Australasian Dermatopathology Society
Perth 2014
Goeffrey Hunter Oration

Borderline Melanocytic Tumors

Artur Zembowicz, MD, PhD

Associate Professor of Pathology, Tufts Medical School, Boston, MA
Medical Director, DermatopathologyConsultations.com, Boston, MA
Founder, Dermpedia.org, Boston, MA
Senior Consultant in Dermatopathology, Lahey Clinic, Burlington, MA

Expert Pathology Consultations Worldwide
DermatopathologyConsultations.com

Lahey CLINIC

Melanoma or Not Paradigm of Classification of Melanocytic Tumors A.D. 1990's

Difficult areas in diagnostic pathology

- Differentiation between atypical nevus and early melanoma
- Recognition of early lentigo maligna
- Nevoid melanoma
- Spitzoid melanocytic tumors
- Atypical variants of special nevi
- Atypical proliferative nodules in congenital nevi

Borderline Diagnostic Categories in Pathology

"Borderline/indeterminate" (MELTUMP/SAMPUS):

- "difficult to classify", "with overlapping histological features between benign or malignant", "challenging", "controversial", "equivocal", etc.

Borderline/intermediate

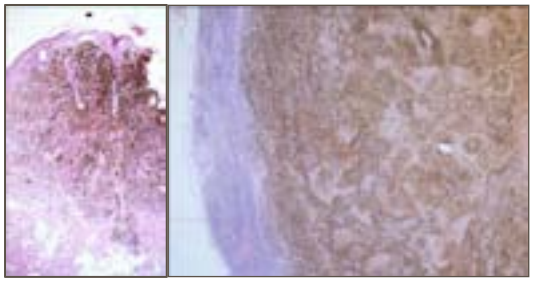
- distinct nozological category, a specific disease or clinicopathological entity of intermediate malignant potential

Pigmented Epithelioid Melanocytoma

A Low-grade Melanocytic Tumor With Metastatic Potential Indistinguishable From Animal-type Melanoma and Epithelioid Blue Nevus

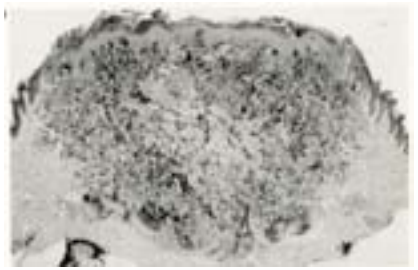
Artur Zembowicz, MD, PhD, J. Aidan Carney,† and Martin C. Mihm**

[*Am J Surg Pathol* 2004;28:31–40]

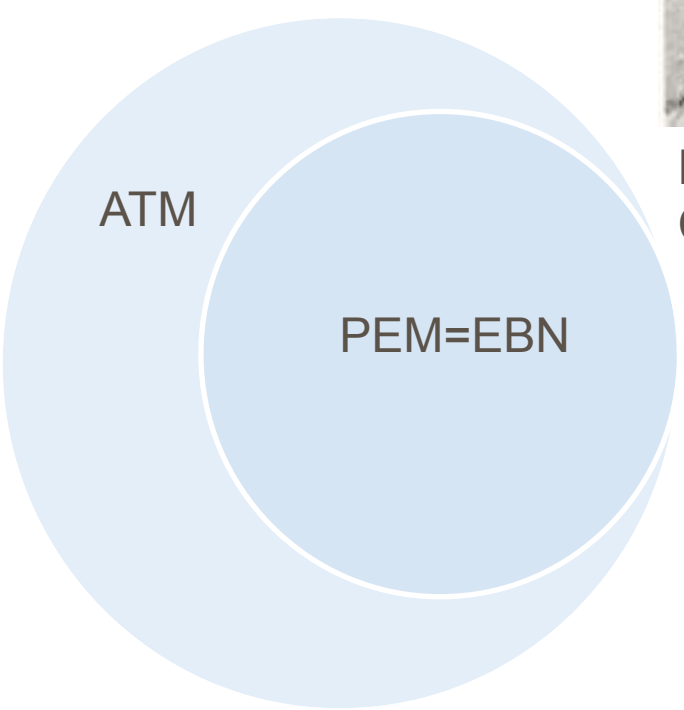


Animal type melanoma (ATM)

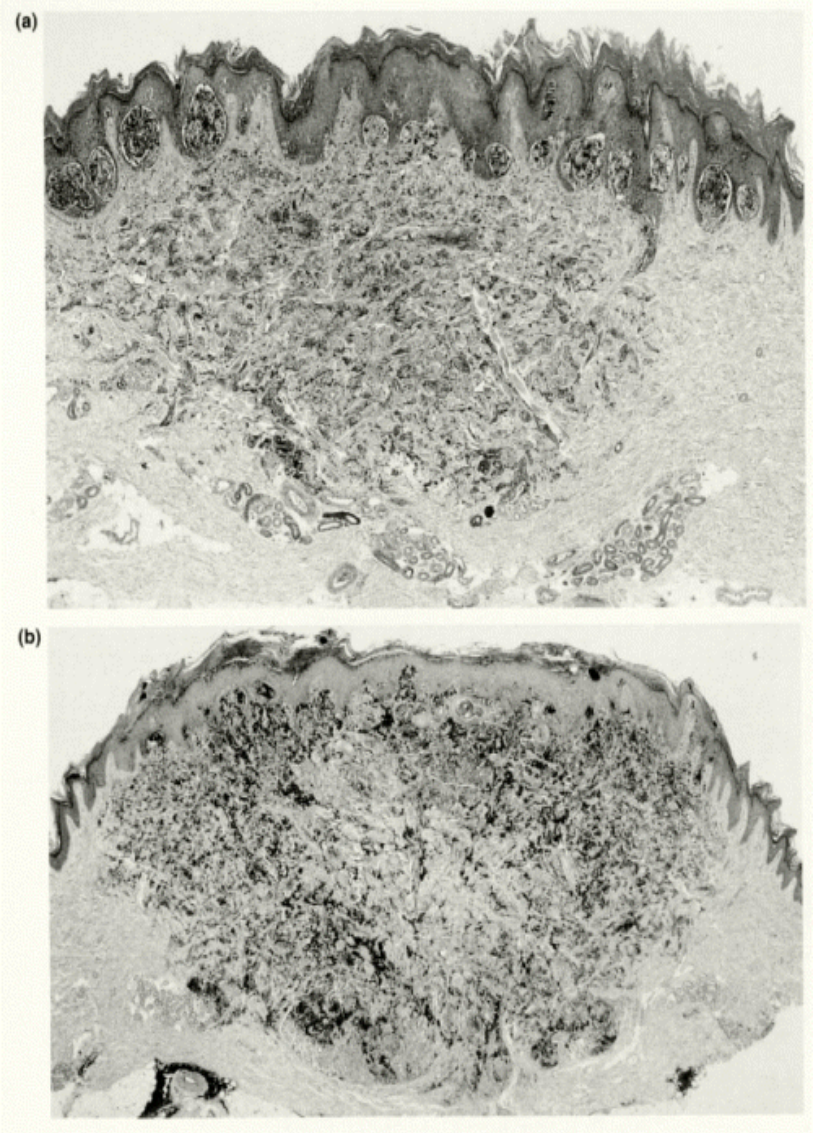
- Mean Breslow thickness = 3.3 mm
- 11/24 patients (46 %) had lymph node metastases

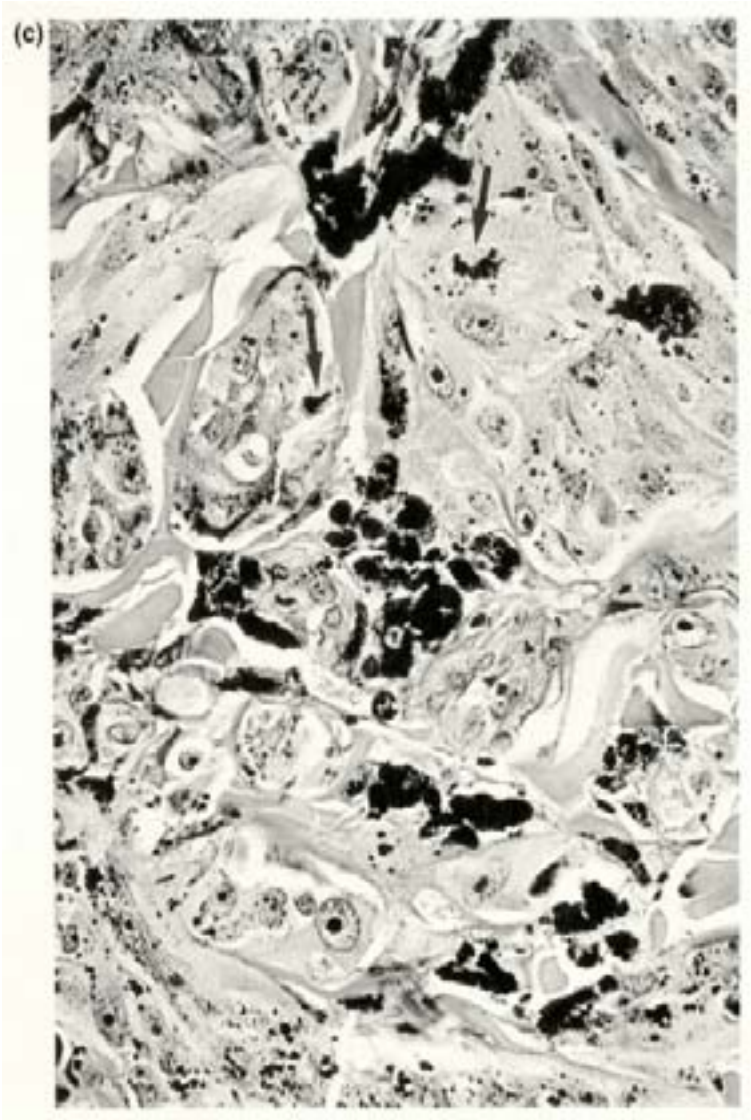


Epithelioid blue nevus of Carney Complex



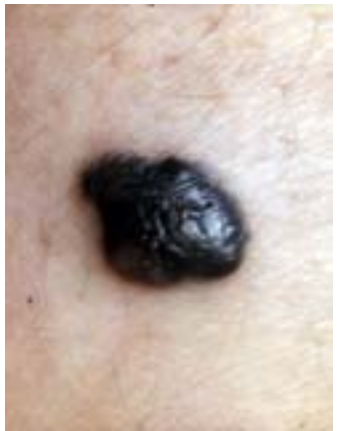
Carney & Ferreiro The Epithelioid Blue Nevus: A Multicentric Familial Tumor With Important Associations, Including Cardiac Myxoma and Psammomatous Melanotic Schwannoma. Am. J. Surg. Path.1996, 259-272

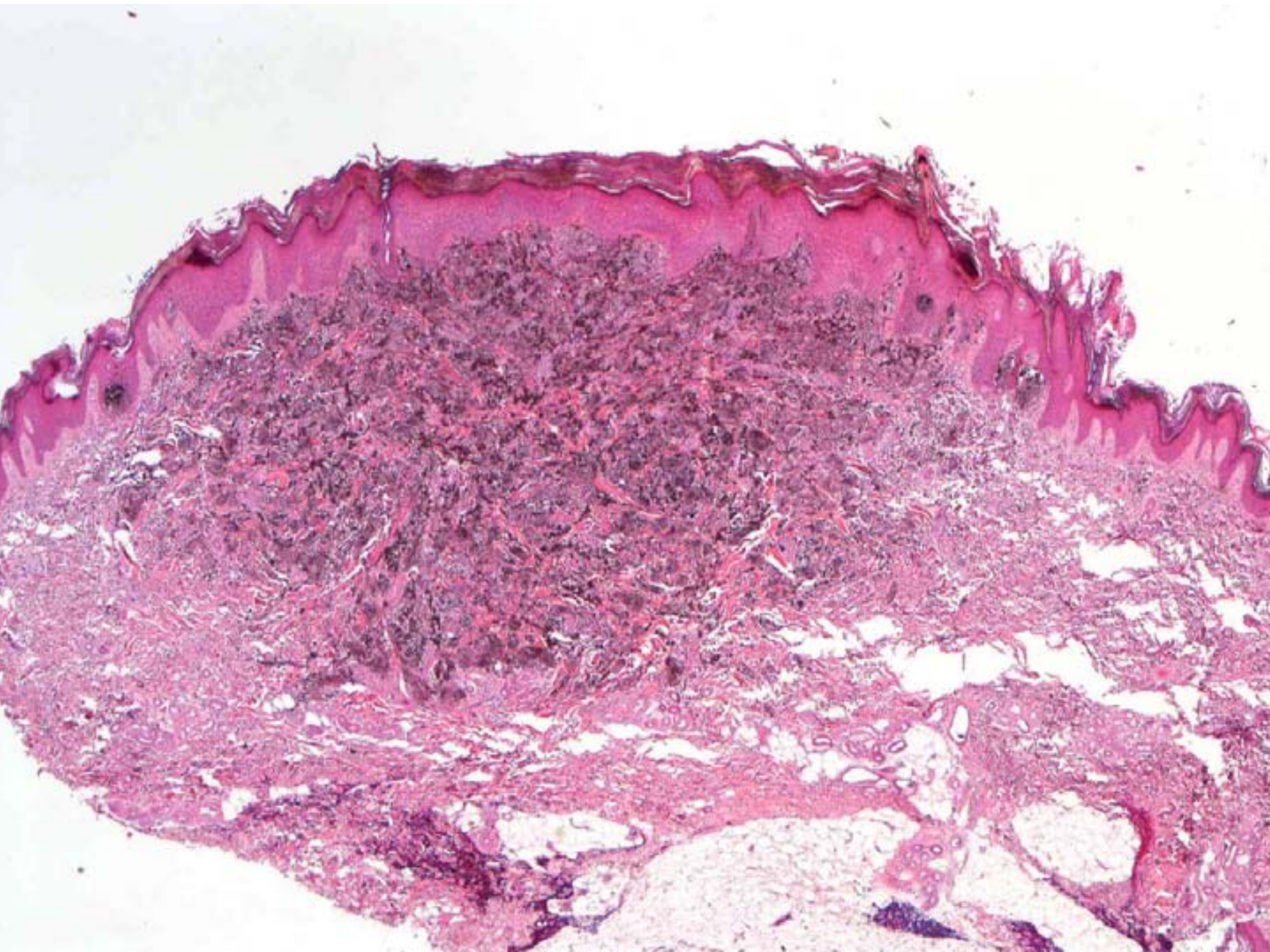


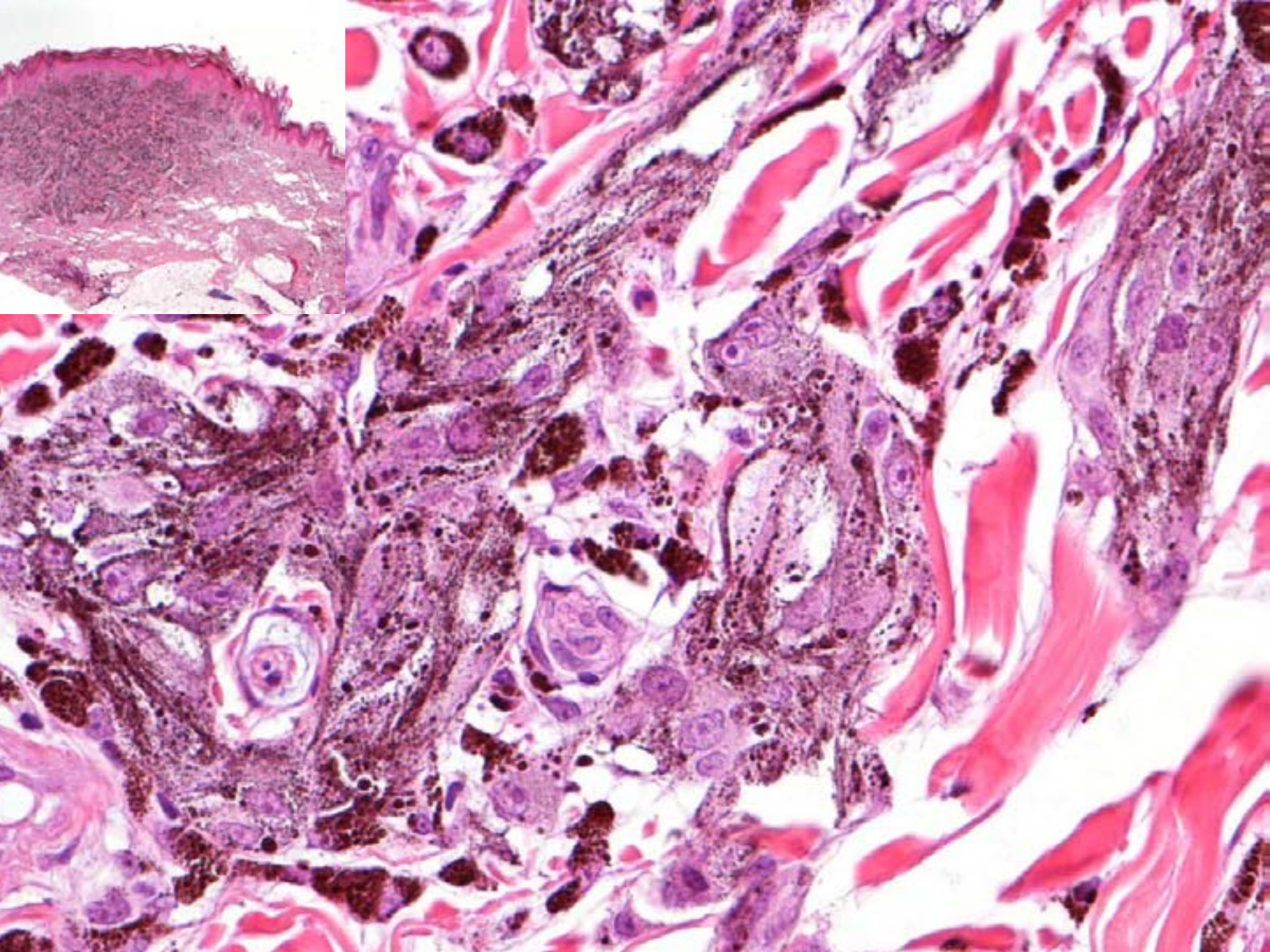


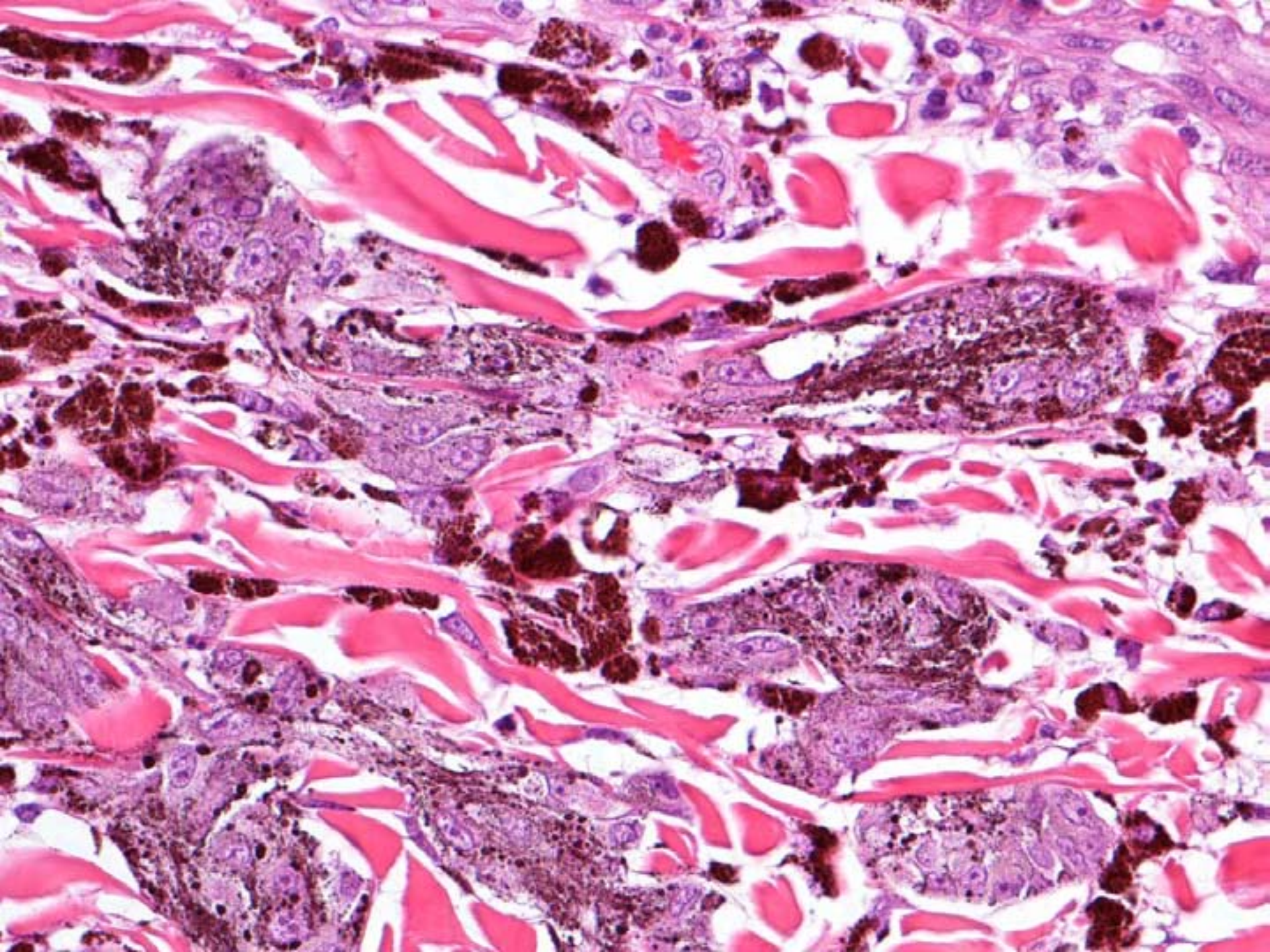
Pigmented Epithelioid Melanocytoma

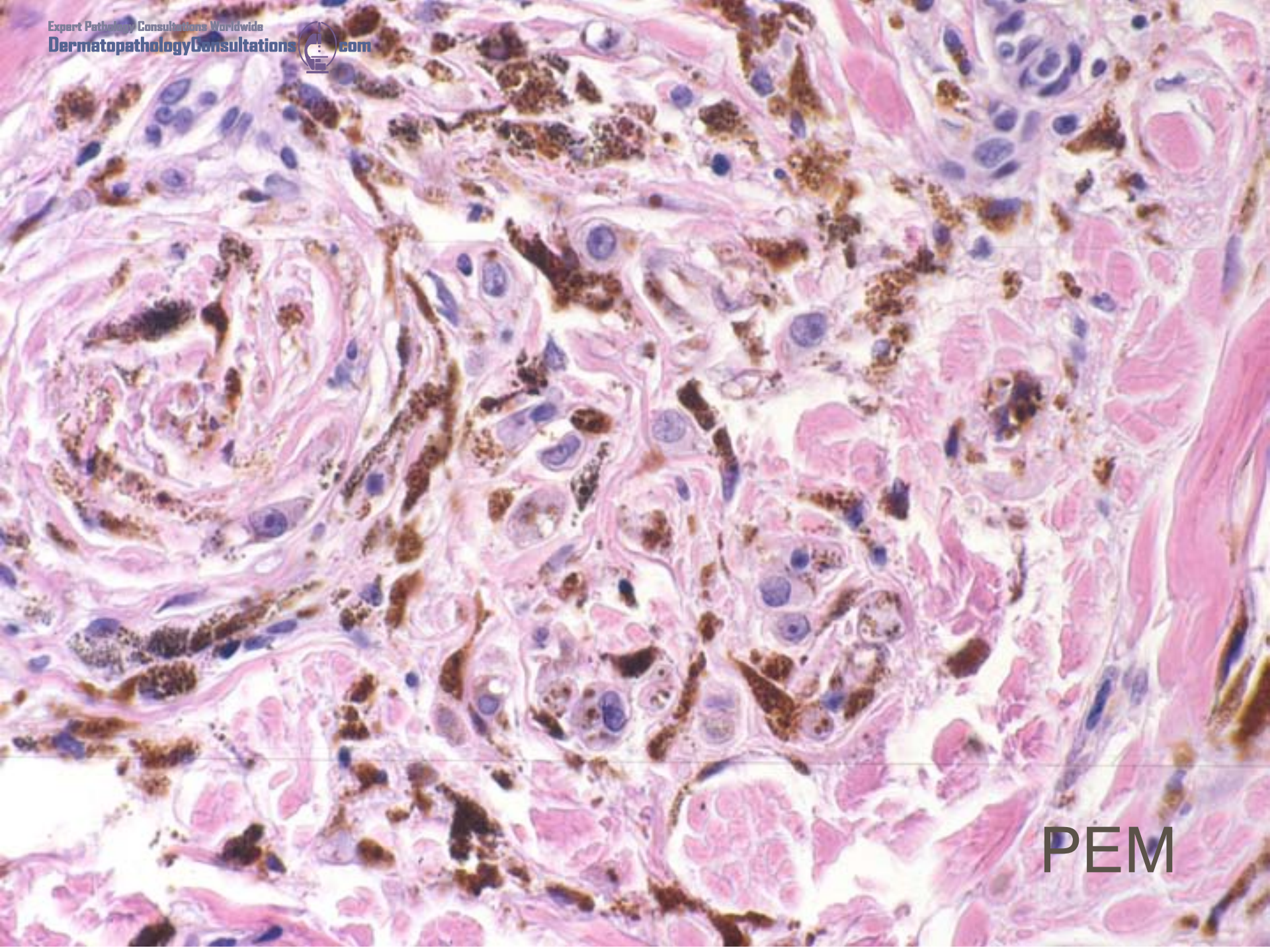
1. Synonymous with epithelioid blue nevus and includes most cases of previously diagnosed as “animal-type” melanoma
2. Can occur in the context of familiar cancer syndrome (Carney complex) and as a sporadic tumor in patients without the complex
3. Unique borderline melanocytic tumor or indolent melanoma capable of lymph node metastases but with limited potential to spread beyond lymph nodes

