The spectrum of melanocytic lesions: From examples to biologically relevant conditions

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BAHRAIN, APRIL 2017

Melanomas and Nevi

- **Significance of melanoma**
  - **Melanomas may persist and recur locally, or may metastasize**
- **Significance of Nevi**
  - **With rare cosmetic exceptions, nevi are important only in relation to melanoma**
  - **As Precursors of melanoma**
    - **potential precursors only; most lesions are stable or senesce**
  - **As Simulants of melanoma**
  - **As Markers of individuals at increased risk of melanoma**

Sources of Uncertainty in Pigmented Lesion Diagnosis

- **Criteria are not universally agreed upon**
- **Some "difficult" lesions present with conflicting or poorly understood criteria**
- **Experts disagree about difficult lesions**
  - **However, most pigmented lesions in routine practice are rapidly and accurately diagnosed**

Difficult Melanocytic Lesions

- **General Principles**
  - **Diagnostic uncertainty should not be "swept under the rug"- uncertainty should be expressed directly**
    - **Patients deserve open and frank discussion of treatment options**
  - **Treatment can be tailored to the differential diagnosis – e.g. melanoma vs. nevus**
    - **Prognostic parameters should be discussed in report to allow rational therapy – WLE, SLN**

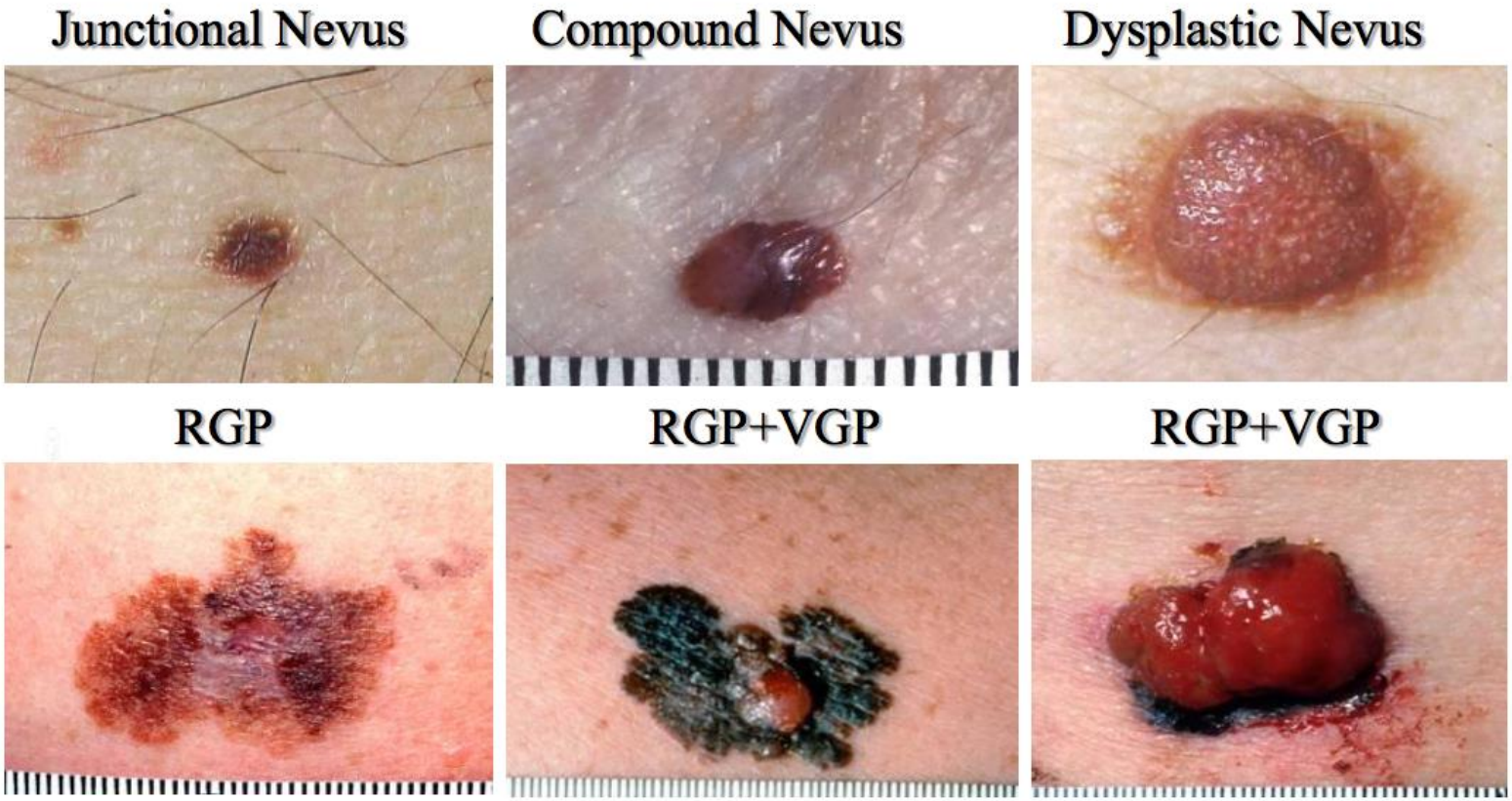
Terminology of Difficult Lesions

- **Borderline Lesions**
  - **Biologicallyborderline**
    - **Lesions that occupy intermediate position in progression**
  - **Diagnostically borderline**
    - **Lesions that lack strong diagnostic features**
    - **Many lesions probably not biologically borderline – unknown biological potential – either benign or malignant but can't tell**
- **Low Malignant Potential (LMP) Lesions**
  - **"Malignant" but with usually good prognosis**
- **Uncertain Malignant Potential Lesions**
  - **A broader term that includes both Biologically and/or Diagnostically "borderline" lesions**
  - **Cases where experts disagree.**

Categories of Uncertainty in Melanocytic Tumors

- **Nontumorigenic Lesions of Uncertain Potential**
  - **Superficial Atypical Melanocytic Proliferation of Uncertain Significance (SAMPUS)**
  - **Locally recurring potential**
- **Tumorigenic Lesions of Uncertain Potential**
  - **Melanocytic Tumor of Uncertain Potential (MELTUMP)**
  - **Locally recurring and metastasizing potential**

Gross Pathology of Tumor Progression Compartments (SSM) in Melanoma

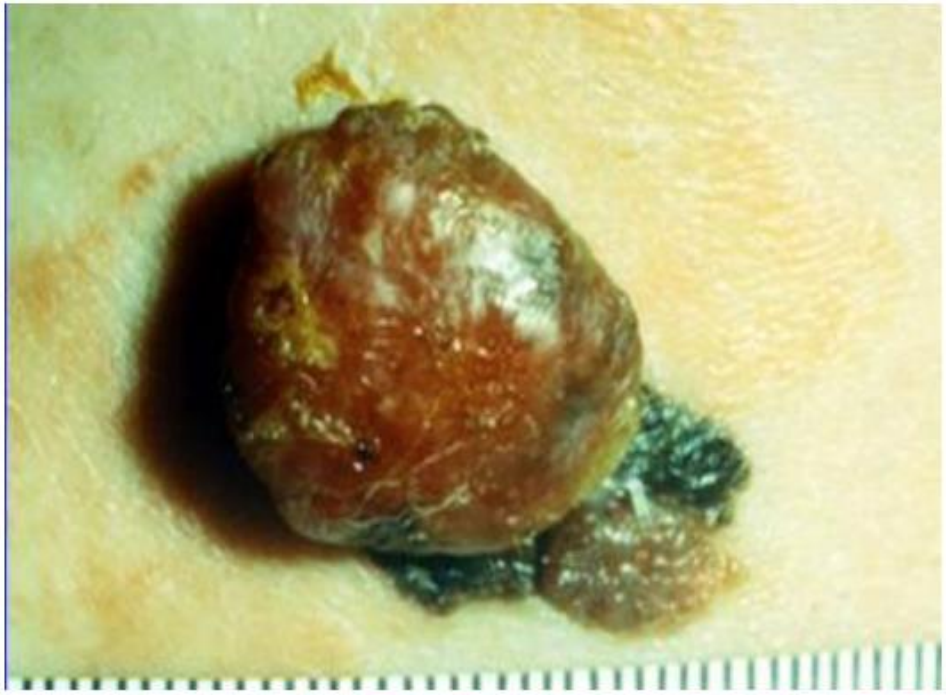


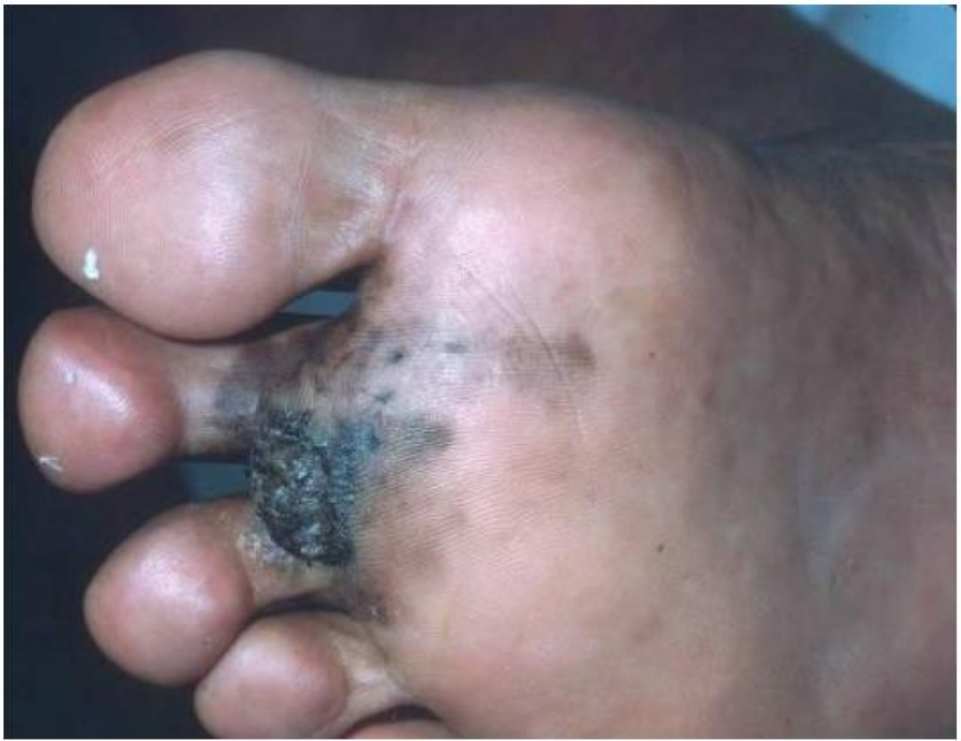
Histogenetic Subtypes

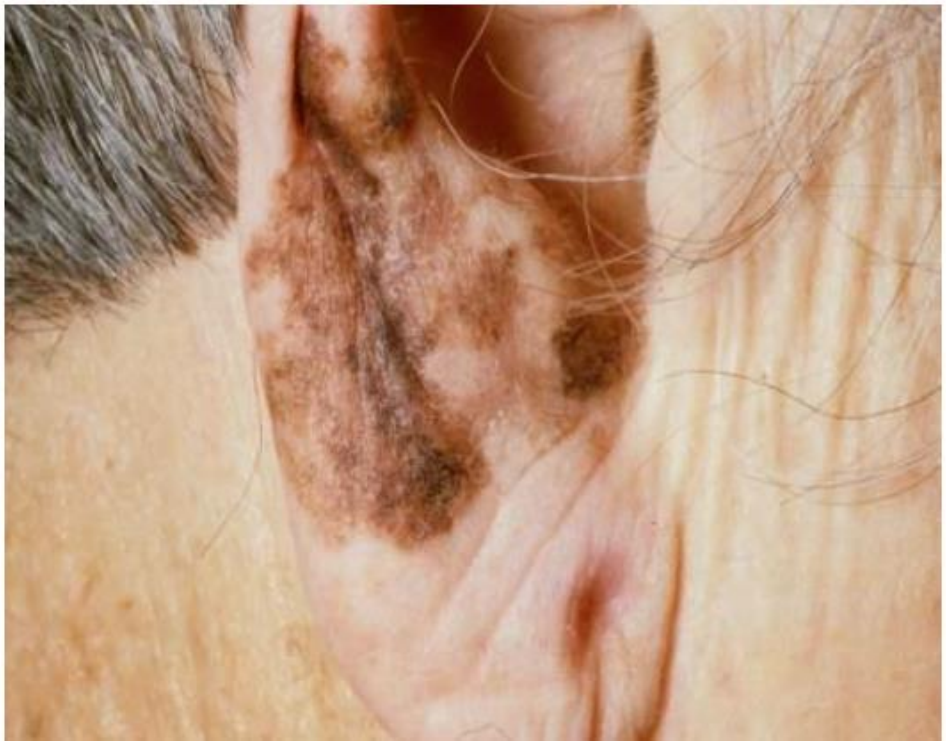
Superficial Spreading (80%)
Intermittent sun exposure

Lentigo maligna (10%)
Chronic continuous exposure

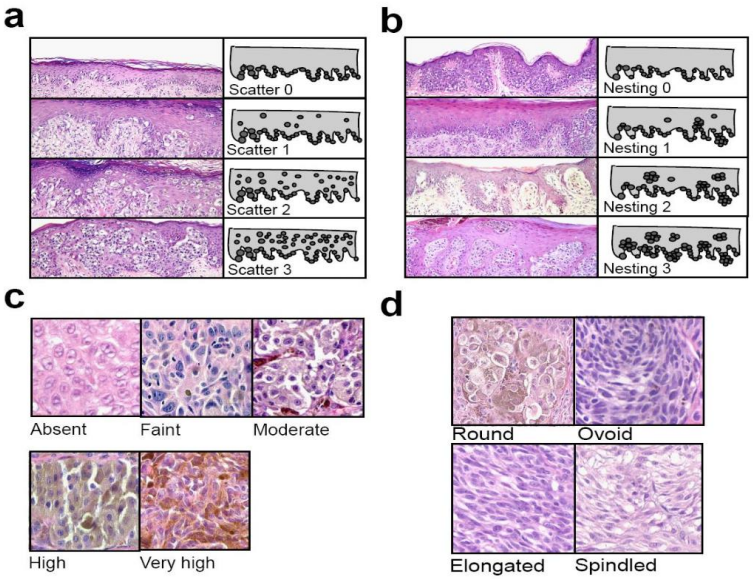
Acral (5%)
No sun exposure

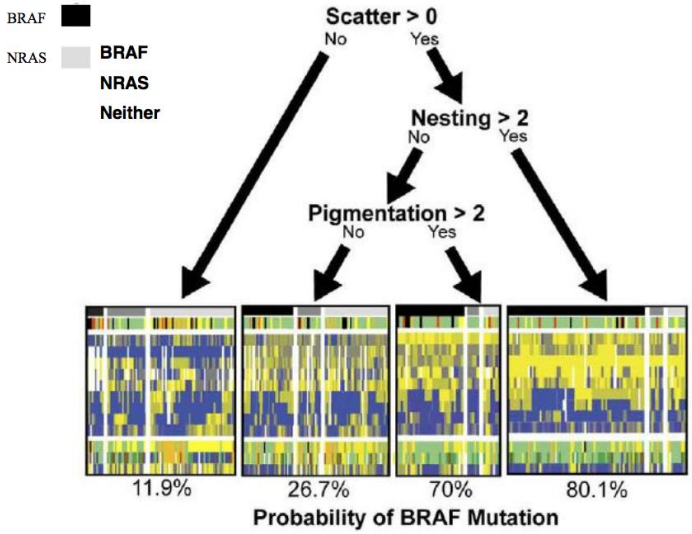


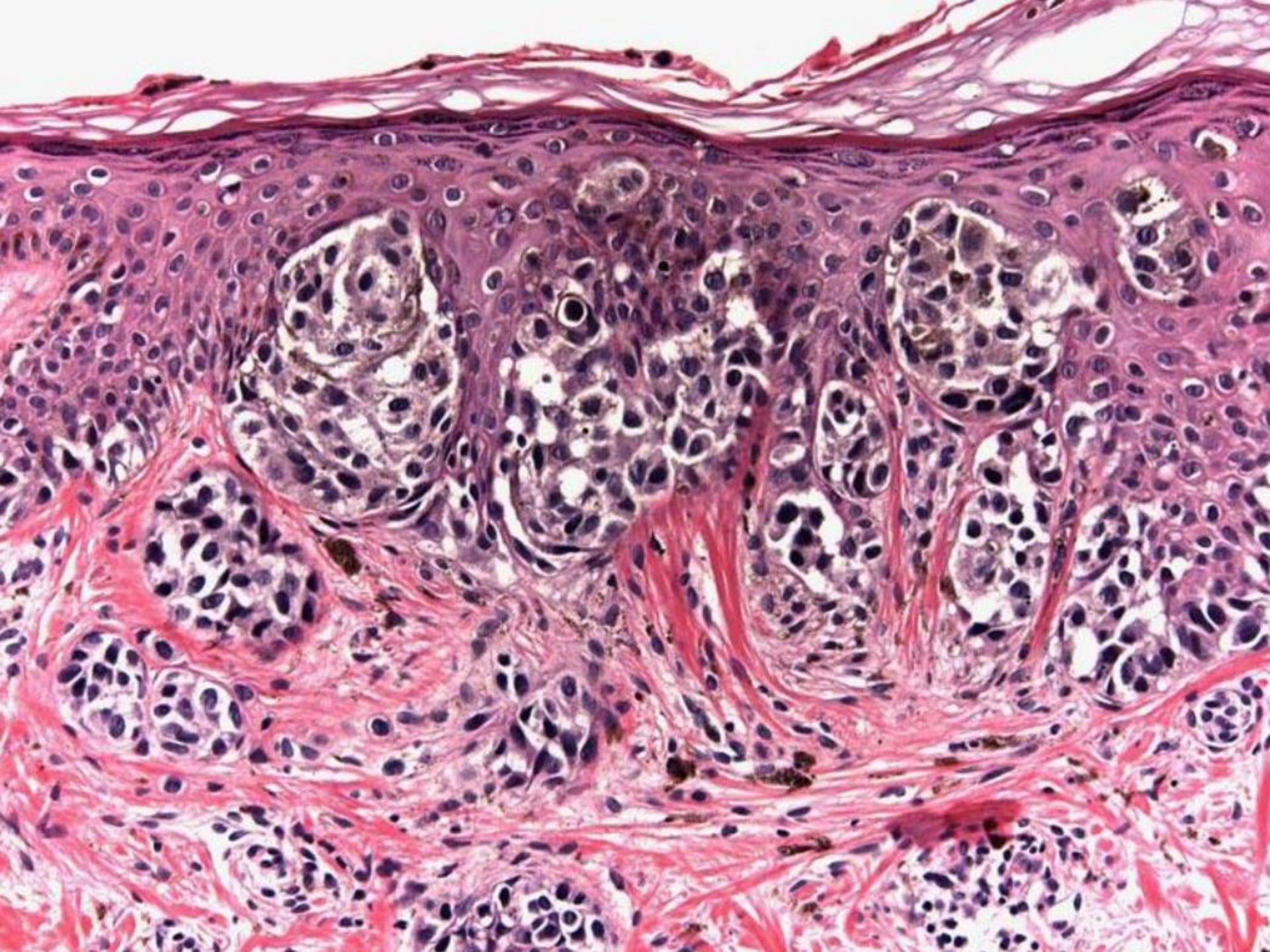


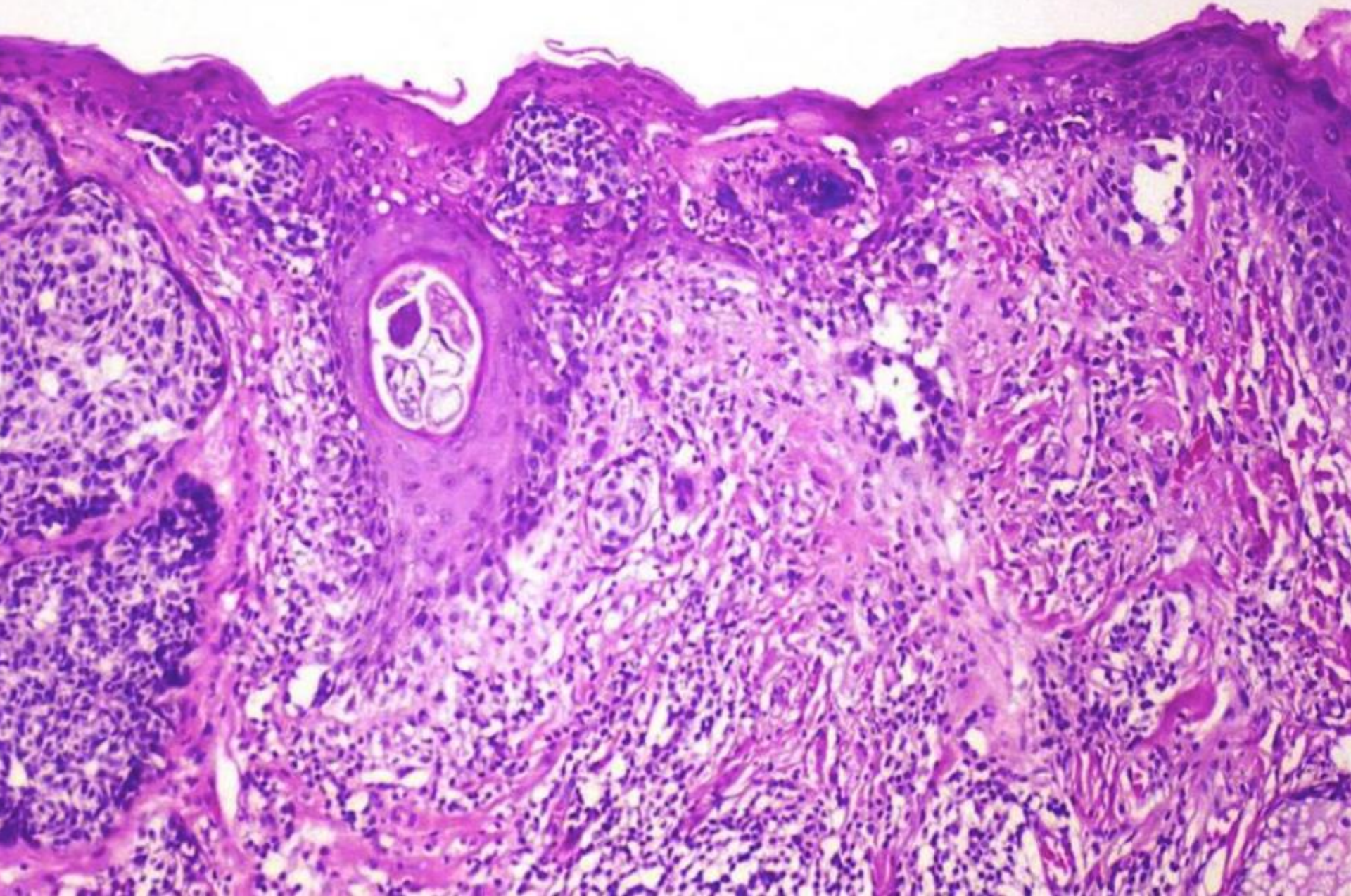


Morphology and Genetic Signature



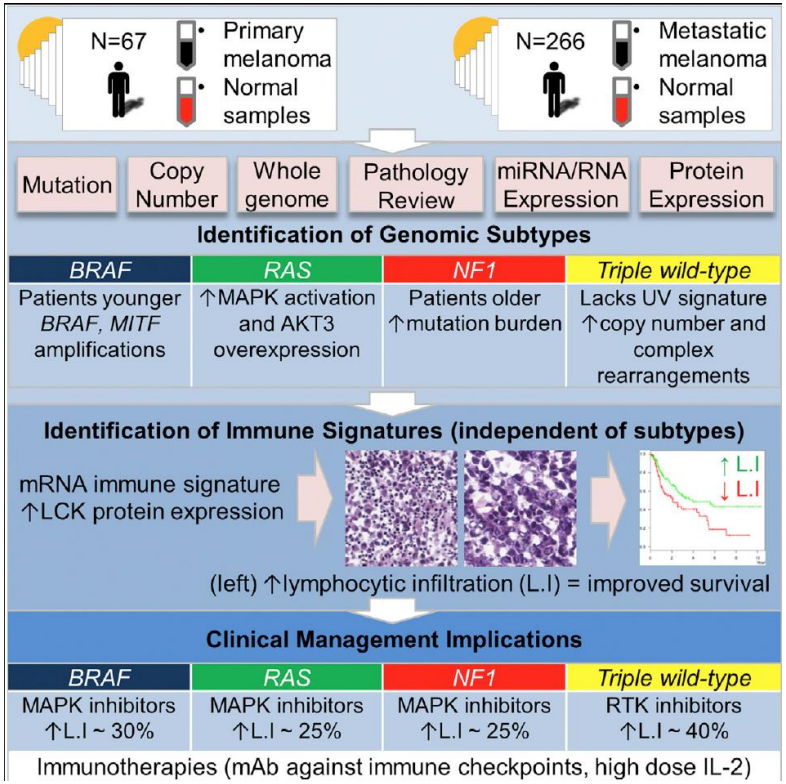






Genomic Pathology in MM

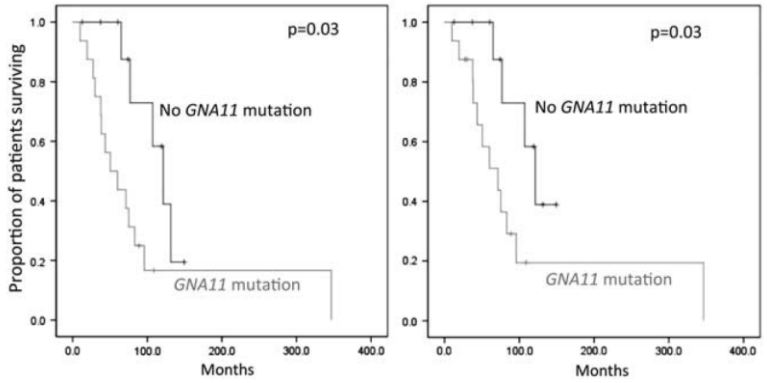
- Represents the largest integrative analysis of cutaneous melanoma (331 patients)
- Establishes a framework for melanoma genomic classification: BRAF, RAS, NF1, and Triple-WT
- Identifies additional subtypes that may benefit from MAPK and RTK-targeted therapies
- Multi-dimensional analyses identify immune signatures associated with improved survival



Akbani et al., 2015, Cell 161, 1681–1696

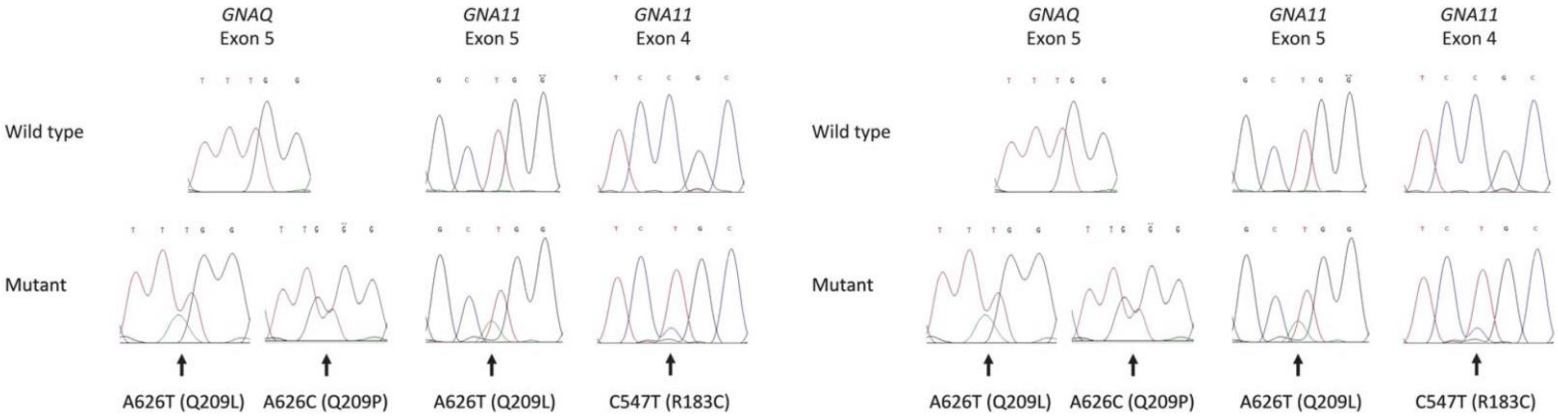
Uveal Melanoma

- **Activating mutations in GNAQ and GNA11, loss-of-function mutations in the tumor suppressor gene BAP1, and recurrent mutations in codon 625 of SF3B1.**
- **Patients with GNA11-mutant tumors had poorer disease-specific survival (60.0 vs 121.4 months, P.0.03) and overall survival (50.6 vs 121.4 months, P.0.03) than those with tumors lacking GNA11 mutations.**



Modern Pathology (2014) 27, 175–183

Uveal Melanoma



Modern Pathology (2014) 27, 175–183

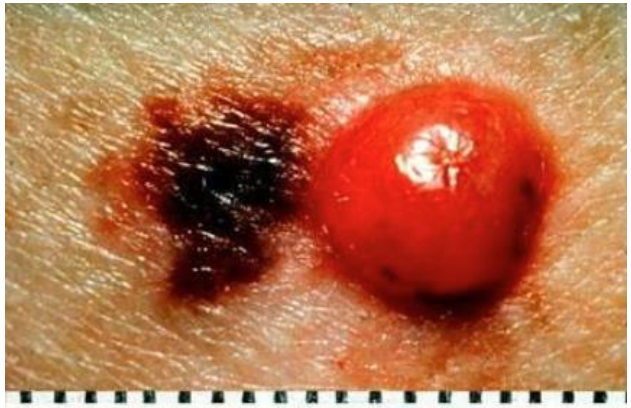
This molecular profile is also shared by primary dermal melanomas and blue melanocytic lesions

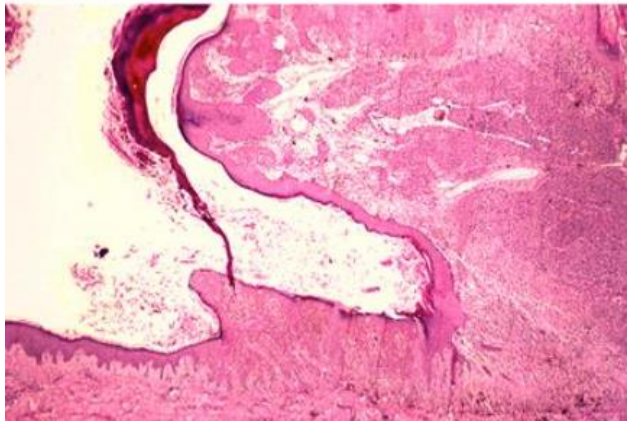
Characteristics of Tumor Progression - Foulds, 1969

- **Not obligate**
  - **most melanocytes will not become nevi, most nevi will not become melanoma, etc**
- **Steps of progression may be skipped**
  - **only 30-50% of melanomas arise in nevi – others presumably arise de novo**
- **Nevertheless, knowledge of tumor progression steps is important**
  - **for accurate diagnosis**
  - **for insight into mechanisms of aggressive behavior**

Tumorigenic & Nontumorigenic melanoma
(Radial & Vertical Growth Phase)

- **ABCD Criteria for RGP**
  - **Asymmetry**
  - **Border irregularity**
  - **Color variegation**
  - **Diameter > 4-6 mm**
- **Vertical Growth Phase**
  - **balloon-like expansion forms nodule**
  - **often symmetrical, smooth borders**
  - **color is often quite uniform**
  - **diameter often less than 6 mm**





Tumorigenic and/or Mitogenic Melanomas (VGP)

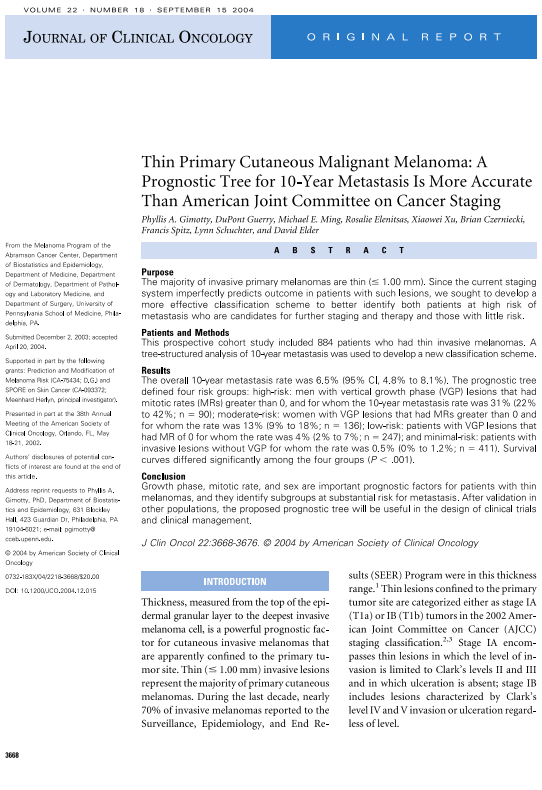
- **Tumorigenic**
  - **Defined as the presence of a mass in the dermis**
  - **Limiting case – there is a cluster of cells in the dermis that is larger than the largest cluster in the epidermis**
- **Mitogenic**
  - **Presence of any mitoses in the dermis**
- **Either finding implies that the lesion has capacity for survival and growth in the dermis and defines it as a VGP melanoma**

Prognosis in Thin Melanoma (AJCC Stage 1)

Tumorigenicity & Mitogenicity -

Both are Prognostic Factors for Metastasis in Thin Melanoma

Thin Primary Cutaneous Malignant Melanoma: A Prognostic Tree for 10-Year Metastasis Is More Accurate Than AJCC Staging



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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Thin Primary Cutaneous Malignant Melanoma: A Prognostic Tree for 10-Year Metastasis Is More Accurate Than American Joint Committee on Cancer Staging

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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A B S T R A C T

Purpose
The majority of invasive primary melanomas are thin (≤ 1.00 mm). Since the current staging system imperfectly predicts outcome in patients with such lesions, we sought to develop a more effective classification scheme to better identify both patients at high risk of metastasis who are candidates for further staging and therapy and those with little risk.

Patients and Methods
This prospective cohort study included 884 patients who had thin invasive melanomas. A tree-structured analysis of 10-year metastasis was used to develop a new classification scheme.

Results
The overall 10-year metastasis rate was 6.5% (95% CI, 4.8% to 8.1%). The prognostic tree defined four risk groups: high-risk: men with vertical growth phase (VGP) lesions that had mitotic rates (MRs) greater than 0, and for whom the 10-year metastasis rate was 31% (22% to 42%; n = 90); moderate-risk: women with VGP lesions that had MRs greater than 0 and for whom the rate was 13% (9% to 18%; n = 136); low-risk: patients with VGP lesions that had MR of 0 for whom the rate was 4% (2% to 7%; n = 247); and minimal-risk: patients with invasive lesions without VGP for whom the rate was 0.5% (0% to 1.2%; n = 411). Survival curves differed significantly among the four groups ($P < .001$).

Conclusion
Growth phase, mitotic rate, and sex are important prognostic factors for patients with thin melanomas, and they identify subgroups at substantial risk for metastasis. After validation in other populations, the proposed prognostic tree will be useful in the design of clinical trials and clinical management.

J Clin Oncol 22:3668-3676. © 2004 by American Society of Clinical Oncology

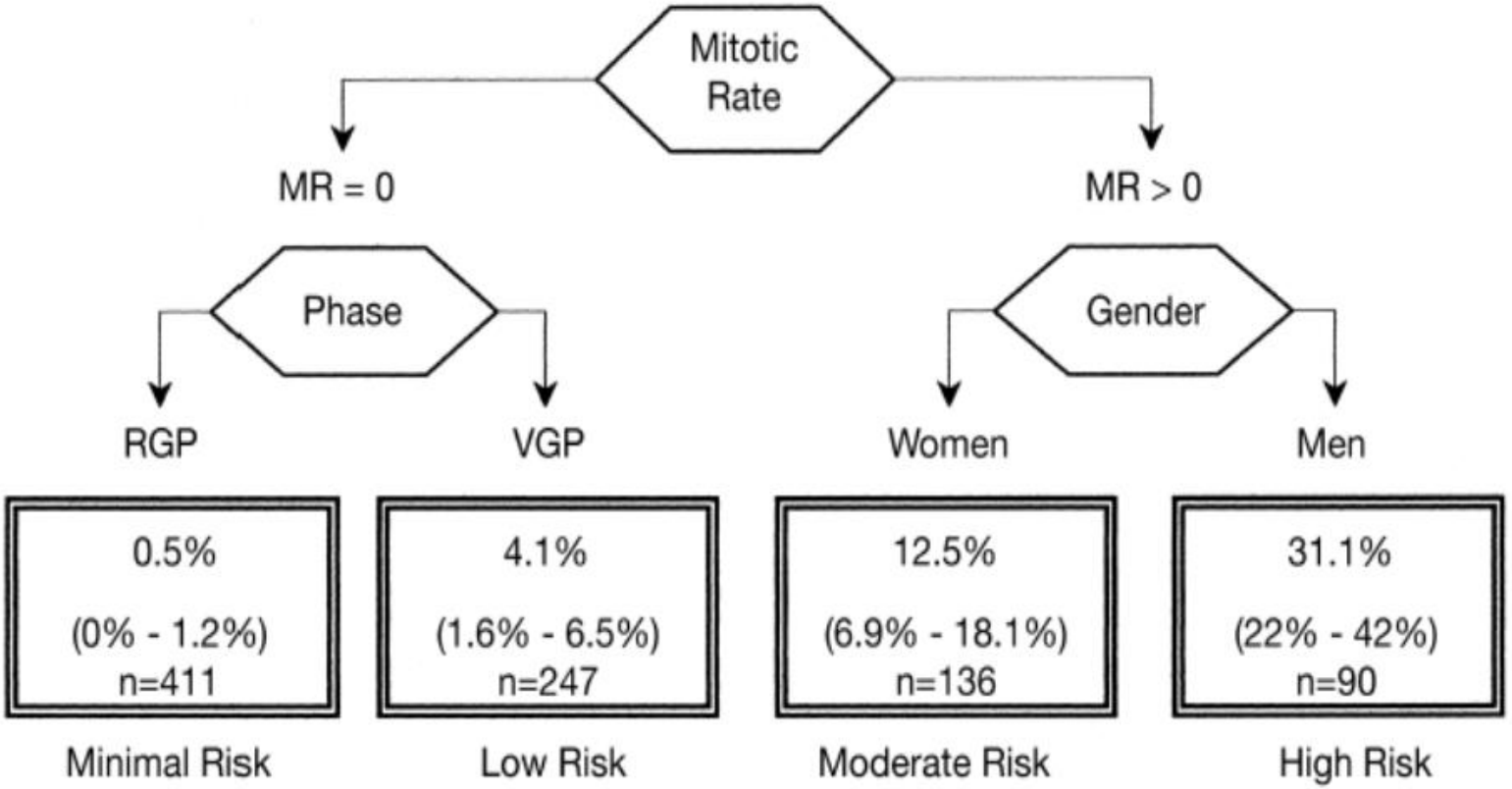
INTRODUCTION

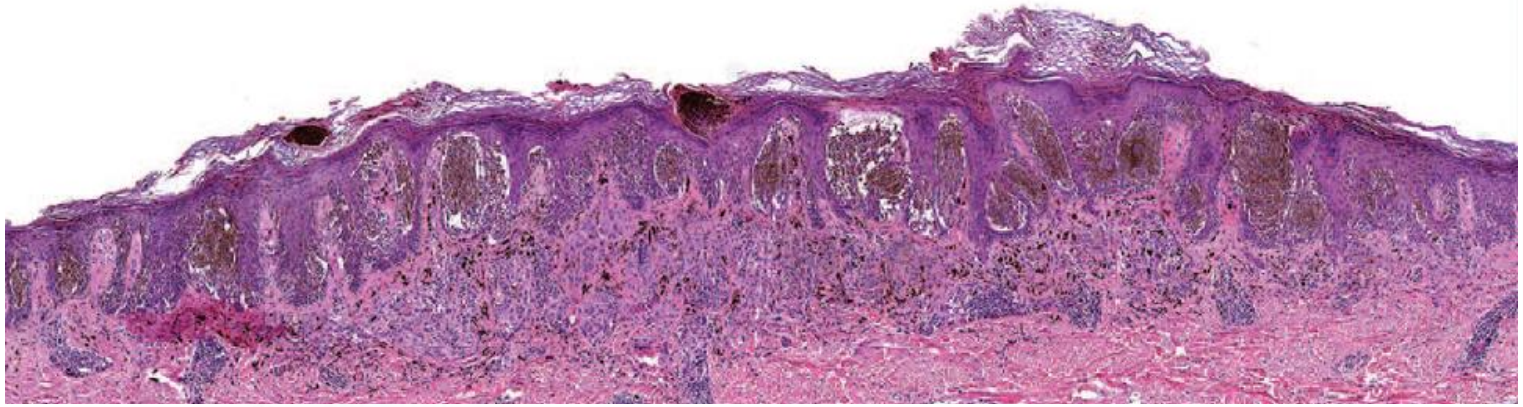
Thickness, measured from the top of the epidermal granular layer to the deepest invasive melanoma cell, is a powerful prognostic factor for cutaneous invasive melanomas that are apparently confined to the primary tumor site. Thin (≤ 1.00 mm) invasive lesions represent the majority of primary cutaneous melanomas. During the last decade, nearly 70% of invasive melanomas reported to the Surveillance, Epidemiology, and End Results (SEER) Program were in this thickness range.[1] Thin lesions confined to the primary tumor site are categorized either as stage IA (T1a) or IB (T1b) tumors in the 2002 American Joint Committee on Cancer (AJCC) staging classification.[2,3] Stage IA encompasses thin lesions in which the level of invasion is limited to Clark's levels II and III and in which ulceration is absent; stage IB includes lesions characterized by Clark's level IV and V invasion or ulceration regardless of level.

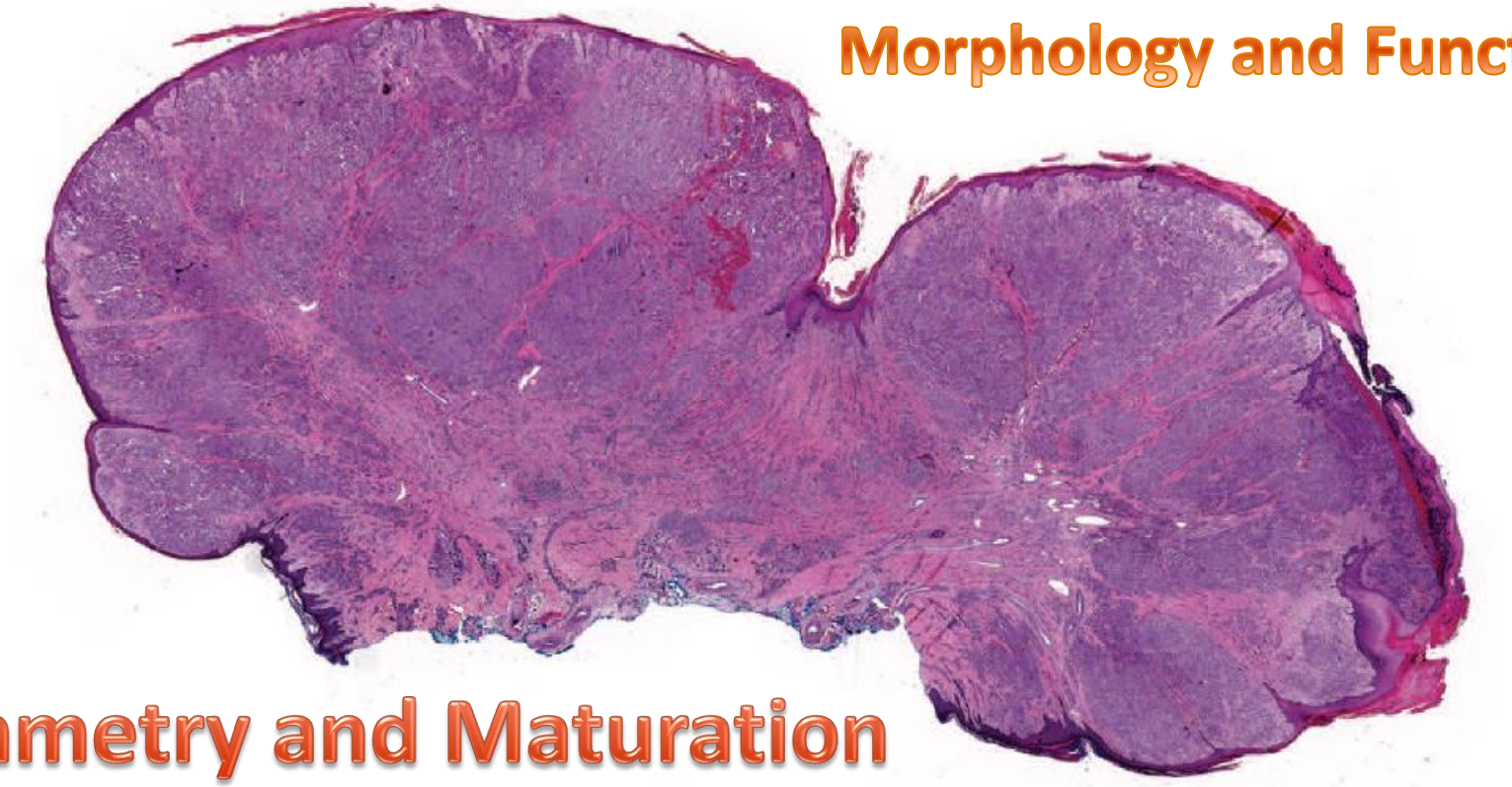
Gimotty PA, Guerry D, Ming M, Elenitsas R, Xu X, Czerniecki B, Spitz F, Schuchter L Elder DE. J Clin Oncol 22:3668-3676 2004.

A Prognostic Tree for 10-Year Metastasis in AJCC Stage 1 Melanoma

(Breslow thickness < 1 mm, n = 884 patients)







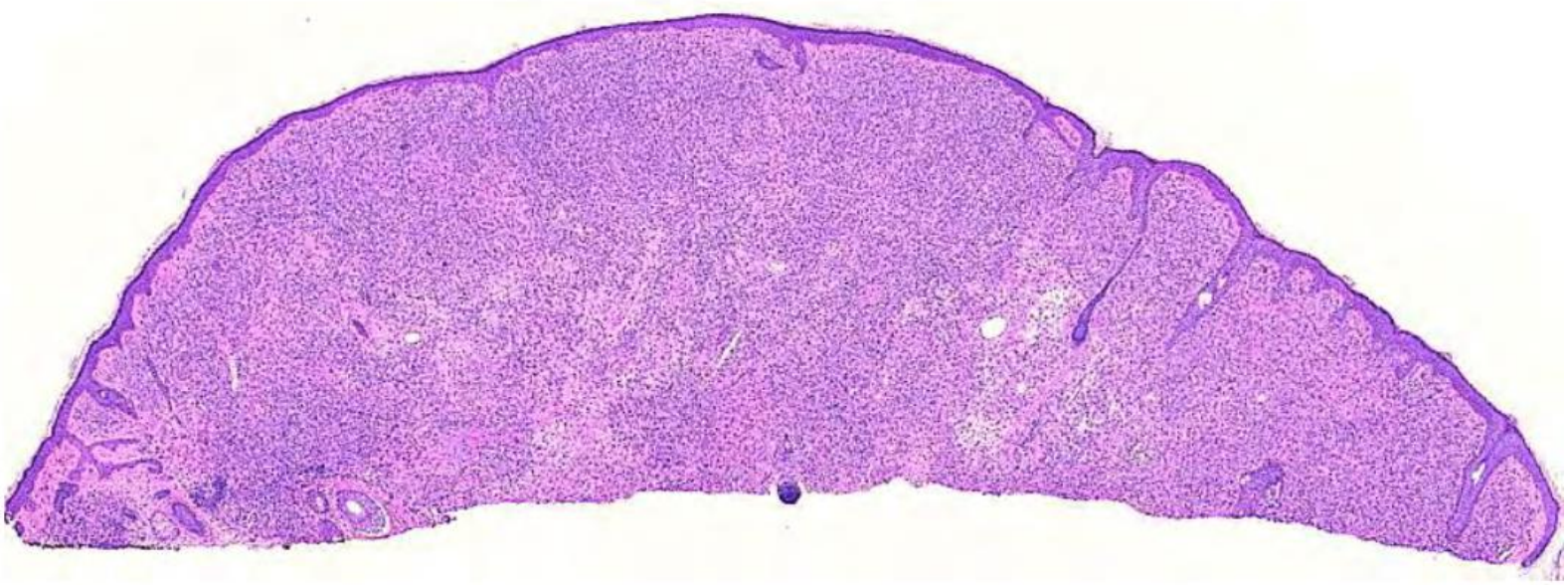
Morphology and Function

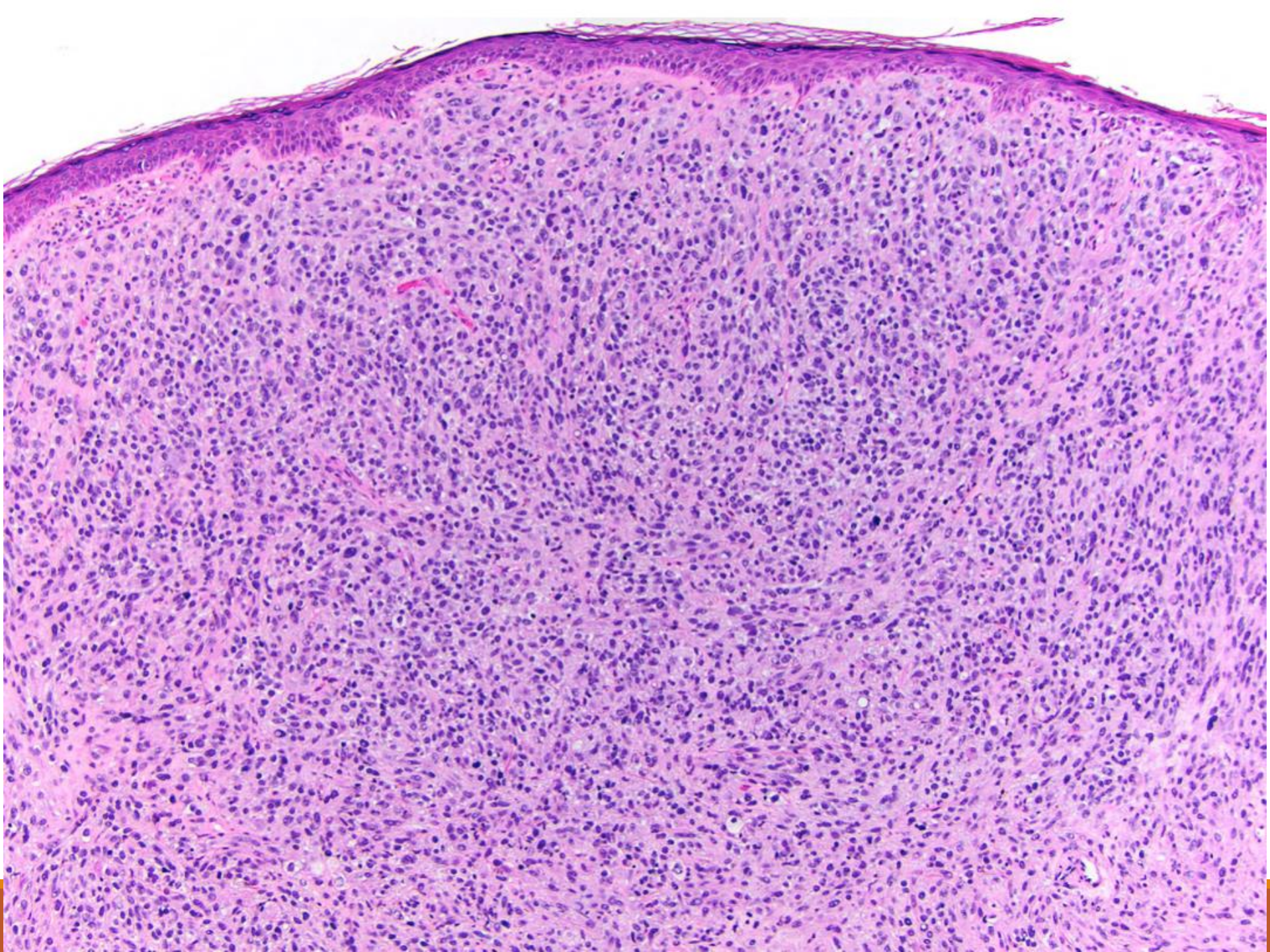
Symmetry and Maturation

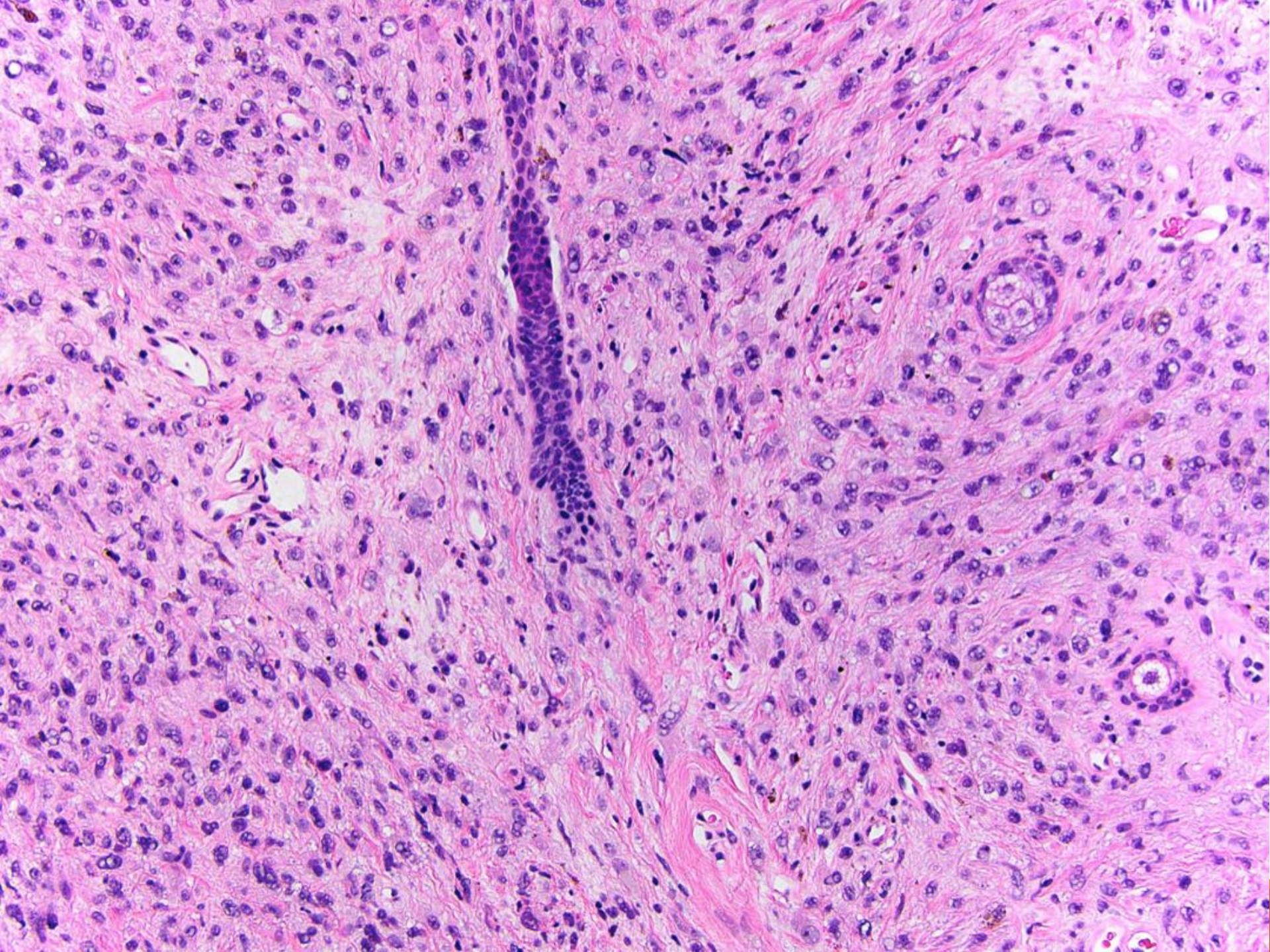
Case 1

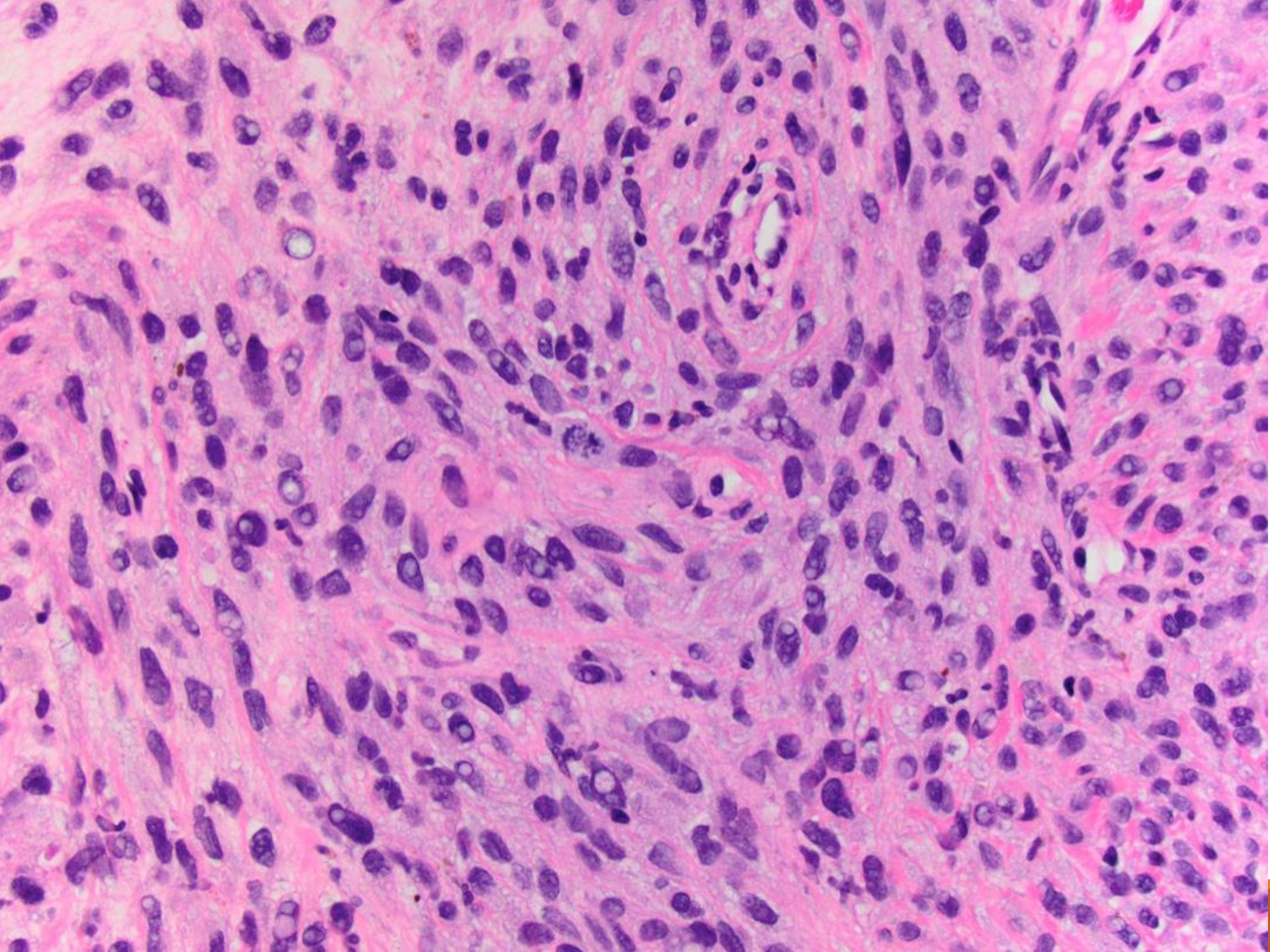
61-YEAR OLD MAN WITH A 9 MM BROWN NODULE ON HIS LEFT MALAR CHEEK; BENIGN KERATOSIS?

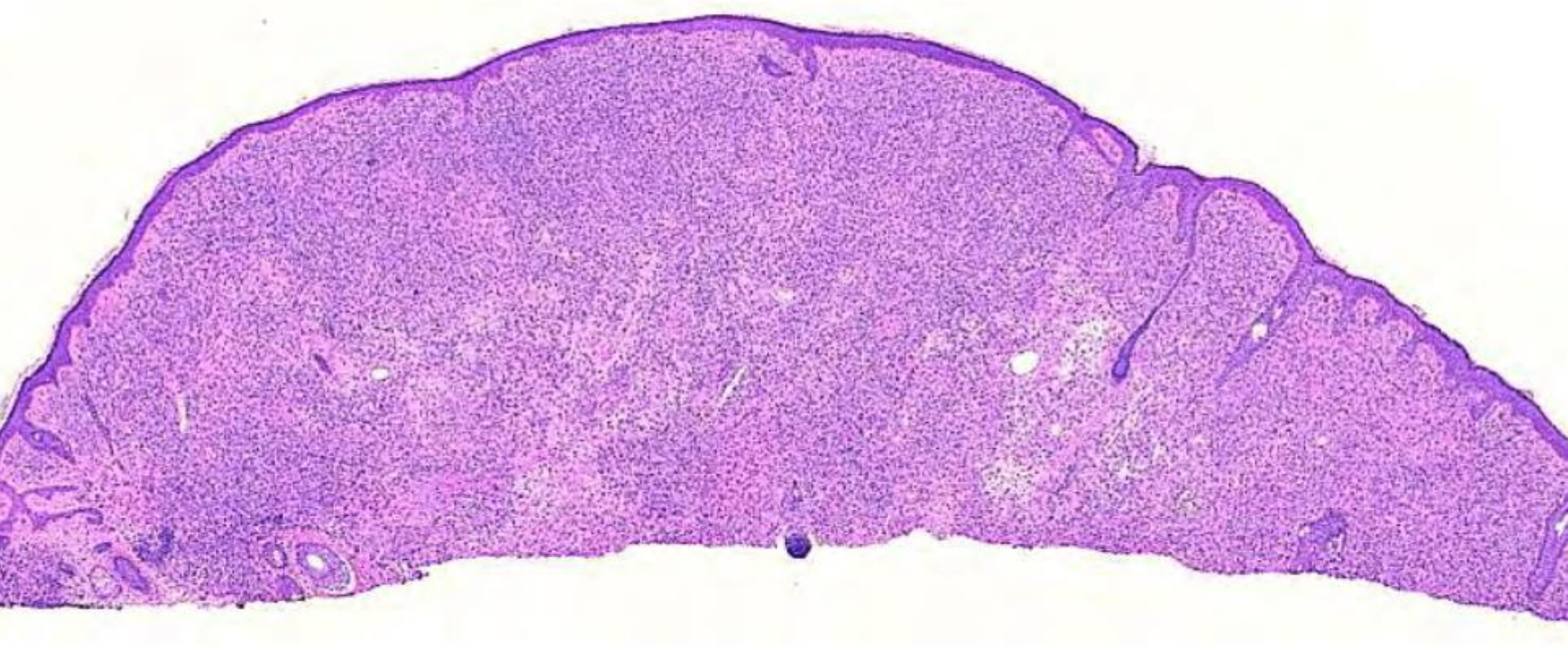
Brown nodule on the malar cheek



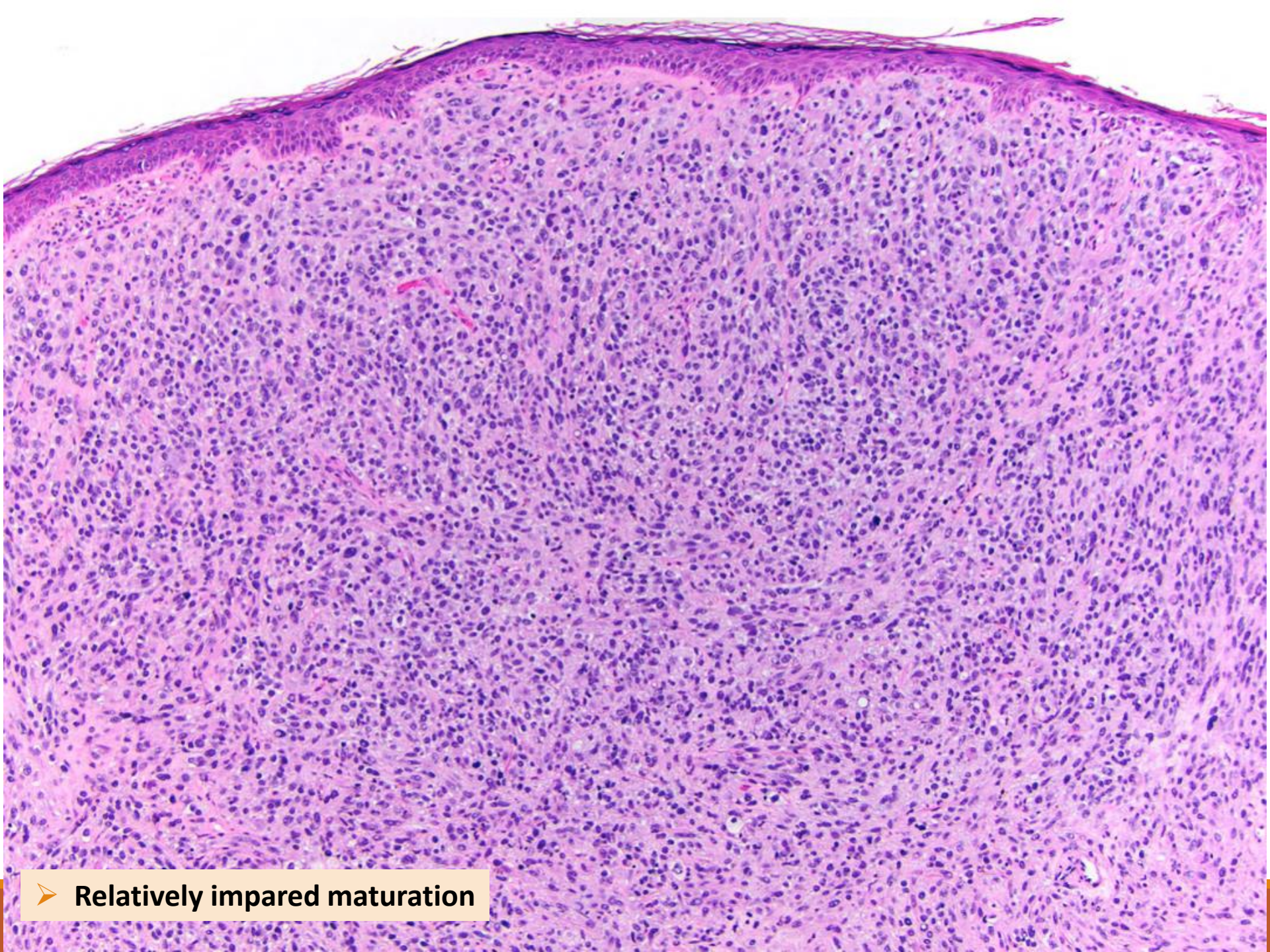


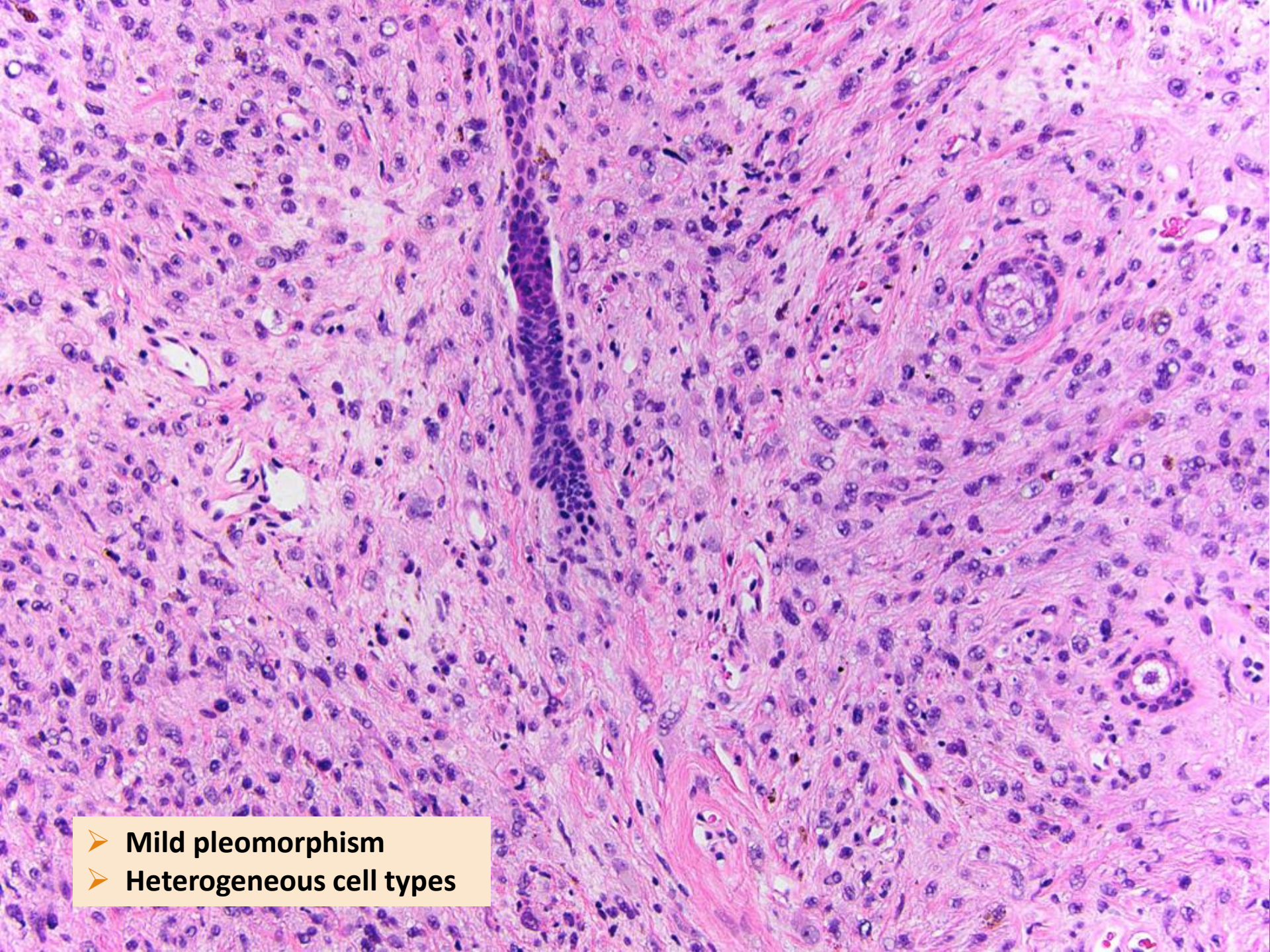


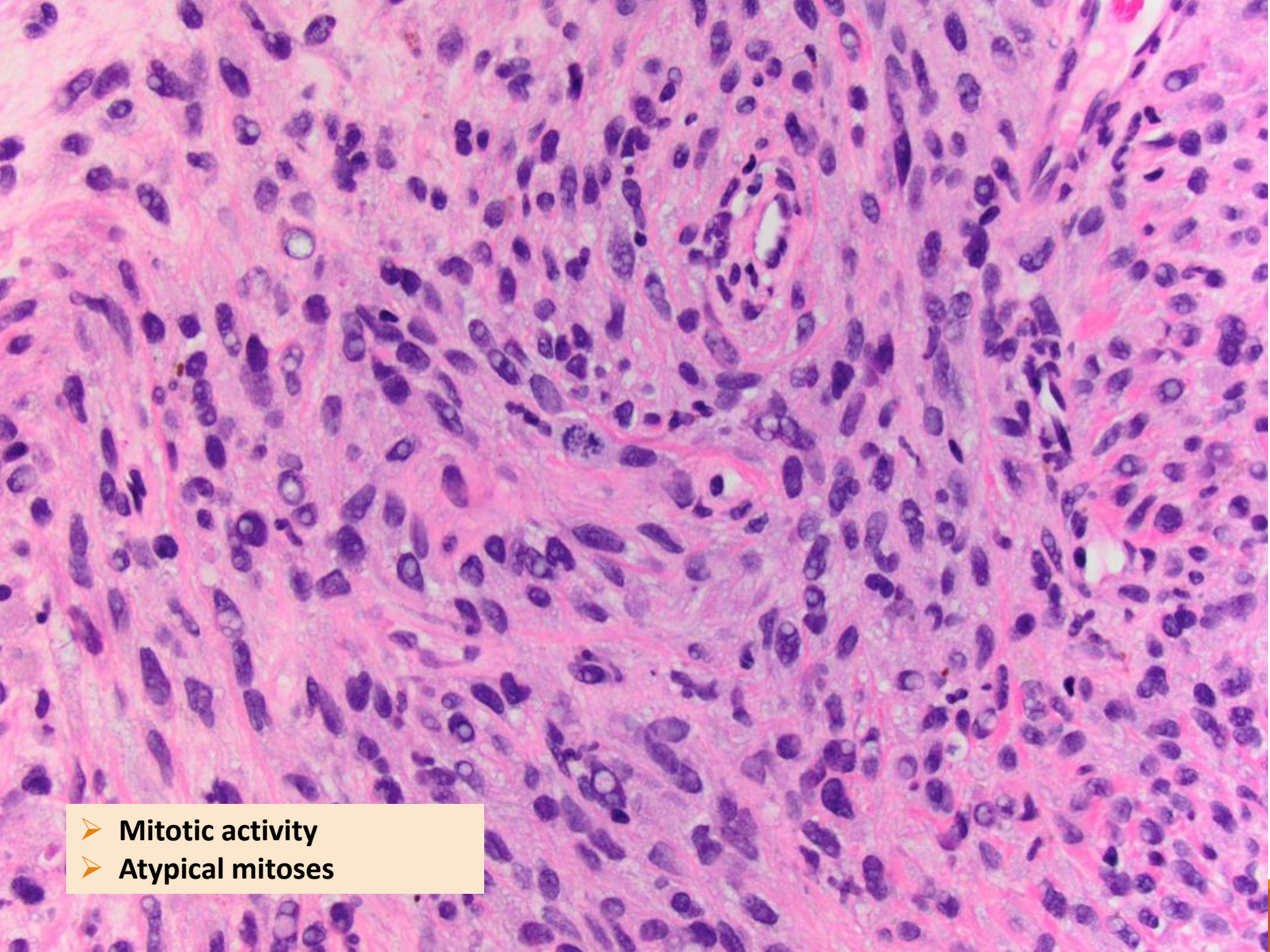




- Relatively asymmetric
- Poorly circumscribed
- No overt junctional component
- Pushing border


➢ Relatively impared maturation


Mild pleomorphism
Heterogeneous cell types


Mitotic activity
Atypical mitoses

Nevoid Melanoma

- **"Diagnosis of a nevus which one later regrets"!**
- **Old terminology:**
  - **"Minimal deviation melanoma"**
  - **"Borderline melanoma"**
- **MELTUMP:**
  - **Melanocytic Tumor of Uncertain Malignant Potential**

Nevoid Melanoma

ARCHITECTURE

- Relatively asymmetric
- Poorly circumscribed
- No overt junctional component
- Relatively impaired maturation
- Pushing border

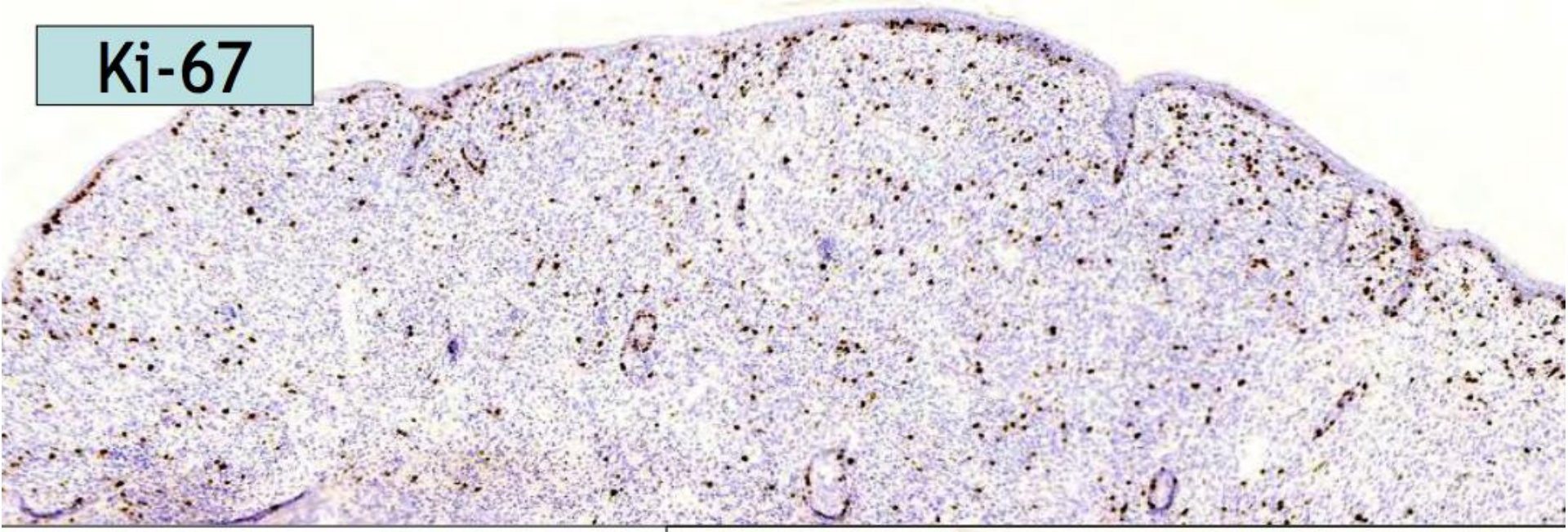
CYTOLOGY

- Mild pleomorphism
- *Mitotic activity
- *Atypical mitoses
- Heterogeneous cell types
- Large nucleoli

Nevoid Melanoma

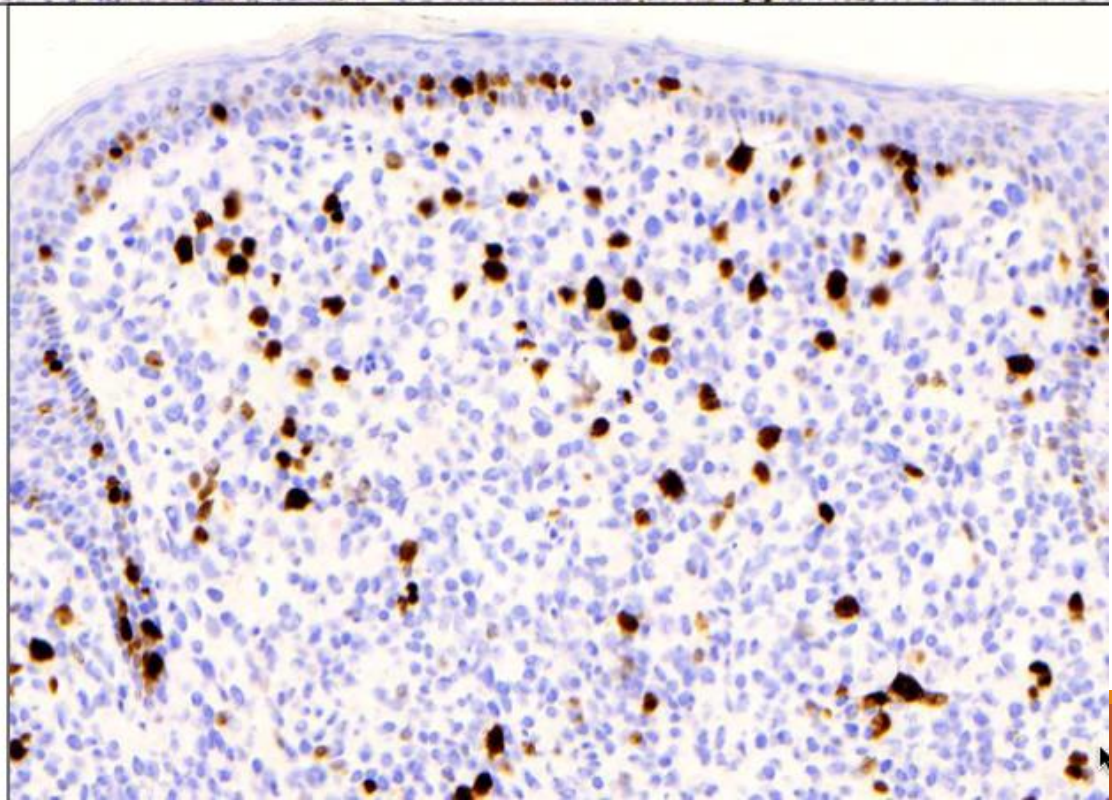
- **Ki-67: brisk & relatively diffuse activity**
- **HMB45: expressed in the deep aspects**
- **Cyclin D1: brisk & relatively diffuse activity**
- **Mart-1/Melan-A, S100, and MiTF: variable positivity**

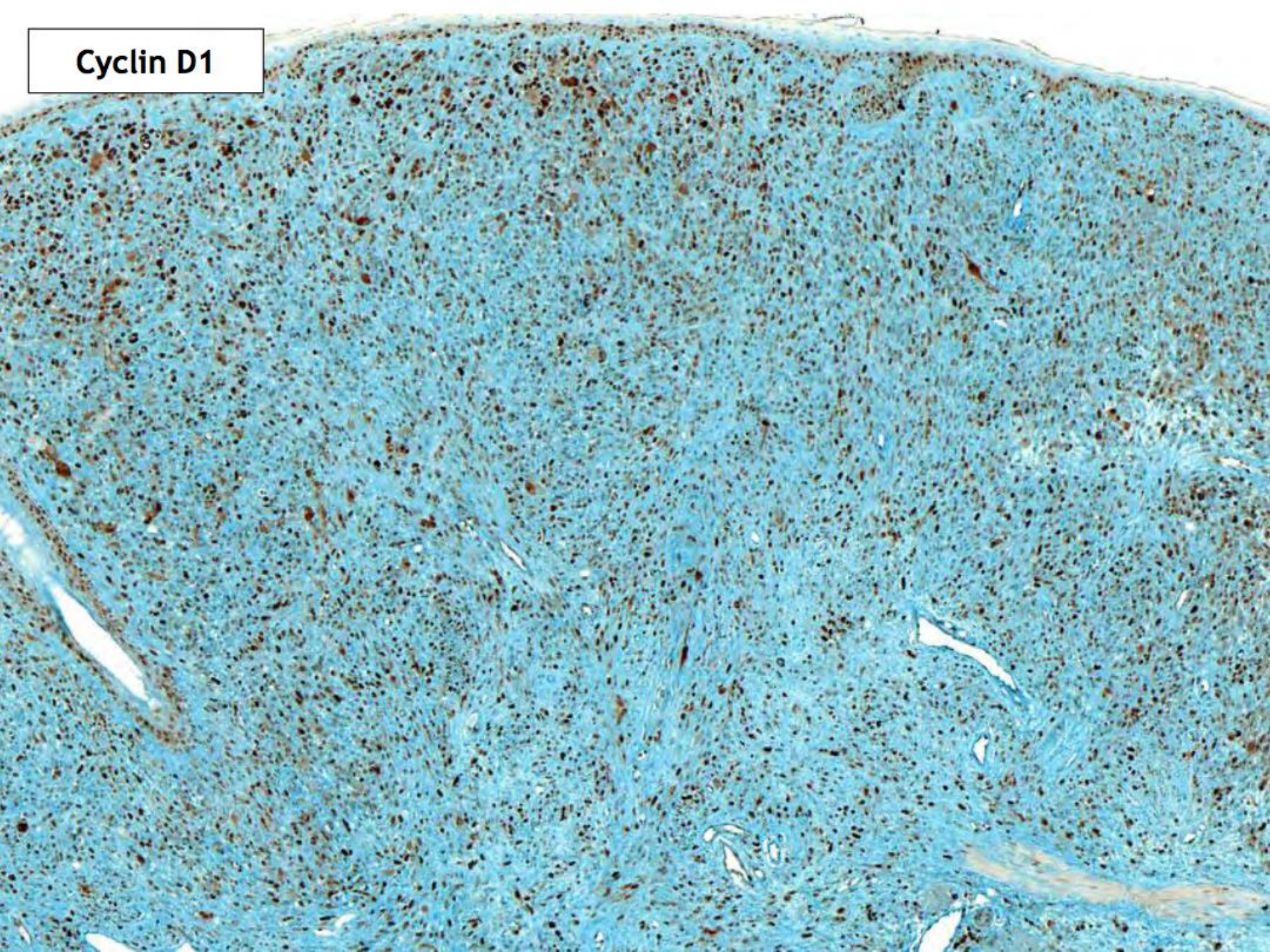
Ki-67

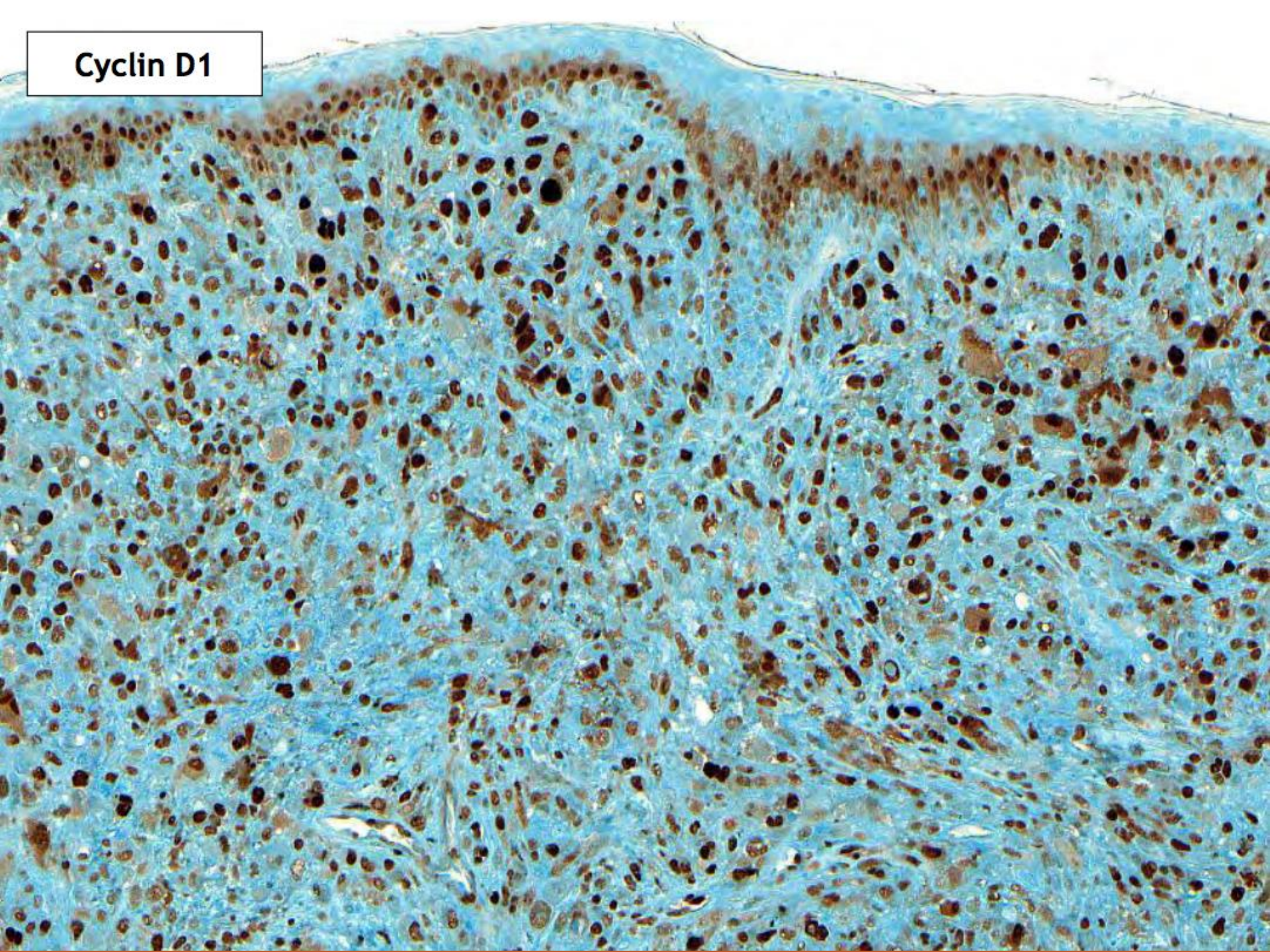


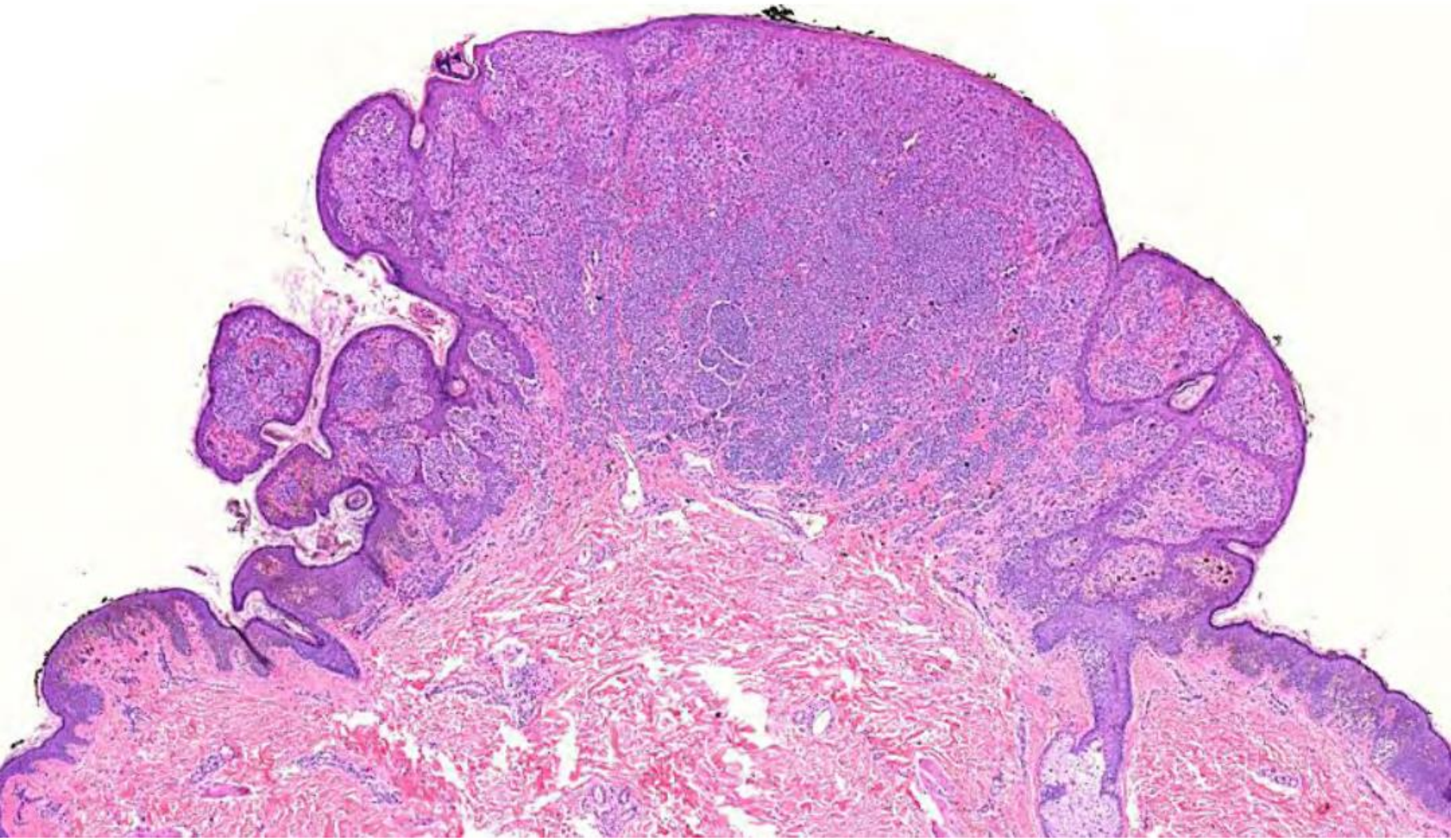
Awareness:

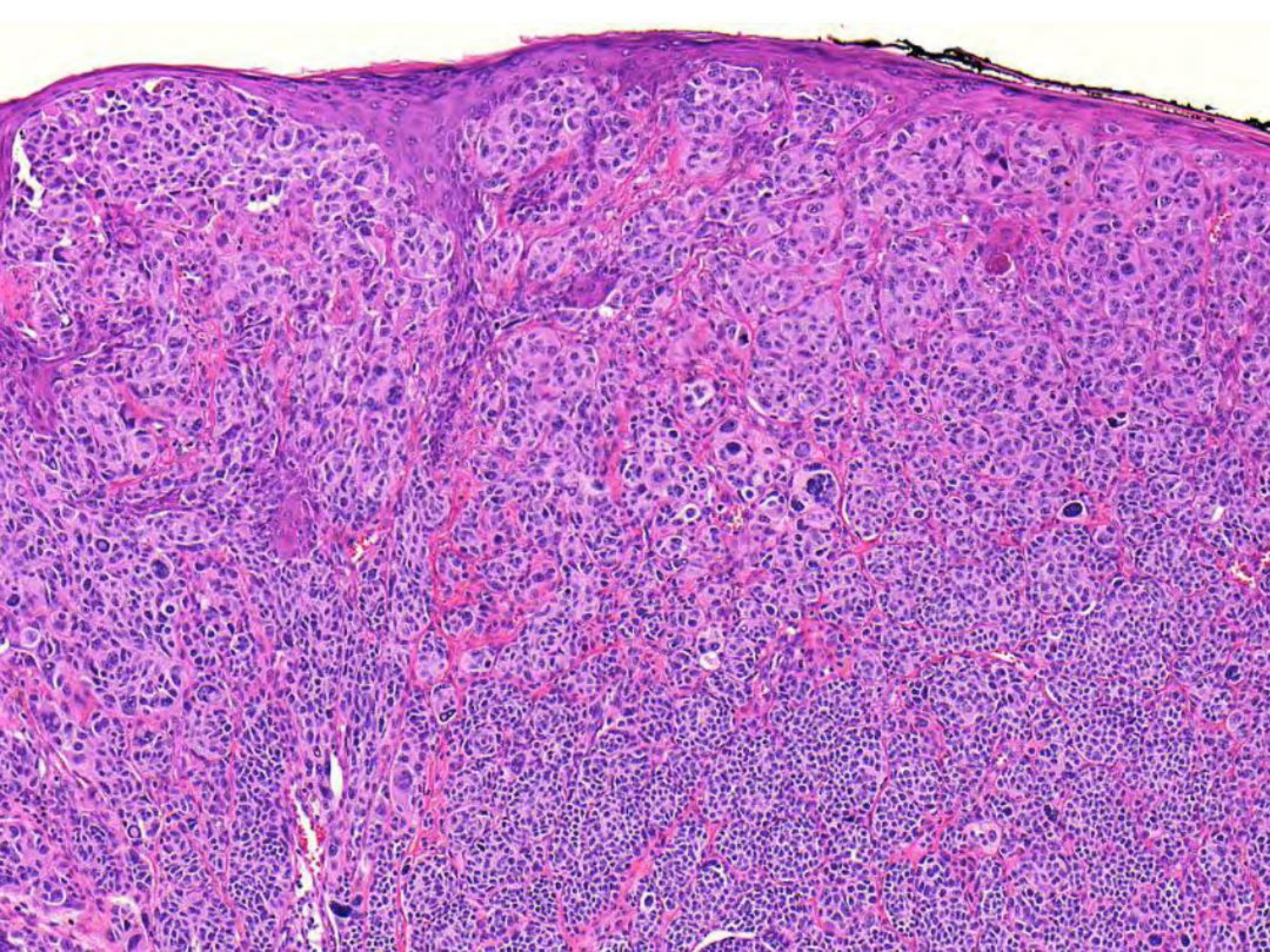
1. Background proliferating cells
   - Lymphocytes
   - Keratinocytes
2. Size of positive cells
3. Superficial vs deep positivity
4. Proliferative index

