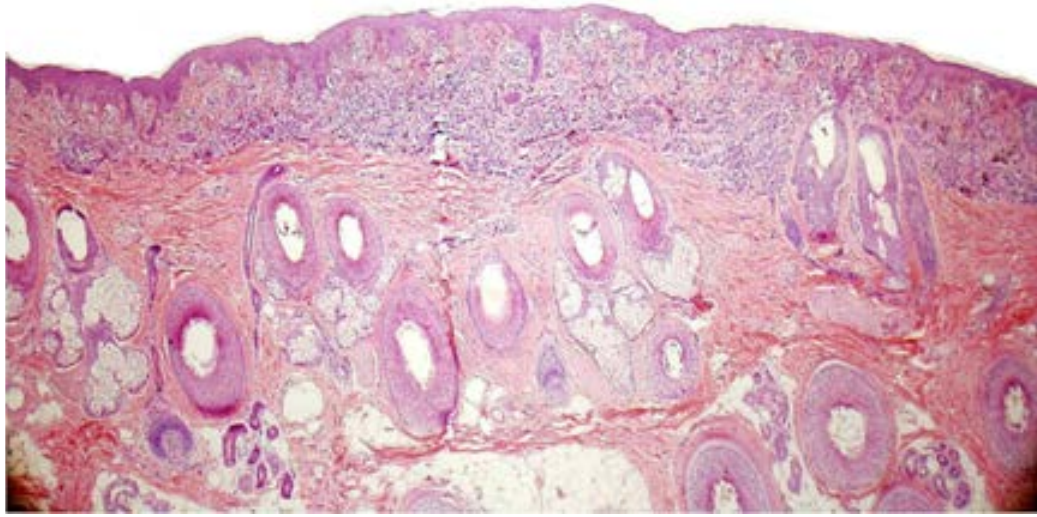
Site Specific Nevi

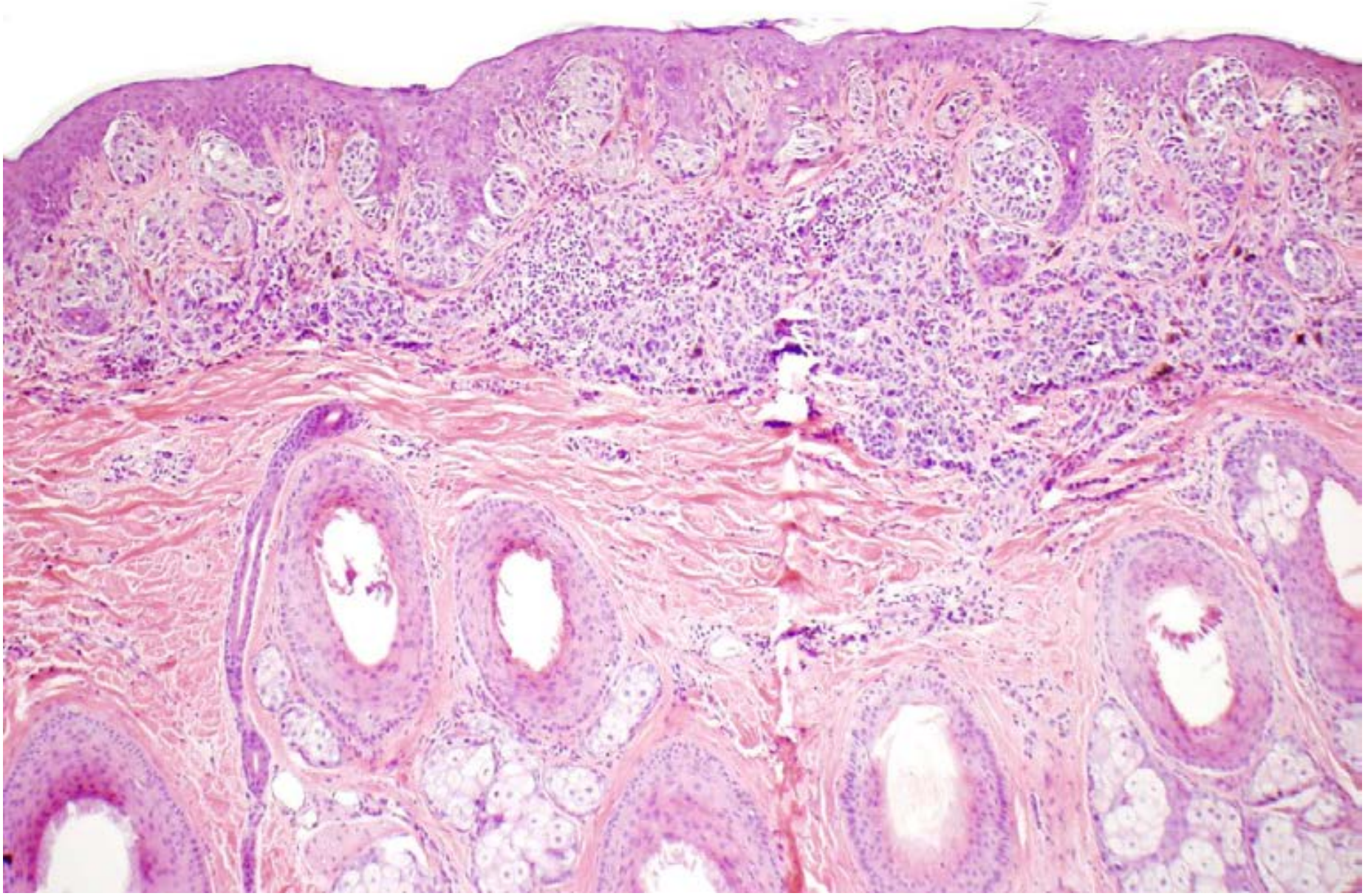
Nevi of Special Site
Mimics of Melanoma

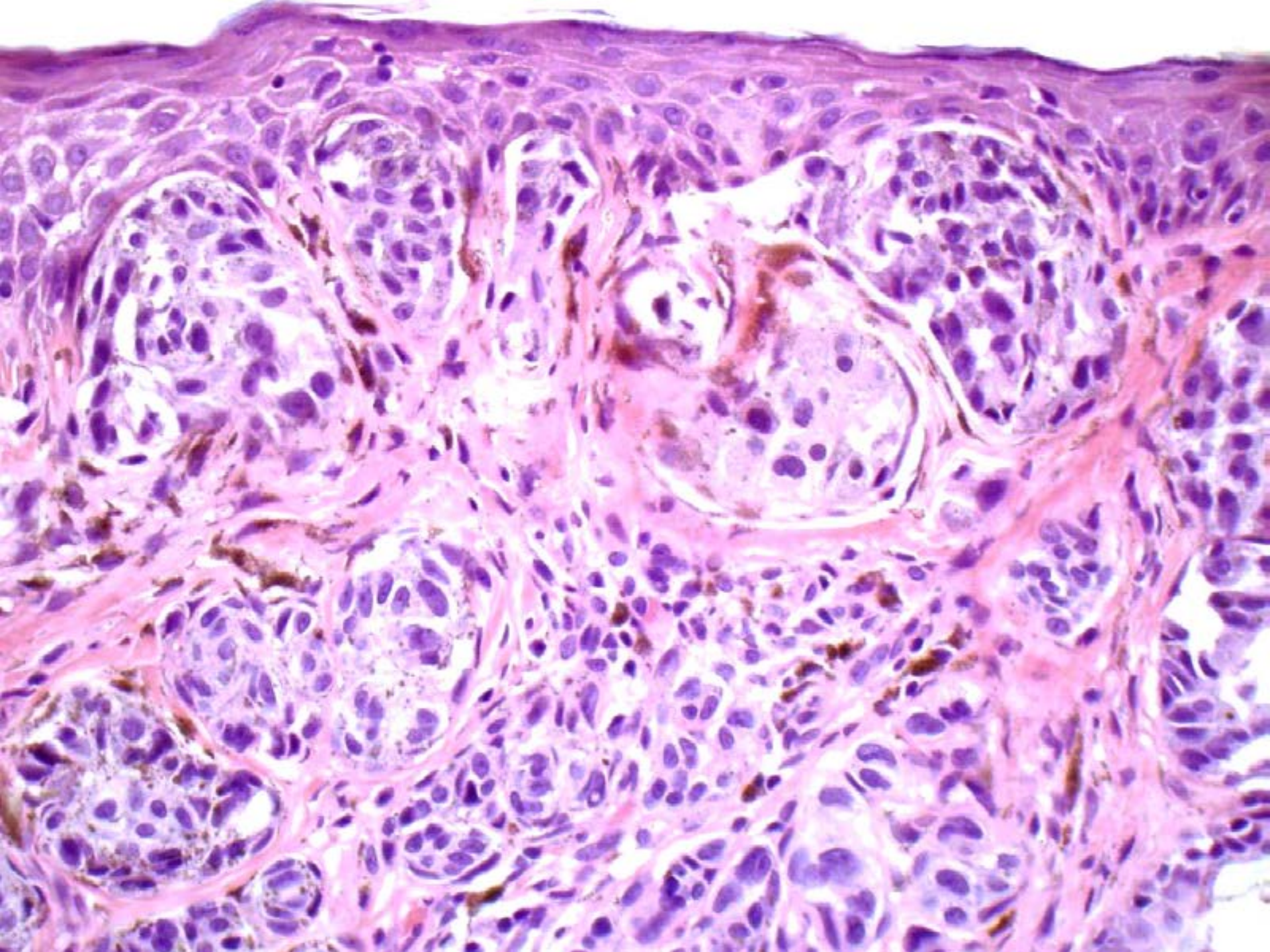


Atypical Compound Nevus, Scalp

- Age: 8 years
- Diameter: 6 mm
- Well circumscribed
- Symmetrical
- Epithelioid nevus phenotype
- Cytological atypia
- Mitotic rate: 1 per mm^2







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

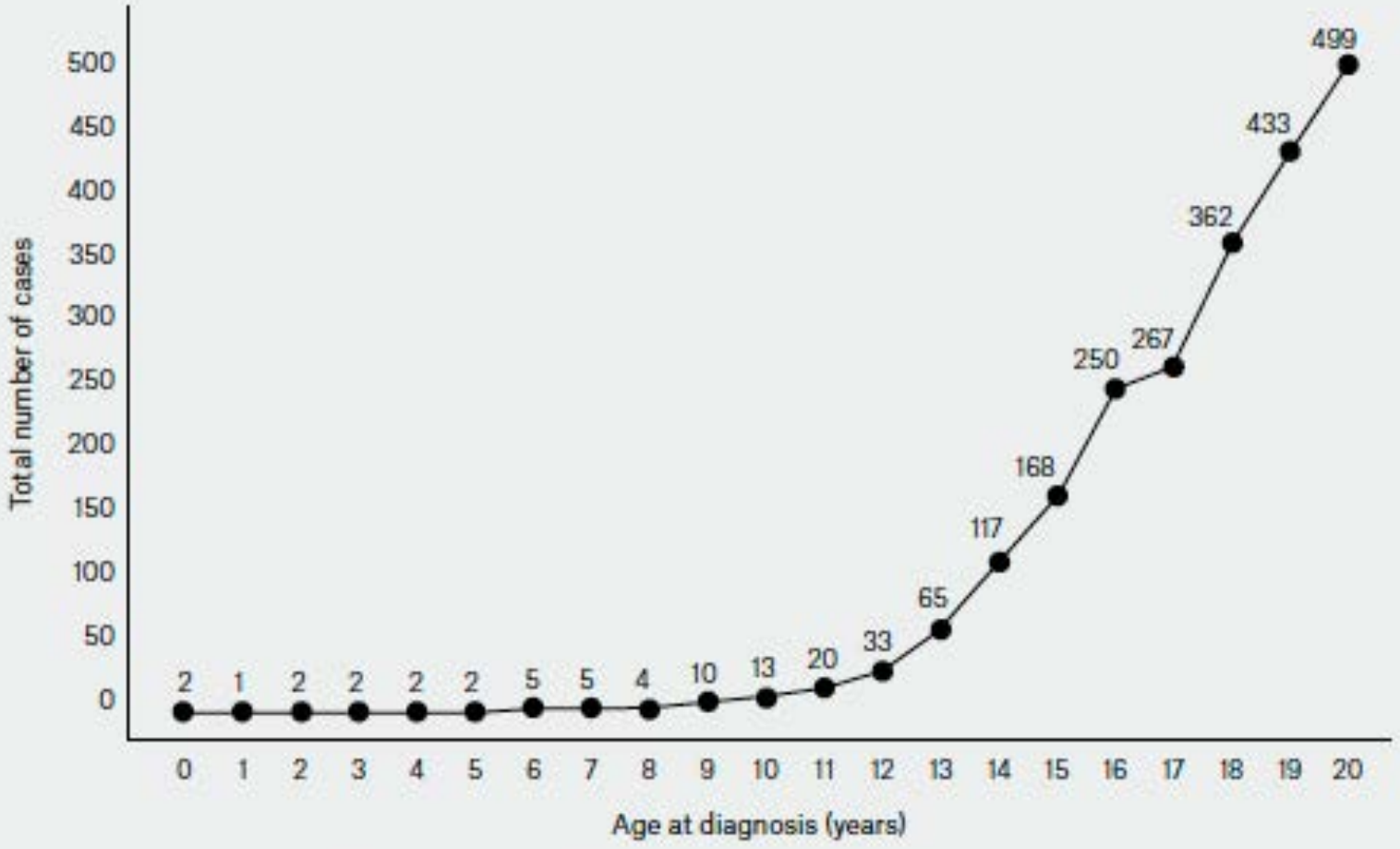


Figure 4. Number of childhood and adolescent melanoma cases in Australia, excluding NSW, from 1982–2014, based on data from the Australian Institute of Health and Welfare

Figure courtesy of Dr Serigne Lo

Two Different Diseases

- Prepubertal melanoma
- Postpubertal melanoma

Prepubertal Melanoma

- De novo melanoma
  - "Nodular" (rapidly evolving)
    - ✓Nevoid ovoid cell
    - ✓Epithelioid cell
    - ✓Spindle cell
  - Conventional melanoma

Prepubertal Melanoma

- Melanoma arising in congenital melanocytic nevi
  - – large and giant types with multiple CMN
  - - leptomeninges/CNS
- Melanoma arising in dysplastic nevi
- Xeroderma pigmentosum
- Immunosuppression

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 phenotype ~ 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