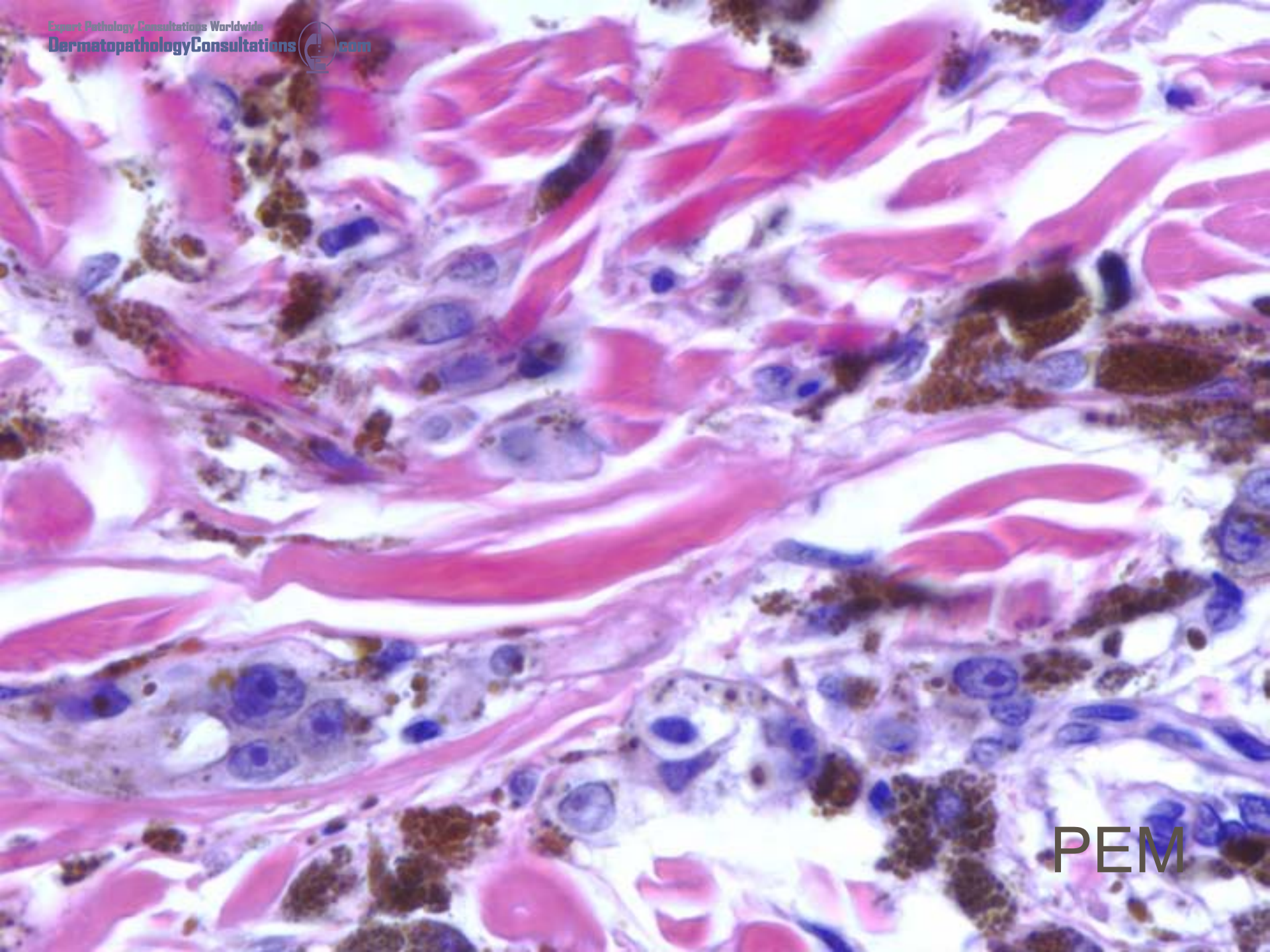


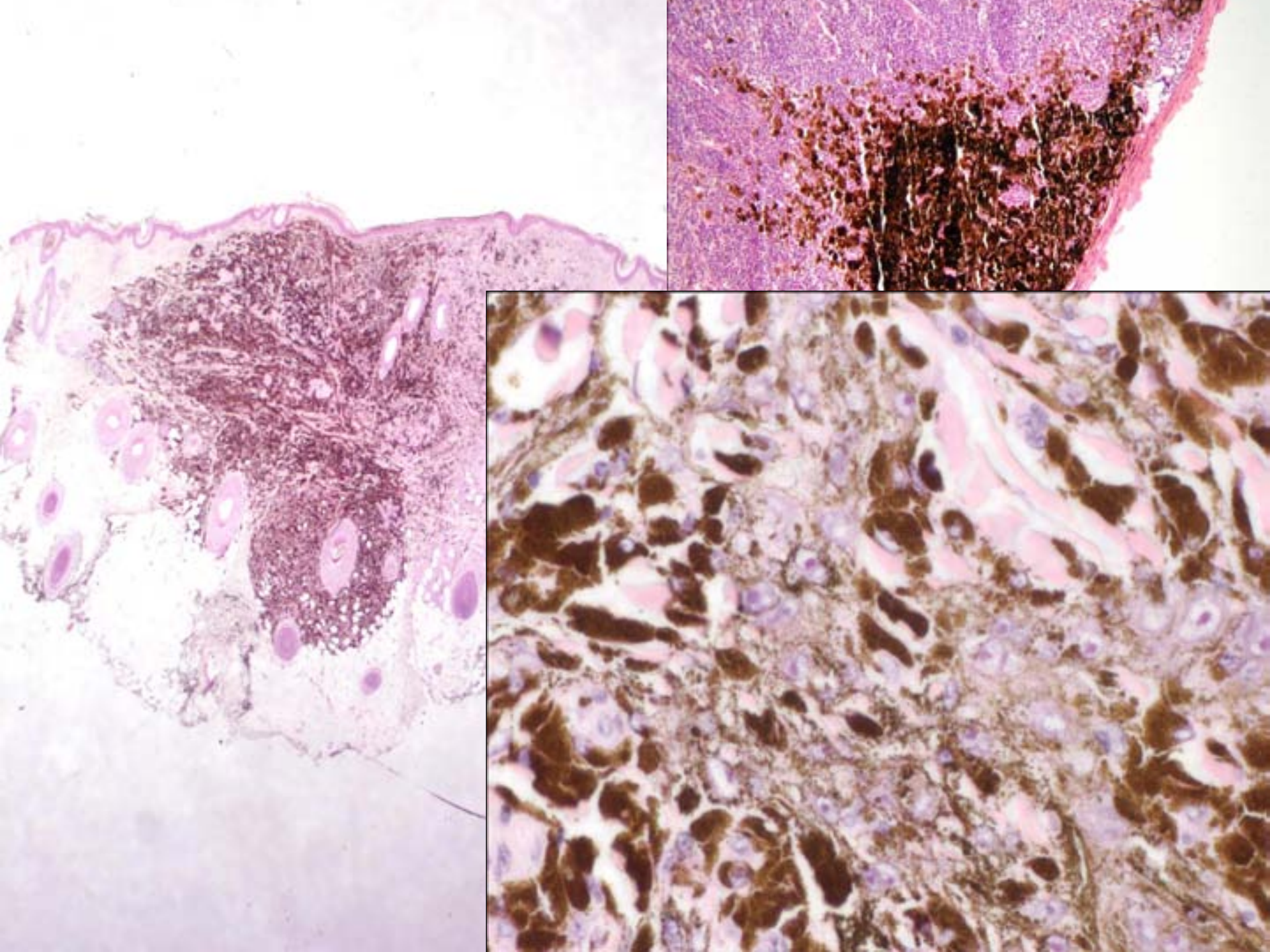






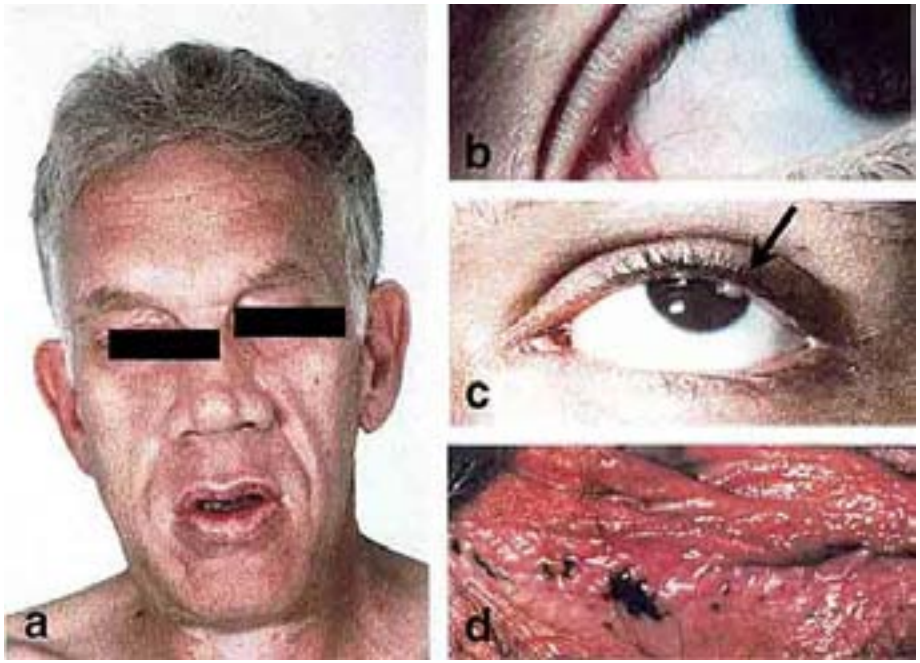






Carney Complex

- MULTIPLE ENDOCRINE NEOPLASIA AND SKIN LENTIGINOSIS SYNDROME
  - PIGMENTED SKIN LESIONS:
    - Lentiginies, blue nevi, and epithelioid blue nevi
  - ENDOCRINE TUMORS:
    - Primary pigmented nodular adrenocortical disease
    - GH and PRL producing pituitary adenoma
    - Large-cell calcifying Sertoli cell tumor
    - Thyroid adenoma and carcinoma
    - Ovarian cysts
  - NON-ENDOCRINE TUMORS:
    - Cardiac and cutaneous myxomas
    - Psammmomatous melanotic schwannoma
    - Breast duct adenoma
    - Osteochondromyxoma of the bone



Genetics of Carney Complex

- Autosomal dominant inheritance

- Carney Complex gene:

  Protein Kinase A Regulatory Subunit 1α (R1α) (17q22-24)

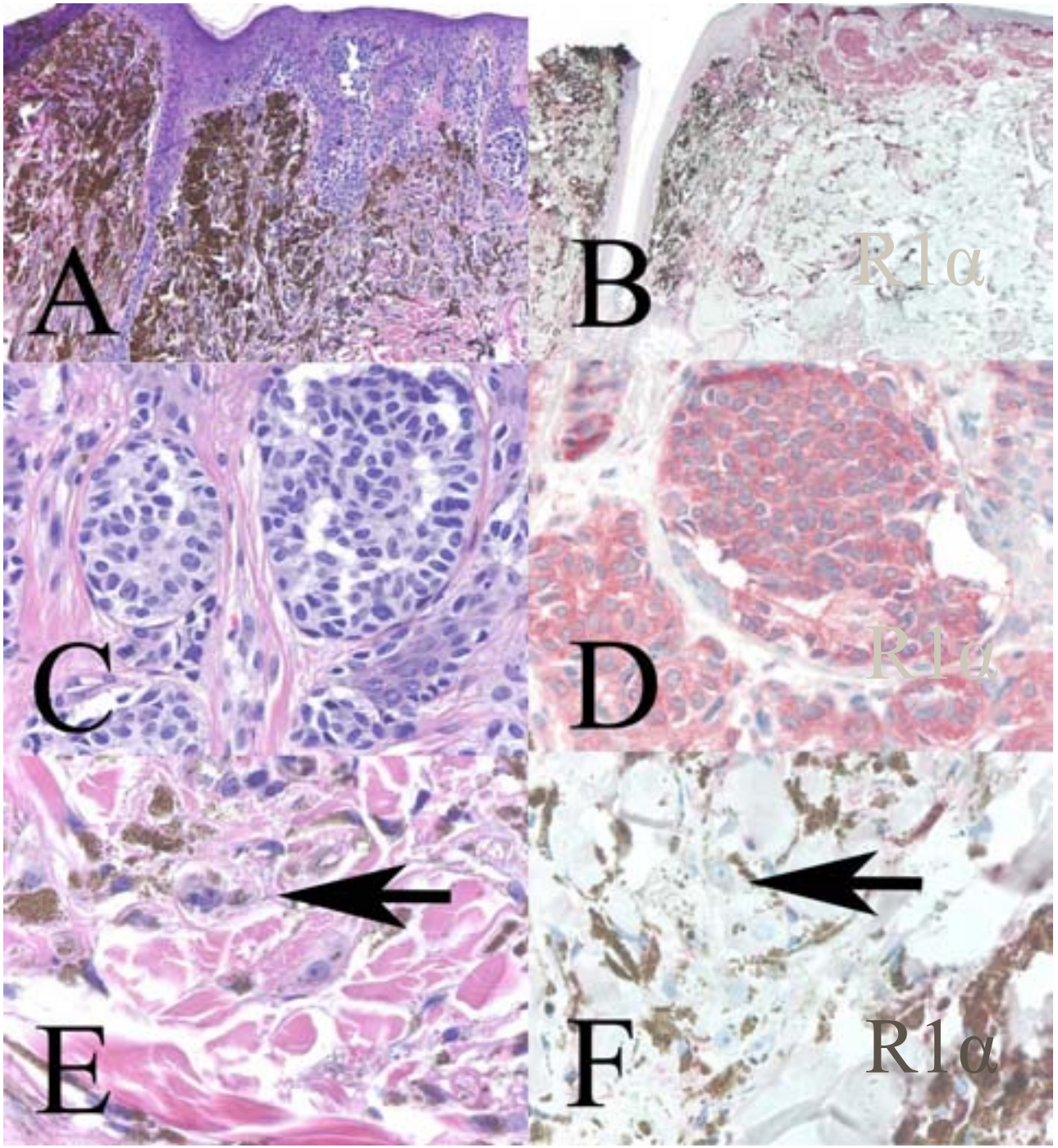
  44 % of families

Am J Hum Genet. 2002 Dec;71(6):1433-42. Epub 2002 Nov 6.

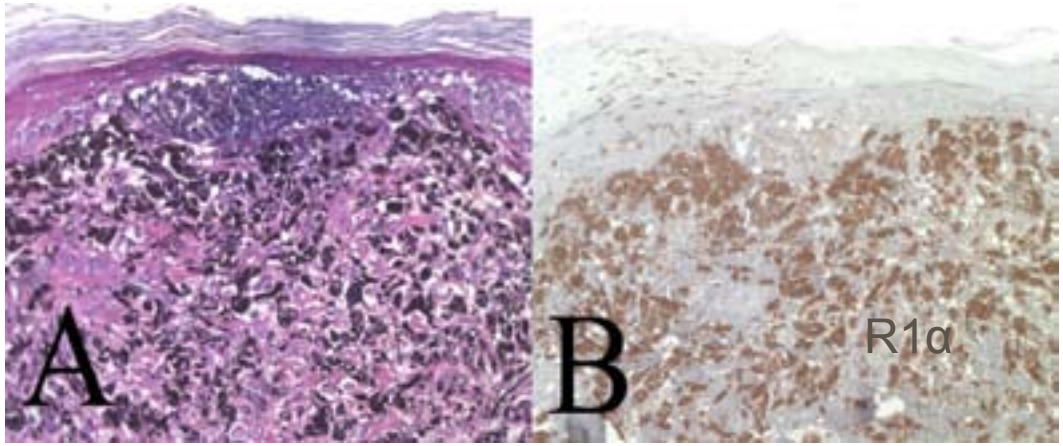
PEM arising in a compound nevus

Nevus component

PEM
(loss of R1a in 82%)



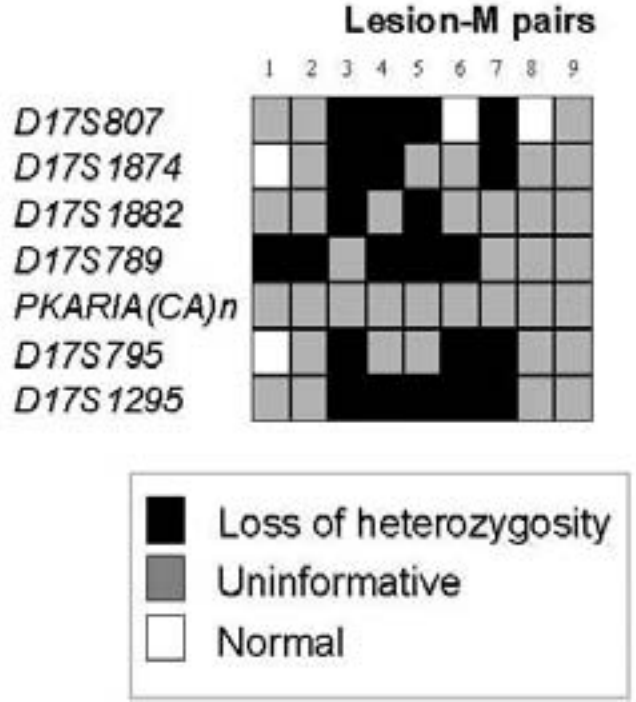
PEM: Genetic studies



LOH for the 17q22-24 locus:

present in < 7% of 28 melanomas

present in 5/7 (71%) PEMs



No mutations of PRKR1a were detected in 60 melanomas or 7 PEM.

No mutations in GNAQ in 9 PEMs (Dr. Bastian's Lab)

Pigmented Epithelioid Melanocytoma

A Low-grade Melanocytic Tumor With Metastatic Potential Indistinguishable From Animal-type Melanoma and Epithelioid Blue Nevus

Artur Zembowicz, MD, PhD, J. Aidan Carney,† and Martin C. Mihm**

"An important implication of this paper is that it supports a recent paradigm shift occurring in melanocytic pathology, which departs from dichotomous classification of all pigmented lesions as either benign nevus or malignant melanoma. Follow-up data of PEM, its histologic similarity to Carney complex-associated epithelioid blue nevus, and the bland histologic features of some cases all suggest that PEM is a unique melanocytic neoplasm with low probability of systemic spread despite its ability to metastasize to regional lymph nodes".

"PEM is not the first example of metastasizing or recurring melanocytic tumor with favorable clinical outcome. Cases of "benign" metastasizing Spitz nevi and spitzoid "nevoid" melanomas have been described. However, histologic features of Spitz nevus and PEM are quite different. Therefore, it is possible that additional borderline melanocytic entities exist within a not uncommon group of atypical spindle and epithelioid cell tumors, which can not be definitively classified as Spitz nevi or melanoma according to present histologic criteria."

Pigmented Epithelioid Melanocytoma: Favorable Outcome After 5-year Follow-up

Rajni V. Mandal, MD, Rajmohan Murali, MBBS,† Kurt F. Lundquist, MD,‡ Bruce D. Ragsdale, MD,‡ Peter Heenan, MD,§ Stanley W. McCarthy, MD,† Martin C. Mihm, Jr, MD,* Richard A. Scolyer, MD,† and Artur Zembowicz, MD, PhD*‖¶*

Abstract: Pigmented epithelioid melanocytoma (PEM) is a recently described entity encompassing epithelioid blue nevus (of Carney complex) and most tumors earlier considered as so-called "animal-type melanoma". Loss of expression of a Carney complex gene, cyclic adenosine 3′,5′ monophosphate-dependent protein kinase regulatory subunit 1α, is observed in the majority of PEMs. Initial reports with short-term follow-up have suggested that although PEMs frequently metastasize to lymph nodes, they have a more favorable outcome than conventional melanomas. In this report, we present the results of long-term follow-up in 26 patients with PEMs from North America and Australia. There were 9 males and 17 females, with a median age of 20 years. The tumors involved the trunk (6 cases), extremities (12 cases), genitalia (1 case), and the head and neck region (7 cases) had a median Breslow thickness of 2.2 mm (range 0.80 to 10.0 mm) and a median Clark level of 4. Eight of the patients developed lymph node metastases. After a median follow-up period of 67 months (range 39 to 216 mo), all patients are alive and free of disease. These findings provide further evidence that PEM is a unique low-grade melanocytic tumor with limited metastatic potential (to lymph nodes), but a favorable long-term clinical course.

Key Words: pigmented epithelioid melanocytoma, nevus, melanoma, equine melanotic disease, epithelioid blue nevus, Carney complex, protein kinase A regulatory subunit 1α, pathology, diagnosis

(*Am J Surg Pathol* 2009;33:1778–1782)

Pigmented epithelioid melanocytoma (PEM) is a recently described entity[22] which subsumes lesions earlier considered to be so-called "animal-type melanomas",[5,6] and epithelioid blue nevi (EBN)[3] occurring in patients with Carney complex (CNC), a familial lentiginosis and neoplasia syndrome.[4]

Most CNC-associated PEMs and sporadic PEMs share loss of expression of cyclic adenosine 3′,5′ mono phosphate (AMP)-dependent protein kinase A regulatory subunit 1α (R1α), a CNC complex-associated gene product.[23] This finding provides a molecular basis supporting the common phenotype of CNC-associated and sporadic cases of PEM. Importantly, no loss of R1α was observed in blue nevi which frequently harbor somatic mutations in GNAQ, a member of the q class of G-protein α-subunits involved in mediating signals between G-protein-coupled receptors.[21]

Initial[22] and subsequent reported series[1,9,17] showed that deposits of PEM were frequently found in sentinel lymph nodes (SLNs), but short-term follow-up suggested a better prognosis for PEM than for conventional metastatic melanoma. In view of these apparently paradoxical findings, we proposed that PEM be considered to be a unique low-grade melanoma or a borderline melanocytic tumor with capacity to metastasize to lymph nodes but with less frequent systemic spread.[22]

In this study, we report clinical outcomes in 26 sporadic PEMs with a long-term follow-up.

26 with median follow-up of 67 months (range 39 to 216 mo)

Median Breslow thickness 2.2 mm (Clark's level IV)

All patients are alive with no evidence of disease

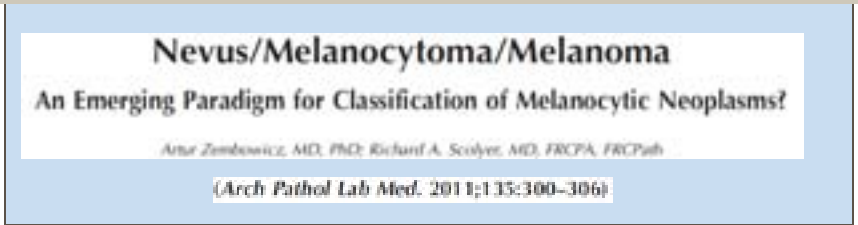
Nevus/Melanocytoma/Melanoma Paradigm

- "borderline/indeterminate" (MELTUMP/SAMPUS):
  - "difficult to classify", "with overlapping histological features between benign or malignant", "challenging", "controversial", "equivocal", etc.

Clinicopathological and molecular correlation

- Nevus
- Borderline/intermediate melanocytic tumor (Melanocytoma)
  - distinct nozological category, a specific disease or clinicopathological entity of intermediate malignant potential
- Melanoma

Click here



Other “Melanocytomas”

- BAPoma
- Atypical Spitz Tumor
- Other

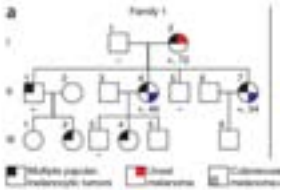
BAPoma

Nature Genetics VOLUME 43 |
NUMBER 10 |
OCTOBER 2011

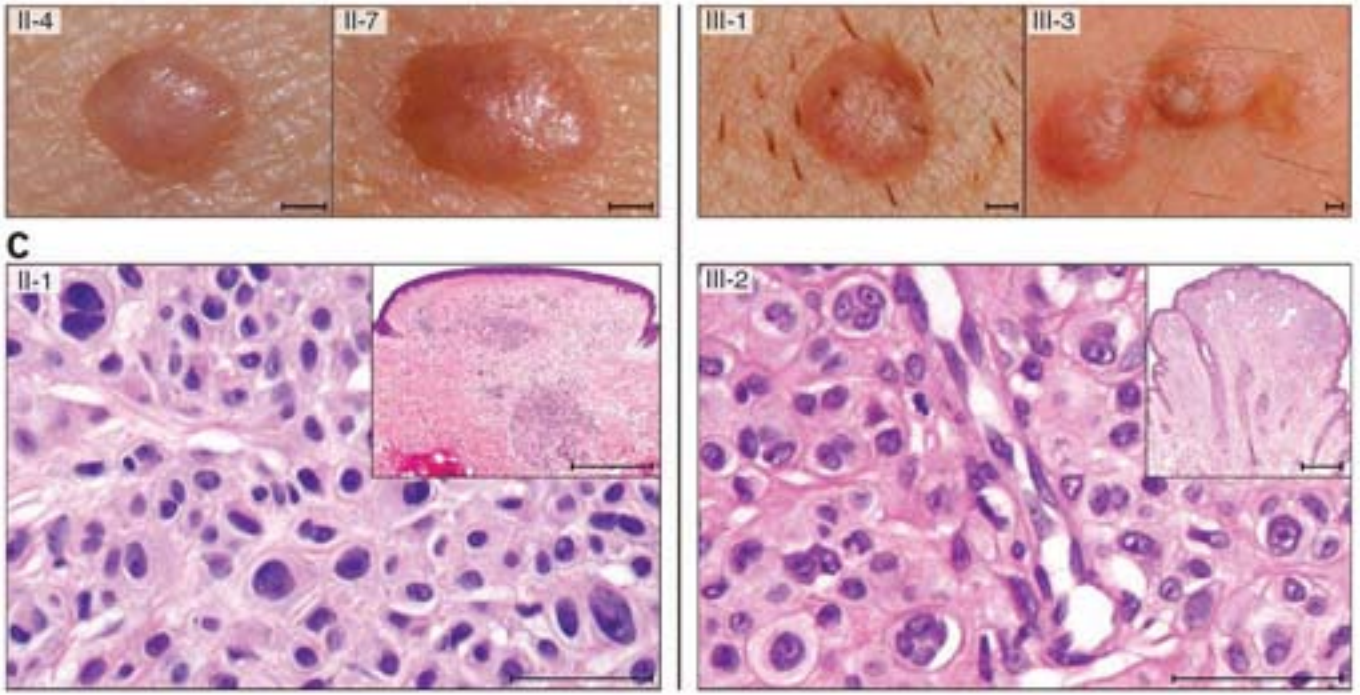
nature genetics

Germline mutations in *BAP1* predispose to melanocytic tumors

Thomas Wiesner[1,2], Anna C Obenauf[3,4], Rajmohan Murali[1], Isabella Fried[5], Klaus G Griewank[5], Peter Ulz[3], Christian Windpassinger[3], Werner Wackernagel[6], Shea Loy[1], Ingrid Wolf[7], Agnes Viale[8], Alex E Lash[7], Mono Pirun[7], Nicholas D Socci[7], Arno Büttner[9], Gabriele Palmedo[9], David Abramson[10], Kenneth Offit[4,10], Arthur Ott[11], Jürgen C Becker[5], Lorenzo Cerroni[5], Heinz Kutzner[9], Boris C Bastian[1,2,12,13] & Michael R Speicher[3,4]



Biallelic loss of BAP1 expression (mutations or loss of 3p25)



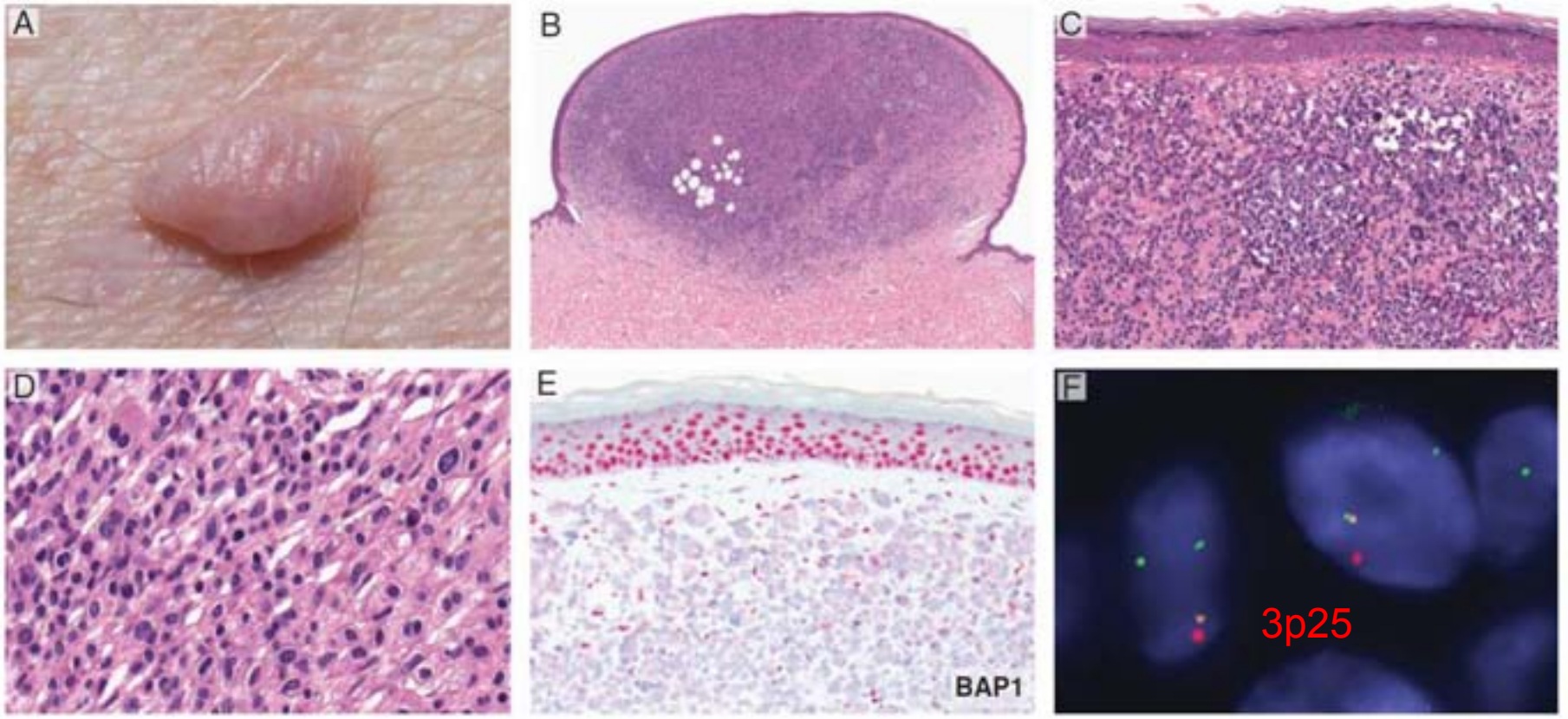
BAP1 tumors:

- ✓ Uveal melanoma
- ✓ Melanocytic BAPoma
- ✓ Mesothelioma

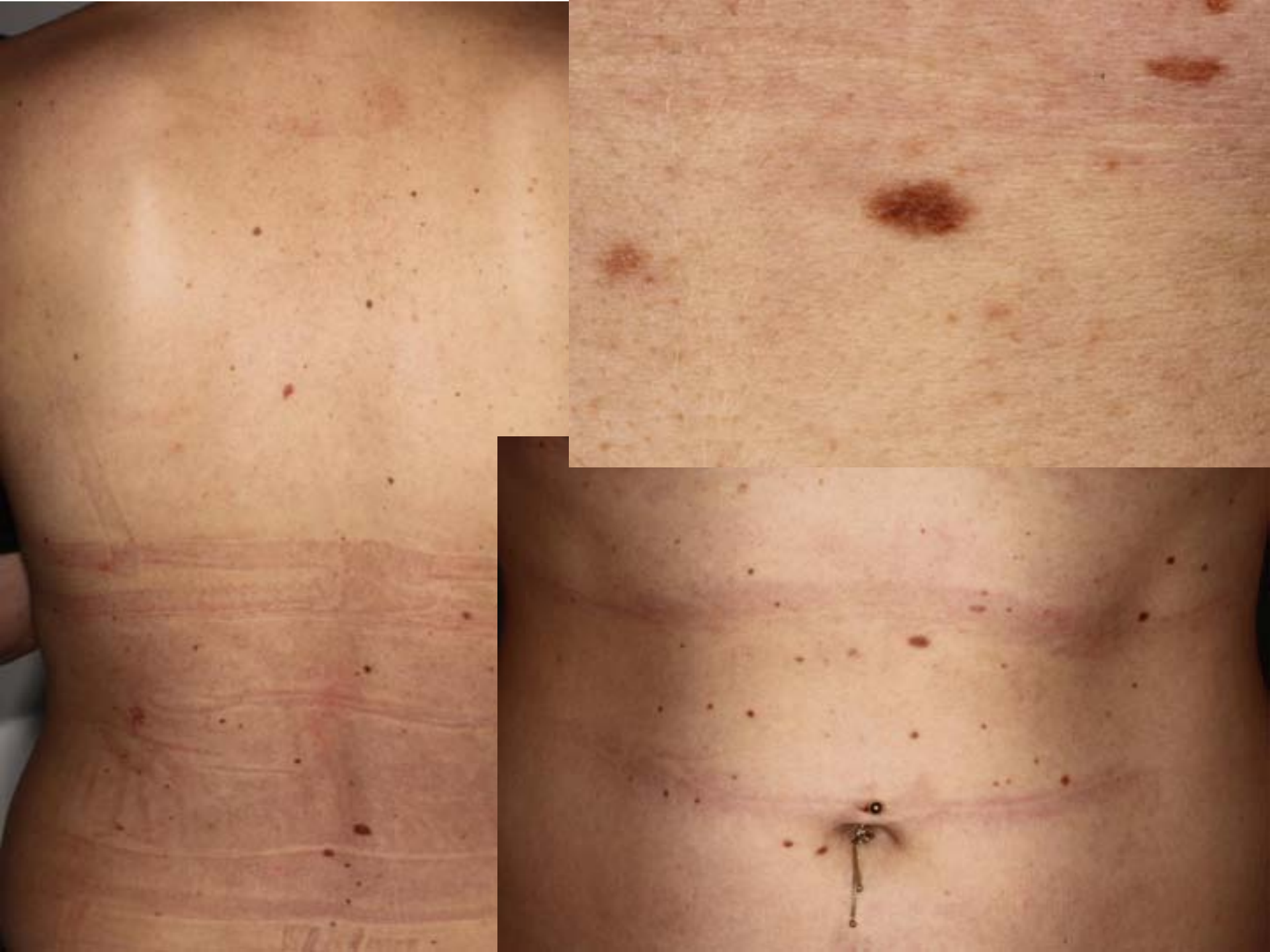
A Distinct Subset of Atypical Spitz Tumors is Characterized by *BRAF* Mutation and Loss of BAP1 Expression

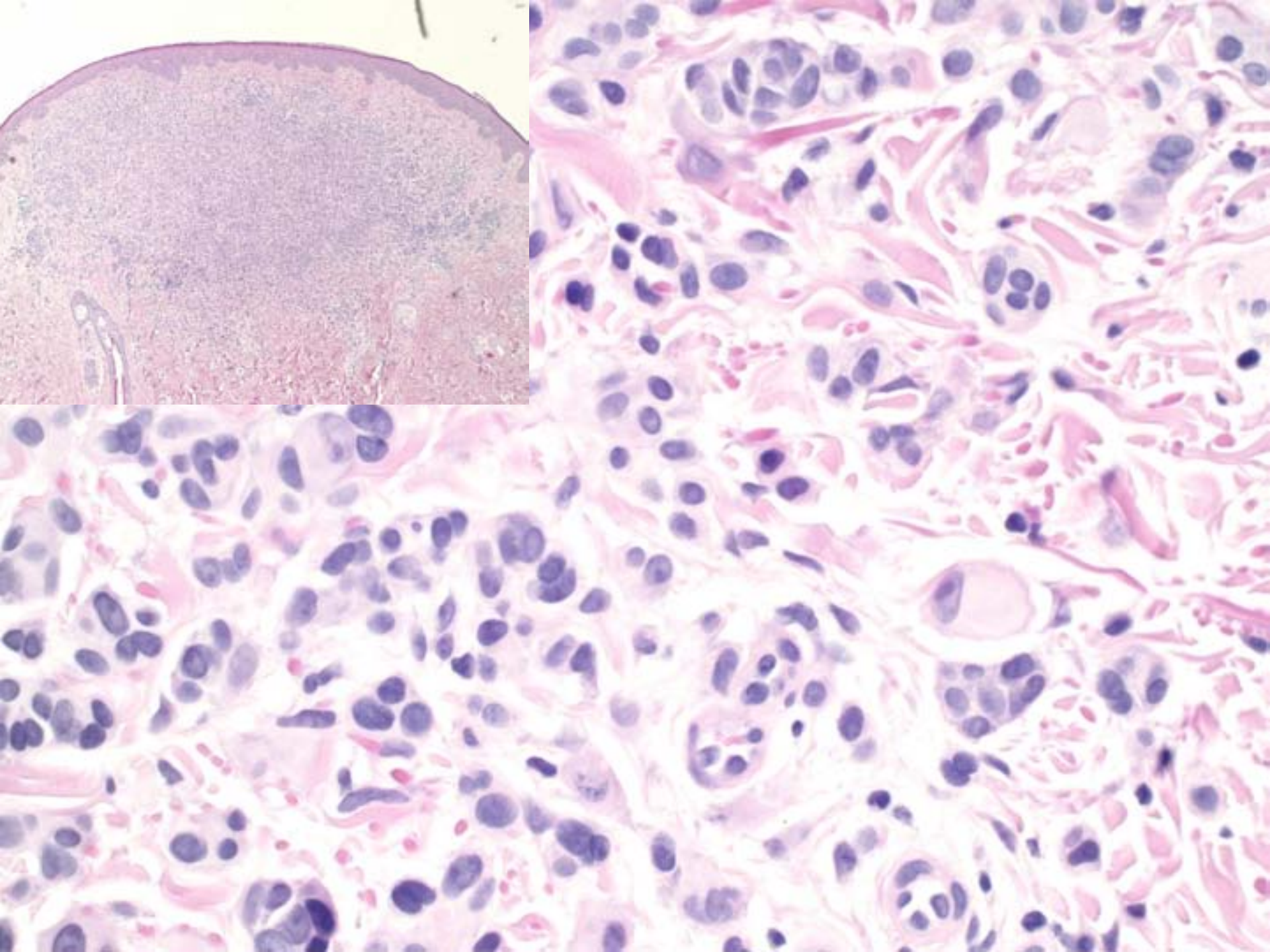
Thomas Wiesner, MD,*† Rajmohan Murali, MBBS, MD,*‡ Isabella Fried, MD,†
Lorenzo Cerroni, MD,† Klaus Busam, MD,‡ Heinz Kutzner, MD,†§ and Boris C. Bastian, MD*‡¶

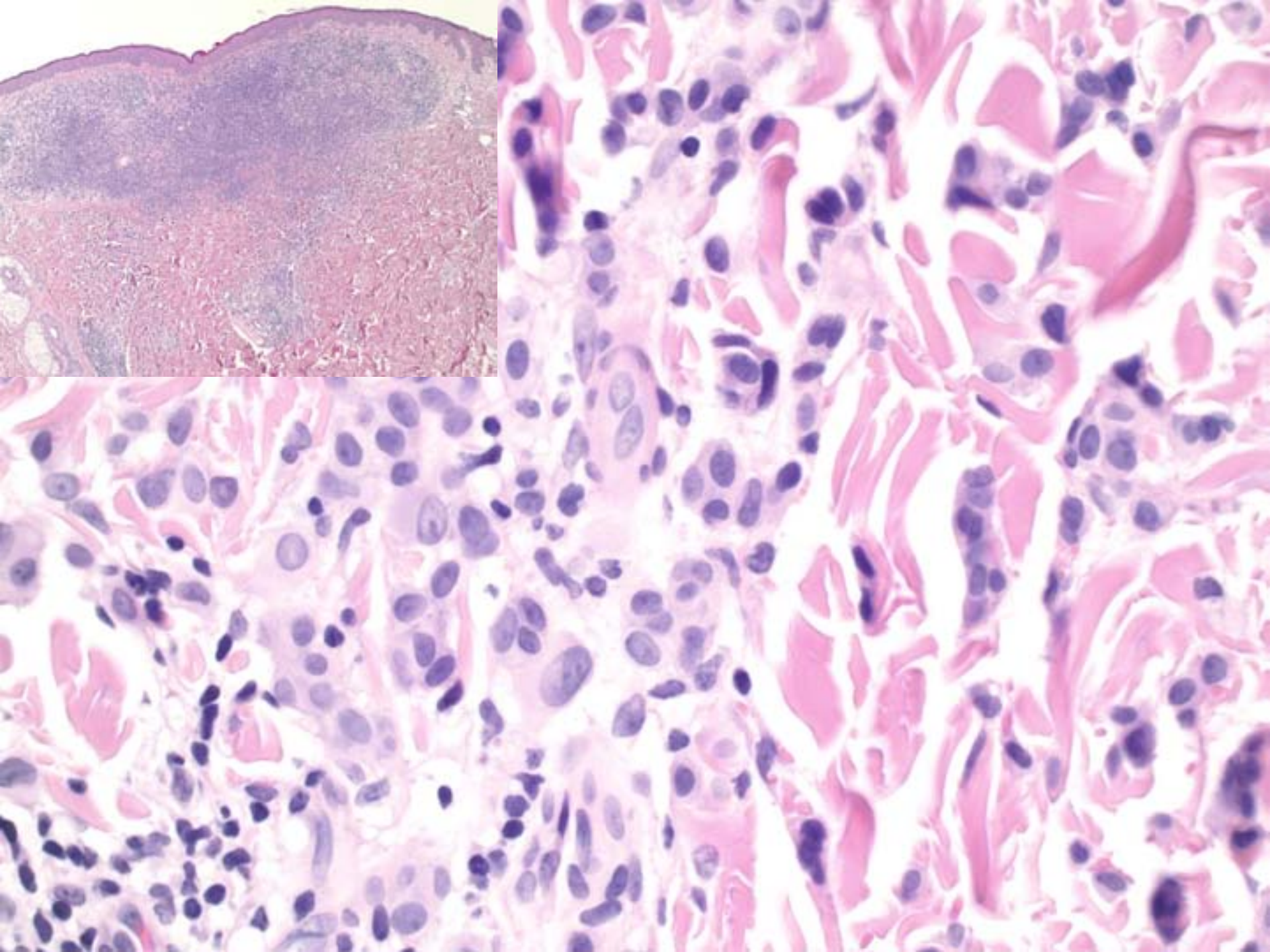
(Am J Surg Pathol 2012;36:818–830)

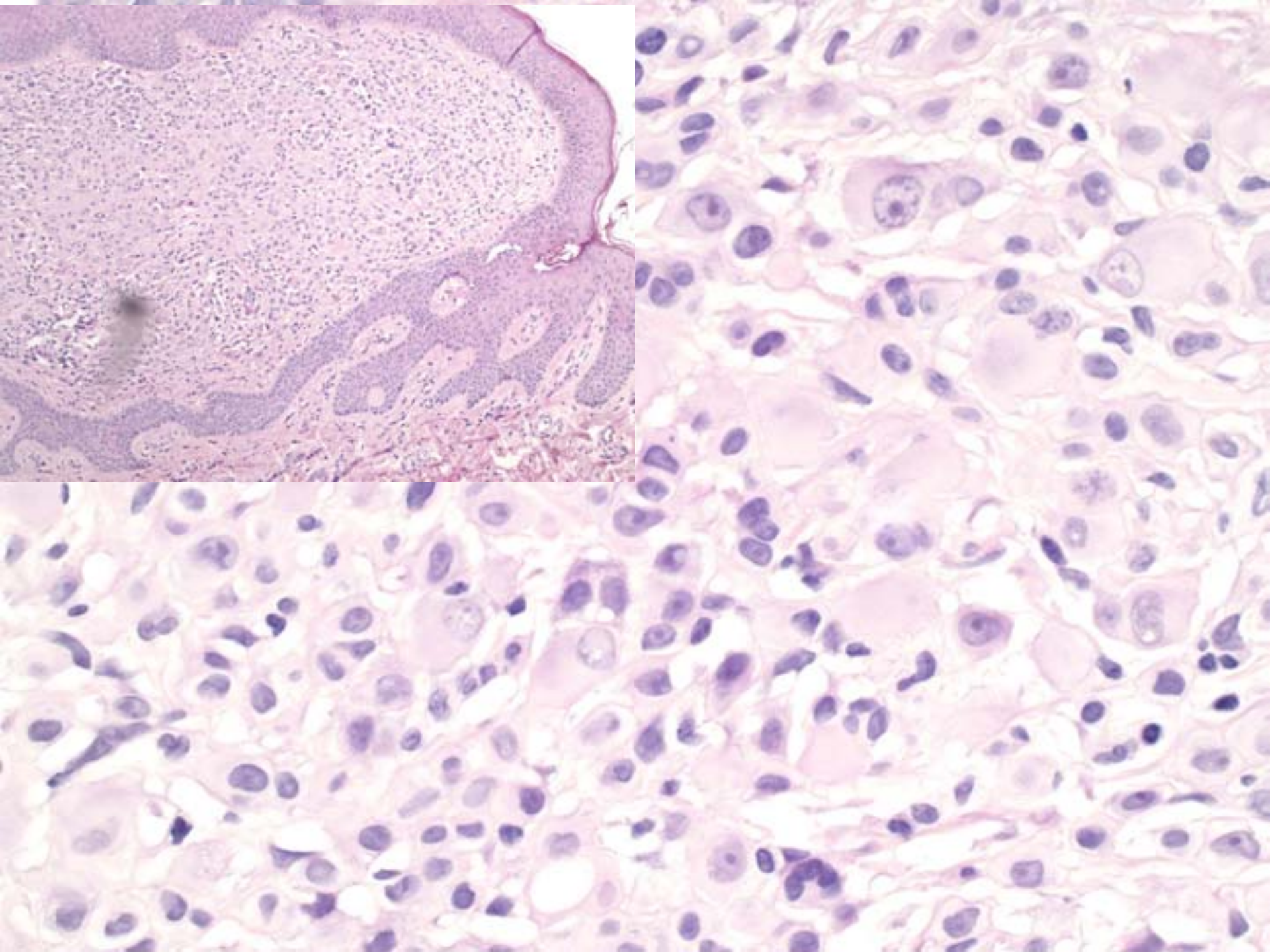


BRAFV600E/BAP1neg









Atypical Spitz Tumor

145 cases with Sentinel LN + 25-45%

No deaths with mean 35 months F/U

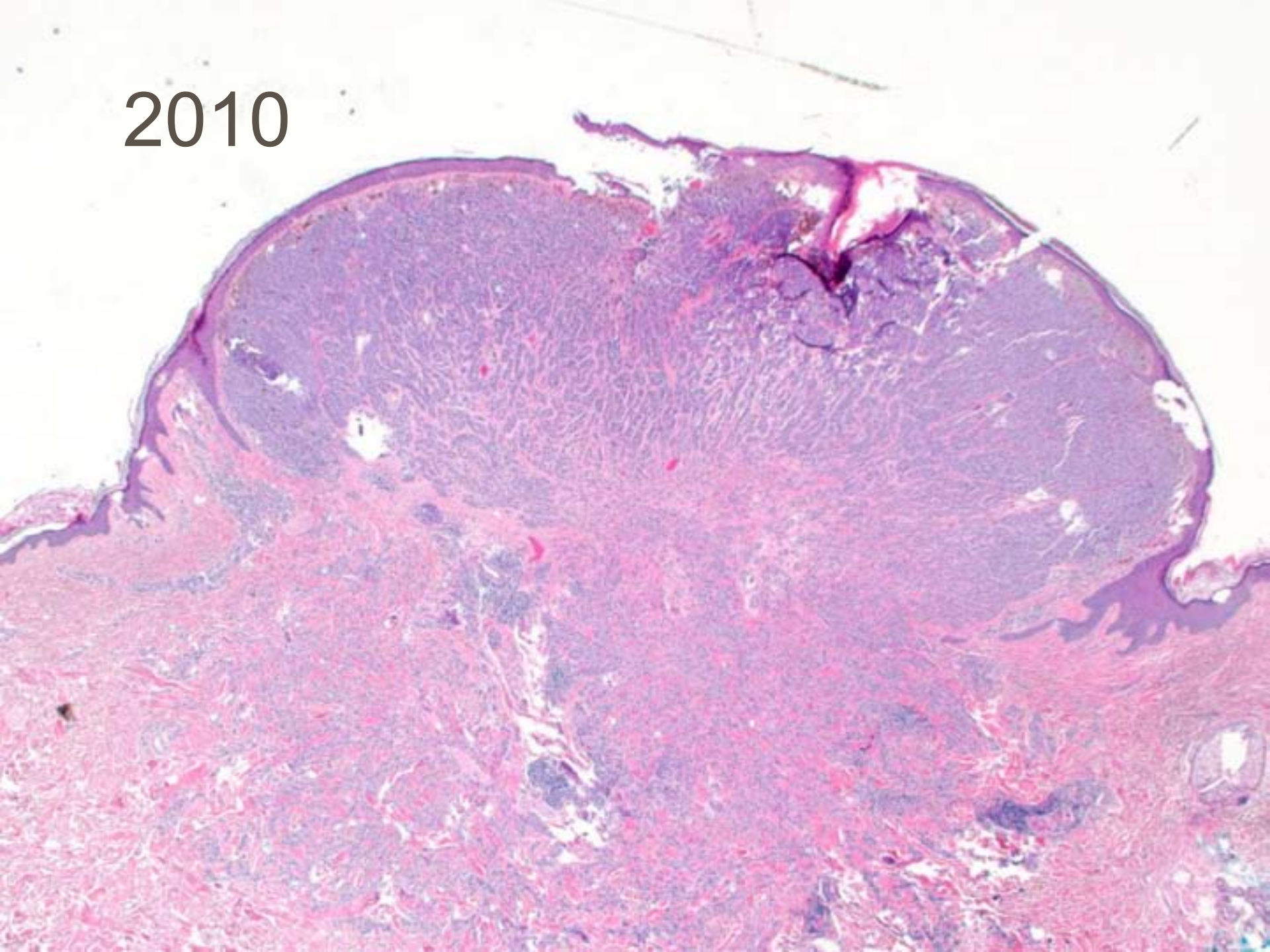
High risk vs. Low risk

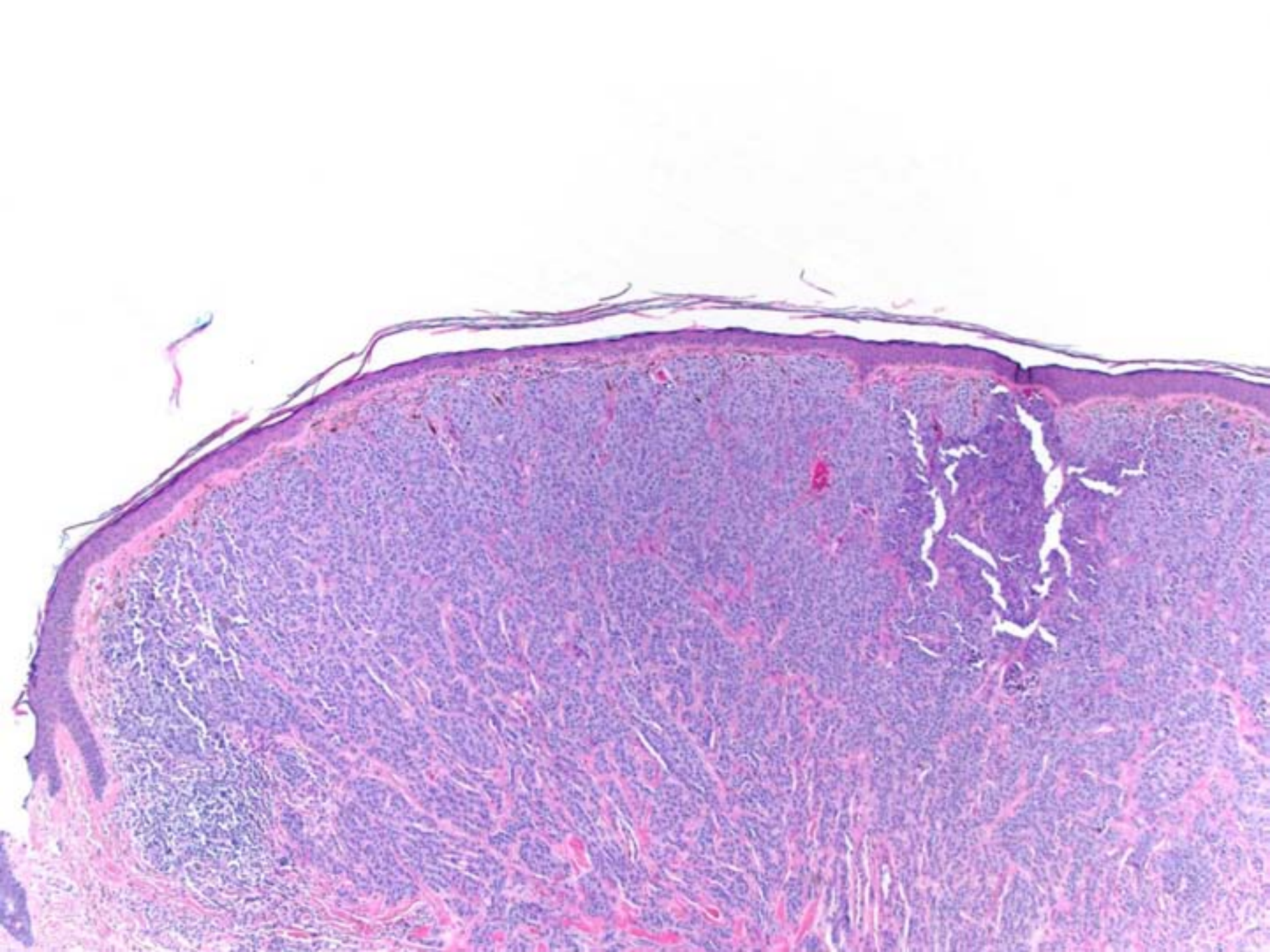
2013 Dermpedia Course
Didactic Session III:
Friday, 3:00pm-3:30pm

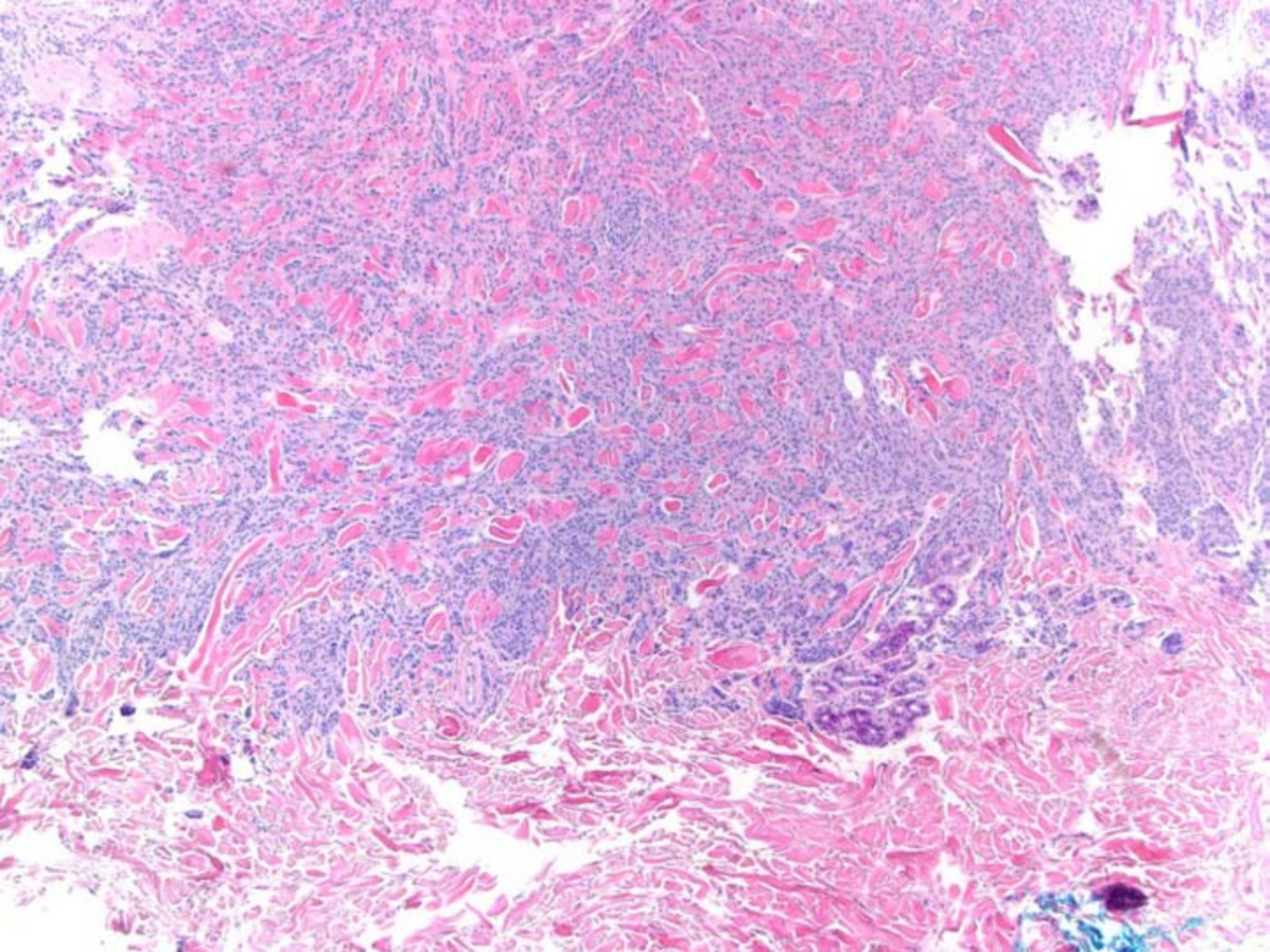
Artur Zembowicz, M.D., Ph.D.

