THE PATHOLOGY OF MELANOMA:

AN INTERNATIONAL COURSE

JANUARY 16 & 17 • 2020

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MERCK

myriad WHEN DECISIONS MATTER

DIAGNOMICS

PATHOLOGY WATCH


STRIKE
SNCF
EN MARCHE!

Criteria for Melanocytic Lesions: An Introduction

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PSL UNIVERSITÉ PARIS

International Melanoma Pathology Study Group IMPSG

institutCurie

Road Map

- Mission of the pathologist
- Classification
- Intermediate lesions
- Uncertain lesions
- MPath project, classification tool, and study
- Criteria for diagnosis
  - Clinical criteria
  - Histopathological criteria

Mission of the Pathologist
Re: Melanocytic Lesions

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

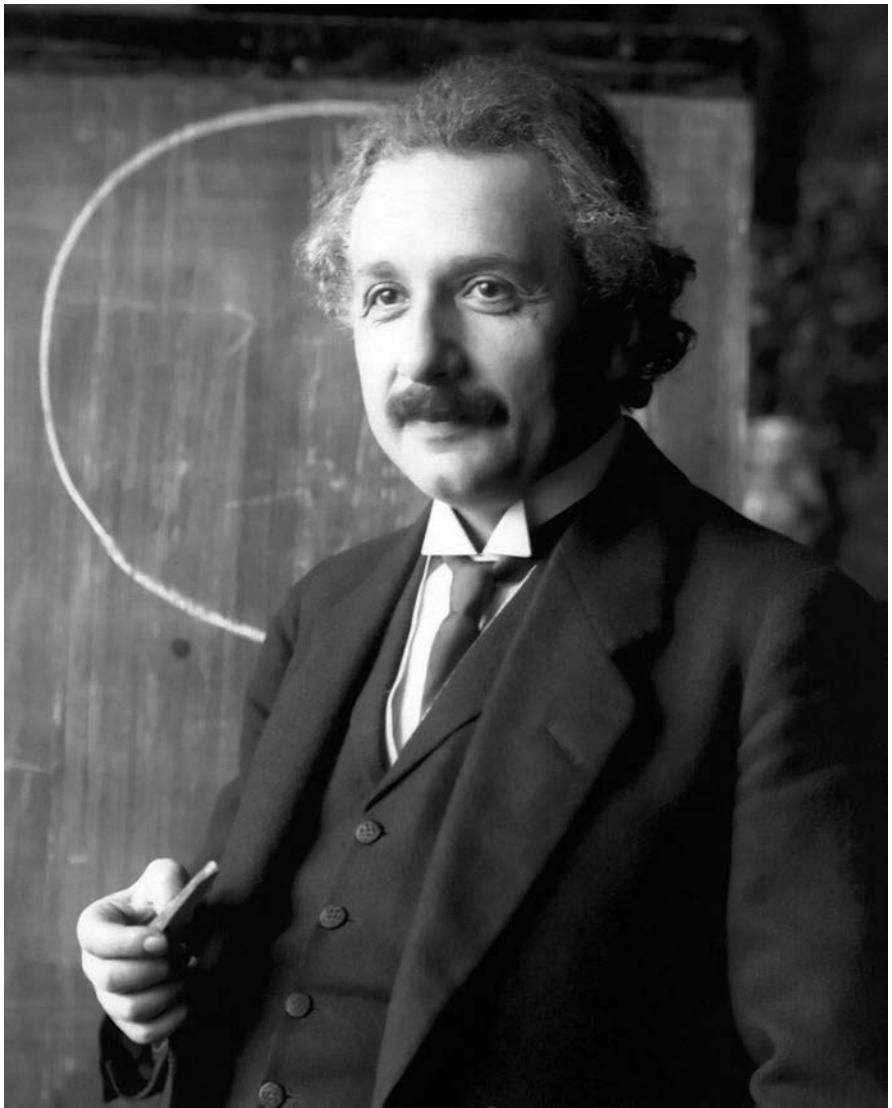
Classification: A Longstanding Dogma

- Benign

  or

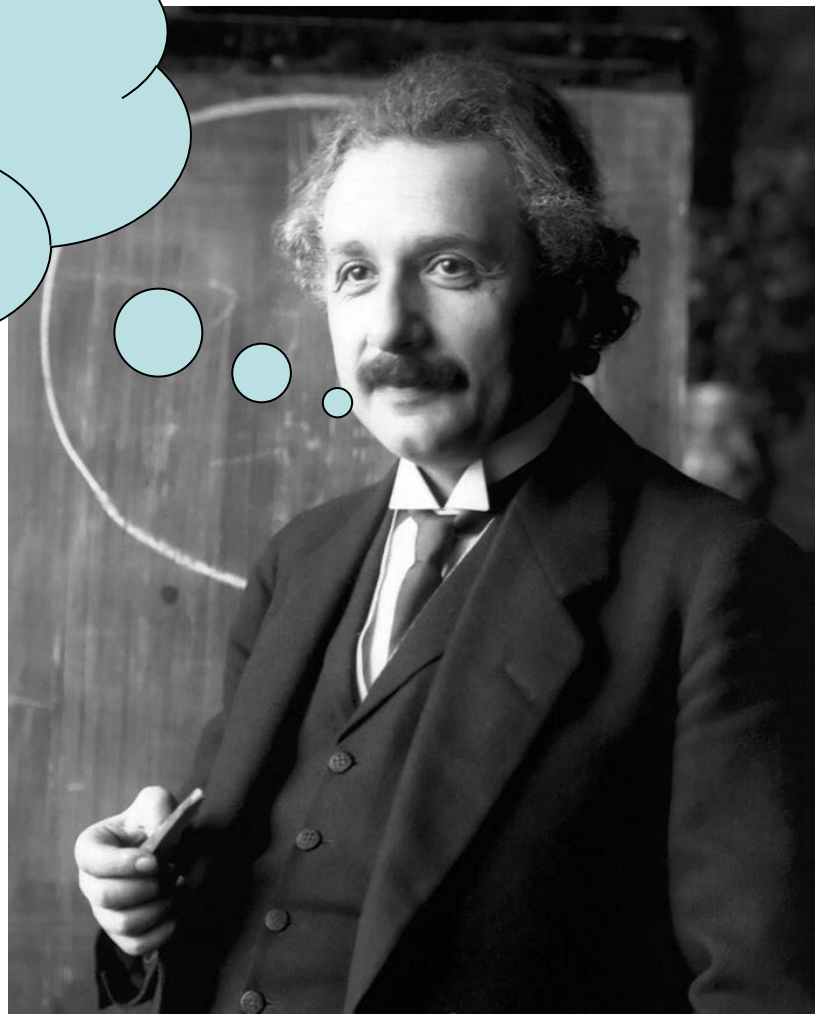
- Malignant

One should try to make things simpler but not too simple.



Classification of Melanocytic Lesions

Too simple! This leads to over-diagnosis and missed melanomas! And harm to patients.

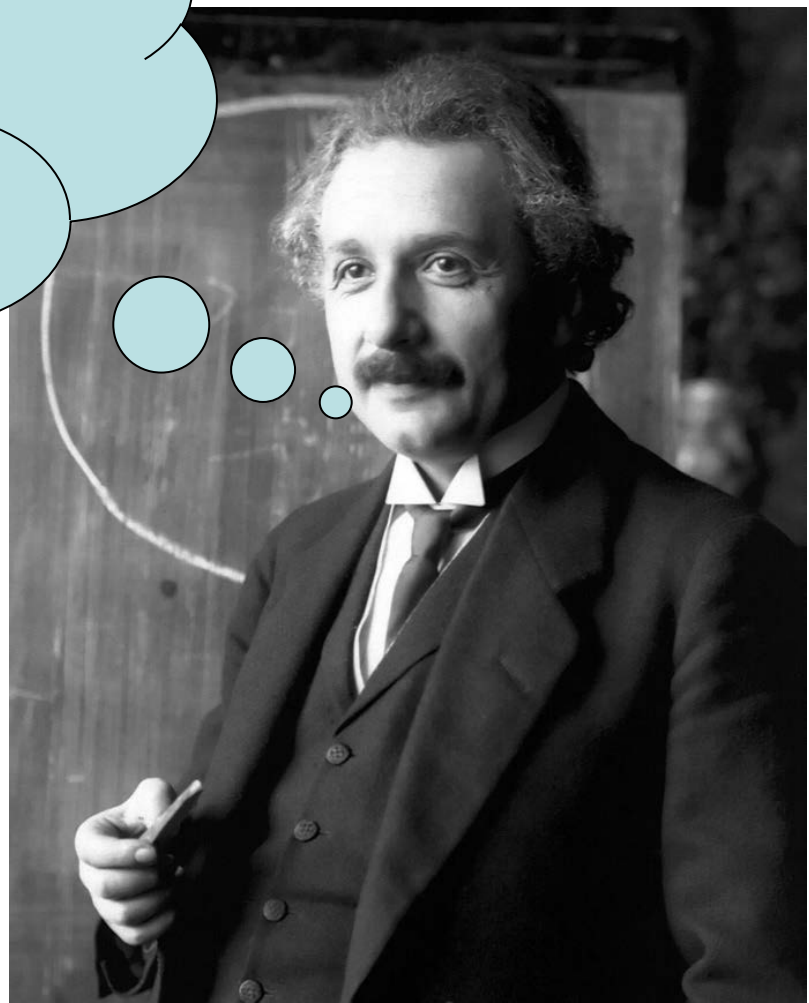


- Benign
- Malignant


TWEET
NUKE
CHAPPATTE
International New York Times

MPATH and WHO 4th Edition Classification

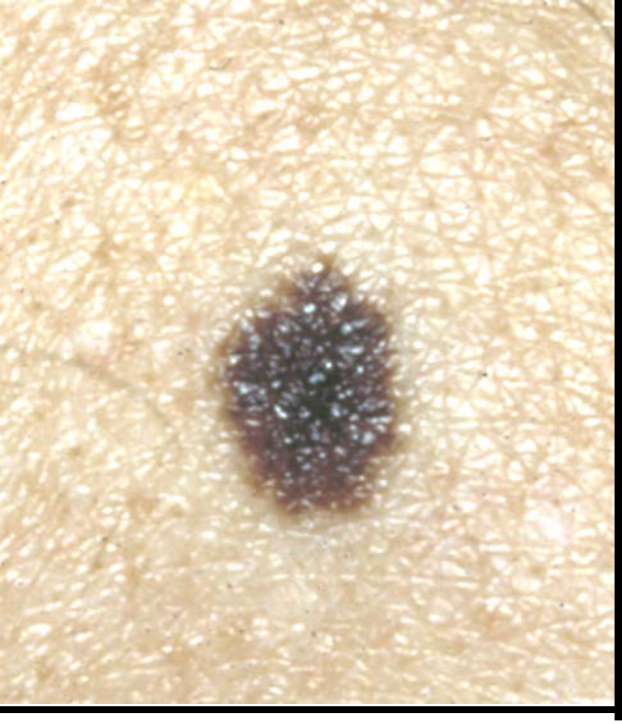
Much better! This acknowledges intermediate and uncertain lesions

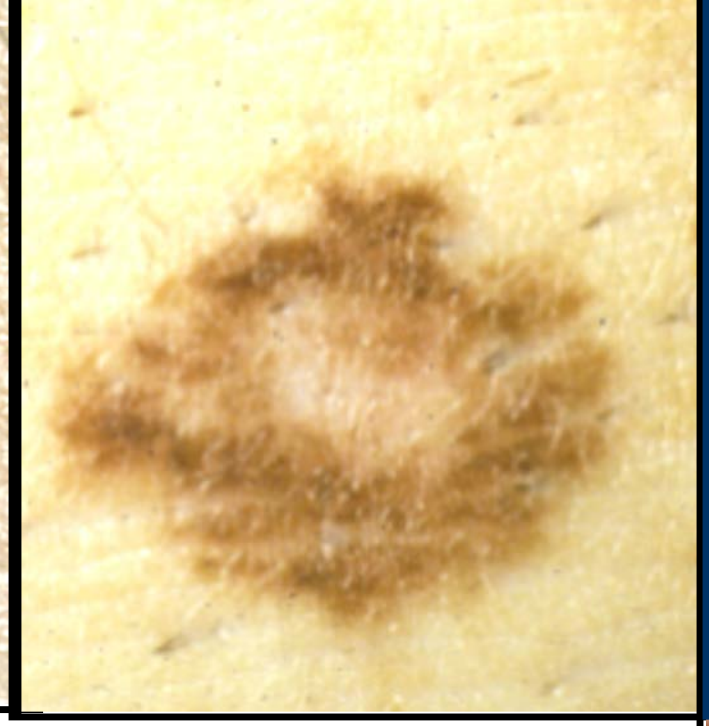


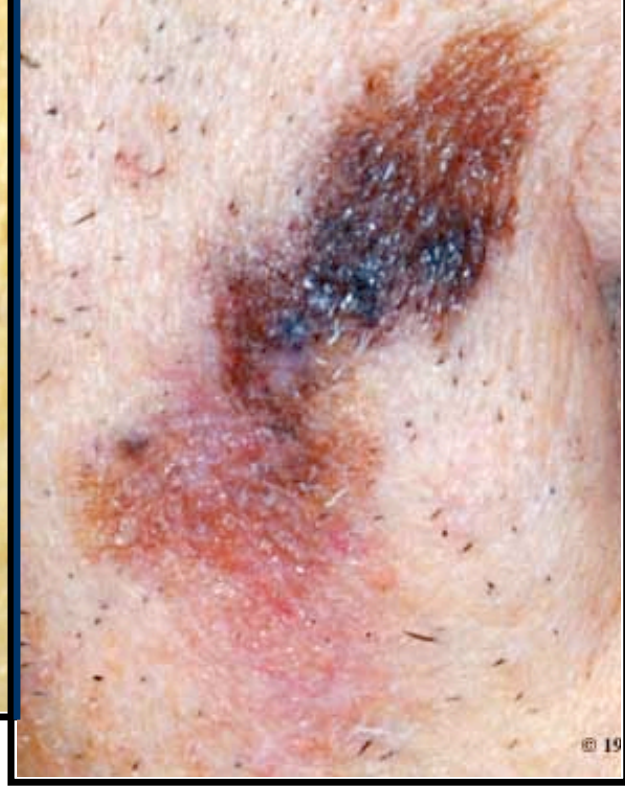
- Benign
- Intermediate
- Malignant

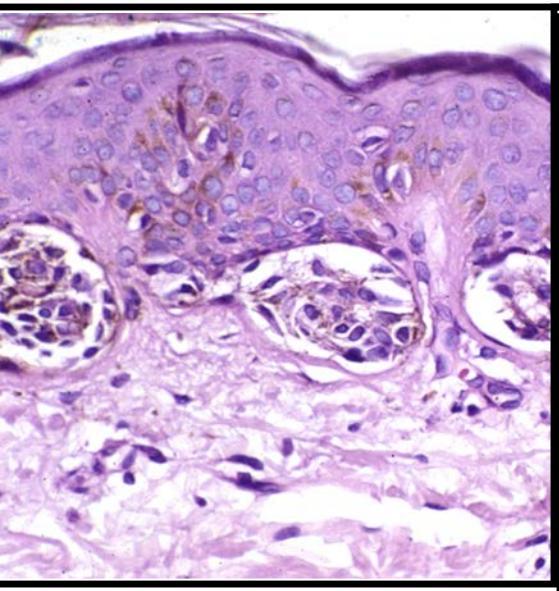
What is an Intermediate Melanocytic Lesion?

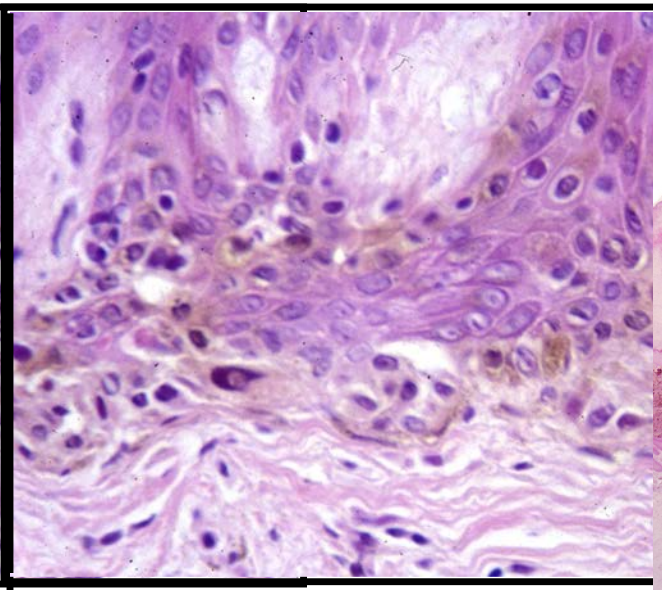
Benign Nevus	• Atypical nevus • Dysplastic nevus • Atypical Spitz tumor • Uncertain lesions (lesions with diagnostic discordance) • Lesions with uncertain malignant potential 	Clear-cut Melanoma

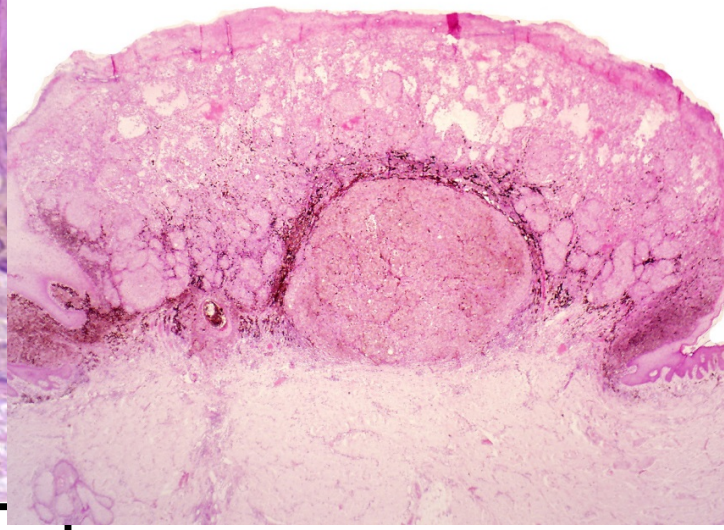












What is an Uncertain Melanocytic Lesion?

- A lesion difficult to interpret as benign or malignant
- A lesion with uncertain potential for :
  - Recurrence, persistence, progression, or metastasis

“Medicine is a science of uncertainty and an art of probability”

…….Sir William Osler

Uncertainty about melanocytic lesions exists and must be communicated for patient care

MPATH Study: Discordance in Diagnosis of Melanocytic Lesions

- NIH grants: Joann Elmore and expert panel: RB, DE, MP 2009 to present
- Study set: 240 melanocytic lesions
- MPATH-Dx classification schema: 5 Classes of melanocytic lesions related to degree of atypia
- Recruitment of 187 pathologists in USA
- Rate of agreement with a consensus diagnosis of the expert panel

MPATH-Dx* Class	Perceived Risk for Progression	Suggested treatment consideration	Examples
0	Incomplete study due to sampling or technical limitations	Repeat biopsy or short-term follow up	N/A
I	Very low risk	No further treatment	-Common melanocy nevus -Blue nevus -Mildly dysplastic nevus
II	Low risk	Narrow but complete excision (< 5 mm)	-Moderately dysplastic nevus -Spitz nevus
III	Slightly higher risk, greater need for intervention.	Complete excision with at least 5 mm but <1 cm margins	-Severely dysplastic nevus -Melanoma in situ -Atypical Spitz tum
IV	Substantial risk for local or regional progression	Wide local excision with ≥ 1 cm margins	Thin, invasive melanoma (e.g., T1a)
V	Greatest risk for regional and/or distant metastases	Wide local excision with ≥ 1 cm margins. Consideration of staging sentinel lymph node biopsy, adjuvant therapy	Thicker invasive melanomas (e.g., T1b, T2 or greater)

MPath Project

Pathologists' diagnosis of invasive melanoma and melanocytic proliferations: observer accuracy and reproducibility study

Joann G Elmore,[1] Raymond L Barnhill,[2] David E Elder,[3] Gary M Longton,[4] Margaret S Pepe,[4] Lisa M Reisch,[1] Patricia A Carney,[5] Linda J Titus,[6] Heidi D Nelson,[7,8] Tracy Onega,[9,10] Anna N A Tosteson,[11] Martin A Weinstock,[12,13] Stevan R Knezevich,[14] Michael W Piepkorn[15,16]

ABSTRACT

OBJECTIVE

To quantify the accuracy and reproducibility of pathologists' diagnoses of melanocytic skin lesions.

DESIGN

Observer accuracy and reproducibility study.

SETTING

10 US states.

PARTICIPANTS

Skin biopsy cases (n=240), grouped into sets of 36 or 48. Pathologists from 10 US states were randomized to independently interpret the same set on two occasions

concordance rates were lower, but with similar trends. Accuracy using a consensus diagnosis of experienced pathologists as reference varied by class: I, 92% (95% confidence interval 90% to 94%); II, 25% (22% to 28%); III, 40% (37% to 44%); IV, 43% (39% to 46%); and V, 72% (69% to 75%). It is estimated that at a population level, 82.8% (81.0% to 84.5%) of melanocytic skin biopsy diagnoses would have their diagnosis verified if reviewed by a consensus reference panel of experienced pathologists, with 8.0% (6.2% to 9.9%) of cases overinterpreted by the initial pathologist and 9.2% (8.8% to 9.6%) underinterpreted.

British Medical Journal 2017:357: j2813

Accuracy of 187 Pathologists' Interpretations Compared with Consensus Reference Diagnoses

MPATH Class		% Concordance with consensus reference diagnosis†
Class I	**Nevus, no or mild atypia**	**92 %**
Class II	**Nevus, moderate atypia**	**25 %**
Class III	**Nevus, severe atypia** **Melanoma in situ**	**40 %**
Class IV	**Melanoma invasive < 0.8 mm**	**43 %**
Class V	**Meanoma invasive > 0.8 mm**	**72 %**

†Reference diagnosis was obtained from consensus of three experienced dermatopathologists (RB, DE, MP).

Greatest Concordance and Certainty: Banal Nevi and Thicker Melanomas

MPATH Class		% Concordance with consensus reference diagnosis† (95% CI)
Class I	**Nevus, no or mild atypia**	**92 %**
Class II	**Nevus, moderate atypia**	**25 %**
Class III	**Nevus, severe atypia** **Melanoma in situ**	**40 %**
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Class V	**Melanoma invasive > 0.8 mm**	**72 %**

†Reference diagnosis was obtained from consensus of three experienced dermatopathologists.

Worst Concordance and Greatest Uncertainty: Intermediate Lesions

MPATH Class		% Concordance with consensus reference diagnosis†
Class I	**Nevus, no or mild atypia**	**92 %**
Class II	**Nevus, moderate atypia**	**25 %**
Class III	**Nevus, severe atypia** **Melanoma in situ**	**40 %**
Class IV	**Melanoma invasive < 0.8 mm**	**43 %**
Class V	**Meanoma invasive > 0.8 mm**	**72 %**

†Reference diagnosis was obtained from consensus of three experienced dermatopathologists.

Due Diligence

Standardized, Methodical, and Comprehensive Approach to Difficult/Intermediate and Uncertain Melanocytic Lesions

Clinical Criteria*

Histopathological Criteria*

Ancillary Technique Criteria

Guidelines for Criteria

- Obtain as much information as possible
- Always use several/multiple criteria
- No single criterion is diagnostic
- There are exceptions to every criterion… often leading to uncertainty!

I.
Clinical Criteria

Obtain as much information as possible, especially all clinical information before finalizing a diagnosis

- ✓ Age
- ✓ Gender (sex)
- ✓ Anatomic site
- ✓ Size
- ✓ Clinical features of the lesion
- ✓ Clinical history

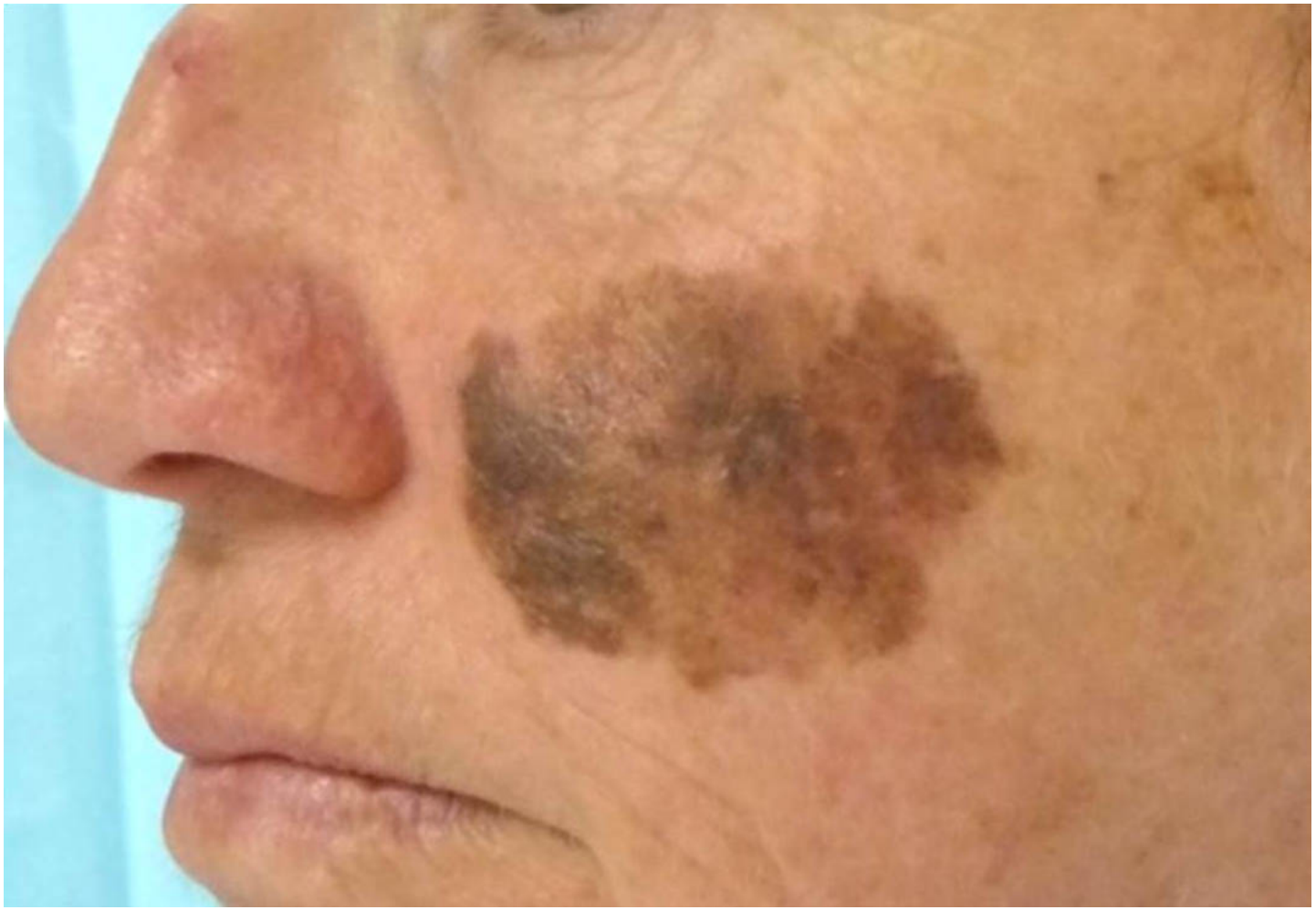
Clinical Criteria

Criterion	Benign	Melanoma
Age	Young age, especially < 10-12 years	Increasing age Increasing prevalence
Gender	Hormonal effects in women	Older men - increased risk
Anatomic site	Extremities favor Spitz, special sites: acral, vulvar	Scalp, neck, back, trunk, lower legs women
Gross morphological features	< 5 mm, well circumscribed, symmetrical, regular borders, uniform color	> 5 mm >10mm, poorly circumscribed asymmetrical, irregular color, black, ulceration, amelanotic
Clinical history	Stable, long-standing lesion, history of trauma	Changing lesion, new lesion, itching, pain, bleeding

Clinical Criteria

Criterion	Benign	Melanoma
Age	Young age < 10 years	Increasing age Increasing prevalence

Age – 60 years

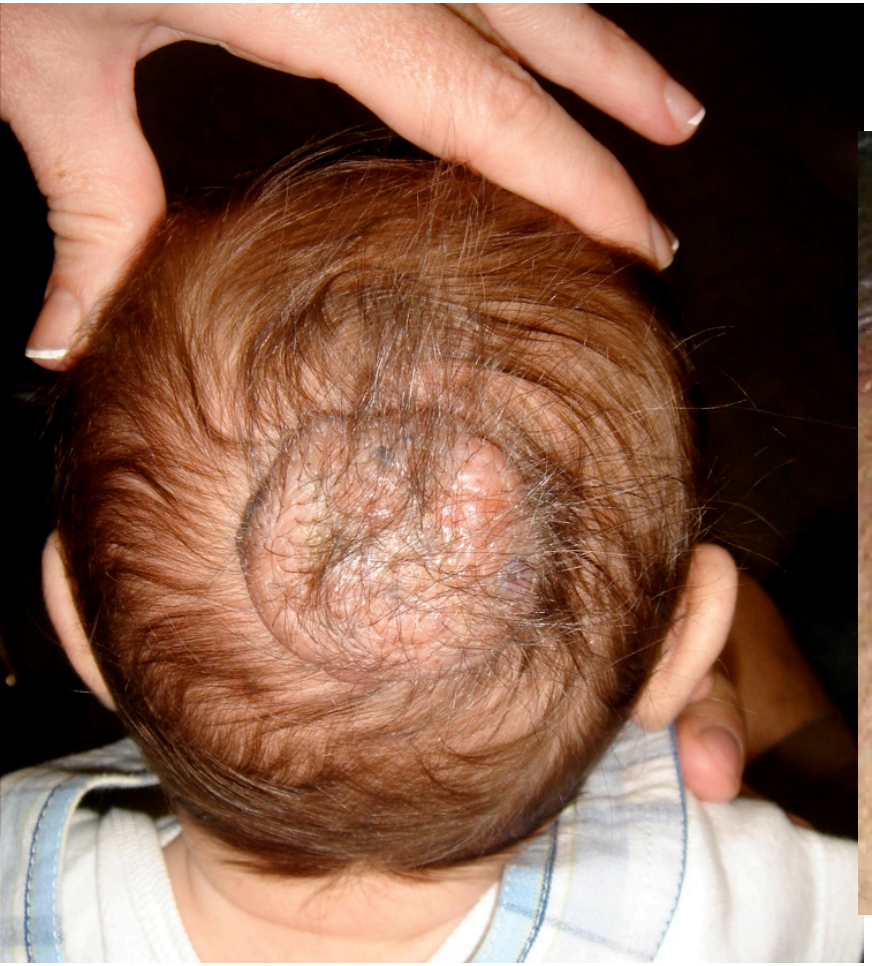


Lentigo Maligna Melanoma

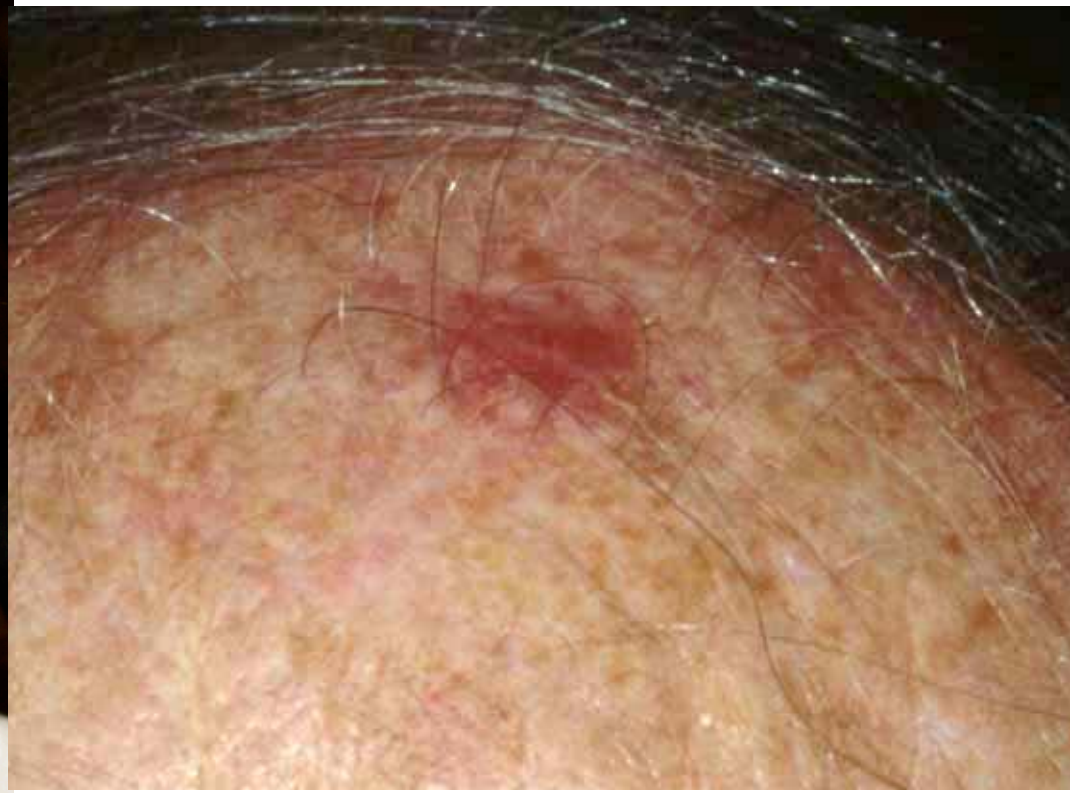
Clinical Criteria

Criterion	Benign	Melanoma
Anatomic site	Extremities favor Spitz Special sites: acral, vulvar *Can mimic melanoma*	Scalp, neck, back, trunk, lower legs in women