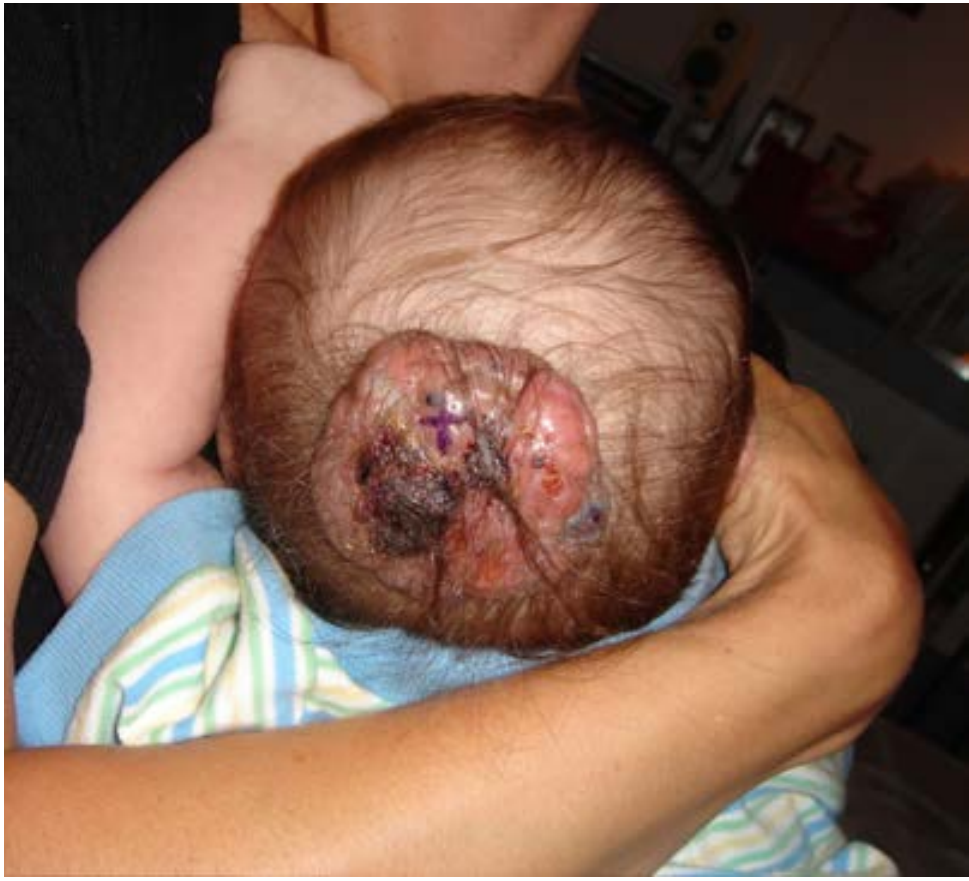
INTRODUCTION

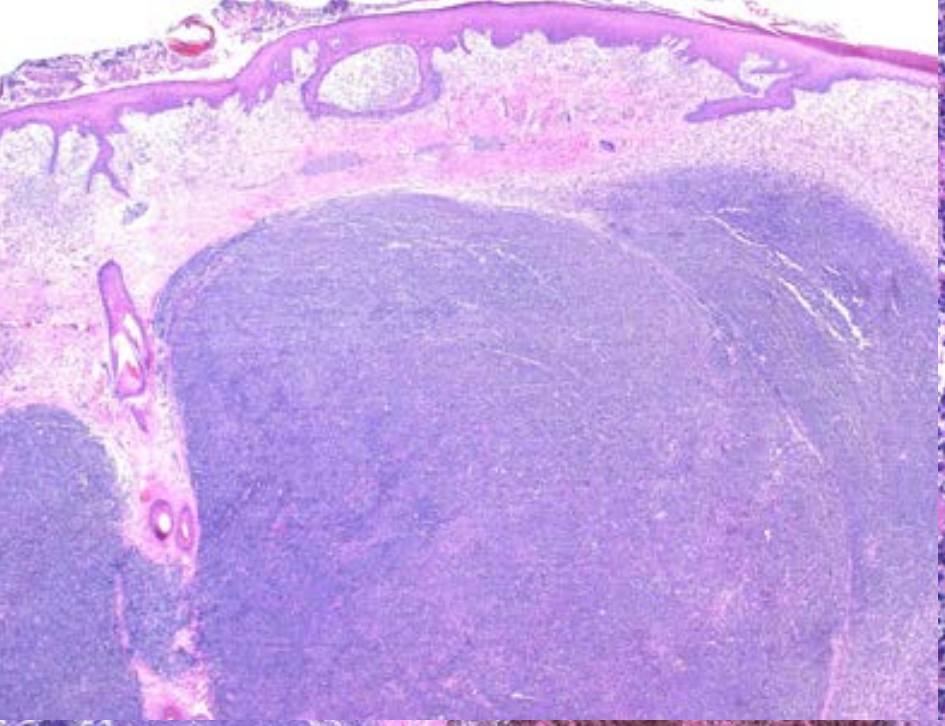
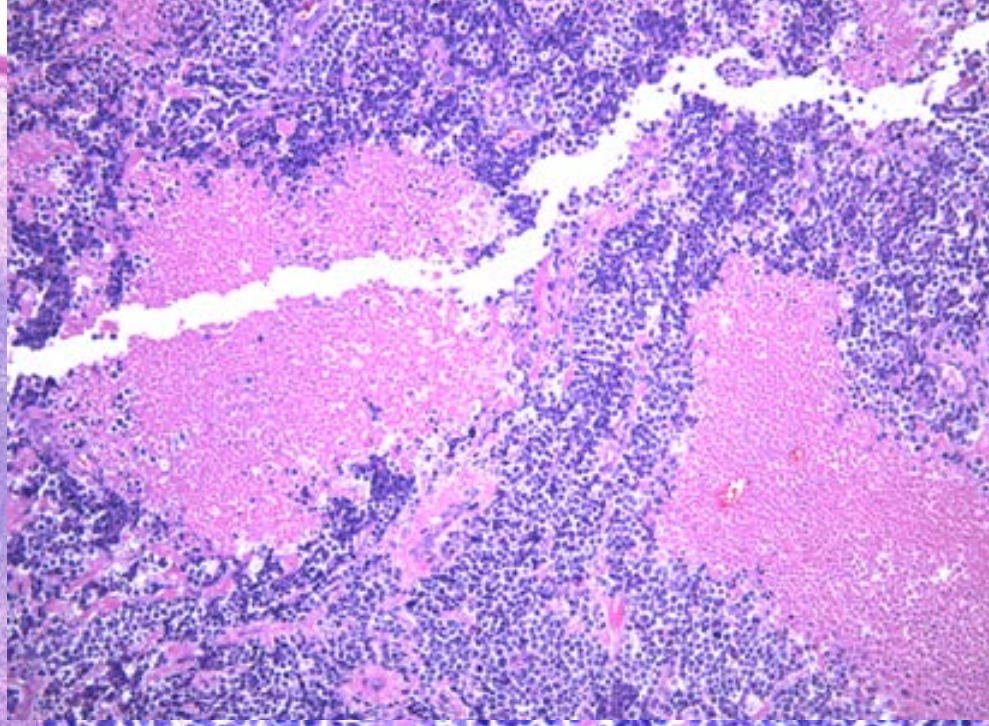
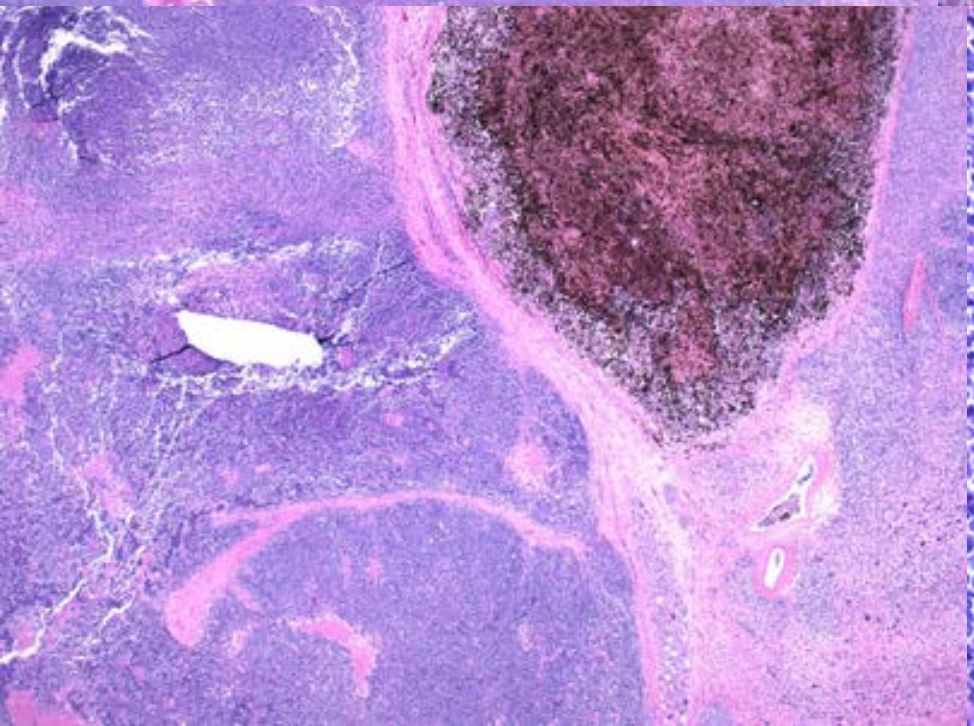
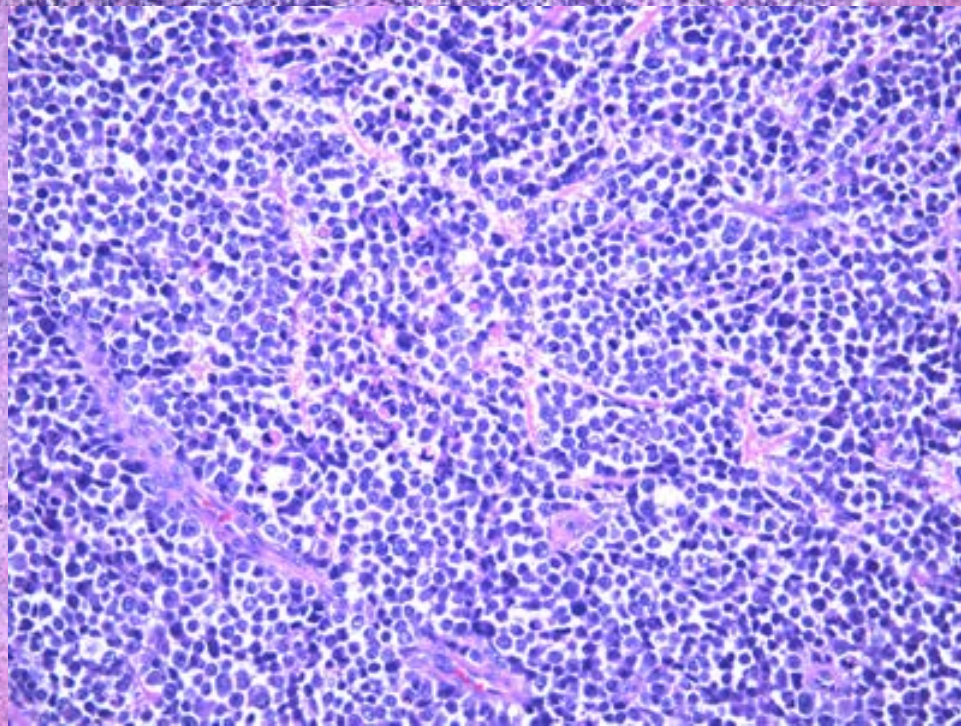
Congenital or infantile melanoma is extraordinarily rare; according to a recent review of the literature, 27 cases have been reported.[1] Three types of congenital melanoma have been described: transplacental metastases from the mother,[2–4] de novo congenital melanoma,[1,5,6] and melanoma occurring 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-

Am J Dermatopathol 2014

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]

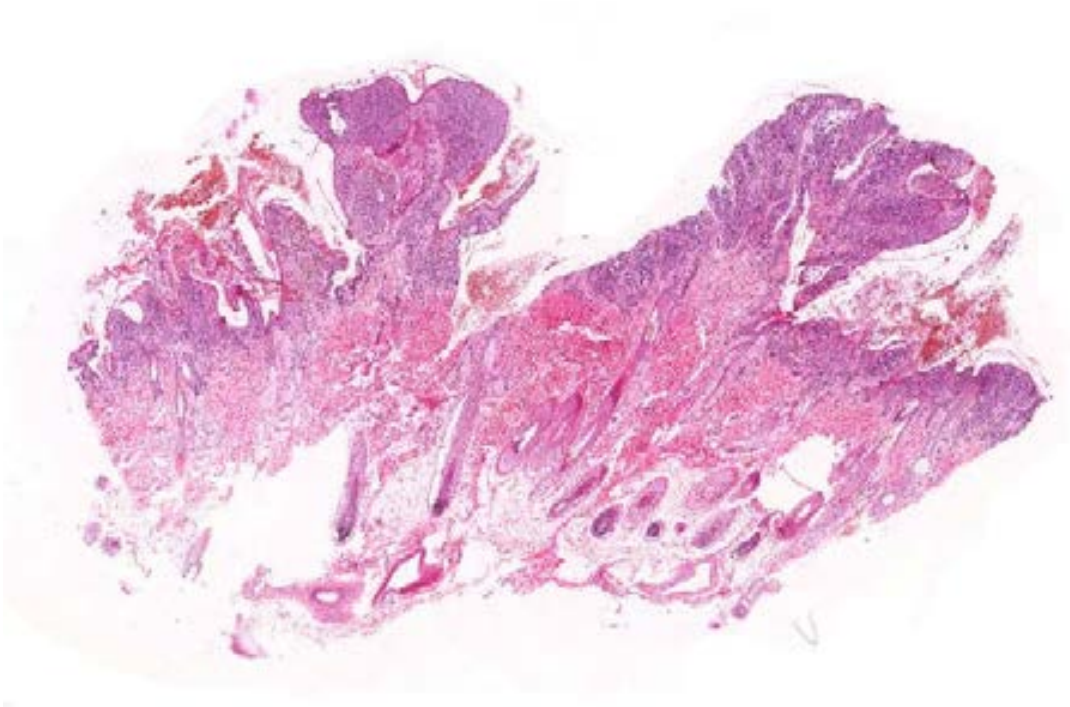
- De novo
- Melanoma arising in congenital nevus