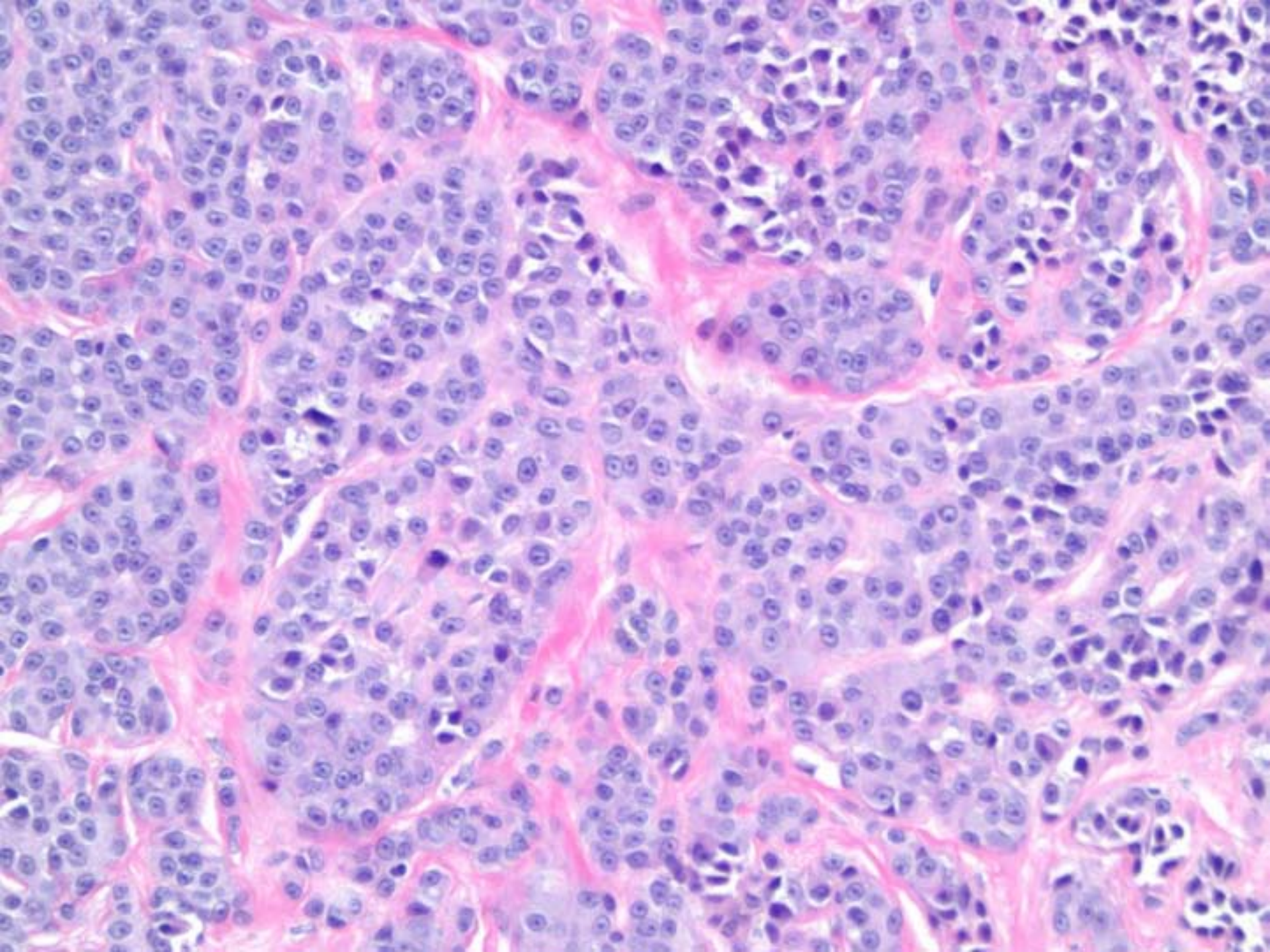
Case vignette 3:

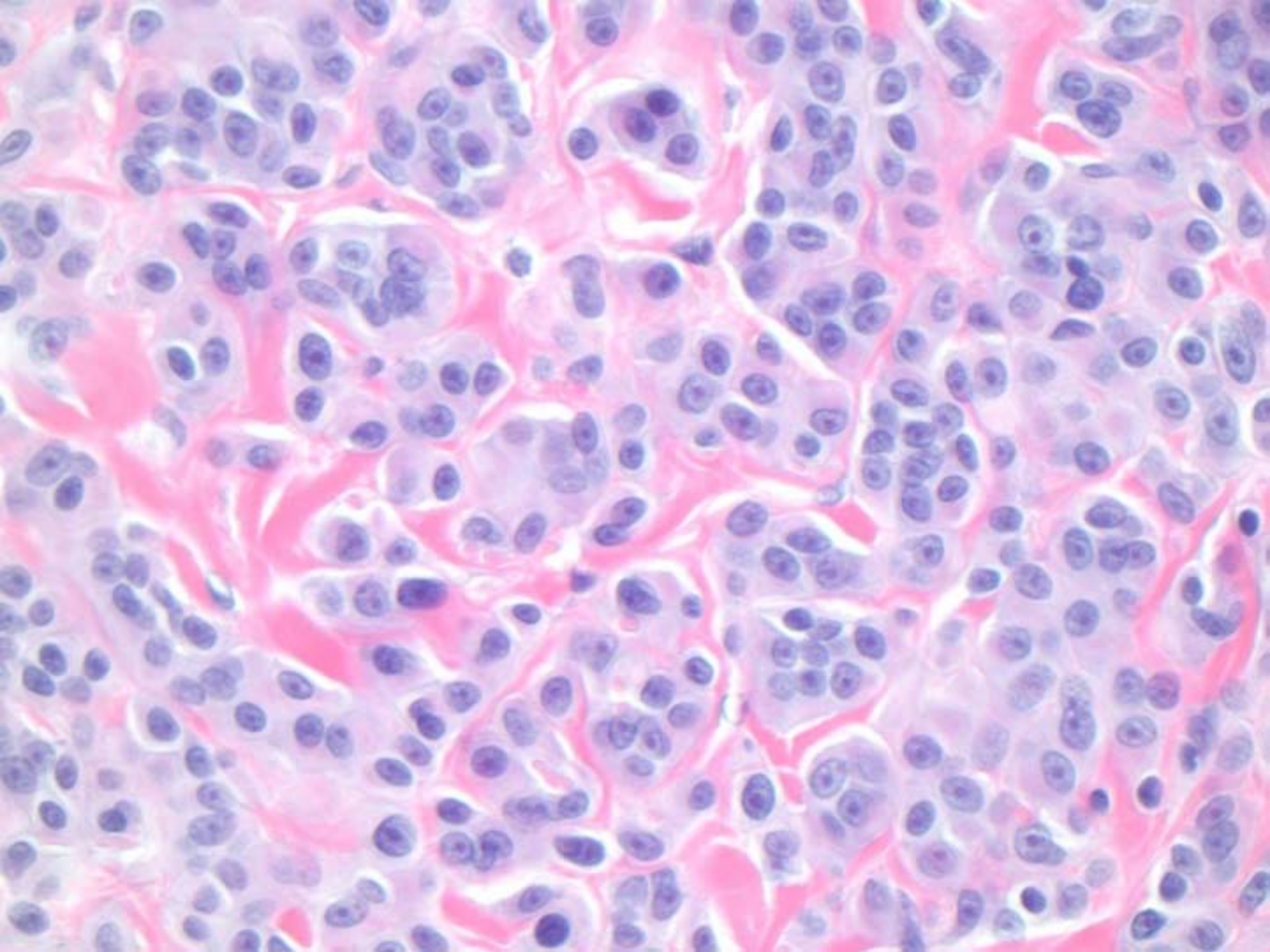
A 68 year old female with a third recurrence of a "melanocytic nevus", previously biopsied in 1997 and 2005.

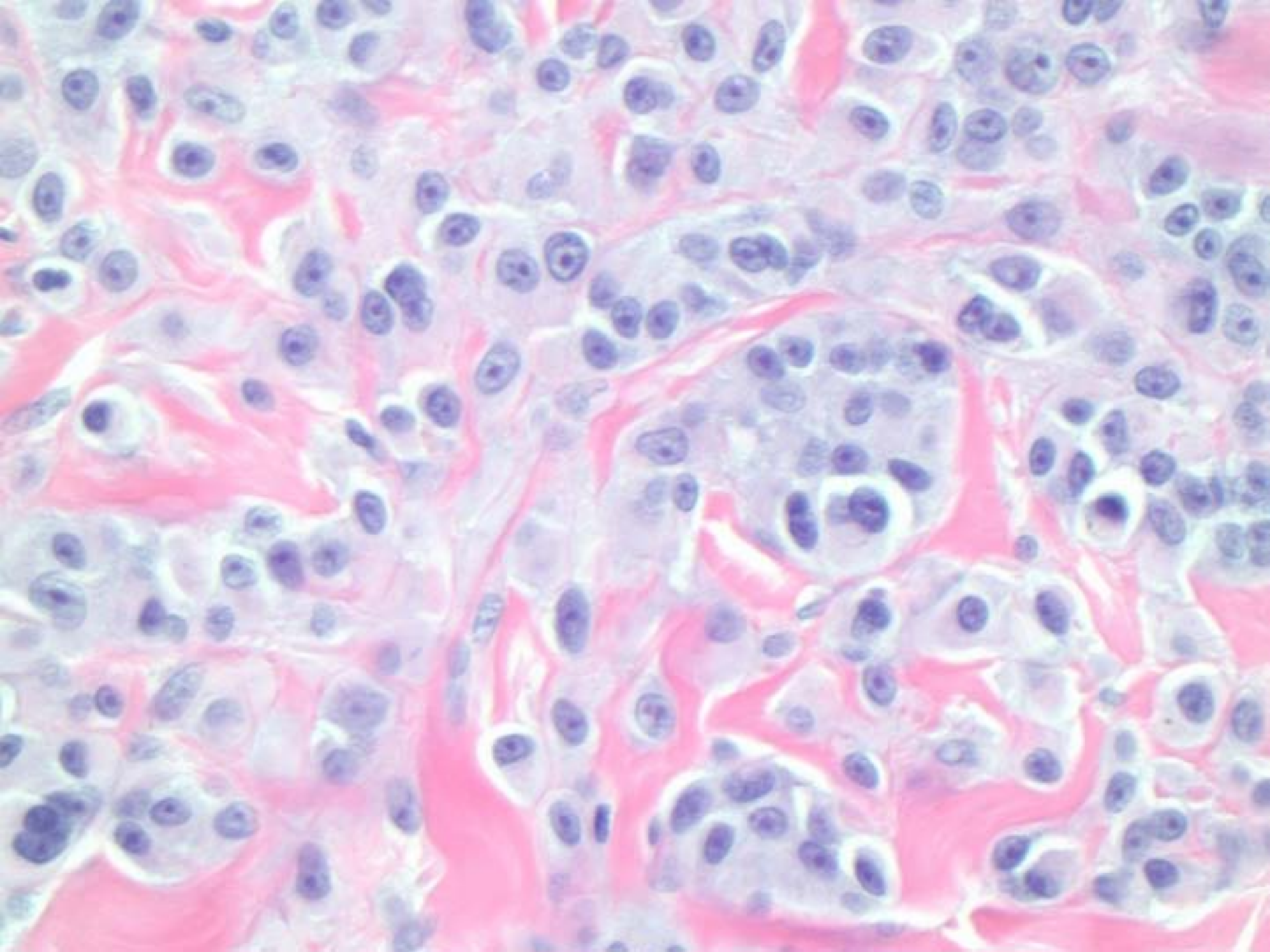

2010

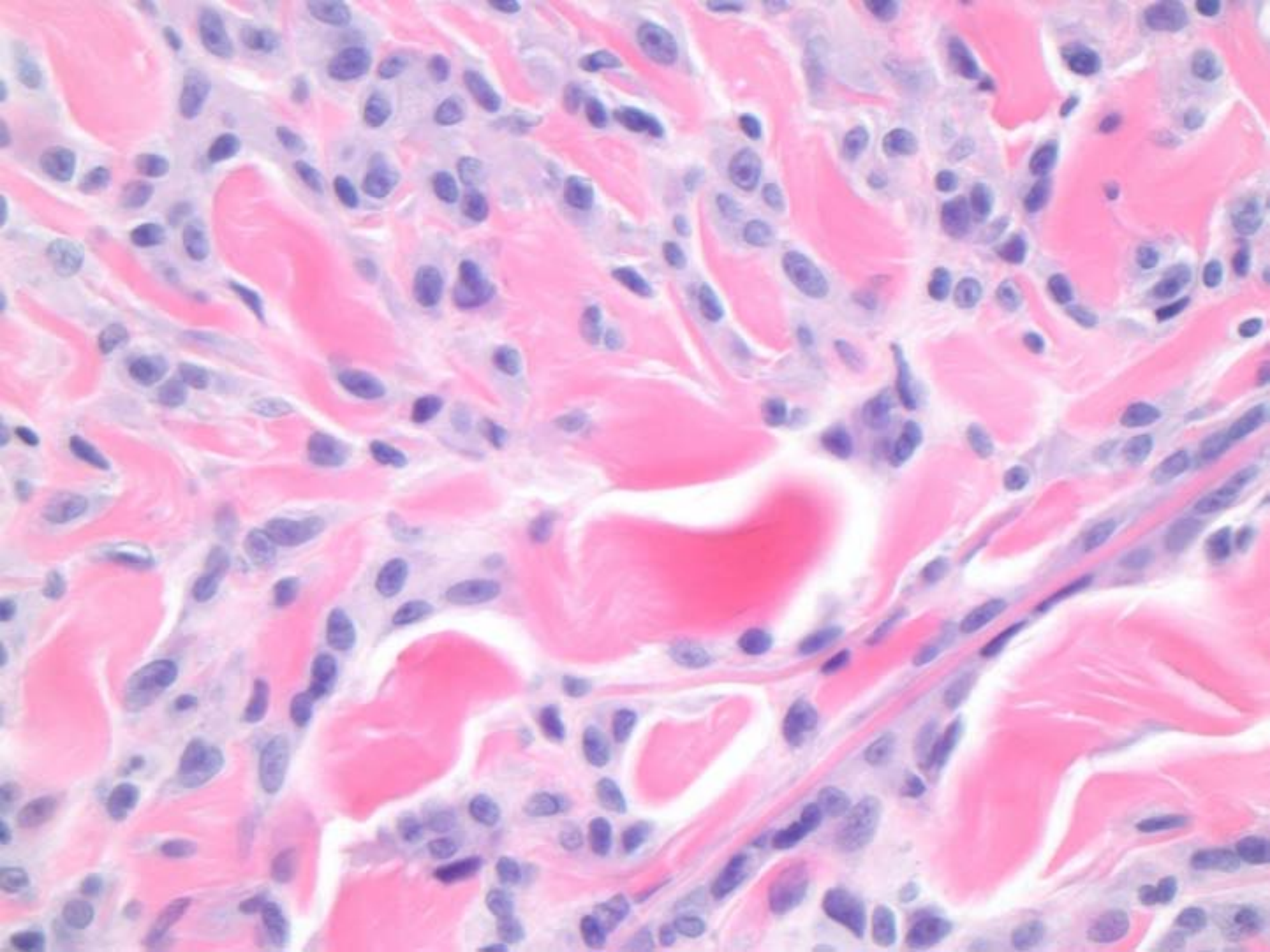








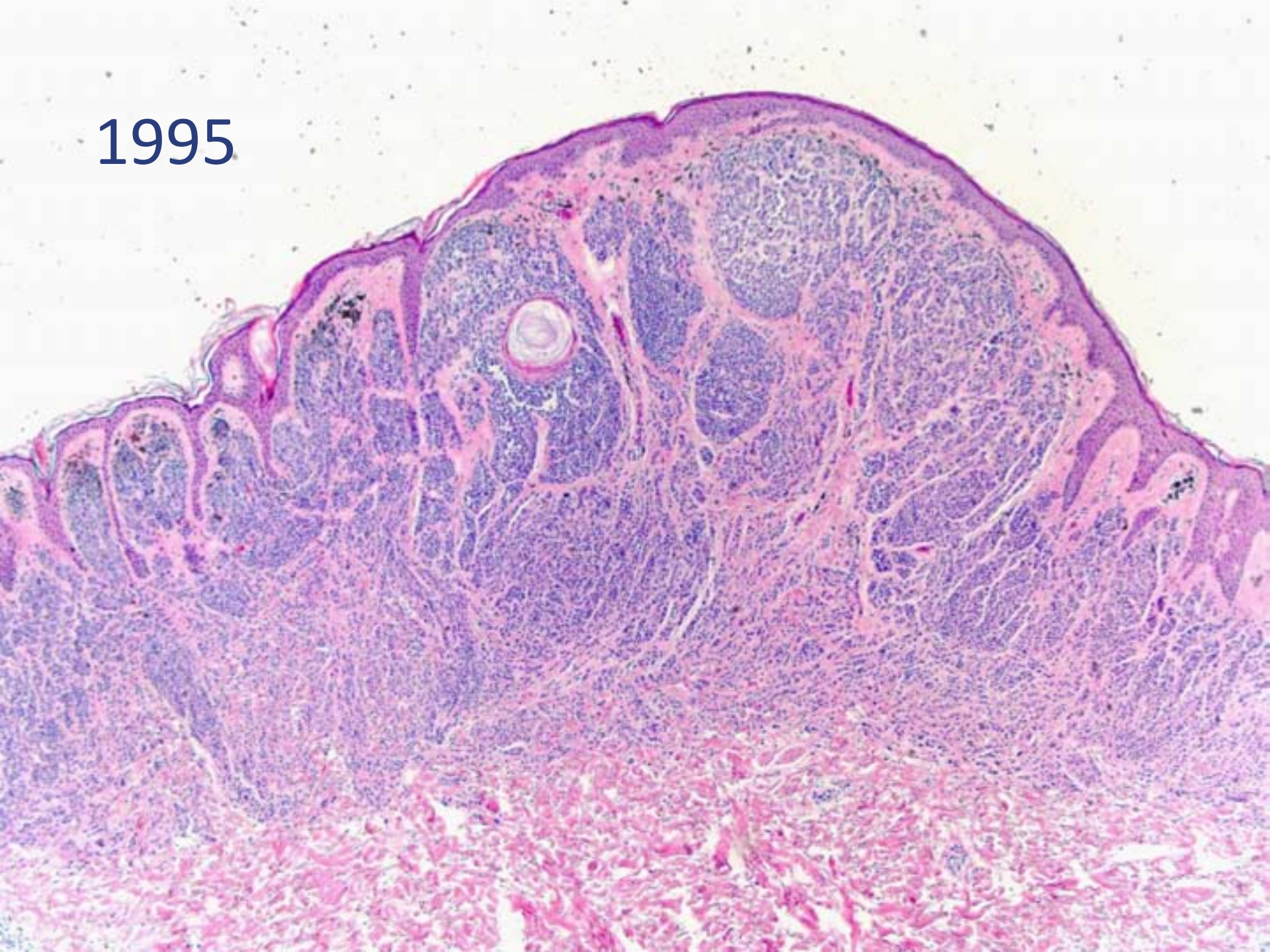


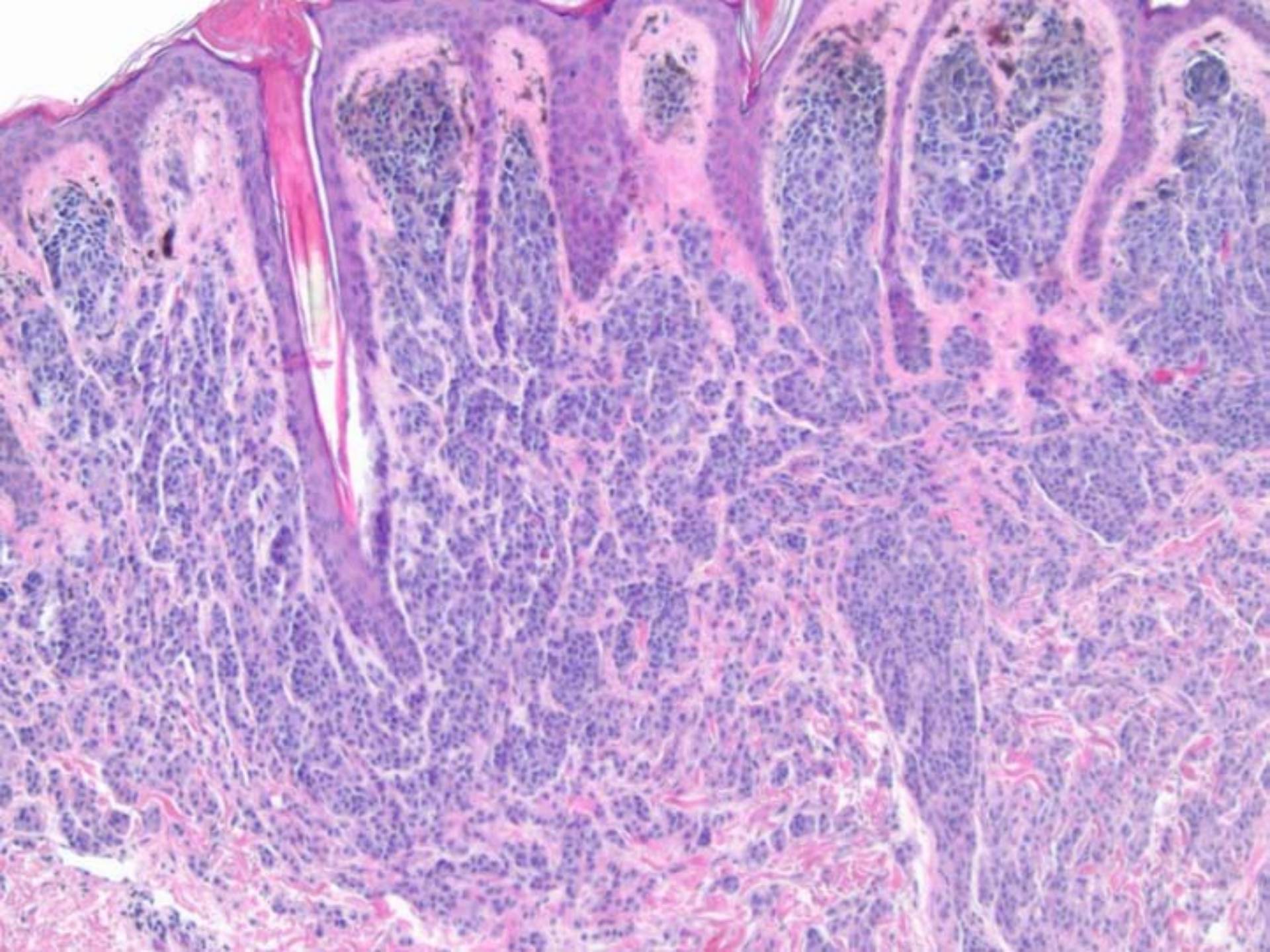


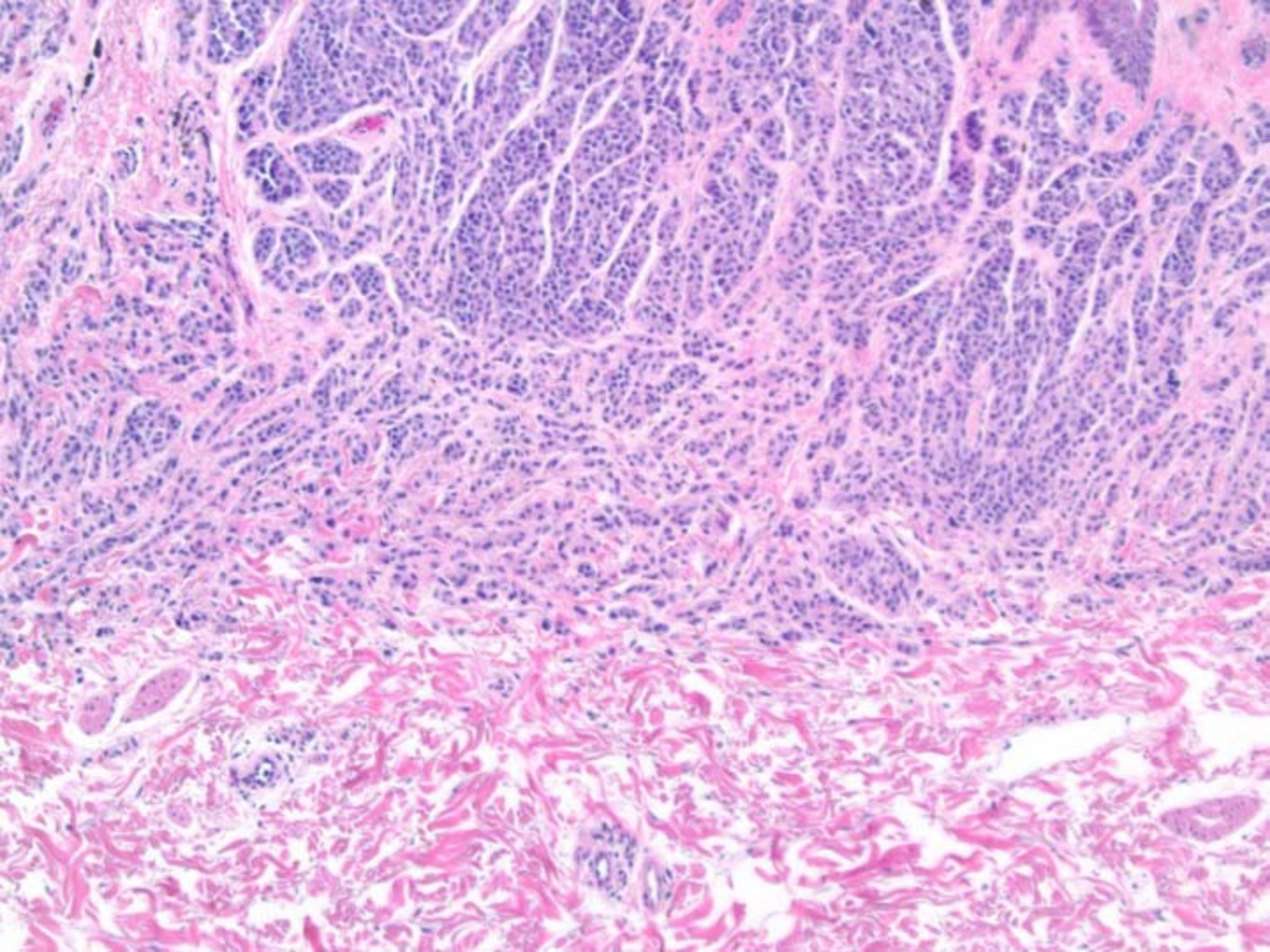
Department of Pathology, 6th Floor
133 Brookline Ave, Boston, MA 02215
Tel. 617 549 1168
Fax. 866 877 9094

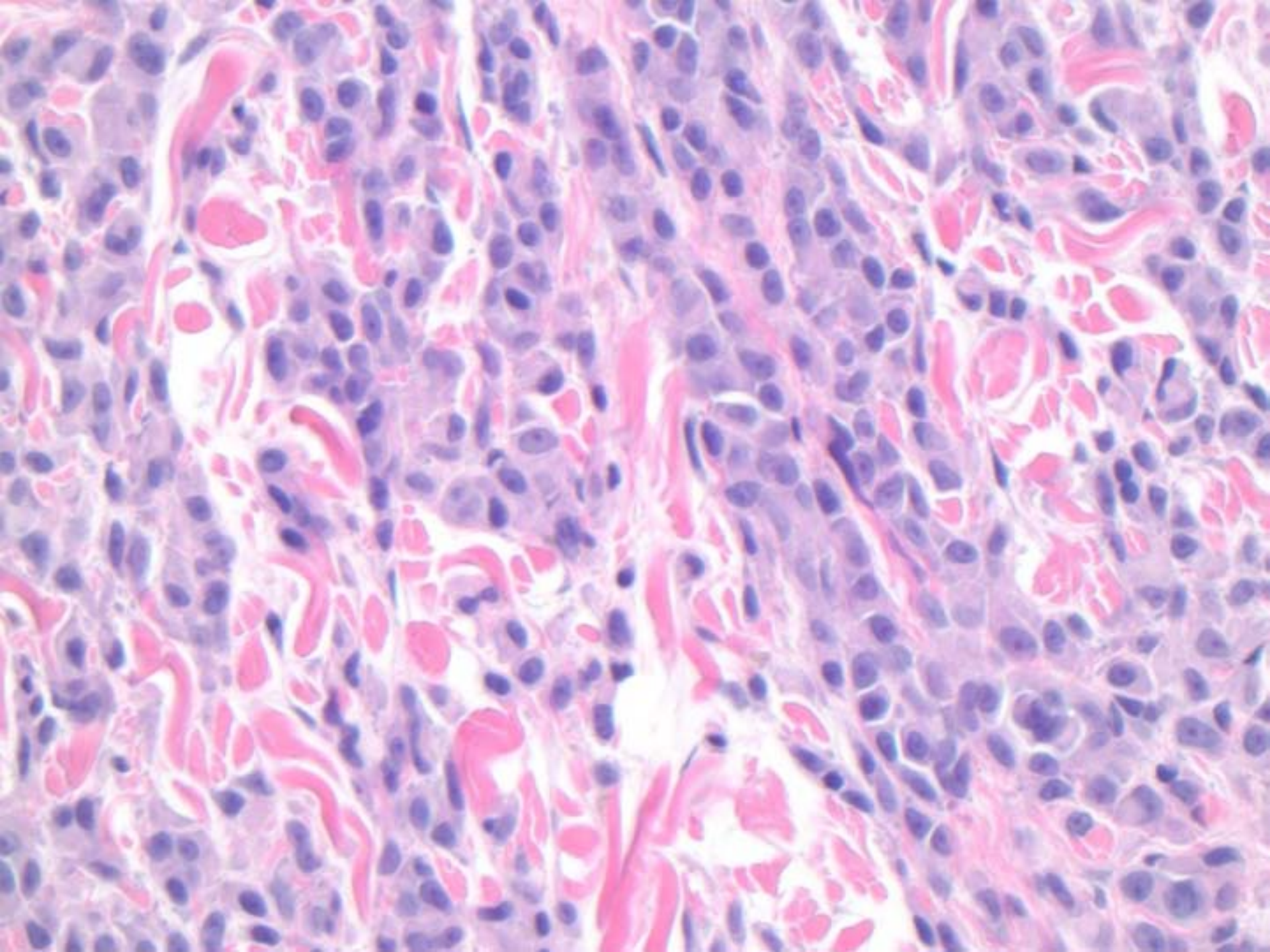
Medical Director:
Artur Zembowicz, M.D., Ph.D
CLIA No: 22D1049112

