

Diverticula in Dermatopathology

Benjamin A Wood



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franklin.ai



 THE 47TH ANNUAL SCIENTIFIC MEETING

of the Australasian Division of the
International Academy of Pathology

Disclosure of Relevant Financial Relationships

No relevant financial relationships.

“WAYSIDE HOUSES OF ILL-REPUTE”

— DIVERTICULAR DISEASE OF THE COLON

By T. W. BALFOUR

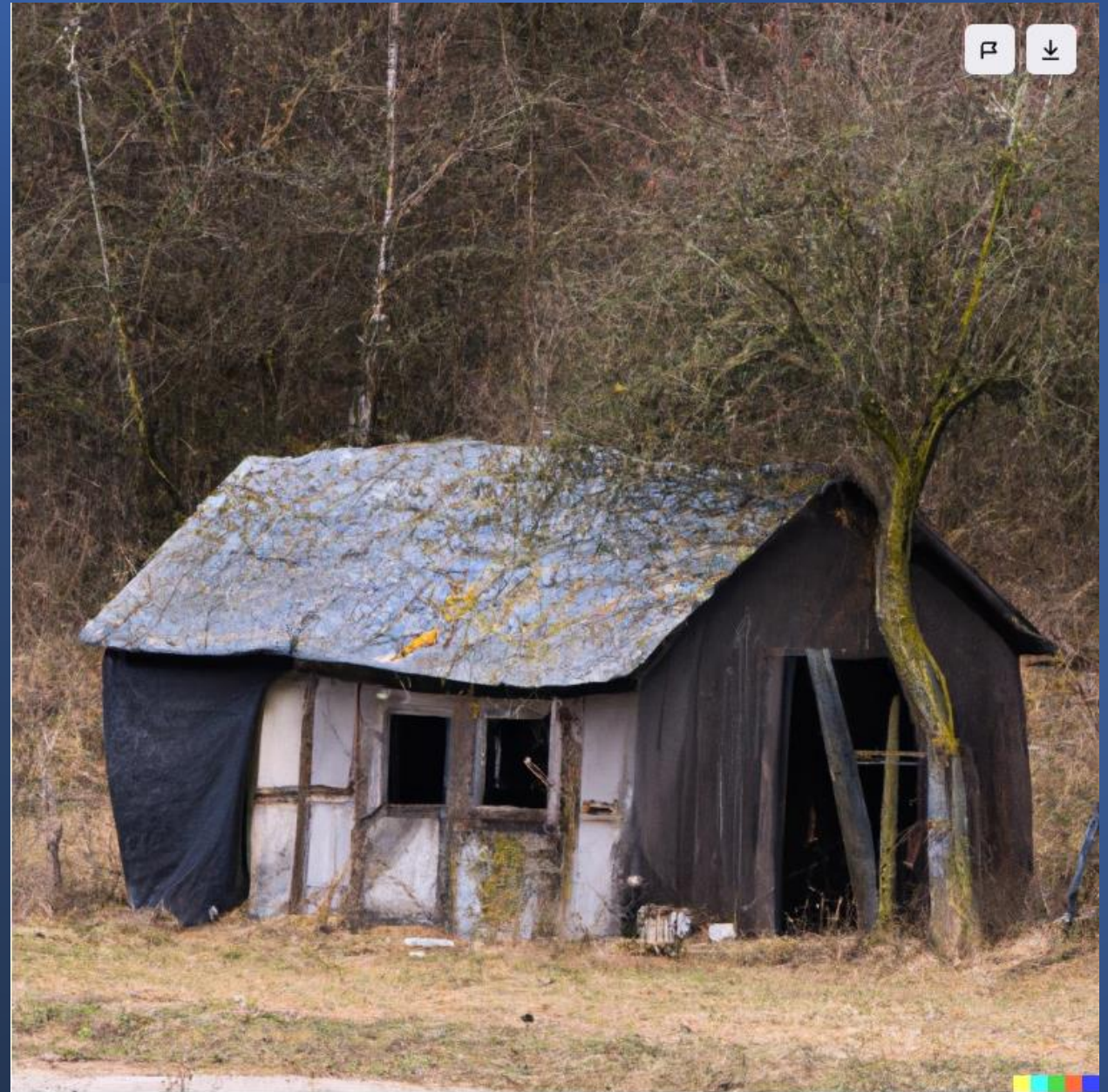
*From a Dissertation delivered before the Royal Medical Society
on January 29th, 1965.*

“He was never in London before but one week
and then he was kidnapp’d into a House of ill
Repute.”

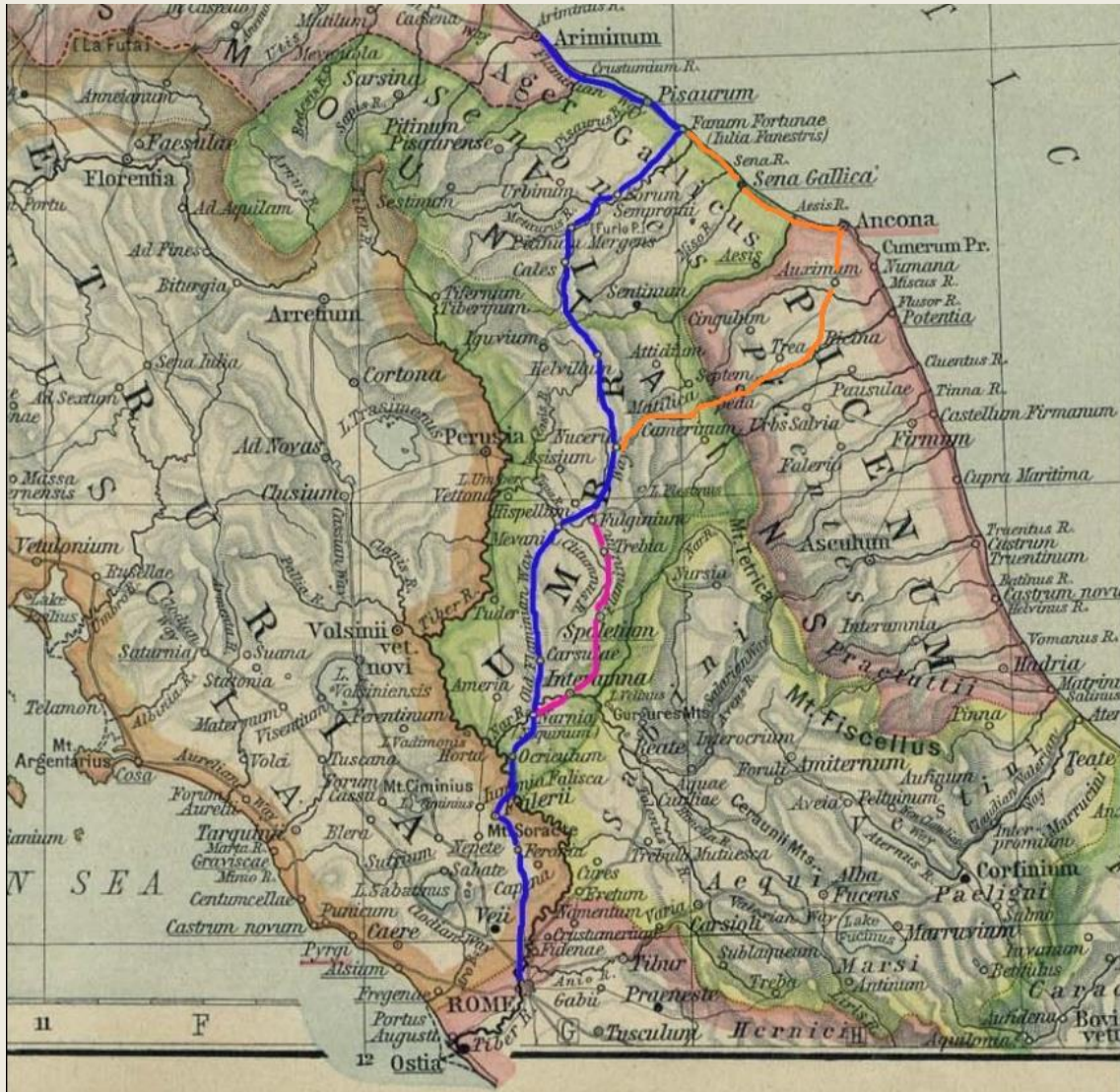
Jon Vanbrugh, *A Journey to London*, 1728

“A wayside house of ill-repute”

Image generated by DALL.E.2



The classical definition...

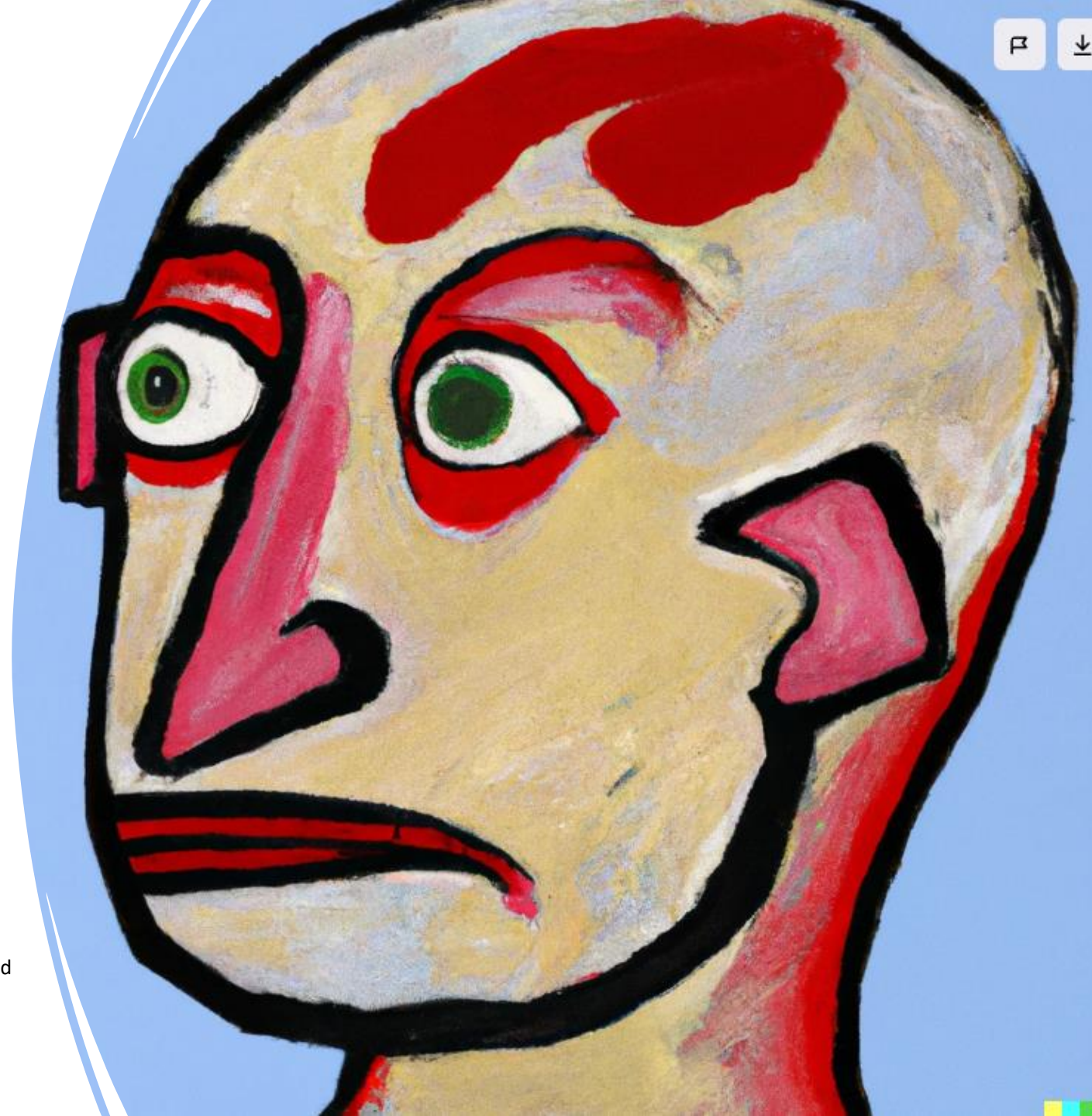


Today's diverticula....

- Atypical Fibroxanthoma
- Melanoma "Overdiagnosis"
- Squamous Dysplasia



Atypical Fibroxanthoma



- “Painting in the style of Picasso of a bald man with a red ulcerated fungating tumour growing from his scalp”
- Image generated by DALL.E.2

Helwig, E. Texas State Journal of Medicine, July 1963

History.—For one year a 75 year old man noted a swelling on his neck which gradually increased in size until it measured 3 cm. in diameter. It was covered with skin except for a small central focus of ulceration. The cut surface was grayish-white with a suggestion of yellow.

Submitted Diagnoses.—Sarcoma (rhabdo-, 16; lipo-, 8; leio-, 2; fibro-, 3; pleomorphic cell, 1) 31; reticulohistiocytoma, 10; reticulohistiocytic granuloma, 4; malignant granular cell myoblastoma, 3; dermatofibrosarcoma protuberans, 1; malignant melanoma, 1; squamous cell carcinoma, 1; malignant fibrous xanthoma, 1; dermatofibroma, 1; neuroxanthoma, 1; granular cell myoblastoma, benign, 1.

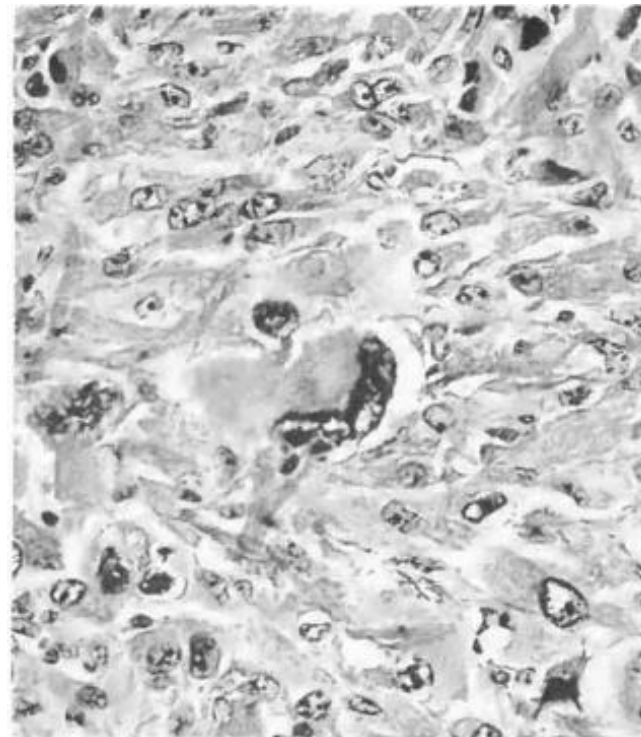


Fig. 6. Case 6. (Atypical fibroxanthoma). The cells appear fibroblastic and histiocytic. Some cells are large with bizarre nuclei. X 300

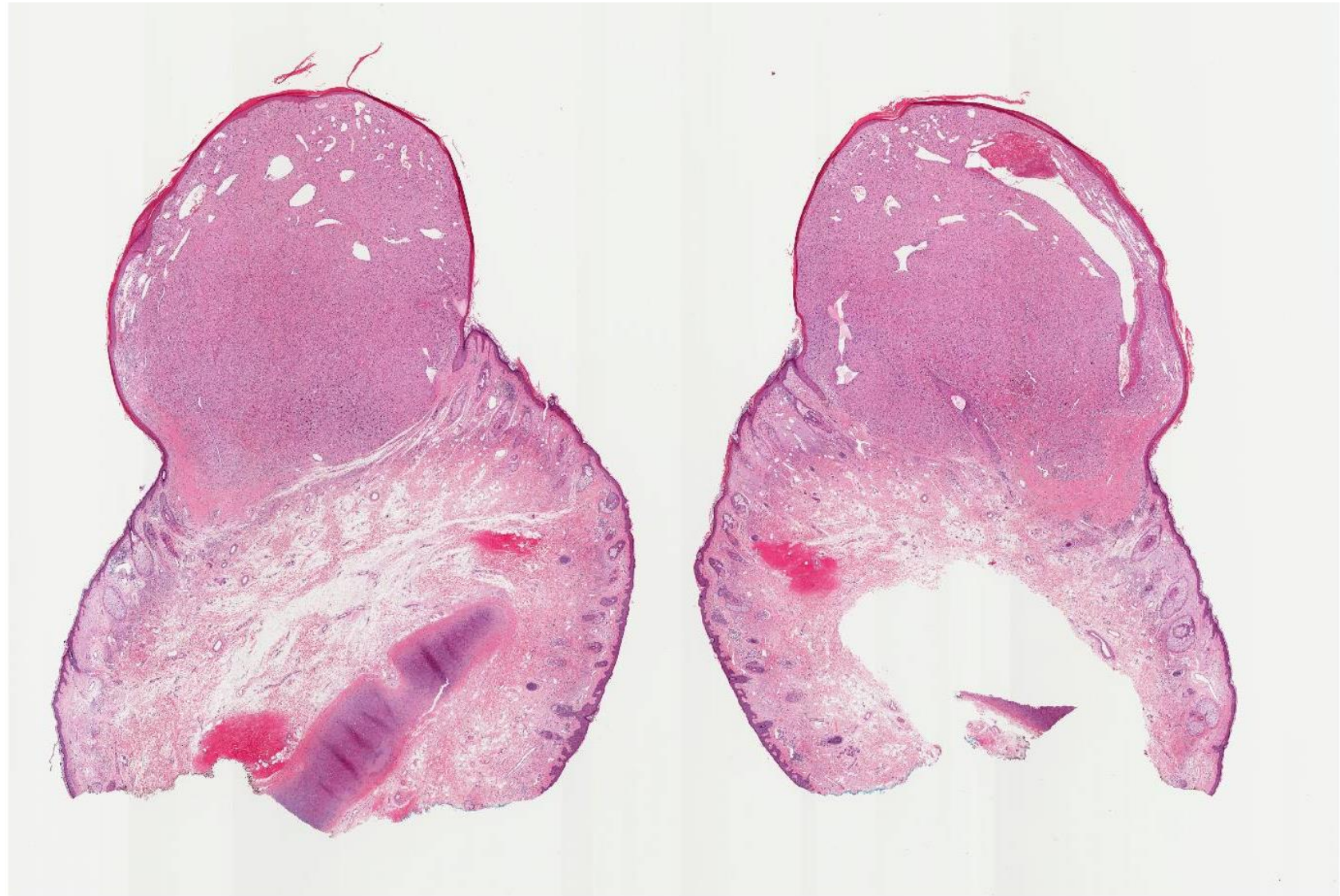
I'm putting this case out as a sort of trial balloon. My interpretation is an "atypical fibroxanthoma", a name we have used for several years at the Armed Forces Institute of Pathology. After looking at the microscopic pictures I will tell you what we know about these lesions.



Elson B.
Helwig, MD

Atypical Fibroxanthoma

Elderly male,
ear



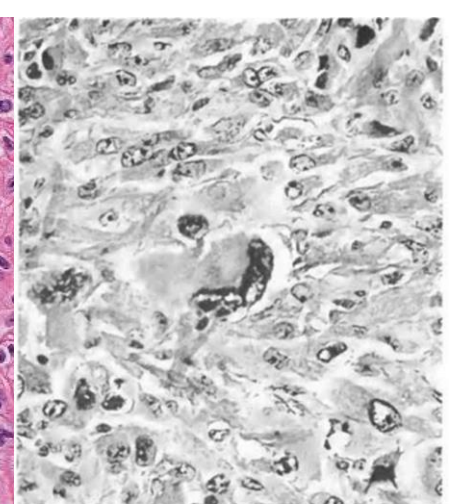
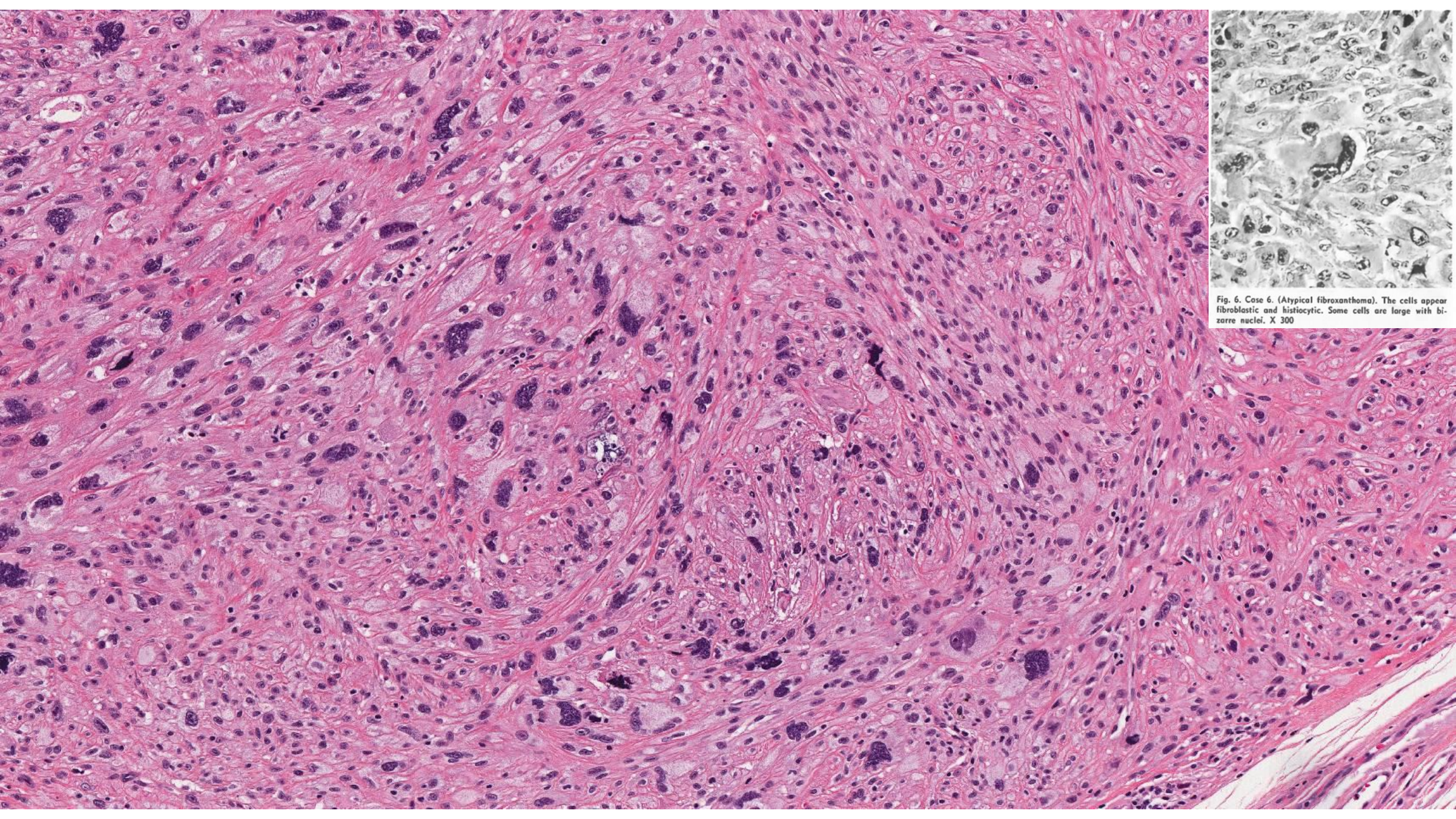


Fig. 6. Case 6. (Atypical fibroxanthoma). The cells appear fibroblastic and histiocytic. Some cells are large with bizarre nuclei. X 300

ATYPICAL FIBROXANTHOMA OF THE SKIN

A Clinicopathologic Study of 140 Cases

DAVID F. FRETZIN, MD,* AND ELSON B. HELWIG, MD†

CANCER June 1973

- 2 clinicopathological variants
 - Sun damaged head and neck skin in elderly
 - Younger patients on the limbs
- 140 cases, 9 recurrences, no metastases
 - “most” recurrent lesions involved subcutis
 - 6 had involved margins
- Hypothesized reactive/“pseudosarcomatous” nature, with discussion of sarcomatoid SCC alternative

Among 101 patients followed for periods up to 15 years, no metastatic lesions were found and only nine lesions recurred. Correlation of the clinical and follow-up data support the concept that in spite of its alarming histologic appearance, atypical fibroxanthoma of skin appears to behave in a benign manner.

...in a distinctly younger age group. The atypical fibroxanthoma has a malignant cytologic appearance often simulating that seen in soft tissue sarcomas, yet it behaves in a clinically benign manner. The pathogenesis of this lesion is uncertain. Most authorities have considered it to be a reactive or reparative process, possibly the cutaneous counterpart of the pseudosarcomas of soft tissue.^{14,16,18} Other

Of the nine lesions that recurred, most were poorly circumscribed and had infiltrated into the subcutis. Six of the lesions appeared inadequately excised, with the tumor extending to

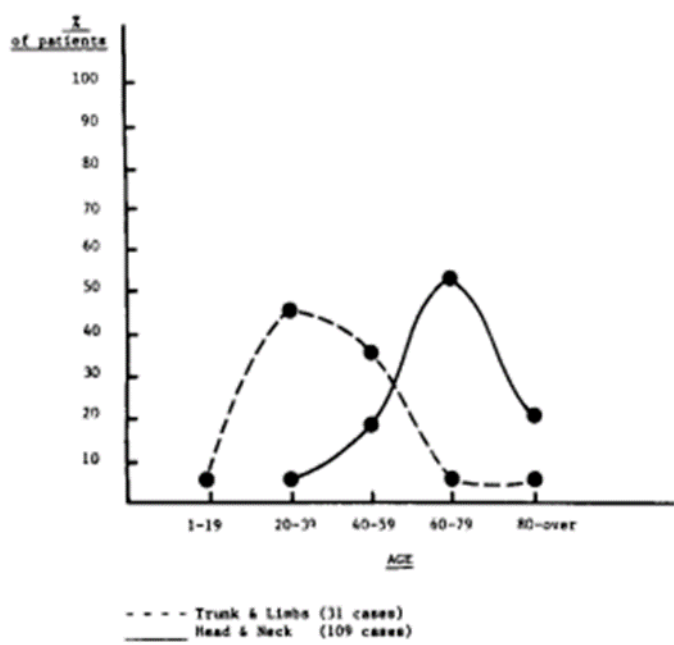
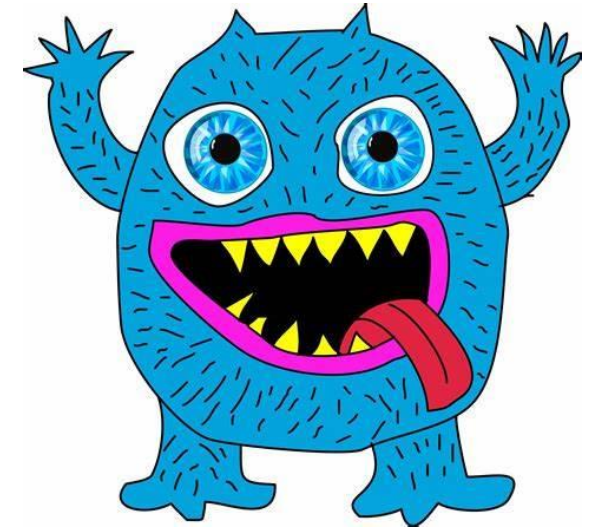
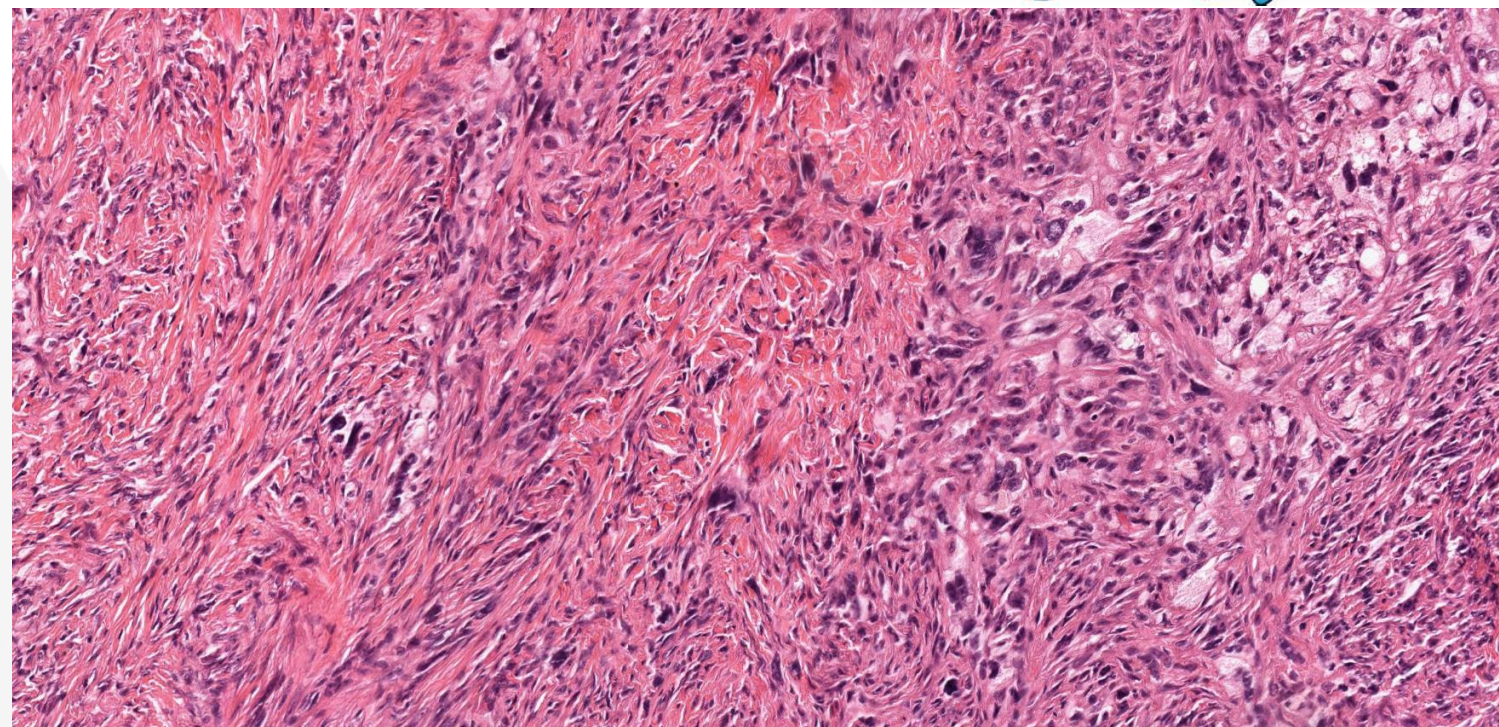
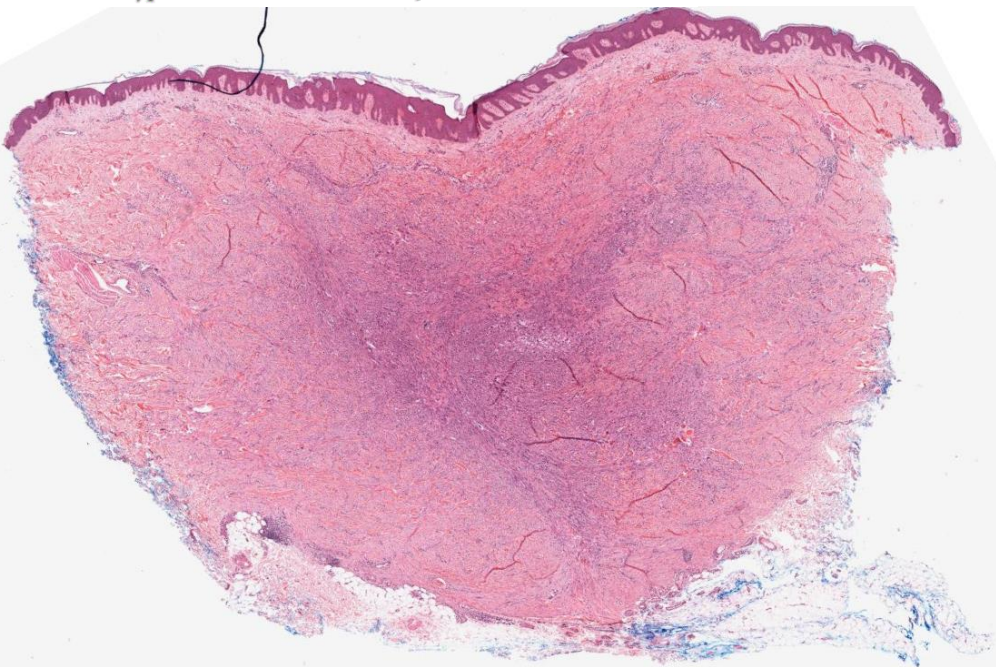


FIG. 1. Chart showing age distribution of 140 patients with atypical fibroxanthoma by site of lesions.



“Atypical” fibrous histiocytoma



Atypical Fibroxanthoma: A Histological and Immunohistochemical Review of 171 Cases

*Trevor W. Beer, MBChB, MRCPATH, FRCPA, Paul Drury, BSc (Med Sci),
and Peter J. Heenan, MBBS, FRCPath, FRCPA*

Am J Dermatopathol • Volume 32, Number 6, August 2010

- Median age 74, in sun-damaged skin
- Morphological variants:
 - Keloidal
 - Clear cell
 - Granular cell
 - Plaque-like
 - Myxoid
 - Regressing
- 2 cases recurred locally, no metastases
 - Recurrences at 6 and 11 months
 - F/U from <12 months to 9 years (T Beer, pers. Com.)

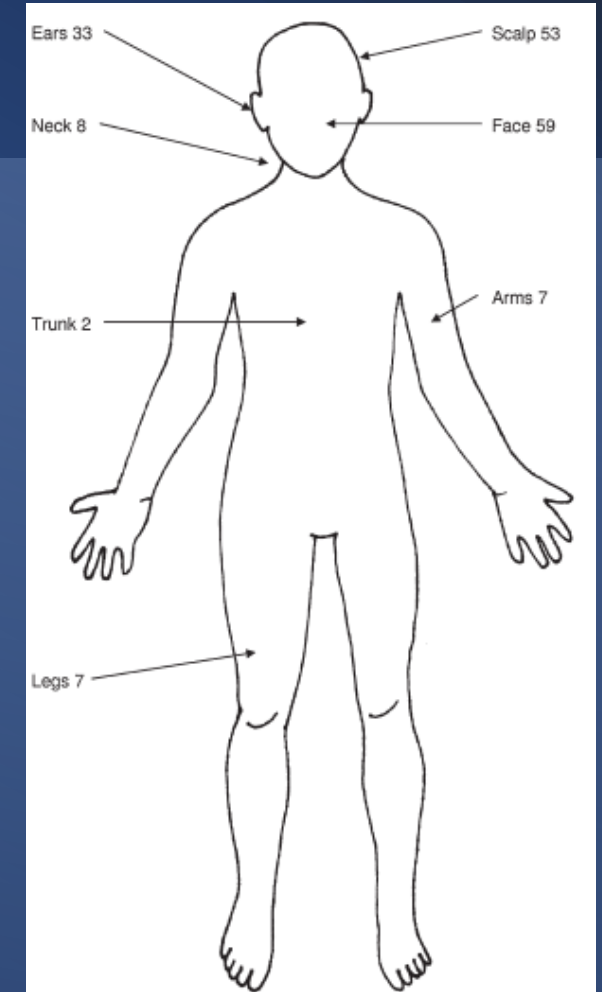


FIGURE 2. Anatomical location of the 171 AFXs. Ninety-one percent were present on the head and neck, and 99% were seen on sun-damaged skin.

Two points of interest:

TABLE 1. Review of the Clinical, Histological, and Immunohistochemical Findings in the Original 183 AFXs Led to Reclassification of 12 Cases

Revised Diagnosis	No. Cases	Comment
Metastatic melanoma	1	Original partial excision was negative for S100, HMB45, and Melan A
Squamous cell carcinoma	5	Cytokeratin staining was patchy but more clearly seen in several cases with subsequent 34betaE12 staining
MFH	3	Reclassified due to extensive or deep tissue invasion, extensive necrosis, and repeated recurrences
Unclassified	3	Clinical, histological, or immunohistochemical features were equivocal, so firm diagnosis was not possible

1

2

Invasion of subcutis in 26% - “generally only focal and of limited extent”

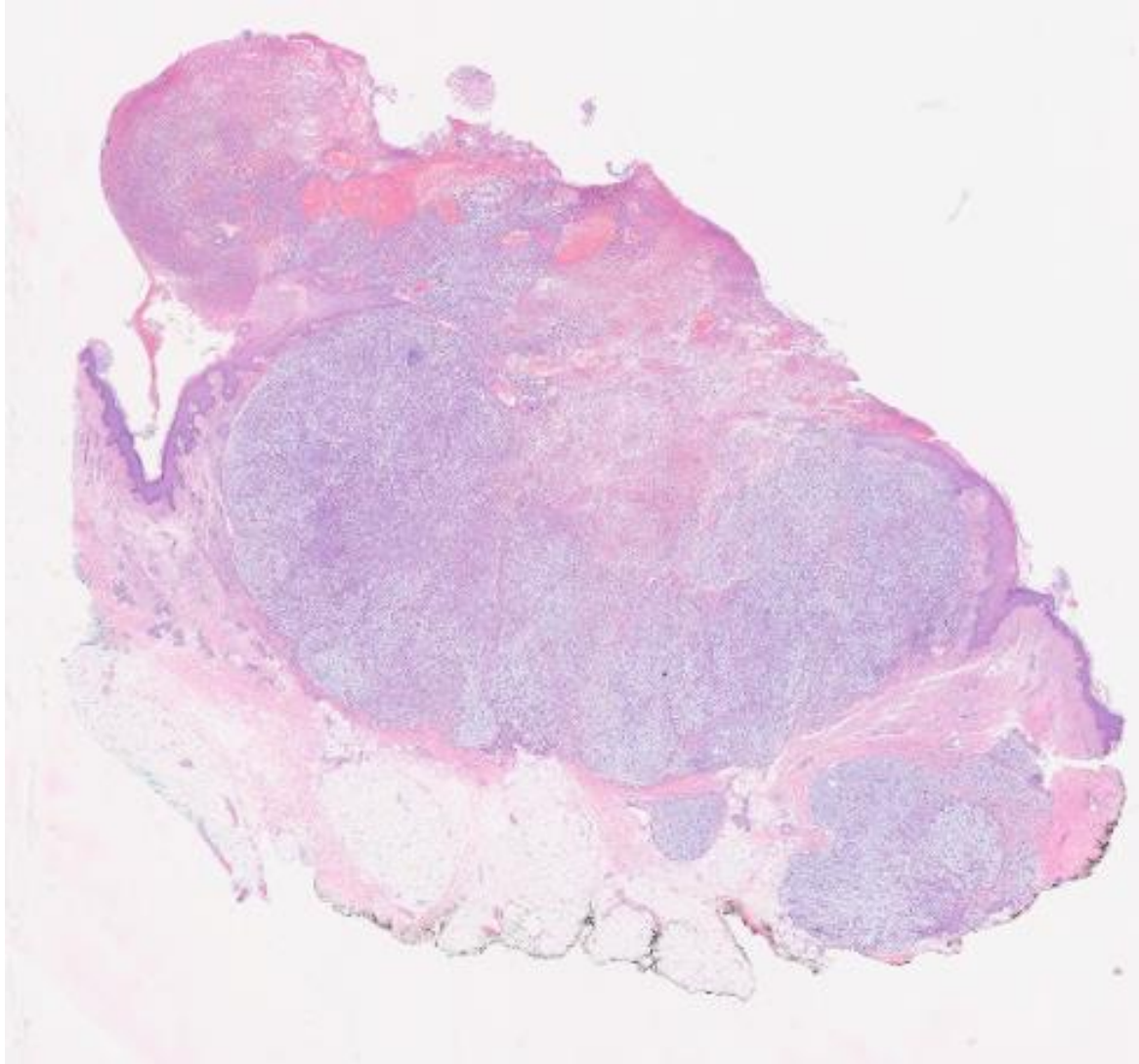
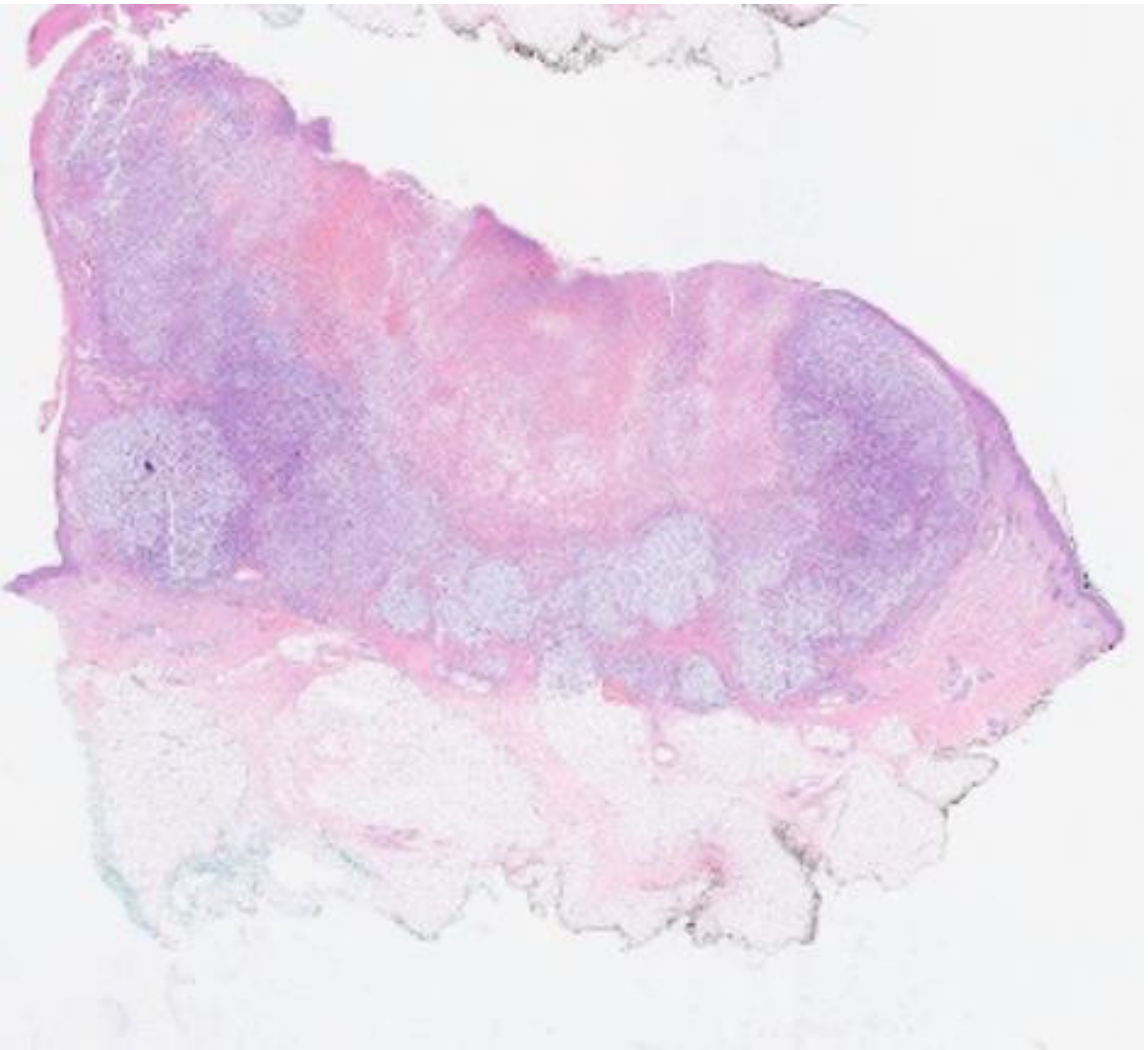
DR. R. E. BRIERTY, Brooke General Hospital: Dr. Helwig, was a trichrome stain done to bear out the fibrous portion of the stroma here, as your diagnosis indicates?