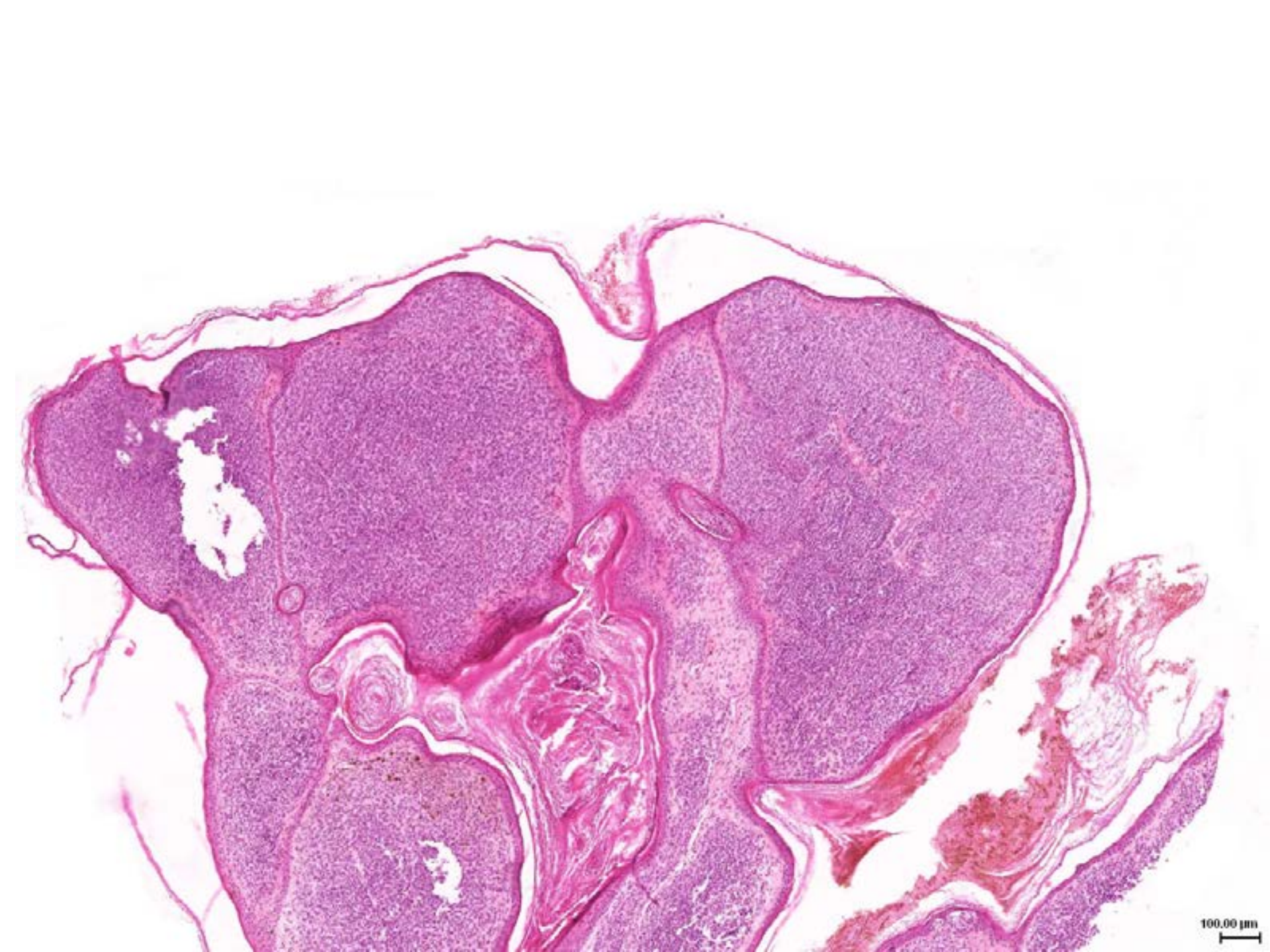
De Novo Nevoid Melanoma

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

Nevoid Melanoma

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

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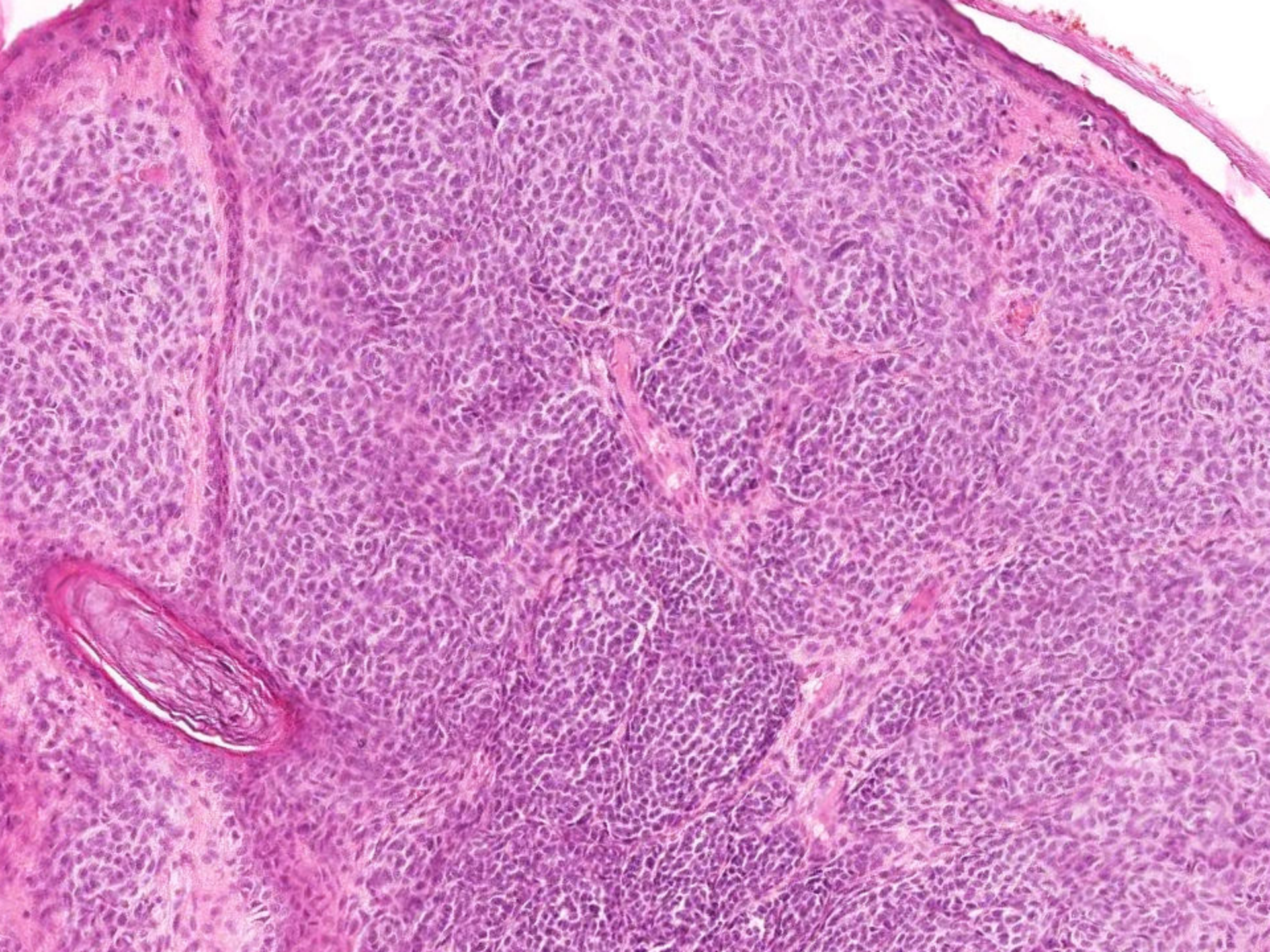
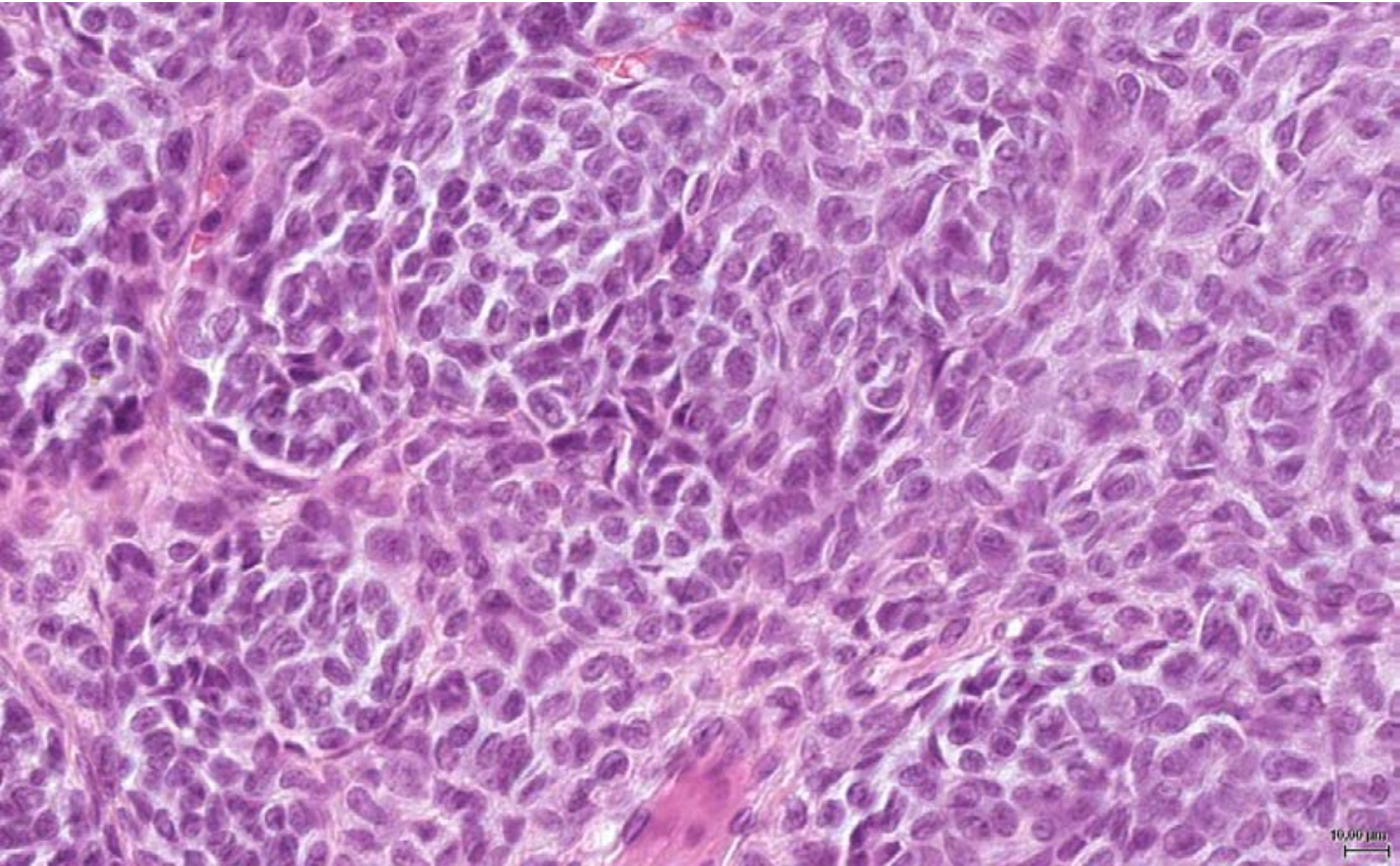