Anatomic Site - Scalp

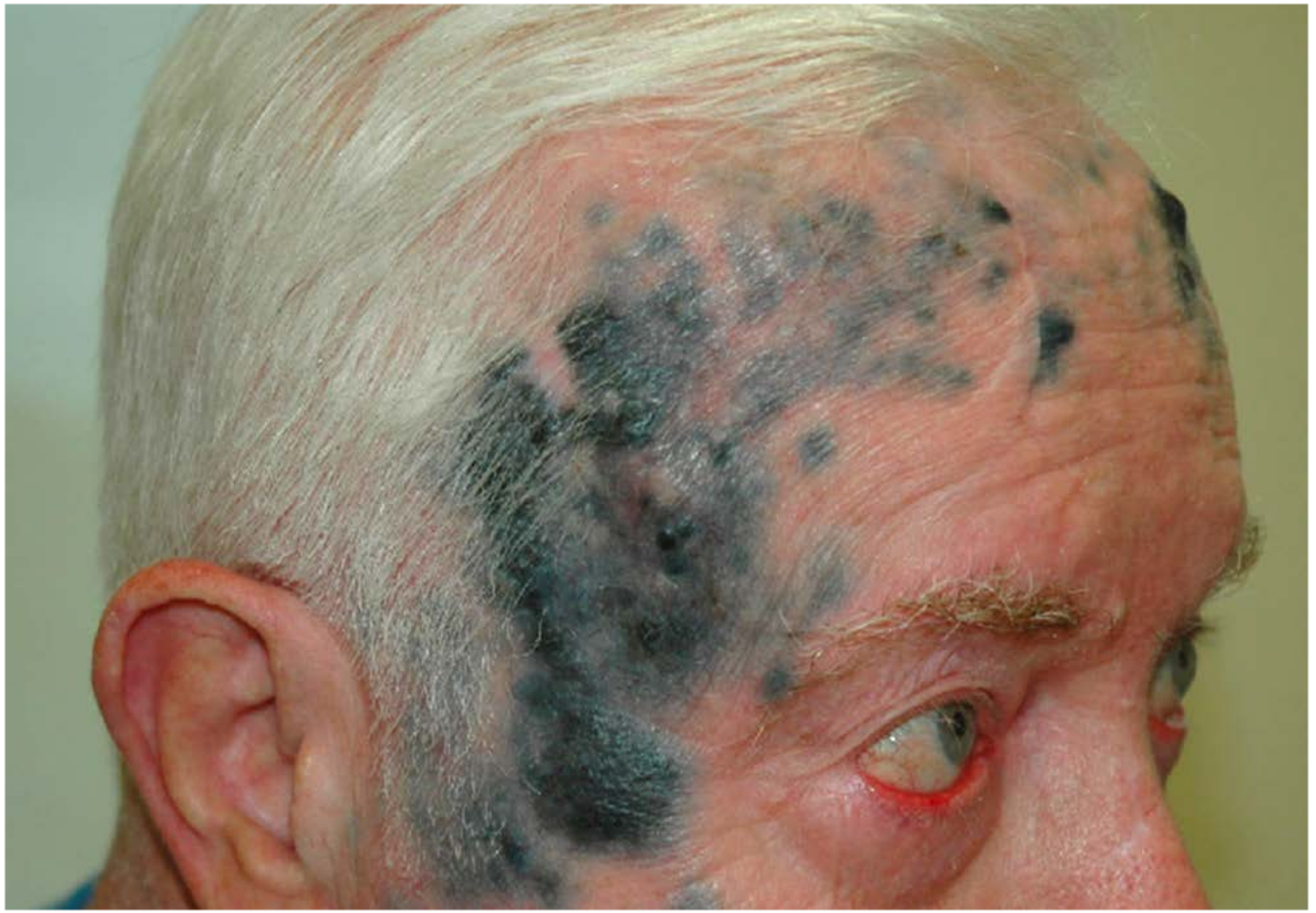


Congenital/Pediatric Melanoma



Desmoplastic Melanoma

Anatomic Site - Scalp

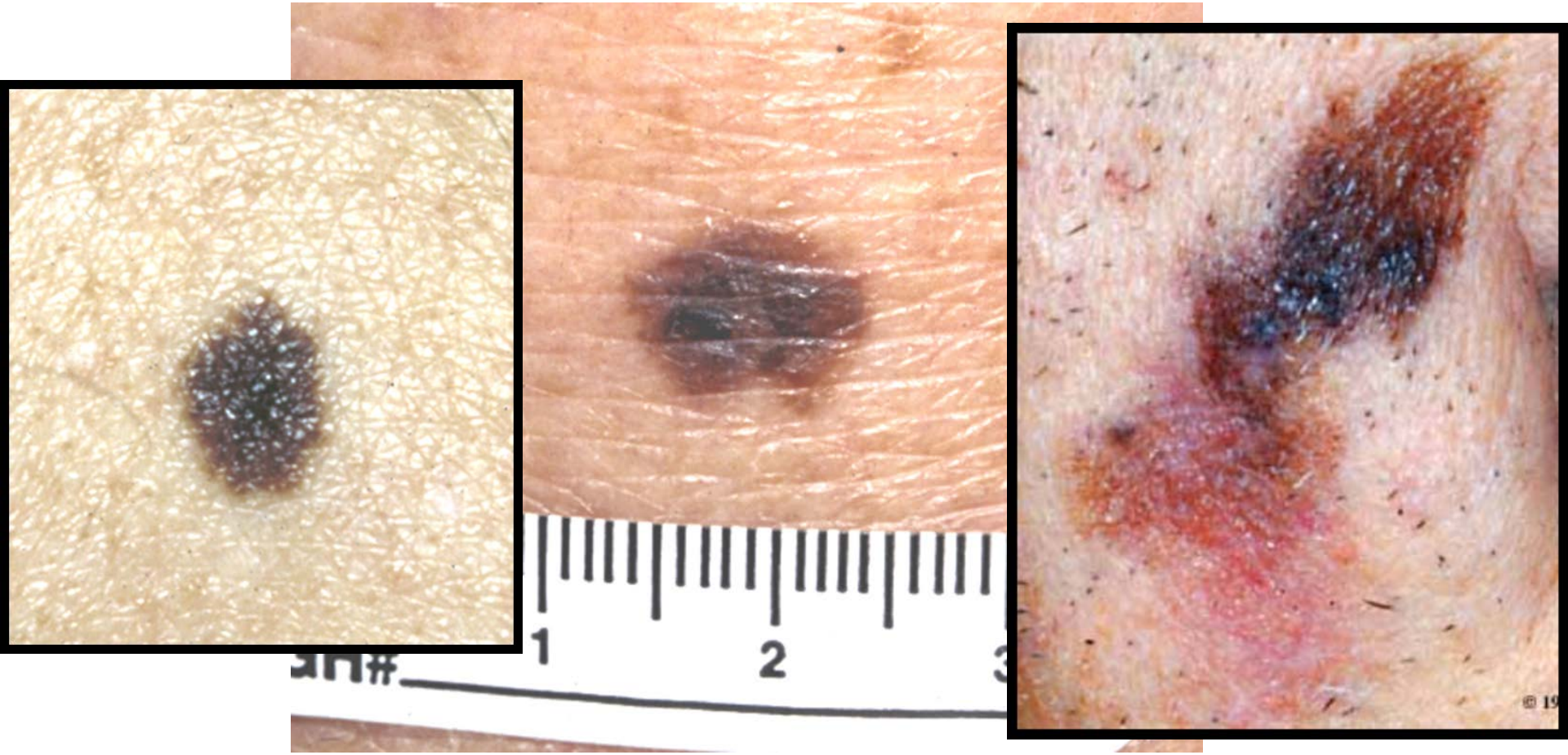


Melanoma arising in Blue Nevus

Clinical Criteria ["ABCDEs"]
Clinical Diagnosis is 80 to 90%

Gross Morphological Features	Benign Nevus	Melanoma
• **Diameter (size)**	• < 5 mm,	• > 6 mm >10mm,
• **Symmetry**	• Symmetry	• Asymmetry
• **Circumscription (borders)**	• Well circumscribed	• Poor circumscription
• **Color**	• Uniform color	• Non uniform color -Black -Amelanotic

Clinical Features



< 5 mm

5- 10 mm

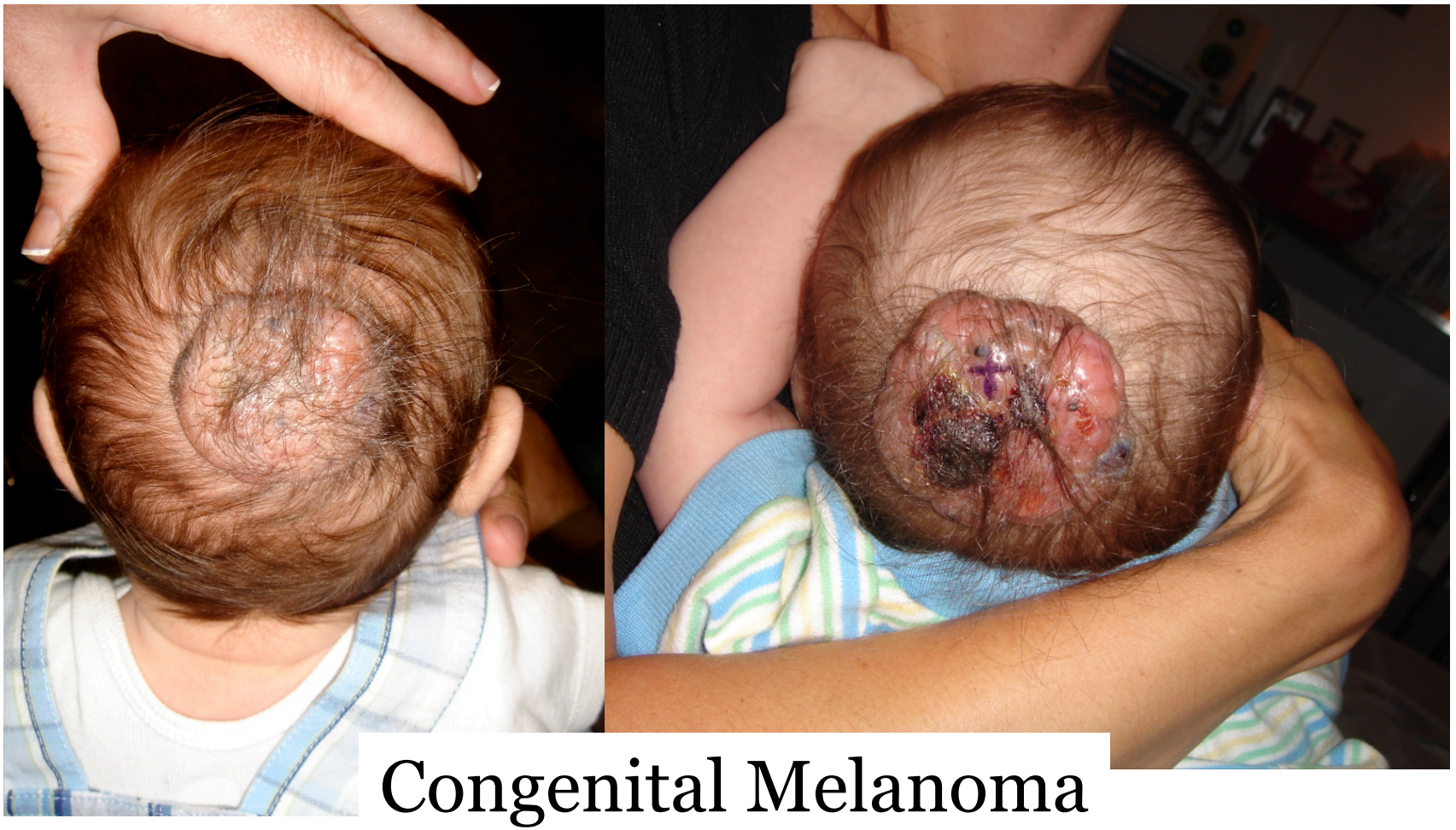
> 6 mm , >10 mm

Clinical Criteria

Criterion	Benign	Melanoma
Clinical History [Evolution]	• Stable • Long-standing lesion • History of trauma	• Changing • New lesion • Itching, pain, bleeding

Clinical History

Enlarging and Changing Lesion



Congenital Melanoma

II. Histopathological Criteria

WHO 4th Edition
Histopathology is the Gold Standard

How Does Histopathology Really Function?

Benign Nevus	• Gray or intermediate zone: suboptimal gold standard	Clear-cut Melanoma
		

Why Does Histopathology Function So Poorly in This Intermediate Zone?

- The lack of correlation between histopathological criteria and precise molecular data and neoplastic progression
- The problem of defining cancer

Perspective
DECEMBER 12, 2019

Machine Learning and the Cancer-Diagnosis Problem — No Gold Standard

Adewole S. Adamson, M.D., M.P.P., and H. Gilbert Welch, M.D., M.P.H.

Artificial intelligence is a branch of computer science devoted to the performance of tasks that normally require human intelligence. A major subbranch of this field is machine learning, in which computers learn to perform tasks by analyzing data rather than requiring specific programming instructions from humans — that is, they generate

delays in diagnosis.[1] Automation of tedious and repetitive tasks, such as the examination of multiple lymph nodes for histologic evidence of metastatic disease, is

derstand why, it's important to appreciate how the technology works. Most machine-learning algorithms used in medicine are trained by means of a process called supervised learning, in which the computer is presented with images that have been labeled using an external standard that serves as the "ground truth."

A simplified version of the

New England J Medicine 2019; 381: 2285

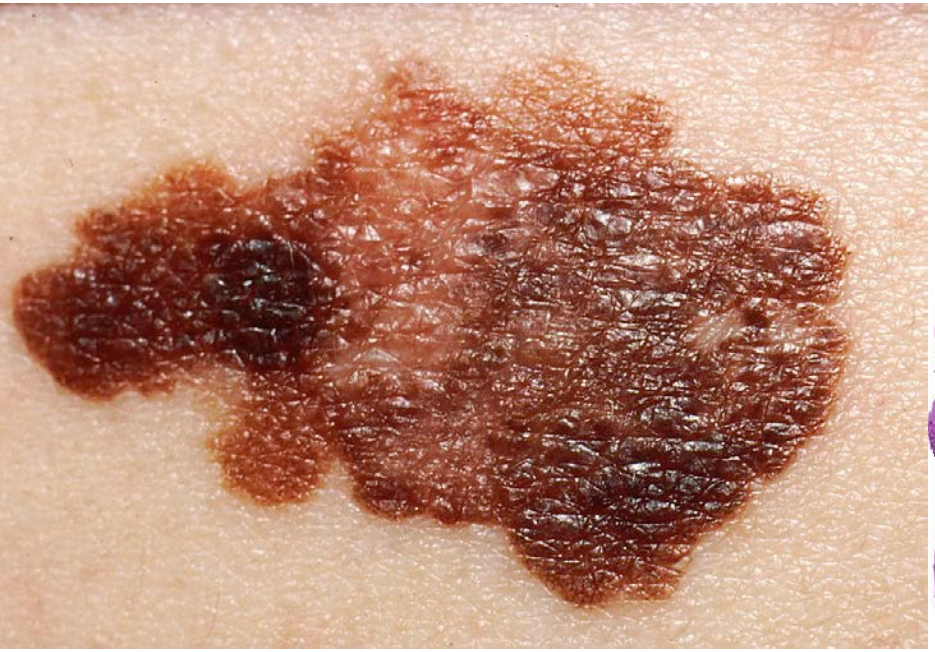
5. Elmore JG, Barnhill RL, Elder DE, et al. Pathologists' diagnosis of invasive melanoma and melanocytic proliferations: observer accuracy and reproducibility study. BMJ 2017; 357:j2813.

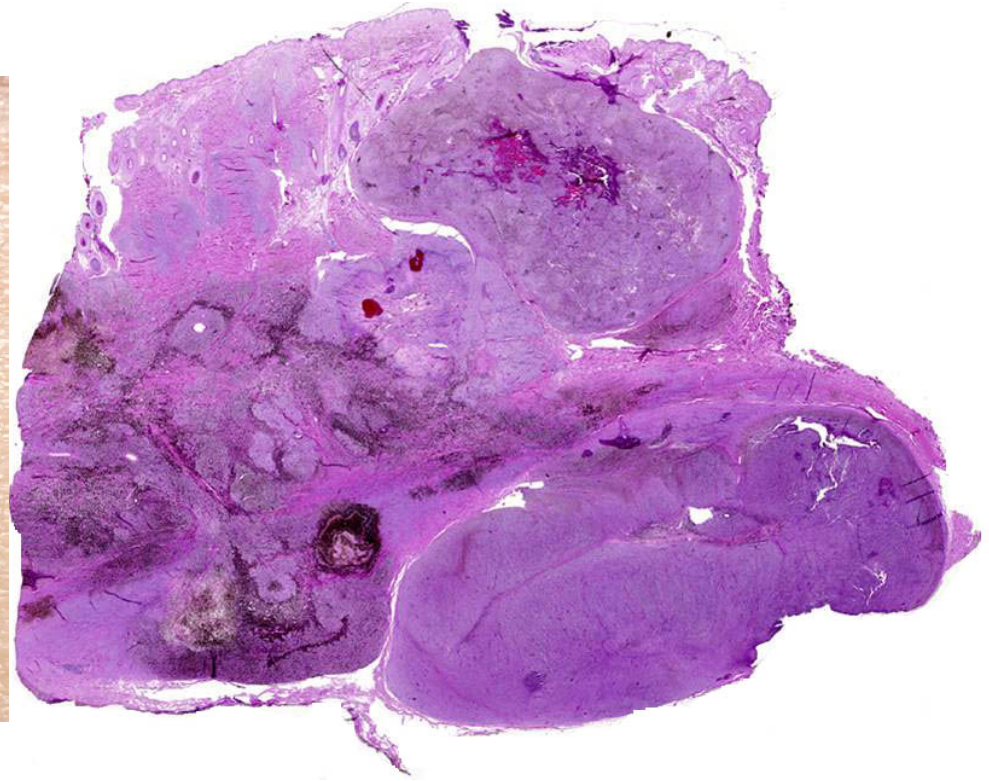
Machine Learning the Cancer-Diagnosis Problem

- Risk for greatly over-diagnosing cancer!
- The potential to utilize a three-tiered system: benign, intermediate/uncertain lesions, malignant
- Facilitate recognizing intermediate/uncertain lesions for further study and analysis by pathologists

The Certain Lesion

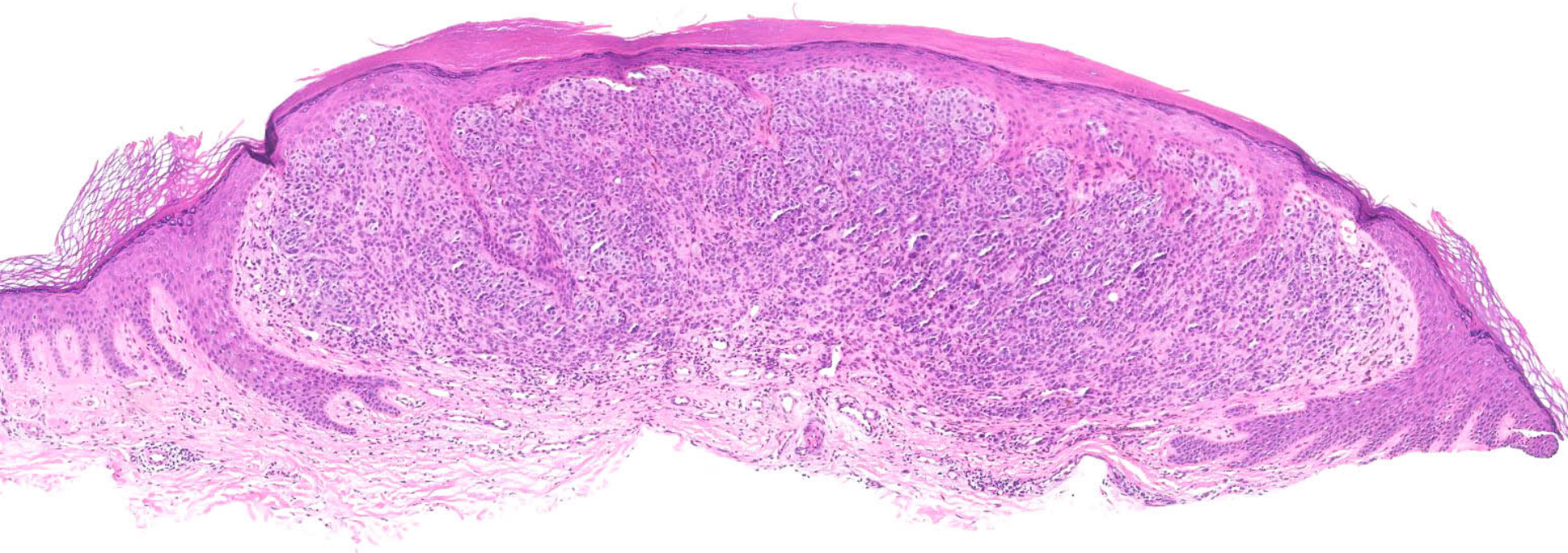
Diagnosis by Gestalt



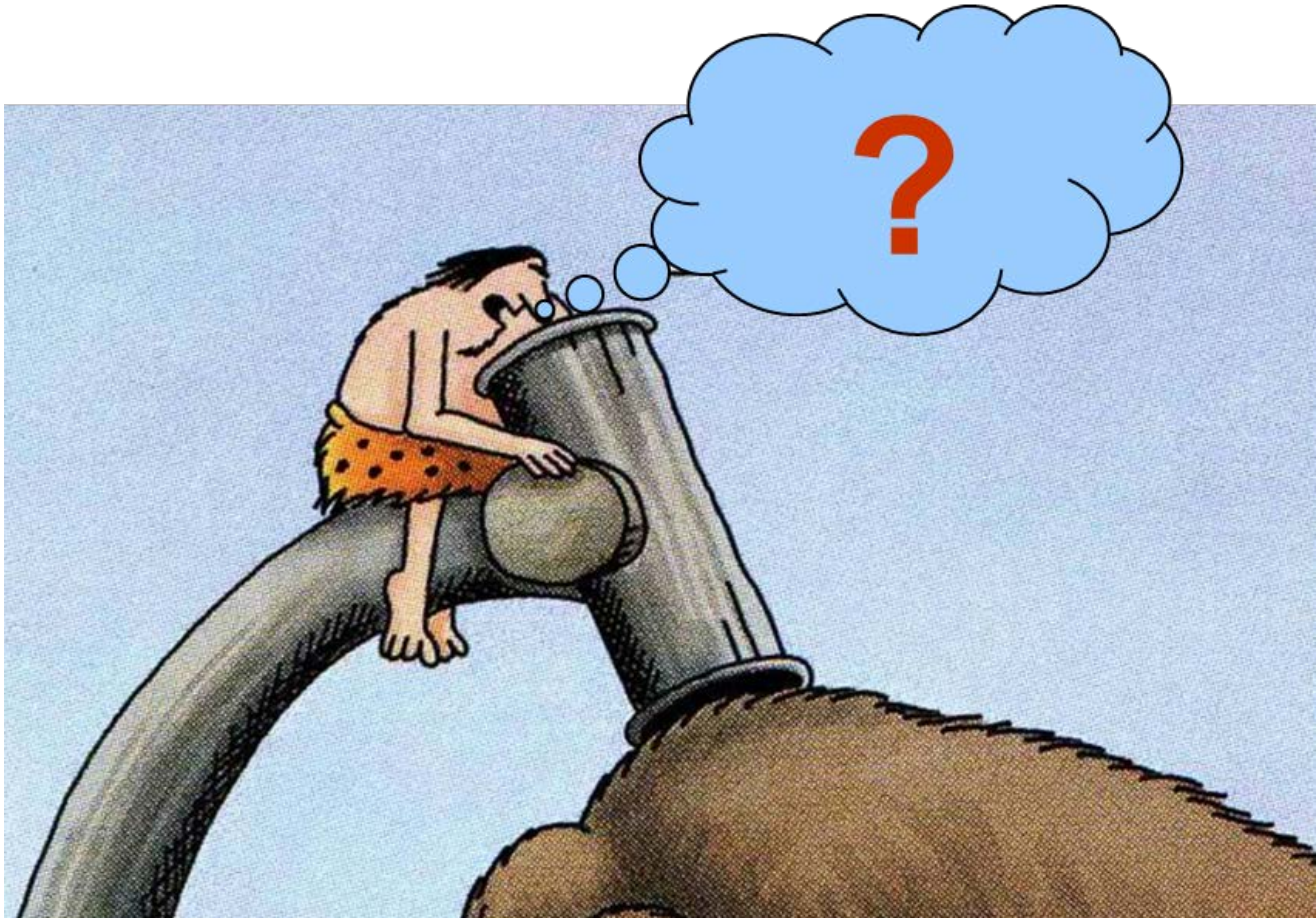


The Uncertain Lesion

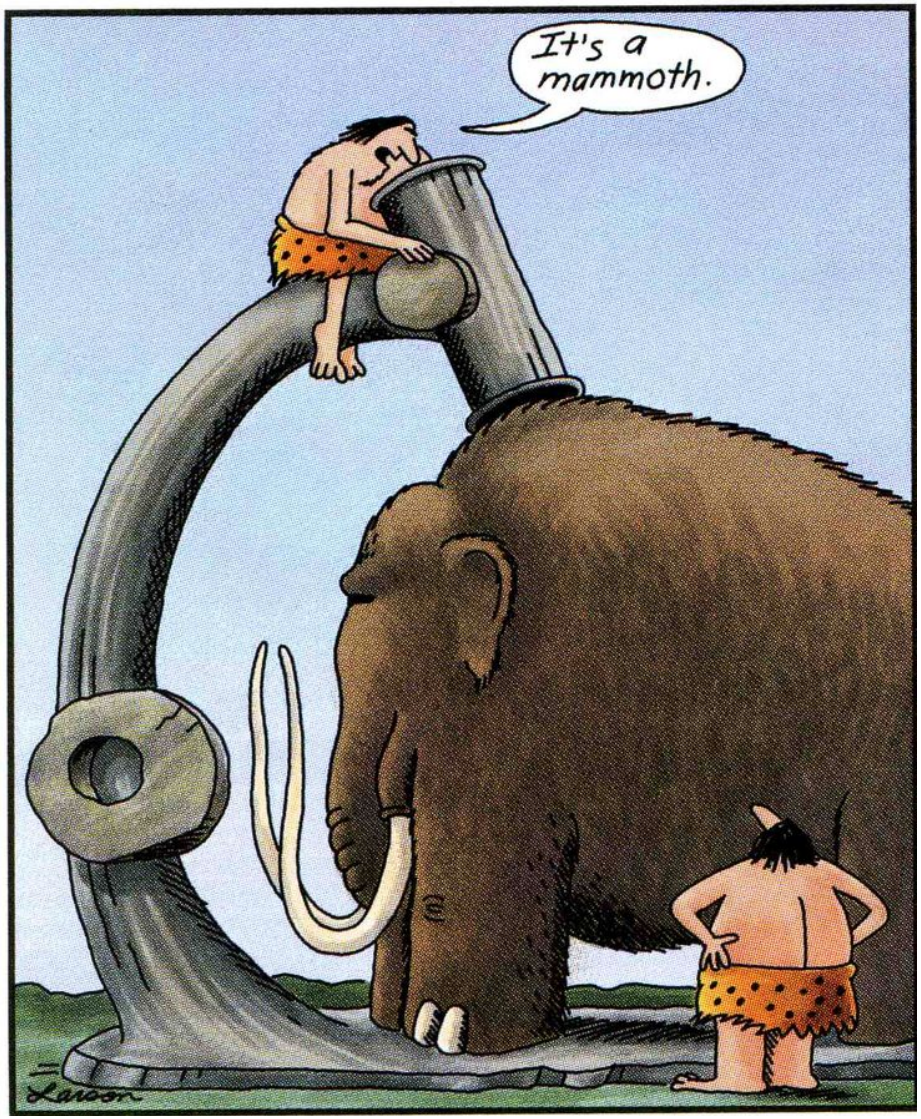
Use of Multiple Criteria



In addition, is your specimen representative of the whole lesion?...



Examine the entire lesion before final diagnosis!



Histopathological Criteria

Criterion	Benign	Intermediate	Melanoma
Diameter (size)	< 4 mm	4 – 12 mm	> 5 mm >10mm
Symmetry	Symmetry	± Symmetry	Asymmetry
Circumscription	Sharp	Sharp to poor	Poor
Pagetoid melanocytosis	Usually none	± , focal	Often present
Architecture of nesting Confluence melanocytes	Regular nests	Often irregular ± Confluence	Irregular nesting
Cellularity	Low cellularity	Increasing cellularity	High cellularity
Maturation	Present	±	Absent
Mitoses	Usually absent	±	Often present
Cytological atypia	Usually none	Variable	Moderate - severe
Solar elastosis	Usually none	±	Often present
Host response	Usually absent	Increasing	Prominent

Histopathological Criteria

1. How many are needed?
2. What are the most important criteria?

Histopathological Criteria

1. Objective or quantifiable criteria are better than subjective (fuzzy) criteria
   - Size, diameter
   - Ulceration
   - Mitotic rate
   - Cellular and nuclear sizes

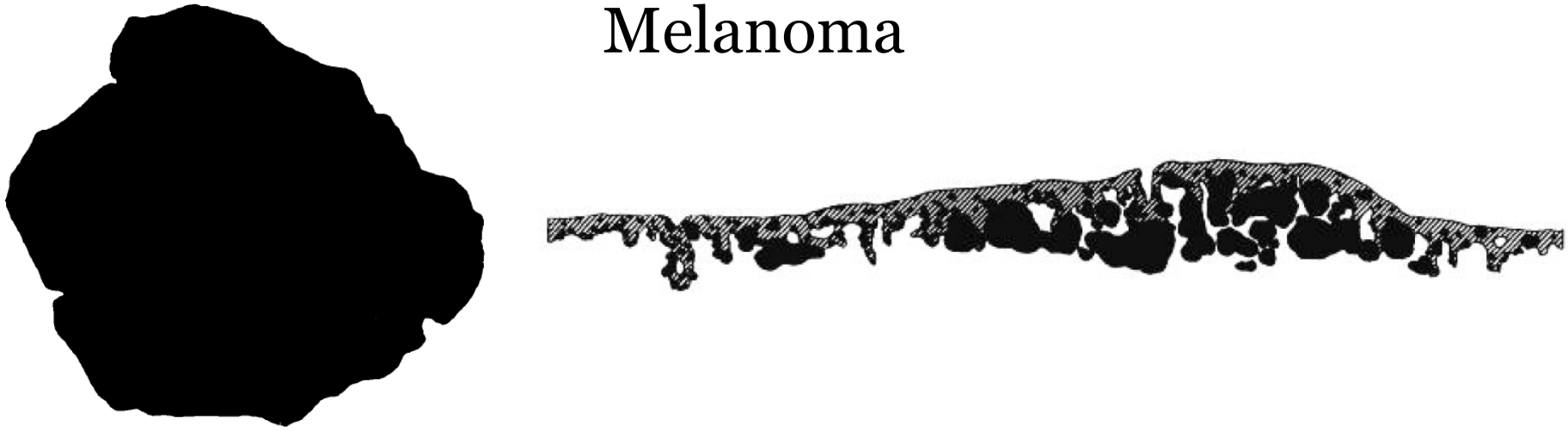
Histopathological Criteria

1. Architecture - Low/scanning magnification
2. Cytology – High magnification

Gross Morphology and Microscopic Silhouette at Low/Scanning Magnification Are Complementary

Architecture/Silhouette

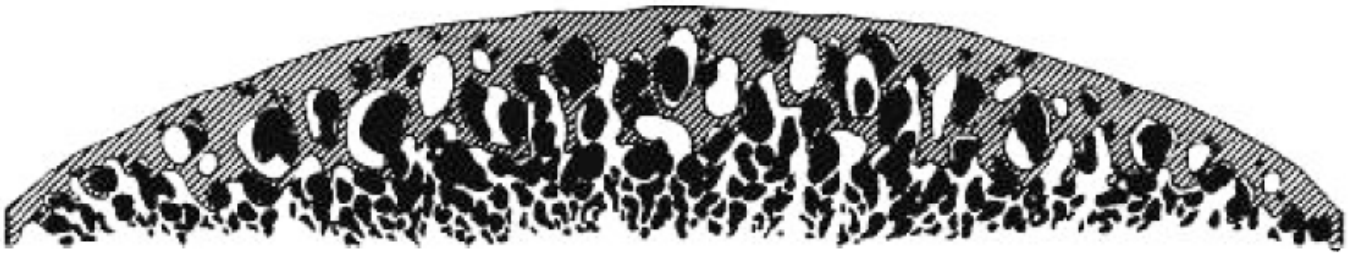
Melanoma



Accurate diagnosis in approximately

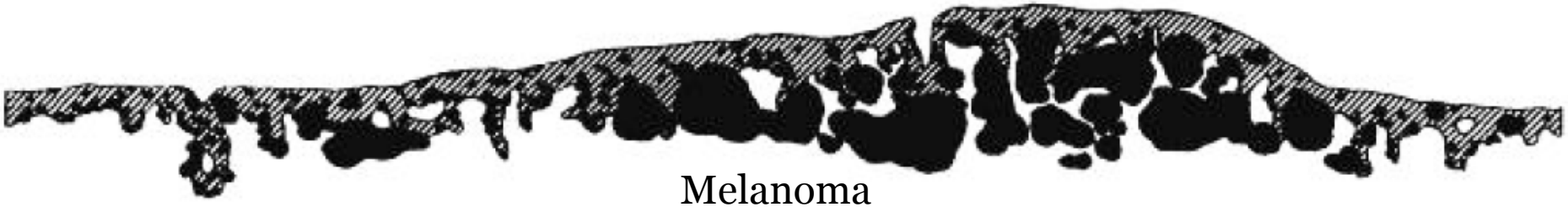
80 to 90% of melanomas

Evaluation of Microscopic Architecture by Silhouette



Benign nevus

Intermediate lesion



Melanoma

Ackerman AB Am J Dermatopathol 1989;11:297-300.

