BEYOND DERMATOFIBROMA: A CONTEMPORARY UPDATE OF CUTANEOUS MESENCHYMAL TUMORS

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“Fibrohistiocytic”

- Concept established 60 years ago
- First applied to pleomorphic sarcomas
- Morphology: composed of fibroblasts and histiocytes
- Tissue culture: ameboid growth and phagocytic properties (“facultative fibroblasts” thought to be histiocytic in origin)
- Also applied to benign and intermediate lesions of skin and superficial soft tissue

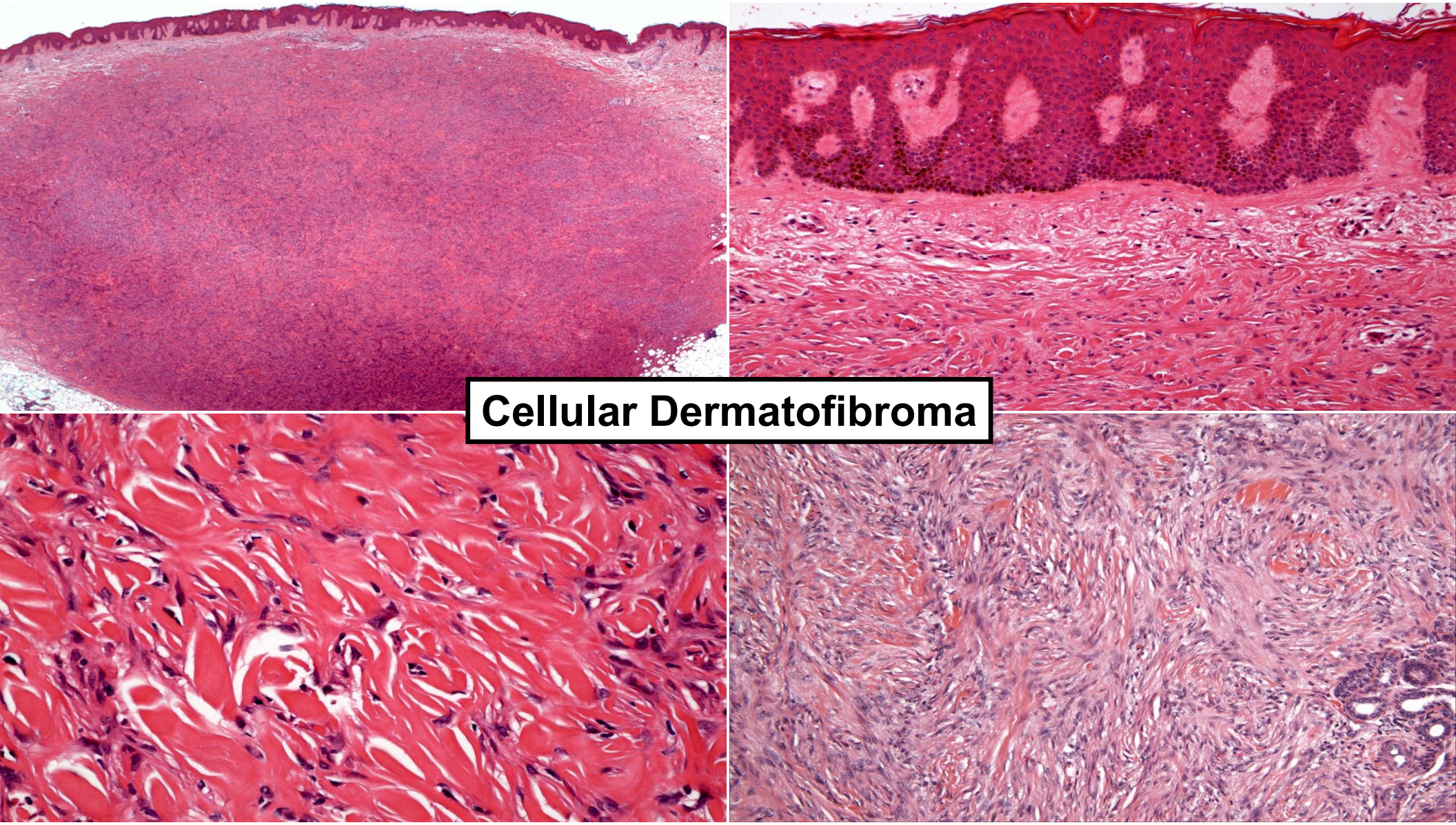
“Fibrous histiocytomas”

- **Neither benign nor malignant lesions derived from histiocytes**
- **Fibroblastic/myofibroblastic differentiation**
- **“MFH” (malignant fibrous histiocytoma) can be subclassified into distinct sarcoma types – prognostic significance**
- **Dermatofibroma is more appropriate designation than fibrous histiocytoma (sorry, soft tissue pathology!)**

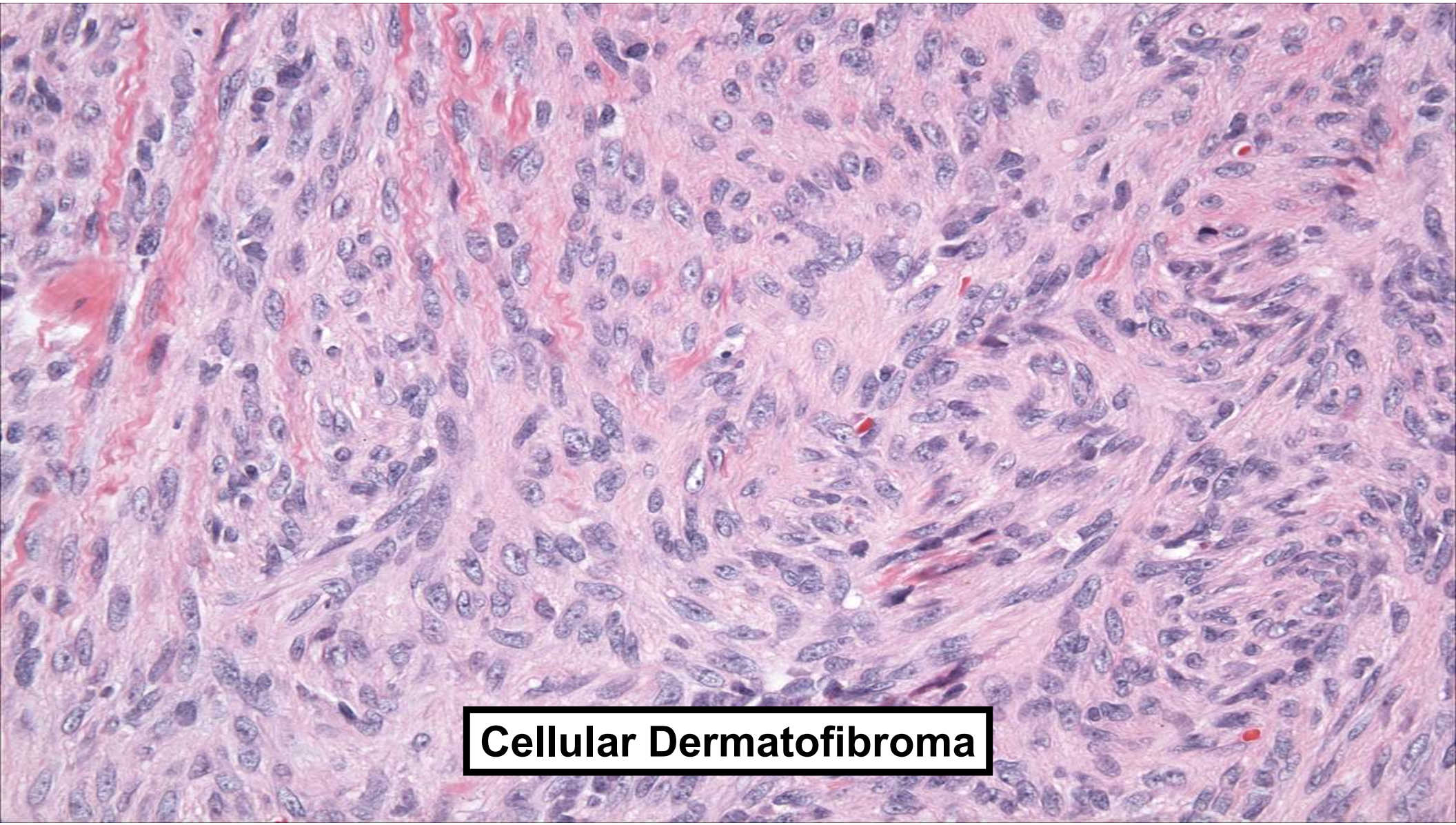
Dermatofibroma and variants

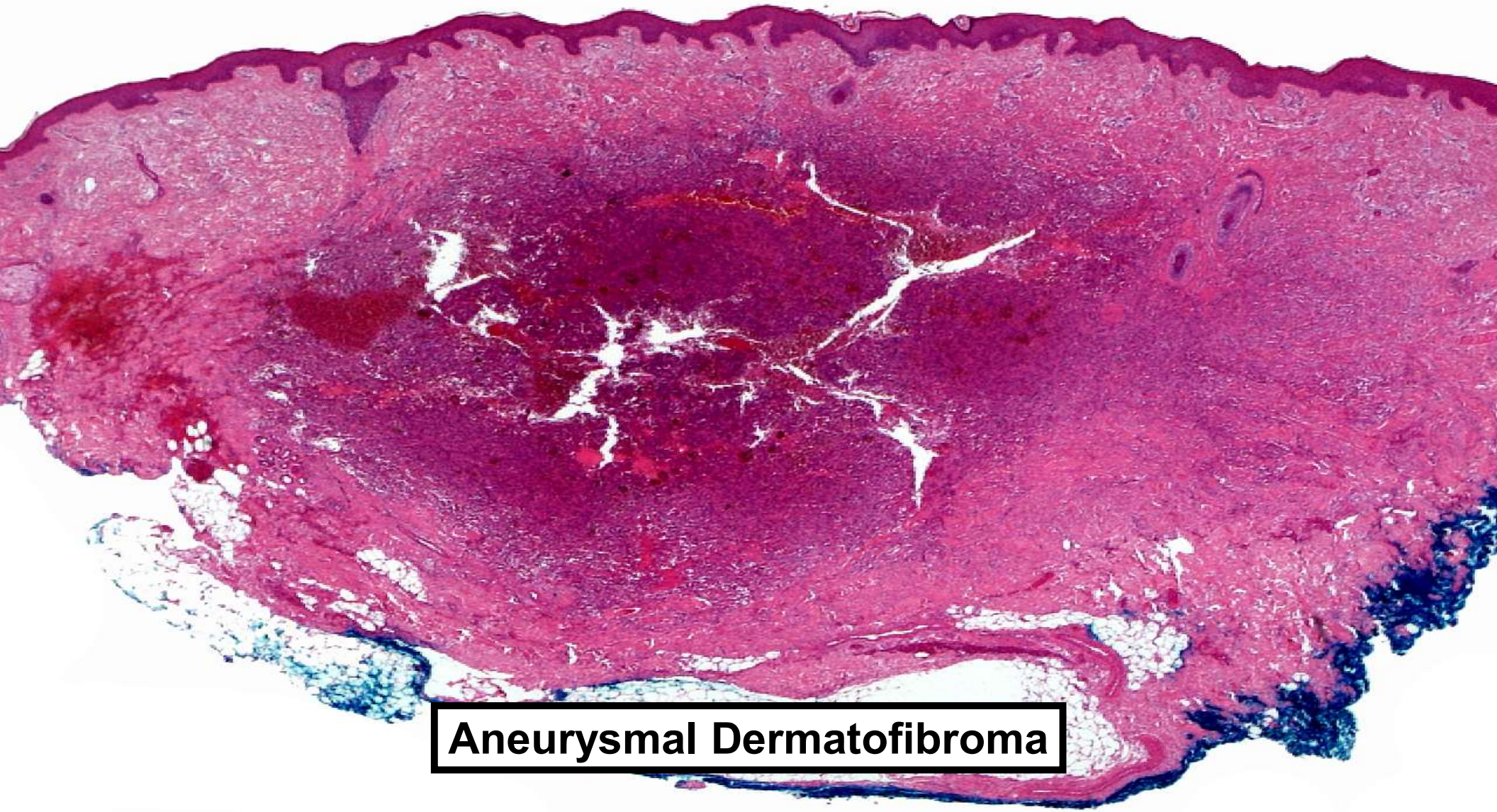
- Peak in young to middle-aged adults
- Predilection for trunk and extremities
- Differences in recurrence rates:

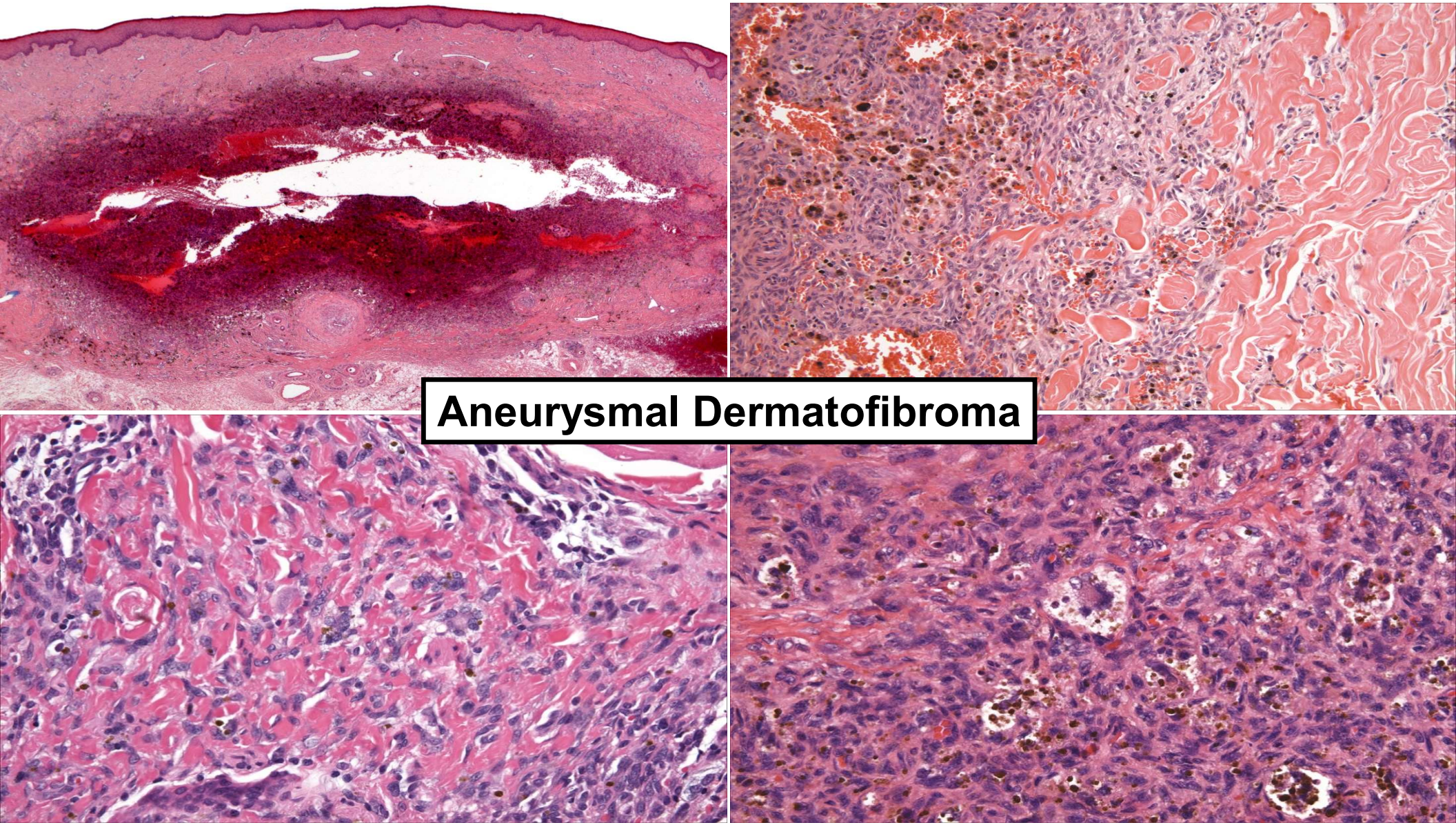
Variant	Recurrence
Common DF	<5%
Cellular	20%
Aneurysmal	20%
Atypical	20%

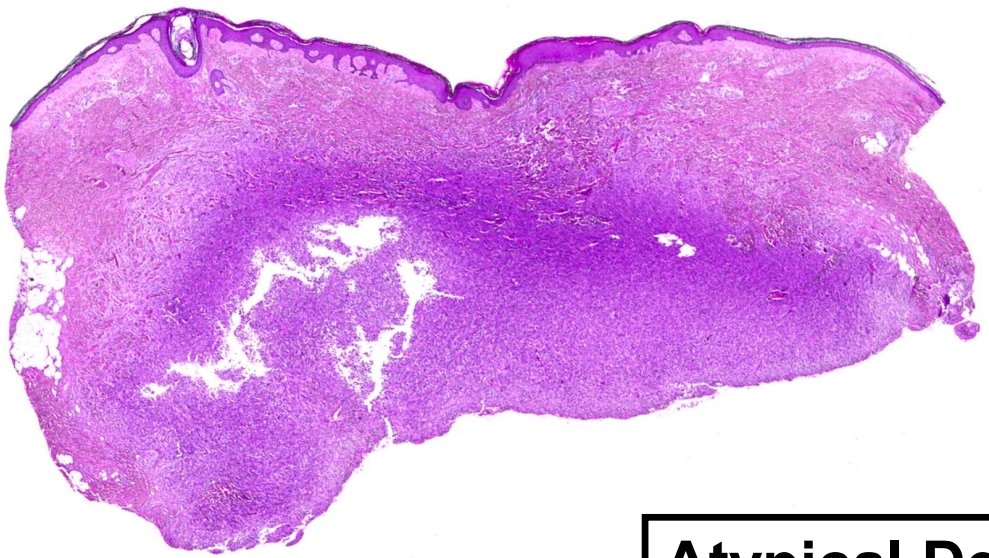


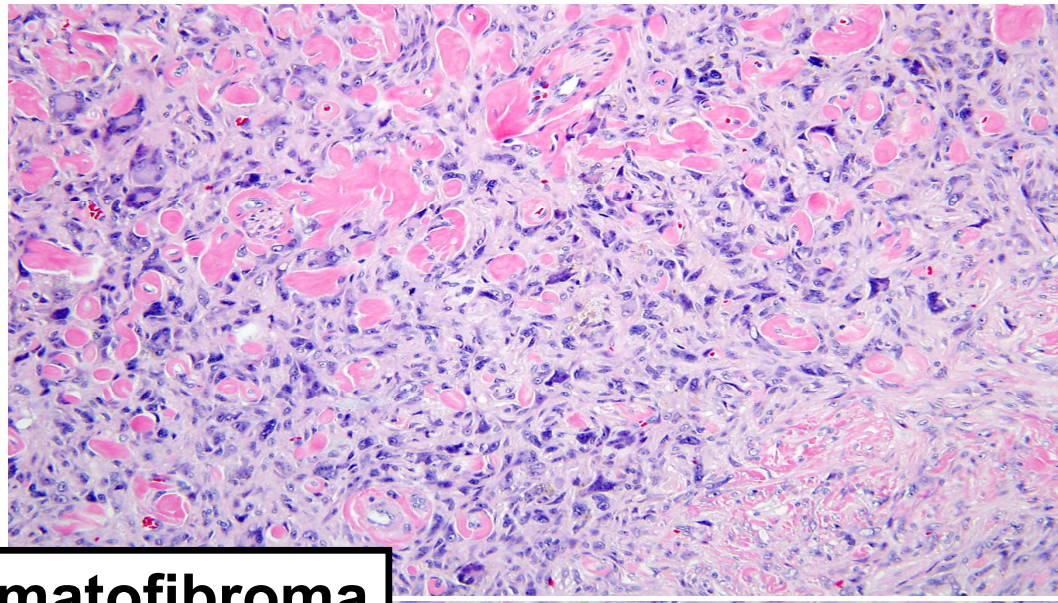
Cellular Dermatofibroma


Cellular Dermatofibroma

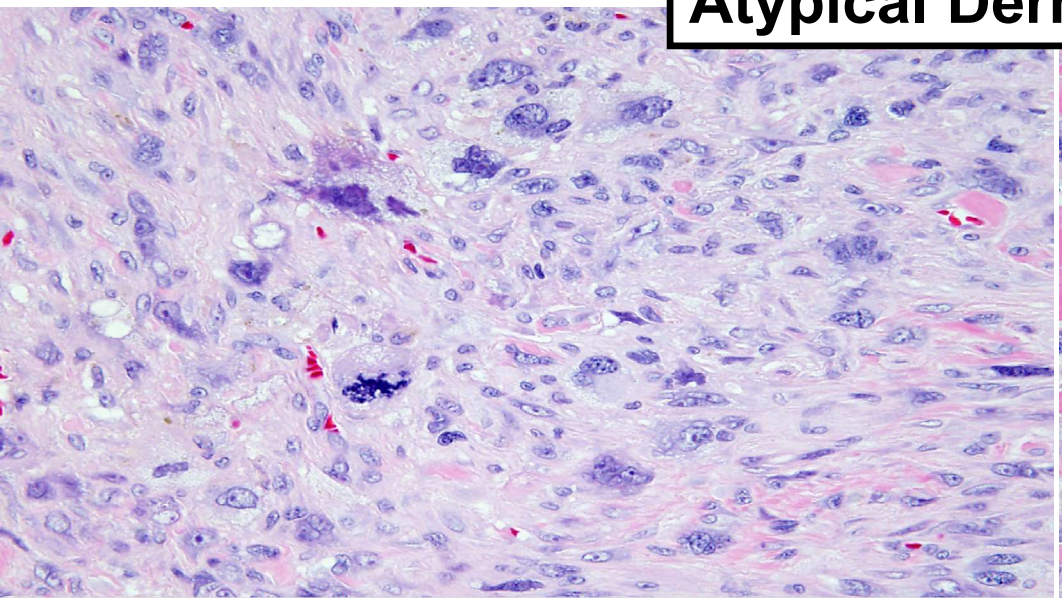

Aneurysmal Dermatofibroma

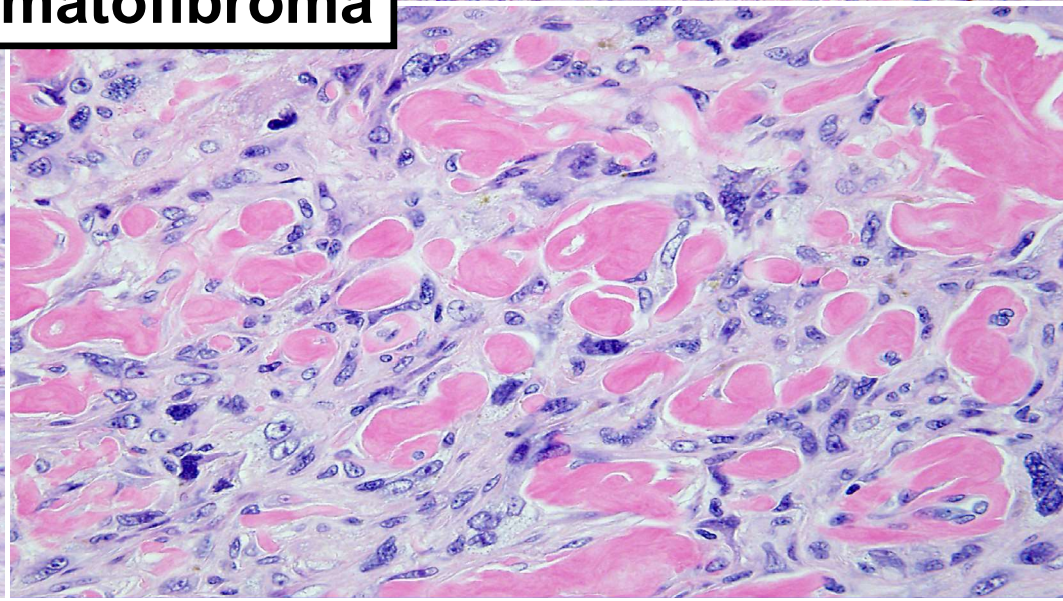

Aneurysmal Dermatofibroma





Atypical Dermatofibroma





Immunohistochemistry

Marker	Positive
SMA (multifocal)	95%
Desmin (focal)	32%
CD34 (focal)	6%

Factor XIIIa positive in surrounding dermal fibroblasts ("dendrocytes"), less often in tumor cells!