- Metastases
- Death in 12 months

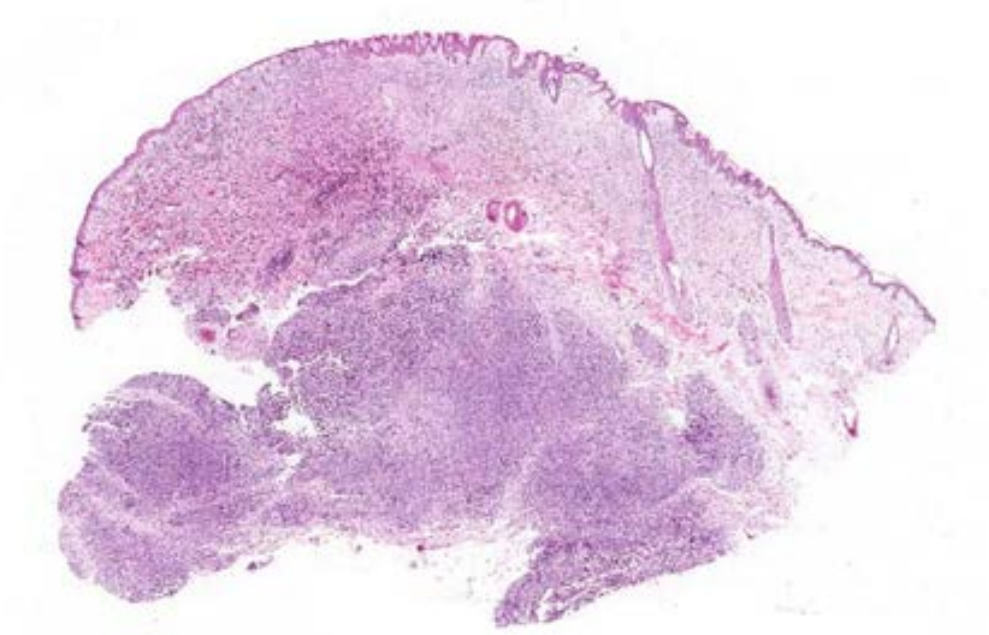


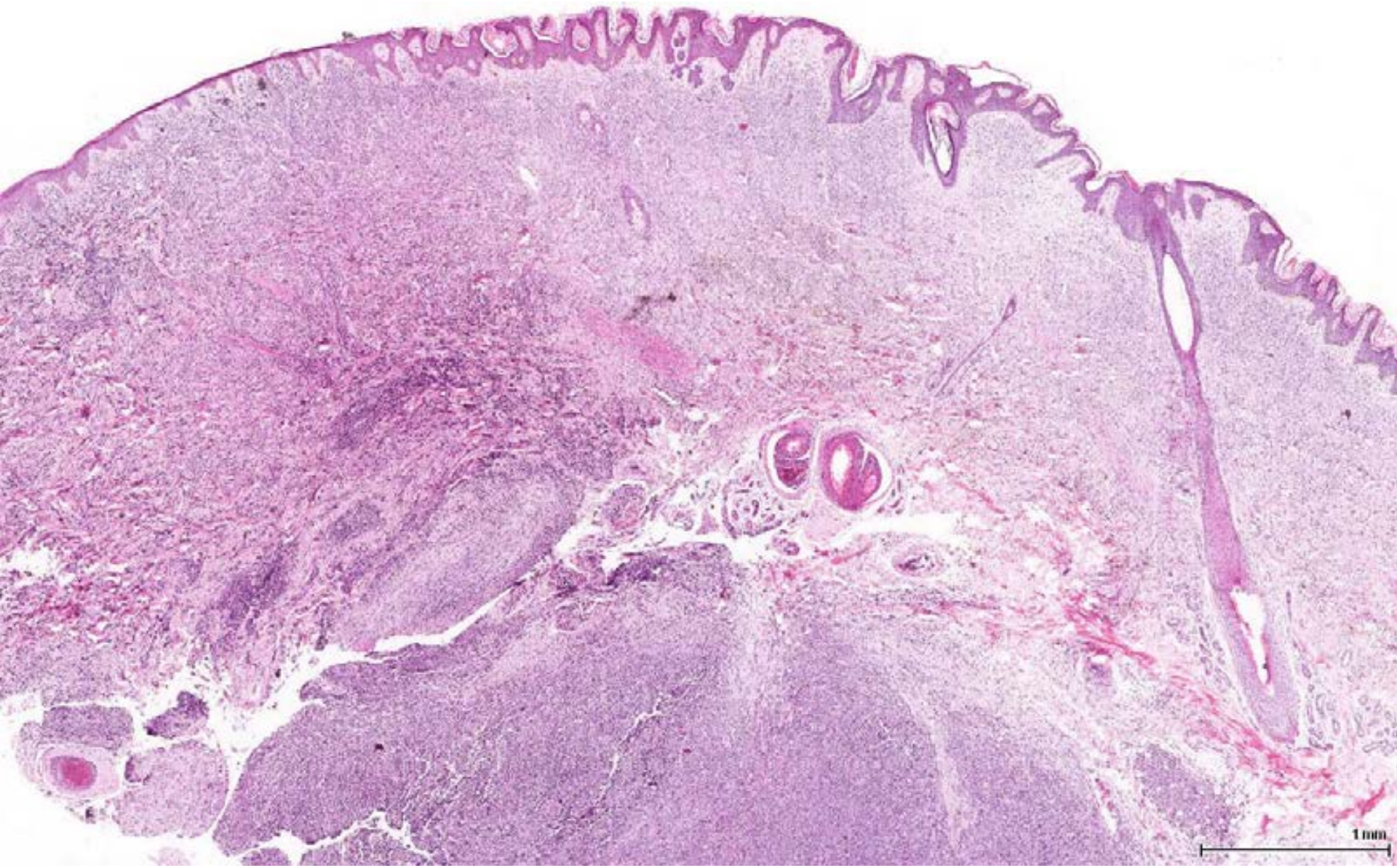
Nevoid Melanoma

- Nevoid melanoma in congenital nevus

Nevoid Melanoma

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

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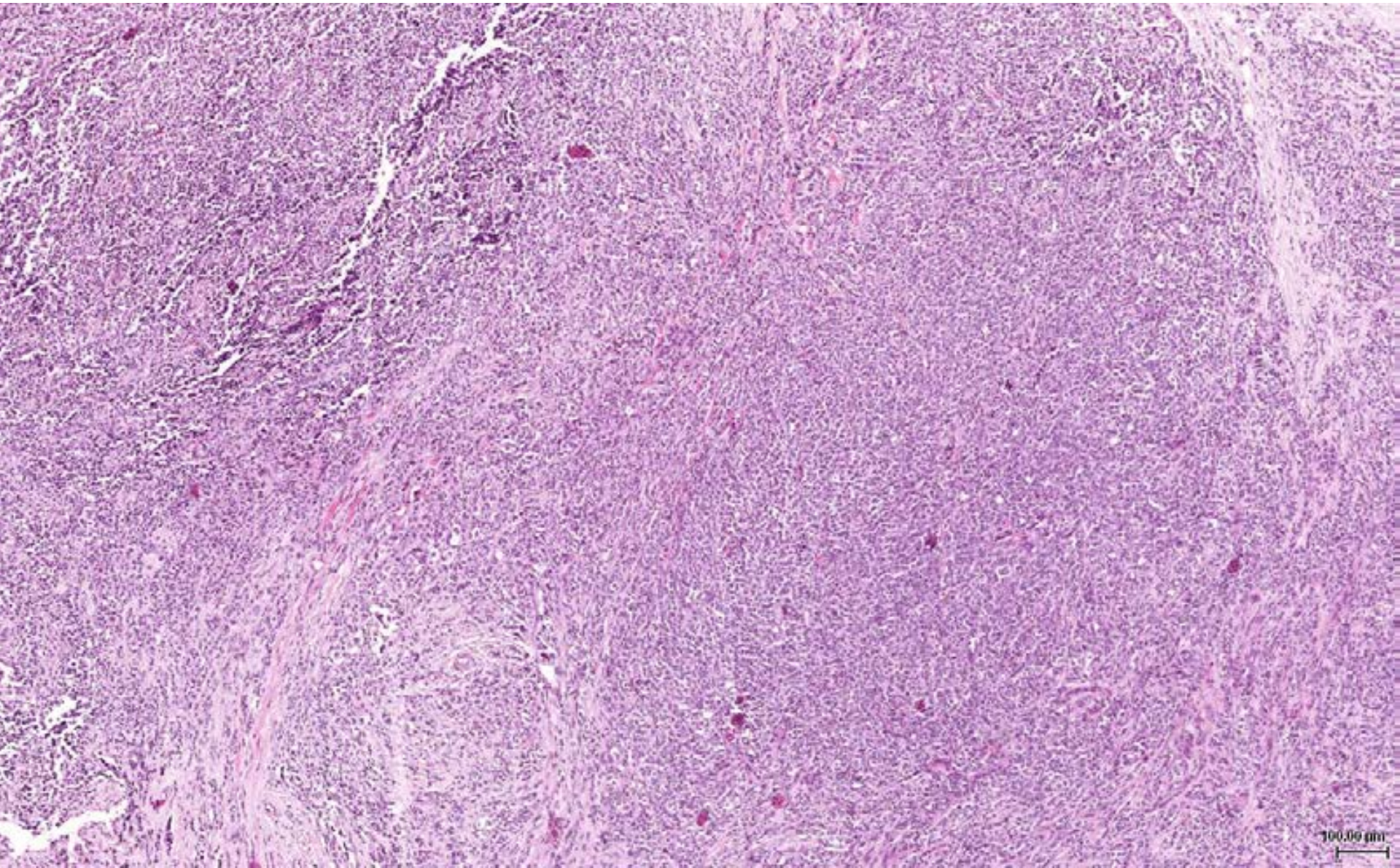
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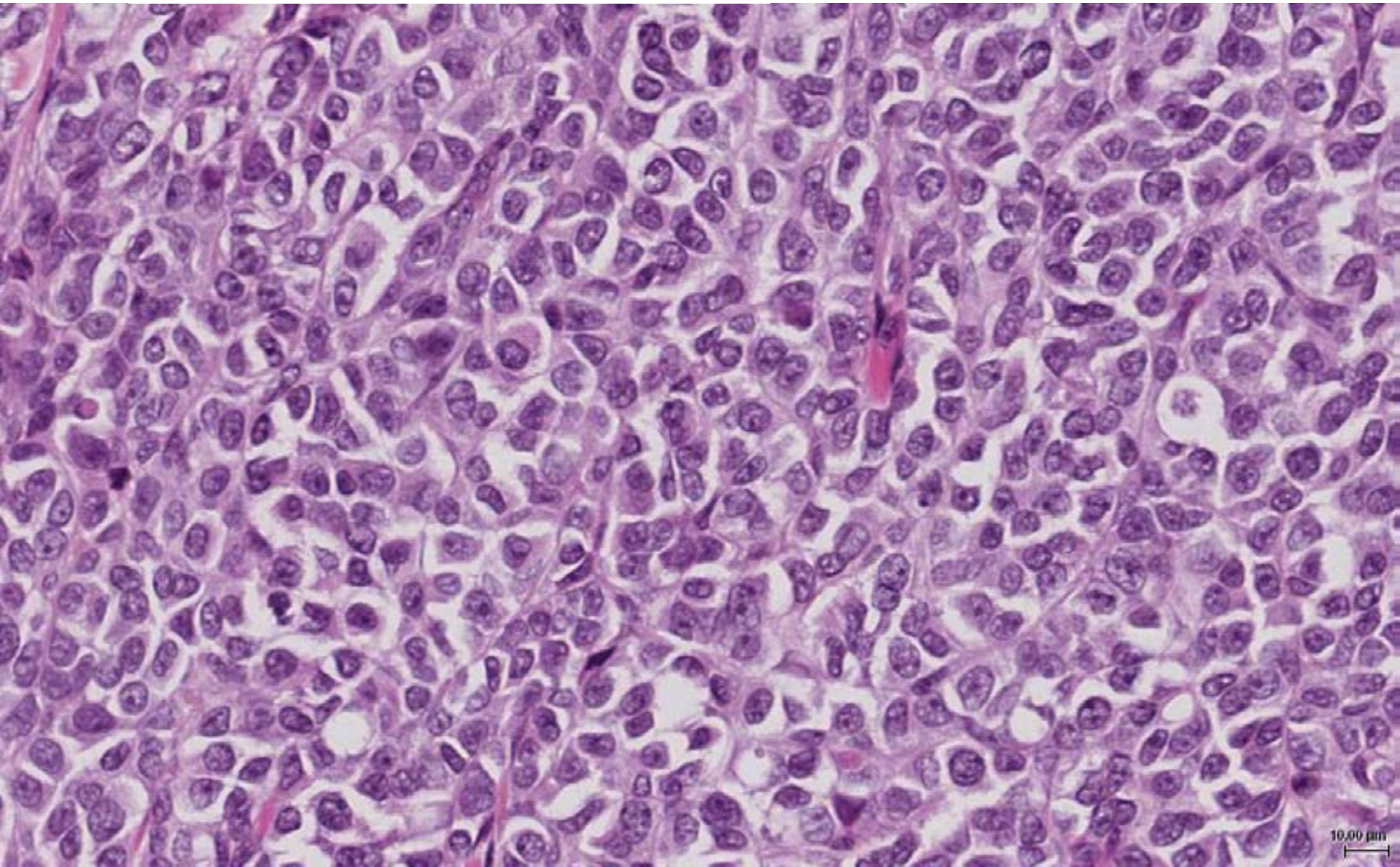
- Distant metastases
- Death in 6 months