Evaluation of Microscopic Architecture by Silhouette

- Diameter (size)
- Breslow thickness
- Symmetry
- Circumscription
- Pagetoid melanocytosis
- Architecture of nesting
- Confluence of melanocytes
- Cellularity
- Maturation

Histopathological Criteria

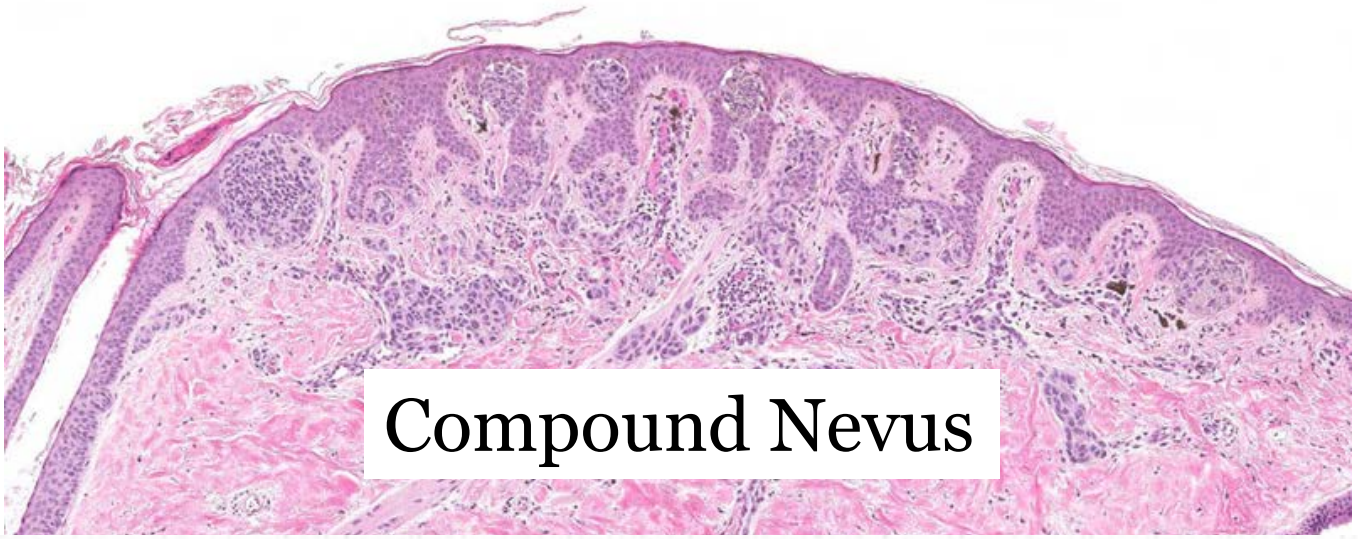
Criterion	Benign	Intermediate	Melanoma
Diameter	≤ 4 mm Common nevi	4 – 12 mm Dysplastic nevi	> 5 mm >10 mm

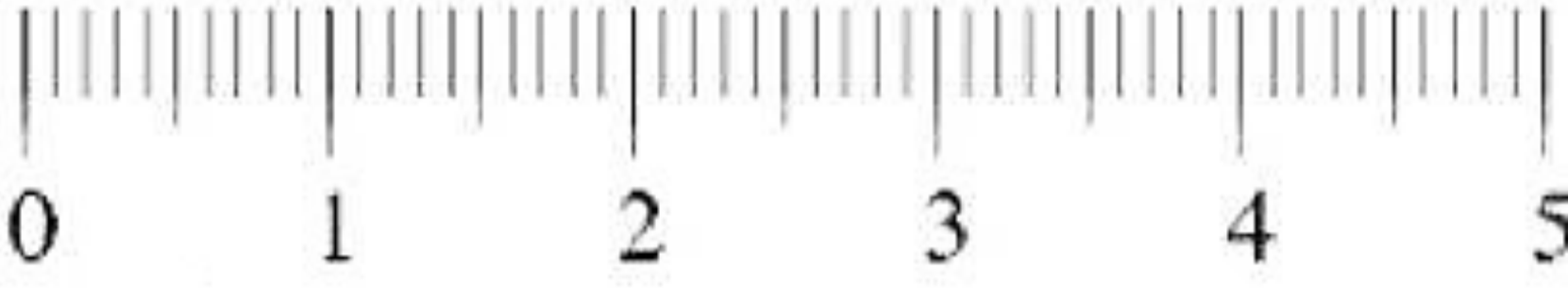
Diameter of Dysplastic Nevi Is a More Robust Biomarker of Increased Melanoma Risk Than Degree of Histologic Dysplasia: A Case-Control Study

Xiong MY, Rabkin MS, Piepkorn MW, Barnhill RL, Argenyi Z, Erickson L, Guitart J, Lowe L, Shea CR, Trotter MJ, Lew RA, Weinstock MA. J Am Acad Dermatol. 2014 Dec;71(6):1257-1258.e4.

Diameter

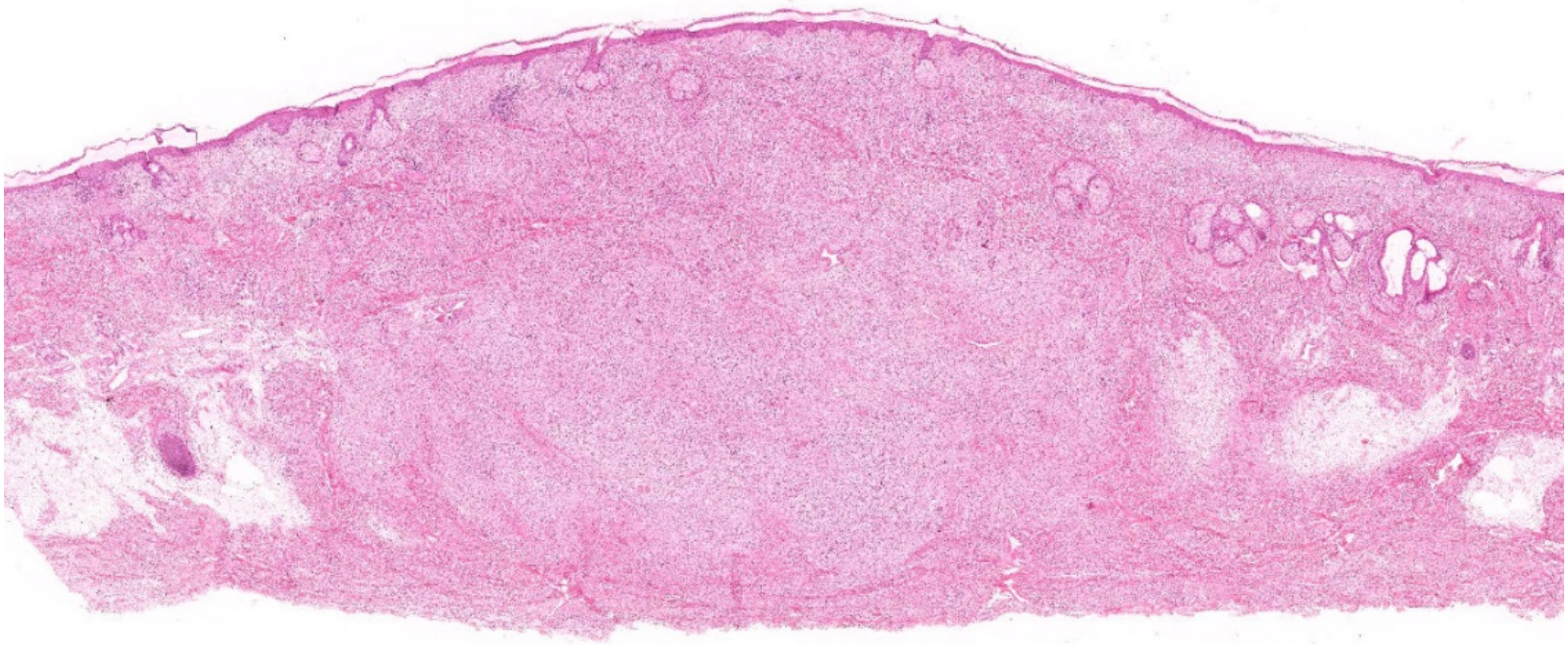
Diameter - 3 mm





Diameter

Diameter - 2 cm



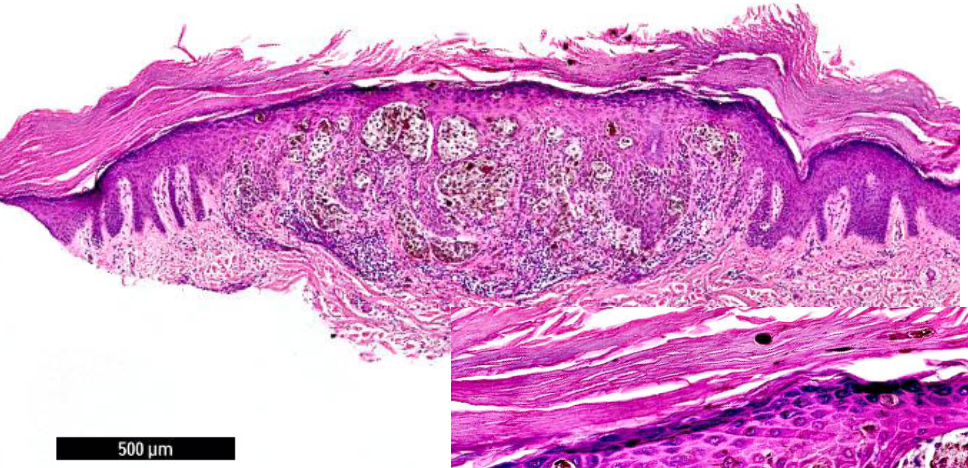
Desmoplastic Melanoma

Diameter

Exceptions

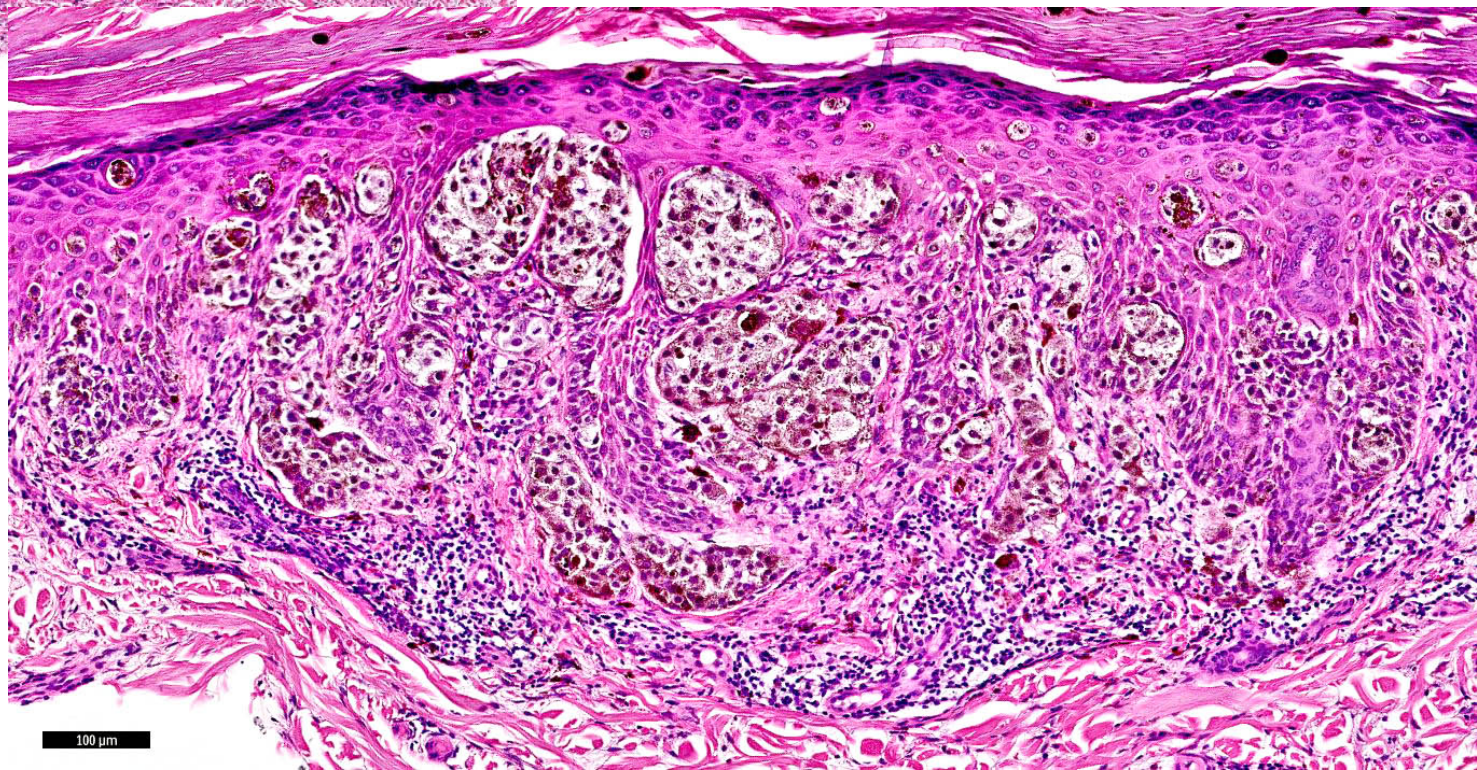
Lesions with Uncertainty

Diameter



Acral Melanoma

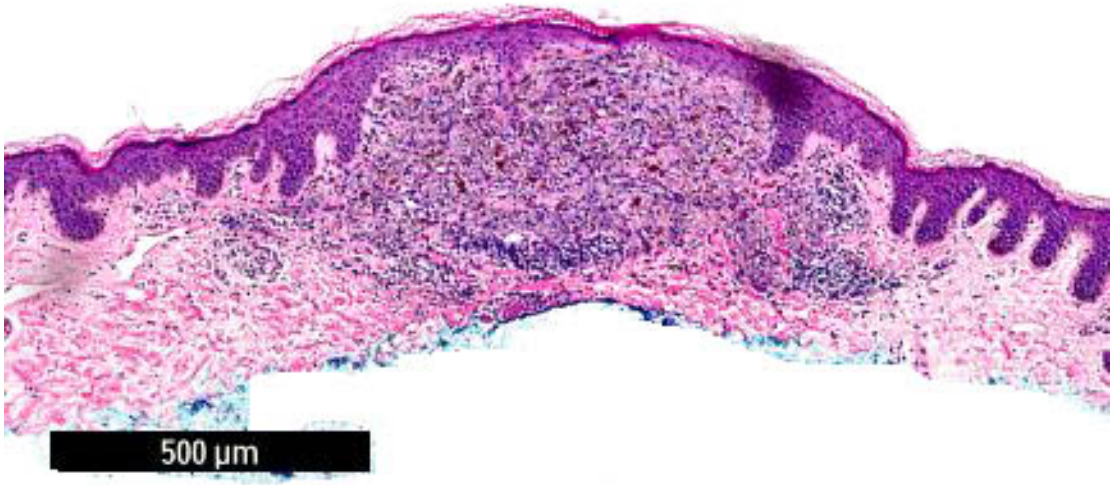
Diameter = 2 mm



Diameter

Metastatic Melanoma !

Diameter < 4 mm



Clinical History!

Histopathological Criteria

Criterion	Benign	Intermediate	Melanoma
Breslow thickness	Not applicable	Useful metric for dermal neoplasm	Prognostic factor Guides therapy

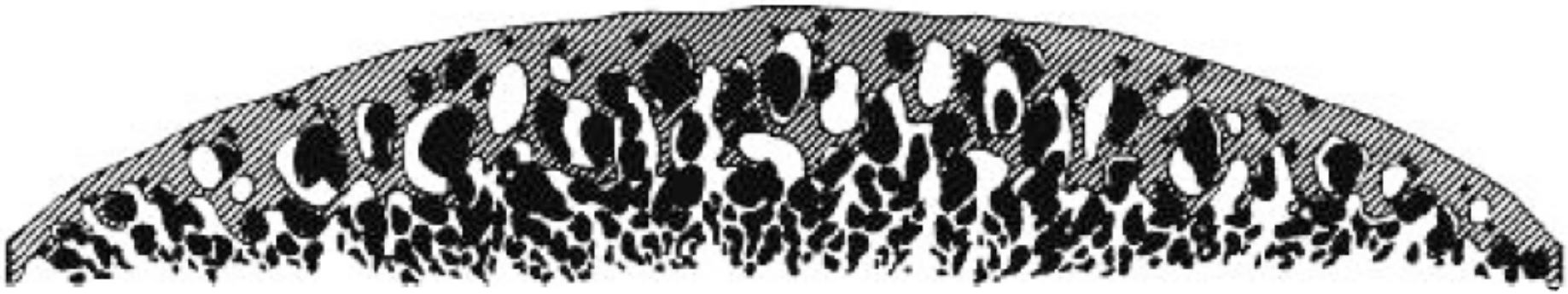
Histopathological Criteria*

Criterion	Benign	Intermediate	Melanoma
Symmetry ➢ Silhouette • Epidermal contour • Melanocytes • Melanin • Host response	Symmetry	Symmetry or asymmetry	Asymmetry

Mirror Image Symmetry

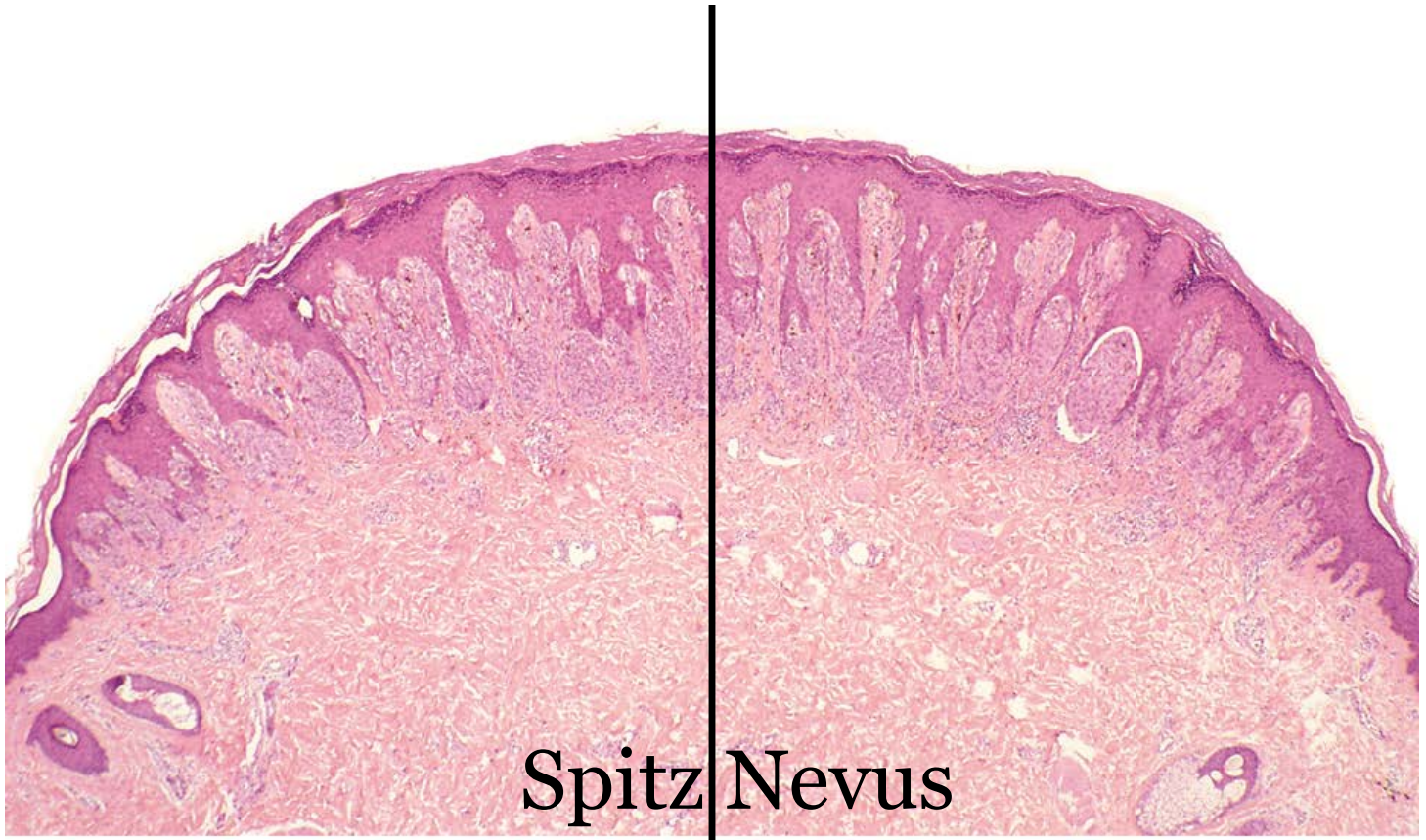
- Overall silhouette
- ? Biphasic silhouette
- Detailed comparison of individual elements
    - ✓ Melanocytes
    - ✓ Melanin
    - ✓ Host response
    - ✓ Epidermal contour

Symmetry



Spitz Nevus

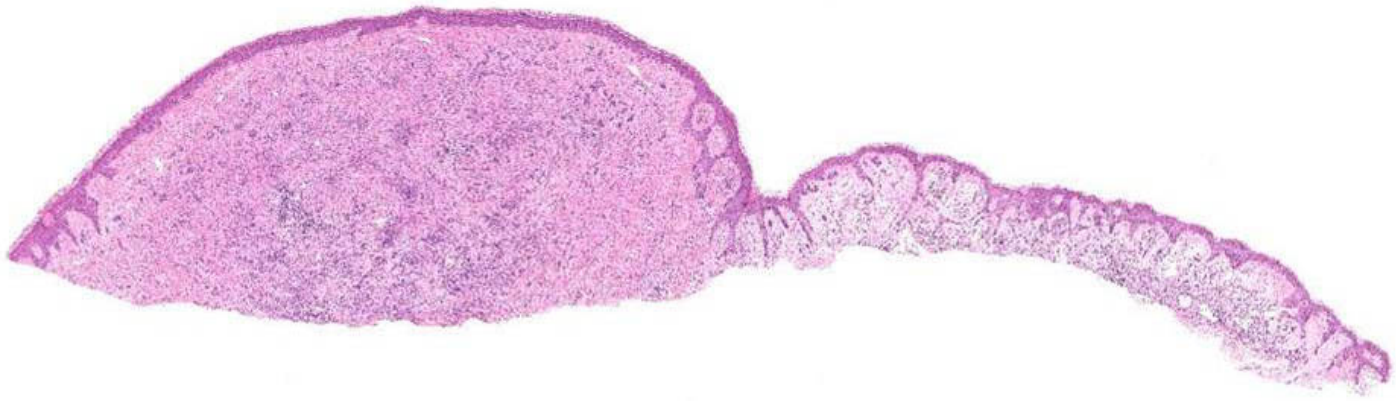
Mirror Image Symmetry

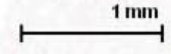


Asymmetry

The Biphasic Lesion

Two distinct components

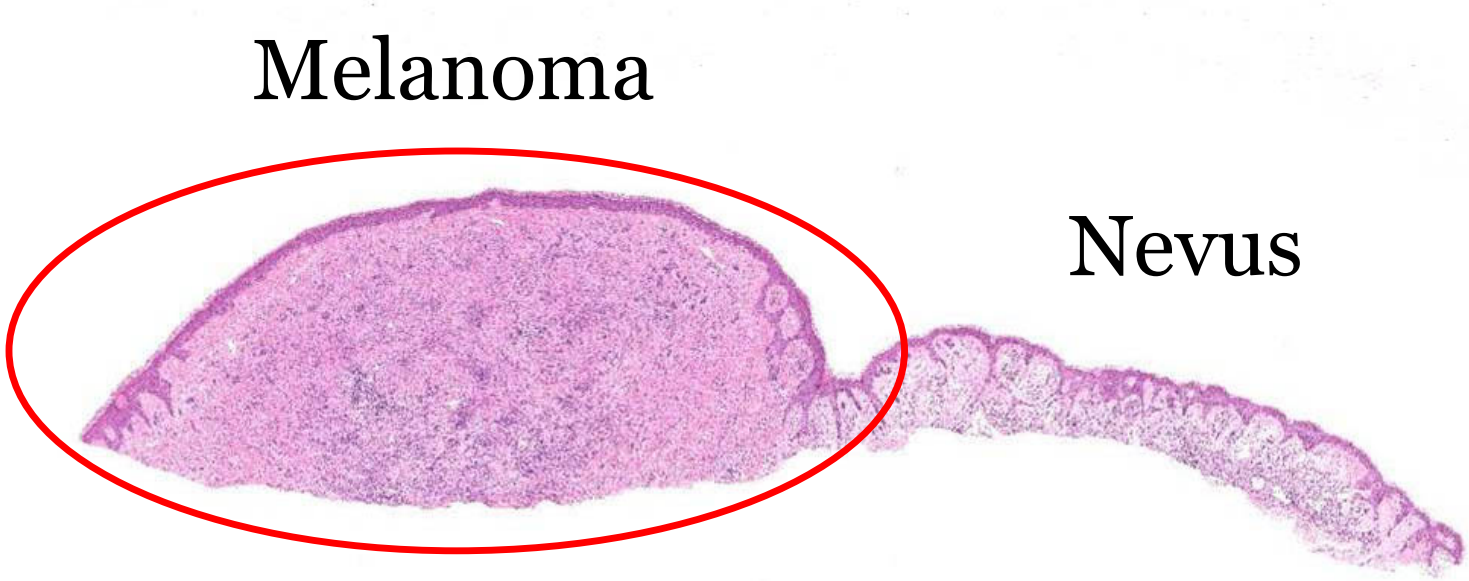




Asymmetry

The Biphasic Lesion

Marker of Neoplastic Progression

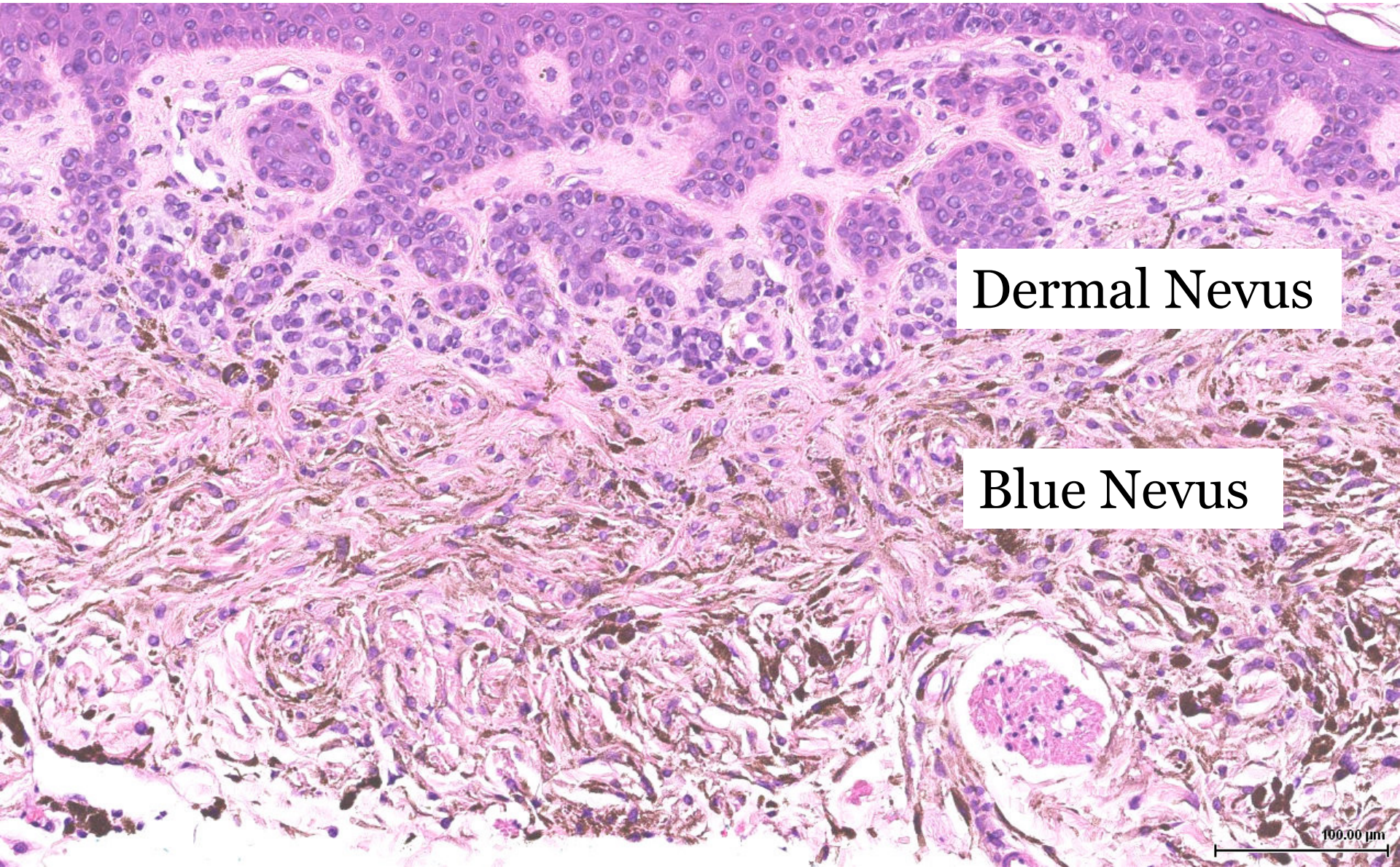


Biphasic Melanocytic Lesions

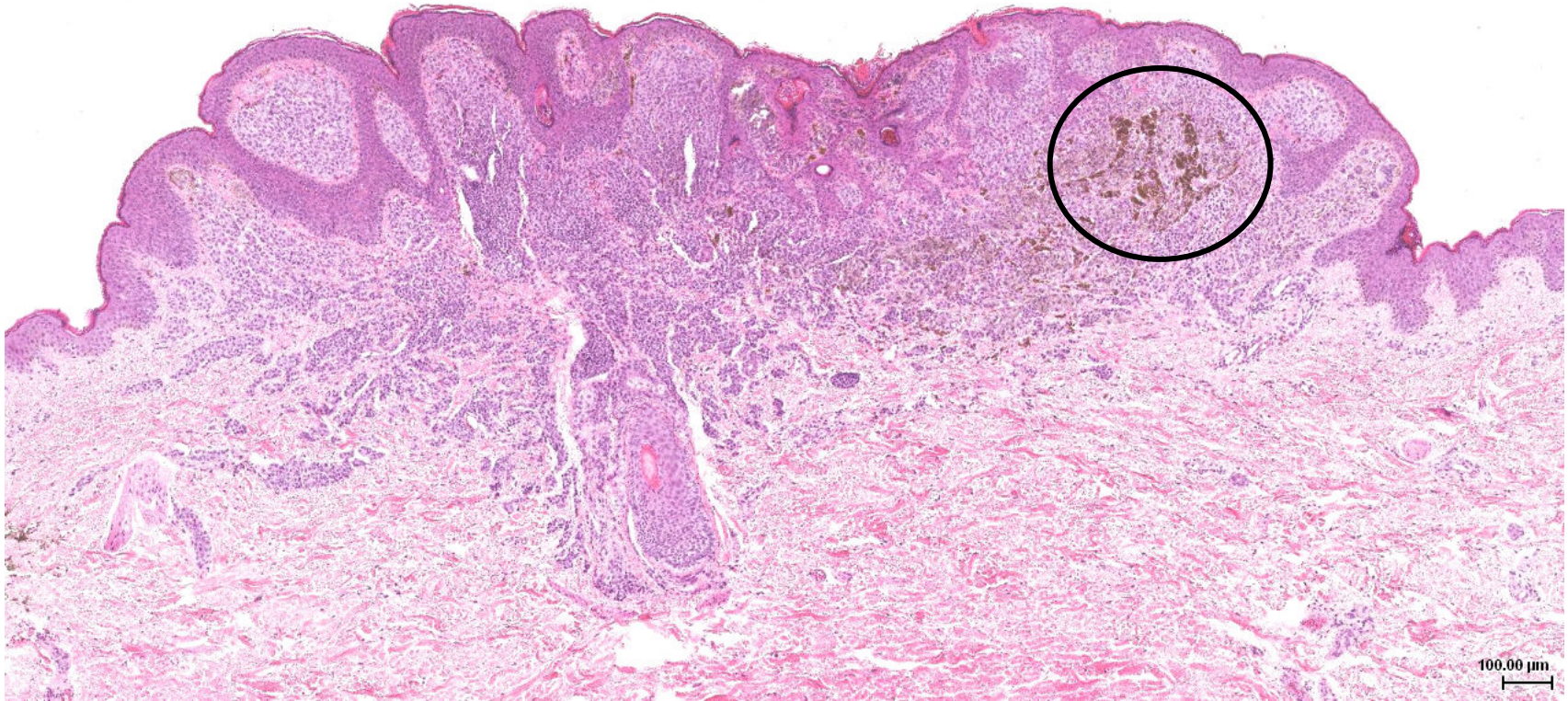
Two distinct components

Benign	Intermediate	Malignant
• Combined nevus • ? Malignant transformation	• Benign + ✓Atypical ✓Uncertain ✓Malignant transformation	• Conventional radial + ✓vertical growth phases ✓Clonal progression

Benign Biphasic Lesion: Combined Nevus



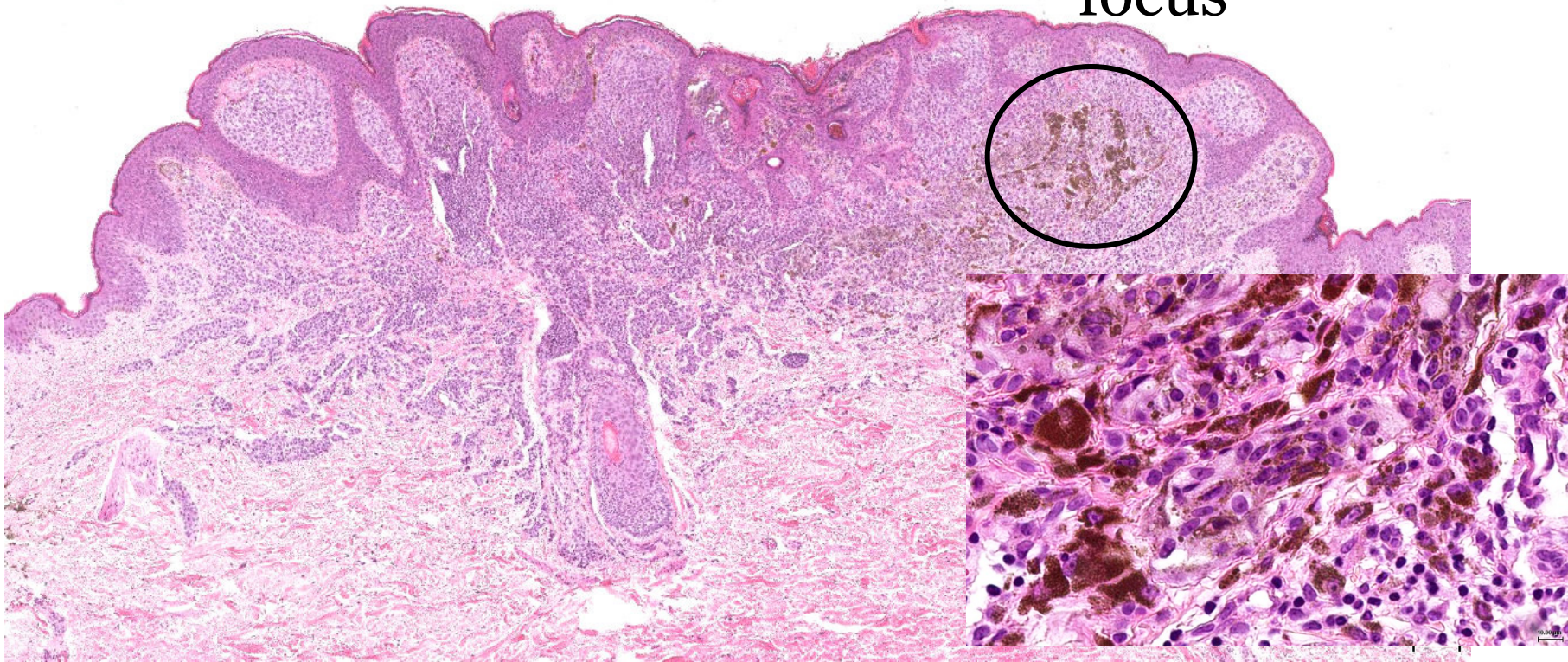
Atypical Biphasic Lesion: Combined Nevus or Neoplastic Progression?