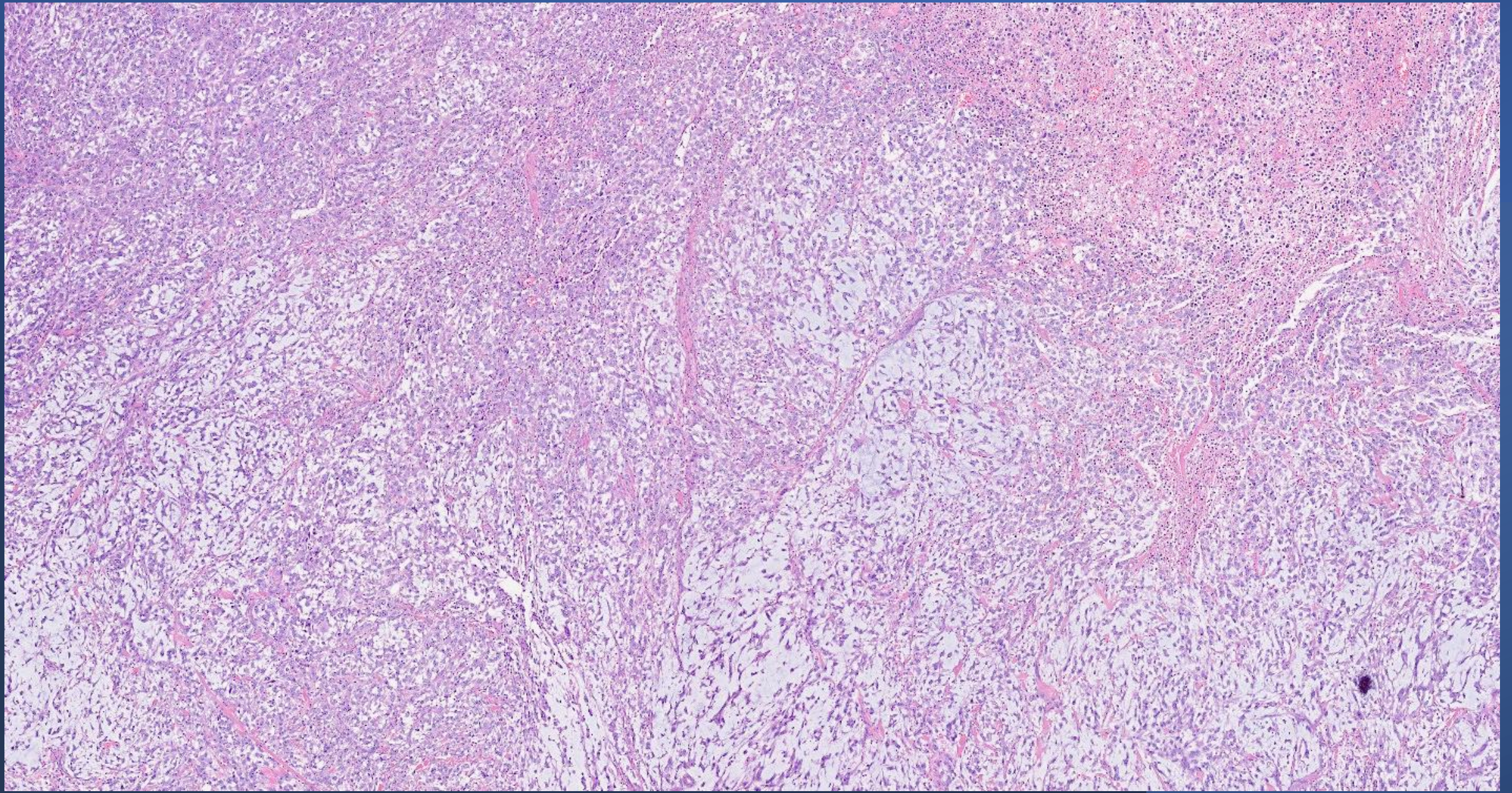
Immunohistochemistry

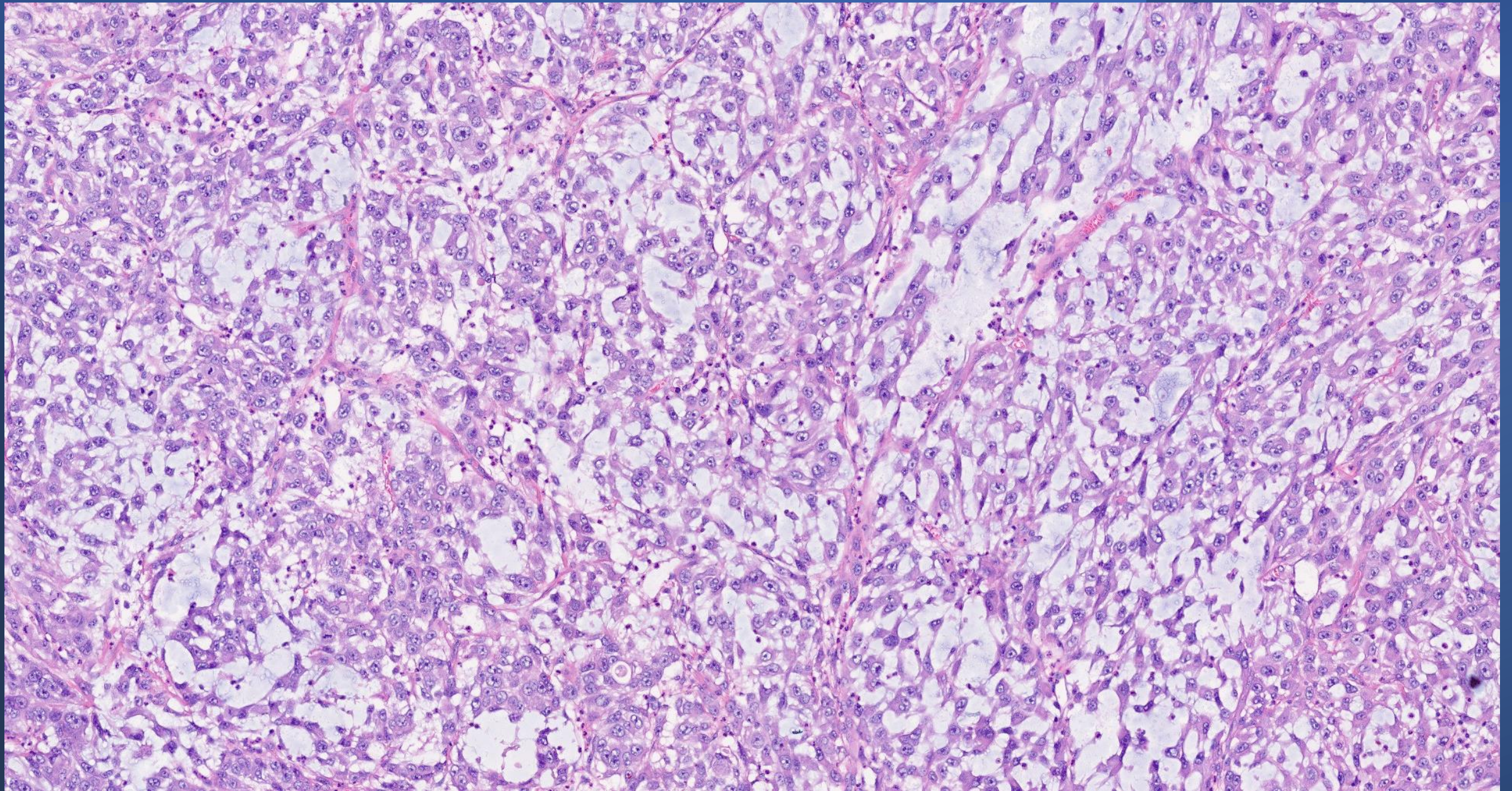
- AFX remains a diagnosis of exclusion:
 - Negative CK (broad spectrum, HMWK)
 - Negative melanocytic markers
 - Negative Desmin, ERG...
- Positive stains CD10, Procollagen-1 etc. are non-contributory



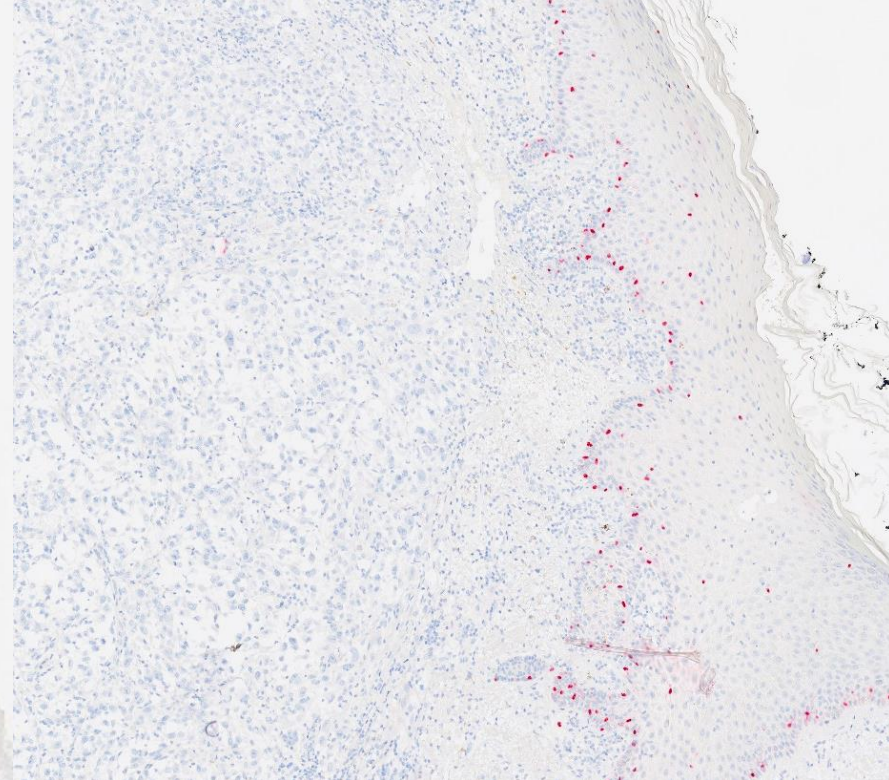
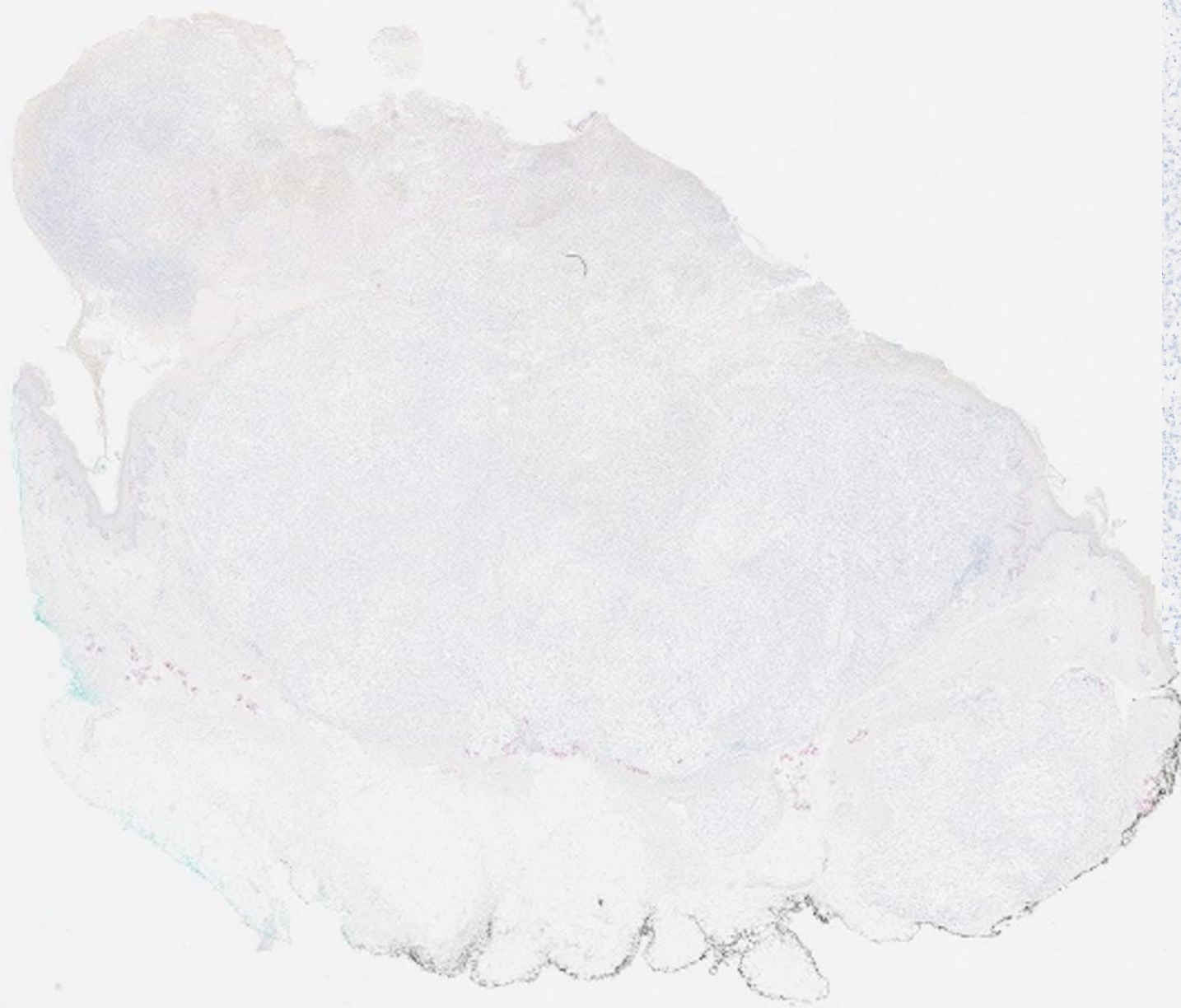
80F. Left cubital fossa.
Case courtesy of Dr M Gera





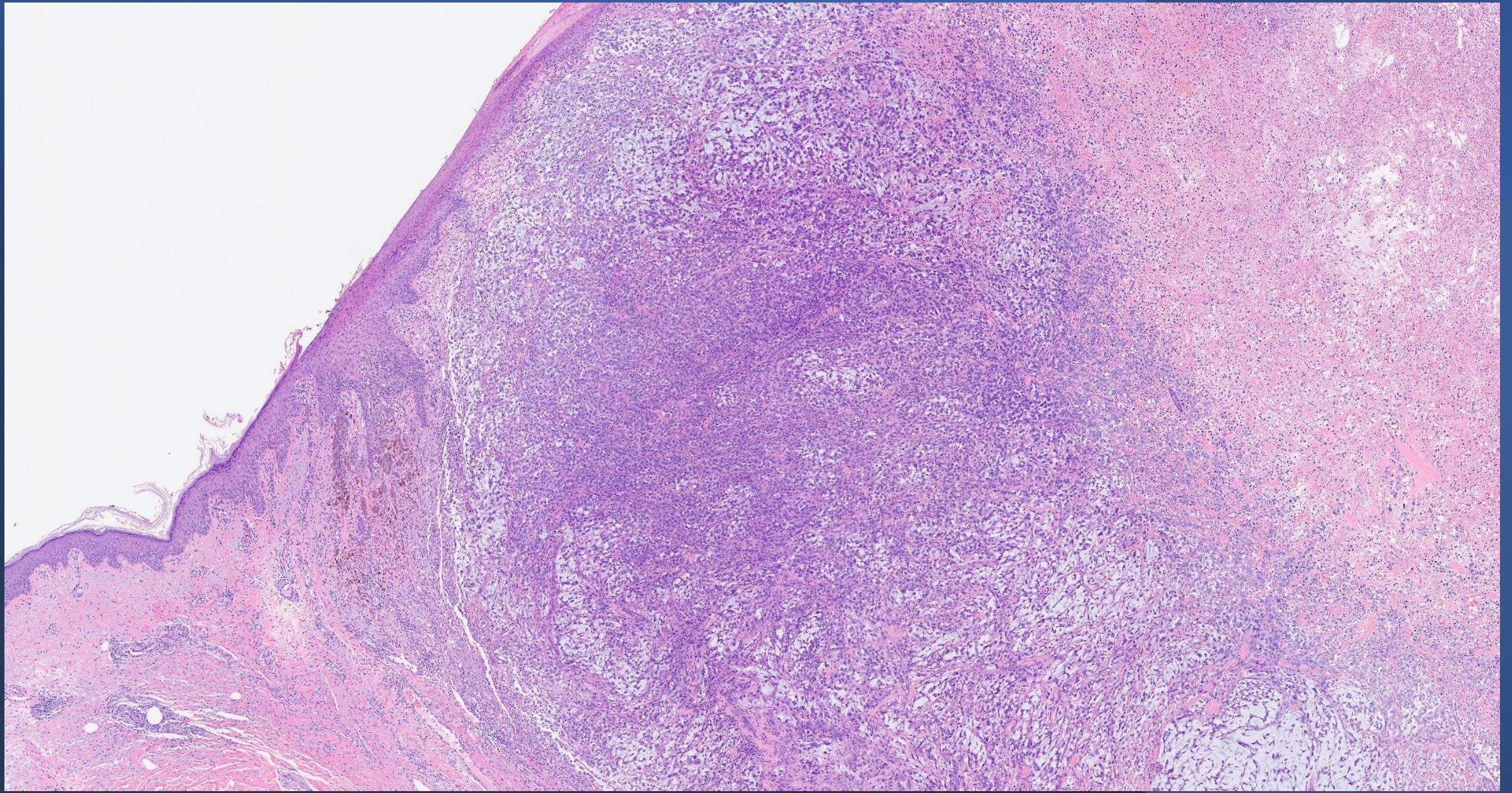


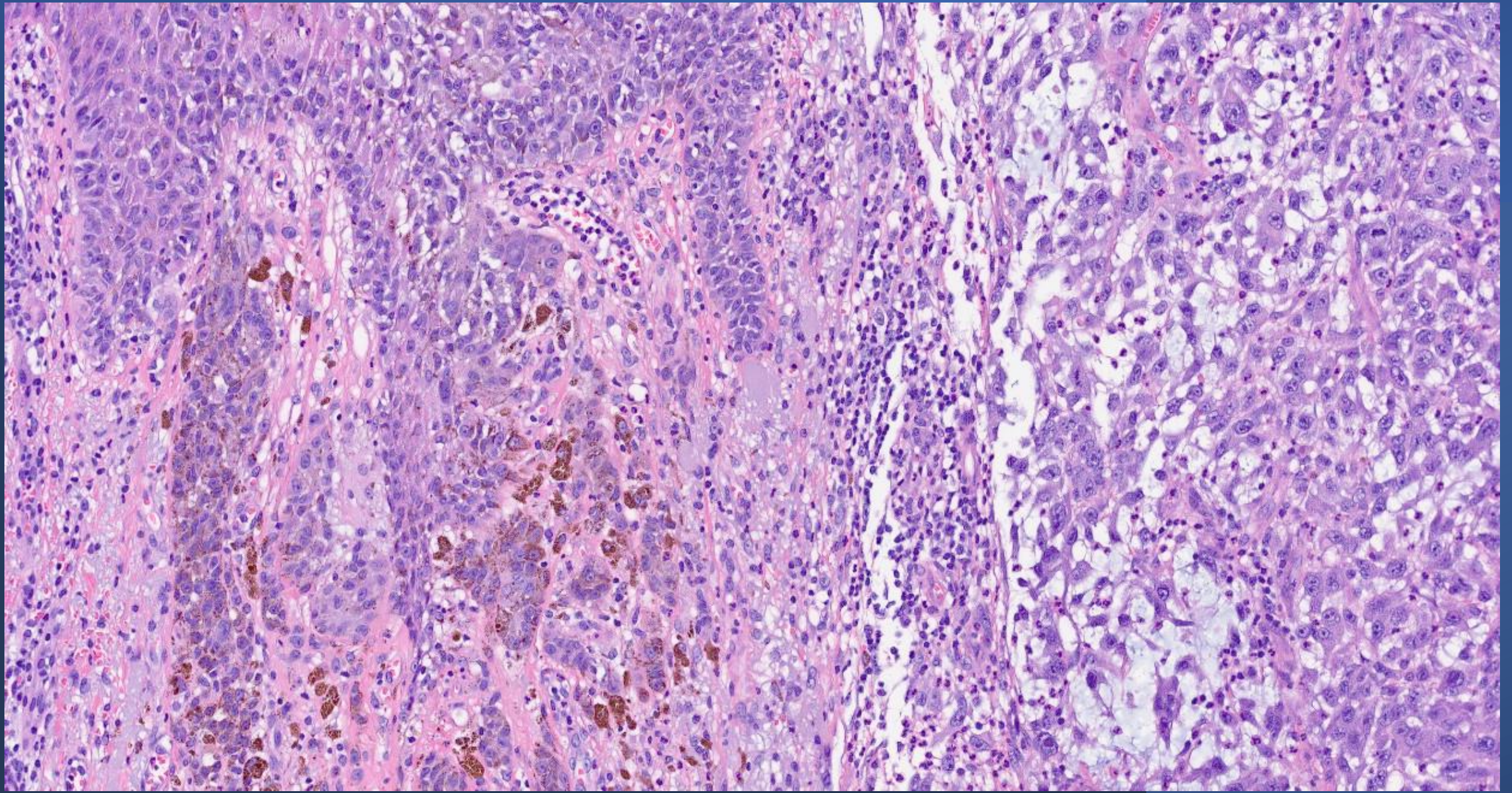
Sox10



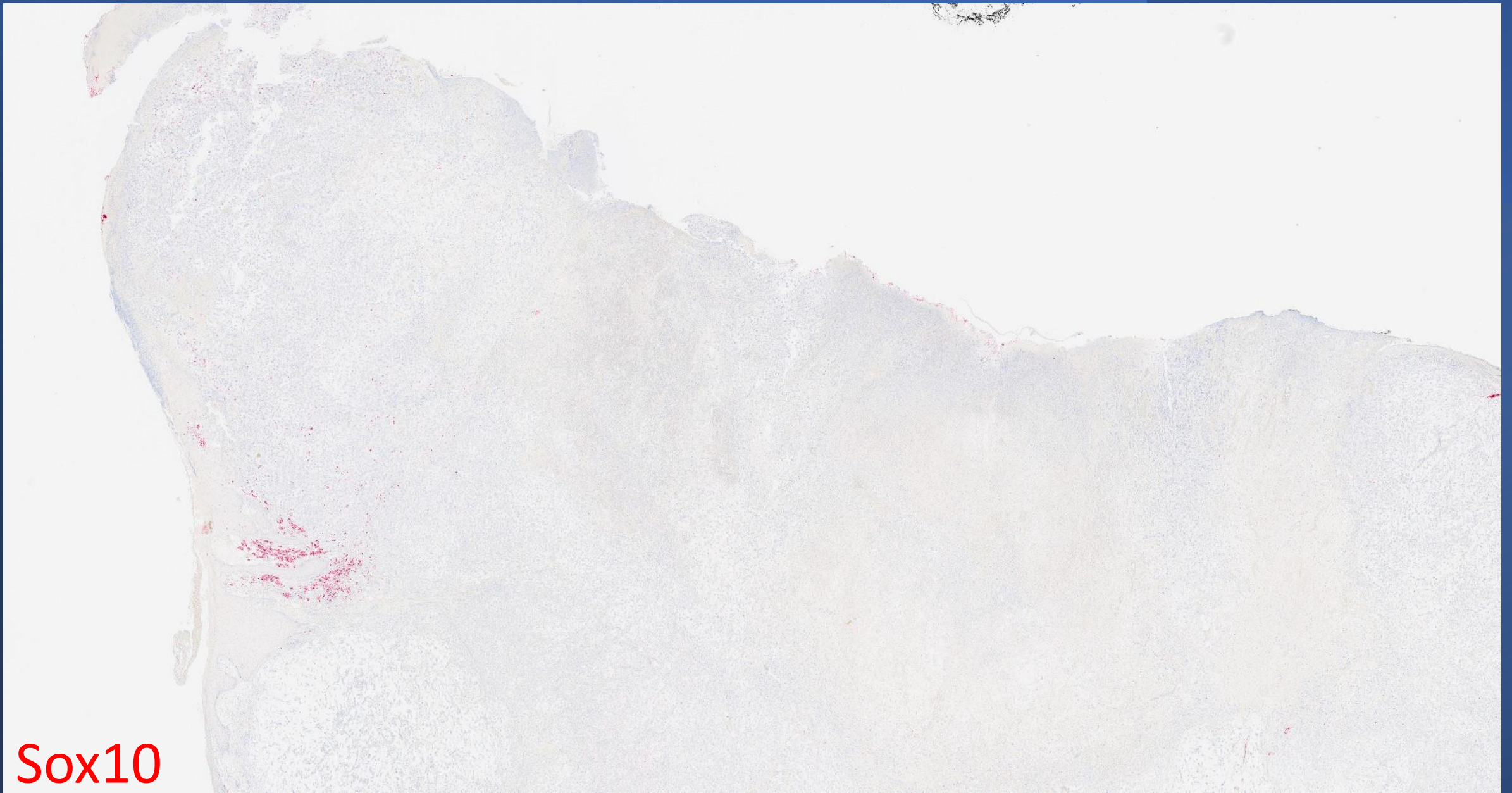
All IHC negative

Is this AFX/PDS?

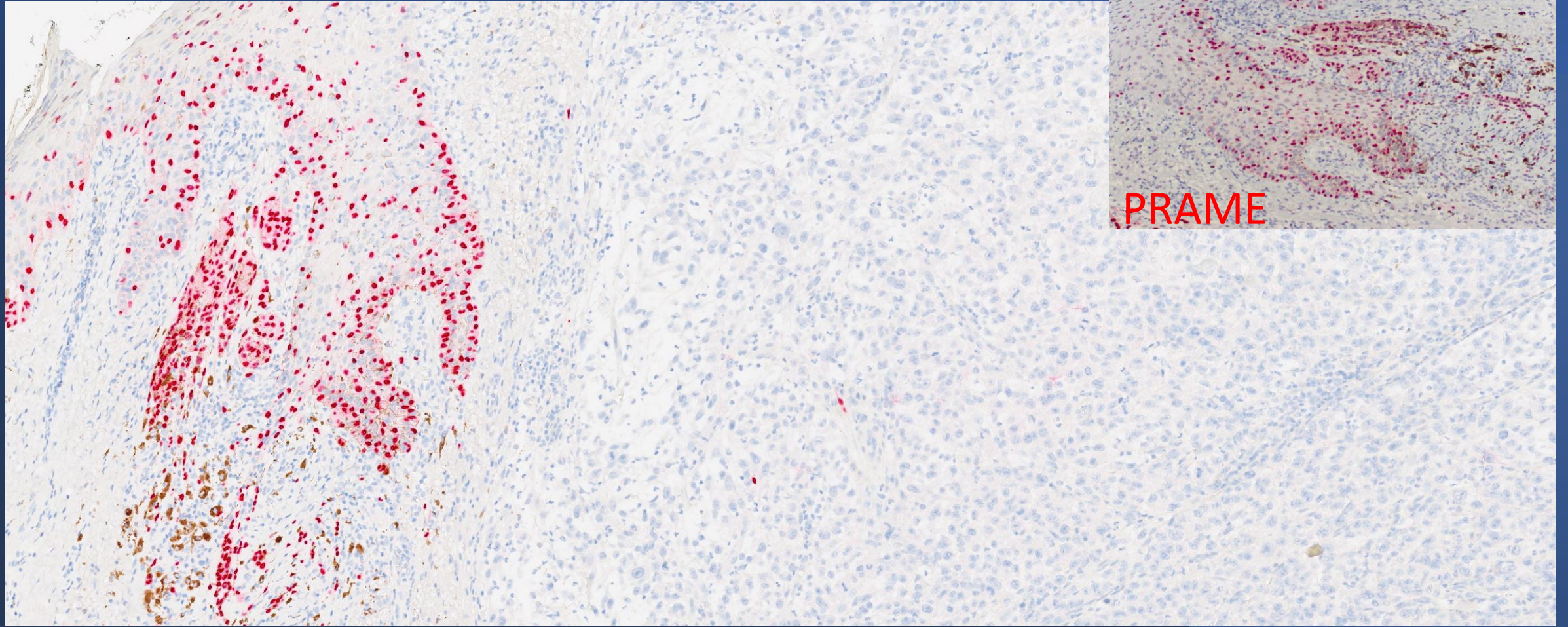




Sox10



Dedifferentiated melanoma



Sox10

Metastatic Malignant Melanoma With Complete
Loss of Differentiation Markers
(Undifferentiated/Dedifferentiated Melanoma)

*Analysis of 14 Patients Emphasizing Phenotypic Plasticity and the Value
of Molecular Testing as Surrogate Diagnostic Marker*

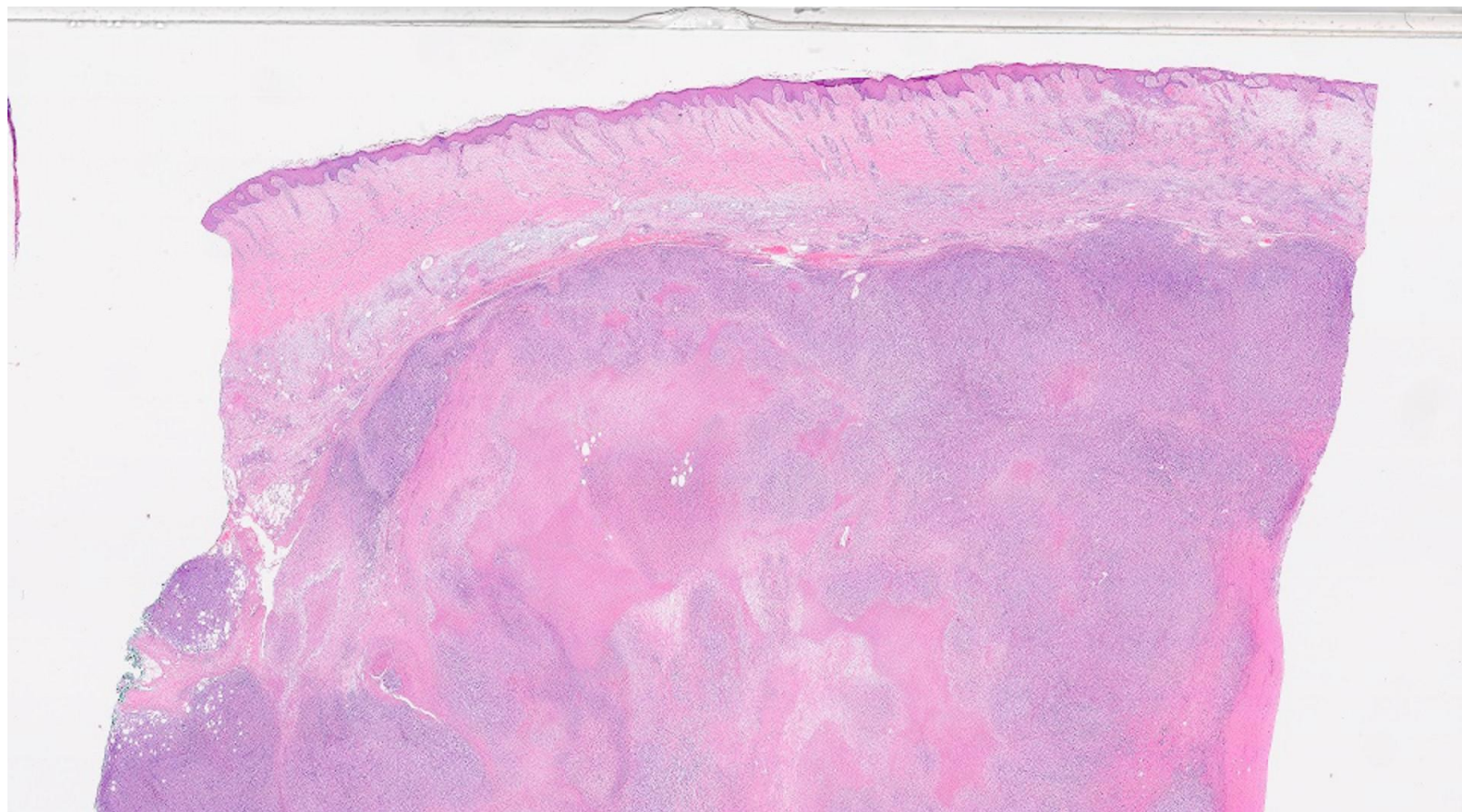
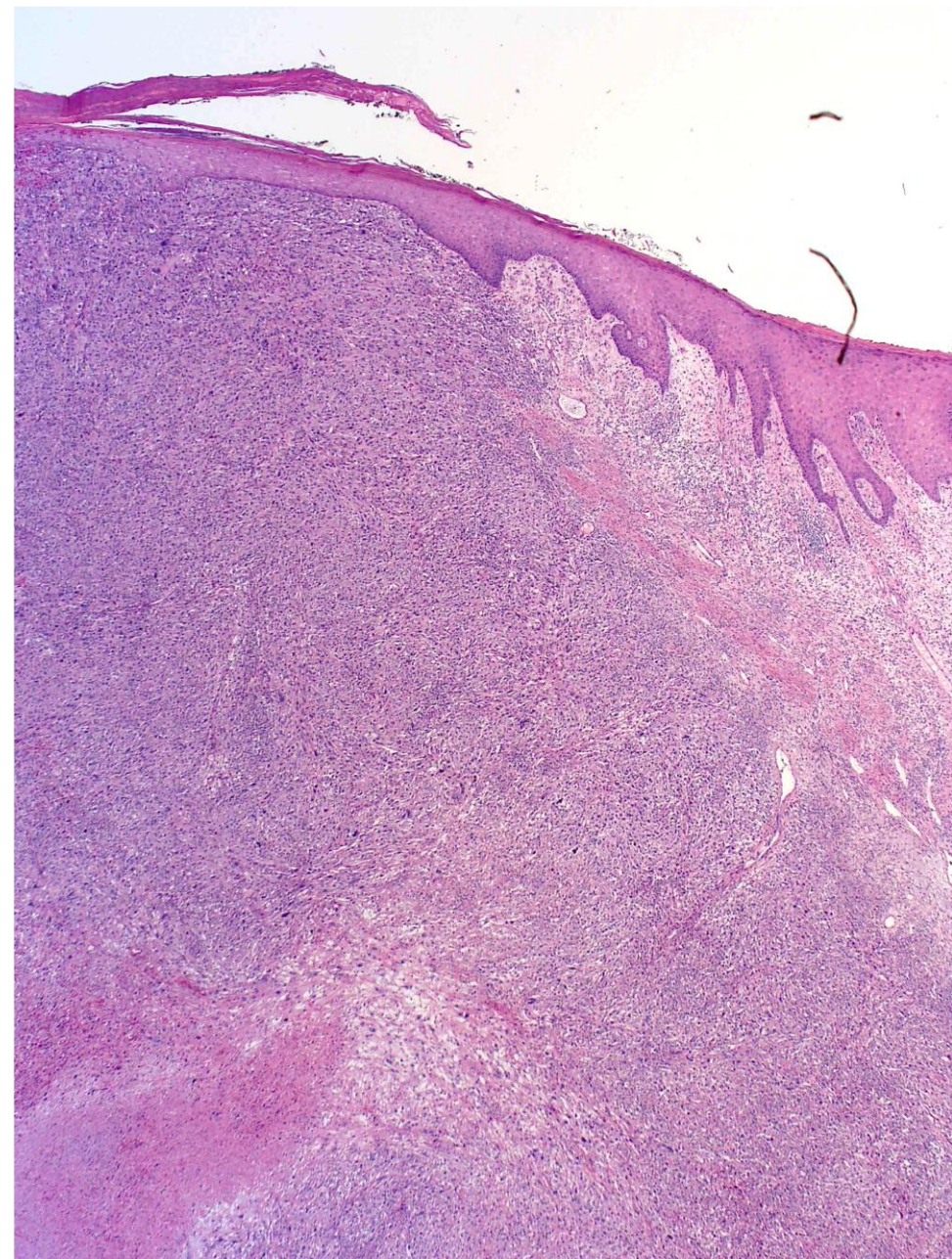
Abbas Agaimy, MD, Katja Specht, MD,† Robert Stoehr, PhD,* Thomas Lorey, MD,‡
Bruno Märkl, MD,§ Gerald Niedobitek, MD,|| Melanie Straub, MD,† Thomas Hager, MD,¶
Anna-Carina Reis, MD,¶ Bastian Schilling, MD,# Regine Schneider-Stock, PhD,*
Arndt Hartmann, MD,* and Thomas Mentzel, MD***

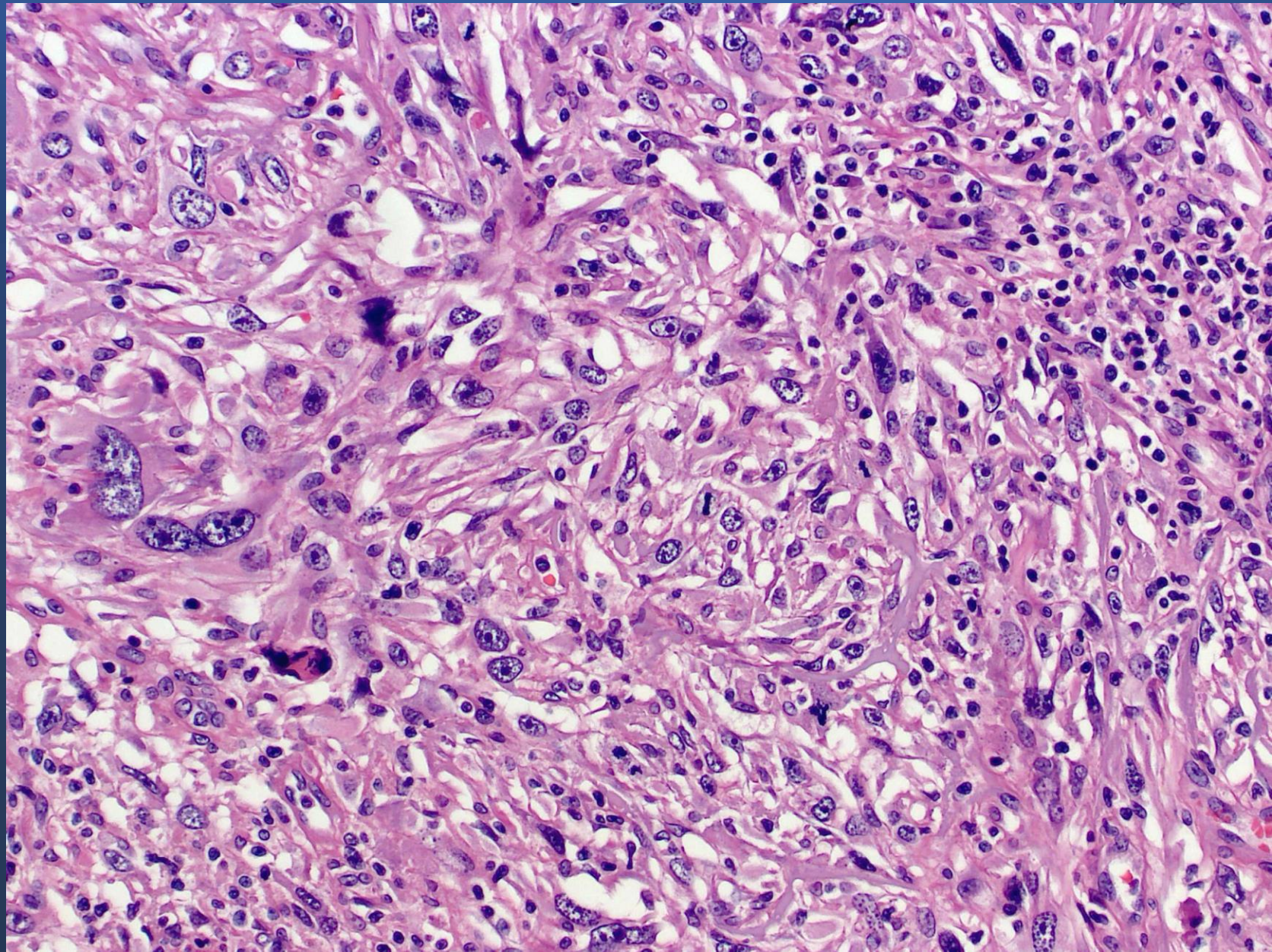
(Am J Surg Pathol 2016;40:181–191)