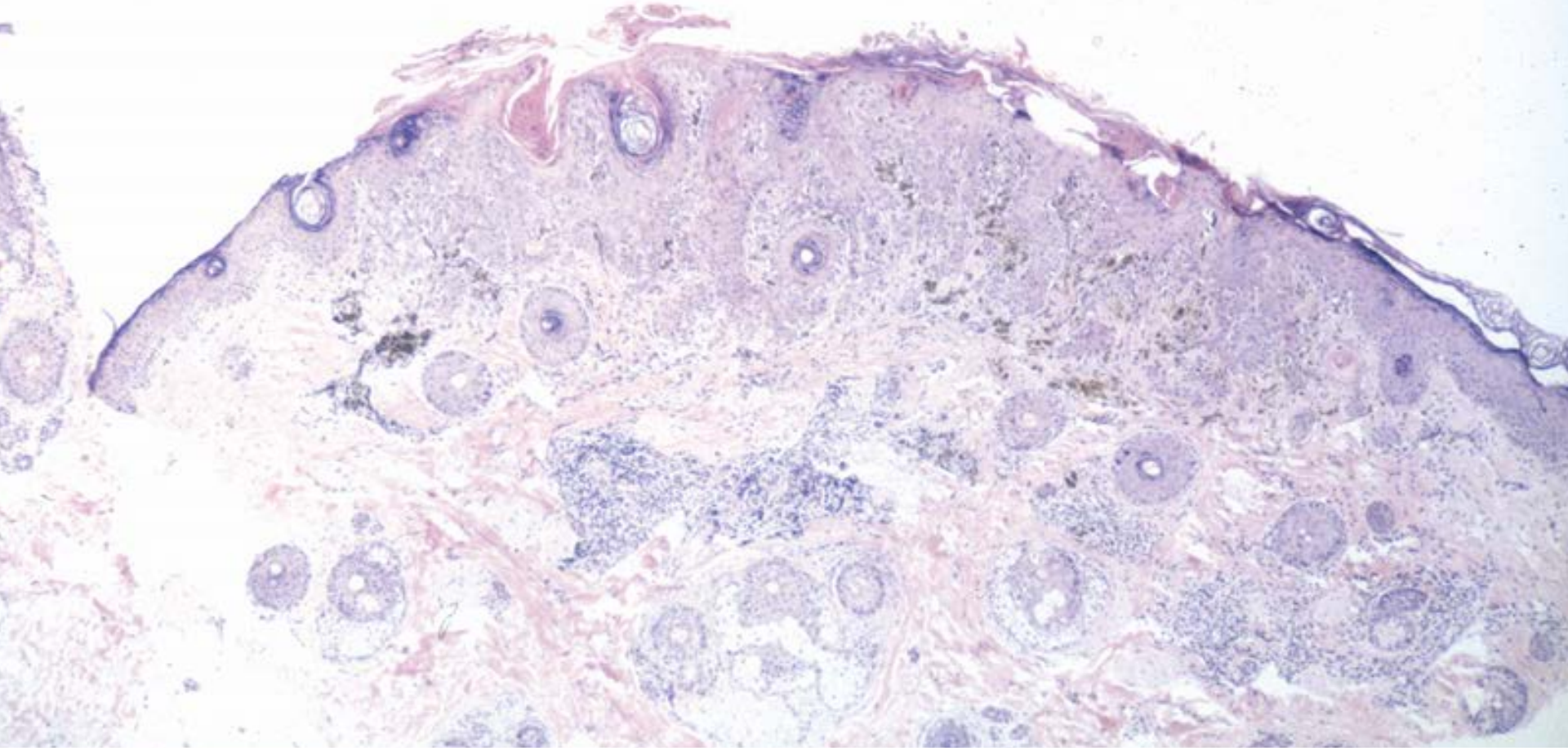


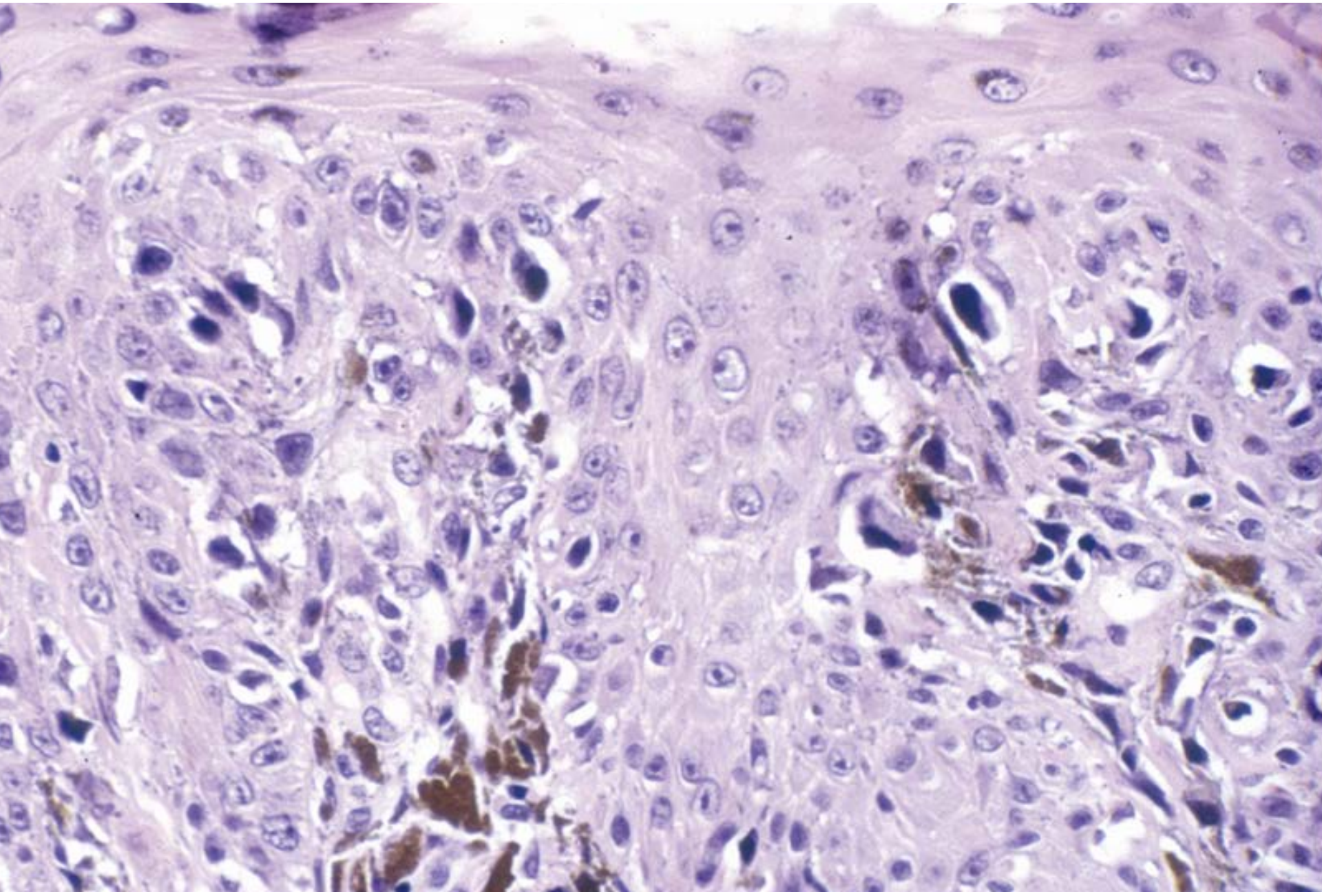
Xeroderma Pigmentosa

Lentiginous Melanoma

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

Lentiginous Melanoma Resembling Lentigo Maligna





Postpubertal Melanoma

Postpubertal Melanoma

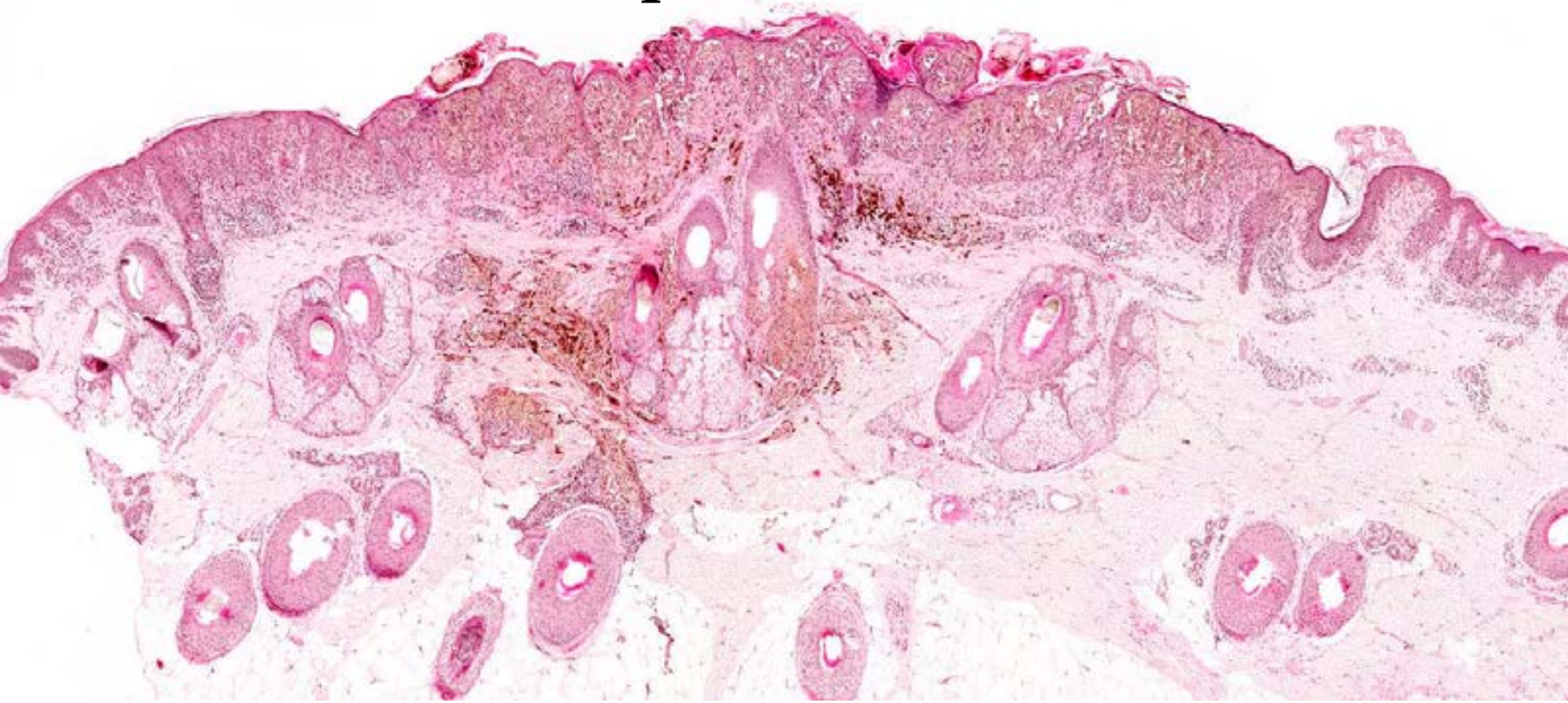
- Melanoma arising in congenital melanocytic nevi
- De Novo melanoma
- Conventional adult melanomas
- Spitz melanoma