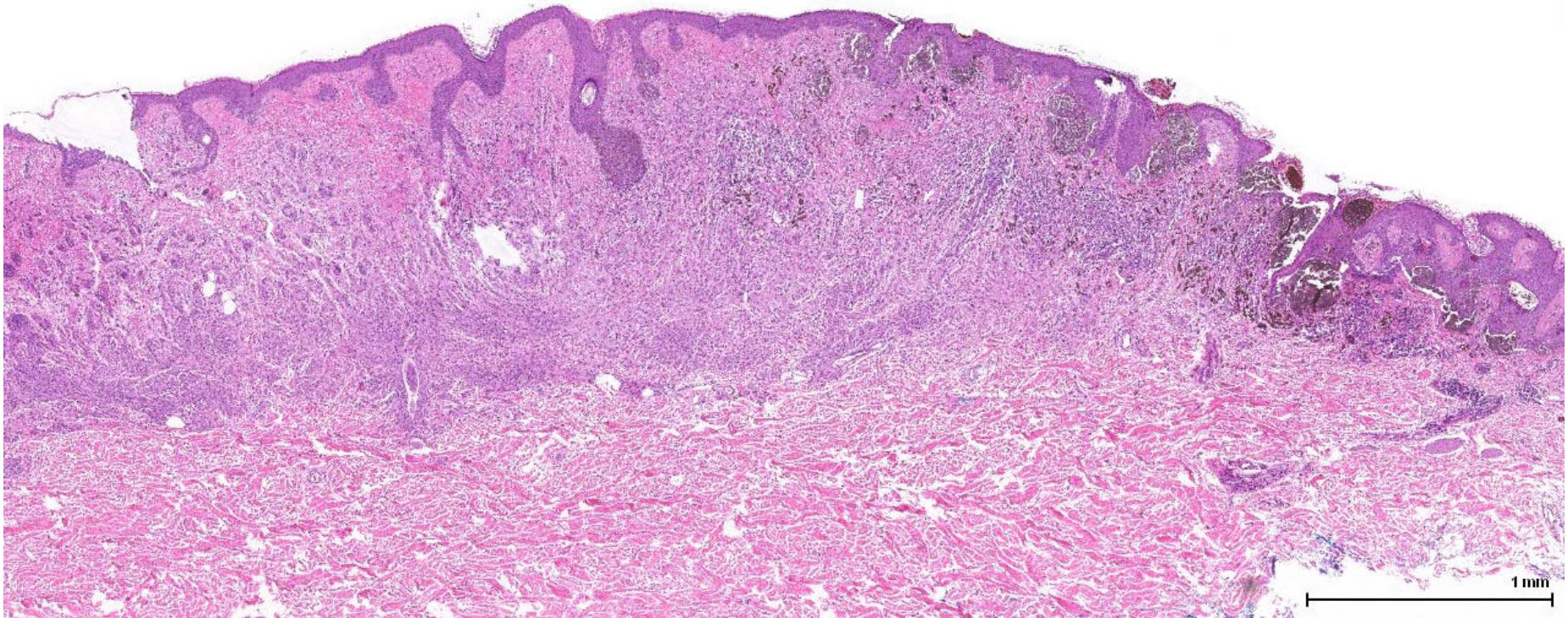
Atypical Biphasic Lesion: Combined Nevus or Neoplastic Progression?

Nevus

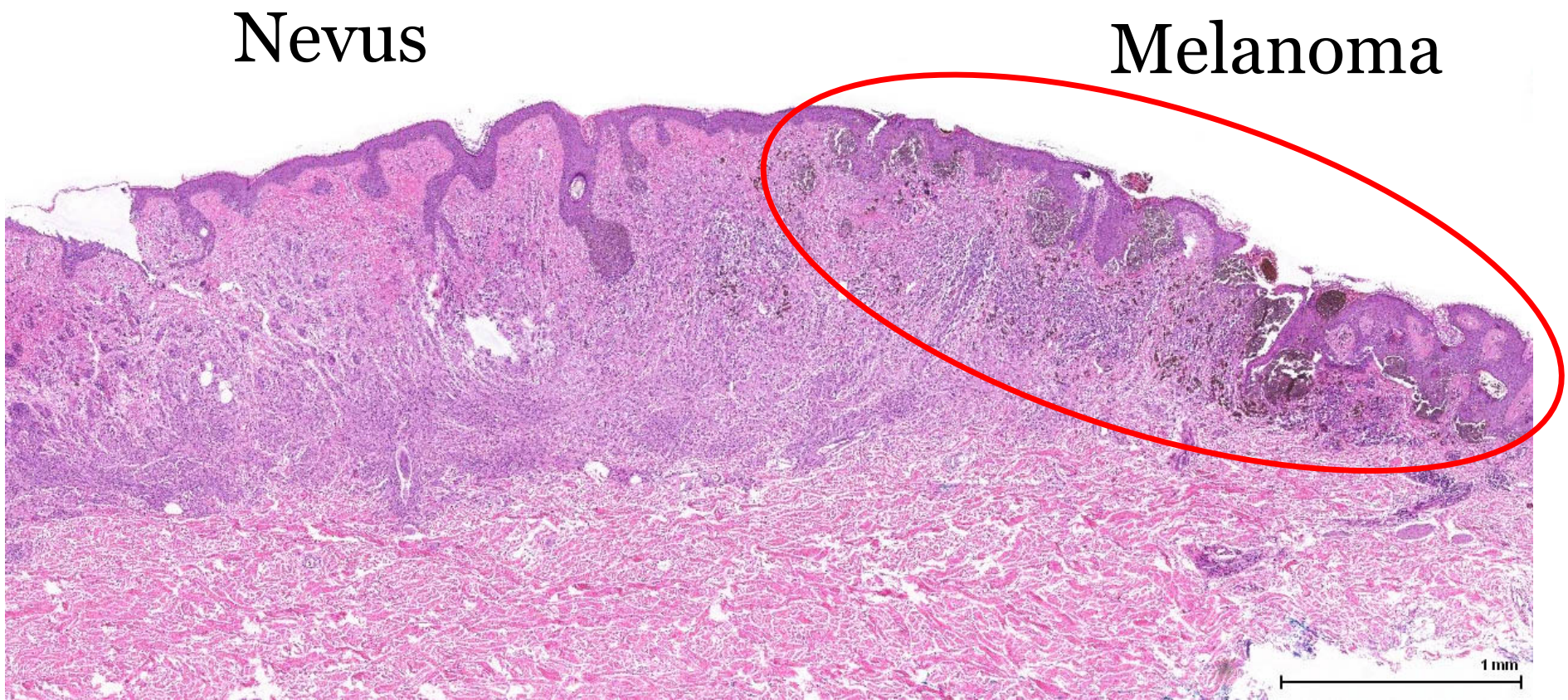
Pigmented spindle/epithelioid cell focus



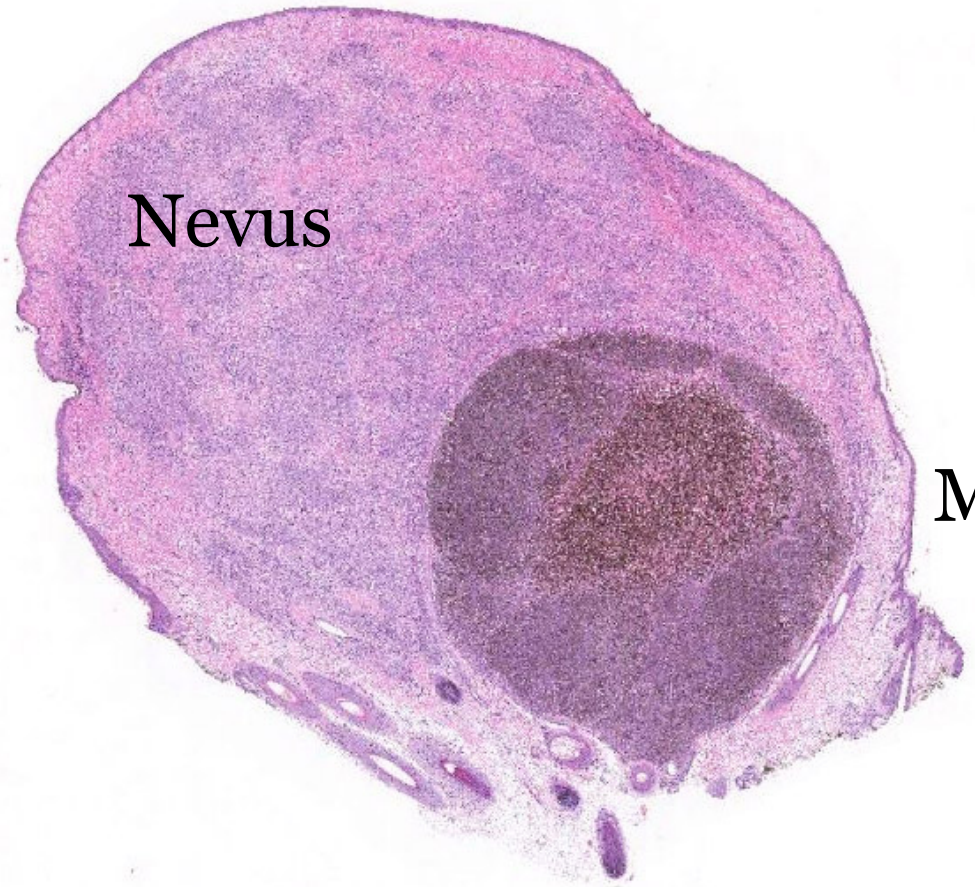
Atypical Biphasic Lesion: Nevus and Melanoma



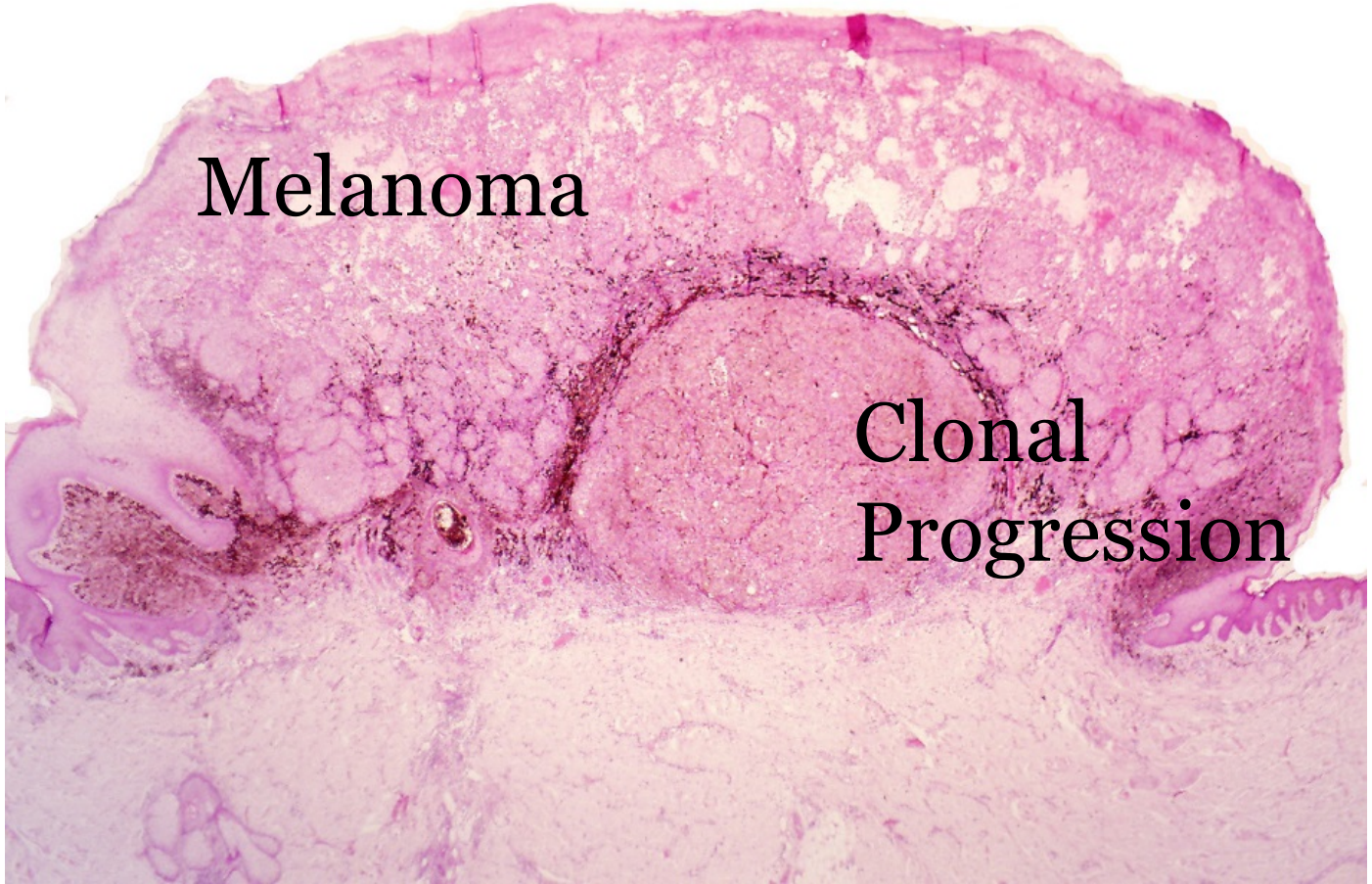
Atypical Biphasic Lesion: Nevus and Melanoma



Atypical Biphasic Lesion: Nevus and Melanoma



Malignant Biphasic Lesion: Melanoma with Clonal Progression



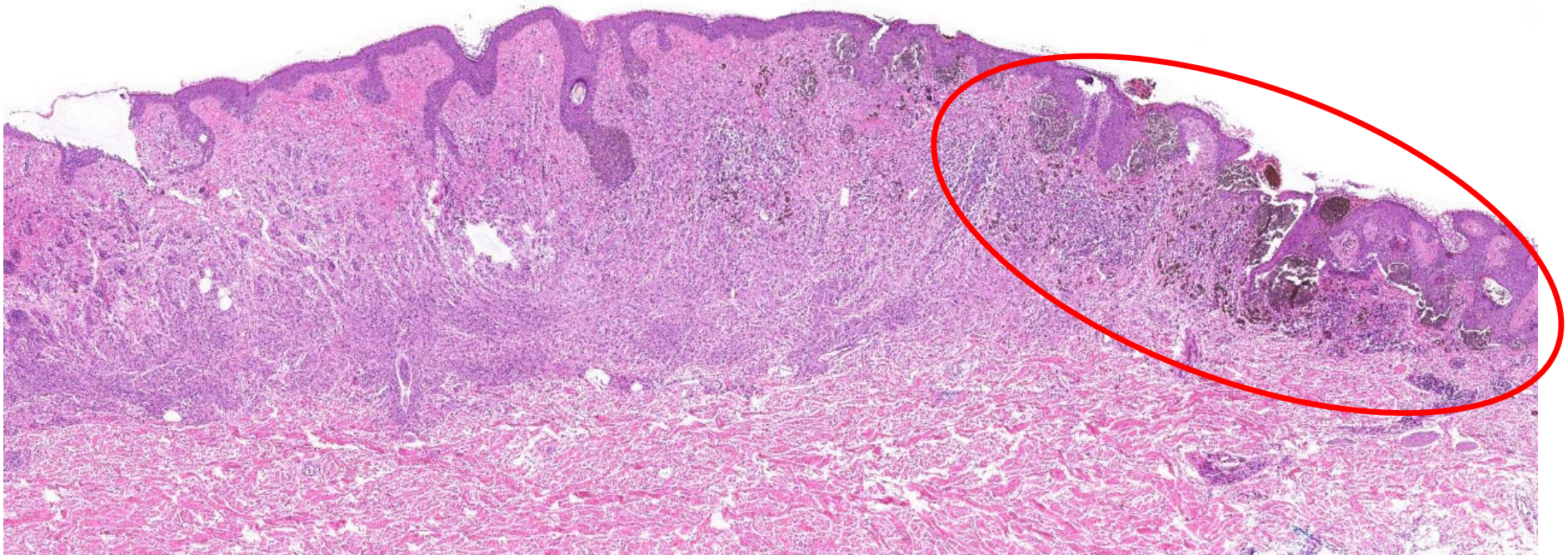
Asymmetry:
Individual Elements

- Melanocytes
  - Density
  - Pattern of distribution, e.g.
    - ✓ Junctional vs pagetoid
    - ✓ Single cells vs nests
  - Cytological features
- Melanin
- Host response

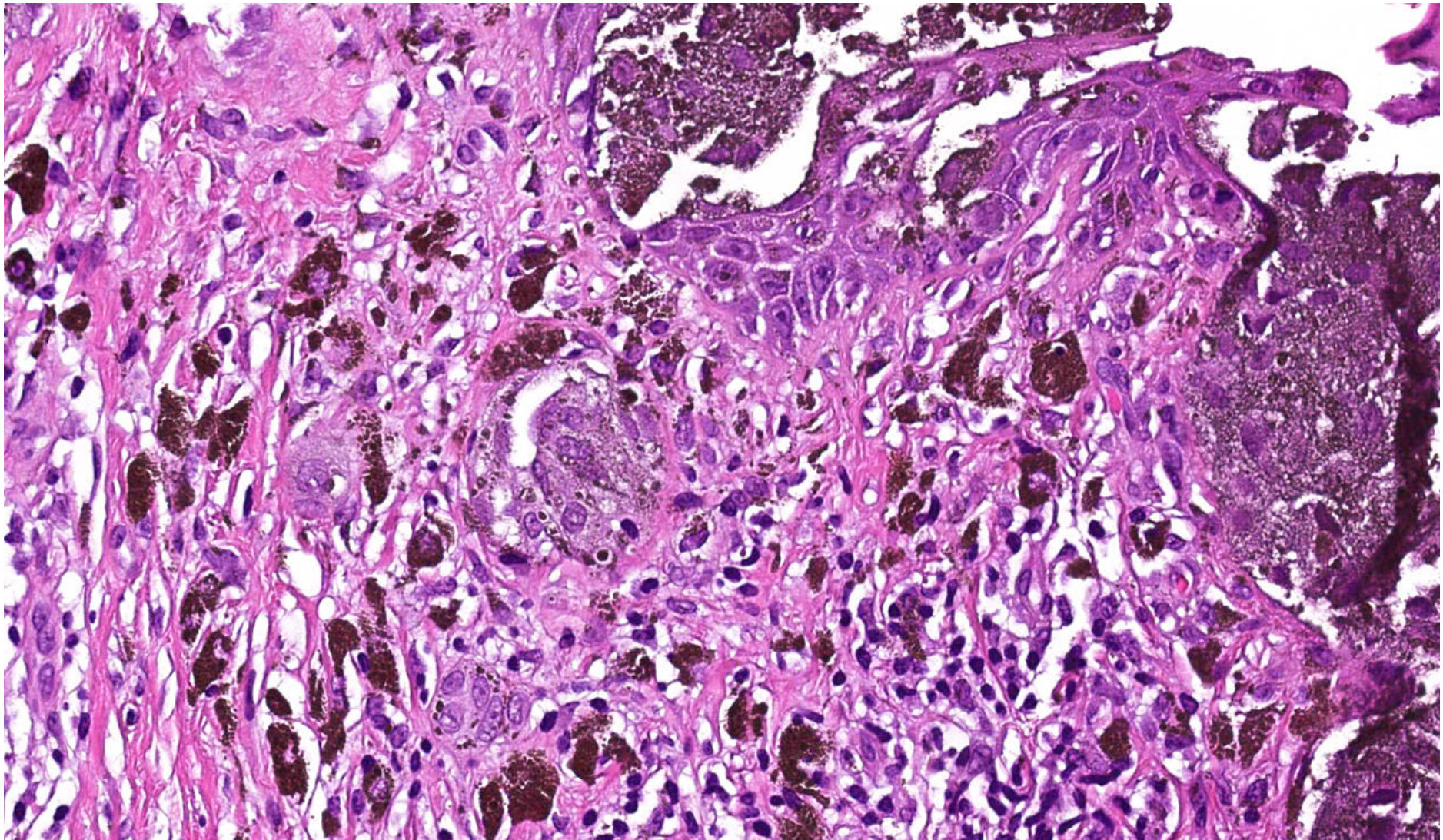
Atypical Biphasic Lesion:
Nevus and Melanoma

Nevus

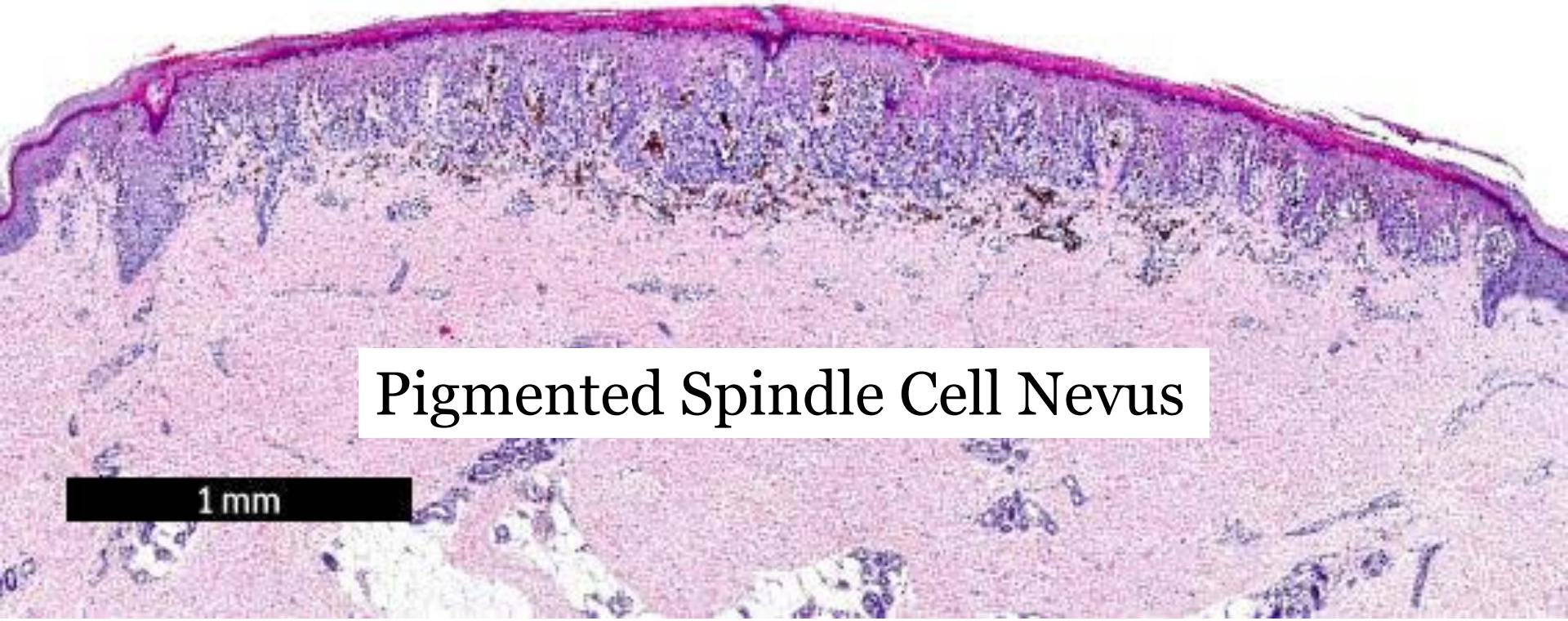
Melanoma



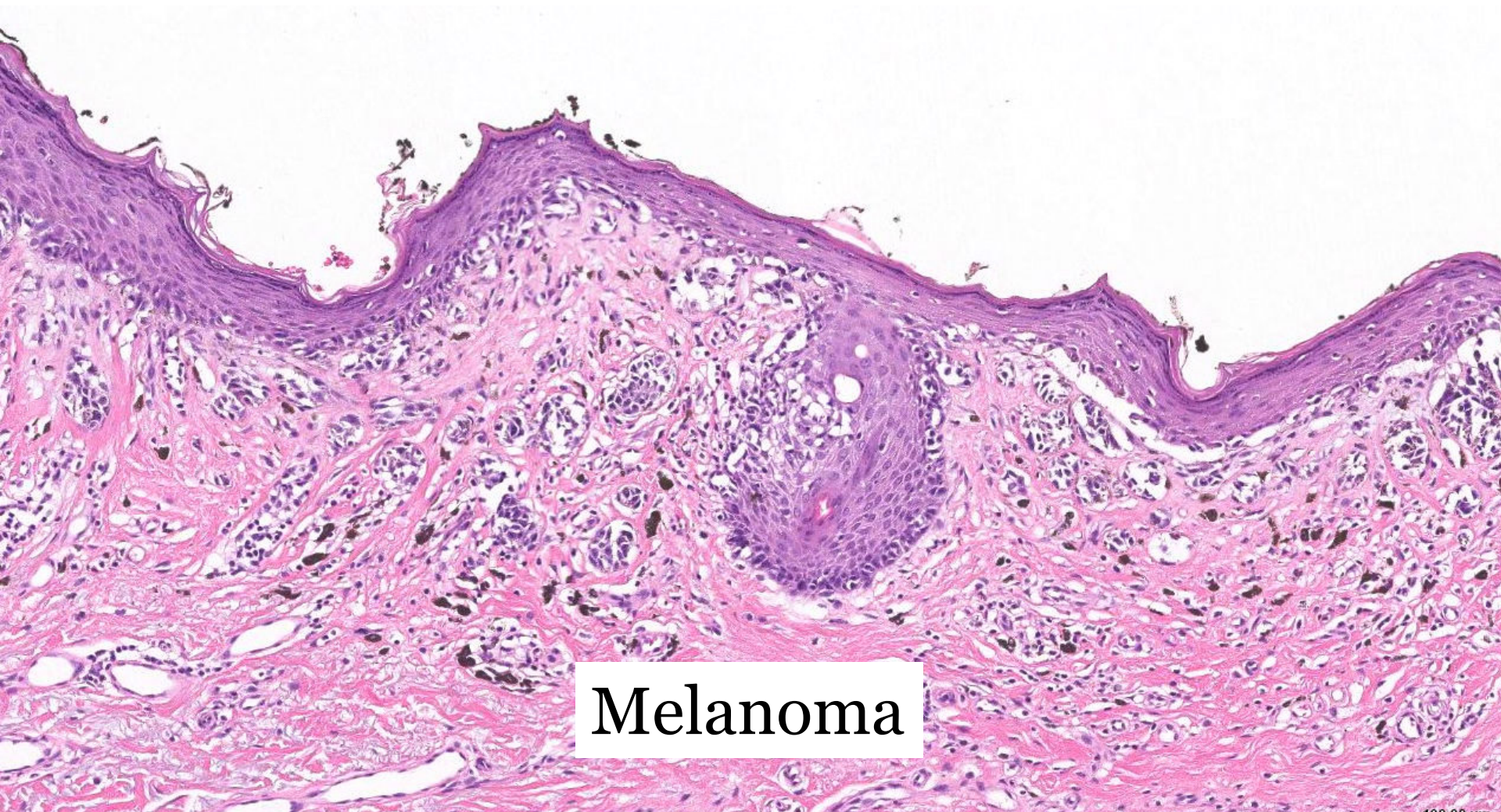
Asymmetry:
Individual Elements



Epidermal Contour
Uniform

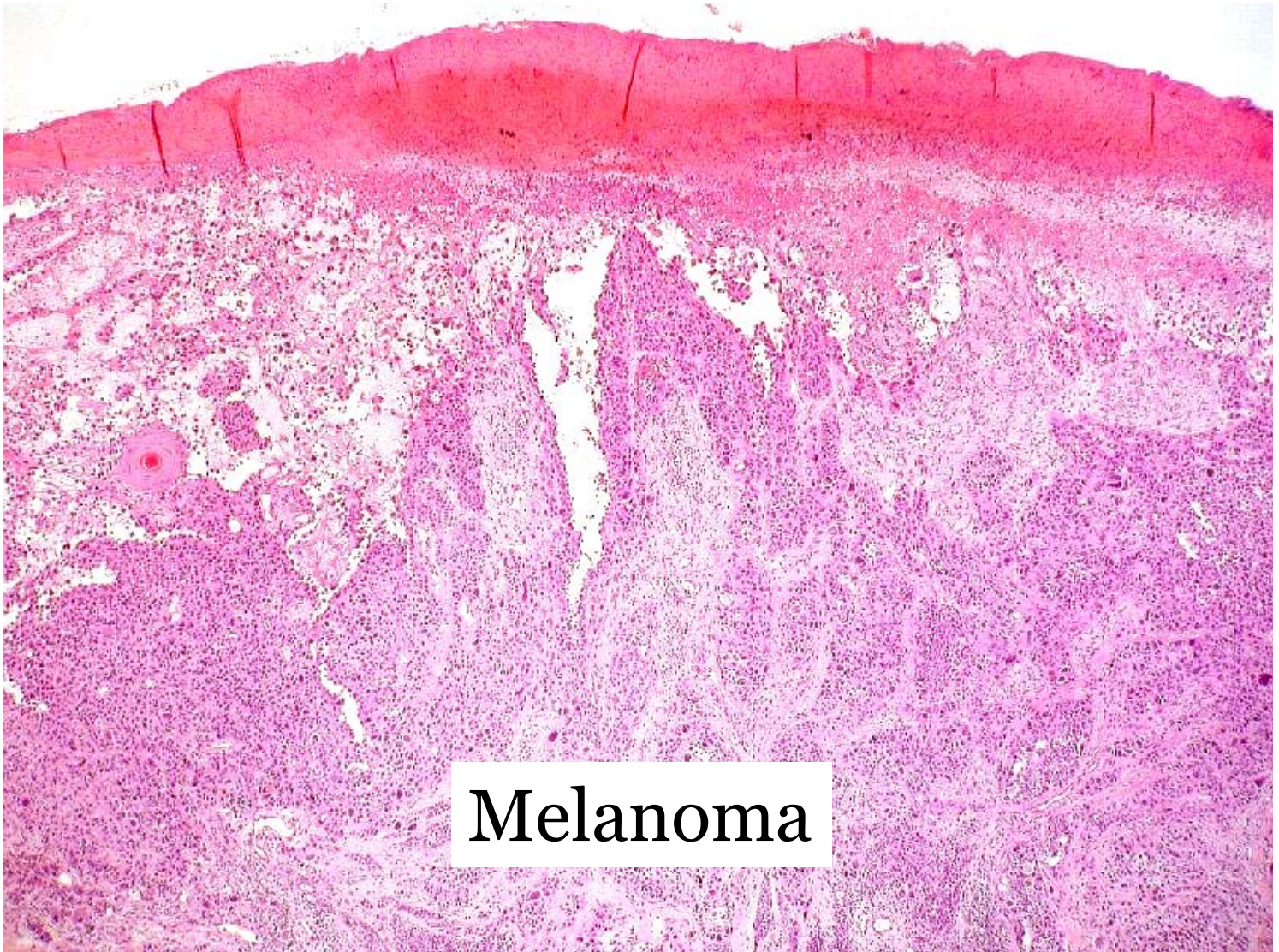


Epidermal Contour
Effacement



Epidermal Contour

Ulceration



Symmetry

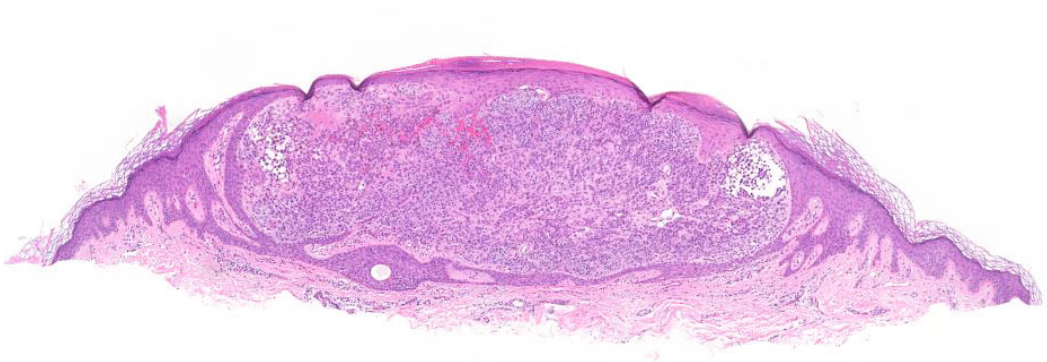
Exceptions

Lesions with Uncertainty

Symmetry

Nevoid Melanoma
Metastatic Melanoma!