- Partial or complete loss of melanocytic markers can occur in melanoma

85M. Lesion on Leg

Case courtesy Drs K Francis and C Ly

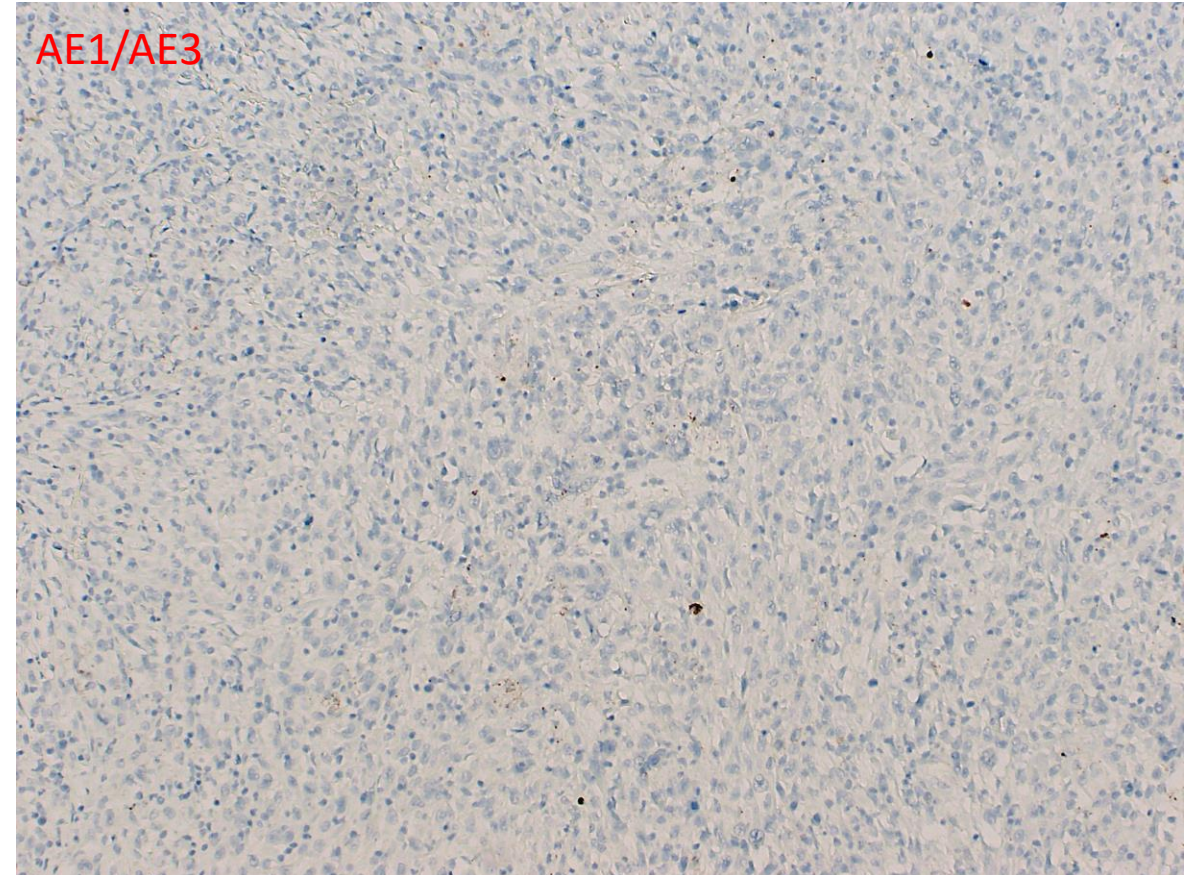
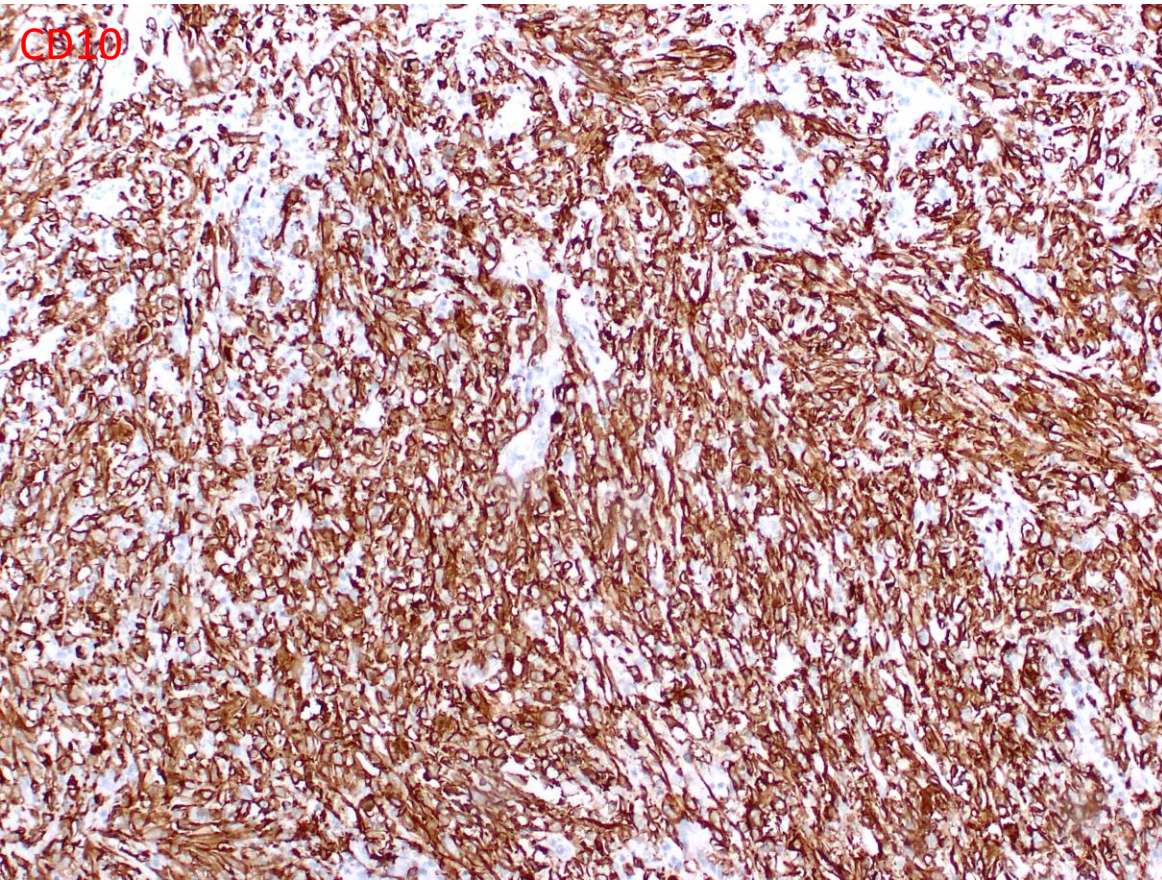




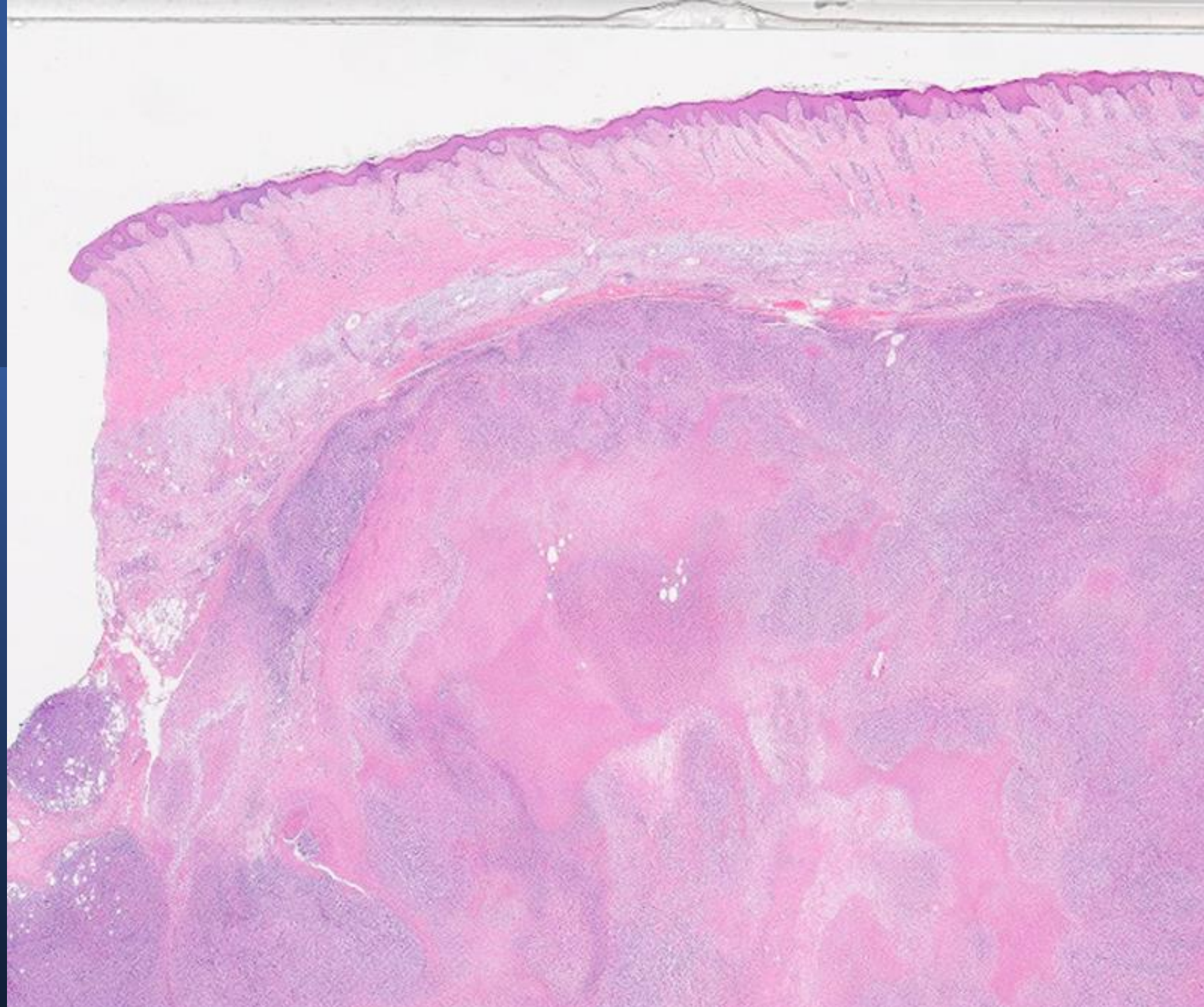
Immunohistochemistry:

Positive: CD10

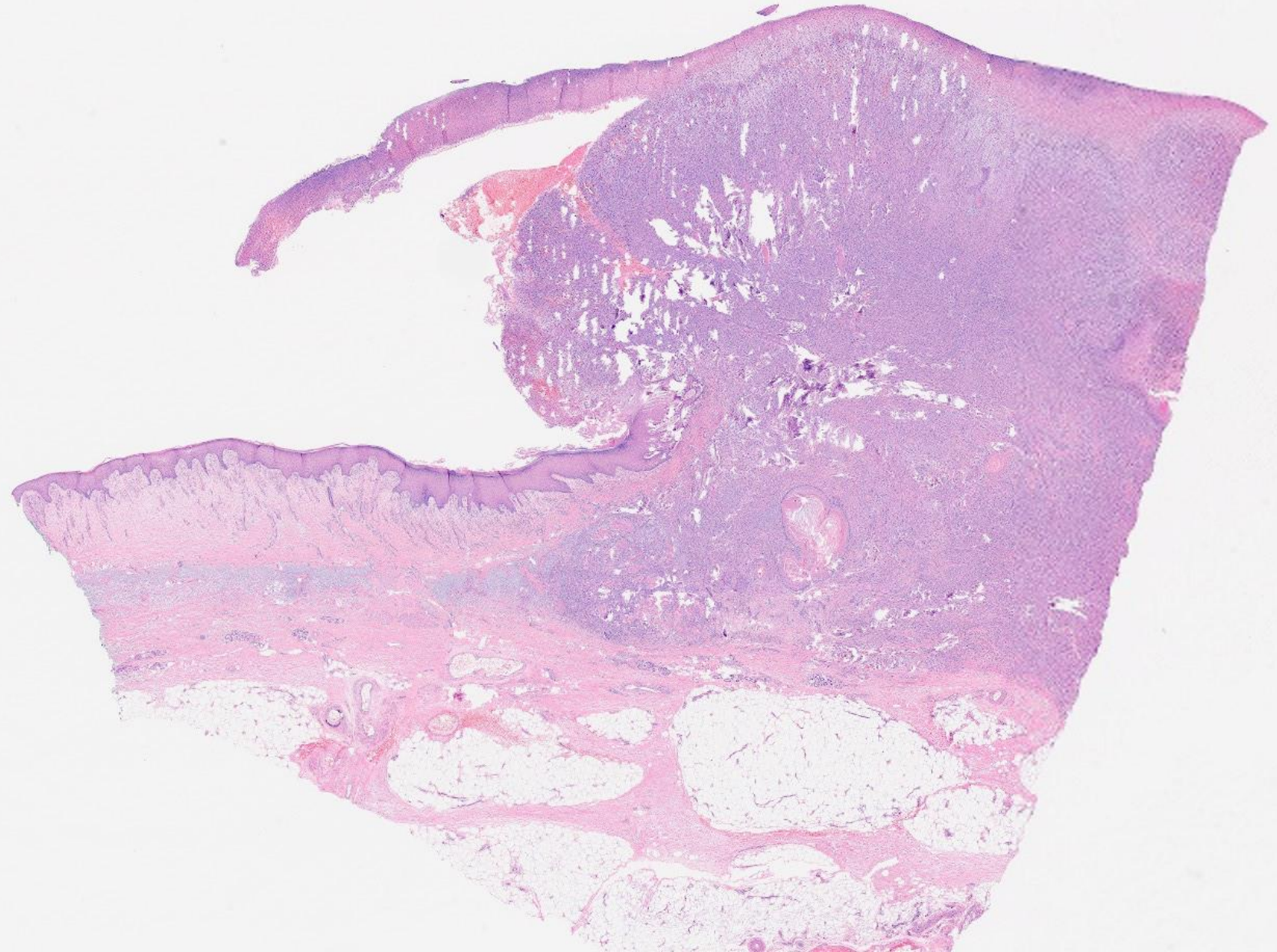
Negative: Everything else that could be contributory; on multiple sections

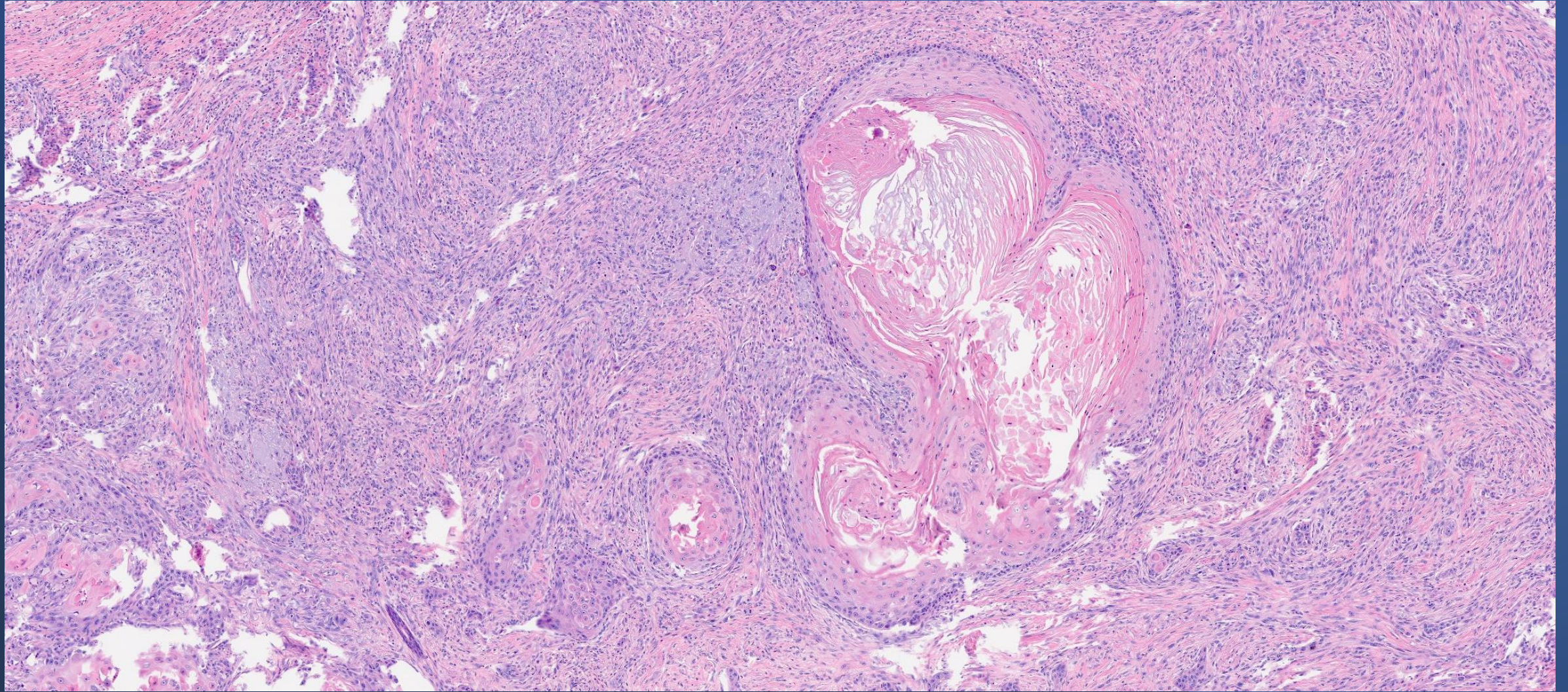


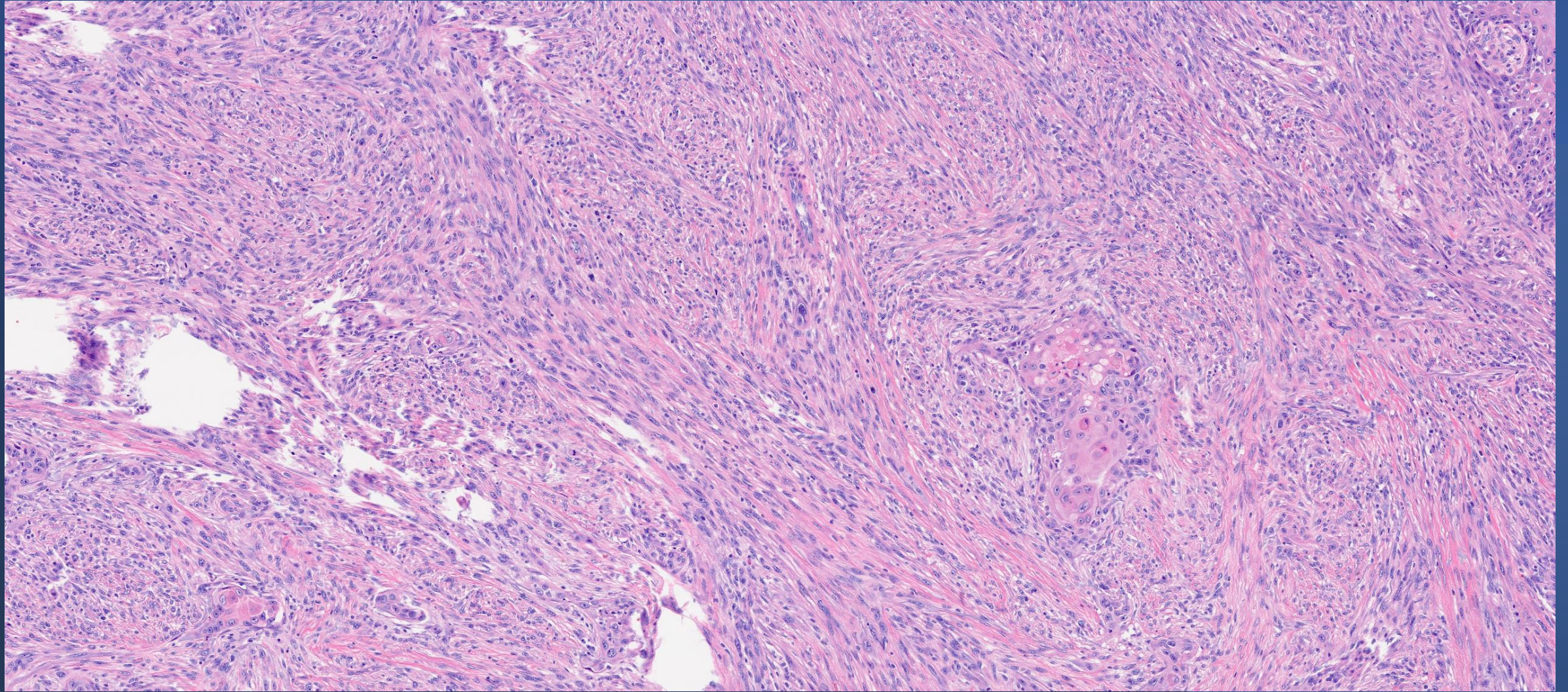
Is this
pleomorphic
dermal
sarcoma?



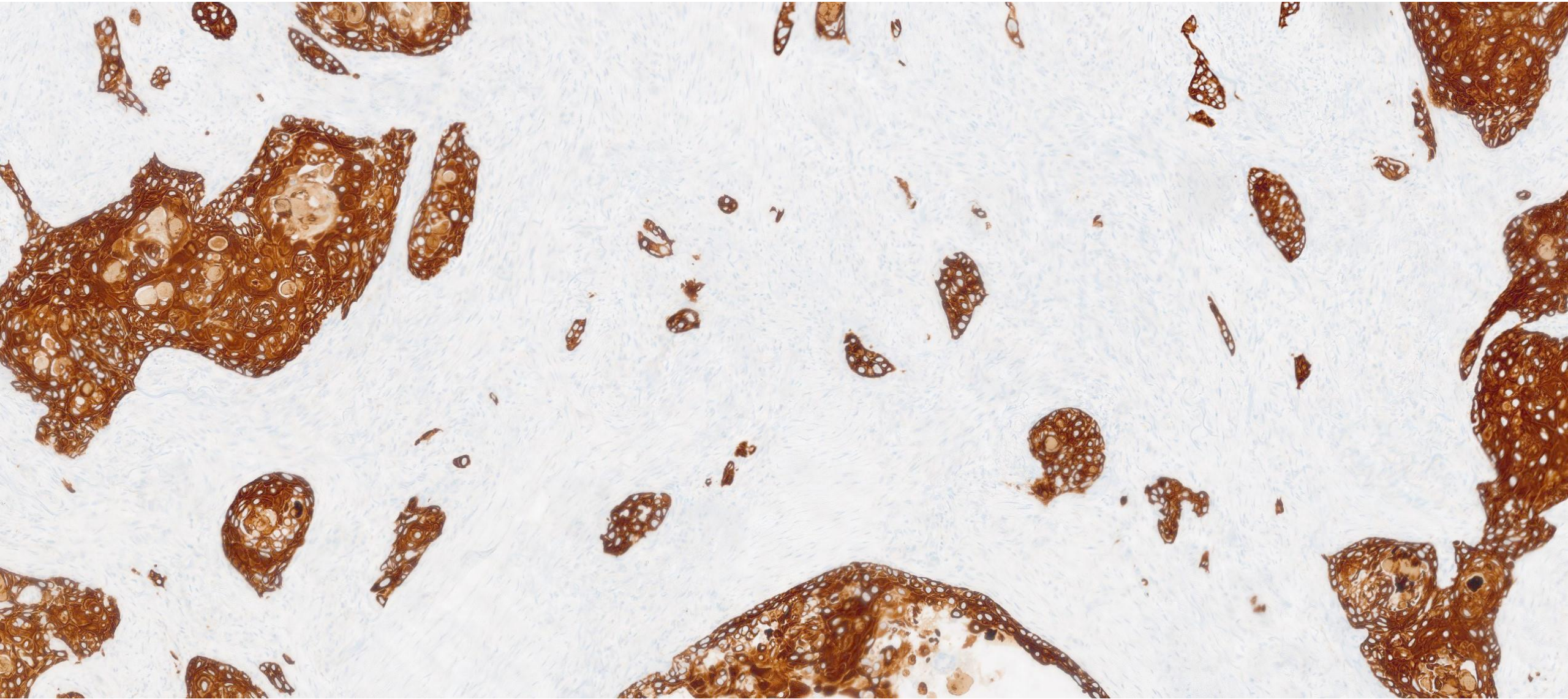
3 years earlier at the same site....







Spindle cell (sarcomatoid) SCC



AE1/AE3

Other immunohistochemical issues:

- CD31 positivity is not rare in AFX (10% +); also occurs in sarcomatoid SCC (unpublished data)
- Isolated p63 positivity is common in AFX-like tumours
 - Probably not sufficient for Dx of SCC
- SMA positivity is very common in AFX- no diagnostic use for distinction with leiomyosarcoma

Sarcoma-like Tumor of Head and Neck Skin

Daisuke Nonaka, MD† and Paul W. Bishop, BA, MB, BCh, FRCPath‡*

Am J Surg Pathol • Volume 38, Number 7, July 2014

Two points of interest:

1 **TABLE 1. Review of the Clinical, Histological, and Immunohistochemical Findings in the Original 183 AFXs Led to Reclassification of 12 Cases**

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Unclassified	3	Clinical, histological, or immunohistochemical features were equivocal, so firm diagnosis was not possible

2 Invasion of subcutis in 26% - “generally only focal and of limited extent”

Pleomorphic Dermal Sarcoma

Adverse Histologic Features Predict Aggressive Behavior and Allow Distinction From Atypical Fibroxanthoma

Keith Miller, FRCPath, John R. Goodlad, MD, FRCPath,†
and Thomas Brenn, MD, PhD, FRCPath†*

(Am J Surg Pathol 2012;36:1317–1326)

Surgical pathology files of the Department of Pathology, NHS Lothian University Hospitals Trust, Edinburgh, UK, were searched for diagnoses coded as “malignant fibrous histiocytoma” and “skin” or “atypical fibroxanthoma.” Inclusion criteria were dermal-based tumors with histologic and immunohistochemical features of AFX but invasion of deep subcutis (ie, at least into the deep reaches of subcutaneous adipose tissue, skeletal muscle, fascia, or galea) and/or tumor necrosis, lymphovascular invasion, or perineural infiltration. Immunohistochemical negativity against cytokeratins, S100, CD34, and desmin was a further requirement. A total of 32 cases fulfilled inclusion criteria.

Pleomorphic Dermal Sarcoma

- 32 cases
- Epidemiology, immunohistochemistry and histological appearances identical to AFX
- Follow up limited (due to age etc.)
 - 28% local recurrence
 - 10% metastasis

Letter to the Editor

Atypical fibroxanthoma

Keywords: atypical fibroxanthoma, Humpty Dumpty, pleomorphic dermal sarcoma

To the Editor,



Having had a life-long interest in atypical fibroxanthoma,¹⁻³ a not uncommon tumor in the sun-ravaged skin of some Australians, I read with interest Dr McCalmont's original editorial on the subject⁴ and his clarification of the terms 'atypical fibroxanthoma' and 'pleomorphic dermal sarcoma', based on correspondence with Dr Christopher Fletcher.⁵

With apologies to my two very learned colleagues, Humpty Dumpty said it all 140 years ago: 'When I use a word it means just what I choose it to mean – neither more nor less'.⁶

David Weedon, AO, MD

Mitchell Van Deurse

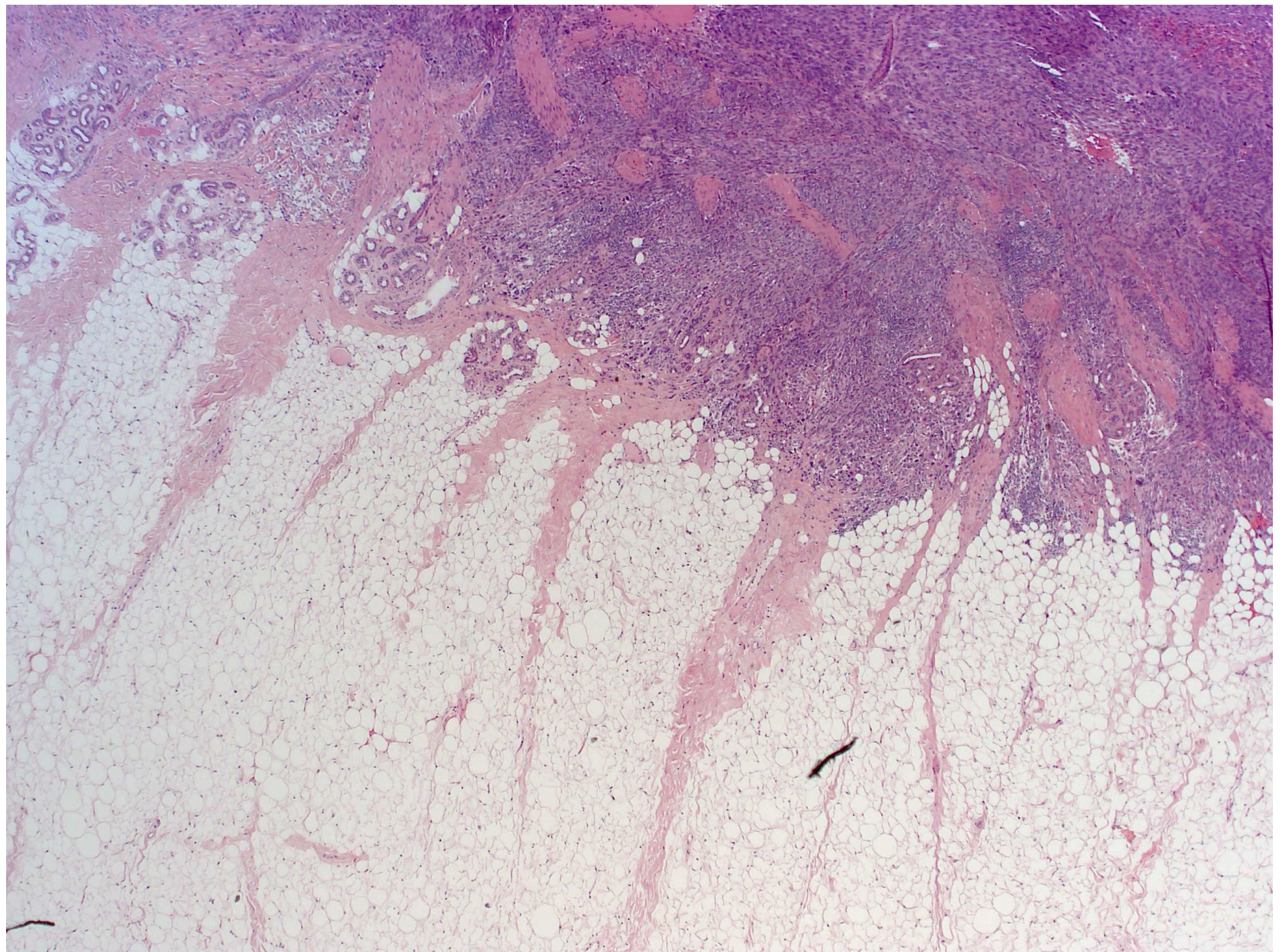
Skin Laboratory, Sullivan Nicolaides Pathology,
Brisbane, Australia

e-mail: d_weedon@snp.com.au

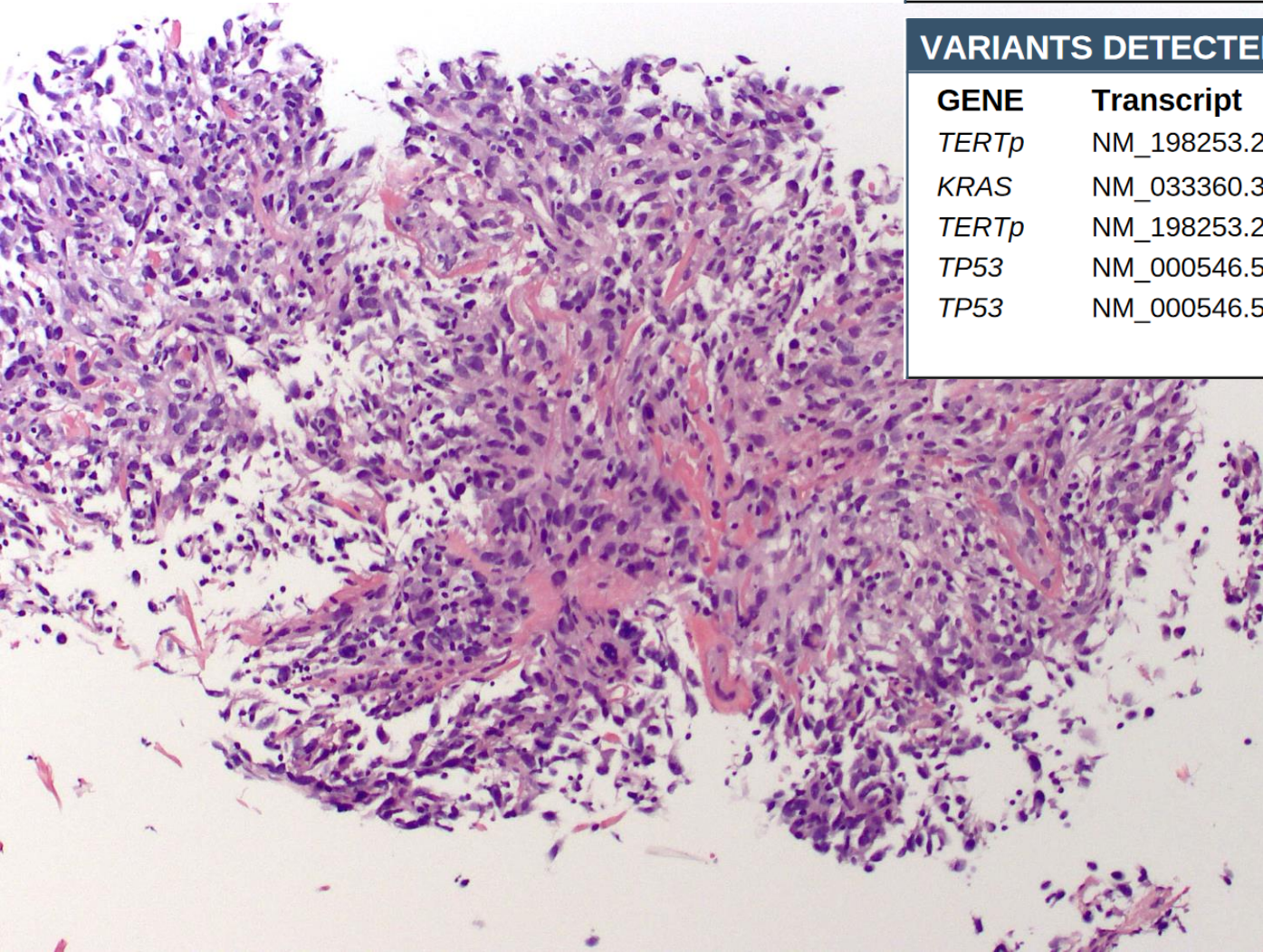
78M. Scalp
2021



Not "deep subcutis"



Lung core, 2023



VARIANTS DETECTED Scalp

GENE	Transcript	HGVSc	HGVSp	Read Depth	VOF(%)
<i>TERTp</i>	NM_198253.2	c.-148C>A		377	19.8
<i>TERTp</i>	NM_198253.2	c.-124C	C228T	372	20.4
<i>KRAS</i>	NM_033360.3	c.106A>T	p.(Ile36Leu)	2404	13.9
<i>TP53</i>	NM_000546.5	c.380_381delinsTT	p.(Ser127Phe)	1962	31.4
<i>TP53</i>	NM_000546.5	c.580C>T	p.(Leu194Phe)	1056	28.5

VARIANTS DETECTED Lung

GENE	Transcript	HGVSc	HGVSp	Read Depth	VOF(%)
<i>TERTp</i>	NM_198253.2	c.-252C		1105	14.8
<i>KRAS</i>	NM_033360.3	c.106A>T	p.(Ile36Leu)	3955	14.7
<i>TERTp</i>	NM_198253.2	c.-124C	C228T	1084	14.7
<i>TP53</i>	NM_000546.5	c.380_381delinsTT	p.(Ser127Phe)	5330	28.5
<i>TP53</i>	NM_000546.5	c.580C>T	p.(Leu194Phe)	4410	26.5

The definition of PDS has become more aggressive....

Essential and desirable diagnostic criteria

Essential:

Pleomorphic dermal based neoplasm

Invasion of subcutis, necrosis, perineurial infiltration or lymphovascular invasion

Exclusion of epithelial, vascular, smooth muscle and melanocytic tumours by immunohistochemistry

AFX

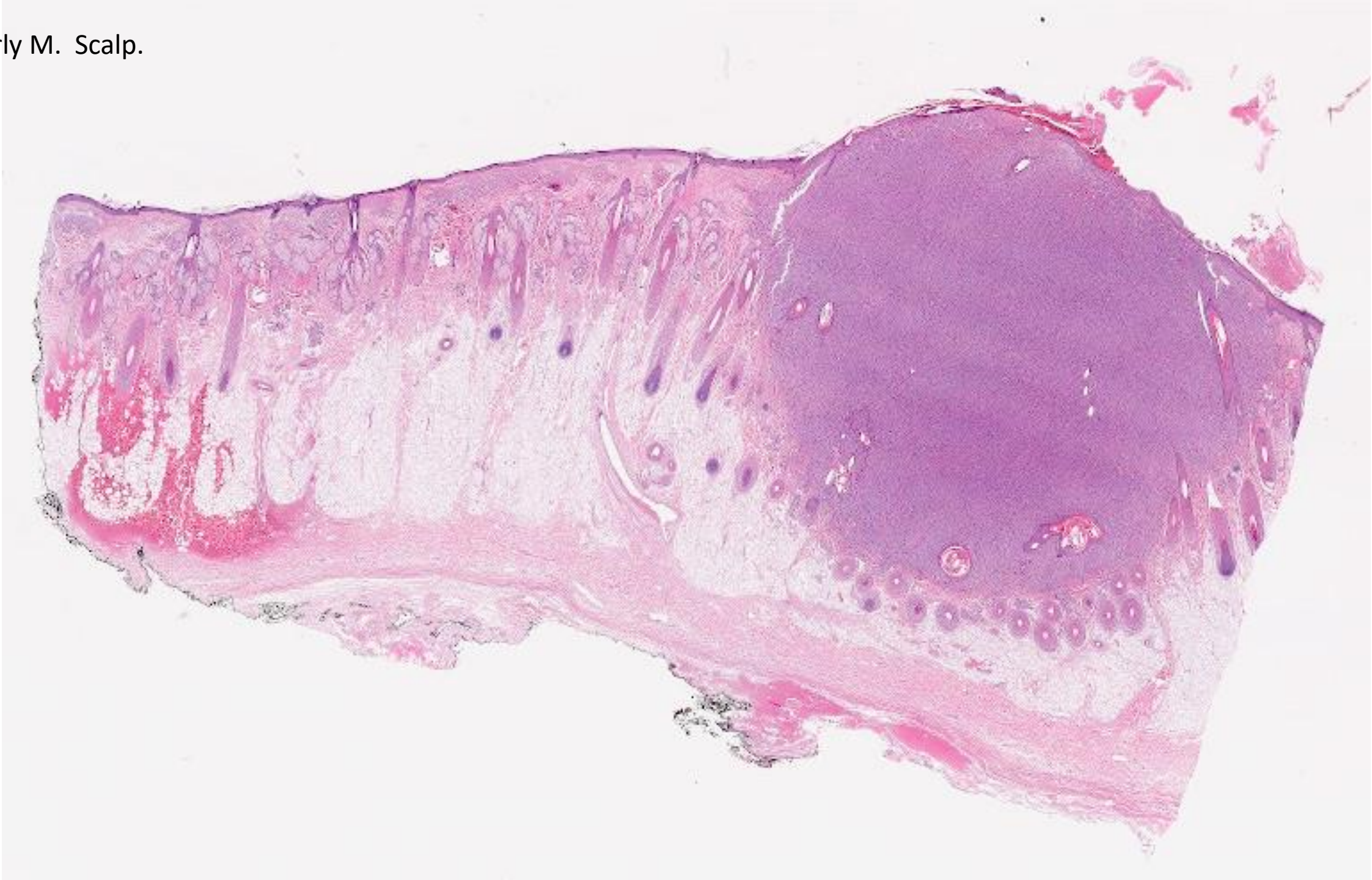
Essential and desirable diagnostic criteria

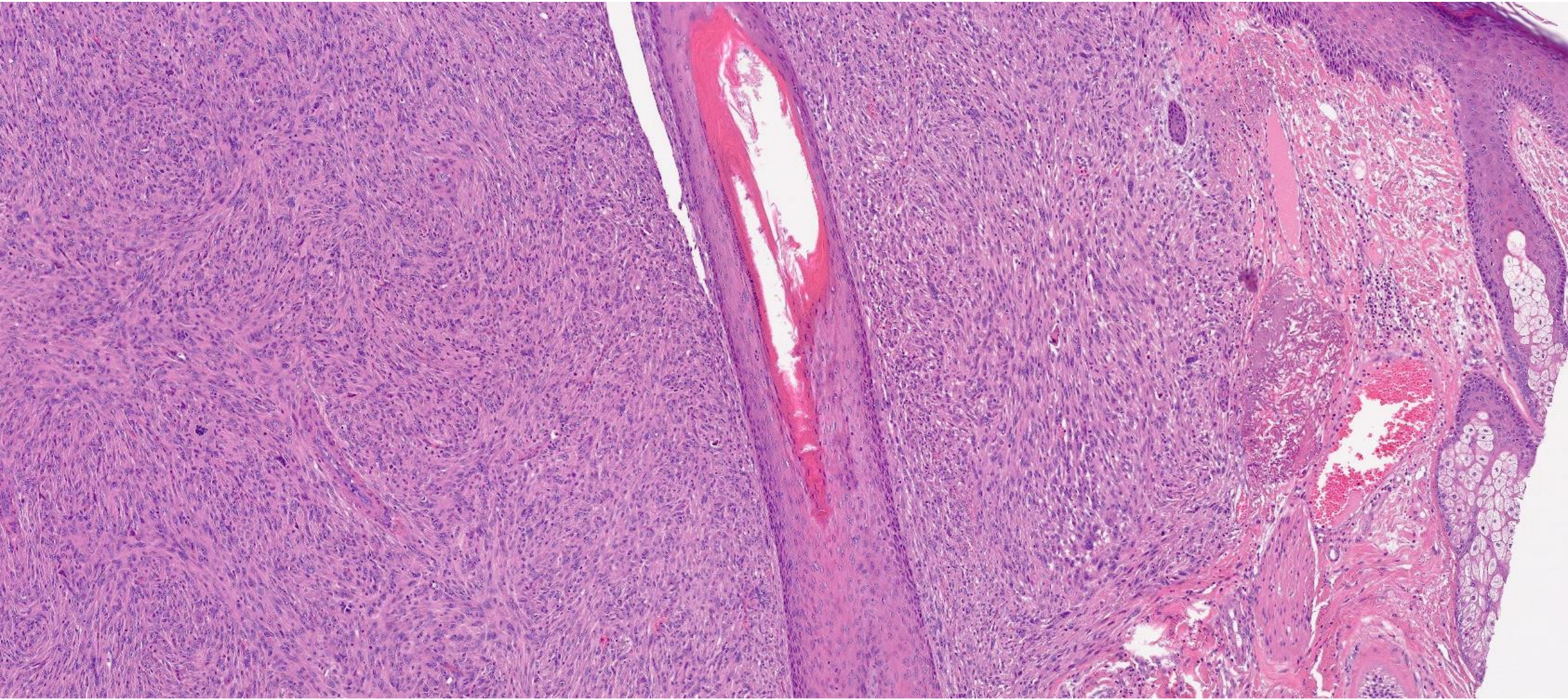
Essential: usually pleomorphic (but variable) morphology; strict confinement to the dermis; immunonegativity for at least two epithelial and melanocytic markers, e.g. keratins, P63, S100, HMB45, Melan-A, and SOX10.