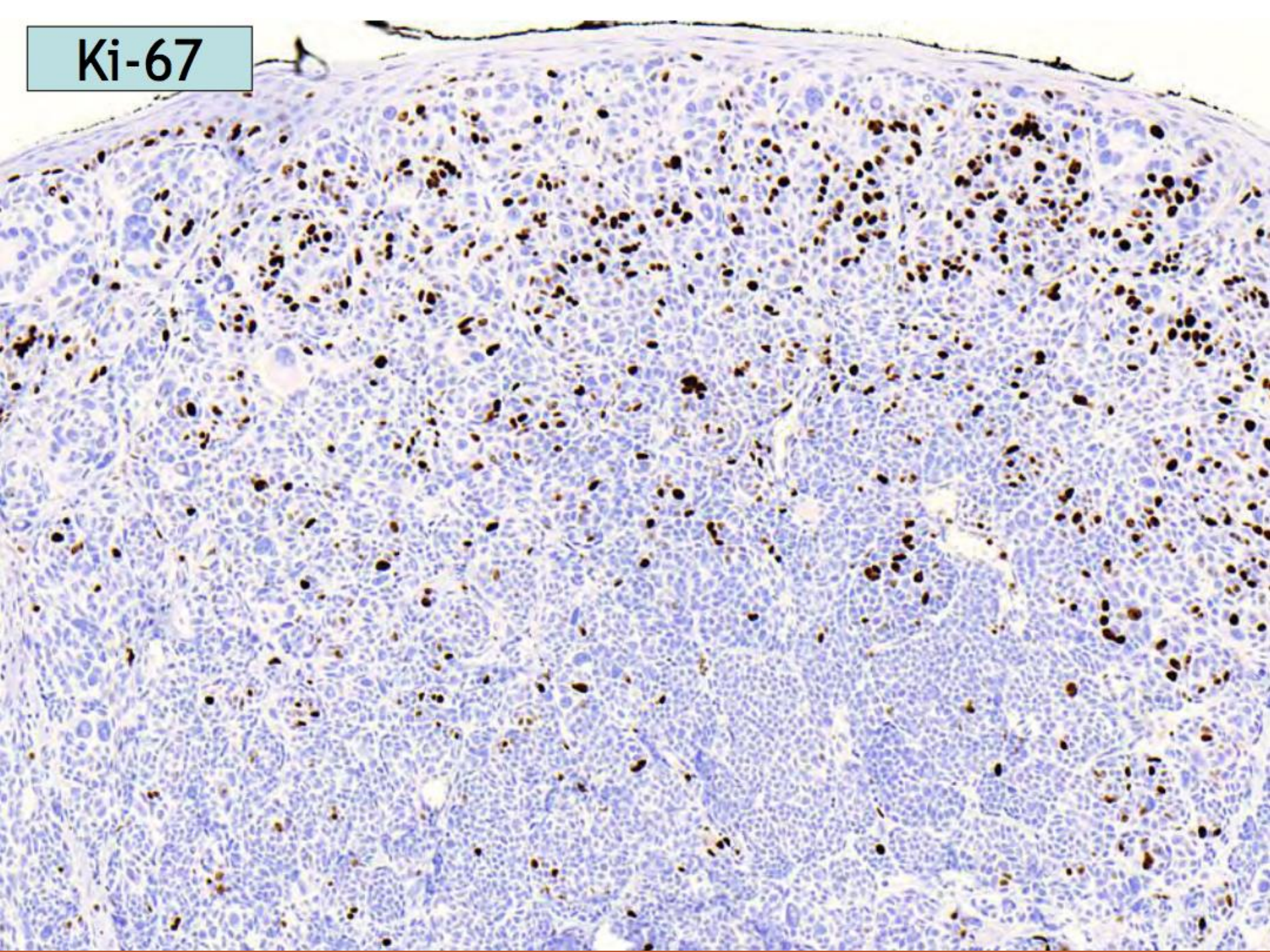


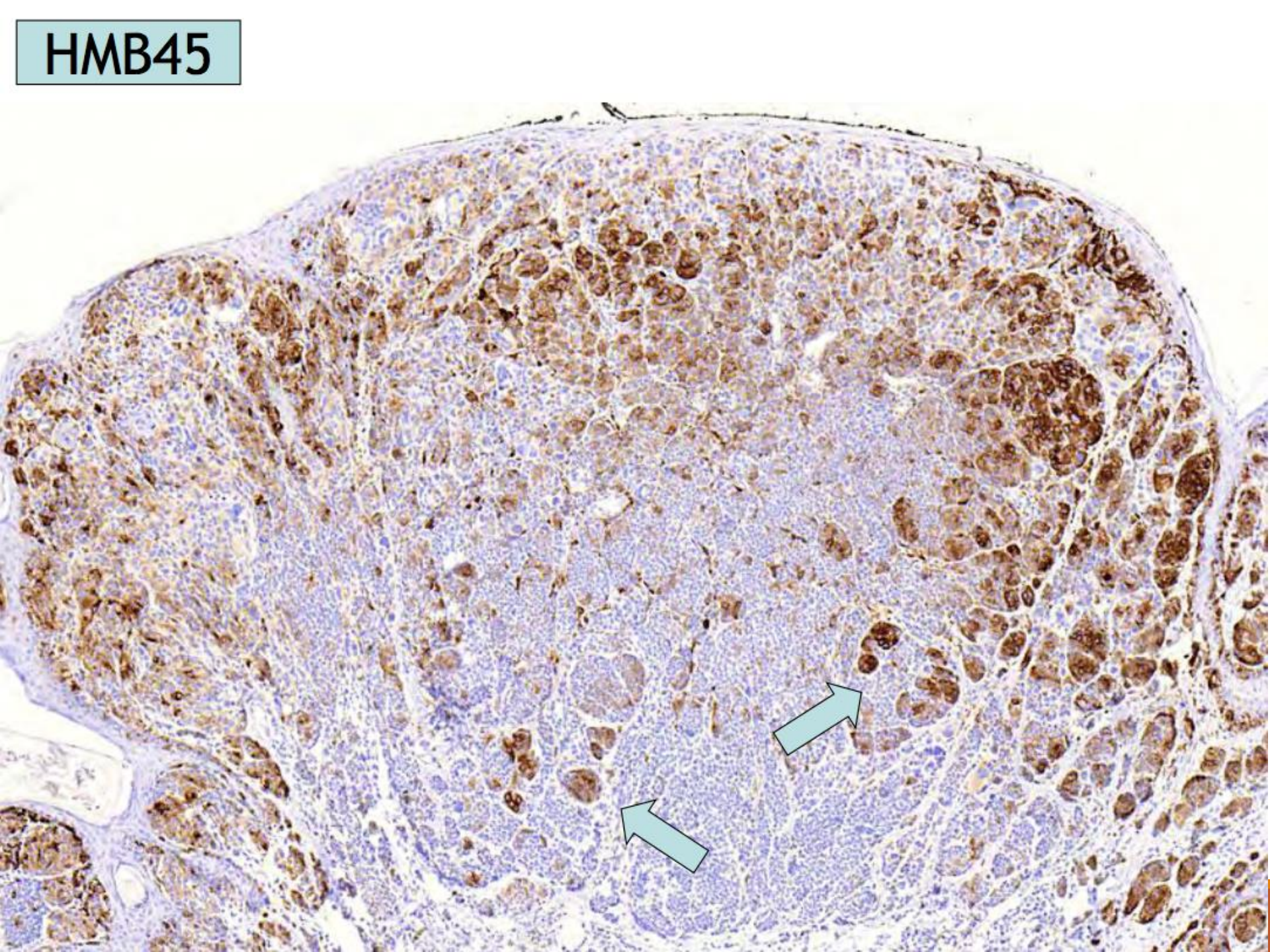

Cyclin D1

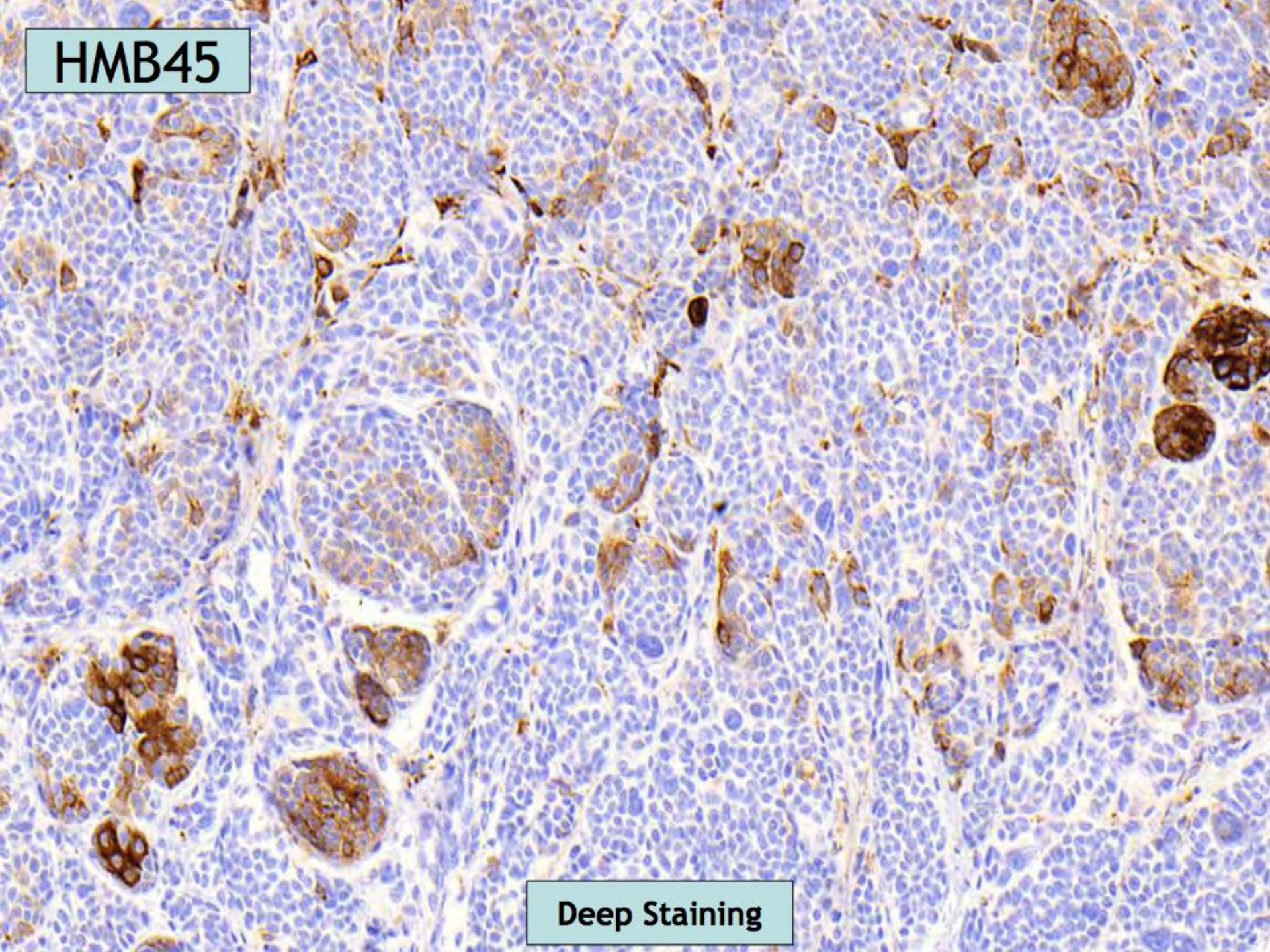

Cyclin D1





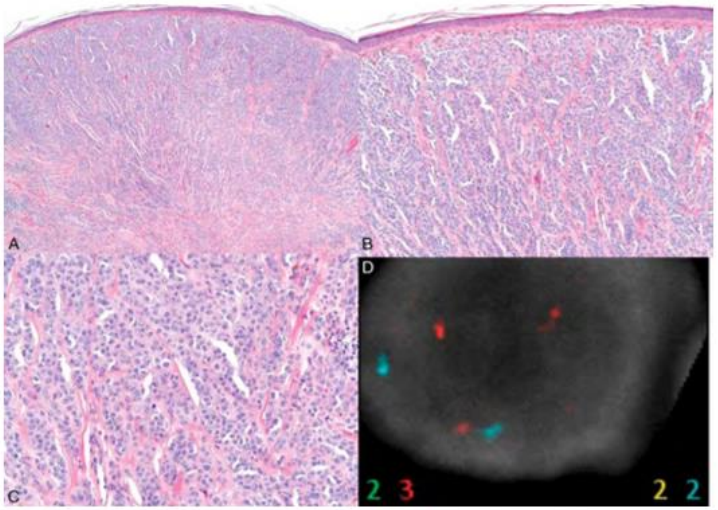

Ki-67


HMB45


HMB45
Deep Staining

Fluorescence In-Situ Hybridization (FISH)

- **Probes:**
  - **6p25 (RREB1)**
  - **6q23 (MYB)**
  - **11q13 (CCND1) – CEP6**
- **Sensitivity: 83%**
- **Specificity: 98%**



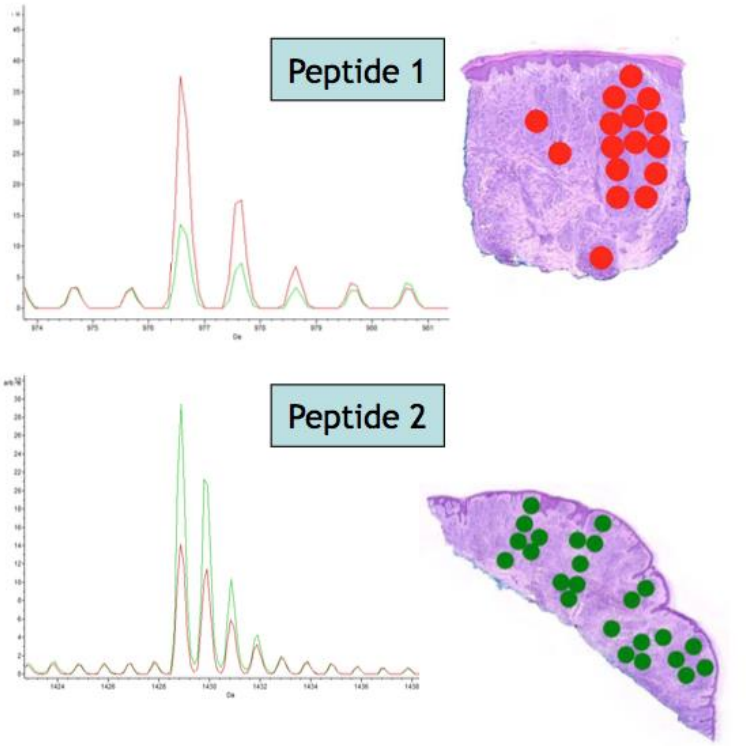
➢ 59-year-old woman; ? atypical nevus

FISH: 3 signals with *RREB1* (red) and 2 signals with CEP6 (aqua) probes. The numbers (2, 3, 2, 2) indicate the number of signals with CCND1 (green), *RREB1* (red), *MYB* (yellow), and CEP6 (aqua) probes. Amplification of the *RREB1* locus is c/w nevoid melanoma.

Zembowicz A et al. Arch Pathol Lab Med, 2012

MALDI Imaging Mass Spectrometry (MALDI IMS)

- **Probes:**
  - **12-peptide algorithm**
  - **15-peptide algorithm**
- **Sensitivity: 85%**
- **Specificity: 100%**



Sepehr A, et al. Modern Pathology 2013

Key Elements

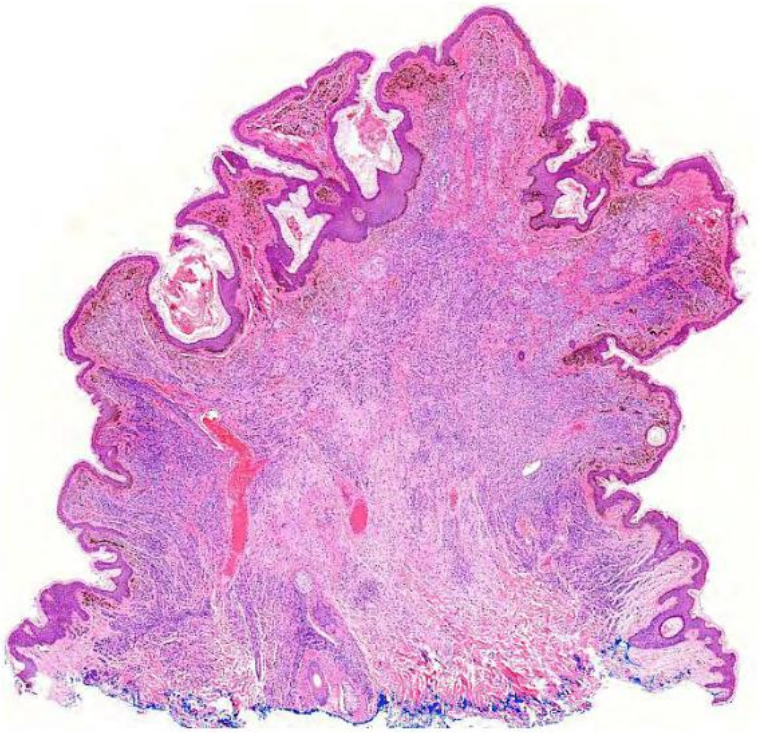
- Patient's age
- History of change or prior trauma
- Pregnancy or hormonal influence
- Deceiving "benign" architecture and/or pseudo-maturation
- No excessive cytologic pleomorphism
- Presence of mitotic figures, especially in low numbers and in the deep aspects
- Diffuse and deep HMB45 staining pattern
- High levels of Ki-67 and cyclin D1 activity
- Utility and limitations of FISH/MALDI IMS

Key Elements

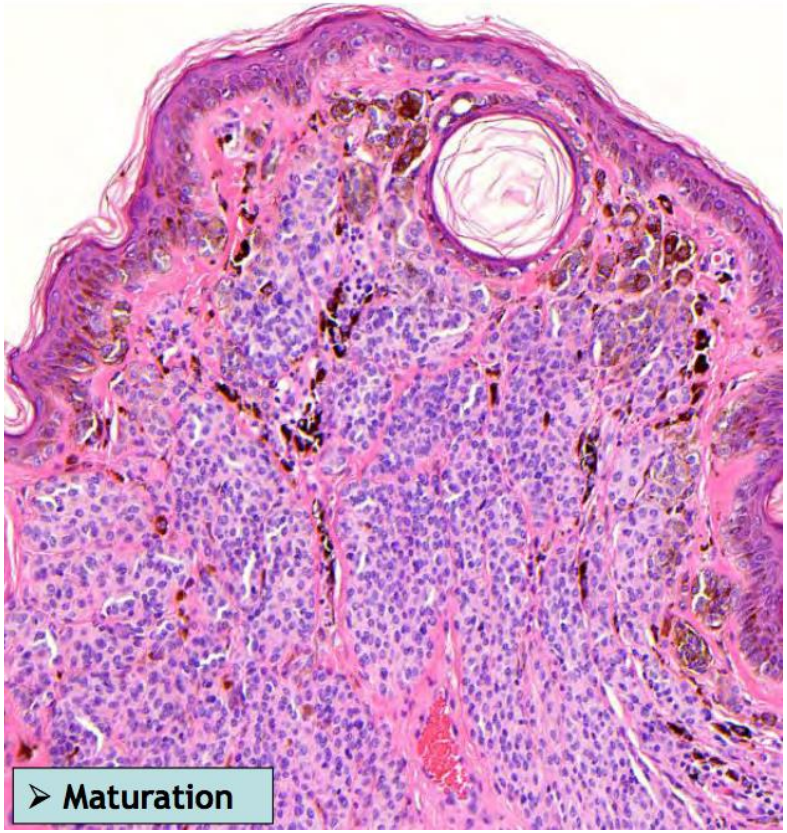
- **Deceiving “nevic” architecture in lower magnifications**
- **Minimal cytologic atypia in high power**
- **Non-brisk mitotic activity**

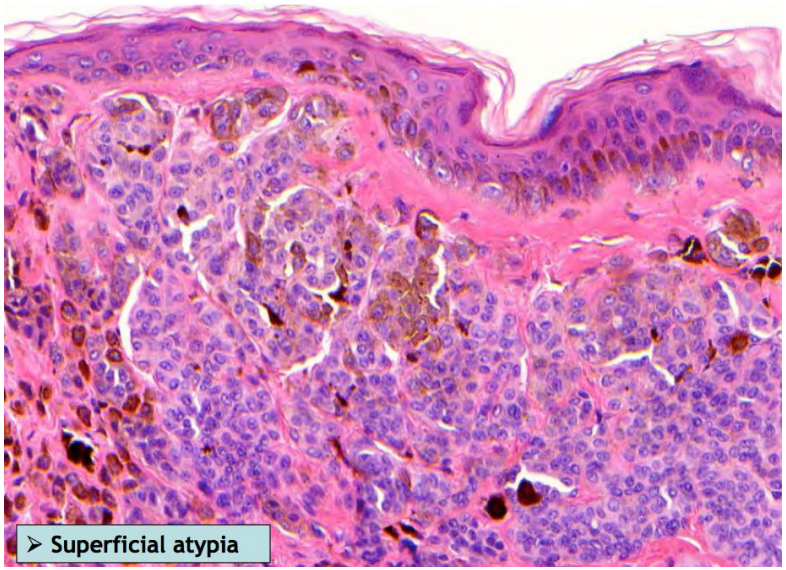
Dermal Nevus with Irritation Effect

- **Only superficial (if any) cytological atypia, mostly in the irritated zone**
- **Rare (if any) superficial mitoses, mostly in the irritated zone**
- **HMB45 or cyclin D1 are negative in deeper aspects of the nevus**
- **Ki-67 is usually < 5%**



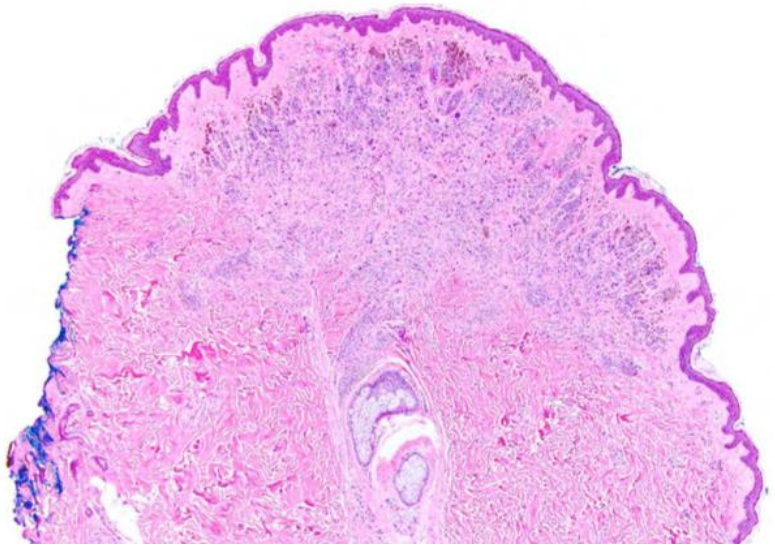
Dermal Nevus with Irritation Effect



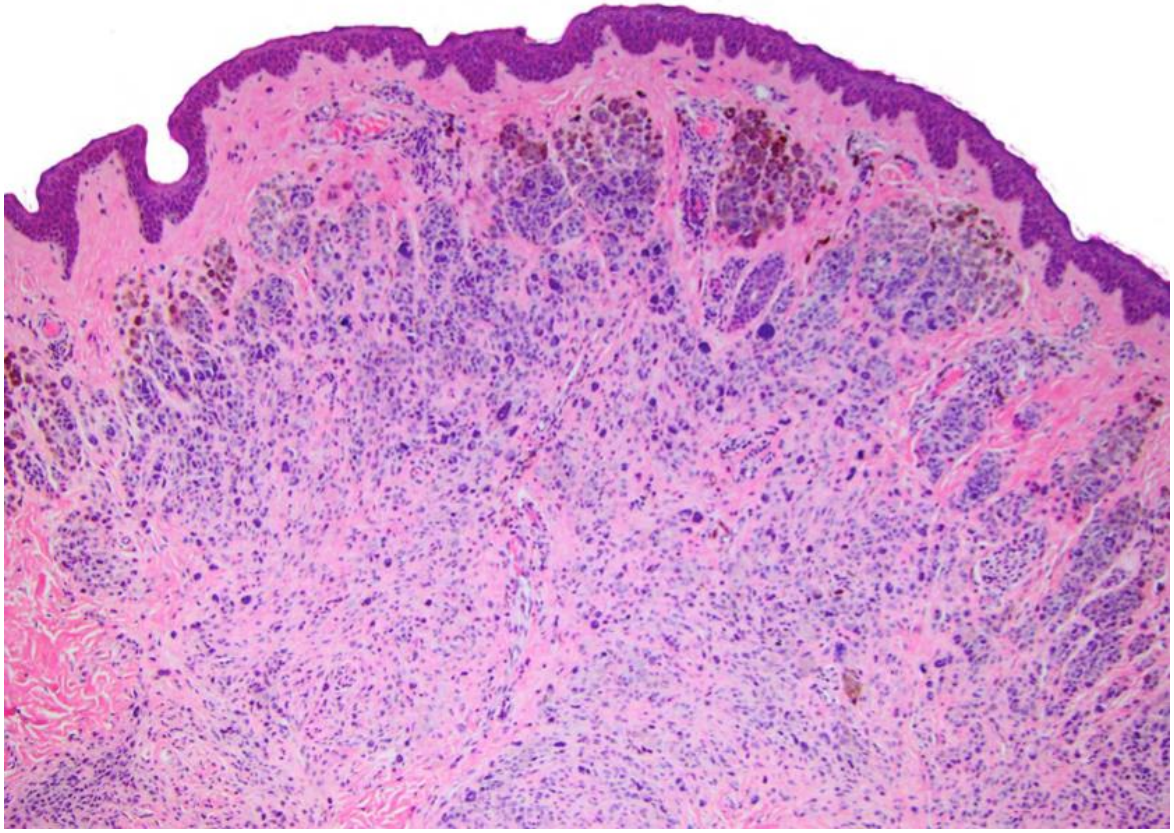


Dermal Nevus with "Senescence" Changes

- **Some cytological atypia of senescence type is usually present**
- **Usually no mitotic activity seen**
- **HMB45 or cyclin D1 are negative in deeper aspects of the nevus**
- **Ki-67 is usually < 5%**



Dermal Nevus with "Senescence" Changes

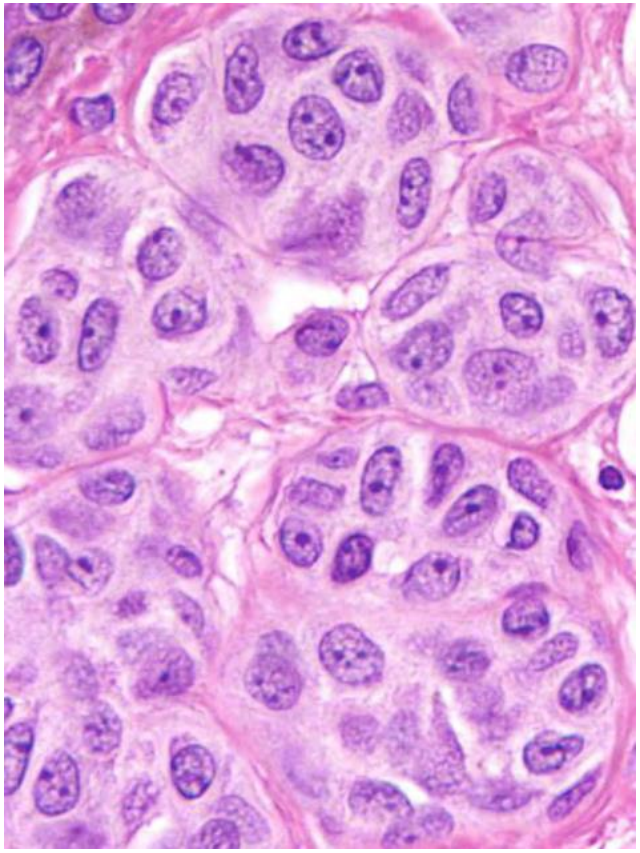


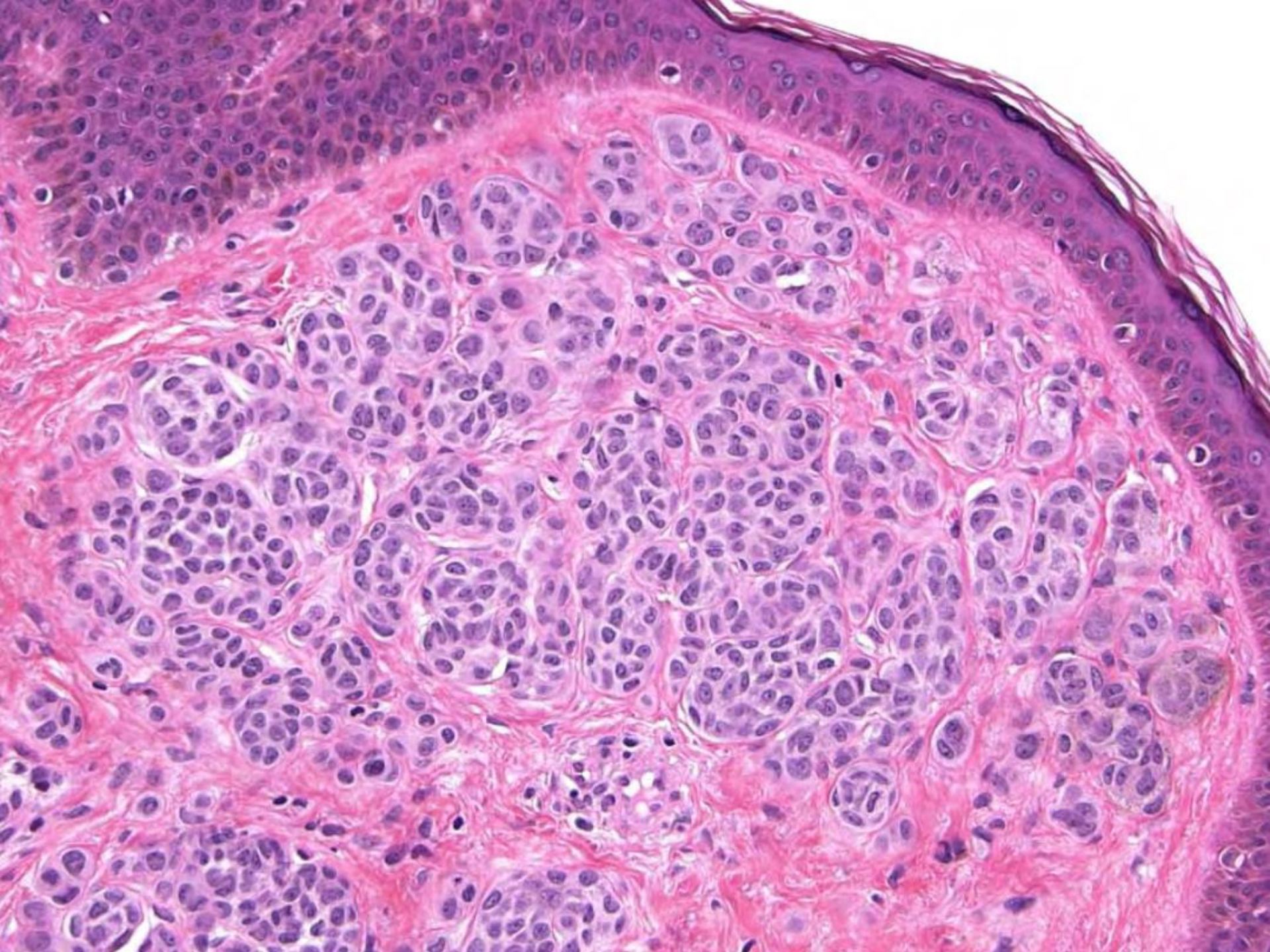
Nevi with Pregnancy-Related Changes

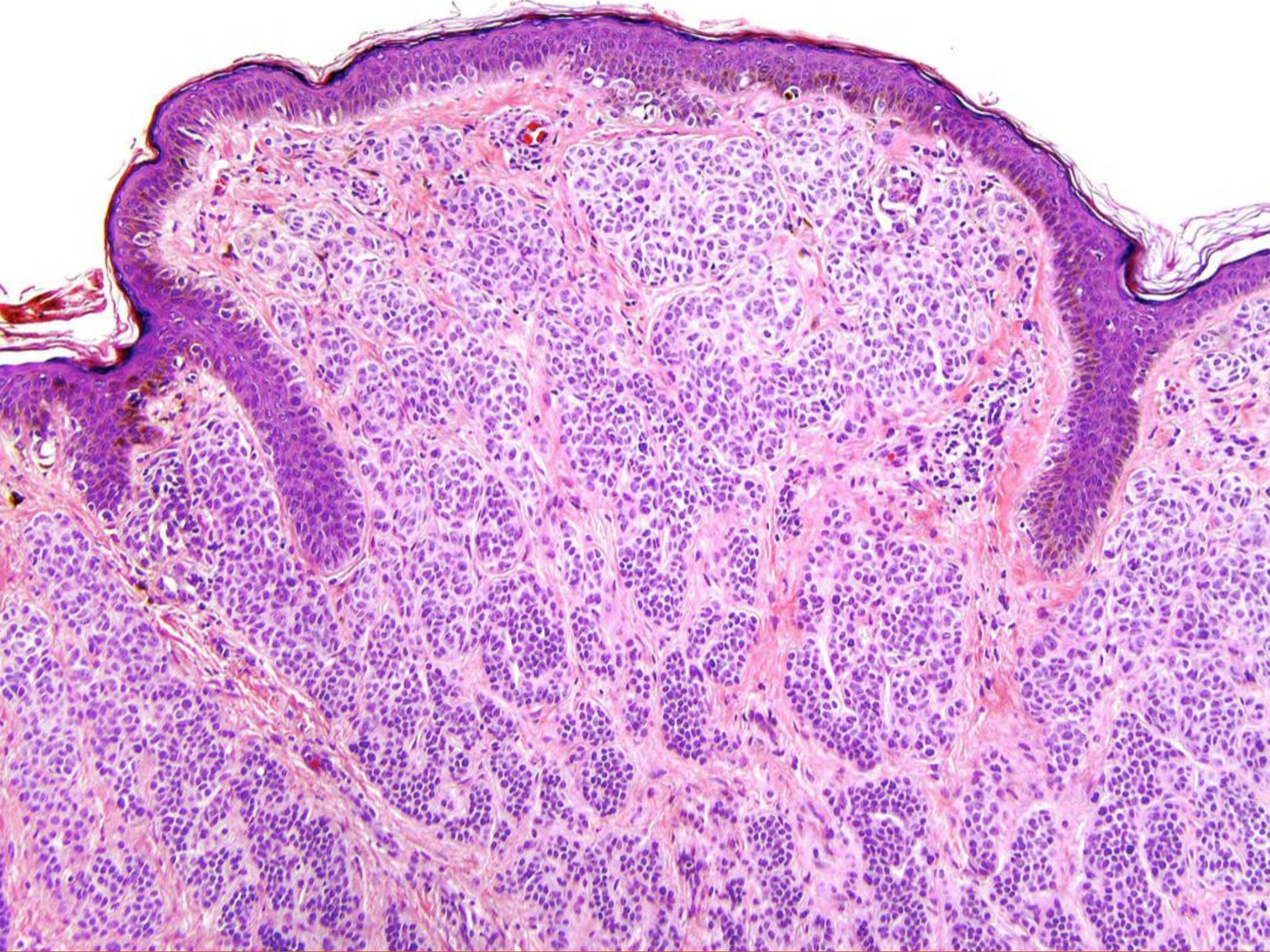
- Symmetry and circumscription (polypoid)
- Superficial micronodules of pregnancy (SMOPs)
- Lack of nuclear atypia or pleomorphism
- Complete maturation of the deeper cells
- Mitotic figures may be present, but the rate is low (1- 2/mm2) and are mostly superficial
- Ki-67 proliferation index usually < 5%
- HMB45 stratification

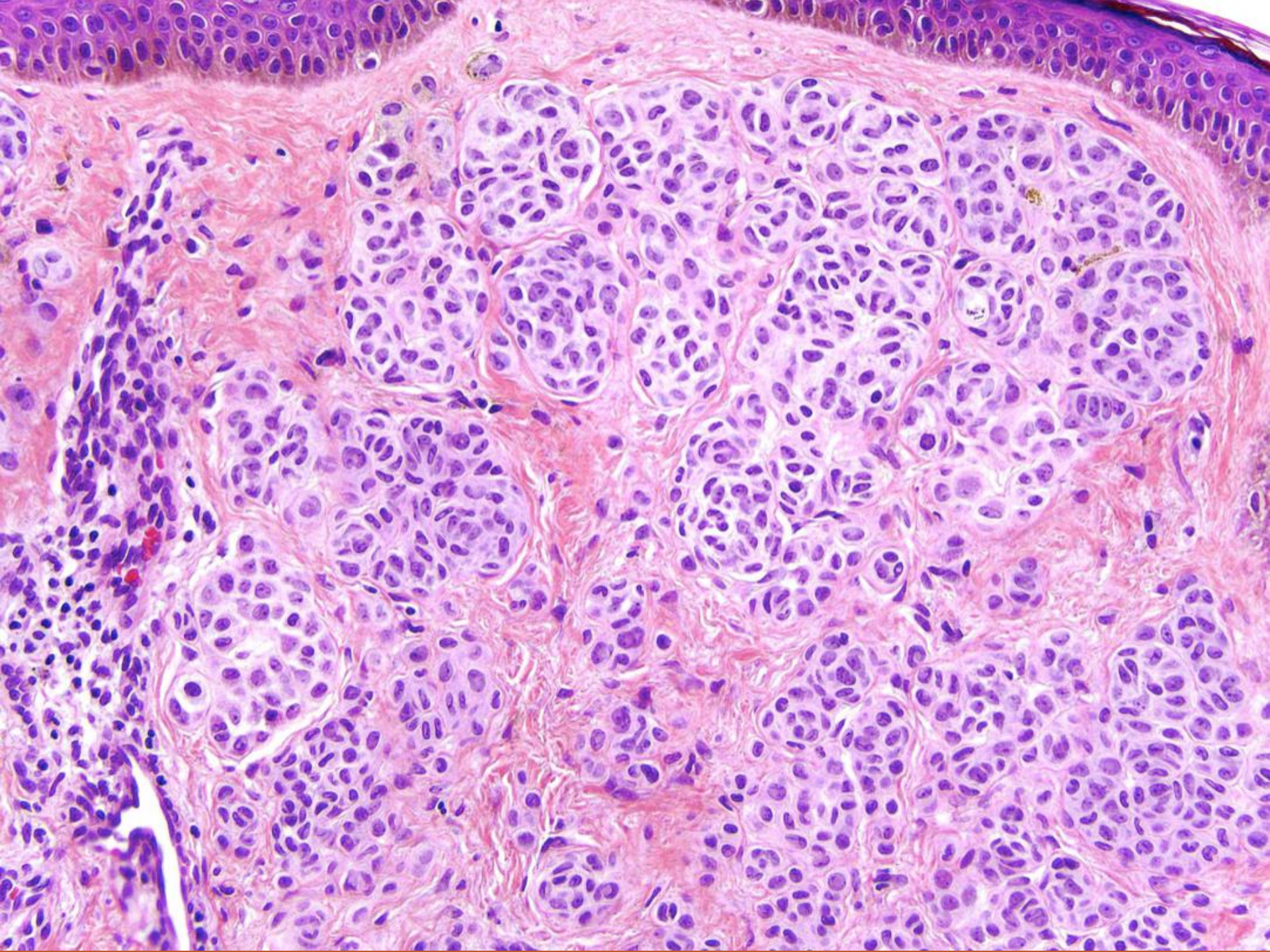
“Superficial Micronodules”

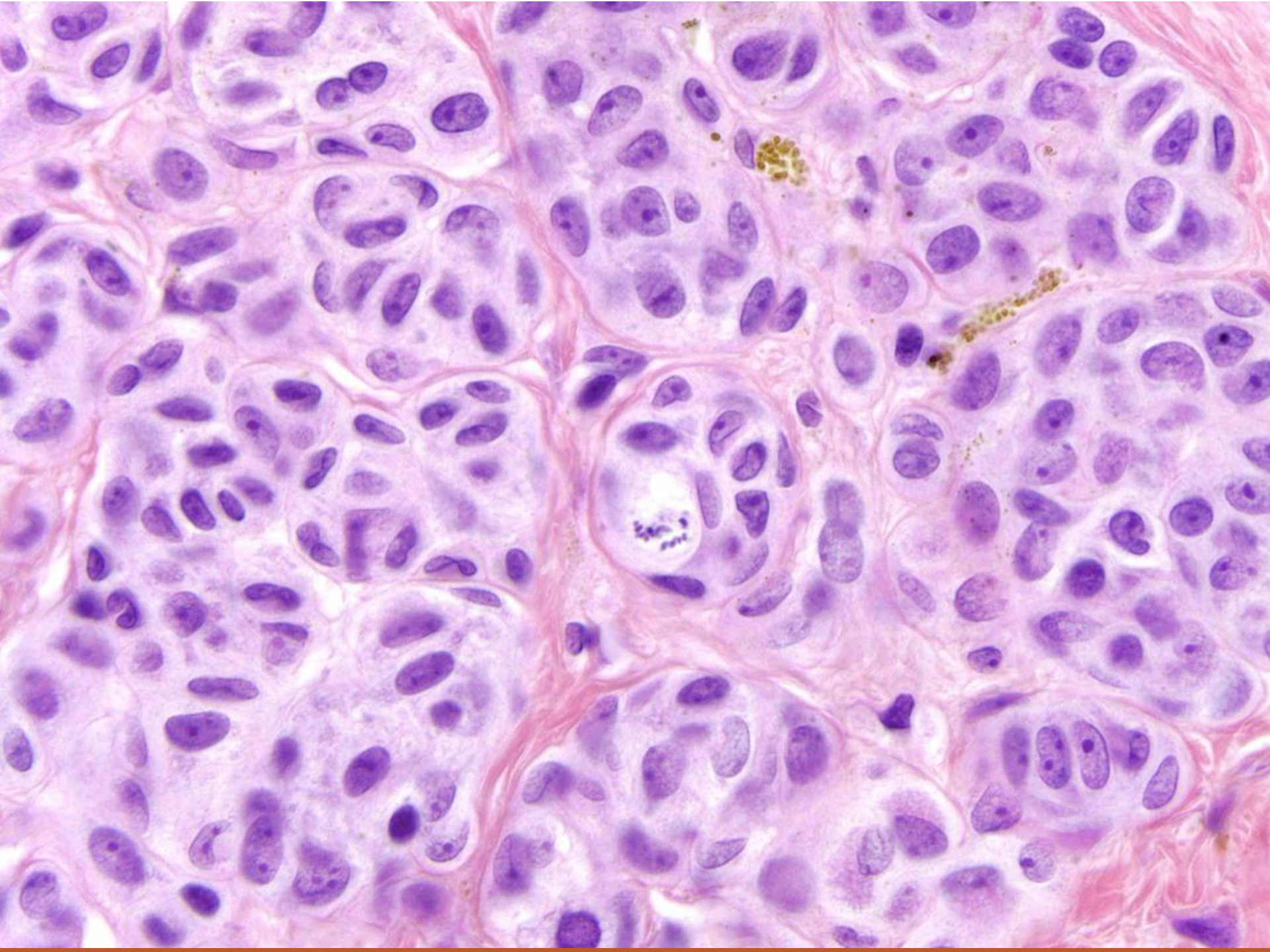
- **Rounded nests of plump epithelioid melanocytes with abundant cytoplasm, smooth regular nuclei, and central nucleoli**
- **More prominent than type A cells, and distinctively larger than the type B cells**
- **Fill and slightly expand dermal papillae → bosselated surface**

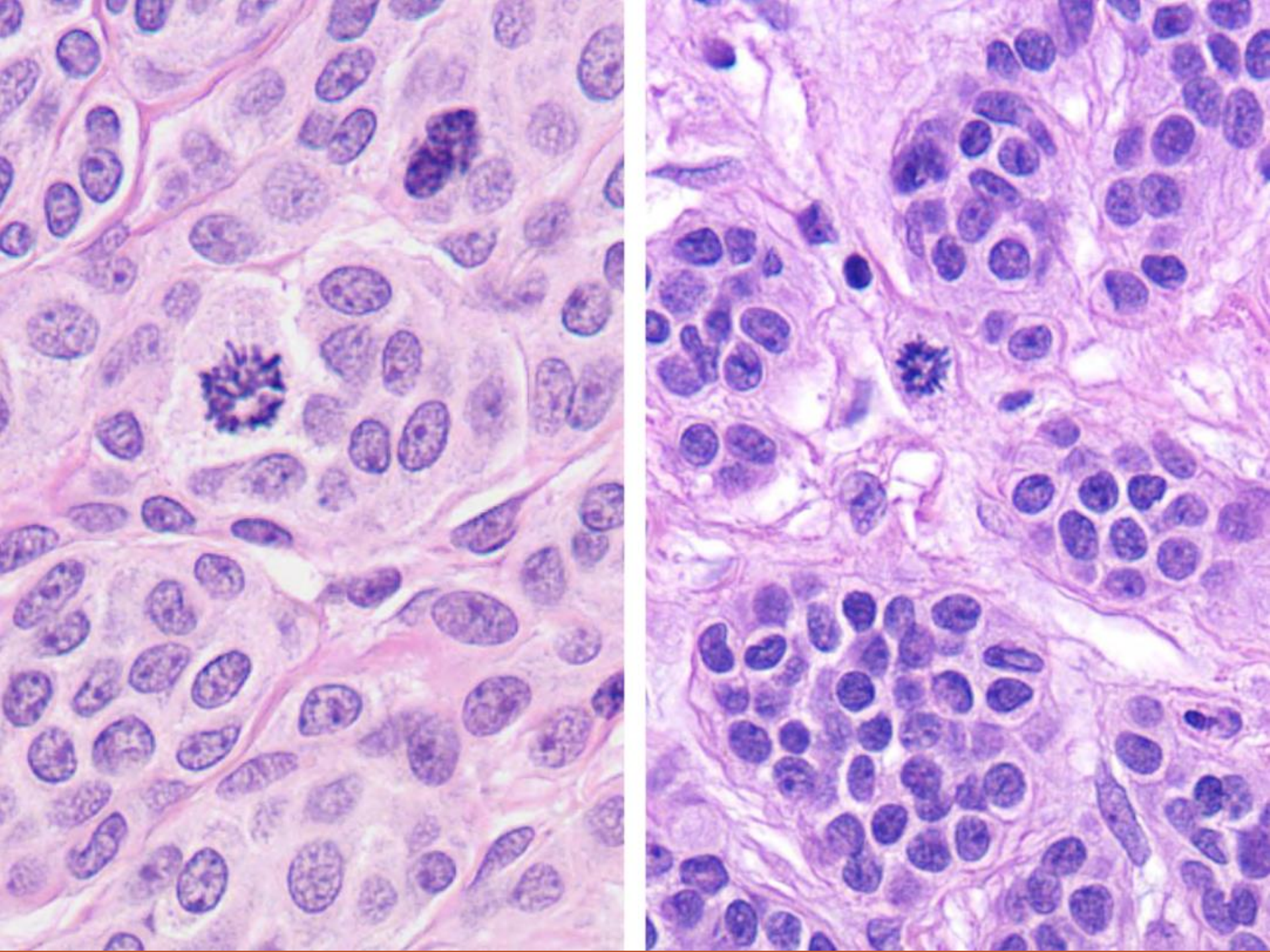




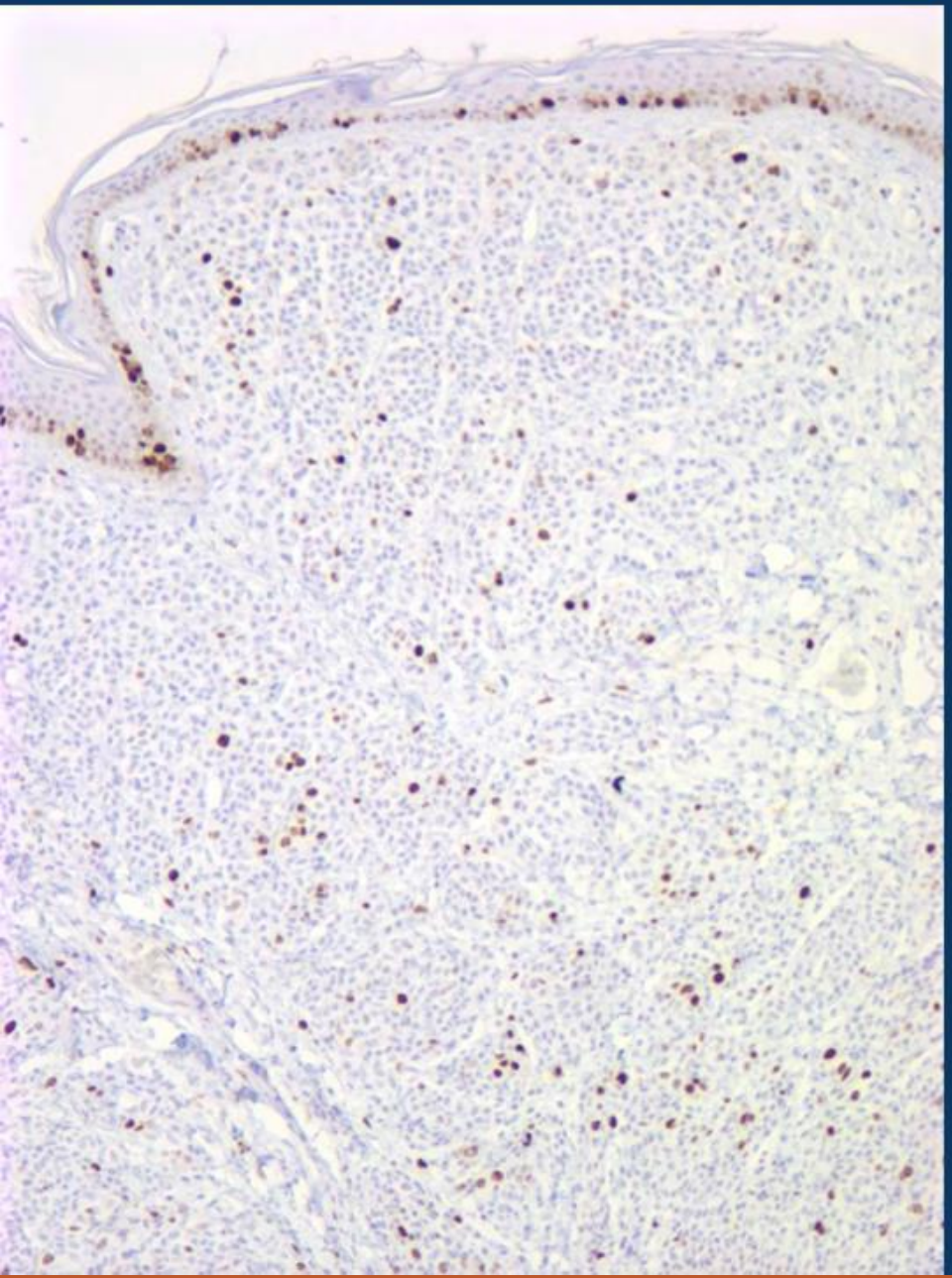




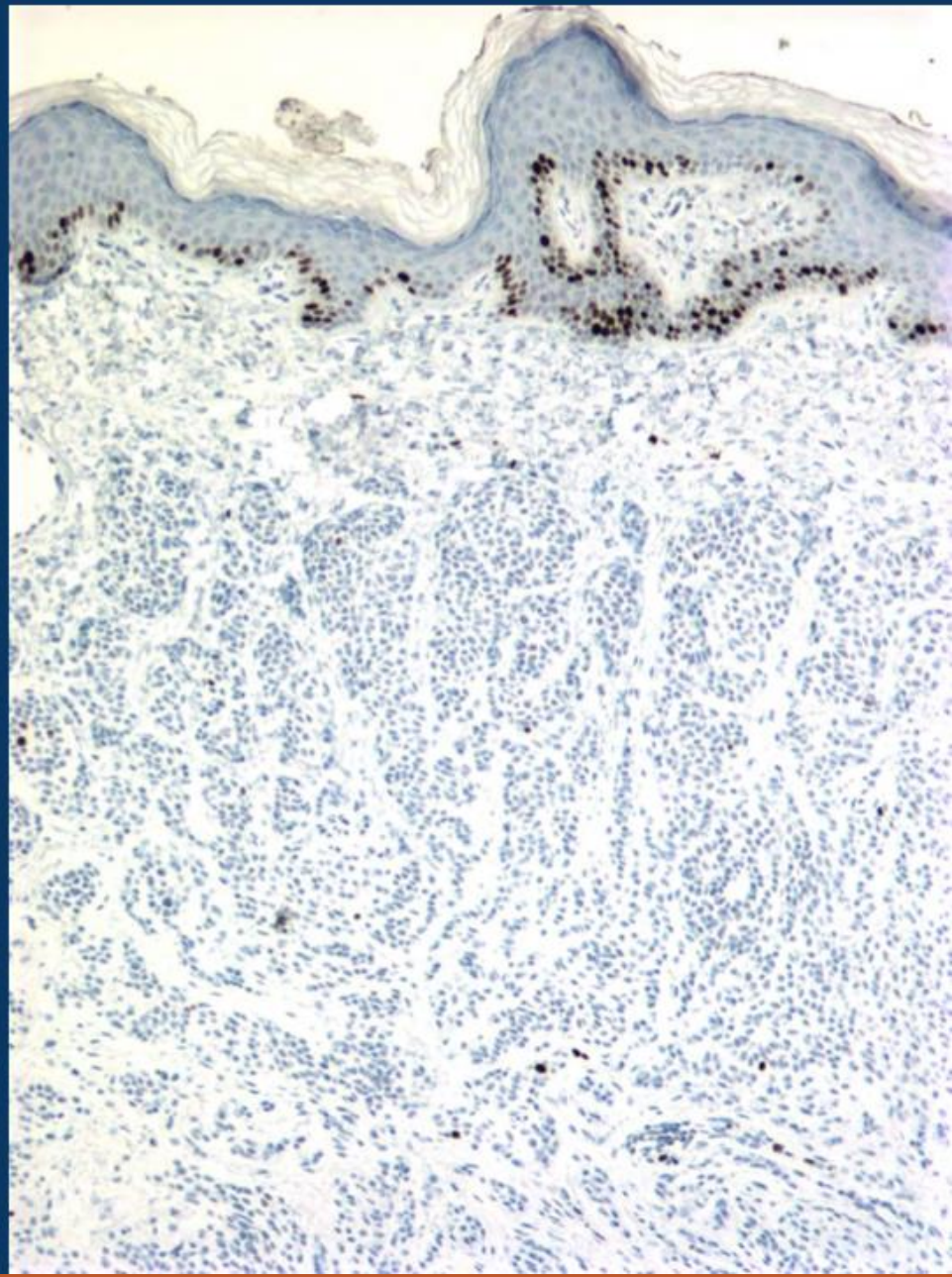




Pregnancy (mean Ki-67 = 3%)

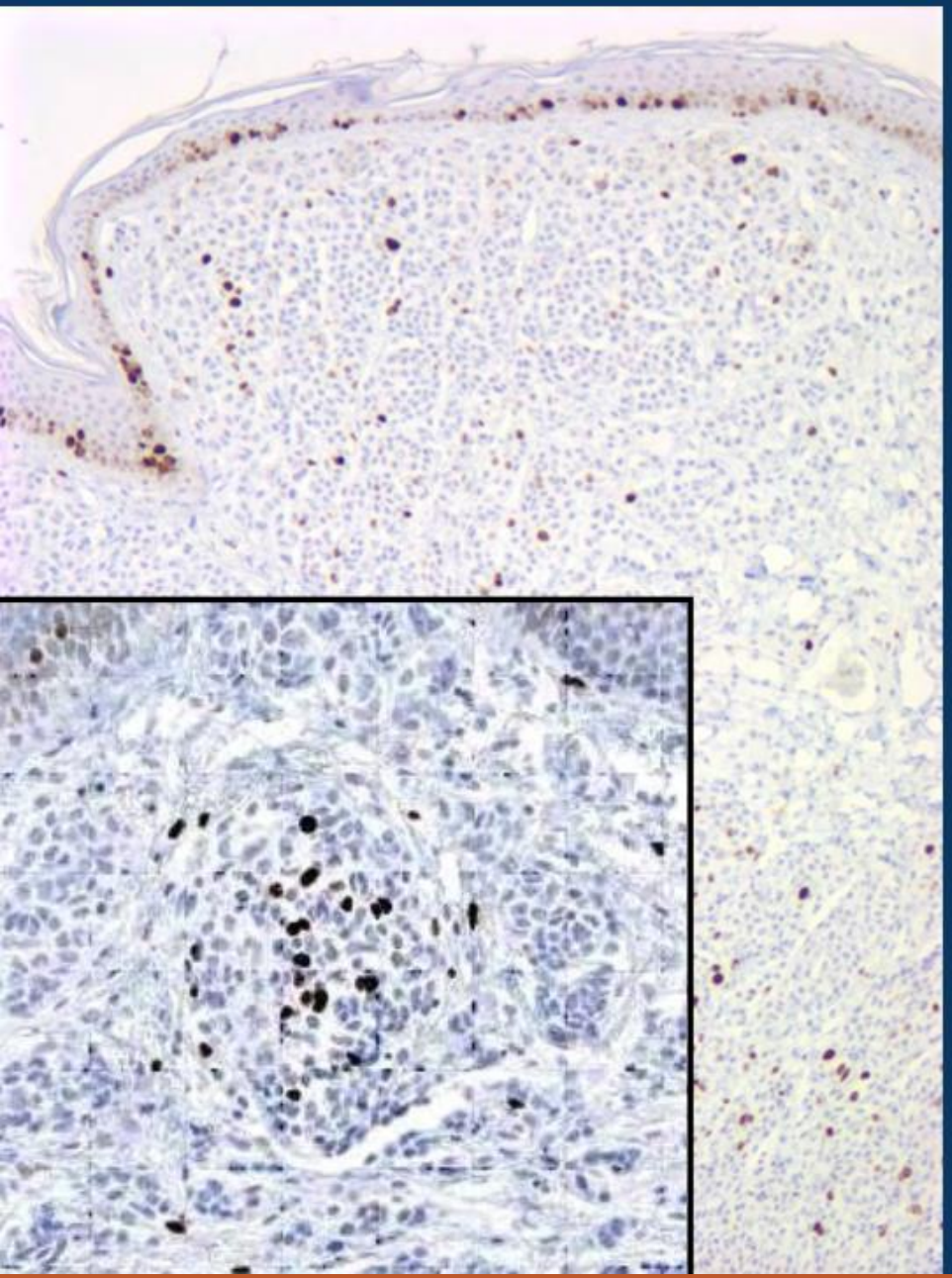


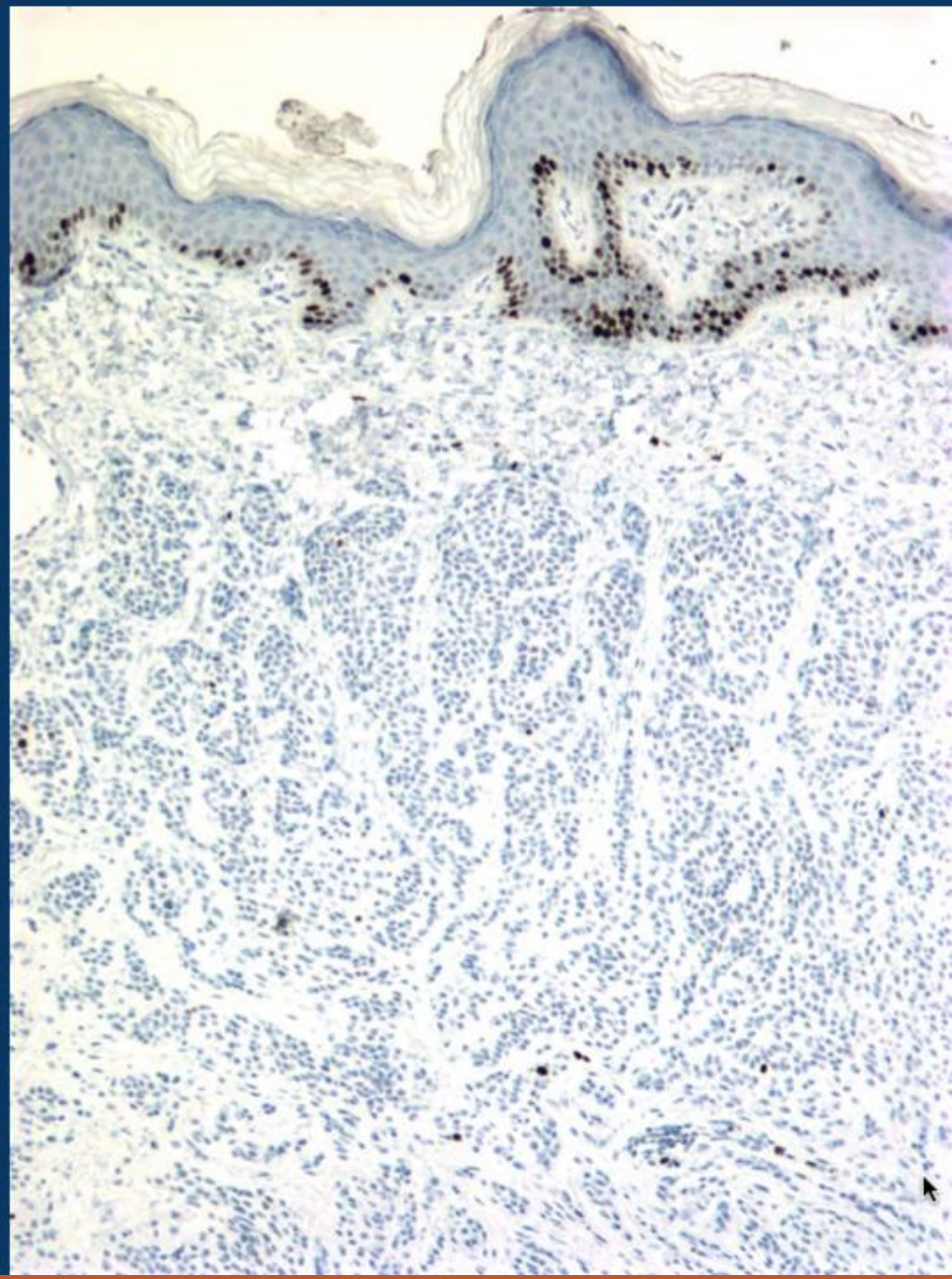
Control (mean Ki-67 = 1%)

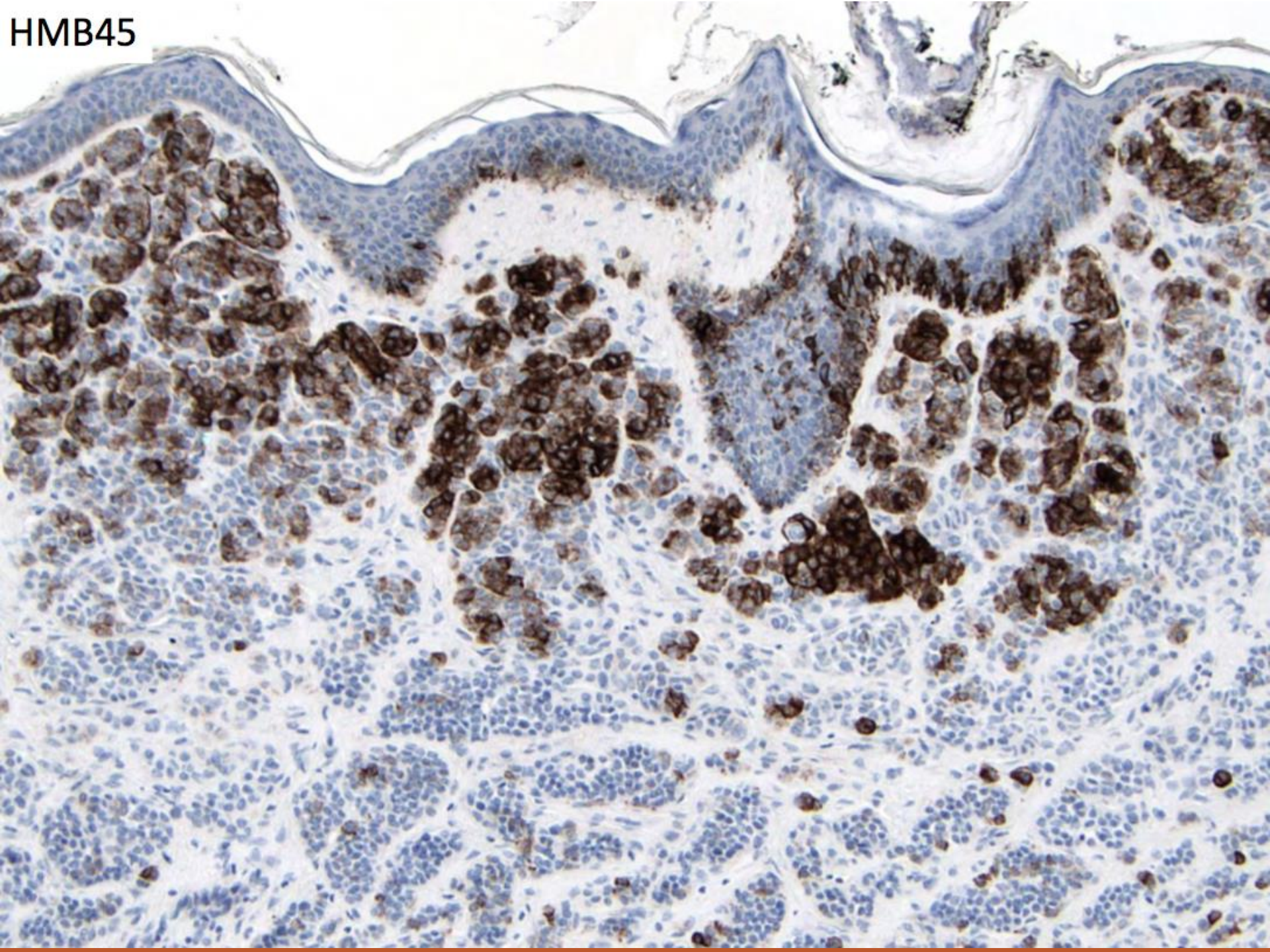


Pregnancy (mean Ki-67 = 3%)

Control (mean Ki-67 = 1%)

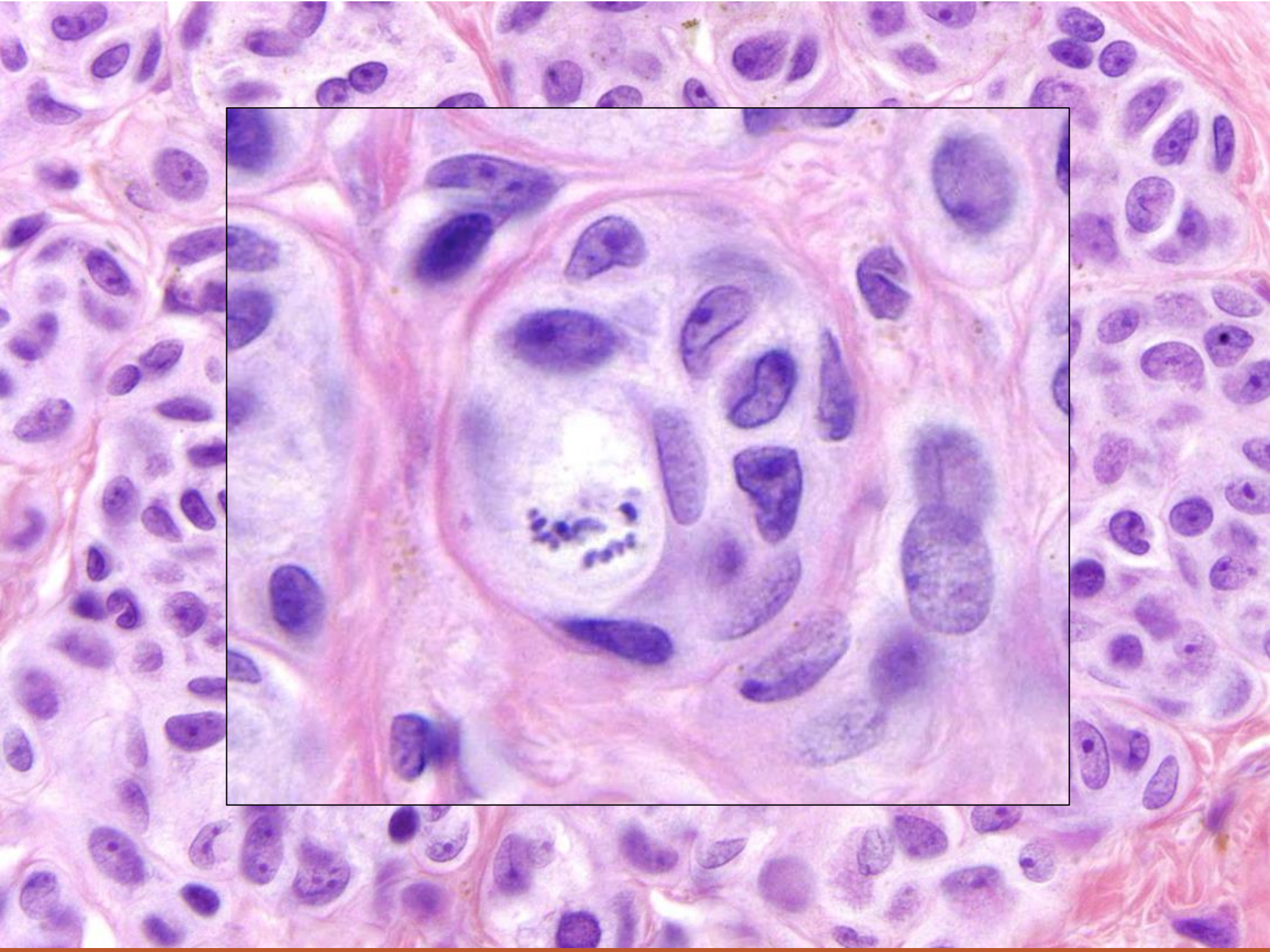





HMB45

Other Mitotically Active Nevi

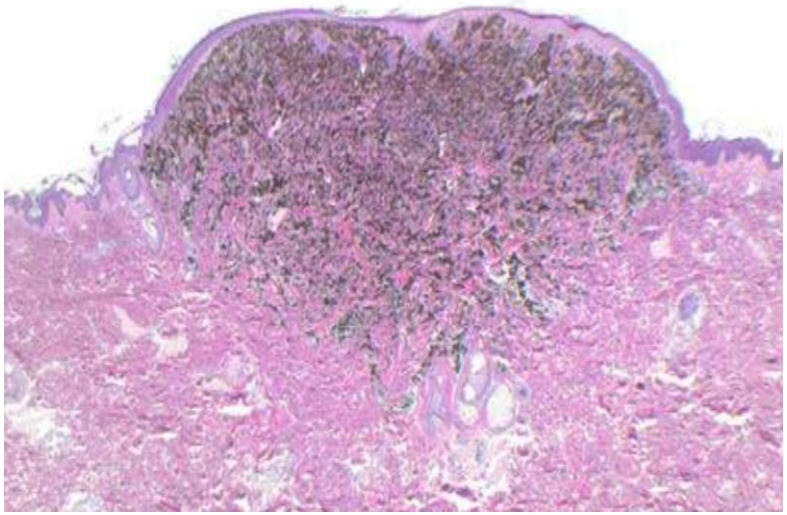
- **Up to ~20% of banal nevi contain mitoses**
- **Most contain single mitosis**
- **Nevi from younger patients, and those traumatized or inflamed are more likely to have multiple and/or deeper mitoses**

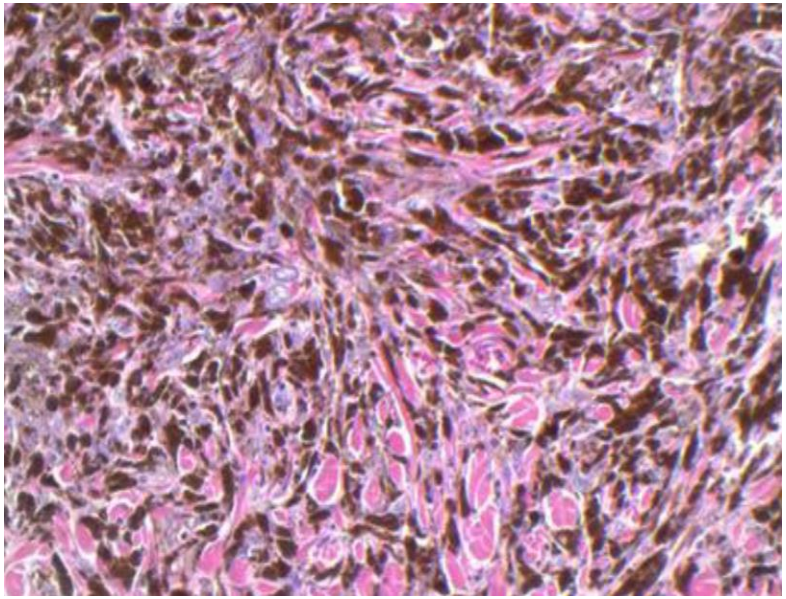


Case 2

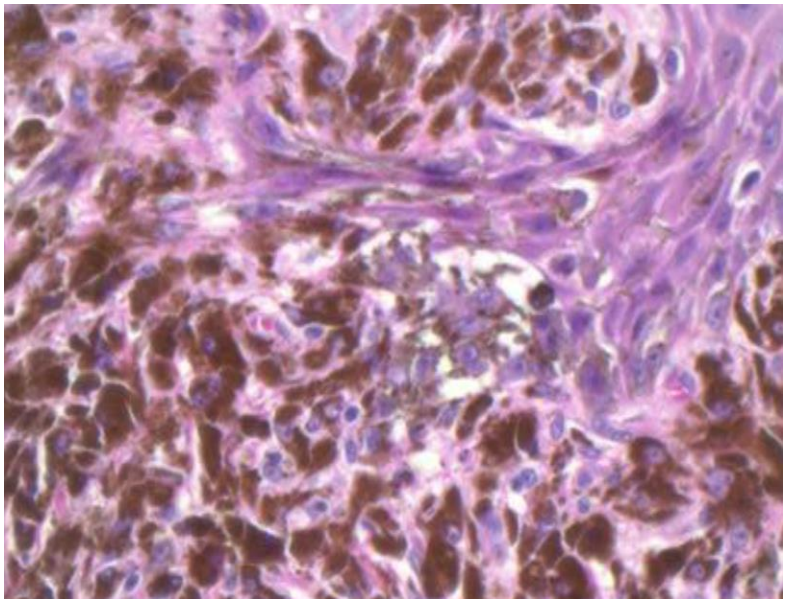
21 YO MAN PRESENTED WITH A DARKLY PIGMENTED NODULE ON THE BACK. CLINICAL DIFFERENTIAL DIAGNOSIS INCLUDED BLUE NEVUS VERSUS MALIGNANT MELANOMA. THE LESION WAS EXCISED.

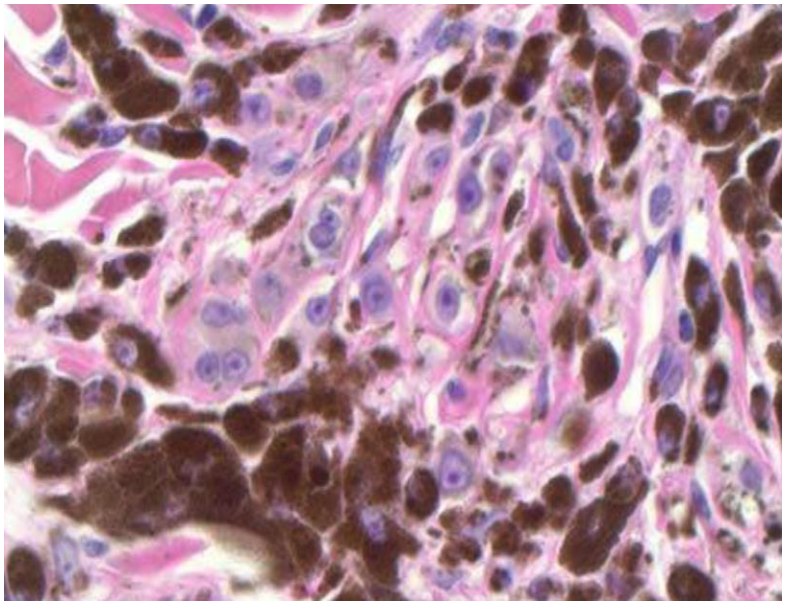
Darkly pigmented nodule on the back





Darkly pigmented nodule on the back

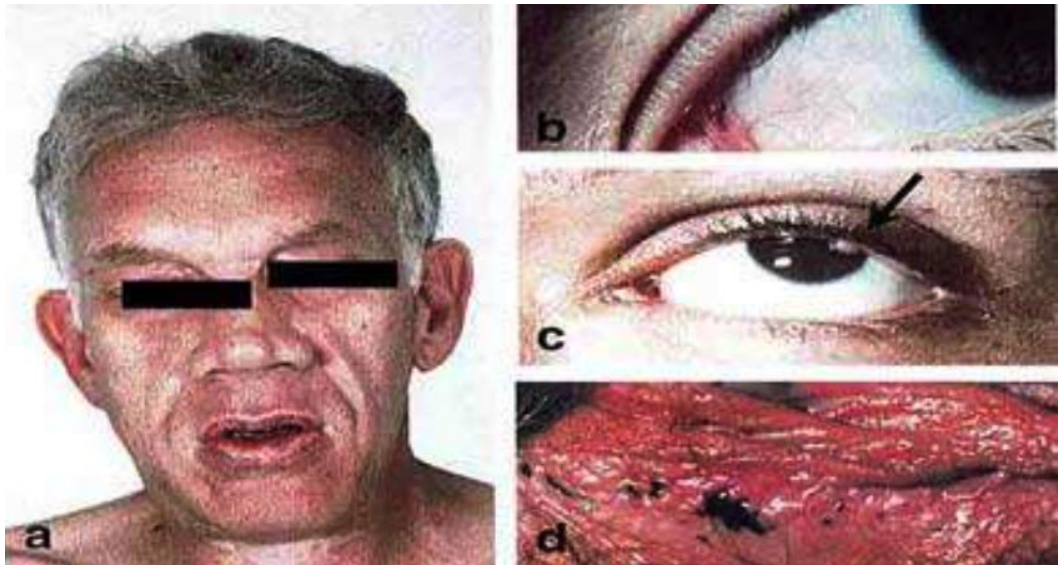




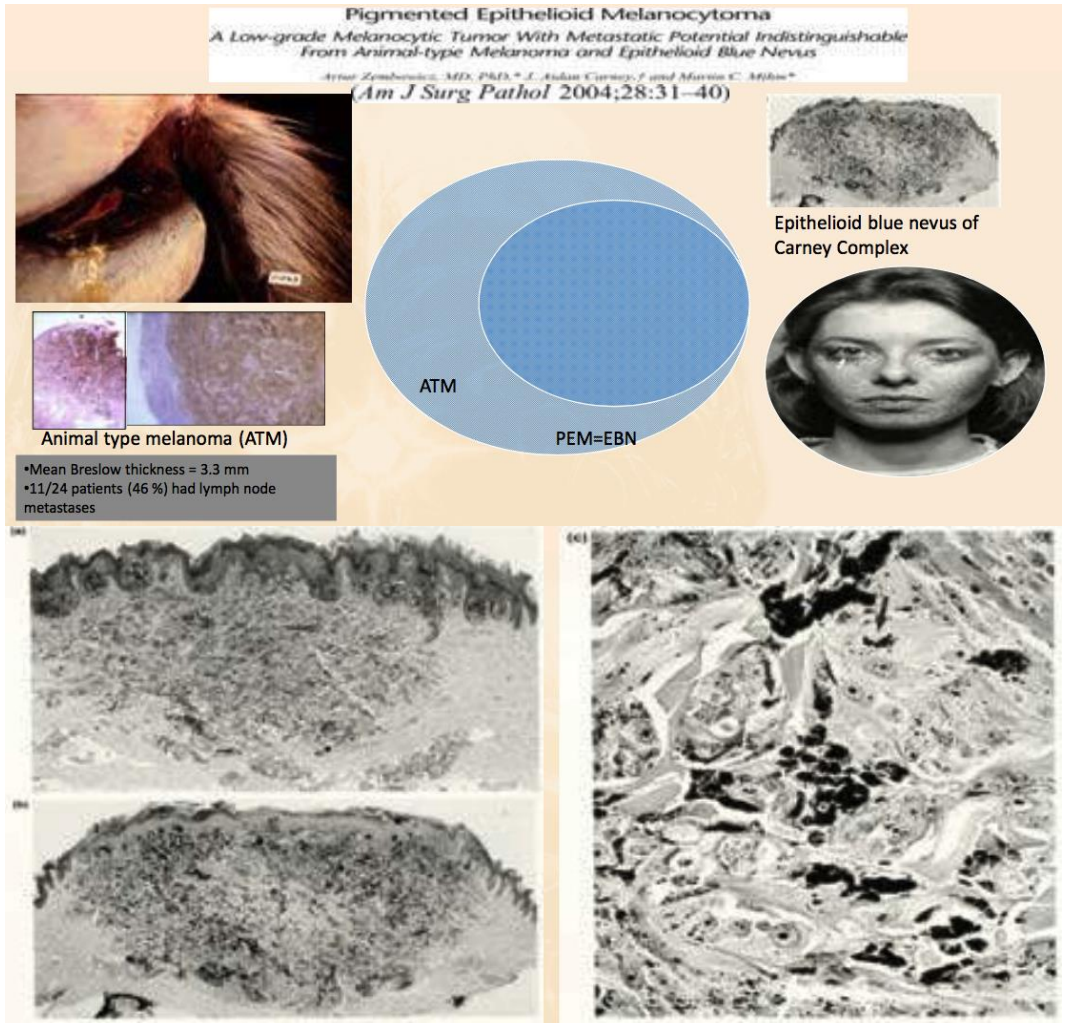
Historical Perspective

- **Pigmented cutaneous neoplasms of old gray horses, also pigs, have been occurring at the base of the tail, the anogenital area and orofacially have been recognized for years as "Equine melanotic disease". (Dick 1832)**
- **Lesions metastasize in 20-30% often following a benign course.**
- **Darier (1925) was the first to describe these lesions in humans.**
- **Levene (1978) and Lerner, Tuthill and Clark (1982) described these lesions as resembling the equine tumor. Clark (1988 and 1990) designated them as animal type melanoma. Levene (1978) also reported a similar tumor occurring in backfries of Xiphorous fish.**
- **Crowson et al also described a series with death in one patient. (Crowson et al 1999)**

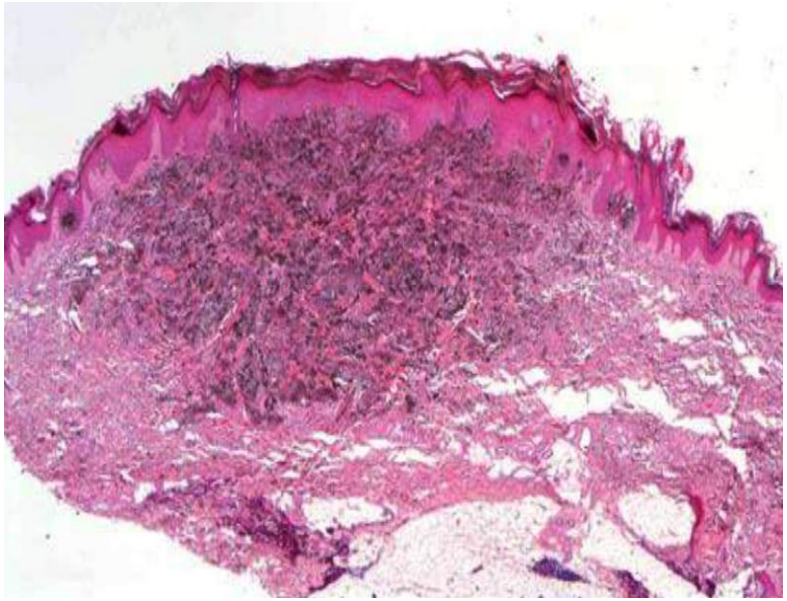
- Carney Complex includes multiple lentigines, blue nevi, and so- called epithelioid blue nevi. (Carney 1985)
- There are multiple endocrine and non-endocrine tumors associated with the disorder including myxomas and schwannomas
- There has been no evidence of metastatic disease from any of the pigmented tumors of the Carney Complex.
- Autosomal dominant inheritance: 44 % of families Carney Complex gene: Protein Kinase A Regulatory Subunit 1α (R1α) (17q22-24)

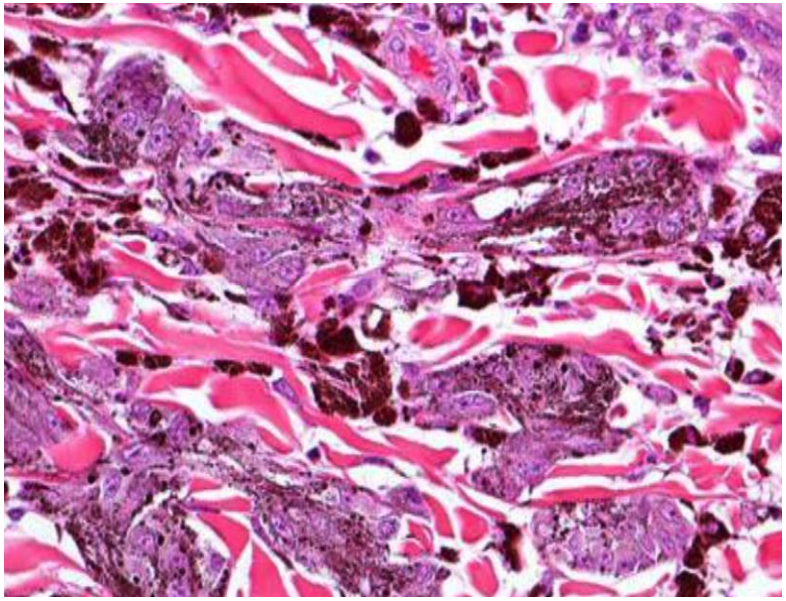


- Dr. Carney reviewed all his cases of epithelioid blue nevus with all collected cases of “animal type melanoma” with A. Zembowicz and M. Mihm in 2003.
- No significant difference found.
- Because of benign behavior of all collected lesions at that time a new terminology was proffered namely pigmented epithelioid melanocytoma (PEM).