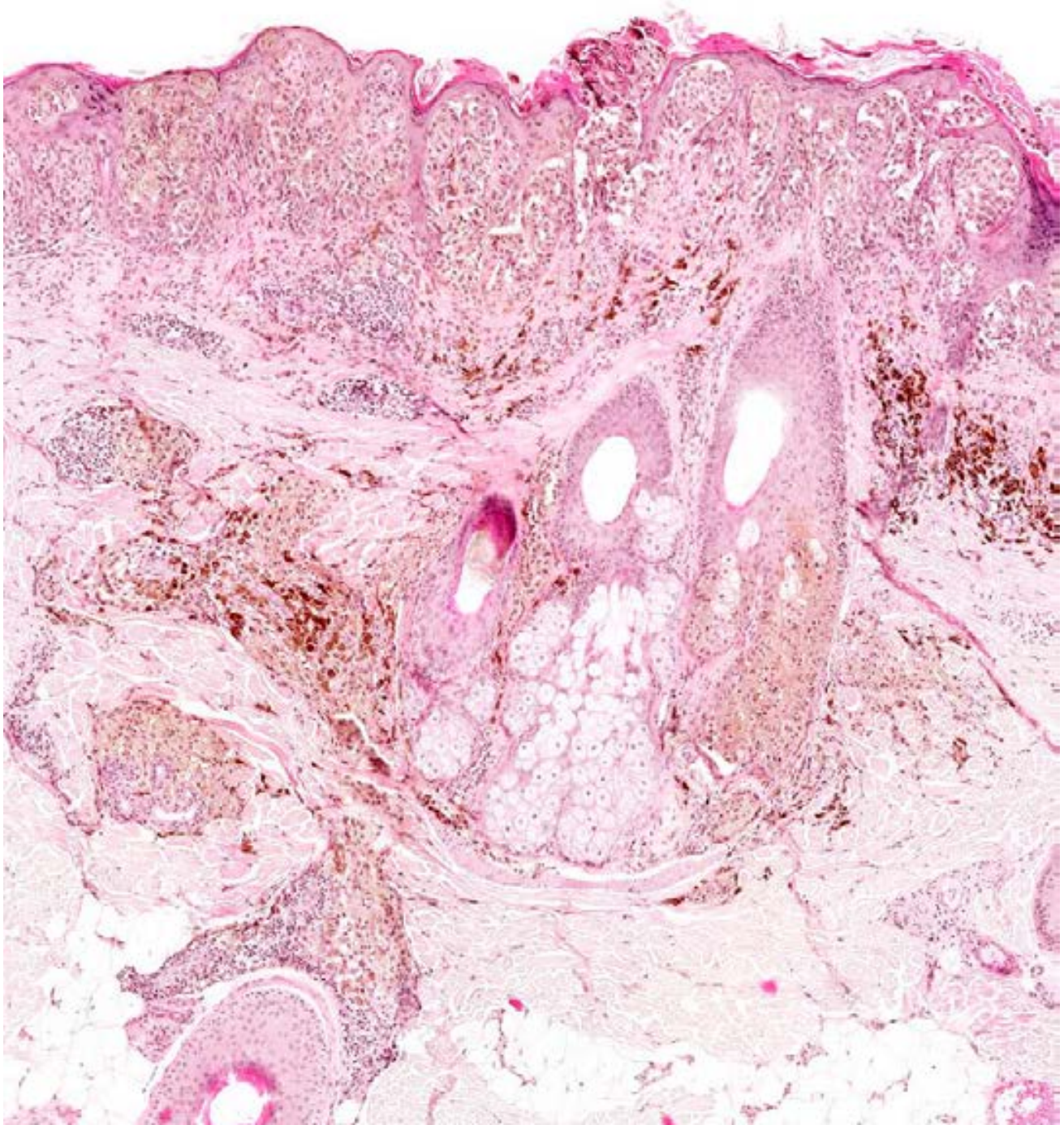
Adolescent Melanoma

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

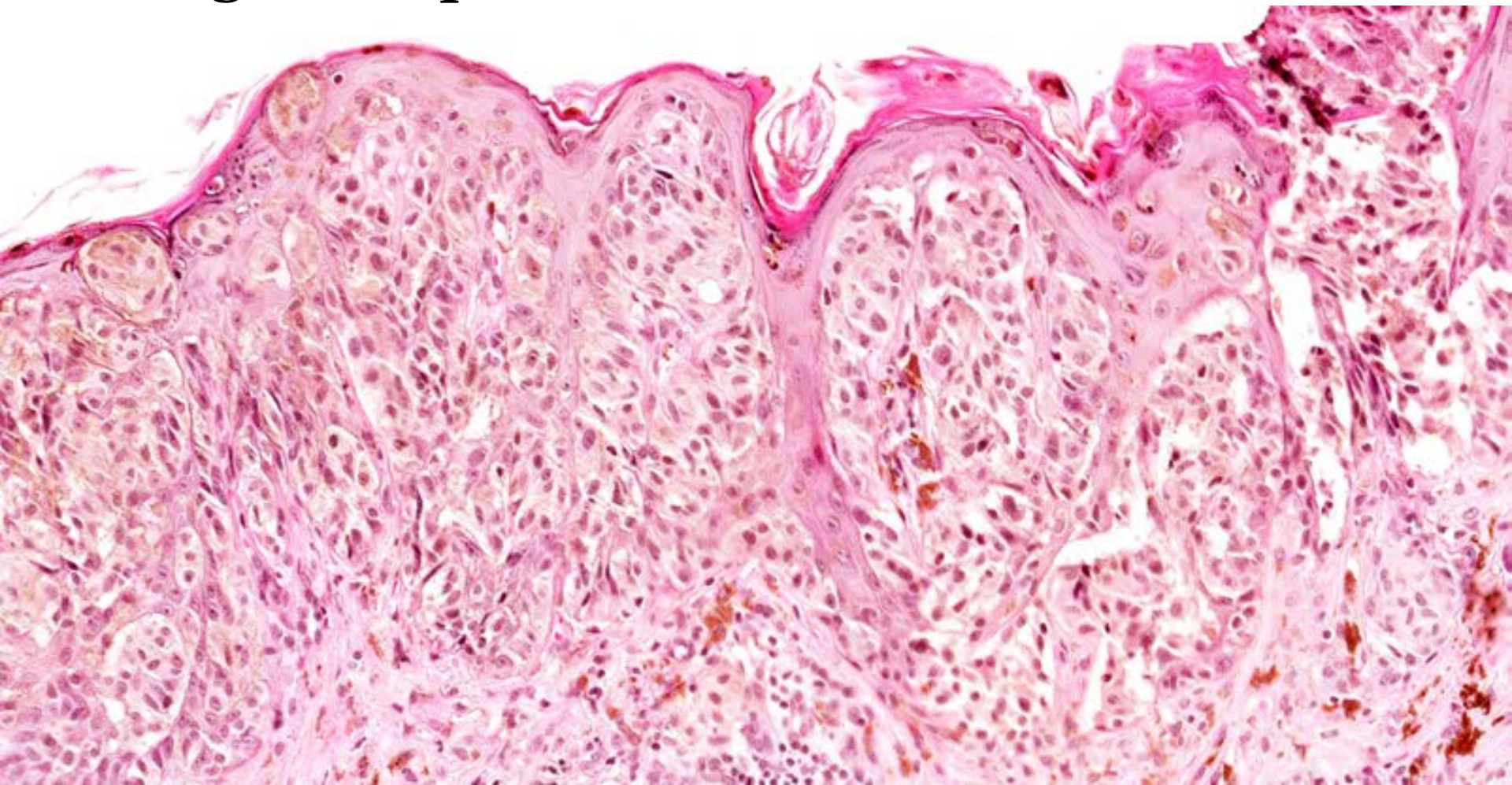
Adolescent Melanoma

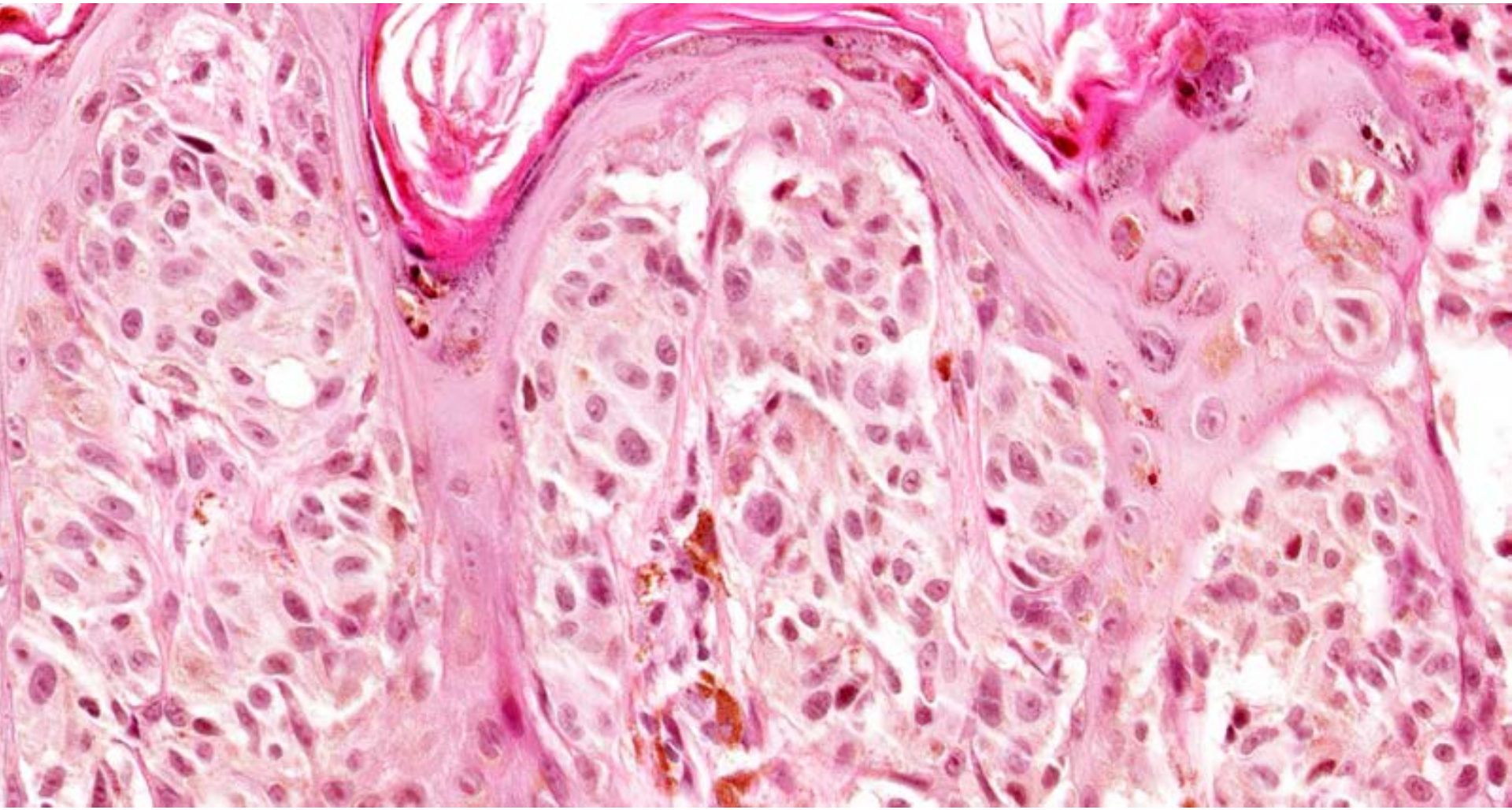
- Asymmetry
- Poor circumscription

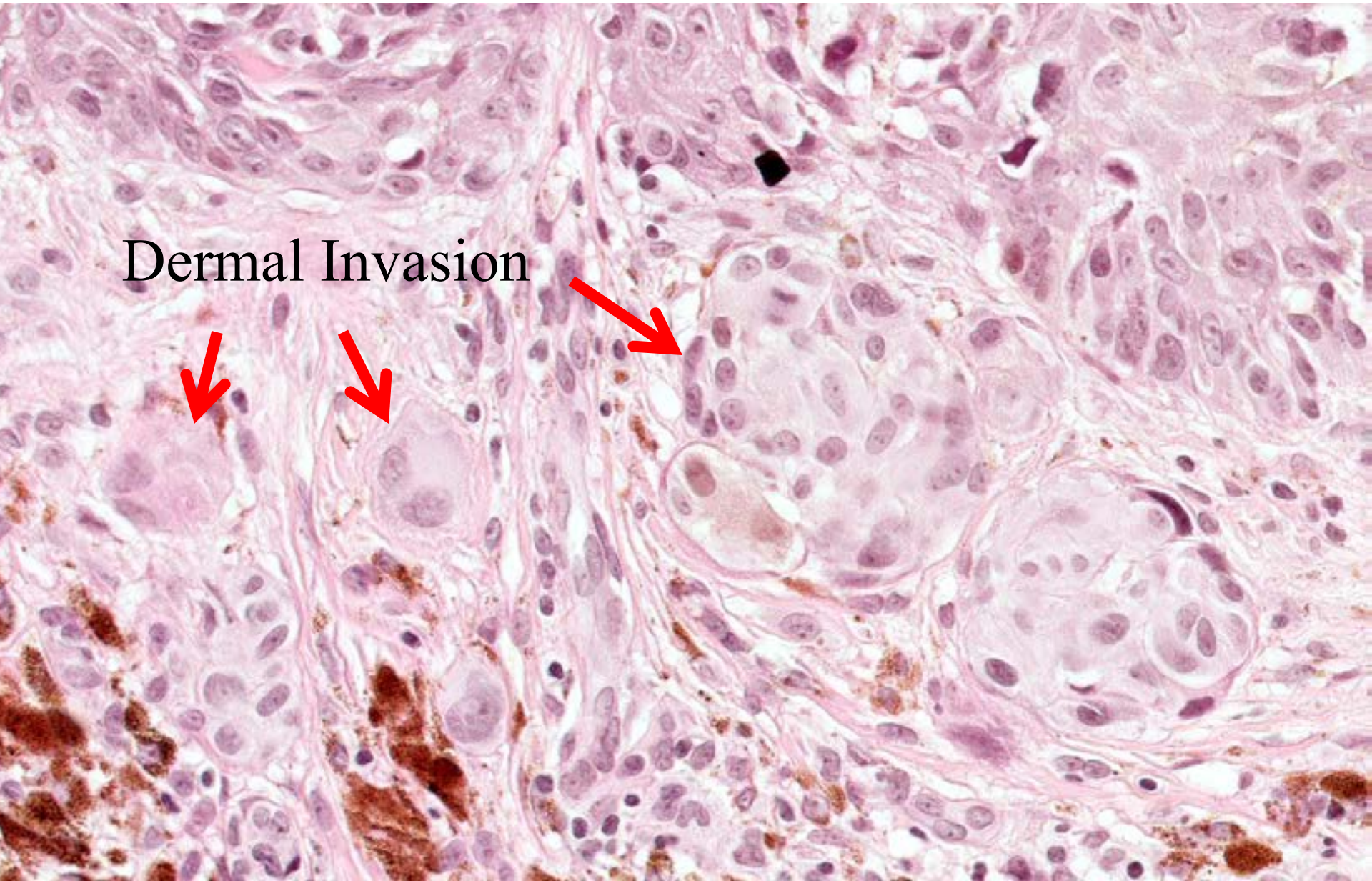




- Replacement of epidermis
- Pagetoid spread

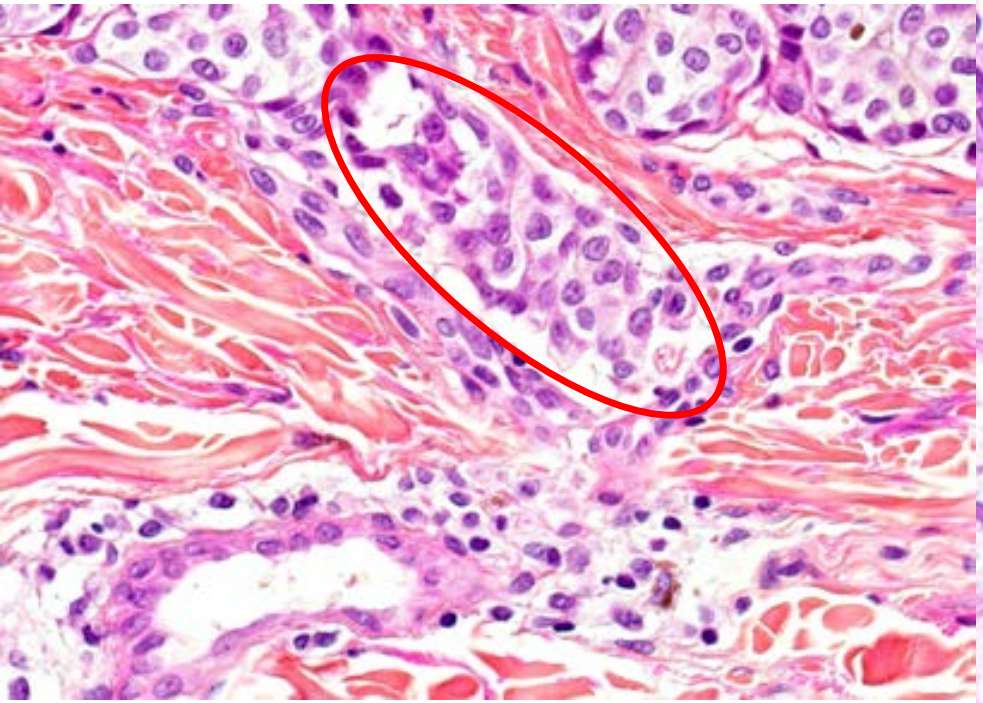


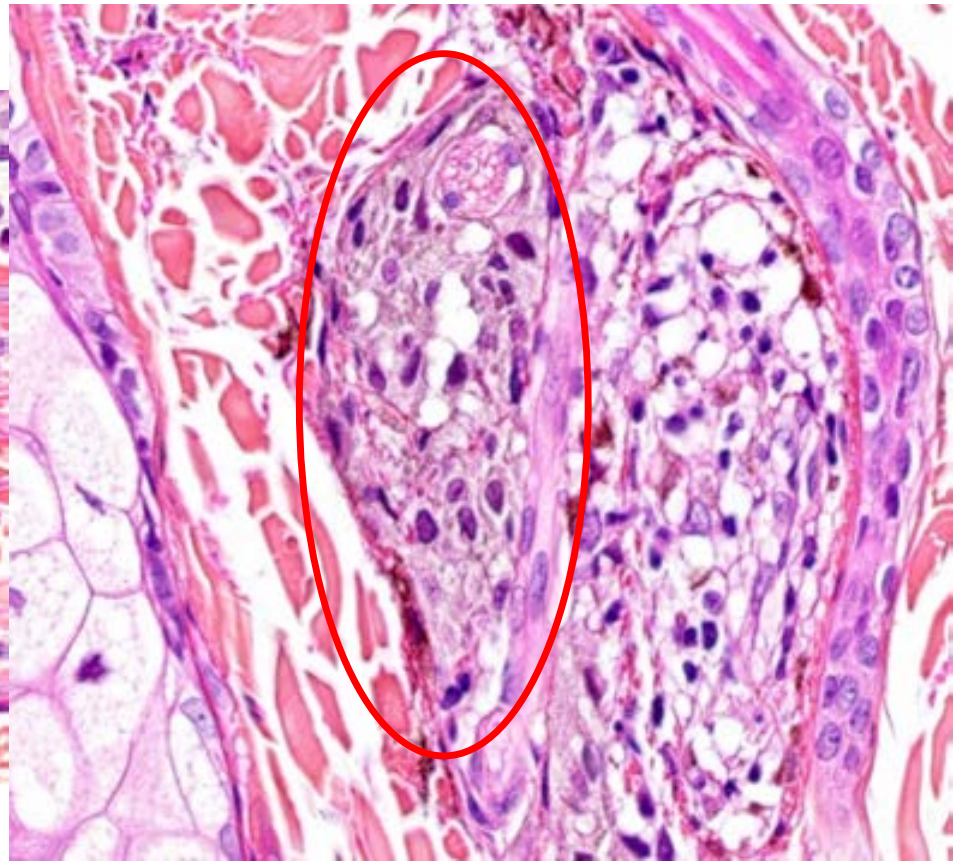



Dermal Invasion

Adolescent Melanoma

- Angiotropism
- Neurotropism

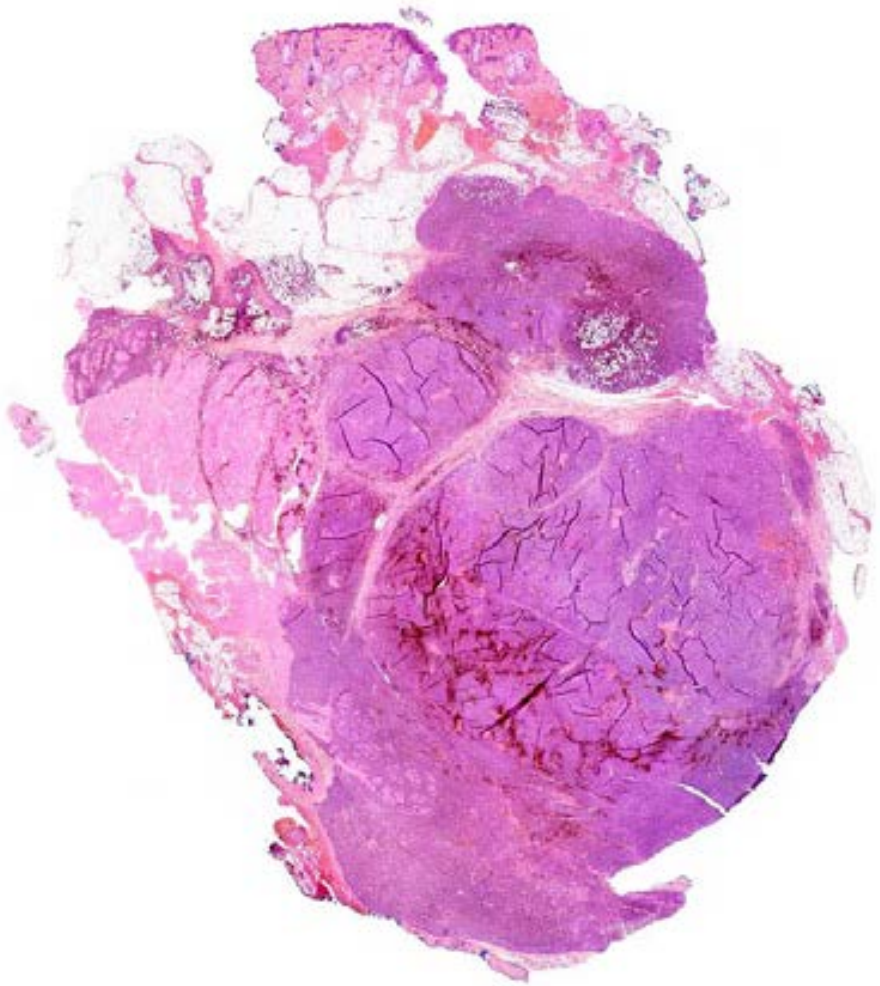


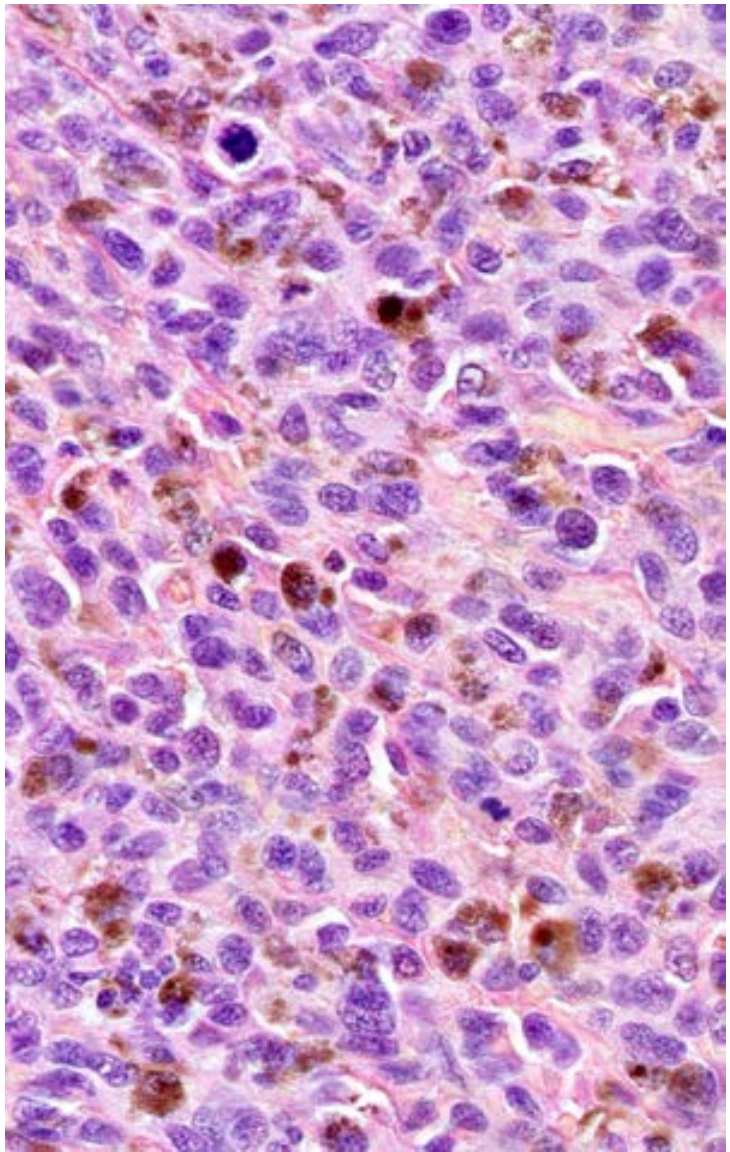


Superficial Spreading Melanoma

- Breslow: 1.6 mm
- Level V
- Ulceration: absent
- Mitotic rate: 1 per mm^2
- Neurotropism
- Angiotropism

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