Desmin and CD34 positivity in cellular fibrous histiocytoma: an immunohistochemical analysis of 100 cases

Journal of Cutaneous Pathology

Elgida R. Volpicelli and Christopher D. M. Fletcher

Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

The International Journal of Biochemistry & Cell Biology 53 (2014) 475–481

Contents lists available at ScienceDirect

The International Journal of Biochemistry & Cell Biology

journal homepage: www.elsevier.com/locate/biocel

Fusions involving protein kinase C and membrane-associated proteins in benign fibrous histiocytoma☆

Anna Płaszczyca[a], Jenny Nilsson[a], Linda Magnusson[a], Otte Brosjö[b], Olle Larsson[c], Fredrik Vult von Steyern[d], Henryk A. Domanski[e], Henrik Lilljebjörn[a], Thoas Fioretos[a], Johnbosco Tayebwa[a], Nils Mandahl[a], Karolin H. Nord[a], Fredrik Mertens[a,*]

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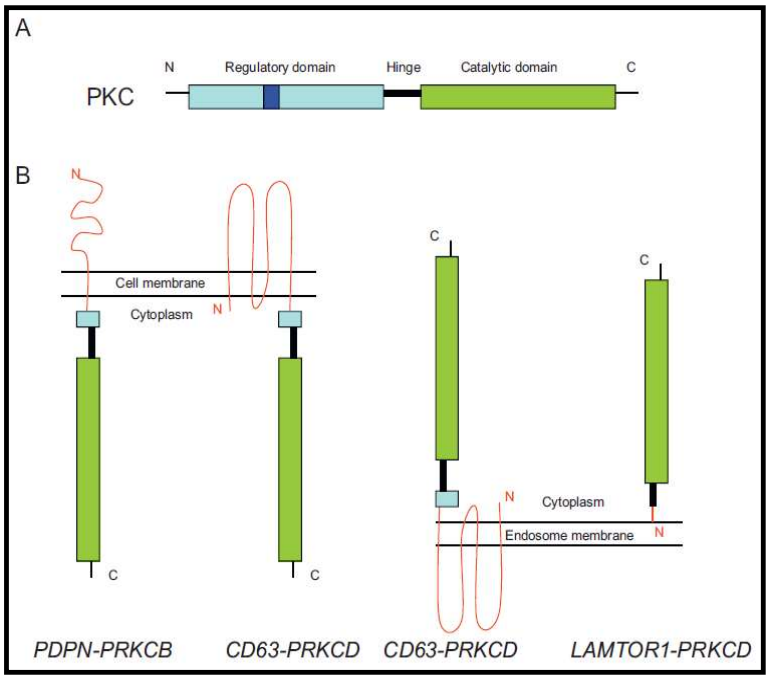
[e] *Department of Pathology, University and Regional Laboratories, Lund University, SE-221 85 Lund, Sweden*

Protein Kinase C Fusions in Dermatofibromas



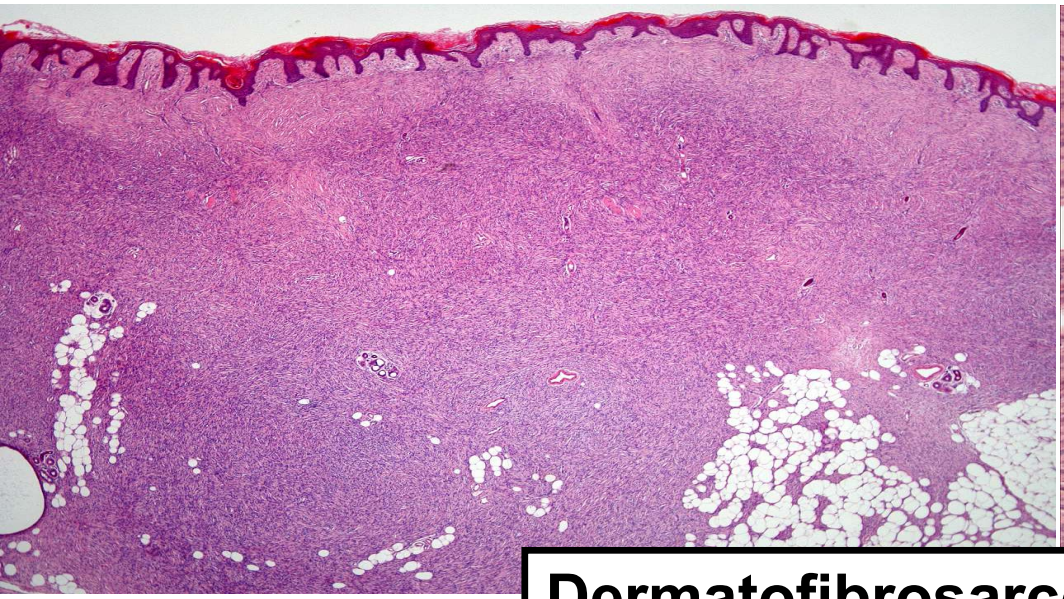
Protein kinase C isoform	Fusion partner
PRKCA	*KIRREL*
PRKCB	*PDPN*
PRKCD	*CD63*
PRKCD	*LAMTOR1*

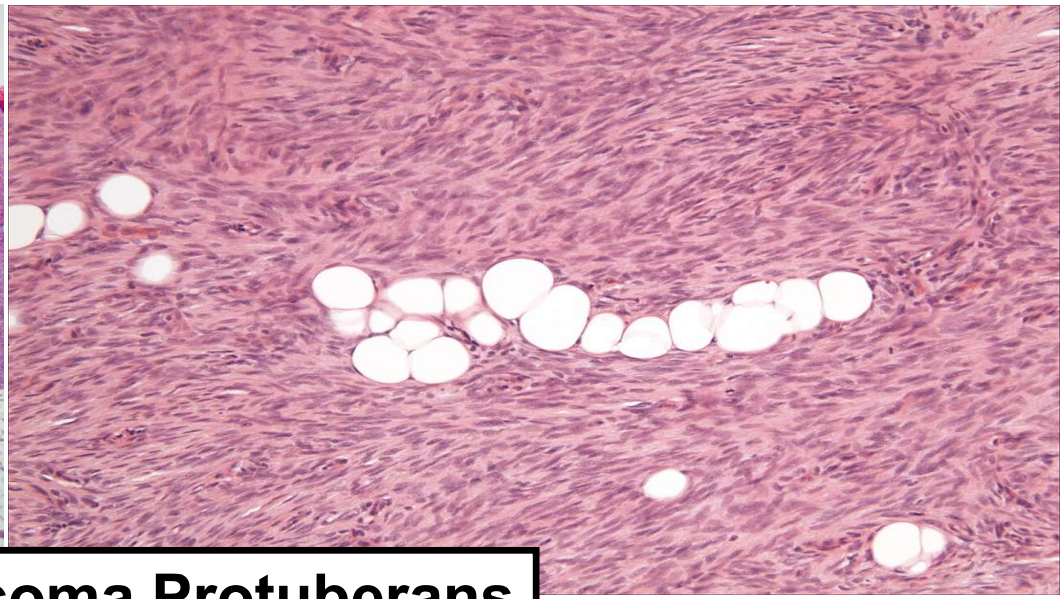
Gene fusions only found in minority of cases

Walther et al. *Lab Invest* 2015

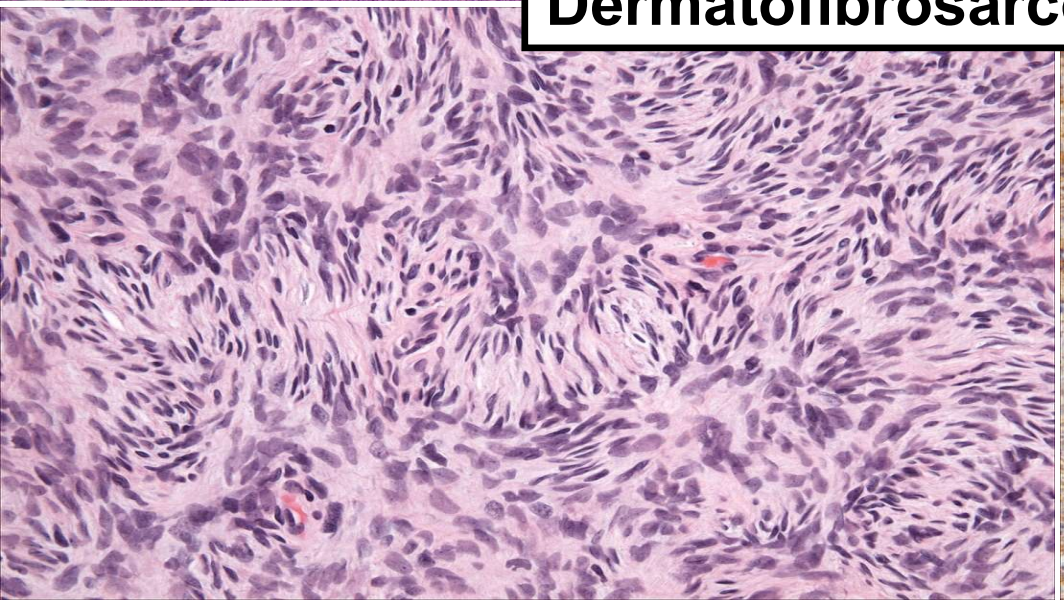
Płaszczyca et al. *Int J Biochem Cell Biol* 2014

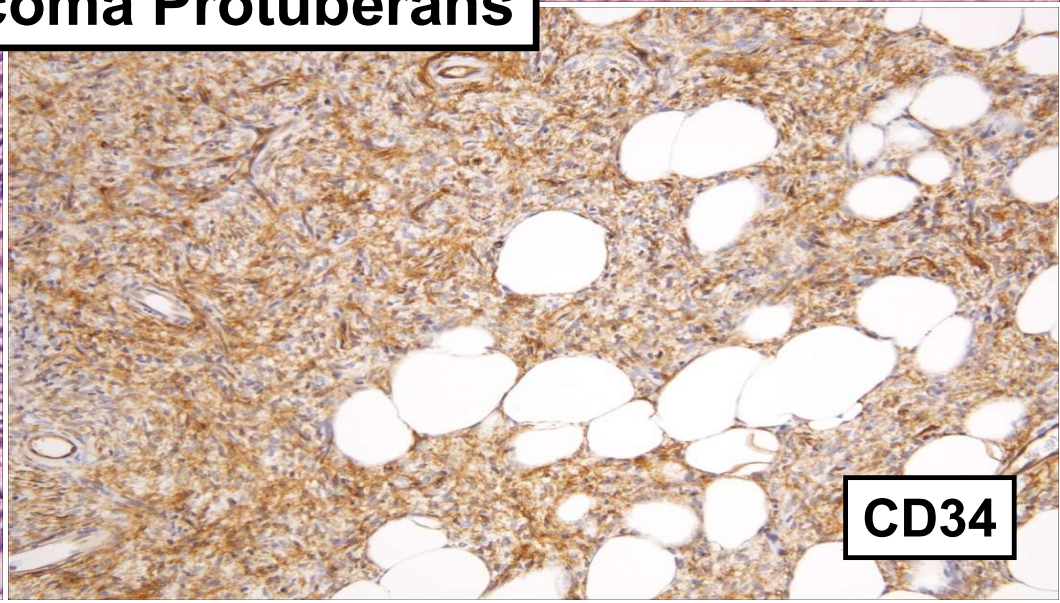
Dermatofibrosarcoma protuberans





Dermatofibrosarcoma Protuberans





Cellular Dermatofibroma	DFSP
Epidermal hyperplasia	None
Lateral hyaline collagen entrapment	Diffuse infiltration
Mixed fascicular and storiform pattern	Tight storiform pattern
Pale eosinophilic cytoplasm	Minimal cytoplasm
Superficial fat entrapment	Diffuse infiltration of fat
CD34 usually negative	CD34 positive
SMA patchy positive	SMA negative