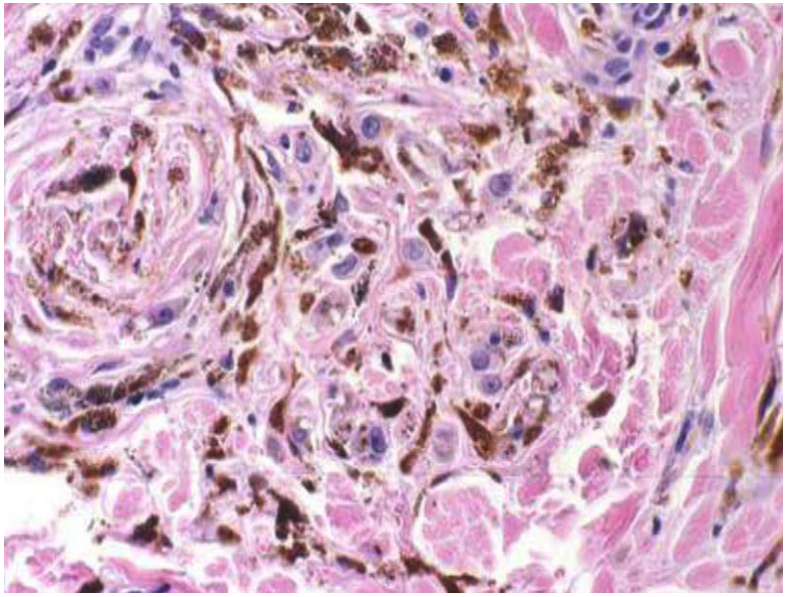


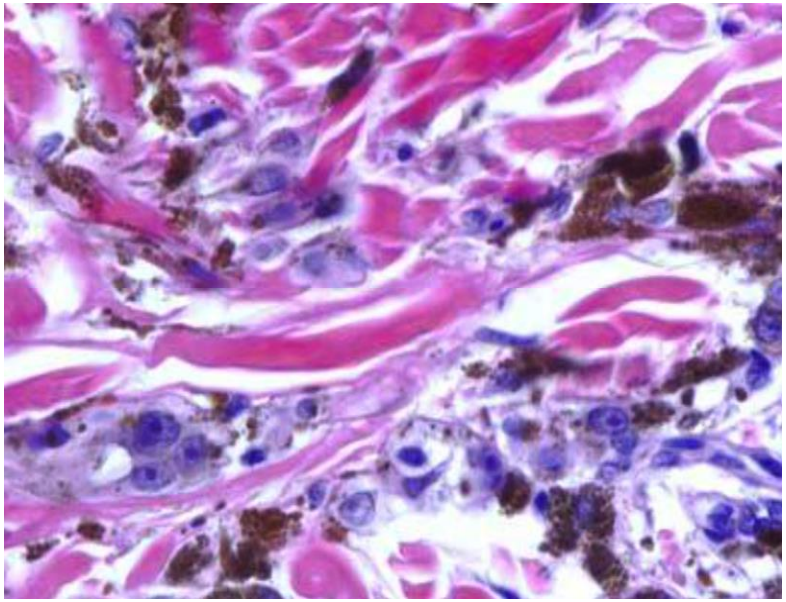
Pigmented Epithelioid Melanocytoma





Pigmented Epithelioid Melanocytoma





Pigmented Epithelioid Melanocytoma

- **Blue plaques or nodules averaging greater than one centimeter in diameter.**
- **Frequently on acral surfaces, buttocks, and scalp**
- **Skewed to the younger population**
- **No association with familial dysplastic nevus syndrome, sun exposure, or family history of malignant melanoma.**
- **Precursor lesion: cellular blue nevus, blue nevus**
- **As long as the cytomorphology is well differentiated, the clinical course is in most instances indolent**

Pigmented Epithelioid Melanocytoma

- **Stratification scheme can be potentially applied separating PEM into high risk and low risk lesions in regards to regional metastatic disease**
- ***Features denoting a low risk for regional metastatic potential***
  - **Small size less than 2 mm in depth**
  - **Lack of involvement of the deeper dermis and subcutis**
  - **Rare mitoses**
  - **Well differentiated cytomorphology**

Pigmented Epithelioid Melanocytoma

- **Mitotic activity is low.**
- **A host response is absent.**
- **Ulceration is uncommon.**
- **Majority of cells are polygonal and or spindle shaped with abundant cytoplasm/well differentiated**
- **The central portion exhibits large aggregates of epithelioid cells that transform into fascicles of thick spindle cells extending into the periphery.**
- **Intraepidermal involvement is commonly found**
- **Cases with an overtly malignant cytology are not categorized as PEM but rather as melanoma, animal type, or as malignant blue nevus**

Pigmented Epithelioid Melanocytoma

High Risk for regional metastatic disease:

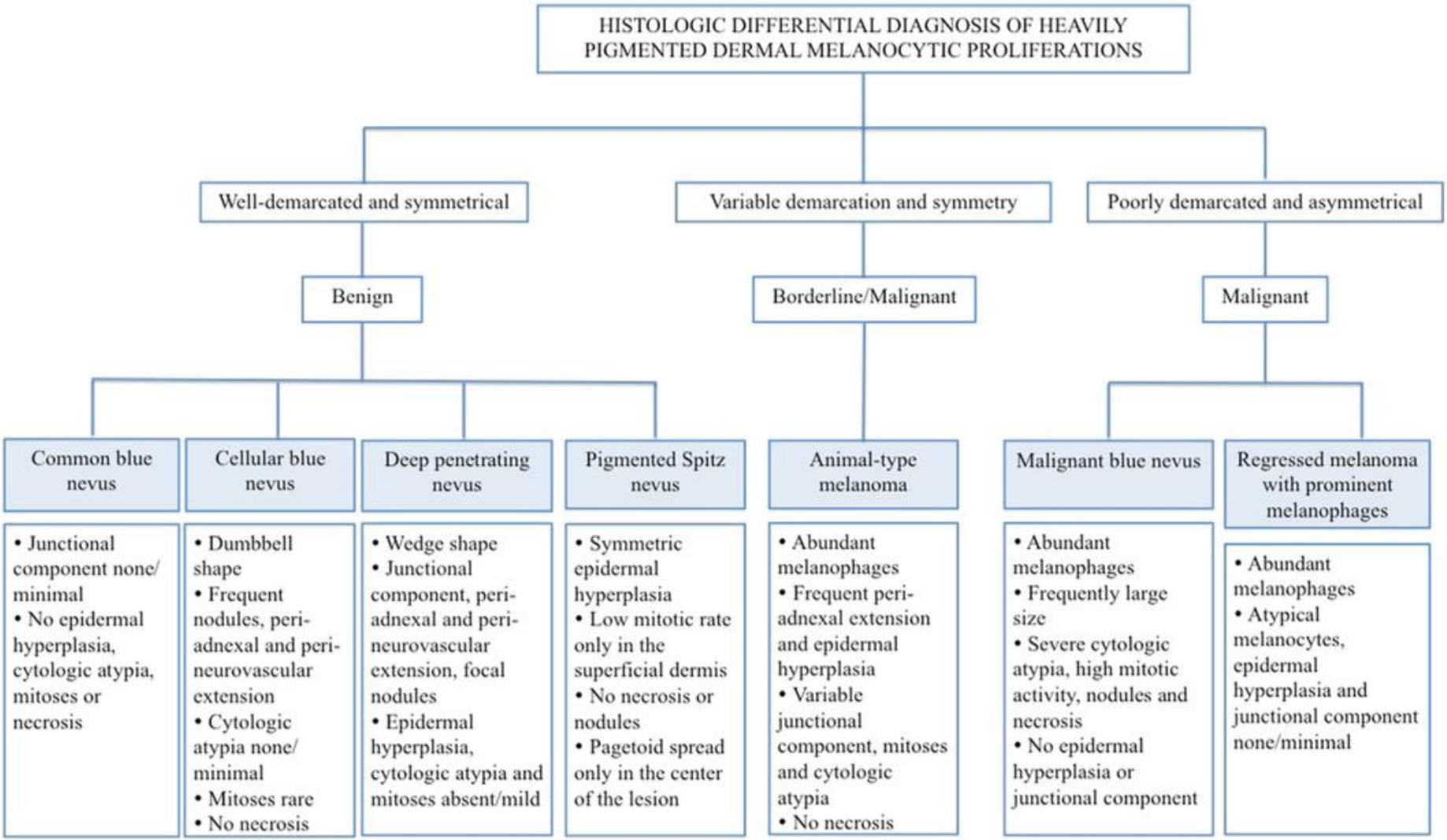
- **Deeper than 2 mm frequently with involvement of the deep dermis and subcutis, with high mitotic activity and necrosis**
- **As long as the cells appear well differentiated/ low mitotic activity the prognosis, after wide excision/sentinel lymph node biopsy, is excellent**

Pigmented Epithelioid Melanocytoma

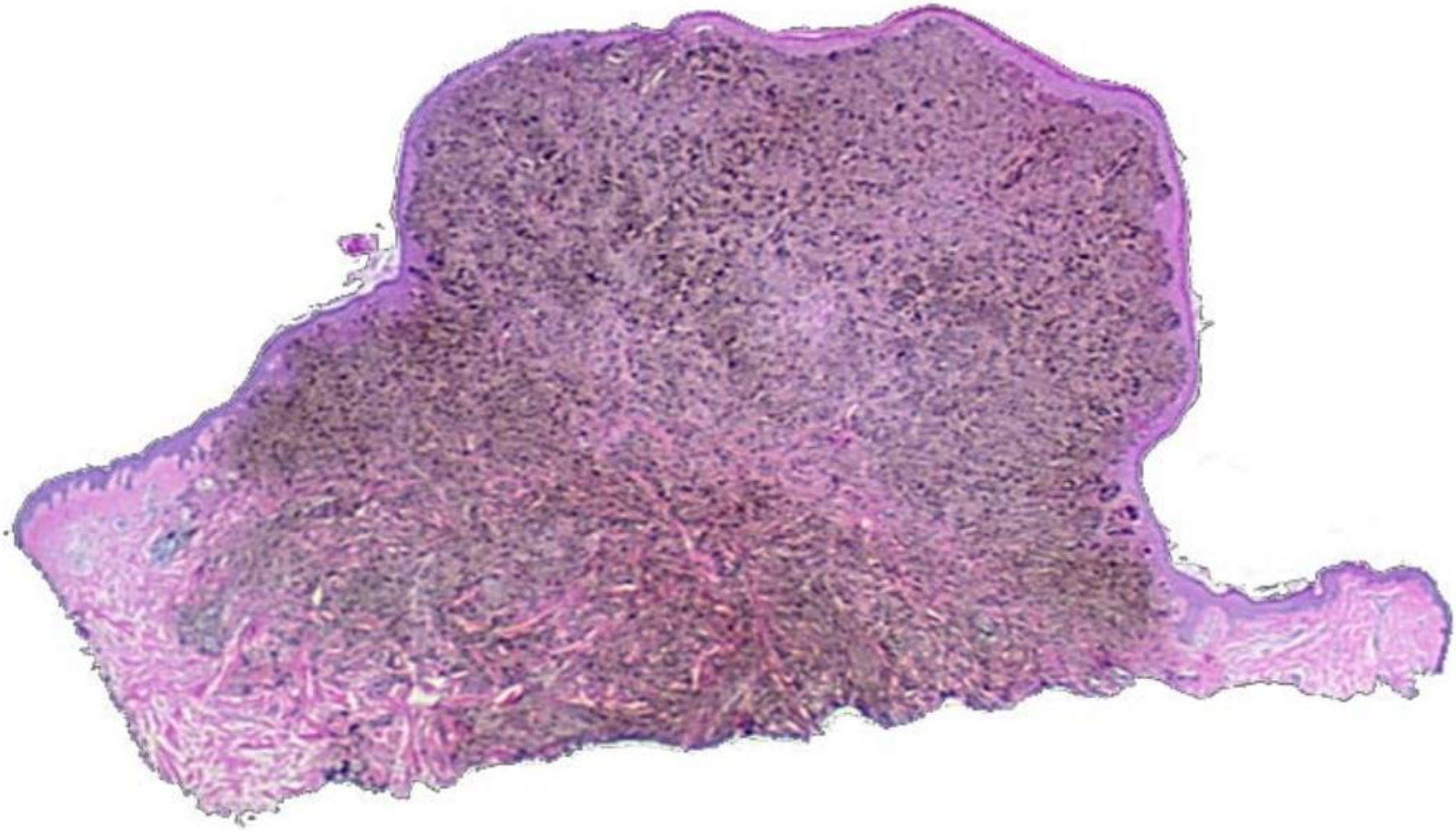
- **Mutations of the protein kinase A regulatory subunit type 1alpha (R1α) (coded by the *PRKAR1α* gene) were studied.**
- **Loss found in PEM and in lesions of Carney's syndrome but not in nevi, melanomas, equine melanomas.**
- **PEM a distinct tumor different from ordinary nevi and melanomas and equine melanomas**

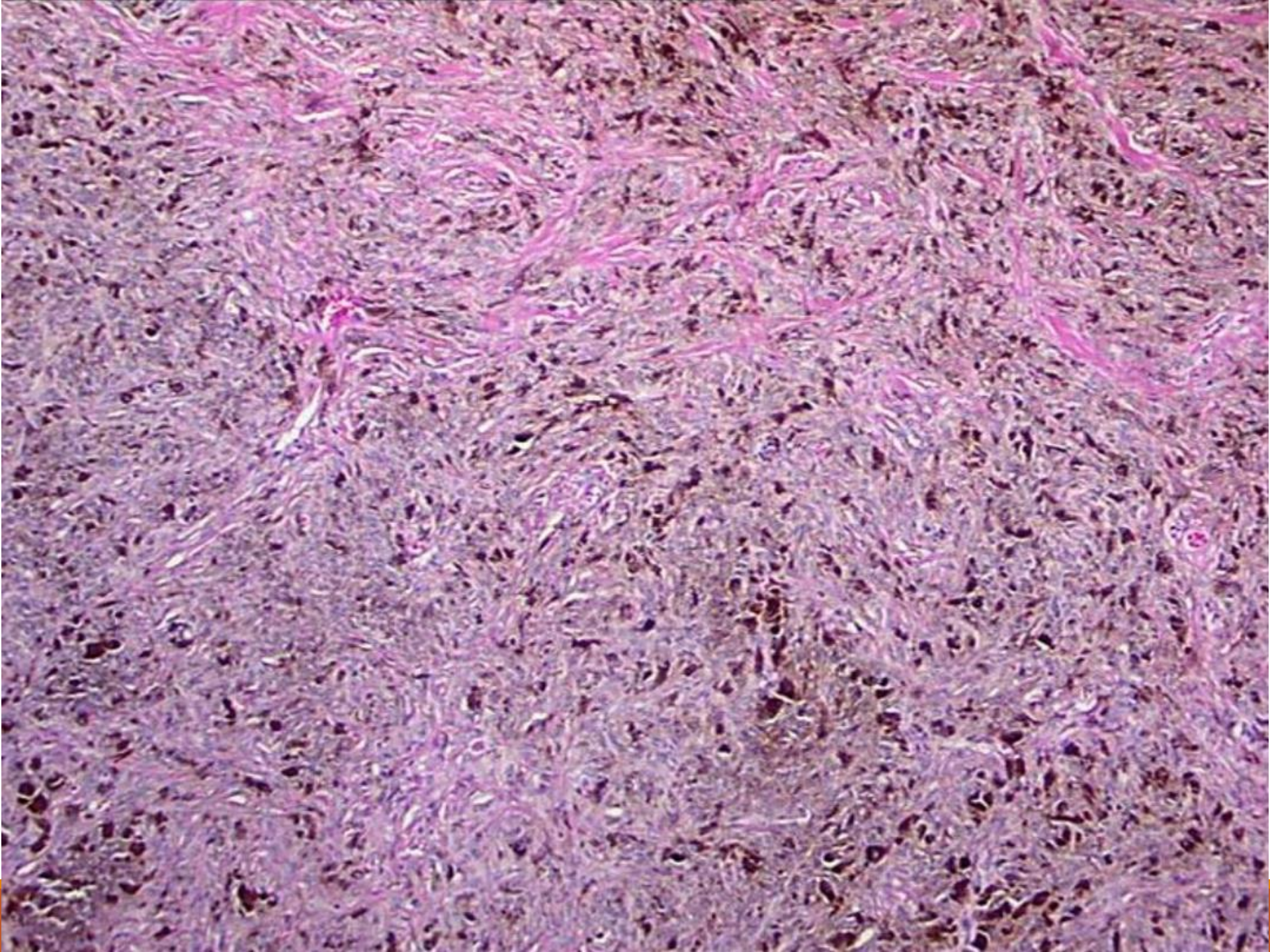
Pigmented Epithelioid Melanocytoma

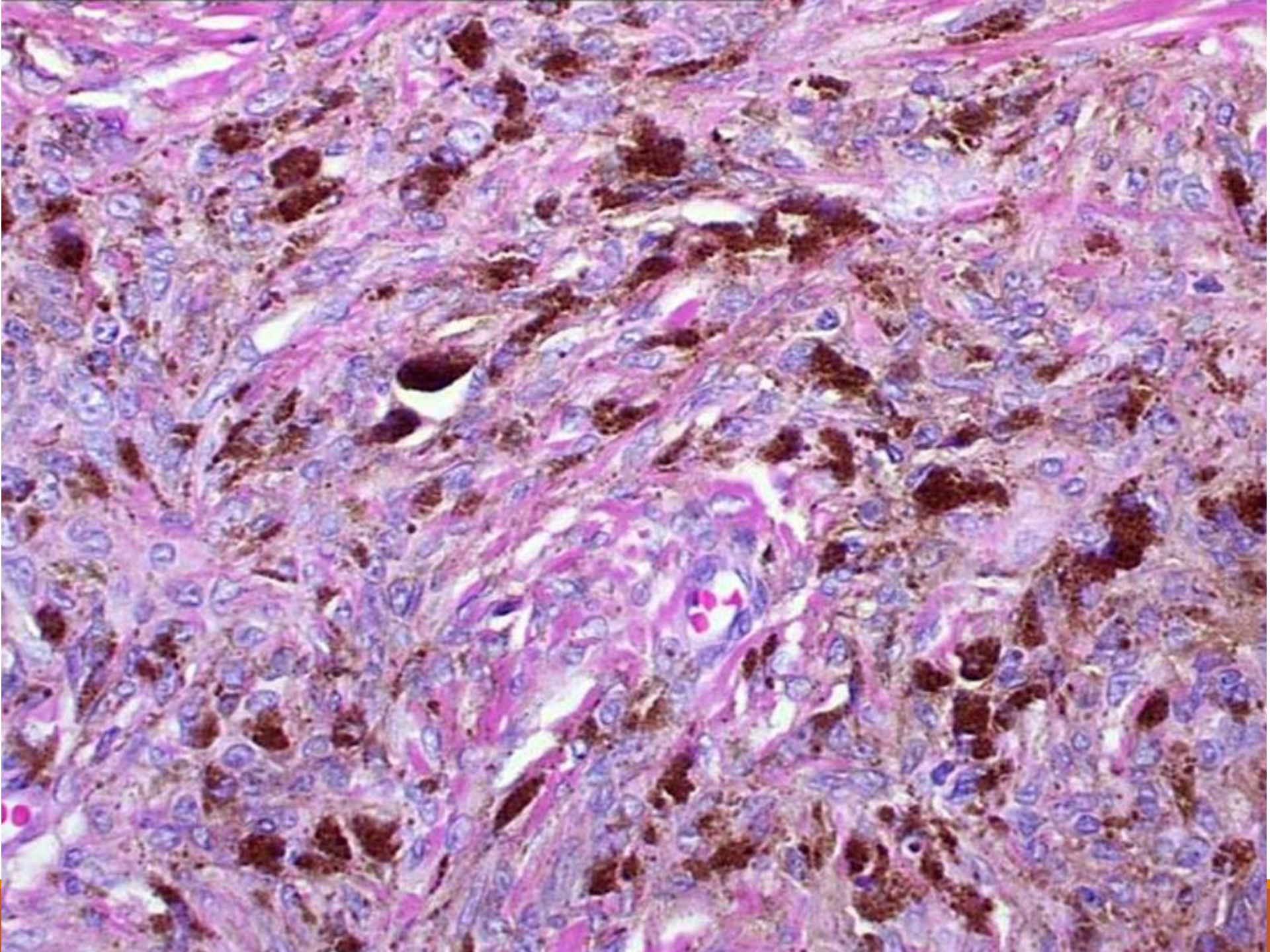
- **190 cases affecting men and women equally with 53% Caucasian race. 55% had wide excision and SLND biopsy**
- **Breslow median, 3.8 mm; mitoses ≥ 1/mm2; ulceration, 27%.**
- **SLNB, CLND: 41%, 34% positivity respectively.**
- **Loco-regional recurrence, distant metastases and death in 15, 6 and 2 patients.**
  - **Median follow up 36 months; range 0 to 348 months**

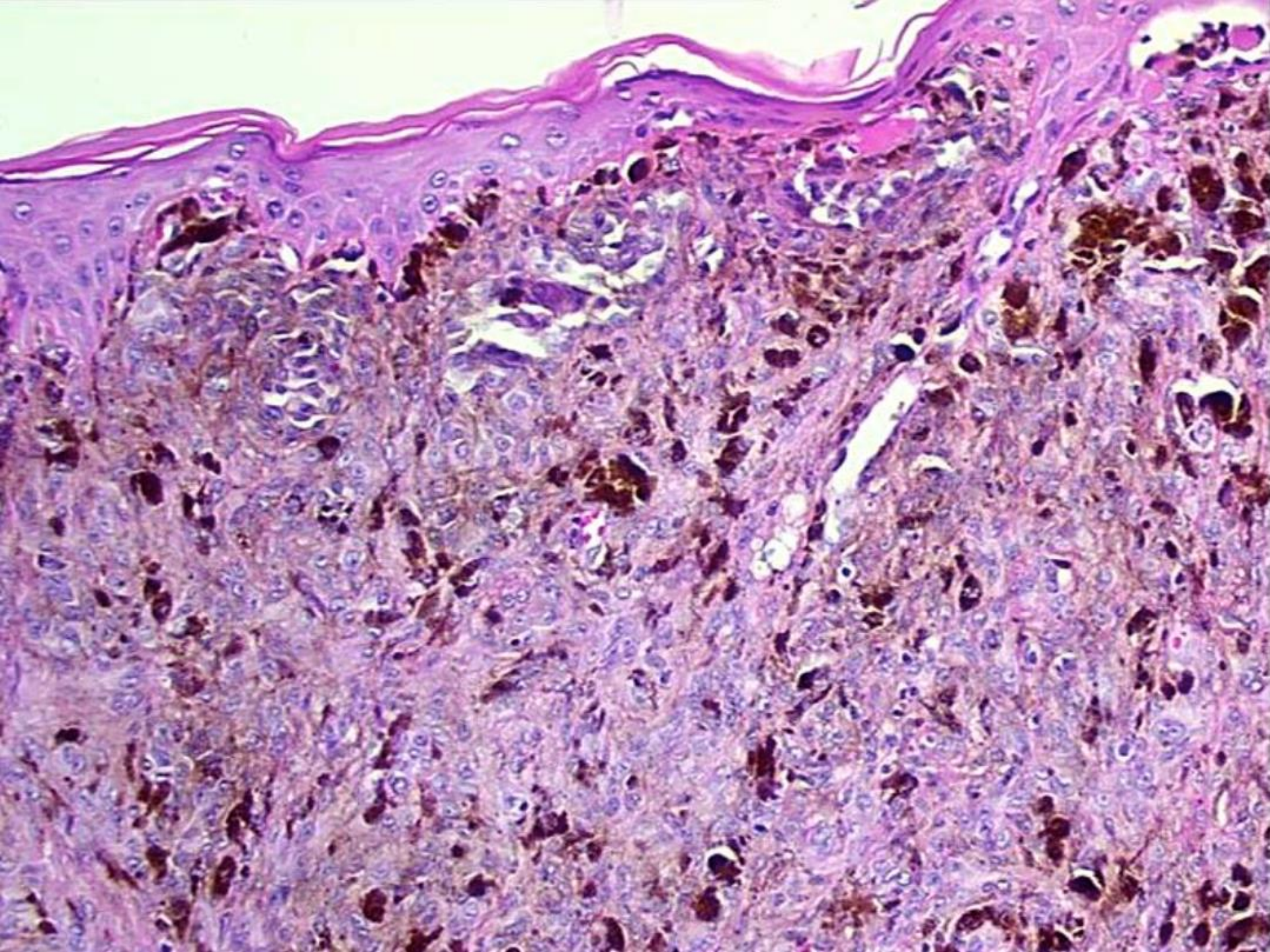

HISTOLOGIC DIFFERENTIAL DIAGNOSIS OF HEAVILY PIGMENTED DERMAL MELANOCYTIC PROLIFERATIONS
Well-demarcated and symmetrical
Variable demarcation and symmetry
Poorly demarcated and asymmetrical
Benign
Borderline/Malignant
Malignant
Common blue nevus
Cellular blue nevus
Deep penetrating nevus
Pigmented Spitz nevus
Animal-type melanoma
Malignant blue nevus
Regressed melanoma with prominent melanophages
• Junctional component none/ minimal
• No epidermal hyperplasia, cytologic atypia, mitoses or necrosis
• Dumbbell shape
• Frequent nodules, peri-adnexal and peri-neurovascular extension
• Cytologic atypia none/ minimal
• Mitoses rare
• No necrosis
• Wedge shape
• Junctional component, peri-adnexal and peri-neurovascular extension, focal nodules
• Epidermal hyperplasia, cytologic atypia and mitoses absent/mild
• Symmetric epidermal hyperplasia
• Low mitotic rate only in the superficial dermis
• No necrosis or nodules
• Pagetoid spread only in the center of the lesion
• Abundant melanophages
• Frequent peri-adnexal extension and epidermal hyperplasia
• Variable junctional component, mitoses and cytologic atypia
• No necrosis
• Abundant melanophages
• Frequently large size
• Severe cytologic atypia, high mitotic activity, nodules and necrosis
• No epidermal hyperplasia or junctional component
• Abundant melanophages
• Atypical melanocytes, epidermal hyperplasia and junctional component none/minimal

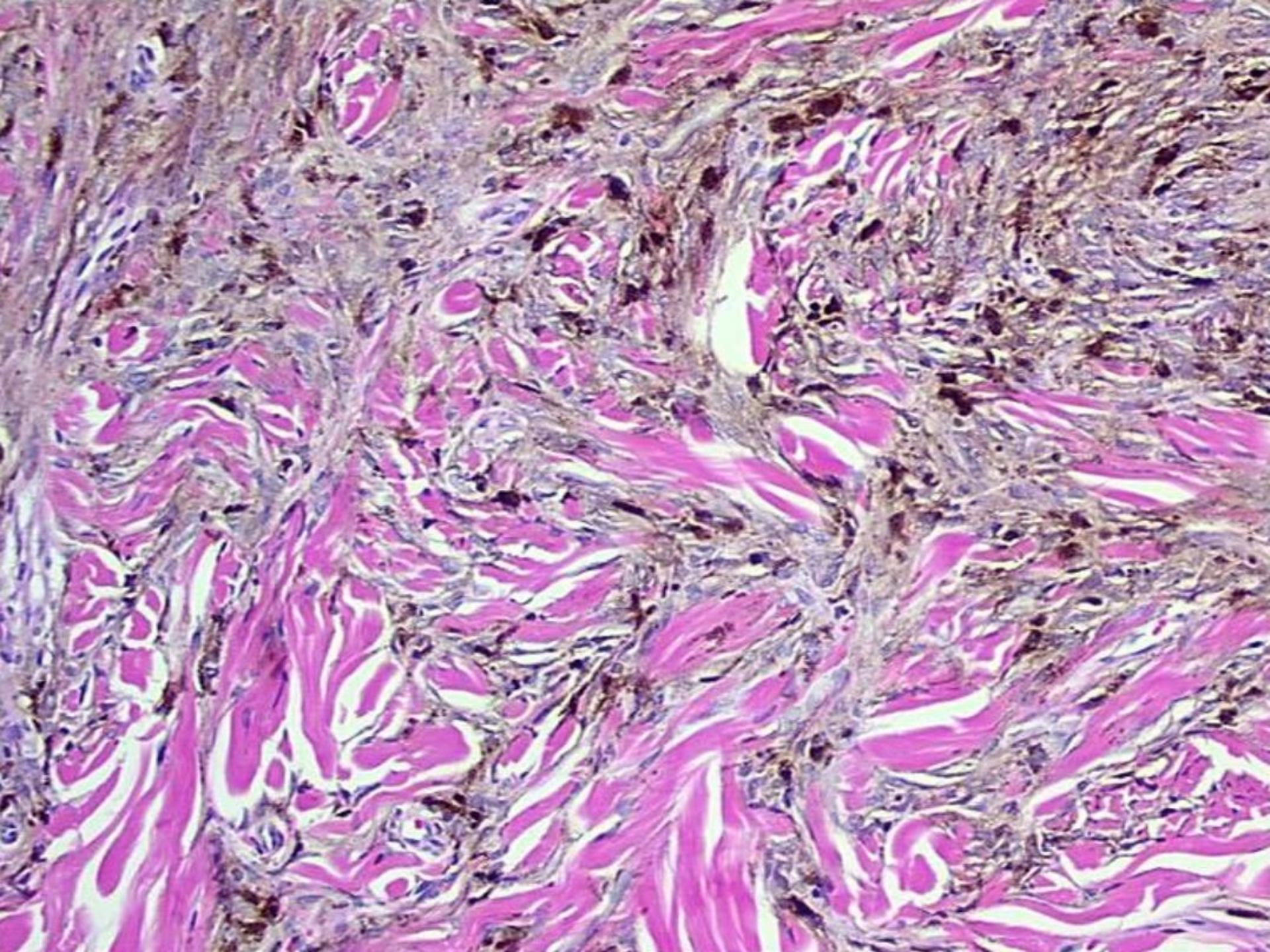

cm
1
2
3











Animal Type Melanoma

- **William Dick (1832) reported the existence in horses of skin neoplasms comprising nodules of heavily melanized cells, termed equine melanotic disease.**
- **Biologic behavior was unpredictable but characteristically indolent**

Animal Type Melanoma

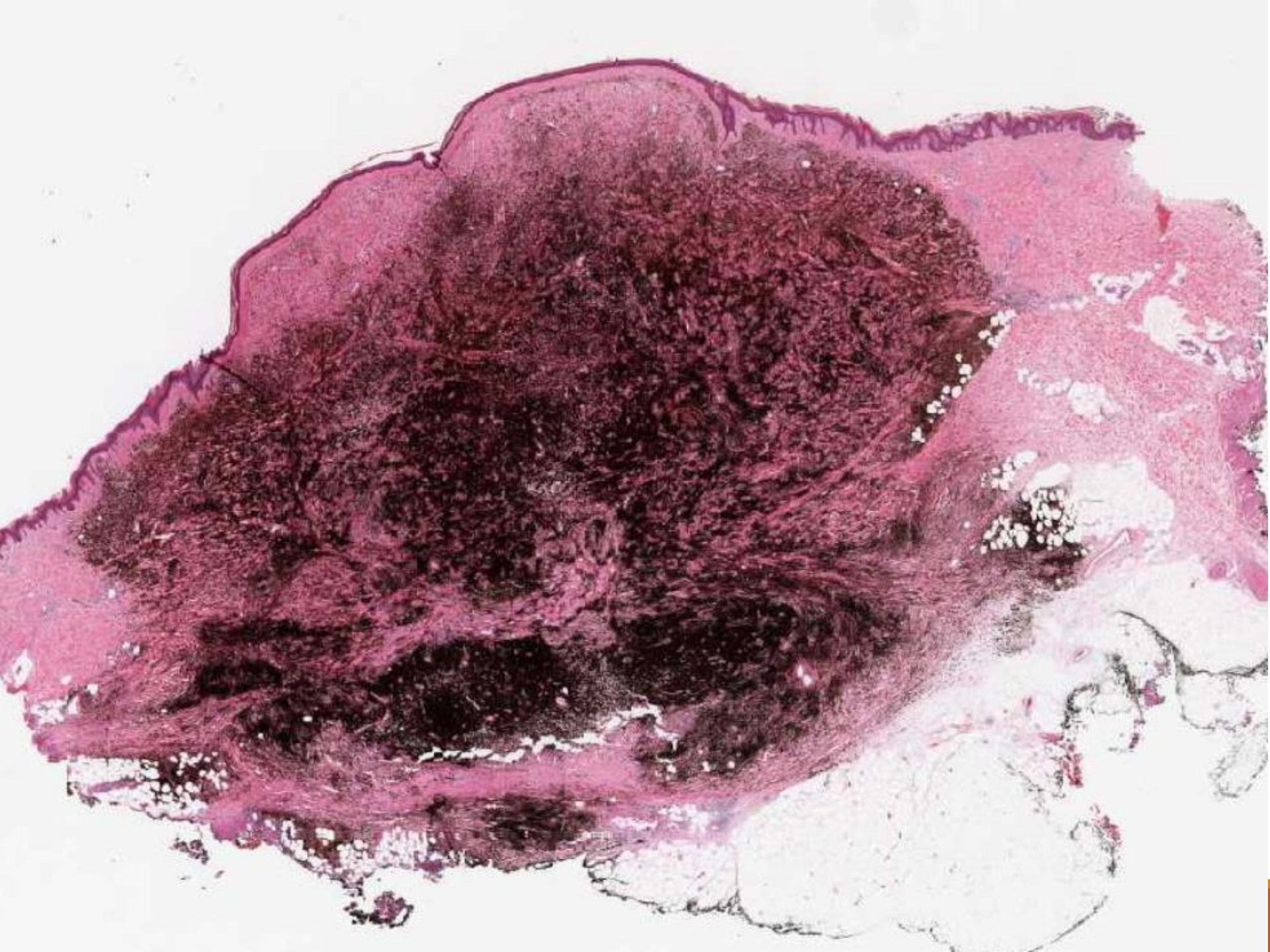
- **The morphological parallel between such lesions and a similar process in humans was first drawn by Darier in 1925, who introduced the term melanosarcoma.**
  - **Darier J: Le melanome malin mesenchymateaux ou melanosarcome. Bull Assoc Fr Cancer 14:221-249, 1925**

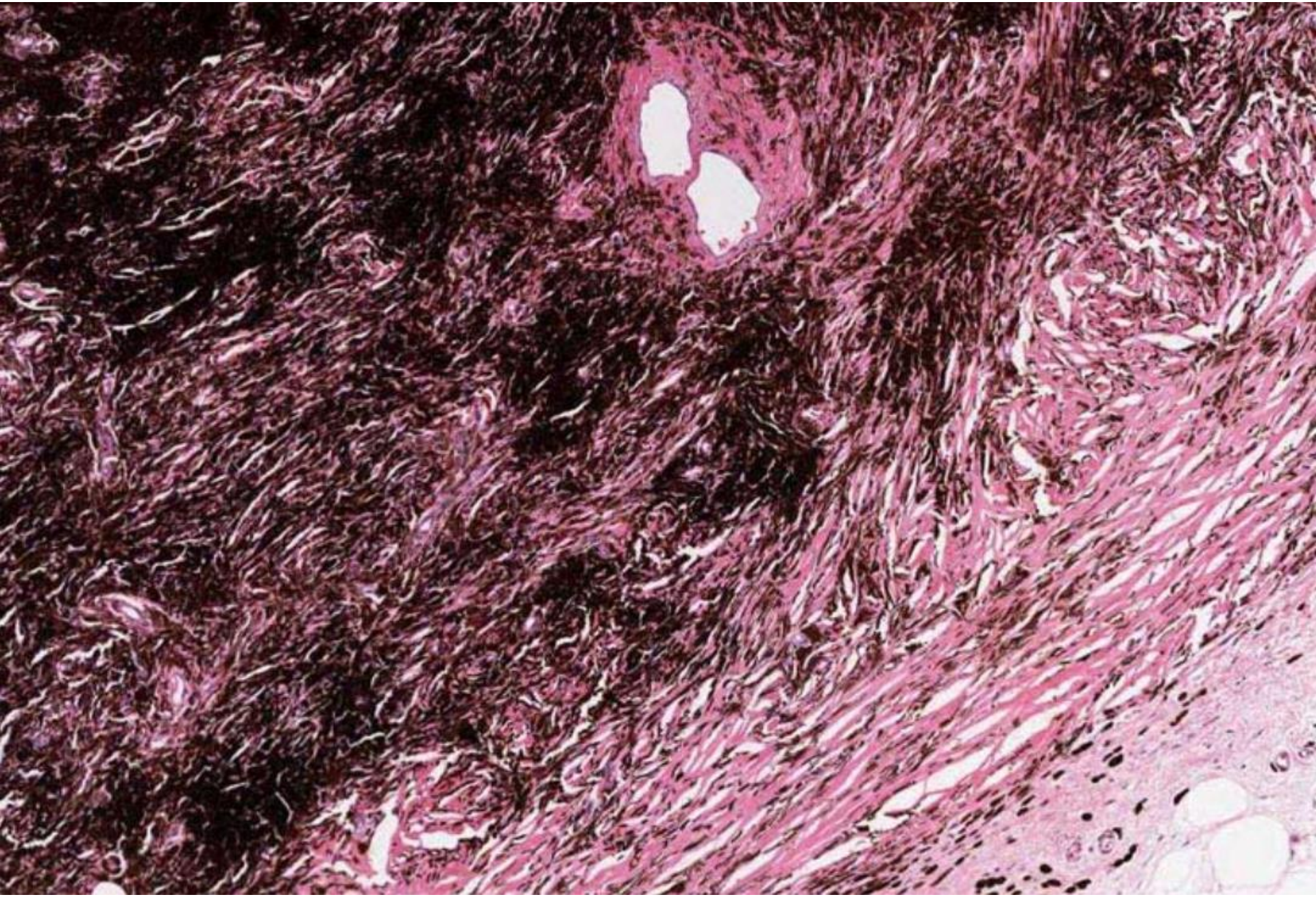
Animal Type Melanoma

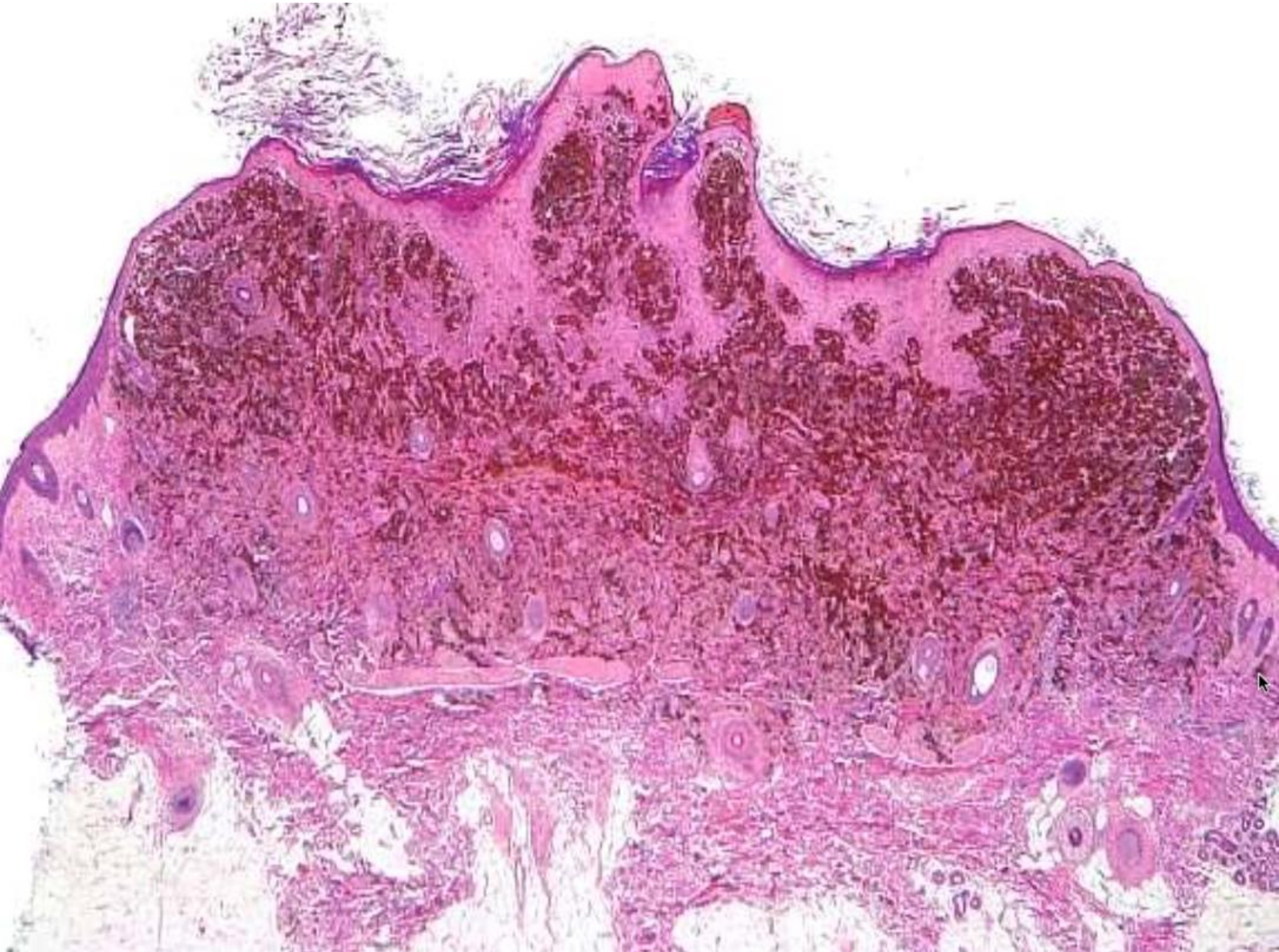
- **Blue plaques or nodules averaging greater than one centimeter in diameter, often on acral surfaces,buttocks, and scalp**
- **Skewed to the younger population**
- **No association with familial dysplastic nevus syndrome, sun exposure, or family history of malignant melanoma**
- **Precursor lesion: cellular blue nevus, blue nevus**
- **As long as the cytology is well differentiated, clinical course is in most cases indolent**

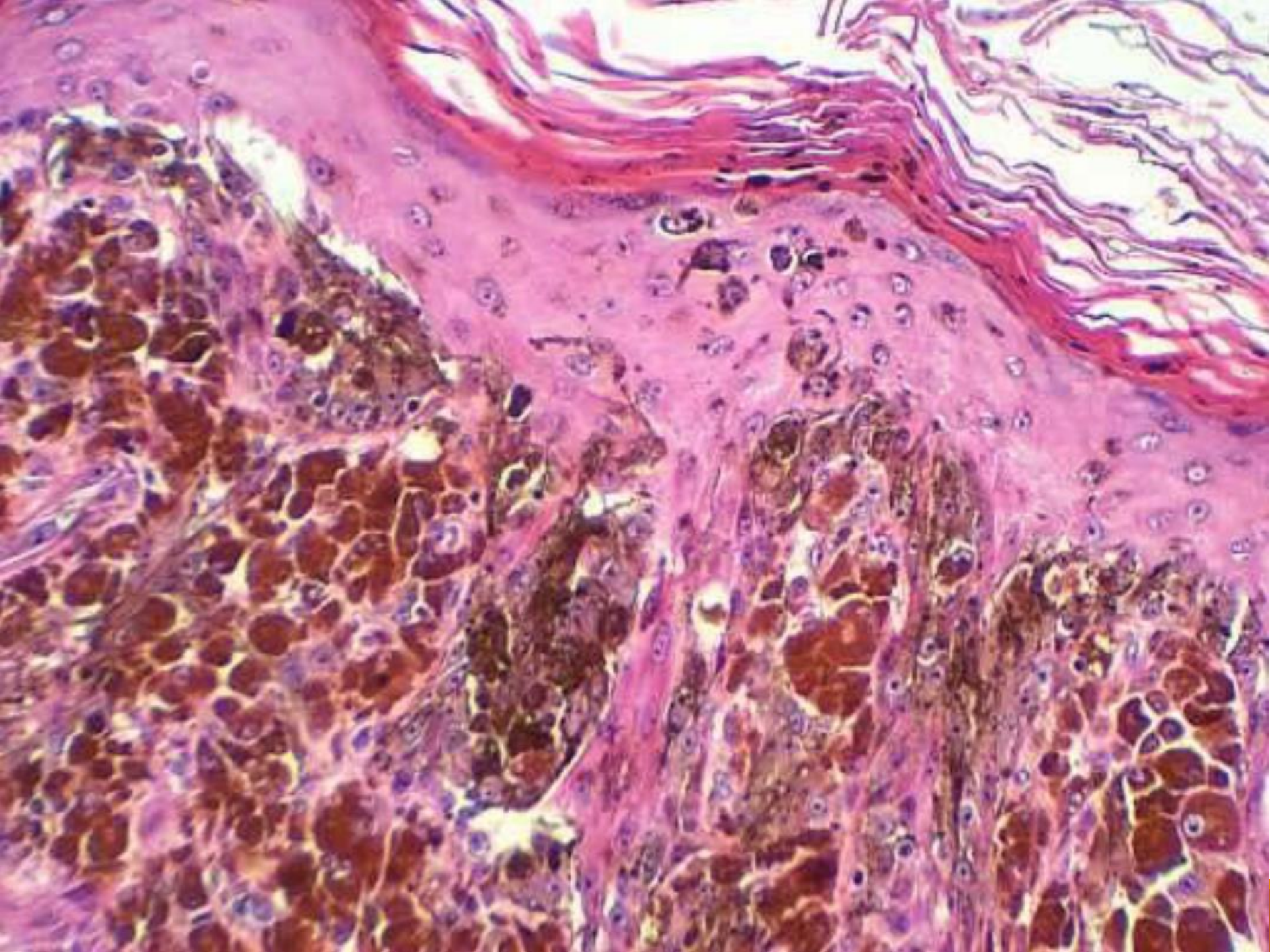
Animal Type Melanoma

- **Prominent dermal involvement with extension to the dermal subcutaneous interface.**
- **No significant Grenz zone of papillary dermal sparing.**
- **Pattern of pigmentation: fine granular light brown deposits allowing easy identification of nuclear detail, to dark brown coarse deposits that obscured the nuclei.**



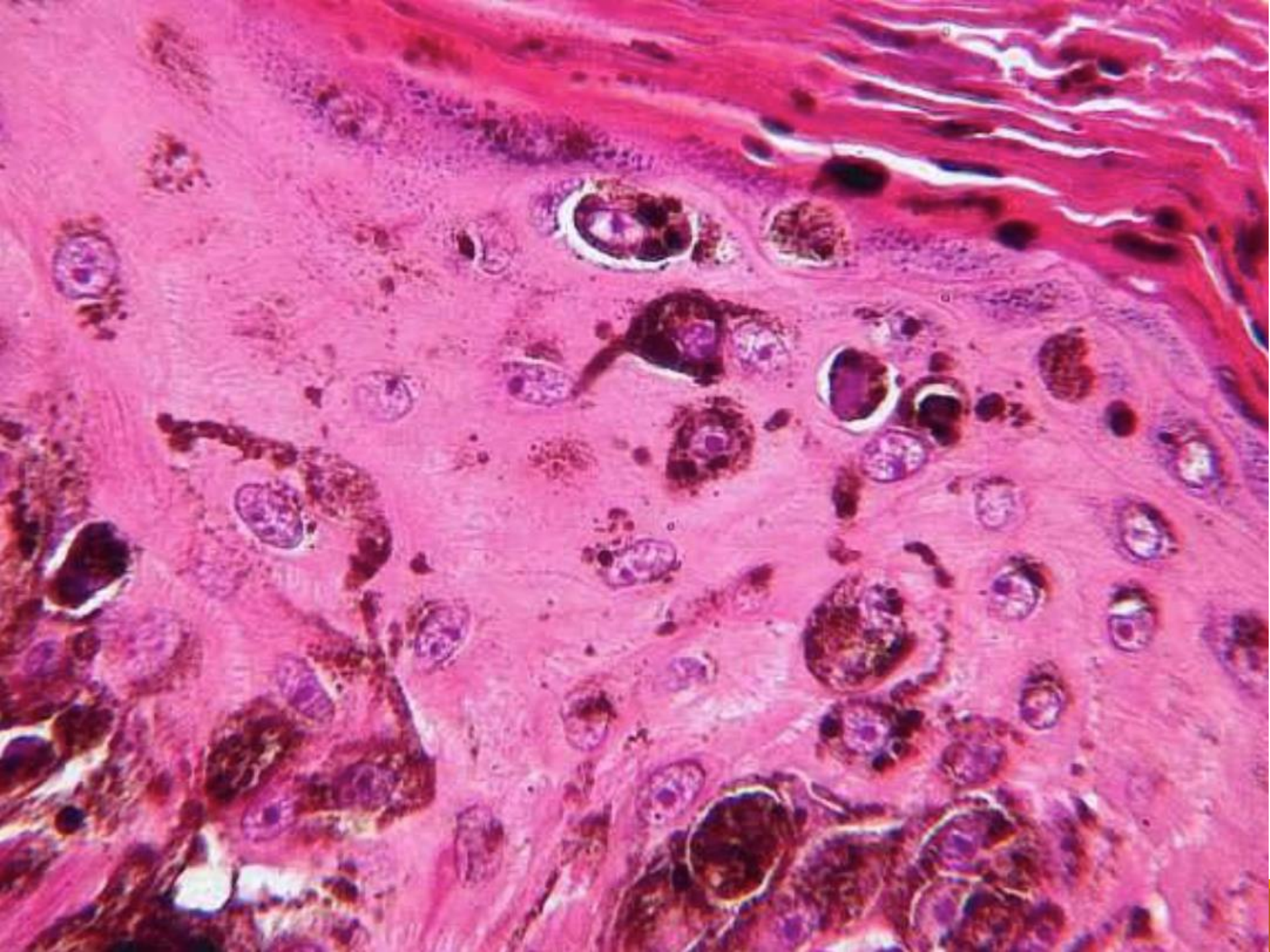


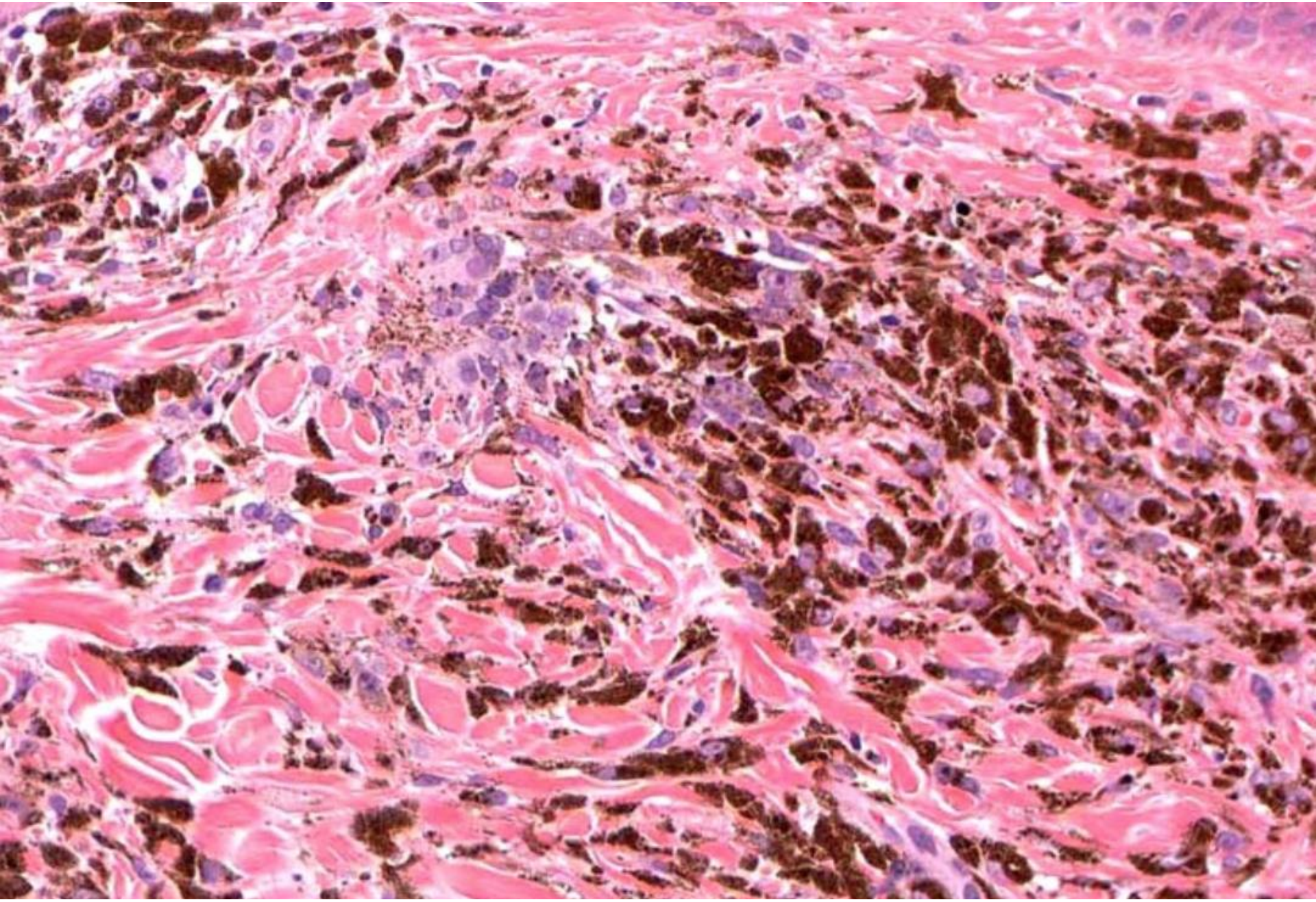




Animal Type Melanoma

- **Cytomorphology : Spindled or polygonal/rounded morphology, difficult to distinguish from melanophages.**
- **Dissipation in cellularity occurred at the periphery of the lesion, where the cells manifested a dendritic appearance producing a morphology reminiscent of a blue nevus.**





Animal Type Melanoma

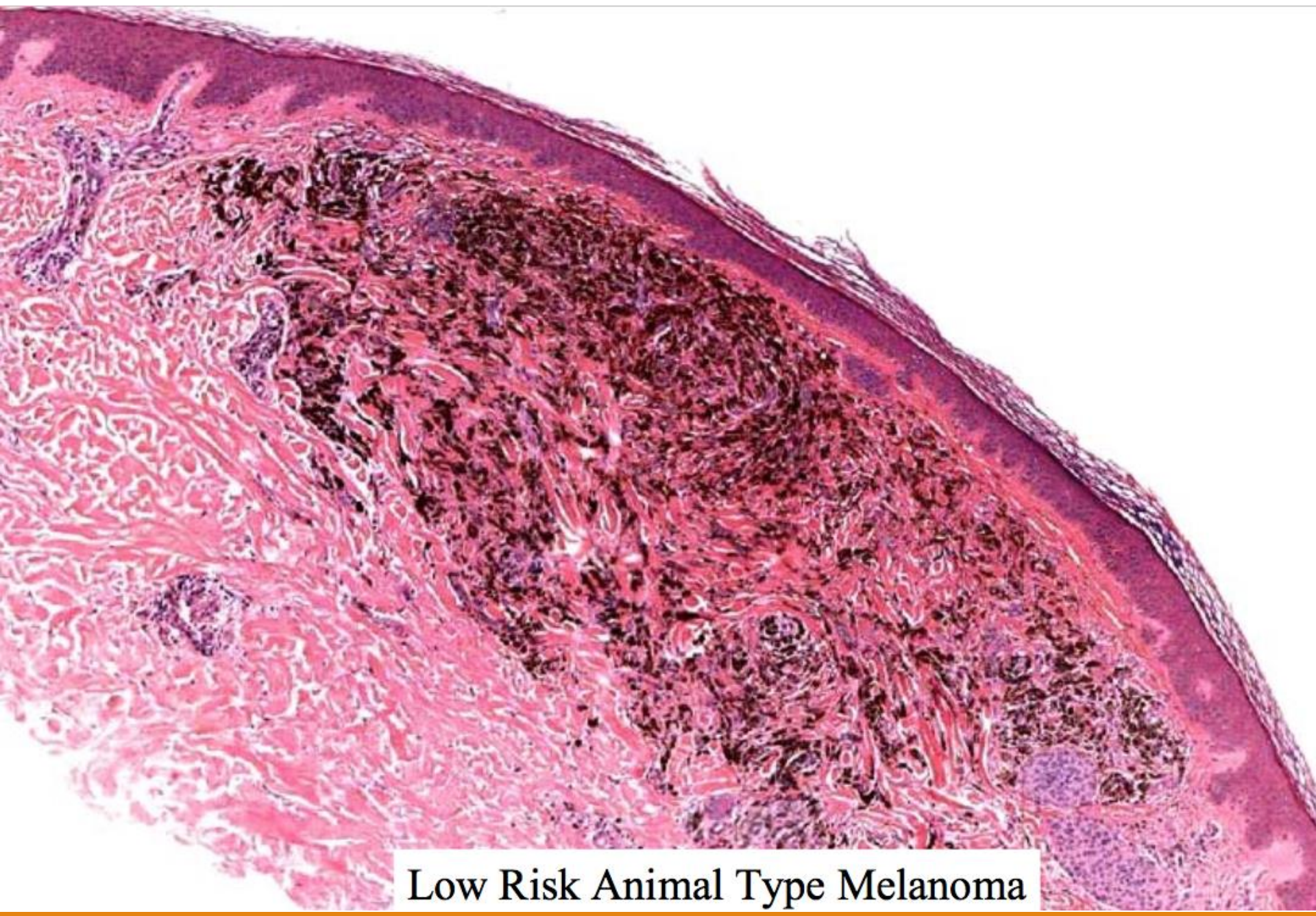
- **Recent studies (ie Zembowicz et al, 2002) have shown sentinel node positivity in 33% of cases**
- **Patients with +ve nodes appear not to manifest progressive disease in limited follow-up obtained today**
- **In general, the prognosis is vastly better compared to other types of melanoma manifesting a similar depth of penetration**

Pigmented Epithelioid Melanocytoma

- **Morphologically identical to animal type melanoma and epithelioid blue nevus of Carney's complex**
- **Young median age (27years); extremities most common**
- **Deep dermal extension (mean Breslow's thickness 3.3 mm)**
- **Five lesions part of combined nevus.**
- **46% with regional lymph node metastases; one with distant metastases although all are alive and well.**
- **Conclusion: PEM is a low-grade melanoma variant with frequent lymph node metastases but indolent clinical course**

Nomenclature

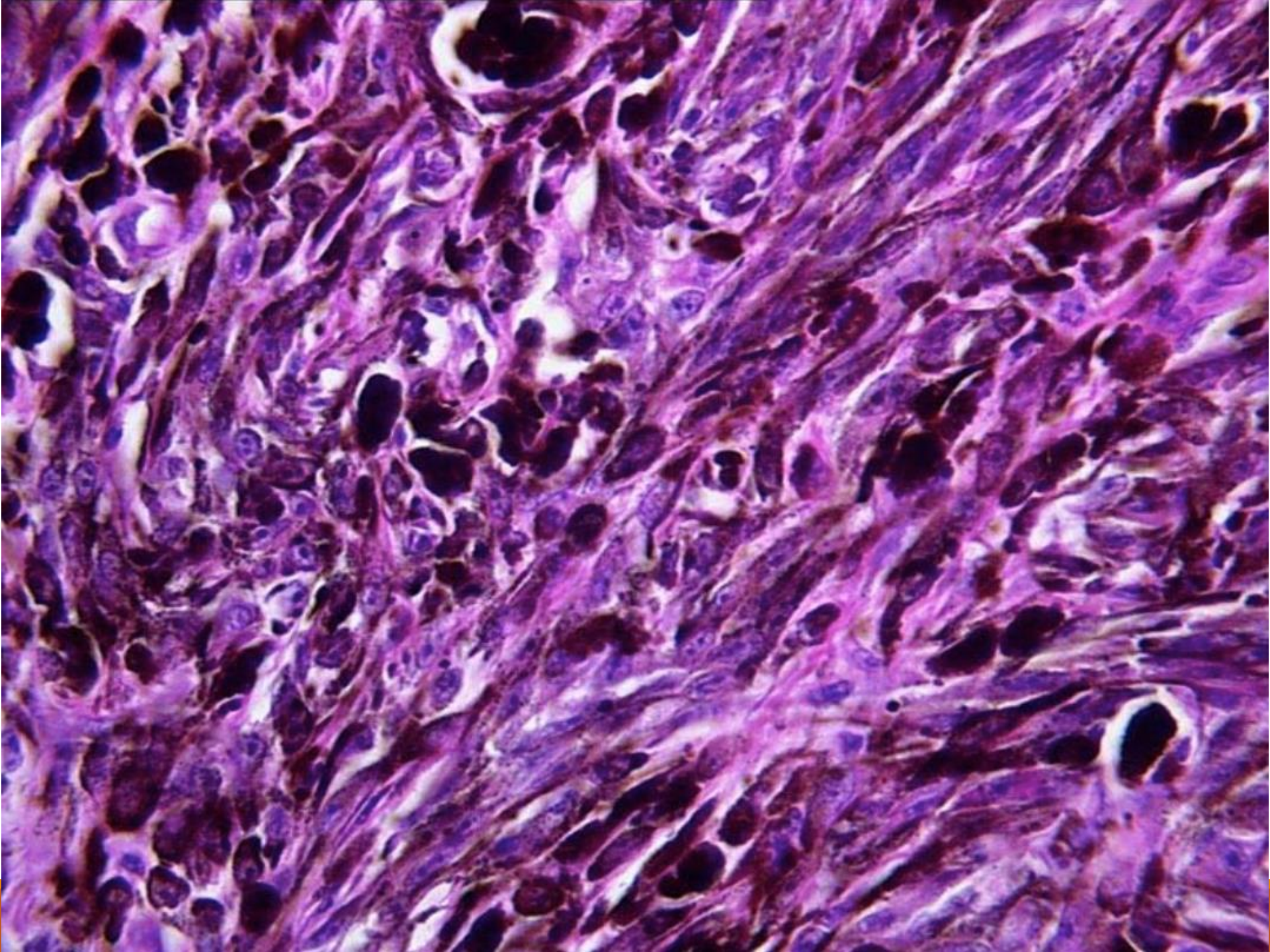
- **Recent: Animal type melanoma (Crowson et al., 1999) and pigmented epithelioid melanocytoma (Zembowicz et al., 2004)**
- **Earlier terms: Dermal melanocytosis resembling equine melanotic disease (Levene, 1979) and pilar neurocristic hamartoma (Tuthill, 1982)**
- **Low risk for RMD: small lesions < 2mm**
- **High risk for RMD: >2mm, extension into fat**
- **Aggressive biological course: cytologic criteria of malignancy and excessive mitotic activity, ? better categorized MBN**



Low Risk Animal Type Melanoma

PEM - Ddx

- Malignant melanoma in vertical growth phase with focal areas of prominent pigment synthesis
- Cellular blue nevus
- Malignant blue nevus
- Malignant melanoma arising in extra-sacral dermal melanocytoses (nevi of Ito, Ota and Sun)
- Deep penetrating nevus
- Plexiform spindle cell nevus
- Pigmented spindle or epithelioid cell nevus
- Regressed melanoma with prominent melanophages

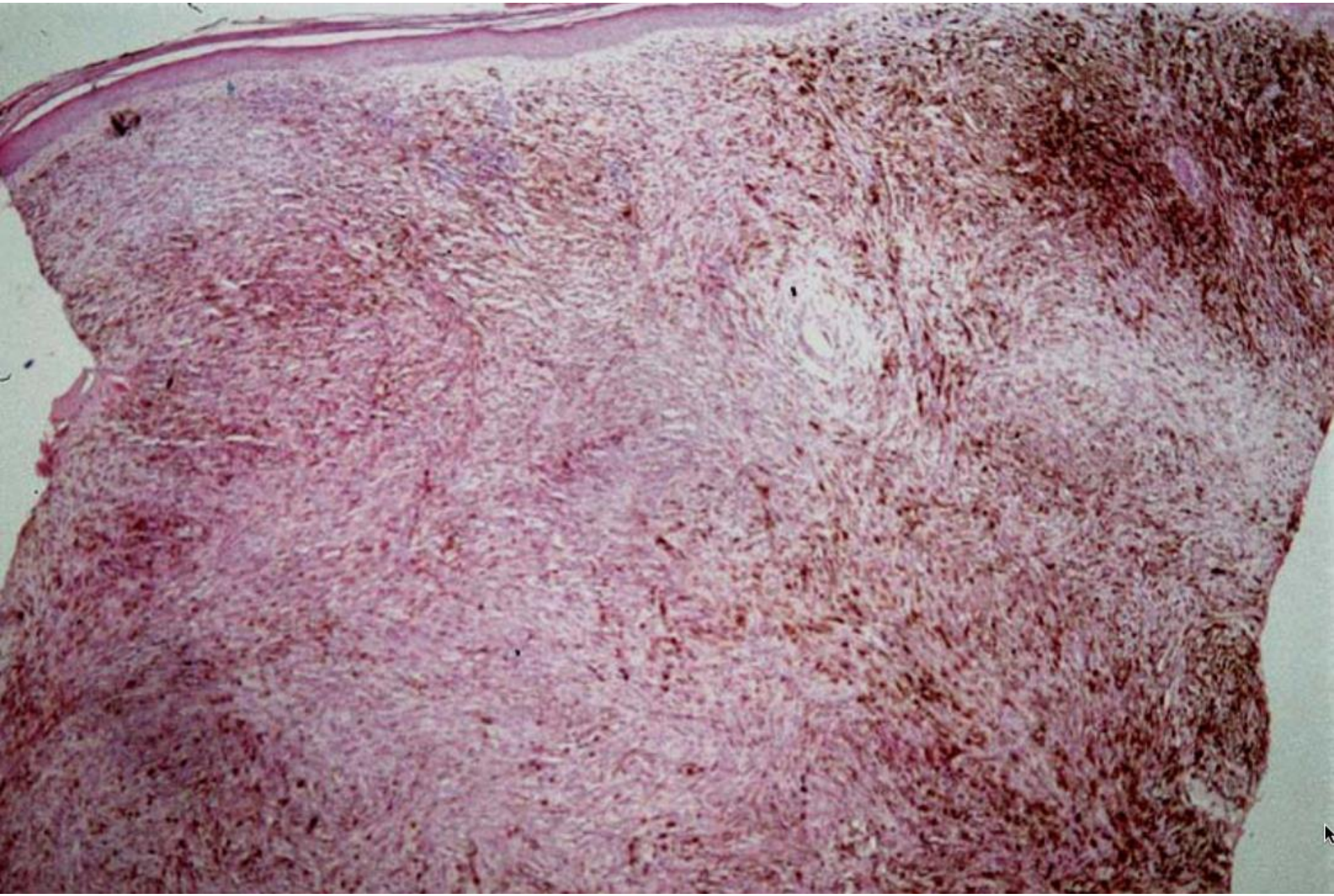


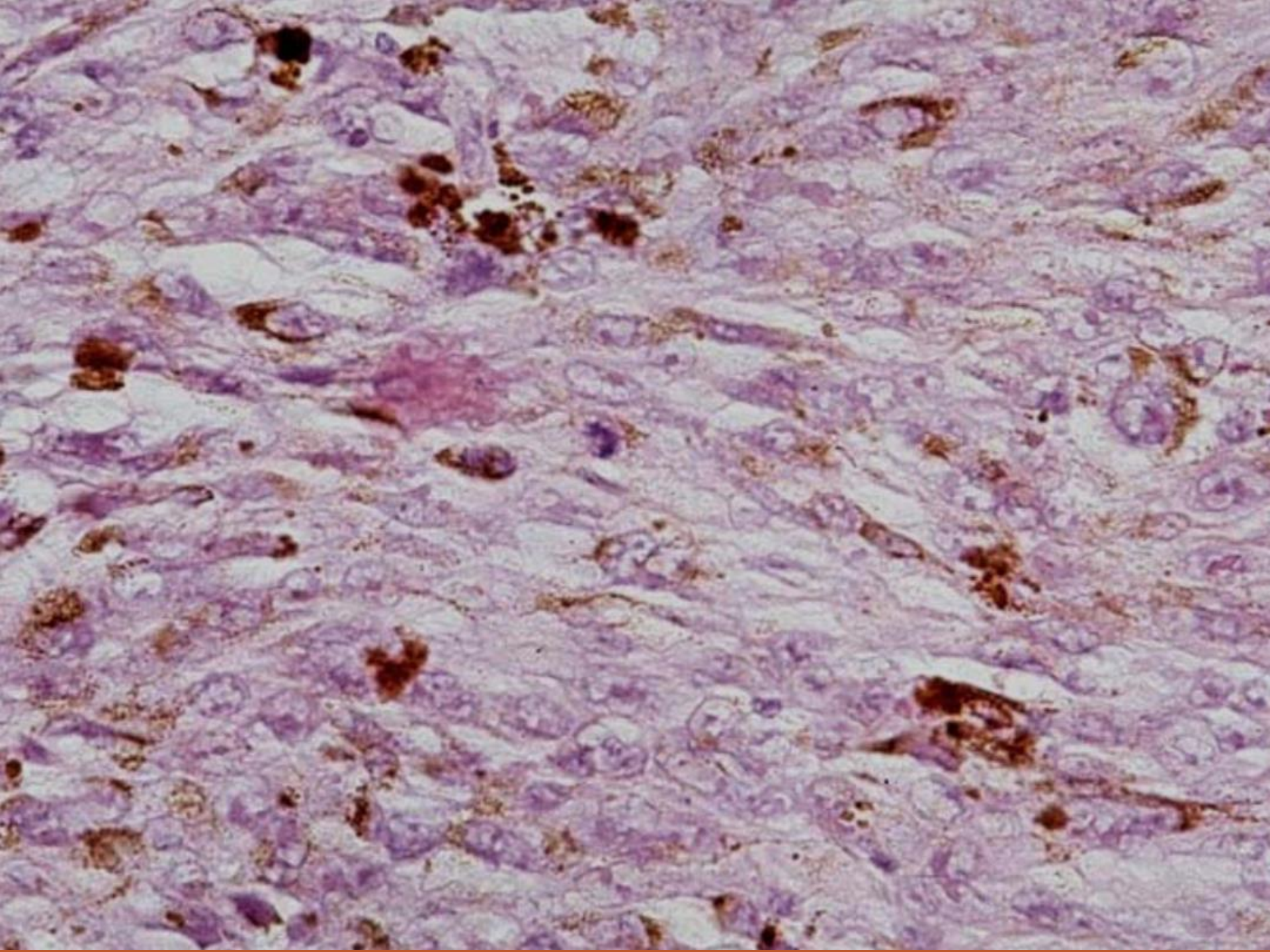
Ddx – Malignant Blue Nevus

- **Background of a cellular/common blue nevus**
- **Equal M to F ratio, range 11 to 77 years (average age, 48.1 years).**
- **The head and neck are the most common location, scalp most common**
- **Tumor size average 1cm.**
- **Most lesions had been present for many years before surgical removal.**
- **The clinical signs: rapid enlargement, and ulceration**
- **Aggressive neoplasms with short survival; metastases to lung is common**

Malignant Blue Nevus

- **Background lesion of cellular or common blue nevus**
- **The malignant component essentially effaces the dermal architecture and may extend into the subcutis**
- **Multiple foci of necrosis with palisading of tumor cells**
- **High grade cytologic atypism**
- **Atypical mitoses**
- **Essentially the overtly malignant counterpart of animal type melanoma**



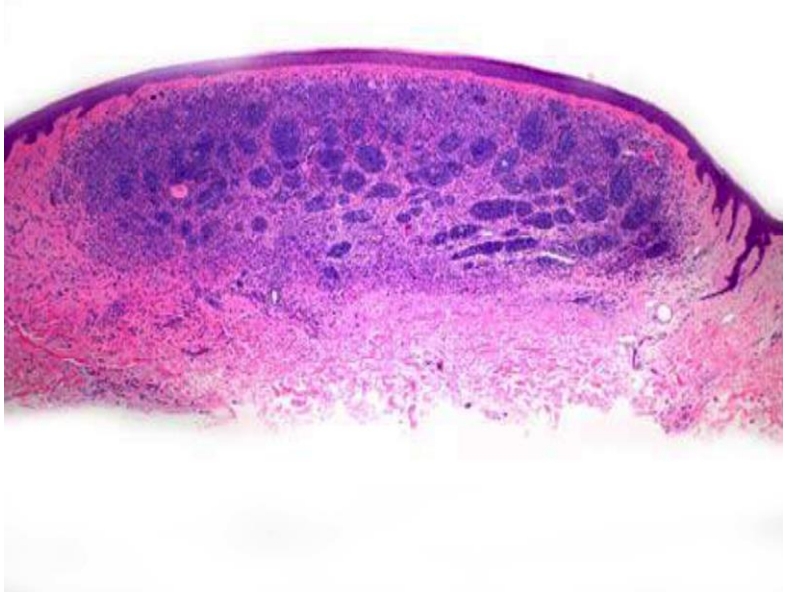


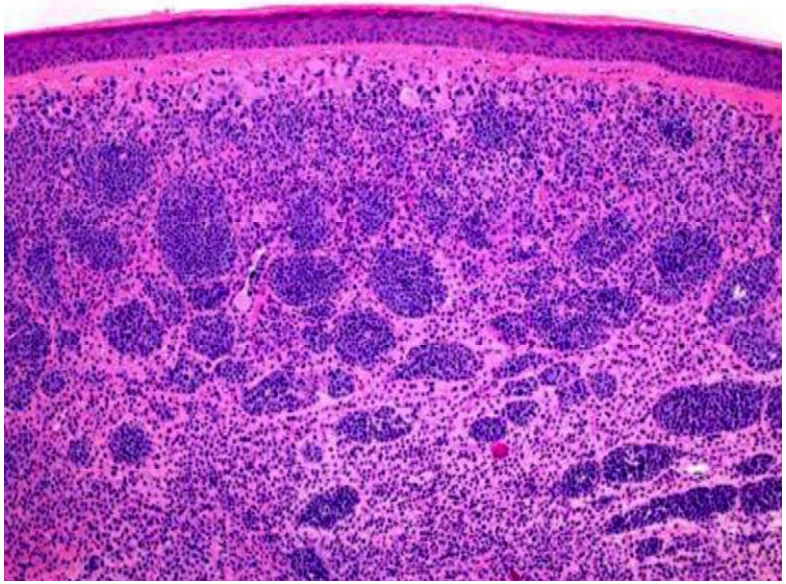
Case 3

35 YO FEMALE WHO PRESENTED WITH MULTIPLE PIGMENTED LESIONS. SEVERAL OF THESE HAD FIRM PALE PALPABLE CENTERS. ONE OF THESE WAS EXCISED. CLINICAL DIFFERENTIAL DIAGNOSIS INCLUDED DYSPLASTIC NEVUS VERSUS MALIGNANT MELANOMA.

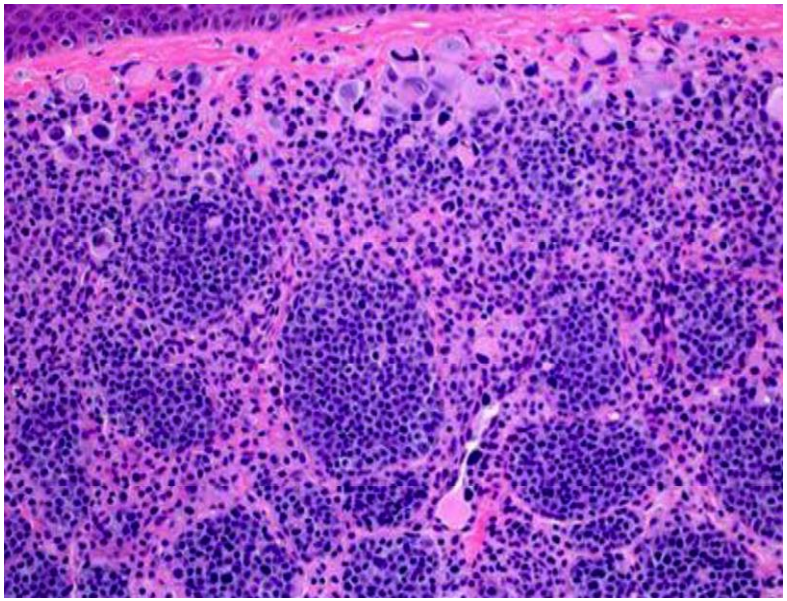
A SIBLING HAD A HISTORY OF OCULAR MELANOMA, AND HER MATERNAL RELATIVES HAD A HISTORY OF NEVI.

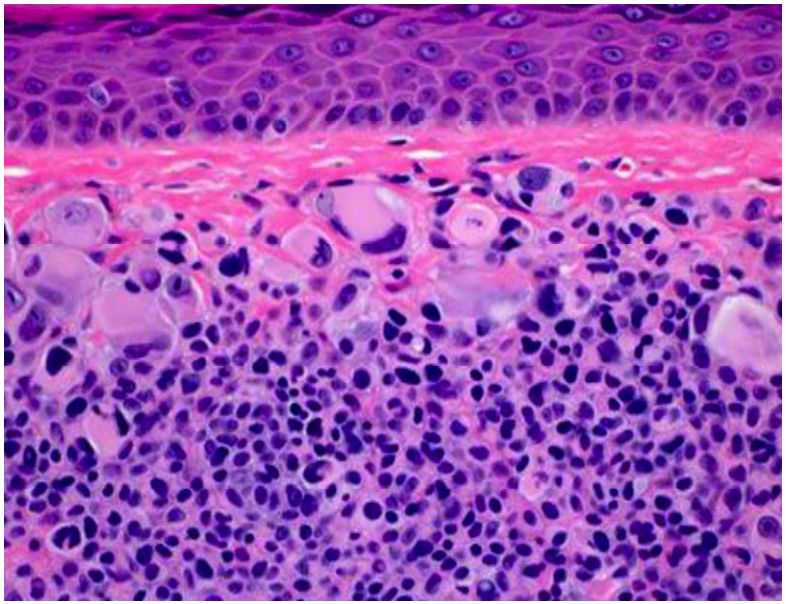
Multiple pigmented lesions with firm pale palpable centers



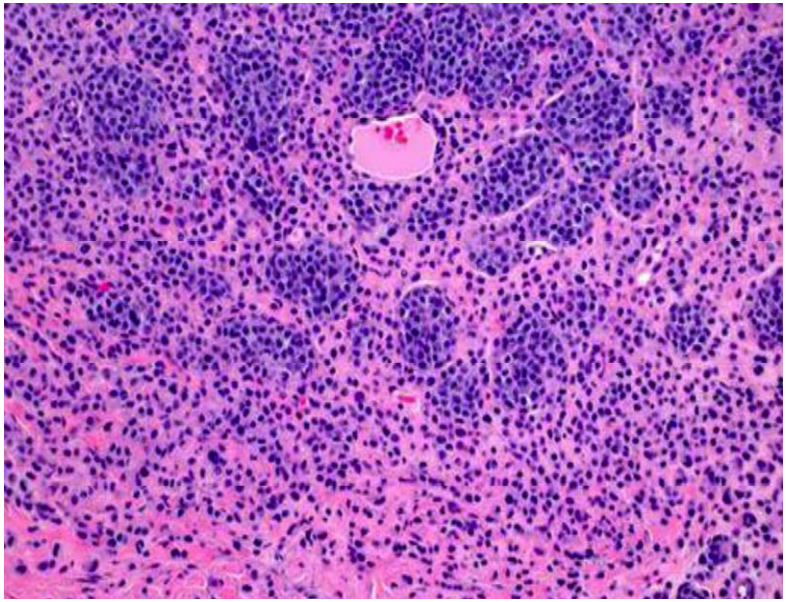


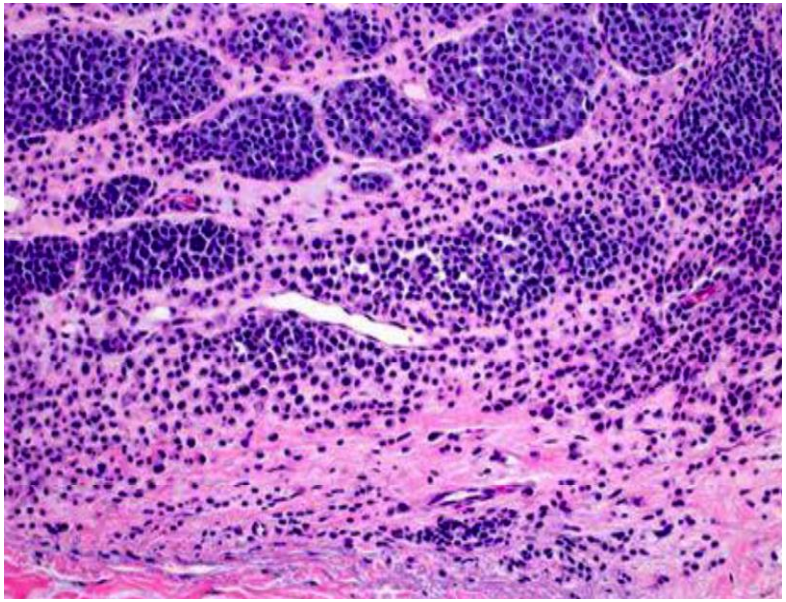
Multiple pigmented lesions with firm pale palpable centers





Multiple pigmented lesions with firm pale palpable centers





BAP1-negative Melanocytic Proliferation – BAPoma

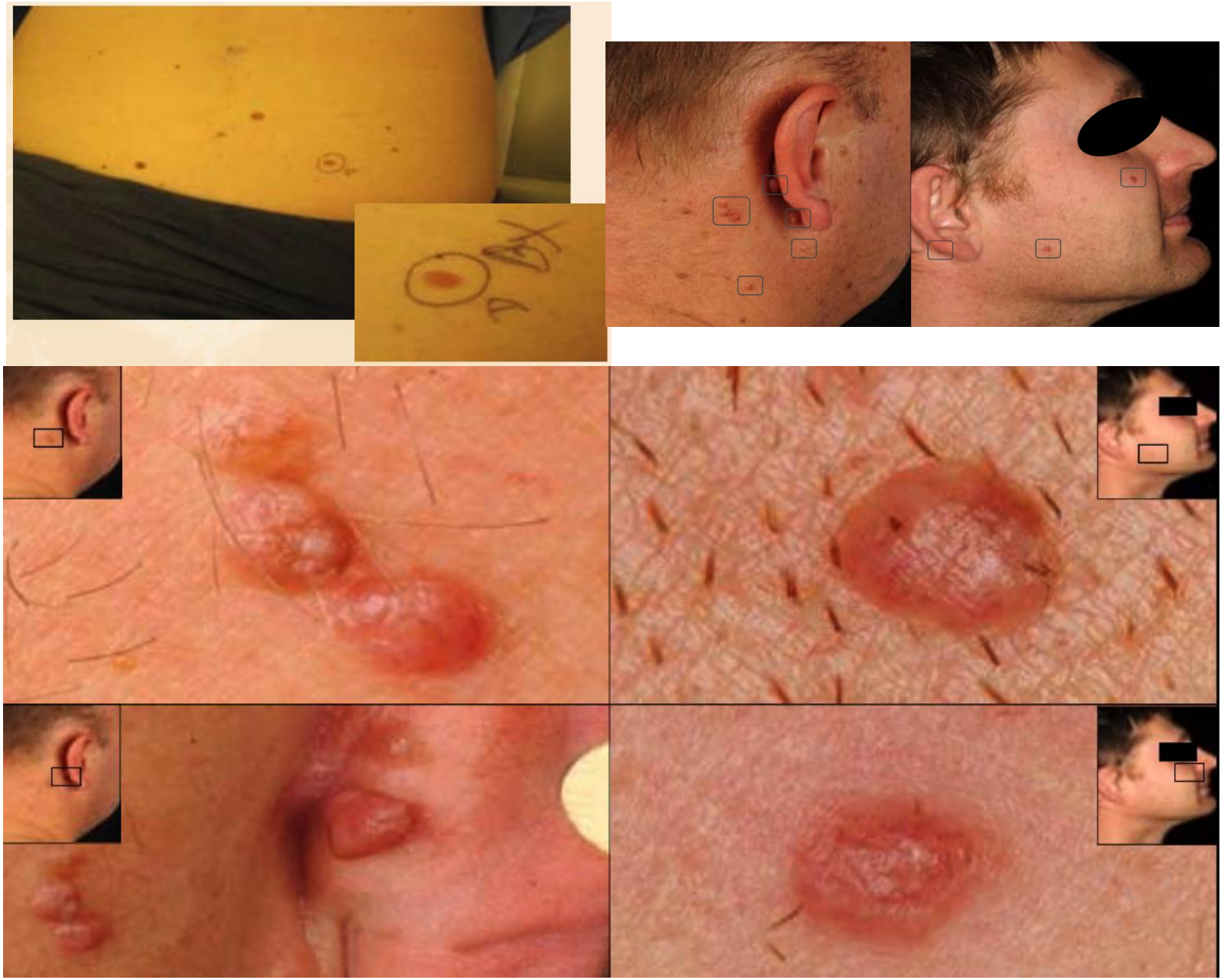
- **Weisner et al first described 2 families that had multiple skin lesions varying from a few to 50 lesions.**
- **Found to show autosomal dominant inheritance.**
- **Families had a history of uveal melanoma as well as cutaneous melanomas.**
- **Genetic studies revealed germ line mutations in the BAP1 (BRCA1-associated protein 1), a tumor suppressor gene located on chromosome 3 (3p21).**
- **Ubiquitin carboxy-terminal hydrolase, functions as a deubiquitylating enzyme for protein substrates.**
- **It was then found that spontaneous cases also occur without germ line mutations.**

BAP1-negative Melanocytic Proliferation – BAPoma

- Other names include:
- NEMMP: highly atypical nevoid melanoma-like melanocytic proliferations
- MBAIT: melanocytic BAP1-mutated atypical intradermal tumors
- BAPoma
- Also likely misclassified in the literature as
  - Epithelioid atypical Spitz tumors
  - Melanoma
- However, these are molecularly distinct and behave non-aggressively

BAP1-negative Melanocytic Proliferation – BAPoma

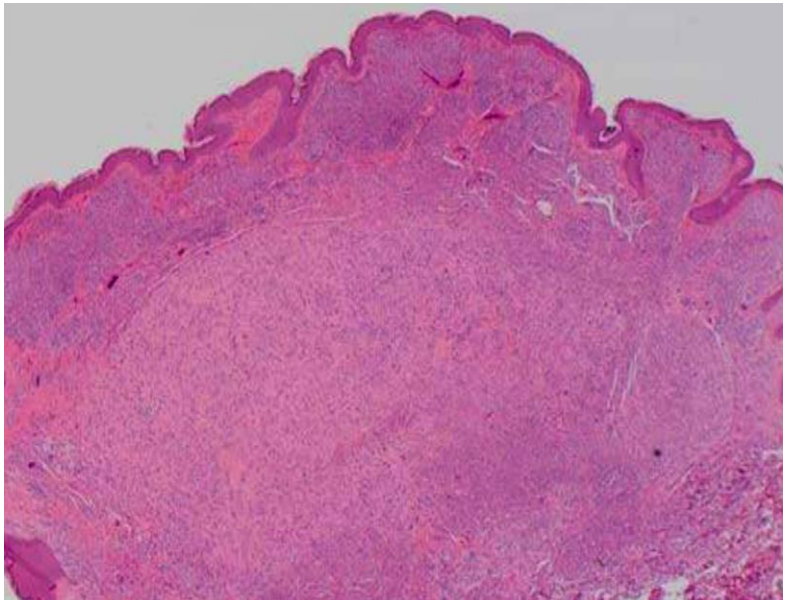
- A family history of cutaneous and/or ocular melanoma
- Orange to red, semitranslucent, papular, or pedunculated lesions, often < 1 cm
- Lesions are usually firm, often surrounded by a halo of pigmentation
- Sun exposed areas are most commonly involved including head, neck, arms, and lower extremities but lesions can occur anywhere
- Studies have shown the BAP1 mutation to occur in melanomas, renal cell carcinoma, meningioma, mesothelioma, and other cancers
- A recent study has shown that basal cell carcinomas in the familial setting show the mutation and may be used for screening

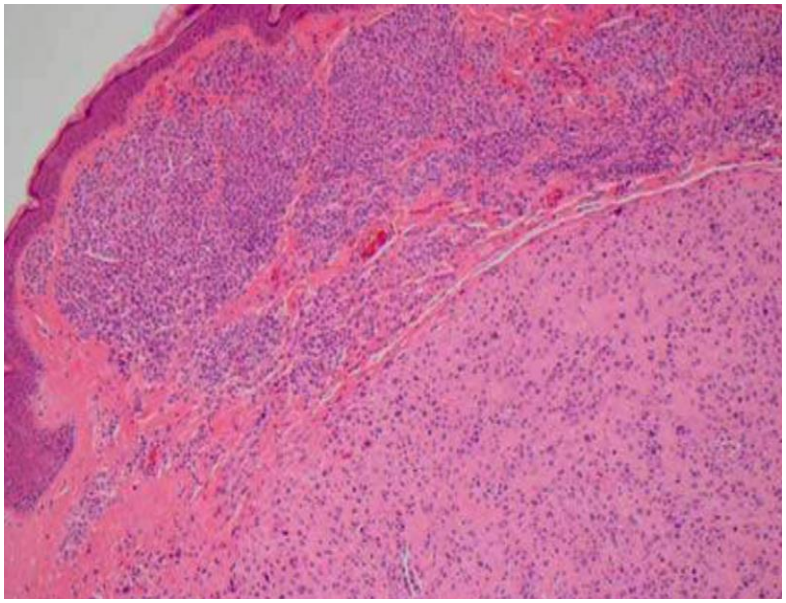


BAP1-negative Melanocytic Proliferation – BAPoma

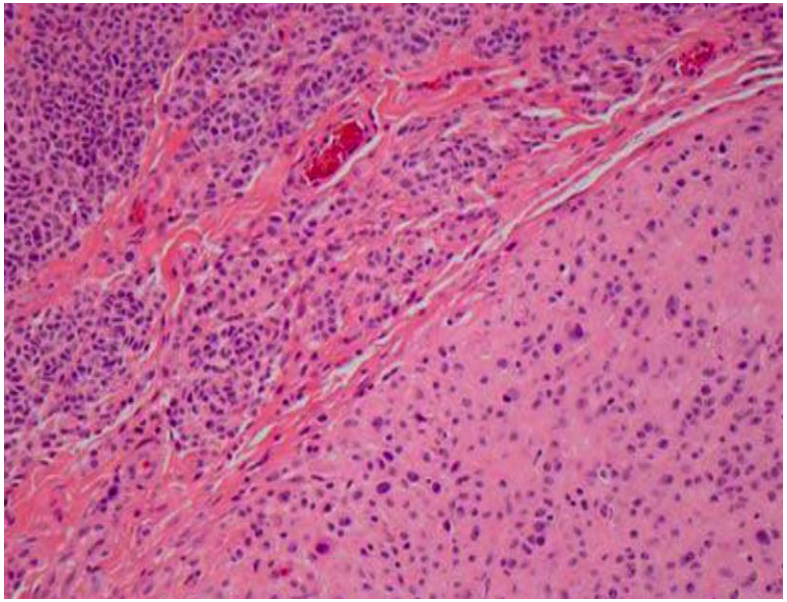
- **Lesions are predominantly dermal but occasionally exhibit junctional nests**
- **The lesion presents as an expansile nodule that often is associated with a peripheral benign dermal nevus**
- **There is a spectrum of prominent epithelioid cells with ample cytoplasm and well defined borders to cells with small cytoplasms and small hyperchromatic nuclei with a nevoid appearance**
- **Many cells resemble Spitz nevus cells but with marked nuclear pleomorphism and hyperchromasia. There is also a clear nucleoplasm with condensed chromatin and a prominent nucleus.**
- **Mitoses are infrequent**

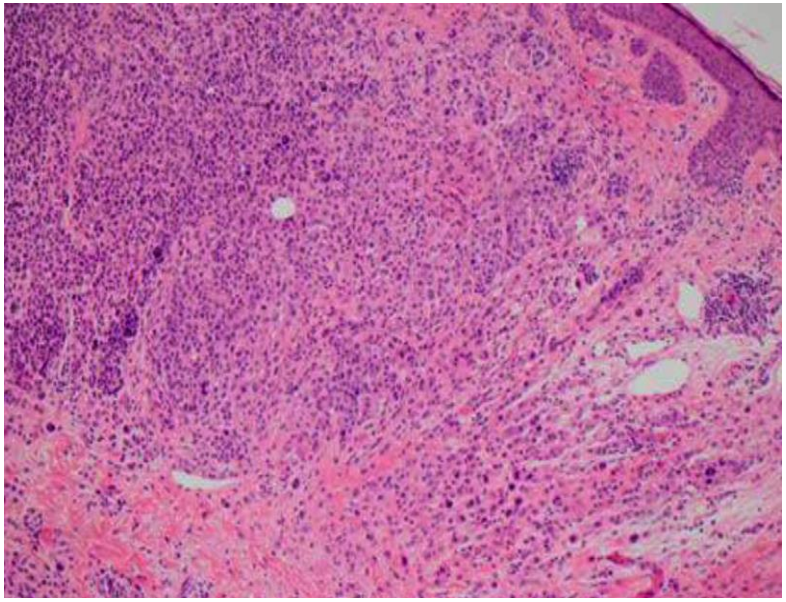
BAP1-negative Melanocytic Proliferation – BAPoma



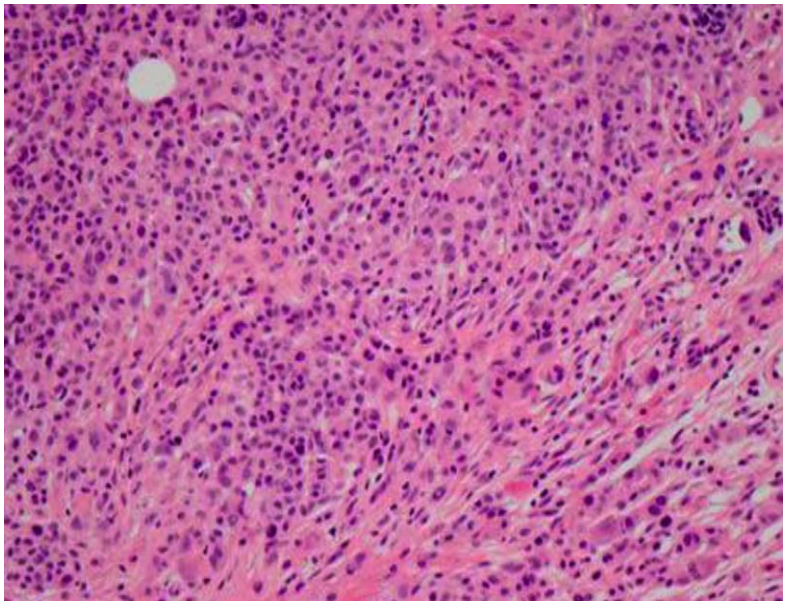


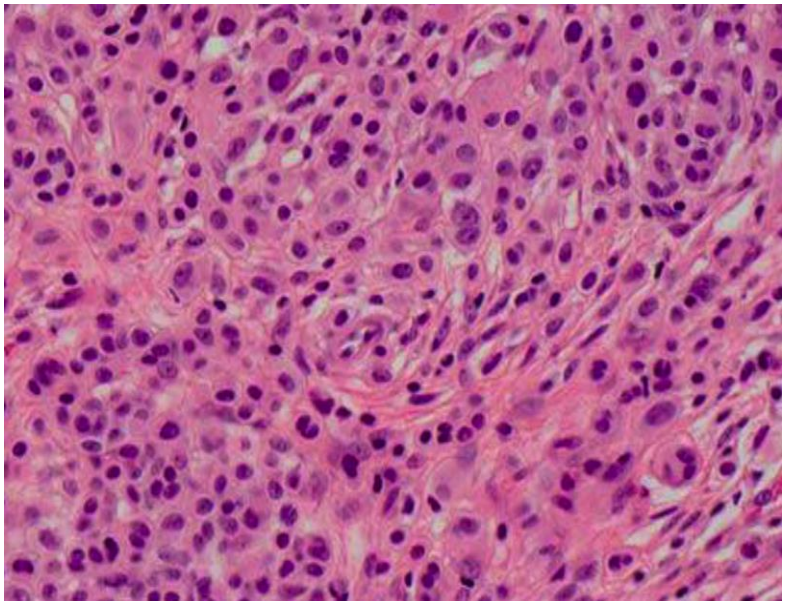
BAP1-negative Melanocytic Proliferation – BAPoma



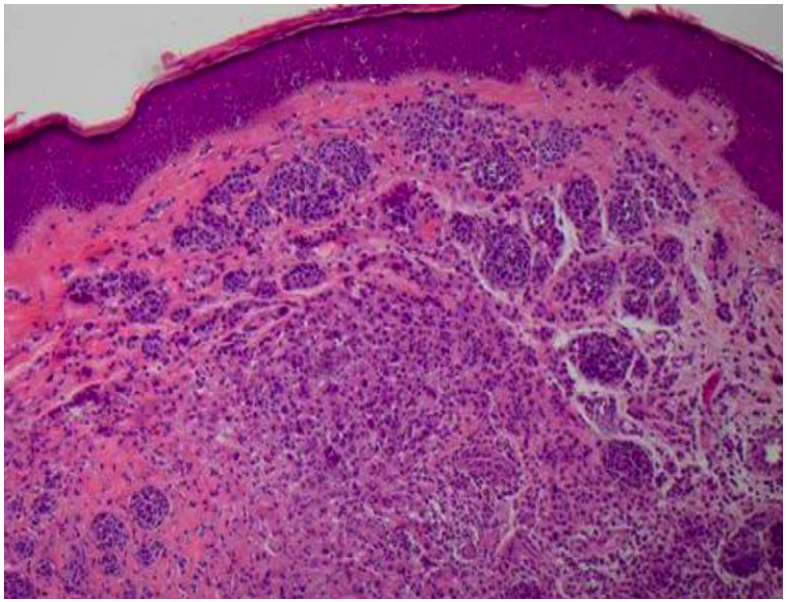


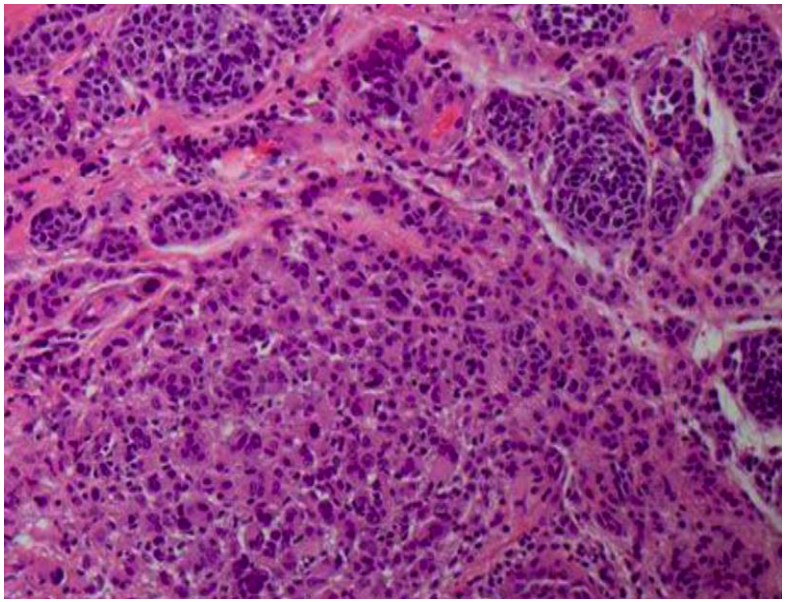
BAP1-negative Melanocytic Proliferation – BAPoma