Adolescent Melanoma

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

Take Home Messages

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

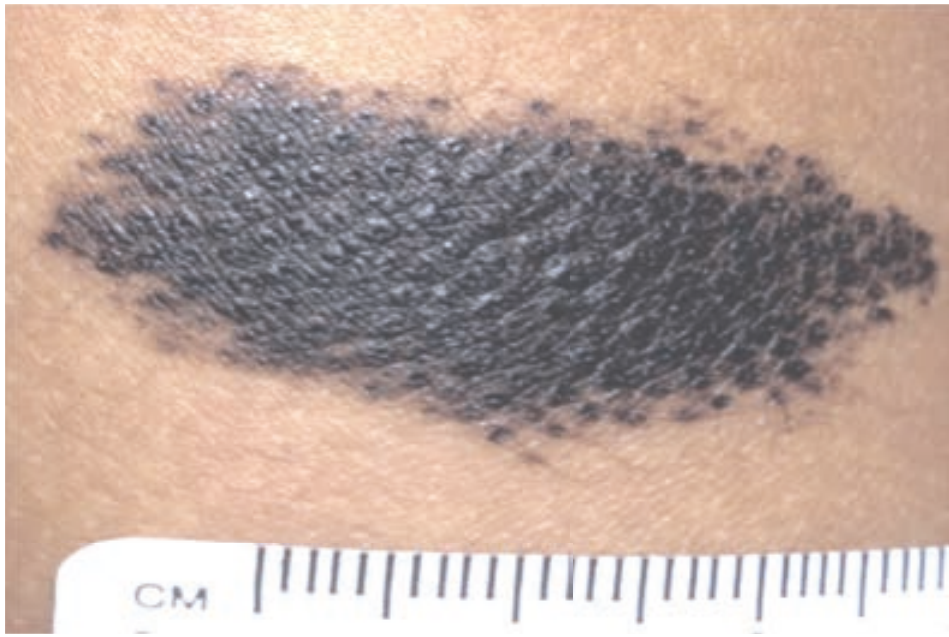
Take Home Messages

3. Melanomas arising in congenital nevi are highly aggressive

4. Consider referral to consultants and institutions with expertise

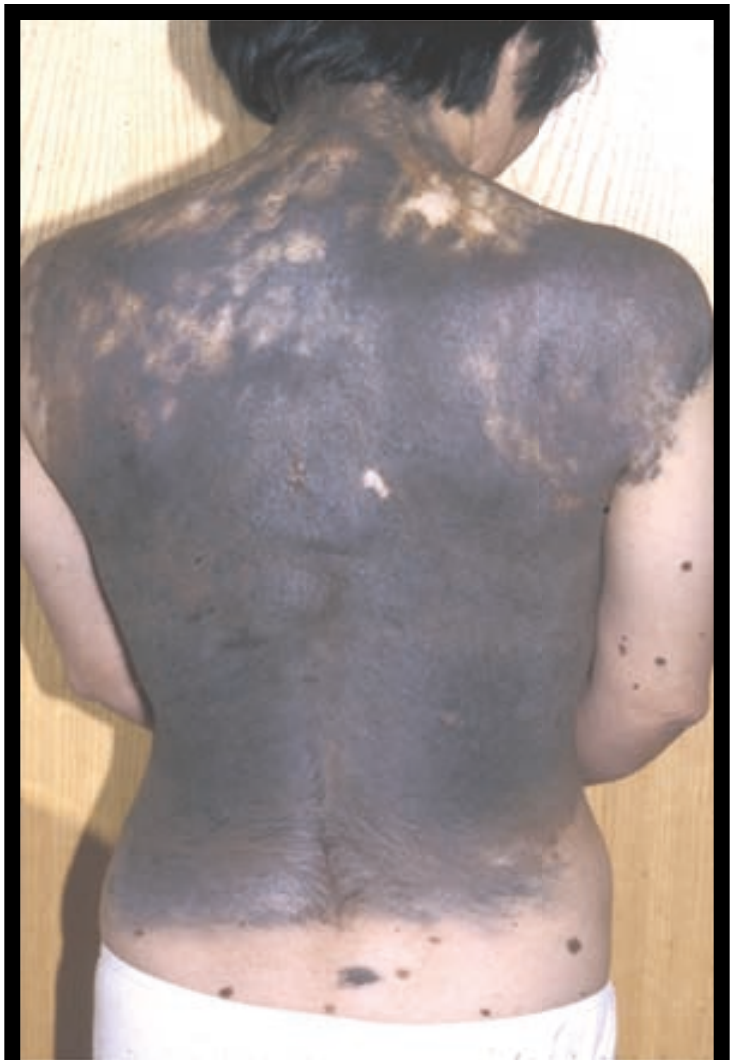
Congenital Nevi
Clinical Features

- 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



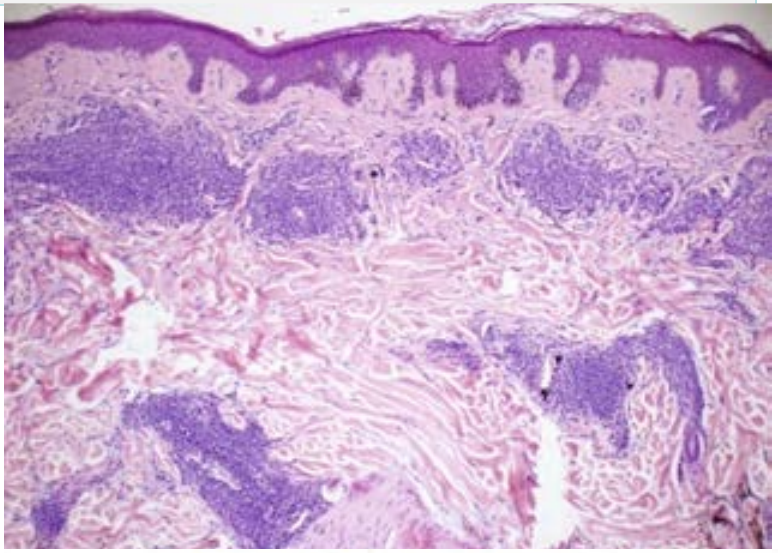
Large/Giant Congenital Nevi Clinical Features

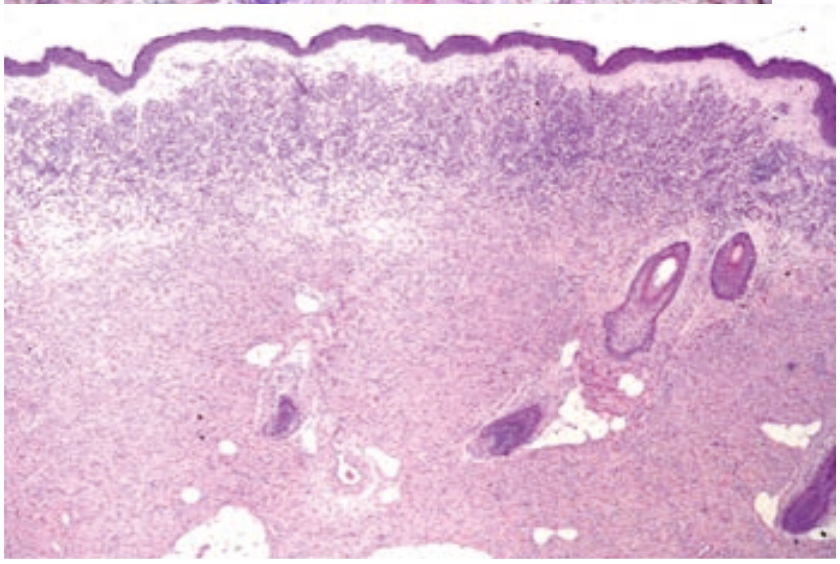
- Prevalence about 1:500,000
- > 20 cm
- > 40 cm
- Major surface area
- Brown-black color
- Rugose, doughy
- Satellite nevi