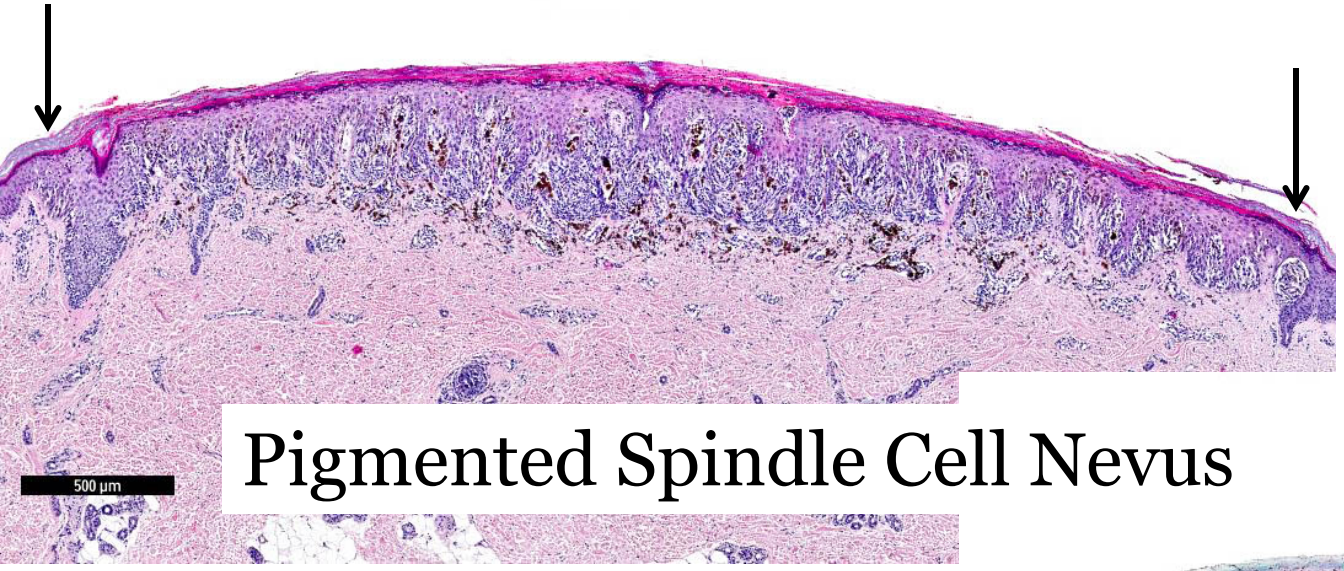
- Size < 4 mm
- Well-circumscribed
- Symmetrical
- No pagetoid scatter
- Nevoid



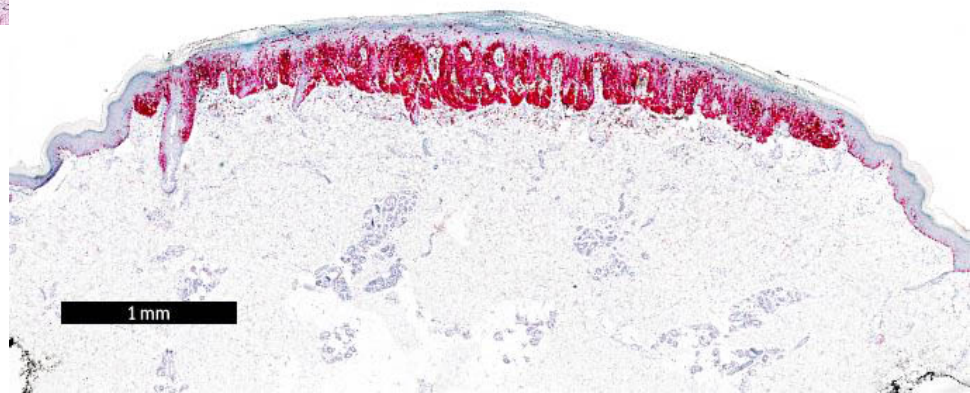
Histopathological Criteria

Criterion	Benign	Intermediate	Melanoma
Circumscription	Sharp borders Nests at periphery	Sharp to poor Dysplastic nevi	Poor Single cells

Sharp Circumscription



Pigmented Spindle Cell Nevus

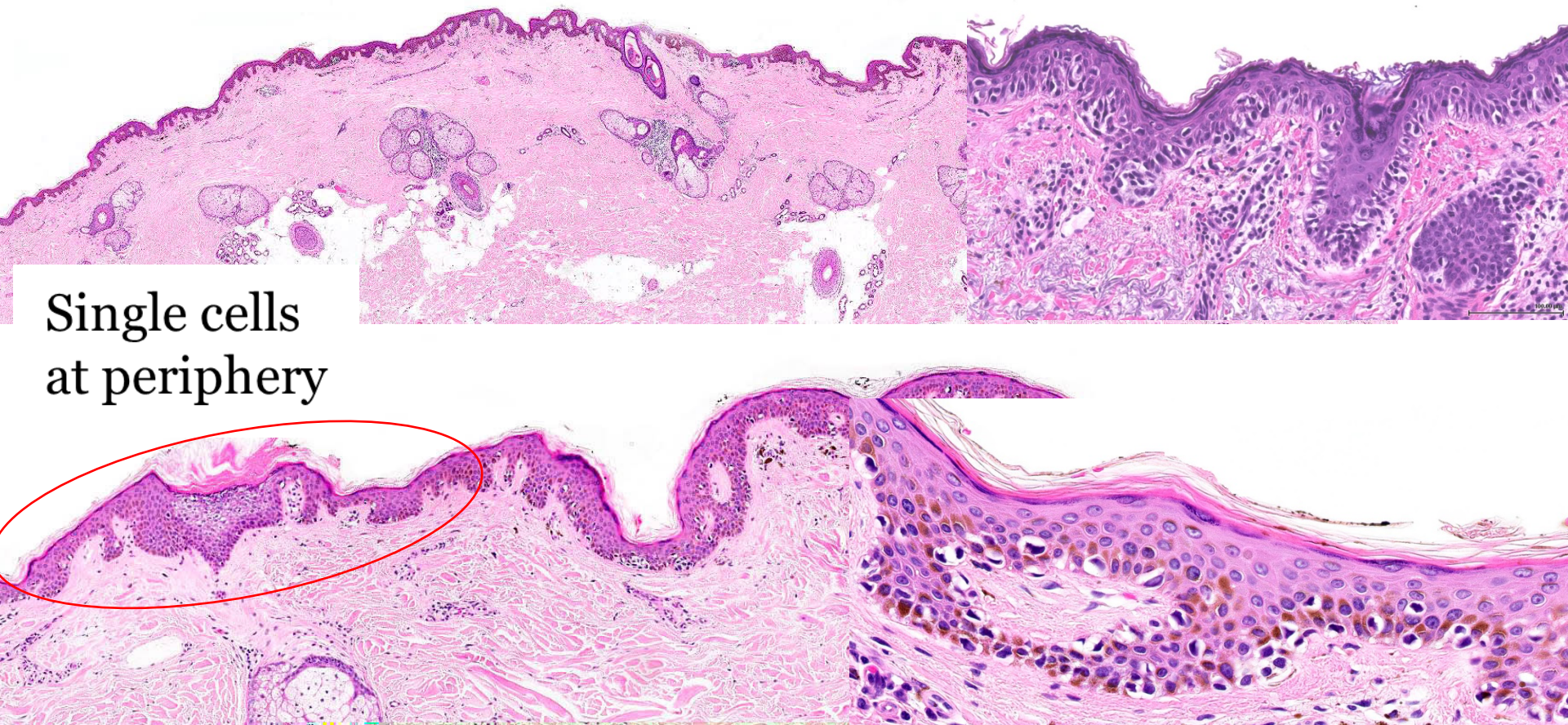


Poor Circumscription

Melanoma

Poor Circumscription

Lentiginous Melanoma in Situ



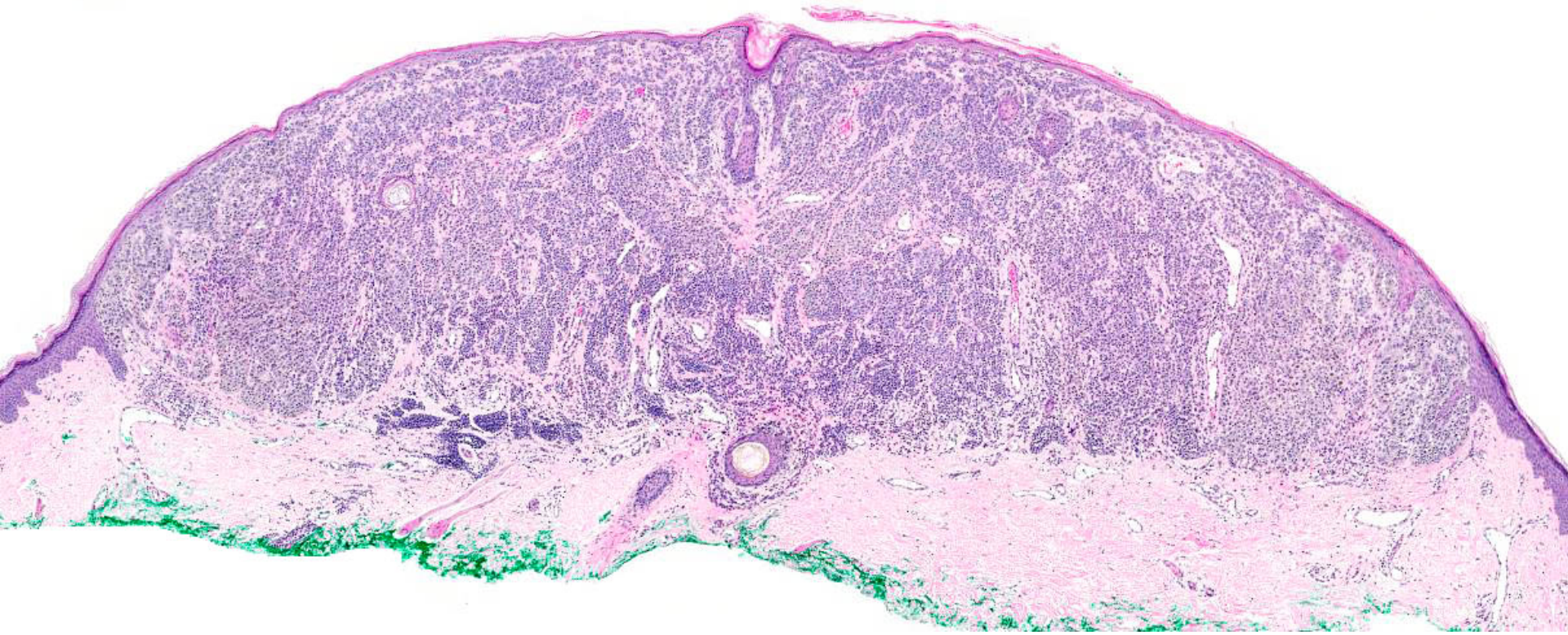
Circumscription

Exceptions

Lesions with Uncertainty

Sharp Circumscription

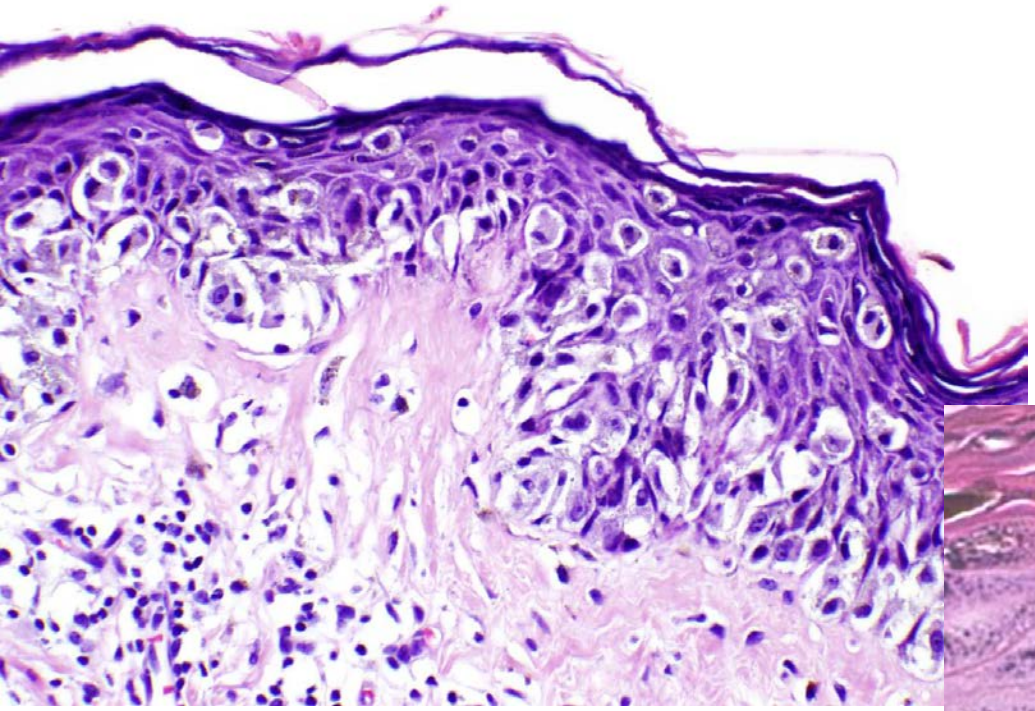
Nevoid Melanoma !



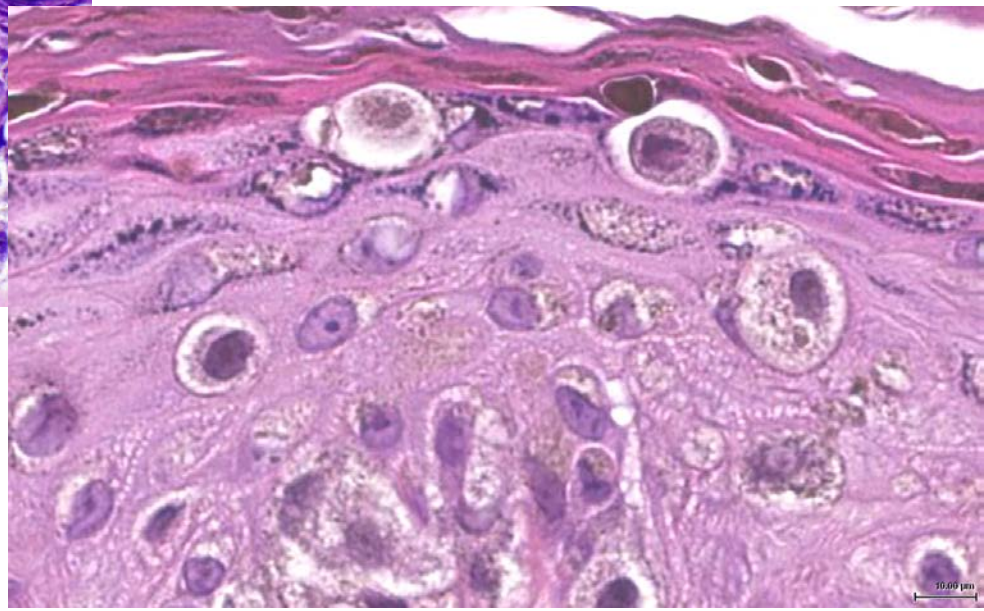
Histopathological Criteria

Criterion	Benign	Intermediate	Melanoma
Pagetoid melanocytosis	Usually absent	Absent Focal	Usually present At least 1 HPF

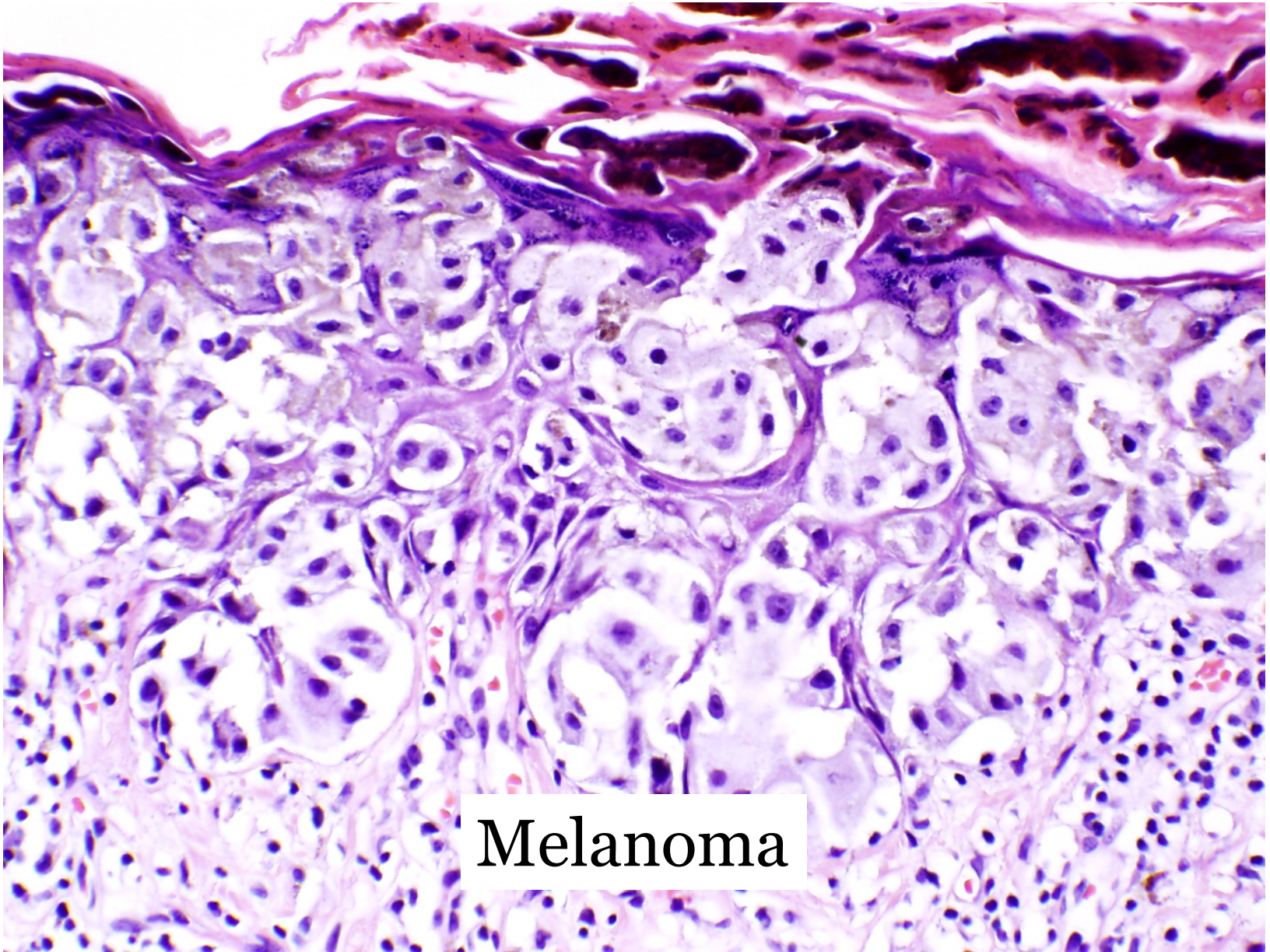
Pagetoid Melanocytosis



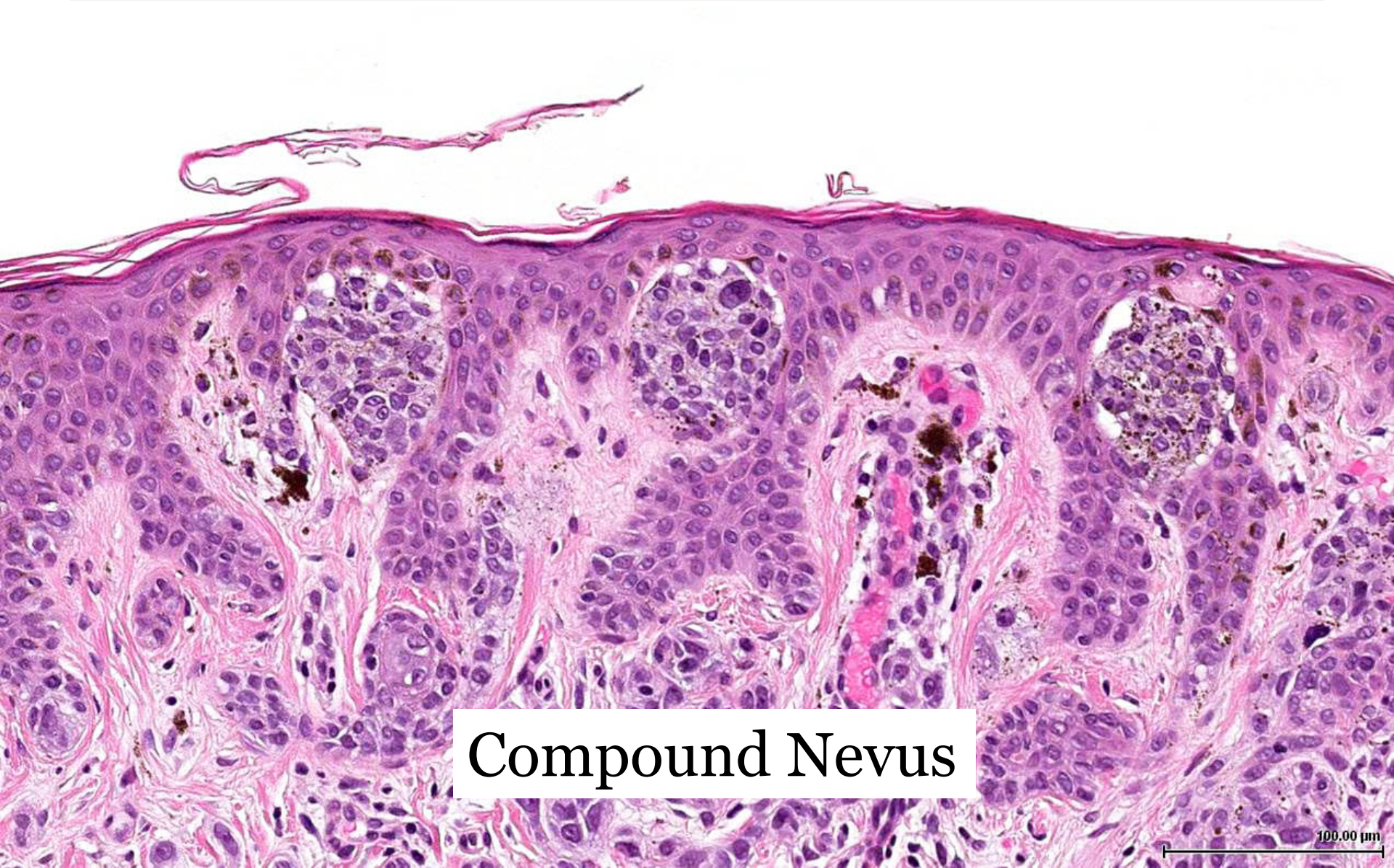
Melanoma



Pagetoid Melanocytosis



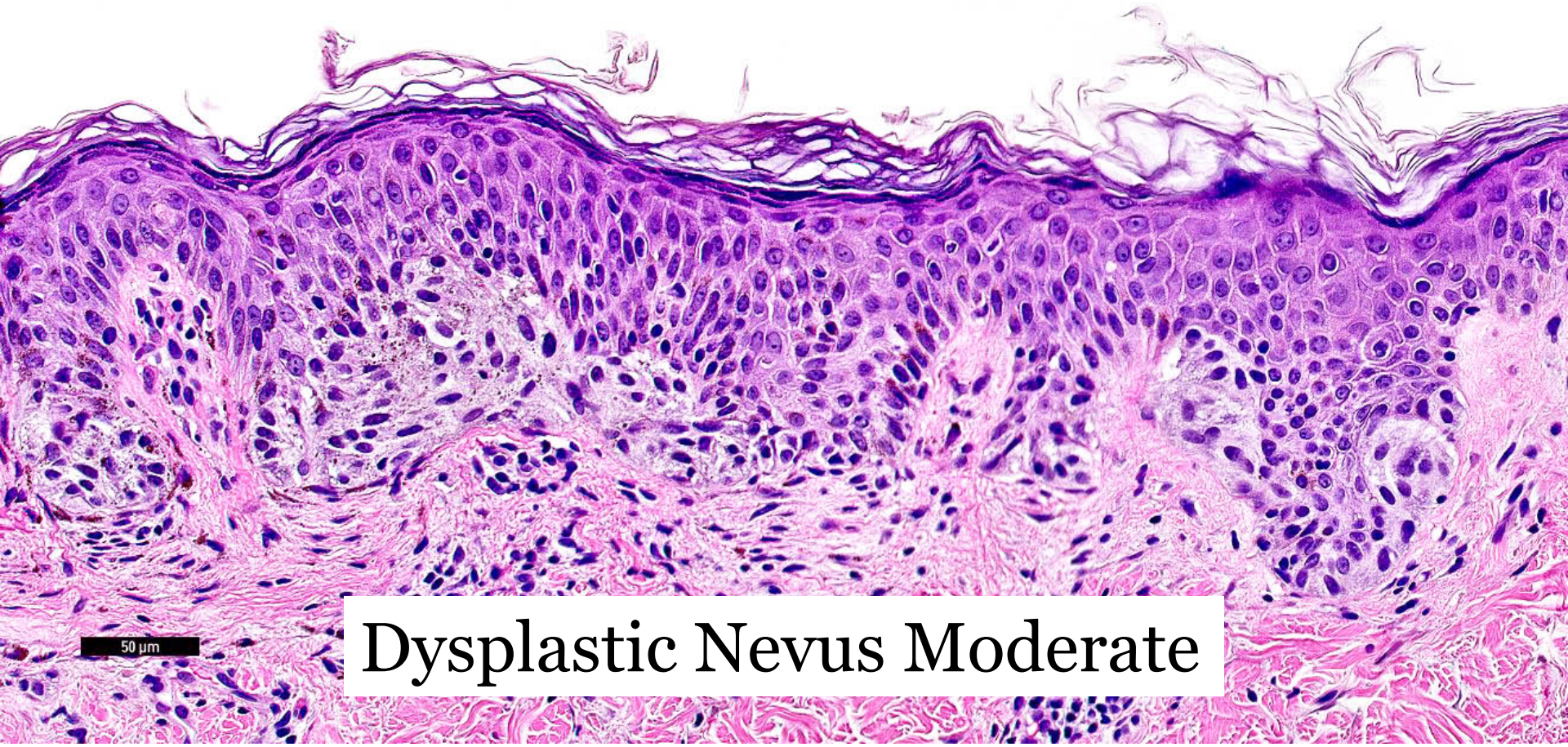
No Pagetoid Melanocytosis



Pagetoid Melanocytosis

Intermediate Lesions

No Pagetoid Melanocytosis



Dysplastic Nevus Moderate

Pagetoid Melanocytosis

Exceptions

Lesions with Uncertainty

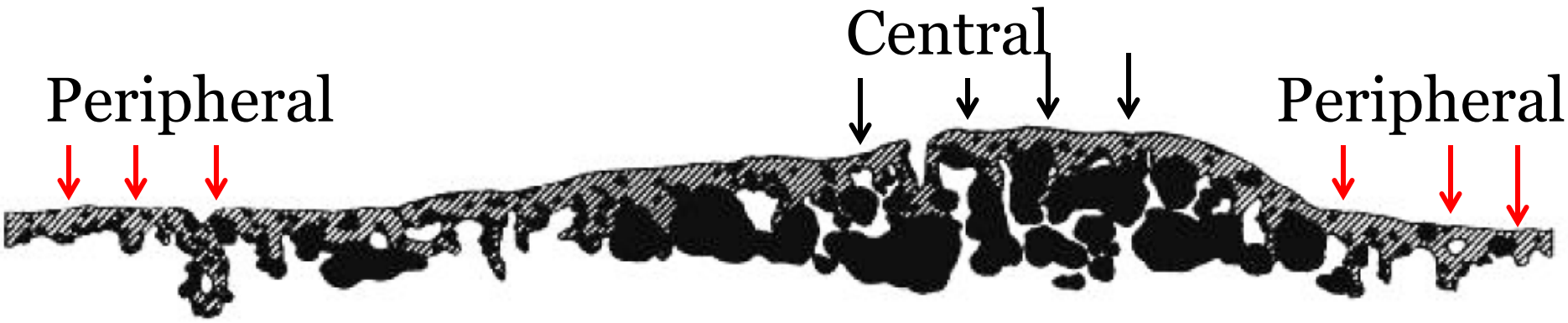
Pagetoid Melanocytosis

- Congenital nevi
- Spitz tumors
  - Pagetoid Spitz nevi
- Pigmented spindle cell nevi
- Acral nevi
- Other special site nevi: vulva
- Nevi with trauma, UV exposure
- Recurrent nevi

Pagetoid Melanocytosis

Criterion	Nevi	Melanoma
Distribution	Focal	Diffuse
Central vs peripheral	Central	Central, peripheral
Density	Sparse	Dense
Level	Suprabasal to mid epidermis	Full thickness
Atypia	Absent or low-grade	Significant