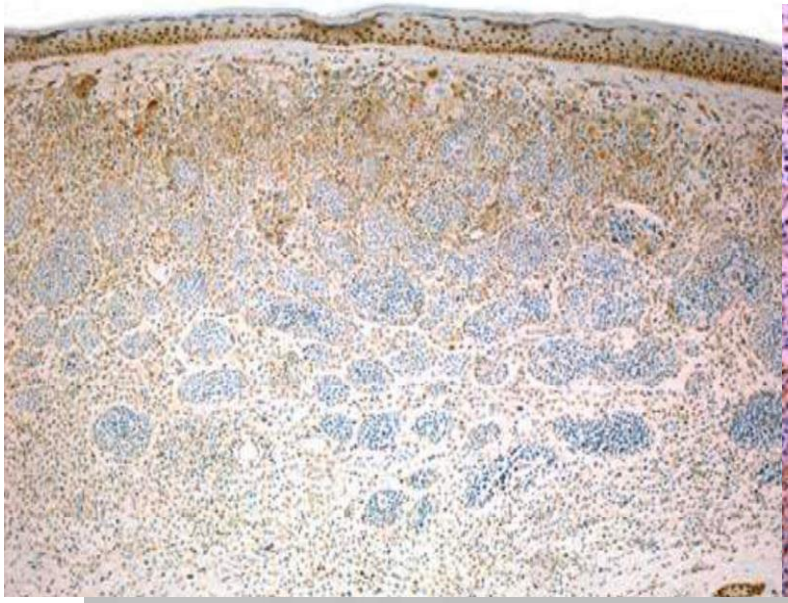


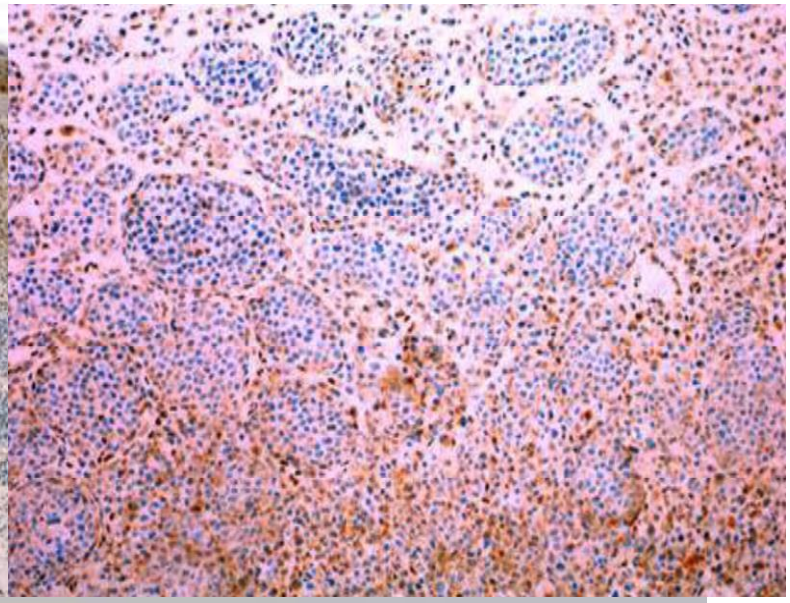


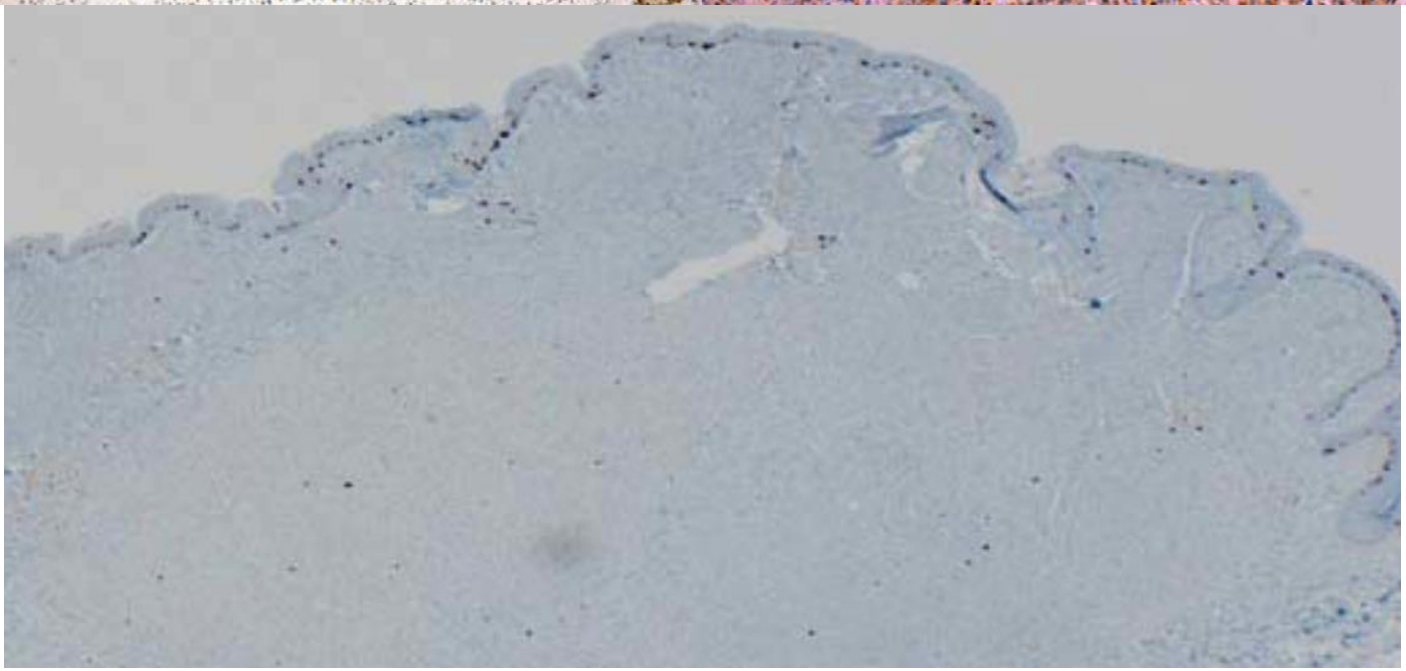
BAP1-negative Melanocytic Proliferation – BAPoma











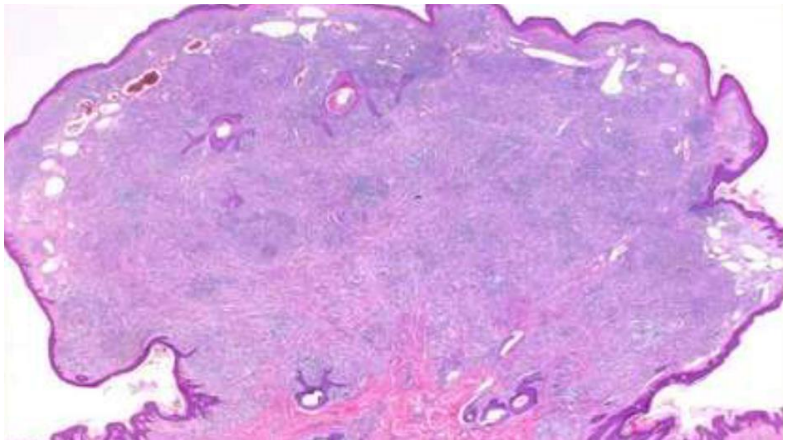
BAP1

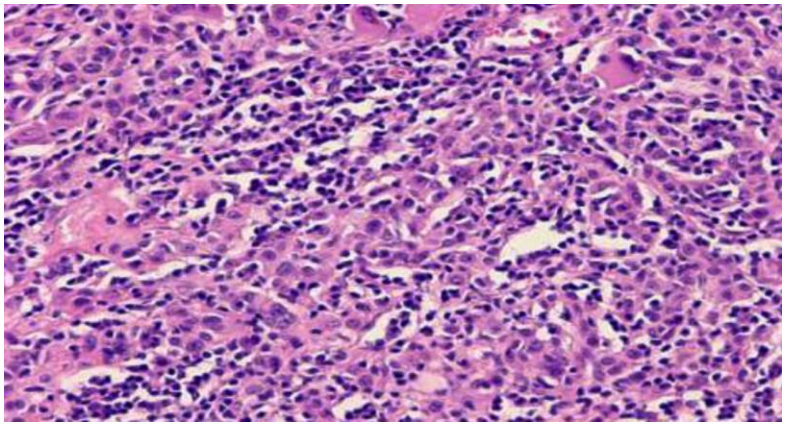
- **Germline BAP1 mutation:**
  - **p.Asp236Glyfs*7 found as carrier status for the three affected members of this family**
- **Tumor BAP1 biallelic inactivation:**
- **(from 7 tumors: 1 SSM, 1 nevoid melanoma, 5 atypical nevomelanocytic proliferations)**
  - **p.Asp236Glyfs*7, a LOH in the nevoid melanoma**
  - **p.Ser123Lysfs*3, a separate somatic BAP1 mutation in a nevomelanocytic proliferation**

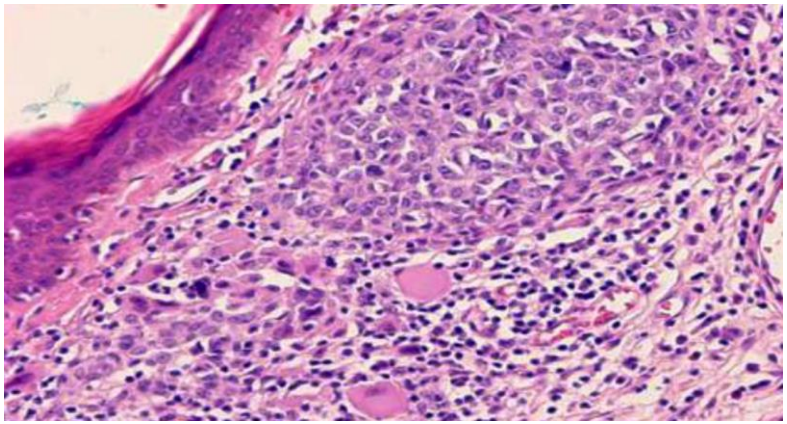
BAP1-negative Melanocytic Proliferation – BAPoma

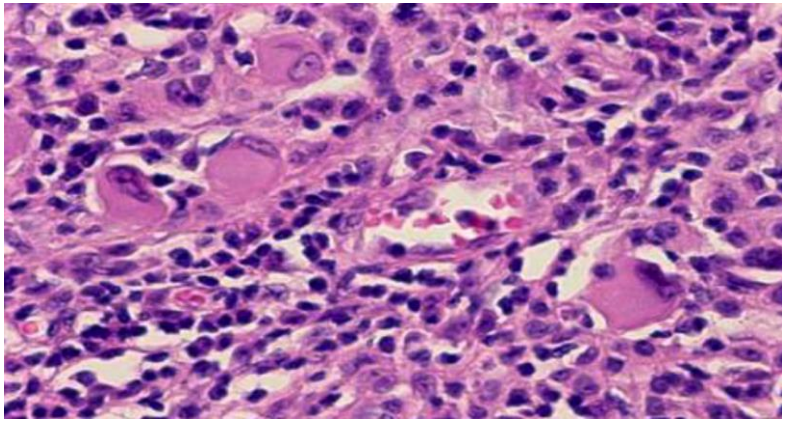
- **In 2004 – 25 yo female history of combined nevus with halo Spitz nevus component excised from temple.**
- **In 2012, she developed two new lesions, one was metastatic melanoma, the other a mesothelioma.**
- **Being aware in 2012 of BAP1 germline mutations, the case from 2004 and the 2 new lesions were tested for BAP1 and were found to have the BAP1 germline mutation.**
- **Subsequent history both cutaneous and uveal melanoma in the family.**

BAP1-negative Melanocytic Proliferation – BAPoma

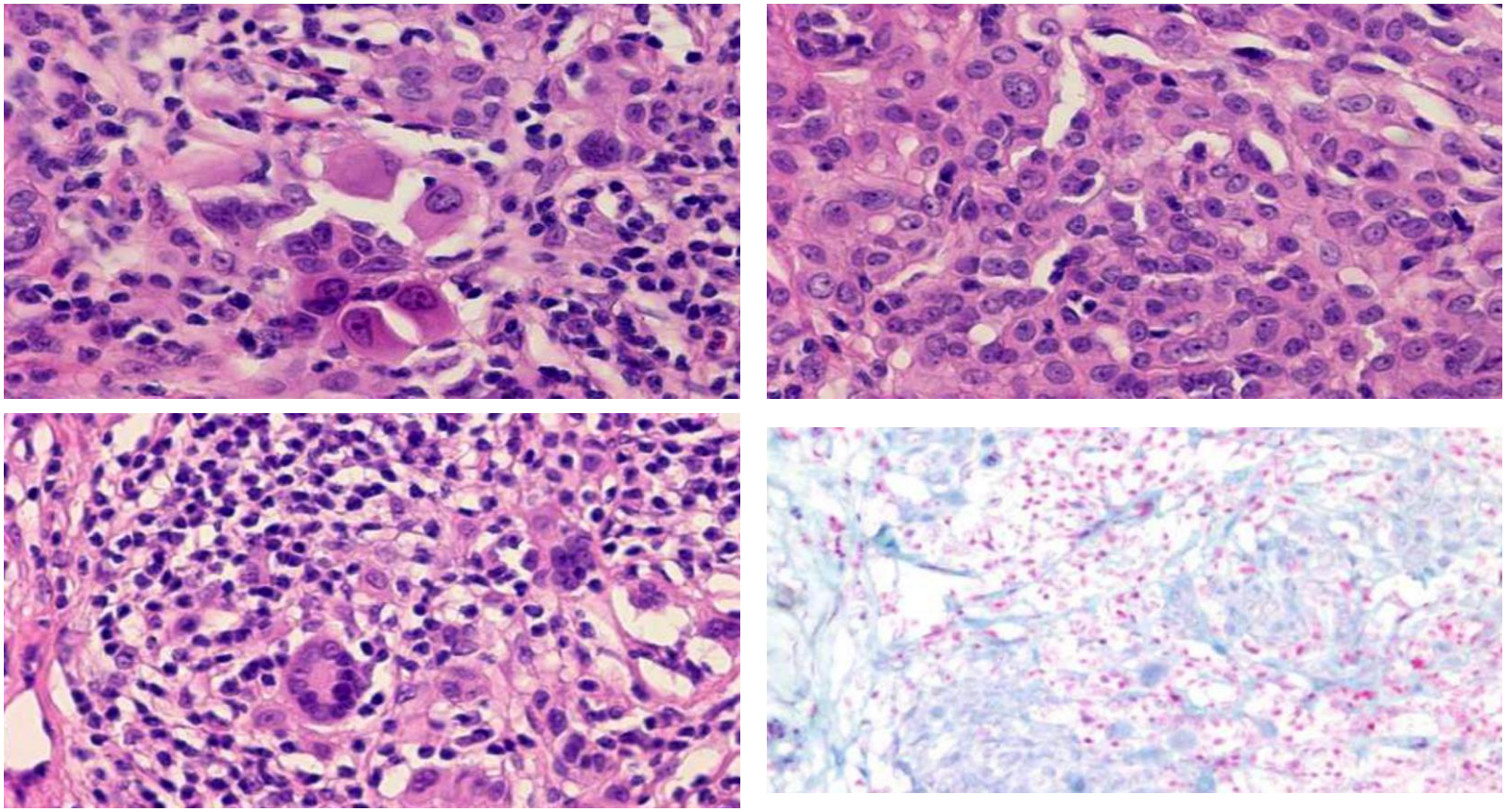




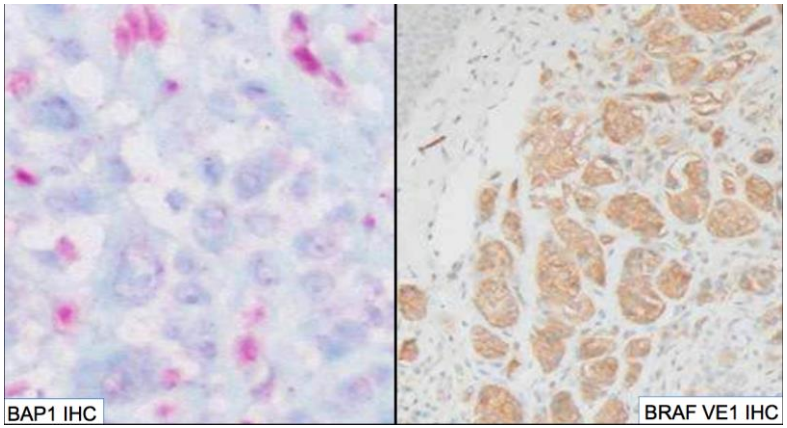


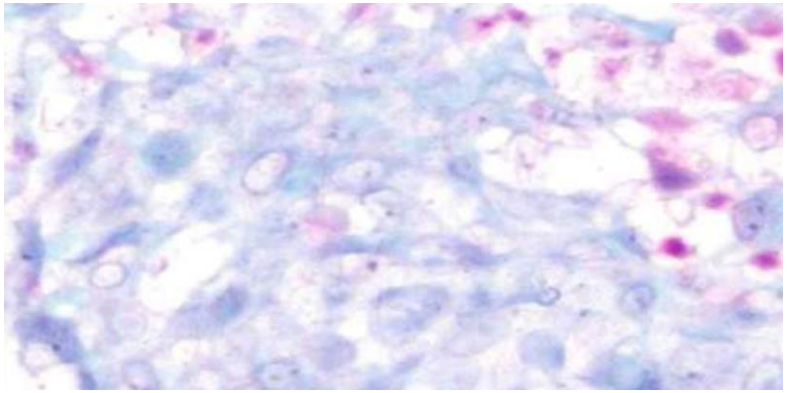


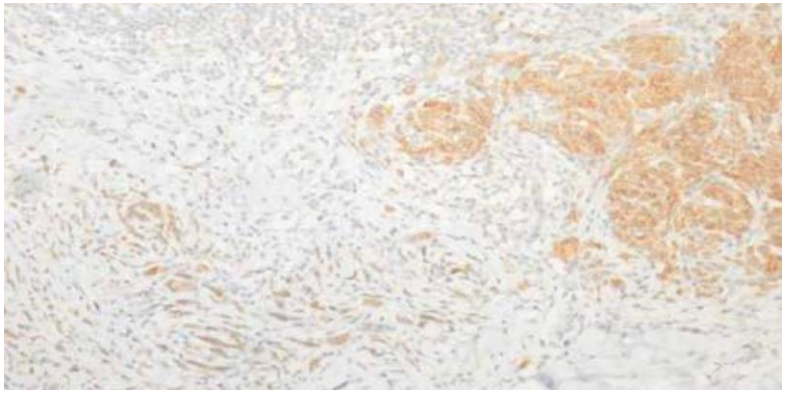
BAP1-negative Melanocytic Proliferation – BAPoma



BAP1 & BRAF







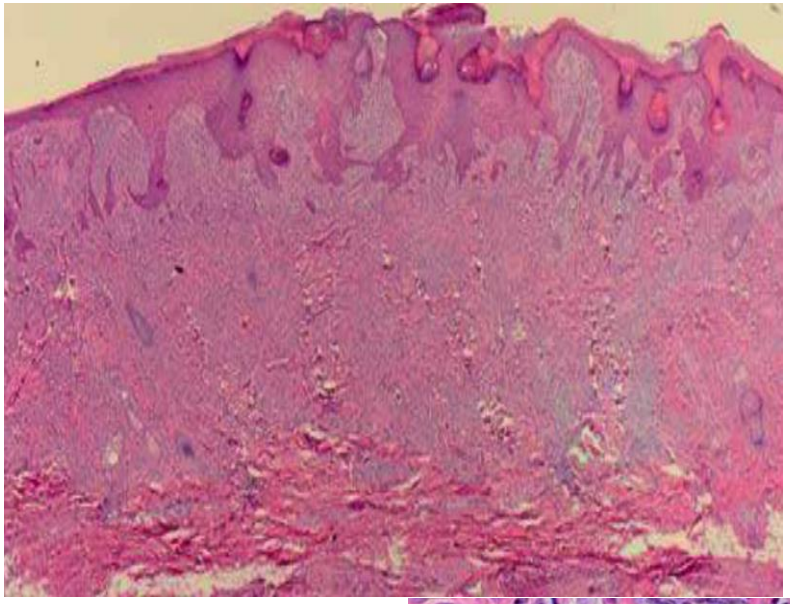
BAP1

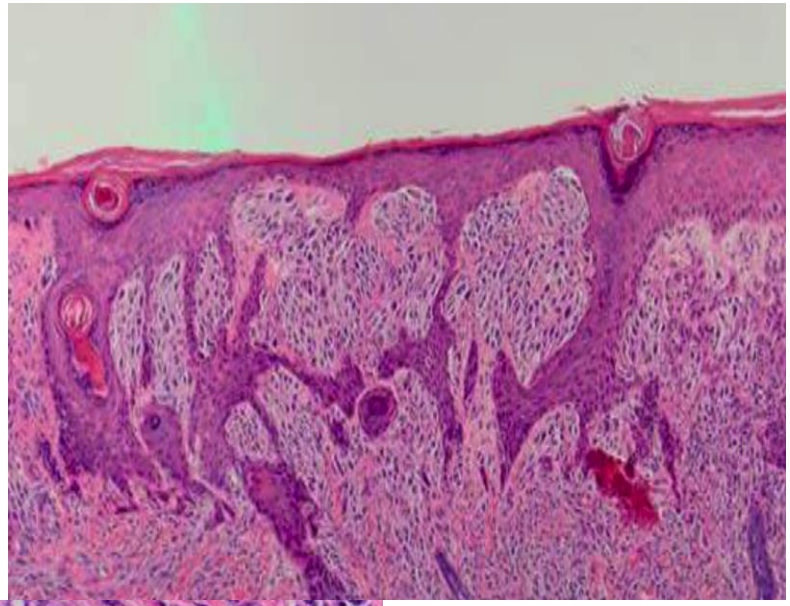
- **The finding of this gene is very significant especially in light of the fact that it may occur spontaneously and apparently predisposes to other malignancies.**
- **Screening for the lesion may be performed by immunohistochemical studies, Sanger sequencing, or screening of basal cell carcinomas or possibly other benign tumors in affected patients.**
- **BAP1, or BRCA1-associated protein 1/ubiquitin carboxy-terminal hydrolase, functions as a deubiquitylating enzyme for protein substrates**
- **BAP1 germline mutations have been seen in familial cancers such as mesotheliomas and meningiomas**
- **Hereditary studies among ocular and cutaneous melanoma kindreds with germline BAP1 mutations have helped identify and molecularly characterize these ubiquitous yet banal acting epithelioid cell melanocytic tumors**

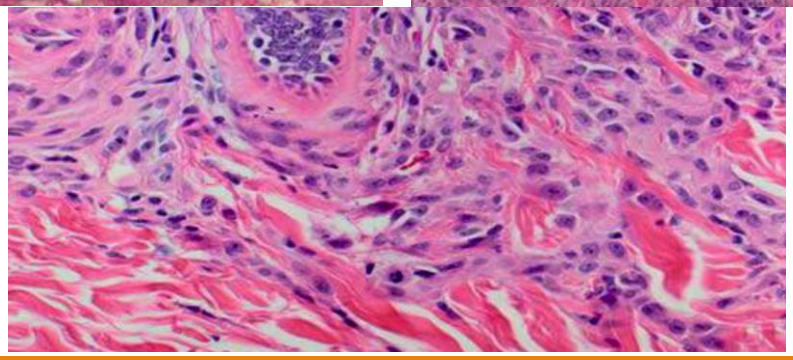
BAP1-negative Melanocytic Proliferation (BAPoma) – Ddx

- **Atypical Spitz nevus**
- **Atypical Spitz's tumor**
- **Malignant melanoma, nodular type**
- **Malignant melanoma, nevoid type**

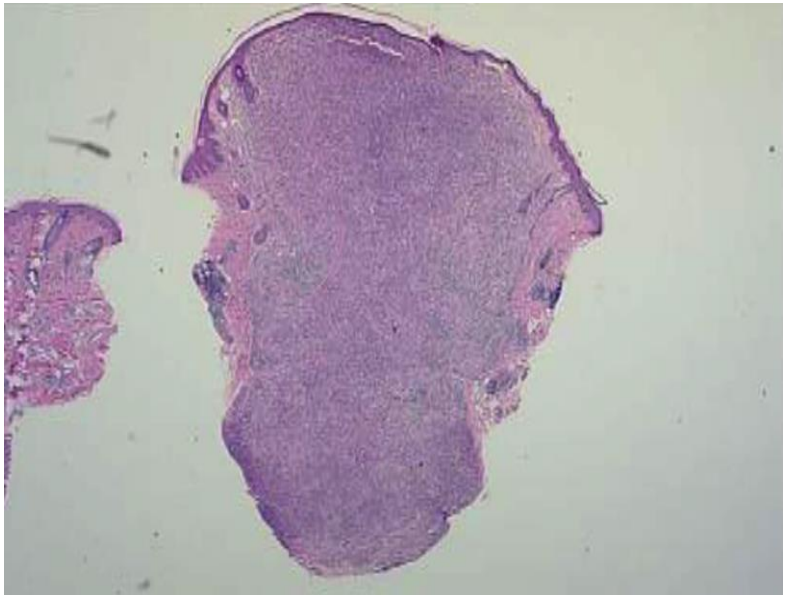
Ddx – Atypical Spitz Nevus

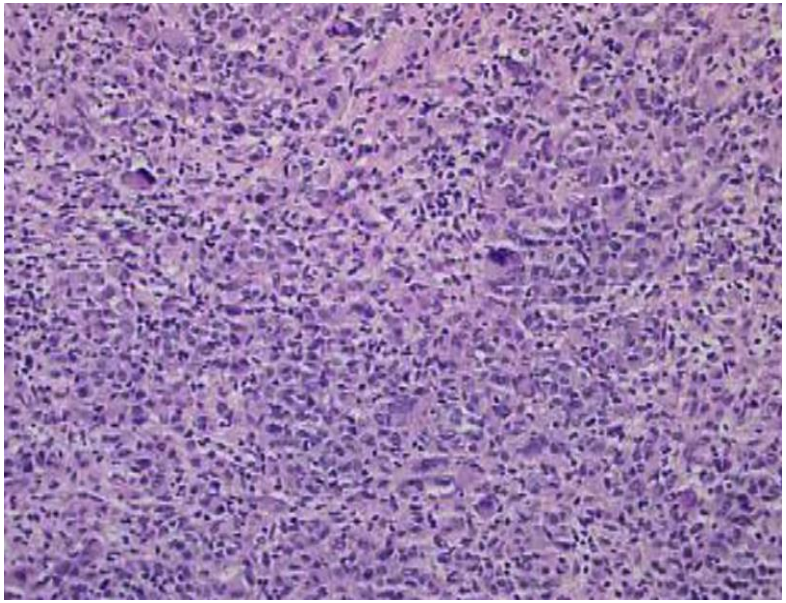






Ddx – Atypical Spitz Tumor



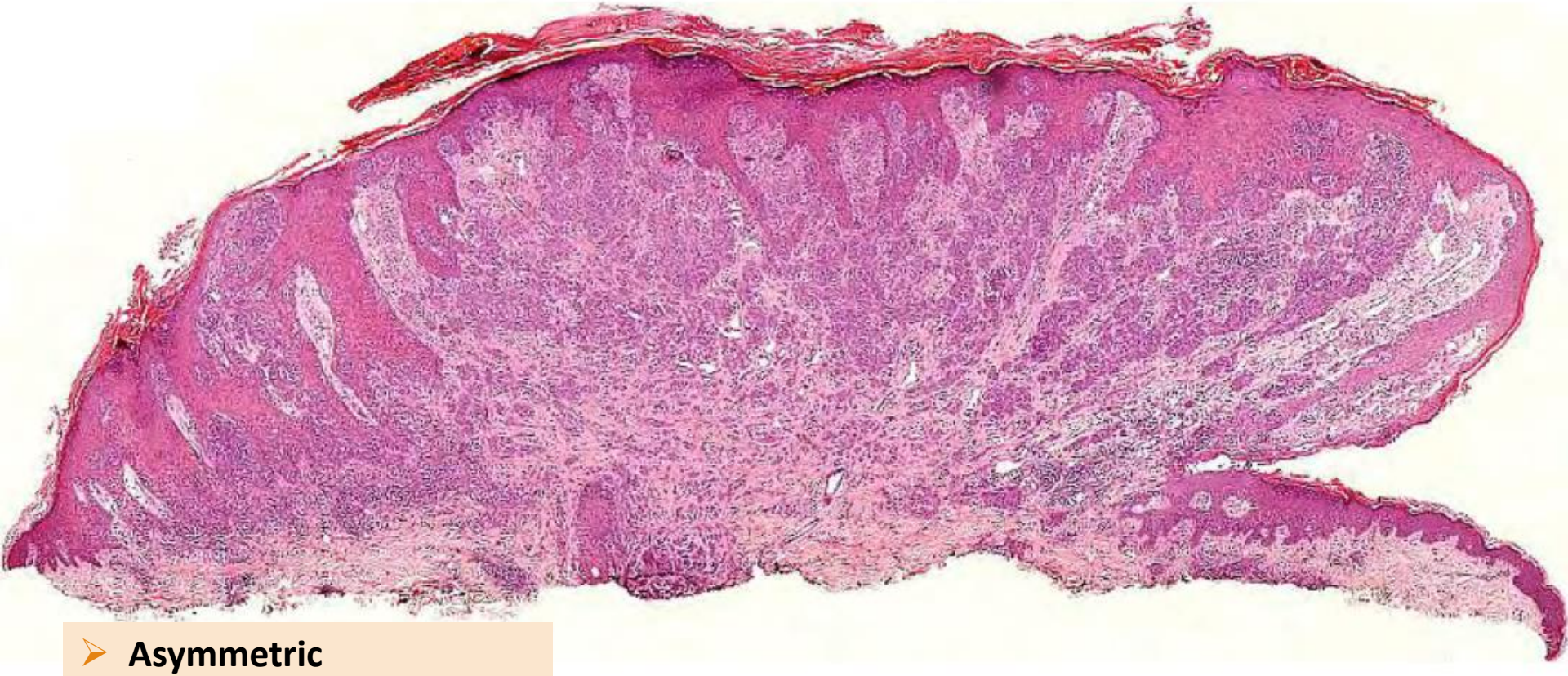


BAP1 & Pathologist's role

The pathologist's expertise is critical in the discovery and documentation of the Bap1 lesion because of the genetic implication. This association of so many tumor with the mutation has now been included Online Mendelian Inheritance in Man (OMIM) database, (#614327).

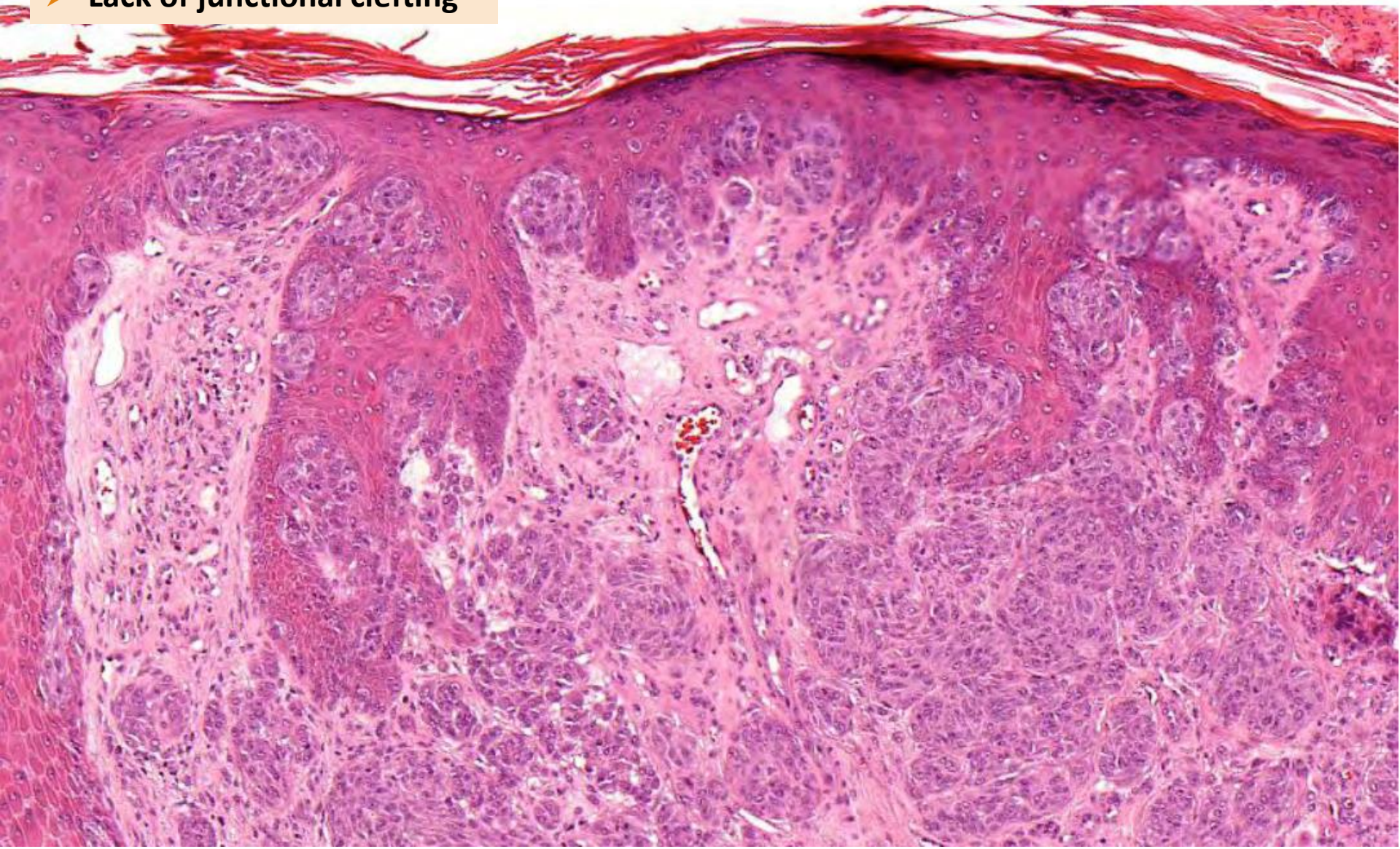
Case 4

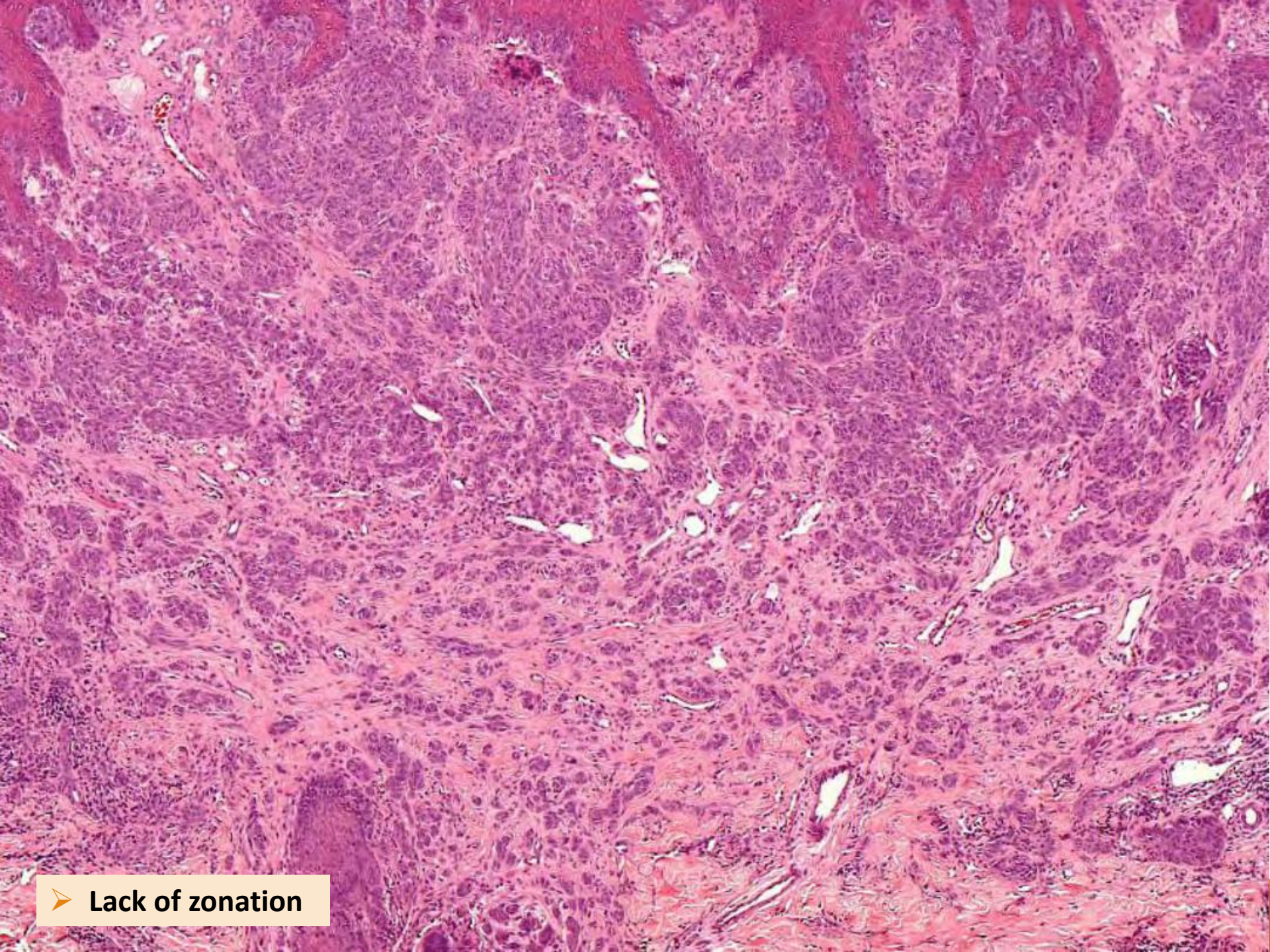
38-YEAR OLD MAN WITH A LESION ON HIS MID BACK; ATYPICAL NEVUS?



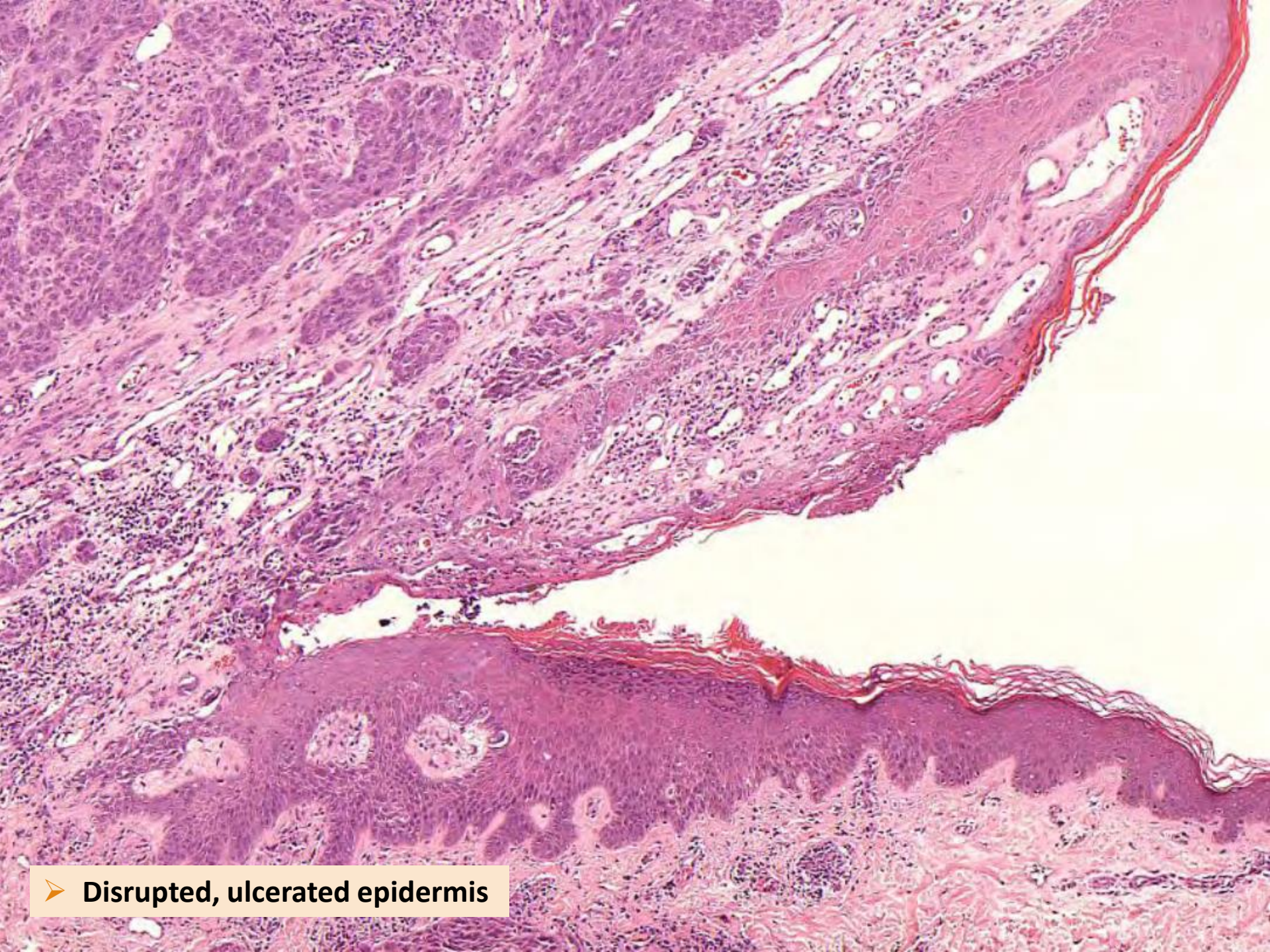
- Asymmetric
- Haphazard architecture
- Poorly circumscribed

- **Lack of junctional clefting**



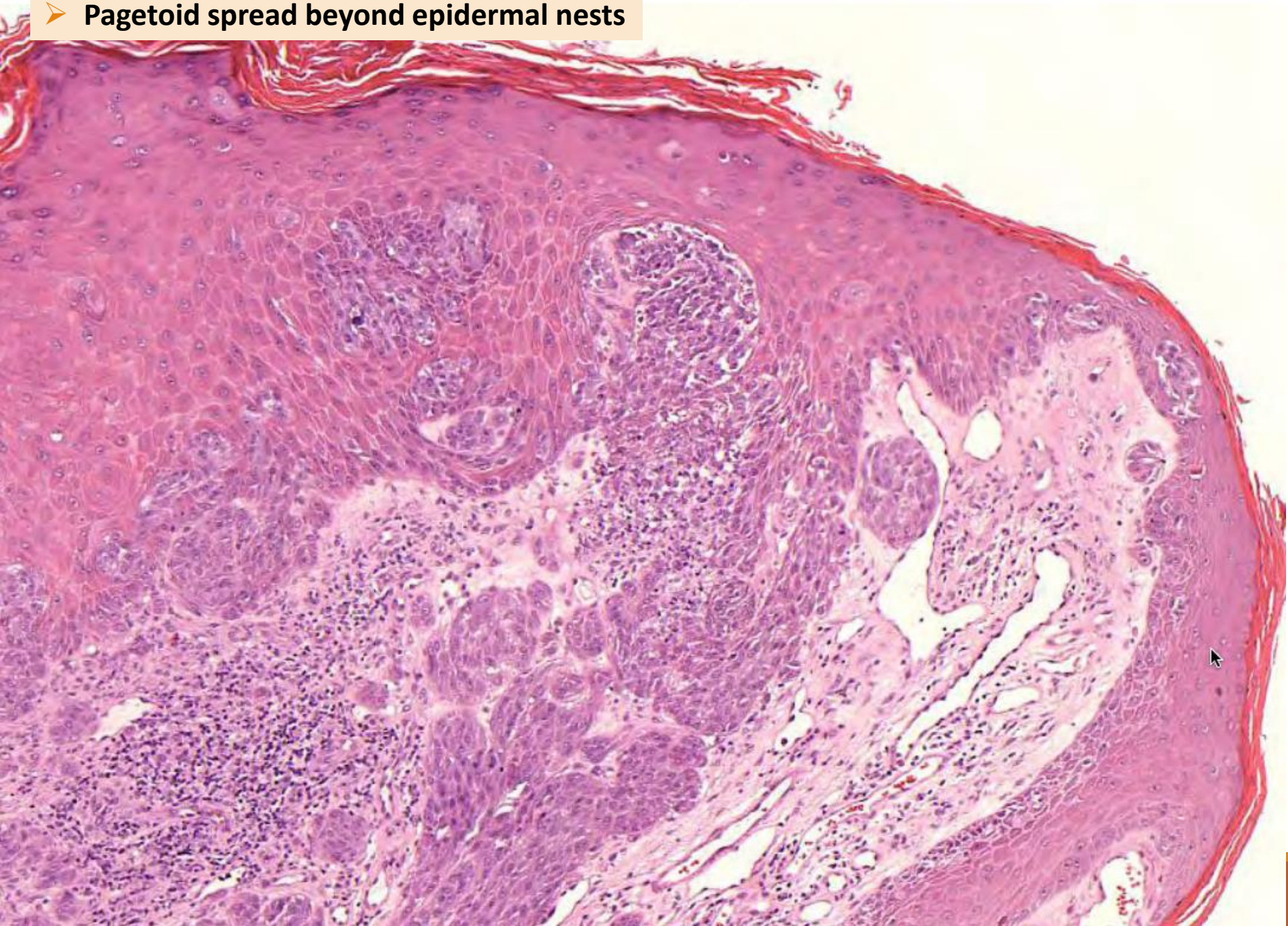


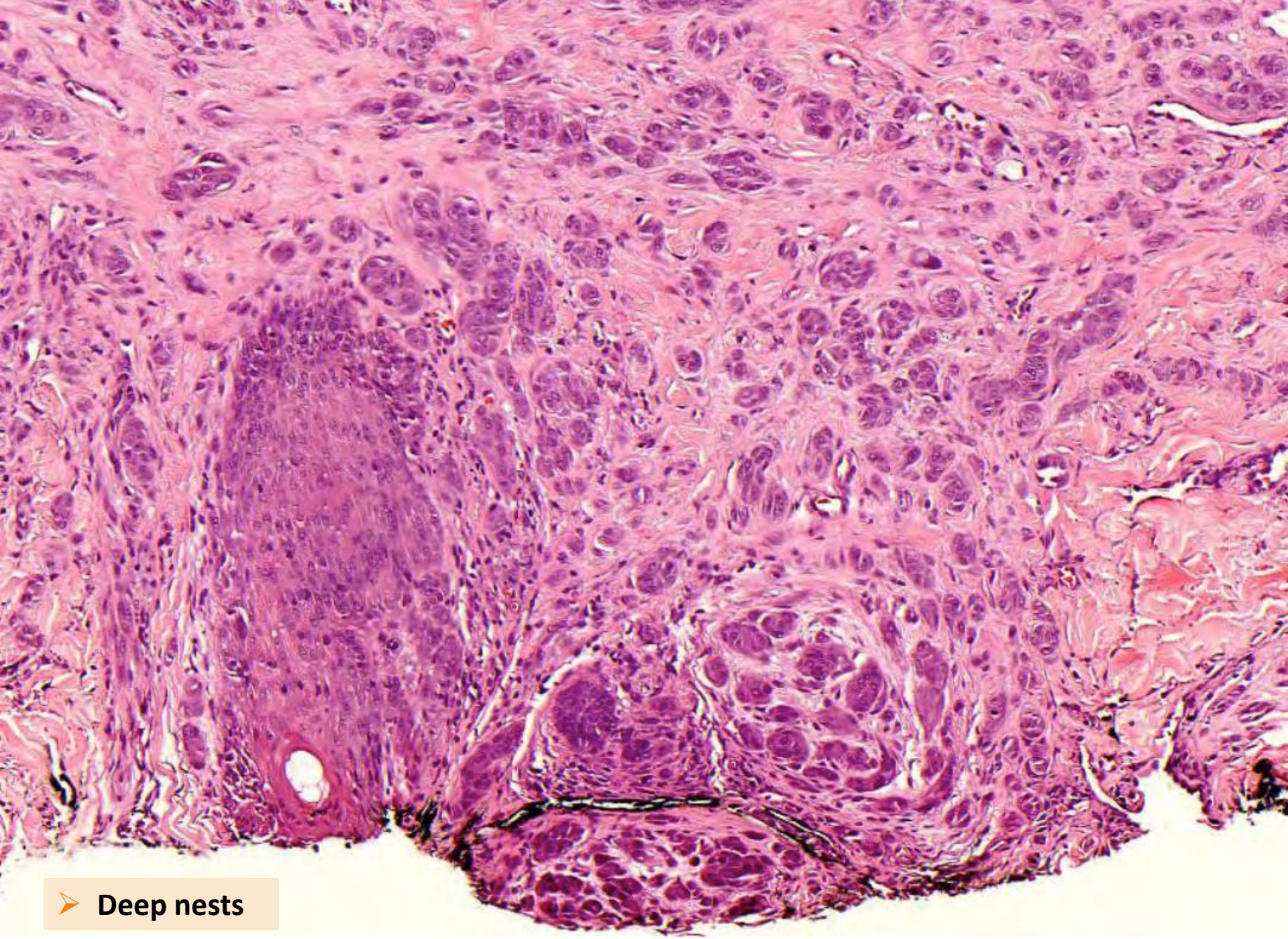
- Lack of zonation



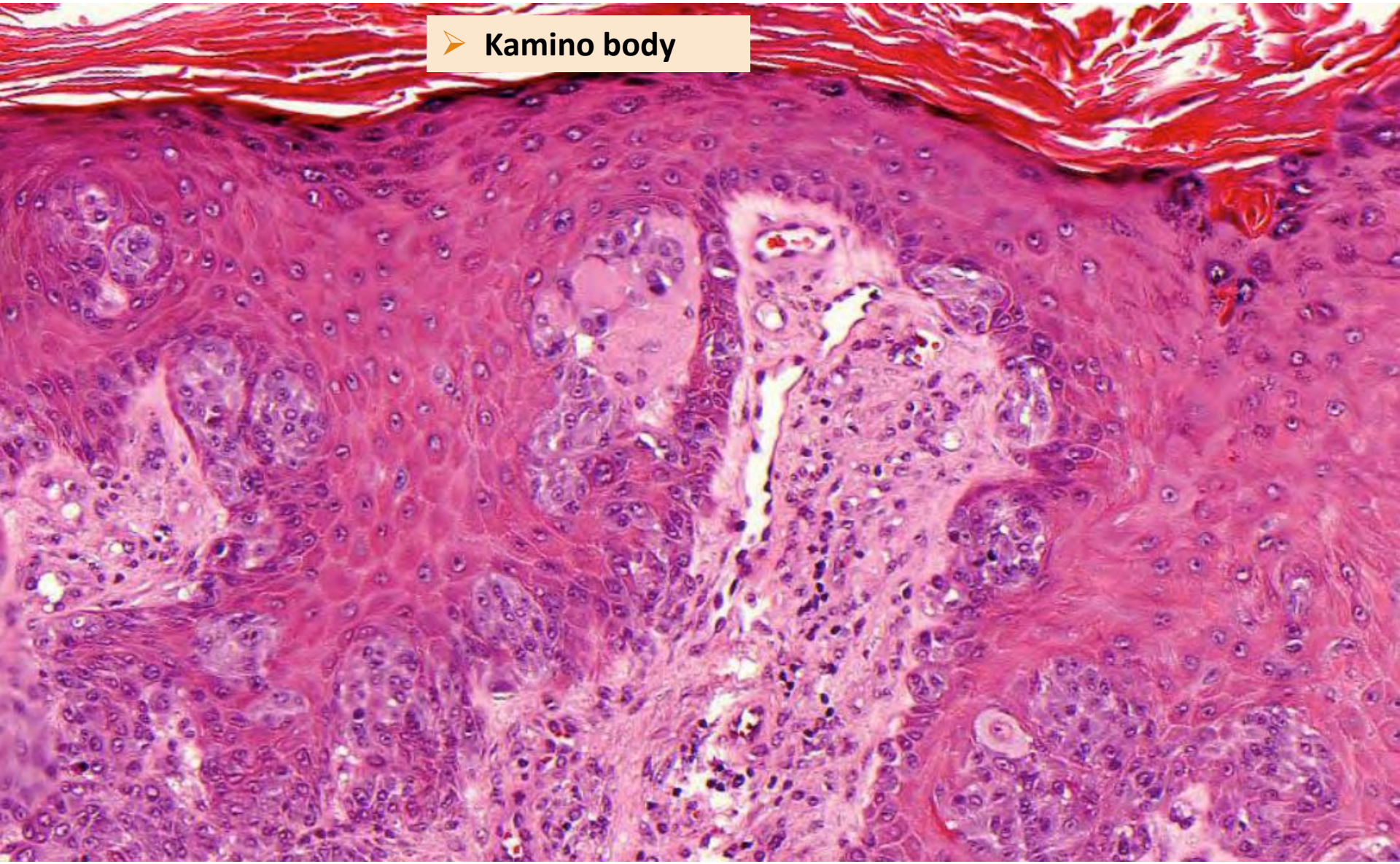
- **Disrupted, ulcerated epidermis**

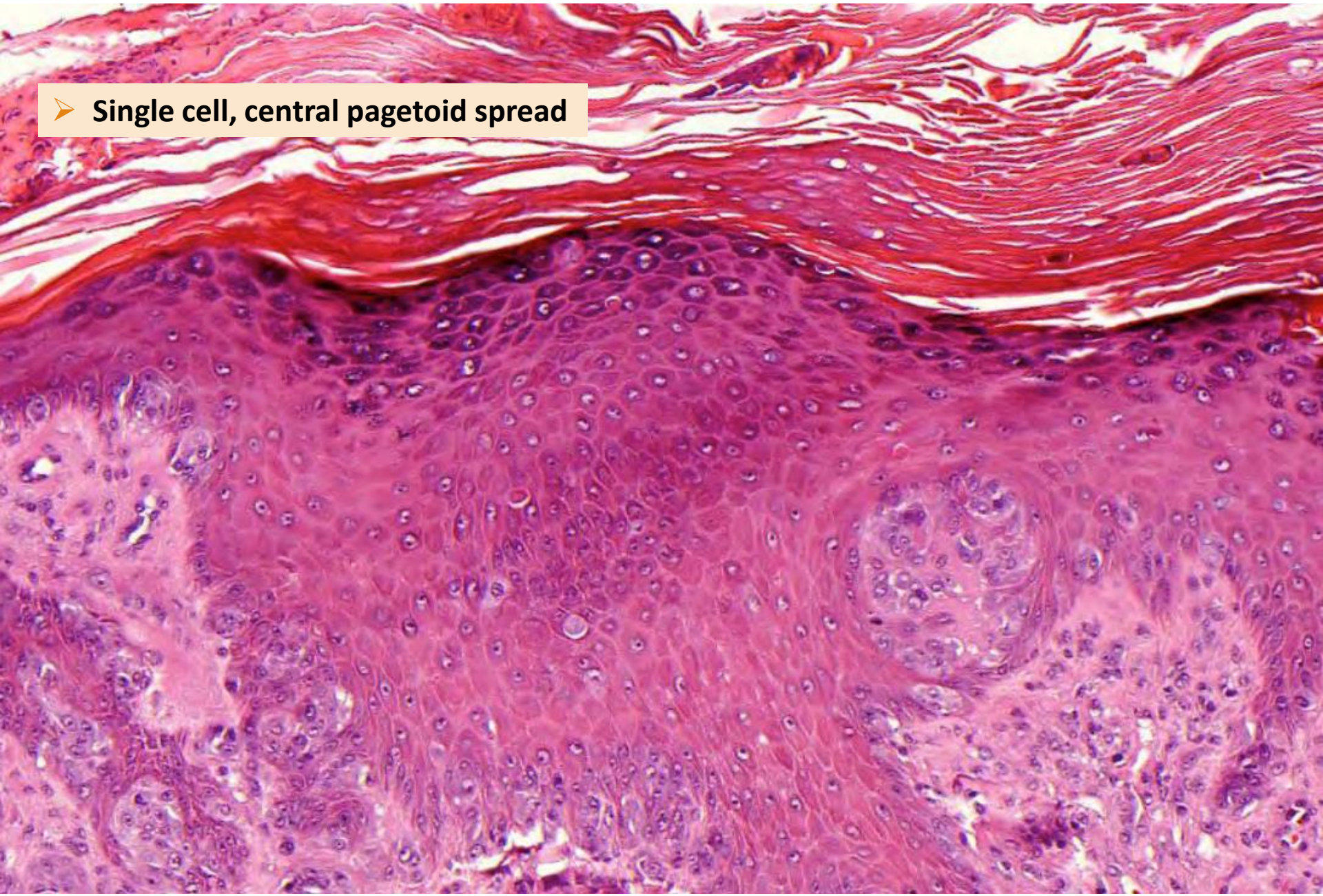
- **Pagetoid spread beyond epidermal nests**

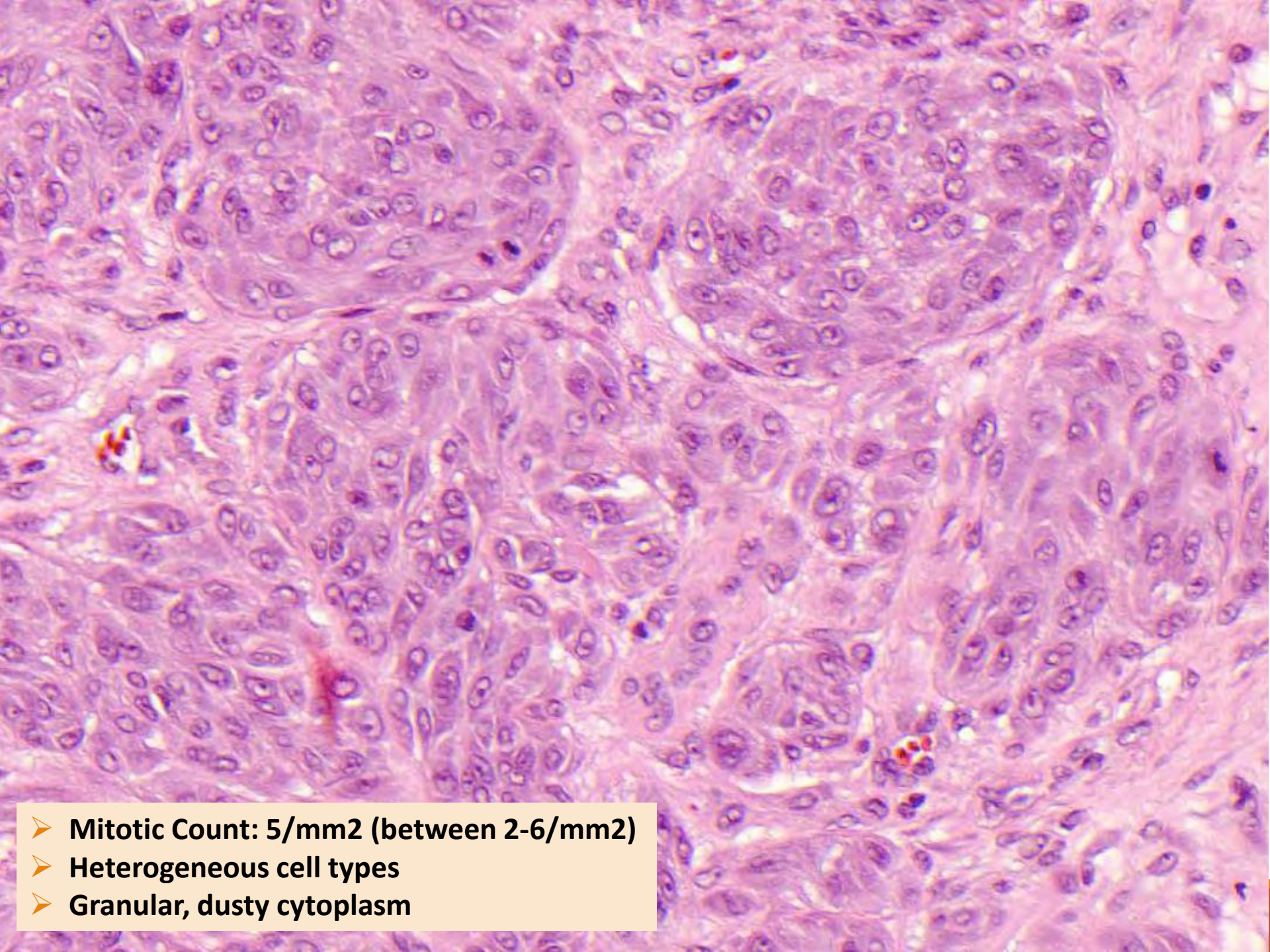




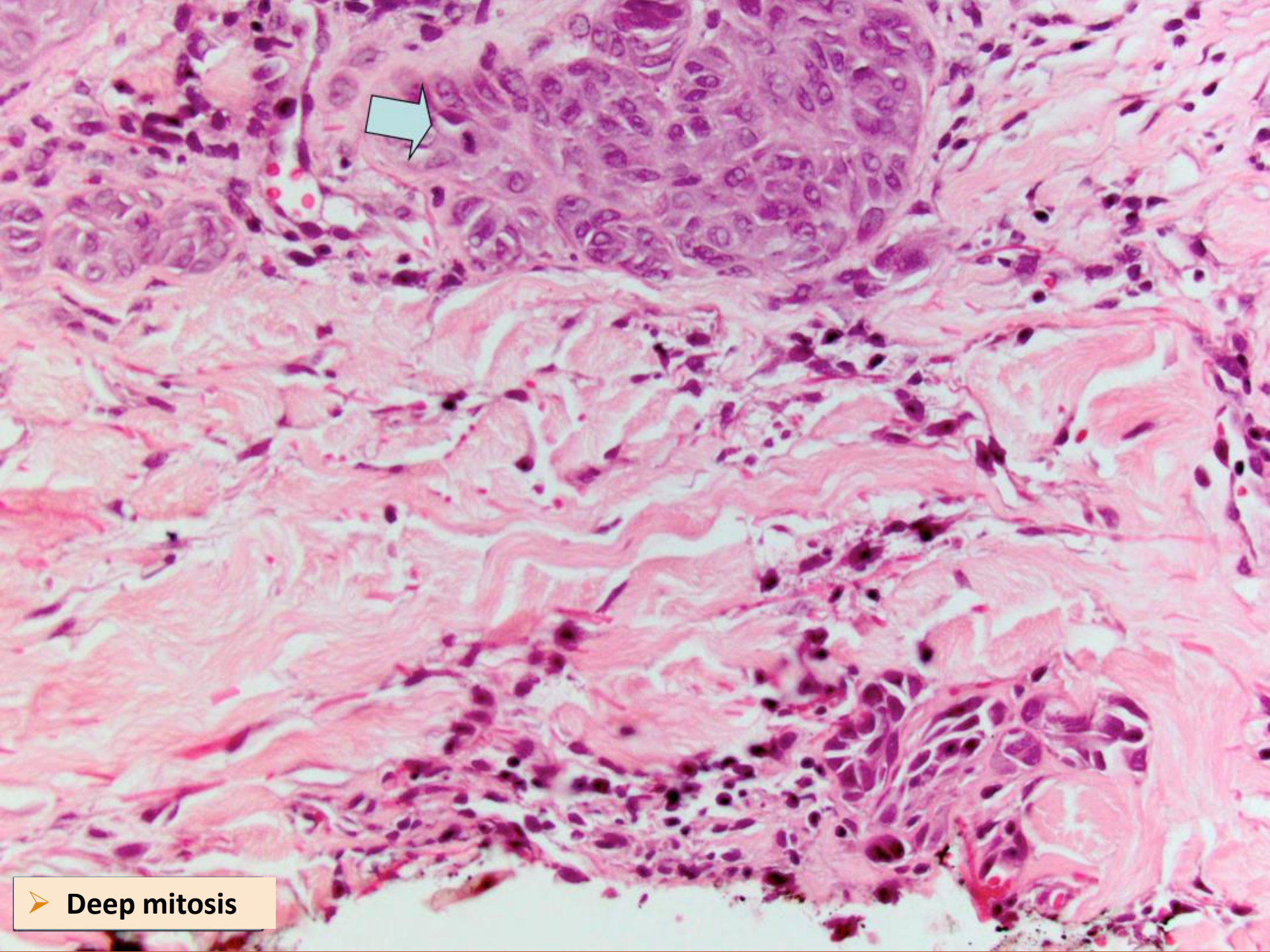
- **Deep nests**


Kamino body


Single cell, central pagetoid spread



- Mitotic Count: 5/mm2 (between 2-6/mm2)
- Heterogeneous cell types
- Granular, dusty cytoplasm



➢ **Deep mitosis**

Atypical Spitz Tumor

ARCHITECTURE

- Haphazard, infiltrative
- Asymmetric
- Poorly circumscribed
- Disrupted, ulcerated epidermis
- Absent or few Kamino bodies
- Lack of junctional clefting
- Subcutaneous involvement
- Prominent, single-cell pagetoid spread beyond epidermal nests
- Confluence, dense cellularity
- Lack of zonation
- Persistent, expansile deep nests

CYTOLOGY

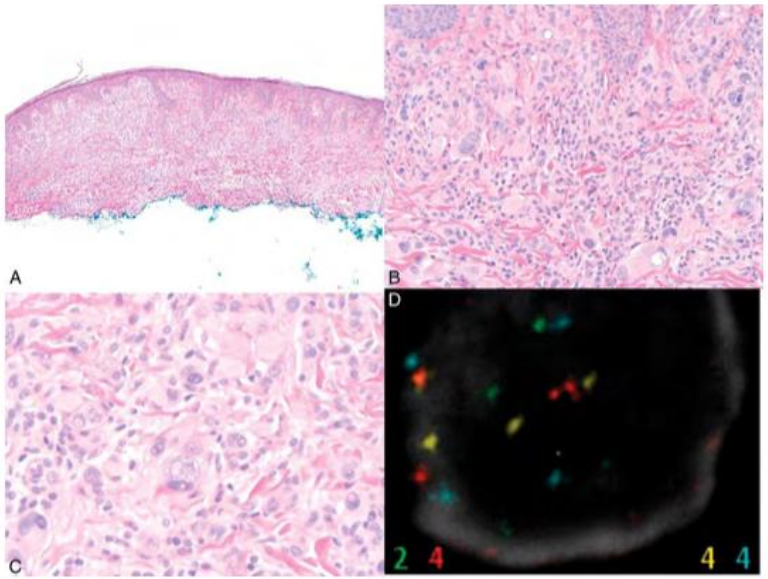
- Mitoses: 2-6/mm2
- Heterogeneous cell types
- Granular, dusty cytoplasm
- High N/C ratio & hyperchromatism
- Large, eosinophilic nucleoli

AST – Immunohistochemistry

- **Variable positivity and non-discriminating between benign versus malignant:**
  - **Mart-1/Melan-A**
  - **S100**
  - **MiTF**
  - **P16**
- **HMB45: deep involvement in melanoma**
- **Cyclin D1: deep involvement in melanoma**
- **Ki-67: >10% (in melanoma)**

Fluorescent in situ hybridization (FISH)

- **Probes:**
  - **6p25 (RREB1)**
  - **6q23 (MYB)**
  - **11q13 (CCND1)**
  - **CEP6**
  - **9p21**
- **Sensitivity:**
  - **4-probe= 70%**
  - **5-probe= 85%**
- **Specificity:100%**

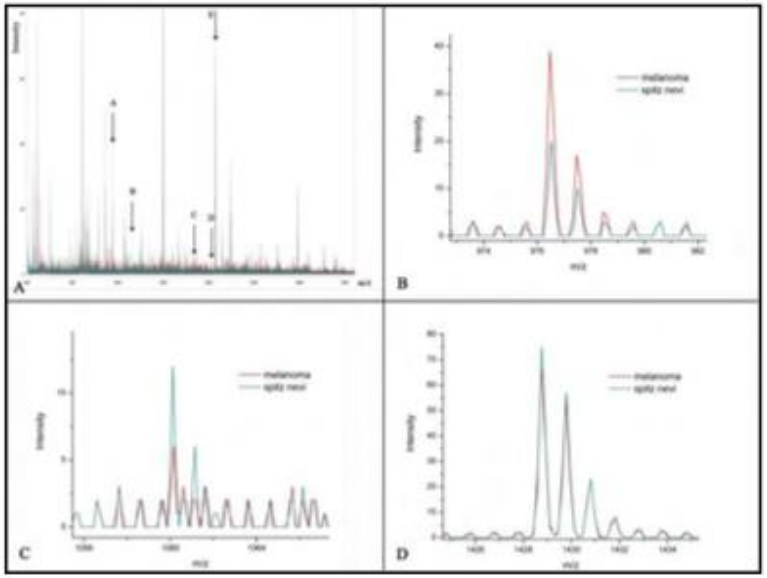


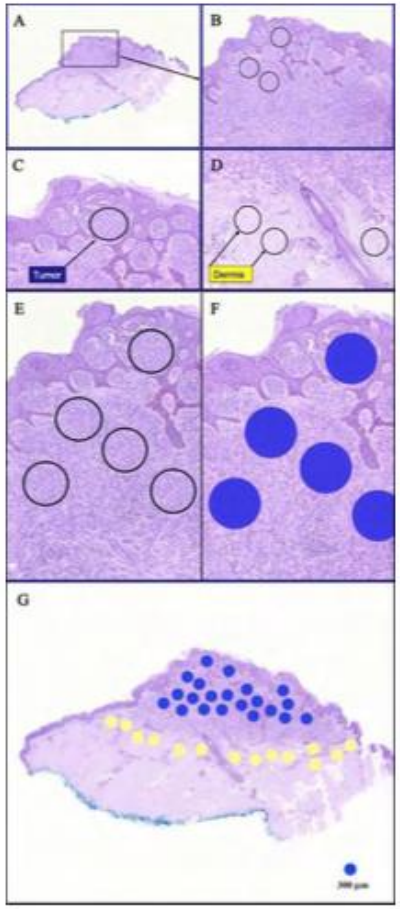
➢ 24-year-old woman. ? Atypical nevus.

FISH: 4 signals with *RREB1* (red), 2 signals with *CCND1* (green), 4 signals with *MYB* (yellow), and 4 signals with CEP6 (aqua) probes, consistent with tetraploidy, favoring ASN.

Zembowicz A et al. Arch Pathol Lab Med, 2012

MALDI Imaging Mass Spectrometry (MALDI IMS)

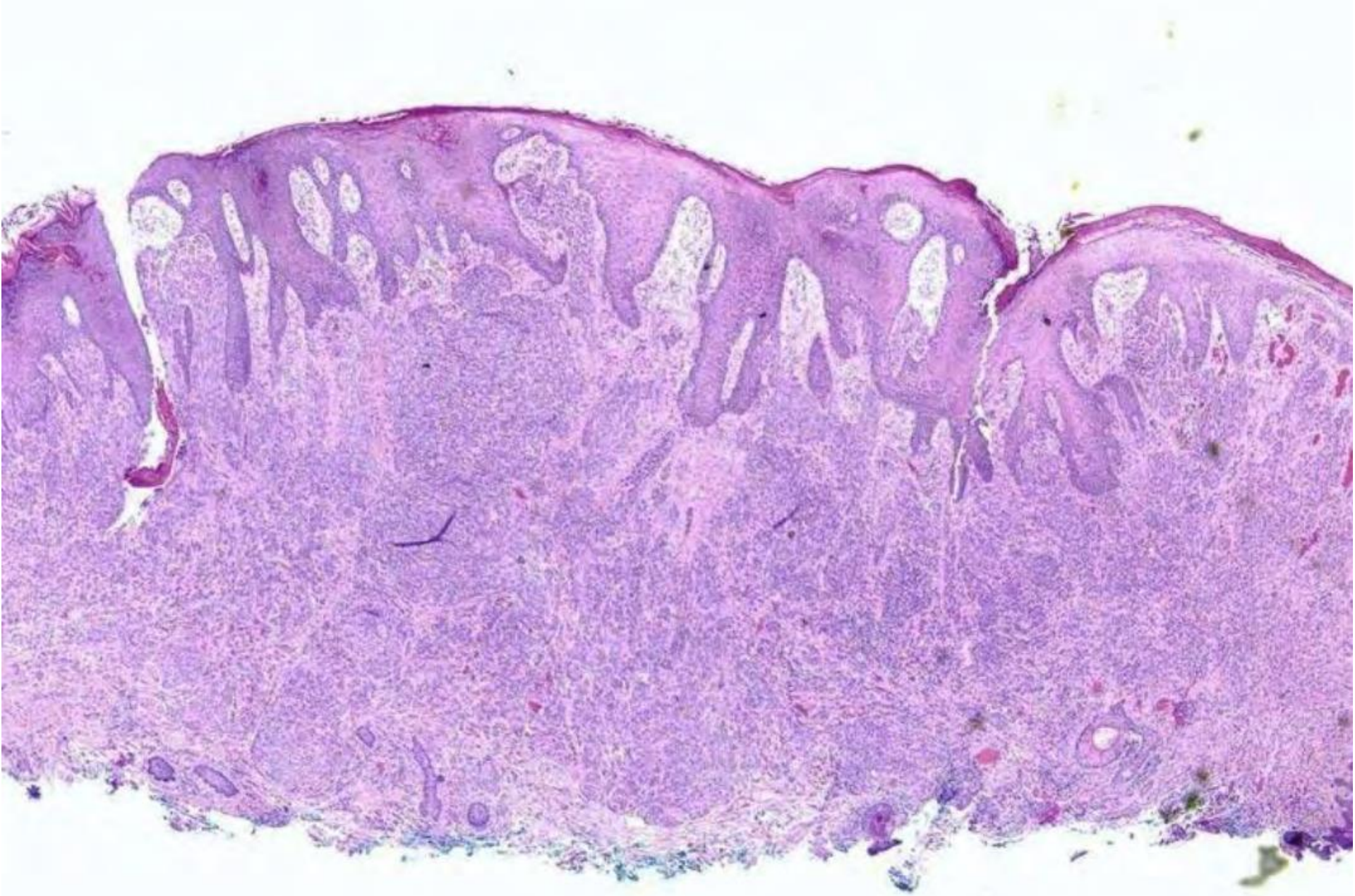




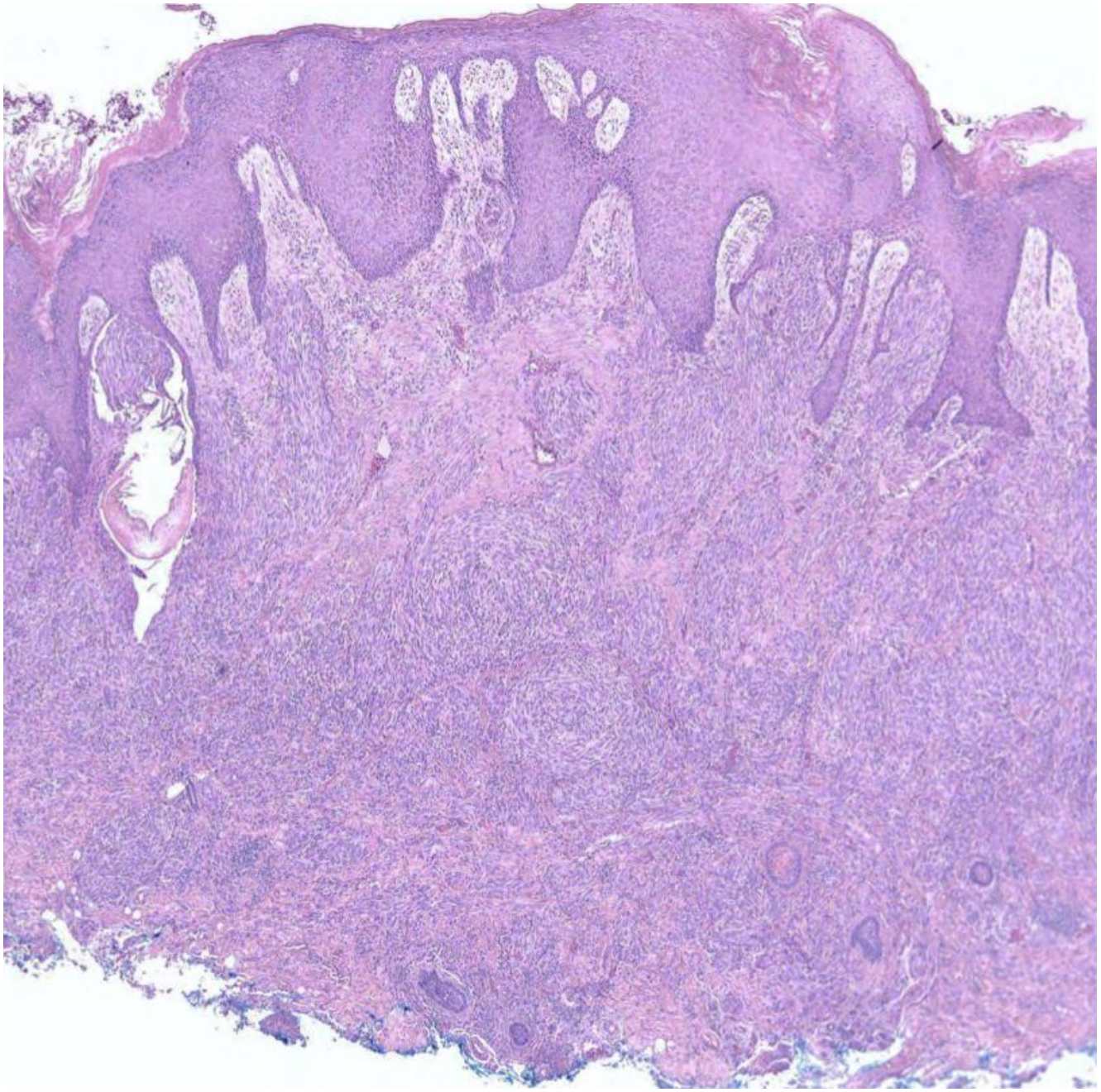
- **Probes:**
  - **5 peptides**
- **Sensitivity: 100%**
- **Specificity: 95%**

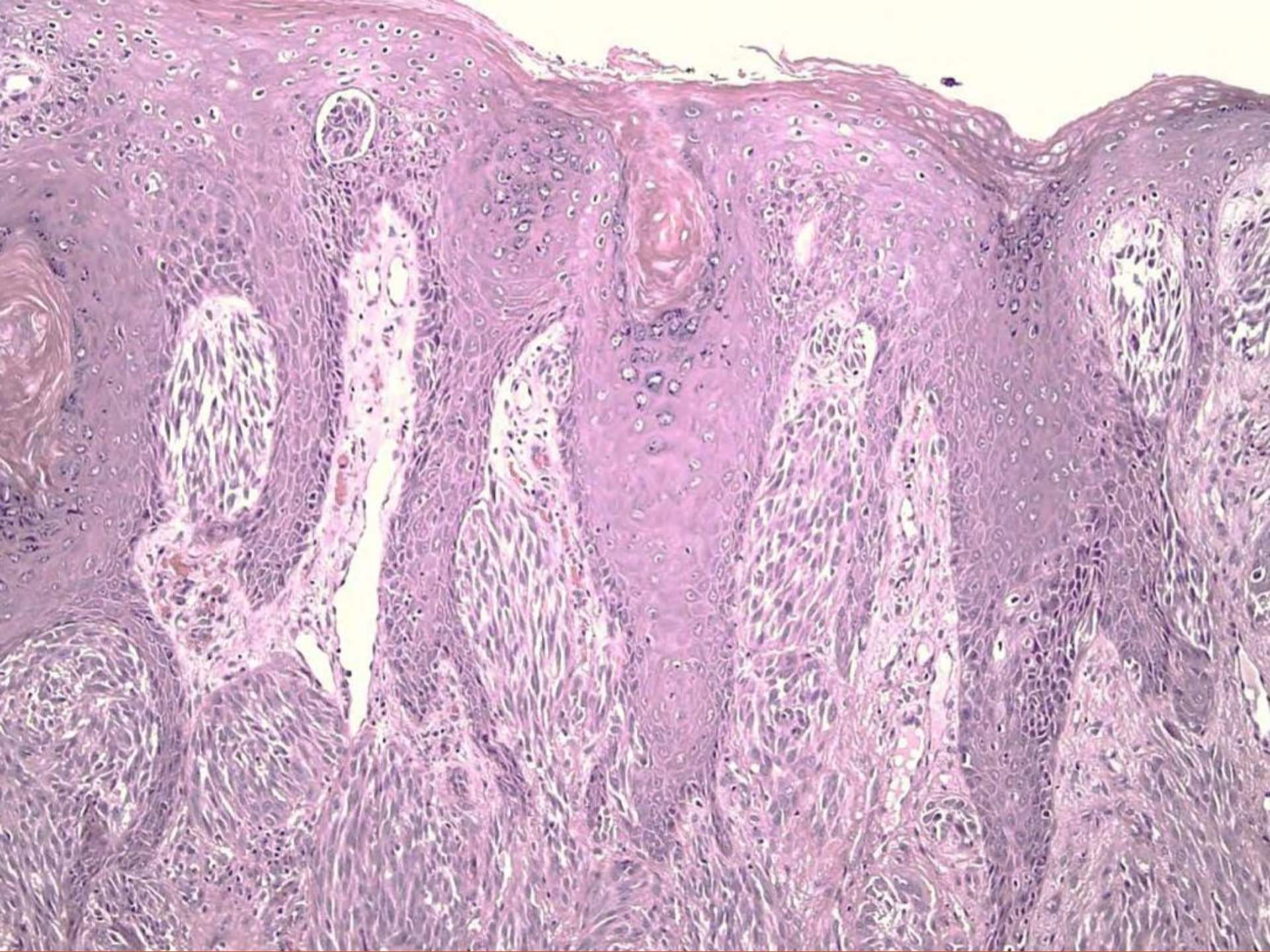
Atypical Spitz Tumor

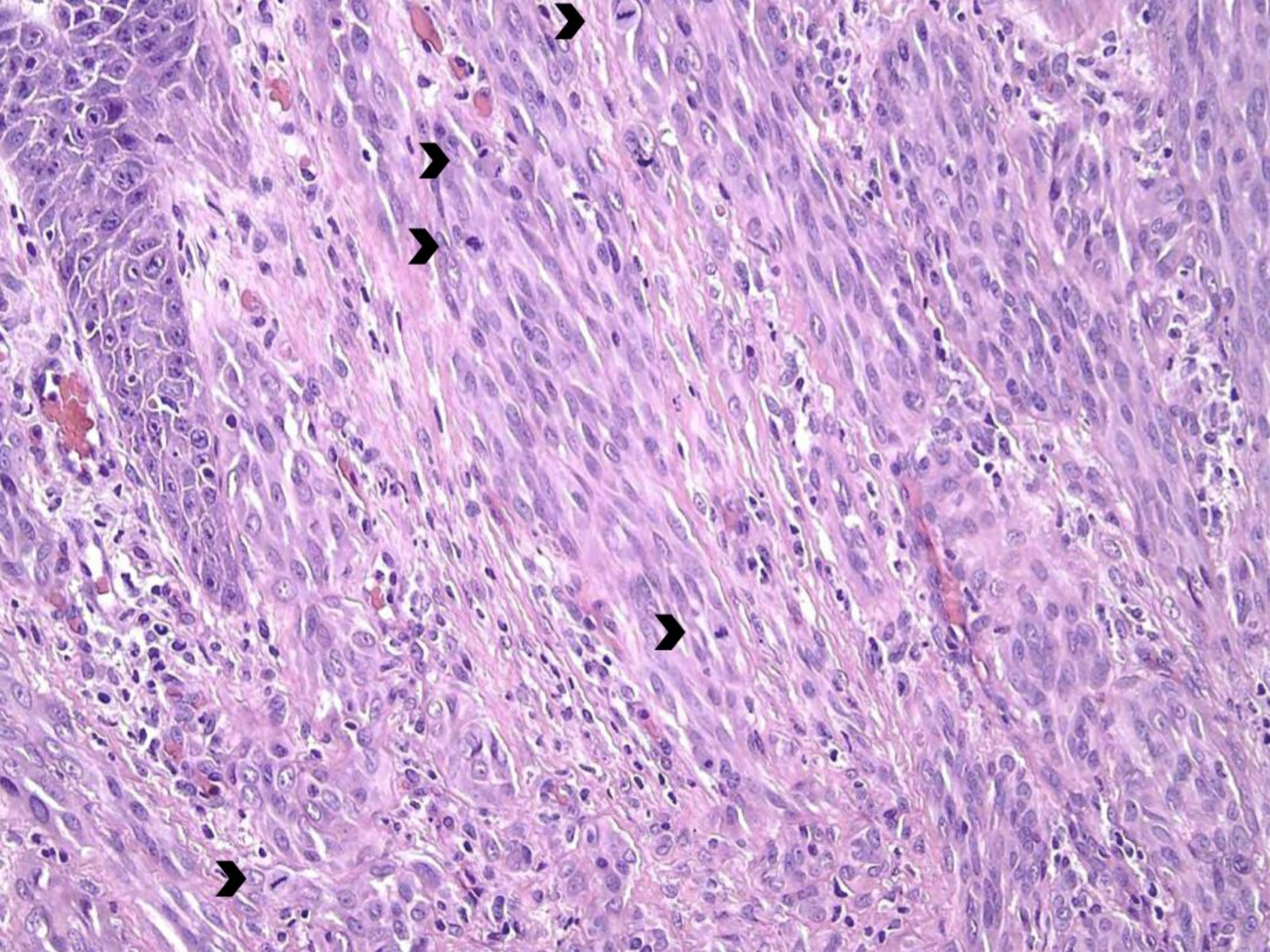
- **There is difficulty in discrimination of atypical Spitz neoplasm from malignant melanoma due to:**
  - **Marked epitheliod/spindle cell cytological atypia**
  - **Presence of some architectural atypia**
  - **Presence of mitotic figures**