Fibrosarcomatous DFSP

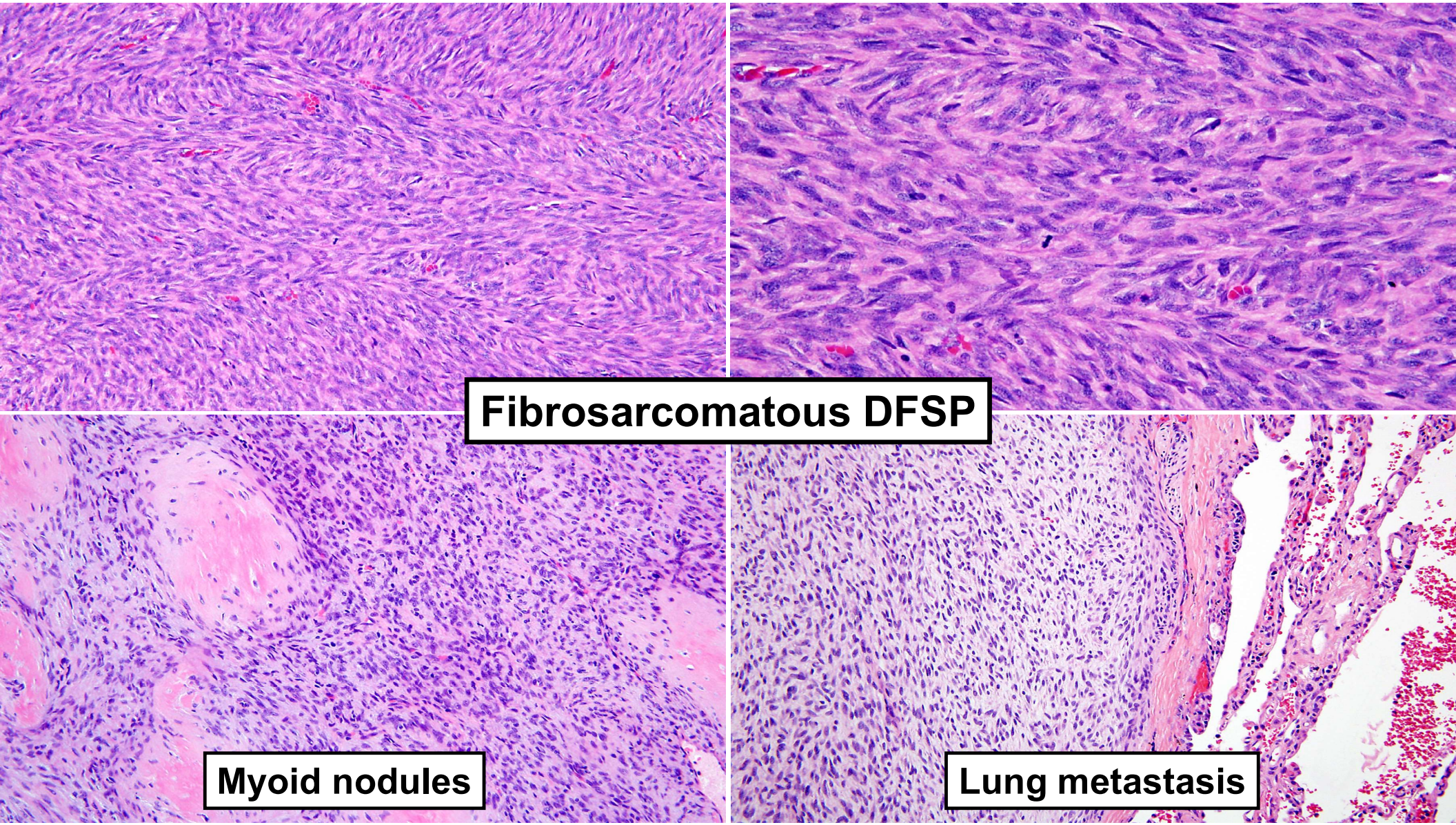
- Progression from storiform DFSP to fascicular, fibrosarcoma-like appearance
- Usually vesicular nuclei, increased mitotic activity
- Often loses expression of CD34
- Acquires 10-15% risk for metastasis (most often to lungs)

Abbott et al. *Am J Surg Pathol* 2006

Goldblum et al. *Am J Surg Pathol* 2000

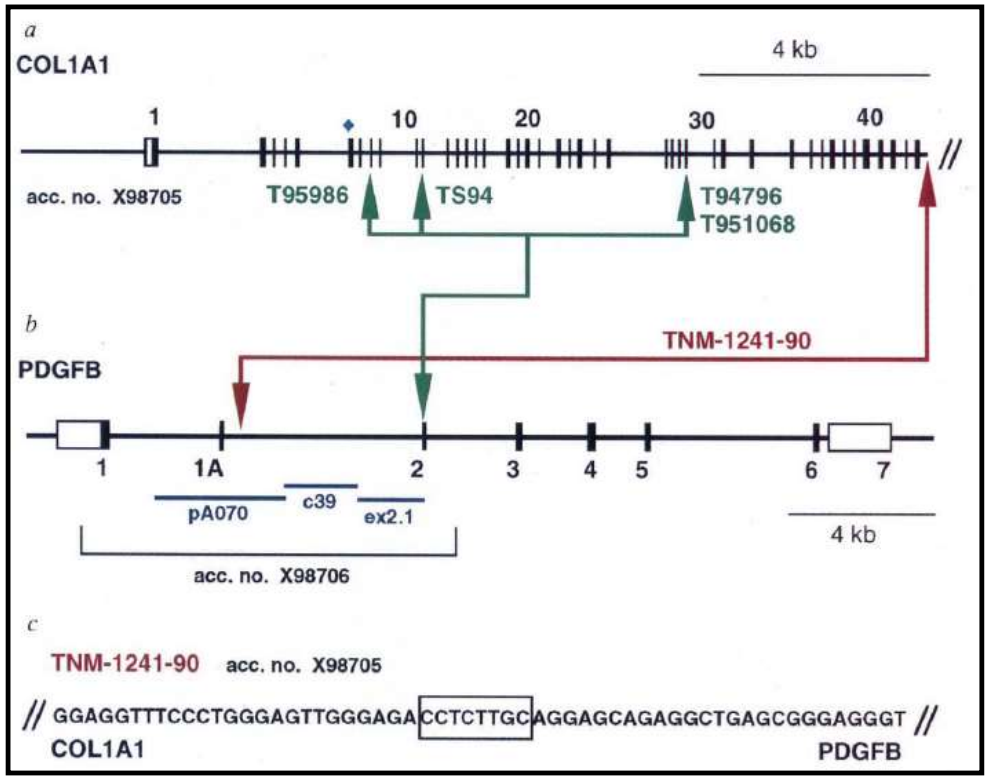
Mentzel et al. *Am J Surg Pathol* 1998

Connelly and Evans *Am J Surg Pathol* 1992


Fibrosarcomatous DFSP
Myoid nodules
Lung metastasis

DFSP Genetics

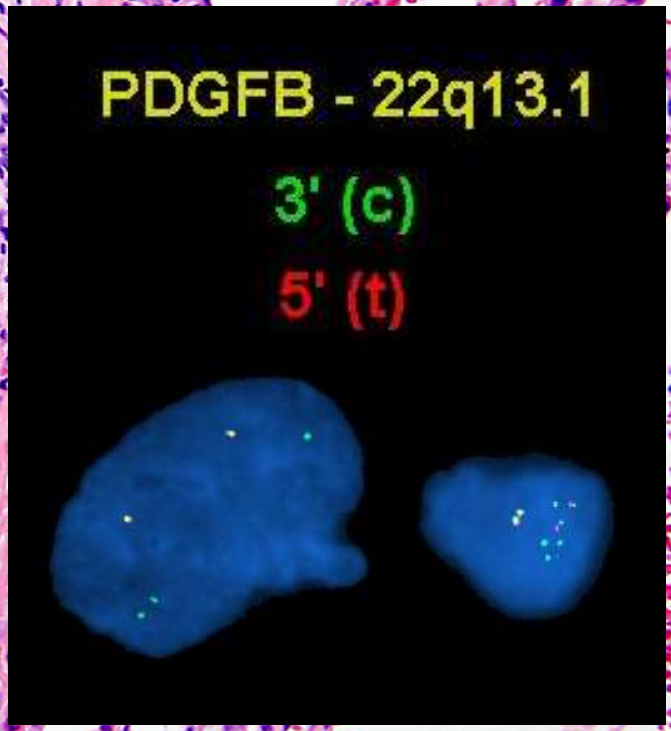
- **Unbalanced translocation**
- **Often ring chromosomes**
- **der(17)(17;22)(q22;q13)**
- ***COL1A1::PDGFB***
- **Strong promoter drives expression of growth factor**
- **FISH for *PDGFB***



Karanian et al. *Mod Pathol* 2015

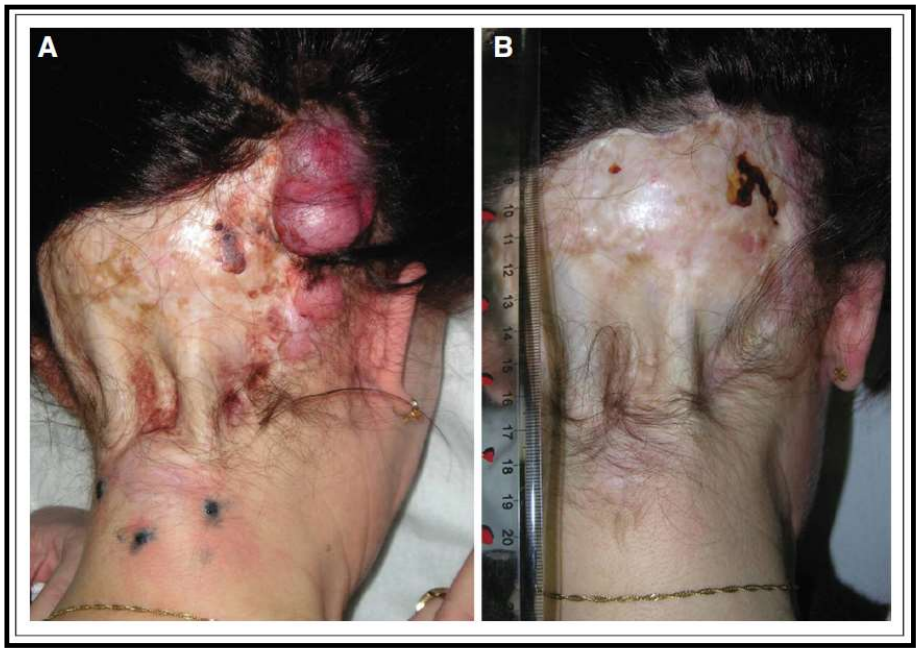
Simon et al. *Nat Genet* 1997

Metastatic Fibrosarcomatous DFSP



DFSP Targeted Therapy

- Imatinib mesylate
- High rate of partial and low rate of complete responses
- Neoadjuvant: “down-stage” prior to surgery
- Shorter responses in with metastatic fibrosarcomatous DFSP