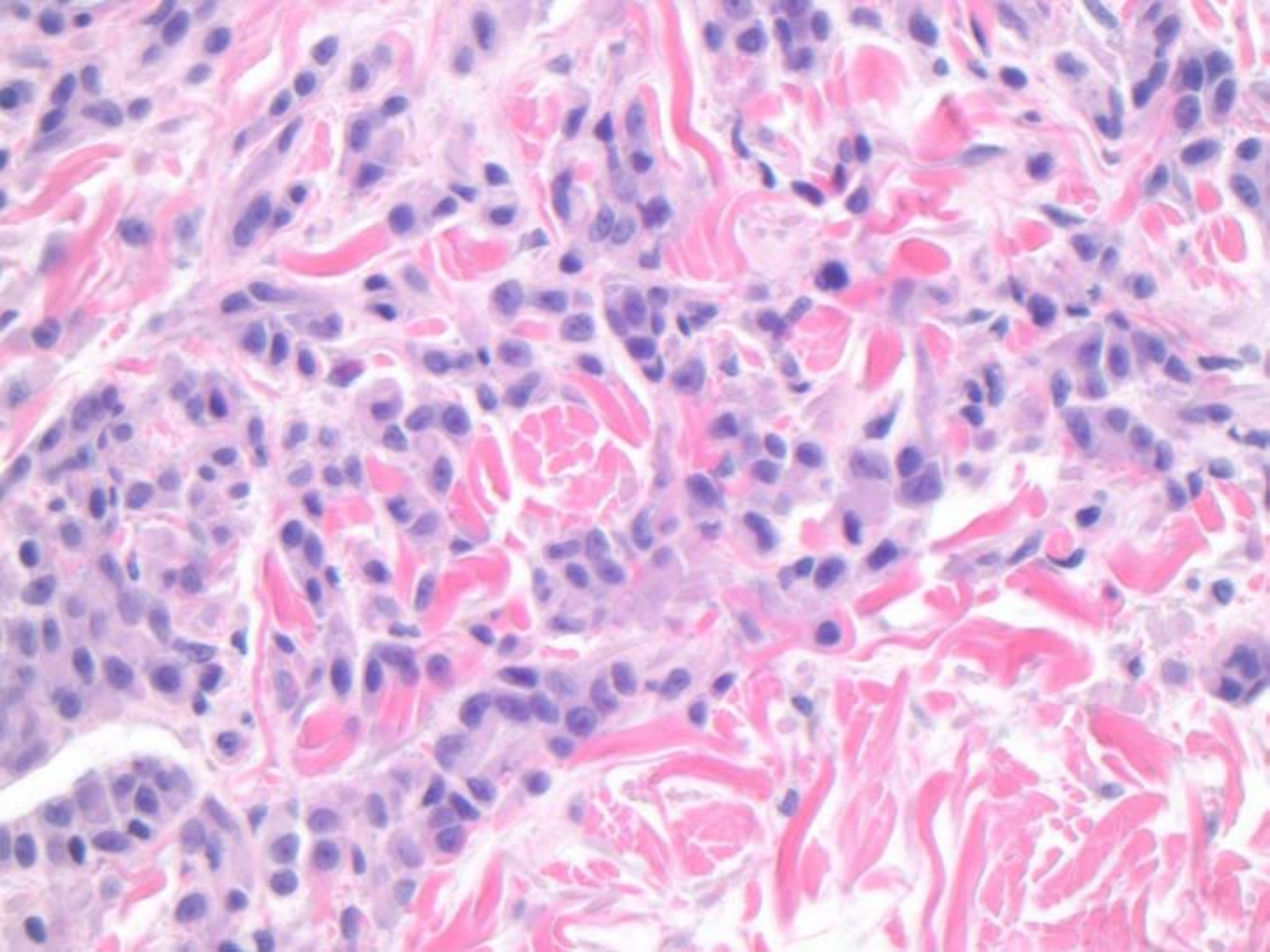
- Malignant melanoma, nevoid type, invasive to 3.5 mm, Clark's level IV

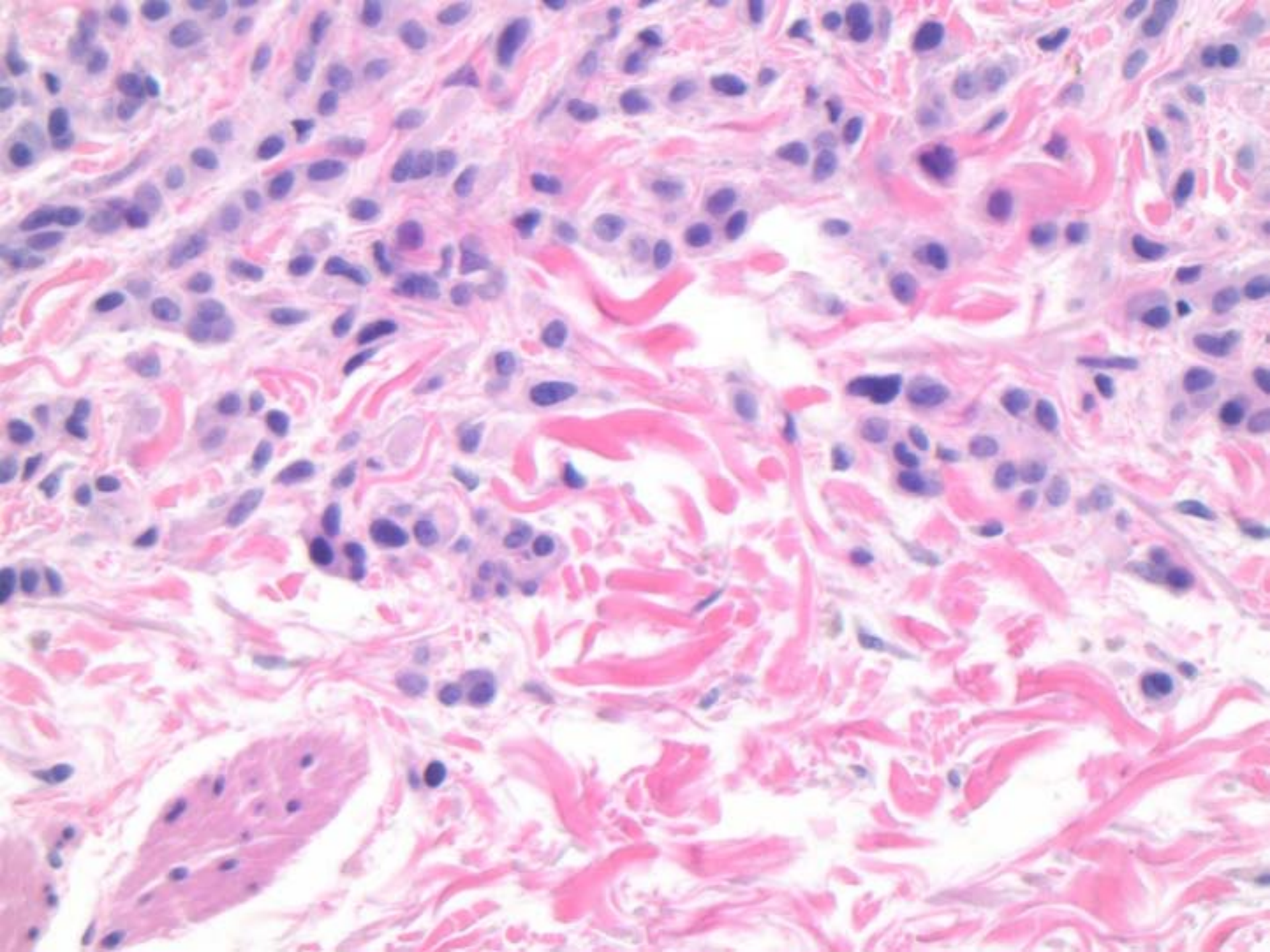

1995









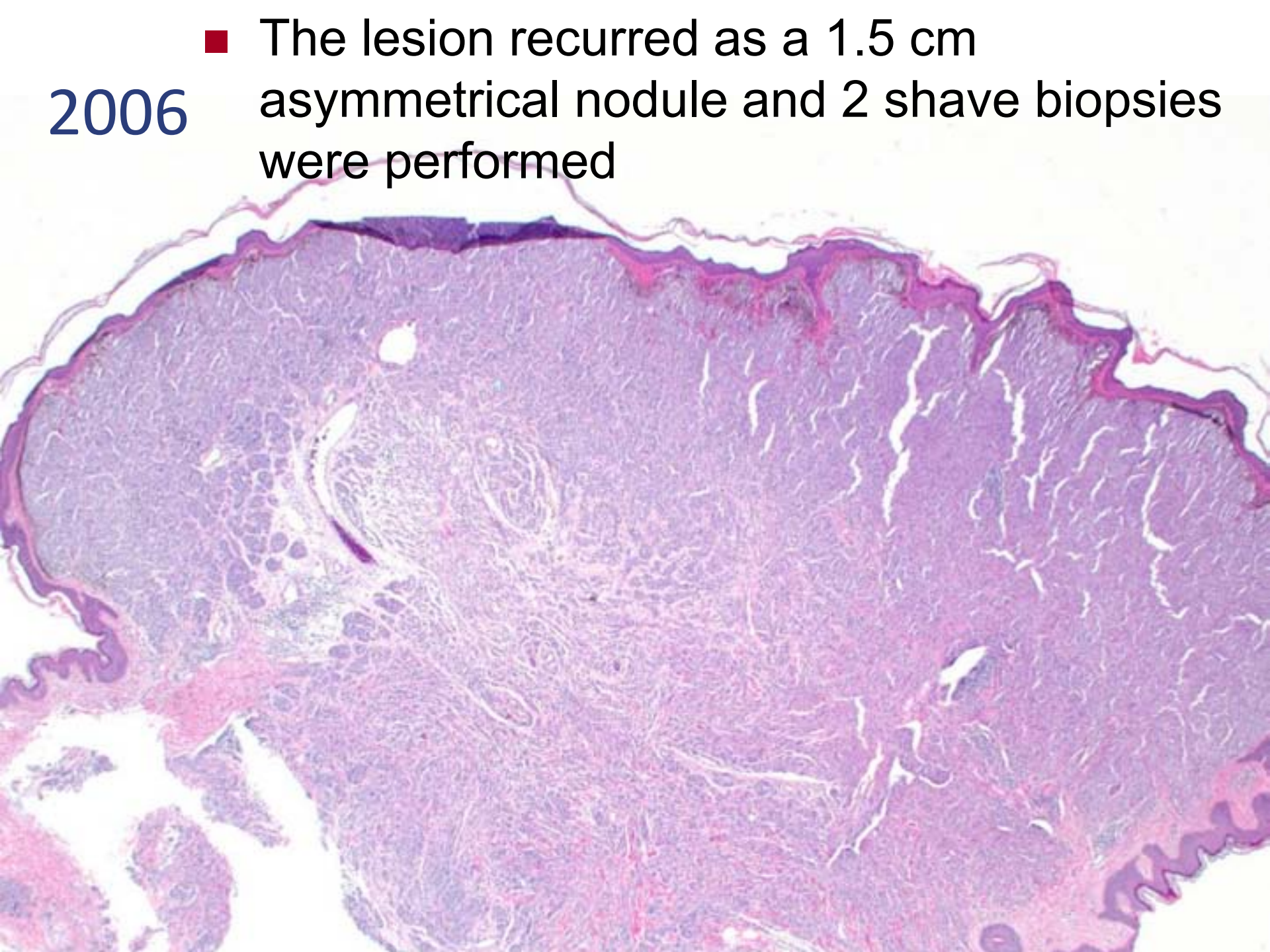


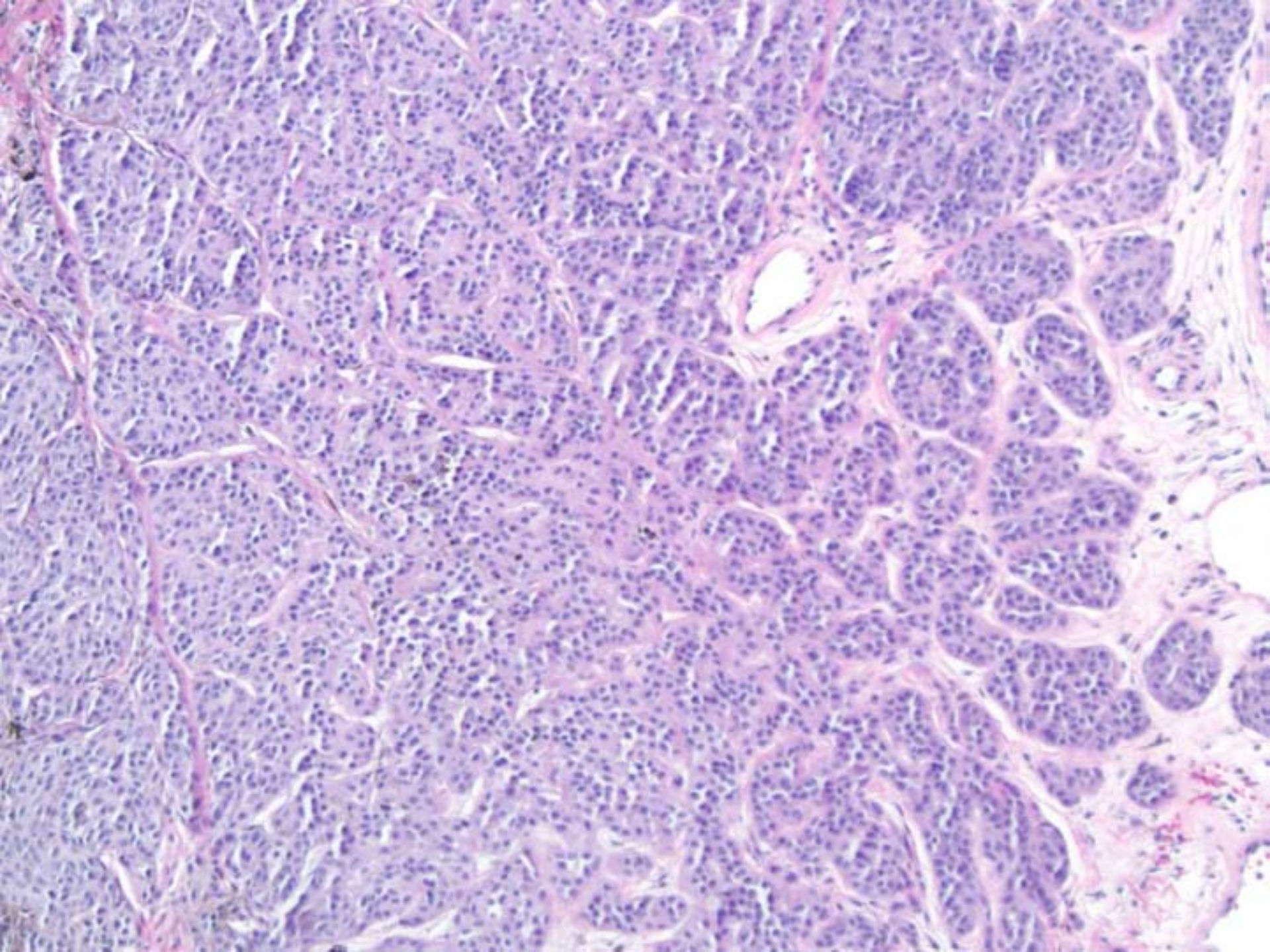
1995: Diagnosis by Pathologist #1

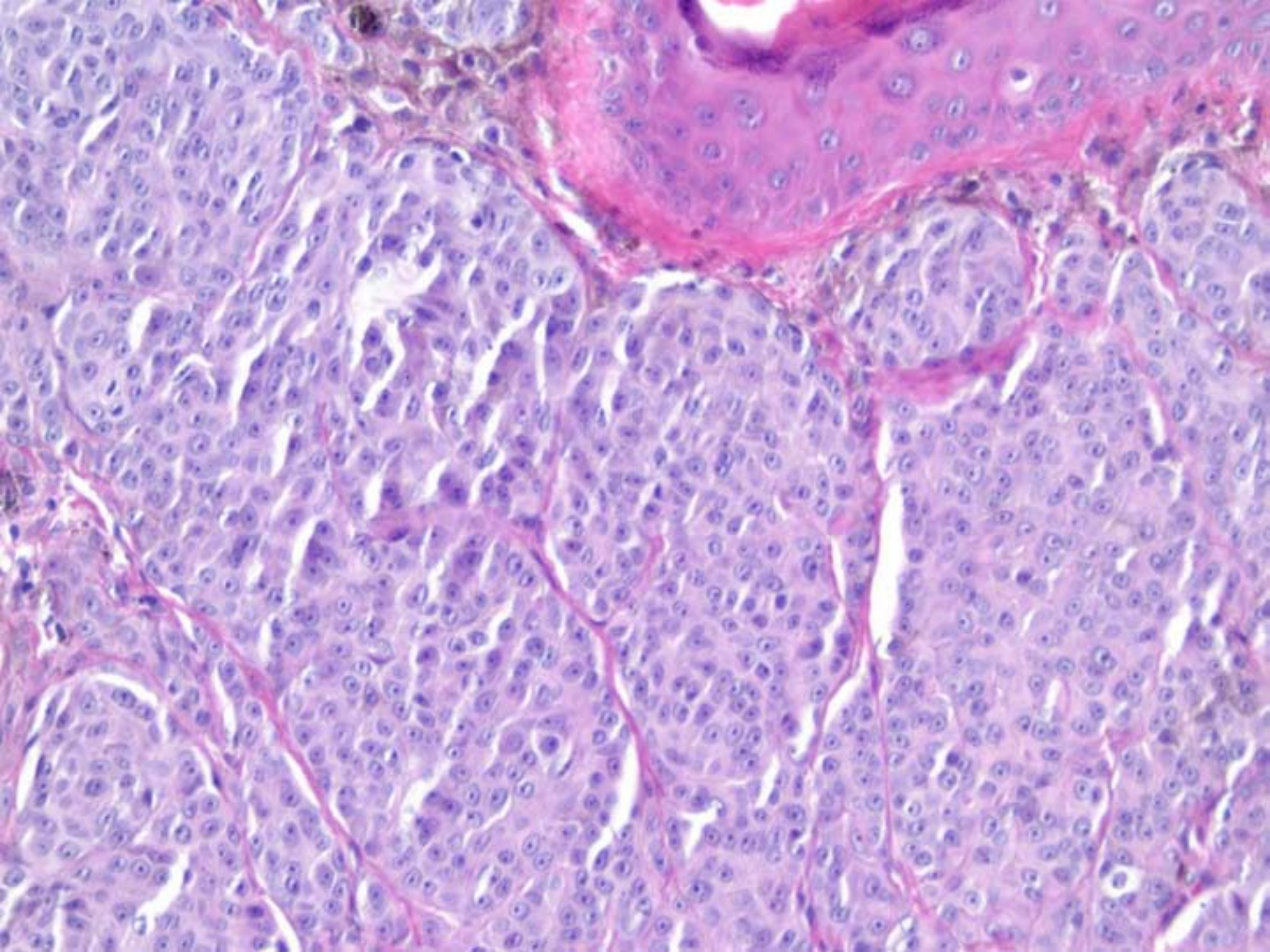
- Dermal nevus

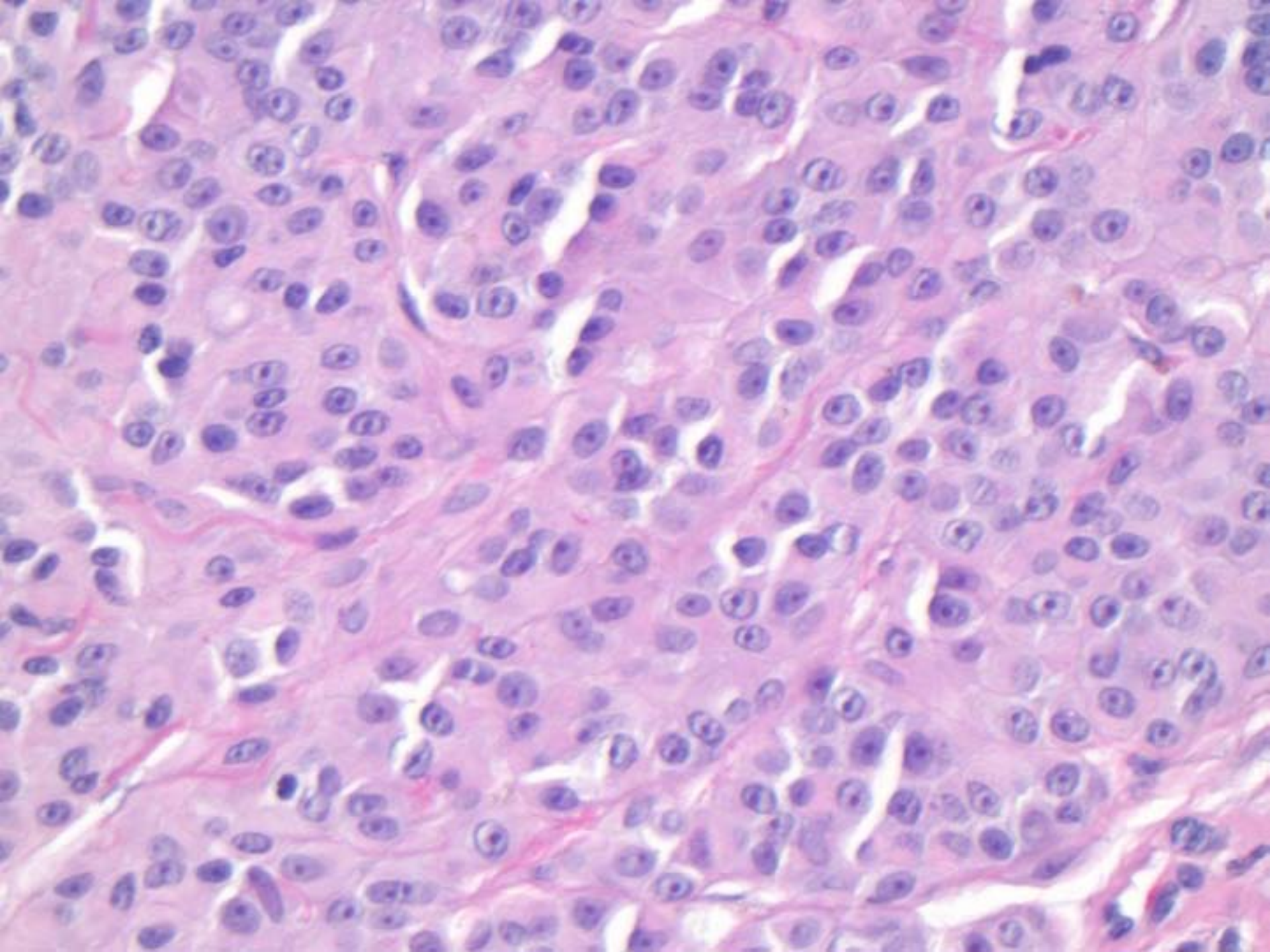
2006

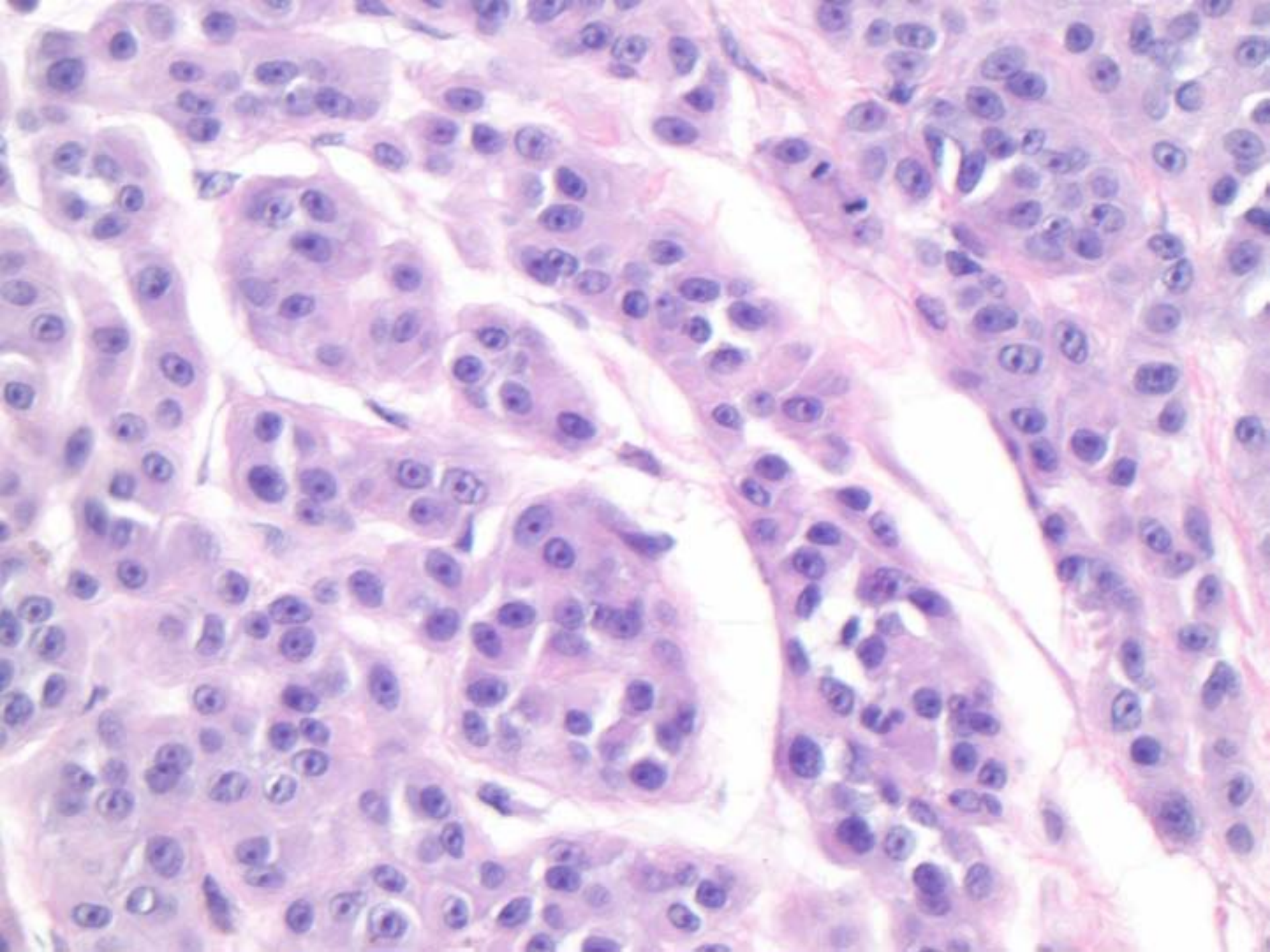
- The lesion recurred as a 1.5 cm asymmetrical nodule and 2 shave biopsies were performed