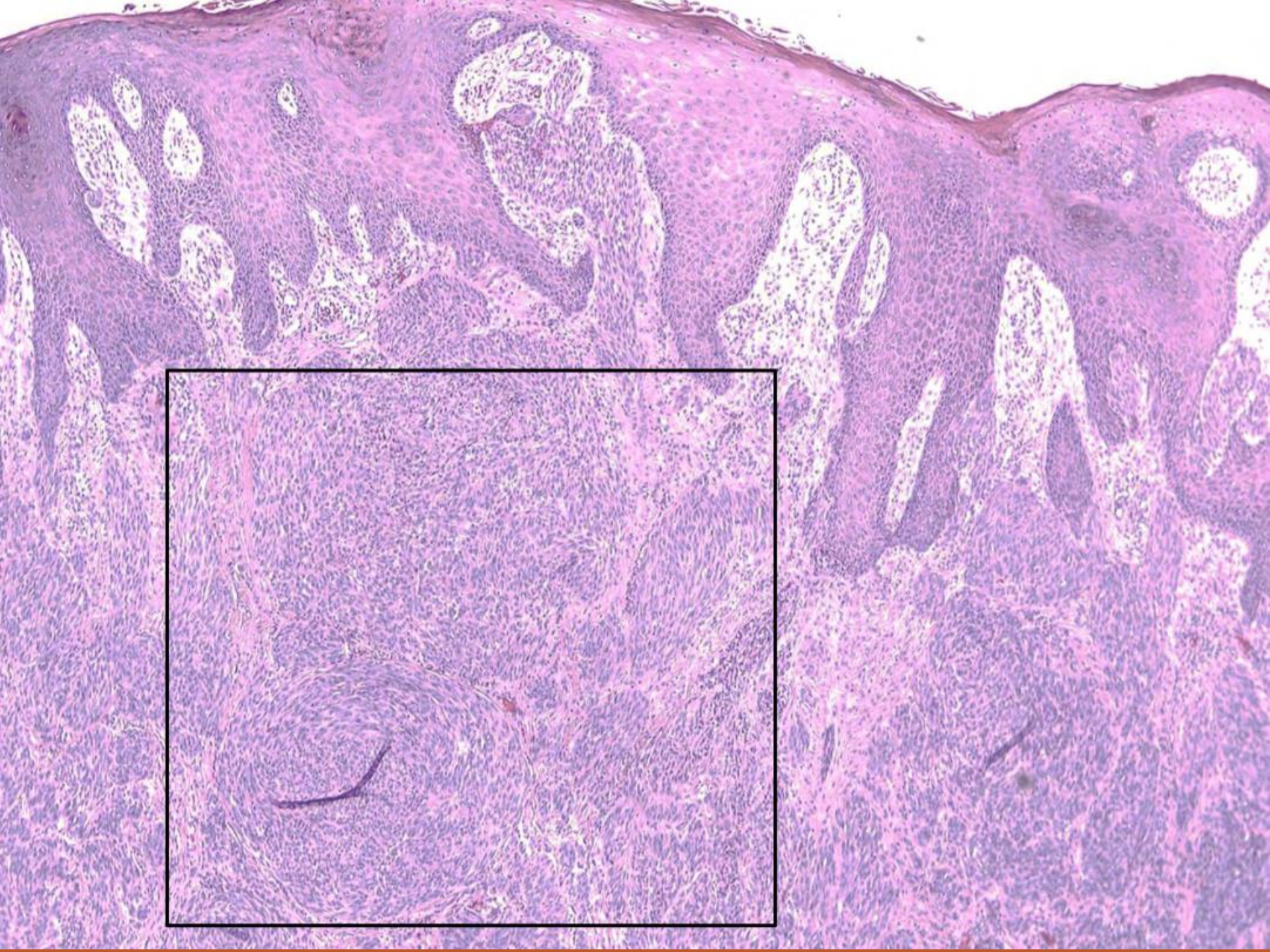


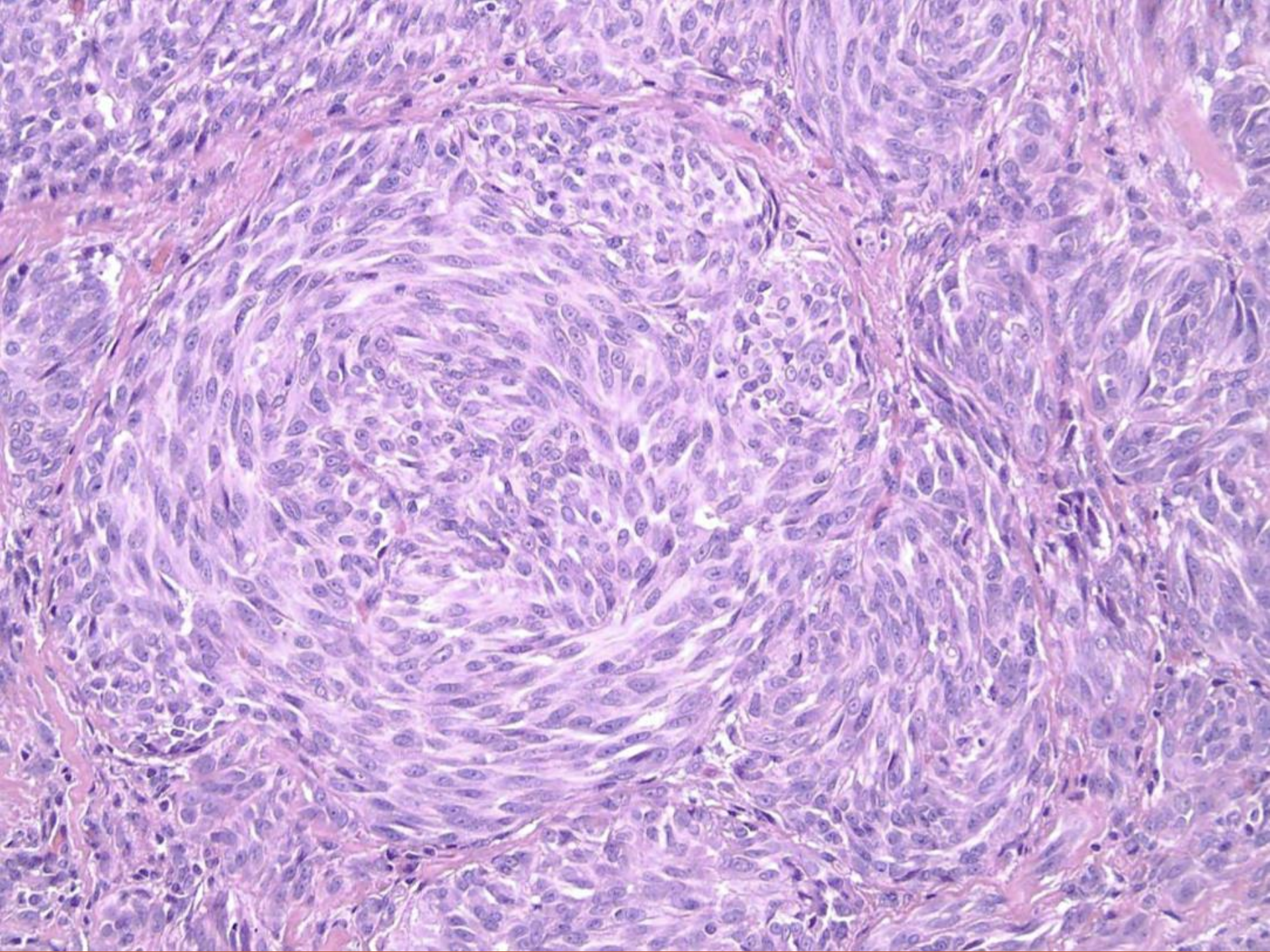
3.0 mm depth

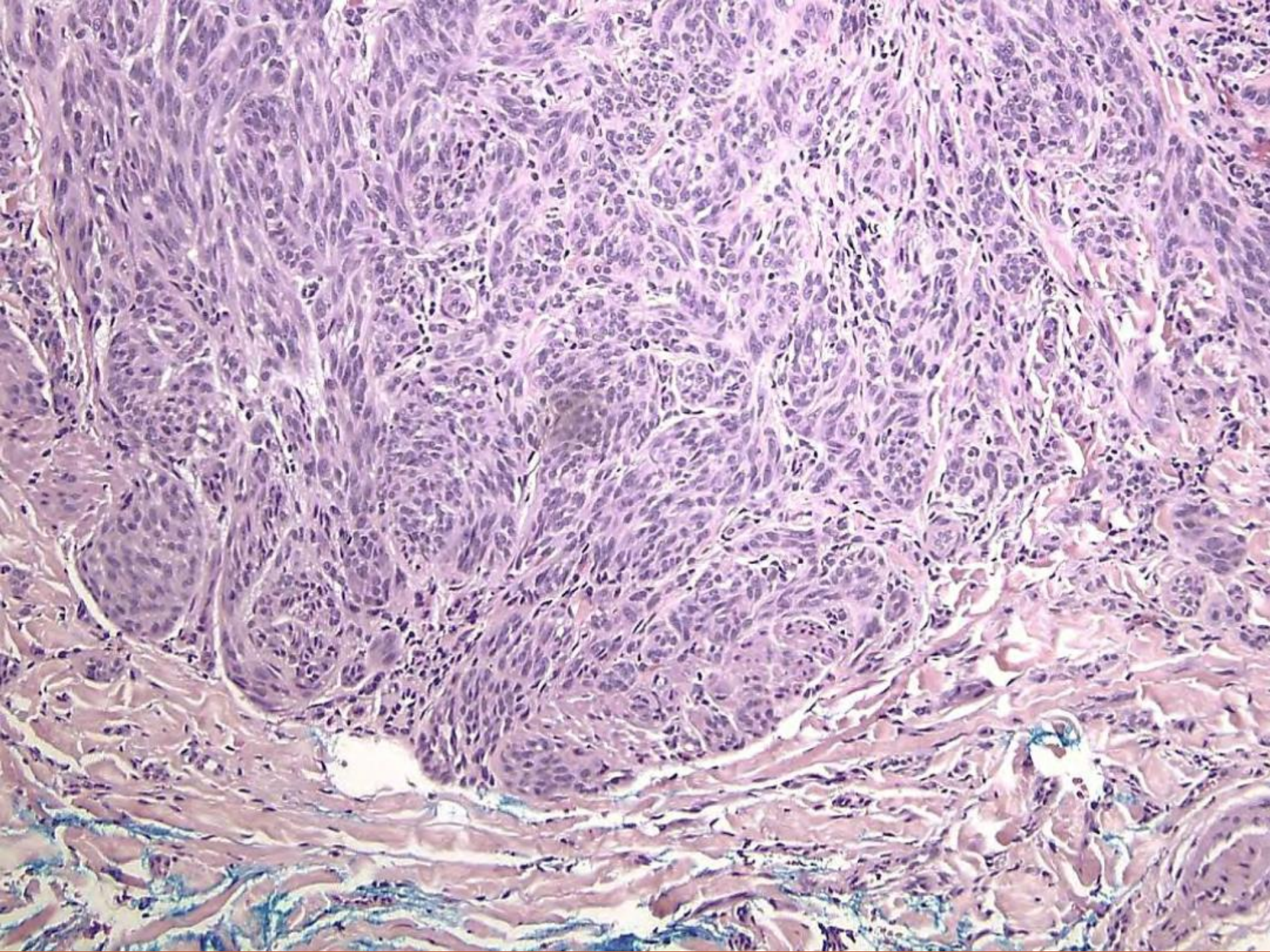


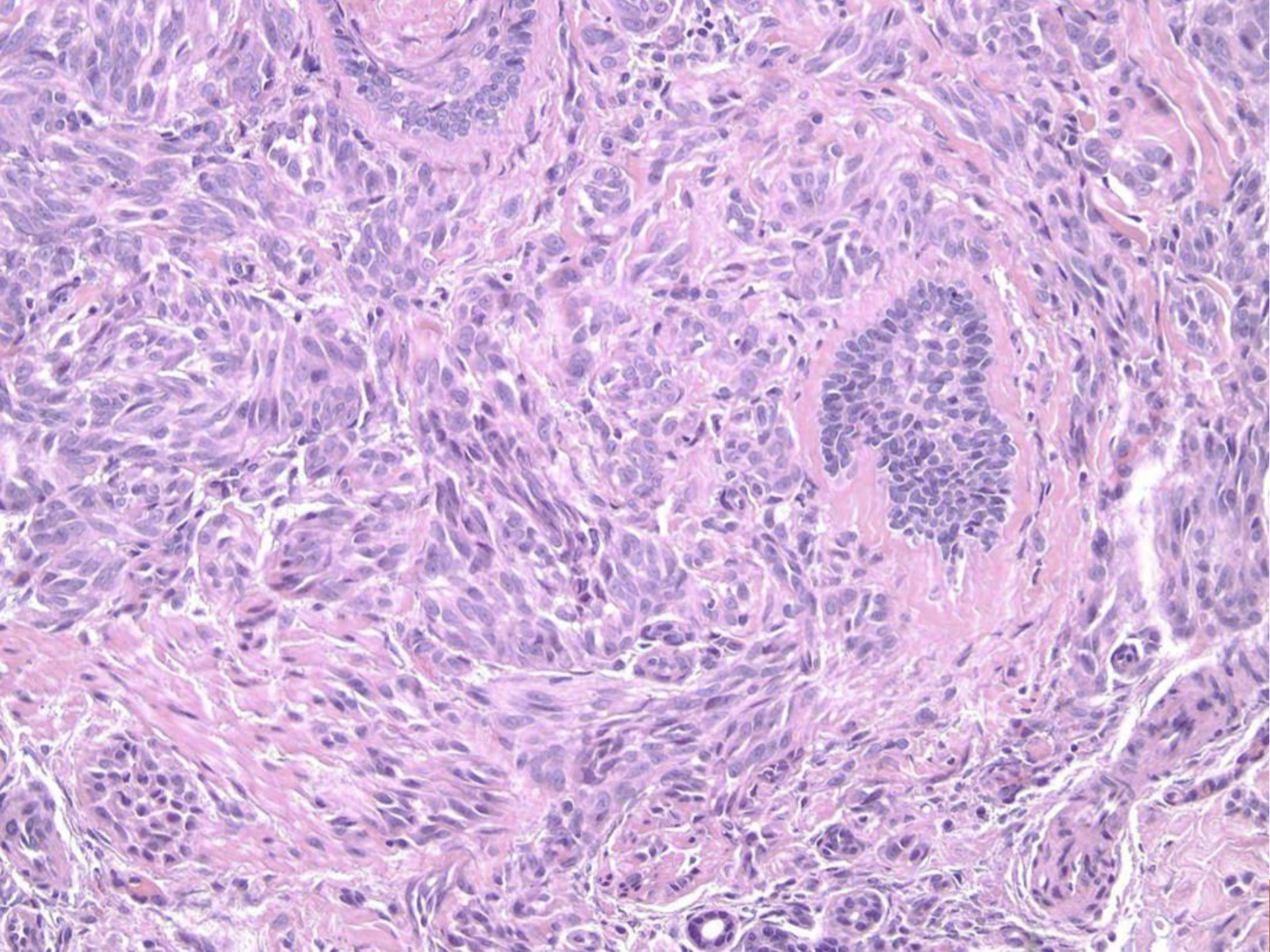


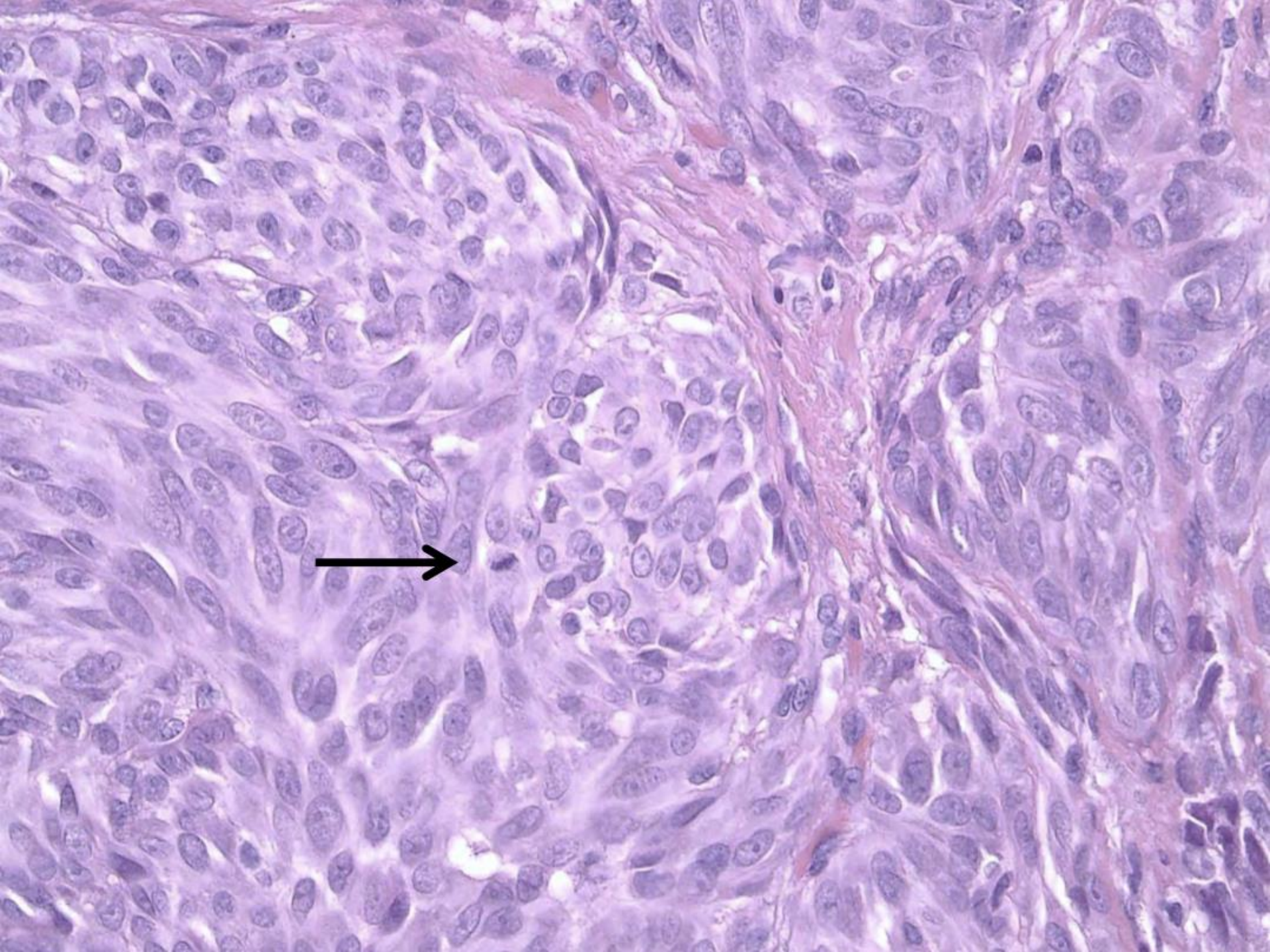




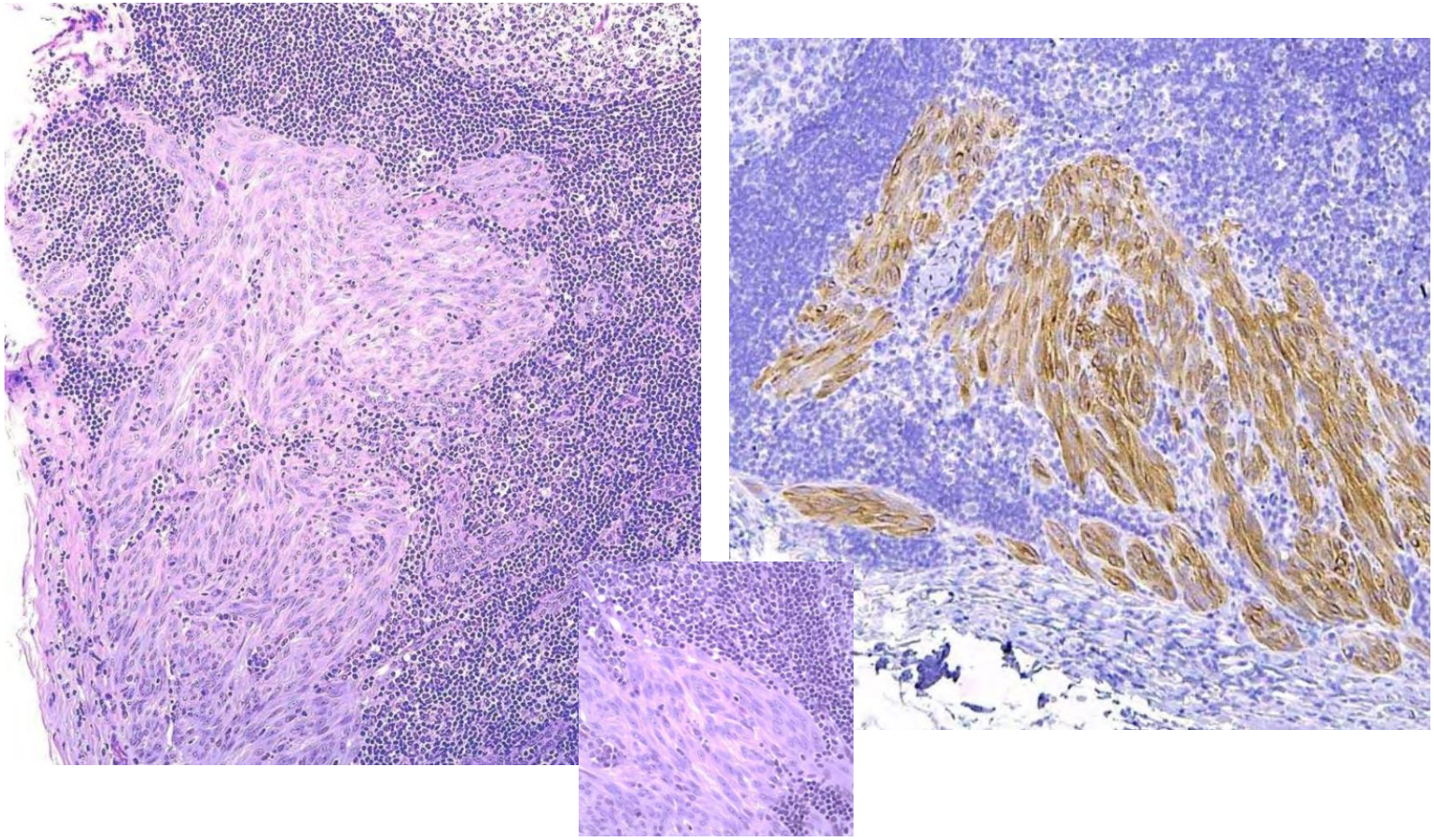








Wide local excision & Sentinel lymph node biopsy



Spitz Nevus

BACKGROUND

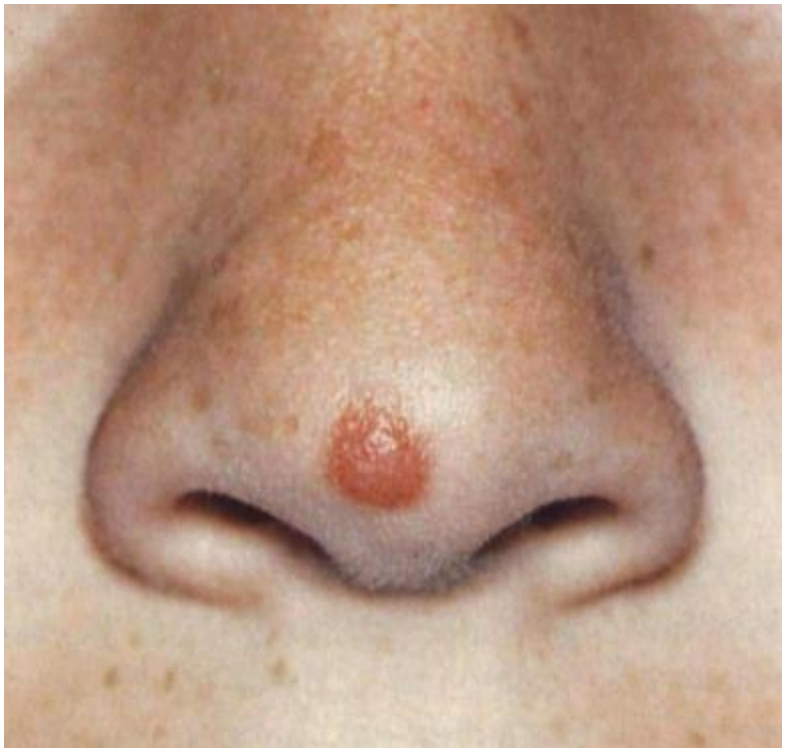
- In1948 Dr. Sophie Spitz published a series of 13 patients with “melanoma of childhood”
  - looked malignant but benign behavior
  - 1 patient (12 y.o.) in series died of metastatic disease
- Spindled and epithelioid cell nevus
- Spitz nevus

CLINICAL FEATURES

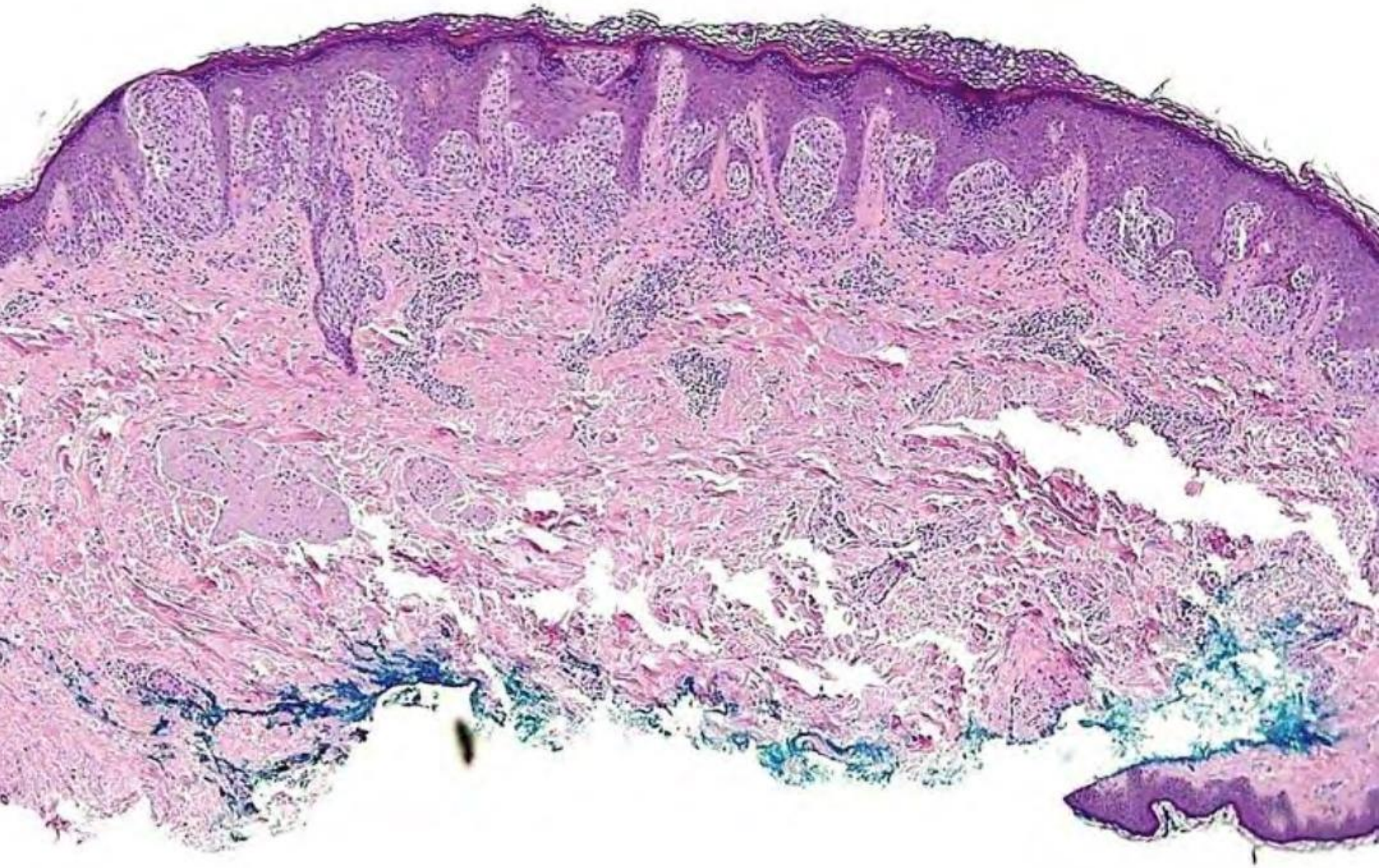
- Predominance in children and young adults; any age
- Predilection for head and neck (children) and extremities (lower extremities of young women)
- Usually < 6 mm diameter

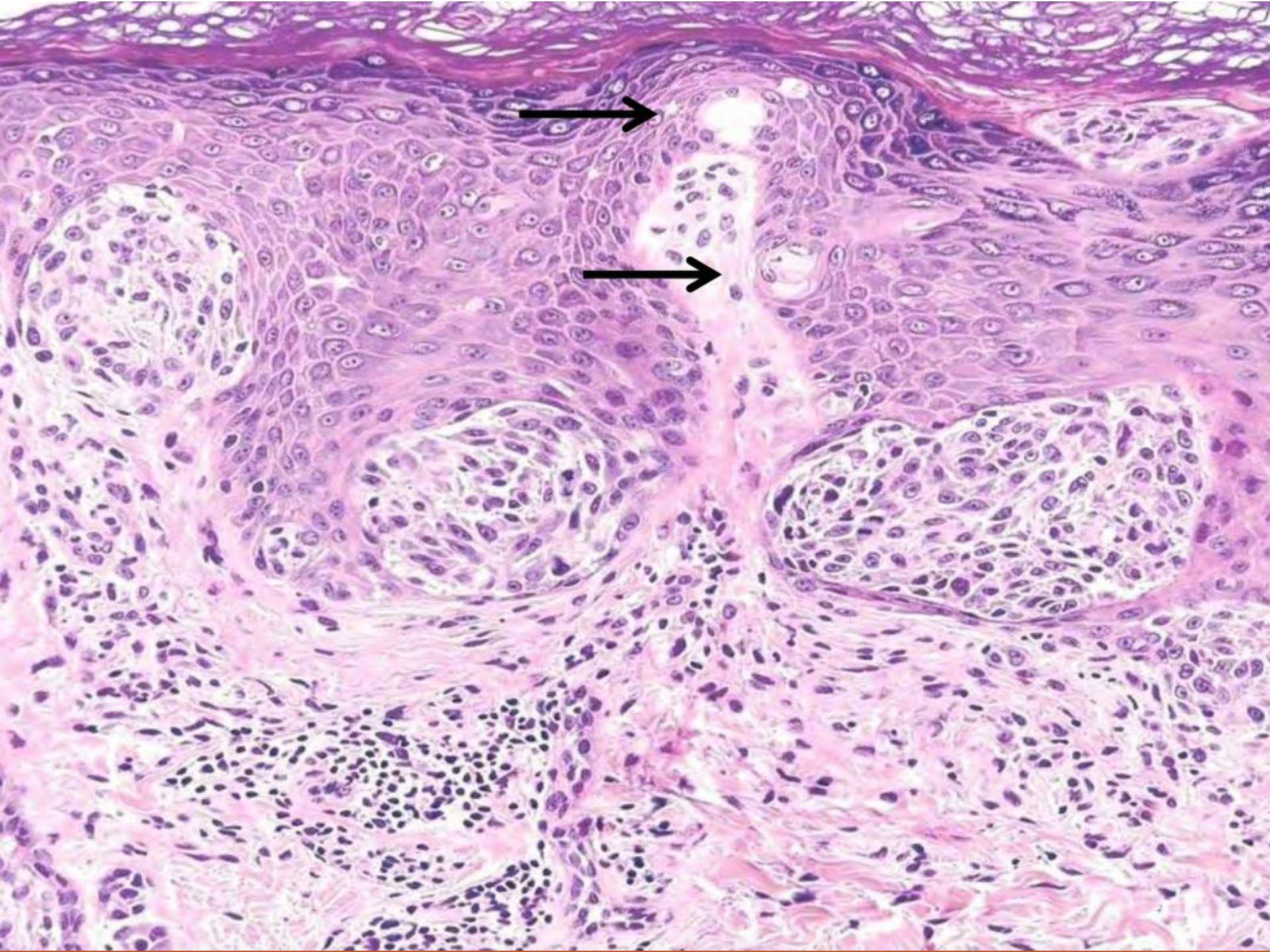
Spitz Nevus

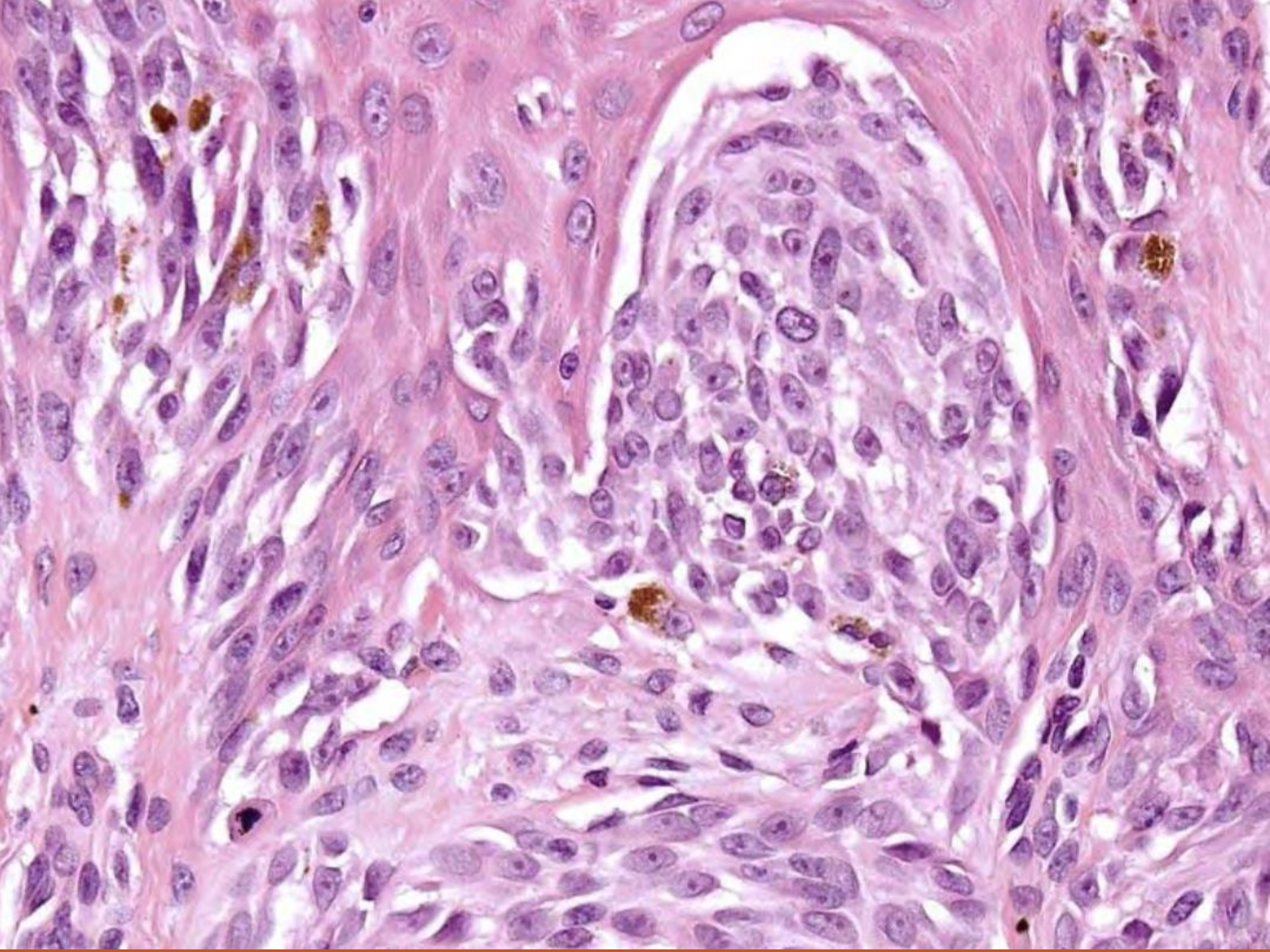
- Pink to red (rarely pigmented) papule; some verrucous or polypoid
- Rapid growth sometimes
- Solitary lesion; multiple or agminated can occur
- Resemble dermatofibroma (desmoplastic variant)

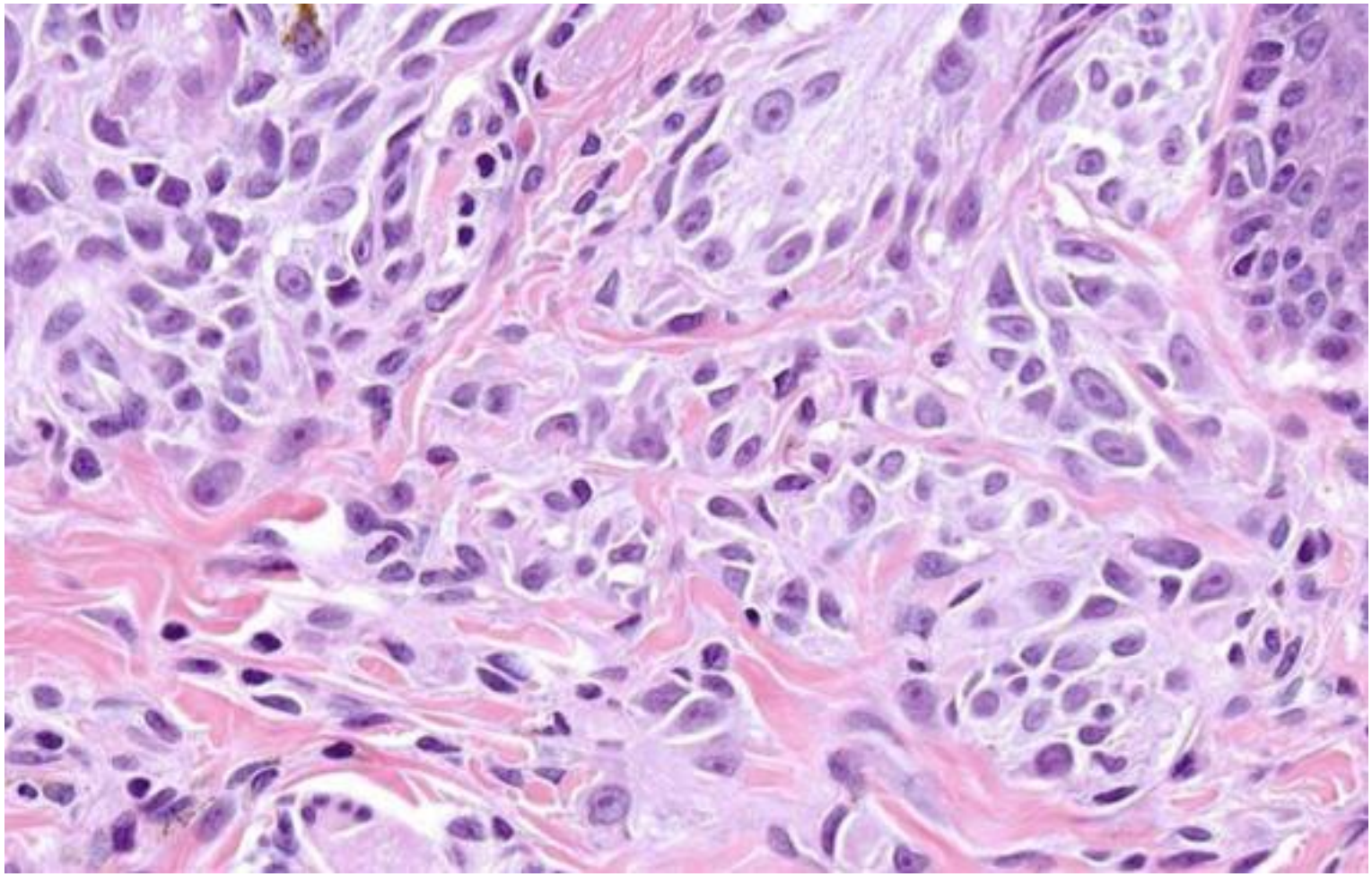


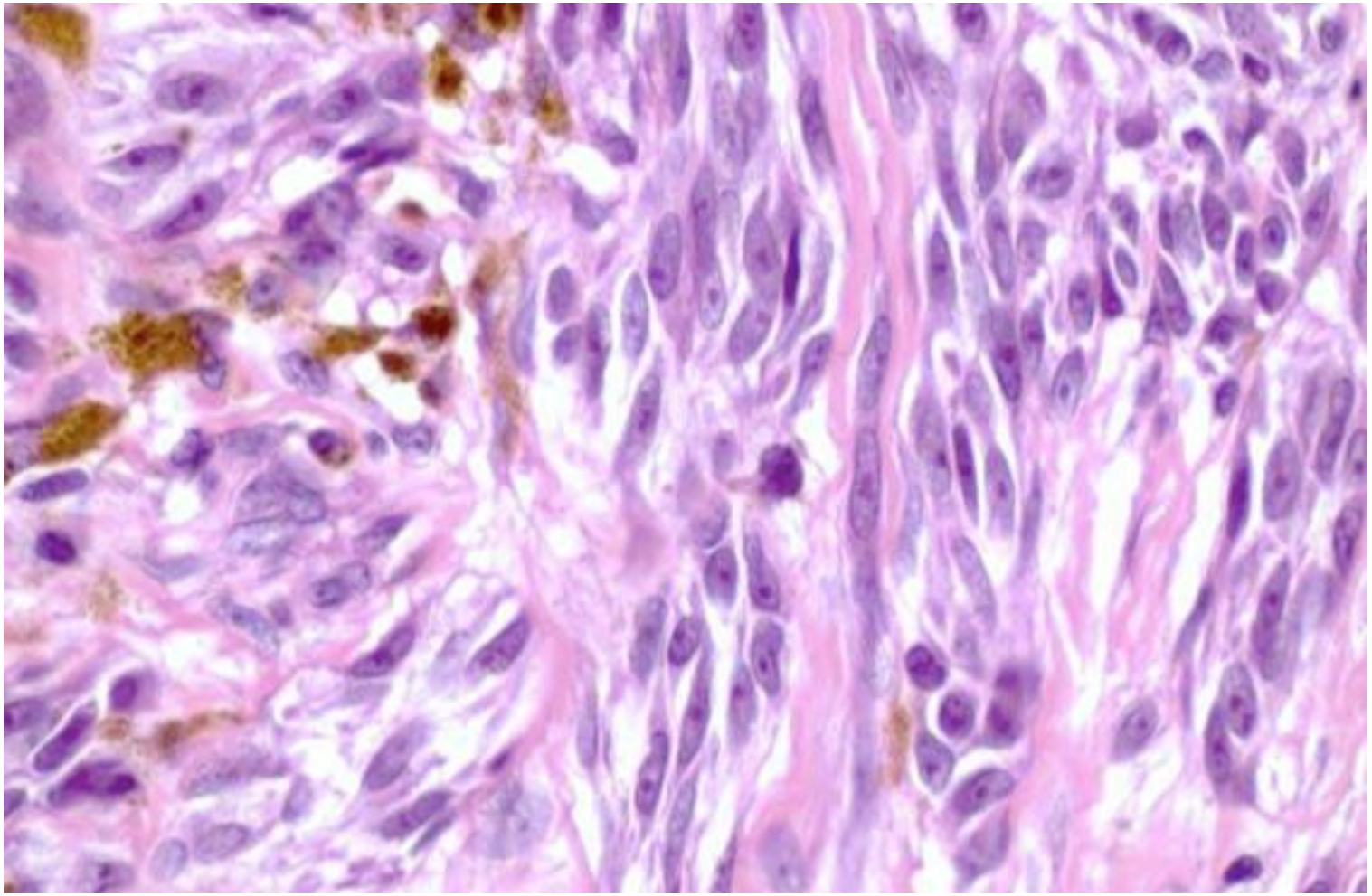
- Symmetrical silhouette
- Lateral circumscription
- Spindled and/or epithelioid cells
- Nests vertically oriented (raining down)
- Epidermal hyperplasia & hypergranulosis
- Clefts around junctional nests
- Eosinophilic globules (Kamino bodies)
- Mitoses (junctional +/- superficial dermis)
- Maturation of dermal component with descent
- Telangiectasias
- Perivascular inflammation
- Stromal fibrosis (desmoplastic variant)

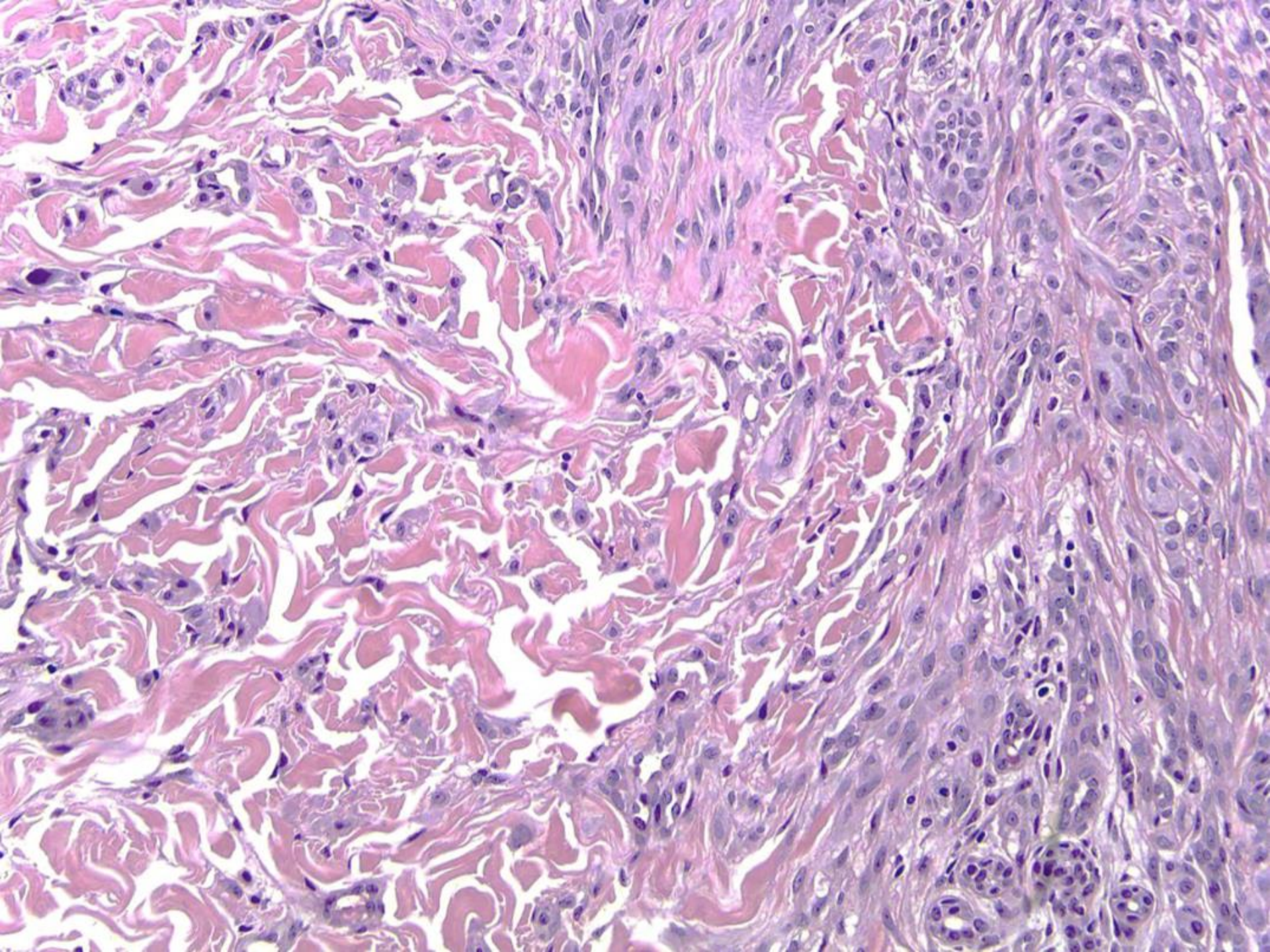


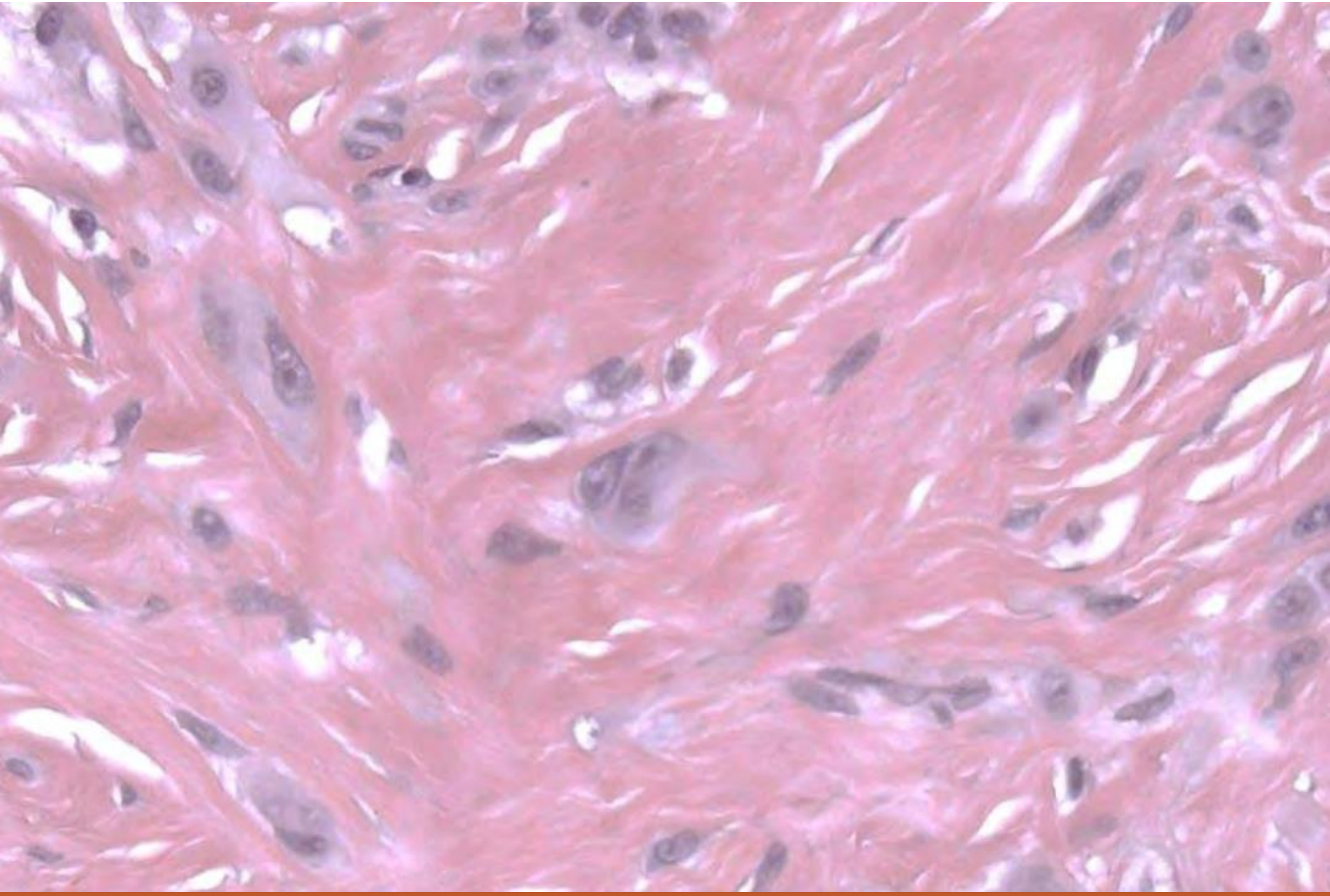






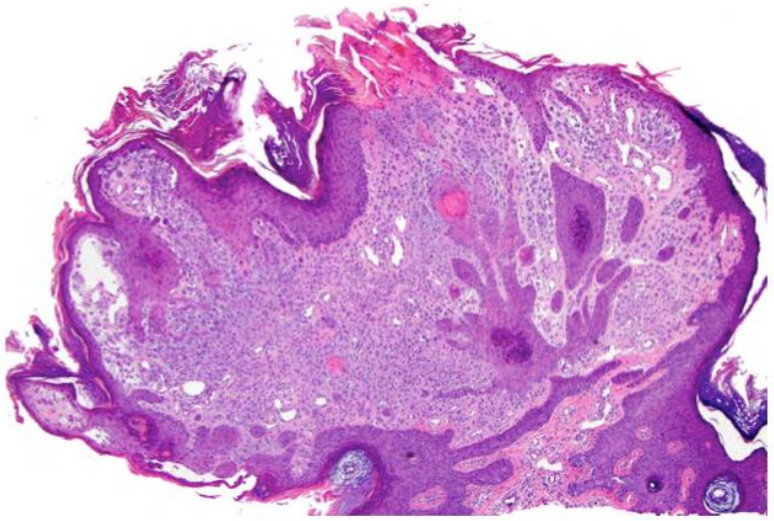




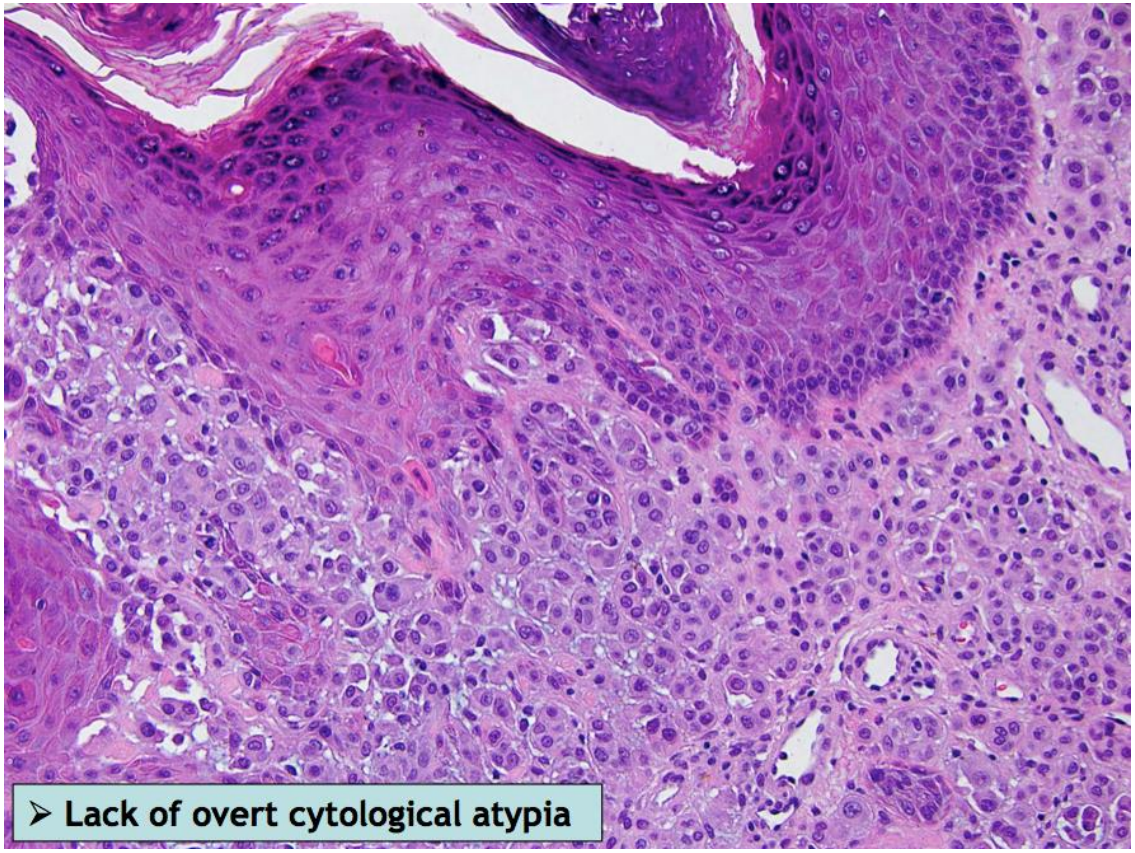


Spitz Nevus

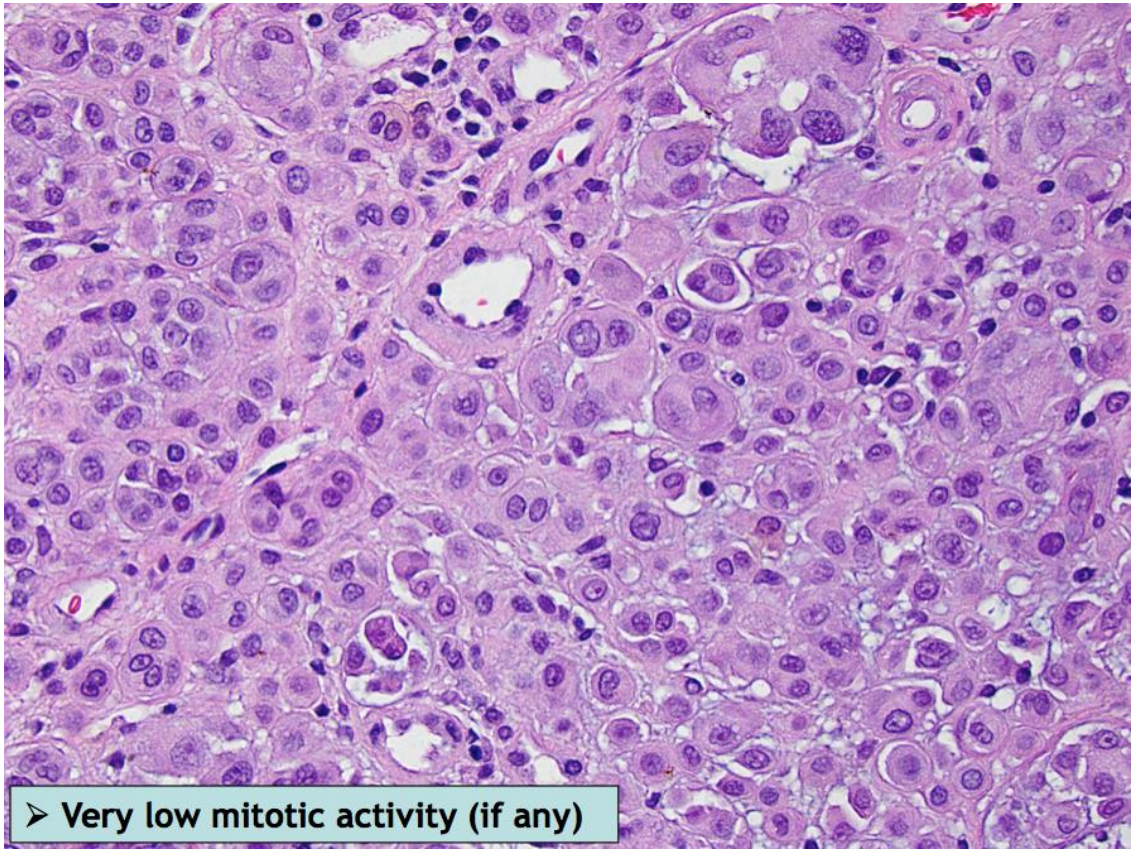
- Absence of architectural atypia
- Lack of overt cytological atypia
- Depth < 1.6 mm
- Low Ki-67 proliferative index
- Absence of strong/diffuse and deep HMB45 staining



Spitz Nevus

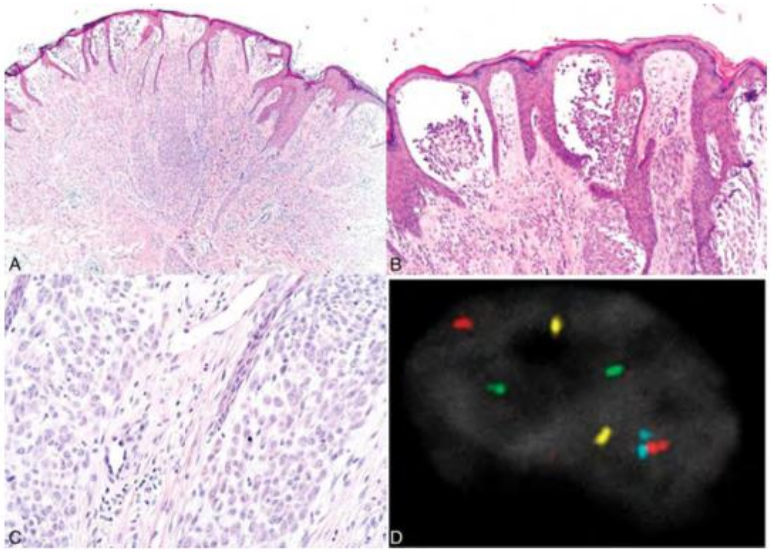


Spitz Nevus



Fluorescent in situ hybridization (FISH)

- **Probes:**
  - **6p25 (RREB1)**
  - **6q23 (MYB)**
  - **11q13 (CCND1)**
  - **CEP6**
  - **9p21**
- **Sensitivity:**
  - **4-probe= 70%**
  - **5-probe= 85%**
- **Specificity: 100%**



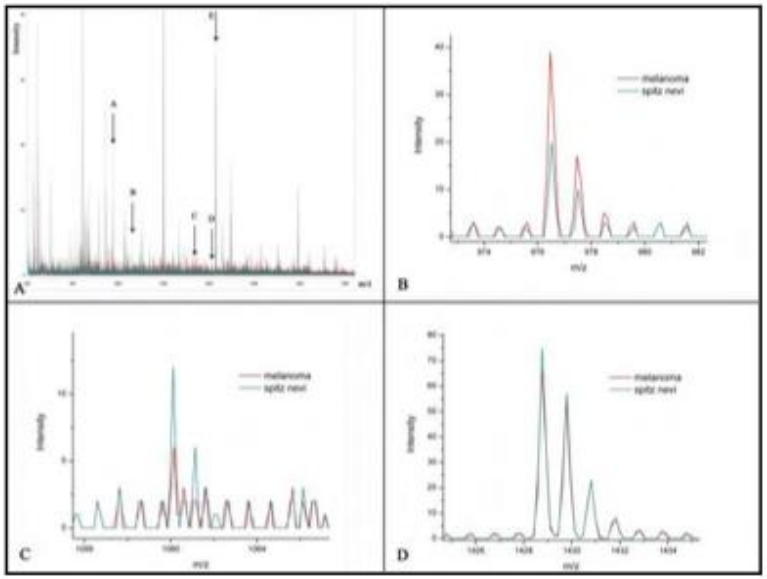
➢ 26-year-old woman - ? Spitz nevus

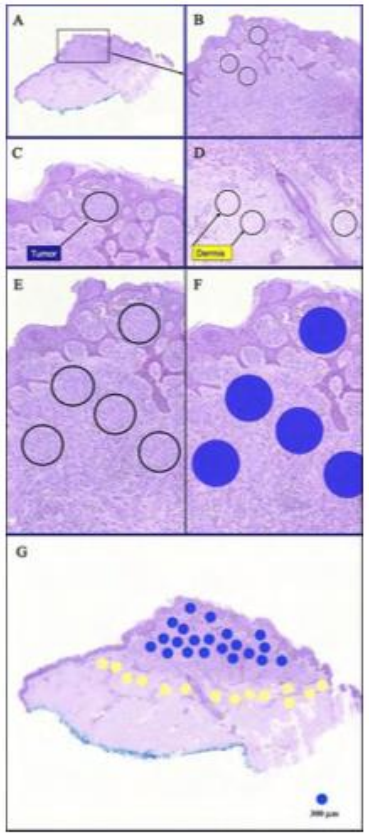
FISH: Normal 2 signals with target *RREB1* (red), *CCND1* (green), *MYB* (yellow) and CEP6 (aqua) probes. FISH favored a benign Spitz nevus.

Zembowicz A et al. Arch Pathol Lab Med, 2012

MALDI Imaging Mass Spectrometry (MALDI IMS)

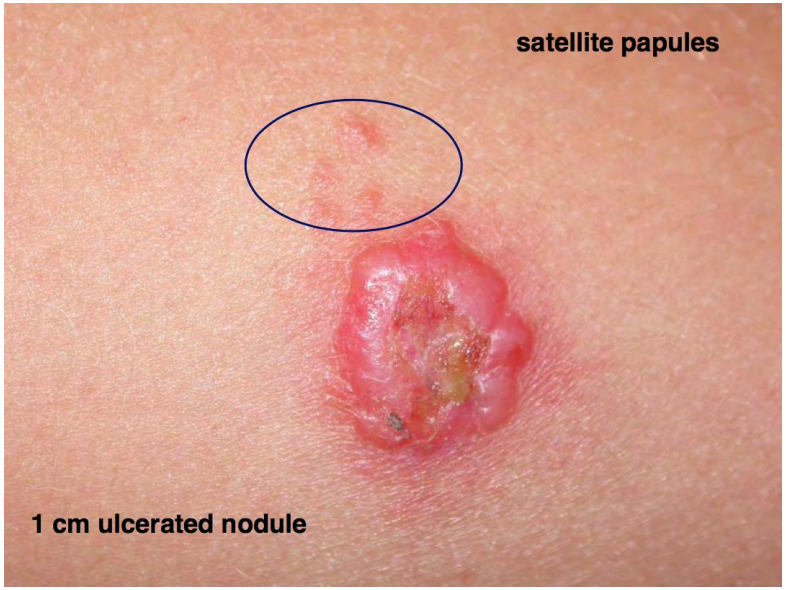
- **Probes:**
  - **m/z: 976.49**
  - **m/z: 1060.18**
  - **m/z: 1336.72**
  - **m/z: 1410.74**
  - **m/z: 1428.77**
- **Sensitivity: 97%**
- **Specificity: 90%**





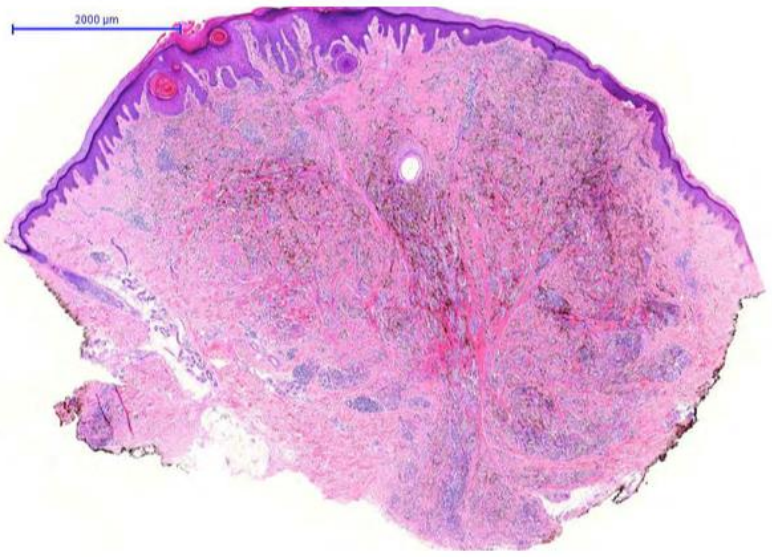
Spitzoid Melanoma

- May occur in adults and children
- Papule, plaque or nodule
- Any anatomic location
- Often > 1 cm in diameter
- Often amelanotic



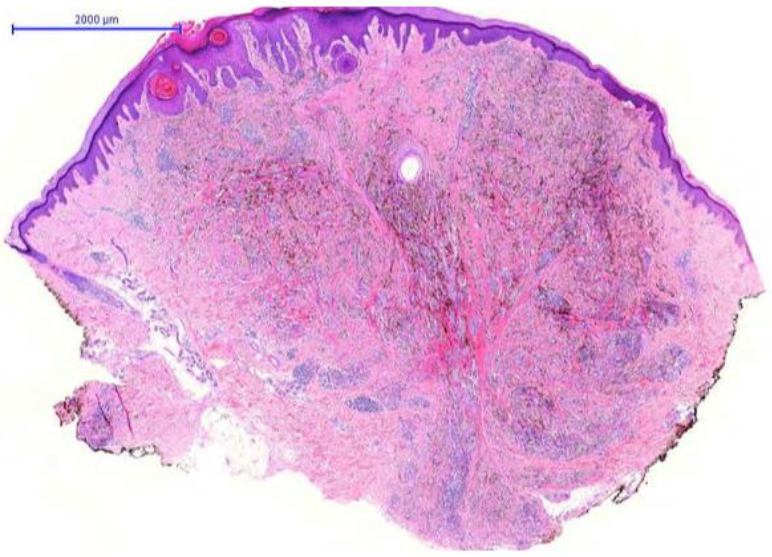
Spitzoid Malignant Melanoma

- Larger in size (clinical > 10 mm)
- Older age
- Unequivocal architectural & cytological atypia, including pleomorphic multinucleate giant cells
- Mitotic activity (usually > 6/mm2)
- Depth > 3.5 mm

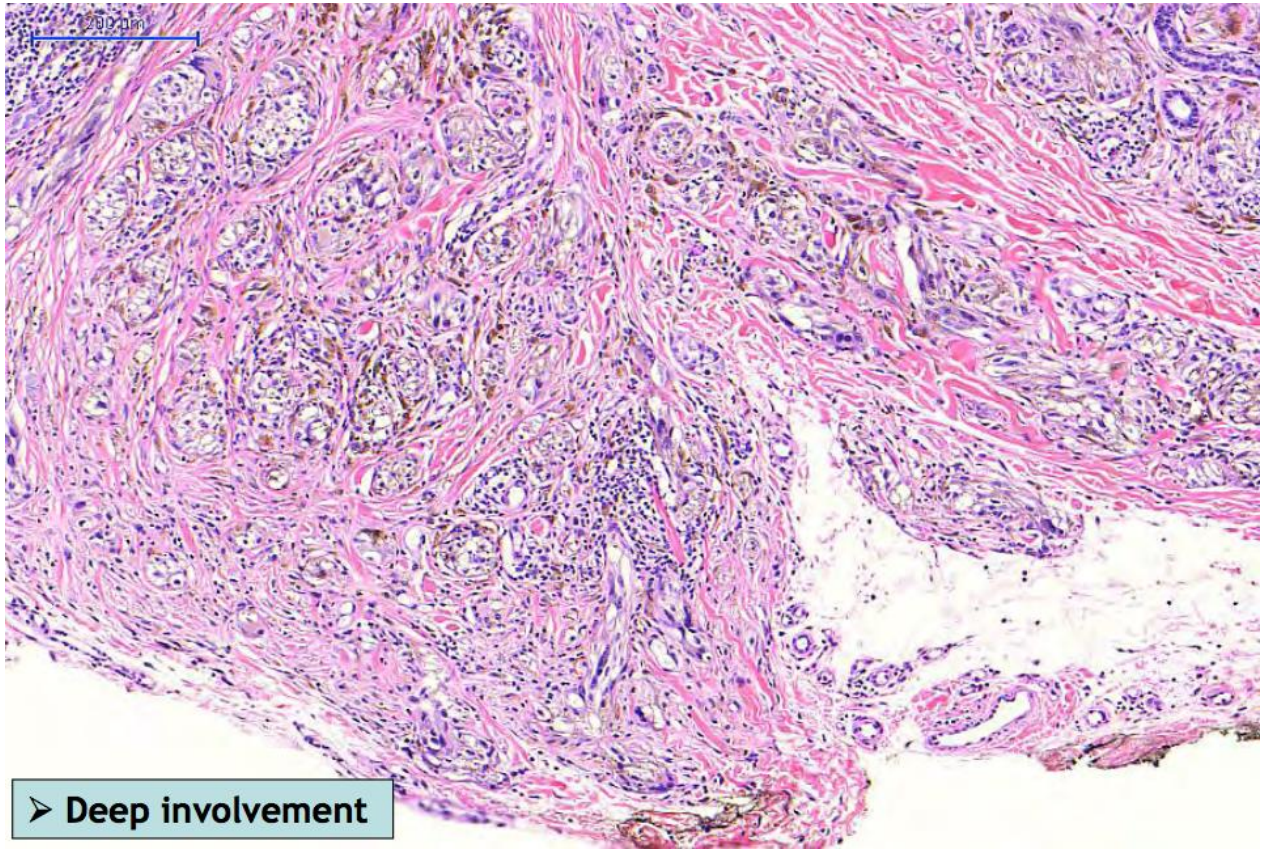


Spitzoid Malignant Melanoma

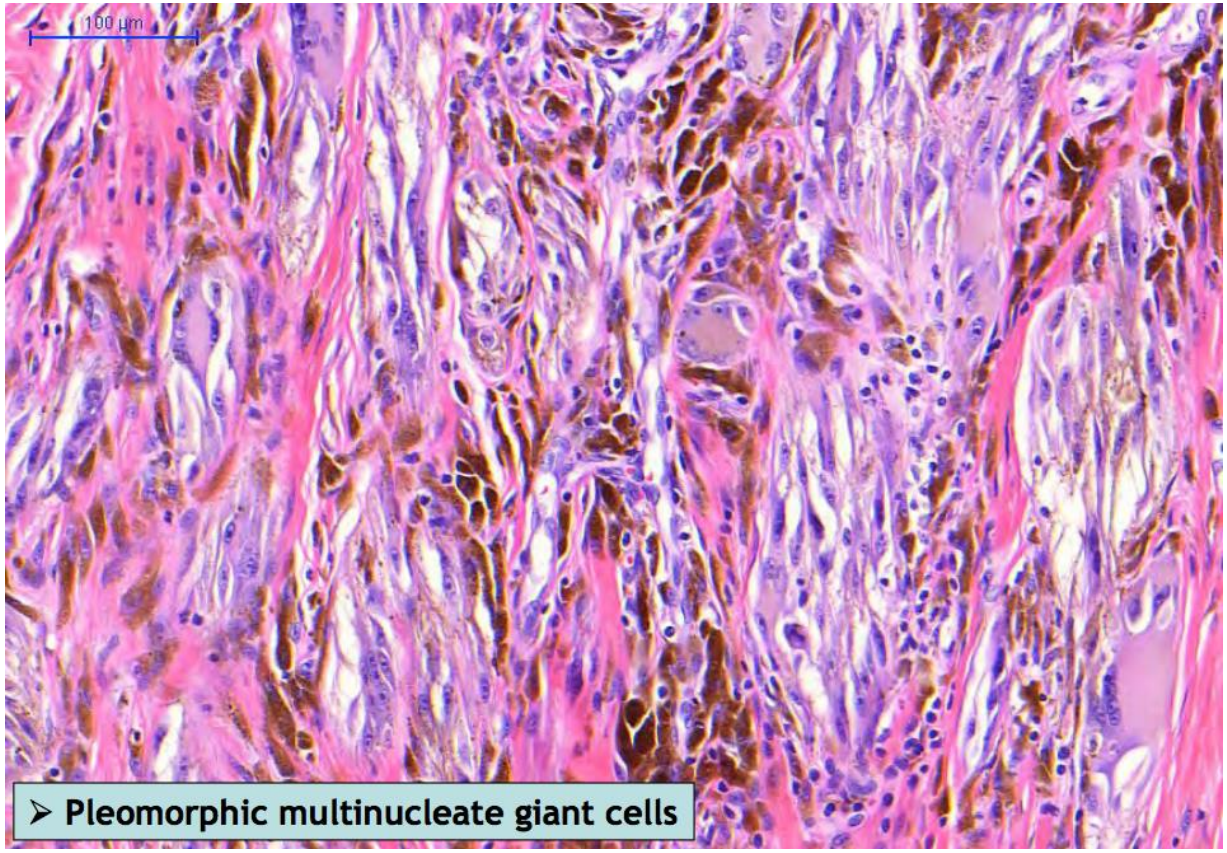
- Extension to deep dermis/subcutaneous adipose tissue with pushing border
- Marked extension of the junctional component and pagetoid spread beyond the dermal component
- Necrosis
- High Ki-67 proliferative index
- Deep HMB45 positivity



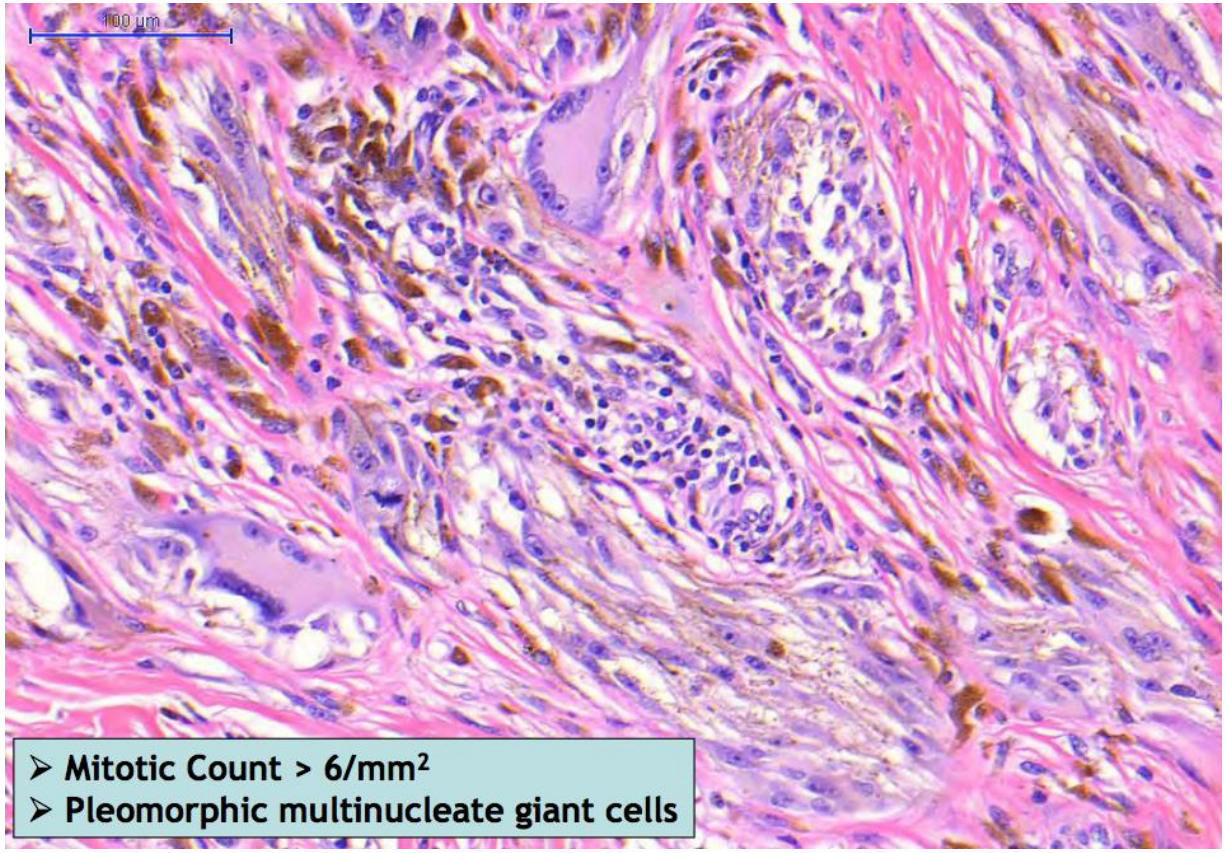
Spitzoid Malignant Melanoma



Sitzoid Malignant Melanoma



Spitzoid Malignant Melanoma



Spitzoid Melanocytic Lesions

Pay very careful attention to the patient's age, biopsy site and/or history of trauma

Spend sufficient time in thorough histopathologic evaluation

Careful assessment of the mitotic rate is always critical!

~ 40% of Spitz nevi show pagetoid spread

Avoid relying on any "single/magical" immunomarker in your decision making

Seek expert opinion in difficult cases

Use tests like FISH and MALDI IMS when indecisive

Avoid practicing defensive medicine and overcalling atypia especially in the younger population and/or in cosmetically sensitive areas

Spitzoid Melanocytic Lesions

While the metastatic potential of atypical Spitz neoplasms has been clearly shown, their true malignant potential is debatable and is an important consideration before surgical interventions

The mortality rate of atypical Spitz neoplasm is close to zero

Sentinel lymph node biopsy (SLNB) does not predict the outcome in atypical Spitz neoplasms

Keep an open mind, communicate with the oncologist/patient and evaluate the utility of SLNB on a case-by-case basis

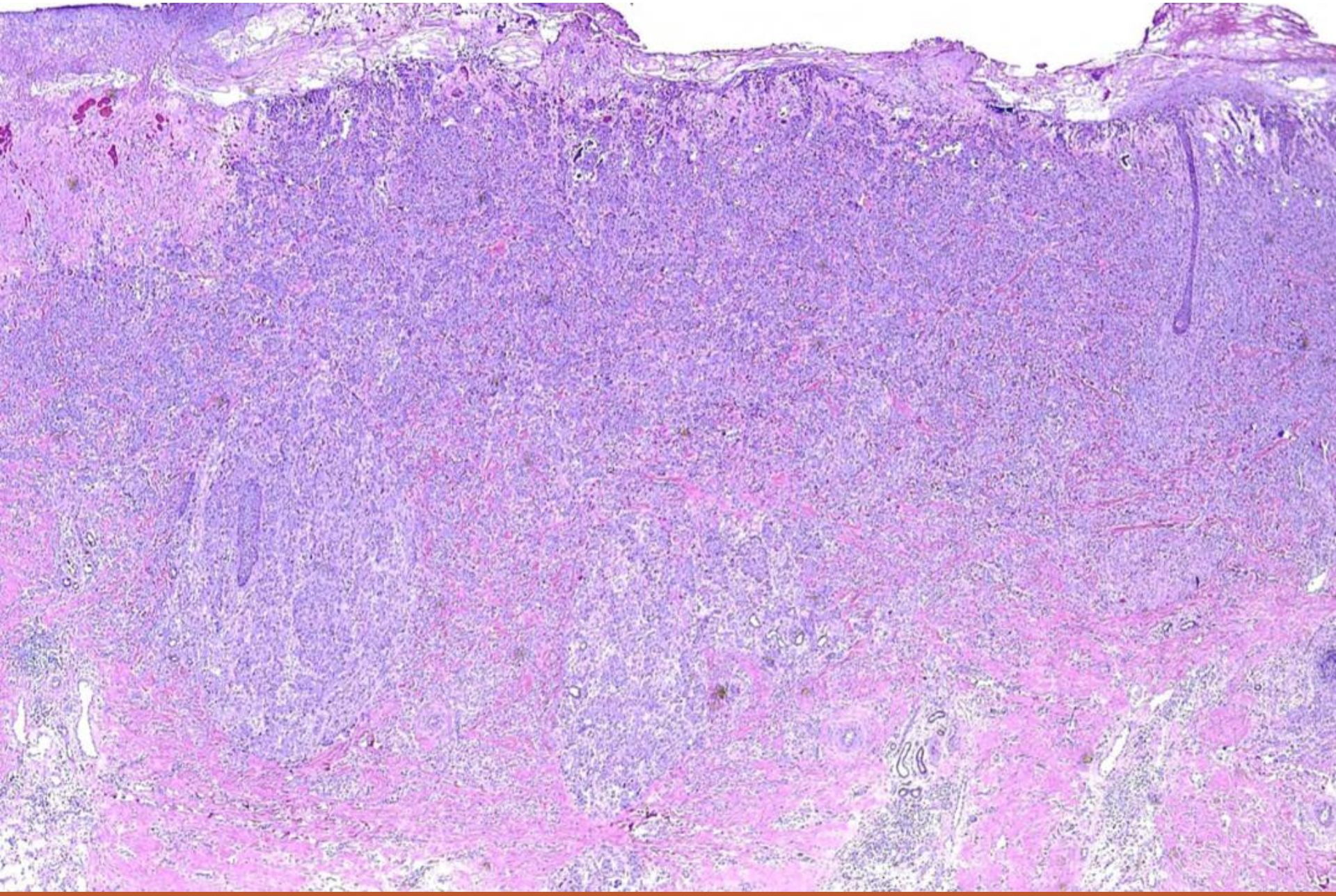
Overall, be cognizant of the immediate impact of your pathology diagnosis on the patient's management such as:

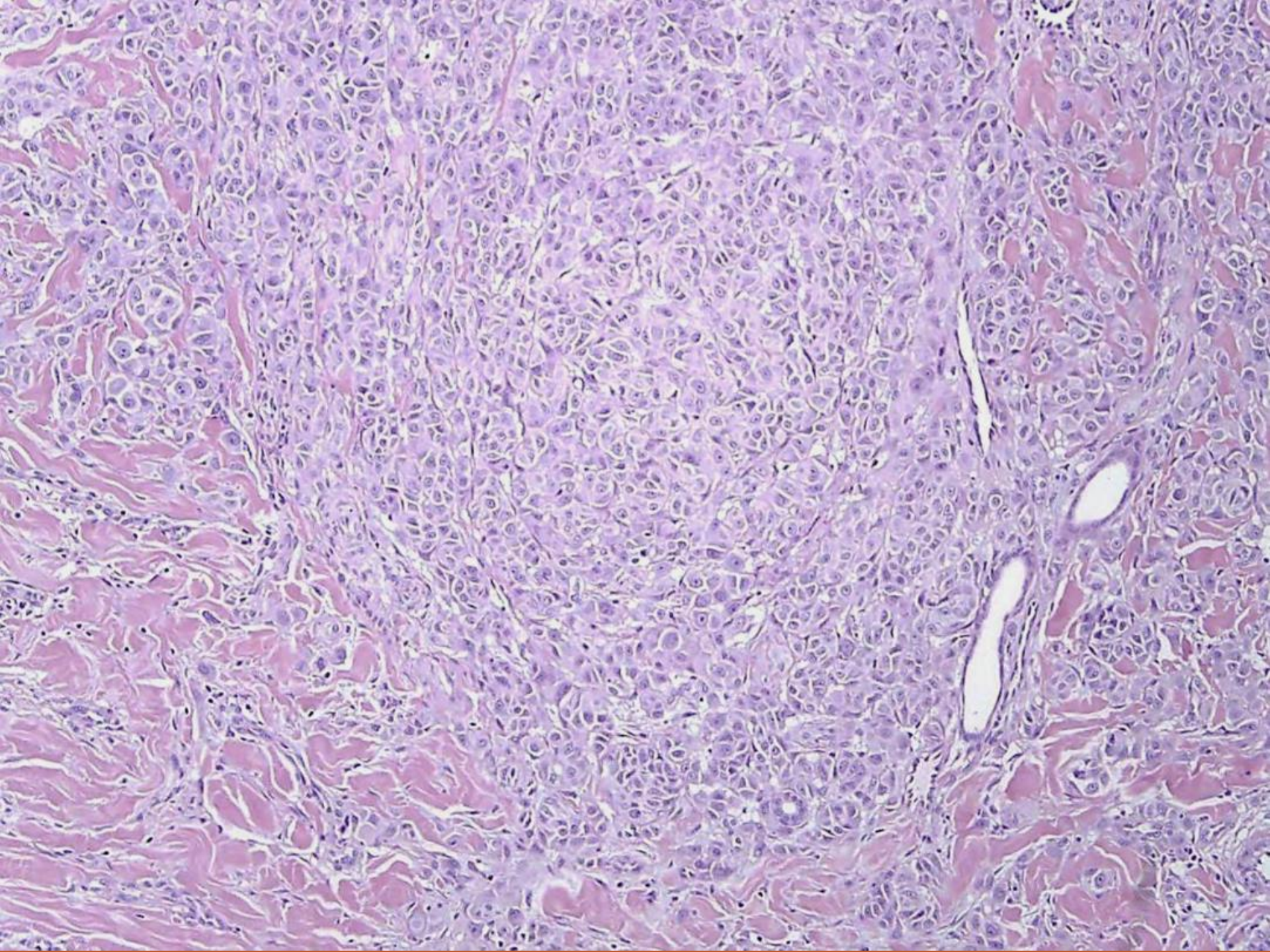
- **Conservative excision**
- **Wide excision**
- **Sentinel lymph node biopsy (SLNB)**
- **Completion lymphadenectomy**
- **Chemo- or immunotherapy**

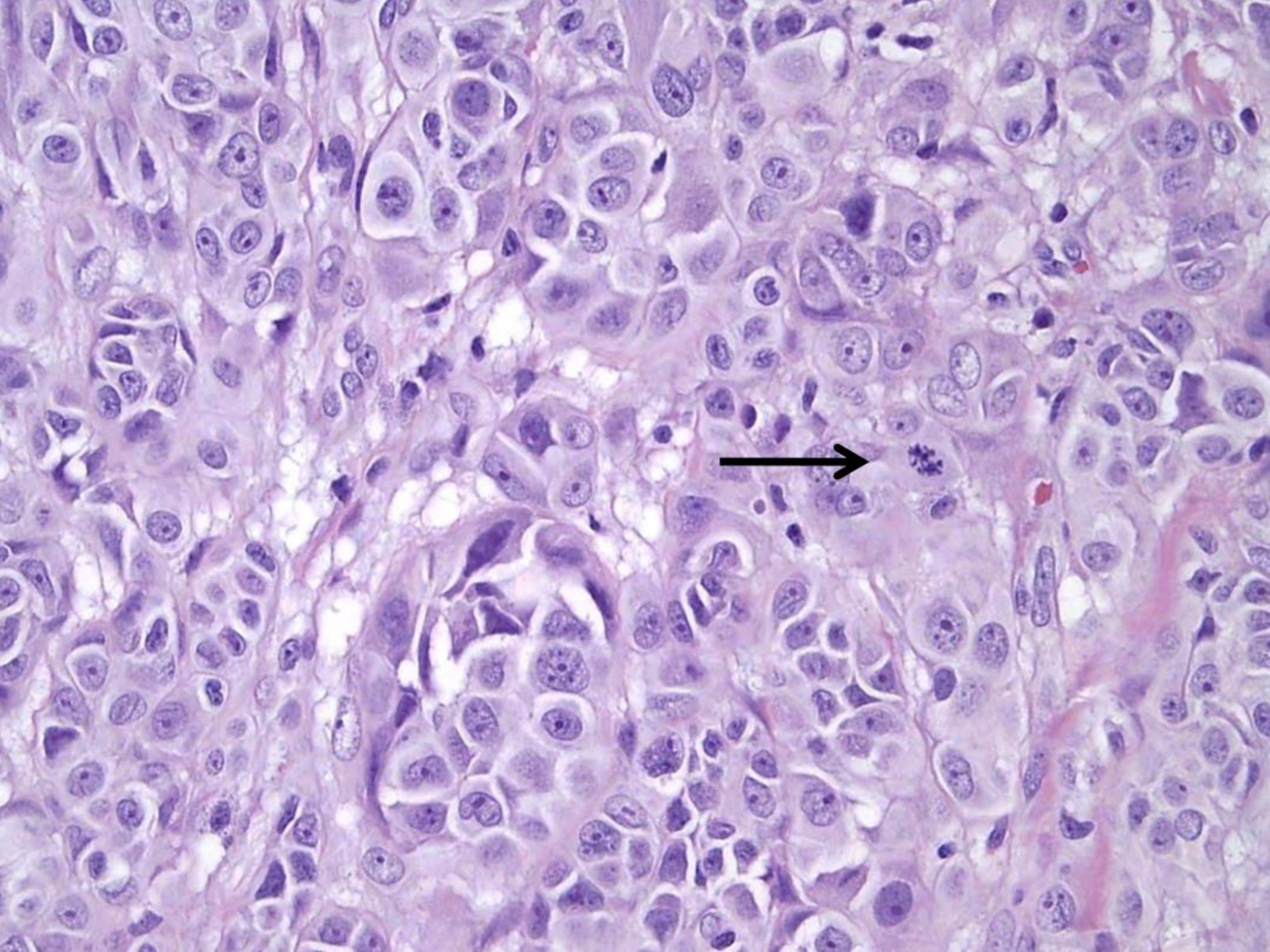
Atypical Spitz Tumor

- **Resemblance to Spitz nevi architecturally and cytologically, but typically have:**
  - **asymmetrical growth – side-to-side at any level**
  - **lack lateral circumscription**
  - **aberrant intraepidermal growth - confluence, pagetoid scatter**
  - **aberrant dermal growth - increased cellularity, compact expansile nests**
  - **lack of maturation of dermal component**

- **Resemblance to Spitz nevi architecturally and cytologically, but typically show:**
  - **cytologic atypia (↑ N:C ratio, coarse chromatin, irregular nuclear contours, larger eosinophilic nucleoli)**
  - **mitoses in deeper dermal component**
  - **atypical mitoses**
  - **necrosis**
  - **variable melanin distribution**

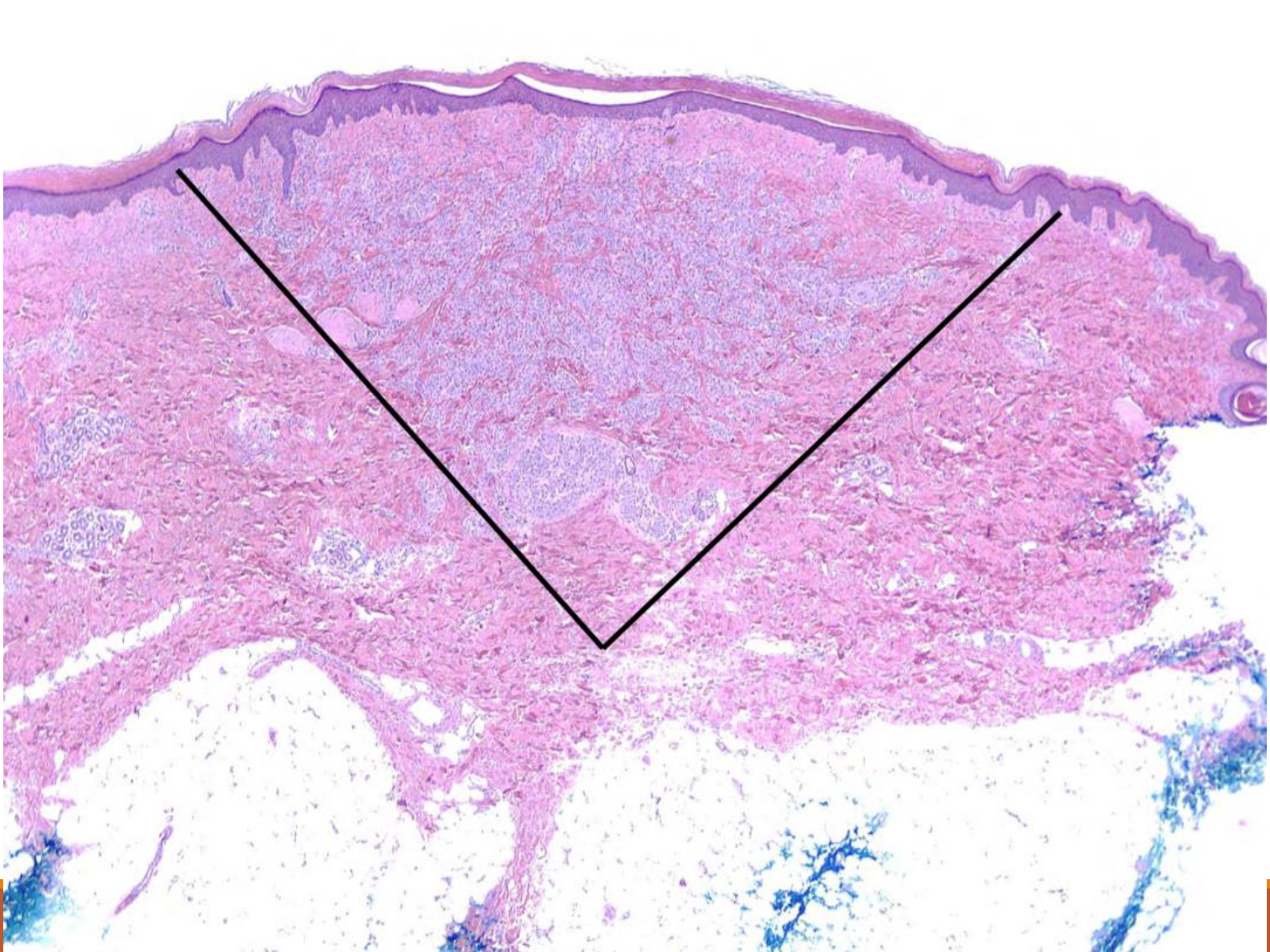


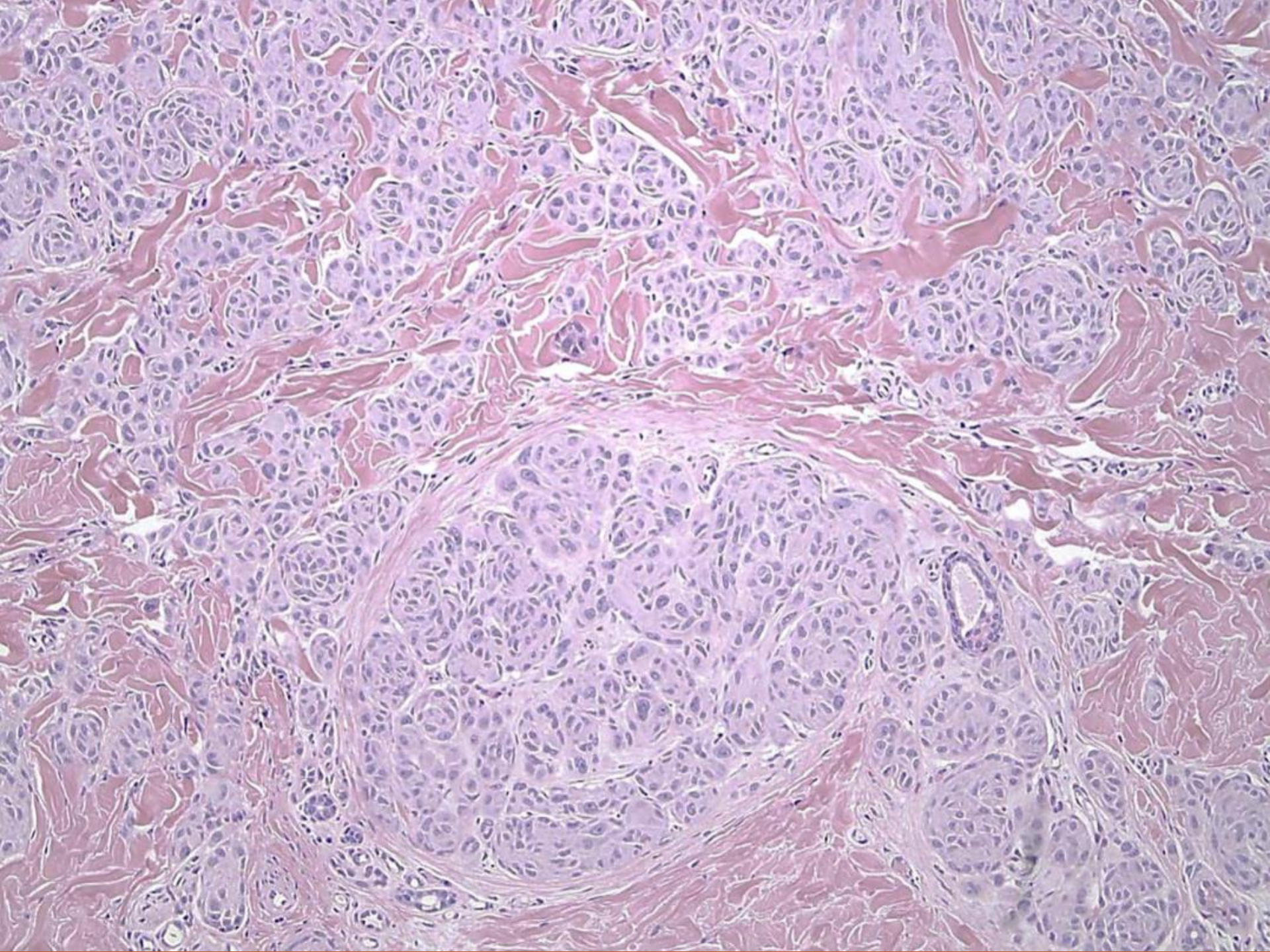


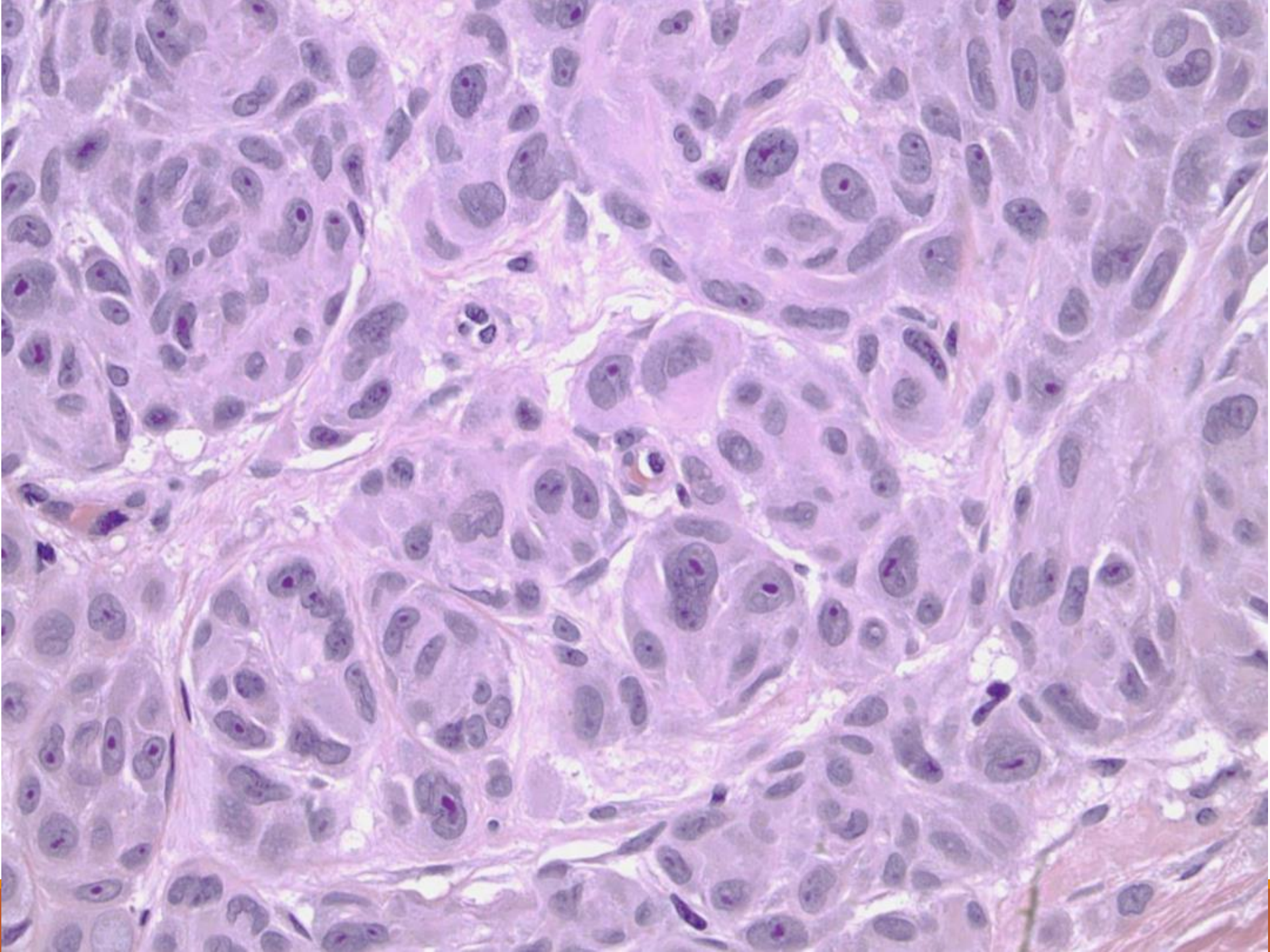


Atypical Spitz Tumor

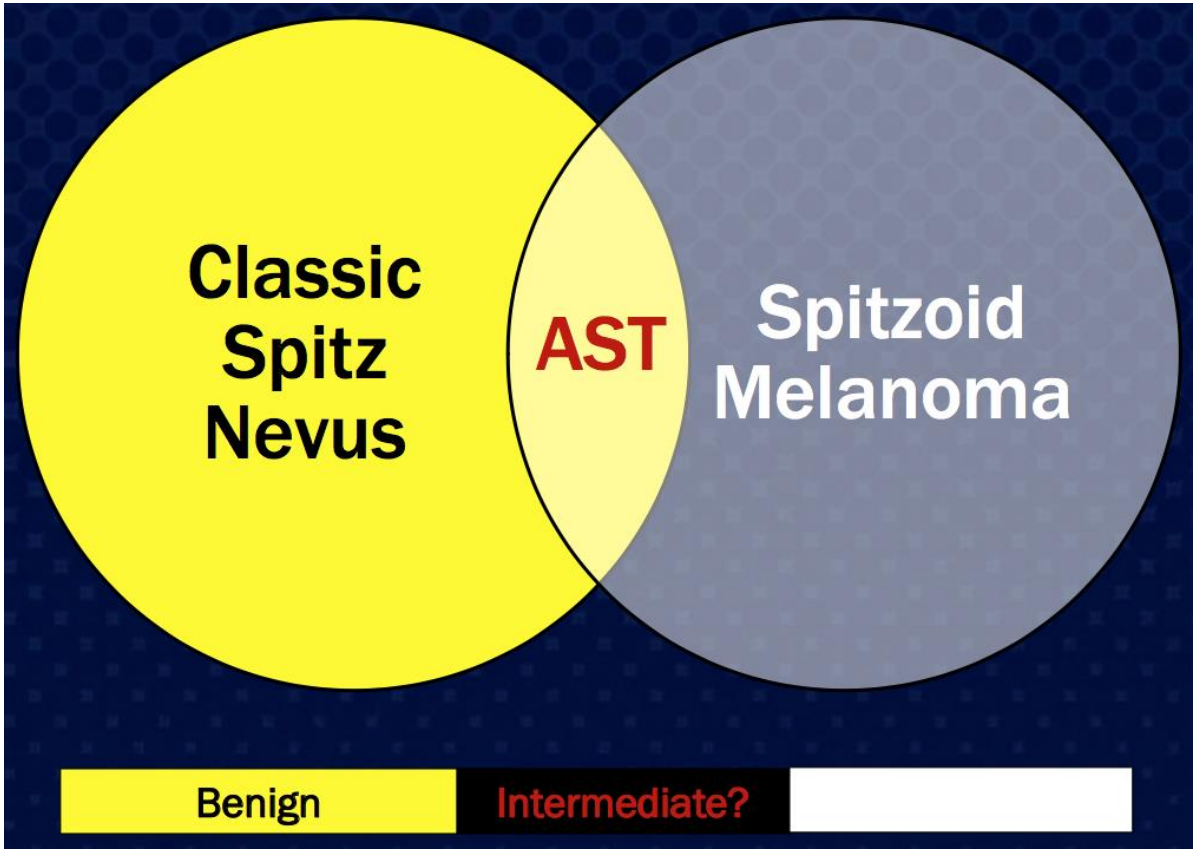
- **Small subset of spitzoid lesions fail to classify well because of histopathologic features overlapping Spitz nevus and melanoma**
- **No distinctive clinical features**
- **Lack reproducible histopathologic features**
- **Other terms: MELTUMP, metastasizing Spitz nevus**





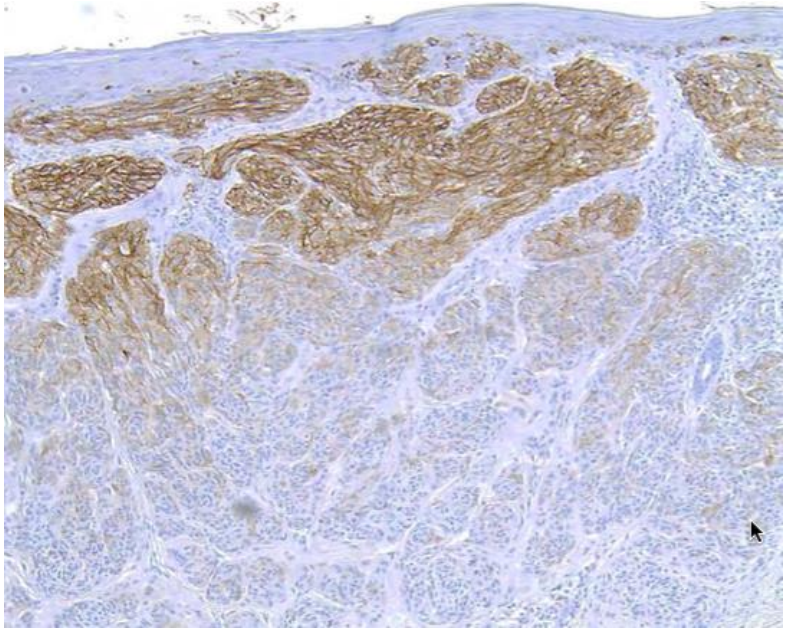


Atypical Spitz Tumor

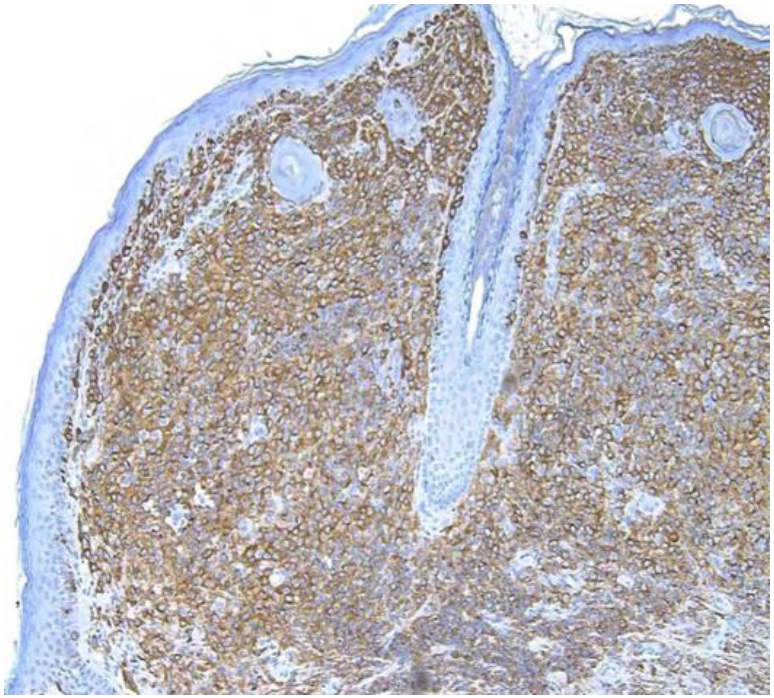


HMB-45 stratification in melanocytic lesions

BENIGN SPITZ TUMOR



SPITZOID MELANOMA



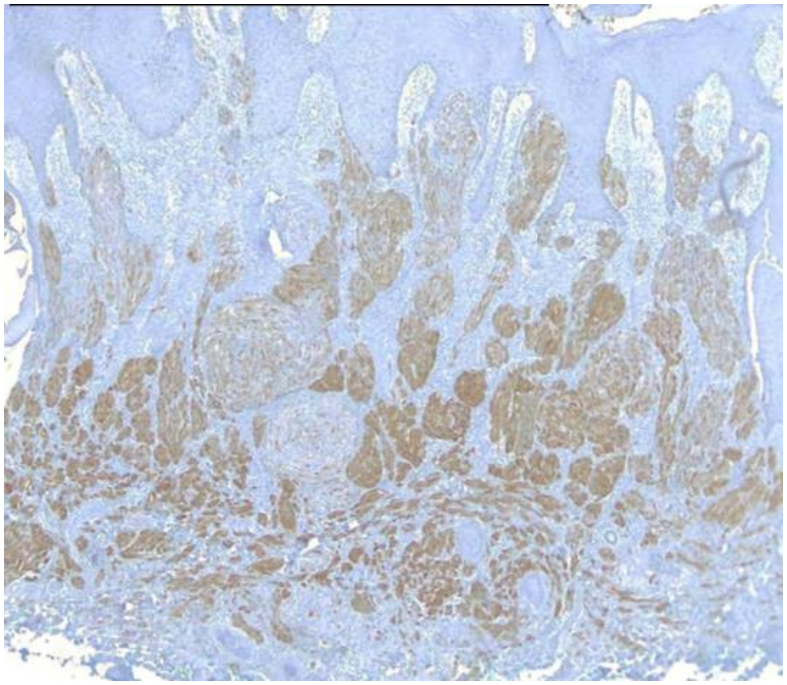
P16 Expression

- **12 compound nevi and 18 Spitz nevi in children:**
  - **diffuse p16 expression in all 30 cases**
- **6 spitzoid melanomas in children:**
  - **absence of p16 expression in all 6 cases**

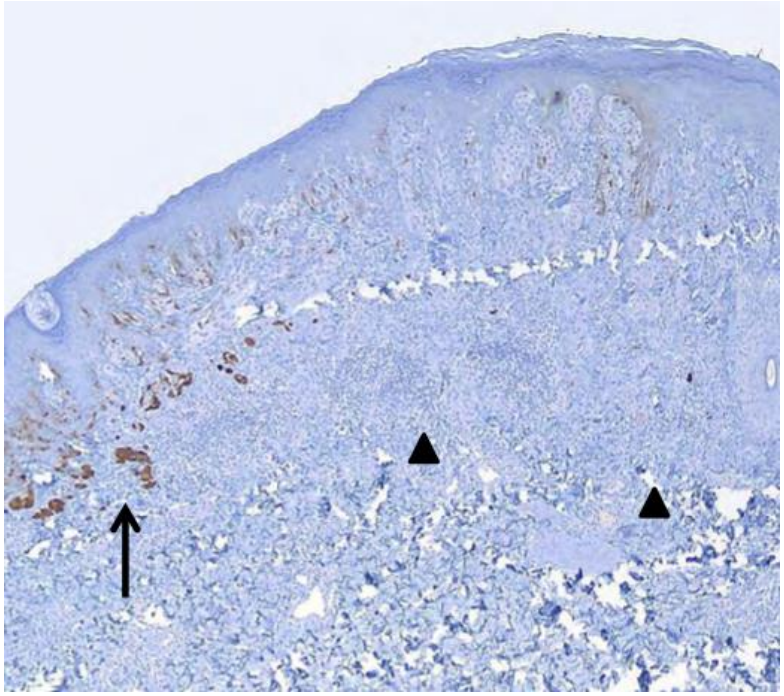
Al Dhaybi R, et al. P16 expression: a marker of differentiation between childhood melanomas and Spitz nevi. J Am Acad Dermatol 2011; 65: 357-363.