Rutkowski et al. *J Clin Oncol* 2010

Rutkowski et al. *Eur J Surg Oncol* 2017

Stacchioti et al. *Clin Cancer Res* 2016

DFSP More Genetics

- **Small subset of DFSP (4%) negative for *PDGFB* rearrangement by FISH**
- **Until recently, molecular pathogenesis unknown**
- **Around half of these cases (2%) harbor "cryptic" *COL1A1-PDGFB* rearrangement**
- **Other half (2%) harbor novel gene fusions:**

  COL6A3-PDGFD* or *EMILIN2-PDGFD

Dadone-Montaudié et al. *Mod Pathol* 2018

Dickson et al. *Genes Chromosomes Cancer* 2018

Dermatofibrosarcoma protuberans with a novel *COL6A3-PDGFD* fusion gene and apparent predilection for breast

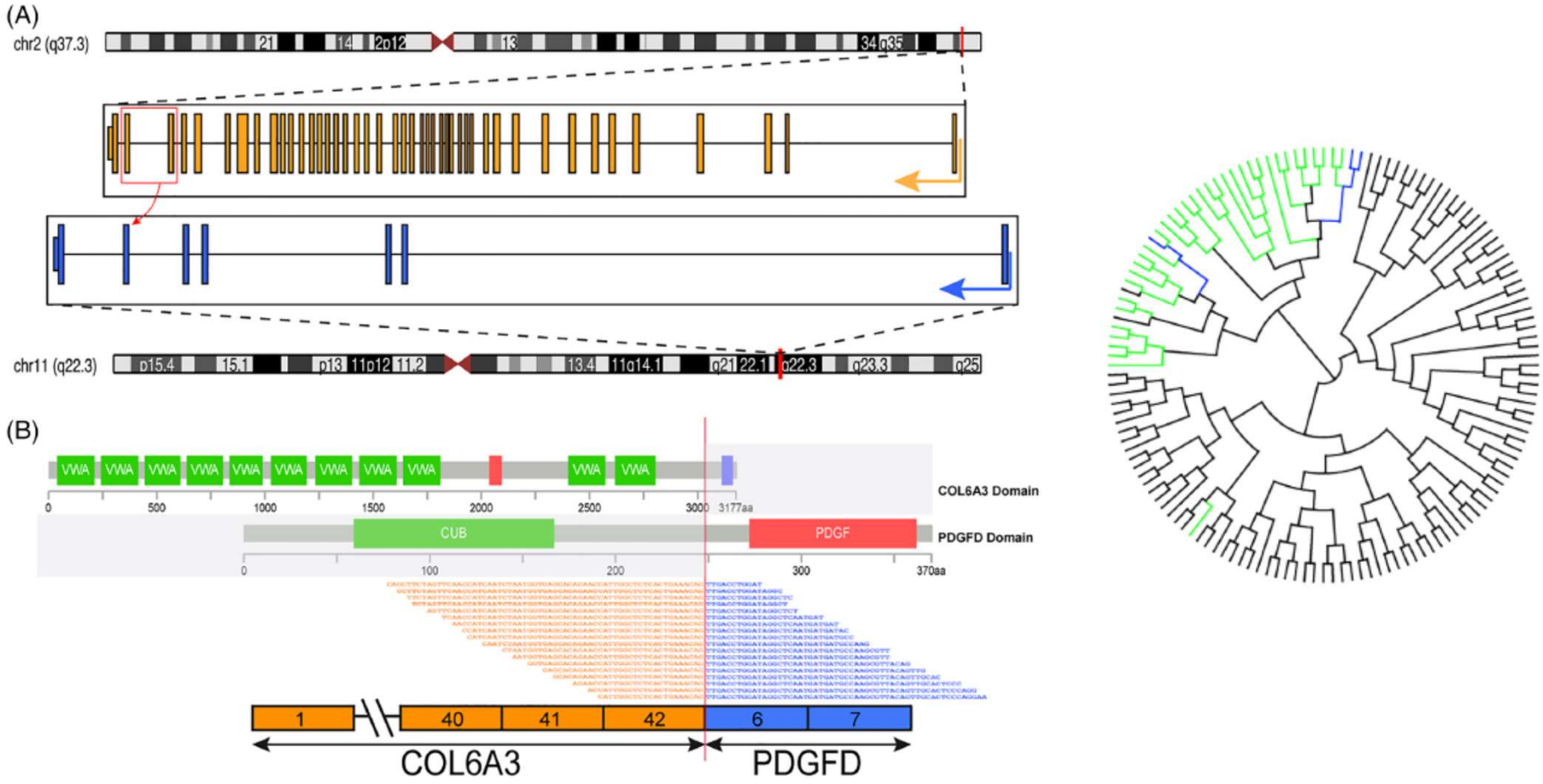
Brendan C. Dickson[1] | Jason L. Hornick[2] | Christopher D. M. Fletcher[2] | Elizabeth G. Demicco[1] | David J. Howarth[1] | David Swanson[1] | Lei Zhang[3] | Yun-Shao Sung[3] | Cristina R. Antonescu[3]

Genes Chromosomes Cancer. 2018;**57**:437–445.

Alternative *PDGFD* rearrangements in dermatofibrosarcomas protuberans without *PDGFB* fusions

Bérengère Dadone-Montaudié[1] · Laurent Alberti[2,3] · Adeline Duc[3] · Lucile Delespaul[4,5,11] · Tom Lesluyes[4,5,11] · Gaëlle Pérot[6] · Agnès Lançon[3] · Sandrine Paindavoine[3] · Ilaria Di Mauro[1] · Jean-Yves Blay[2,7] · Arnaud de la Fouchardière[3] · Frédéric Chibon[4,6,11] · Marie Karanian[3] · Gaëtan MacGrogan[6] · Valérie Kubiniek[1] · Frédérique Keslair[1] · Nathalie Cardot-Leccia[8] · Audrey Michot[9] · Virginie Perrin[10] · Yanis Zekri[10] · Jean-Michel Coindre[5,6] · Franck Tirode[2,10] · Florence Pedeutour[1] · Dominique Ranchère-Vince[3] · François Le Loarer[5,6] · Daniel Pissaloux[2,3]

Modern Pathology (2018) 31:1683–1693



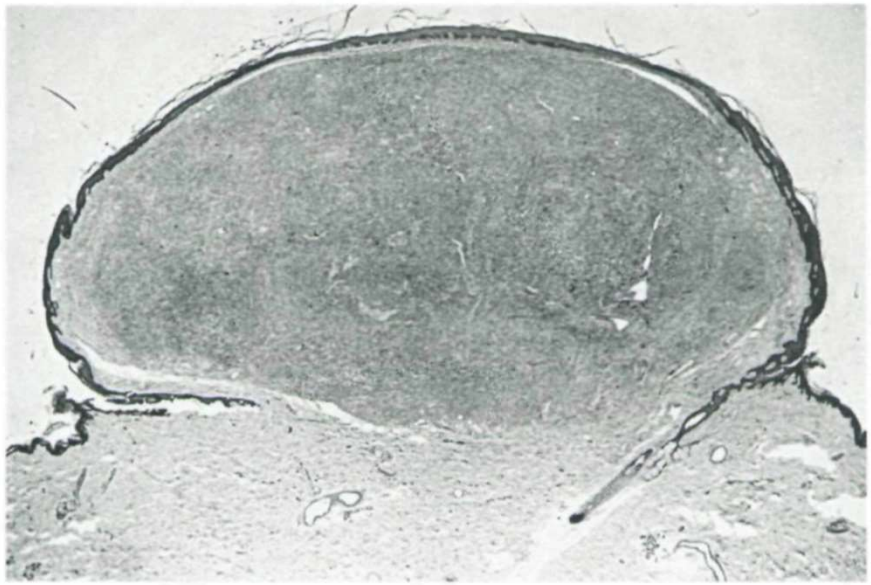
Dickson et al. *Genes Chromosomes Cancer* 2018

Epithelioid cell histiocytoma: a new entity

E.WILSON JONES, R.CERIO AND N.P.SMITH

Institute of Dermatology, United Medical and Dental Schools of Guy's and St. Thomas's Hospitals, St John's Hospital for Diseases of the Skin, London, U.K.

British Journal of Dermatology (1989) **120,** 185–195.



Epithelioid Fibrous Histiocytoma

- Traditionally considered morphologic variant of cutaneous fibrous histiocytoma (dermatofibroma)
- Extremities of young to middle-aged adults
- Exophytic, circumscribed, sometimes with epidermal collarette
- Uniform epithelioid cells, some binucleate
- EMA often positive

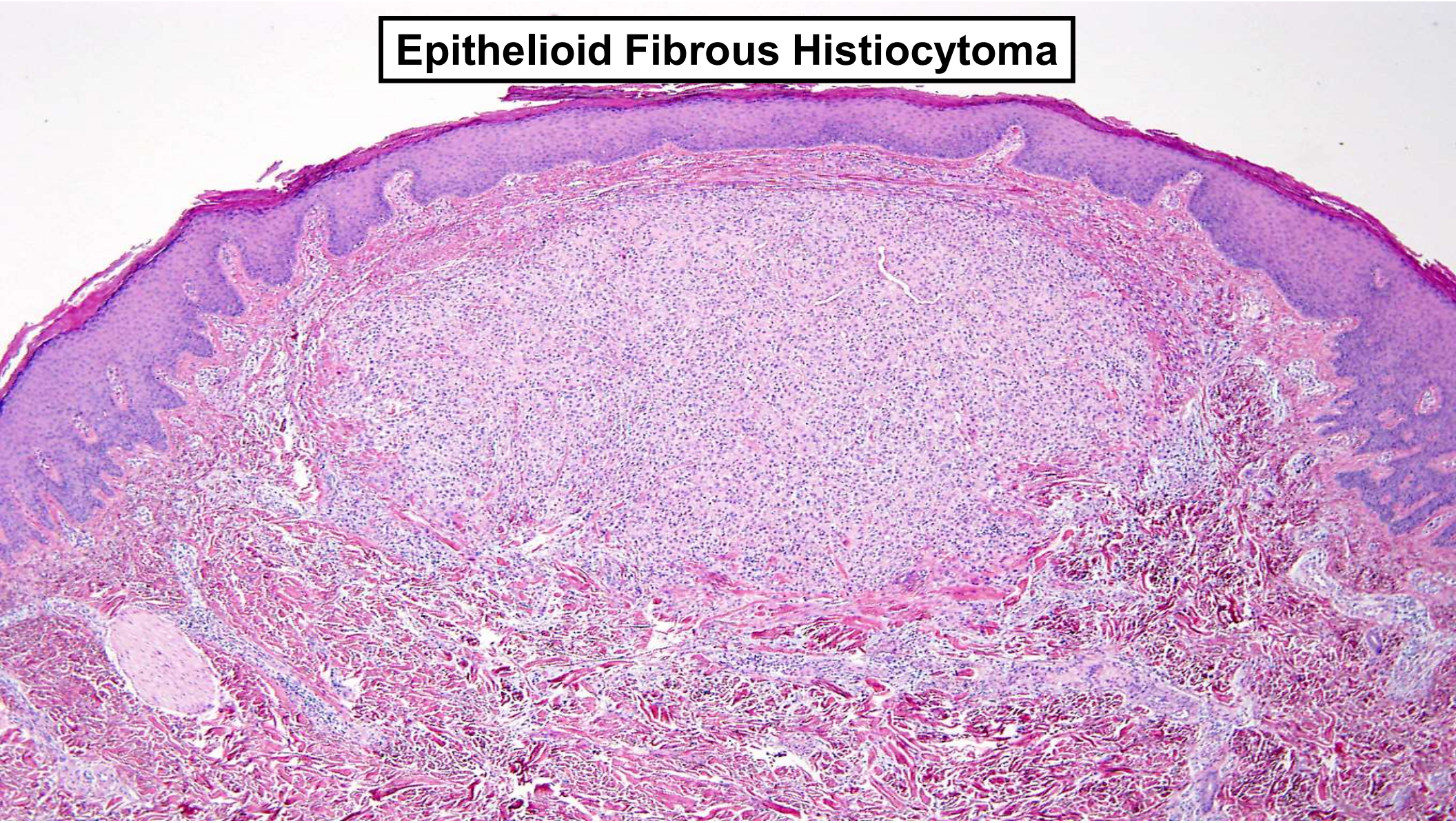
Wilson Jones et al. *Br J Dermatol* 1989