WHO Classification of Tumours [online](#) 

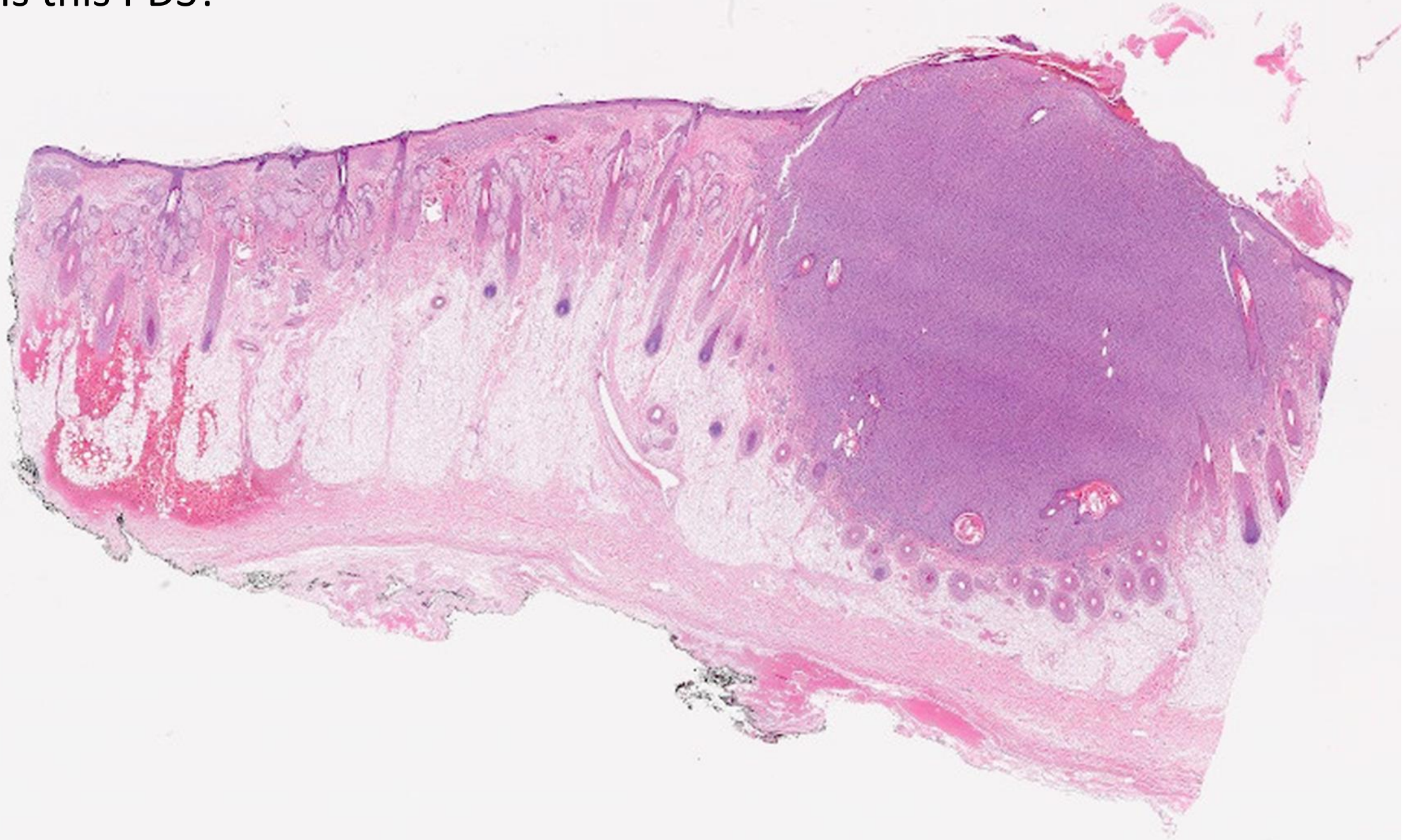
Skin Tumours (5th ed.) // Soft tissue tumours // Tumours of uncertain differentiation // Intermediate neoplasms of uncertain differentiation // Atypical fibroxanthoma 

Elderly M. Scalp.

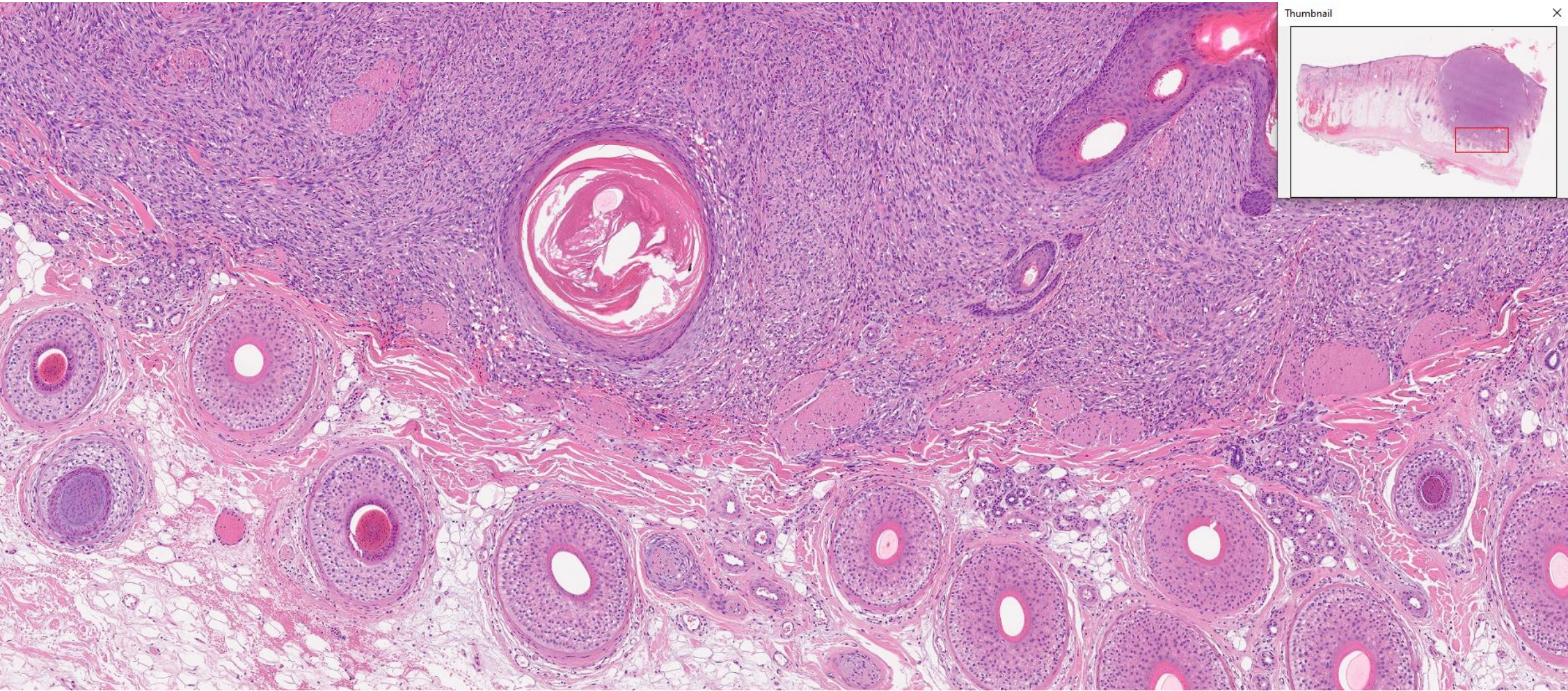




Is this PDS?



Is it still PDS?

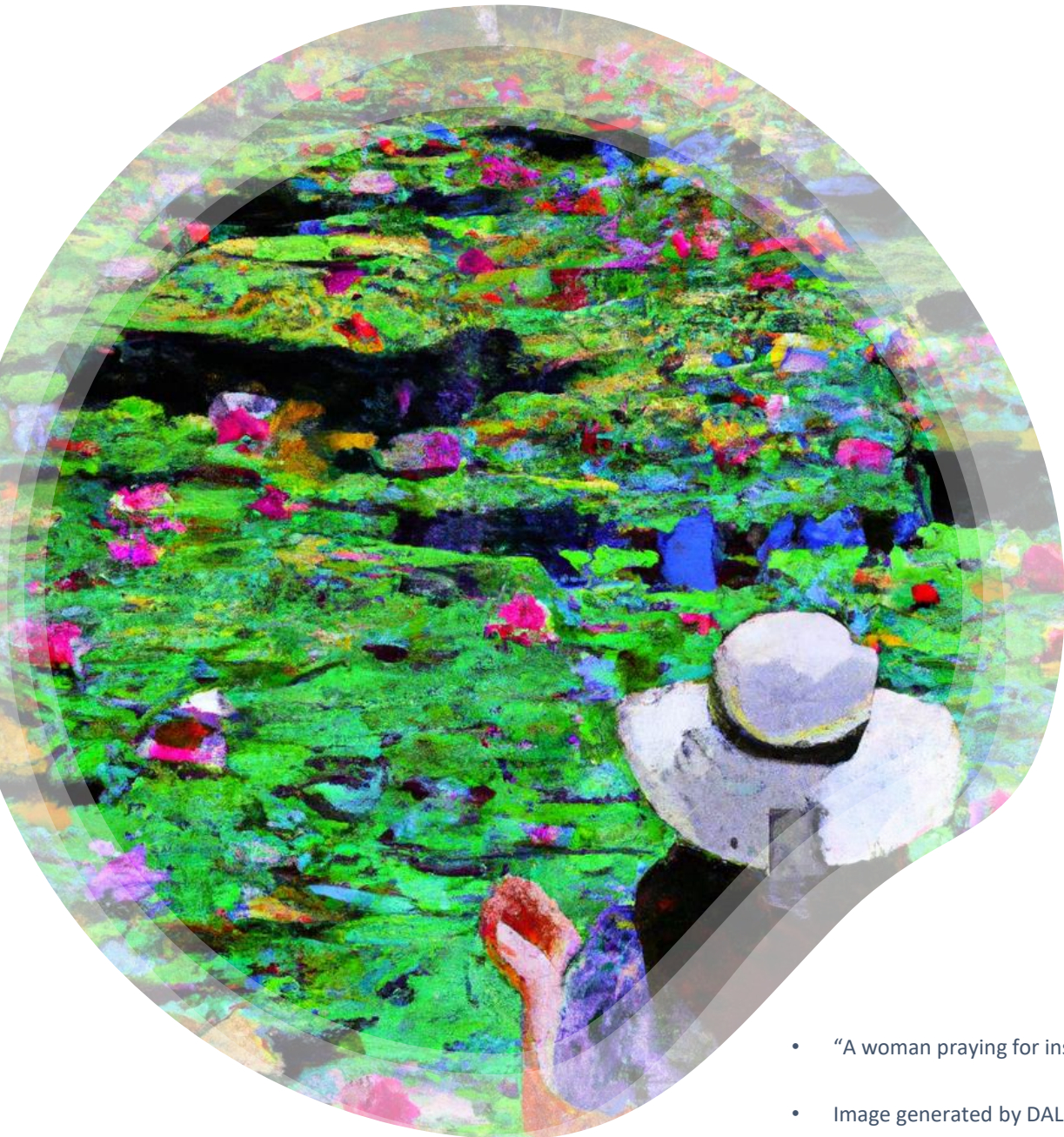


Thumbnail



Getting on track

- Move away from a dichotomous concept of biology:
 - The terms AFX and PDS describe different stages of the same tumour
 - My trial balloon:
 - C-SALT (with staging parameters)
- Do not diagnose AFX/PDS with certainty on partial Bx samples
- Accept that AFX/PDS is always slightly unstable ground
- An aggressive definition of subcutaneous extension is probably appropriate for diagnosing PDS in current practice



Melanoma "overdiagnosis"

- "A woman praying for inspiration by a pond with water lilies in the style of Monet"
- Image generated by DALL.E.2

SOUNDING BOARD

The Rapid Rise in Cutaneous Melanoma Diagnoses

H. Gilbert Welch, M.D., M.P.H., Benjamin L. Mazer, M.D., M.B.A.,
and Adewole S. Adamson, M.D., M.P.P.

N ENGL J MED 384:1 NEJM.ORG JANUARY 7, 2021

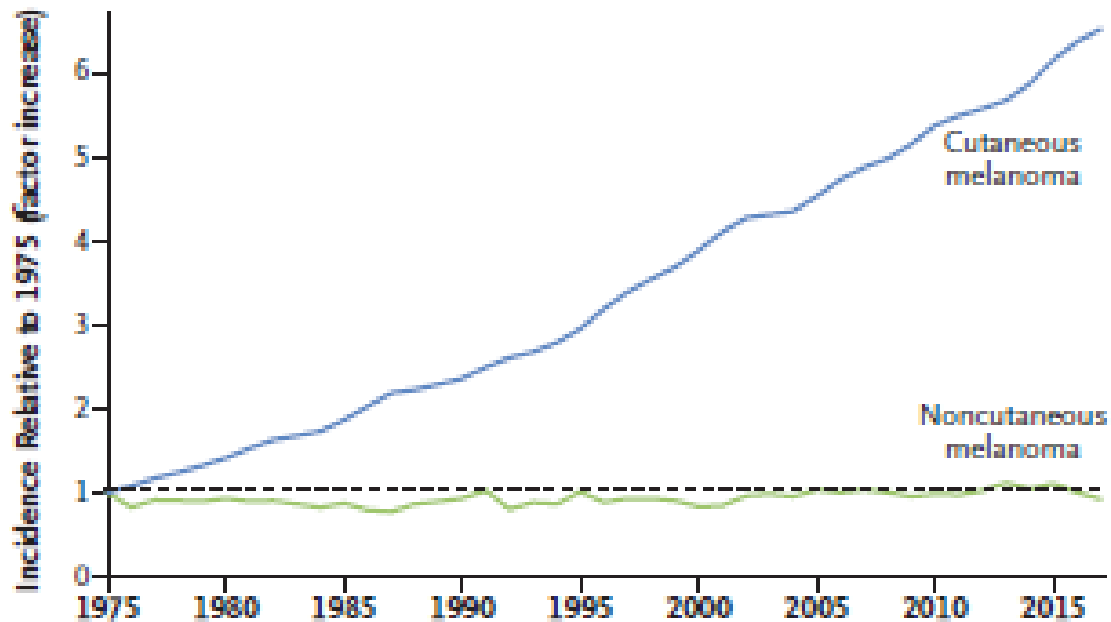


Figure 1. Relative Change in the Incidence of Melanoma in the United States from 1975 through 2017.

J Cutan Pathol 2011; 38: 264–267
doi: 10.1111/j.1509-0560.2010.01600.x
John Wiley & Sons, Printed in Singapore

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Journal of
Cutaneous Pathology

Perspectives in Dermatopathology
The melanoma ‘epidemic’,
a dermatopathologist’s perspective

Earl J. Glusac

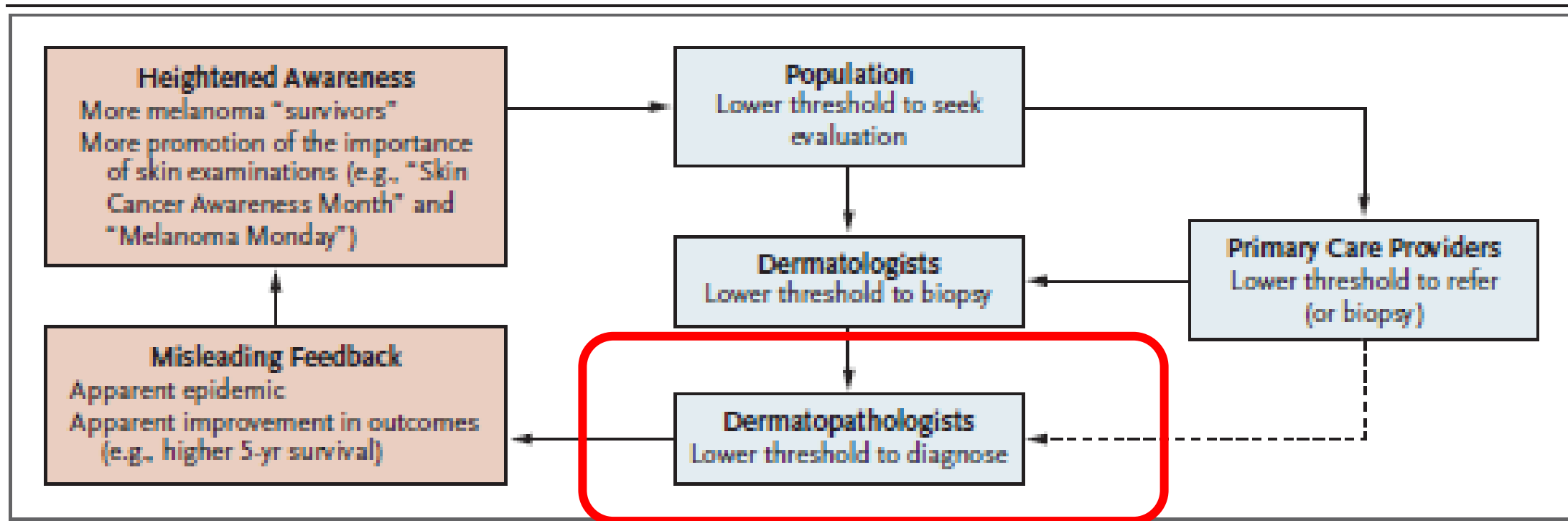


Figure 5. The Cycle of Melanoma Overdiagnosis.

Why might pathology thresholds shift?

1. Shifts in terminology and biological understanding
2. Increasing biopsy of small and ambiguous lesions and increasing use of smaller and partial biopsies.
3. Subjective criteria and difficult grey zones
 - Asymmetric incentive
 - Customer-service relationship



Shifts in terminology

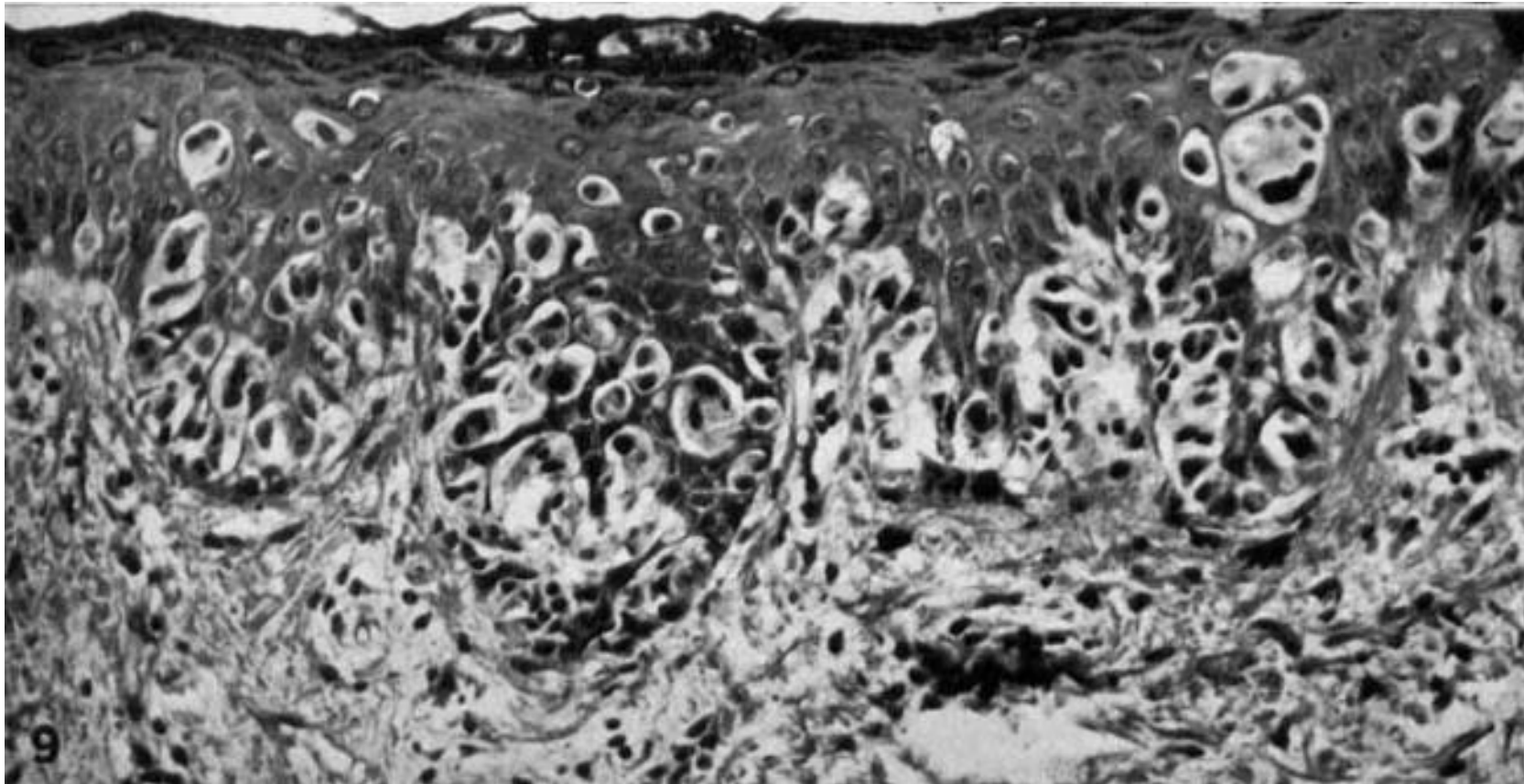


FIG. 9. Activated junctional nevus

MALIGNANT MELANOMA
*A Clinicopathological Analysis of the Criteria for
Diagnosis and Prognosis*
ARTHUR C. ALLEN, M.D., AND SOPHIE SPITZ, M.D.
CANCER January 1953



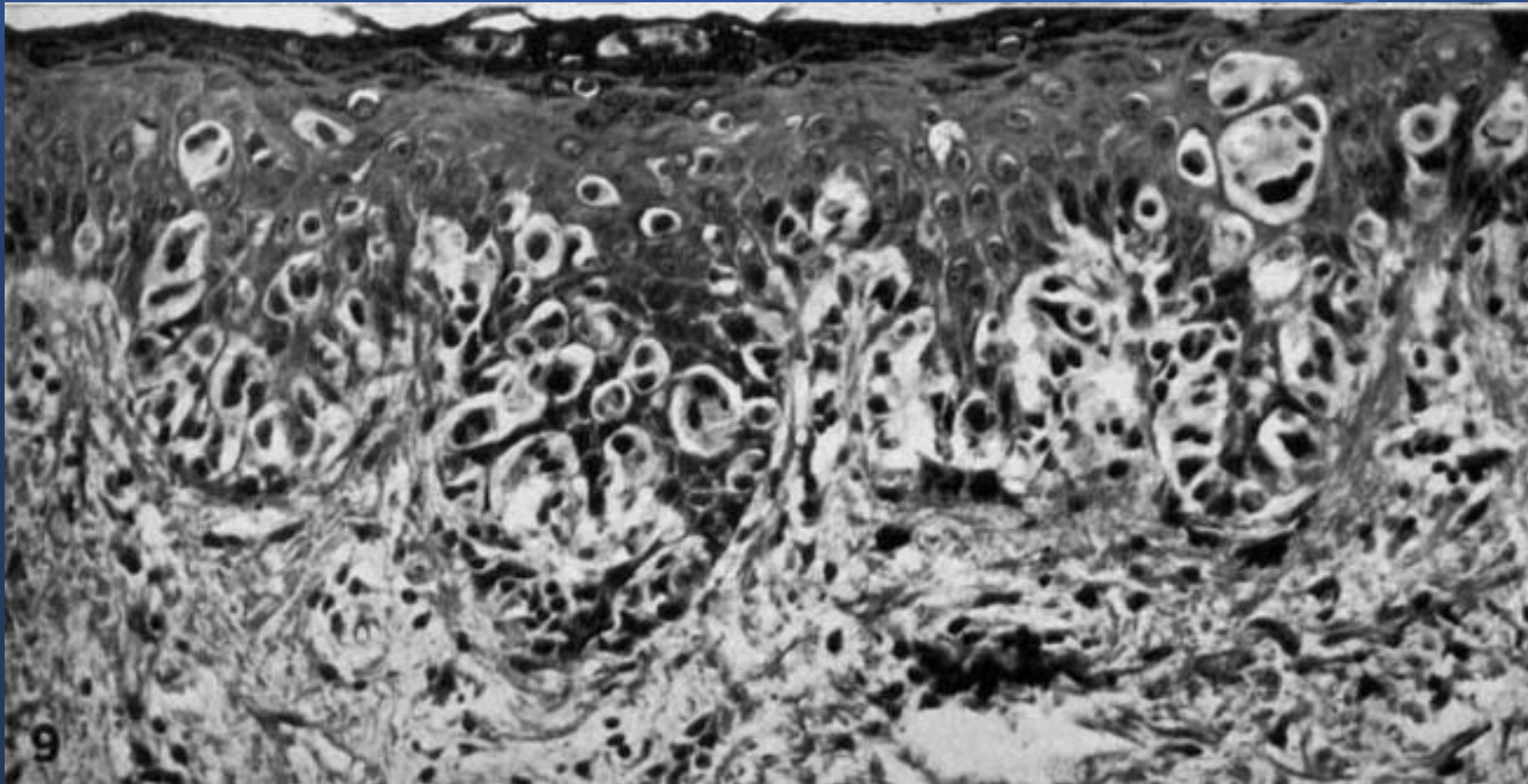
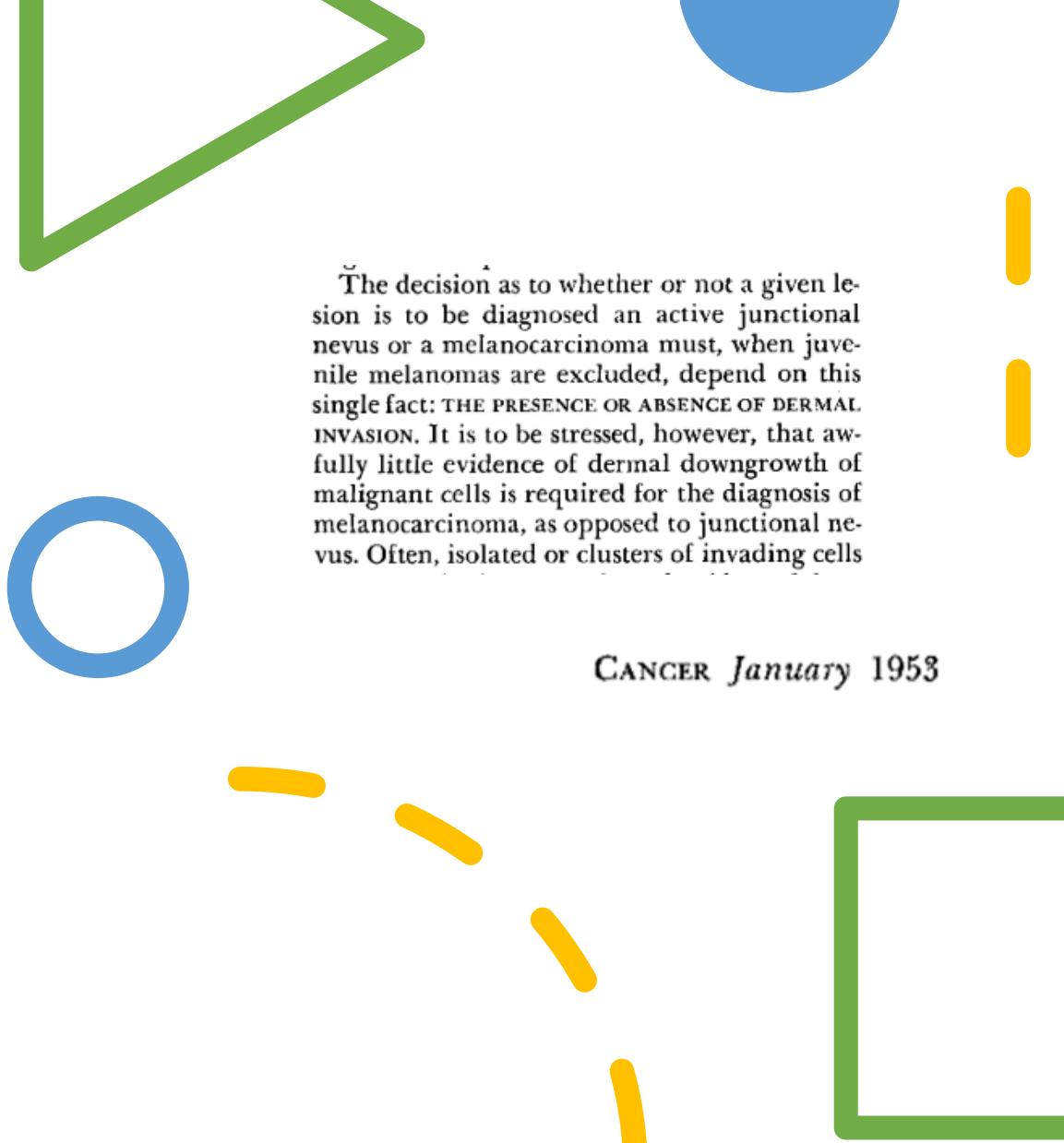


FIG. 9. Activated junctional nevus in the stage immediately preceding the development of infiltrating melanocarcinoma.

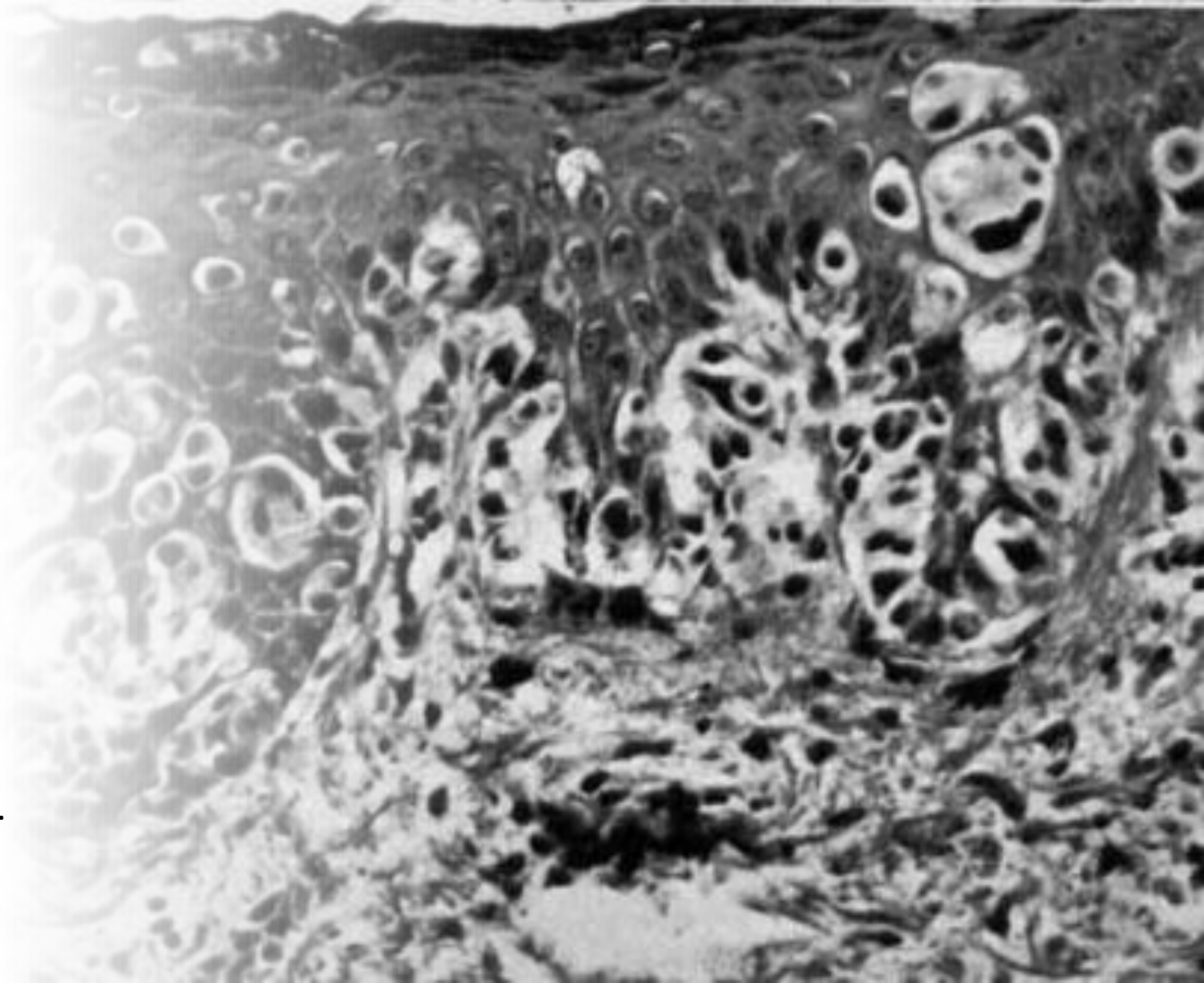
- Arthur Allen's conceptualization:
 - All common types of melanoma arise from "activated junctional naevus"
 - There are a set of morphologic criteria which define "activated junctional naevus" and separate it from common naevus
 - "activated junctional naevus" must be completely excised; if left in the patient it will almost invariably progress to "infiltrating melanocarcinoma"
 - Infiltrating melanocarcinoma can metastasize and kill; "activated junctional naevus" does not



The decision as to whether or not a given lesion is to be diagnosed an active junctional nevus or a melanocarcinoma must, when juvenile melanomas are excluded, depend on this single fact: THE PRESENCE OR ABSENCE OF DERMAL INVASION. It is to be stressed, however, that awfully little evidence of dermal downgrowth of malignant cells is required for the diagnosis of melanocarcinoma, as opposed to junctional nevus. Often, isolated or clusters of invading cells

CANCER *January* 1953

- We agree with Arthur Allen about the morphology of this lesion
- We agree with Arthur Allen about the clinical behaviour of this lesion
- We agree with Arthur Allen about the clinical management of this lesion
- We just have a different name...



What is the definition of “melanoma”?

- “A malignant tumour of melanocytes”

- Malignant:

3 *Pathology.*

a tending to produce death, as bubonic plague.

b (of a tumor) characterized by uncontrolled growth; cancerous, invasive, or metastatic.



OVERVIEW

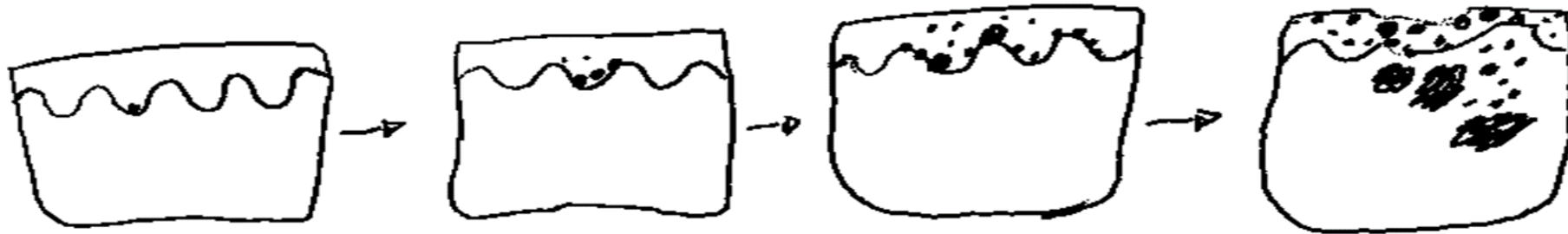
What is a malignant neoplasm?

A malignant neoplasm (NEE-oh-plaz-um) is another term for a cancerous [tumor](#). The term “neoplasm” refers to an abnormal growth of tissue. The term “malignant” means the tumor is cancerous and is likely to spread (metastasize) beyond its point of origin.

Cleveland clinic

- 1 : tending to produce death or [deterioration](#)
 - | *malignant* malaria
 - especially* : tending to infiltrate, [metastasize](#), and terminate fatally
 - | a *malignant* tumor

Merriam-Webster
Dictionary



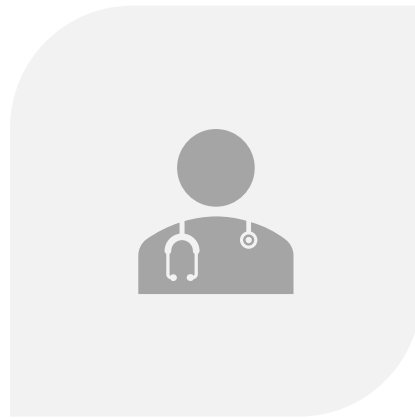
Uncontrolled growth

Invasion,
Metastasis,
Death

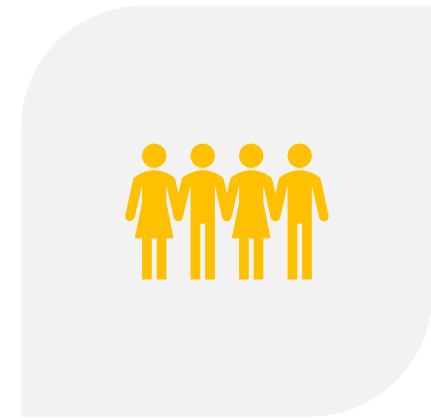
What is the definition of “melanoma”?