P16 staining patterns in melanocytic lesions

BENIGN SPITZ TUMOR

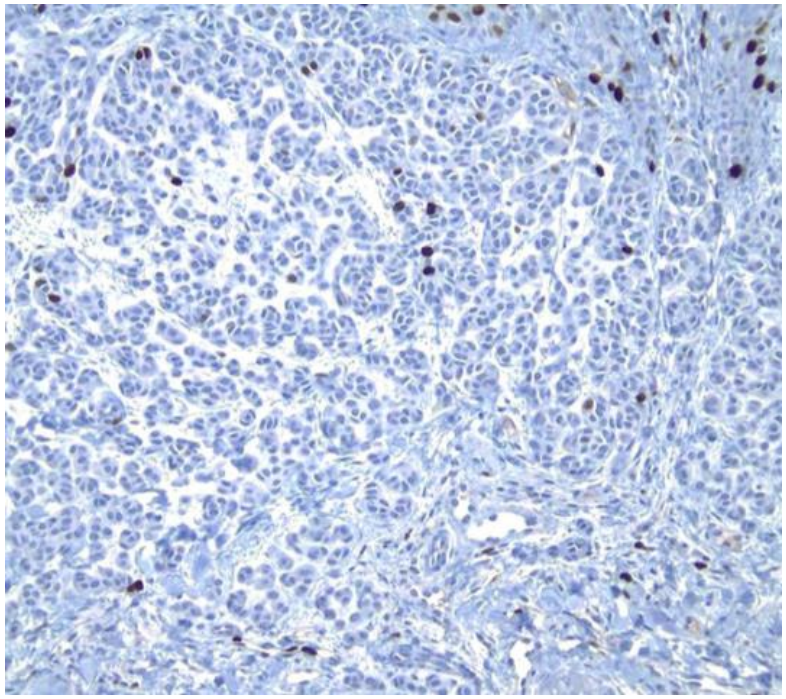


SPITZOID MELANOMA

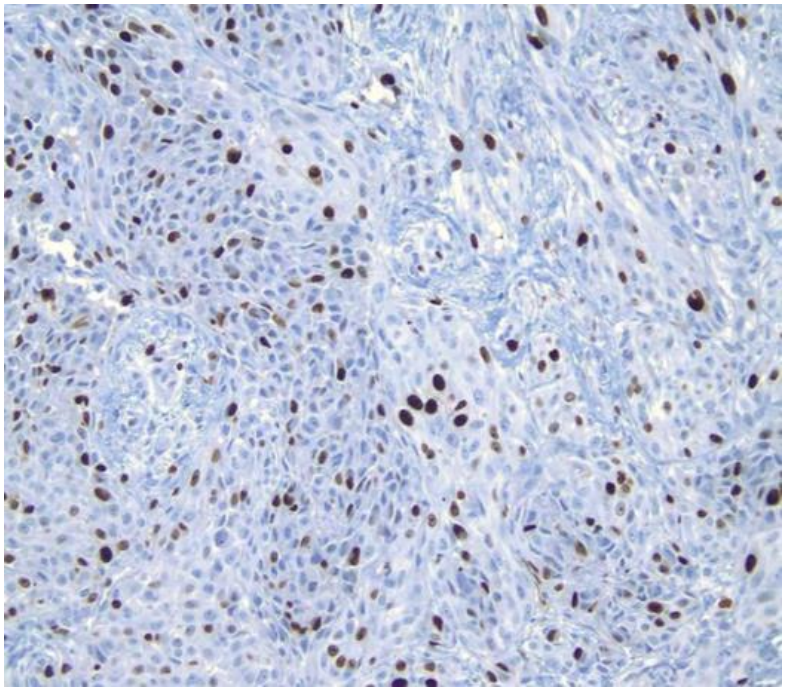


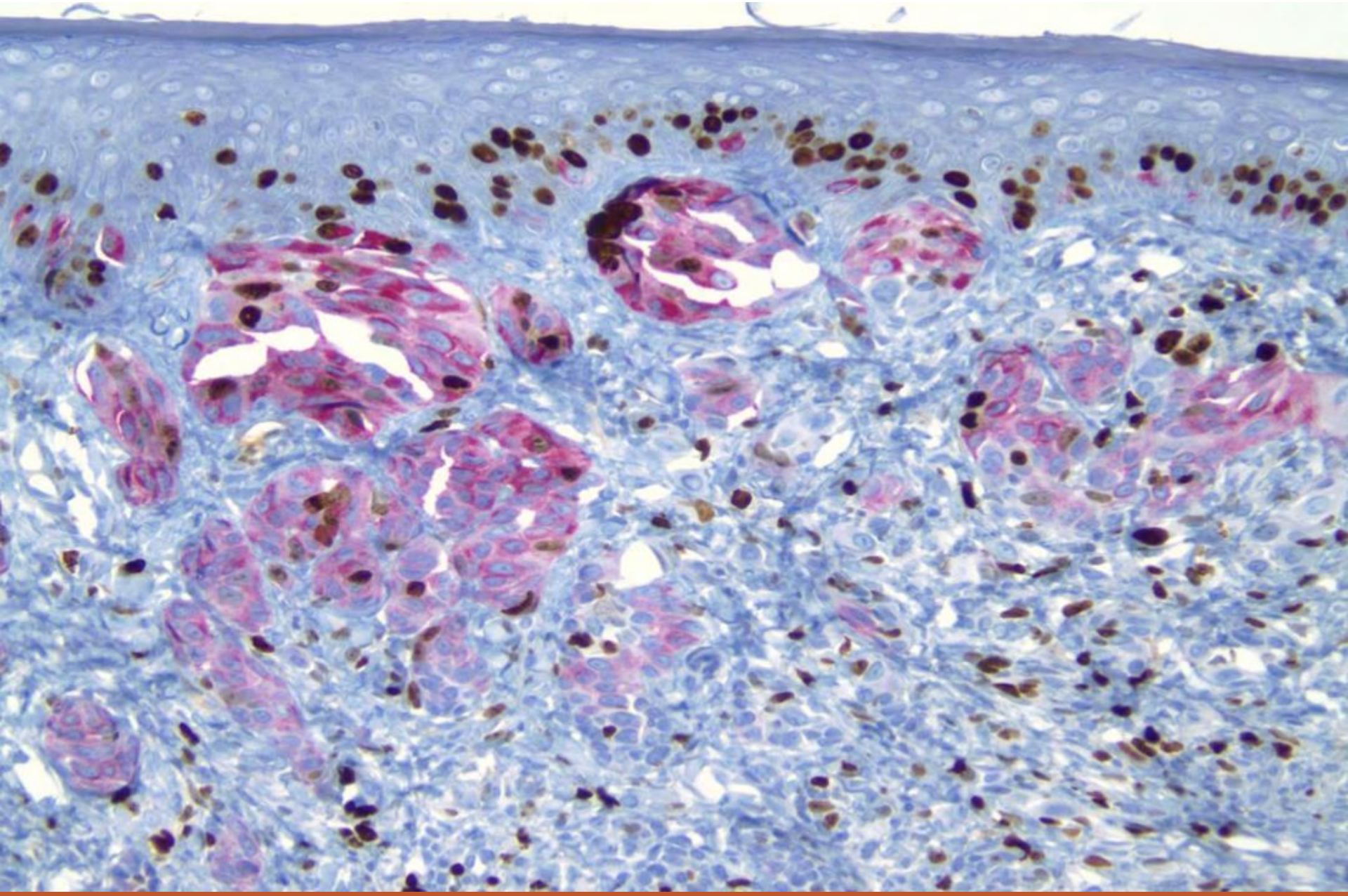
Ki-67 staining patterns in melanocytic lesions

BENIGN SPITZ TUMOR



SPITZOID MELANOMA





CGH

Melanomas

- **vast majority have multiple chromosomal aberrations (gains or losses)**

- **Spitz nevi**
  - **approximately 20% have gains in 11p (H-RAS)**

ASTs (16):

- **7 (44%) ASTs – Chromosomal aberrations; most not common in conventional melanomas**
- **9 (56%) ASTs – No chromosomal aberrations**

Melanoma controls (3):

- **3 (100%) spitzoid (2) and superficial spreading (1) melanomas – Chromosomal aberrations**

Bastian BC, et al. Chromosomal gains and losses in primary cutaneous melanomas detected by comparative genomic hybridization. Cancer Res 1998; 58: 2170-2175.
Bastian BC, et al. Molecular cytogenetic analysis of Spitz nevi shows clear differences to melanoma. J Invest Dermatol 1999; 113(6): 1065-1069.
Raskin L, et al. Copy number variations and clinical outcome in atypical Spitz tumors. Am J Surg Pathol 2011; 35(2): 243-252.

FISH

ASTs (16):

- **– 0% (0/16) were positive, including 1 with fatal outcome**

Melanoma controls (3):

- **– 66% (2/3; 1 spitzoid and 1 superficial spreading) were positive**

Raskin L, et al. Copy number variations and clinical outcome in atypical Spitz tumors. Am J Surg Pathol 2011; 35(2): 243-252.

Prognosis

- **Spitz nevi are benign**
- **Atypical Spitz tumors should be regarded as having uncertain biologic potential**
- **Spitzoid melanomas are malignant tumors:**
  - **Children – more indolent (low-grade)**
  - **Adults – more aggressive**

AST – Key Points

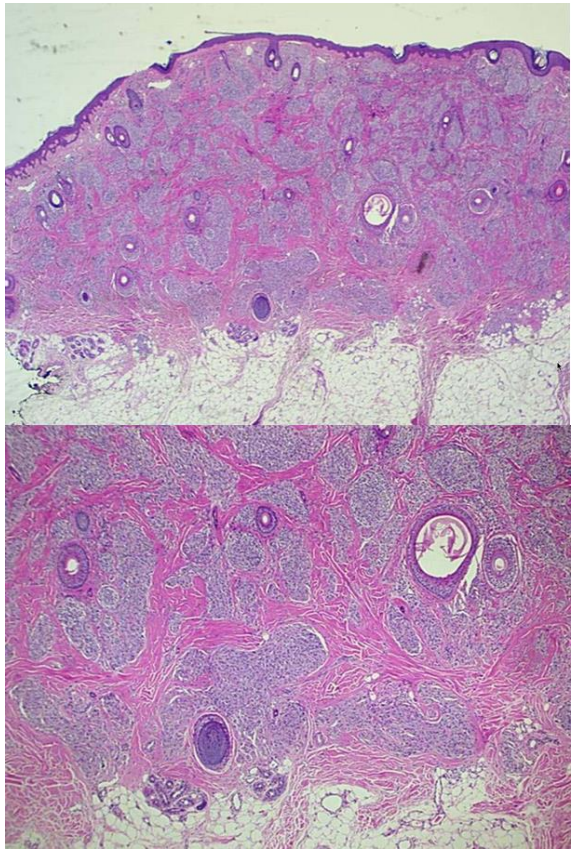
- **Most spitzoid lesions can be diagnosed as Spitz nevi or melanoma by adherence to established criteria**
- **Subset of spitzoid lesions defy classification as benign or malignant histopathologically (AST, MELTUMP) – advisable to seek consultation**
- **IHC and molecular analysis (CGH) may help to further define the risk of an individual lesion**
- **ASTs should be excised for complete removal and SLNB (controversial) considered for high risk lesions**

AST – Barnhill et al, 1999

- **Subset of Spitzoid melanocytic proliferations with a worrisome histology but indeterminate biologic behaviour**
  - **Architecture resembles VGP melanoma**
  - **Cytology resembles conventional Spitz**
  - **Metastases, when present, tend to confine to regional lymph nodes**
- **Often larger than usual Spitz nevus: >12cm**

AST – Spatz et al, Arch Dermatol 1999

- High risk for metastatic disease (at least regional)
  - Deep extent greater than 2 millimeters/fat
  - Marginal mitoses/mitoses > 6/mm2
  - Lack of maturation
  - Pushing nodular borders
  - Lymphatic extension
  - Ulceration
  - Diameter greater than 1 cm/older age



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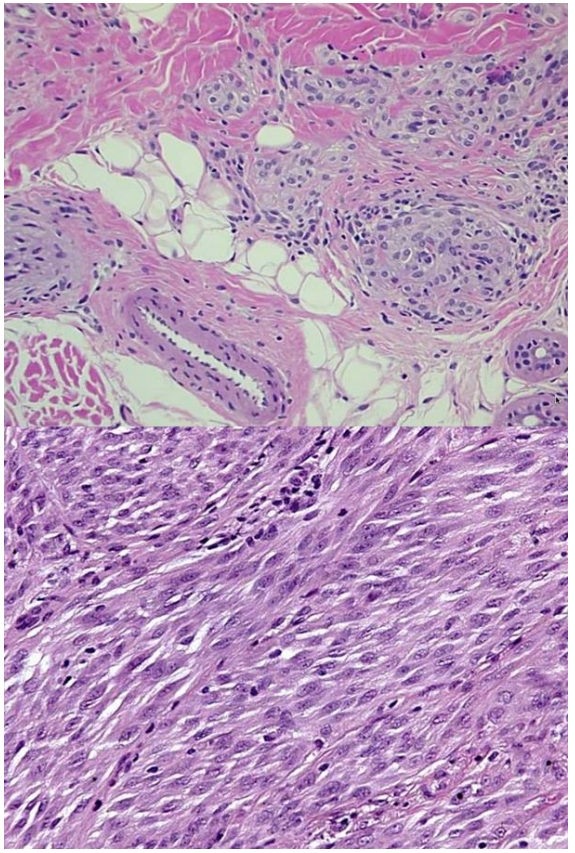
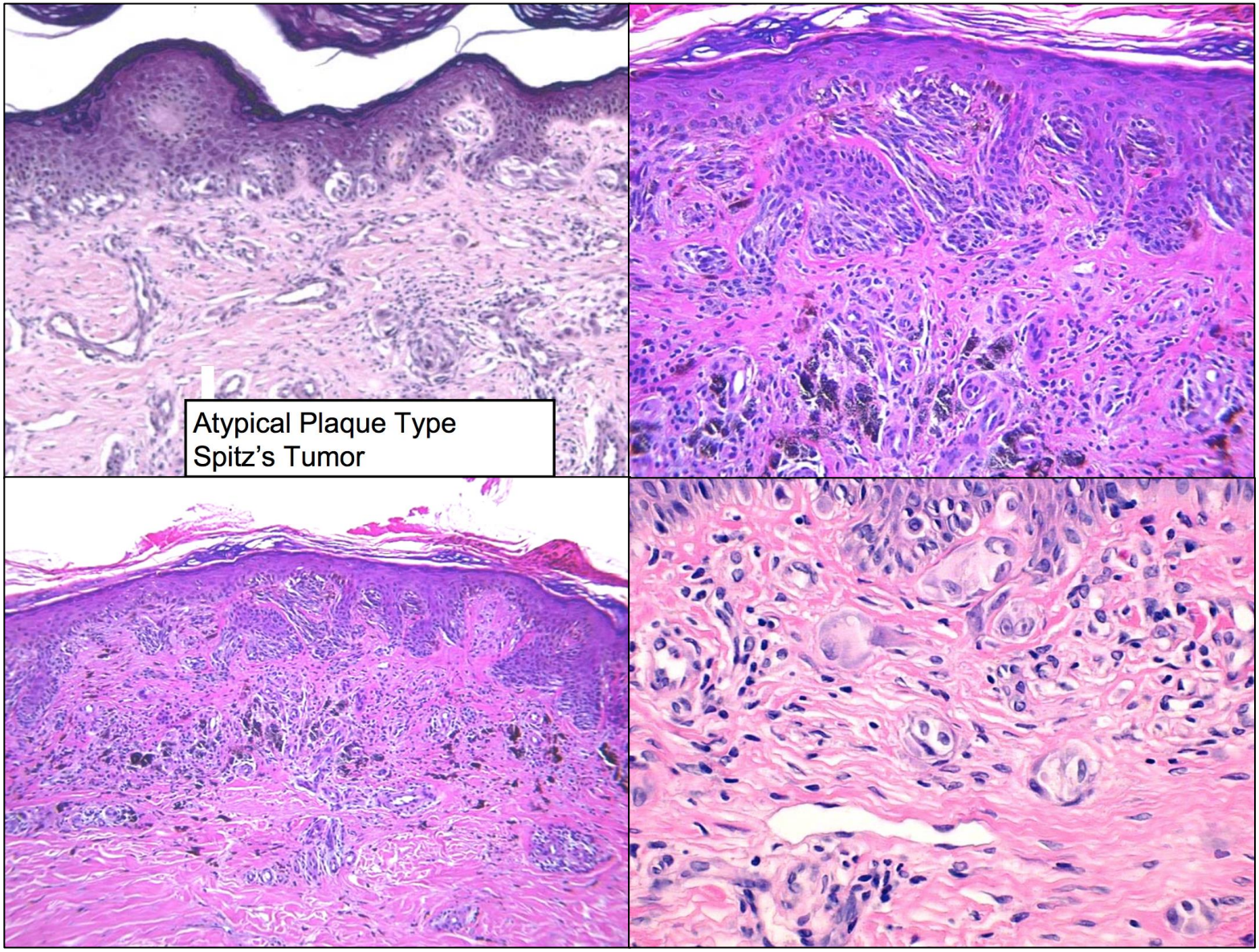



Atypical Plaque Type
Spitz's Tumor

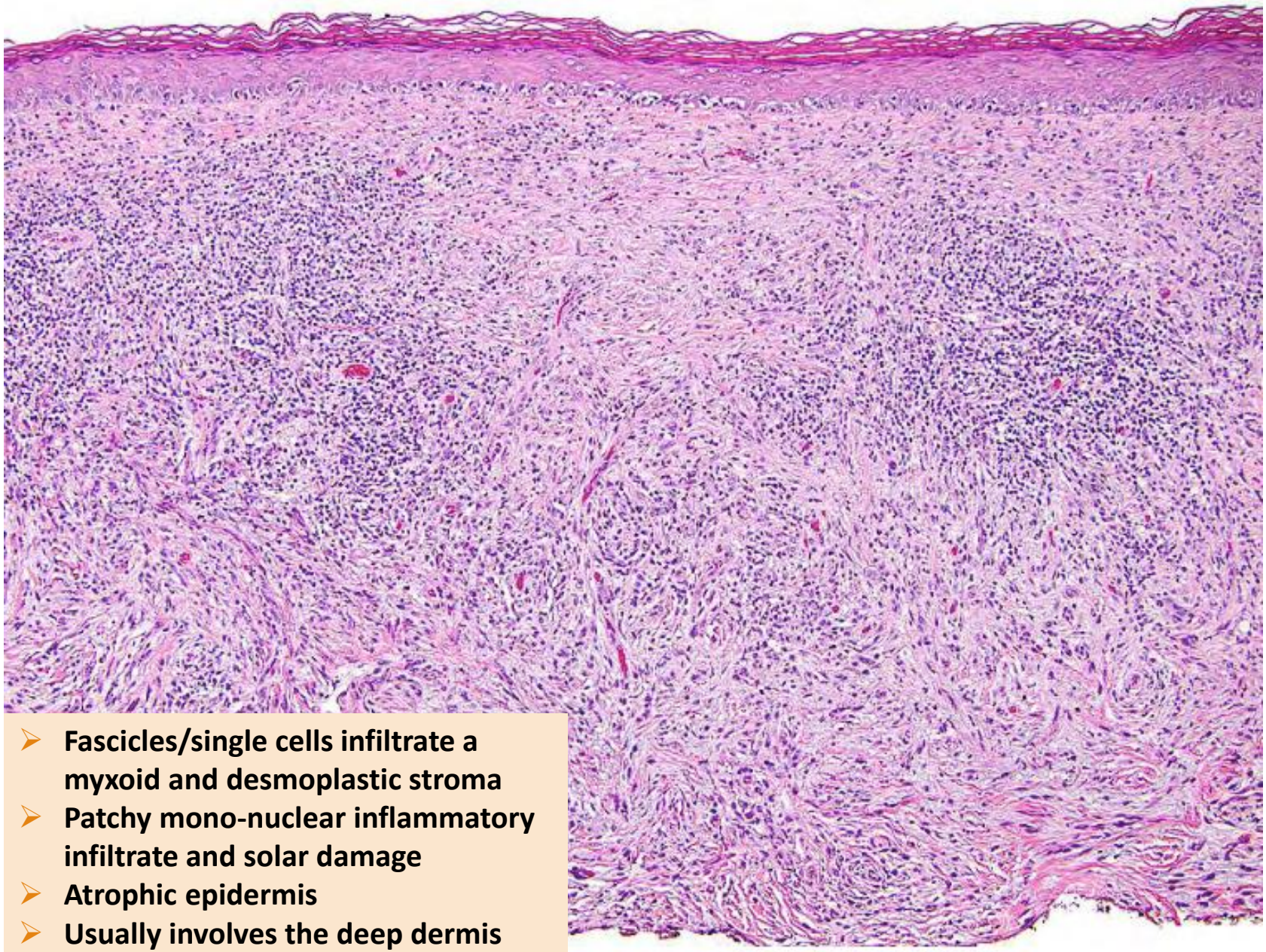
Prognosis in the Atypical Spitz Tumor

- **Patient population: problematic spitzoid neoplasms**
- **18 patients; 8 to 32 years of age**
- **Deep dermal mitoses**
- **Sheet like growth**
- **No maturation**
- **Nuclear pleomorphism**
- **44% had positive SNL and one had an additional positive node on completion lymphadenectomy**
- **All are alive and well(mean follow up of 12 months)**

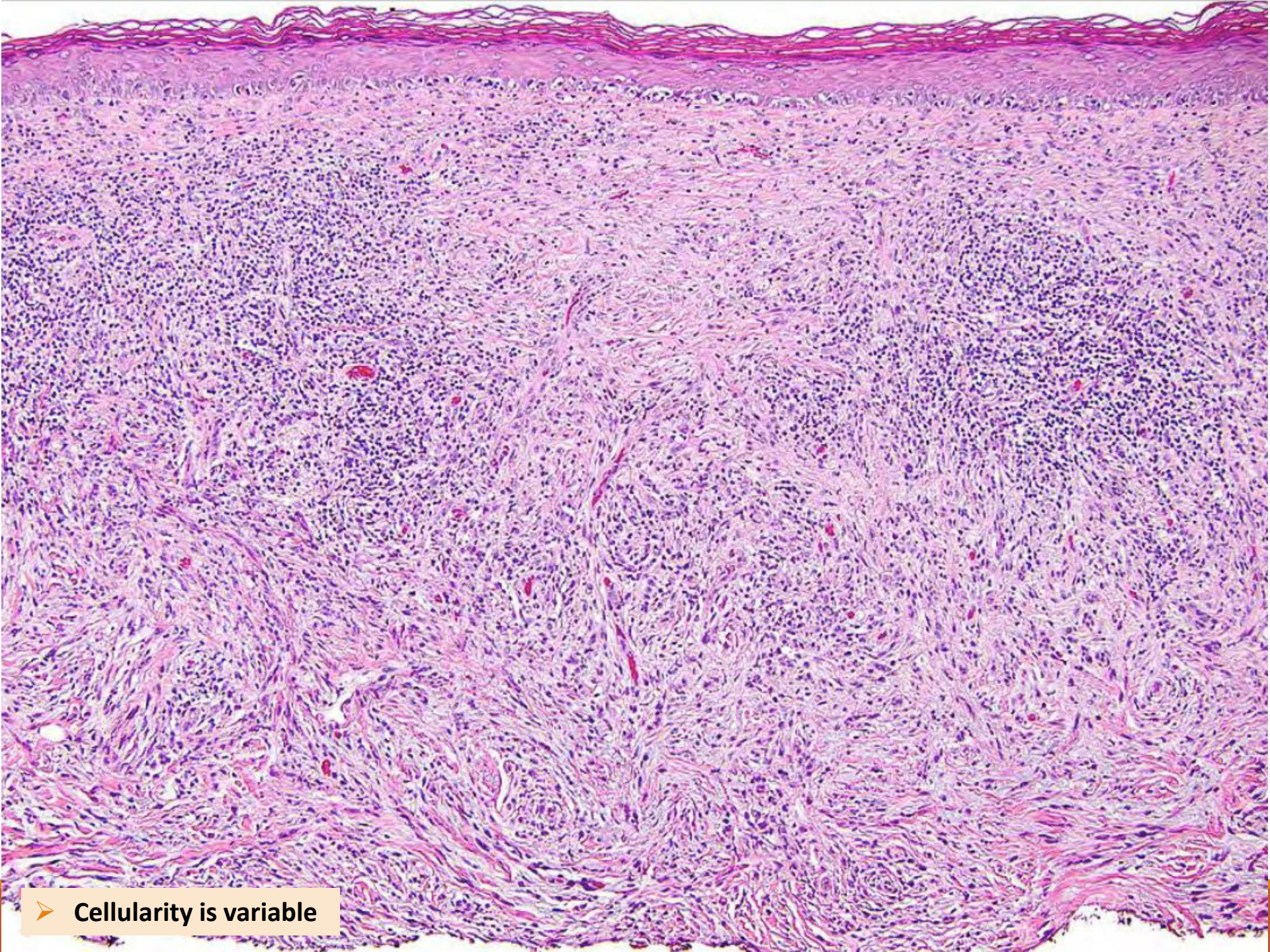
Cancer. 2003 Jan 15;97(2):499-507. Sentinel lymph node biopsy for patients with problematic spitzoid melanocytic lesions: a report on 18 patients. Su LD, Fullen DR, Sondak VK, Johnson TM, Lowe L.

Case 5

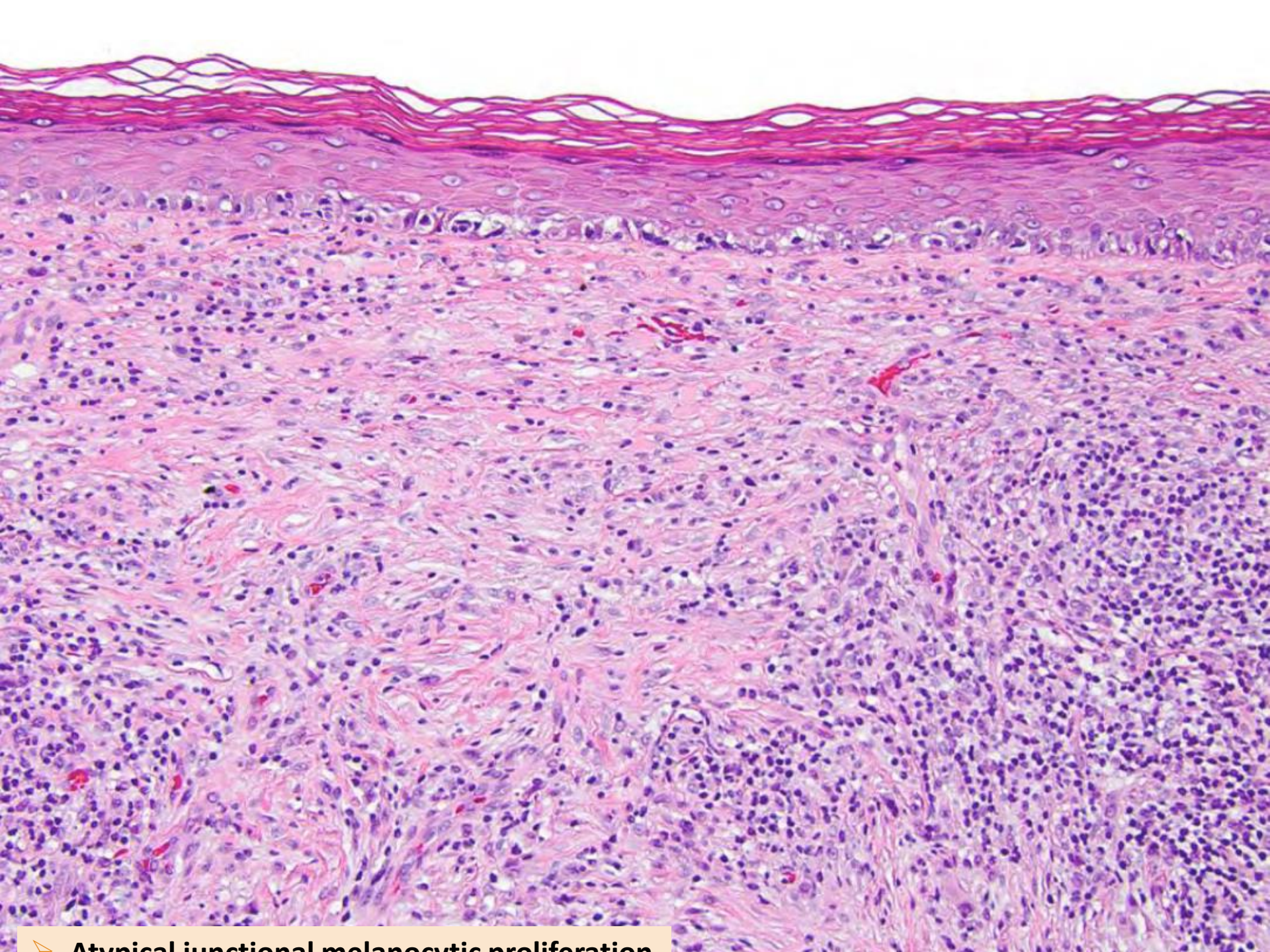
86-YEAR OLD WOMAN WITH A LESION ON HER BACK; BCC?

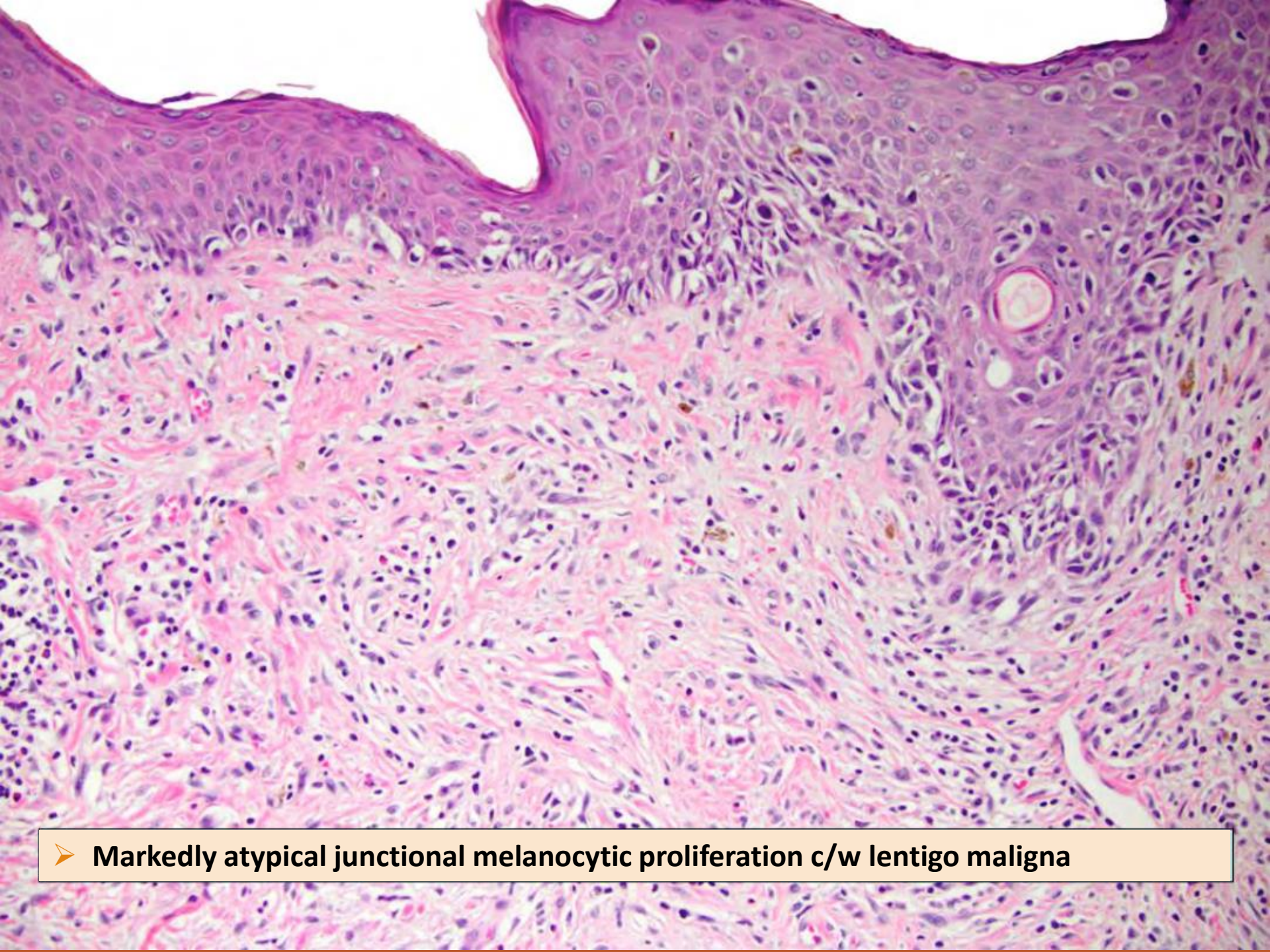


- Fascicles/single cells infiltrate a myxoid and desmoplastic stroma
- Patchy mono-nuclear inflammatory infiltrate and solar damage
- Atrophic epidermis
- Usually involves the deep dermis

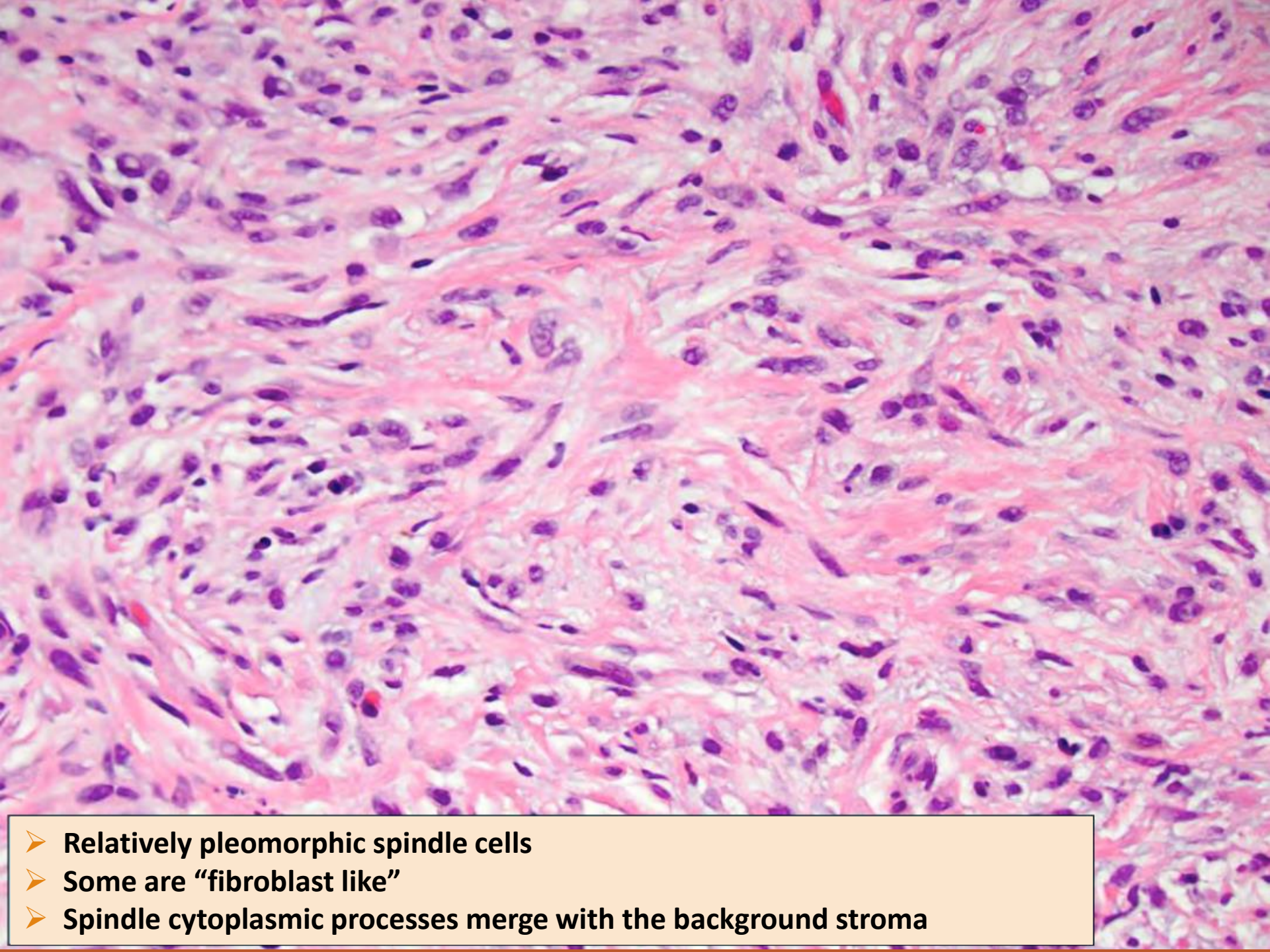


- **Cellularity is variable**

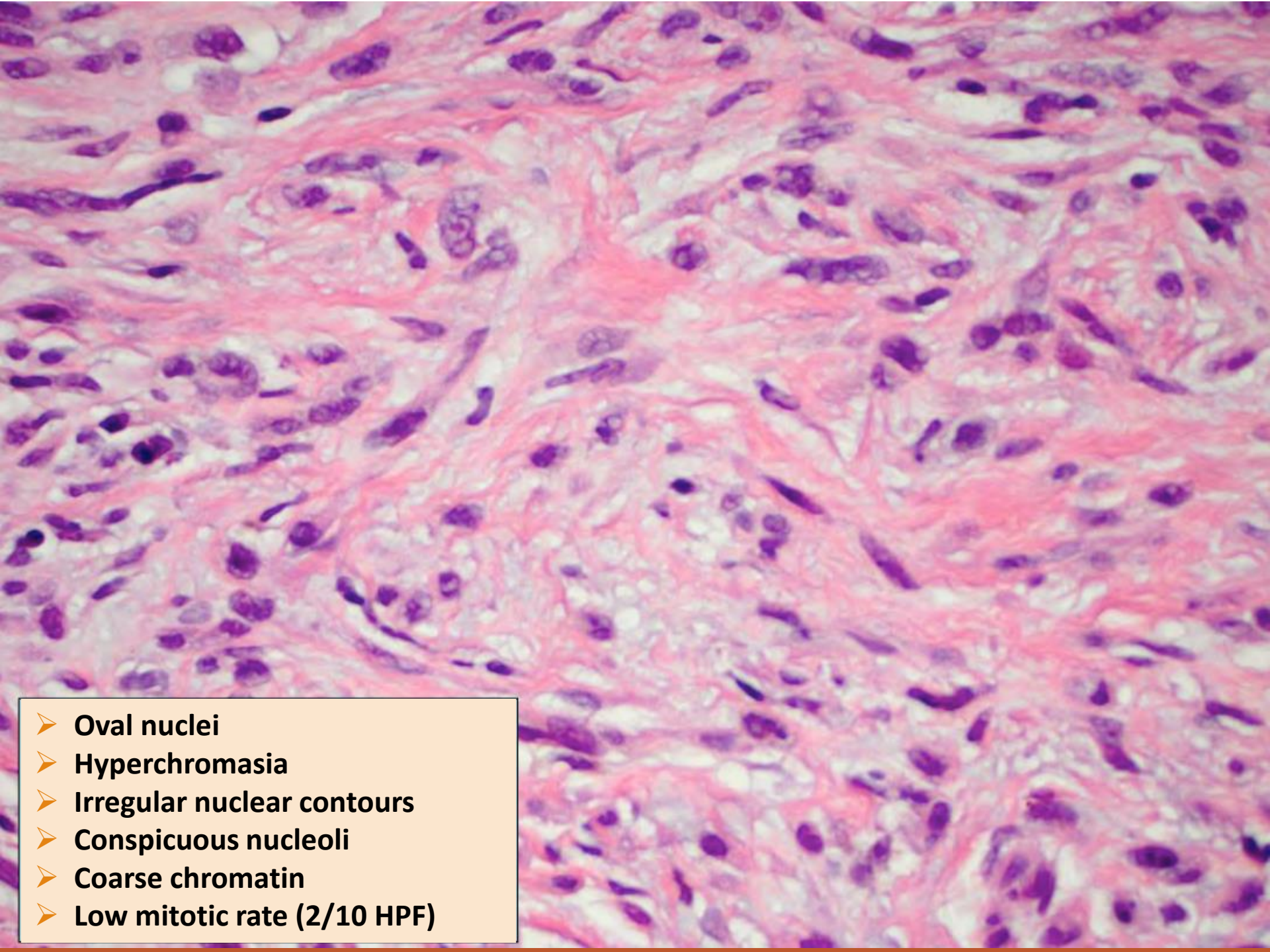

Atypical junctional melanocytic proliferation



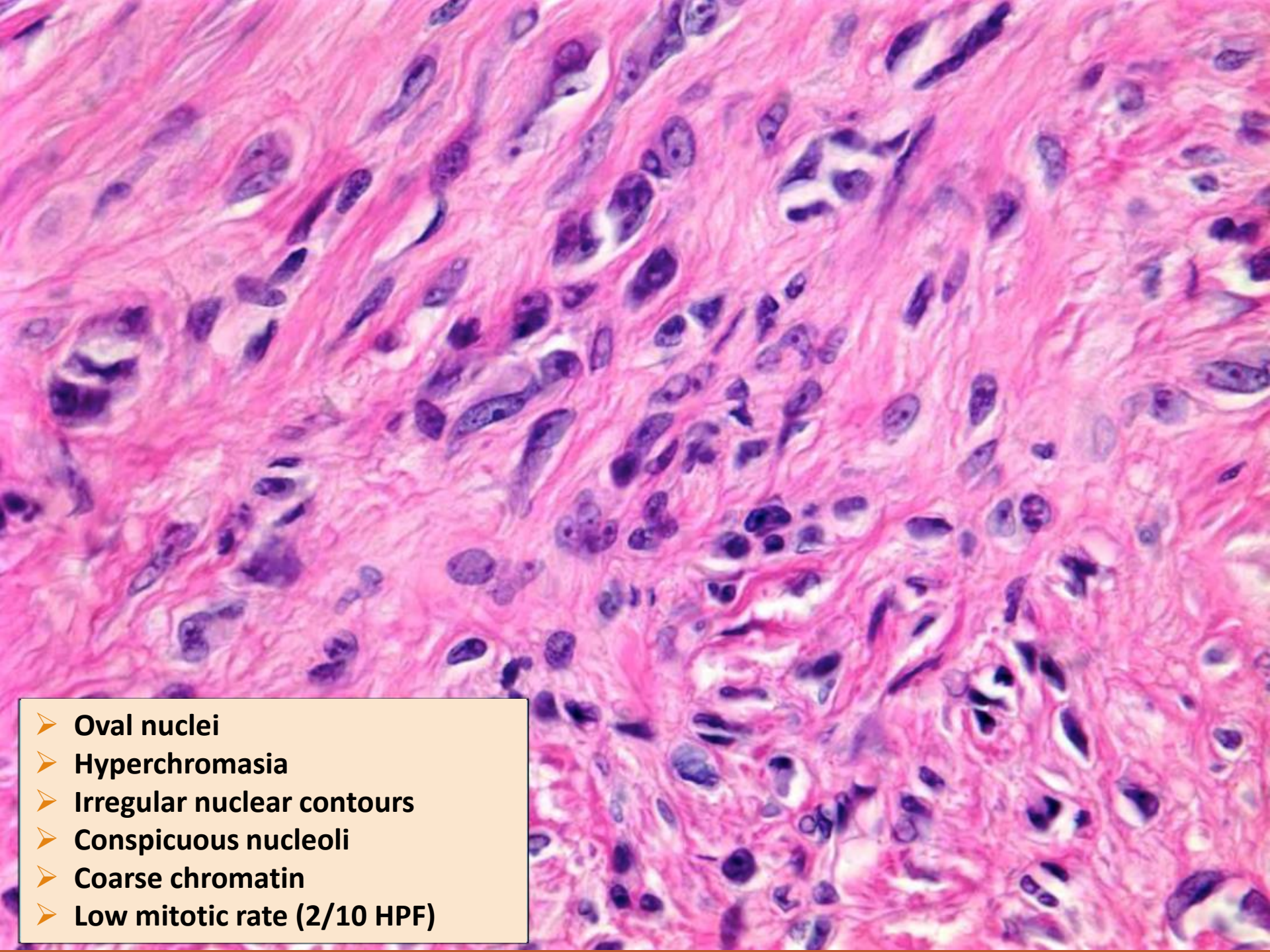
- **Markedly atypical junctional melanocytic proliferation c/w lentigo maligna**



- Relatively pleomorphic spindle cells
- Some are “fibroblast like”
- Spindle cytoplasmic processes merge with the background stroma



- Oval nuclei
- Hyperchromasia
- Irregular nuclear contours
- Conspicuous nucleoli
- Coarse chromatin
- Low mitotic rate (2/10 HPF)


Oval nuclei
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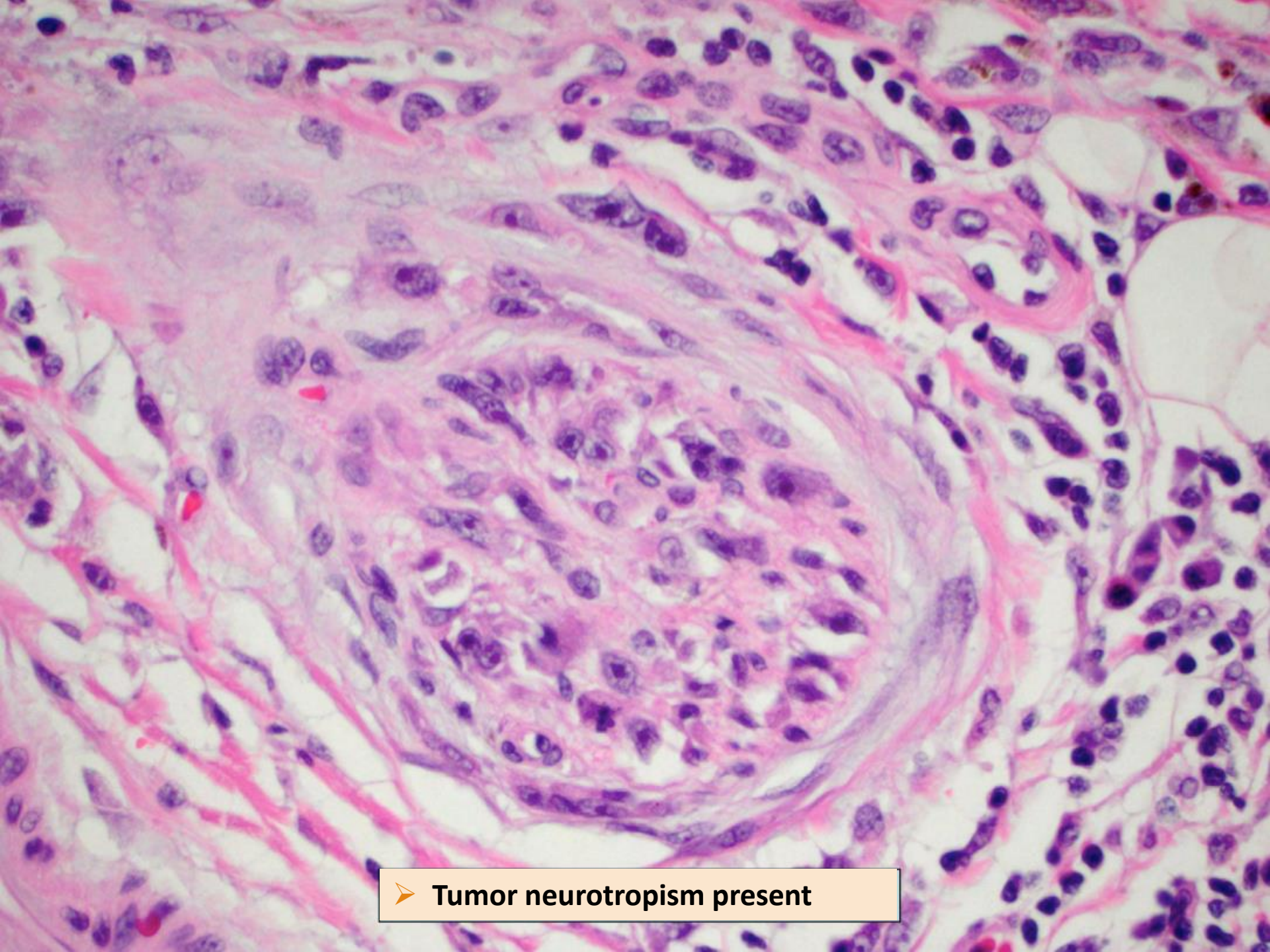
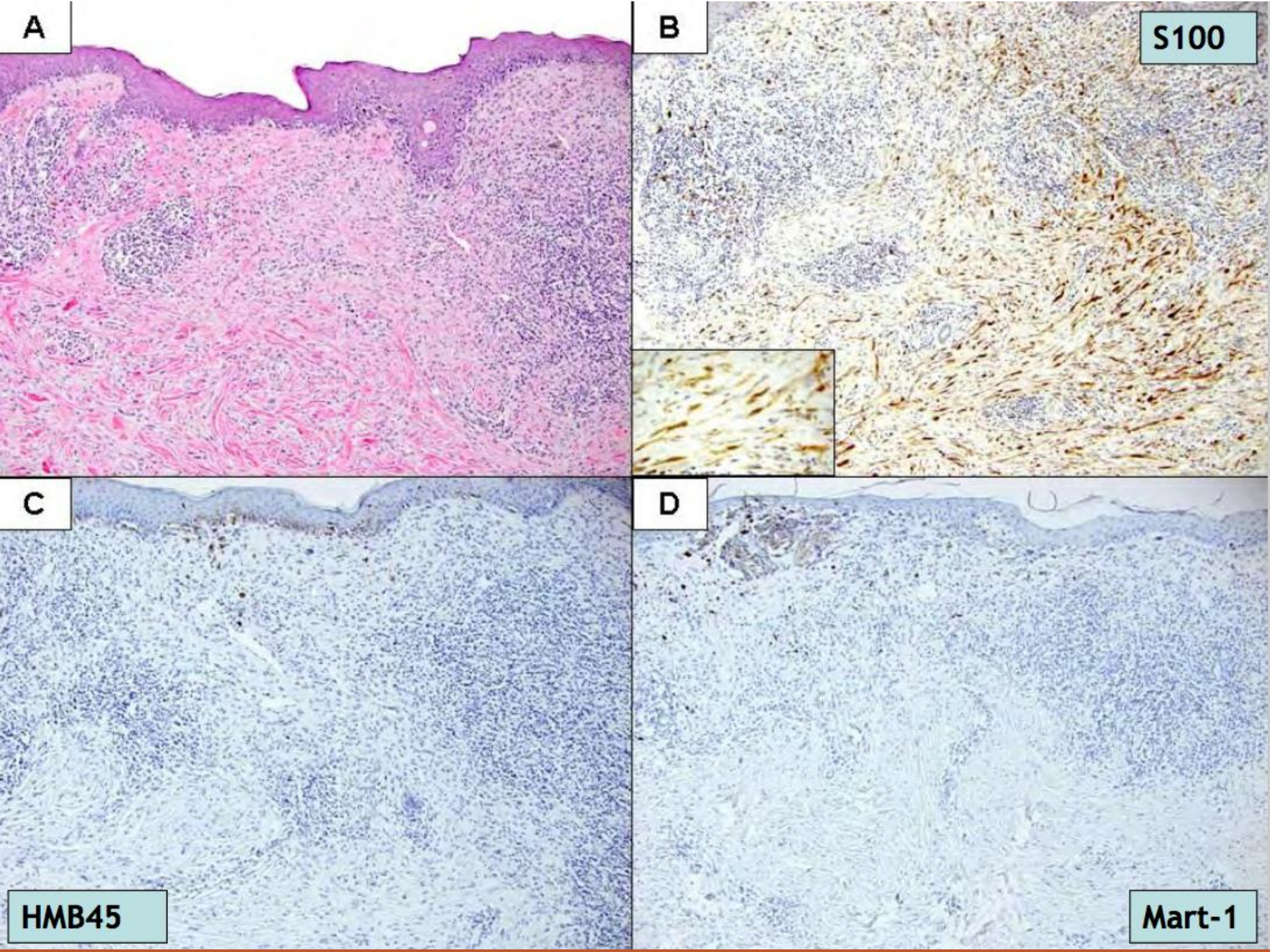
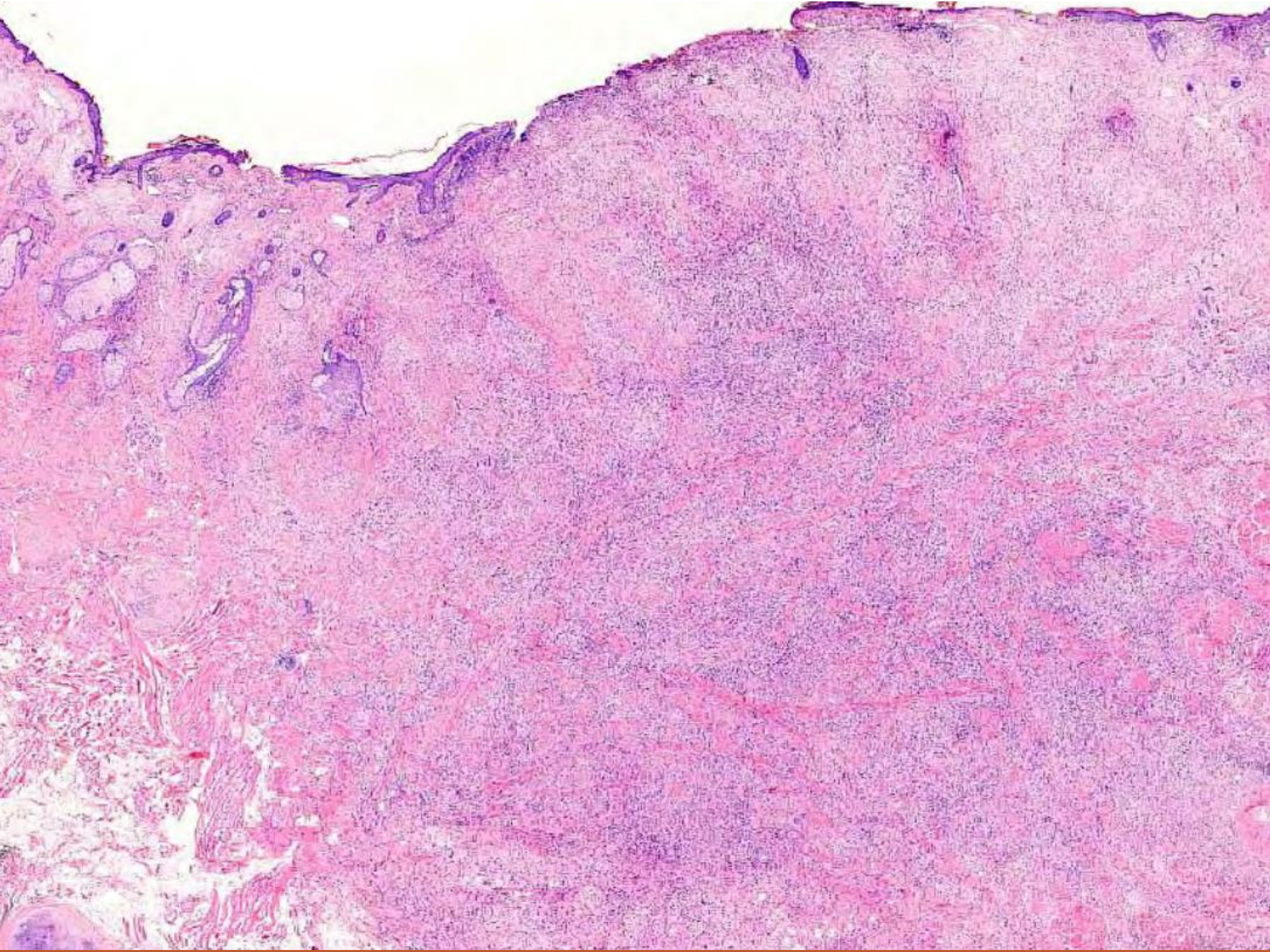
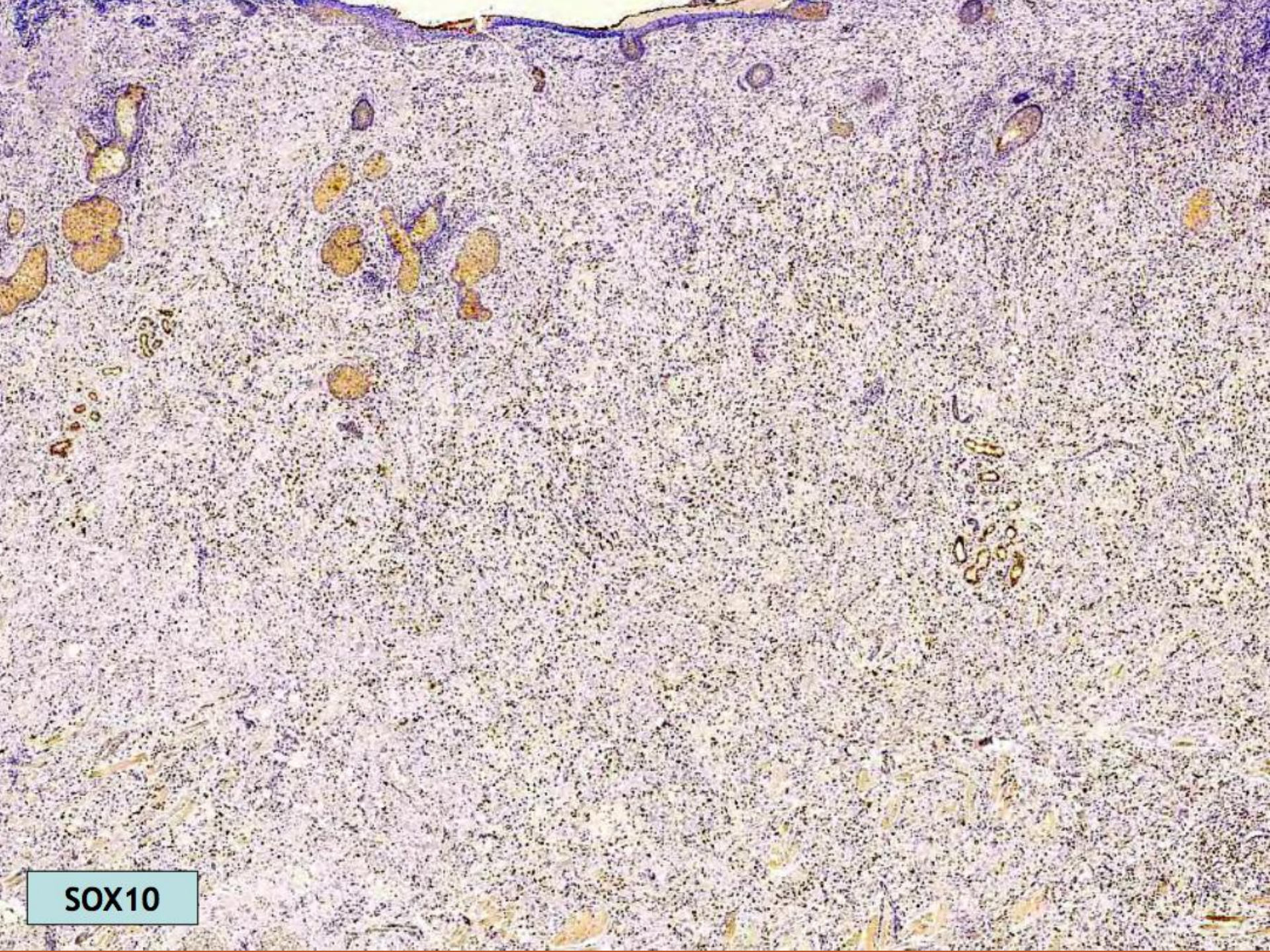

Tumor neurotropism present

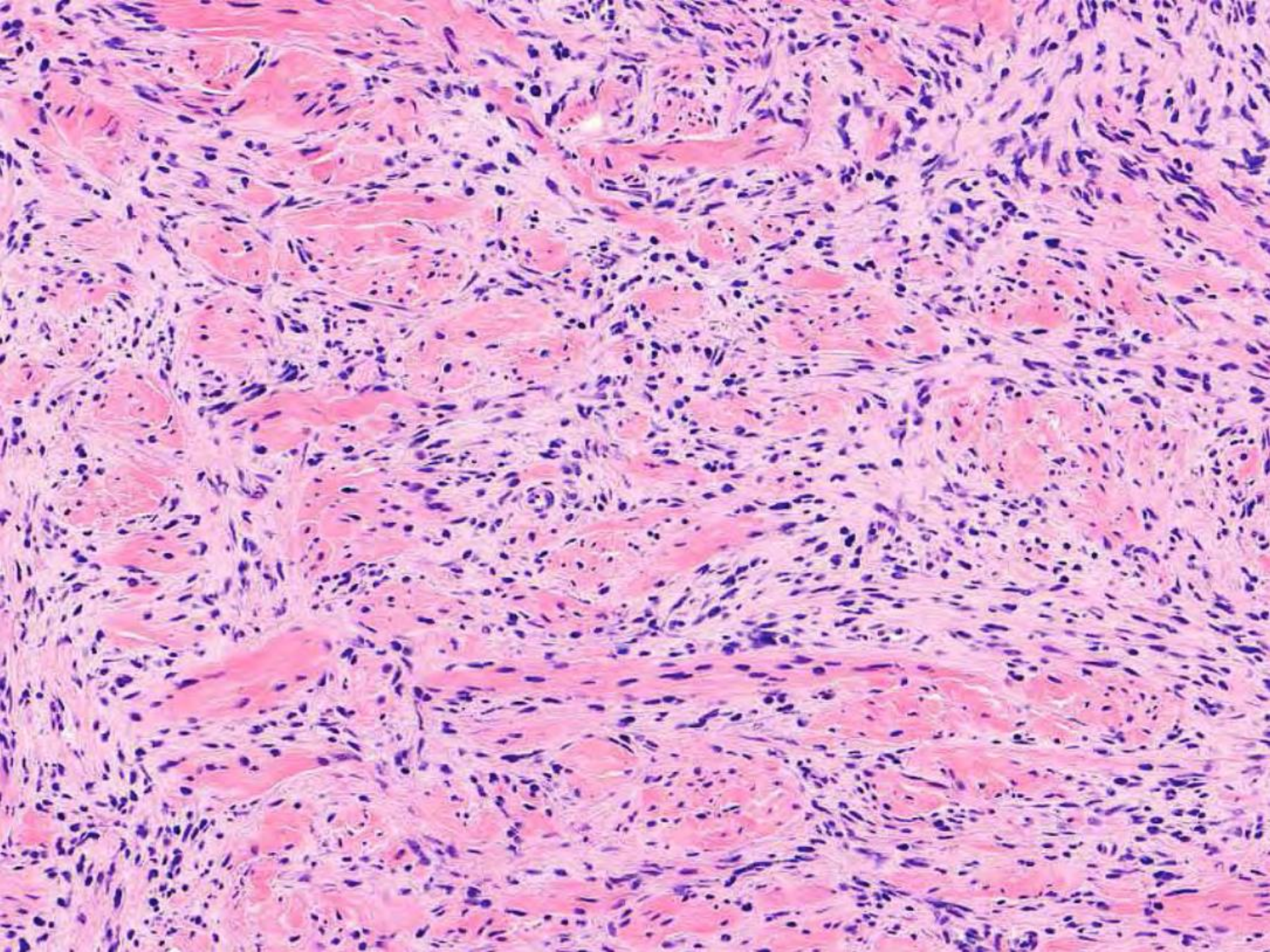
Desmoplastic Melanoma

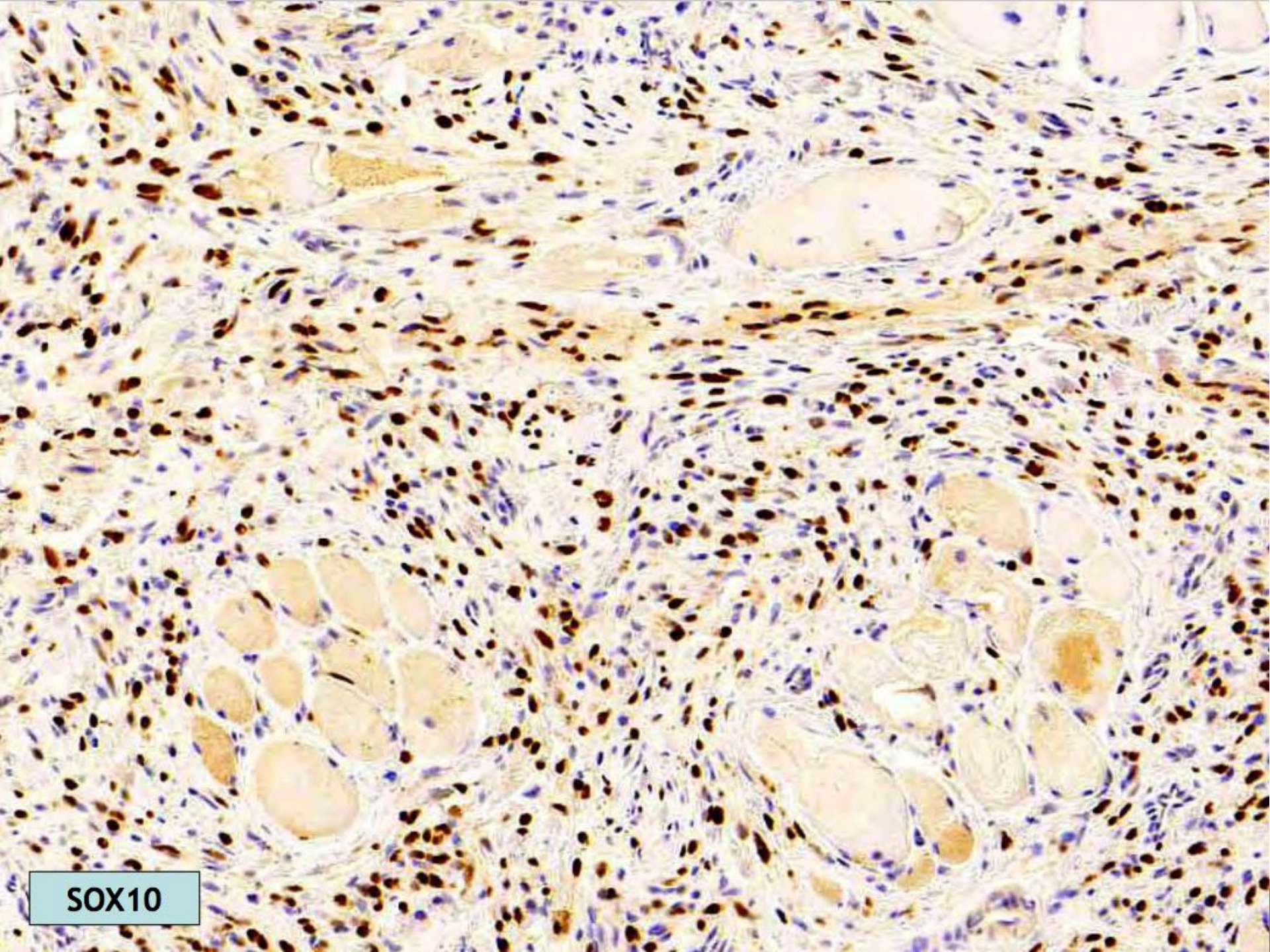
- **S100: diffuse and uniform positivity**
- **SOX10: diffuse and uniform nuclear positivity**
- **HMB45: differential staining in 20% of cases (positivity in the junctional component, or patchy dermal positivity in mixed variants)**
- **Ki-67: ≥10%**
- **P75 (NGFR): diffuse and uniform positivity**
- **Mart-1/Melan-A and MiTF: negative (except for the junctional component, or patchy dermal positivity in mixed variants)**


A
B
S100
C
HMB45
D
Mart-1




SOX10




SOX10

Fluorescent in situ hybridization (FISH)

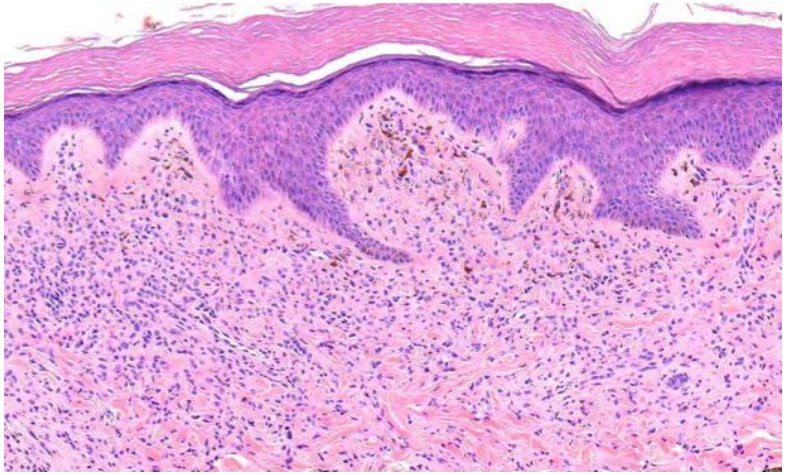
- **Probes:**
  - **6p25 (RREB1)**
  - **6q23 (MYB)**
  - **11q13 (CCND1)**
  - **CEP6**
- **Sensitivity: 47%**
- **Specificity: 100%**

Desmoplastic Melanoma - Ddx

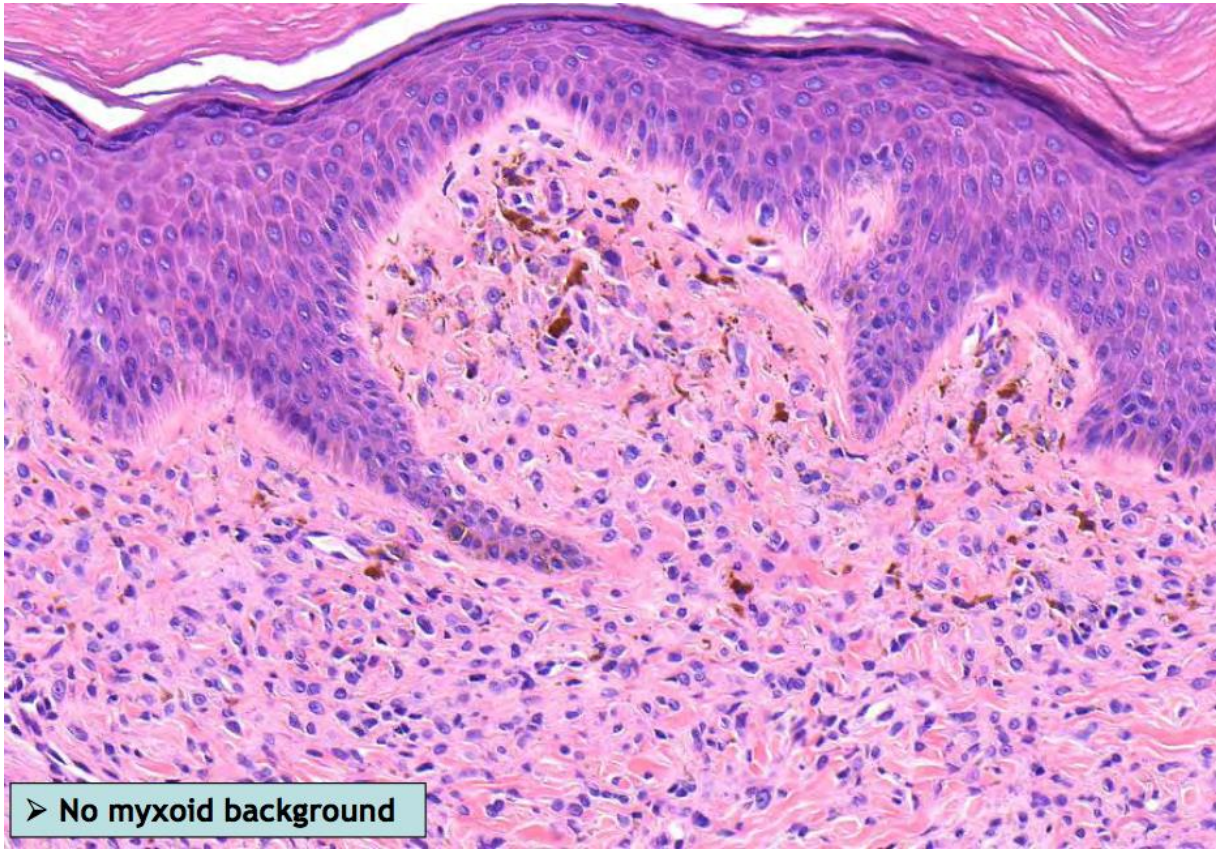
- Sclerosing nevus
- Sclerosing blue nevus
- Sclerosing Spitz nevus
- Dermatofibroma
- Scar
- Neurofibroma
- Malignant Peripheral Nerve Sheath Tumor (MPNST)
- Neurocristic hamartoma
- Atypical spindle cell proliferations; NOS
  - Sarcomatoid squamous cell carcinoma
  - Atypical fibroxanthoma (“AFX”)
  - Dermatofibrosarcoma protuberans
  - Atypical fibrohistiocytic tumors

Sclerosing Melanocytic Nevus

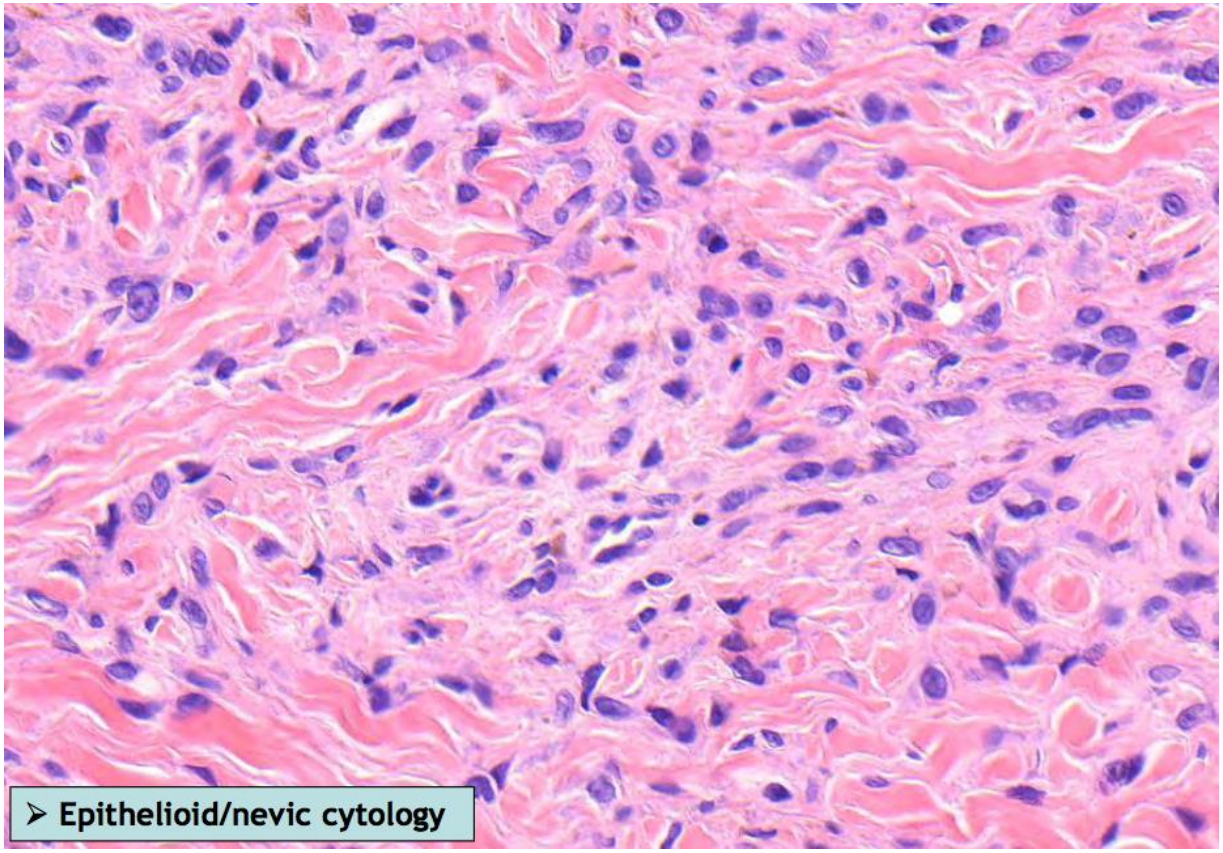
- No myxoid/mucinous background
- Lack of atypical junctional component (often)
- Maturation present
- Mart-1 is diffusely positive in tumor cells
- SOX10 is negative

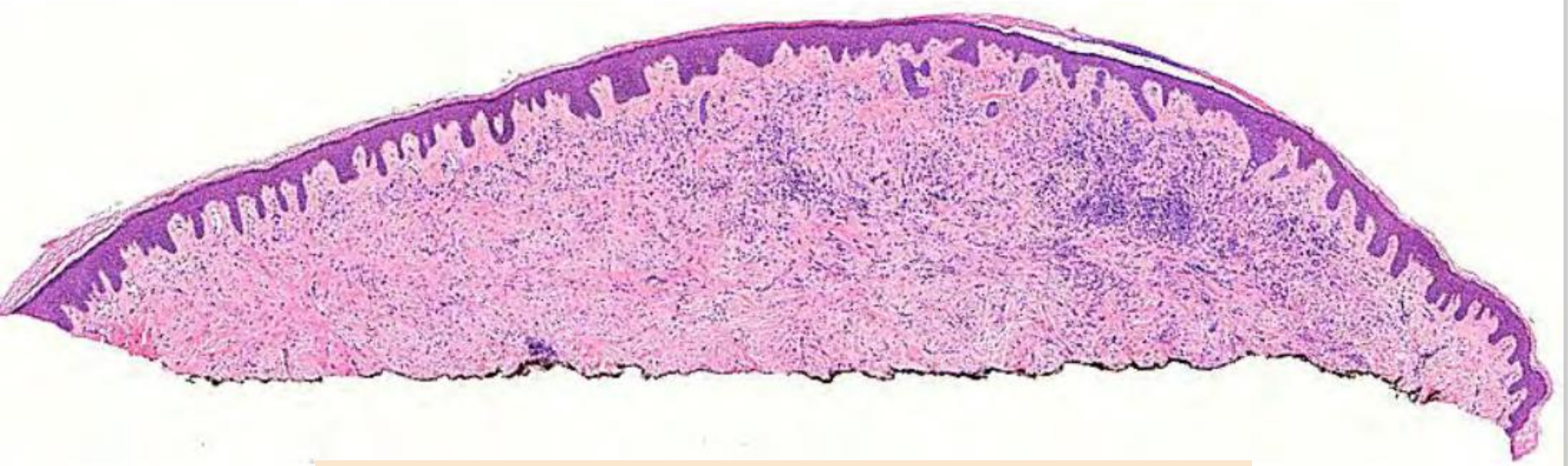


Sclerosing Melanocytic Nevus

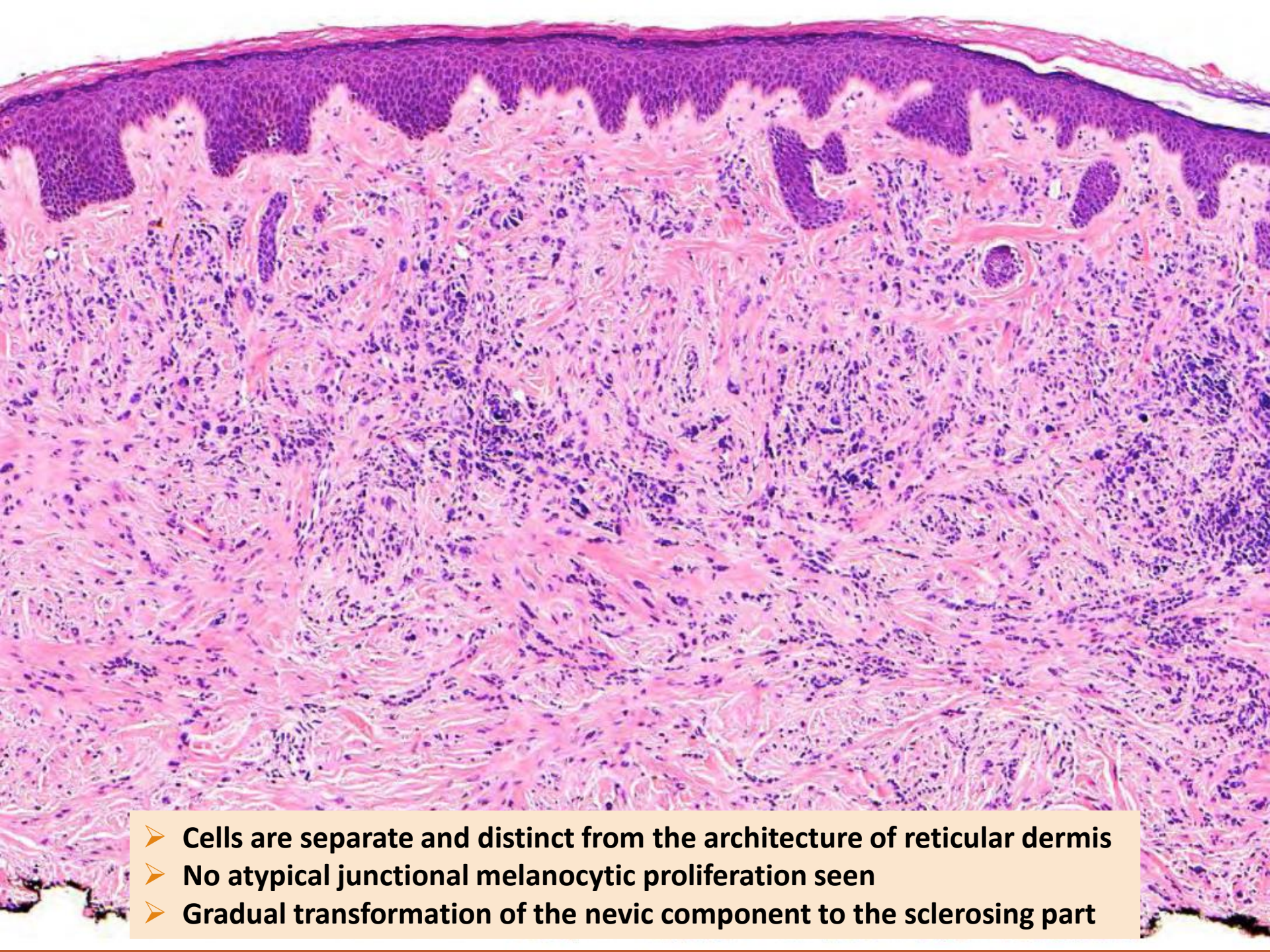


Sclerosing Melanocytic Nevus

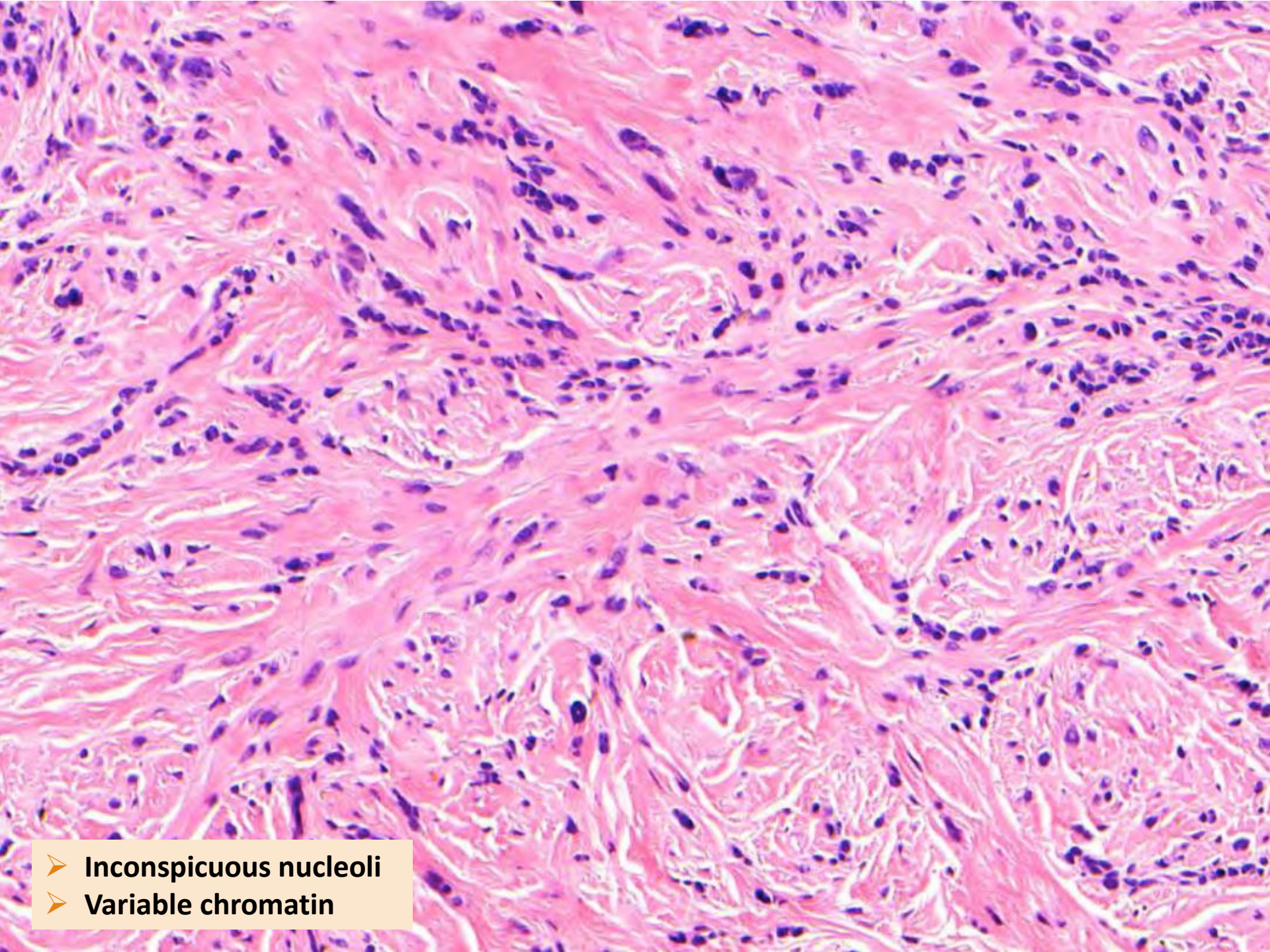


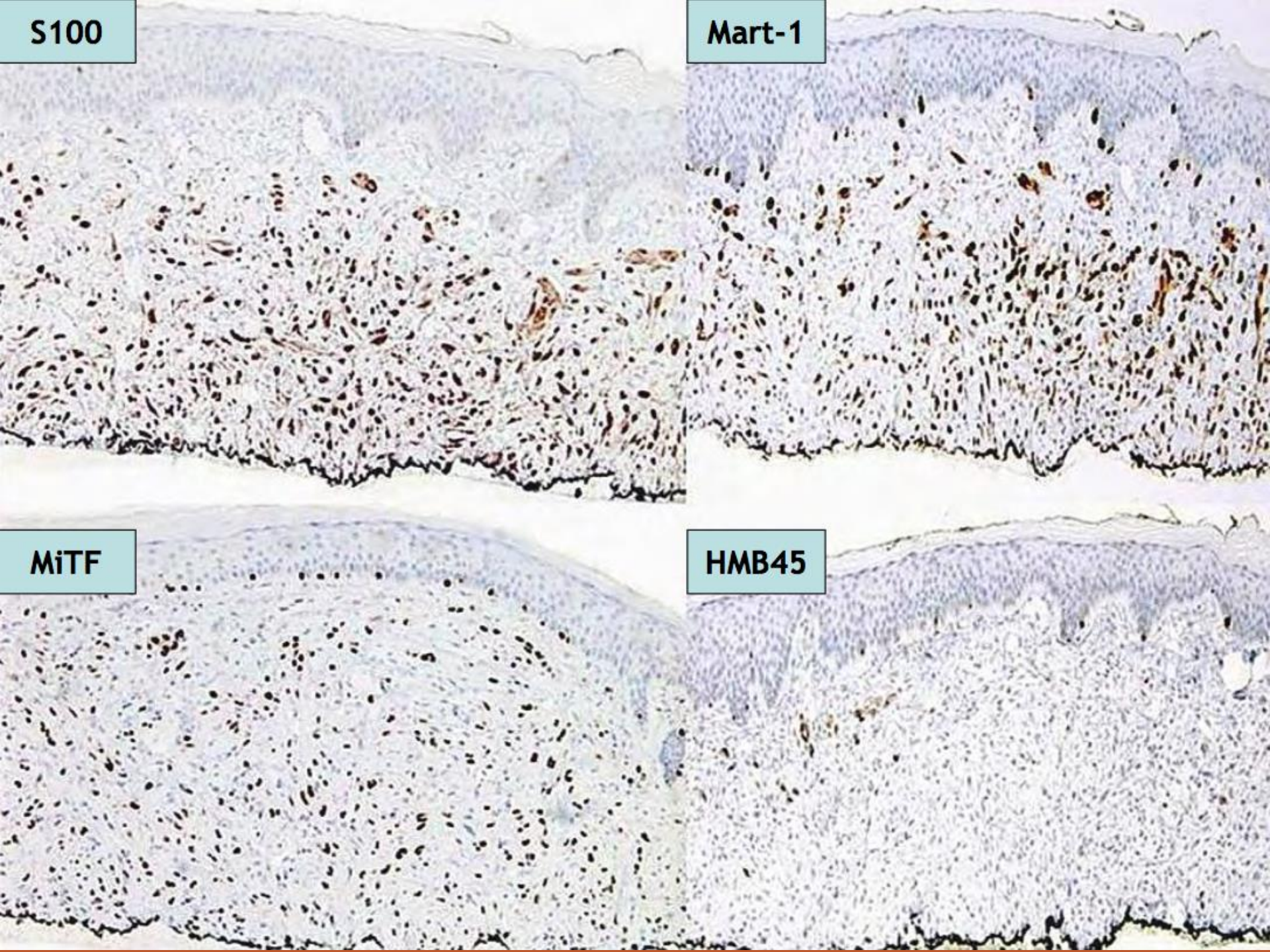


- Single cells and nests infiltrate a collagenous stroma
- Inflammation is usually absent
- Epidermis is not atrophic
- Cellularity is low