Singh Gomez et al. *Histopathology* 1994

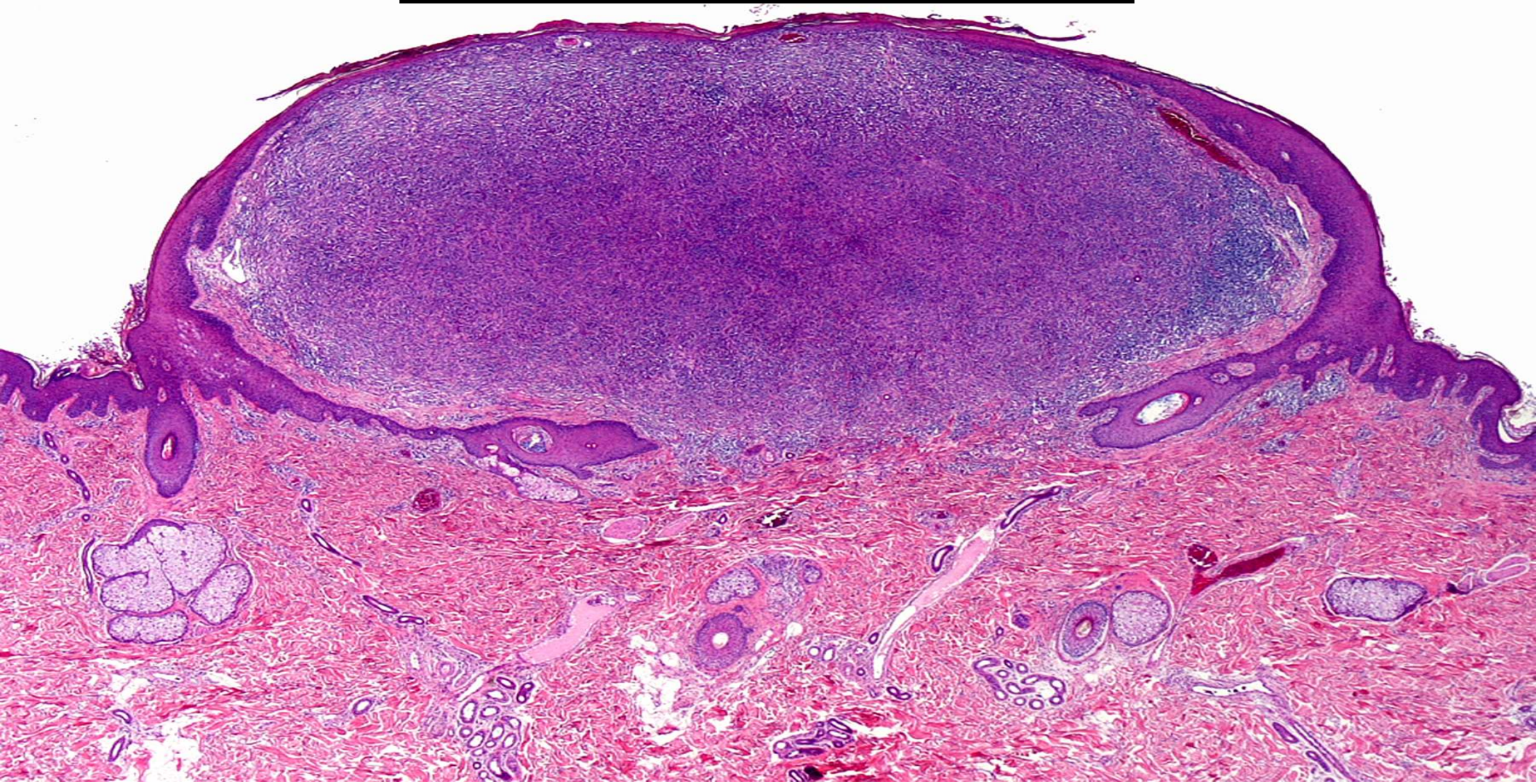
Glusac et al. *Am J Surg Pathol* 1994

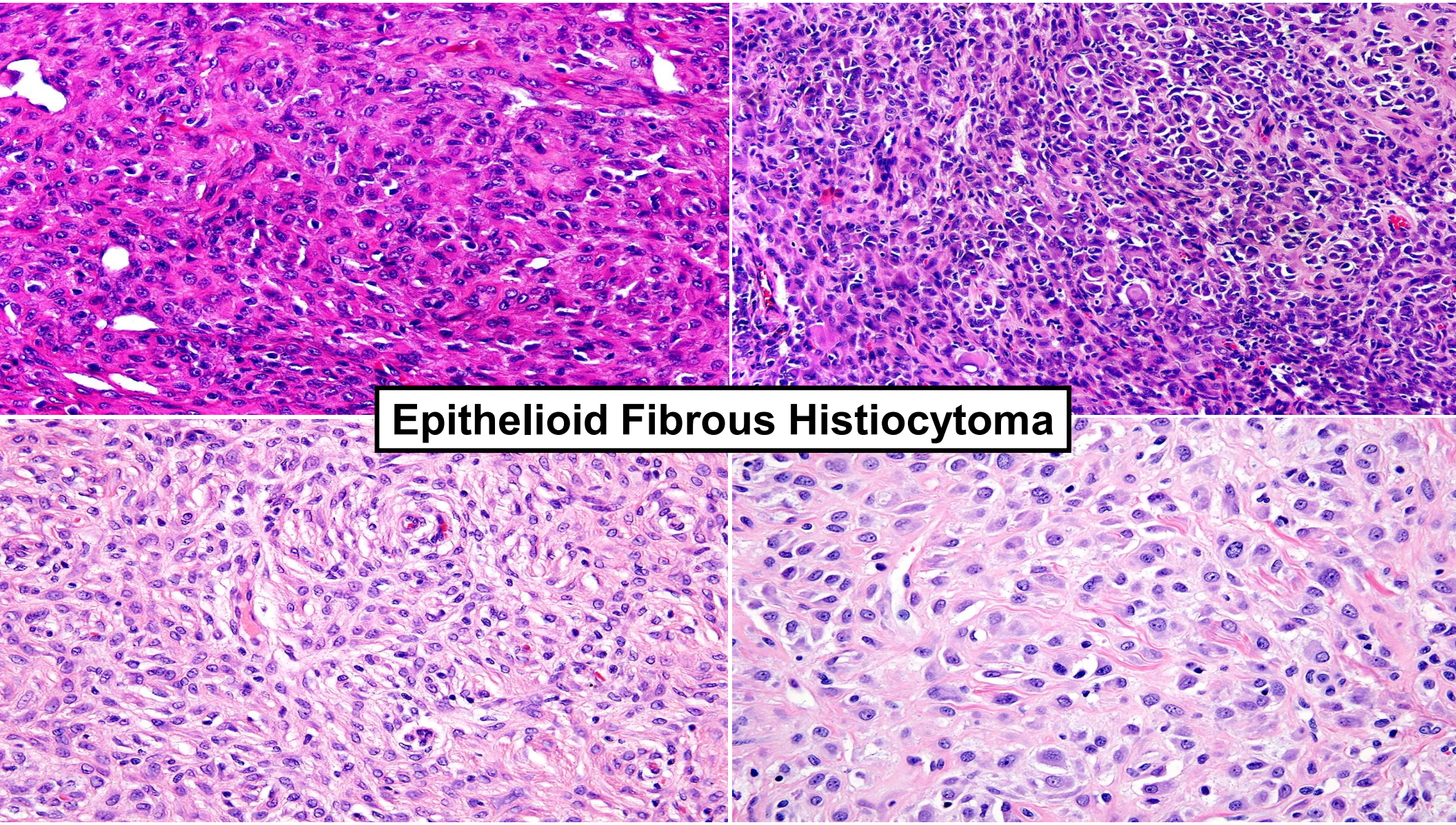
Doyle and Fletcher *J Cutan Pathol* 2011

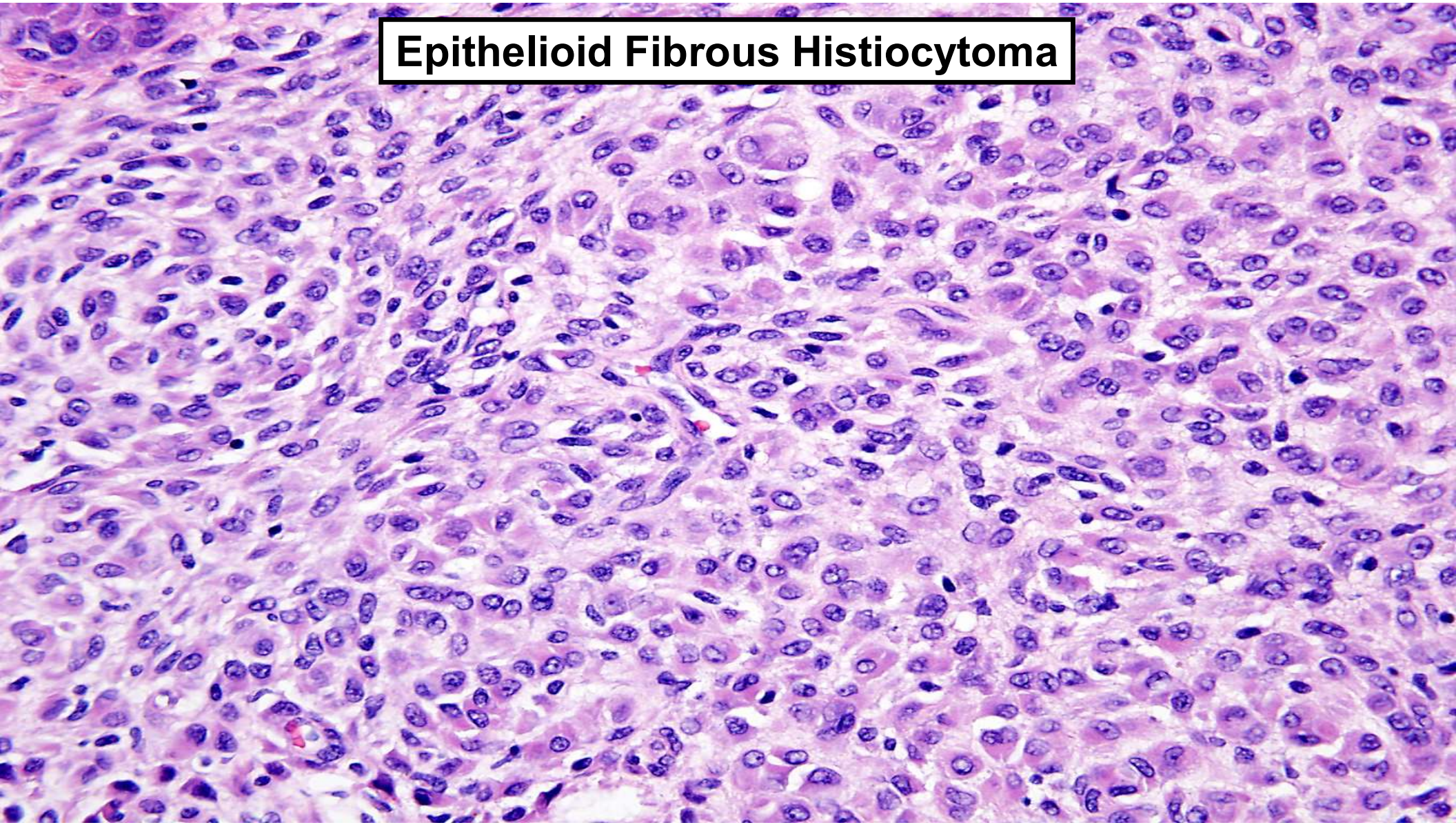
Epithelioid Fibrous Histiocytoma



Epithelioid Fibrous Histiocytoma




Epithelioid Fibrous Histiocytoma


Epithelioid Fibrous Histiocytoma

Is epithelioid fibrous histiocytoma related to conventional dermatofibromas?