WE NOW FOCUS ON THE
“UNCONTROLLED GROWTH” ASPECT

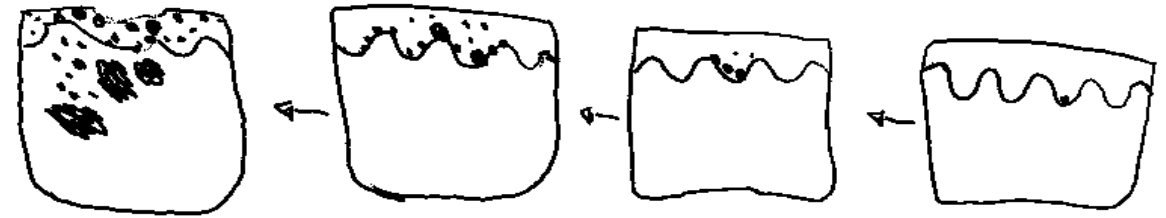
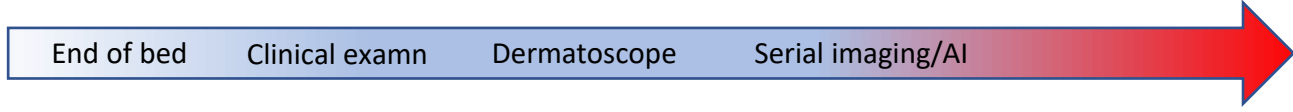


PATHOLOGISTS OF THE MID-20TH
CENTURY FOCUSED ON THE INVASIVE,
METASTATIC AND MORTALITY ASPECTS



THE GENERAL COMMUNITY HAS NOT
COME WITH US ON THIS JOURNEY

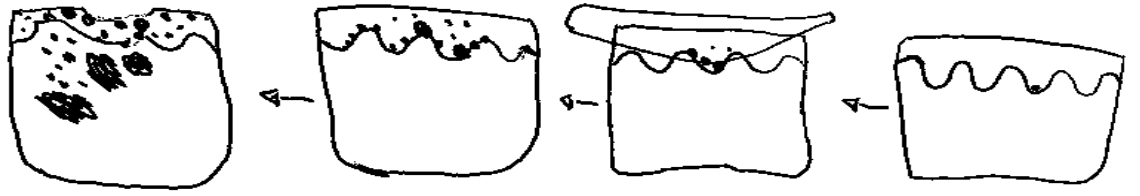
Clinical recognition



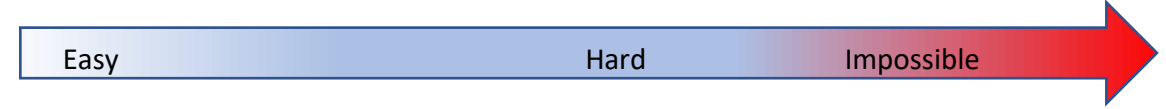
Commonly used biopsy Approach

Excision

Shave/Punch



Pathological diagnosis



Concordance and Reproducibility

- "Diagnoses spanning moderately dysplastic naevi to early stage invasive melanoma were neither reproducible nor accurate...."

Table 5 | Accuracy of 187 participating pathologists' when phase 1 interpretations are compared with the consensus reference diagnoses*

Consensus reference diagnosis†	Study pathologists' interpretation					Total interpretations (No)	% Concordance with reference diagnosis (95% CI)
	Class I	Class II	Class III	Class IV	Class V		
Class I	862	50	19	3	1	935	92 (90 to 94)
Class II	843	331	131	26	11	1342	25 (22 to 28)
Class III	695	520	908	113	11	2247	40 (37 to 44)
Class IV	150	176	717	928	198	2169	43 (39 to 46)
Class V	68	87	161	321	1646	2283	72 (69 to 75)
Total	2618	1164	1936	1391	1867	8976	

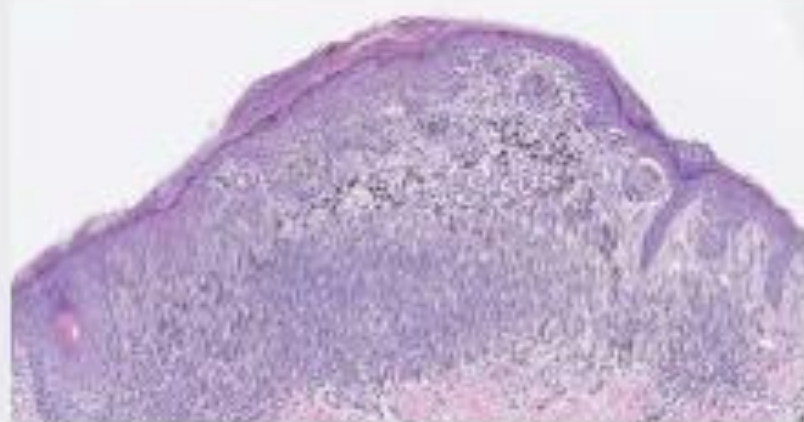
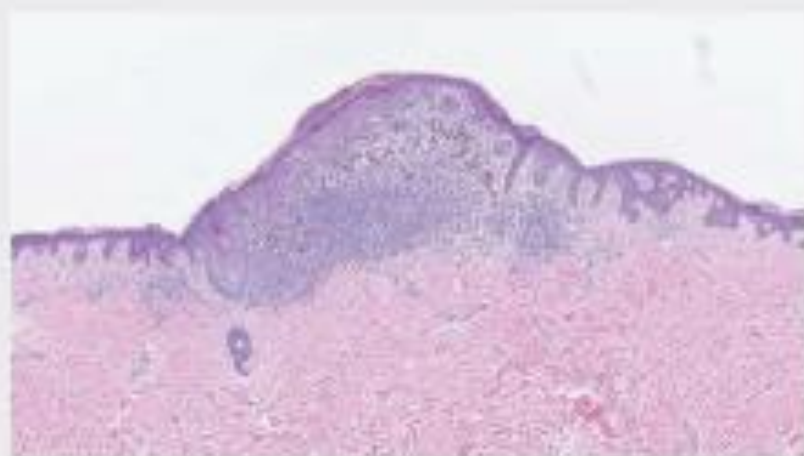
*Concordance in interpretation is emboldened.

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

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

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

thebmj | BMJ 2017;357:j2813 | doi: 10.1136/bmj.j2813



Diagnostic terms given

No of pathologists

MPATH-Dx class I

- Common nevus, junctional 3
- Dysplastic nevus - mild 2
- Halo nevus (1) 1
- Atypical melanocytic neoplasm, junctional (suggested treatment of no further treatment required) 1

MPATH-Dx class II

- Spitz nevus (conventional), (junctional, compound, or intradermal) 4
- Dysplastic nevus - moderate 2
- Pigmented spindle cell nevus (junctional or compound) 1
- Atypical nevus not otherwise specified, including atypical nevus of special anatomic - moderate 1
- Atypical intraepithelial melanocytic proliferation (AIMP) (suggested treatment of repeat excision < 5 mm margins (narrow but complete)) 1
- Atypical melanocytic neoplasm, junctional (suggested treatment of repeat excision < 5 mm margins (narrow but complete)) 1

MPATH-Dx class III

- Atypical/dysplastic Spitz lesion, (junctional, compound, or dermal) 5
- Melanoma in situ, common/pagetoid/superficial spreading 5
- Dysplastic nevus - severe 1
- Atypical nevus not otherwise specified, including atypical nevus of special anatomic site - severe 1
- Melanoma in situ, not otherwise specified 1
- Atypical melanocytic neoplasm, junctional (suggested treatment of repeat excision with at least 5mm (but < 1 cm) margins) 1

MPATH-Dx class IV

- Invasive melanoma, superficial spreading melanoma 4

MPATH-Dx class V

- Invasive melanoma, heavily pigmented melanoma 1

Total 36

Standing on unstable ground:

- Danger of being pushed
- Looking for something to hold on to



Image by DALLE2- photorealistic image of a woman standing on unstable ground by a cliff

We need something to help!

- FISH
- aCGH
- NGS

- IHC

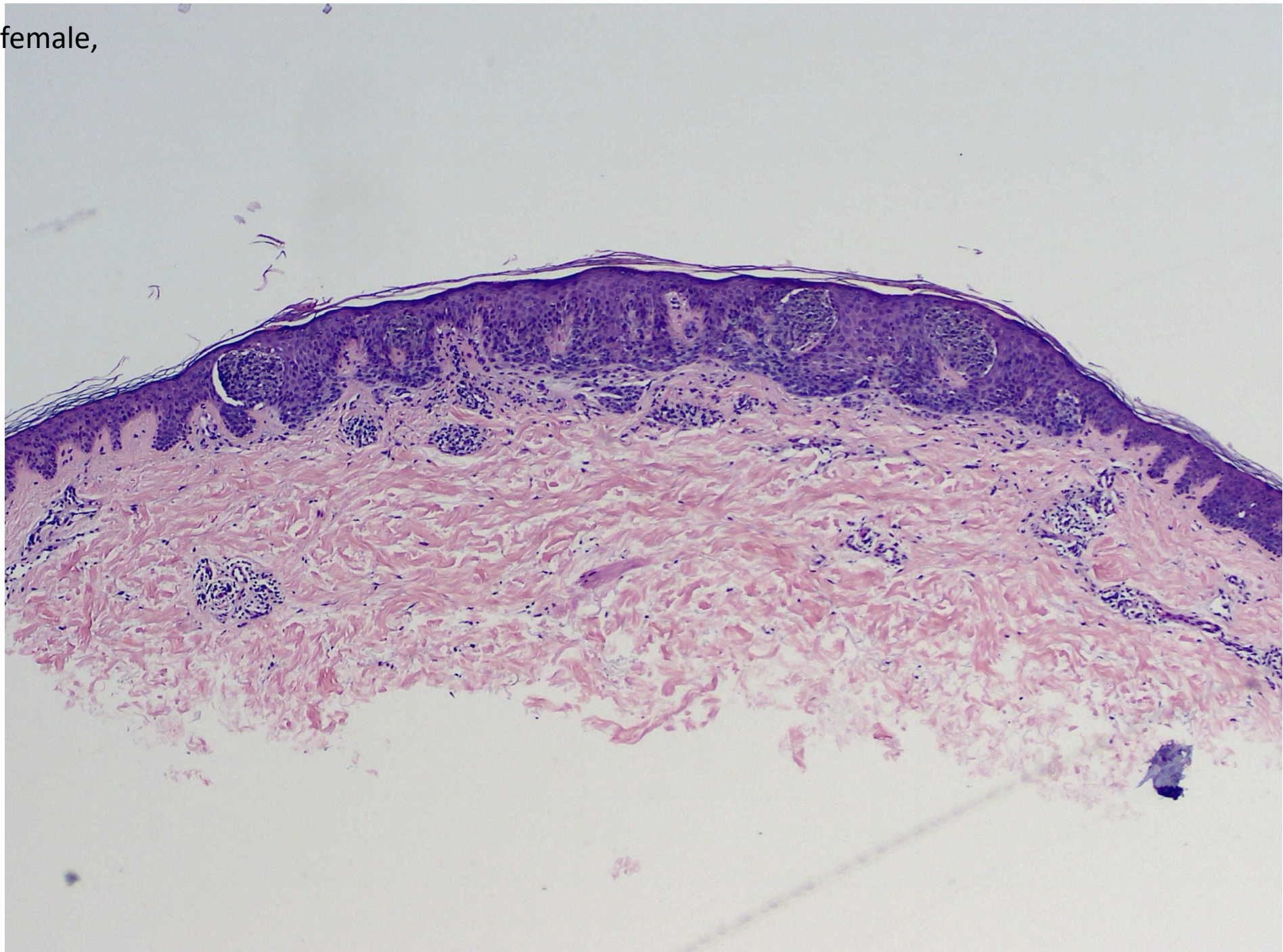
PRAME Expression in Melanocytic Tumors

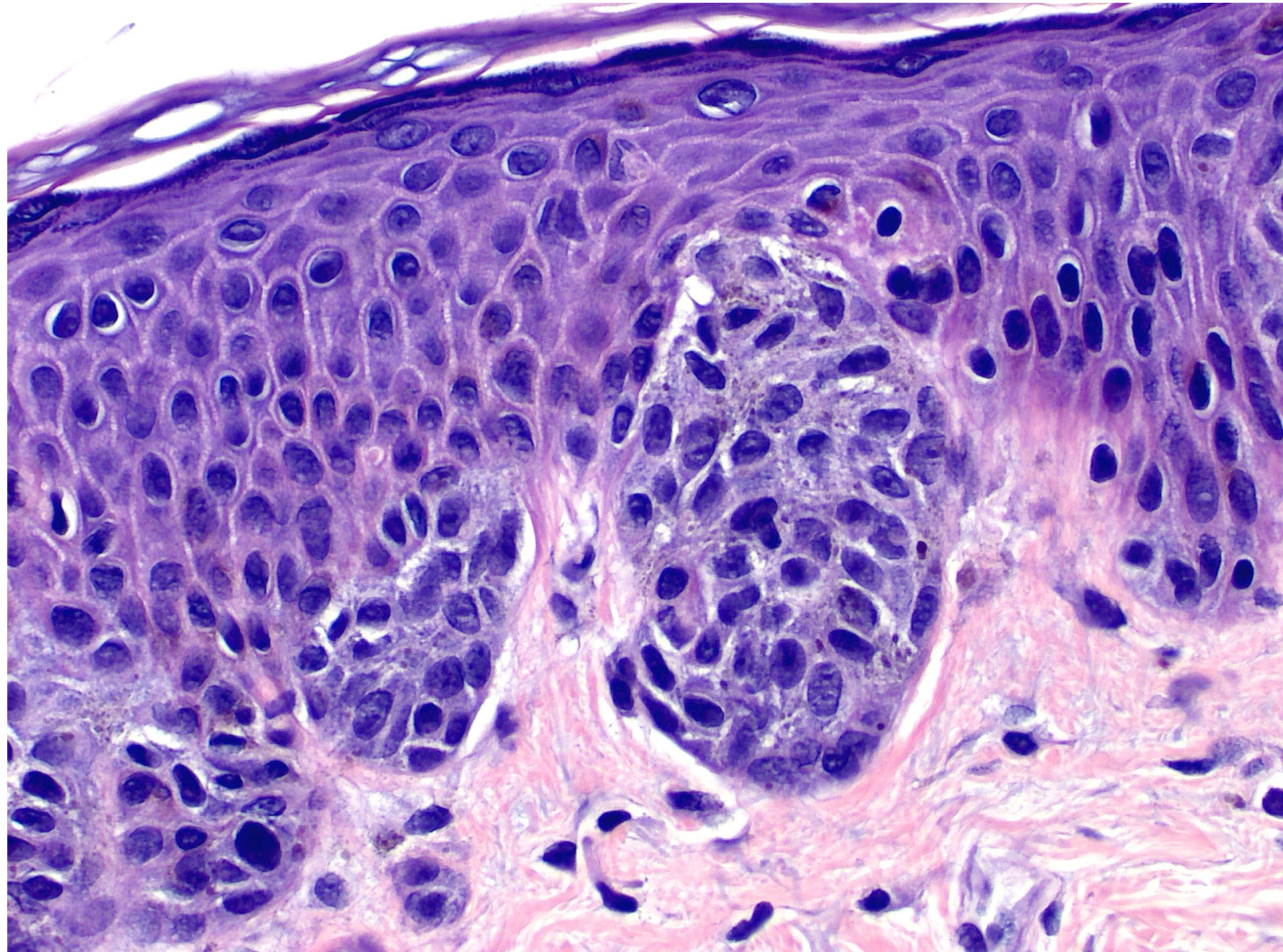
Cecilia Lezcano, MD^{*}, Achim A. Jungbluth, MD^{*}, Kishwer S. Nehal, MD[†], Travis J. Hollmann, MD, PhD^{*}, and Klaus J. Busam, MD^{*}

PRAME

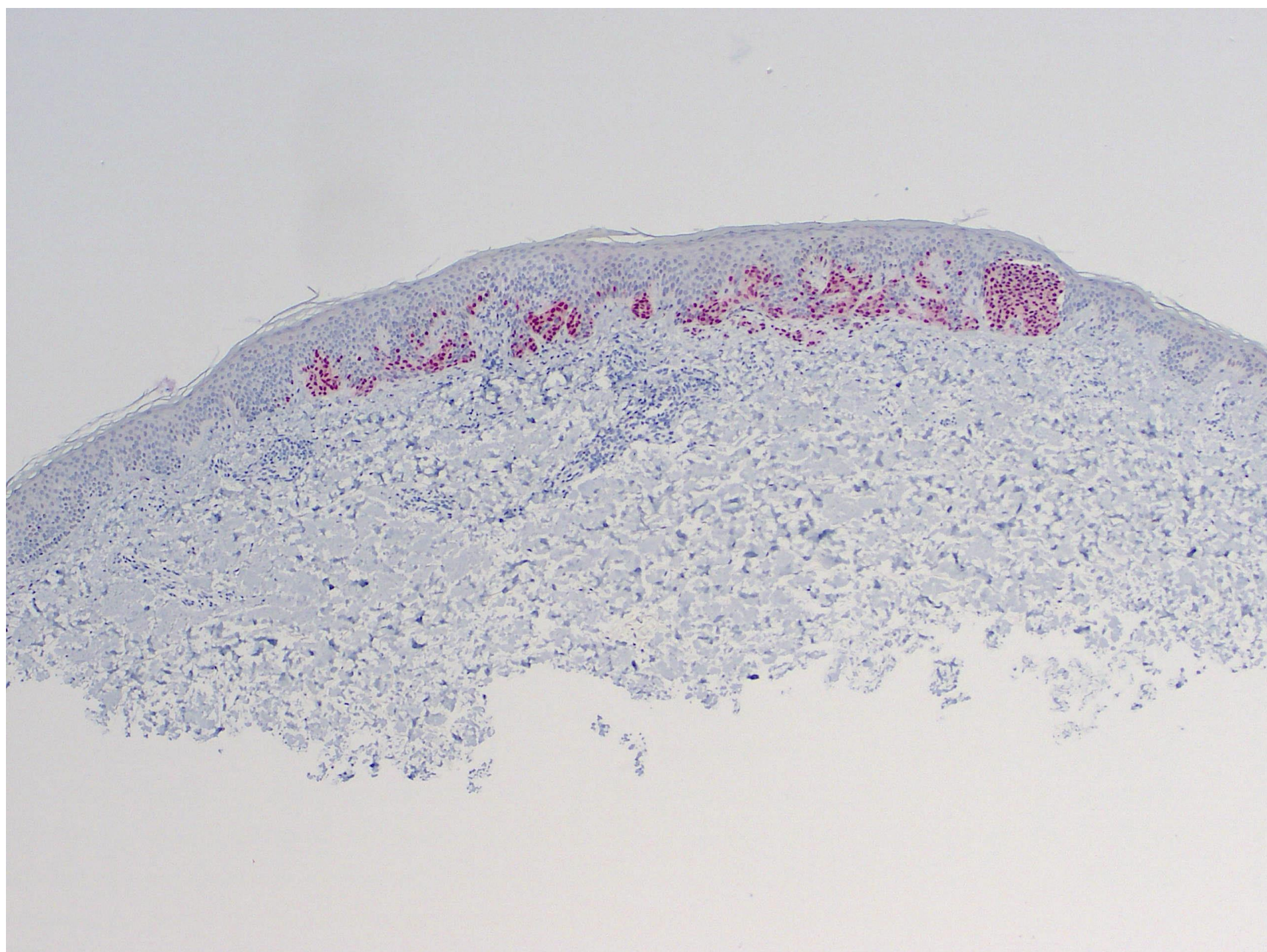
- Multiple studies
 - Tested in multiple scenarios-
 - unequivocal naevi, unequivocal melanoma, Spitz lesions, melanoma arising in naevus, dysplastic naevus vs melanoma, nodal naevus vs metastasis.....
 - Highly specific for melanoma- approx. 95% (some studies 99%, 100%)
 - May be lower in Spitz lesions
 - Sensitivity lower- approx. 75%
 - Probably not great in desmoplastic melanoma
- Problem solved right??

Young adult female,
back

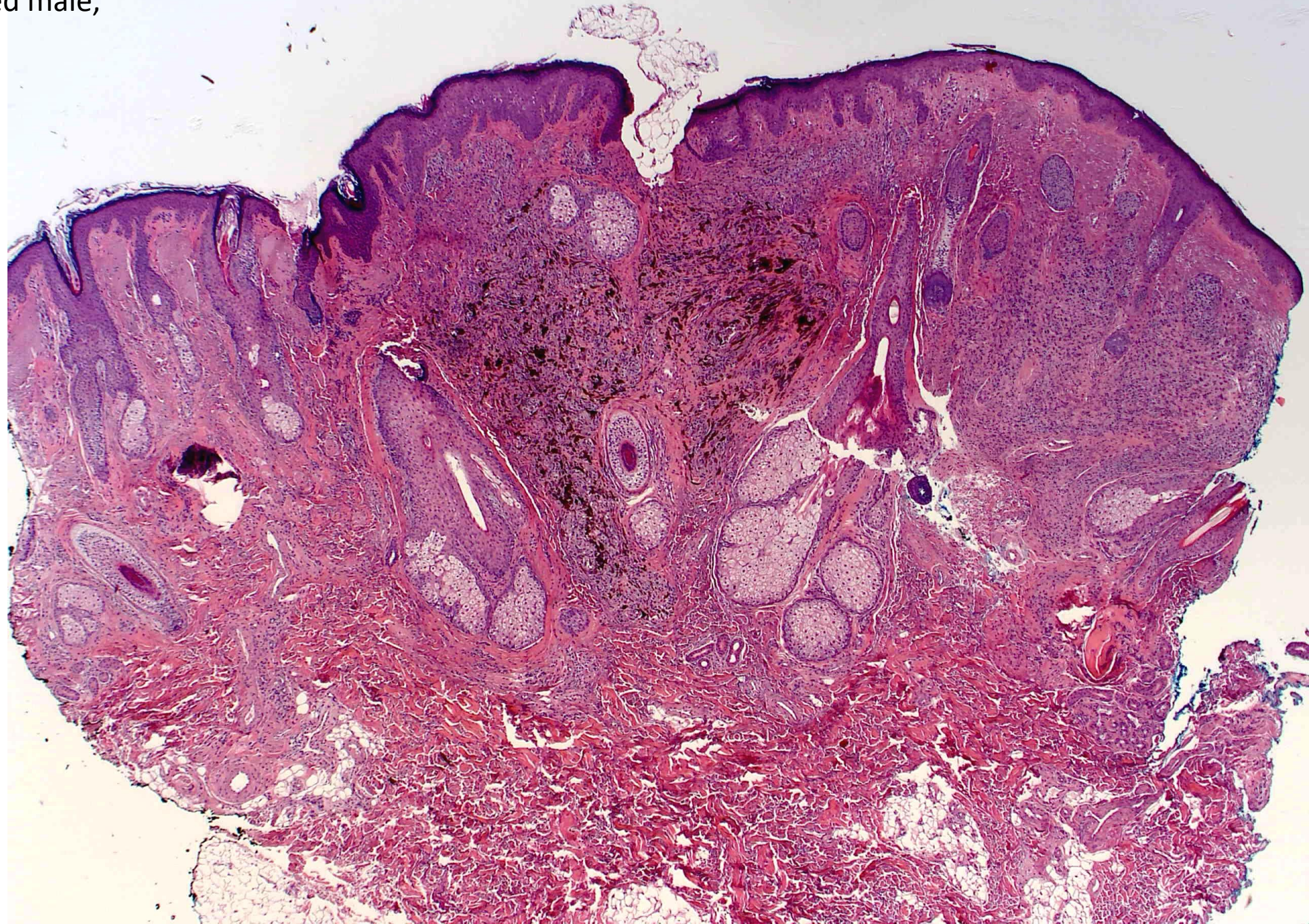


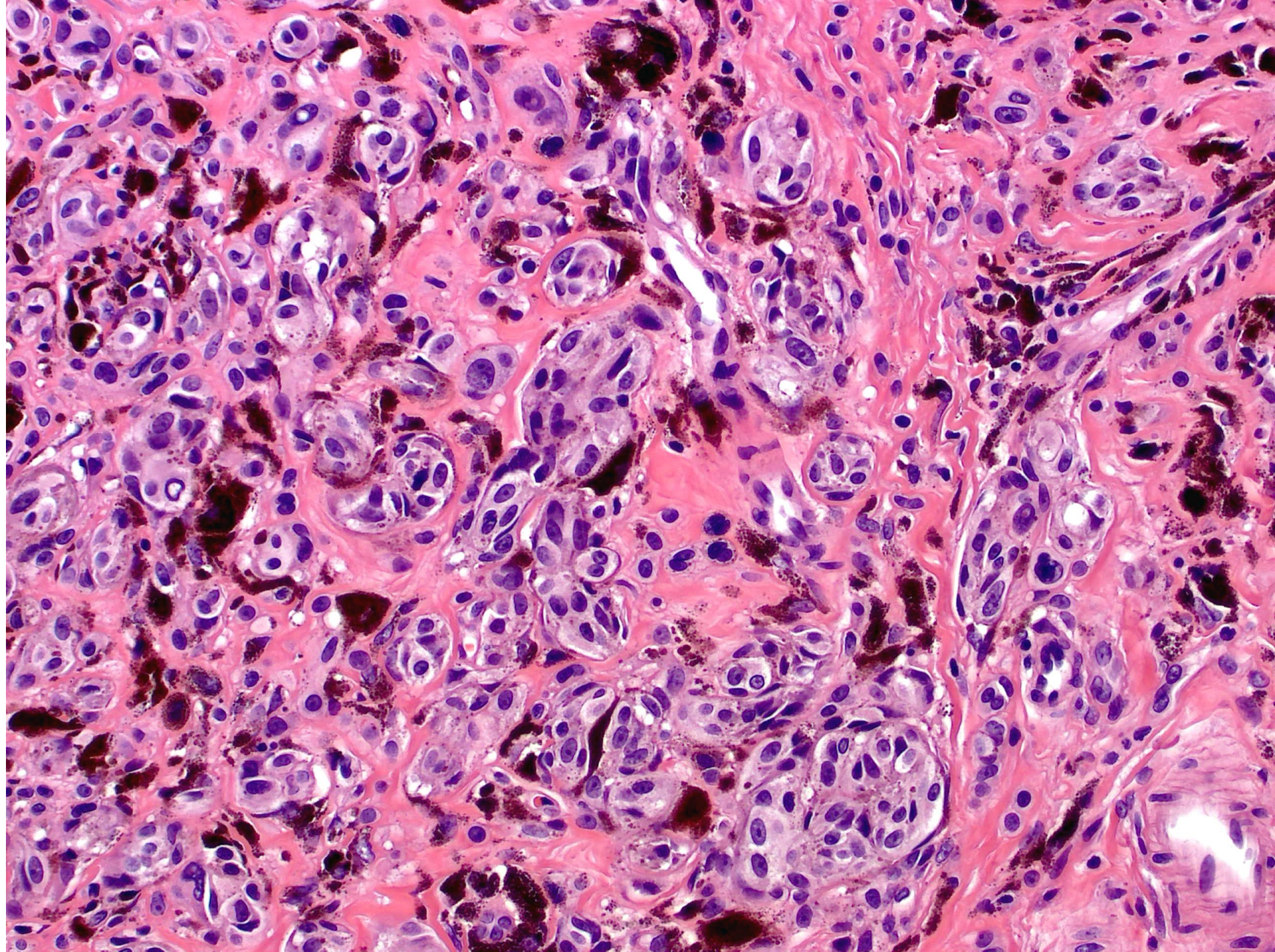


PRAME

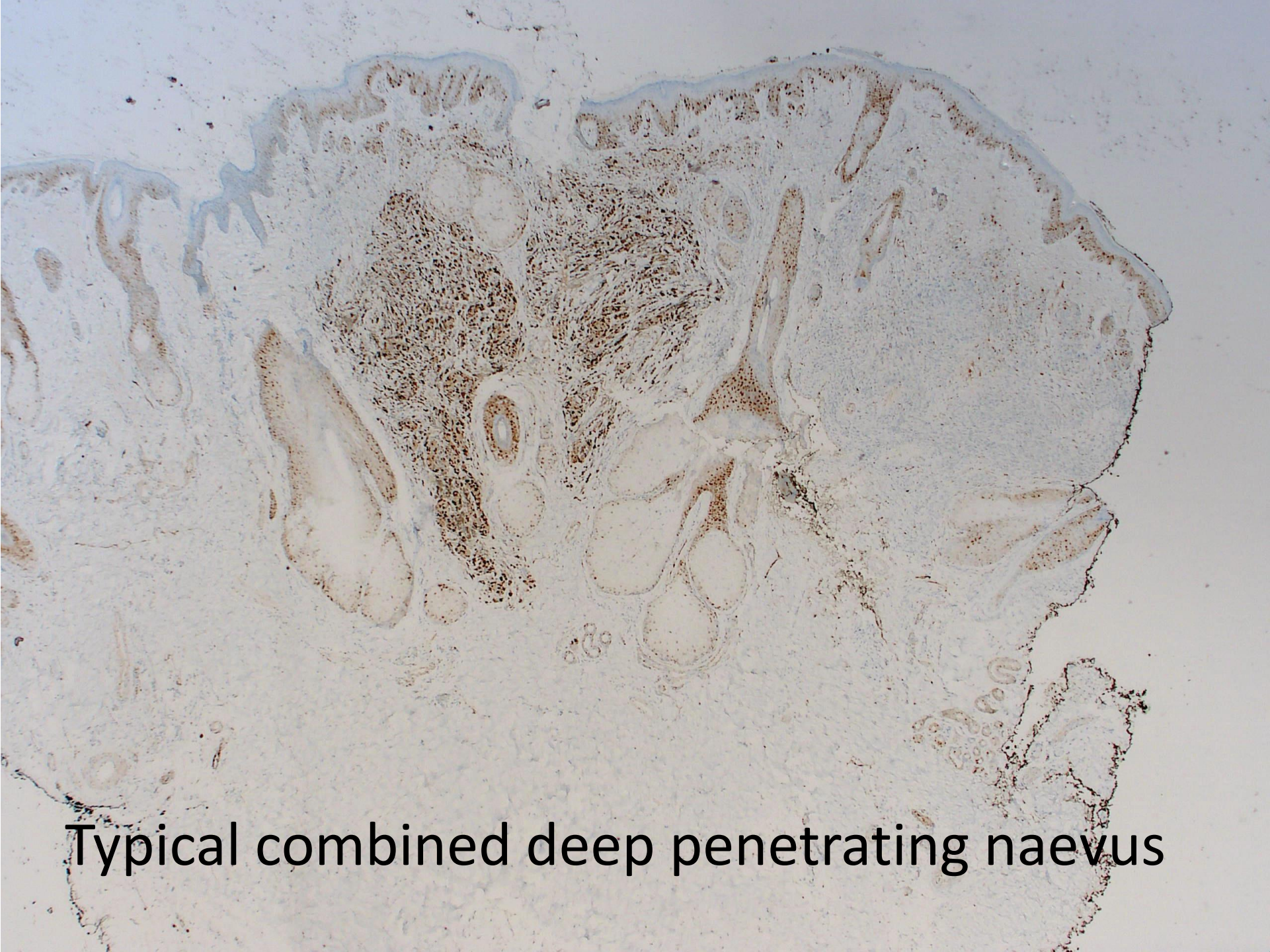


Middle aged male,
cheek



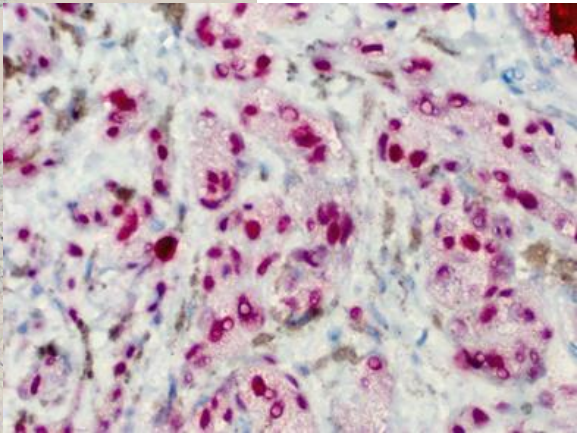
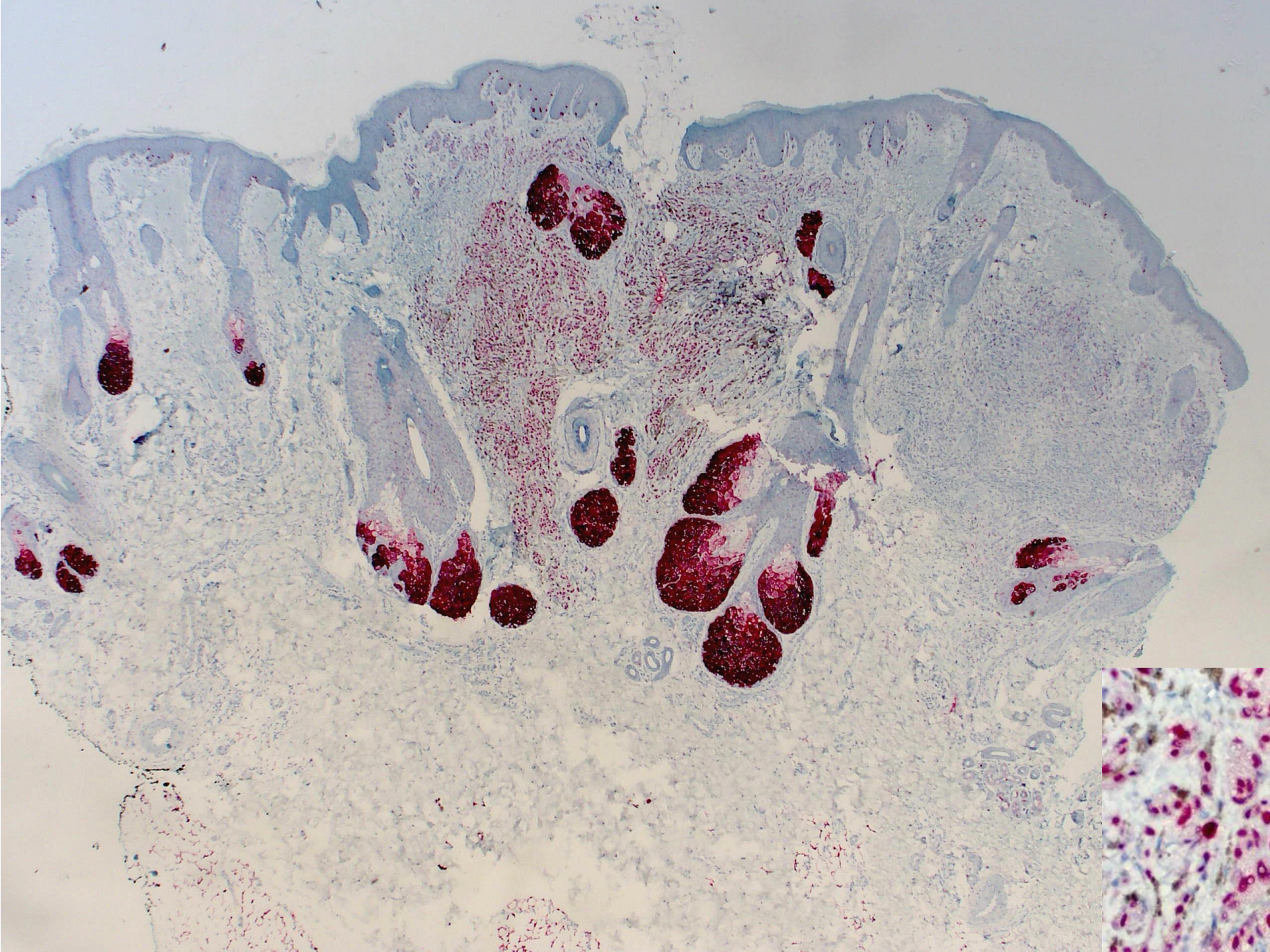


Cyclin D1



Typical combined deep penetrating naevus

PRAME



No problem, just use PRAME judiciously....

- PRAME is performed on 70-80% of melanoma cases diagnosed in our community in 2023 (unpublished data, 5 external laboratories, 2 States)
- The second most common consultation/molecular request in 2022 was for “PRAME positive naevus” (unpublished data, PathWest Dermatopathology)

Why PRAME does not solve our problems (my opinion only, YMMV)

- We know we are on unstable ground, and sometimes PRAME might be better at biology than we are
 - But it is seldom better at identifying lesions with genuine metastatic potential
- Pre-test probability 1% --> Post-test probability 16%
 - What now??
- Thresholds are subjective and subject to wishful thinking
- Staining of some junctional melanocytes in banal compound naevi is common and can be overinterpreted

Why this matters....



"all the dreams I had built of having more than one child seemed suddenly impossible ... then on top of that was this fear that now I have this wonderful little girl ... and I am probably going to die, and she is going to be alone"

Perspectives in Dermatopathology

The melanoma 'epidemic',
a dermatopathologist's perspective

Getting back on track

- Understand that sensitivity and specificity is a trade off
- Acknowledge early/borderline/undiagnosable cases in terminology/reporting (the customer is not always right!)
 - SAMPUS
 - MELPathDx
 - Descriptive
- Don't choose "trick" diagnoses to elicit a desired response
 - Severely dysplastic naevus
 - "Best regarded as" melanoma
- We know the correct approach to management
 - More serious problems arise from partial biopsy/incomplete removal than diagnostic underlabelling

Naevus or melanoma? An inadequate paradigm for a small number of clinically important lesions

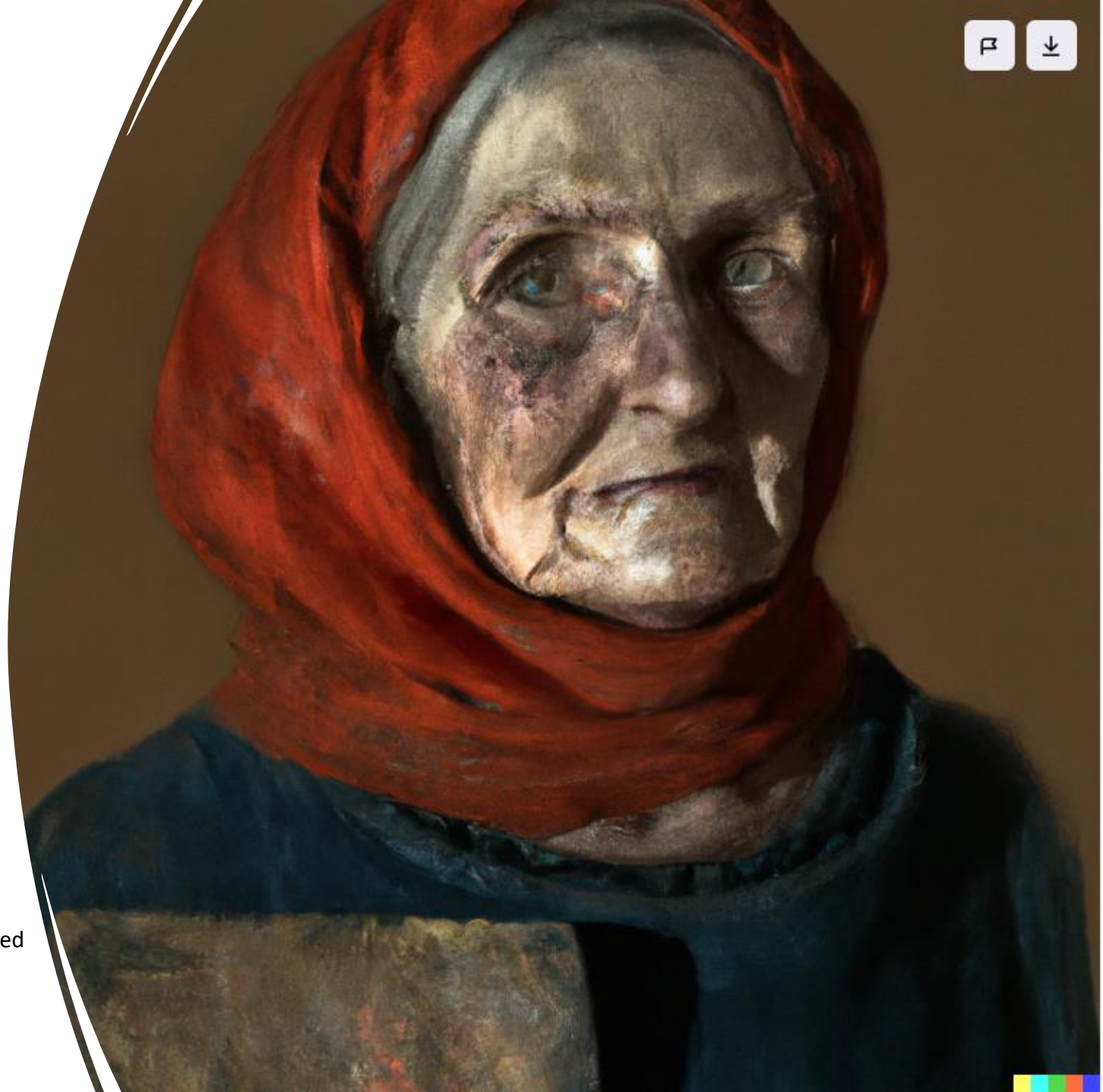
Benjamin A Wood, Nathan T Harvey

Volume 46, Issue 1, January-February 2017

afp
Australian Family Physician
Australian Family Physician

Classification of squamous dysplasia

- “Painting in the style of Rembrandt of a weathered old woman with a scaly red plaque on her face”
- Image generated by DALL.E.2



How good are we at classifying squamous dysplasia?