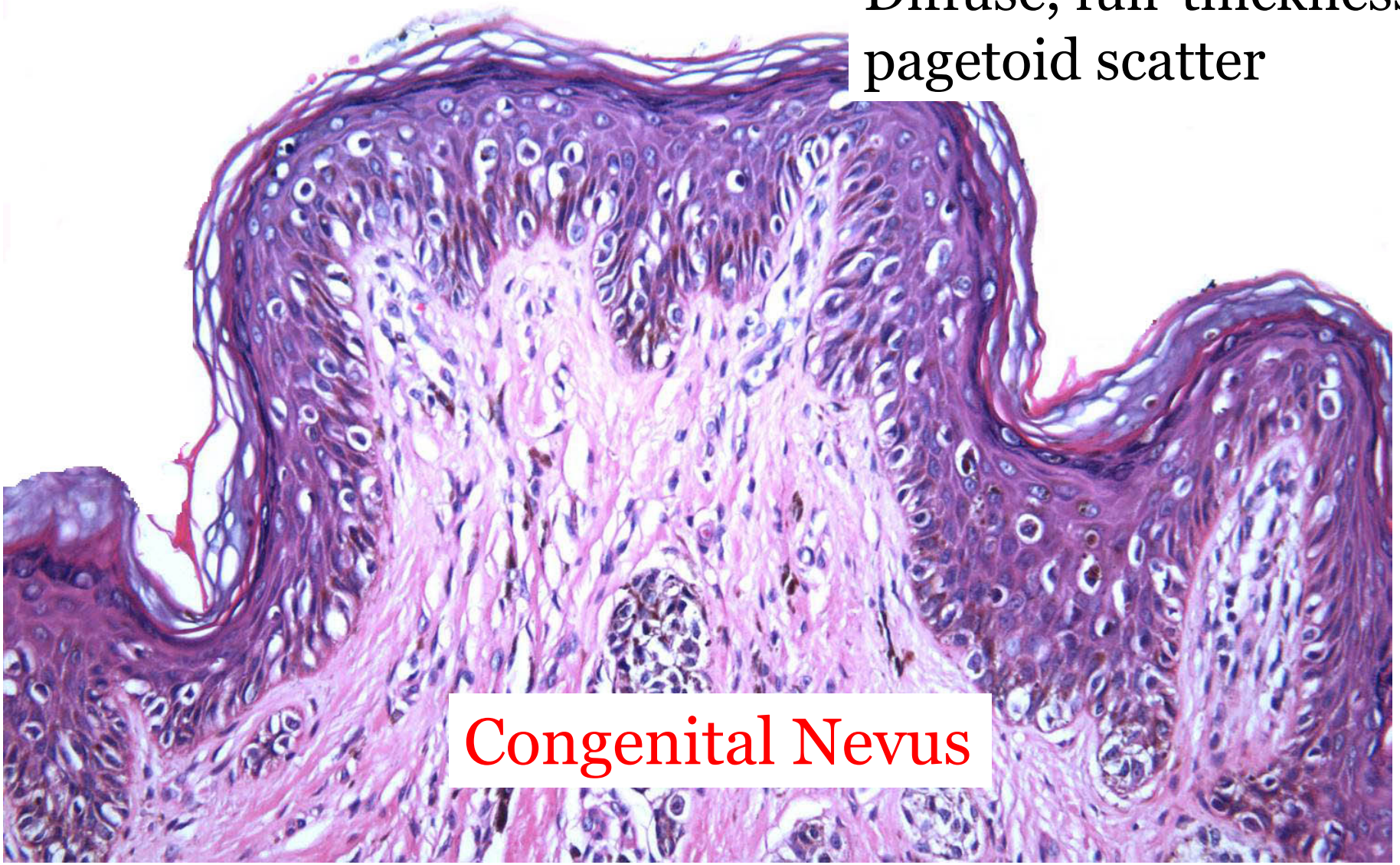
Pagetoid Melanocytosis



Melanoma

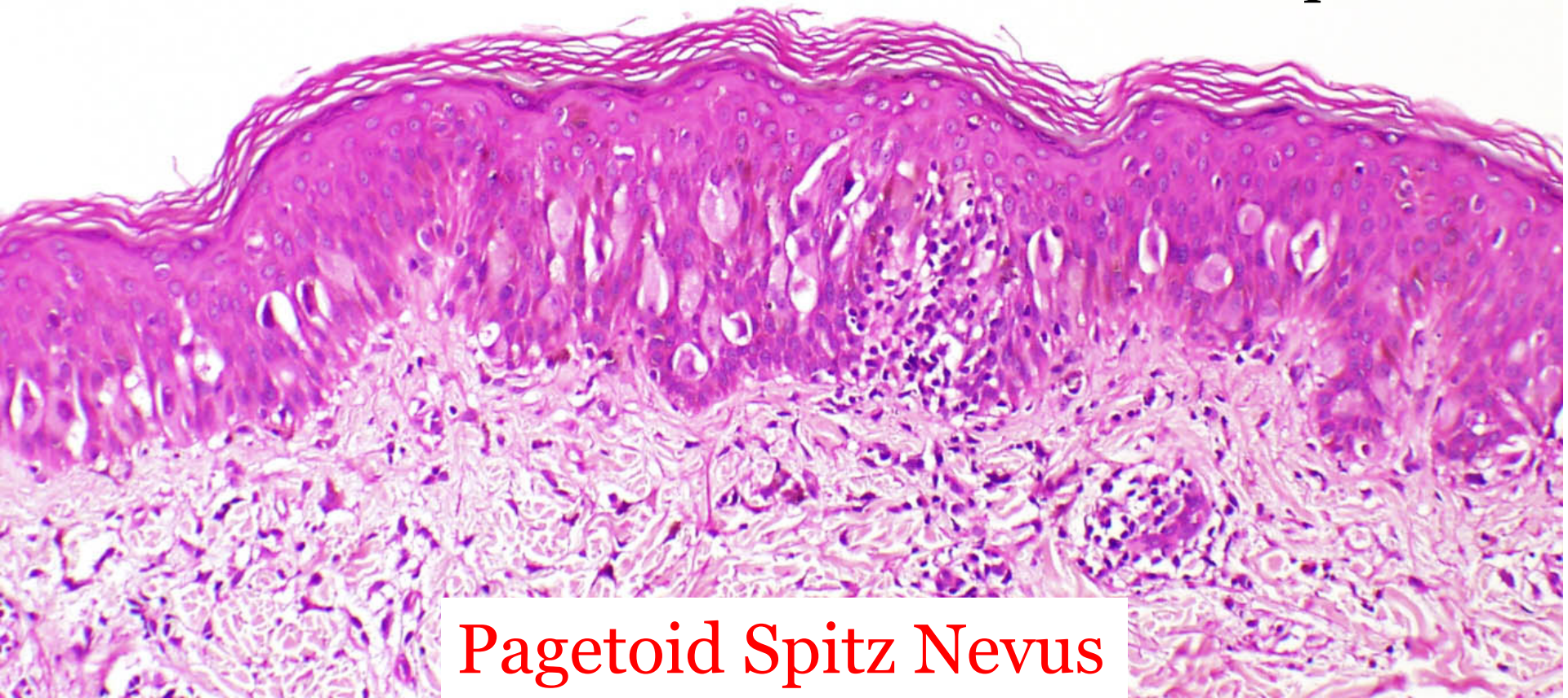
Pagetoid Melanocytosis

Diffuse, full-thickness pagetoid scatter



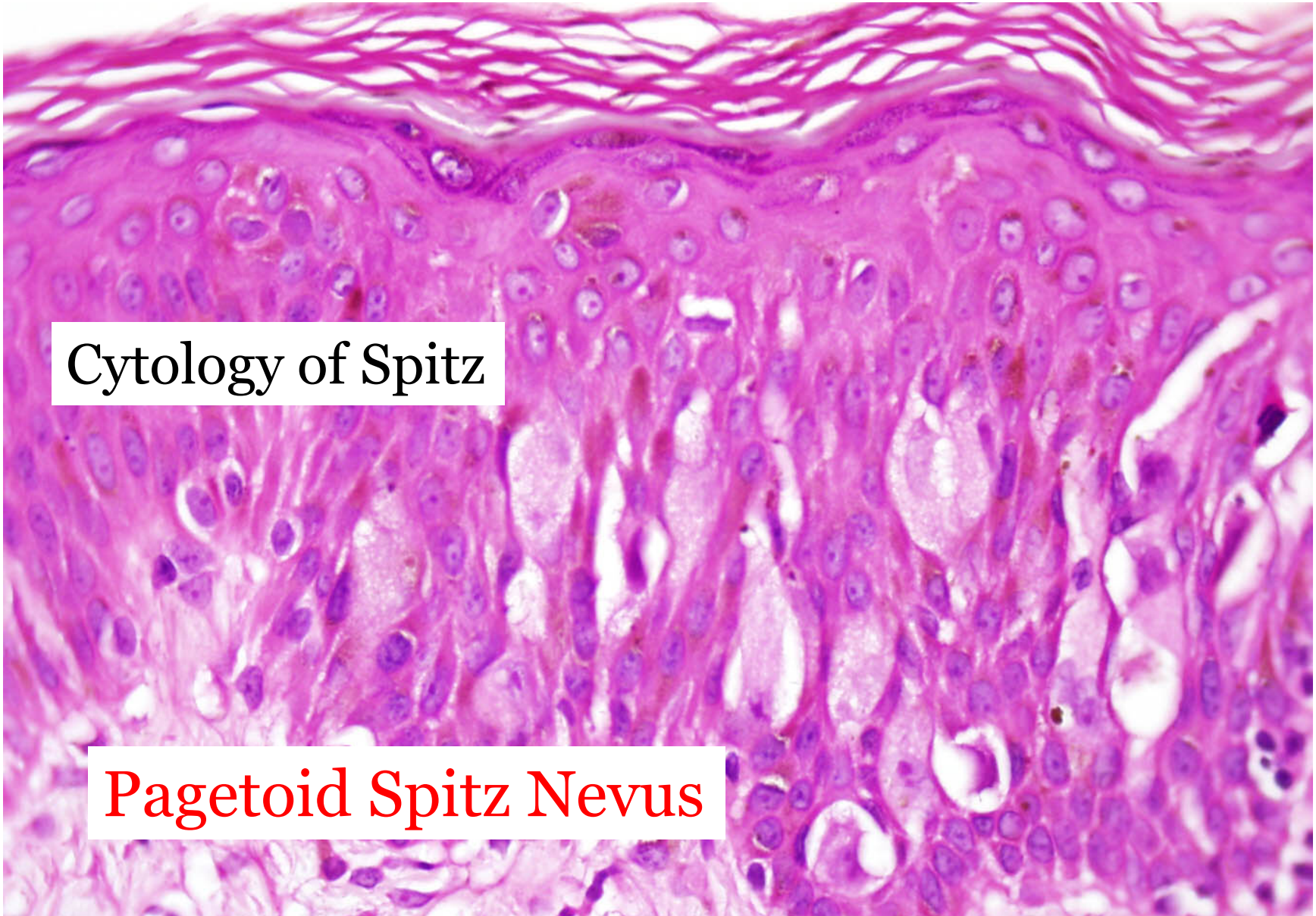
Pagetoid Melanocytosis

Central, sparsely cellular, lower epidermis

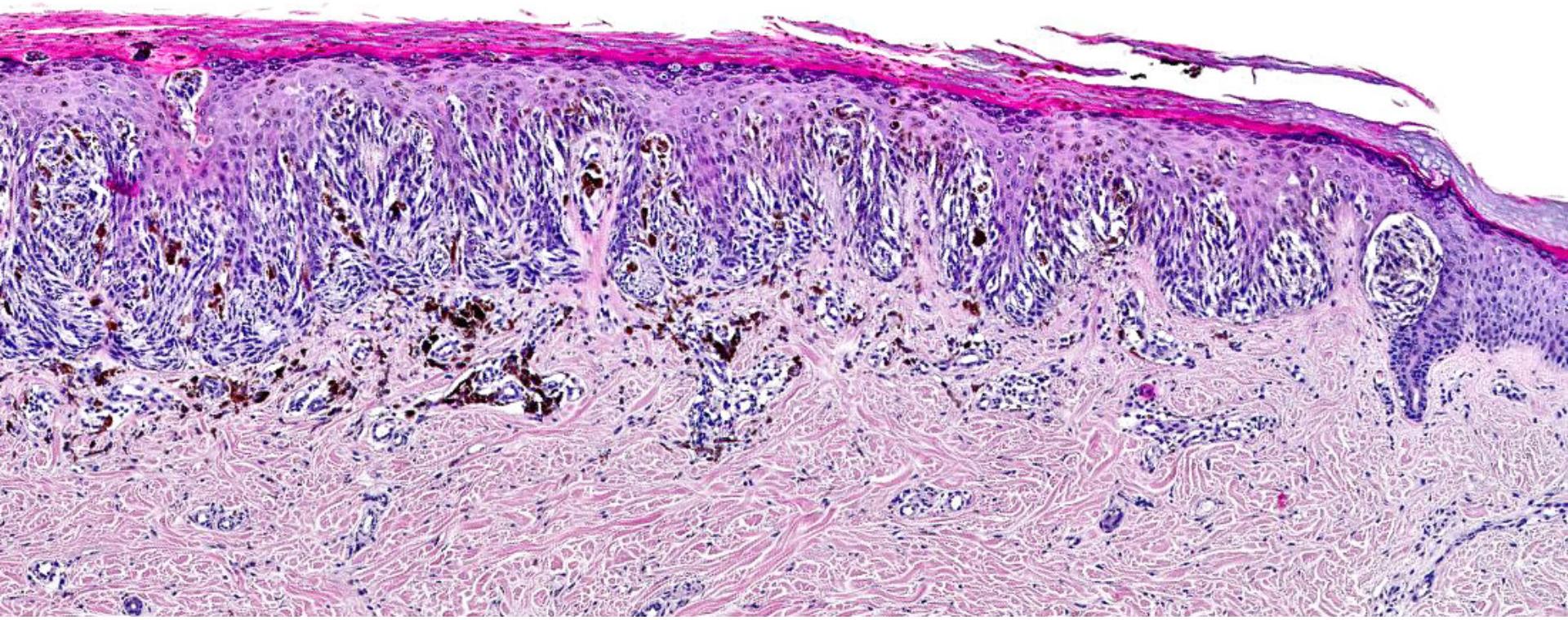


Pagetoid Spitz Nevus

Pagetoid Melanocytosis

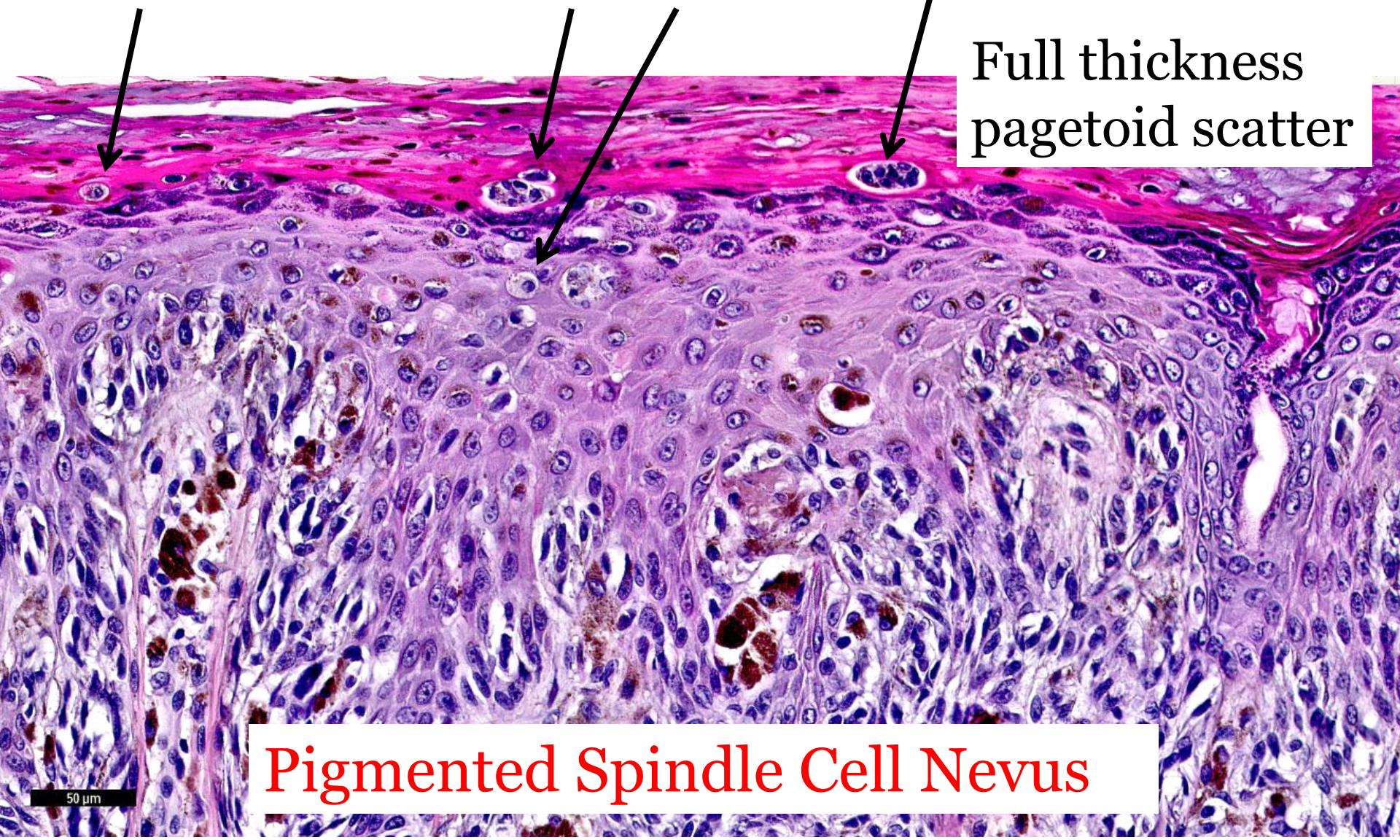


Pagetoid Melanocytosis



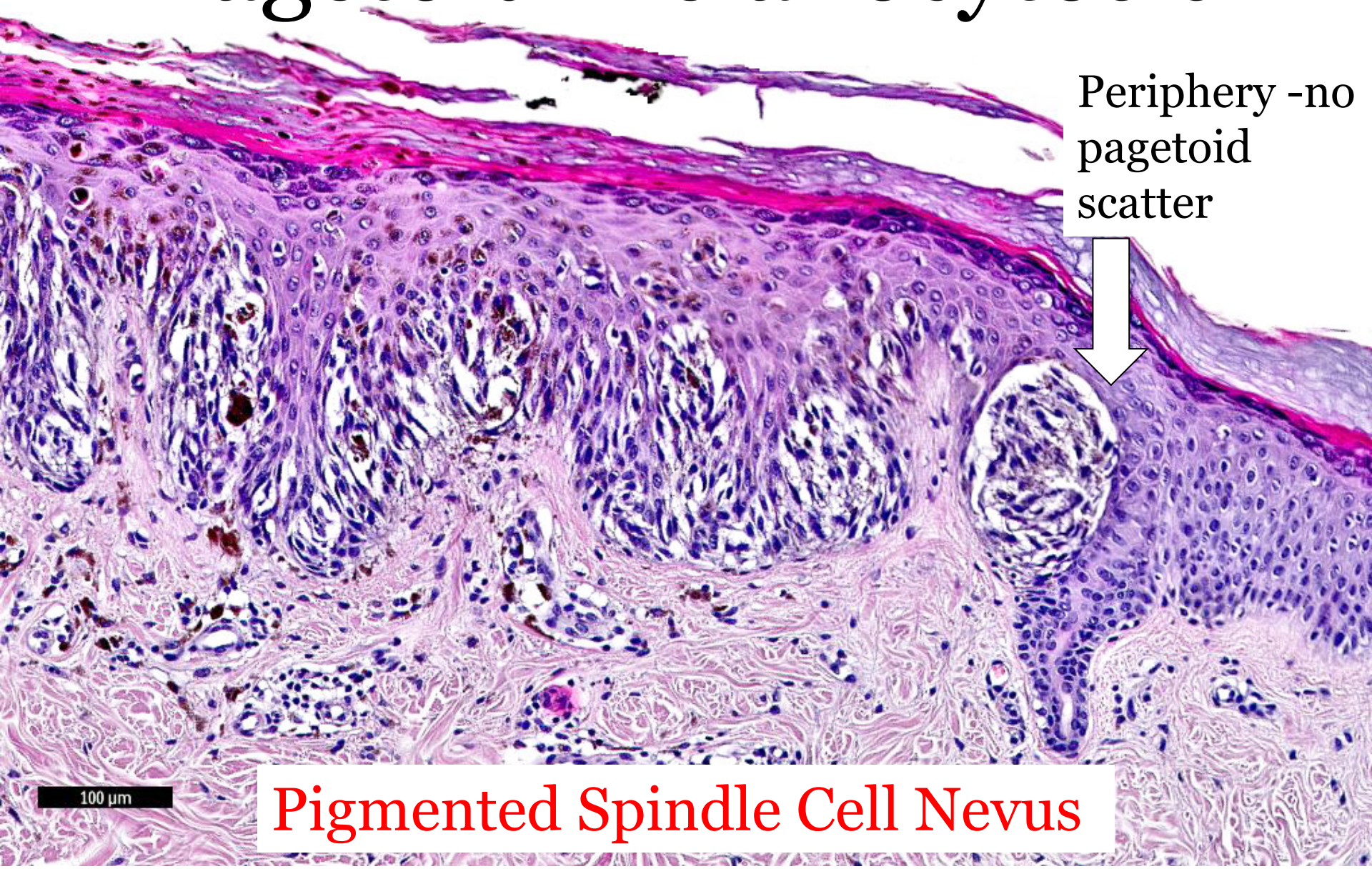
Pigmented Spindle Cell Nevus

Pagetoid Melanocytosis



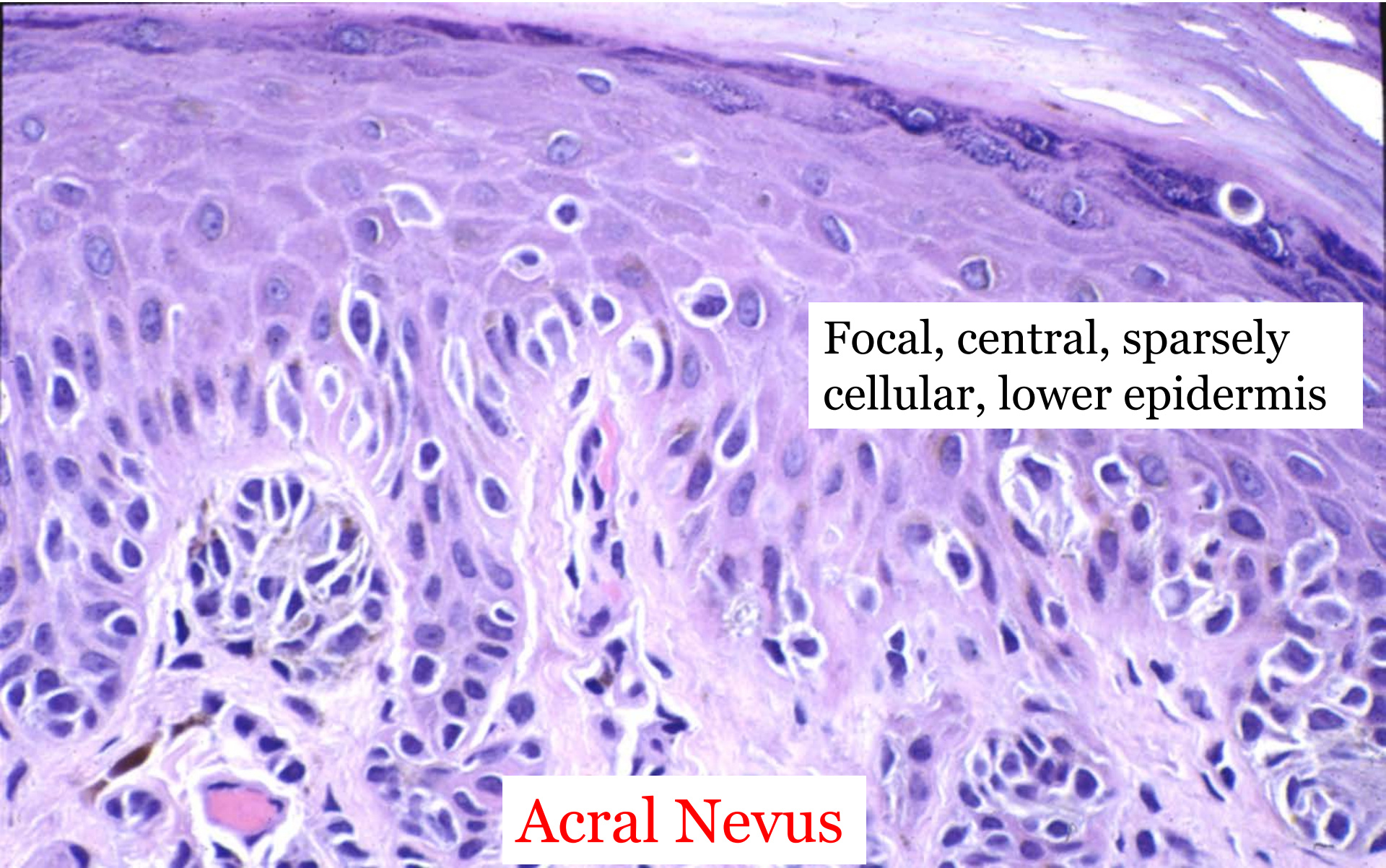
Pigmented Spindle Cell Nevus

Pagetoid Melanocytosis



Pigmented Spindle Cell Nevus

Pagetoid Melanocytosis

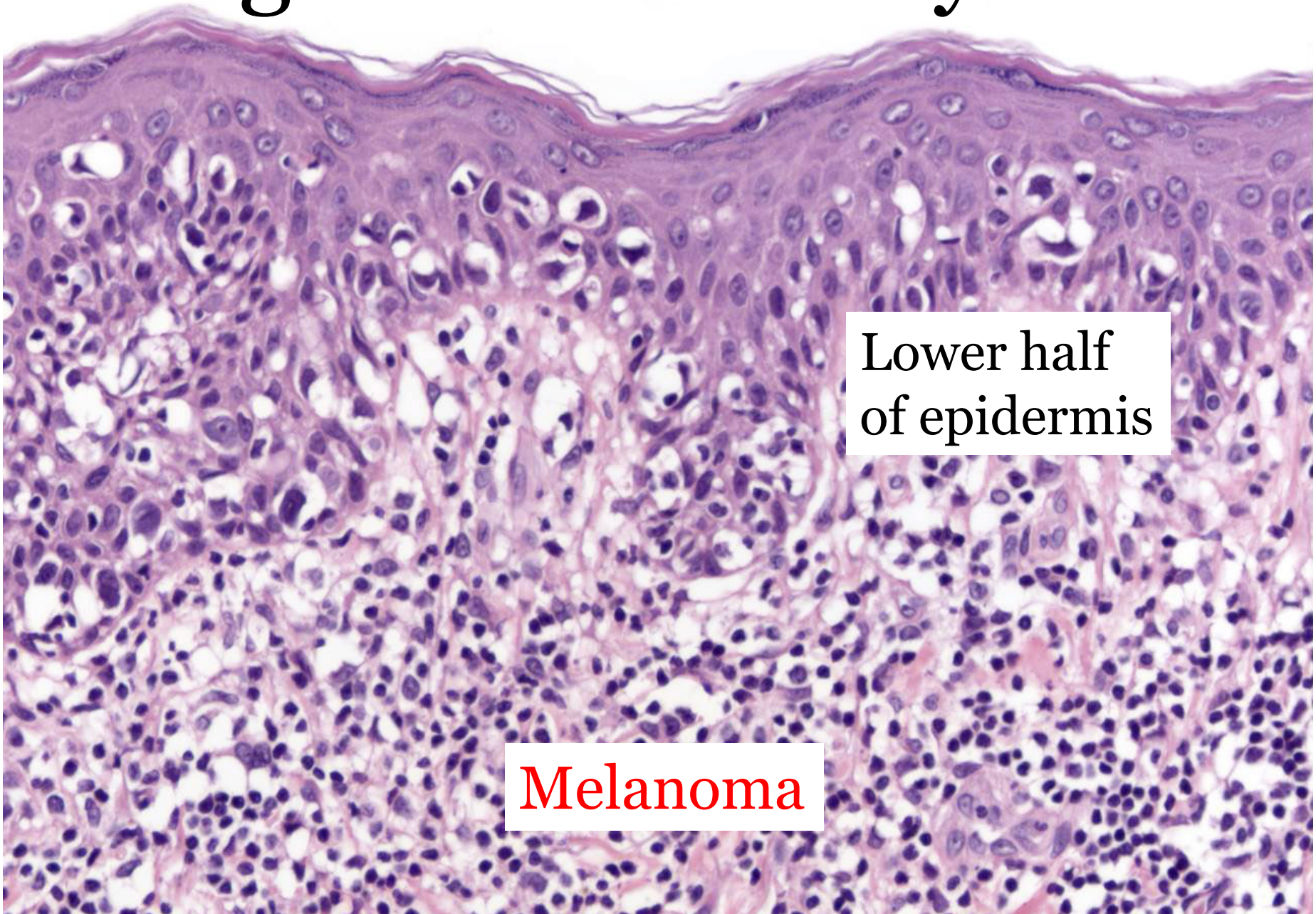


Pagetoid Melanocytosis

Exceptions

Melanoma!

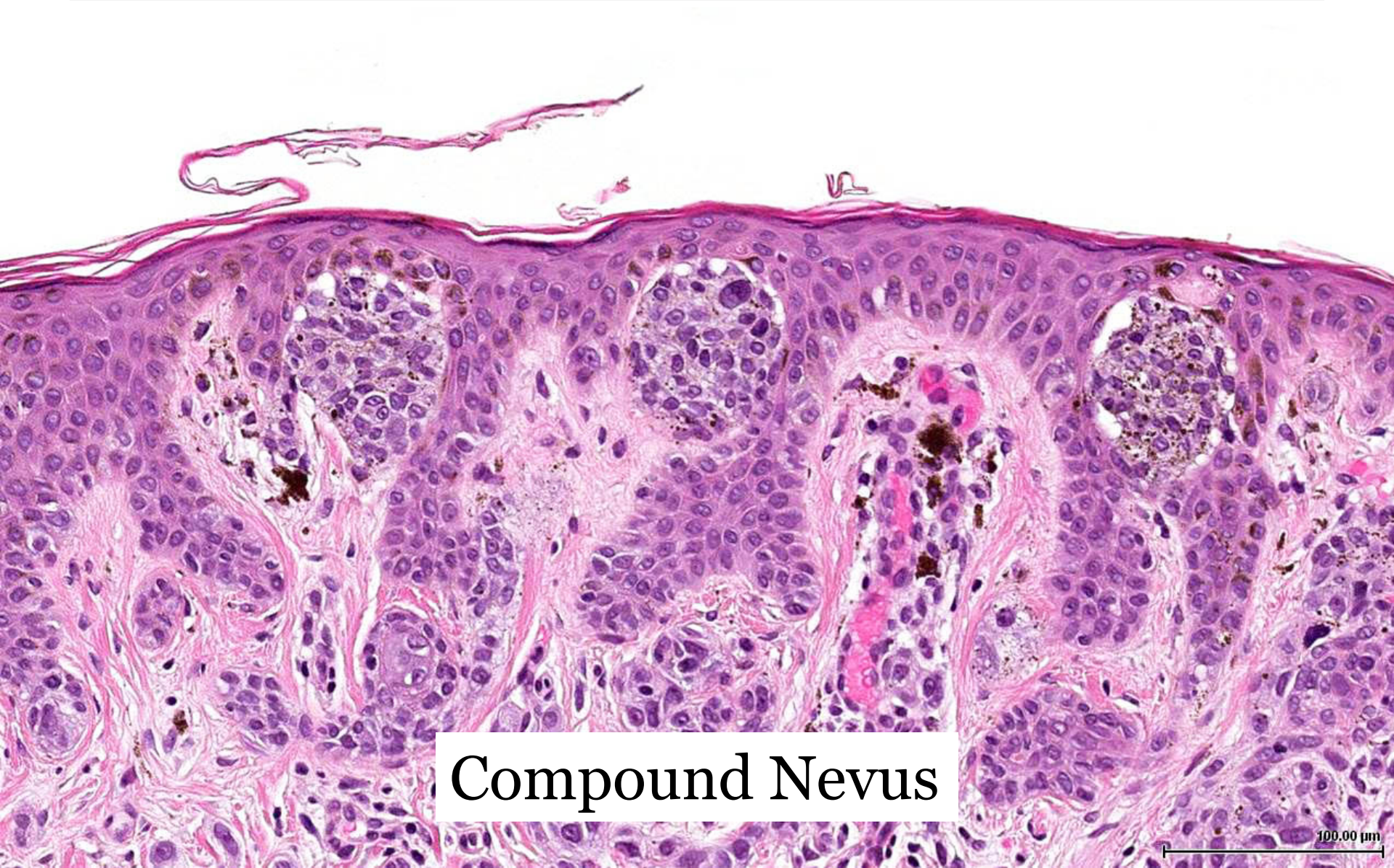
Pagetoid Melanocytosis



Histopathological Criteria

Criterion	Benign	Intermediate	Melanoma
Architecture of nesting **Confluence/ contiguous melanocytes**	Regular	Often irregular Often confluent Bridging	Irregular Confluent