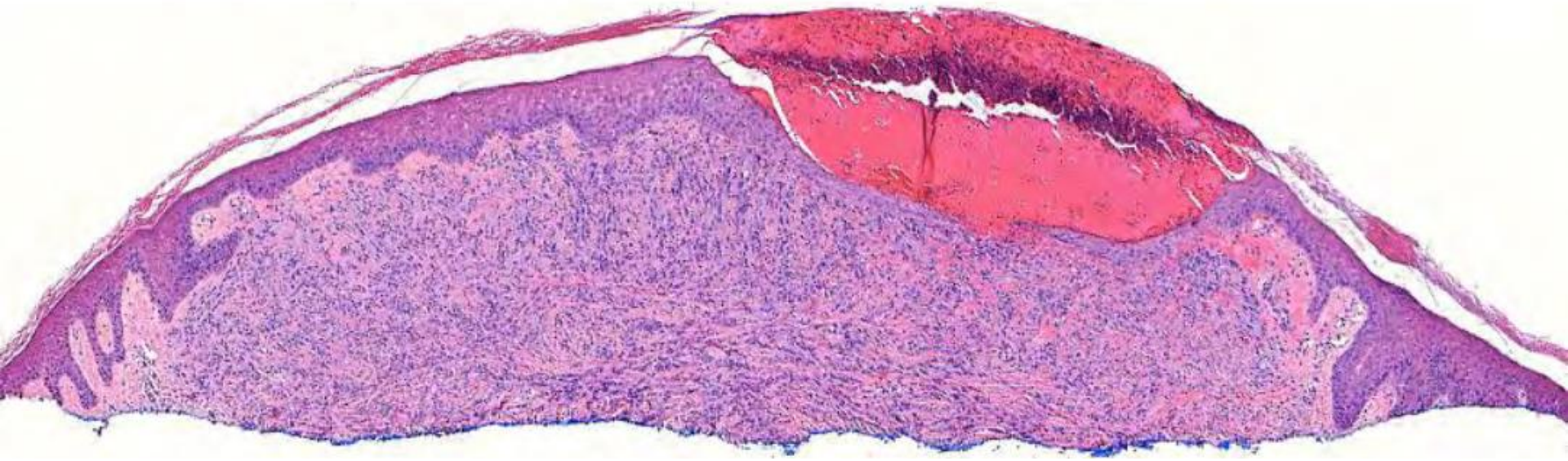
- Cells are separate and distinct from the architecture of reticular dermis
- No atypical junctional melanocytic proliferation seen
- Gradual transformation of the nevic component to the sclerosing part


Inconspicuous nucleoli
Variable chromatin


S100
Mart-1
MiTF
HMB45

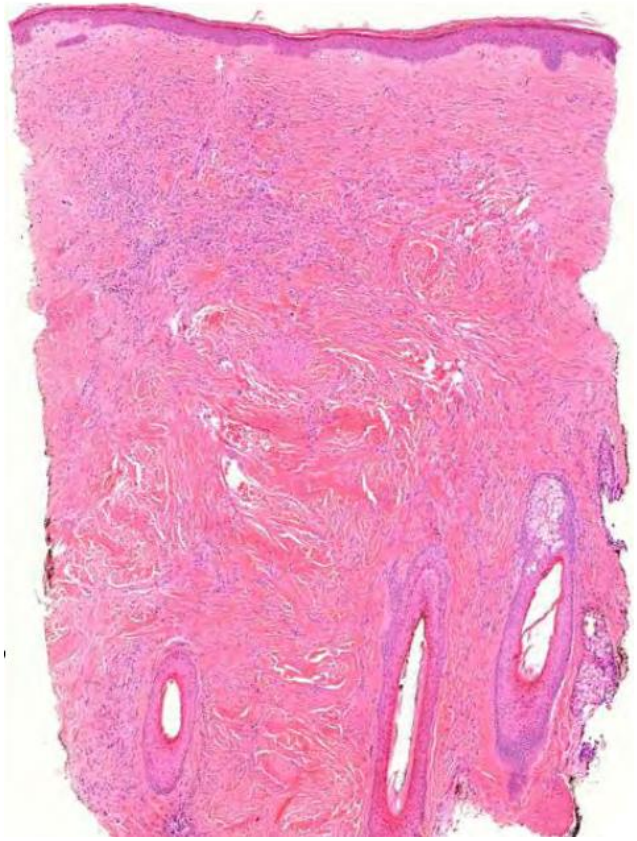
Spindle Cell Melanoma

- Architecture & cytology
- Cellularity
- Marked cytologic atypia
- Lack of maturation
- Mitotic activity
- HMB45 positivity
- High Ki-67 proliferative index



Sclerosing Blue Nevus

- No myxoid/mucinous background
- Lack of junctional component (except for combined nevus)
- Central zone of fibrosis
- Very bland cytology
- Spares the adventitia of hair follicles
- Mart-1 and HMB45 are diffusely positive in tumor cells
- SOX10 is negative



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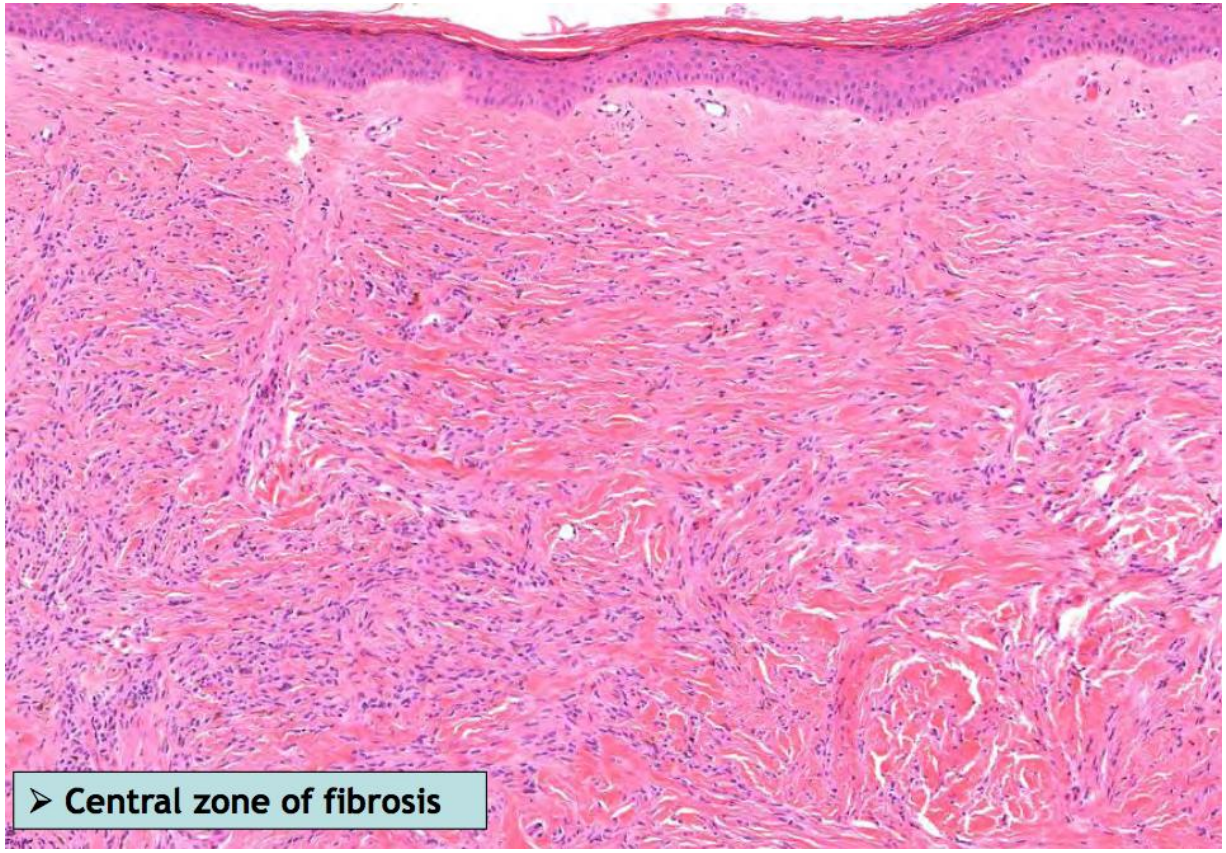
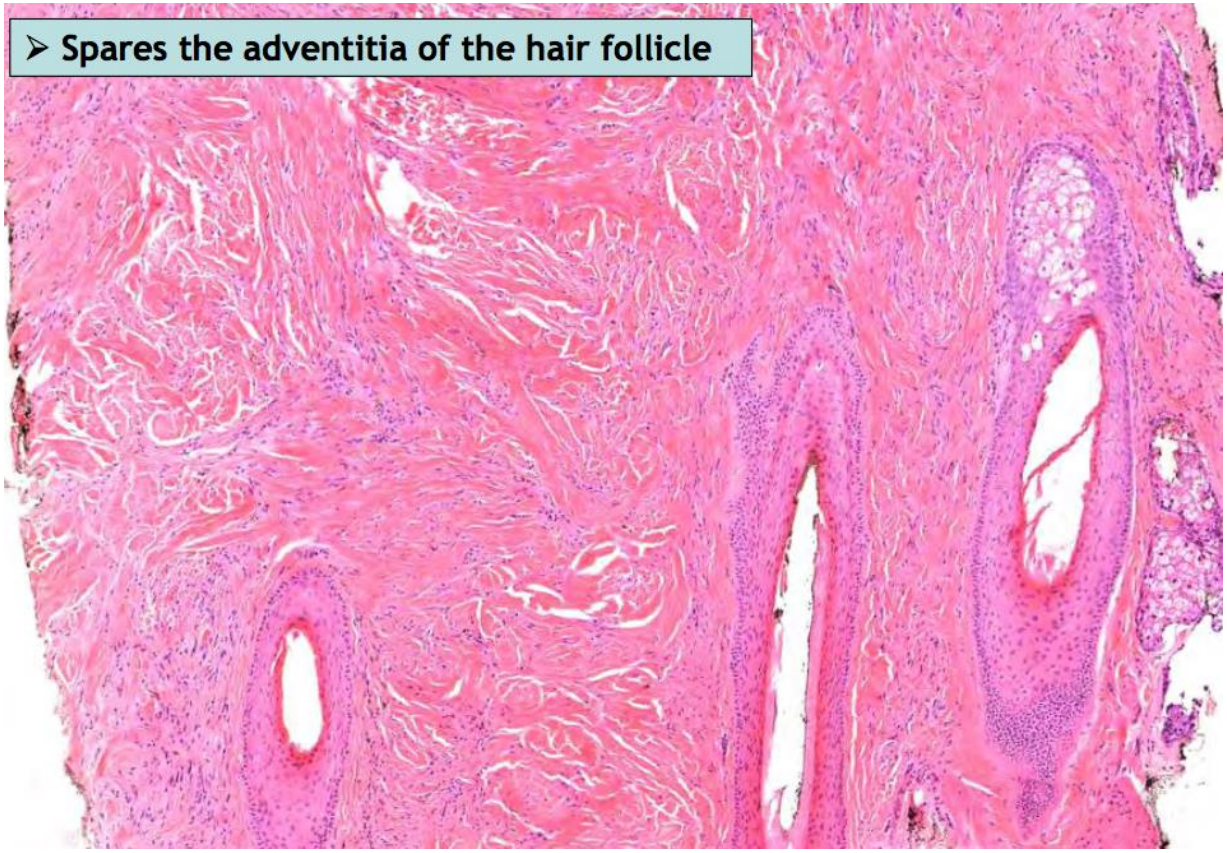
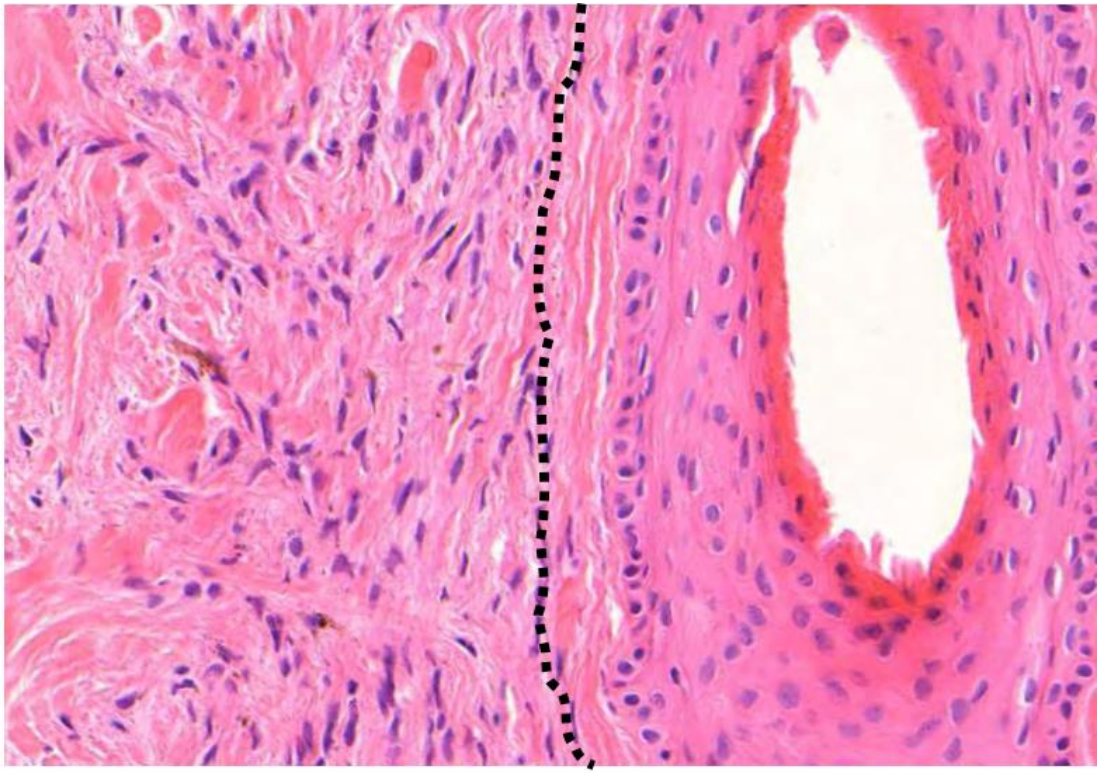


Sclerosing Blue Nevus

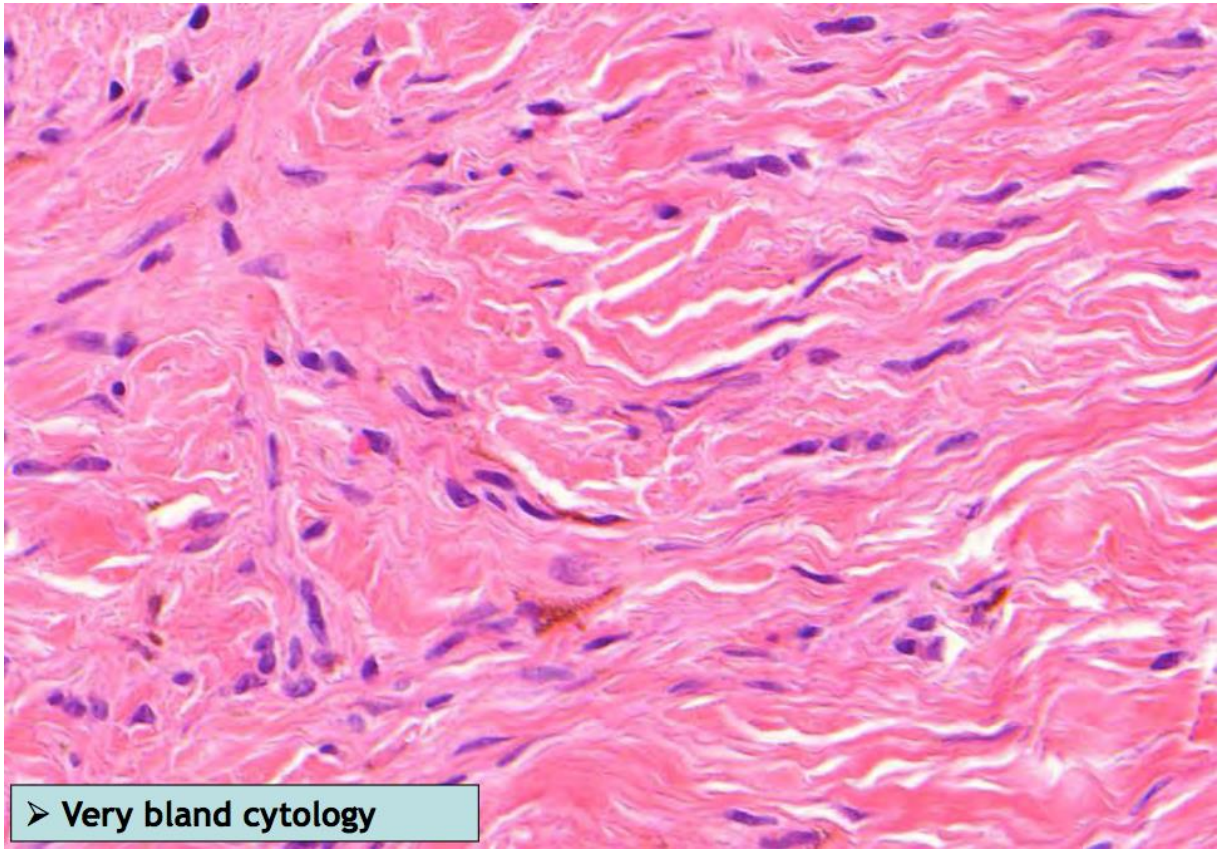


Sclerosing Blue Nevus



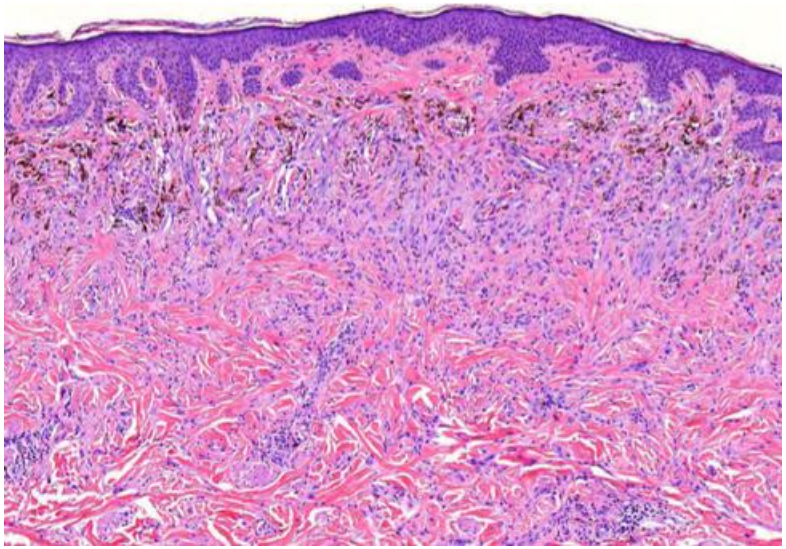
- Spares the adventitia of the hair follicle

Sclerosing Blue Nevus

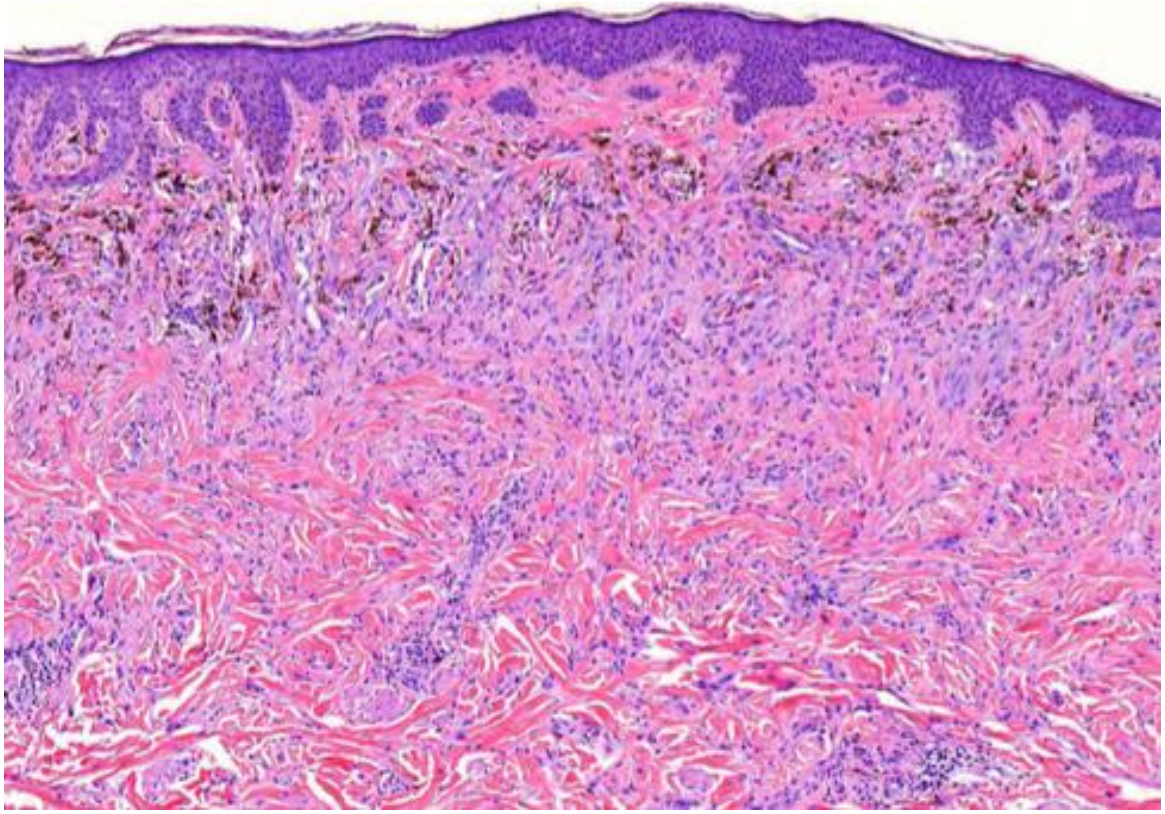


Sclerosing Spitz Nevus

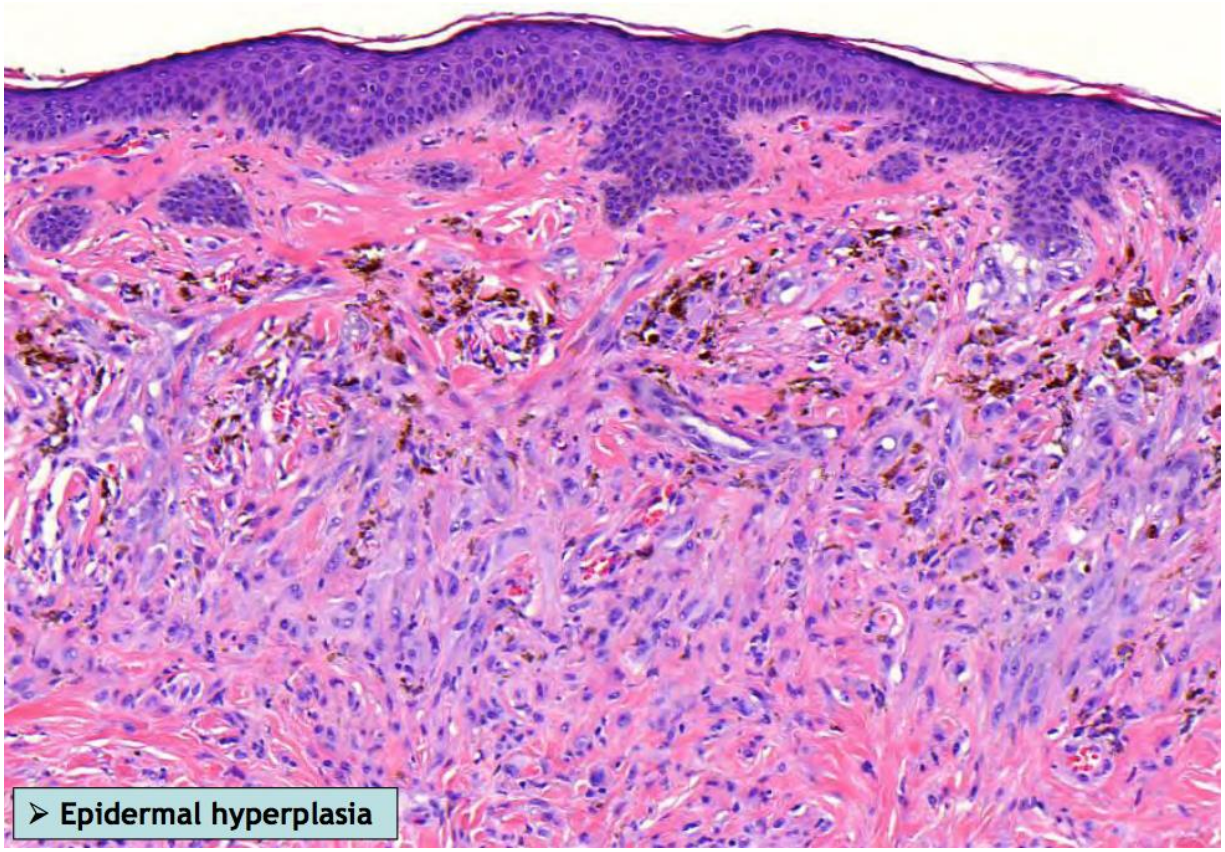
- No myxoid/mucinous background
- No junctional component (except for compound/combined variants)
- More symmetric, wedge shaped, and absence of deep extension
- Absence of solar damage
- Epidermal hyperplasia
- Presence of maturation and no deep mitoses
- Absence of inflammation and neurotropism
- Mart-1 is usually positive and SOX10 is negative



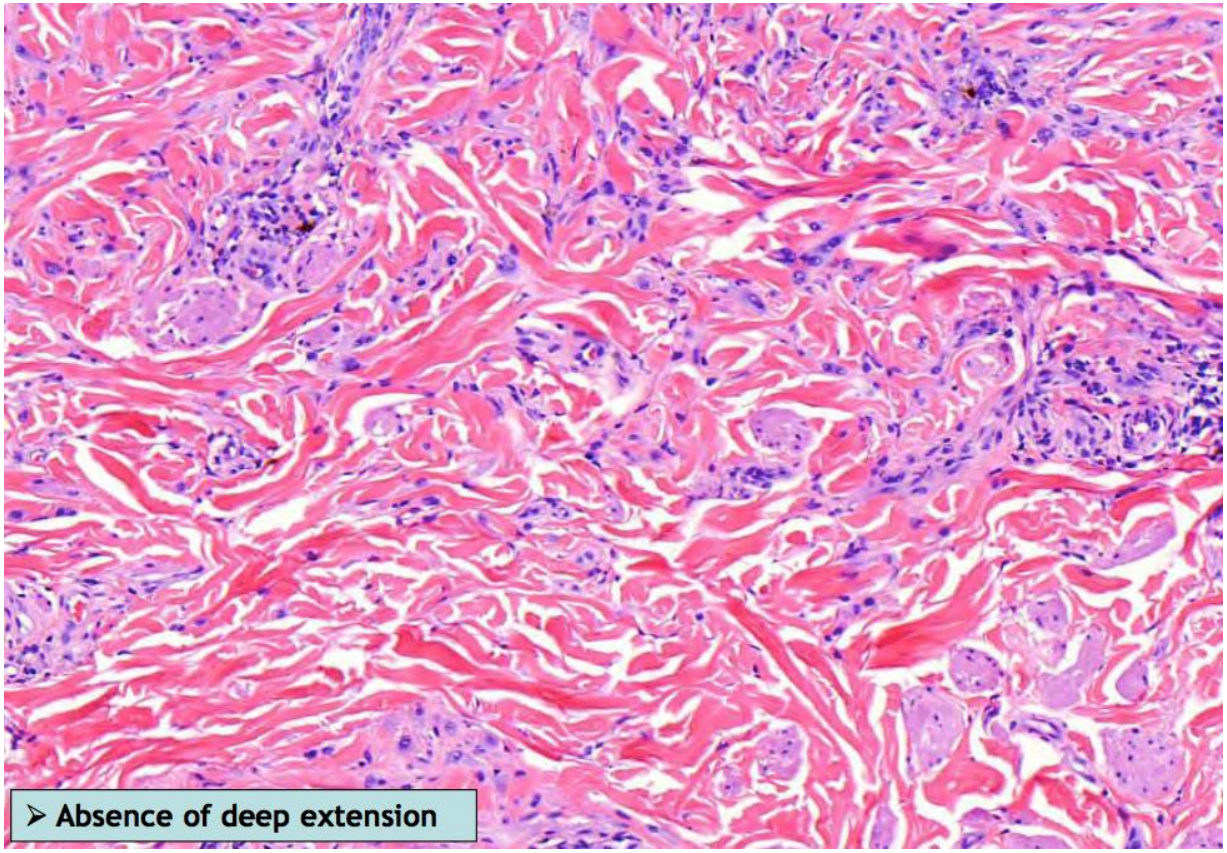
Sclerosing Spitz Nevus



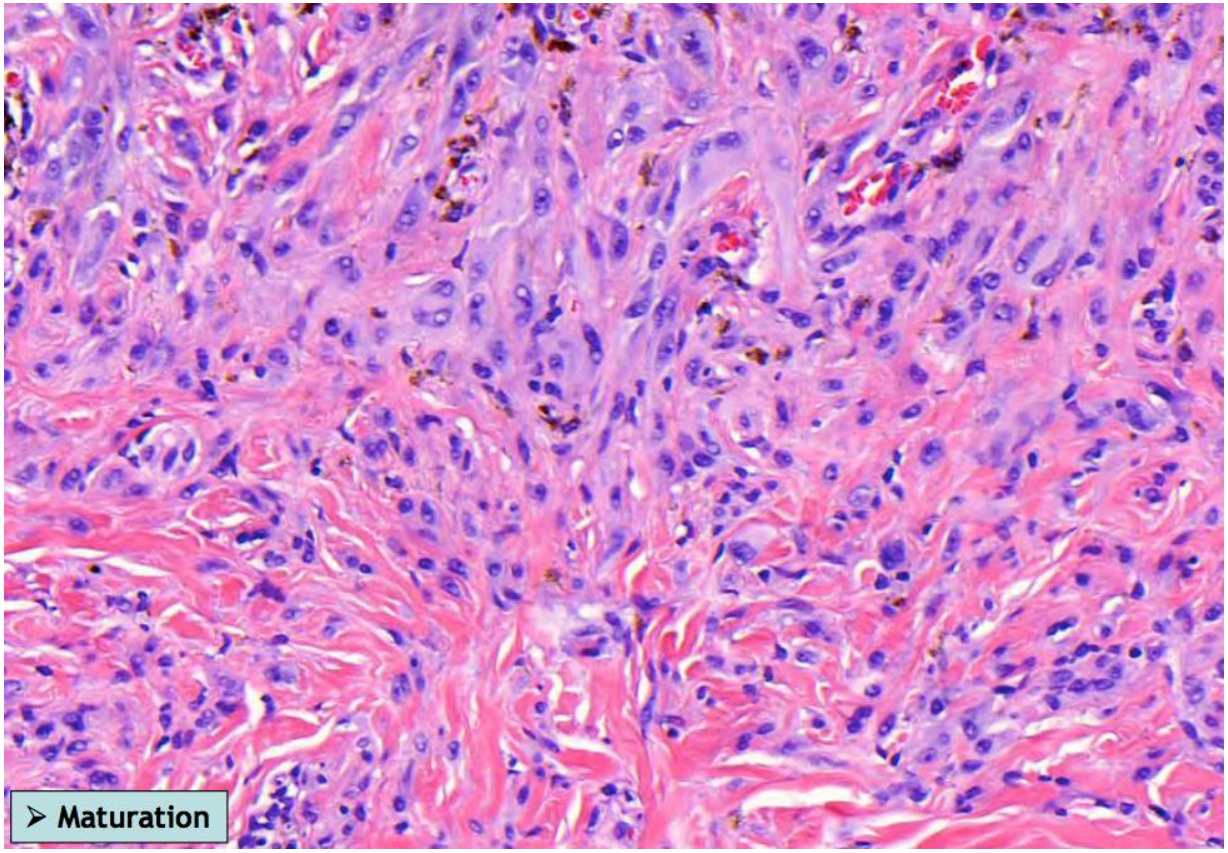
Sclerosing Spitz Nevus



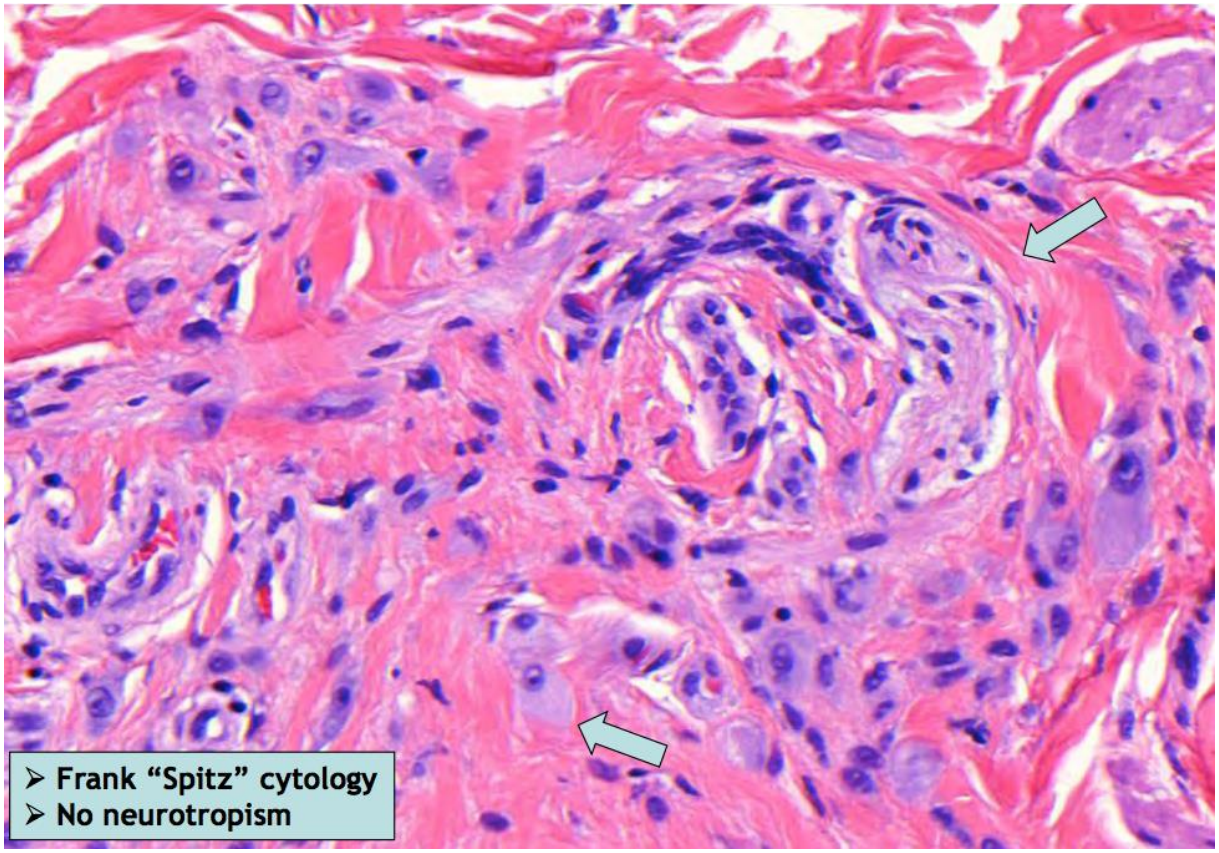
Sclerosing Spitz Nevus



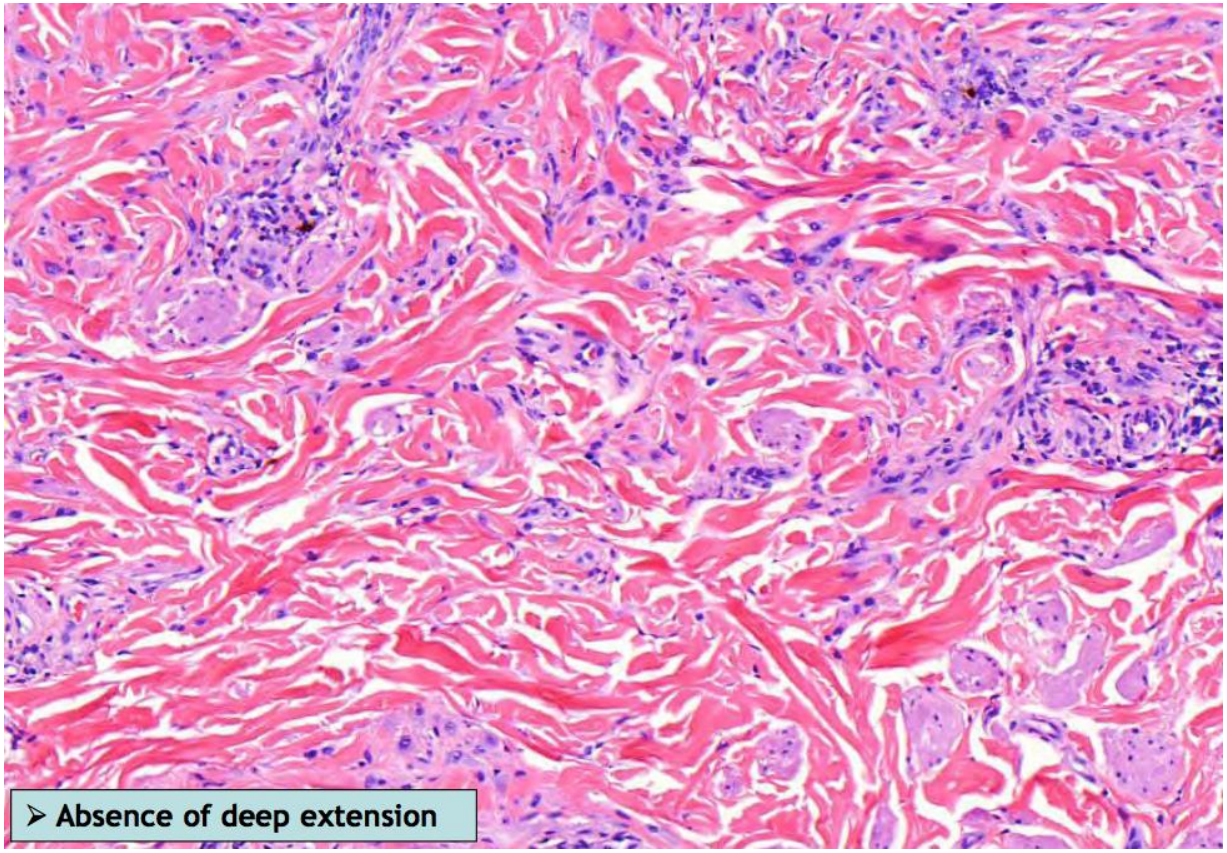
Sclerosing Spitz Nevus



Sclerosing Spitz Nevus

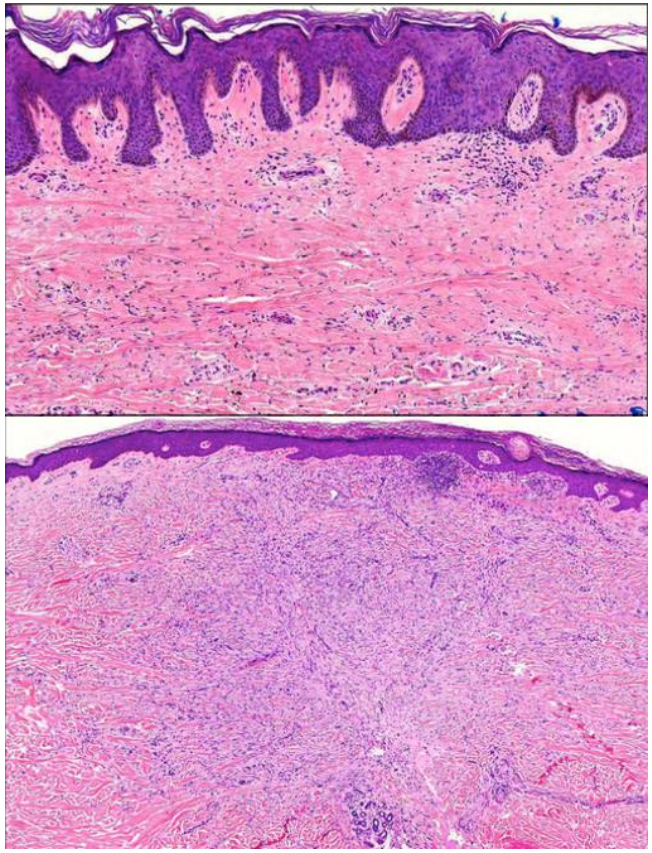


Sclerosing Spitz Nevus

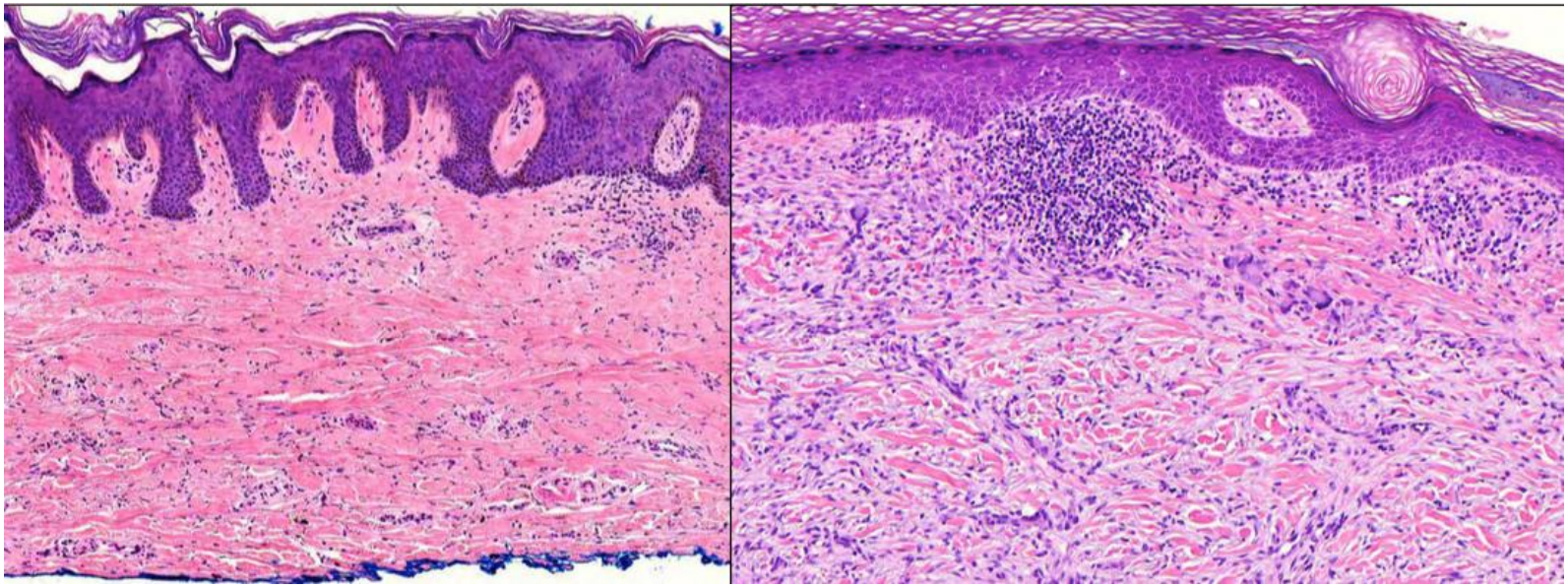


Dermatofibroma

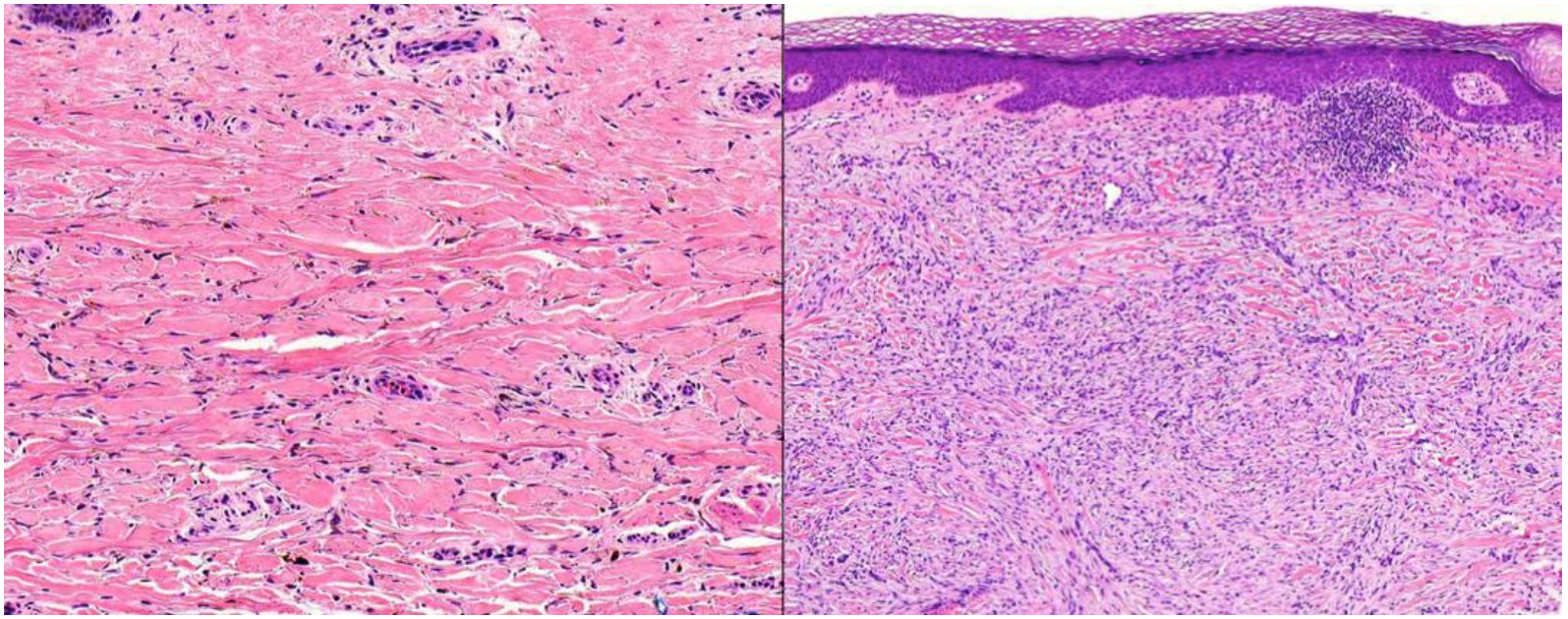
- Architecture & cytology are often very helpful in its discrimination
- Traumatized and superficial dermatofibromas are difficult to distinguish
- They may also show superficial S100 positivity in the dendritic cells
- SOX10 is negative



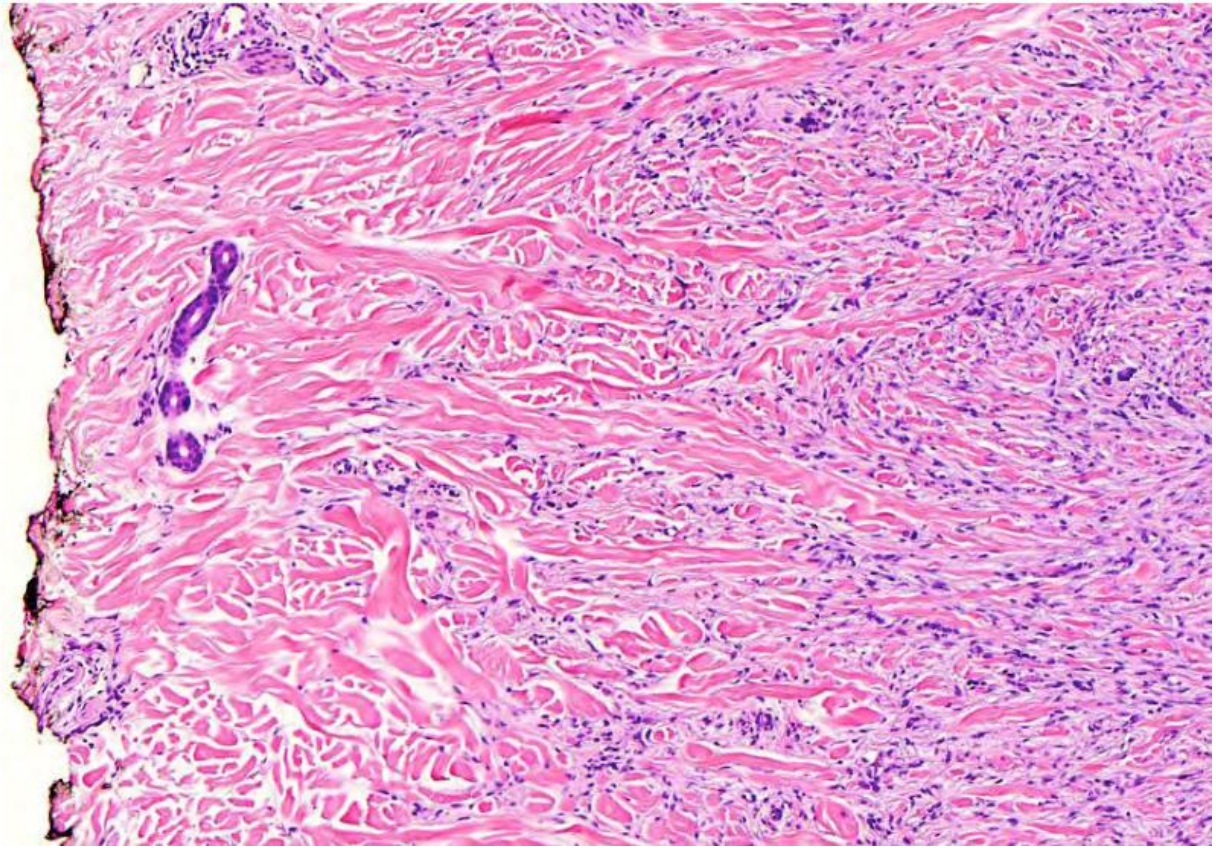
Dermatofibroma



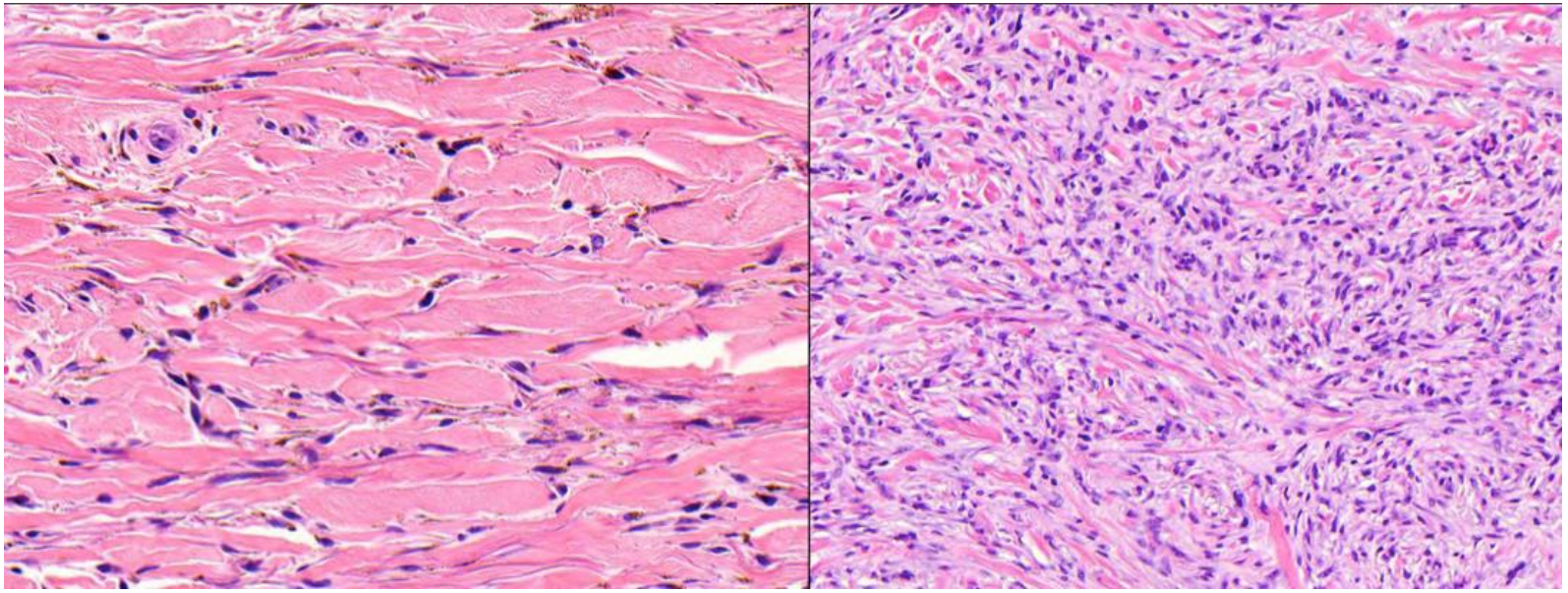
Dermatofibroma



Dermatofibroma

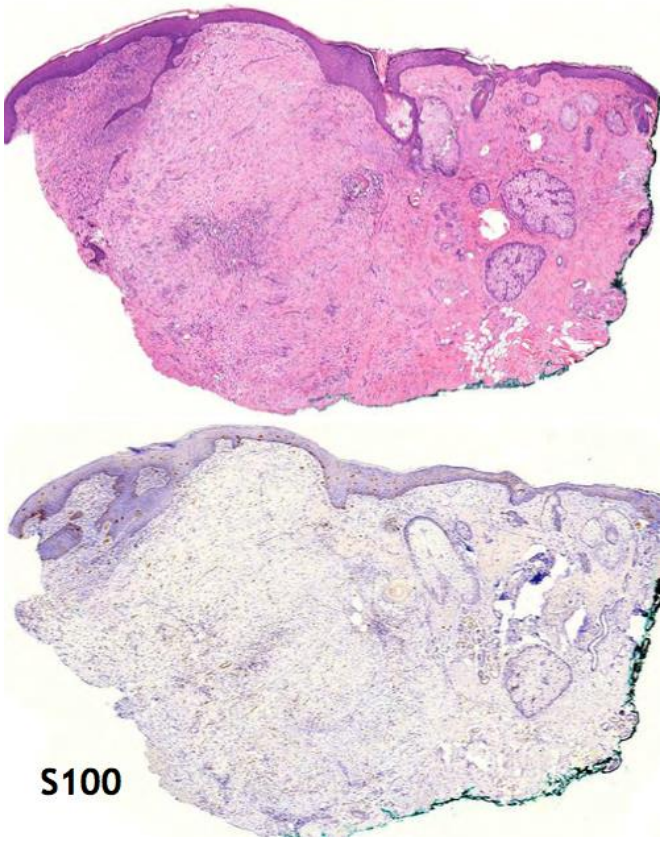


Dermatofibroma

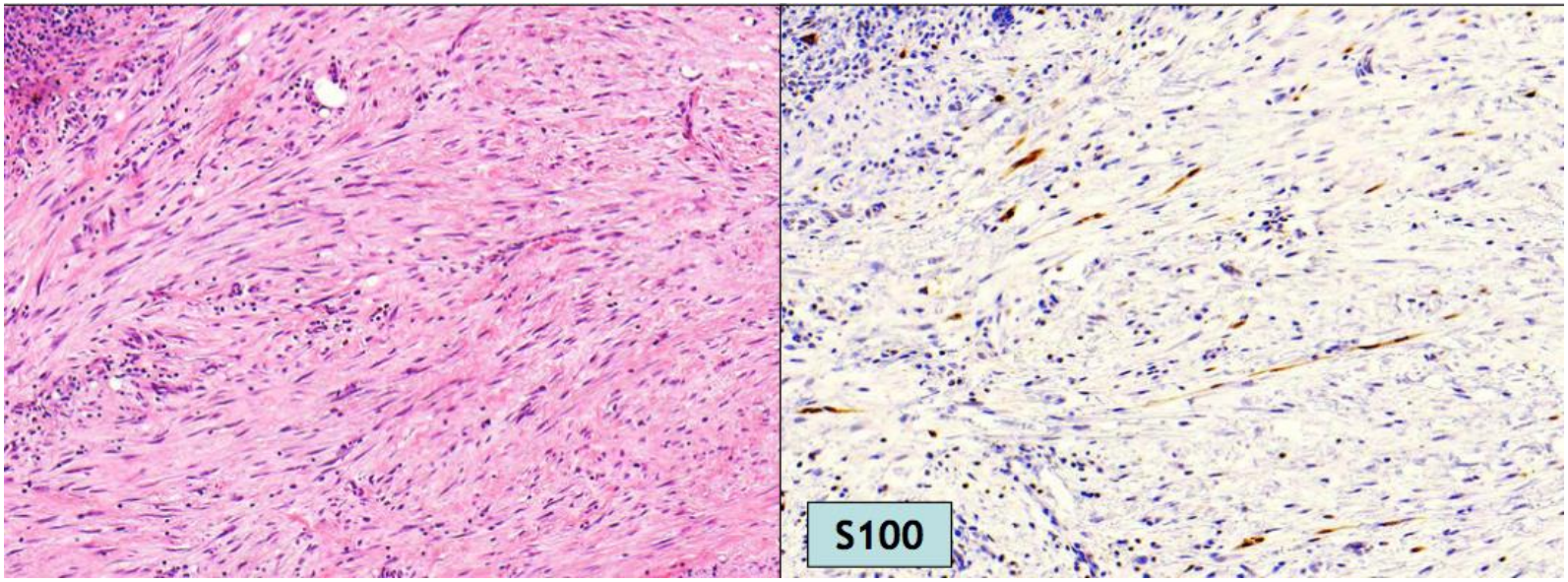


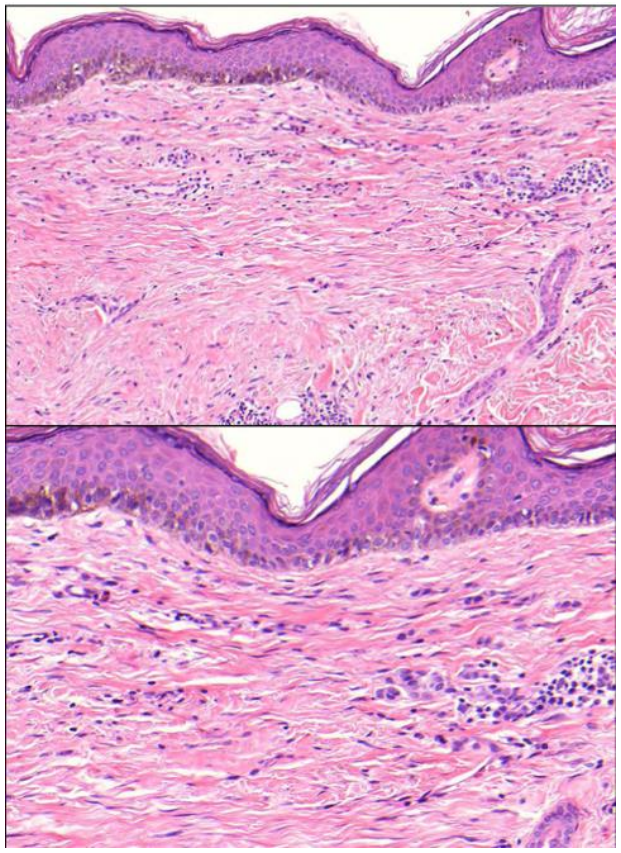
Scar

- Architecture can be deceiving
- Absence of a junctional component
- Be aware of the dermal scar tissue of the recurrent nevus phenomenon vs desmoplastic melanoma w/ junctional component
- S100 can focally stain dendritic cells in the scar and difficult to interpret
- A negative SOX10 is the most helpful immunostain

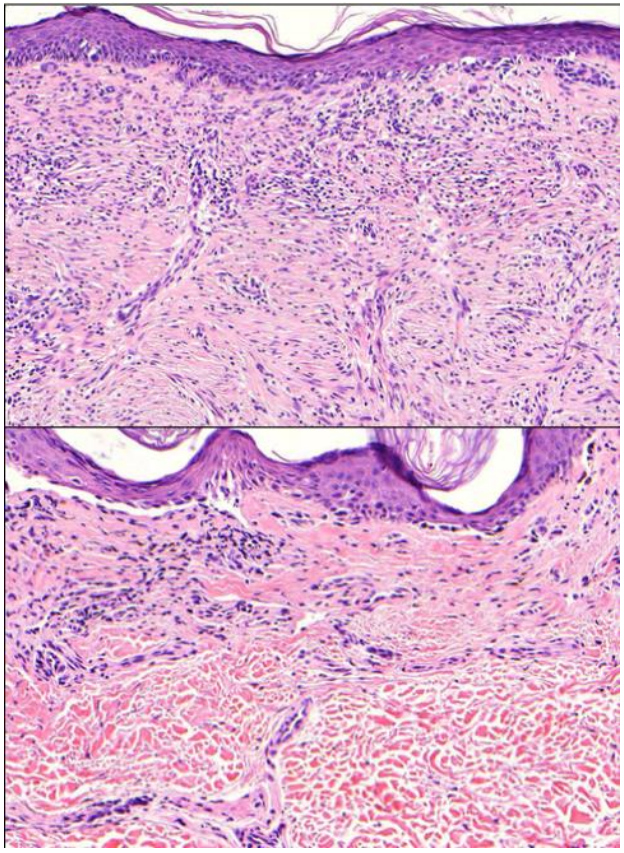


Scar





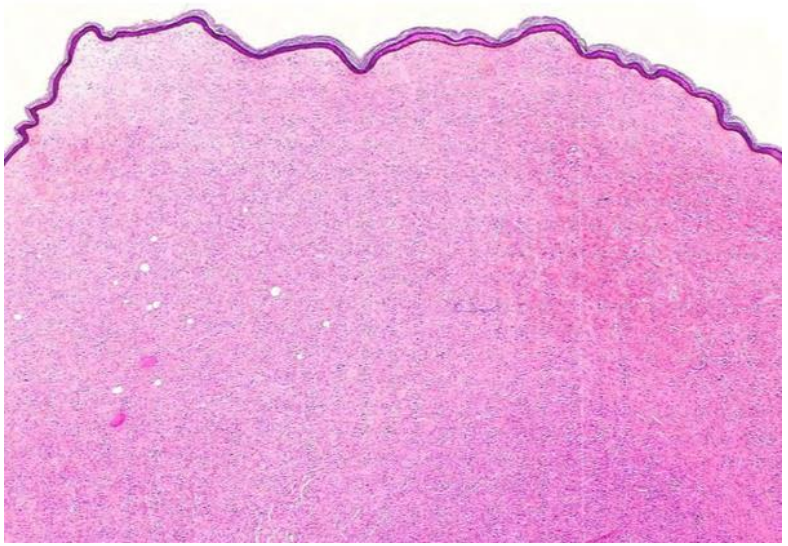
Recurrent MN



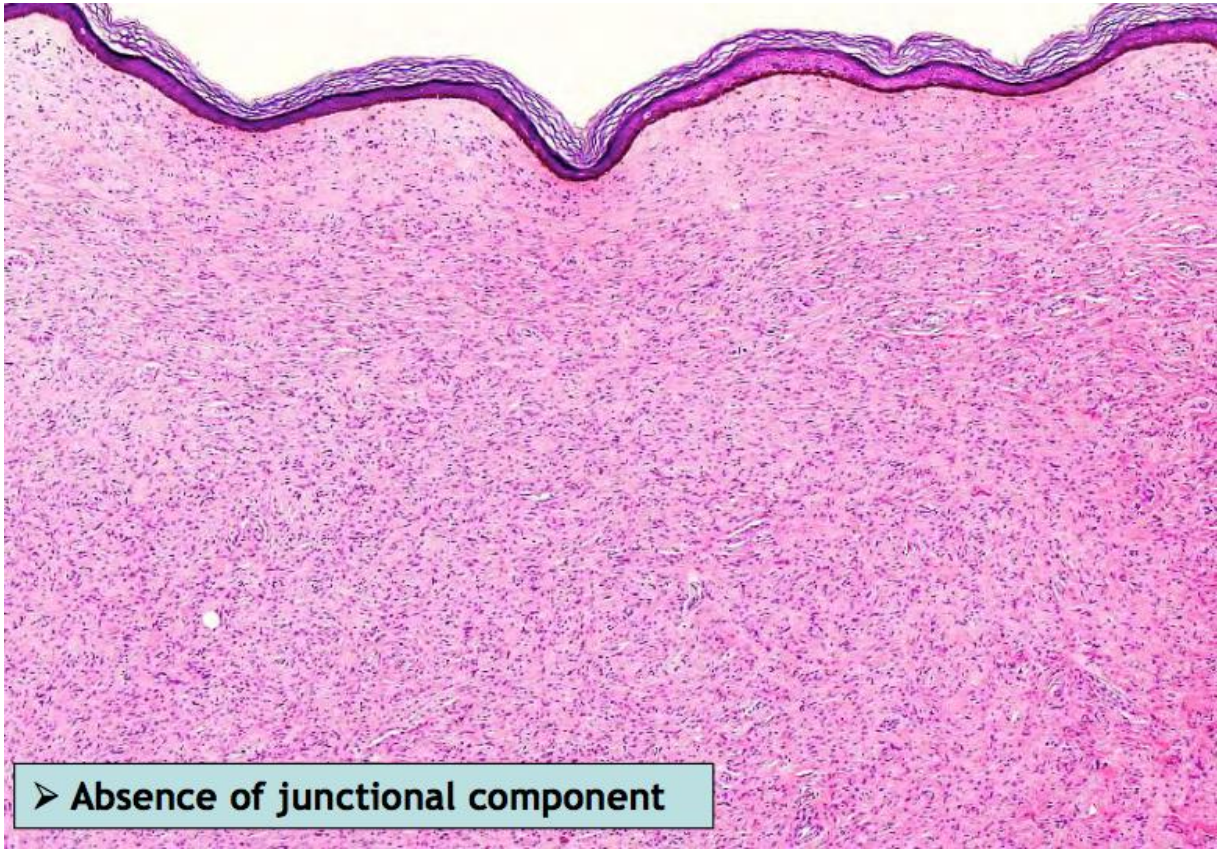
Desmoplastic MM

Neurofibroma

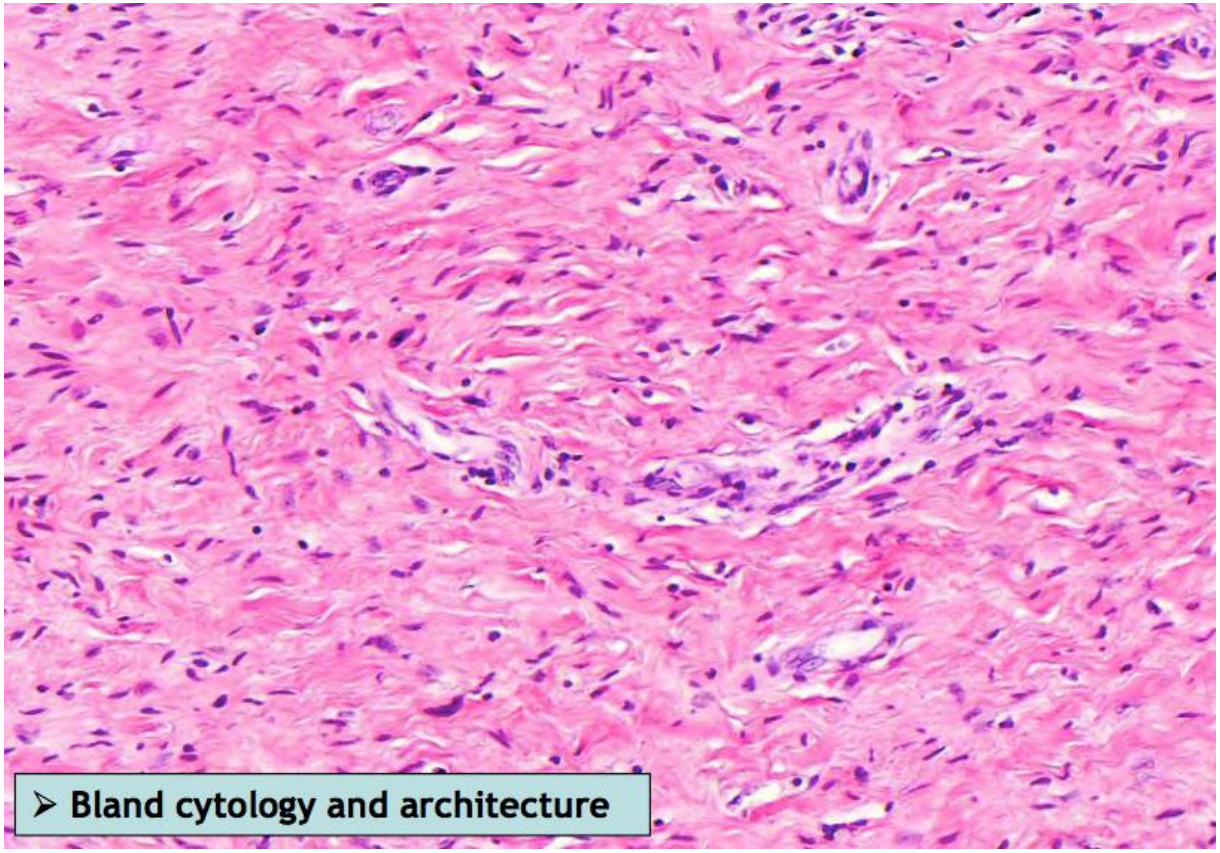
- Architecture and cytology are often very helpful in its discrimination
- Absence of a junctional component
- S100 and SOX10 postivity are not useful
- Any Mart-1 or HMB45 positivity may help



Neurofibroma

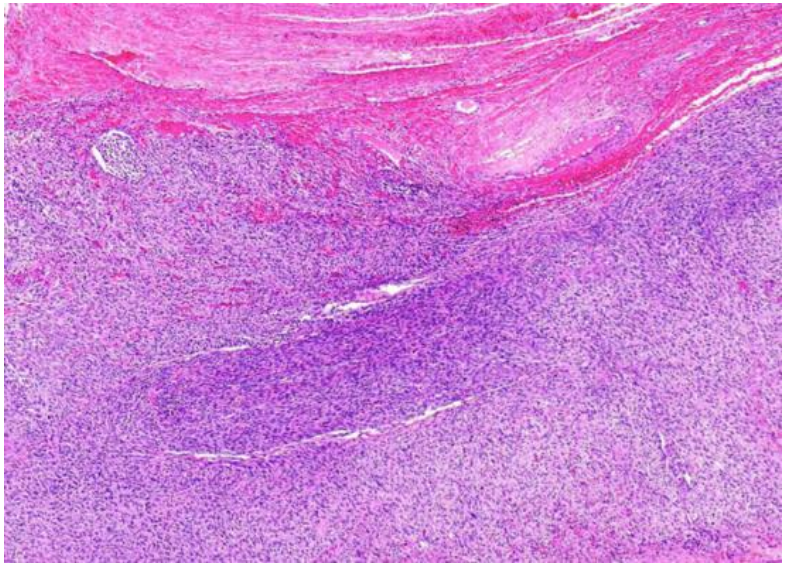


Neurofibroma

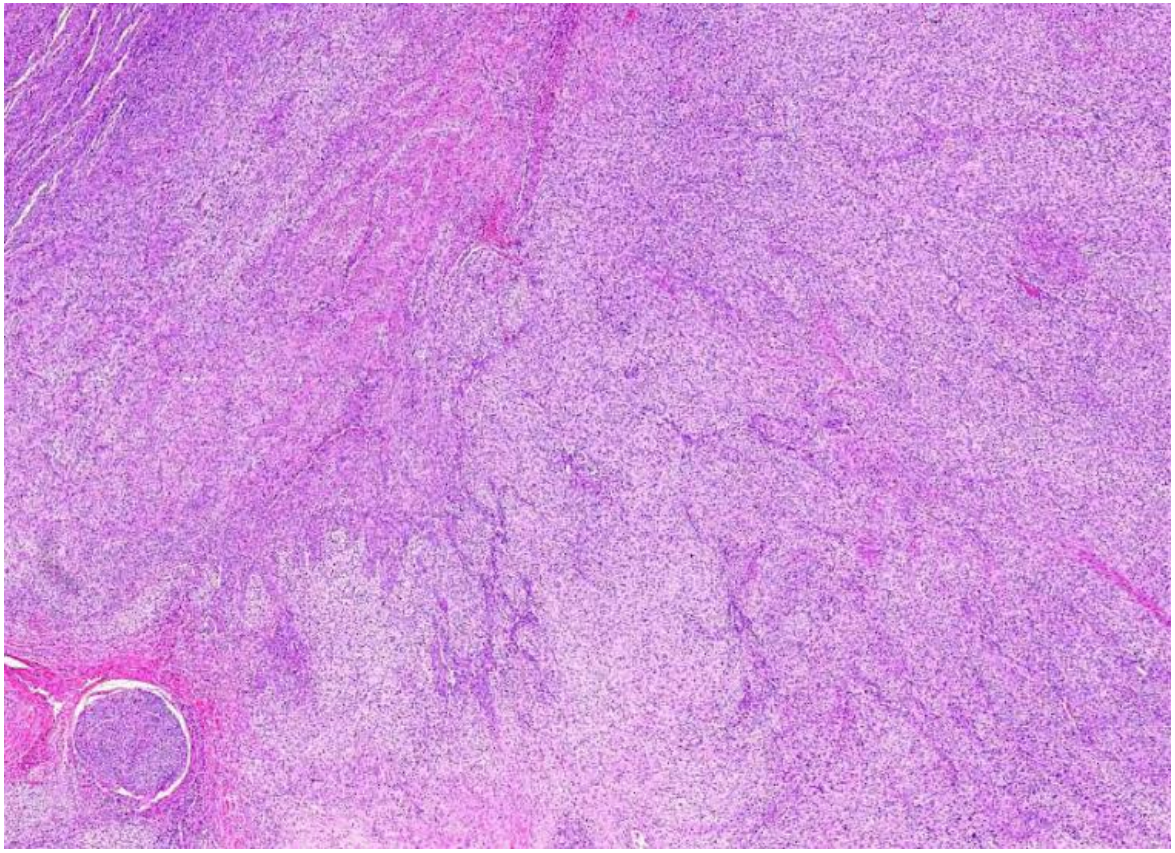


Malignant Peripheral Nerve Sheath Tumor (MPNST)

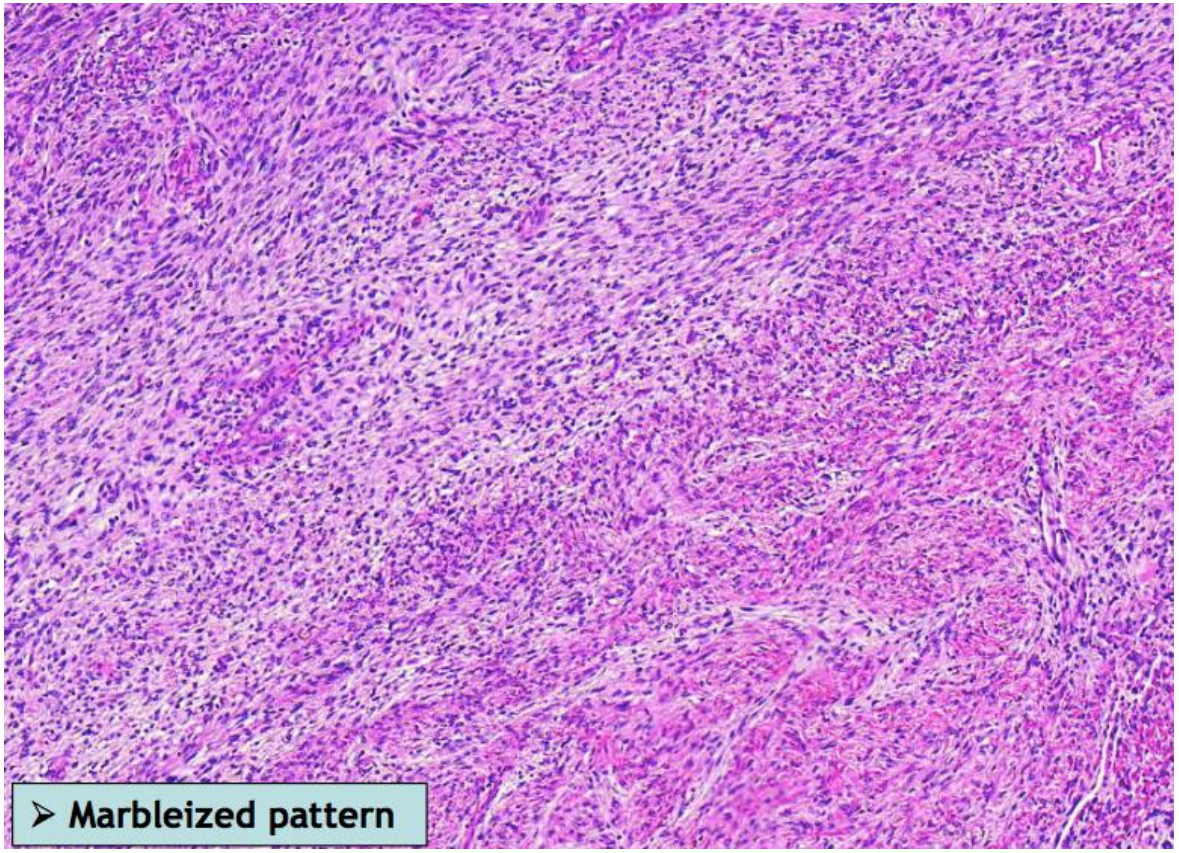
- **Architecture and cytology are often very helpful in its discrimination**
- **Usually presented as deep soft tissue mass not a dermal tumor**
- **Absence of a junctional component**
- **S100 and SOX10 staining is weak**



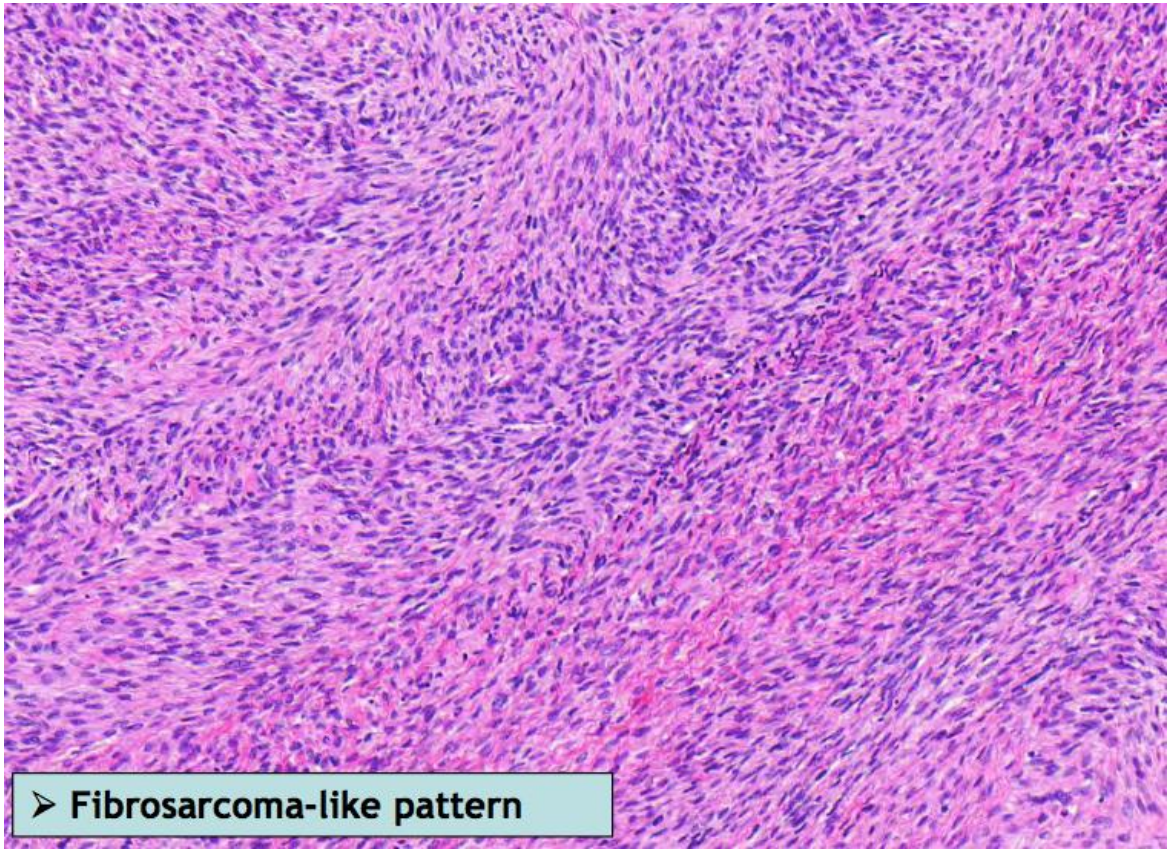
Malignant Peripheral Nerve Sheath Tumor (MPNST)



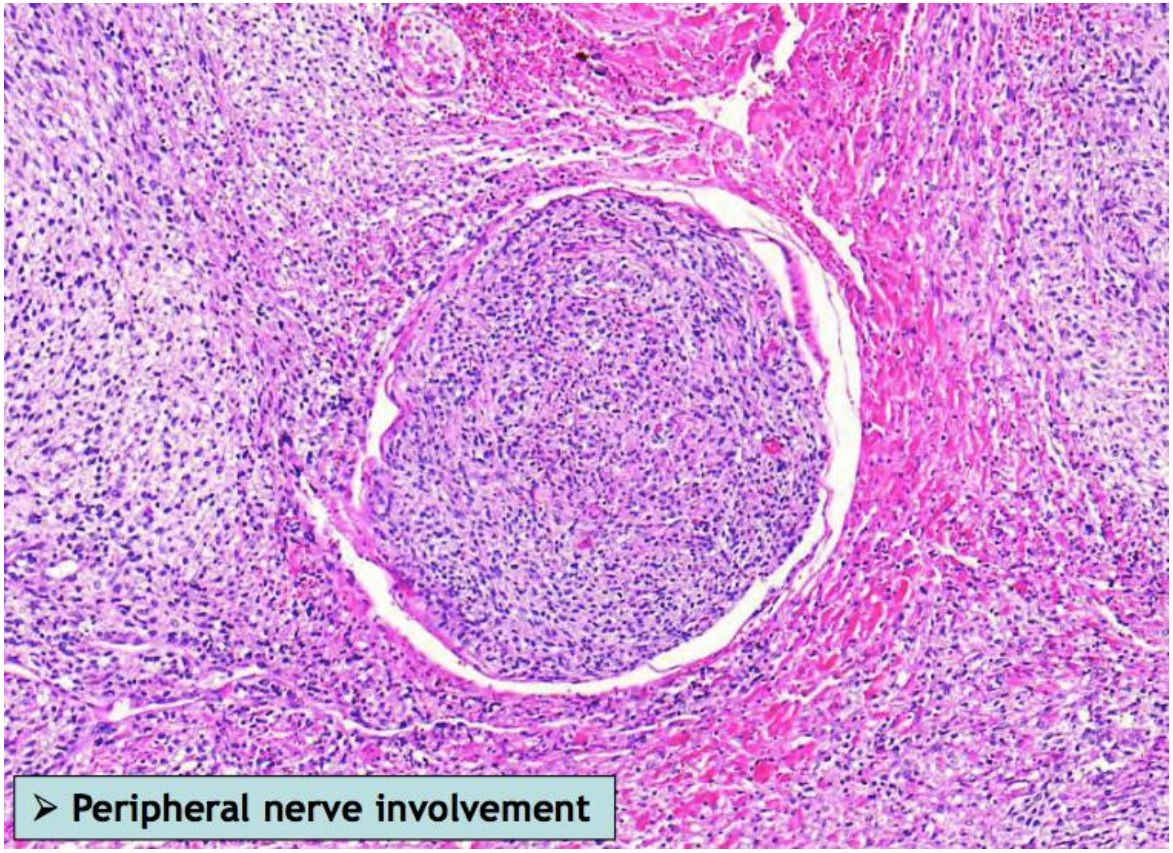
Malignant Peripheral Nerve Sheath Tumor (MPNST)



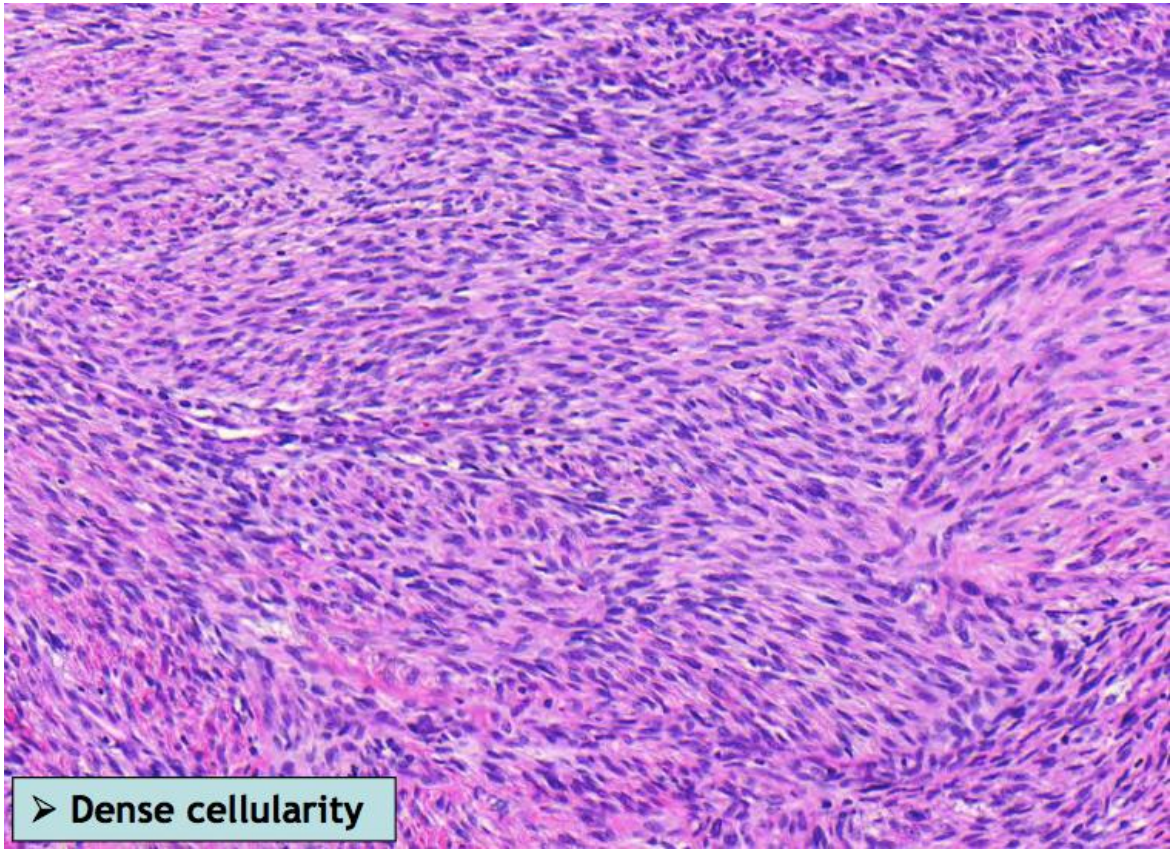
Malignant Peripheral Nerve Sheath Tumor (MPNST)



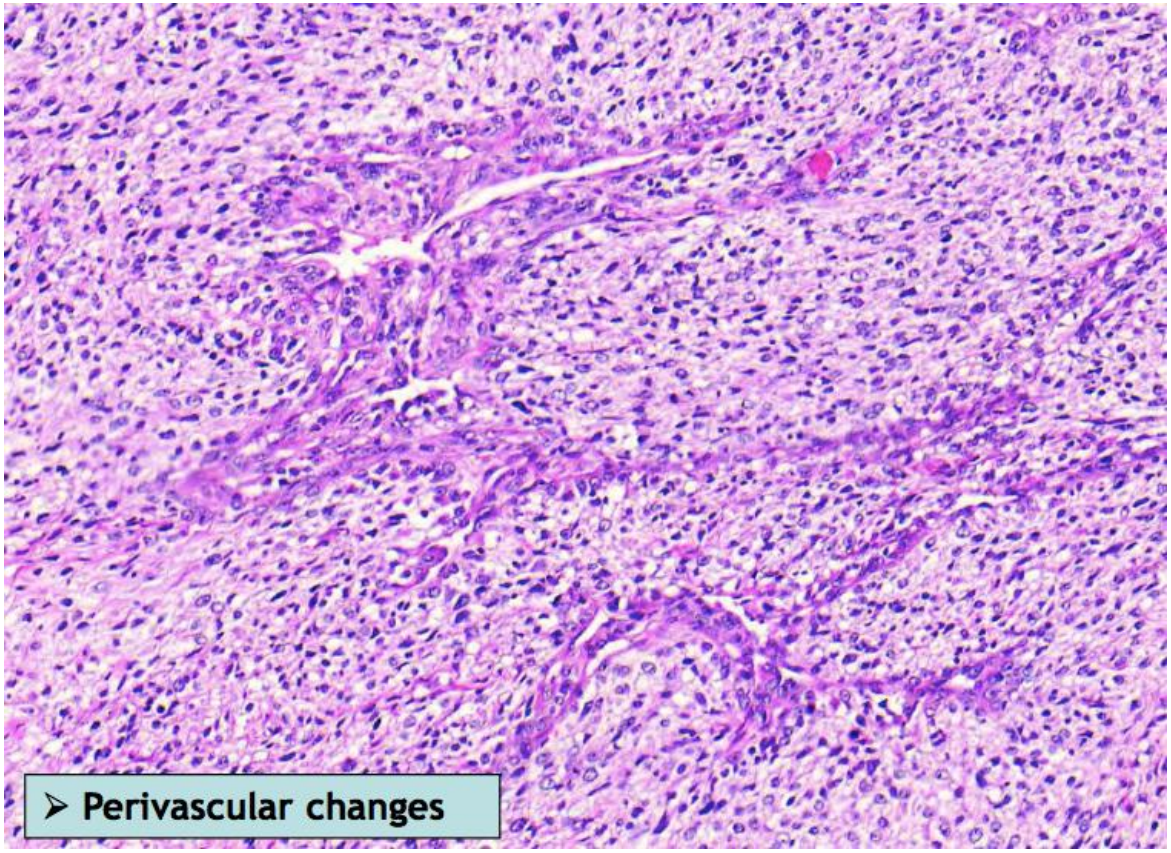
Malignant Peripheral Nerve Sheath Tumor (MPNST)