Histologic feature	Dermatofibroma	Epithelioid fibrous histiocytoma
Overlying epidermal hyperplasia	Present	Absent
Tumor margins	Lateral entrapment of hyaline collagen	Sharply circumscribed
Cytology	Short spindle cells	Epithelioid cells
Inflammatory infiltrate	Prominent lymphocytes, foam cells	Variable lymphocytes

Atypical fibrous histiocytoma of the skin with CD30 and p80/ALK1 positivity and ALK gene rearrangement

Vanessa Szablewski[1], Sara Laurent-Roussel[2], Luc Rethers[3], Antoine Rommel[4], Pascal Vaneechout[5], Alessandra Camboni[5], Pascal Willocz[6], Christiane Copie-Bergman[7] and Nicolas Ortonne[7]

J Cutan Pathol 2014: 41: 715–719

Epithelioid cell histiocytoma of the skin with clonal *ALK* gene rearrangement resulting in *VCL–ALK* and *SQSTM1–ALK* gene fusions

J. Jedrych[1]
M. Nikiforova[2]
T.F. Kennedy[2]
J. Ho[1]

British Journal of Dermatology (2015) **172**, pp1427–1429

ALK rearrangement and overexpression in epithelioid fibrous histiocytoma

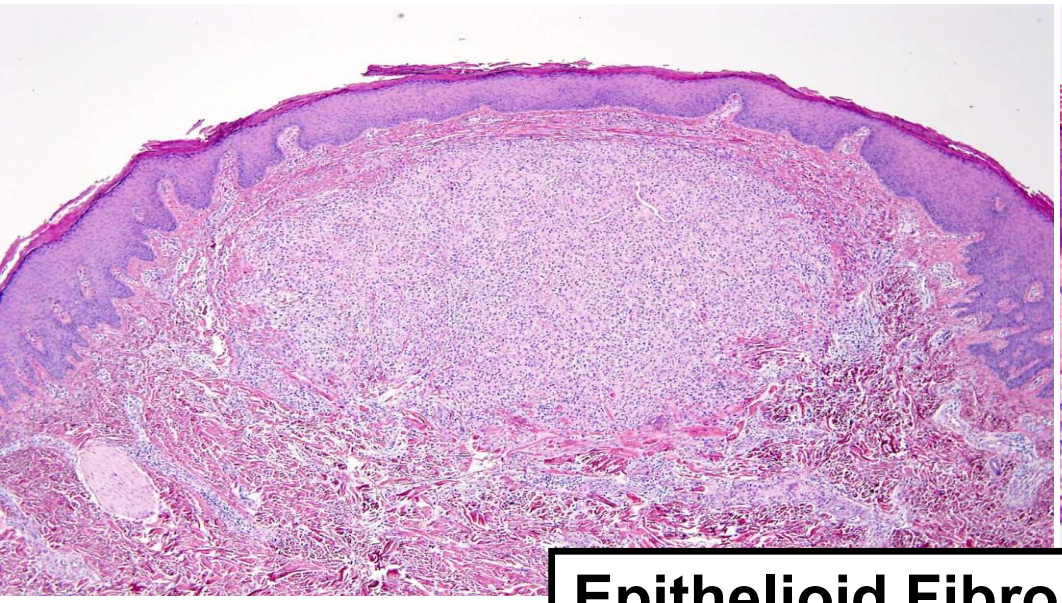
Leona A Doyle, Adrián Mariño-Enriquez, Christopher DM Fletcher and Jason L Hornick

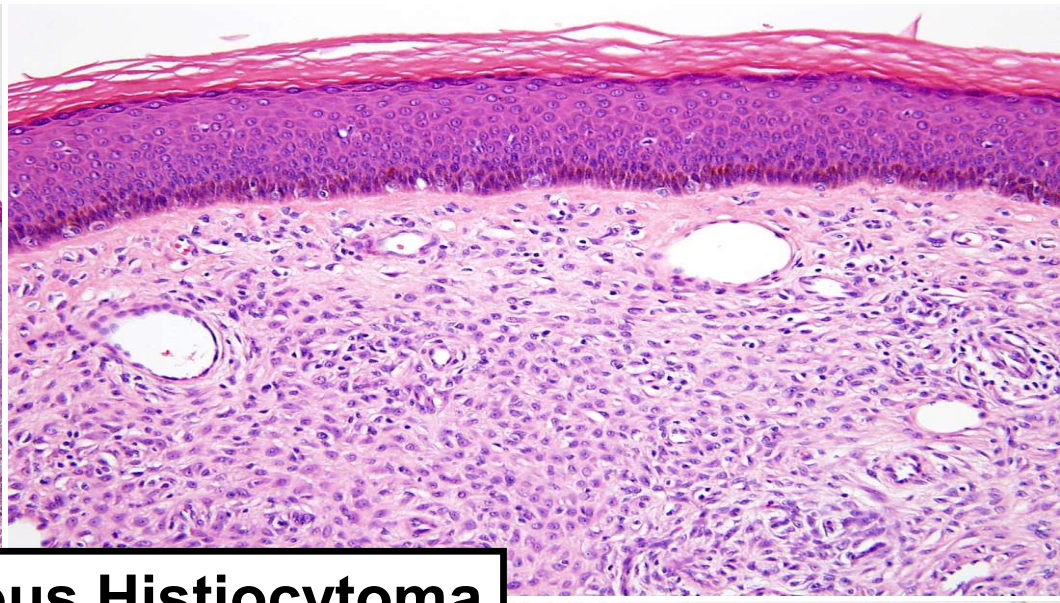
Modern Pathology (2015) 28, 904–912

Table 1 Summary of immunohistochemical staining for ALK in epithelioid fibrous histiocytoma and other tumor types

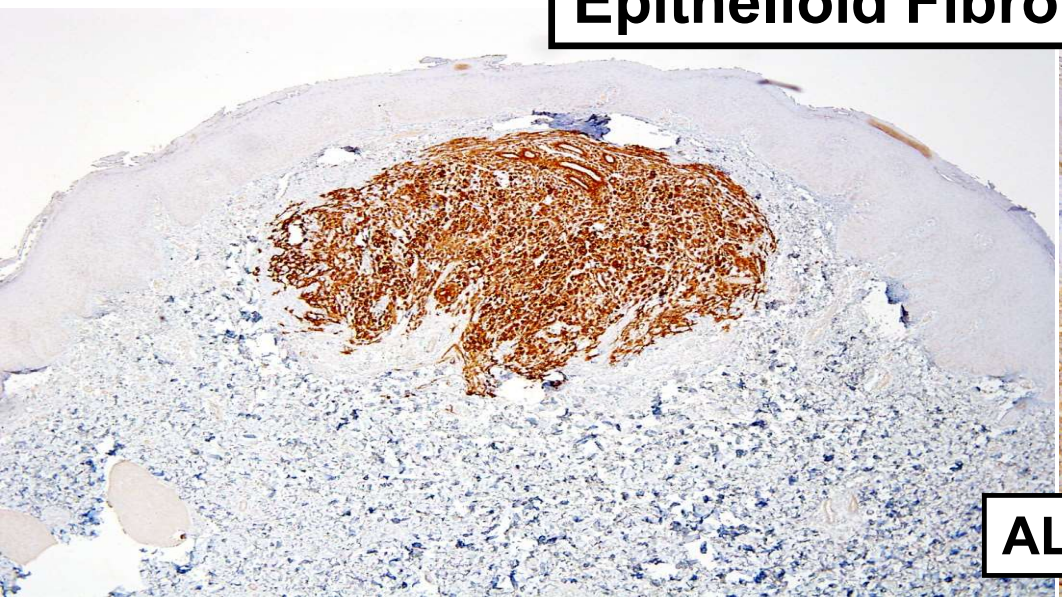
Tumor type	*Total cases*	*ALK positive (%)*
Epithelioid fibrous histiocytoma	33	29 (88)
Aneurysmal fibrous histiocytoma	10	0 (0)
Atypical fibrous histiocytoma	10	0 (0)
Atypical fibroxanthoma	5	0 (0)
Cellular fibrous histiocytoma	10	0 (0)
Conventional fibrous histiocytoma	11	0 (0)
Cutaneous syncytial myoepithelioma	10	0 (0)