Regular Nesting



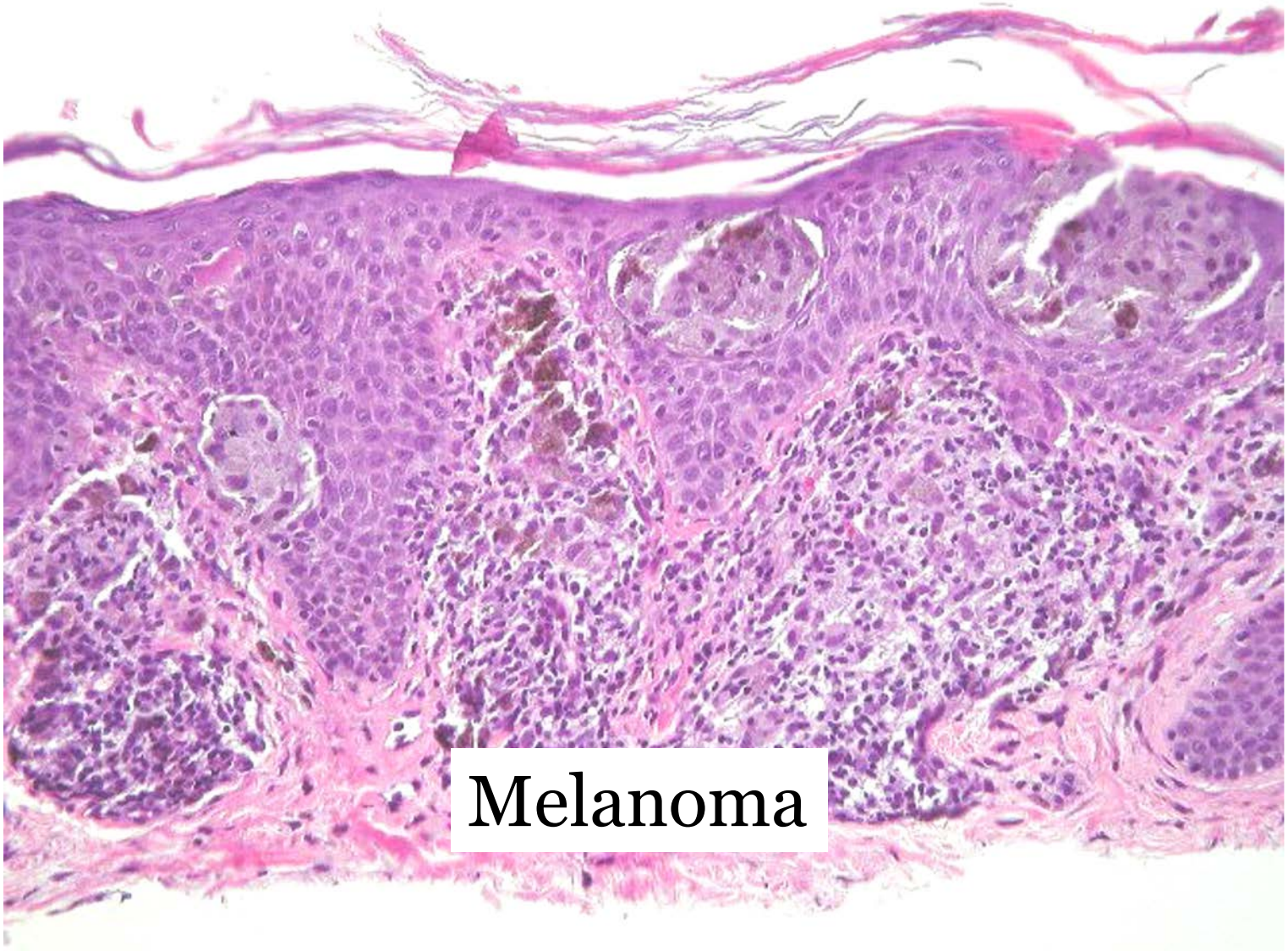
Irregular and Confluent Nesting

Dysplastic Nevus

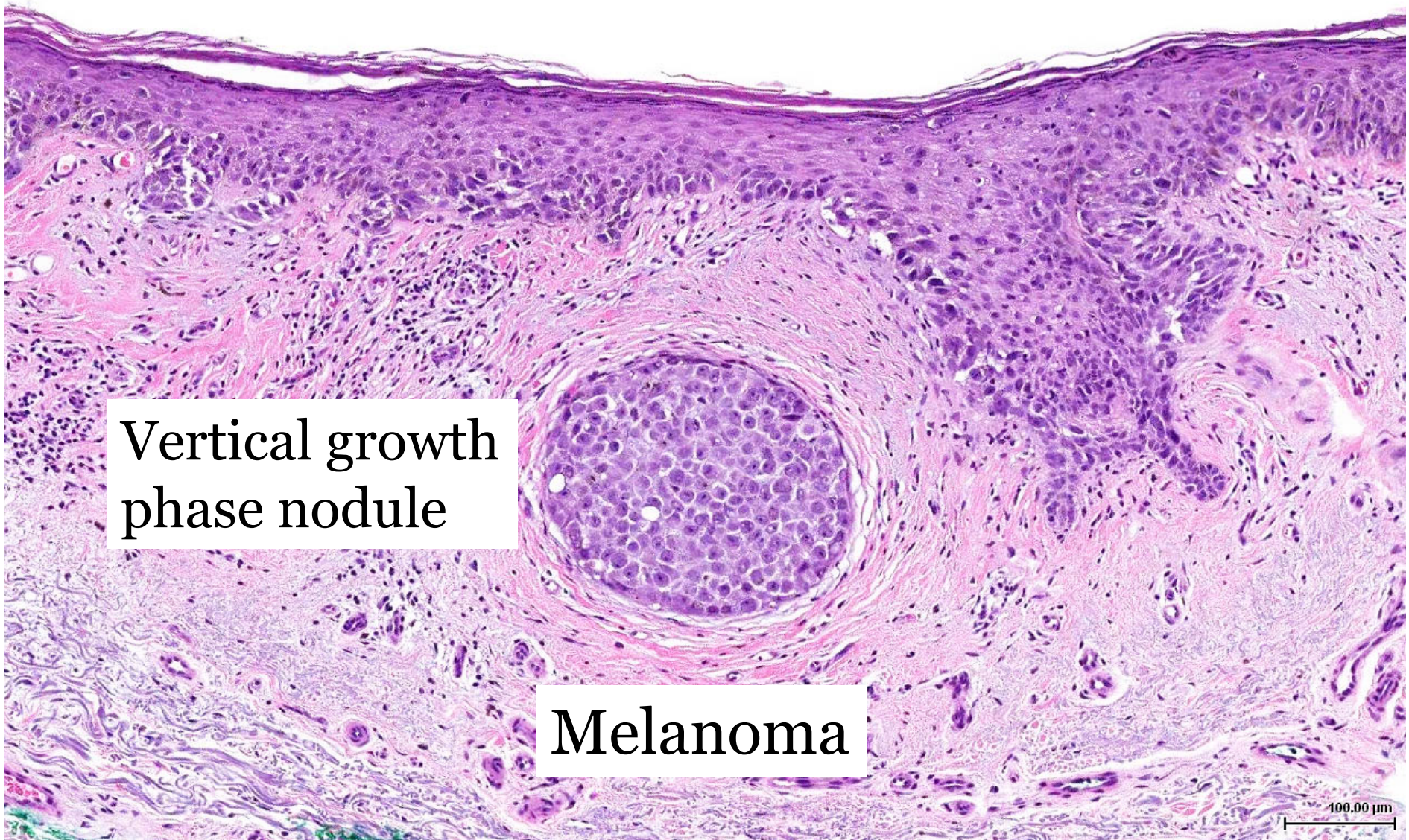
Irregular and Confluent Nesting in Junctional and Dermal Components

Melanoma

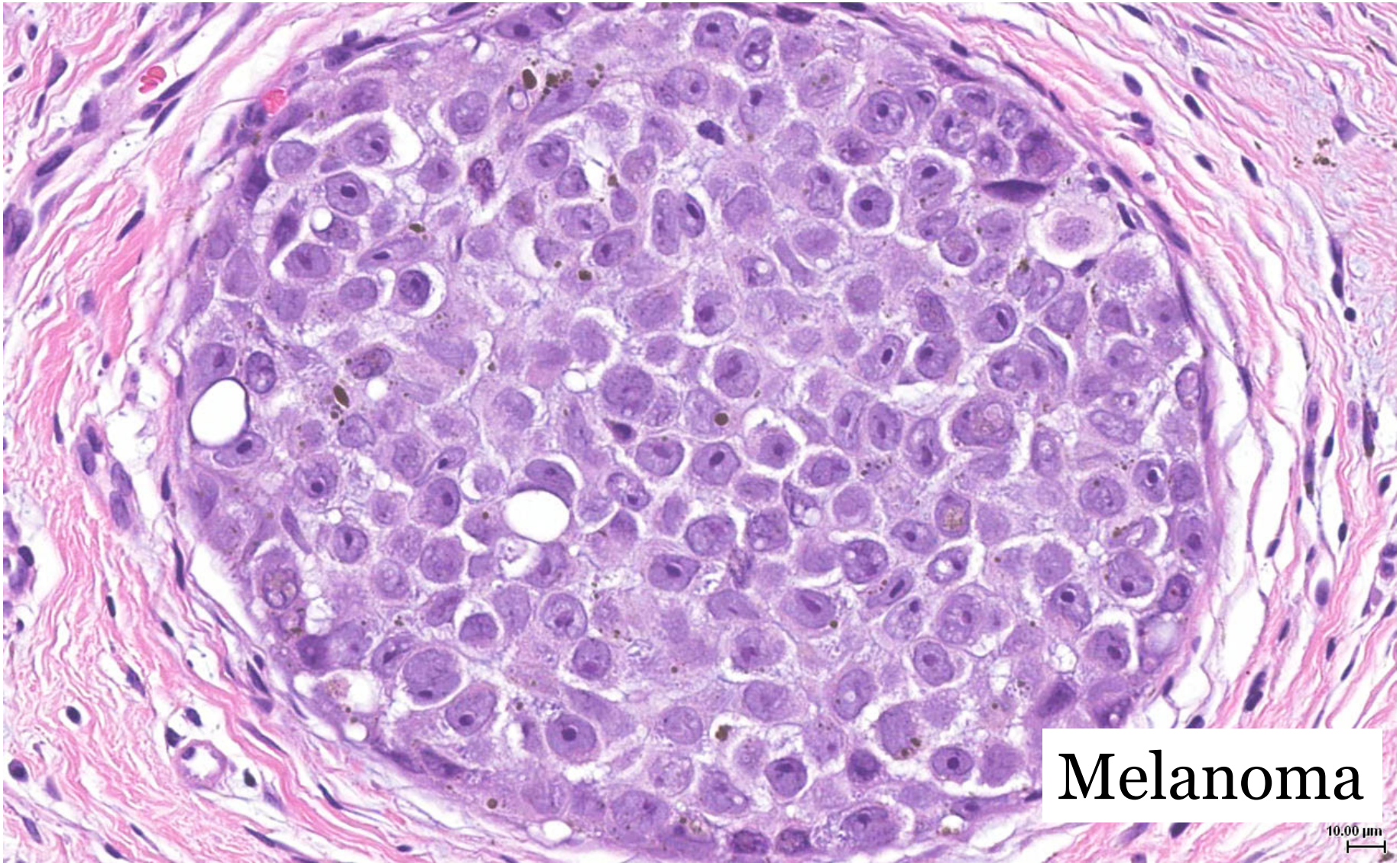
Irregular and Confluent Nesting



Confluent Nesting in Dermis



Confluent Nesting in Dermis



Confluent Nesting

Exceptions

Lesions with Uncertainty

Confluent Nesting

Mimic of melanoma

8 year old female - Vulvar Nevus

Histopathological Criteria

Criterion	Benign	Intermediate	Melanoma
Cellularity	Low cellularity	Increasing cellularity	Dense cellularity

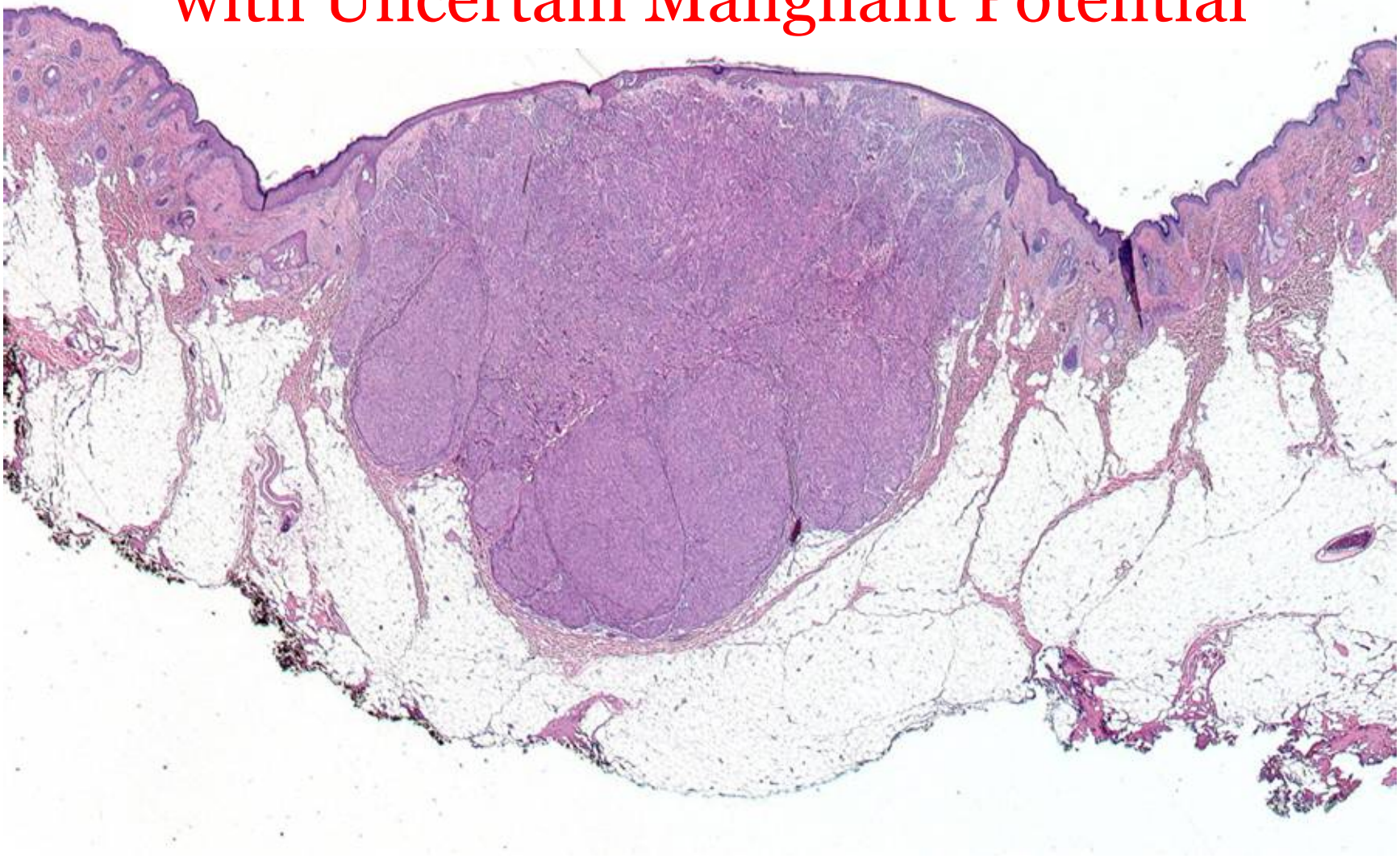
Cellularity

Exceptions

Lesions with Uncertainty

High Cellularity

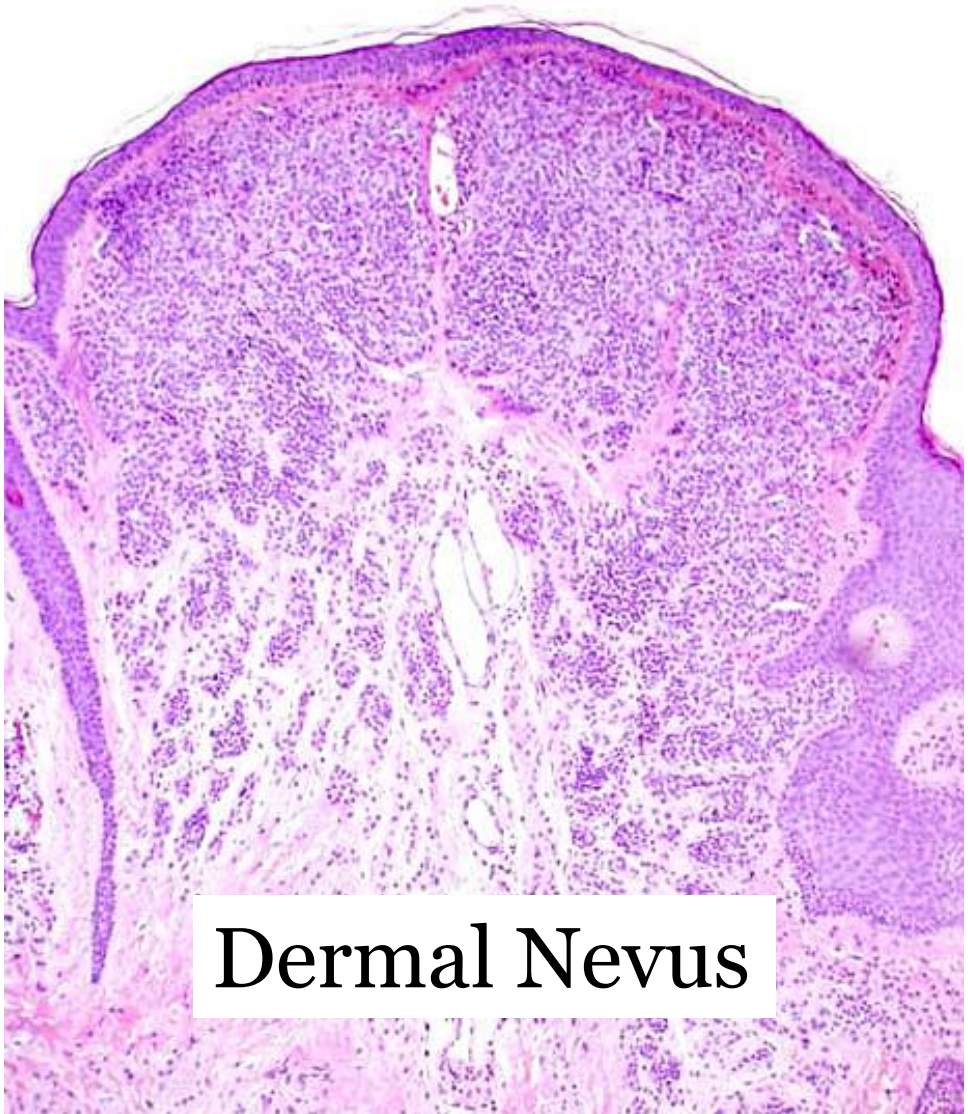
Recurrent Atypical Spitz Tumor with Uncertain Malignant Potential

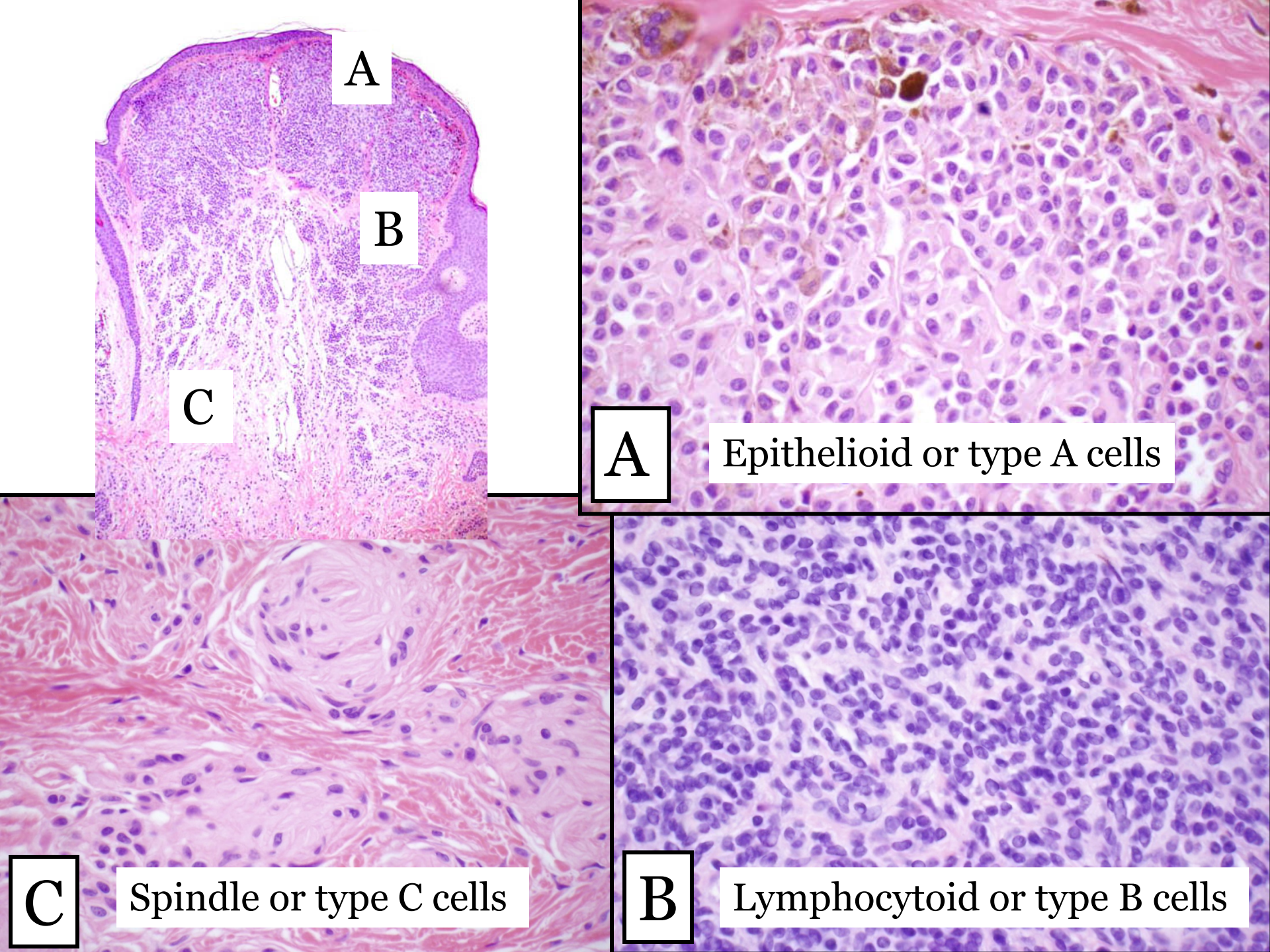


Histopathological Criteria

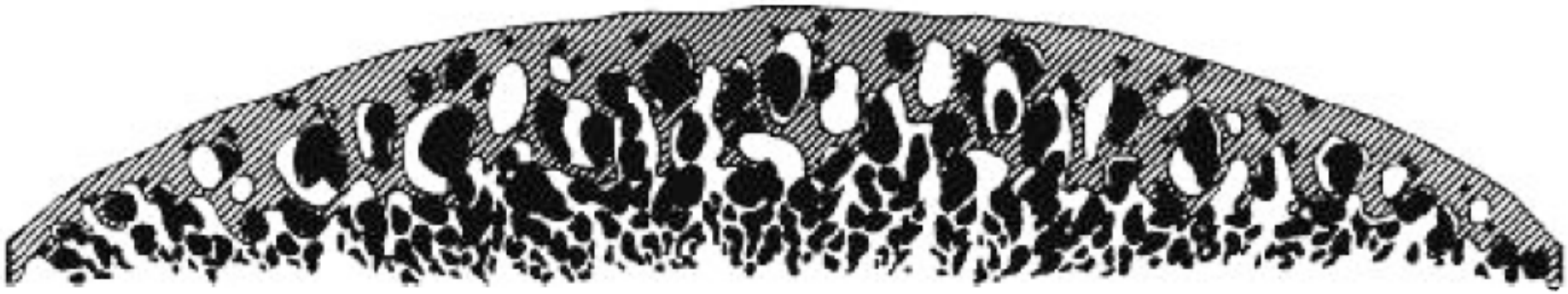
Criterion	Benign	Intermediate	Melanoma
Maturation	Present	Present or diminished	Absent

Maturation



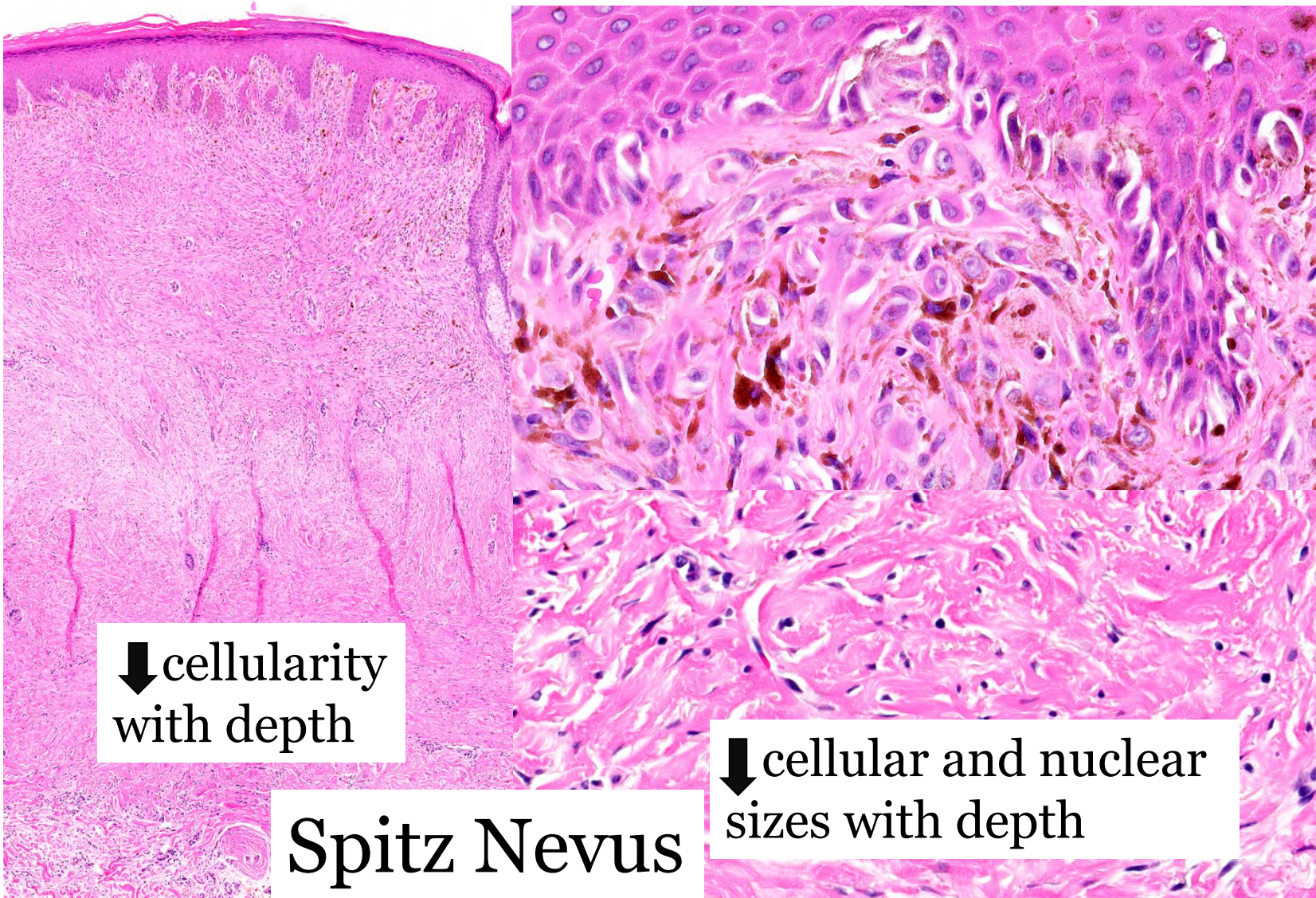

A
B
C
A
Epithelioid or type A cells
C
Spindle or type C cells
B
Lymphocytoid or type B cells