- Personal experience: Not great
- Published data:

Table II. Interobserver agreement

	κ	95% CI	Agreement, %
On diagnosis between reference dermatopathologists			
All diagnoses	0.69	0.67-0.69	76
BCC	0.88	0.84-0.91	94
SCC invasive	0.62	0.52-0.72	88
SCC in situ	0.42	0.29-0.56	93
Actinic keratosis	0.51	0.40-0.62	85
Other	0.71	0.62-0.81	91
On diagnosis between local pathologists and central reference dermatopathologists			
All diagnoses	0.66	0.66-0.67	75
BCC	0.90	0.88-0.91	95
SCC invasive	0.60	0.57-0.64	90
SCC in situ	0.40	0.34-0.45	93
Actinic keratosis	0.51	0.48-0.55	84
Other	0.71	0.58-0.64	88

Reliability of the histopathologic diagnosis of keratinocyte carcinomas

Jared Jagdeo, MS,^{a,b} Martin A. Weinstock, MD, PhD,^{a,b,c} Michael Piepkorn, MD,^d and Stephen E. Bingham, PhD^e; The Department of Veteran Affairs Topical Tretinoin Chemoprevention Trial Group
Providence, Rhode Island; Seattle, Washington; and Perry Point, Maryland

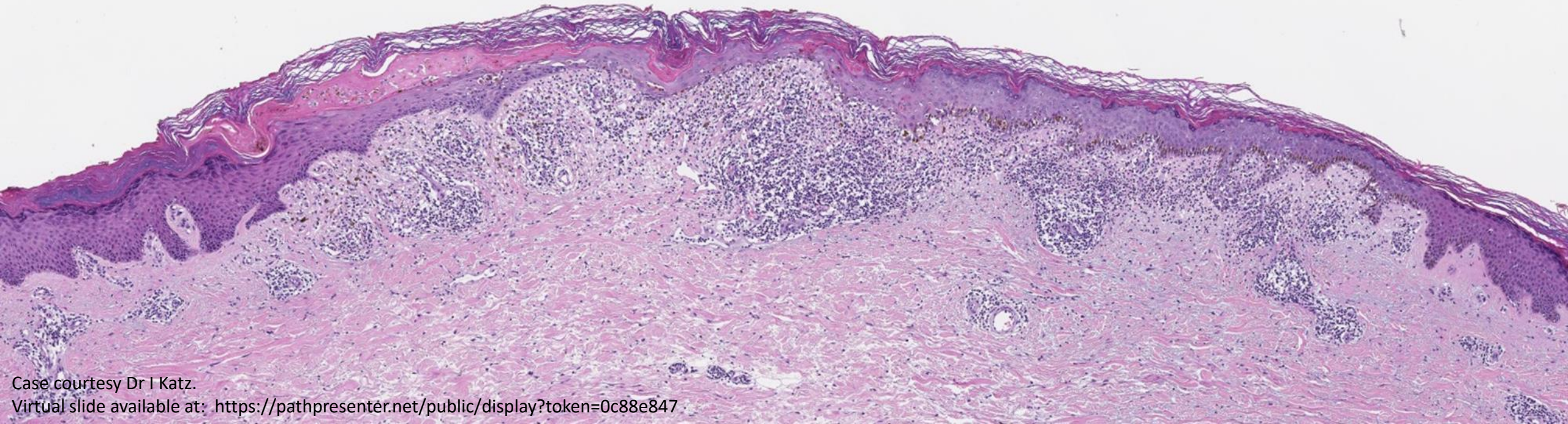
- 44 non-melanocytic lesions from a group of 217 lesions excised to exclude melanoma
- Cases reviewed by 5 experienced dermatopathologists
 - >8 years experience
 - Average >15,000 skin samples/year
- Benign-malignant discrepancy (vs majority Dx): 11%

Variability in the Histopathological Diagnosis of Non-Melanocytic Lesions Excised to Exclude Melanoma

Ian Katz¹, Tony Azzi², Alister Lilleyman², Blake O'Brien³, Brian Schapiro⁴, Curtis Thompson^{4,5}, Tarl Prow^{6,7}

Citation: Katz I, Azzi T, Lilleyman A, O'Brien B, Thompson C, Prow T. Variability in the histopathological diagnosis of non-melanocytic lesions excised to exclude melanoma. *Dermatol Pract Concept*. 2021; 11(4):e2021094. DOI: <https://doi.org/10.5826/dpc.1104a94>

Diagnoses: Benign lichenoid keratosis, seborrheic keratosis, intraepidermal squamous cell carcinoma



Does it matter?

Squamous dysplasia is very common

- Estimated prevalence
 - 40-50% of white Australians over 40
 - 80% in patients in 7th decade
 - Individuals have an average of 6-8 lesions

Marks R. Epidemiology of non-melanoma skin cancer and solar keratoses in Australia: a tale of self immolation in Elysian fields. *Australas J Dermatol* 1997;38(Suppl 1):S26–9.

The cost is high

- NMSC costs at least 1.327 billion (2018/19)- the most expensive cancer
- Many costs associated with treatment (e.g. cryotherapy) are hidden/hard to calculate
- Non-financial costs

We need to get the pathology right for

- Clinical correlation
- Risk prediction and understanding invasive carcinoma
- Future targeted treatment

https://wiki.cancer.org.au/skincancerstats/Skin_cancer_incidence_and_mortality#Economic_impact

WHO Classification of Tumours [online](#) 

Skin Tumours (5th ed.) // Keratinocytic/epidermal tumours // Carcinoma precursors and benign simulants // Premalignant keratoses and precursors

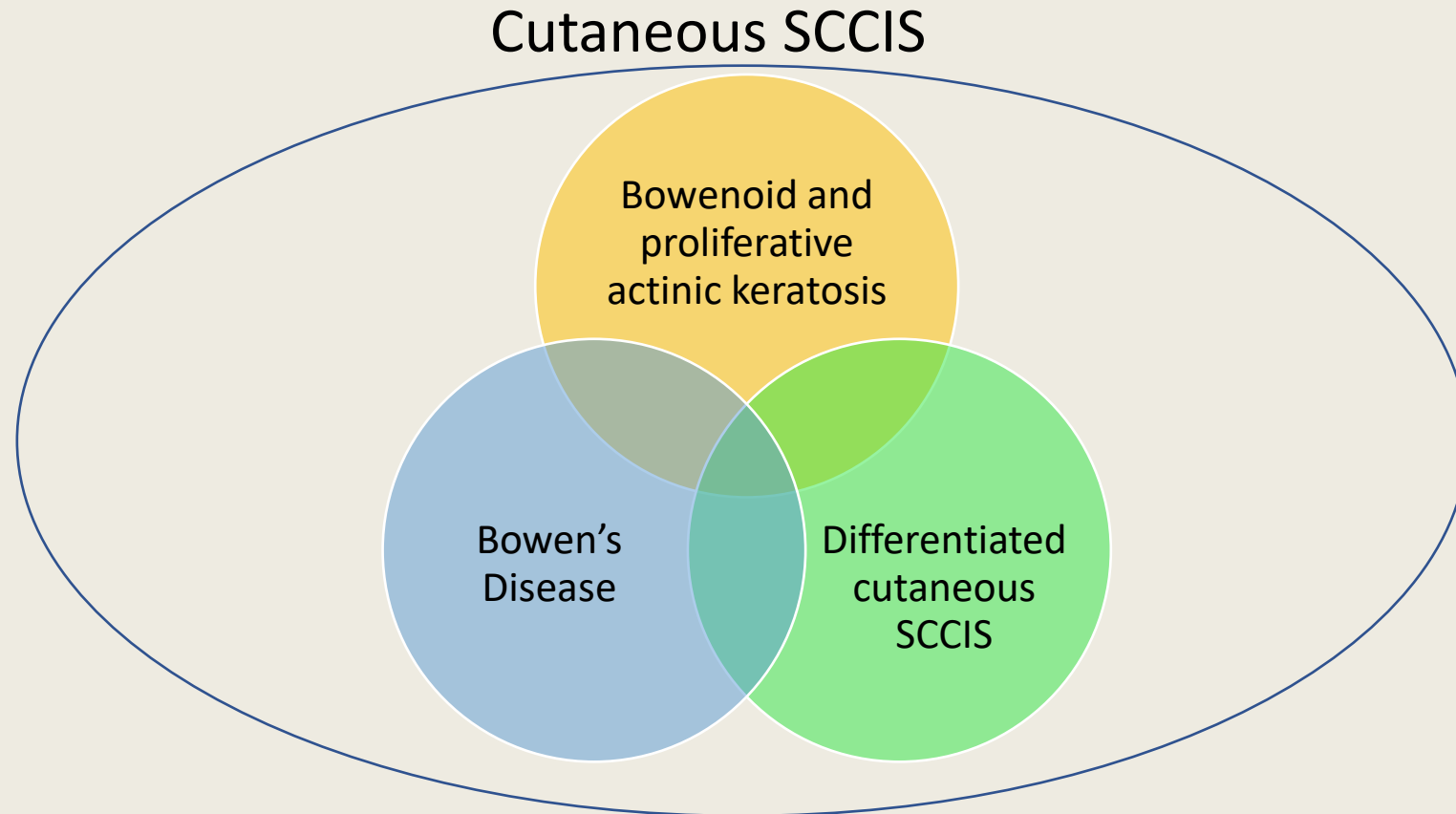
// Squamous cell carcinoma in situ (Bowen disease) 

Squamous cell carcinoma in situ (Bowen disease)

Definition

Squamous cell carcinoma (SCC) in situ, also known as Bowen disease, is SCC confined to the epidermis and superficial adnexal epithelium, further characterized by full-thickness involvement of the epidermis by dysplastic squamous cells.

Alternative View:
(or a diverticulum of my own.....)



Bowen's Disease

May 1912
(*J Cutan Dis Syph* 1912;30:241-255)

PRECANCEROUS DERMATOSES: A STUDY OF TWO CASES OF CHRONIC ATYPICAL EPITHELIAL PROLIFERATION.

By JOHN T. BOWEN, M.D., Boston.

He was first admitted on April 16, 1909. The man was of English birth, a native of Fall River, Massachusetts, 49 years of age, a weaver by occupation, and a man of considerable intelligence. He declared that the affection had first appeared 19 years previously when he was 30 years of age. The first appearances were those of a good sized "pimple" on his gluteal region, which was accompanied by slight itching, but of which he took no notice for several years until he became conscious that it was gradually increasing in size. He complained of some pain in connection with the lesions, chiefly noticeable when seated or after walking, and especially marked at times when the lesion became excoriated and showed a discharge. The inconvenience and pain were chiefly noticeable in the warm weather. During the past 19 years he had used many external applications and at one time he had one treatment of X-rays without producing any marked reaction or results.

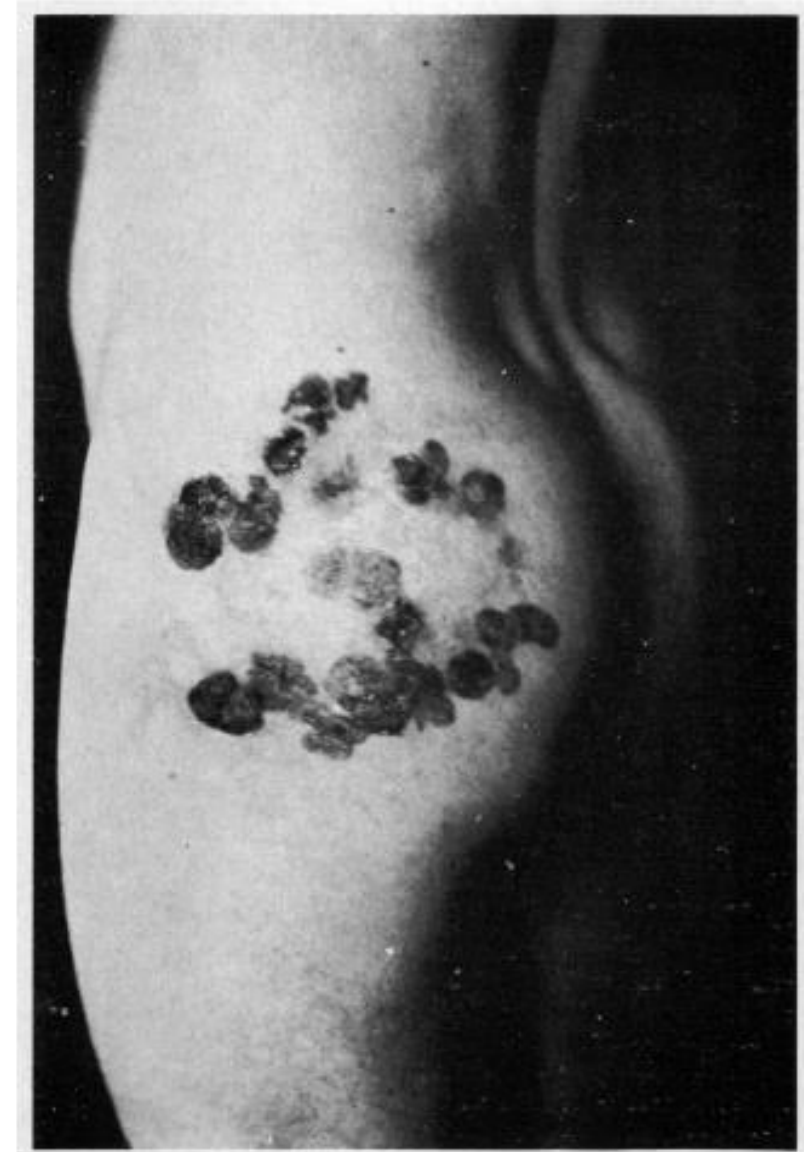


Fig. 1. Case 1.

PLATE XV.—To Illustrate Article by DR. JOHN T. BOWEN.

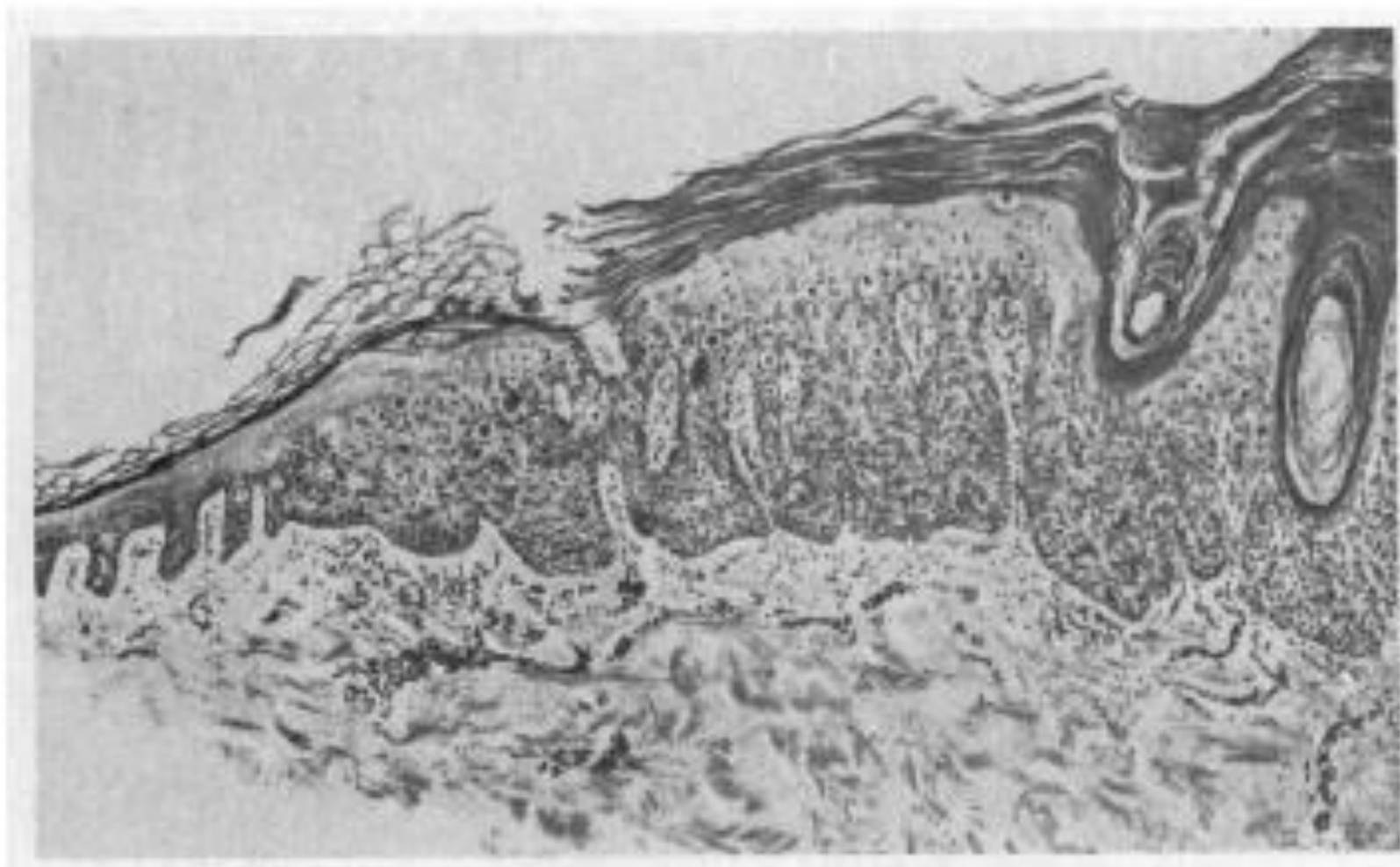
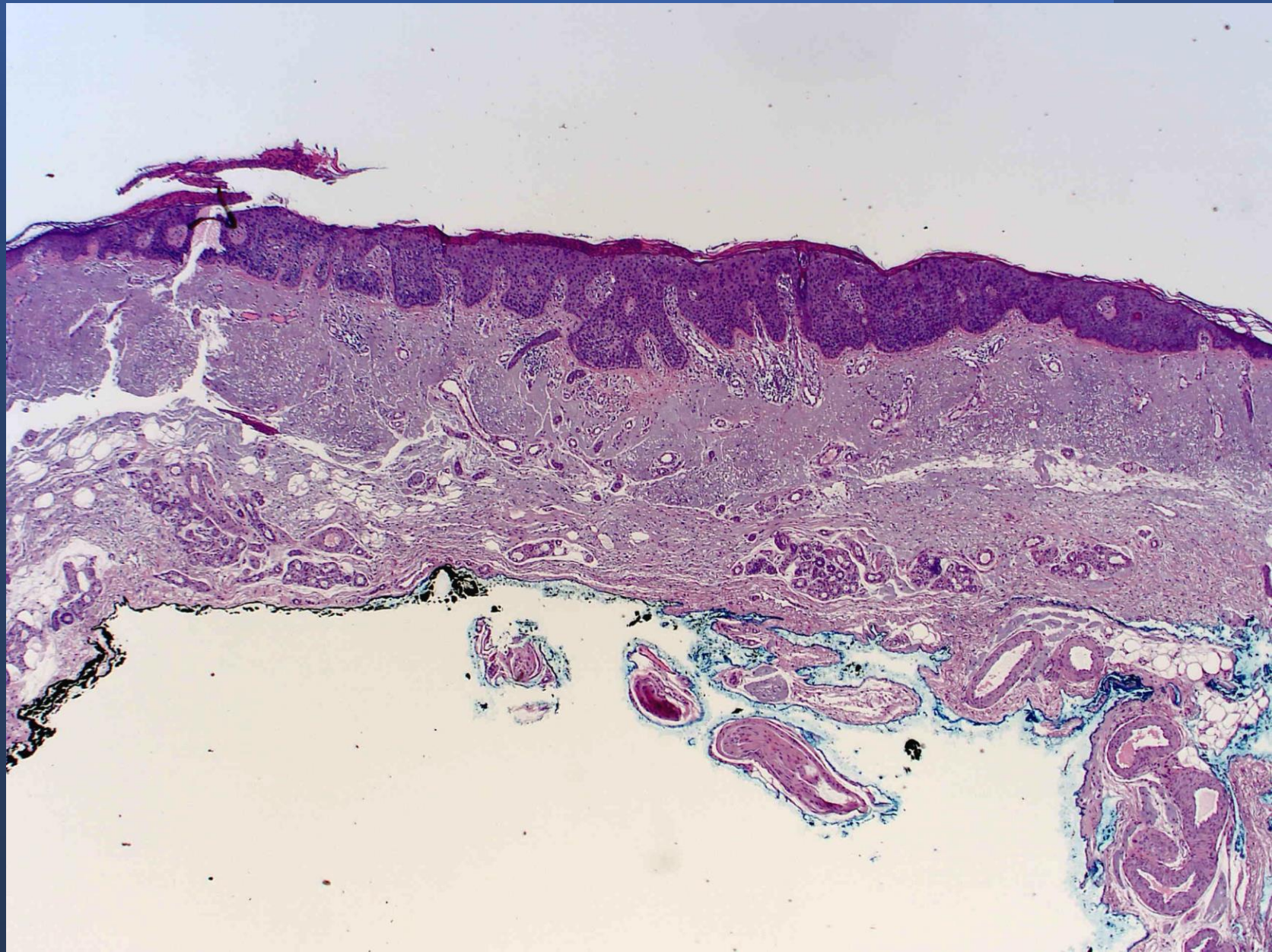


Fig. 2. Case 1.



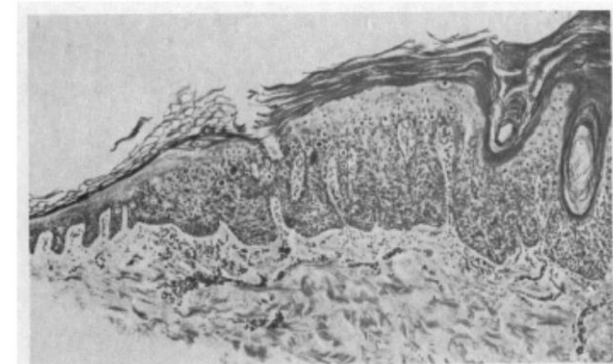
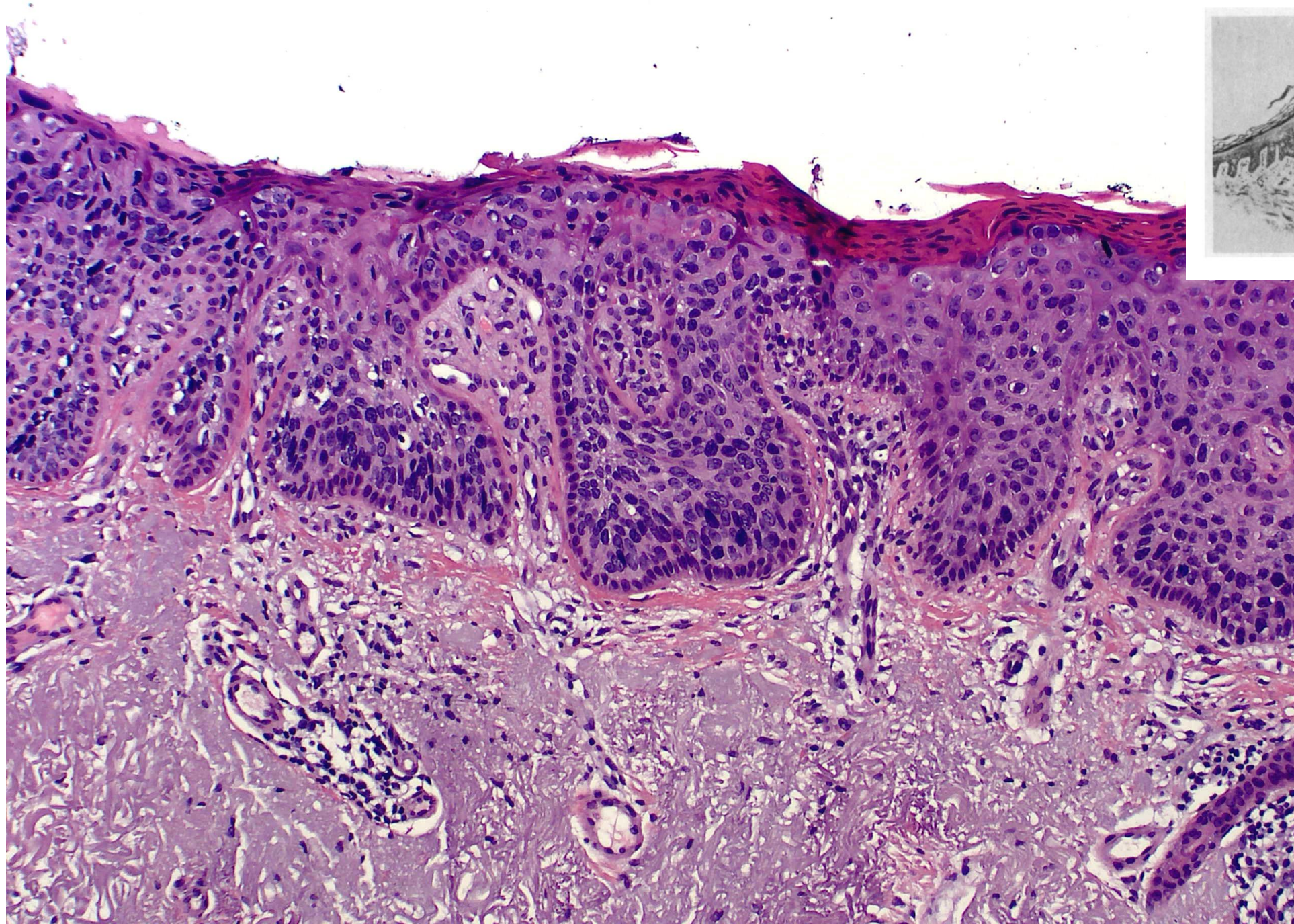
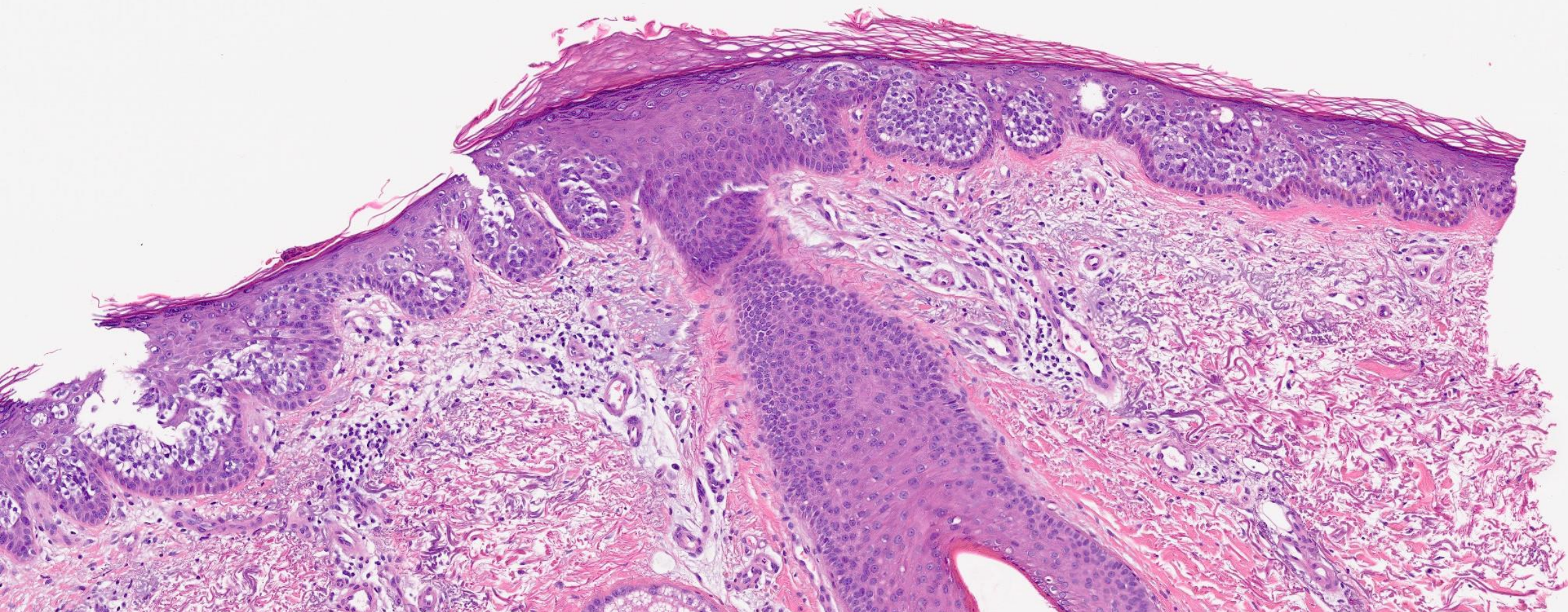


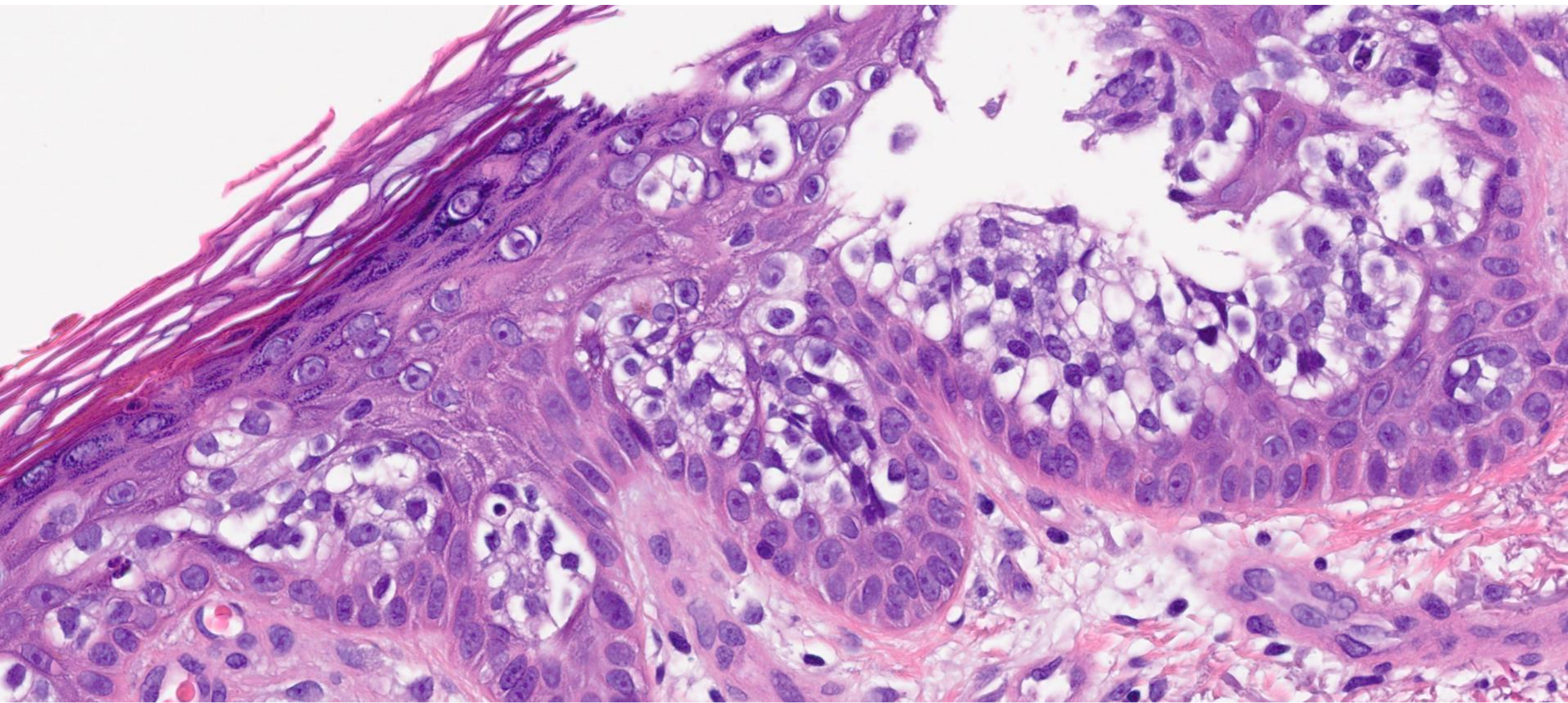
Fig. 2. Case 1.

Essential and desirable diagnostic criteria

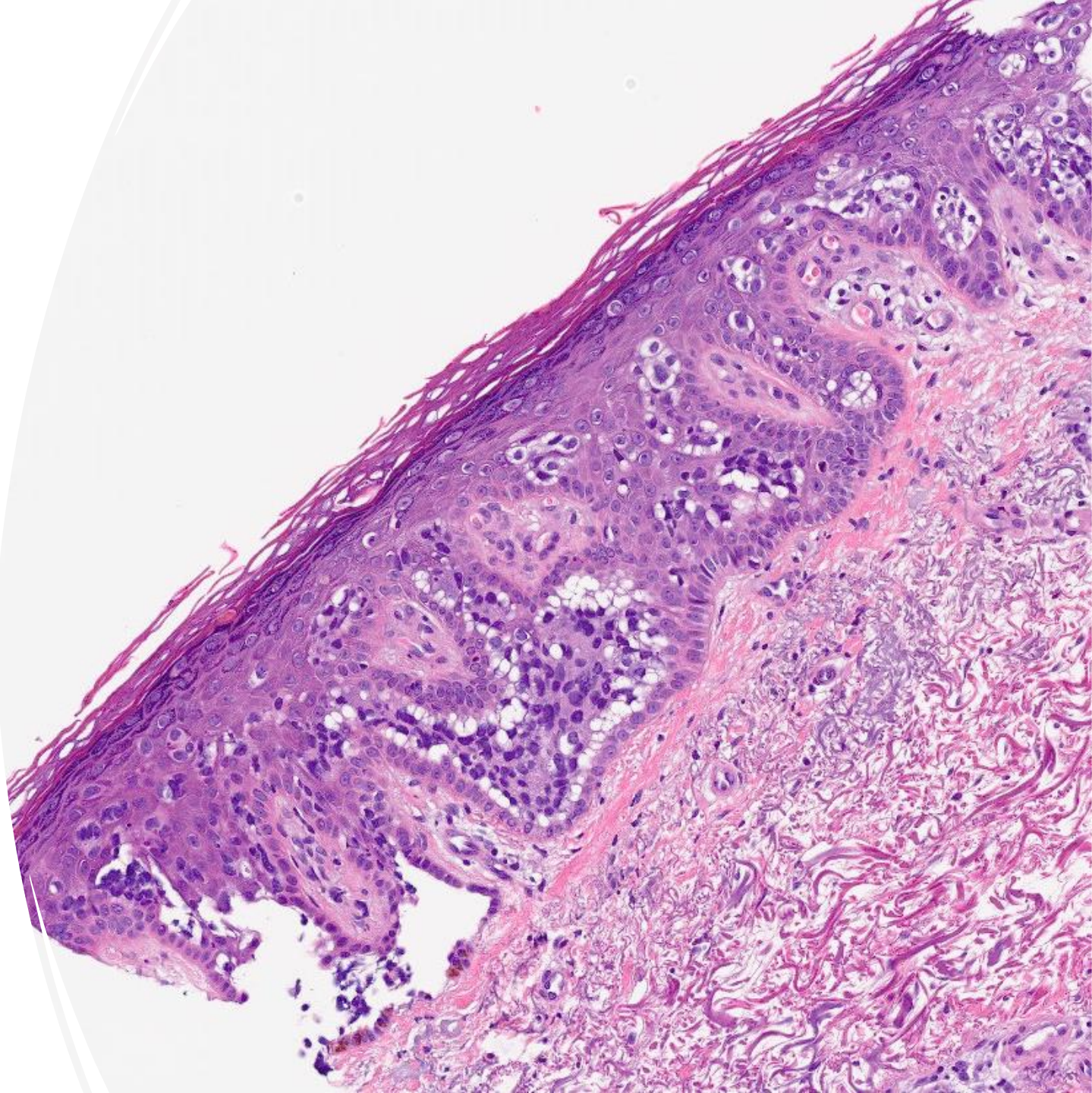
Essential:

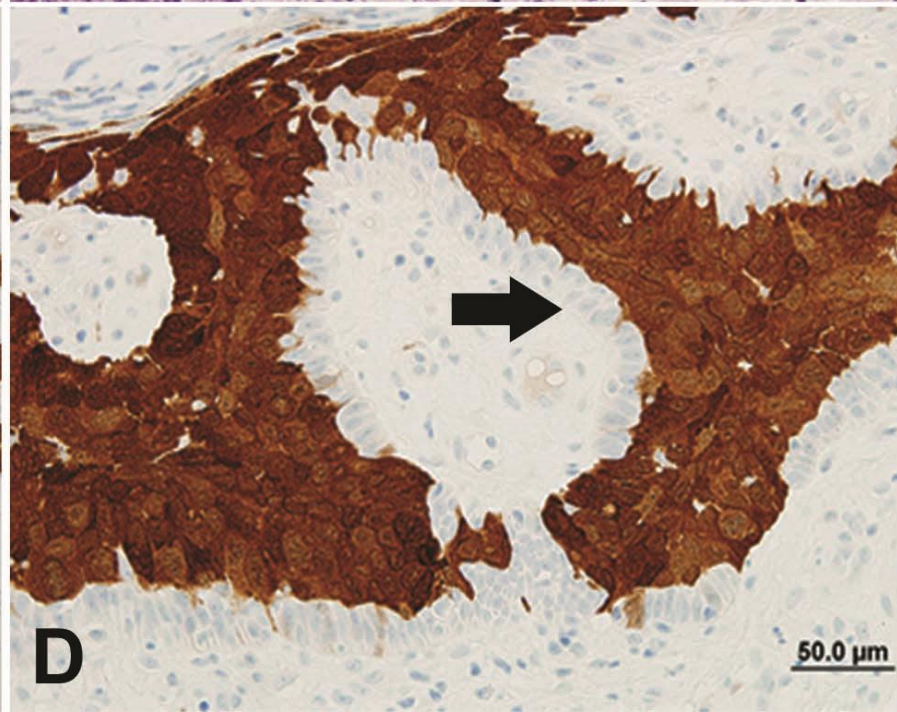
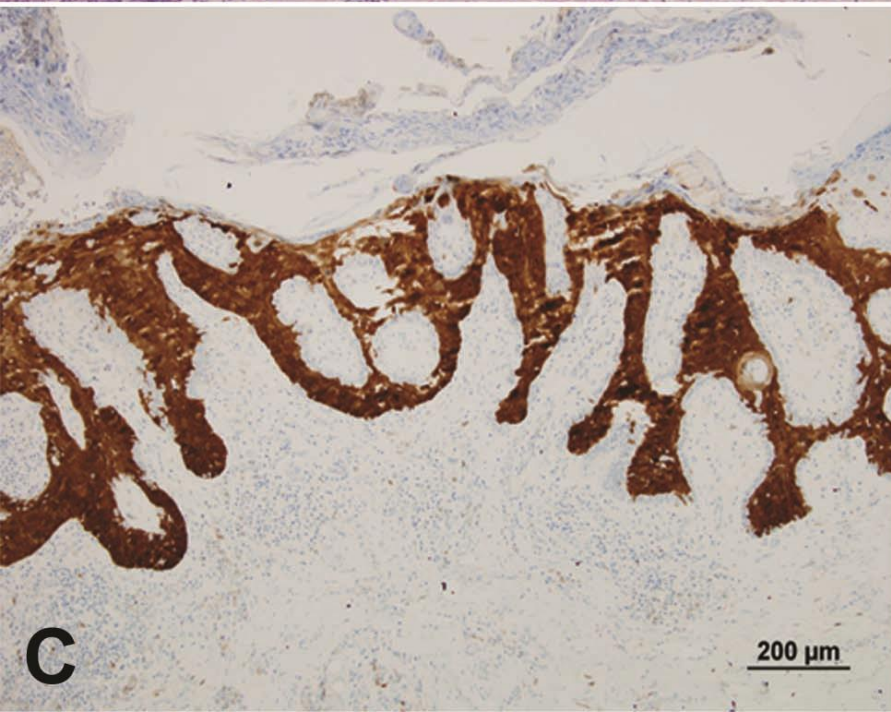
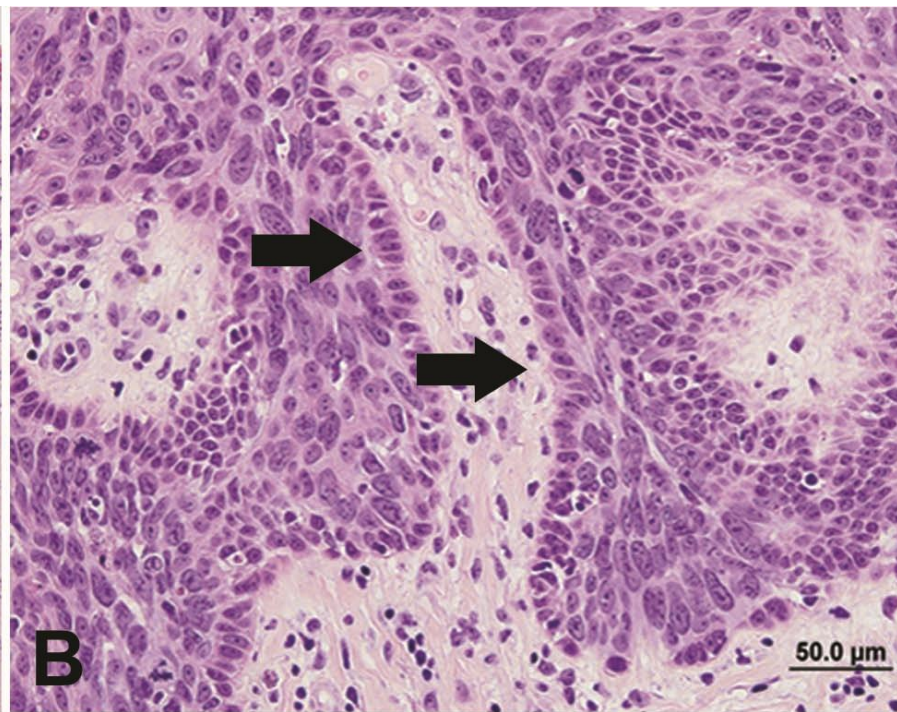
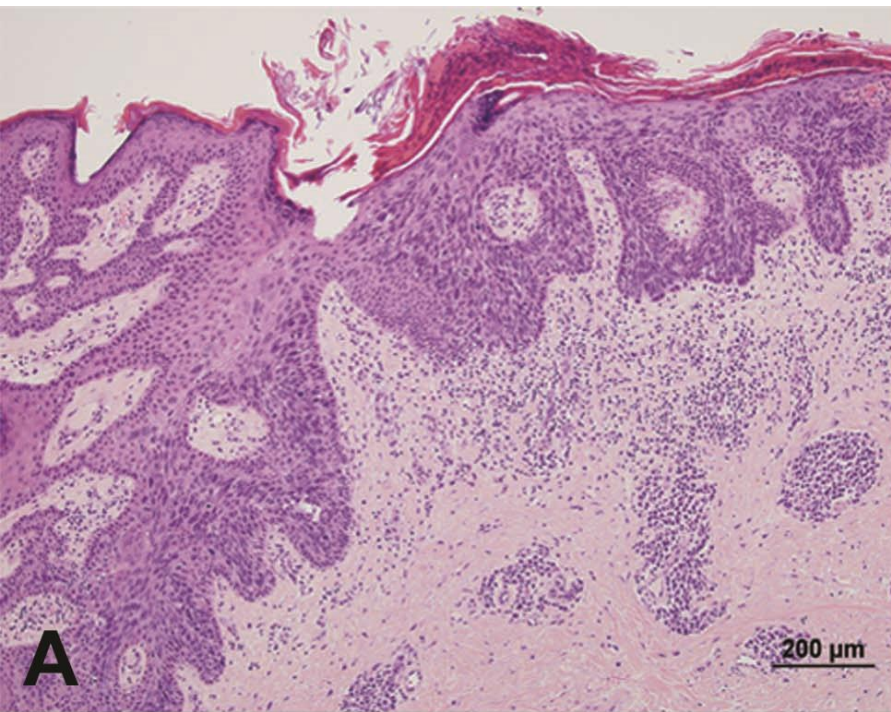
Replacement of full thickness of epidermis by atypical keratinocytes, with absence of maturation and frequent dyskeratotic keratinocytes; the cells may have a pagetoid appearance.