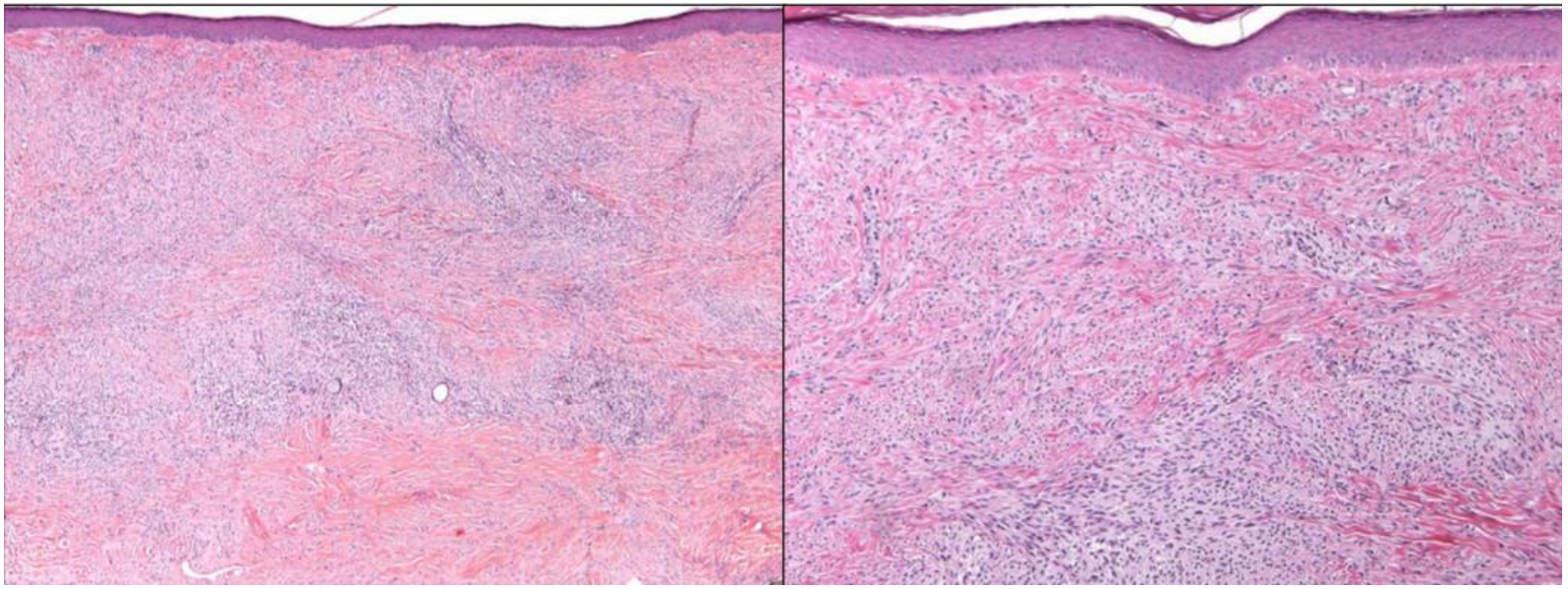
Malignant Peripheral Nerve Sheath Tumor (MPNST)



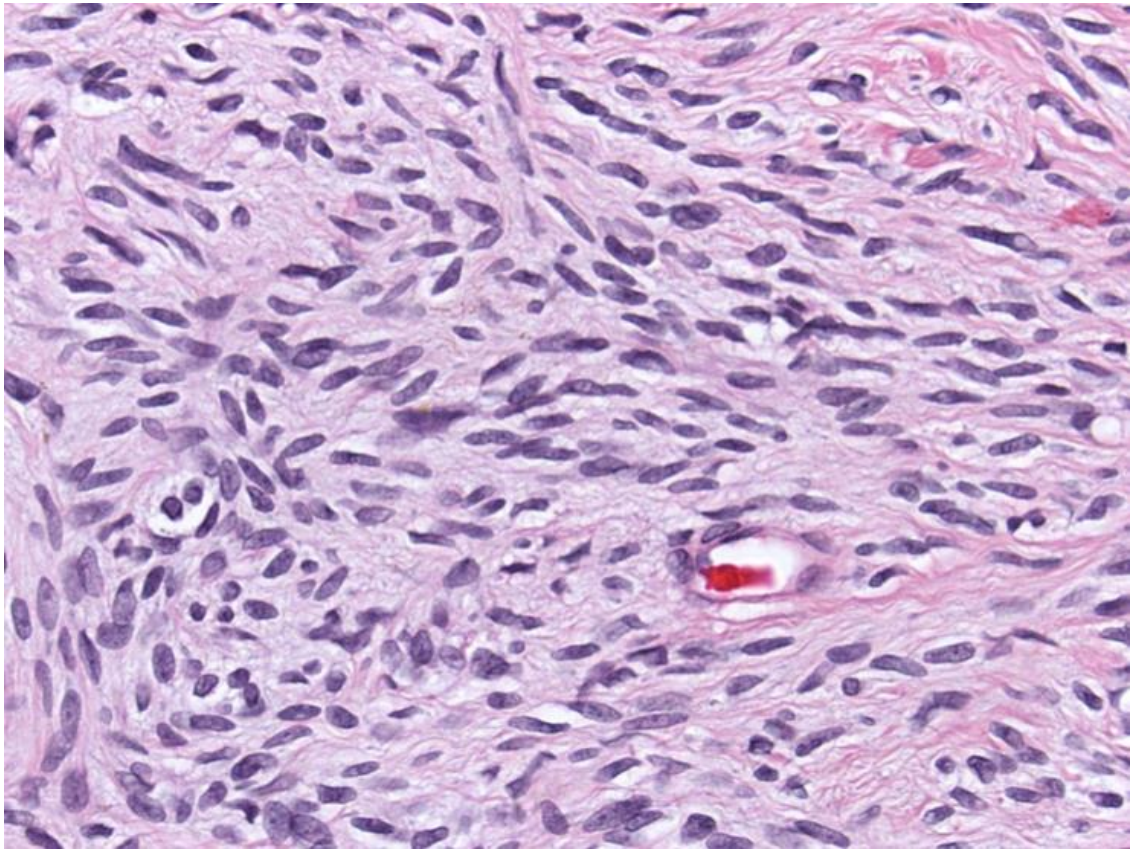
Malignant Peripheral Nerve Sheath Tumor (MPNST)



Neurocristic Hamartoma



Neurocristic Hamartoma



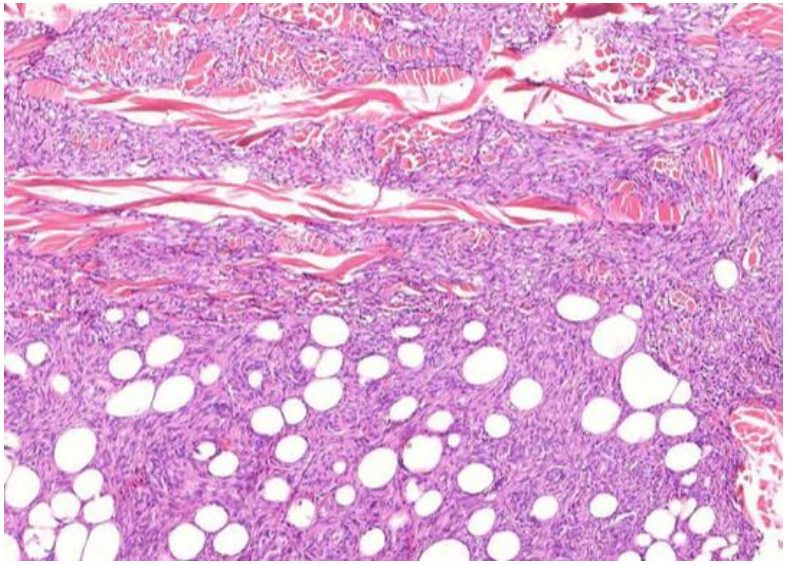
Atypical Spindle Cell Proliferations – NOS

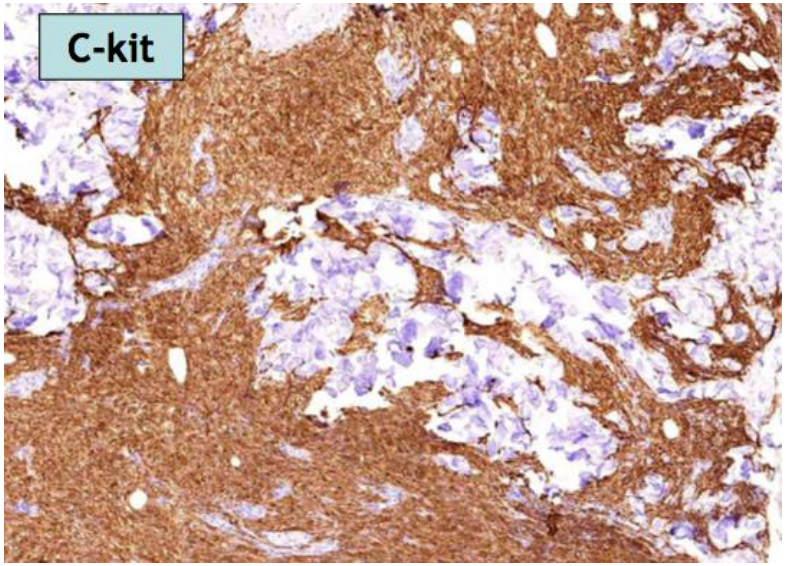
- **Sarcomatoid squamous cell carcinoma**
- **Atypical fibroxanthoma (“AFX”)**
- **Dermatofibrosarcoma protuberans**
- **Atypical fibrohistiocytic tumors**

DIFFERENTIAL DIAGNOSIS	S100	Mart-1	HMB45	MiTF	SOX10
Desmoplastic melanoma	+	-/+	-	-/+	+
Sclerosing nevus	+	+	-	+	-
Sclerosing blue nevus	+	+	+	+	-
Dermatofibroma	-*	-	-	-	-
Scar	-/+	-	-	-	-
"Atypical fibroxanthoma"	-	-	-	-	-
Sarcomatoid SCC	-	-	-	-	-
Sclerosing Spitz nevus	+	+	-/+	+/-	-
MPNST	+/-	-	-	-	-/+
Neurofibroma	+	-	-	-	+

* Sometimes highlights dendritic cells in the superficial aspect of traumatized dermatofibromas

Others





Metastatic Gastrointestinal Stromal Tumor (GIST)

Desmoplastic Melanoma

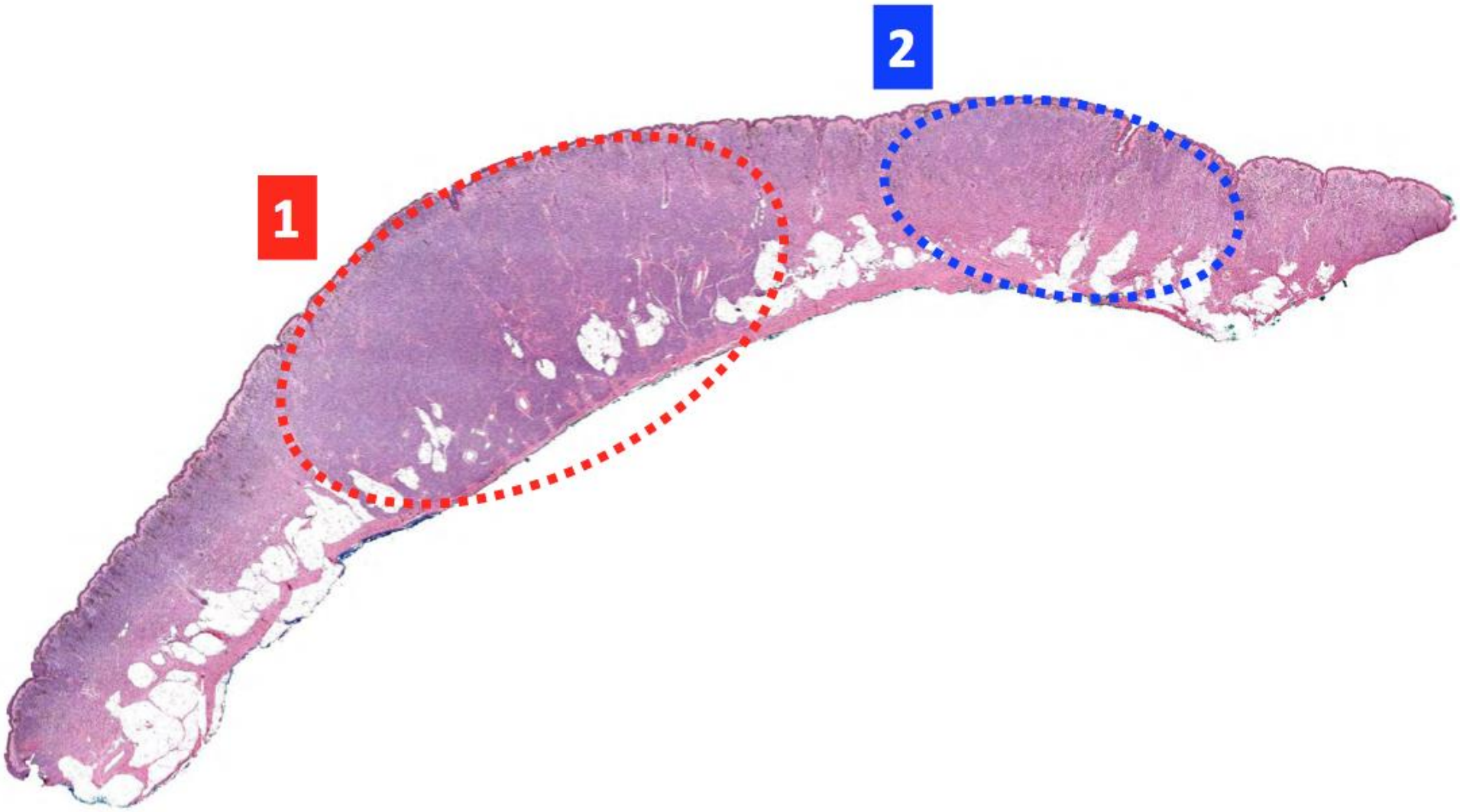
- **Be aware of making a diagnosis of scar when there is no documented history of prior procedure!**
- **Look for mucin/myxoid stroma; if present, be very cautious!**
- **The depth of invasion at the time of first excision is ~ 4 mm on average**
- **Infiltrated nerves may be found in the subcutaneous fat and other locations, and can be relatively far away from the main tumor**
- **Desmoplastic melanoma can appear in a pure form or as a component of a mixed pattern where the second component is non-desmoplastic**
- **Only 50% of desmoplastic melanomas are pigmented**

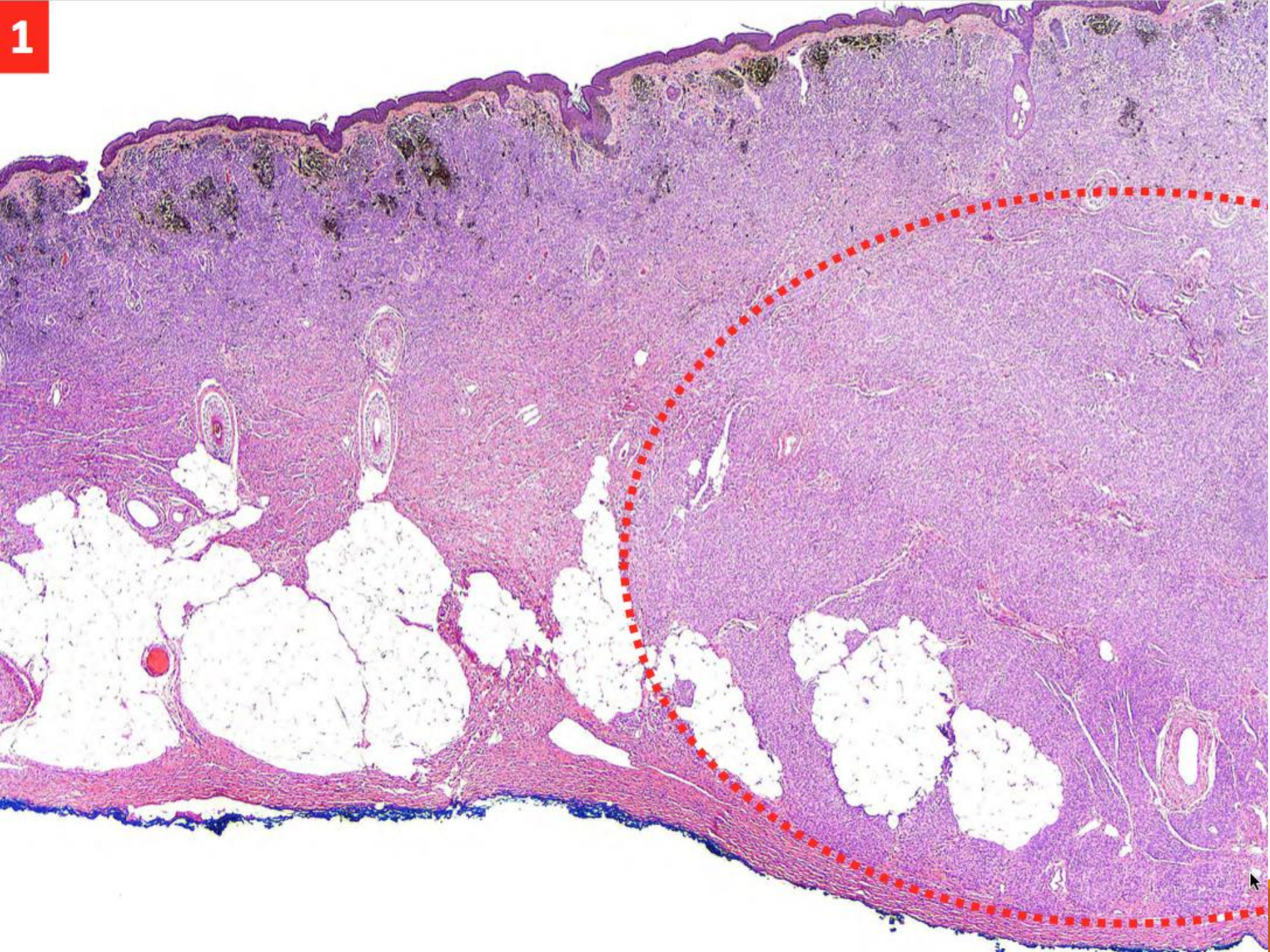
Desmoplastic Melanoma

- Desmoplastic melanoma has a higher local recurrence rate than conventional thickness-matched controlled melanoma
- Pure desmoplastic melanomas are less likely to disseminate to regional lymph nodes and
- Pure desmoplastic melanomas are associated with a longer disease-specific survival than mixed desmoplastic melanomas, which behave similarly to conventional melanomas
- SOX10 is a very sensitive and relatively specific marker in the diagnosis of desmoplastic melanoma and can also be used in evaluation of SLNB
- Approximately ~30-50% of MPNSTs and almost all neurofibromas are positive for SOX10 and S100
- Standard four-probe FISH has a high specificity for the diagnosis of desmoplastic melanoma, but due to its low sensitivity (~ 47%), only positive results are of value

Case 6

A 2-MONTH-OLD BABY GIRL WAS BORN WITH A GIANT CONGENITAL NEVUS INVOLVING THE BACK AND BUTTOCKS, WITHIN WHICH 4-5 NODULAR AREAS ARE NOTED. EXCISION OF ONE OF THE NODULES.


1
2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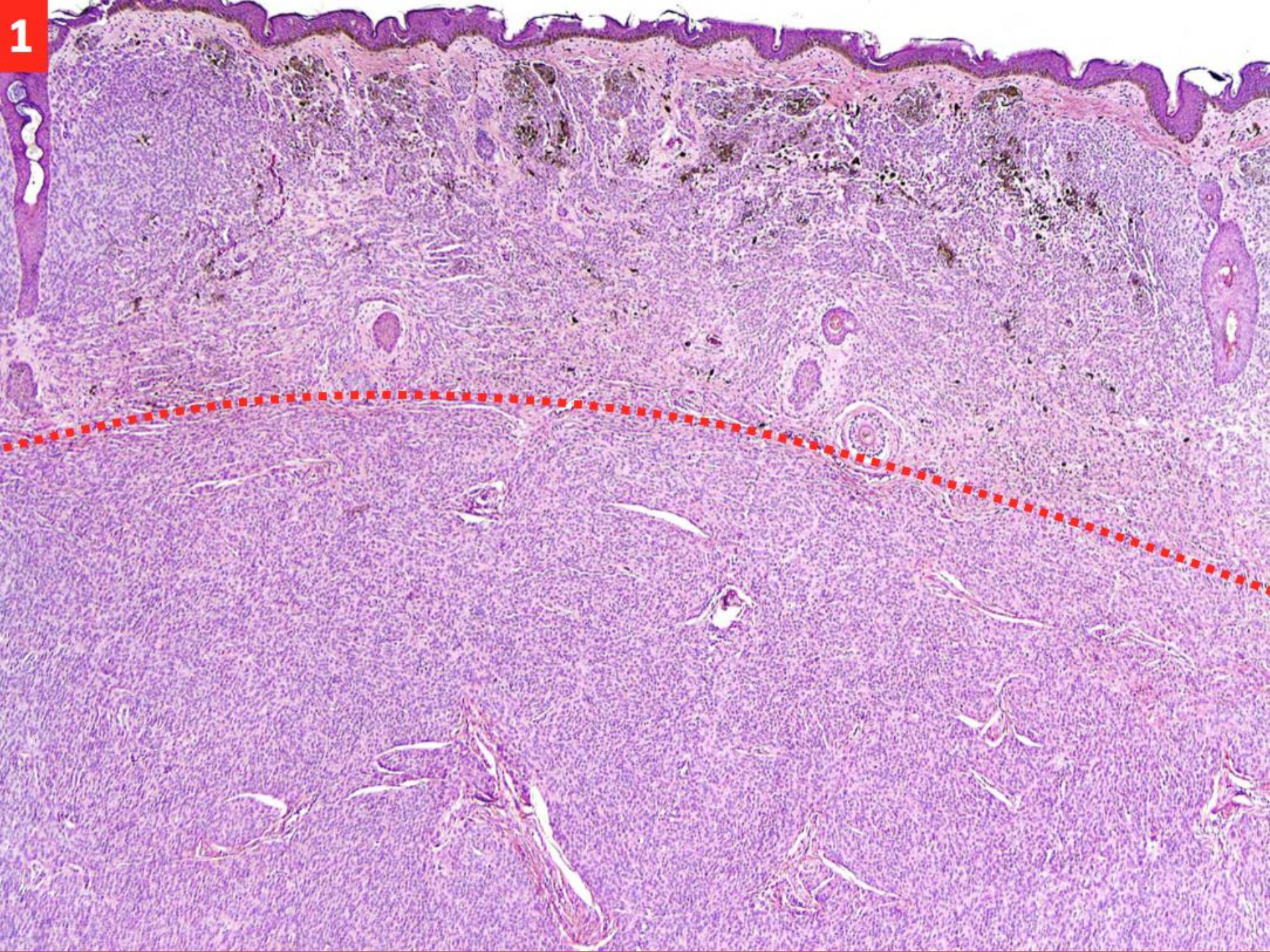
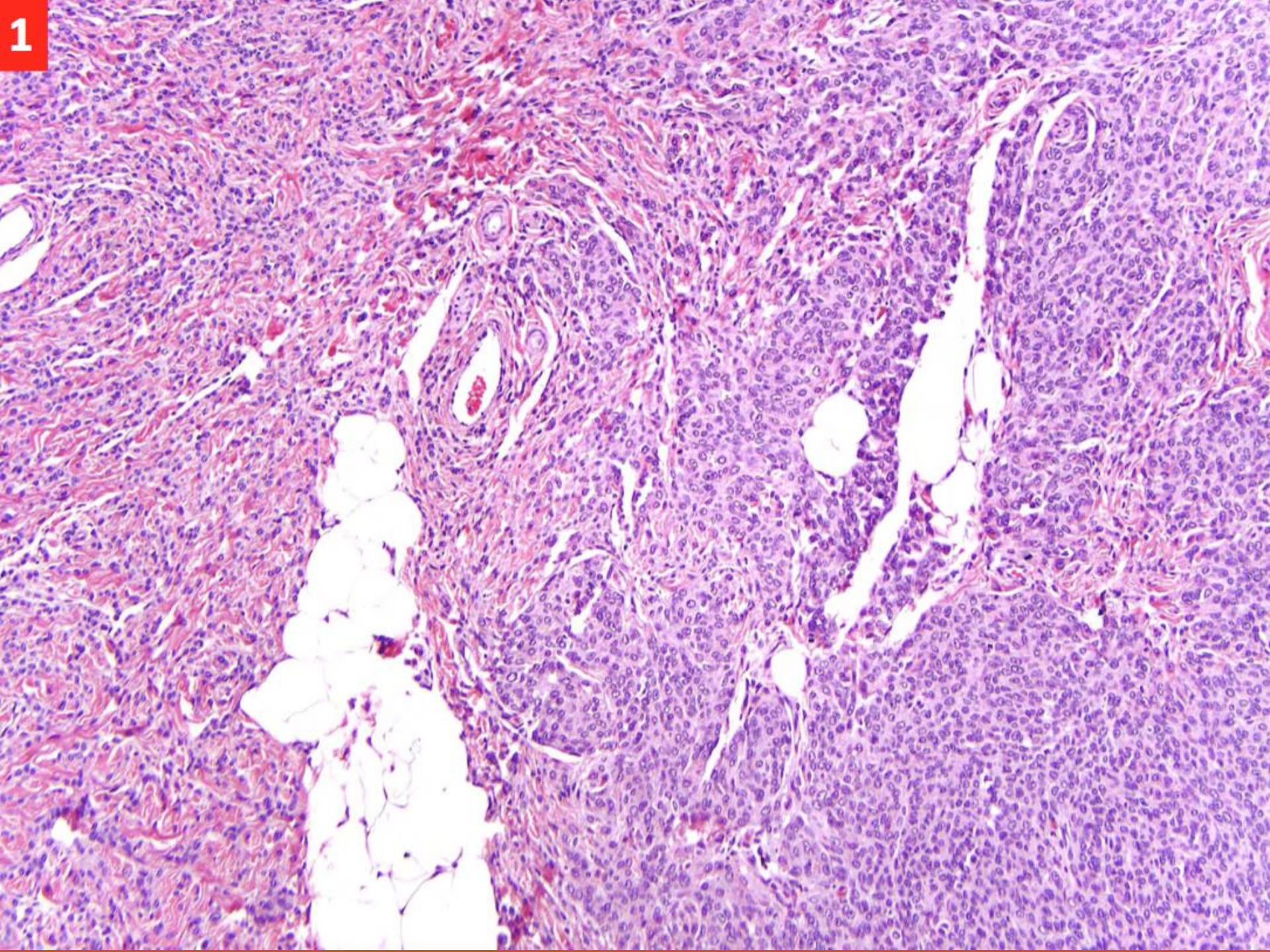
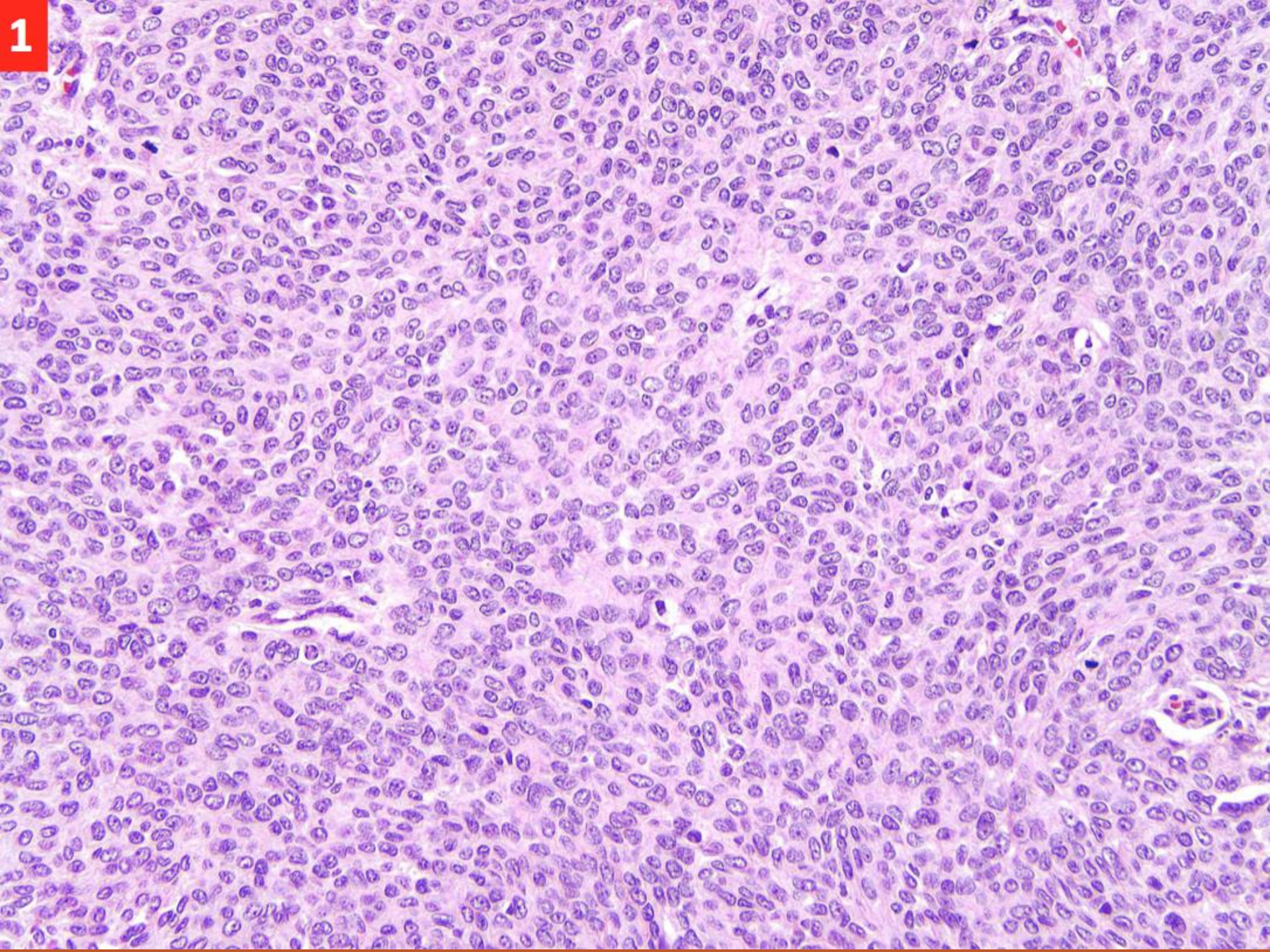
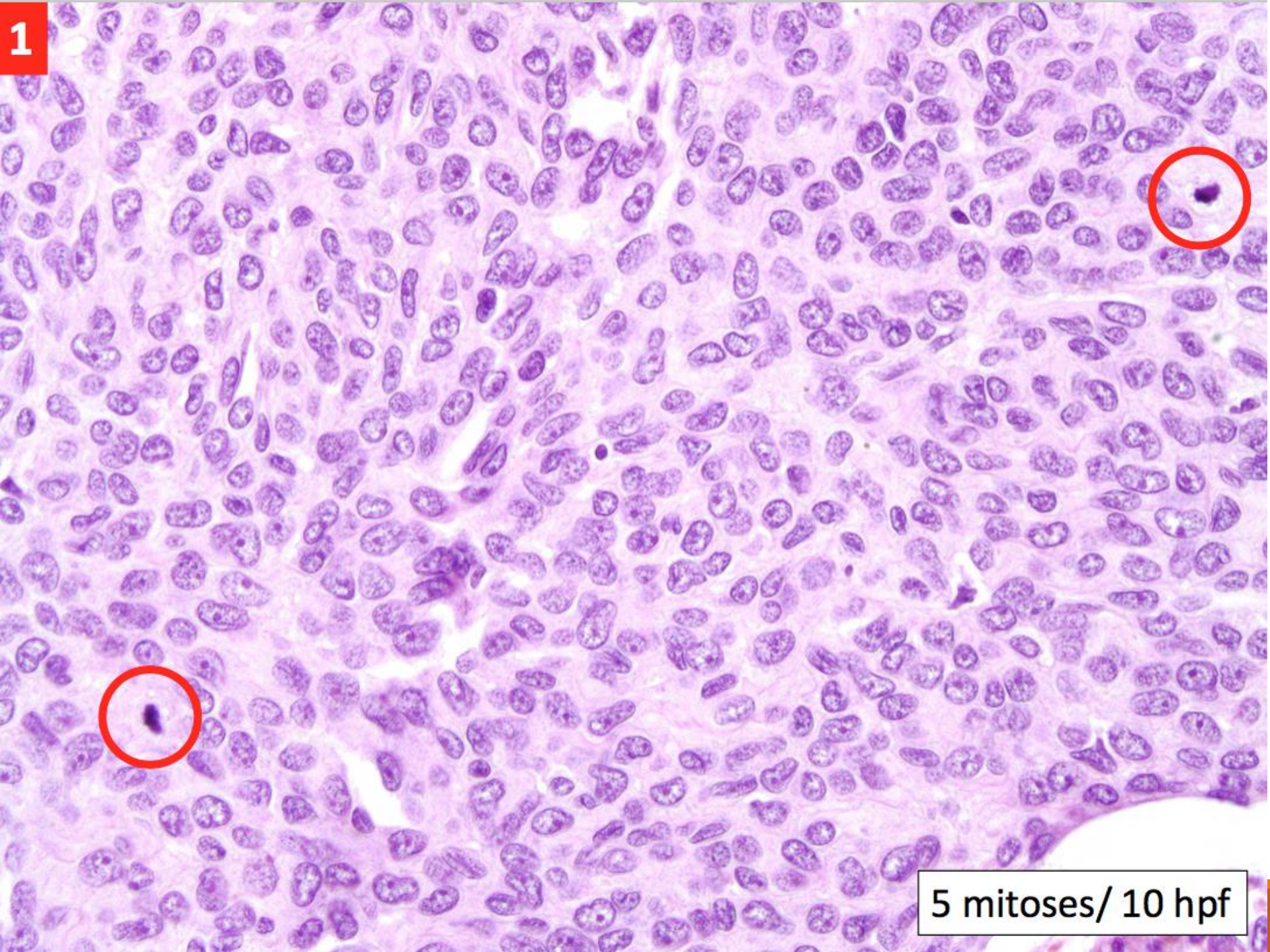
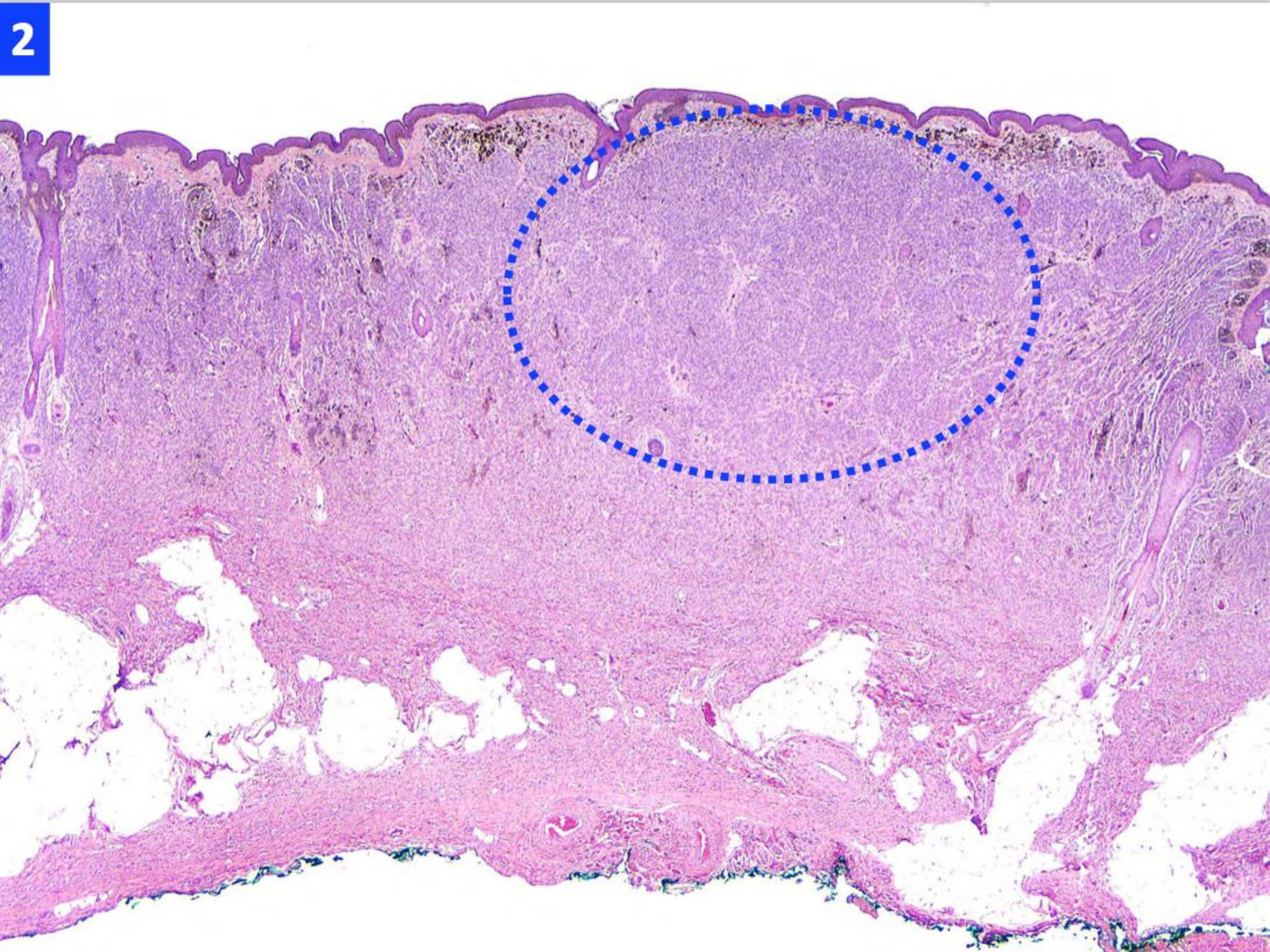

1

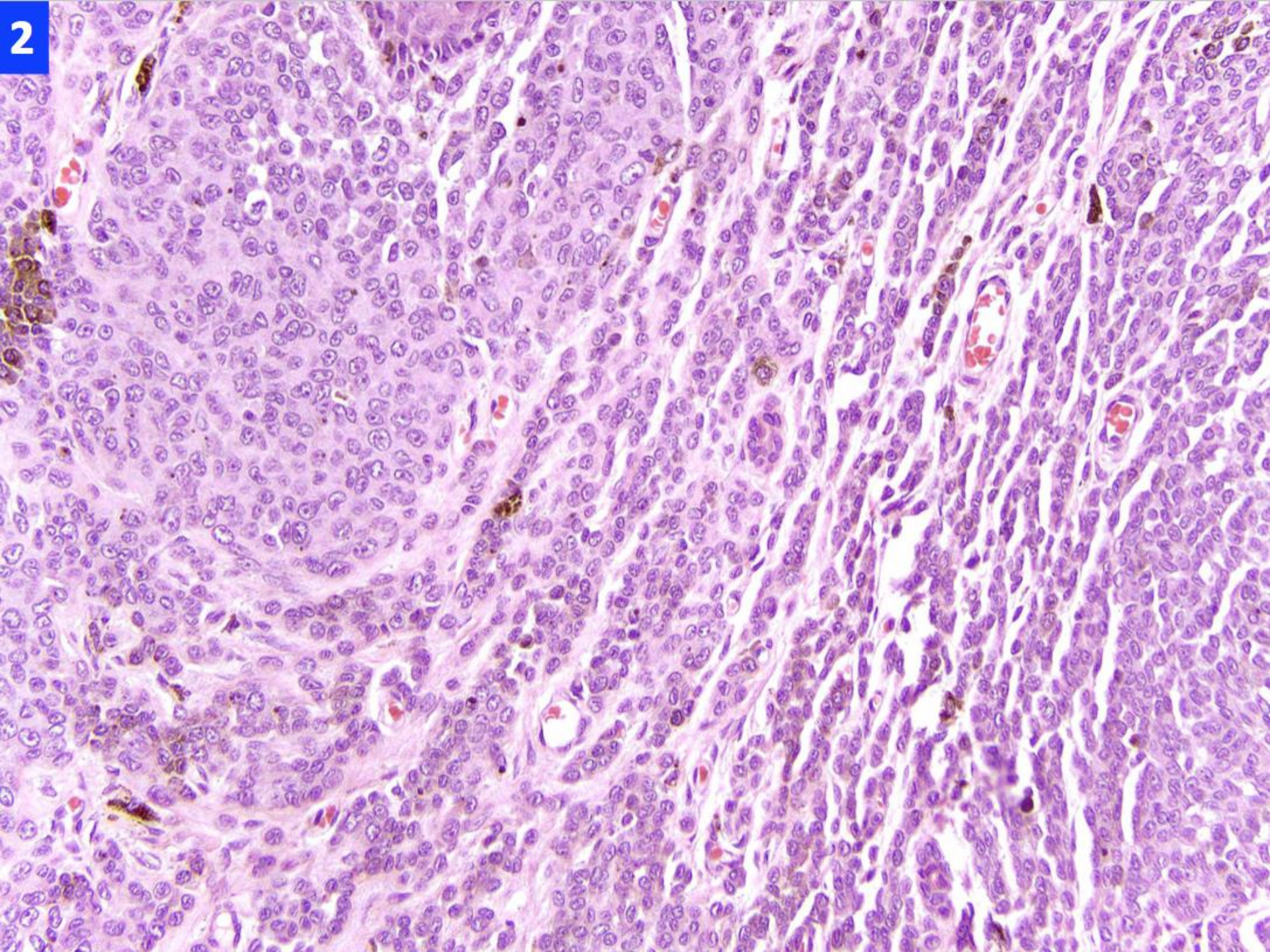

1

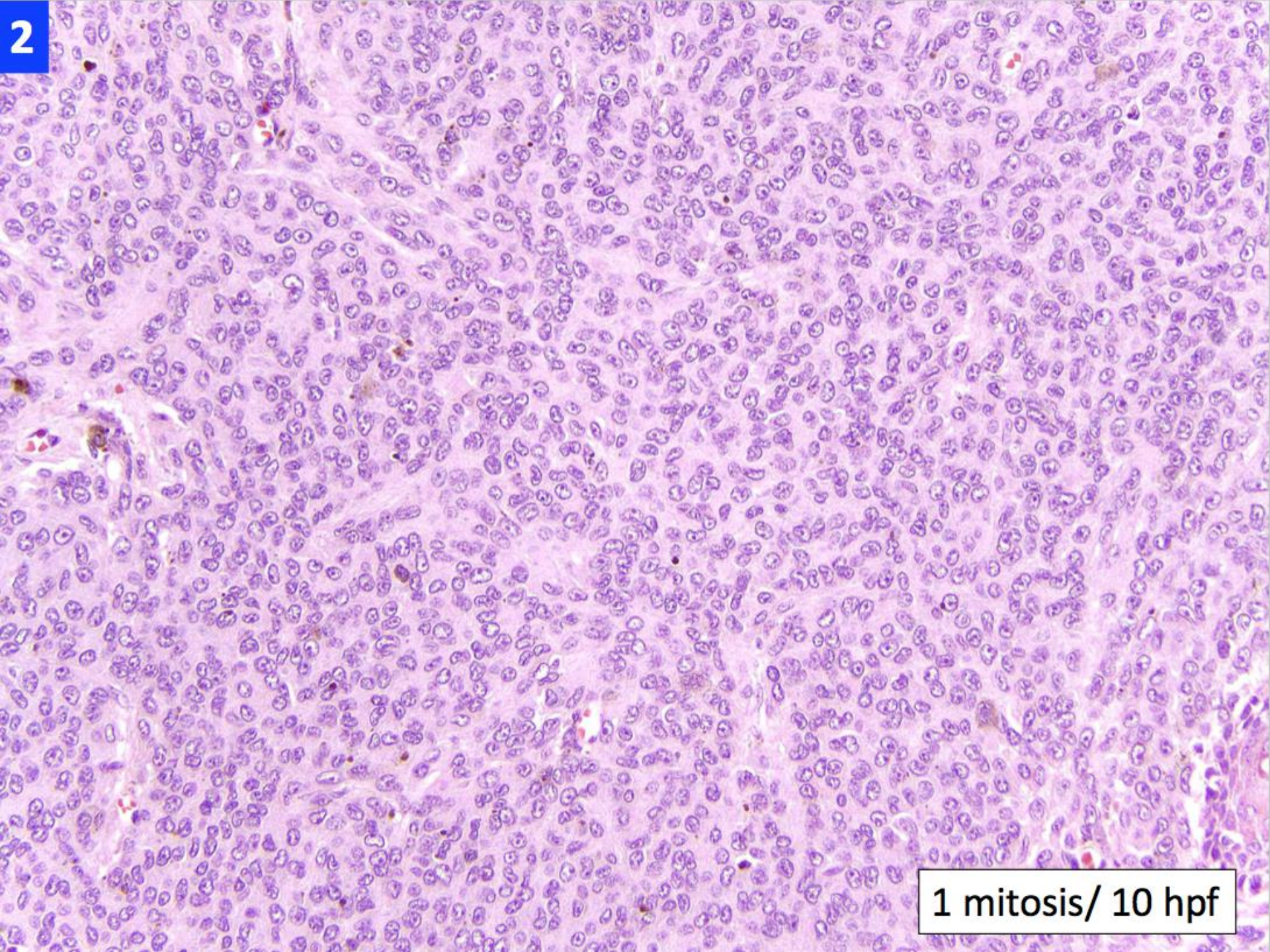

1


1
5 mitoses/ 10 hpf

2




2

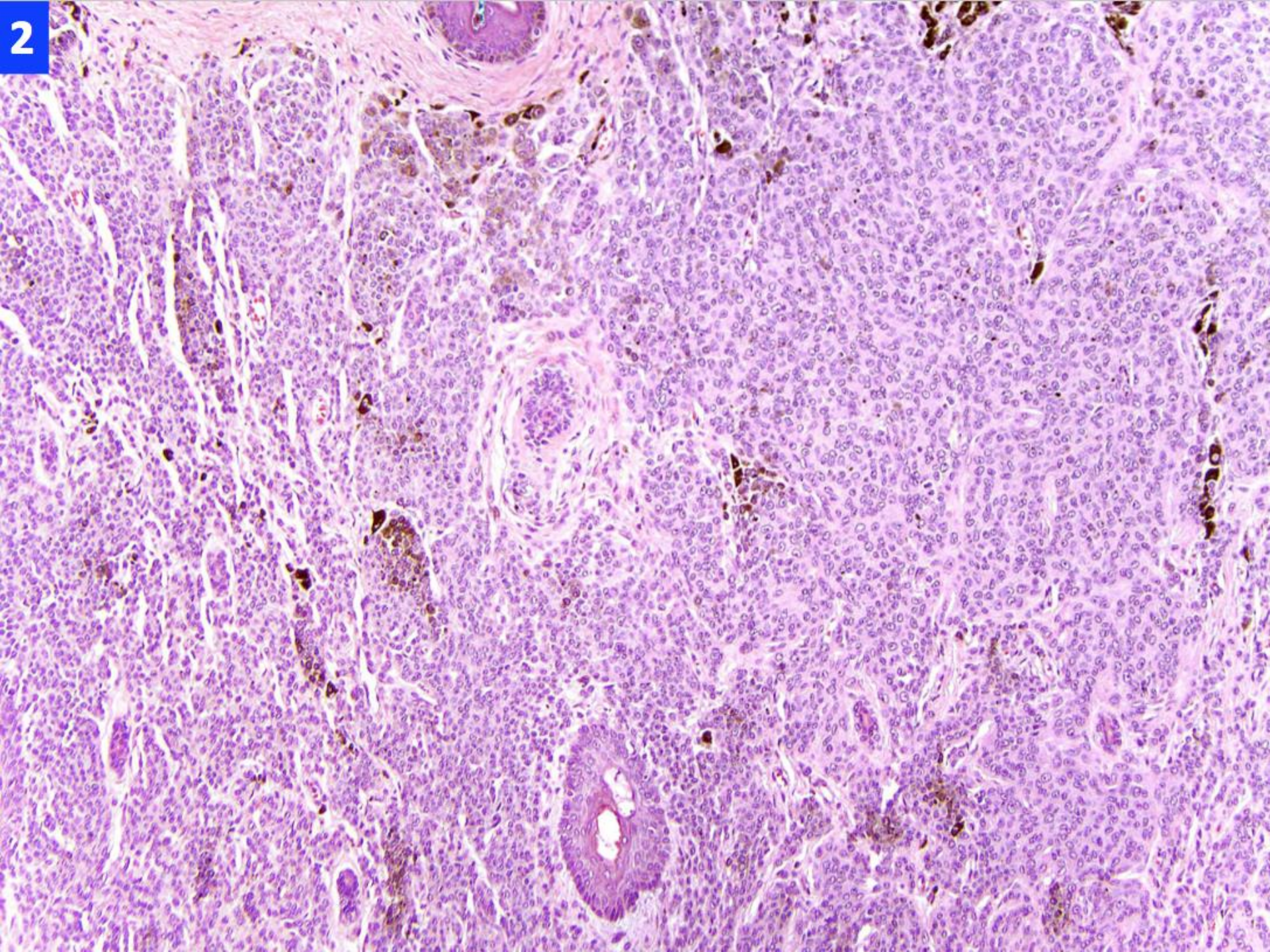

2
1 mitosis/ 10 hpf

What to Consider

- **Is the background nevus a congenital nevus?**
  - **Proliferative nodules only occur in congenital nevi**
- **How big is the background nevus?**
  - **Giant (>20 cm) congenital nevi are more prone to developing melanoma**
- **How old is the patient?**
  - **Proliferative nodules typically affect neonates/infants**
- **How big is the nodule?**
  - **Continuous growth without stabilization in size is worrisome for malignancy**

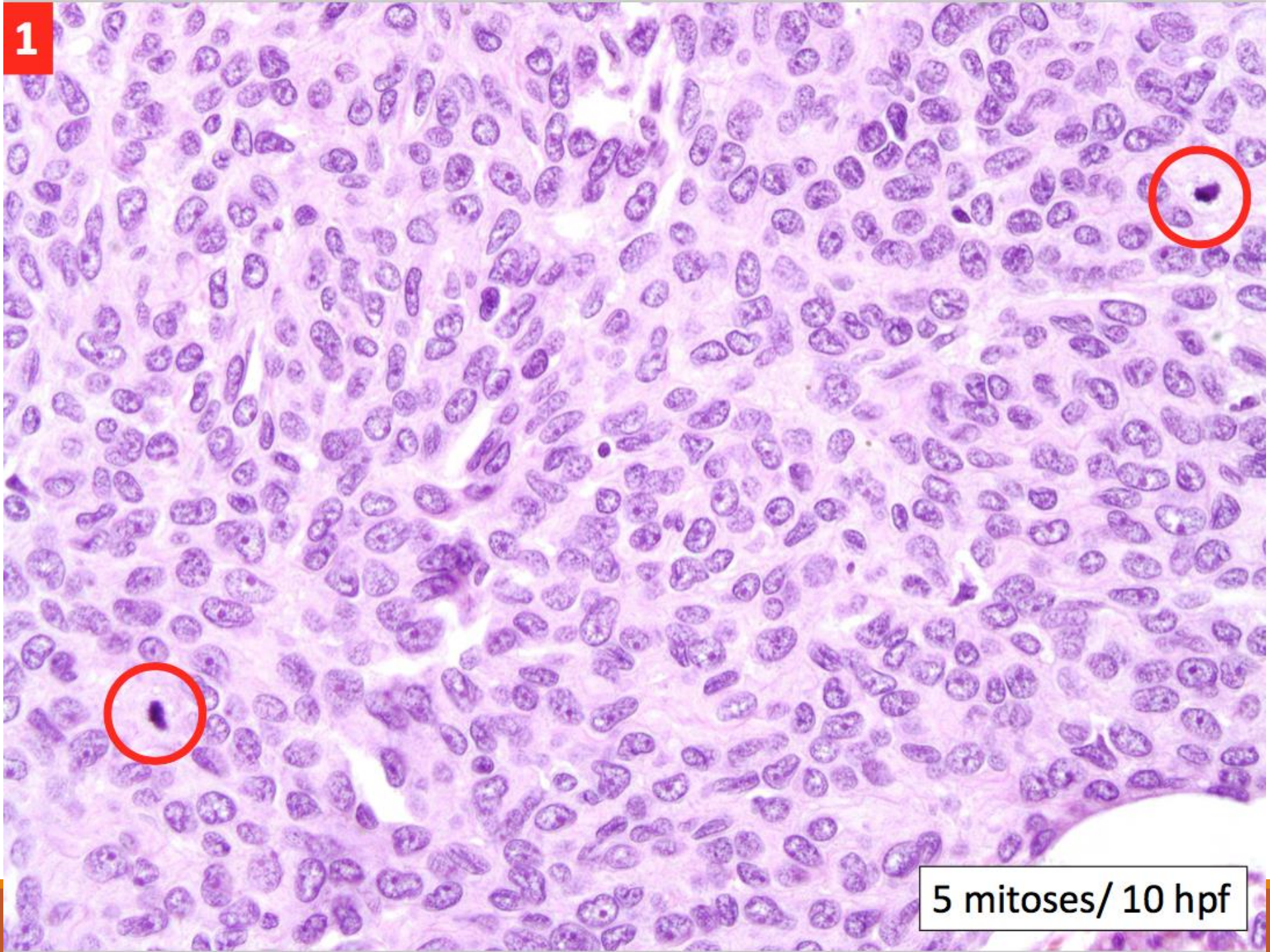
Benign Proliferative Nodule

- Non-expansile, non-destructive
- Smooth interface (blending) with the background congenital nevus
- Minimal cytologic atypia
  - •Nevoid, epithelioid, spitzoid, spindle (blue), DPN-like, etc.
- Low mitotic rate (<2 per 10 hpf) and Ki-67 proliferation index (~1%)
- No epidermal involvement
- Onset during neonatal/infancy period

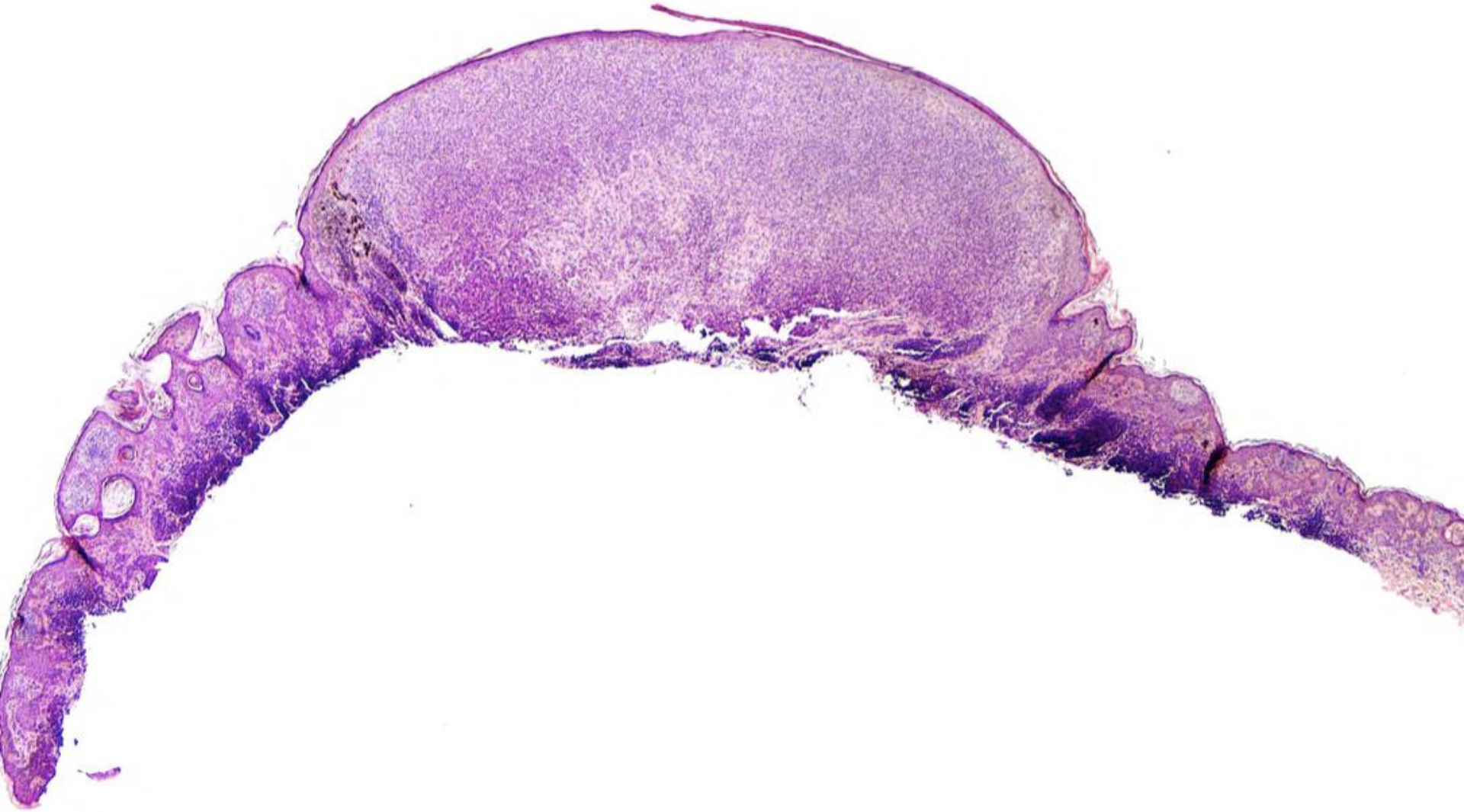

2

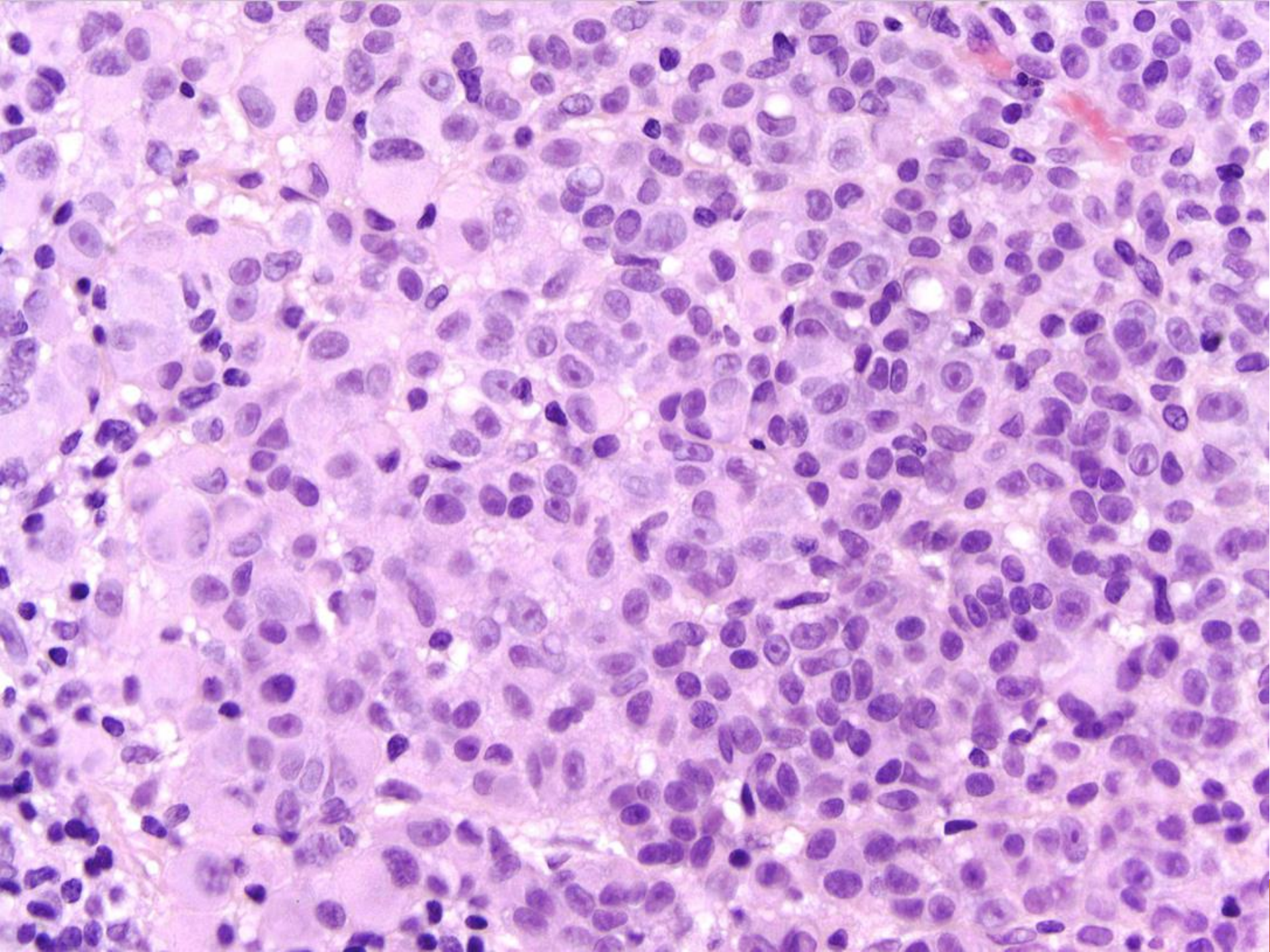
Atypical Proliferative Nodule

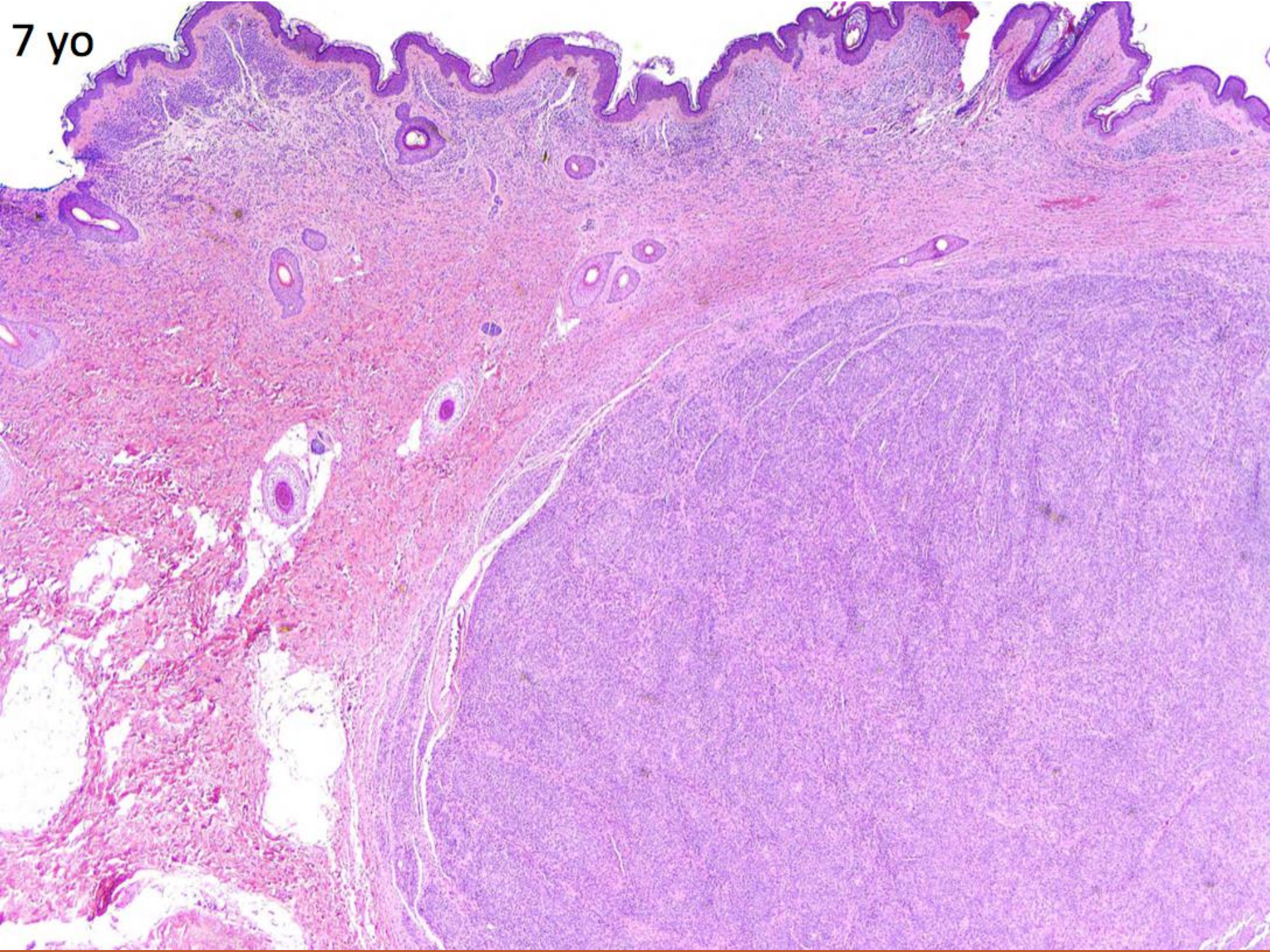
- **Some deviation from a benign proliferative nodule, but insufficient for dx of melanoma**
  - **More discrete from background nevus**
  - **Increased mitoses (>2 per 10 hpf) and Ki-67 proliferation index (1-5%)**
  - **Low-grade cytologic atypia**
  - **Focal epidermal involvement**
- **Same behavior as benign proliferative nodule**

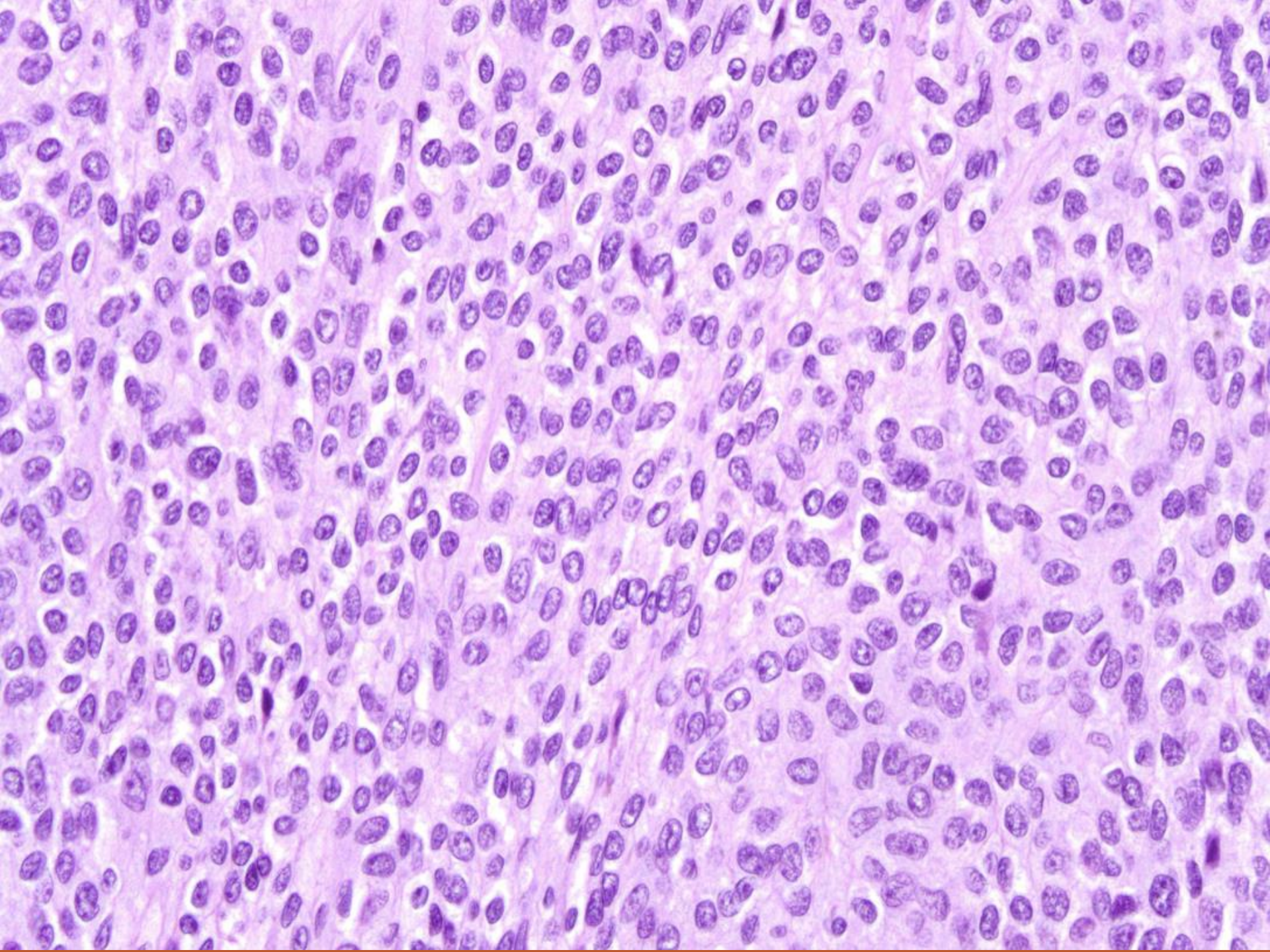

1
5 mitoses/ 10 hpf

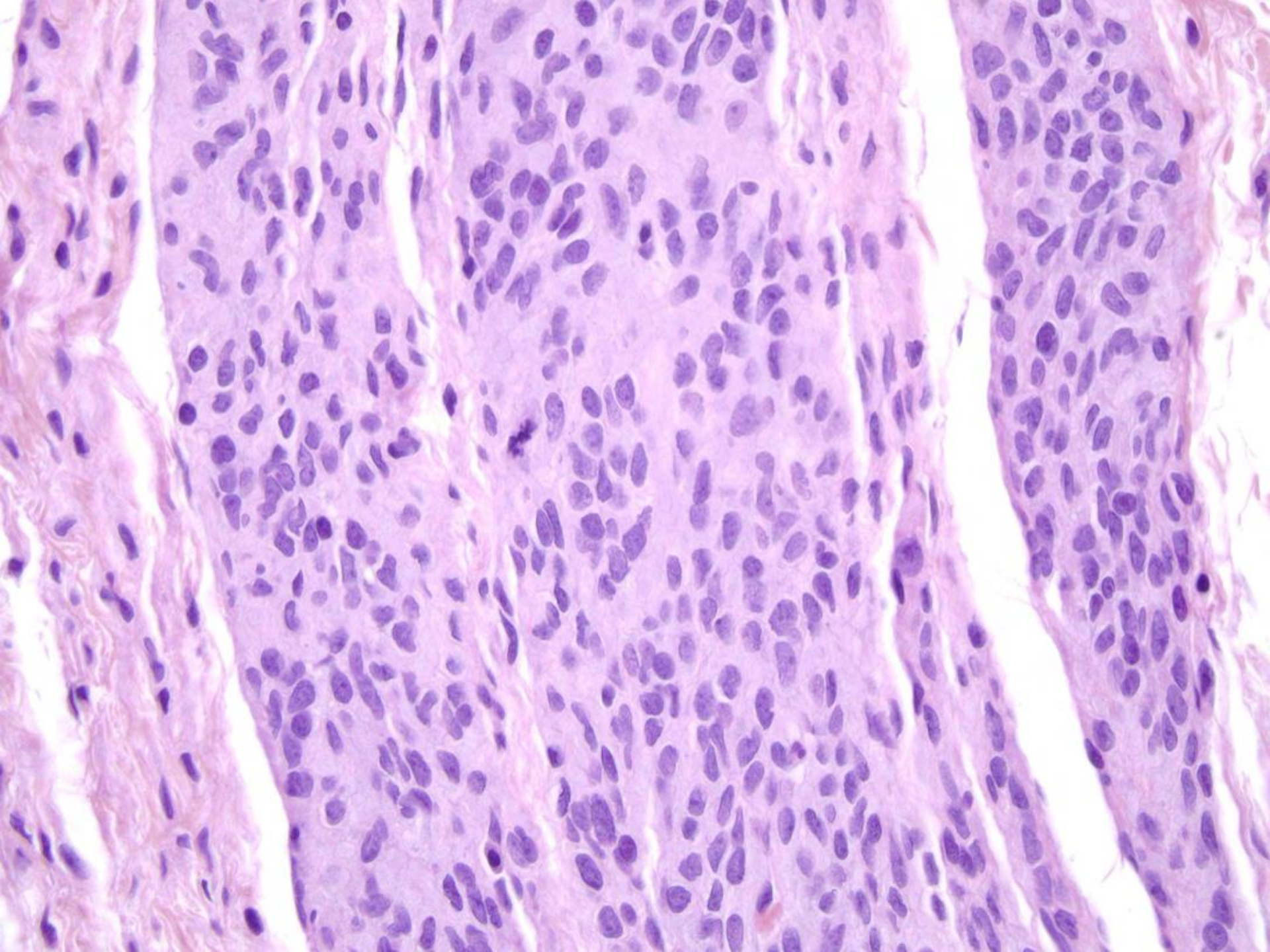
10 yo

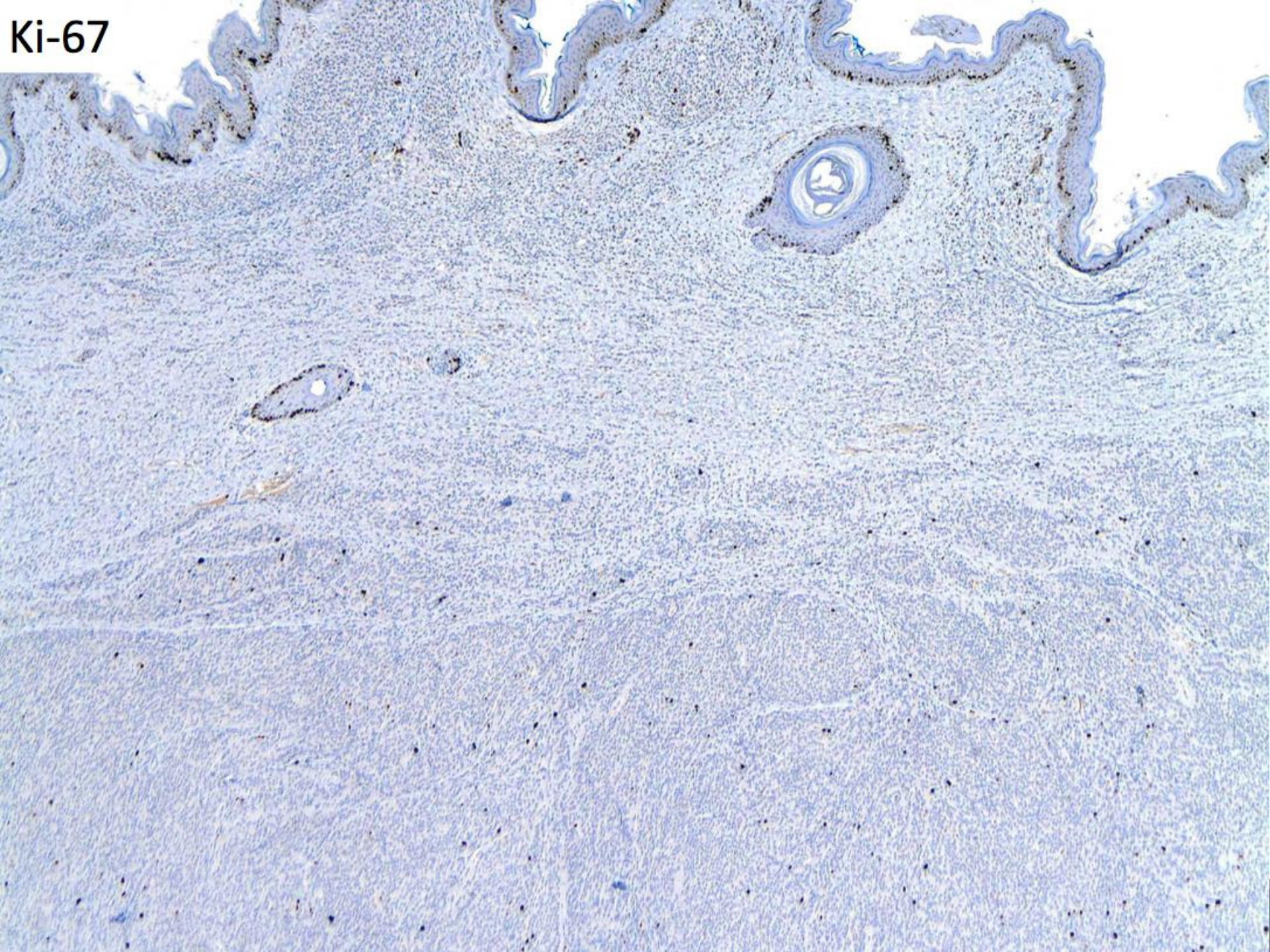


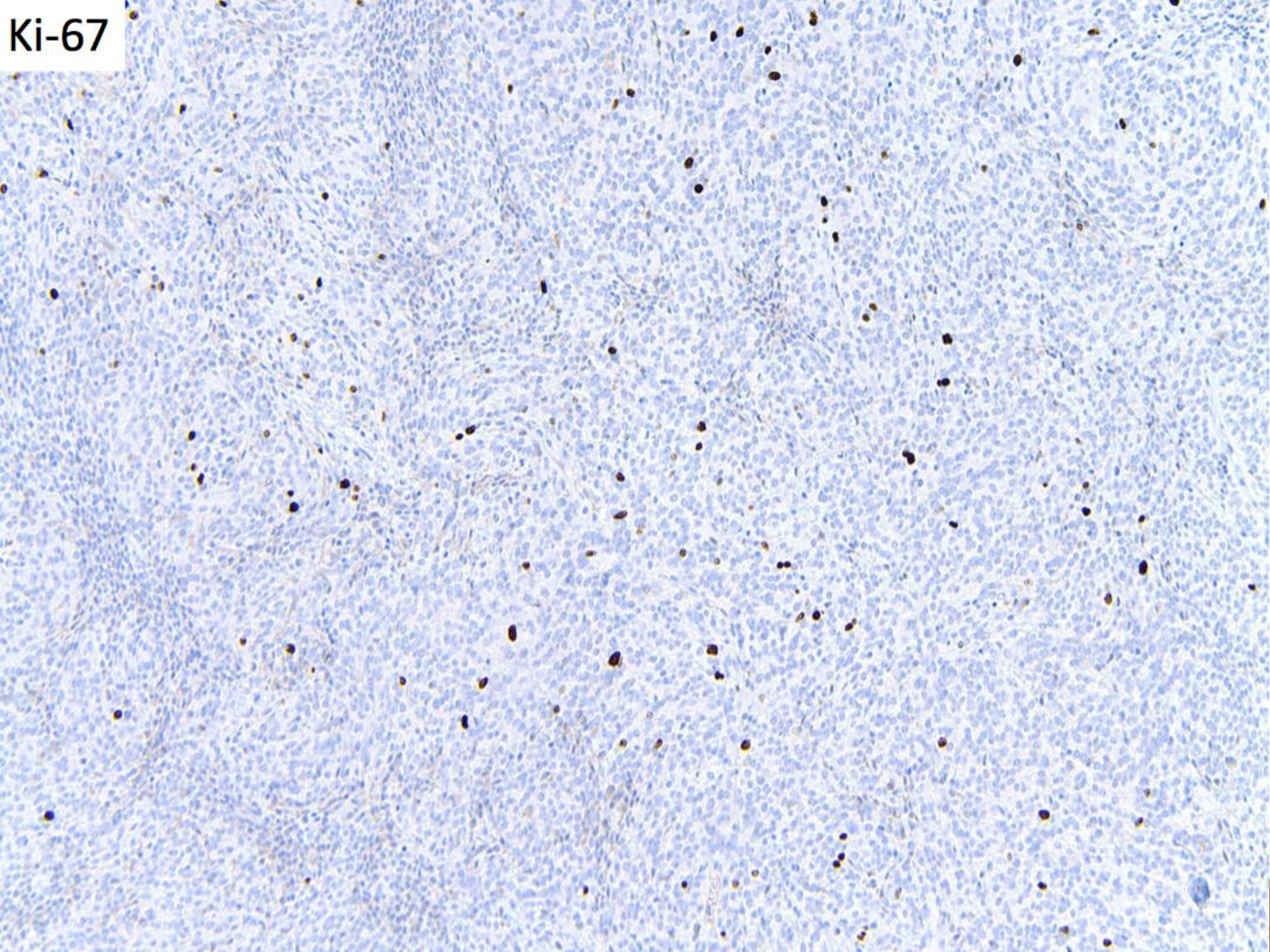


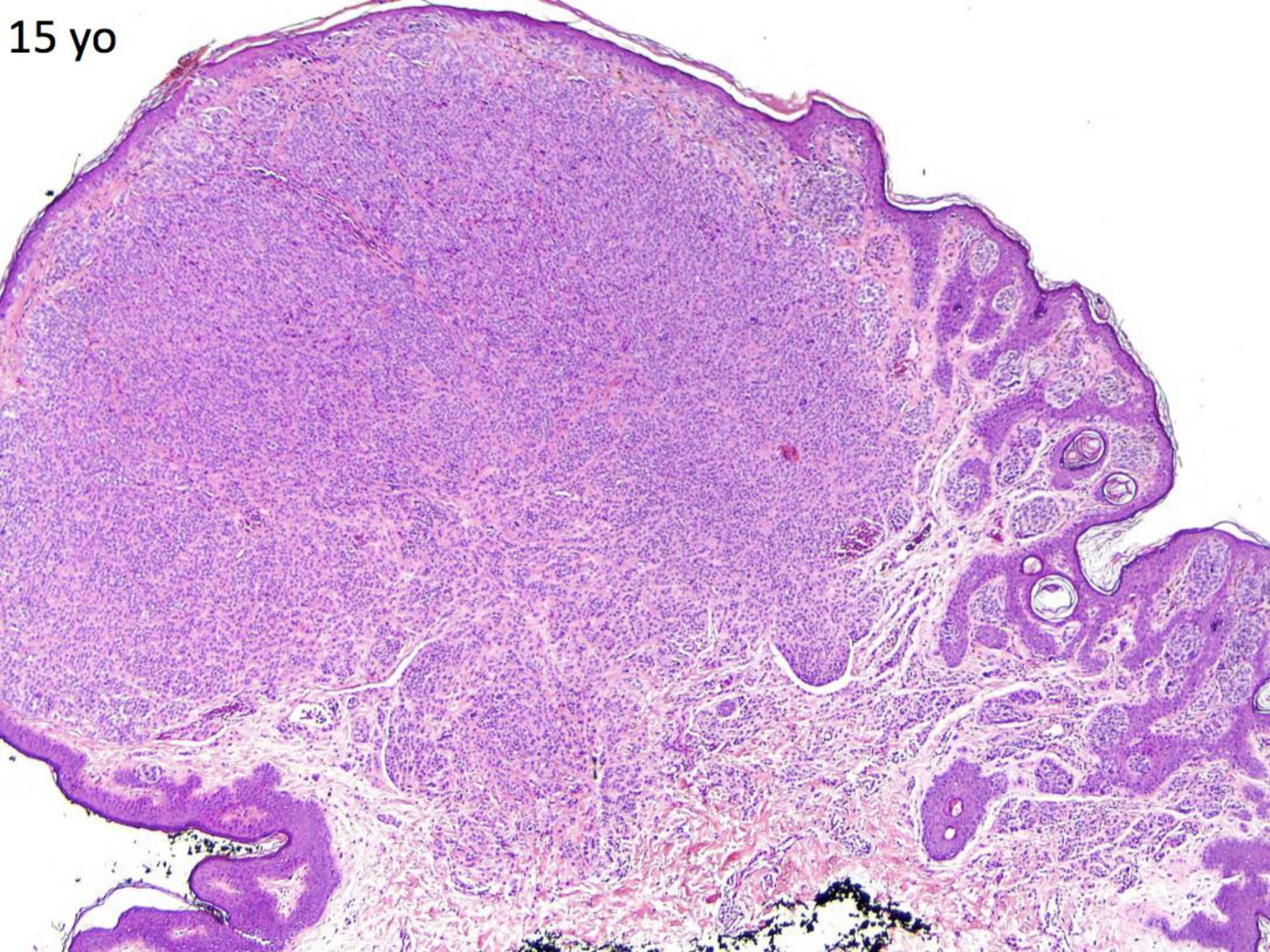

7 yo

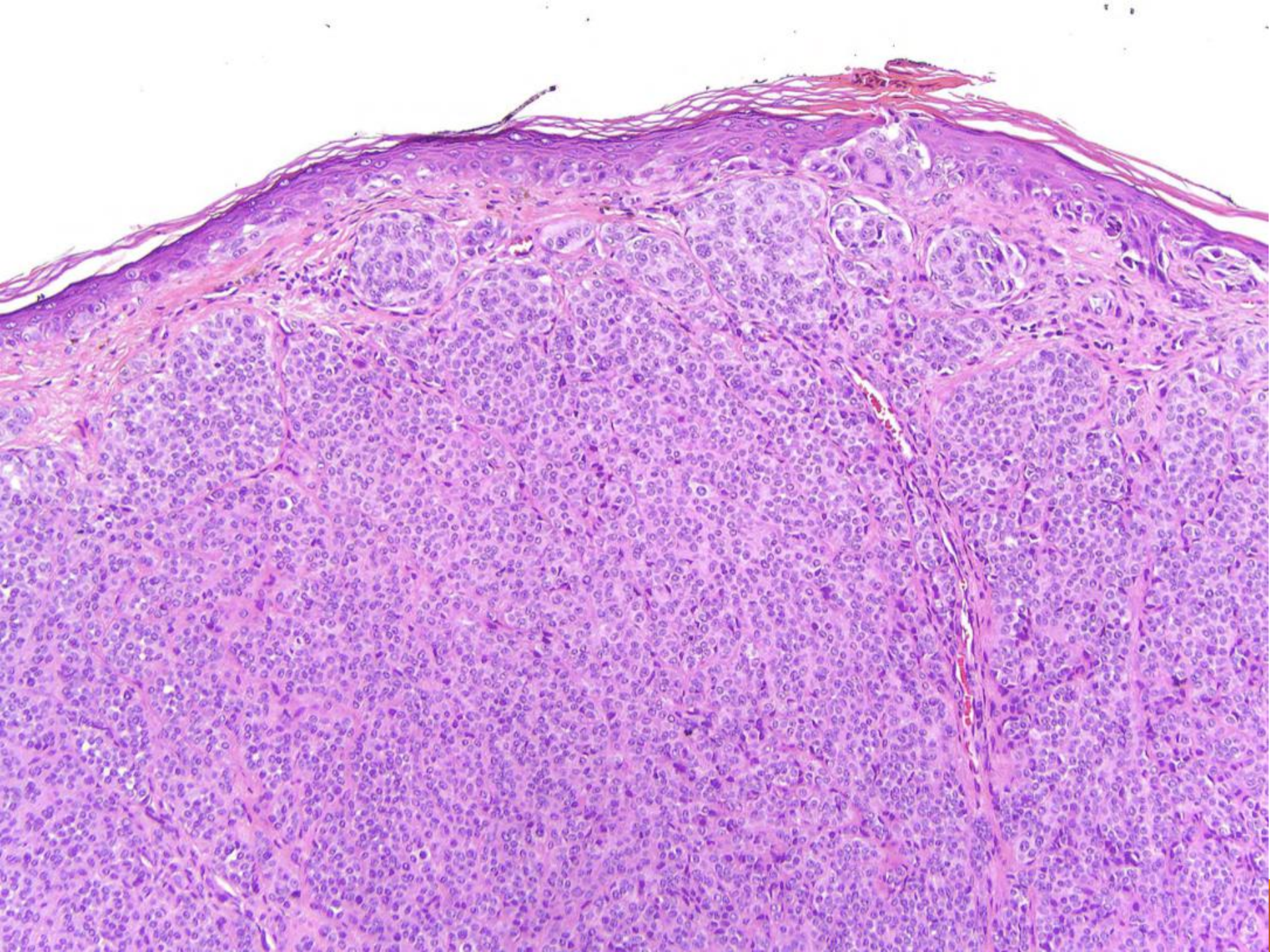


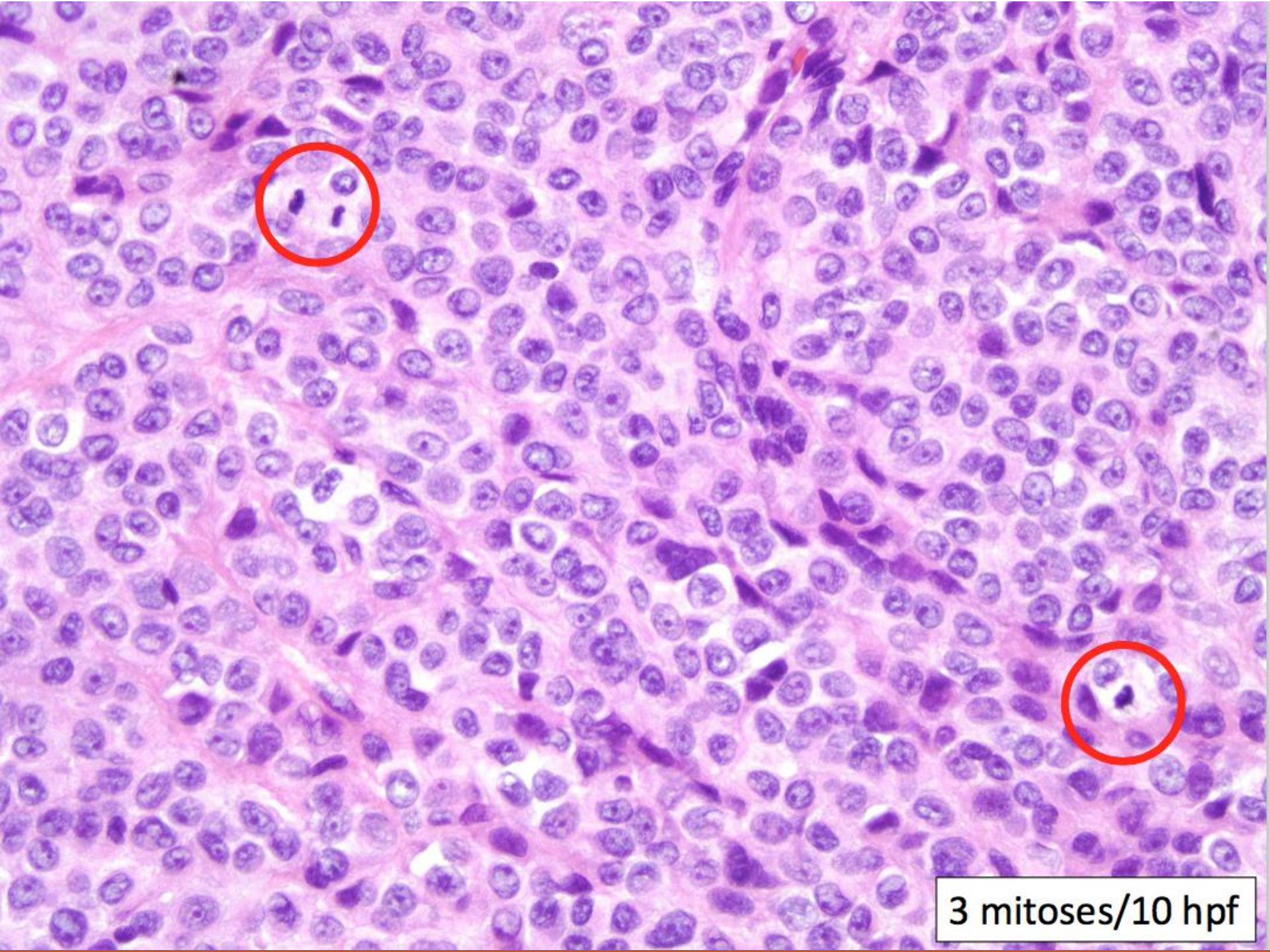



Ki-67


Ki-67


15 yo




3 mitoses/10 hpf

Melanoma Arising in Congenital Nevus

- **Onset during childhood/adulthood (very rare in children < 10 yo)**
- **Expansile, destructive growth**
- **Sharp demarcation from background nevus**
- **Cytologic atypia (high N:C ratio, hyperchromasia, prominent nucleoli)**
- **High mitotic rate and Ki-67 > 5%**
- **Pagetoid spread into epidermis**
- **Necrosis**

	Benign PN	Atypical PN	Melanoma
Clinical:			
Age	Neonates and infants	Neonates and infants	Children and adults
Size (diameter)	Usually <5 mm	Usually <5 mm	Usually >5 mm
Rapid growth	Often	Often	Often
Involution	Often	Often	No
Histologic:			
Interface with background nevus	Smooth and gradual	Somewhat discrete	Well demarcated
Expansile growth	Absent	Absent or slight	Present
Epidermal involvement	Absent	May be present focally	Pagetoid spread into epidermis
Cytologic atypia	Absent or mild	Mild to moderate	Usually high-grade
Mitoses	Few (<2 per 10 hpf)	May be increased (>2 per 10 hpf)	Usually high

Comparative Genomic Hybridization

- **Atypical proliferative nodules:**
  - **No chromosomal aberration, or**
  - **Numerical aberrations (whole chromosome losses/gains)**
- **Melanomas:**
  - **Structural aberrations (partial chromosome losses/gains) almost always present**
  - **+/- Numerical aberrations**

Bastian BC, et al. Am J Pathol 2002;161:1163-9.

Proliferative Dermal Nodules

- **A spectrum of benign, atypical, and malignant nodular proliferations may occur in congenital nevi.**
- **Melanoma is exceptionally rare in infants.**
- **Look for smooth interface, minimal cytologic atypia, low mitotic activity, and low Ki-67 (< 5%) in proliferative nodules.**
- **Atypical proliferative nodules may be extremely difficult to distinguish from melanomas; CGH may be helpful in ambiguous cases.**