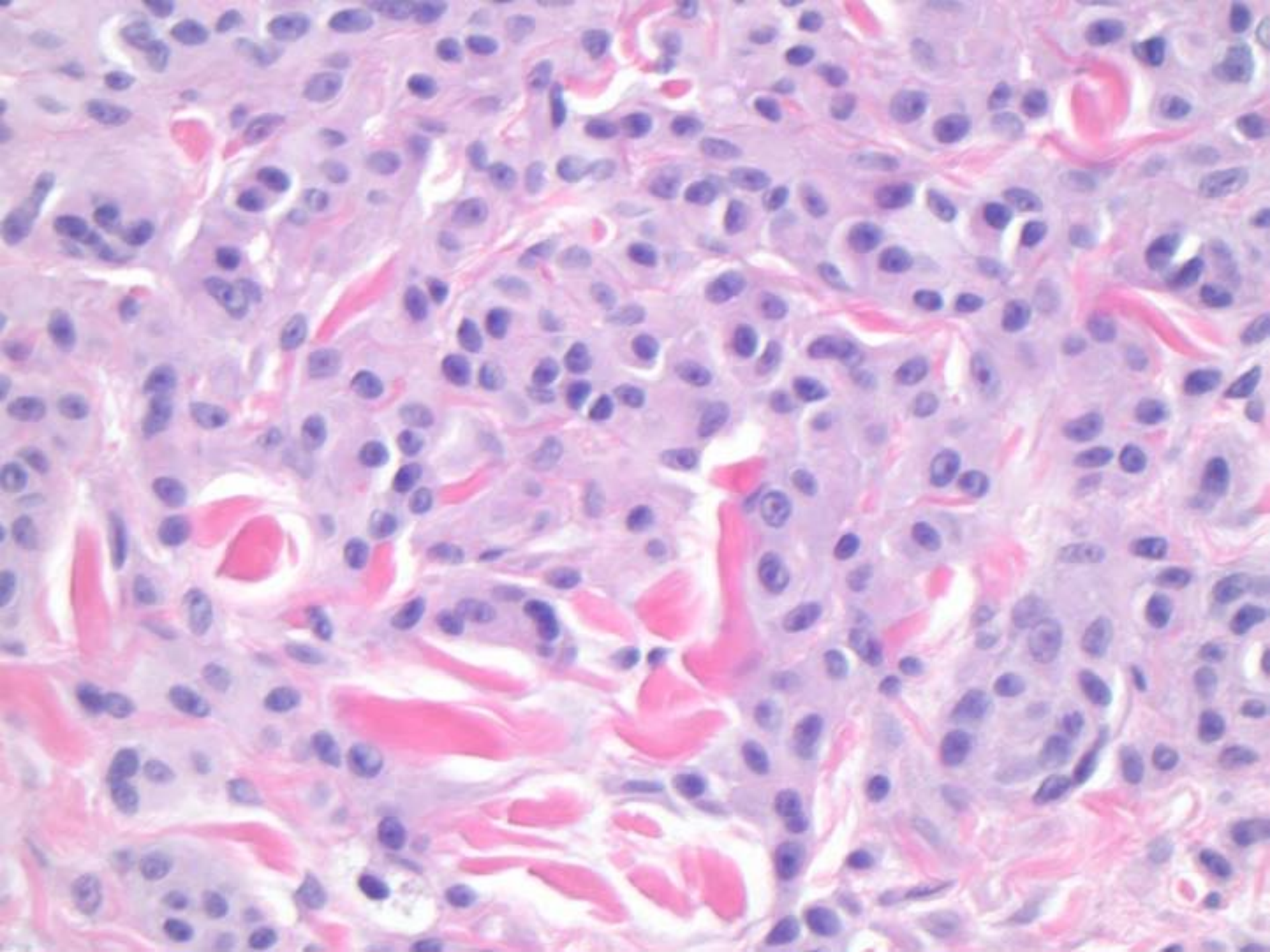












2006: Diagnosis by Pathologist #2

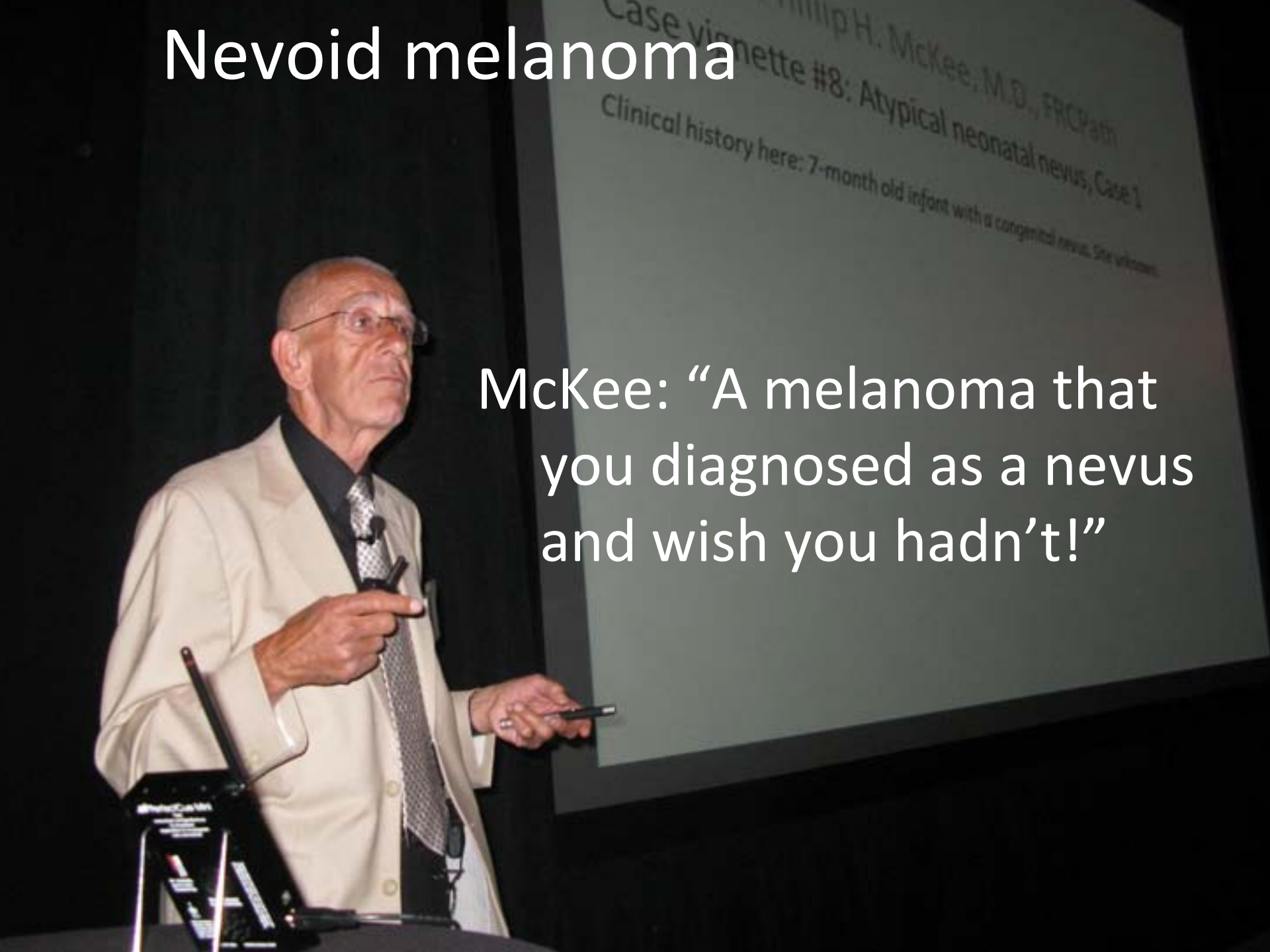
- Dermal nevus, present at margin.

Department of Pathology, 6th Floor
133 Brookline Ave, Boston, MA 02215
Tel. 617 549 1168
Fax. 866 877 9094

Medical Director:
Artur Zembowicz, M.D., Ph.D
CLIA No: 22D1049112

- Nevoid melanoma in 2010
- Favor nevoid melanoma in 2006 and likely in 1995
- MelanoSITE FISH which abnormal (RREB1 amplification) in 2010 and 1995

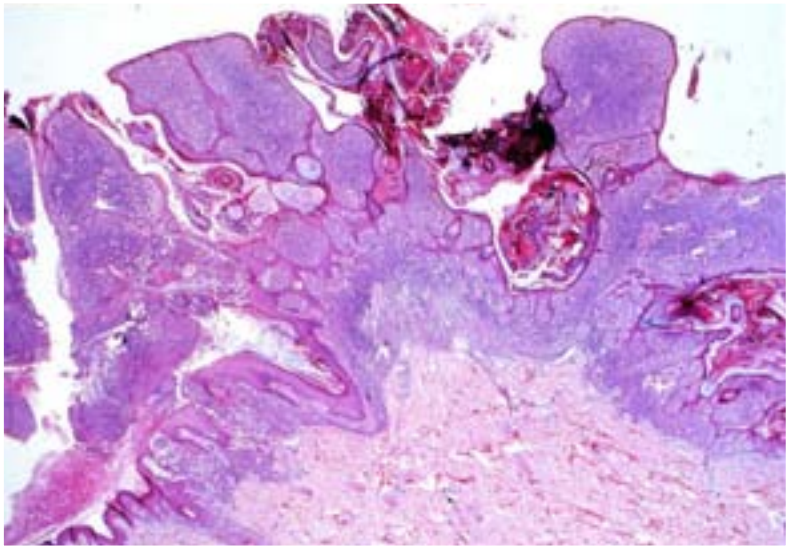
Nevoid melanoma



McKee: “A melanoma that you diagnosed as a nevus and wish you hadn’t!”

Nevoid melanoma: types

- Verrucous
- Nodular
- (Spitzoid)

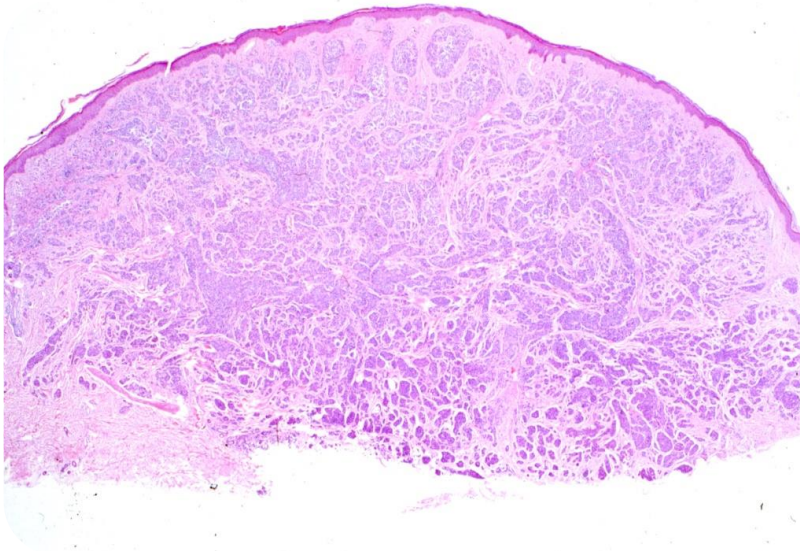


The American Journal of Dermatopathology 23(3): 167-175, 2001

Morphological Analysis of Nevoid Melanoma

A Study of 20 Cases With A Review of the Literature

Artur Zembowicz, M.D., Margaret McCusker, M.D.,
Concetta Chiarelli, M.D., Angelo P. Dei Tos, M.D.,
Scott R. Granter, M.D., Eduardo Calonje, M.D.,
and Phillip H. McKee, M.D.



Pay attention to:

- Maturation
- Infiltrating growth pattern and “indian filing”
- Sheet-like confluent growth and expansile nesting
- Deep dermal mitotic activity
- Subtle but consistent cytological atypia
  - Pleomorphism, nuclear irregulartiy, abundant cytoplasm, plasmacytoid appearance

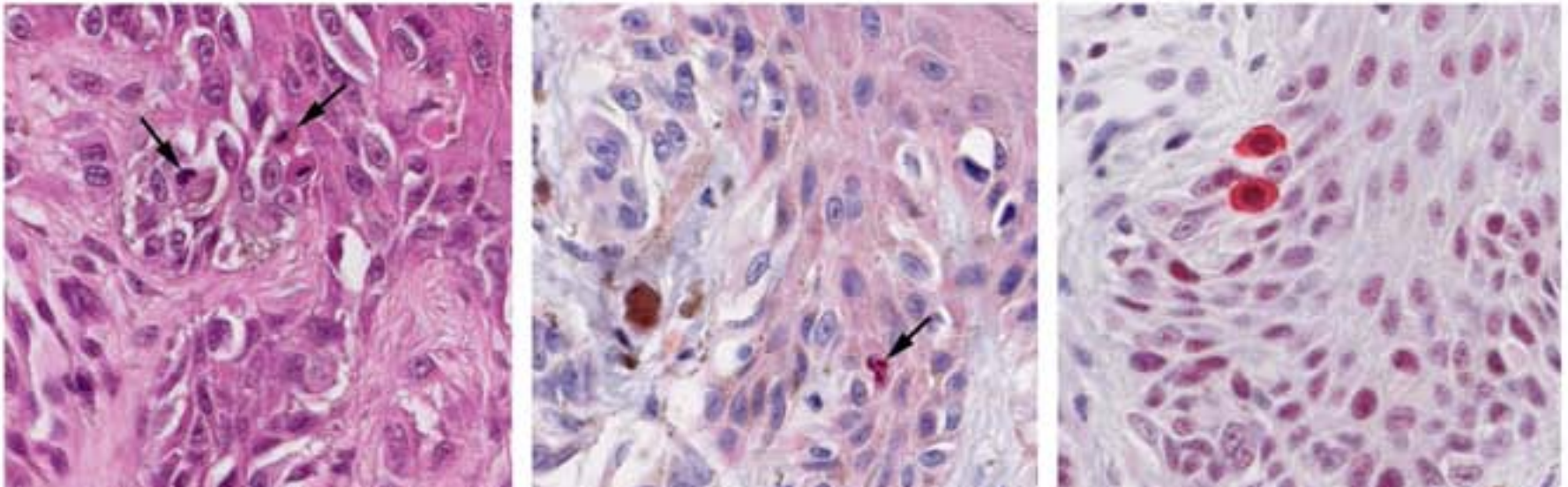
Mitotic Activity in Benign Nevi: More Common Than You Think!

ORIGINAL STUDY

Frequent Mitotic Activity in Banal Melanocytic Nevi Uncovered by Immunohistochemical Analysis

Katharina Glatz, MD, Christoph Hartmann, MD,* Milos Antic, MD,* and Heinz Kutzner, MD†*

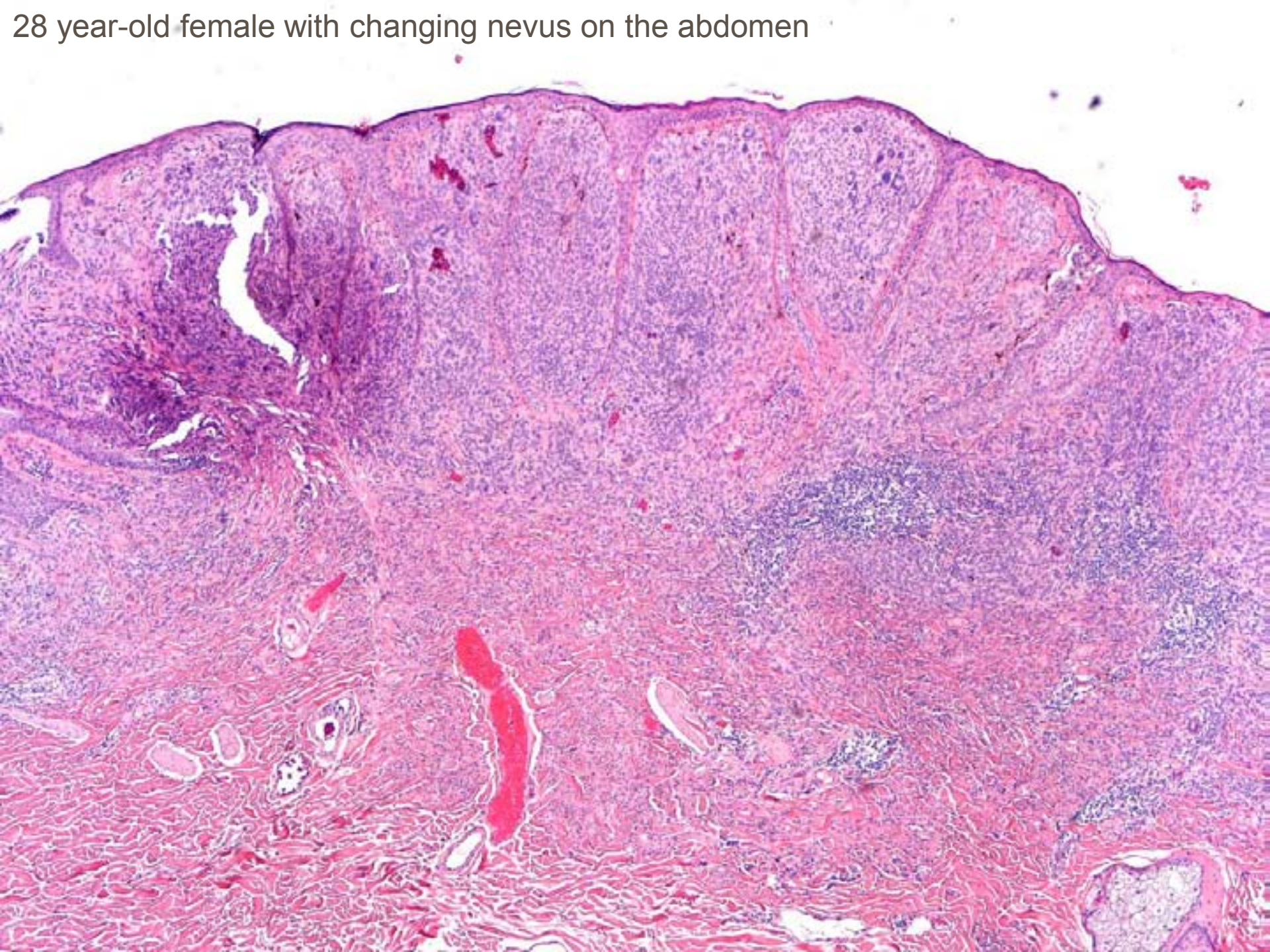
Am J Dermatopathol • Volume 32, Number 7, October 2010 *Occurence and Distribution of Mitotic Figures in Melanocytic Nevi*

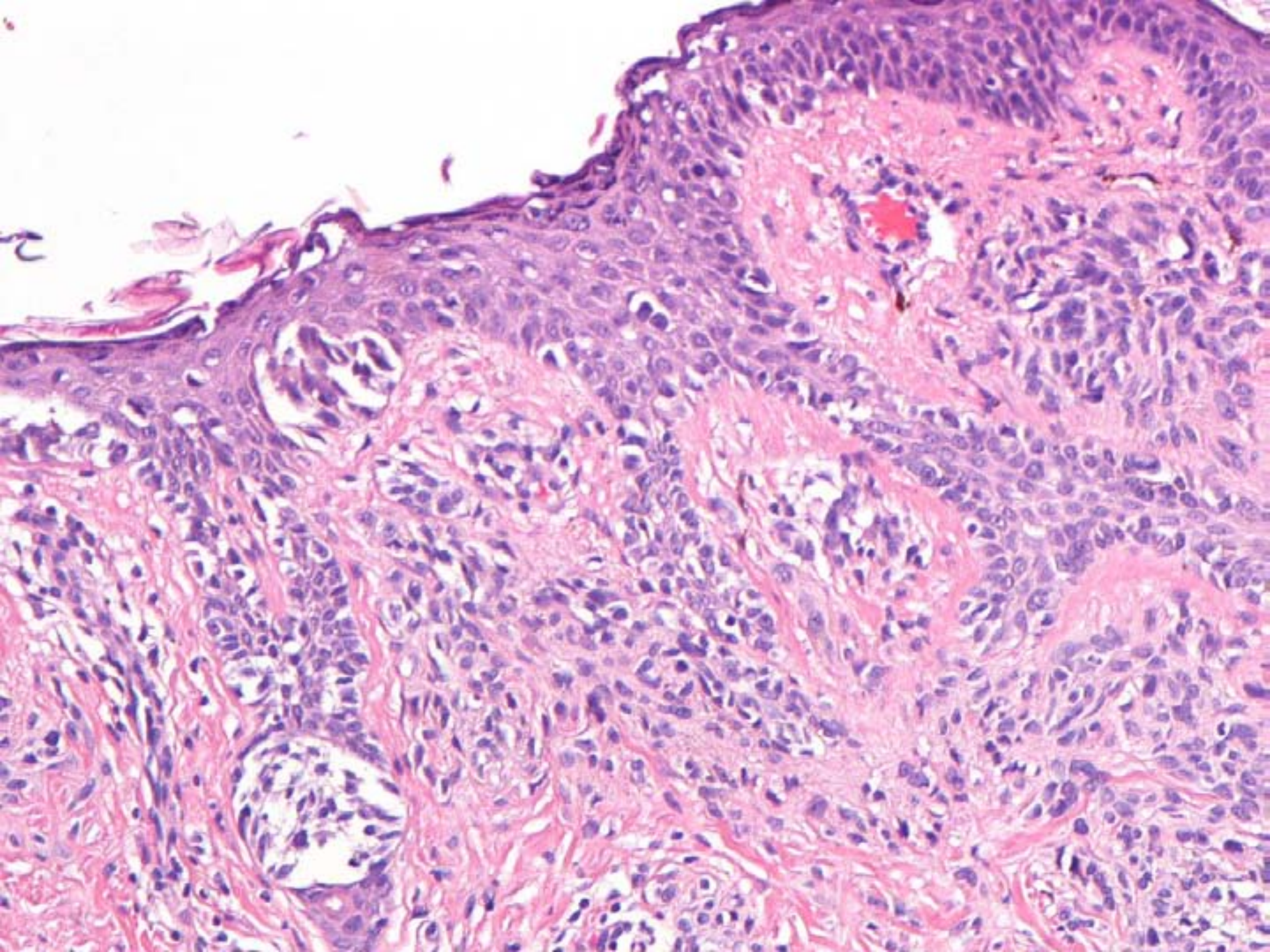


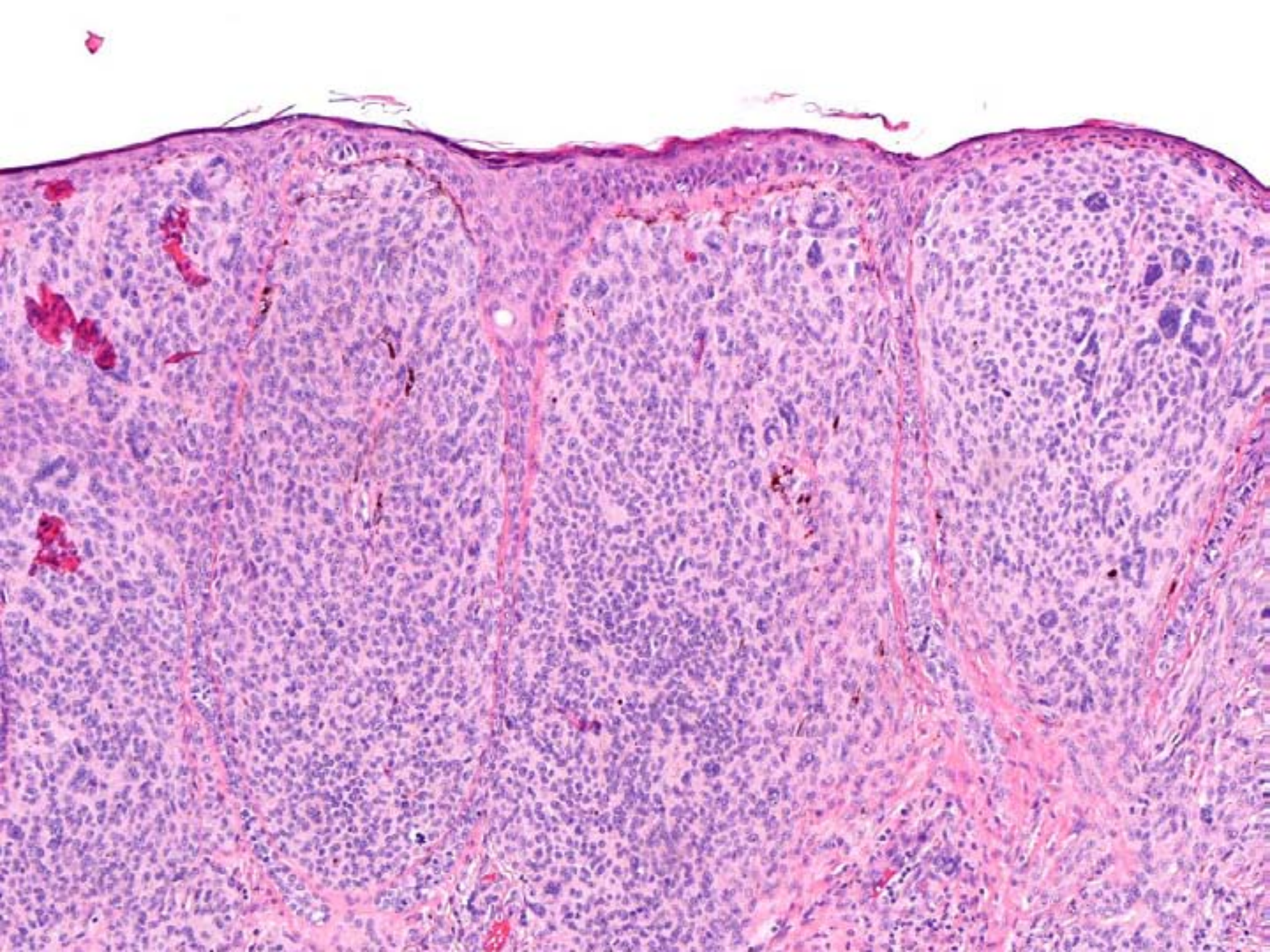
Mitotic activity in benign nevi

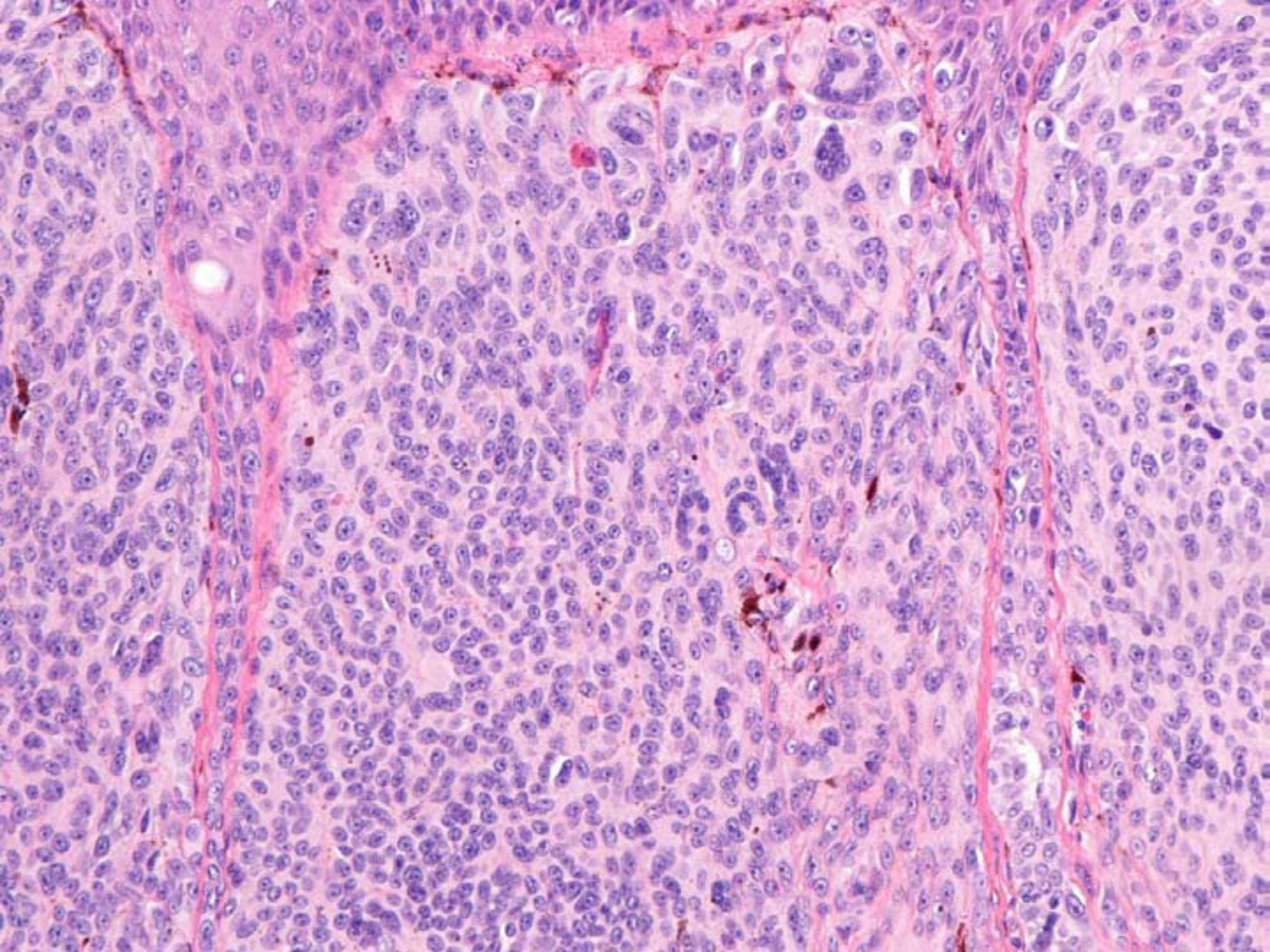
- At least 1 mitotic figure present in 19% (HE) and 30-42% (PHH3-phospho-Histone H3 Ser28, MPM2-mitotic phosphoprotein monoclonal antibody 2)
- Mitoses more frequent lesions from younger (<20 year-old) and older (>50 year-old patients)
- 3x more frequent in the upper ½ of the dermal component
- Traumatized, inflamed and Spitz nevi have higher mitotic activity