-
- Bowen's disease variants:
 - Clear cell
 - Pagetoid
 - Pigmented
 - Papillated/verrucous
 - Subtle
 - ? Others (mucinous, sebaceous...)



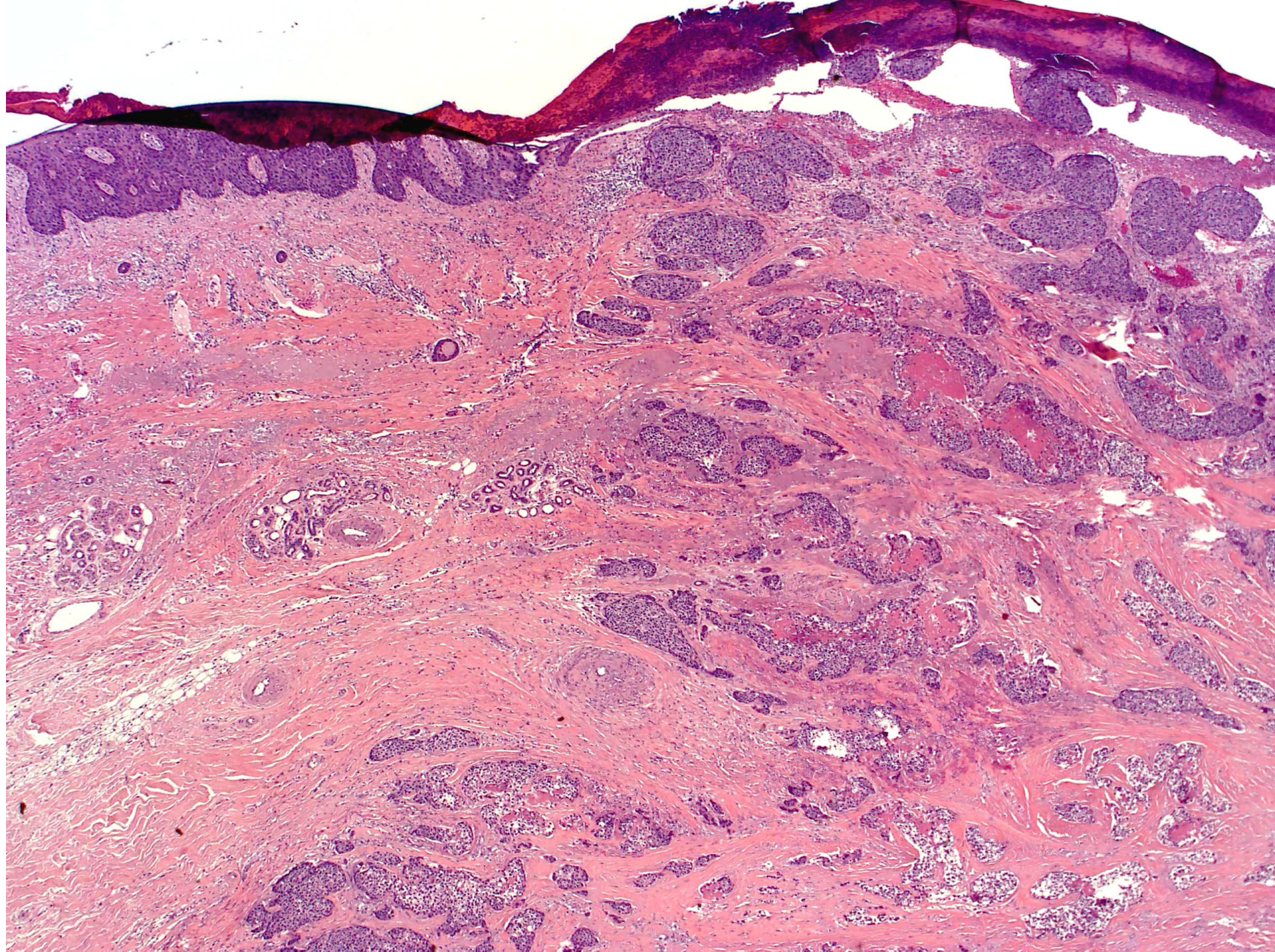


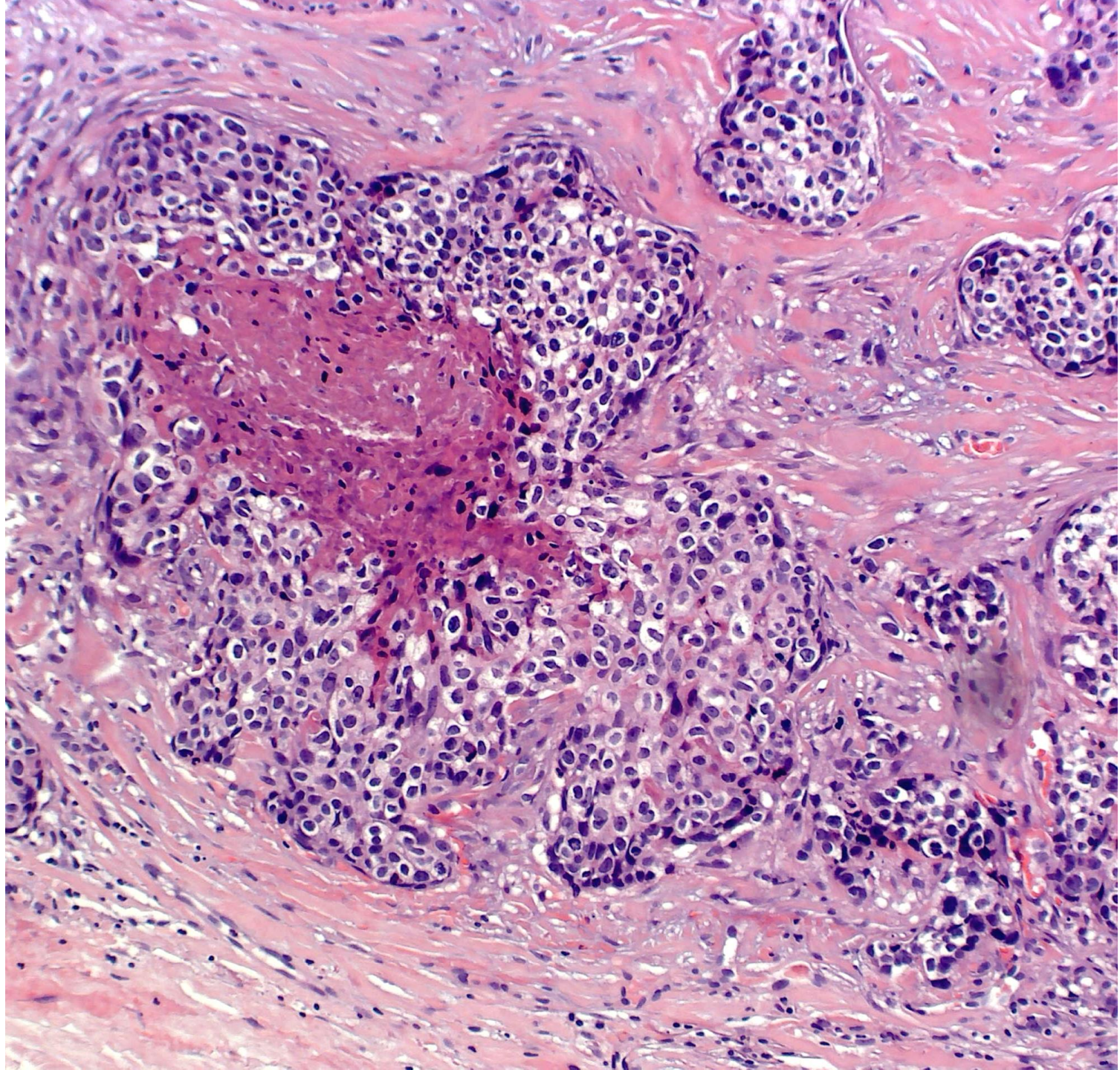
- p16 Diffuse positive, usually with PBS
- RB1 Weak or negative (unpublished data)
- No apparent difference between sun-damaged and non-sun damaged skin

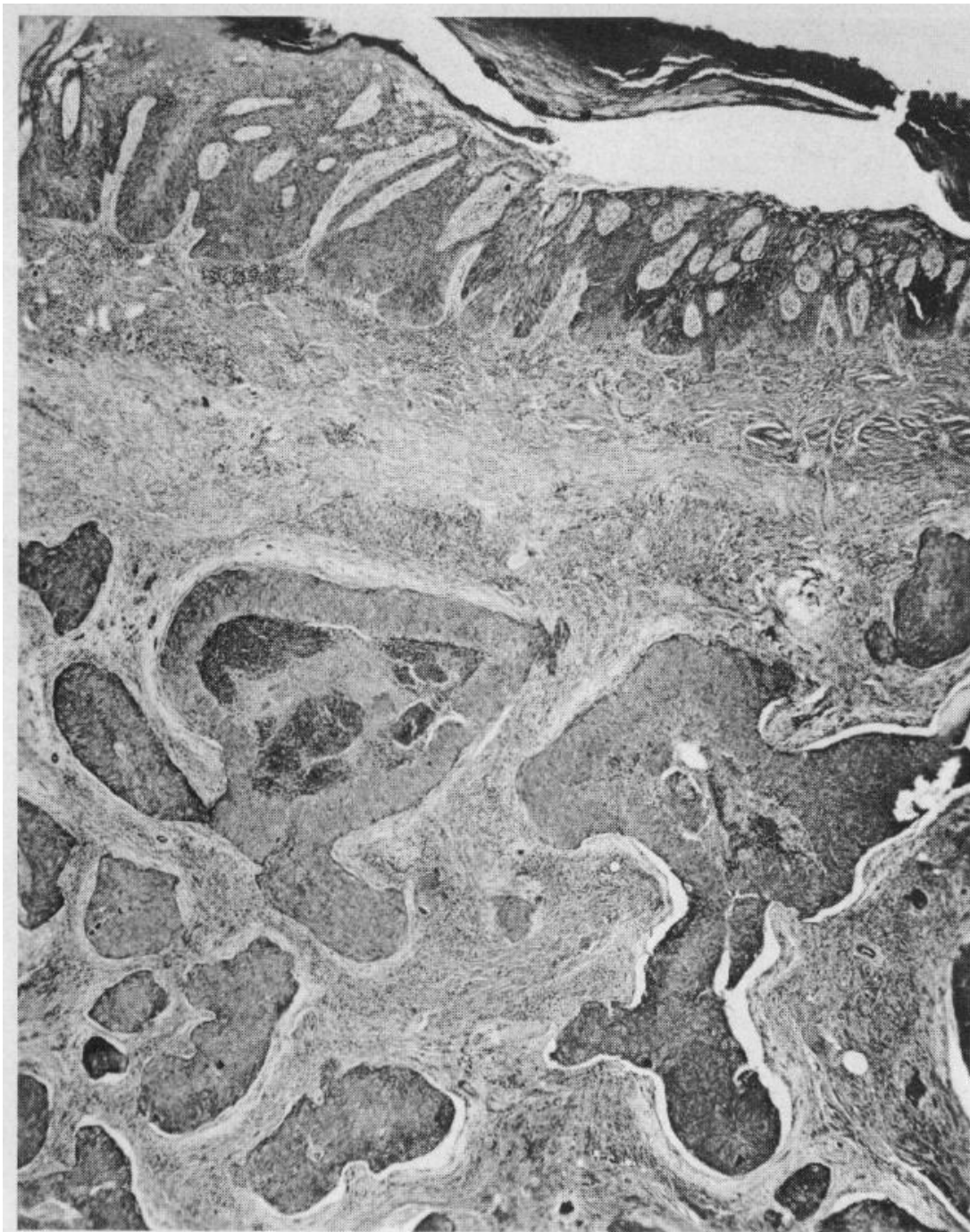
Immunohistochemical staining for p16 is a useful adjunctive test in the diagnosis of Bowen's disease

NATHAN T. HARVEY^{*†}, TAMAZIN LEECY^{**†} AND BENJAMIN ANDREW WOOD^{**†}

^{*}Department of Anatomical Pathology, PathWest, QEII Medical Centre, Nedlands, and [†]School of Pathology and Laboratory Medicine, The University of Western Australia, Crawley, Western Australia, Australia







Bowen's disease (BD) is generally regarded as a premalignant dermatosis.^{1,3} If untreated, 3% to 5% of patients may develop invasive carcinoma, which is capable of metastasizing and may even cause death.^{1,4} Clinically, the lesions of BD present as

Carcinoma arising in BD should be considered a form of adnexal carcinoma that may show various differentiation. These tumors are potentially lethal. Available follow-up information indicates a 13% metastatic rate and that death resulting from widespread dissemination occurs in about 10% of patients.⁴

Carcinoma Arising in Bowen's Disease

Arch Dermatol—Vol 122, Oct 1986

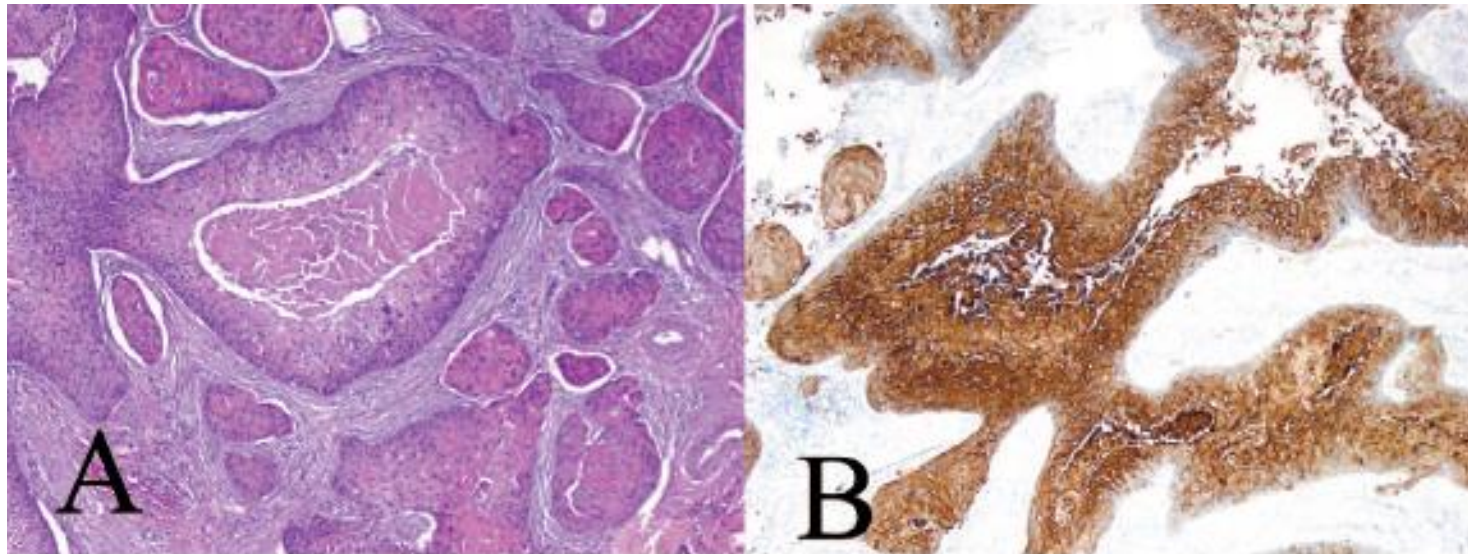
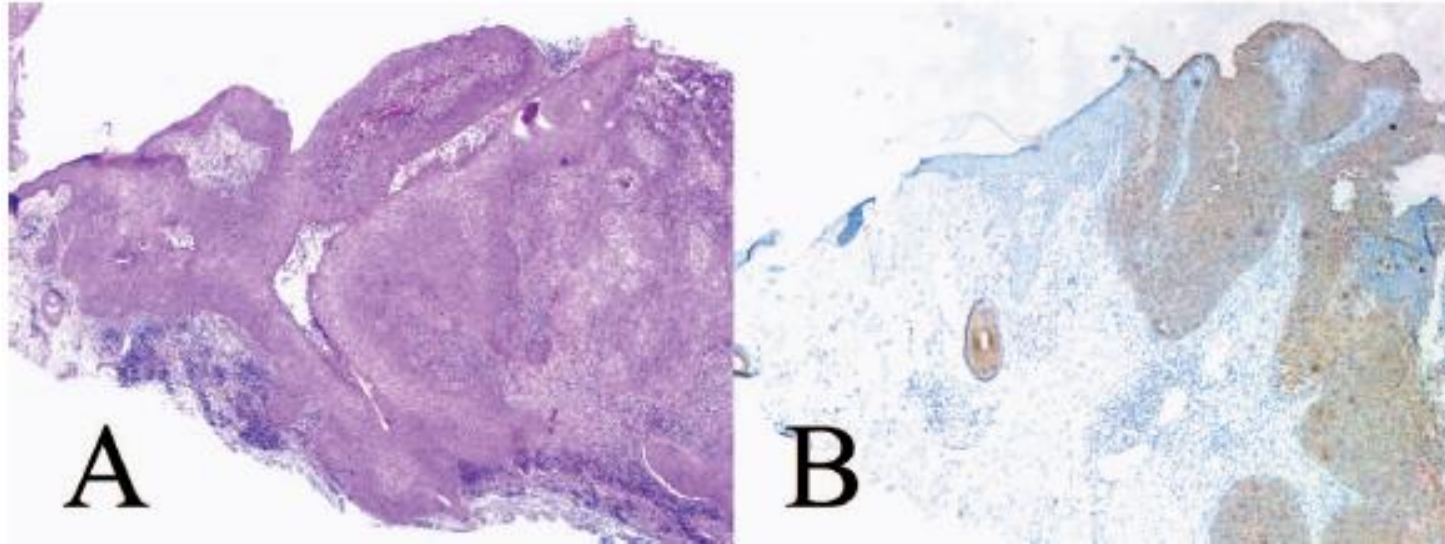
Kao, 1986

Adnexal Clear Cell Carcinoma With Comedonecrosis

Clinicopathologic Analysis of 12 Cases

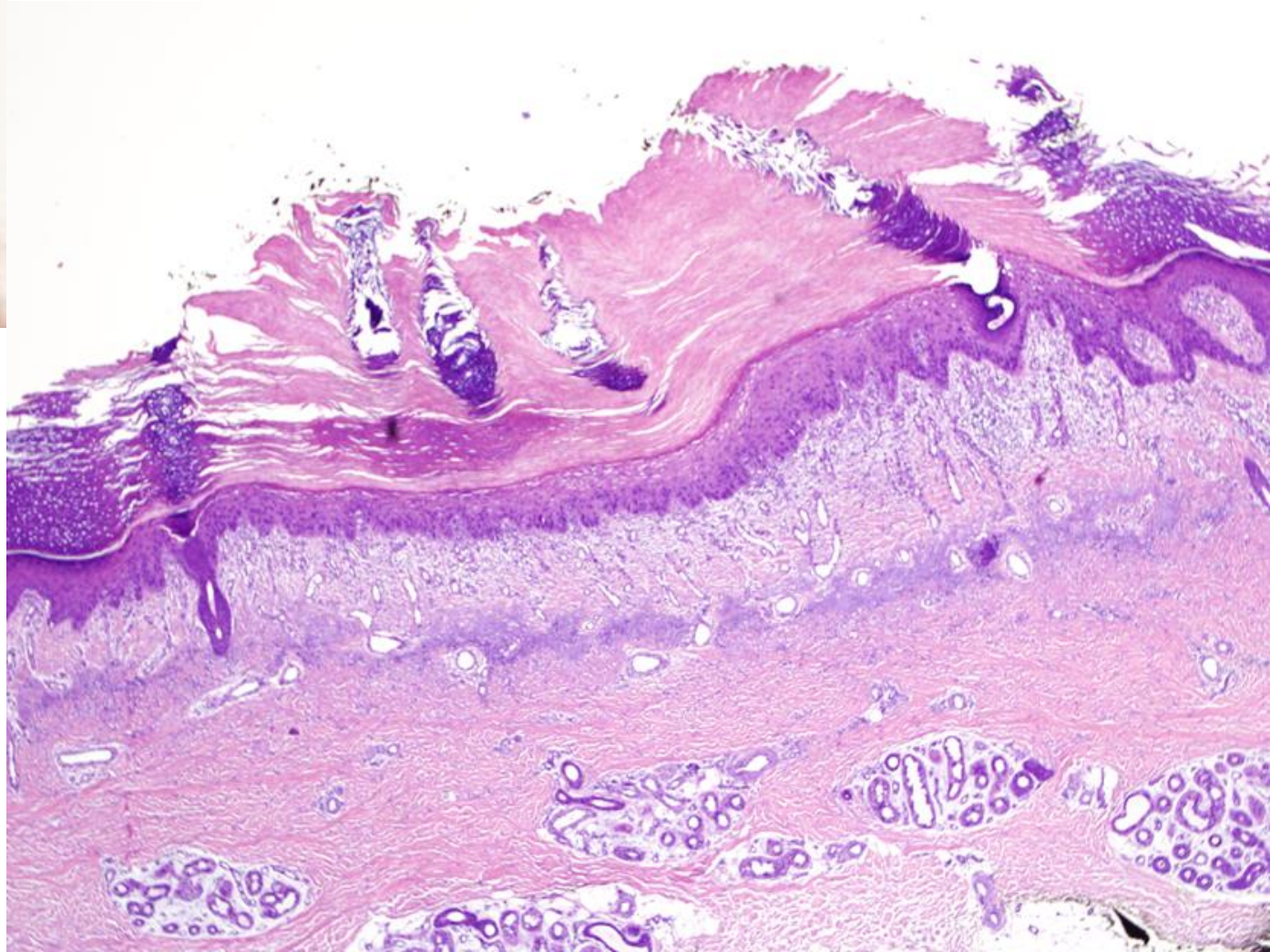
Iskander H. Chaudhry, MRCPATH; Artur Zembowicz, MD, PhD

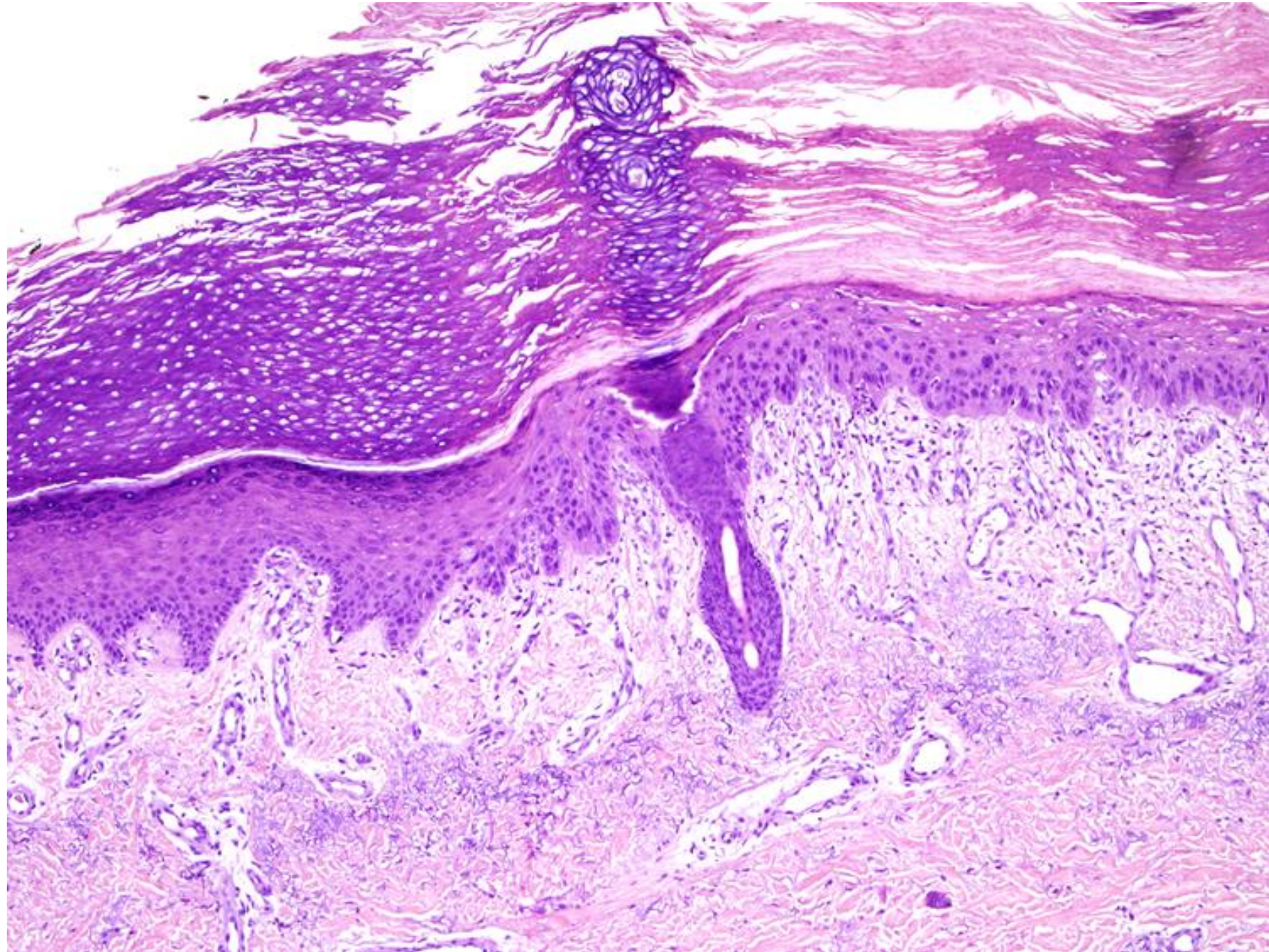
(Arch Pathol Lab Med. 2007;131:1655–1664)

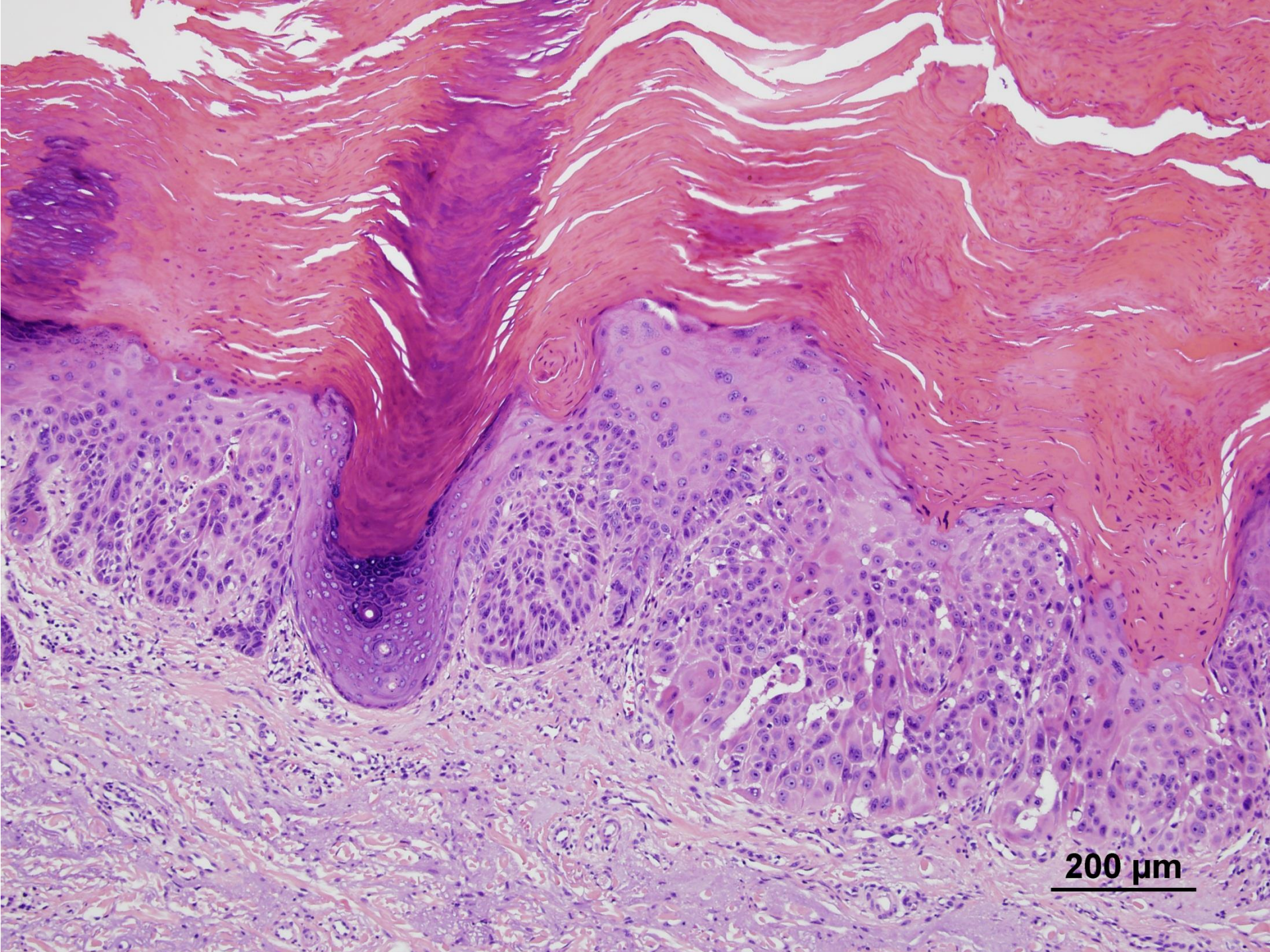


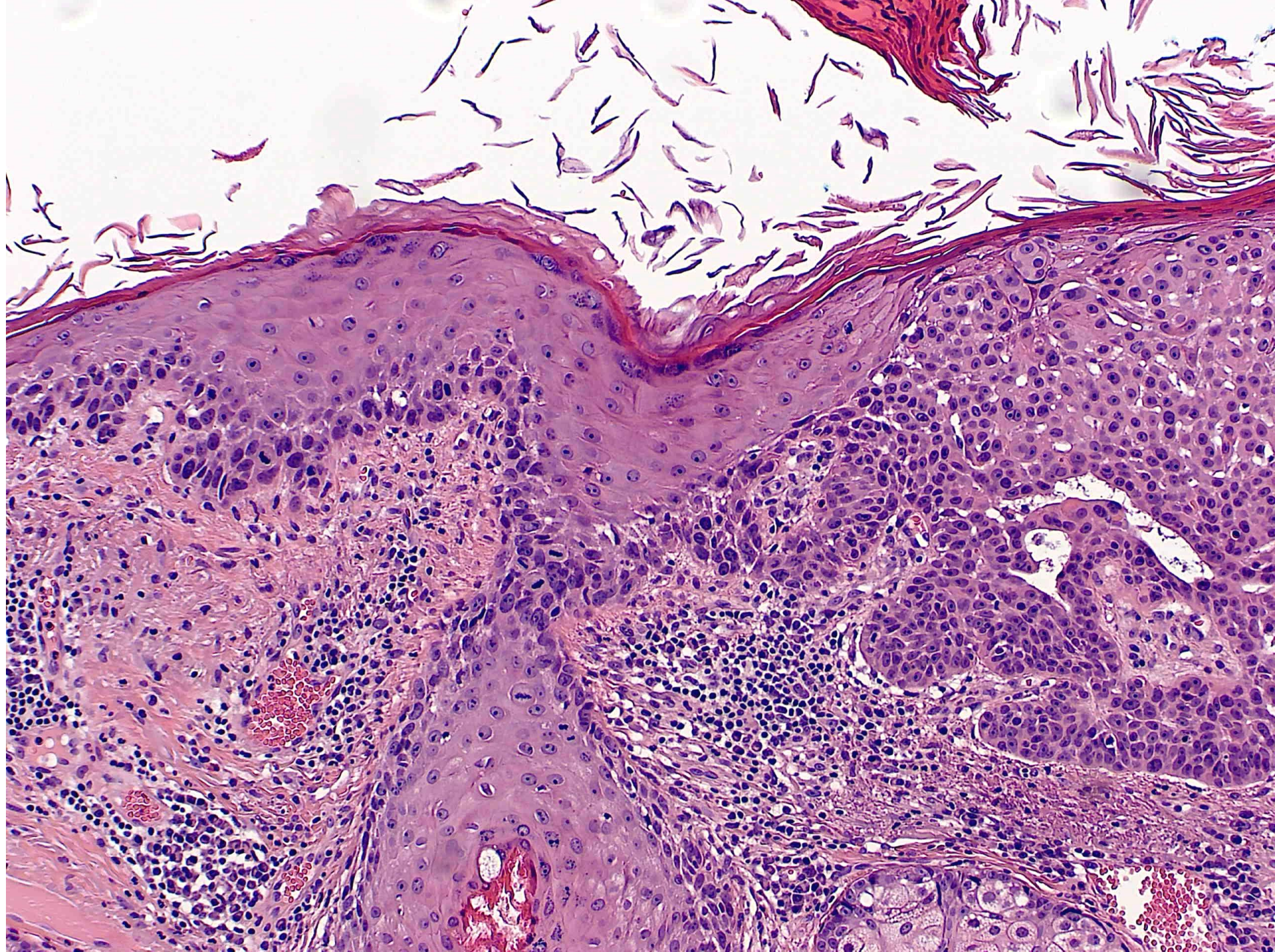
- Differential diagnosis:
 - BCC
 - Sebaceous carcinoma
 - Porocarcinoma