Maturation



Spitz Nevus

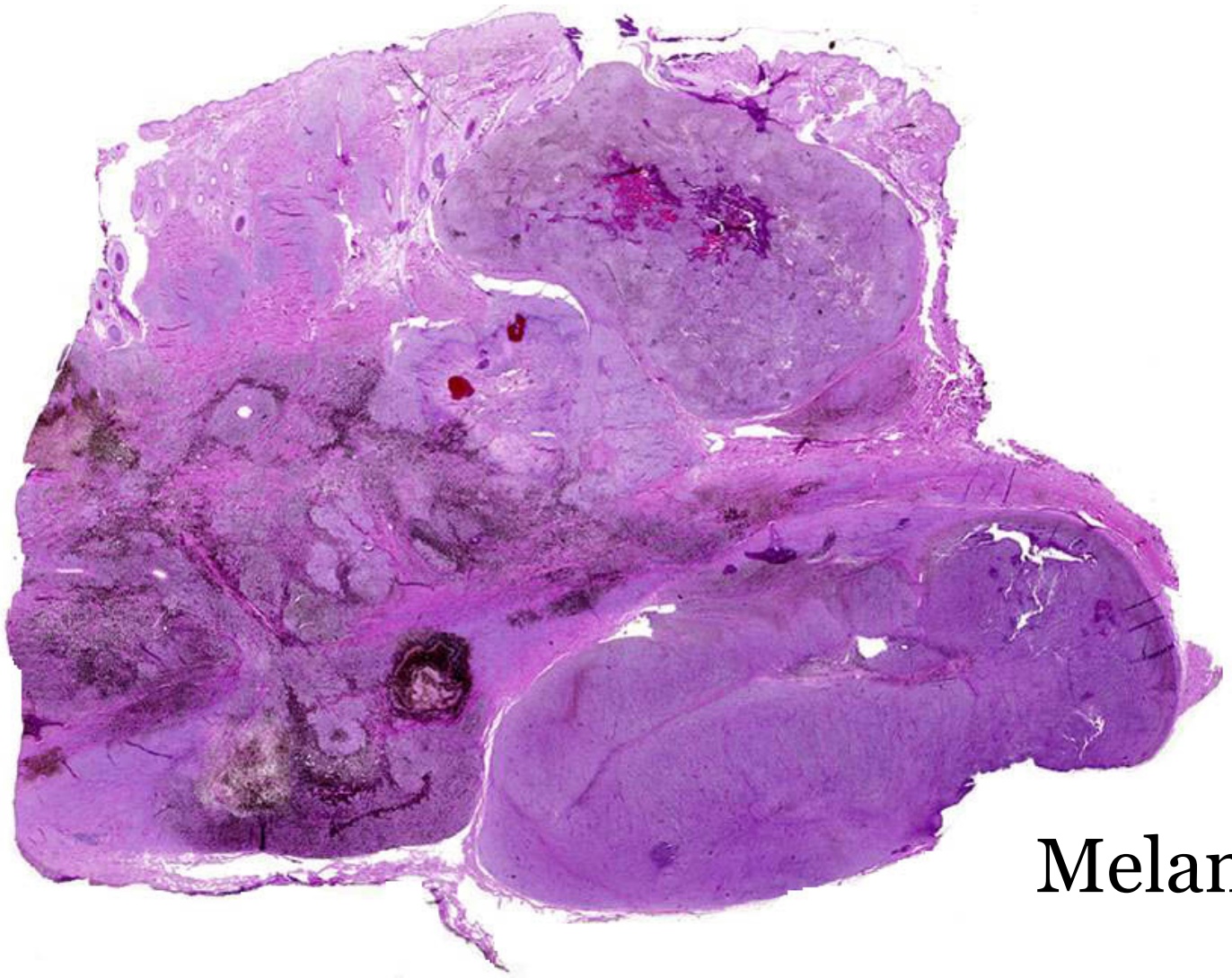
Maturation


⬇cellularity with depth
⬇cellular and nuclear sizes with depth
Spitz Nevus

No Maturation

Melanoma

No Maturation

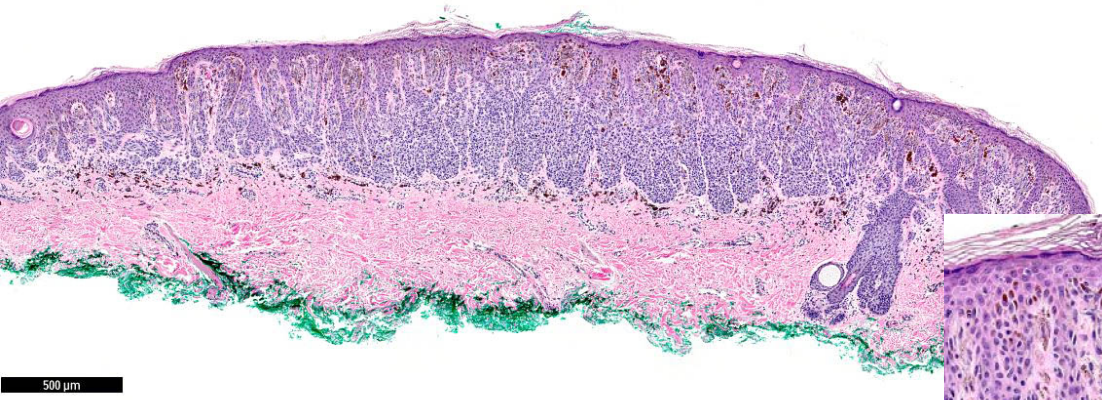


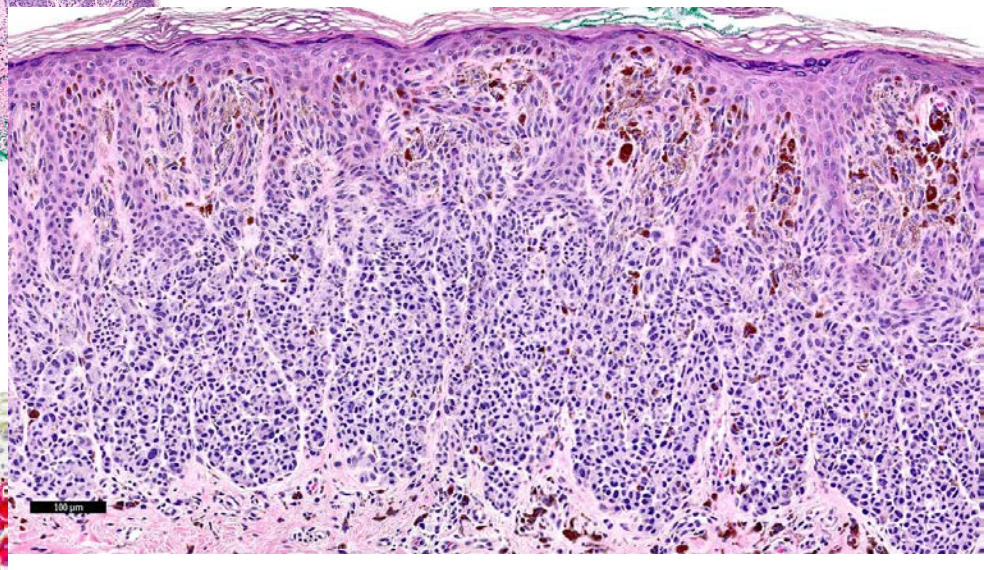
Melanoma

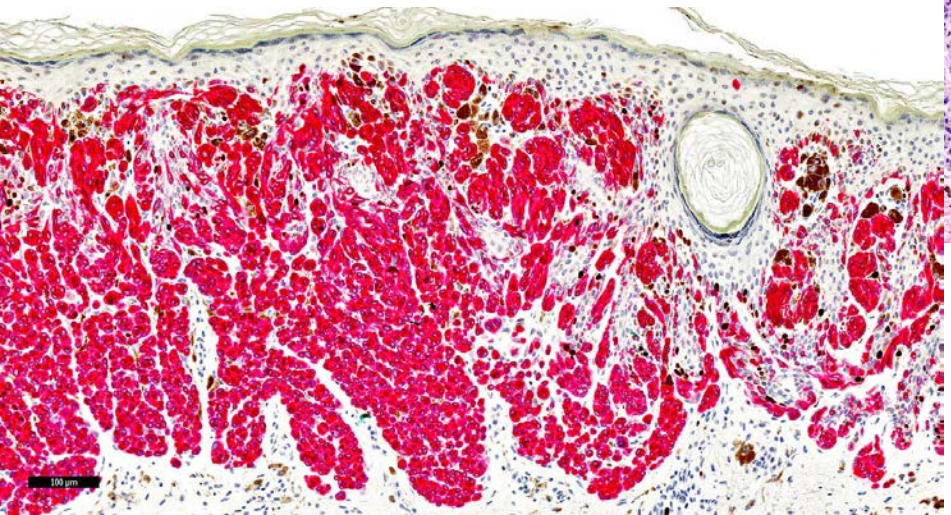
Maturation

Intermediate Lesions

No Maturation







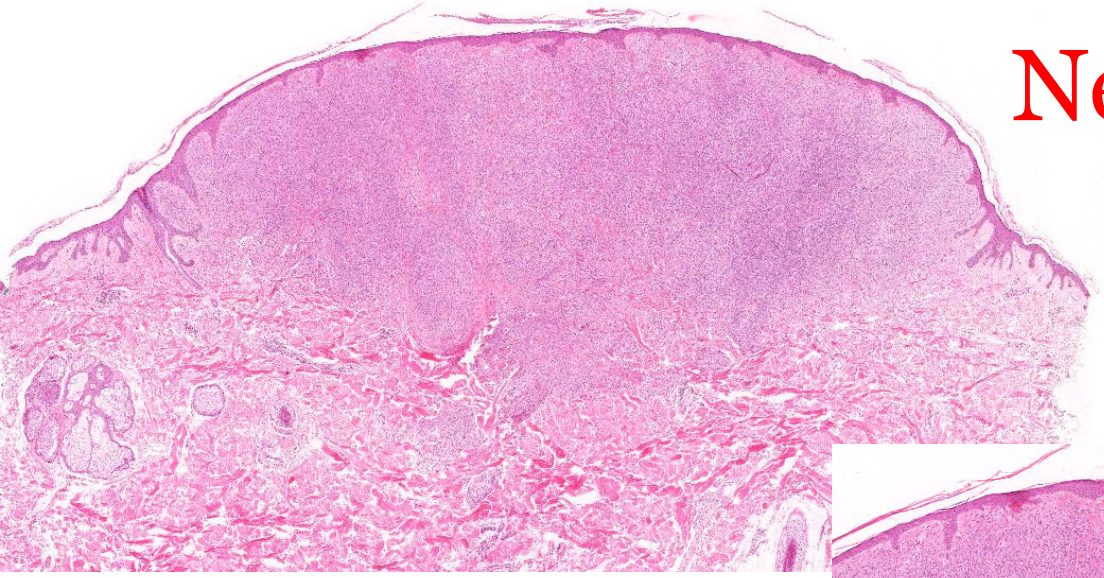
Atypical Pigmented Spindle Cell Nevus

Maturation

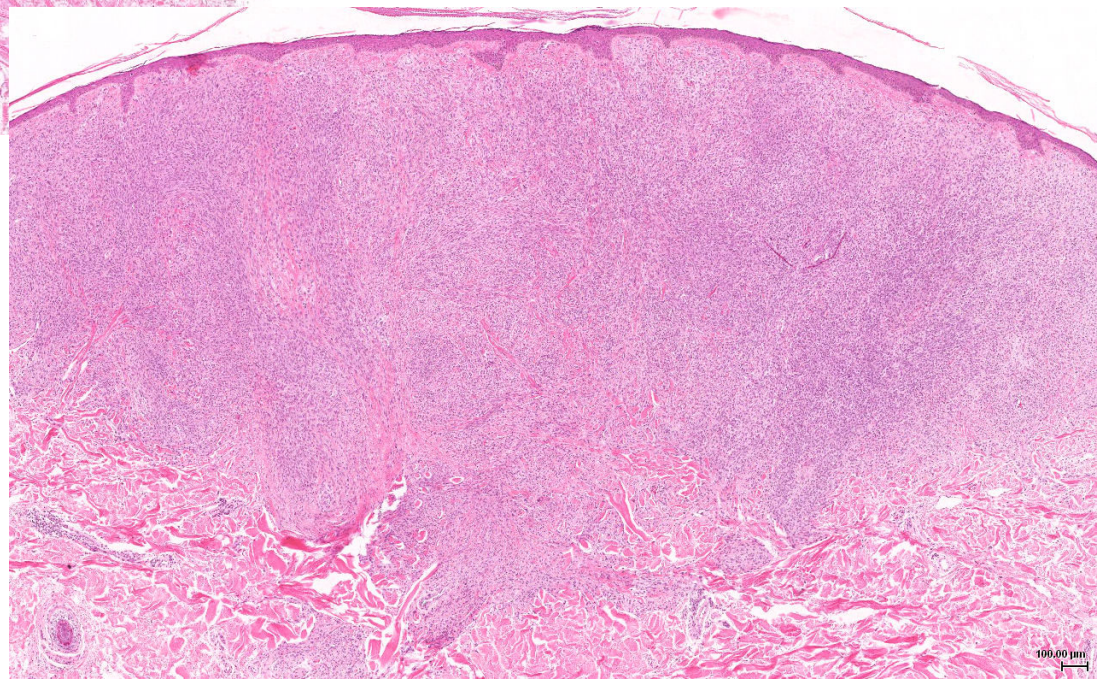
Exceptions

Lesions with Uncertainty

Partial Maturation



Nevoid Melanoma!




En marche!
STREIK
GRÈ
Streik
STOP
Grève
STREIK
ASSEZ!
DER SPIEGEL CHAPPATTE

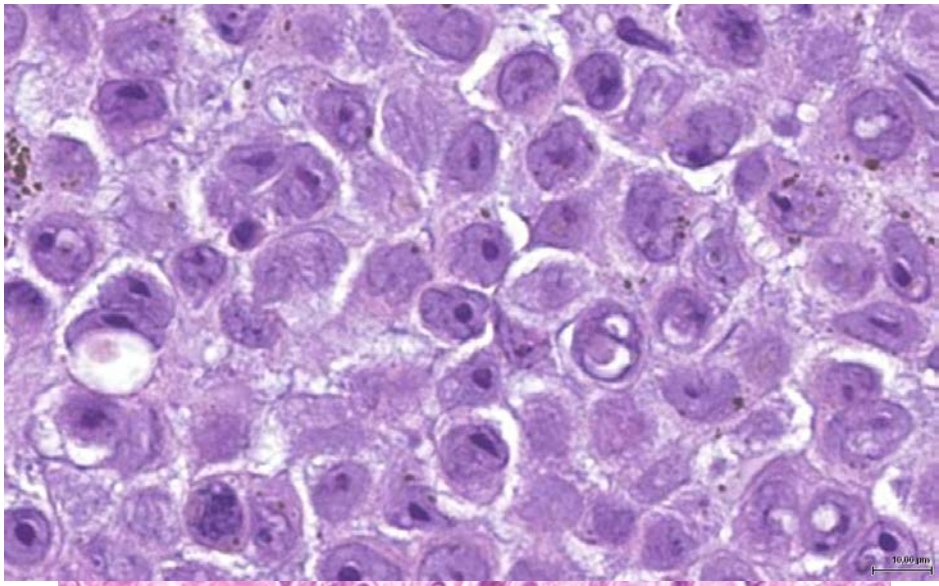
Histopathological Criteria

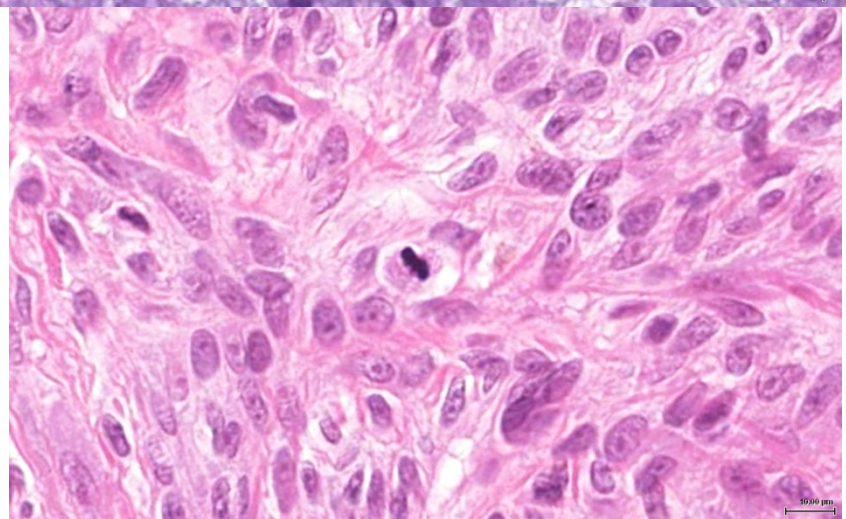
- **Architecture / Silhouette**
  - ✓ Size (Diameter)
  - ✓ Breslow thickness
  - ✓ Circumscription
  - ✓ Symmetry
  - ✓ Pagetoid melanocytosis
  - ✓ Architecture of nesting
  - ✓ Confluence of melanocytes
  - ✓ Cellularity
  - ✓ Maturation

- **Cytological atypia**
- **Mitoses**
- Solar elastosis

Microscopic Evaluation at Medium and High Magnification

- Cytological characteristics
- Cytological atypia
- Mitotic activity

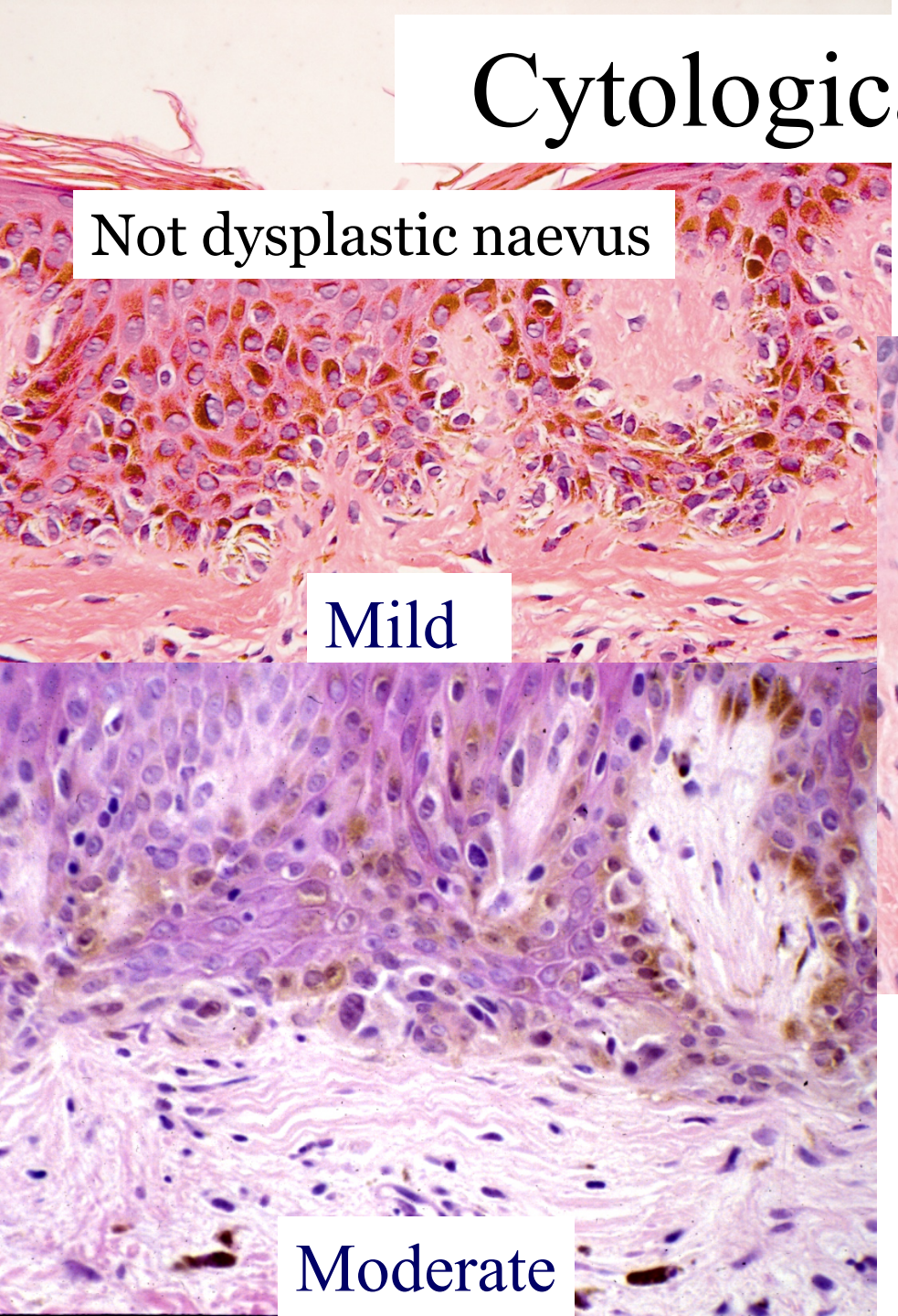


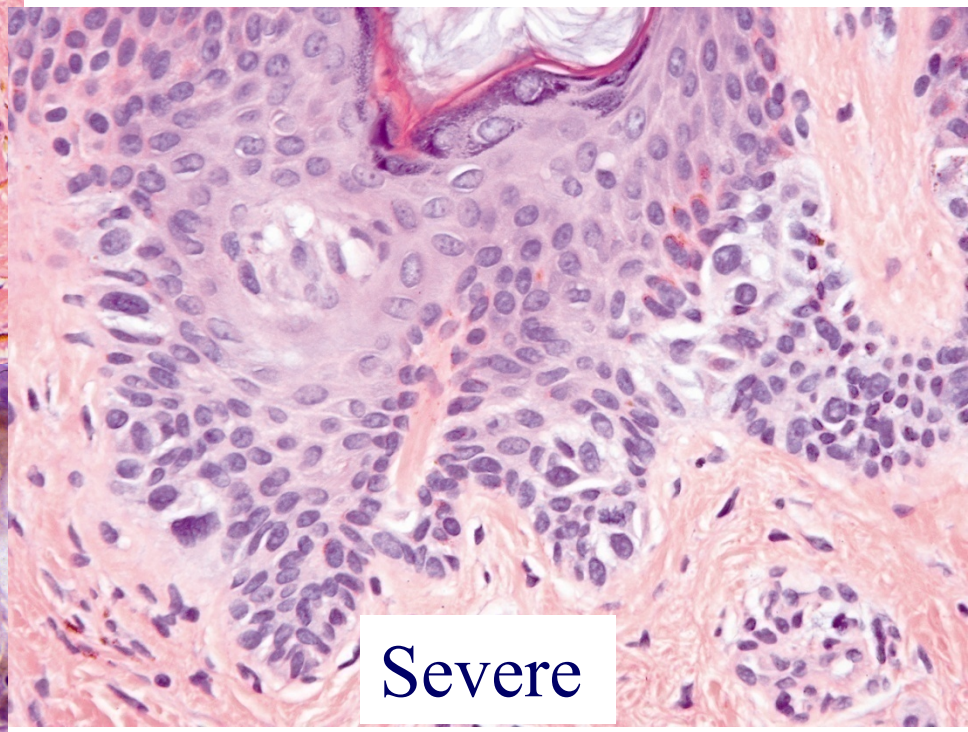


Histopathological Criteria

Criterion	Benign	Intermediate	Melanoma
Cytological atypia Nuclear enlargement Pleomorphism Hyperchromatism Uneven/thickened nuclear membranes Prominent nucleoli Increased nuclear to cytoplasmic ratio	None to mild	Mild to moderate	Moderate to severe

Cytological Atypia



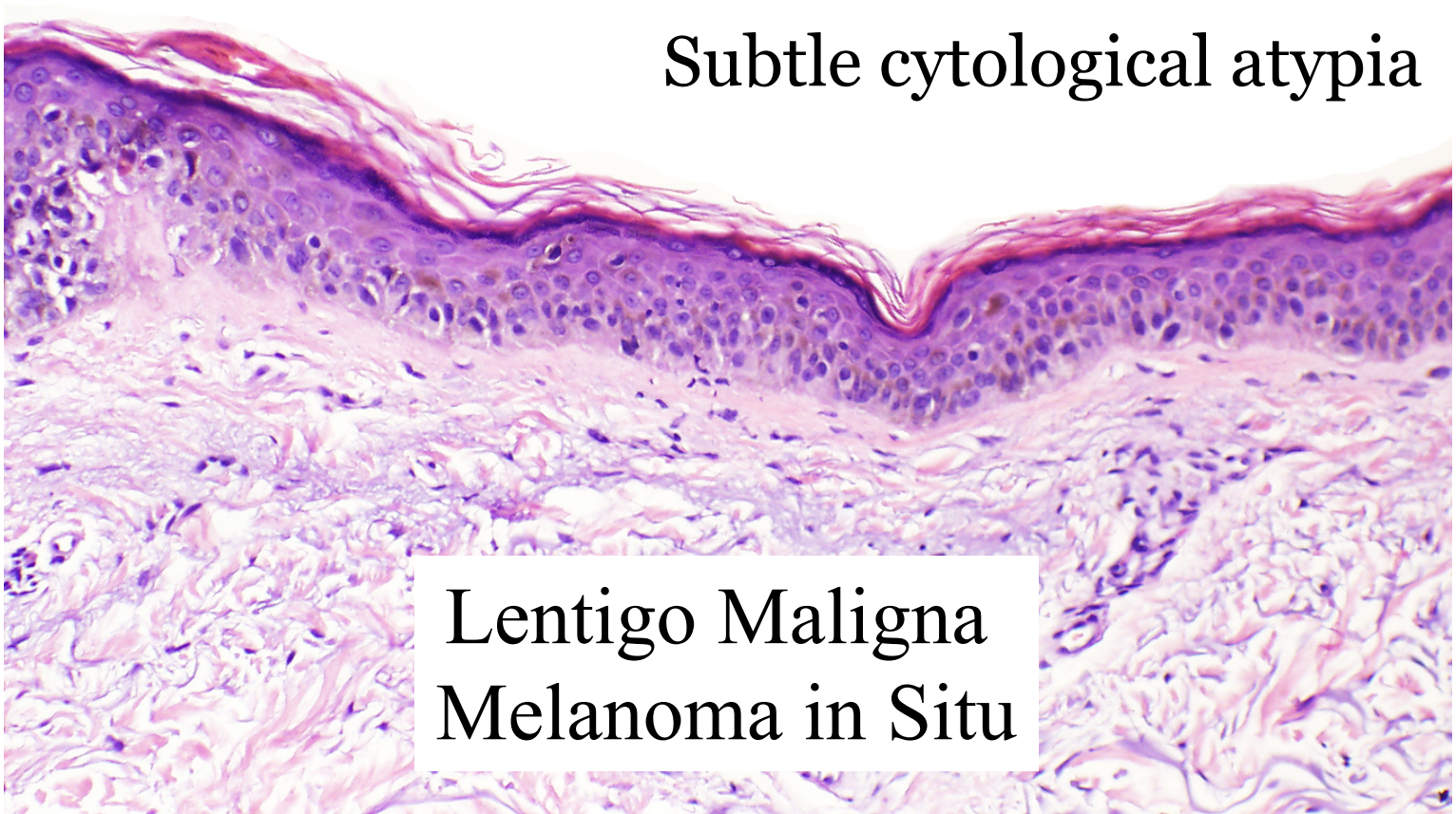


Cytological Atypia

Exceptions

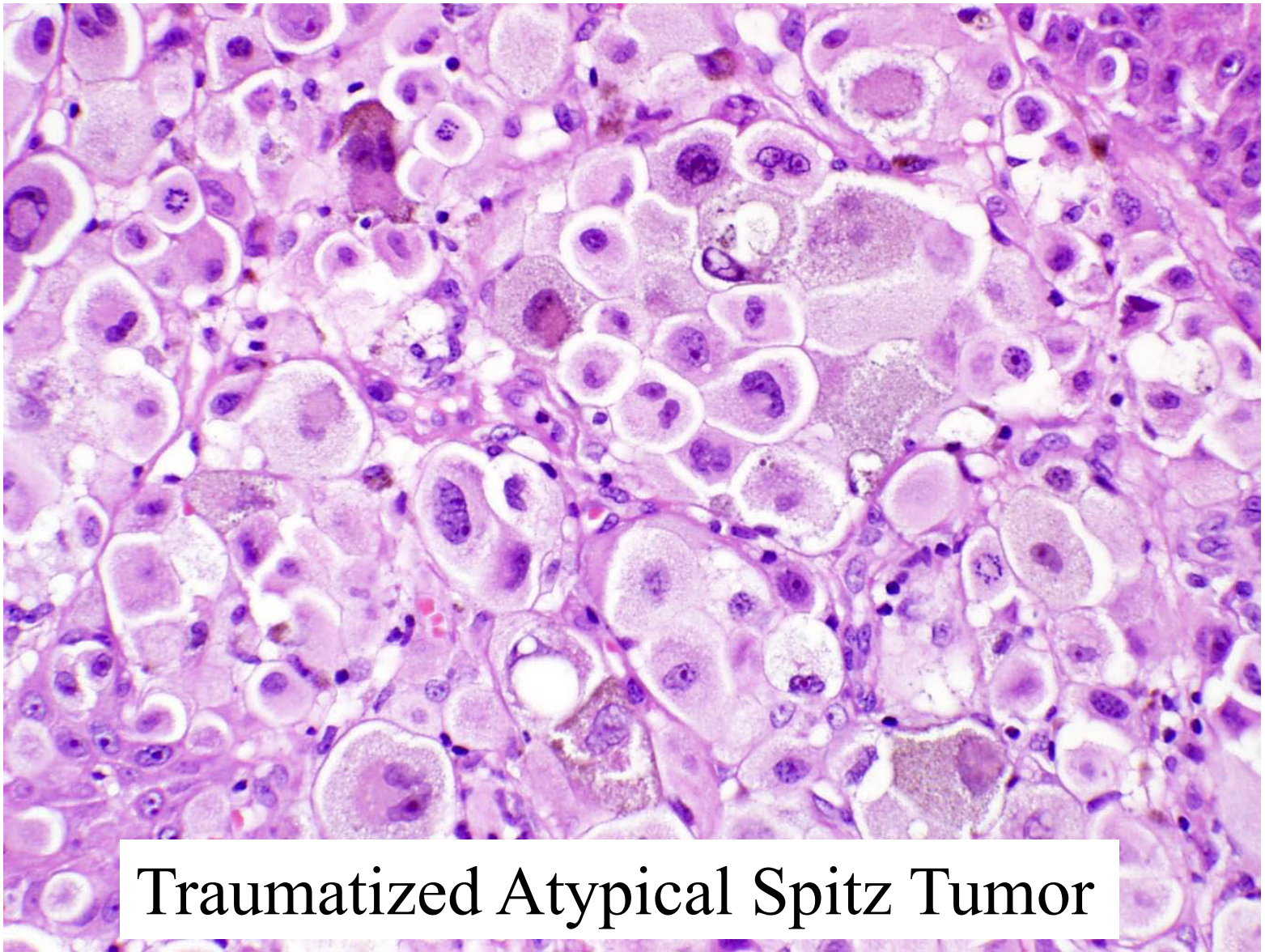
Lesions with Uncertainty

Cytological Atypia



Cytological Atypia:

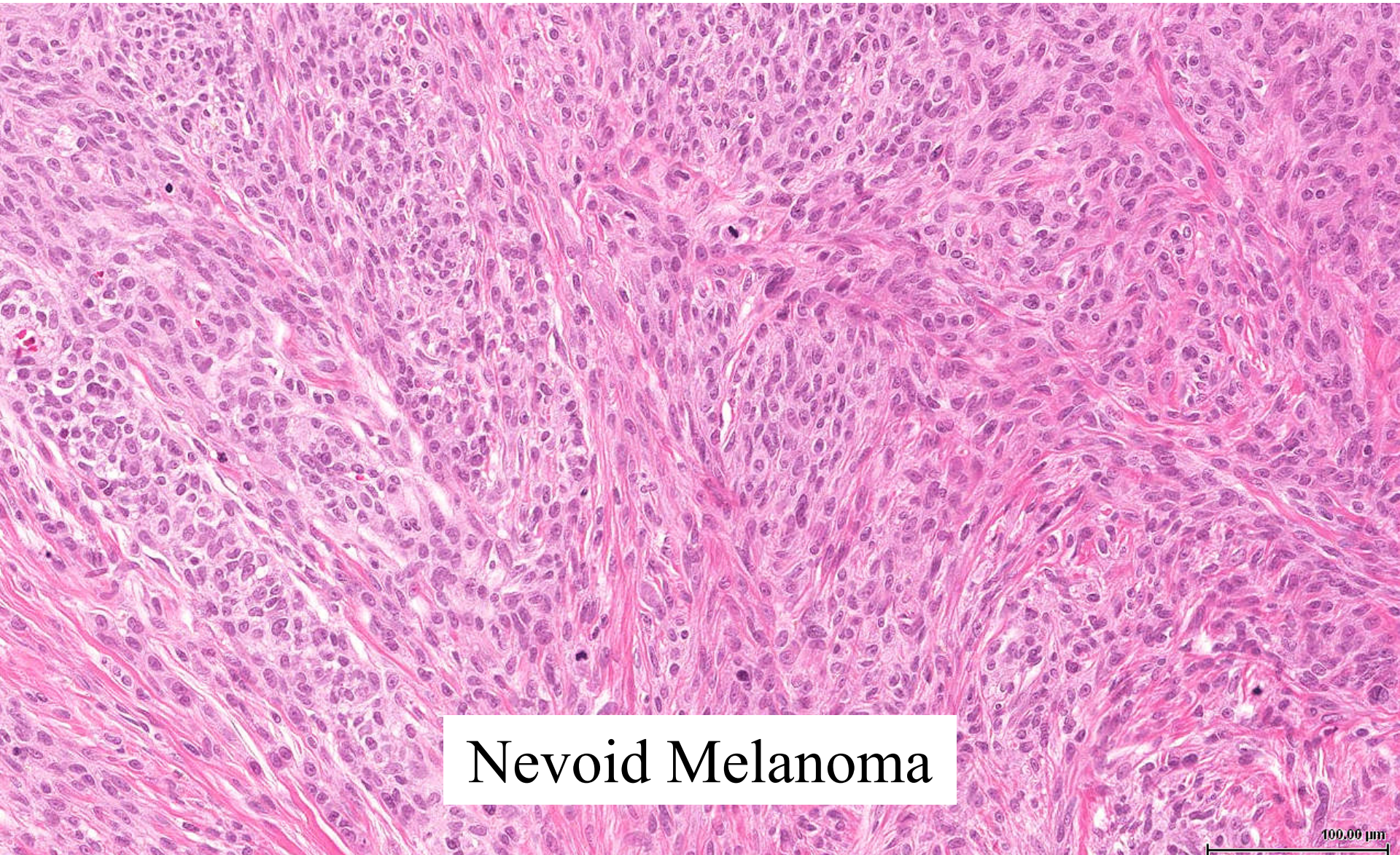
Importance of Clinical History! Mimic of Melanoma



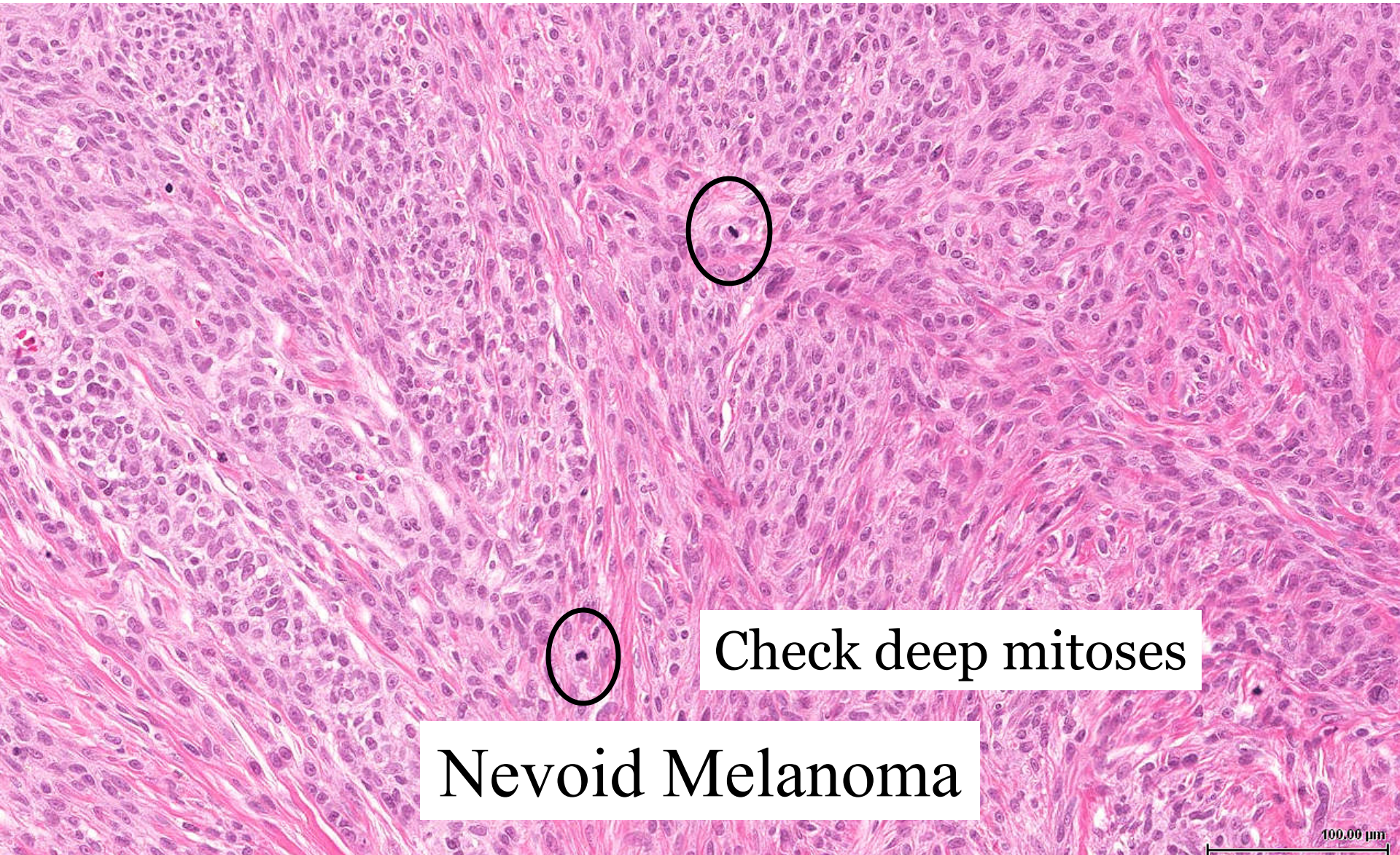
Histopathological Criteria

Criterion	Benign	Intermediate	Melanoma
Mitoses Junctional Dermal	•Usually absent •Superficial	Increased	• Increasing frequency • Hot spots • Deep

Mitoses

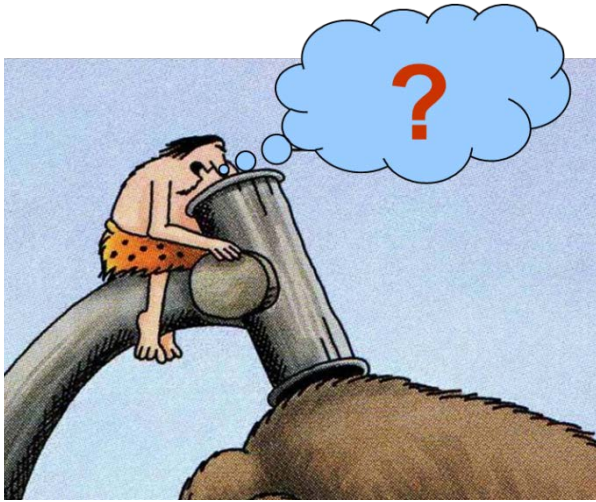


Mitoses



Sampling of Melanocytic Lesions

- Obtain all clinical information!
- Examine the entire lesion!
- Partial biopsies: cannot evaluate:
  - ✓ Size, thickness
  - ✓ Circumscription
  - ✓ Symmetry
  - ✓ Can miss the most important part of the lesion!
- May not be representative!



III.
Ancillary Techniques

Ancillary Techniques

1. Immunohistochemistry
   - Silhouette of a lesion
2. Molecular techniques
   - Increasingly valuable
3. Artificial intelligence and machine learning

Uncertainty about immunohistochemical, molecular, and machine-learning findings in melanocytic lesions exists and must be acknowledged

The Two Most Under-Utilized Special Techniques

1. The human brain

- complex image analysis
- integration of all data
- permits judgement and the human touch

2. The telephone

- direct communication to obtain information

Take Home Messages

1. Do not force benign vs malignant classification; acknowledge intermediate lesions
2. Uncertainty exists in melanocytic lesions and must be communicated
3. Employ due diligence: always have all information and use multiple criteria
4. Always examine the entire lesion

“Medicine is a science of uncertainty and an art of probability”

…….Sir William Osler