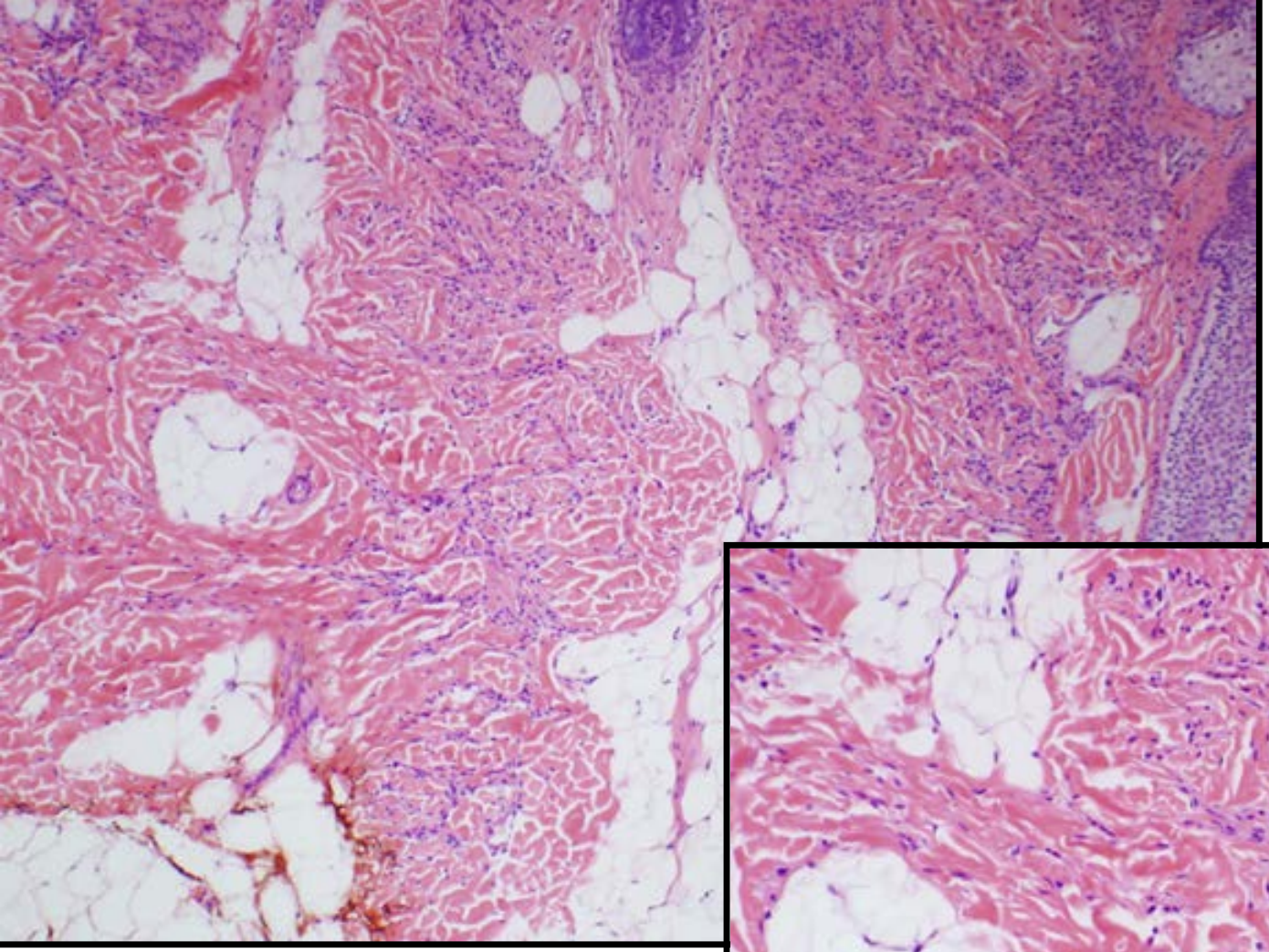


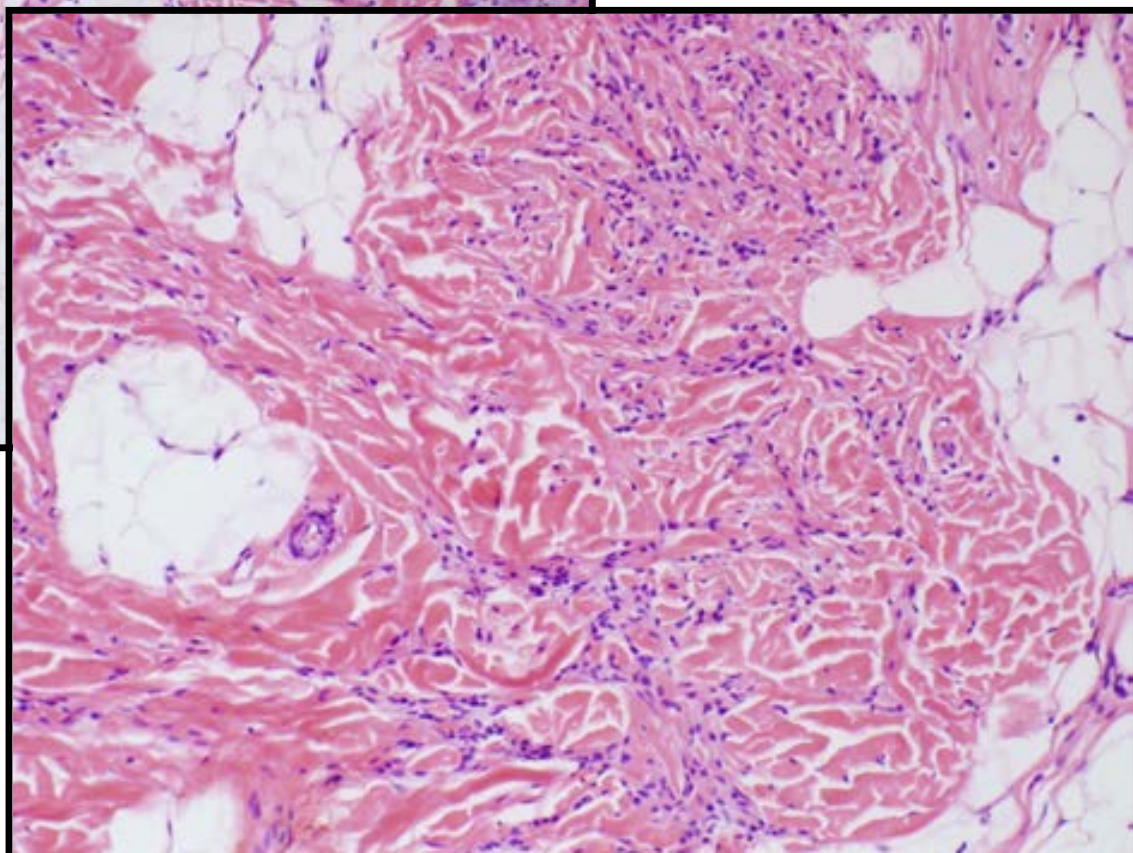
Congenital Nevi
Histological Features

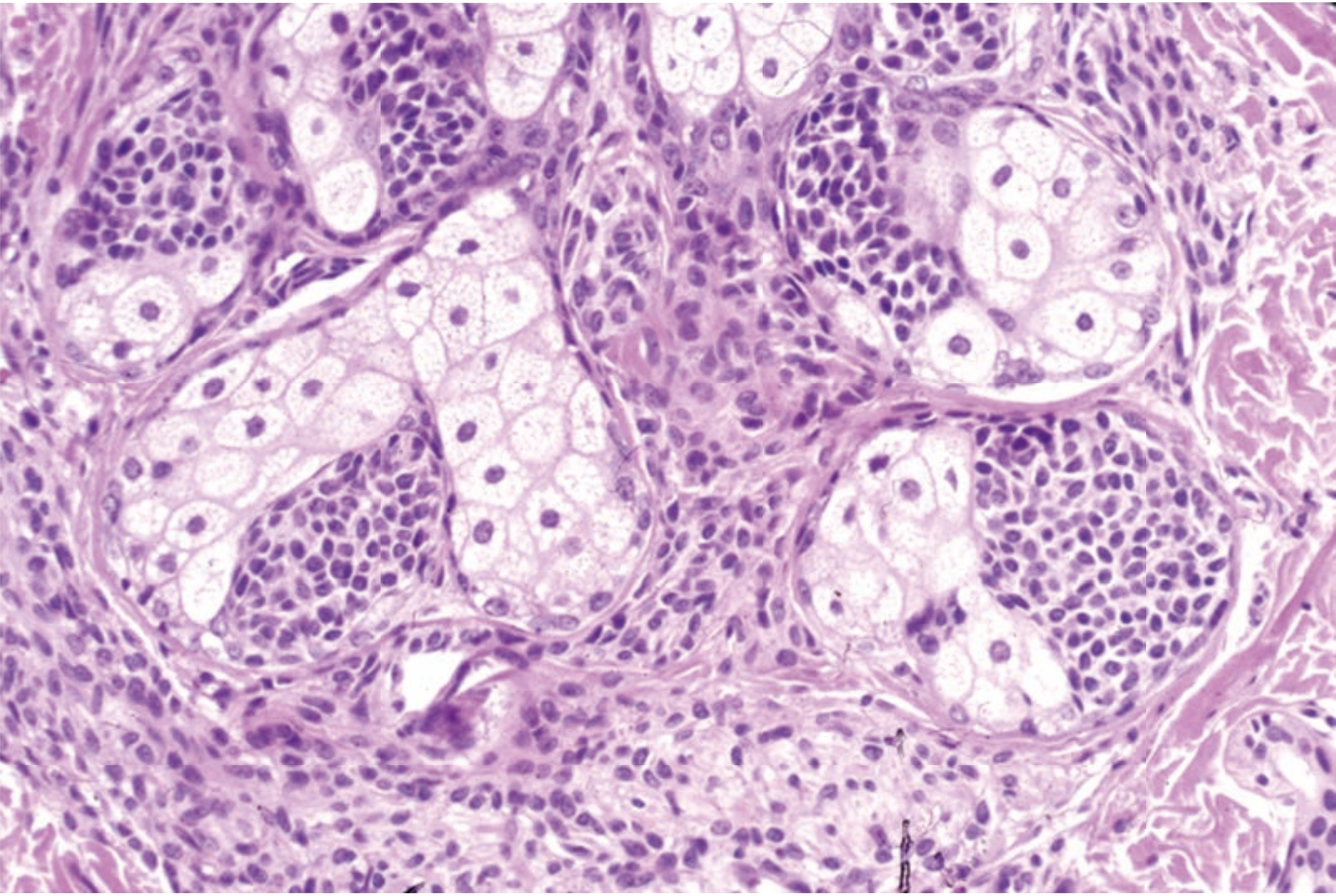
- Nevus cells in discrete aggregates assoc with blood vessels, nerves or appendages
- Nevus cells in diffuse pattern with maturation

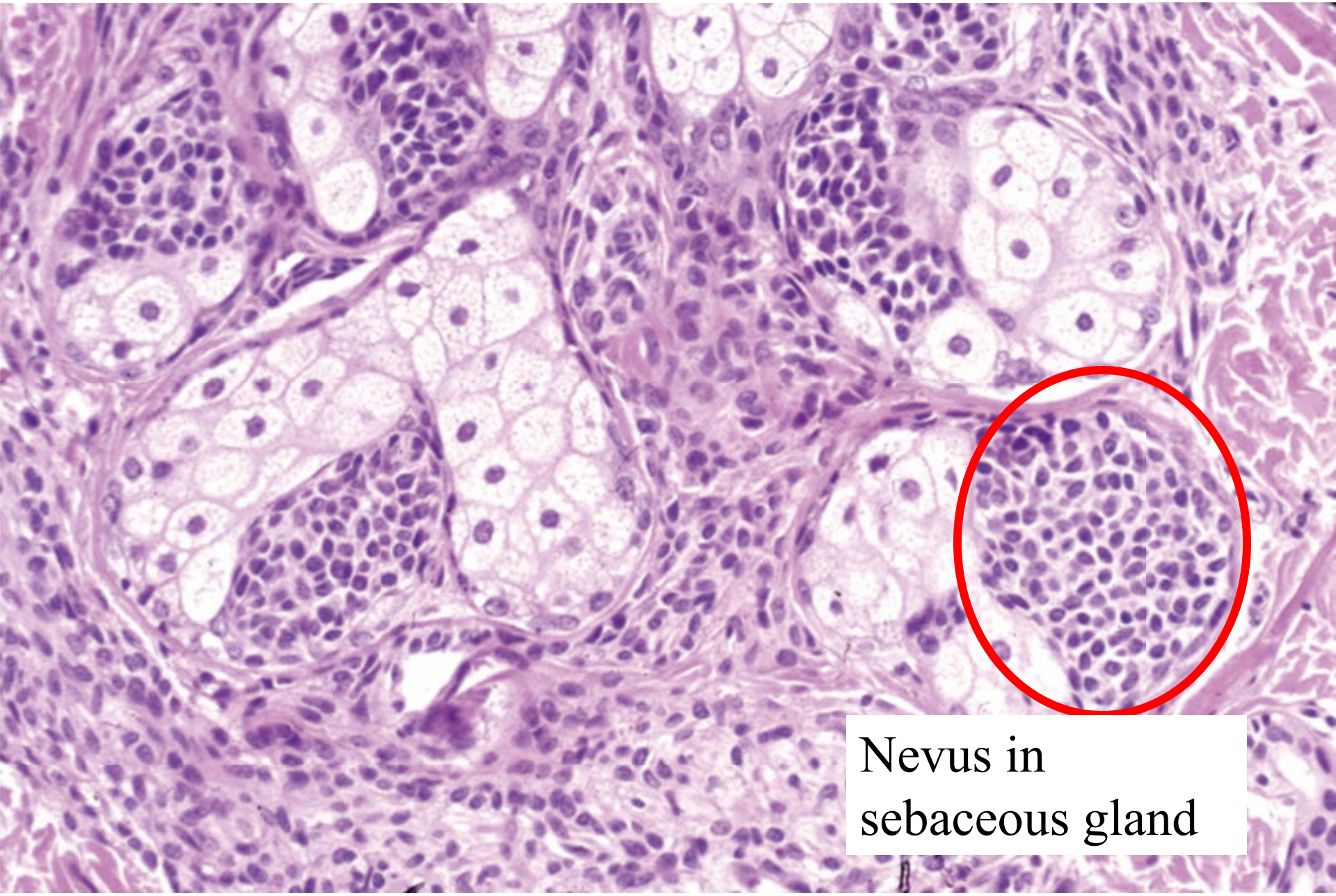


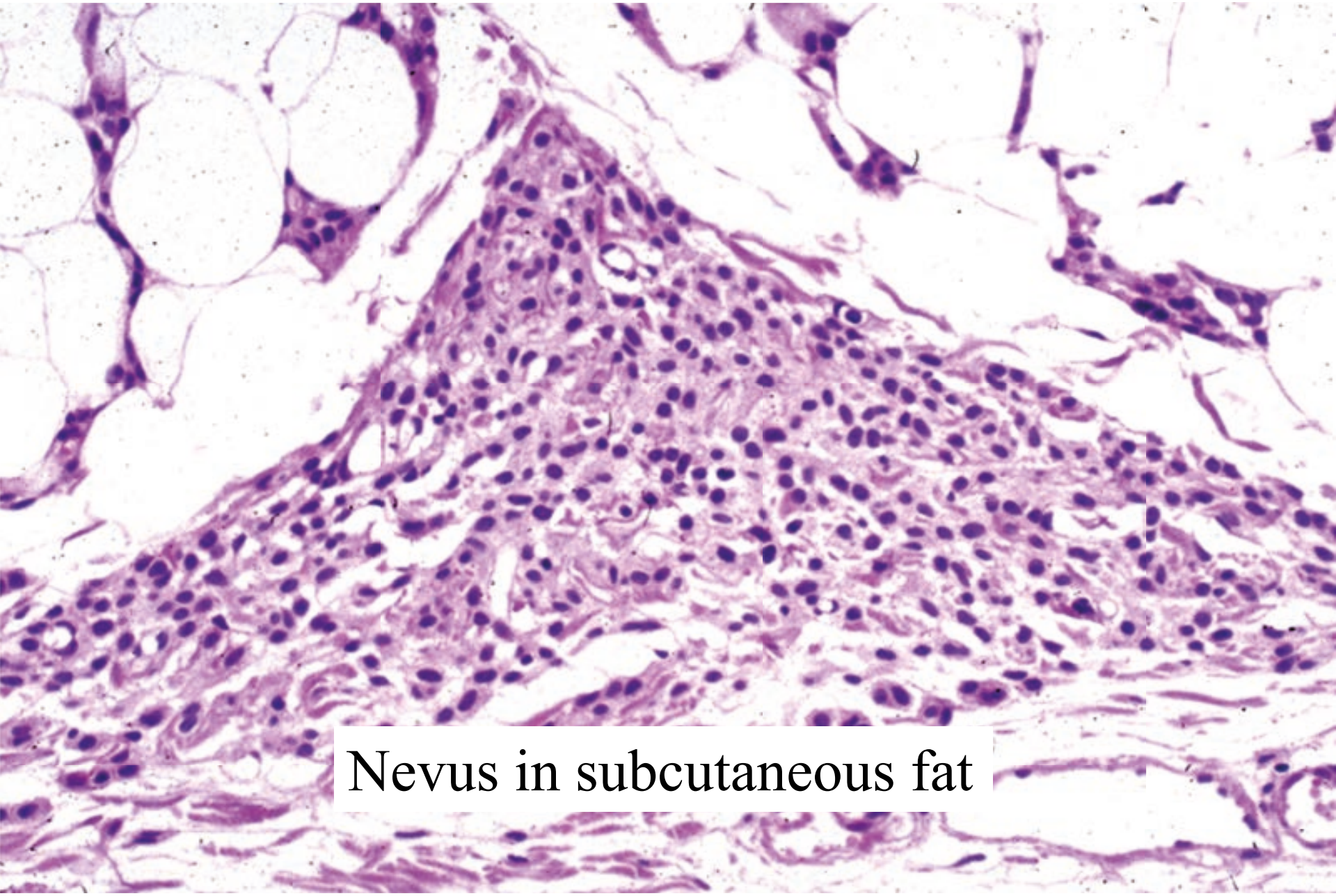









Nevus in
sebaceous gland


Nevus in subcutaneous fat