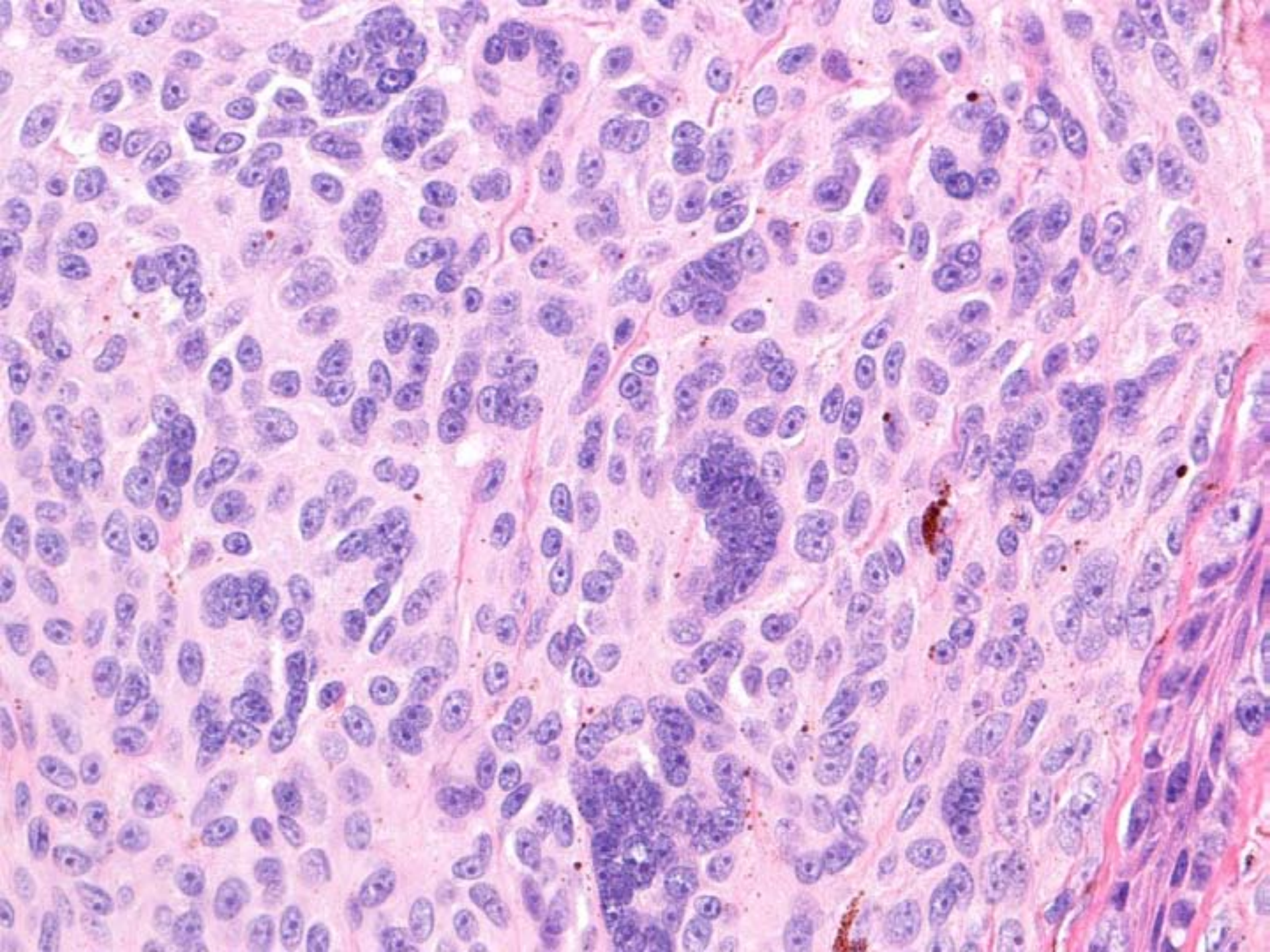
28 year-old female with changing nevus on the abdomen

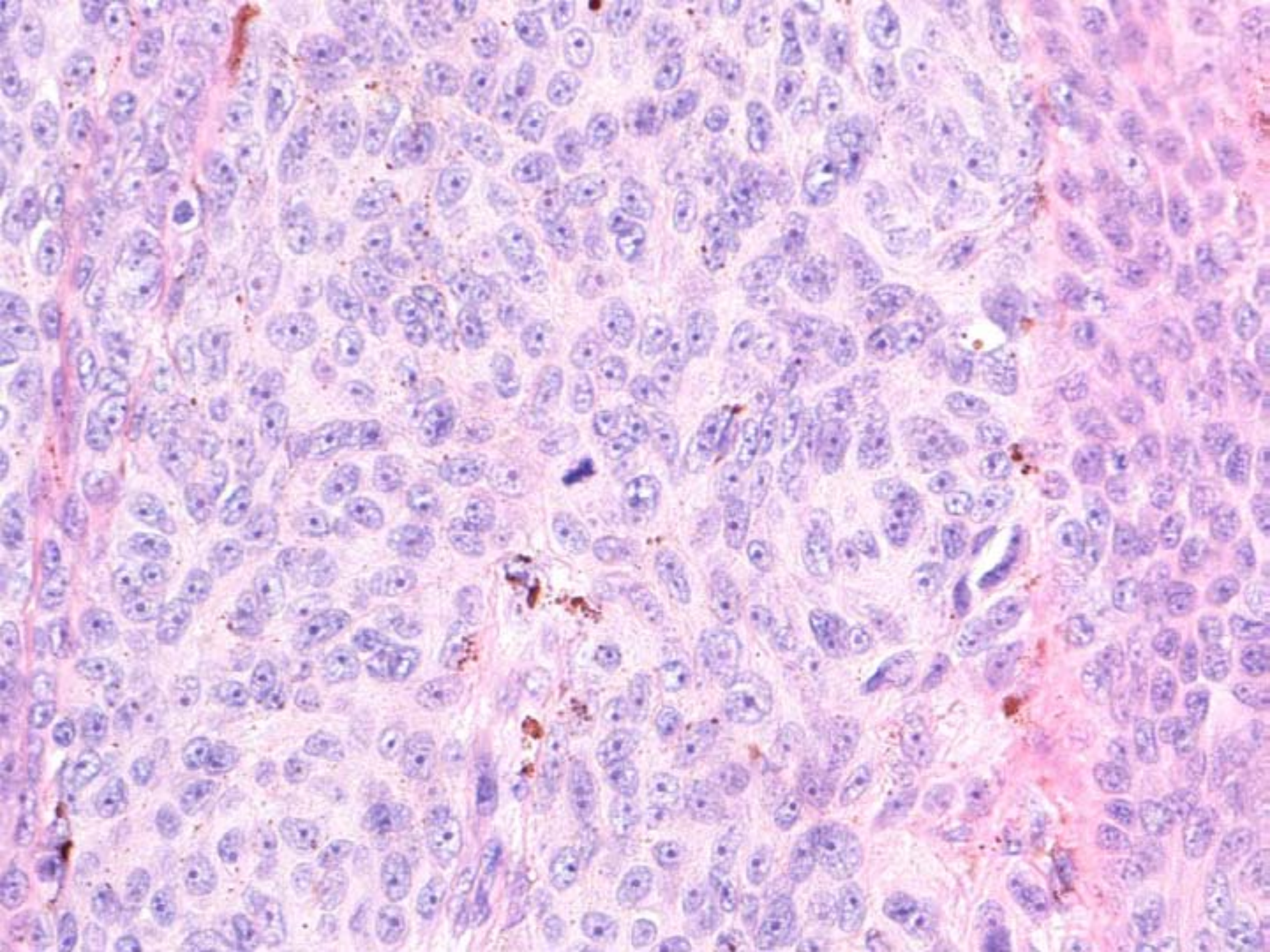


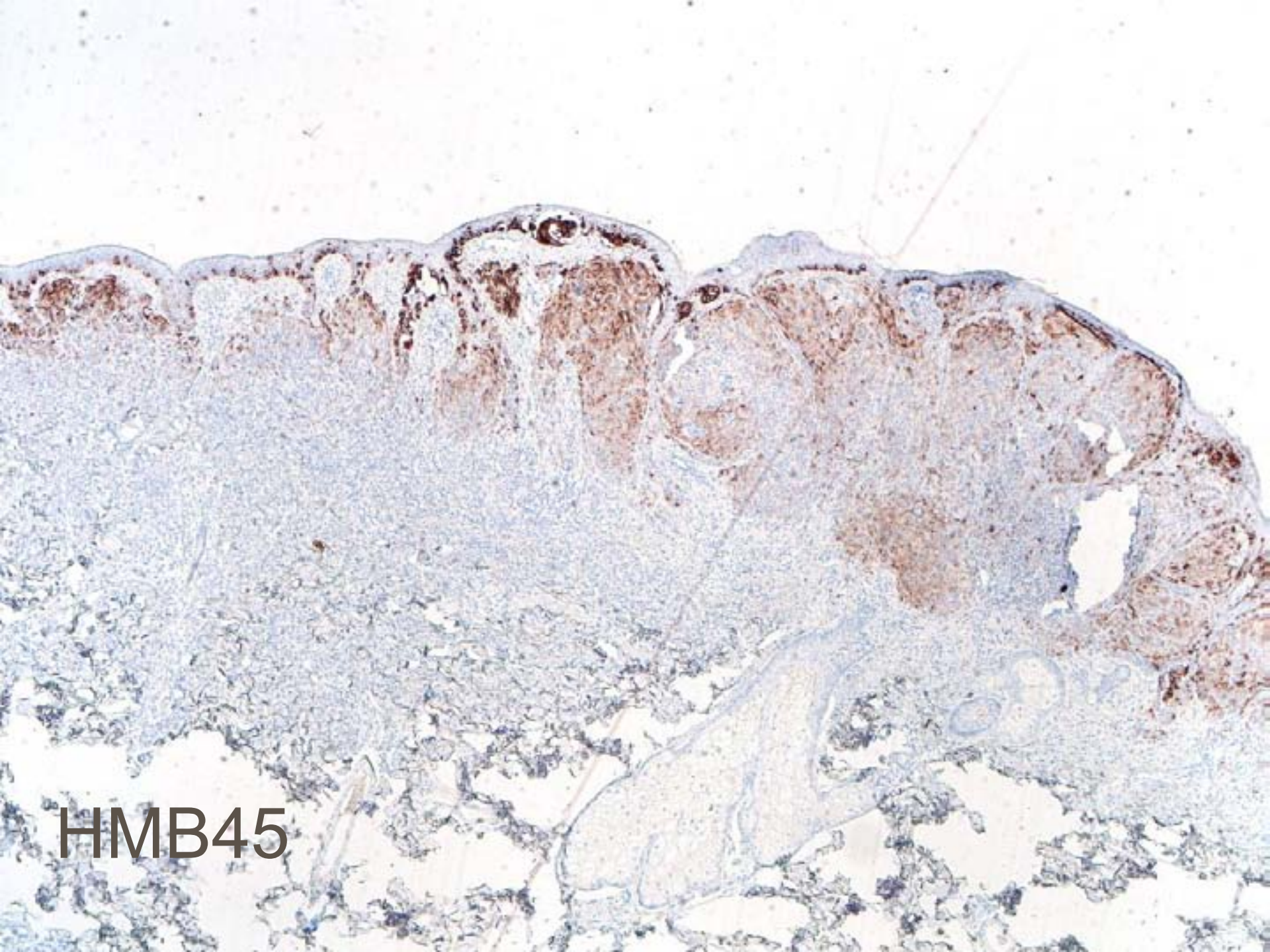











HMB45

Department of Pathology, 6th Floor
133 Brookline Ave, Boston, MA 02215
Tel. 617 549 1168
Fax. 866 877 9094

Medical Director:
Artur Zembowicz, M.D., Ph.D
CLIA No: 22D1049112

Diagnosis

- Atypical nevus of pregnancy

Nevi in pregnancy:

- ↑ mitotic activity (66 % versus 13%)
- ↑ Ki67 proliferation index

- Just “look different”
  - Superficial micronodules of pregnancy

Journal of Cutaneous Pathology

Melanocytic nevi in pregnancy: histologic features and Ki-67 proliferation index

Background: Changes in the clinical appearance of benign dermal nevi during pregnancy may be concerning for malignant transformation. Because the hormonal milieu of pregnancy has not proven to alter their basal behavior, histologic characterization is needed to prevent over-diagnosis and unnecessary treatment.

Methods: Dermal nevi excised from pregnant women (n = 10) were compared with nevi from location- and aged matched control patients (n = 15). Histologic features and Ki-67 proliferation index were evaluated.

Results: Nevi in pregnancy were more likely to have dermal mitotic figures (62.5% vs. 13.3%, p = 0.020) and higher mitotic rates (1.44 vs. 0.20 mitoses/mm^2, p = 0.0027) than control nevi. A distinctive histologic entity, termed *superficial micronodules of pregnancy* (SMOPs), was observed more frequently in the nevi of pregnancy (81.3% vs. 26.7%, p = 0.040), and showed consistent immunoreactivity for HMB45. There was a trend toward higher Ki-67 proliferation index in the nevi of pregnancy (5.0% vs. 1.0%, p = 0.07). Prominent multinucleated melanocytes were seen only in controls. There was no significant difference in pigmentation or irritation changes between groups.

Conclusions: Dermal nevi removed during pregnancy show characteristic histologic features including increased dermal mitoses, *superficial micronodules of pregnancy* (SMOPs), and trend toward increased Ki-67 proliferation index.

Chan MP, Chan MM, Tahan SR. Melanocytic nevi in pregnancy: histologic features and Ki-67 proliferation index. J Cutan Pathol 2010; 37: 945–951. © 2009 John Wiley & Sons A/S.

May P. Chan, Maren M. Chan and Steven R. Tahan

Pregnancy was once regarded as a risk factor and a poor prognostic indicator of melanoma. This is in part due to changes in the clinical appearance of pigmented skin lesions seen during pregnancy.[1,2] Currently, little is known regarding the pathophysiology of these changes. However, recent immunohistochemical findings have shown an increase in estrogen receptor β expression in nevi excised from pregnant women, suggesting an enhanced responsiveness of melanocytes to estrogen during pregnancy.[3] To date, no studies have been able to definitively ascribe the development or progression of melanoma to pregnancy.[4–7]

Only a few articles in the literature have attempted to characterize the histology of melanocytic nevi excised during pregnancy.[8,9] The features examined have included intraepidermal migration of melanocytes above the basal layer, fusiform proliferation of melanocytes, elongation of rete ridges, inflammatory infiltrate, increased nuclear-cytoplasmic ratio, and the presence of maturation. None of these studies have found significant differences between the pregnant and the control groups in any of these parameters. More importantly, guidelines to assist in differentiating the histology of benign hormonal effects of pregnancy from true

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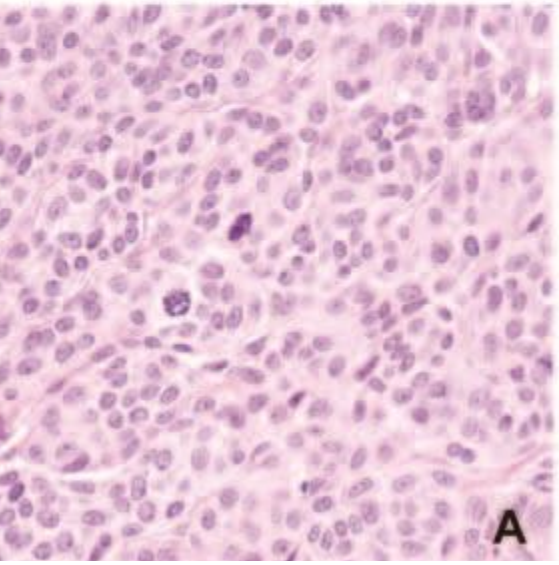
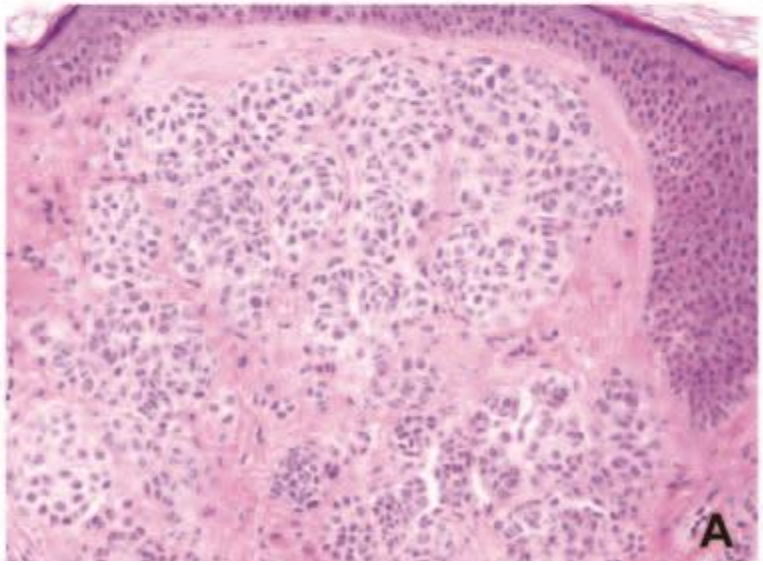
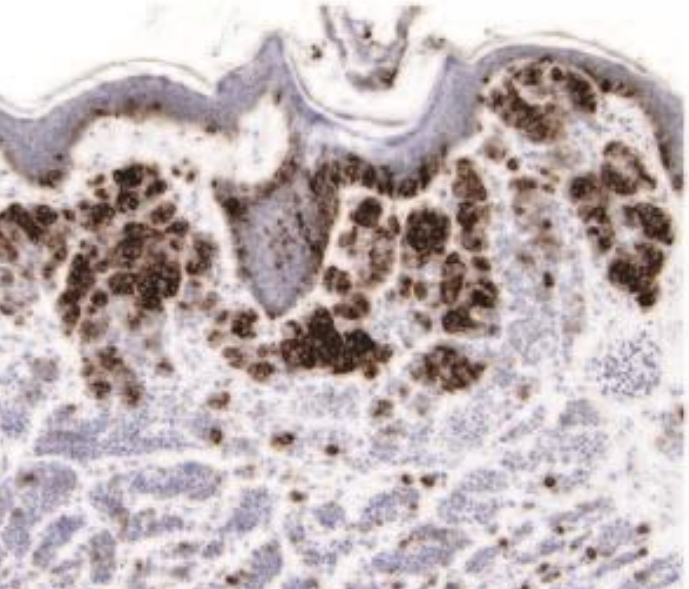


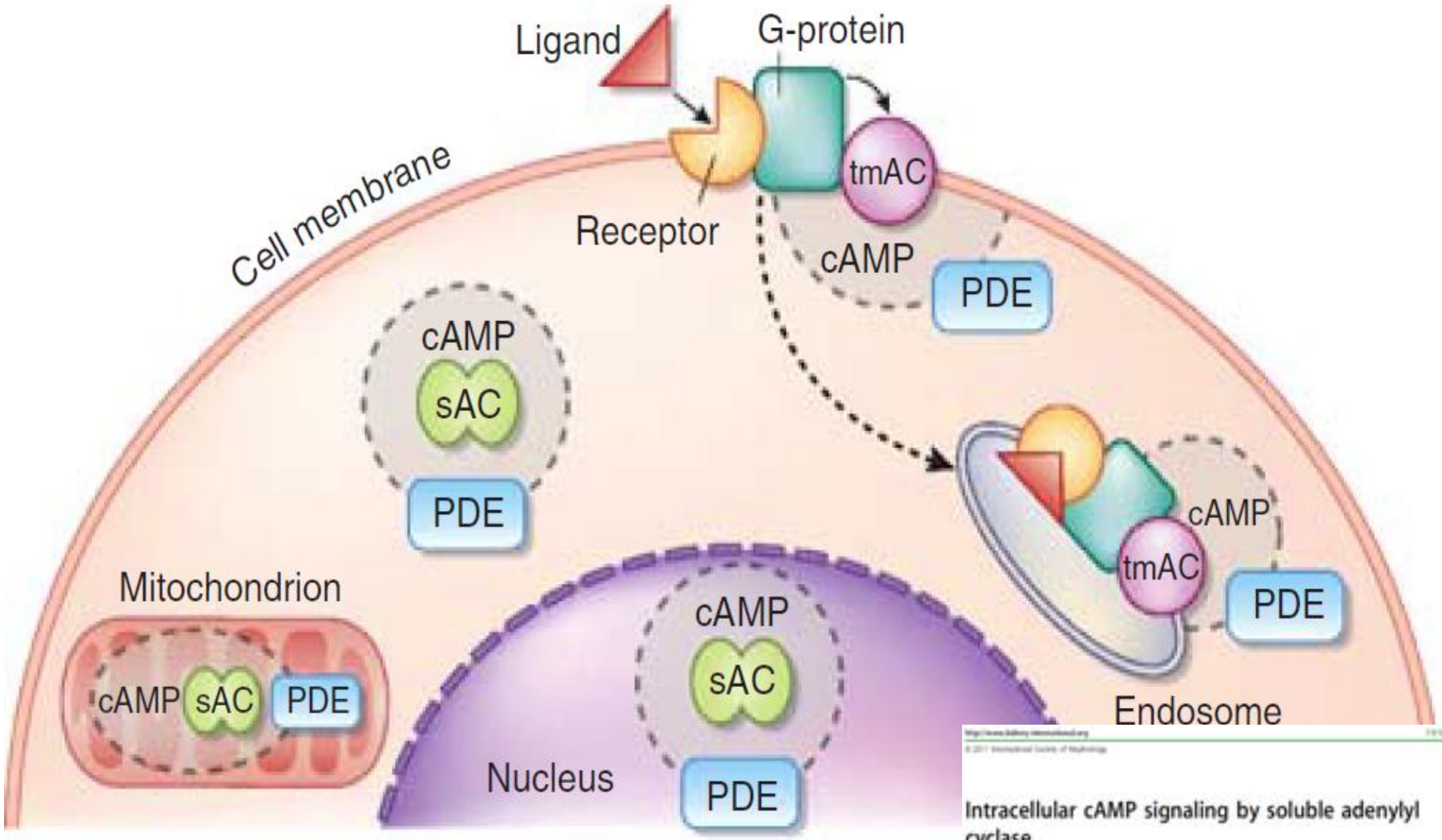




Melanocytic nevi in pregnancy

Only few studies to date have examined the histologic features of benign nevi during pregnancy. Sanchez et al. examined 22 banal melanocytic nevi (predominantly intradermal) from pregnant women and compared them to age-matched controls.[8] These nevi were examined for the presence of melanocytic hyperplasia, elongation of rete ridges, papillary dermal fibroplasia, inflammatory cell infiltrate, melanocytic maturation with depth, vascular dilation, symmetry, circumscription, and melanocytic atypia (defined by pleomorphism, hyperchromatic nuclei, prominent nucleoli, increased nuclear:cytoplasmic ratio, and mitoses). In contrast

Soluble adenylate cyclase (sAC)



Intracellular cAMP signaling by soluble adenylyl cyclase

ONLINE FIRST

Soluble Adenylyl Cyclase Antibody Profile as a Diagnostic Adjunct in the Assessment of Pigmented Lesions

Cynthia M. Magro, MD; A. Neil Crowson, MD; Garrett Desman, MD; Jonathan H. Zippin, MD, PhD

Click here

Objective: To investigate the usefulness of a novel marker for melanocytic proliferations.

Design: Using a novel monoclonal antibody against soluble adenylyl cyclase (sAC), various benign and malignant melanocytic proliferations were immunostained.

Setting: Weill Medical College of Cornell University dermatopathology laboratory.

Main Outcome Measures: The results were qualitative, not quantifiable.

Results: The sAC immunostaining produced distinctive patterns that paralleled melanomagenesis. At one pole of the spectrum were benign nevi, including atypical nevi of special sites and recurrent nevi showing a distinct pattern of dotlike Golgi staining, while at the opposite pole was melanoma, in which many cells demonstrated an intense pannuclear expression pattern, often accompanied by loss of the Golgi expression pattern. Melanomas of lentigo maligna and acral lentiginous subtypes exhibited the most striking pannuclear expression, while nodular melanomas showed the least, although with supervening enhanced diffuse cytoplasmic expression. Loss of the Golgi expression pattern was a feature of malignant melanoma.

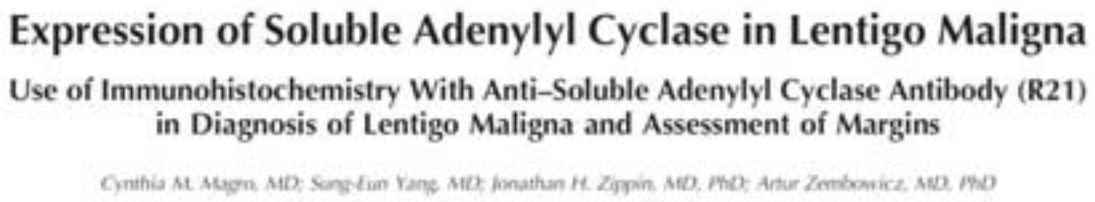
Conclusion: The sAC expression pattern is complex but seems discriminatory, with distinctive and variable staining patterns according to the nature of the lesion biopsied.