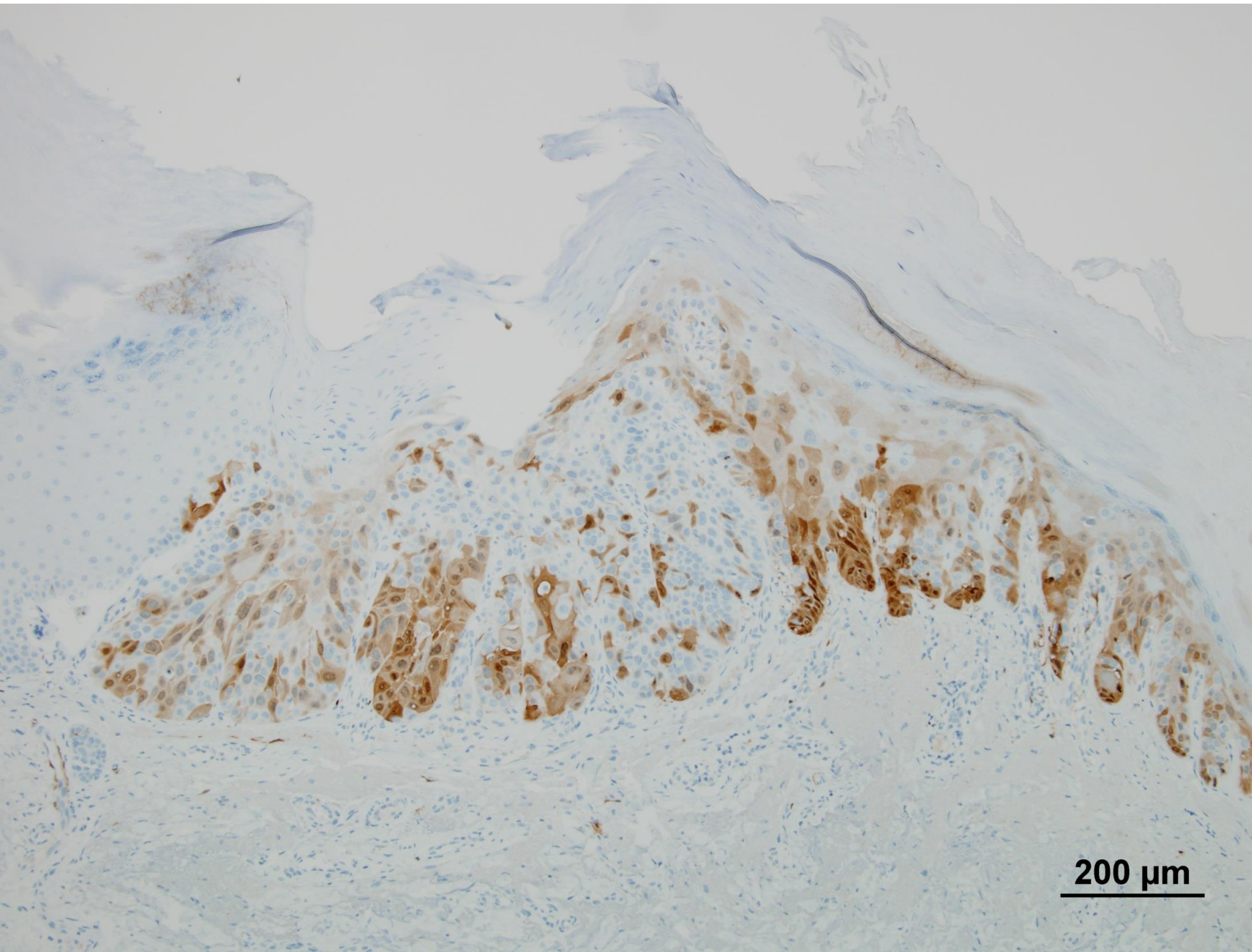
Actinic keratosis



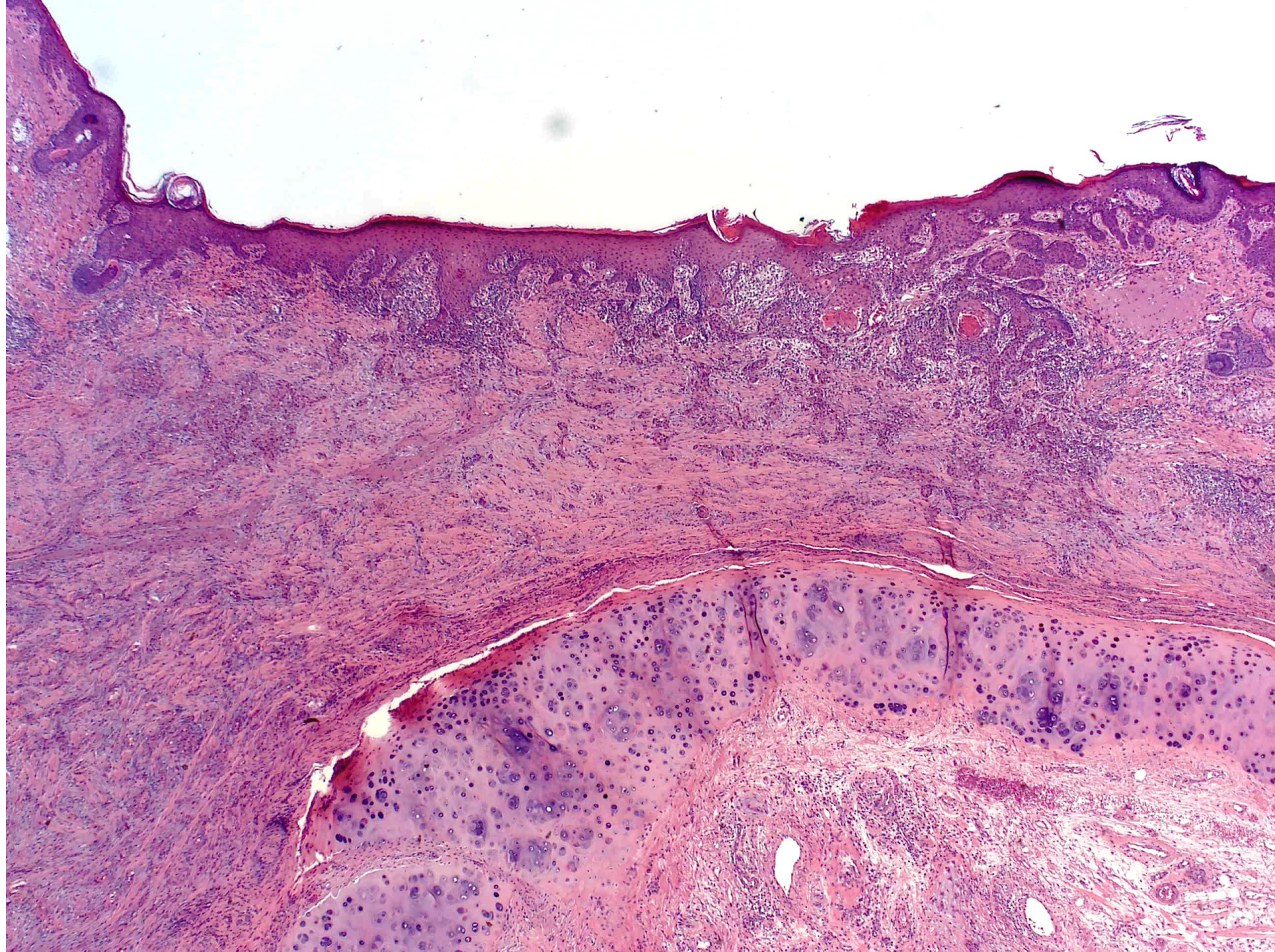


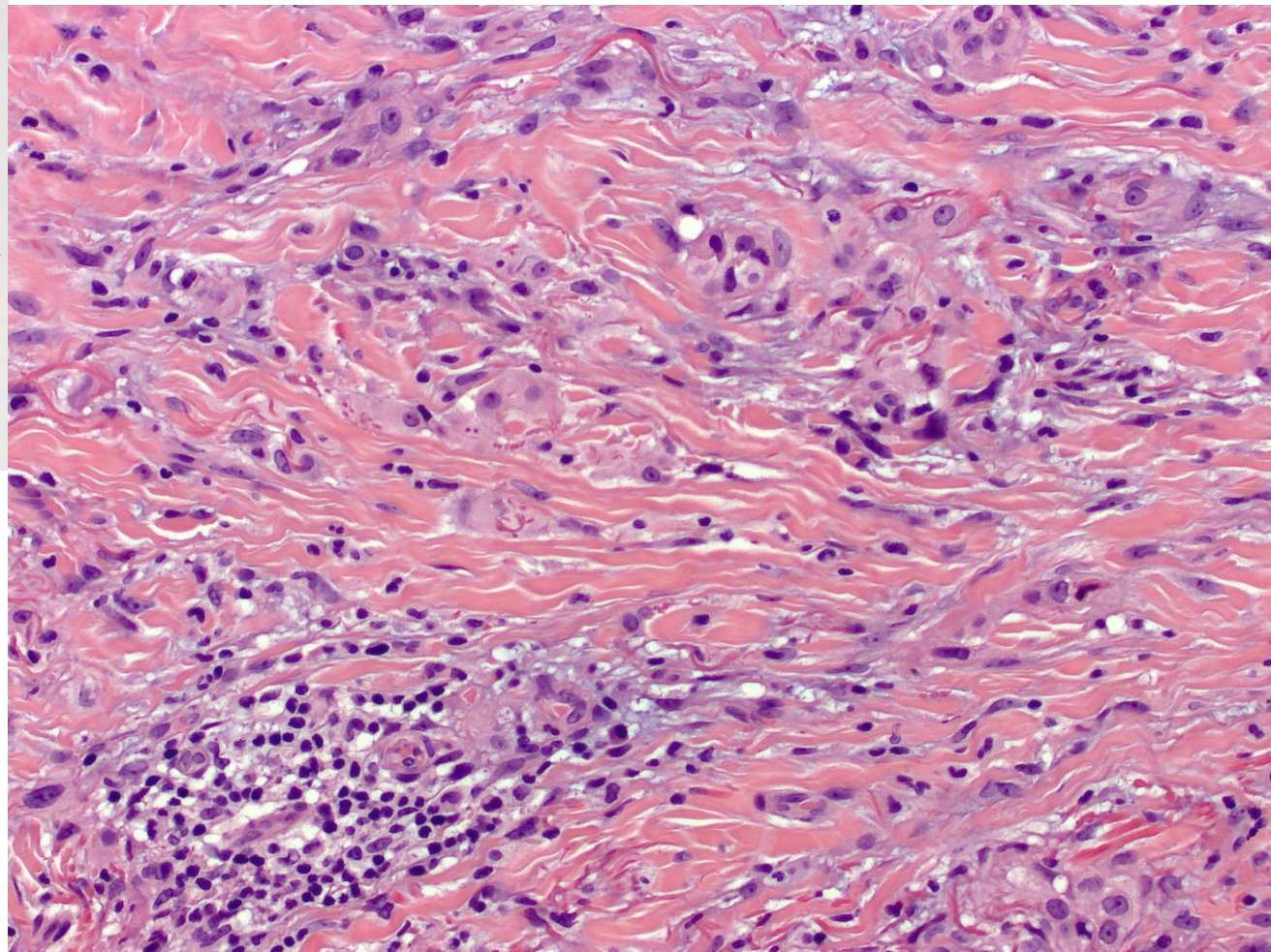
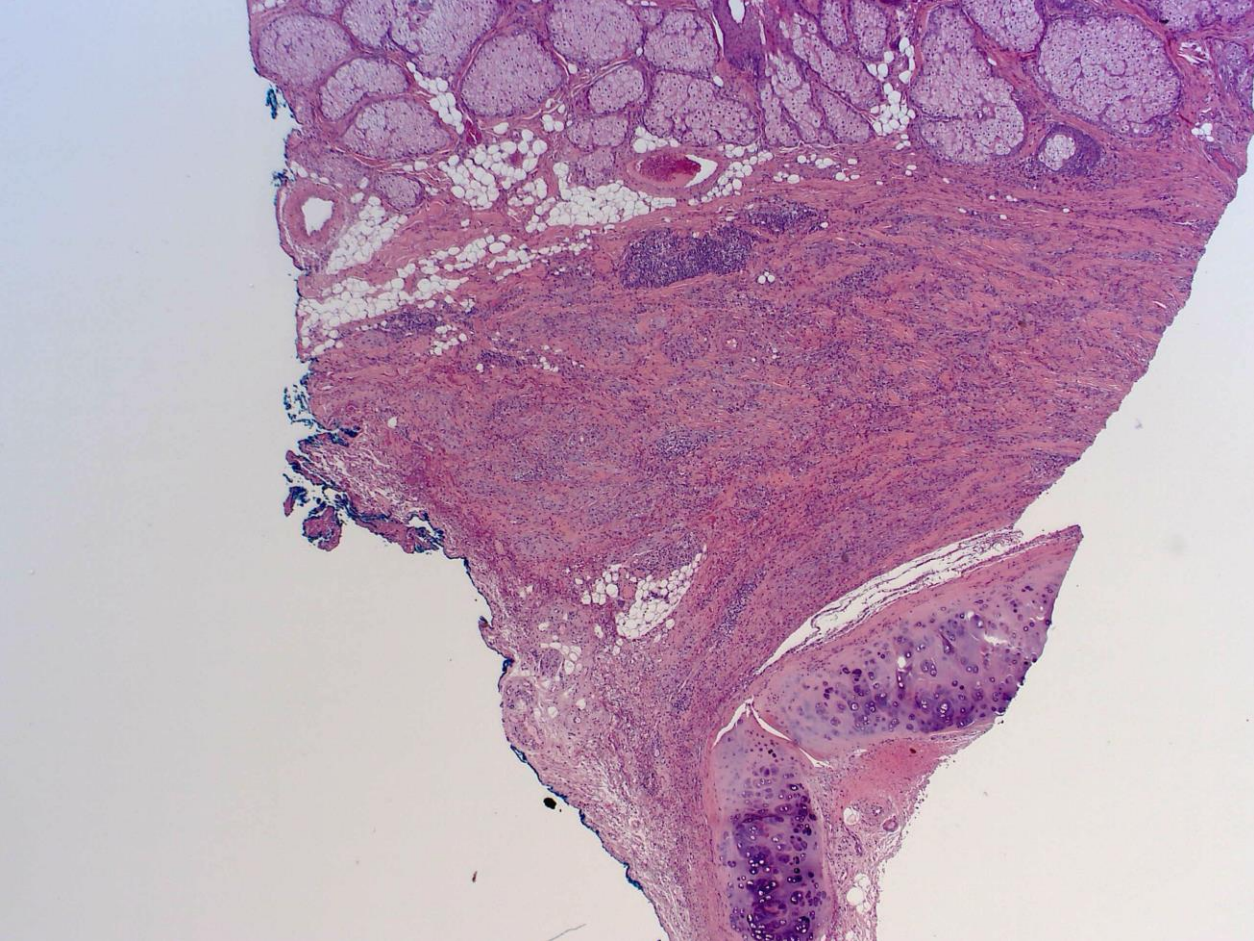


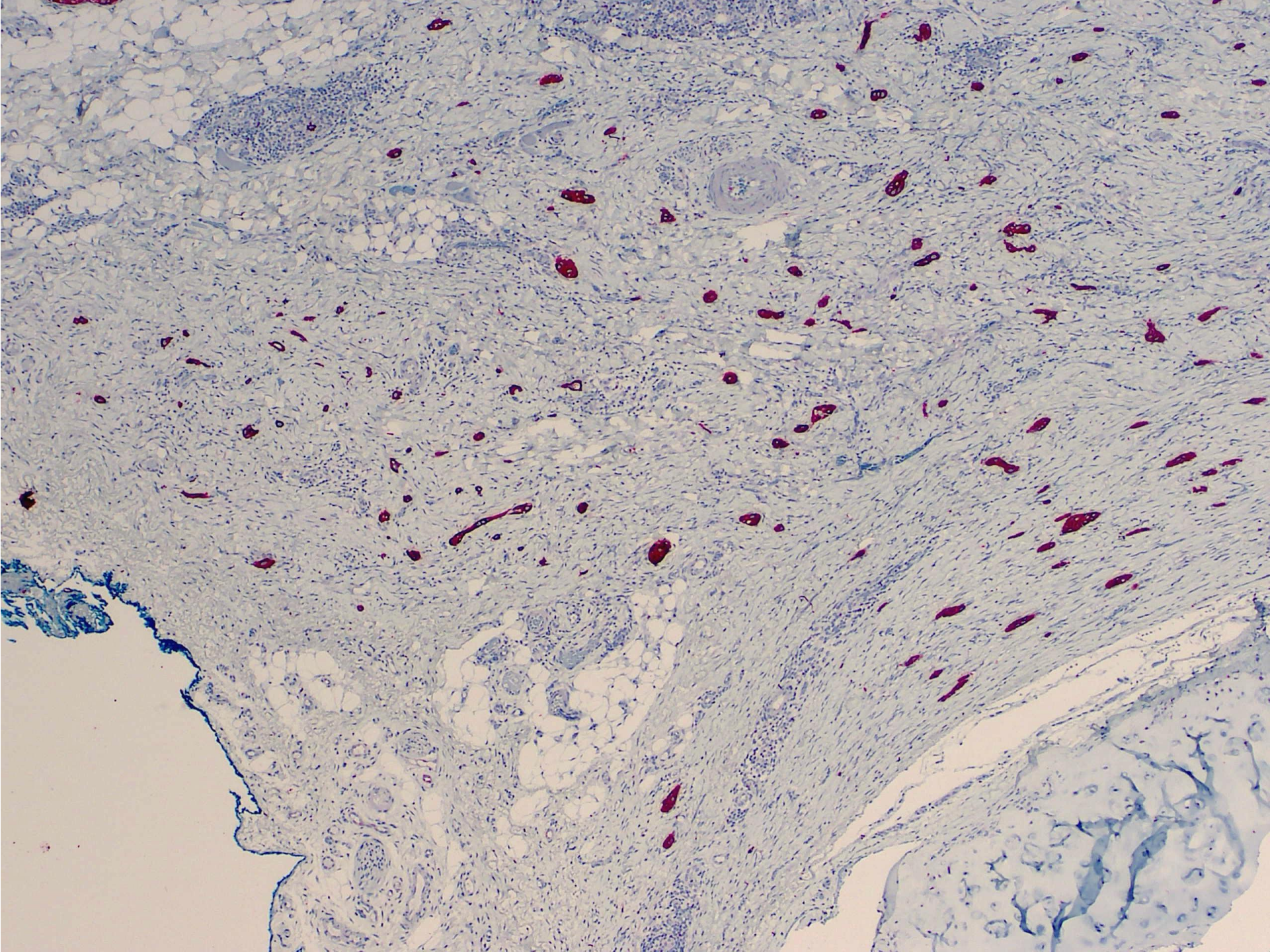




- P16 typically negative or patchwork, no PBS
- RB1 positive
 - More staining in Bowenoid AK
 - (unpublished data)







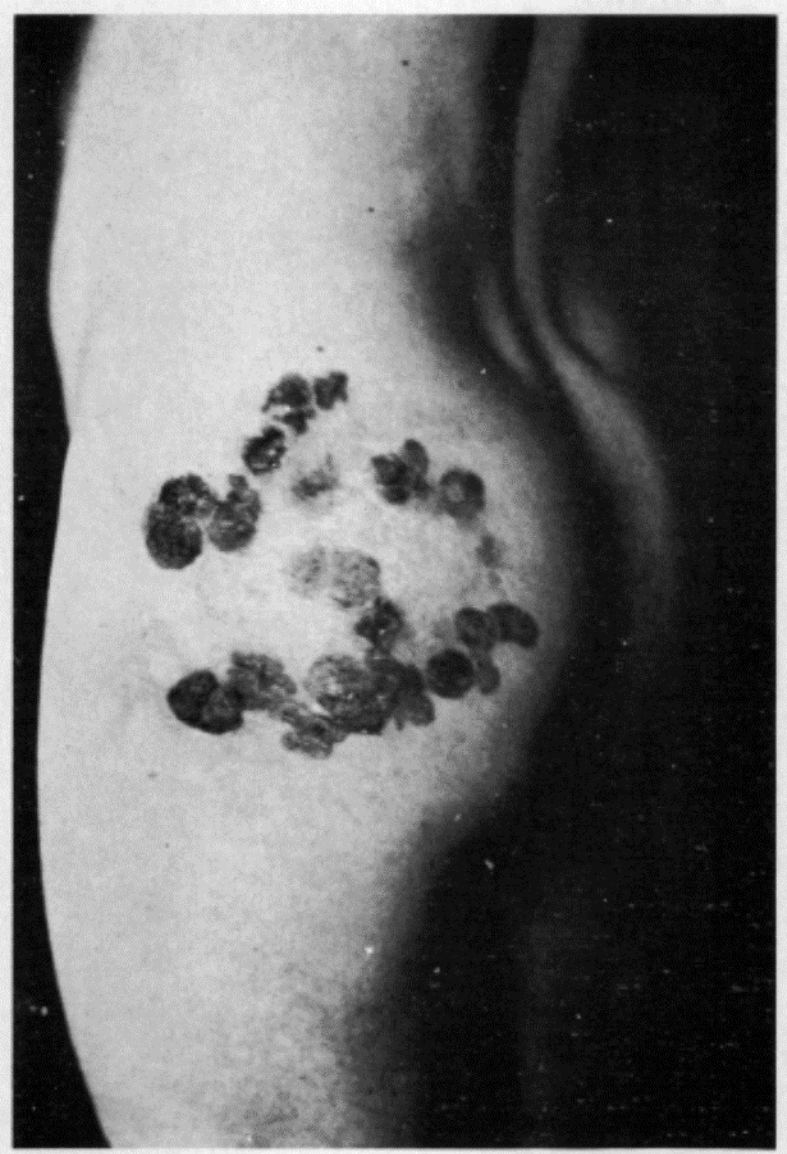
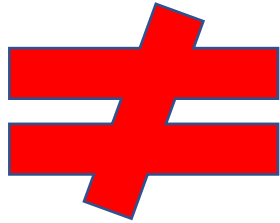
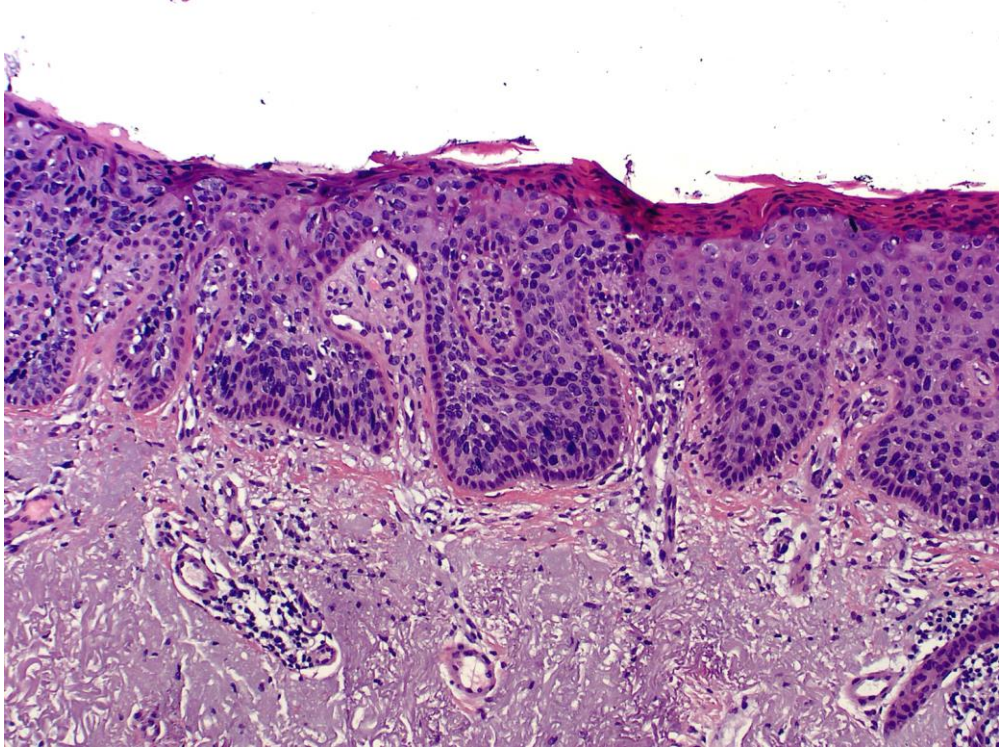


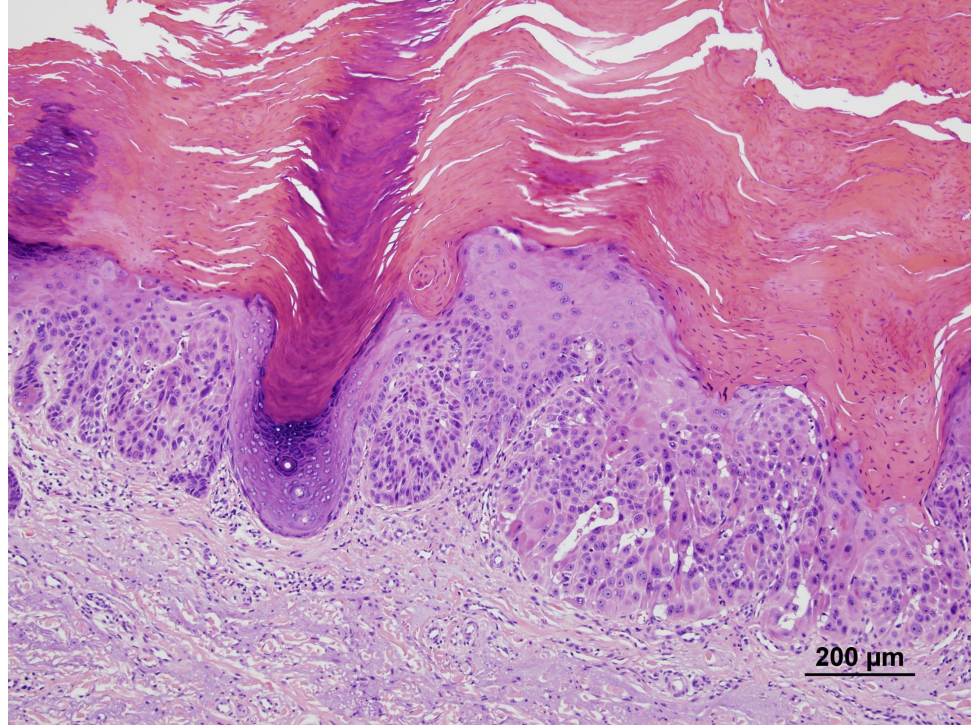
Fig. 1. Case 1.

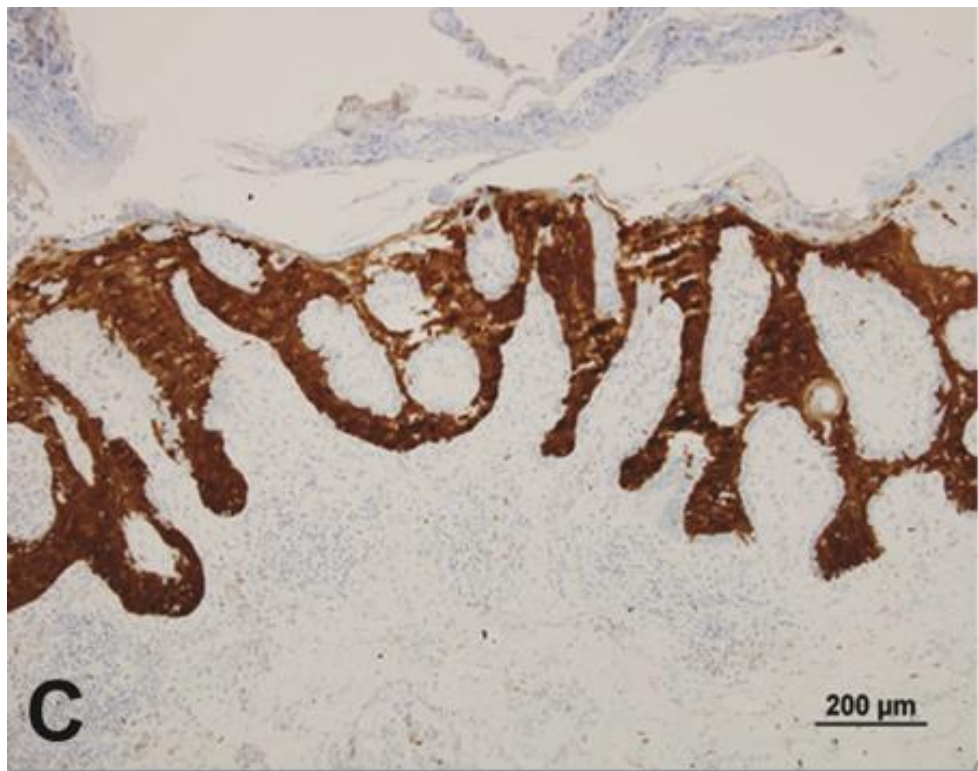
Precancerous Dermatoses.



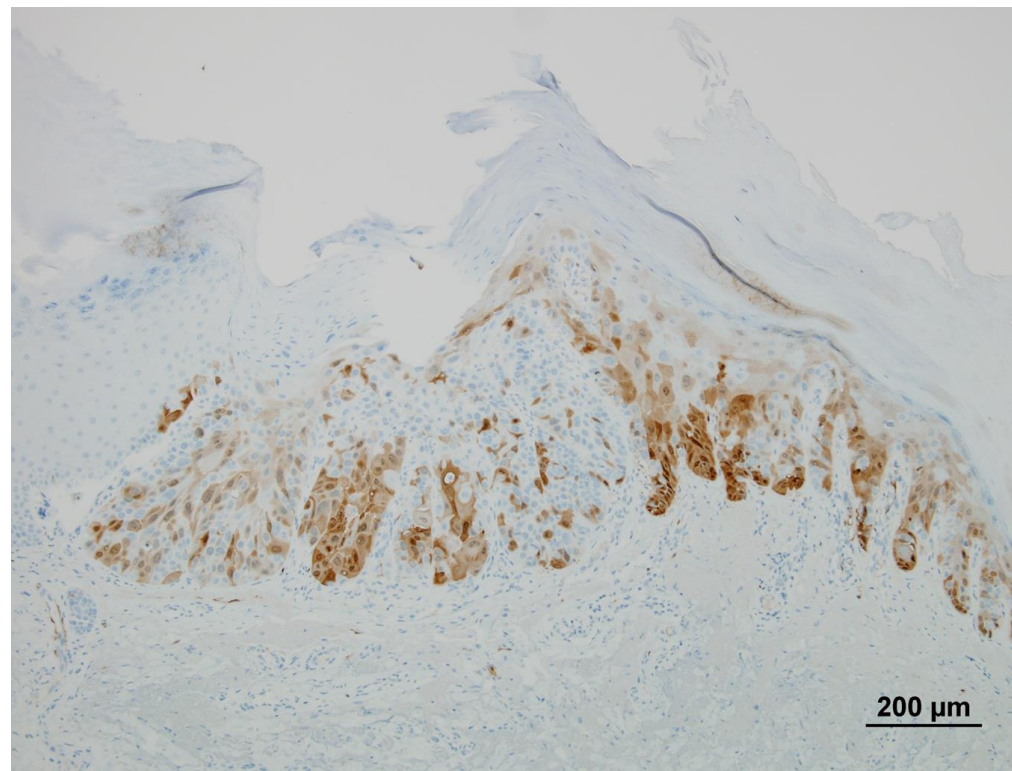


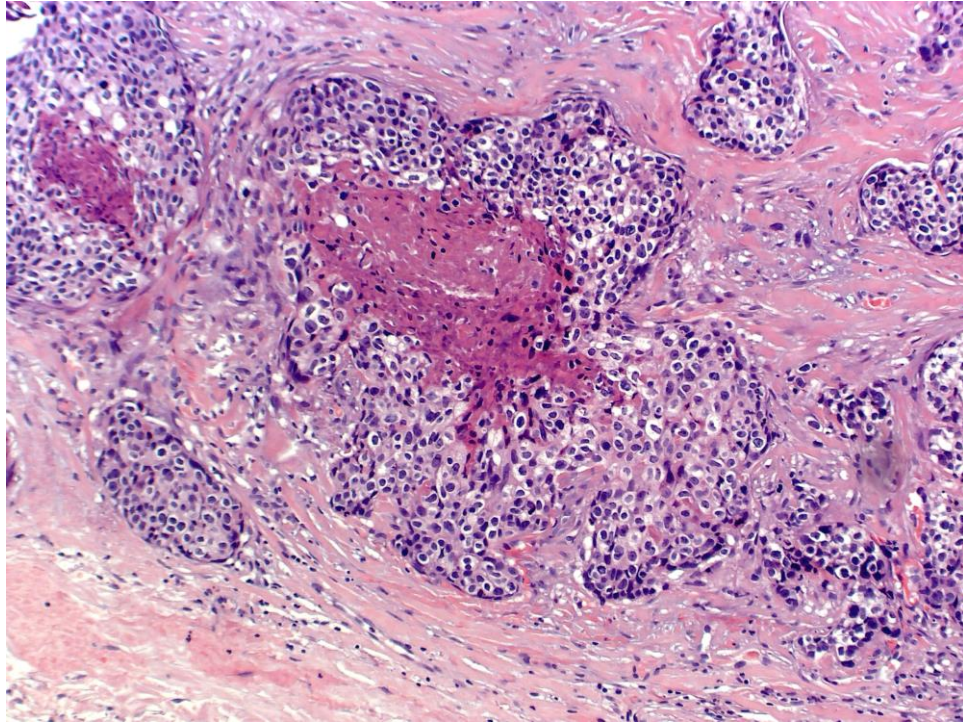
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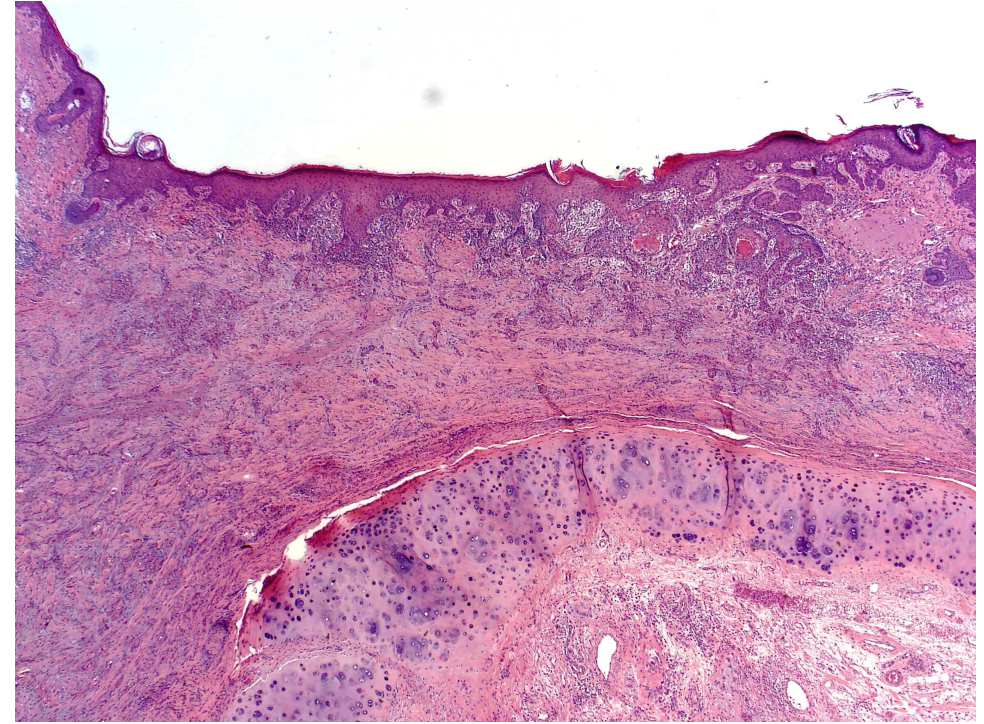


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“Poorly differentiated invasive squamous cell carcinoma”



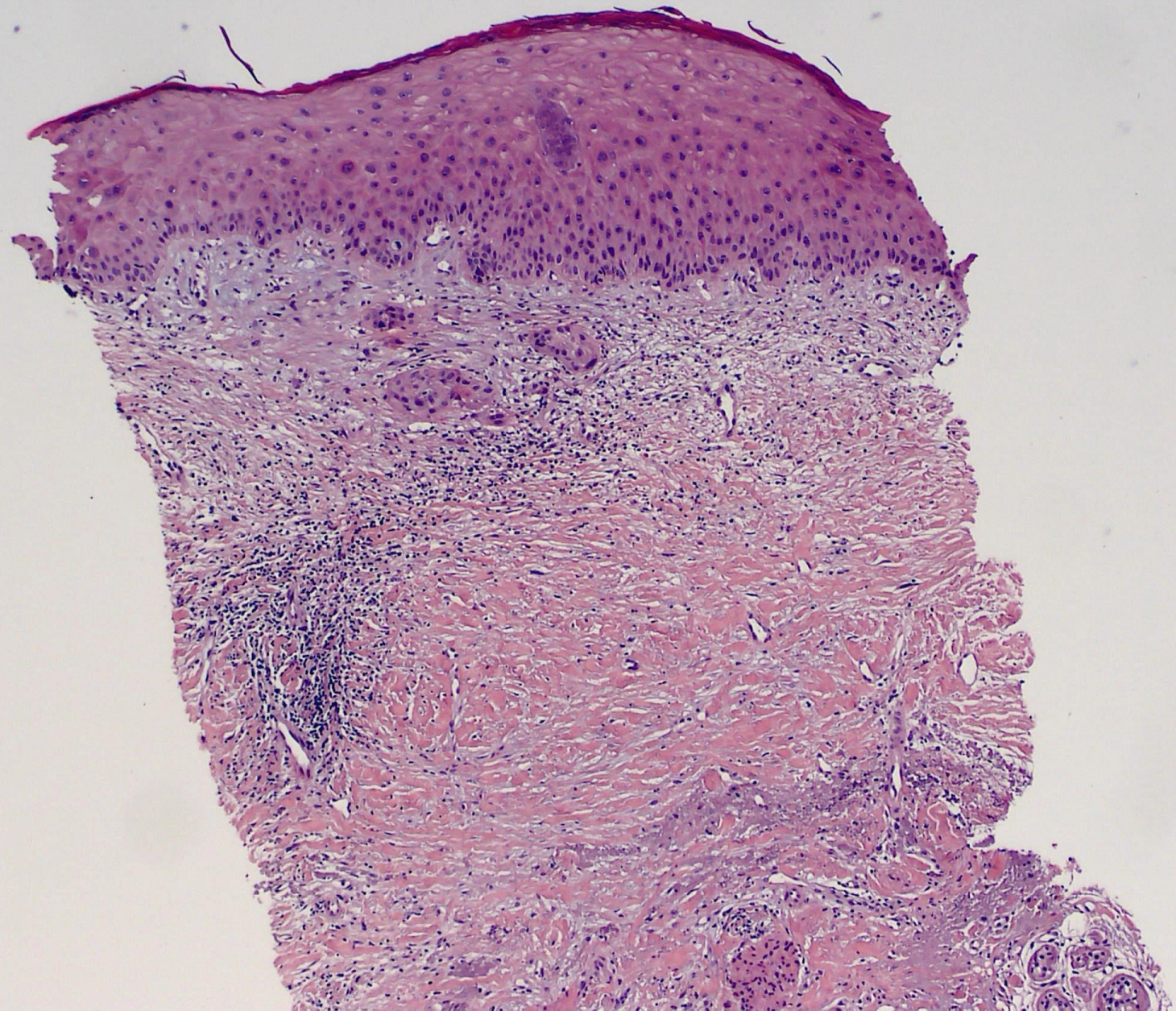
“Poorly differentiated invasive squamous cell carcinoma”

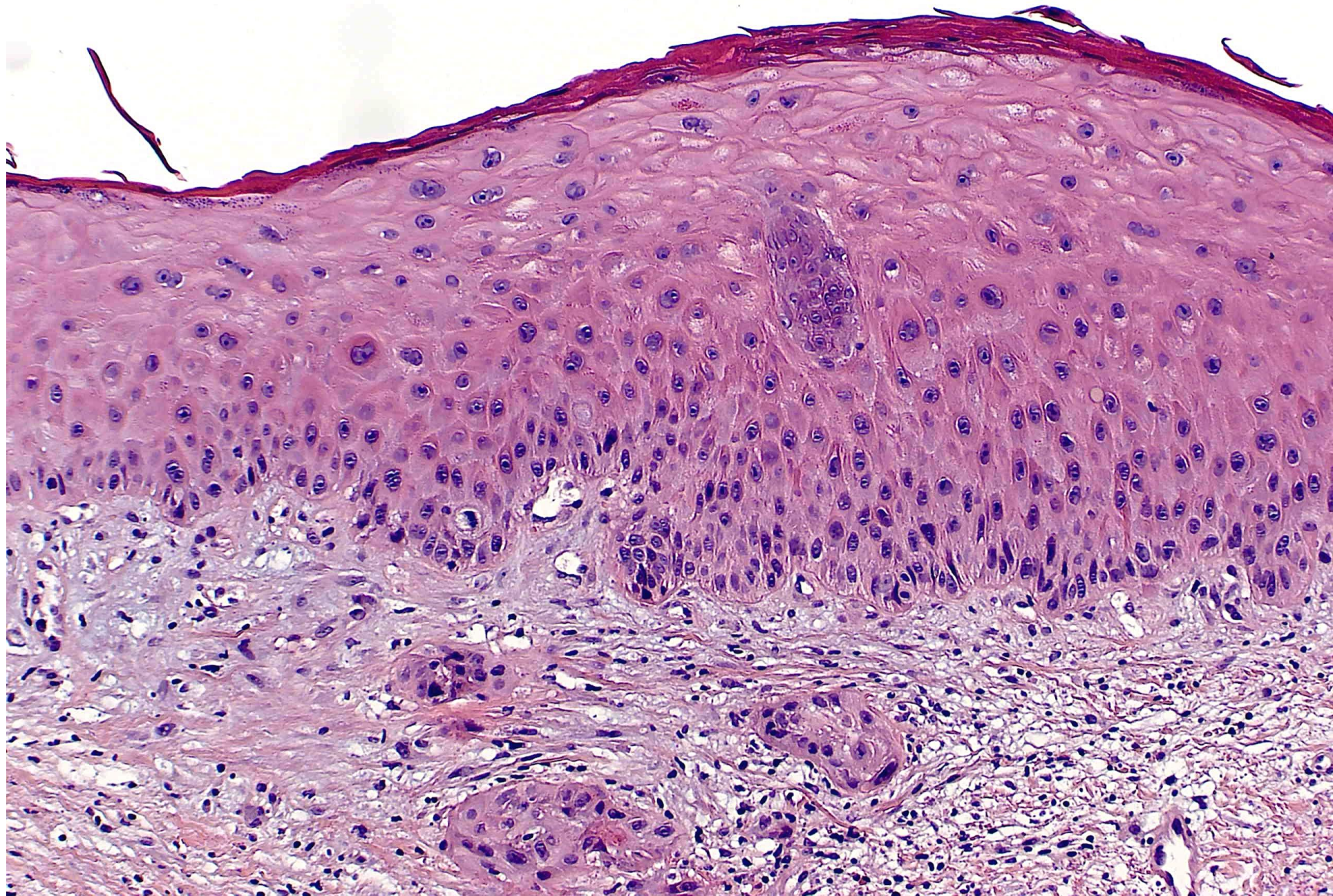
Cutaneous Differentiated SCCIS ??

Well described in
genital skin

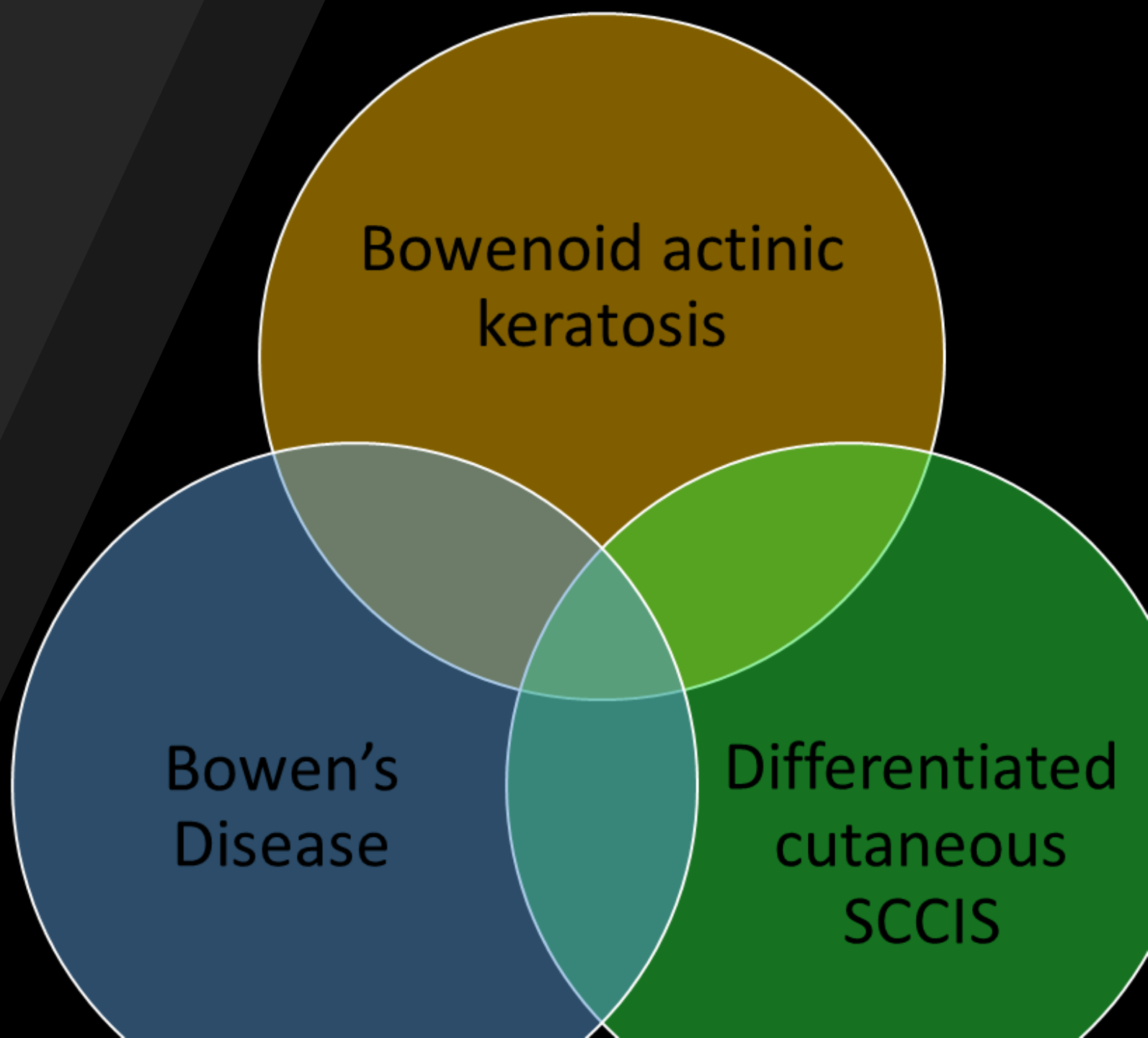
Reproducibility
extremely
challenging

Similar lesions
frequently seen on
extremities,
especially legs





A challenge
for the future



Summary

- Atypical Fibroxanthoma/PDS
- Melanoma “overdiagnosis”
- Squamous dysplasia



Acknowledgements

- Case contributors
- PathWest Dermatopathology:
 - Nathan Harvey, Nima Mesbah Ardakani, Tamazin Leecy, Jean Iacobelli, Lydia Ng, Ben Ryan, Joe Kattampallil
- Clinipath Dermatopathology:
 - Trevor Beer, Gordon Harloe, Stephen Lee, Daniel Ching, Bryan Elston
- Drs Blake O'Brien and Tim Khamu for stimulating melanocytic discussions