Arch Dermatol.
Published online November 21, 2011.
doi:10.1001/archdermatol.2011.338

Lentigo maligna

- Histological differential diagnosis
  - Melanocytic hyperplasia (photoactivation, paracicaticeal)
  - Junctional nevus (dysplastic)
  - Superficial spreading melanoma

- Evaluation of excision margins

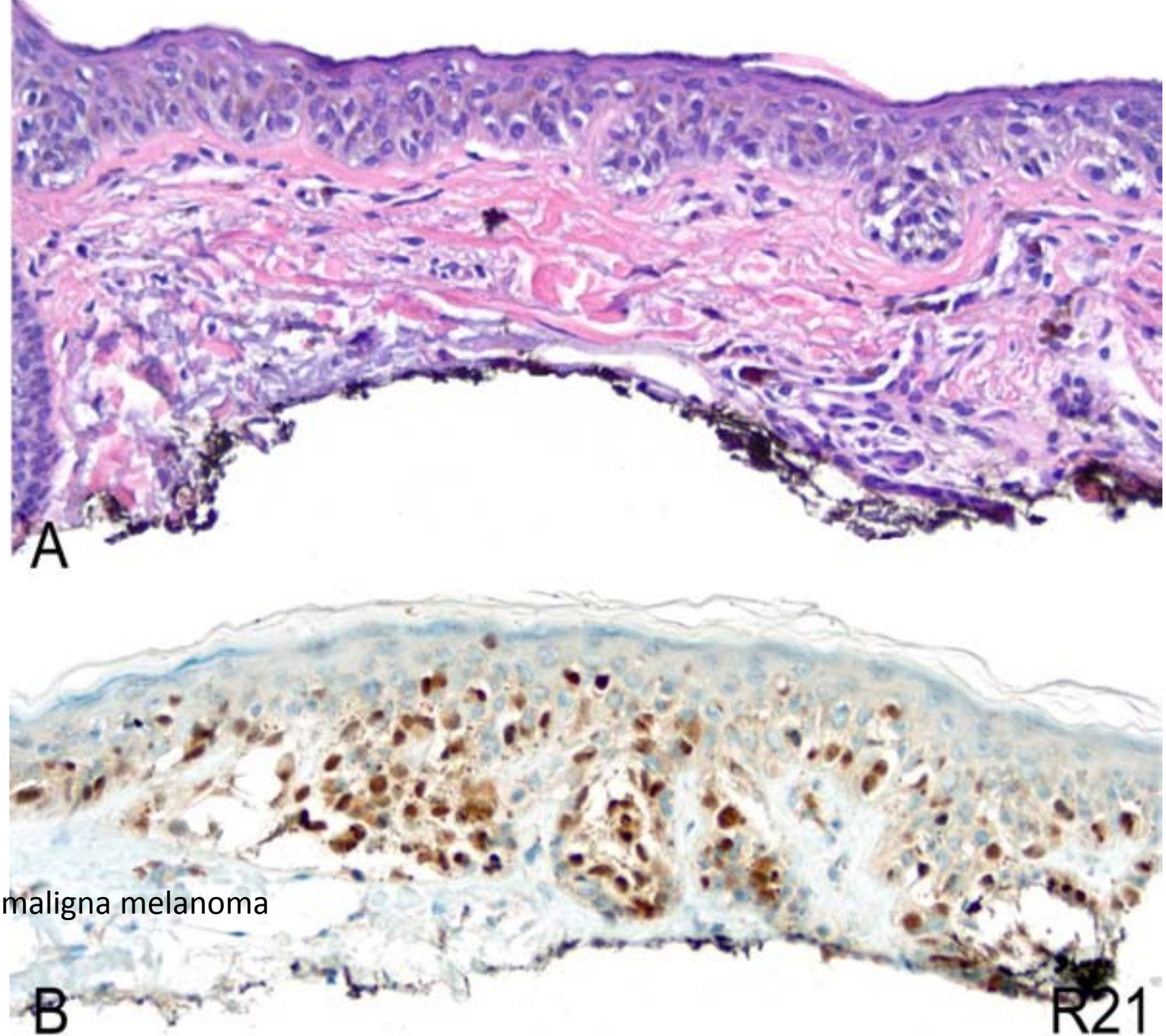


Expression of Soluble Adenylyl Cyclase in Lentigo Maligna

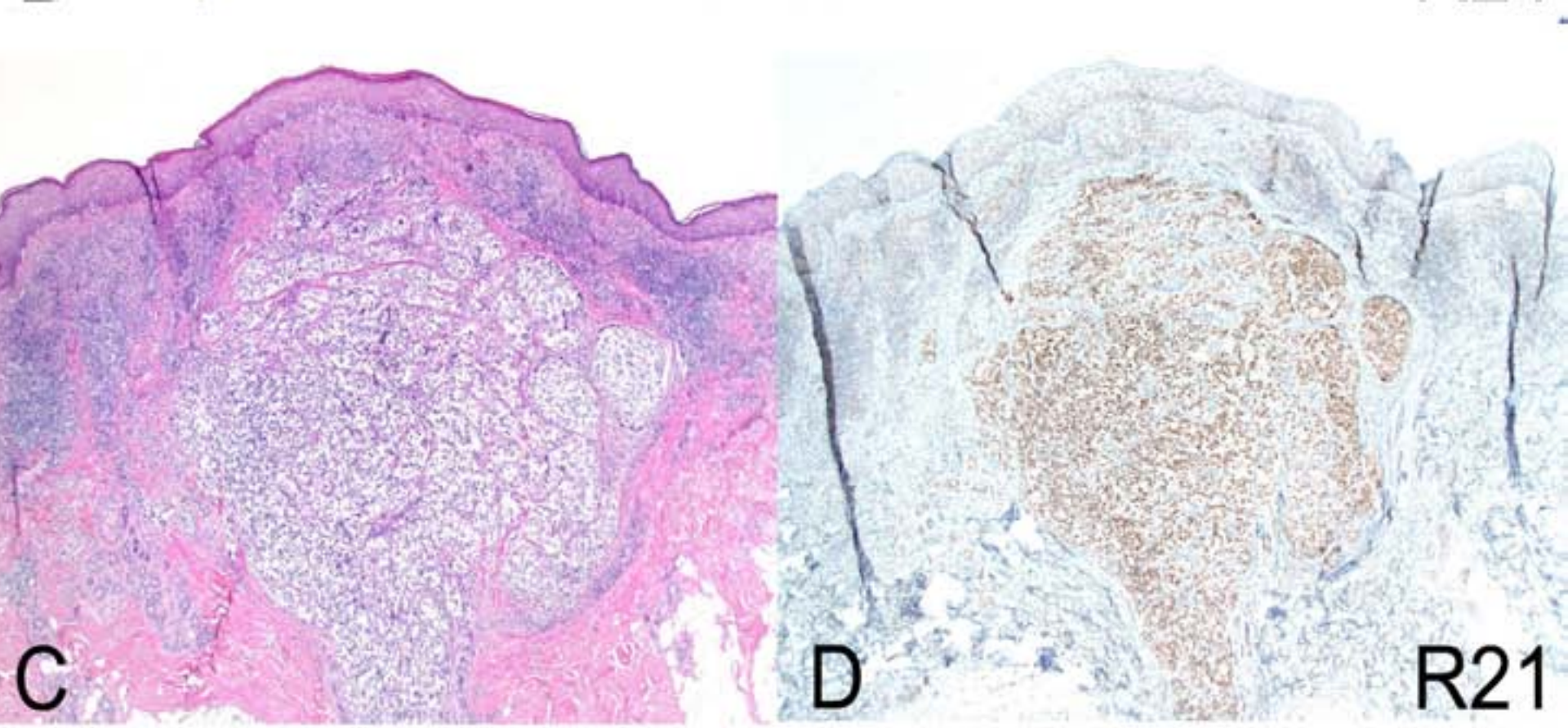
Use of Immunohistochemistry With Anti–Soluble Adenylyl Cyclase Antibody (R21) in Diagnosis of Lentigo Maligna and Assessment of Margins

Cynthia M. Magro, MD; Sung-Eun Yang, MD; Jonathan H. Zippin, MD, PhD; Artur Zembowicz, MD, PhD

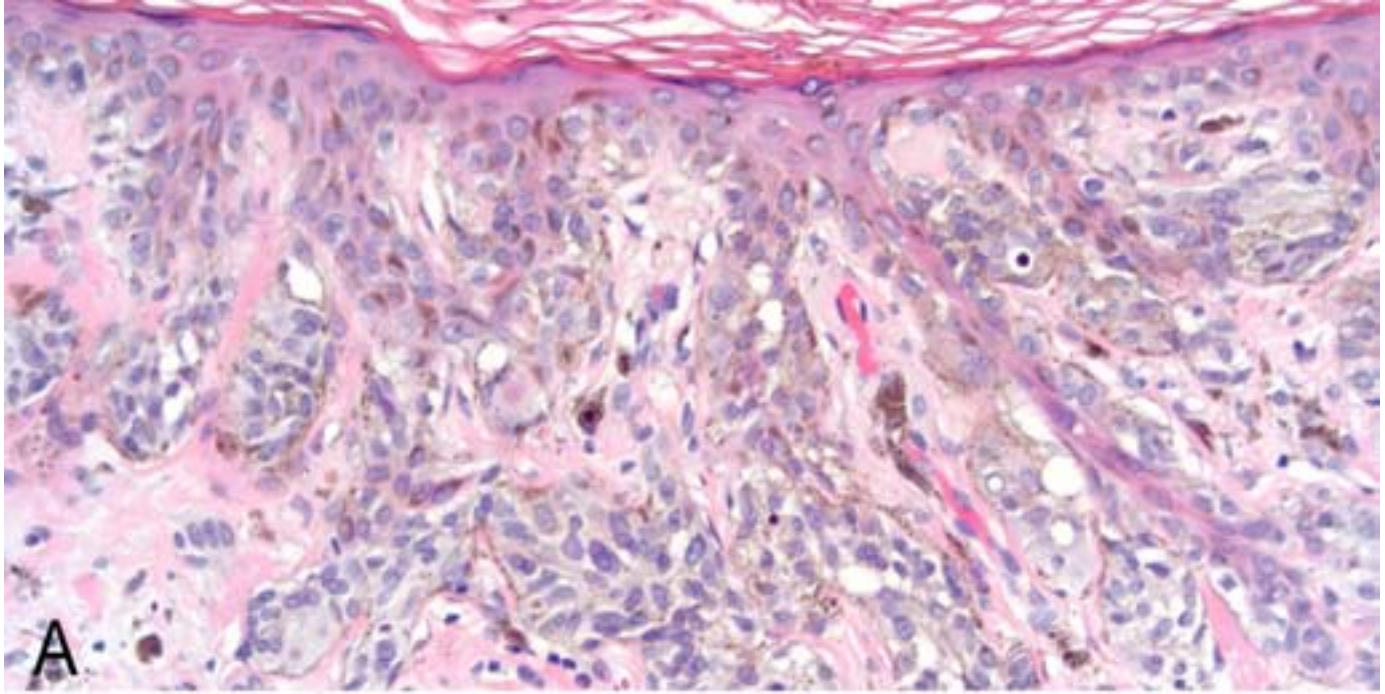
Click here

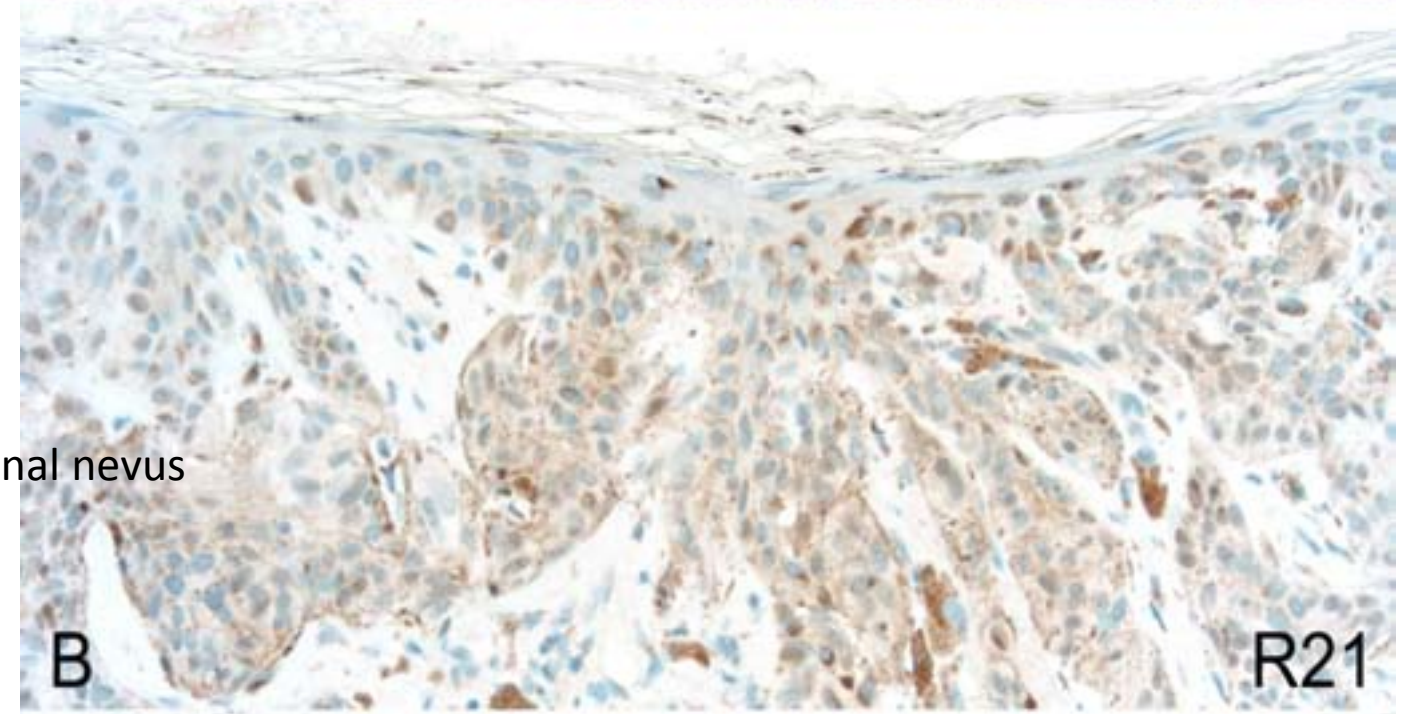


Lentigo maligna melanoma

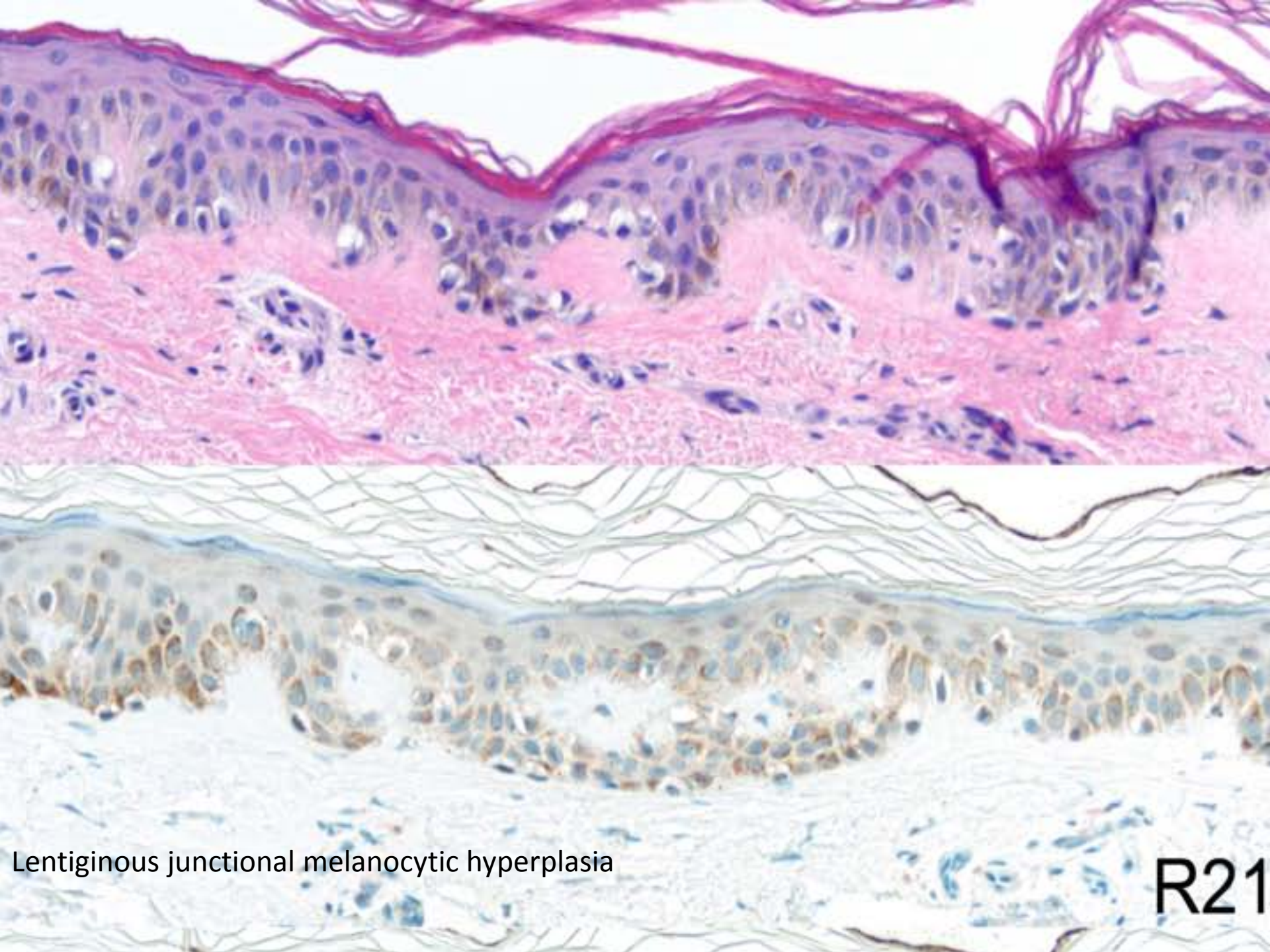


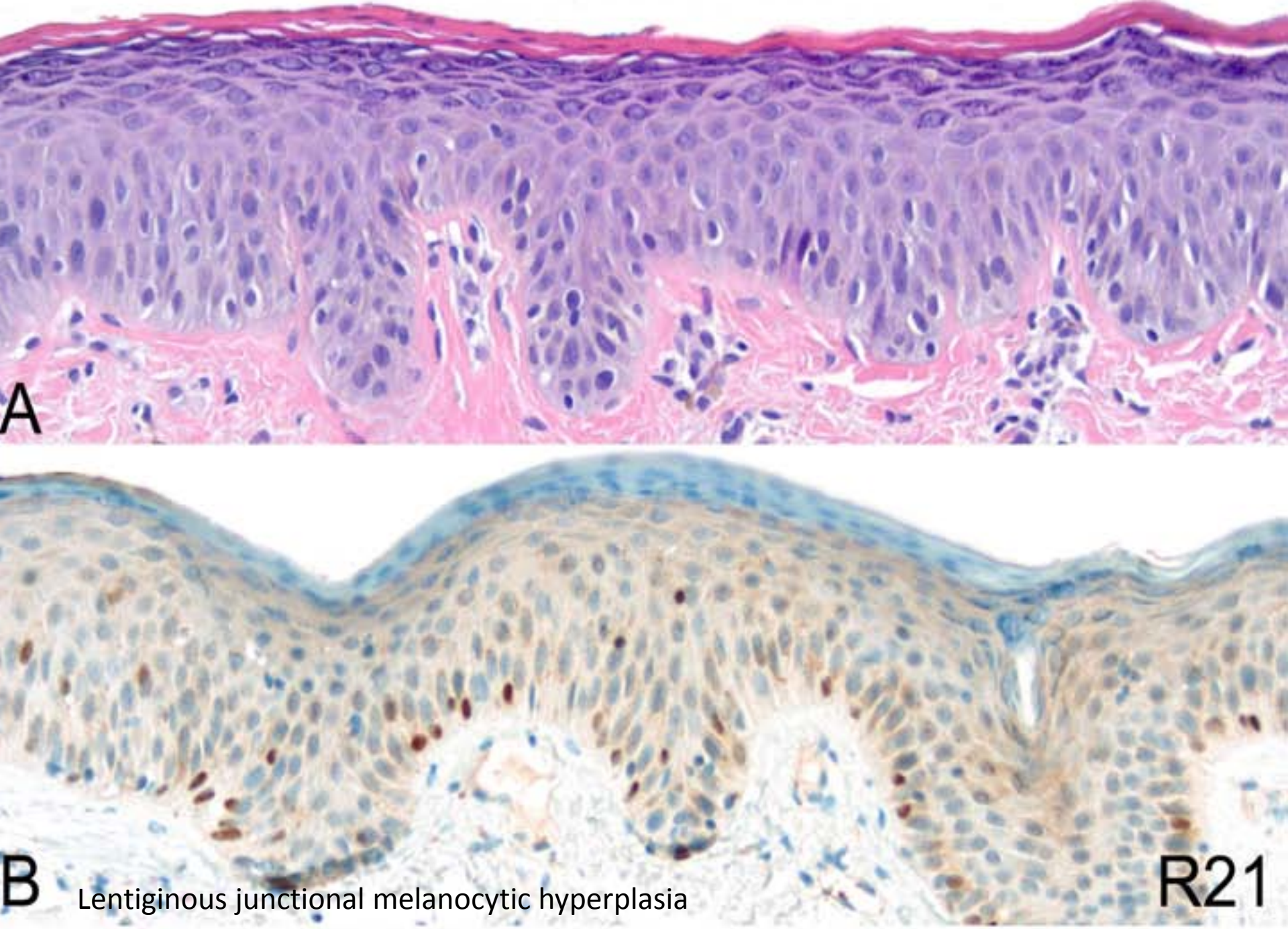
Lentigo maligna melanoma





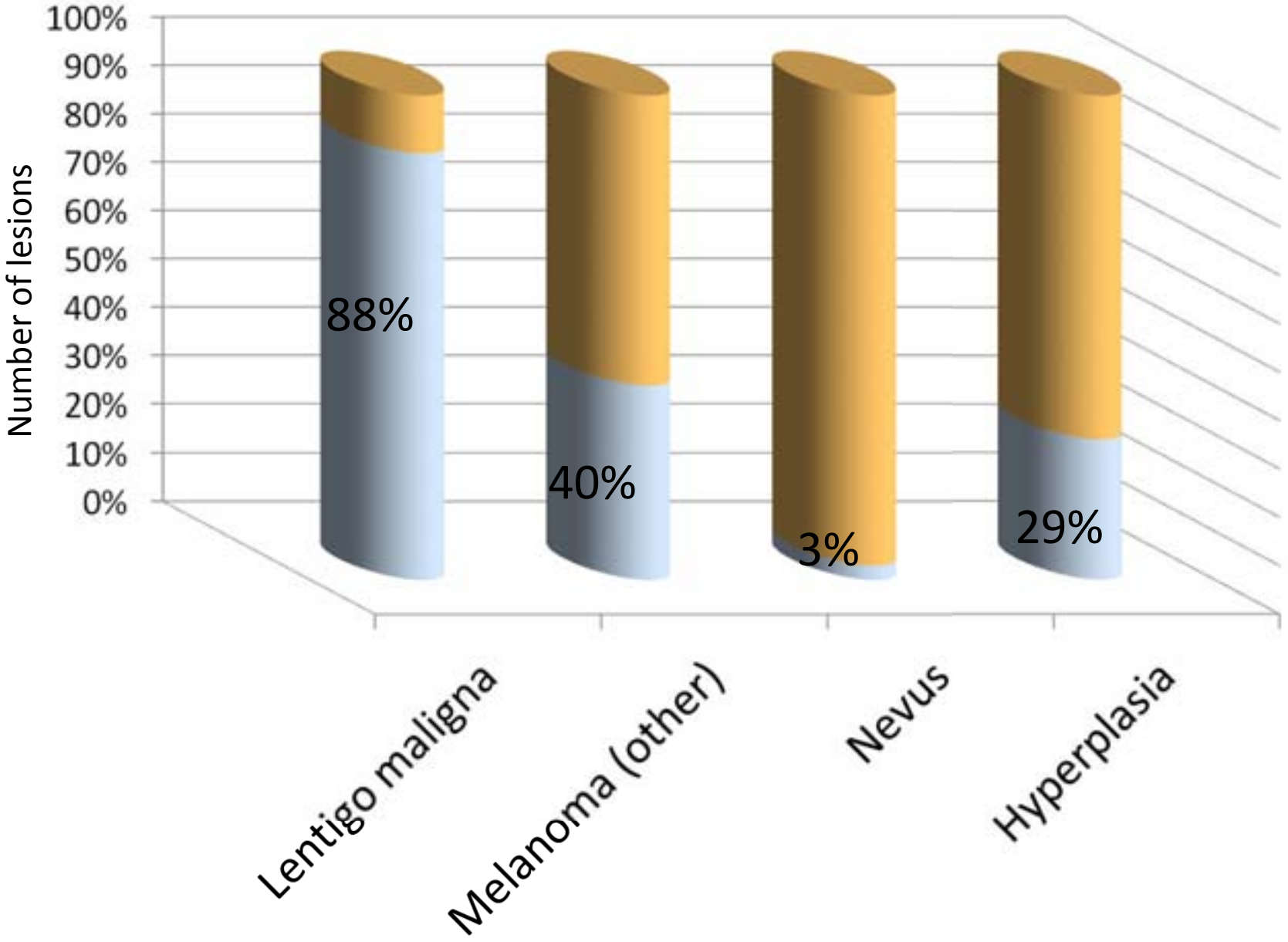
Junctional nevus


Lentiginous junctional melanocytic hyperplasia
R21



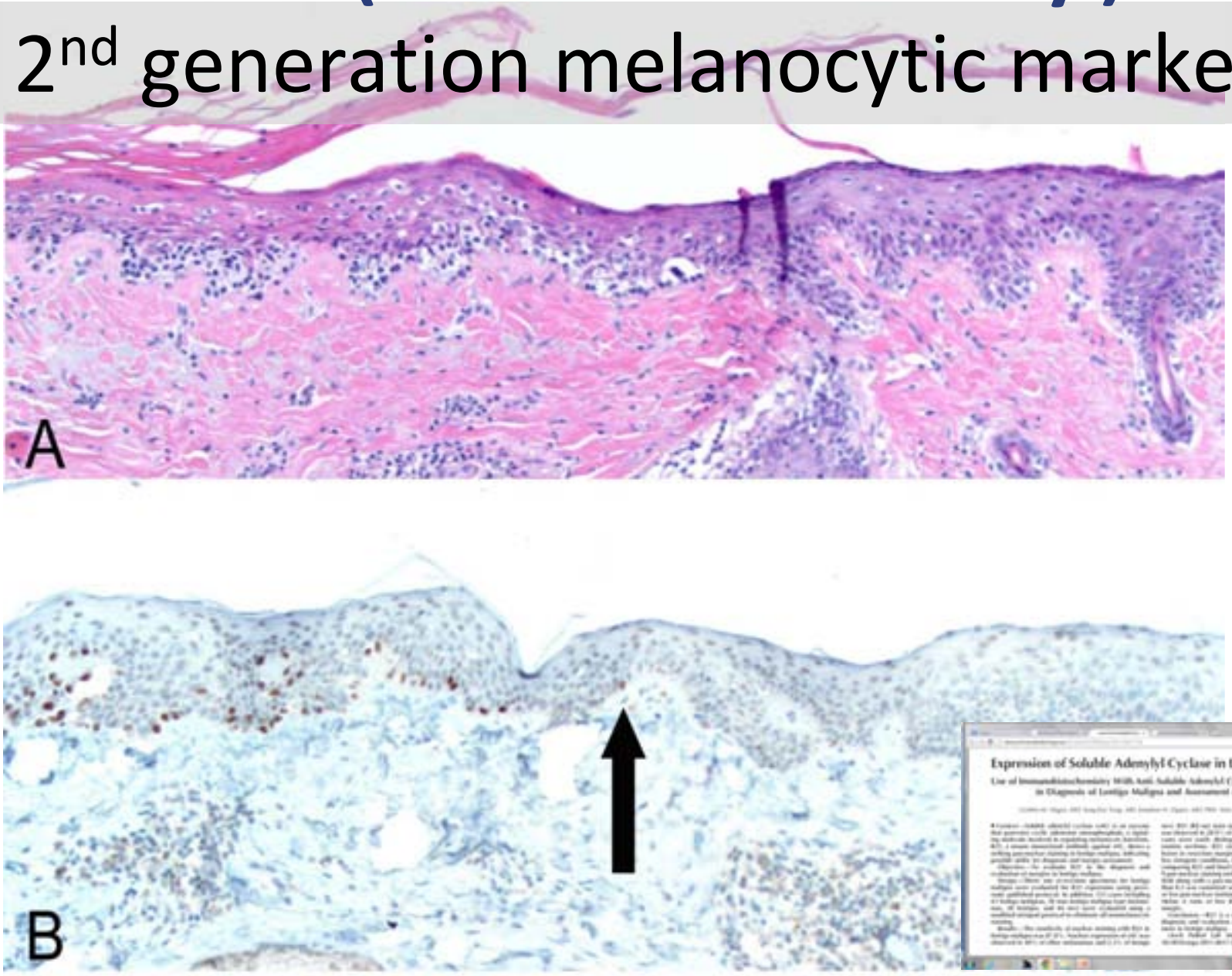
Lentiginous junctional melanocytic hyperplasia

R21 nuclear staining



R21 (sAC antibody)

2nd generation melanocytic marker



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