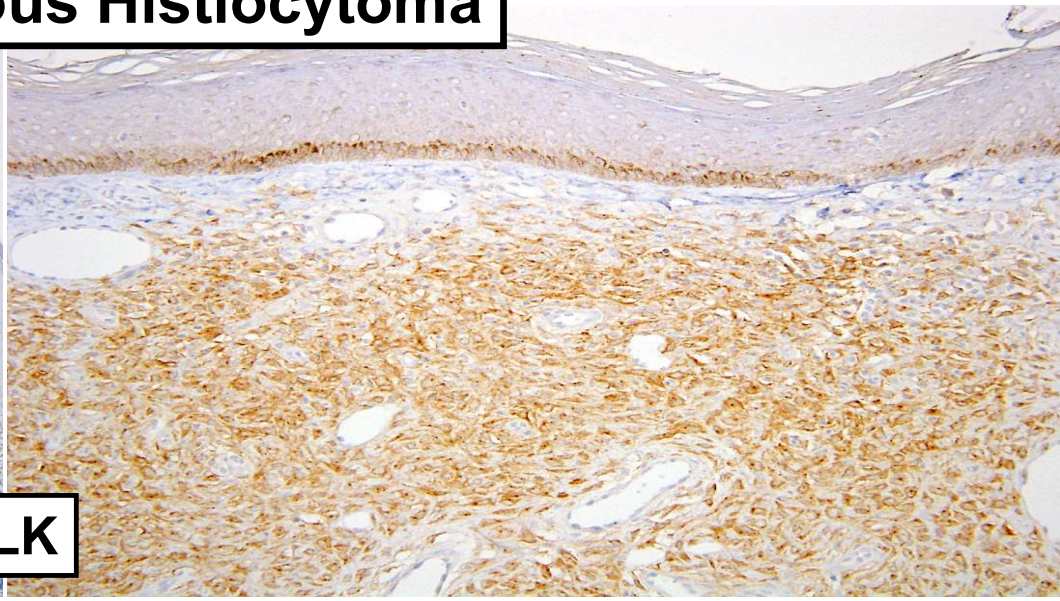
Doyle et al. *Mod Pathol 2015*



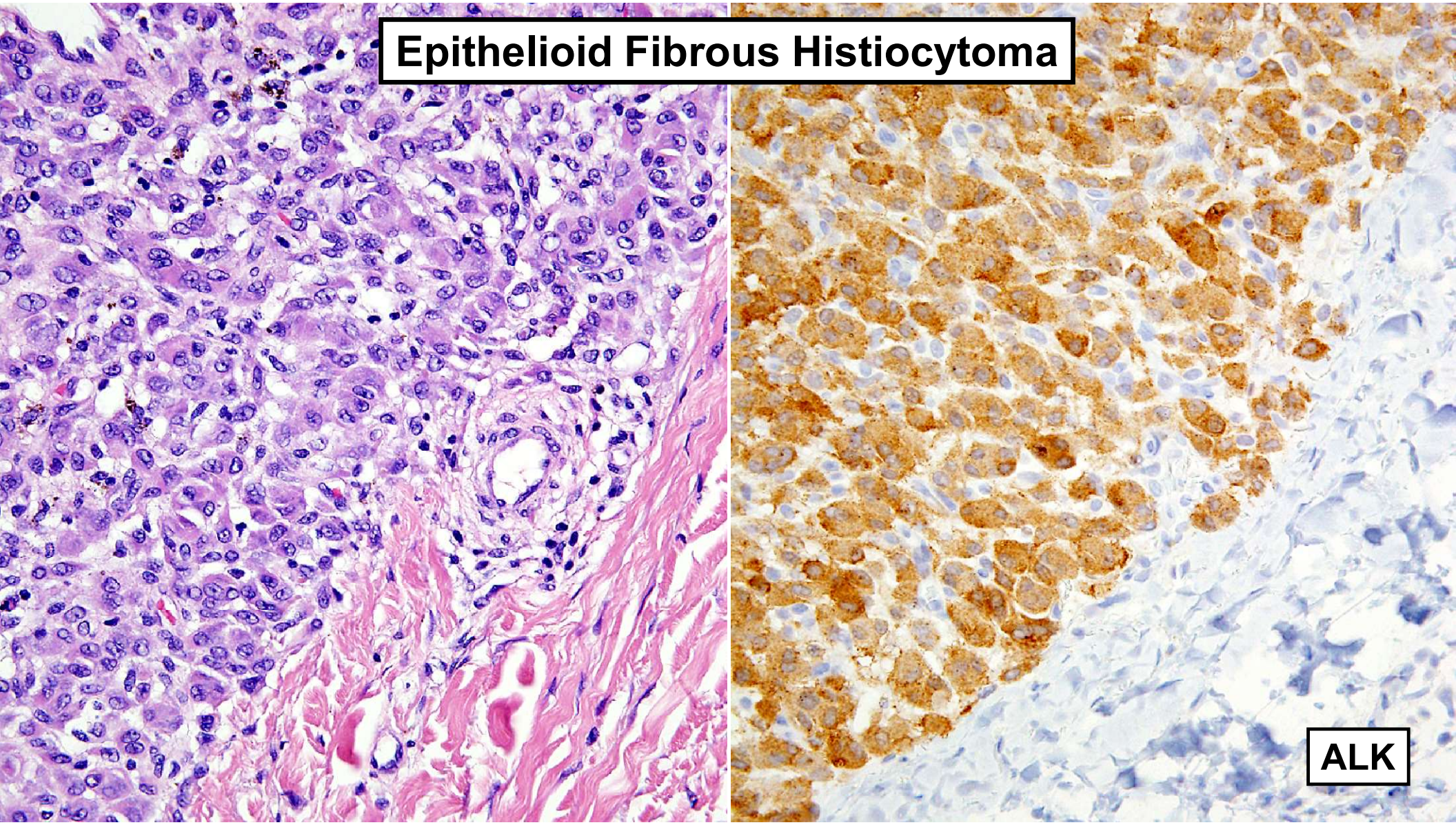


Epithelioid Fibrous Histiocytoma





ALK


Epithelioid Fibrous Histiocytoma
ALK

Epithelioid fibrous histiocytoma: molecular characterization of *ALK* fusion partners in 23 cases

Brendan C Dickson[1,2,3], David Swanson[1,3], George S Charames[1,2,3], Christopher DM Fletcher[4,5] and Jason L Hornick[4,5]

MODERN PATHOLOGY (2018) 31, 753–762

ALK Gene Fusions in Epithelioid Fibrous Histiocytoma: A Study of 14 Cases, With New Histopathological Findings

Dmitry V. Kazakov, MD, PhD,† Liubov Kyrpychova, MD,*† Petr Martinek, PhD,*† Petr Grossmann, PhD,*† Petr Steiner,*† Tomas Vanecek, PhD,*† Michal Pavlovsky, MD,‡ Vladimir Bencik, MD,§ Michael Michal, MD,*† and Michal Michal, MD*†*

Am J Dermatopathol • Volume 40, Number 11, November 2018

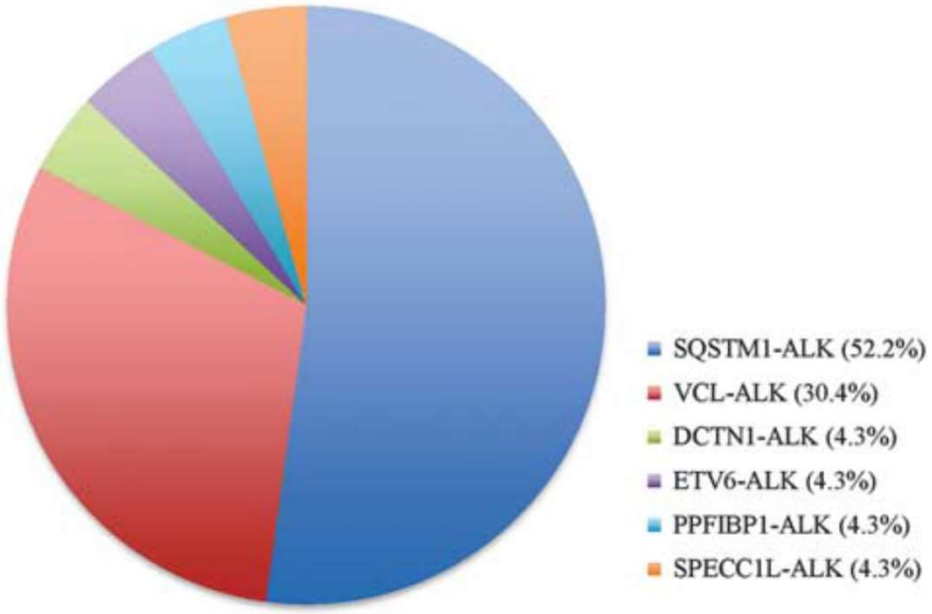


Figure 1 Pie chart demonstrating the relative percentage of each of the *ALK* fusion products within the study cohort.

Gene Fusion	Cases
SQSTM1-ALK	**3**
VCL-ALK	**3**
TPM3-ALK	**2**
PRKAR2A-ALK	**1**
MLPH-ALK	**1**
EML4-ALK	**1**

Nerve Sheath Myxoma

Harkin JC, Reed RJ. Tumors of the peripheral nervous system. Atlas of Tumor Pathology, 2nd Series. Washington, D.C.: AFIP, 1969

Neurothekeoma—A Benign Cutaneous Tumor of Neural Origin

RICHARD L. GALLAGER, MAJOR, USAF, MC, AND ELSON B. HELWIG, M.D.

Am J Clin Pathol 74: 759–764, 1980.

Cellular Neurothekeoma

A Distinctive Variant of Neurothekeoma Mimicking Nevomelanocytic Tumors

Raymond L. Barnhill, M.D., and Martin C. Mihm, Jr., M.D.

The American Journal of Surgical Pathology *14(2): 113–120, 1990*

Dermal Nerve Sheath Myxoma vs “Neurothekeoma”

Nerve Sheath Myxoma

A Clinicopathologic and Immunohistochemical Analysis of 57 Morphologically Distinctive, S-100 Protein- and GFAP-Positive, Myxoid Peripheral Nerve Sheath Tumors With a Predilection for the Extremities and a High Local Recurrence Rate

John F. Fetsch, MD, William B. Laskin, MD,† and Markku Miettinen, MD**

Am J Surg Pathol • Volume 29, Number 12, December 2005

Dermal Nerve Sheath Myxoma vs "Neurothekeoma"

Cellular Neurothekeoma: Detailed Characterization in a Series of 133 Cases

Jason L. Hornick, MD, PhD† and Christopher D. M. Fletcher, MD, FRCPath*†*

Am J Surg Pathol • Volume 31, Number 3, March 2007

Neurothekeoma: An Analysis of 178 Tumors With Detailed Immunohistochemical Data and Long-term Patient Follow-up Information

John F. Fetsch, MD, William B. Laskin, MD,† James R. Hallman, MD,‡ George P. Lupton, MD,‡ and Markku Miettinen, MD**

Am J Surg Pathol • Volume 31, Number 7, July 2007

Dermal Nerve Sheath Myxoma vs “Neurothekeoma”

- **Dermal nerve sheath myxoma – true Schwann cell neoplasm**
- **So-called “cellular neurothekeoma” – line of differentiation unknown (possibly myofibroblastic)**
- **Cellular neurothekeomas may show myxoid stromal change:**

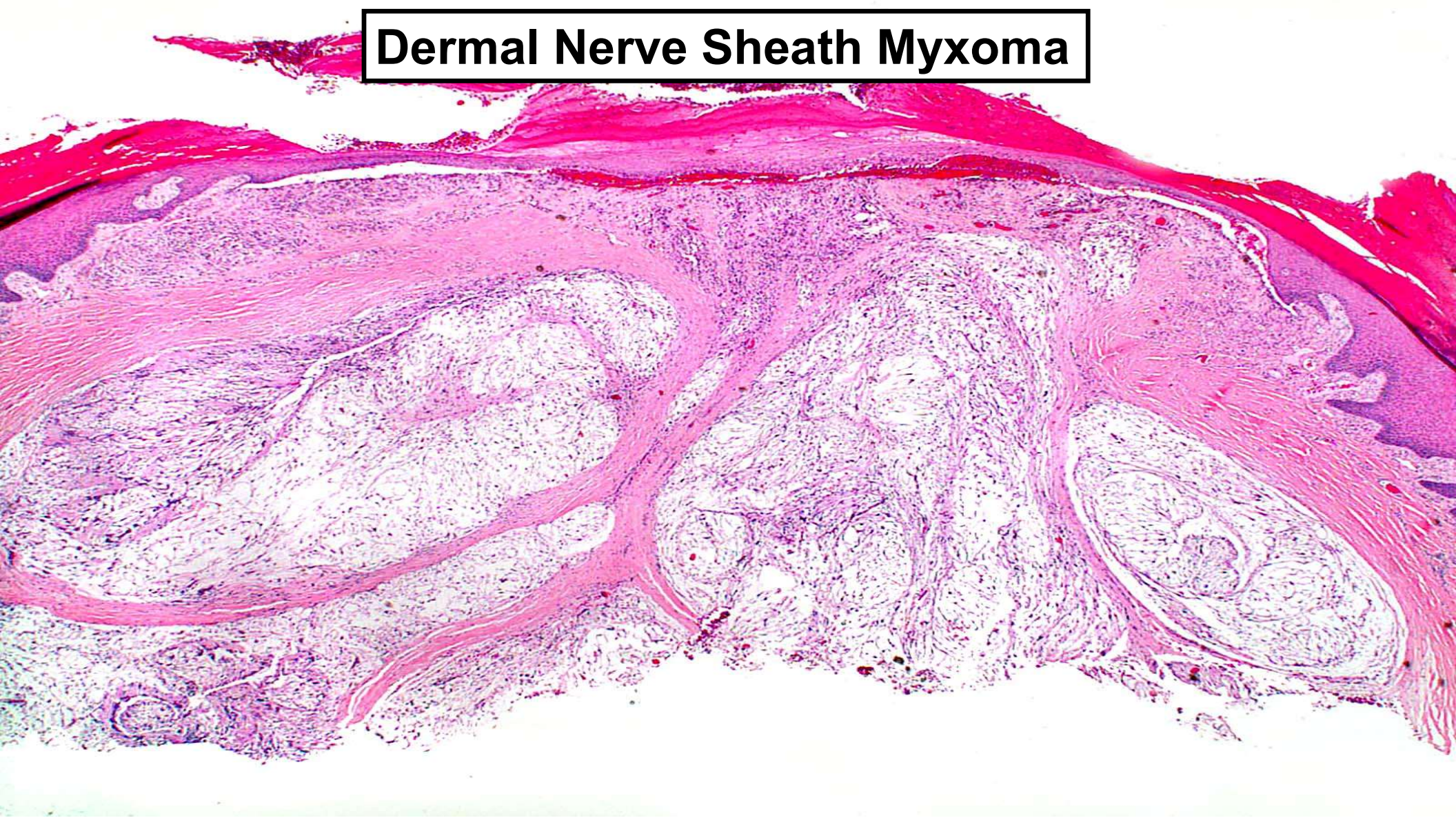
NO RELATIONSHIP TO DNSM

NOT A NERVE SHEATH TUMOR

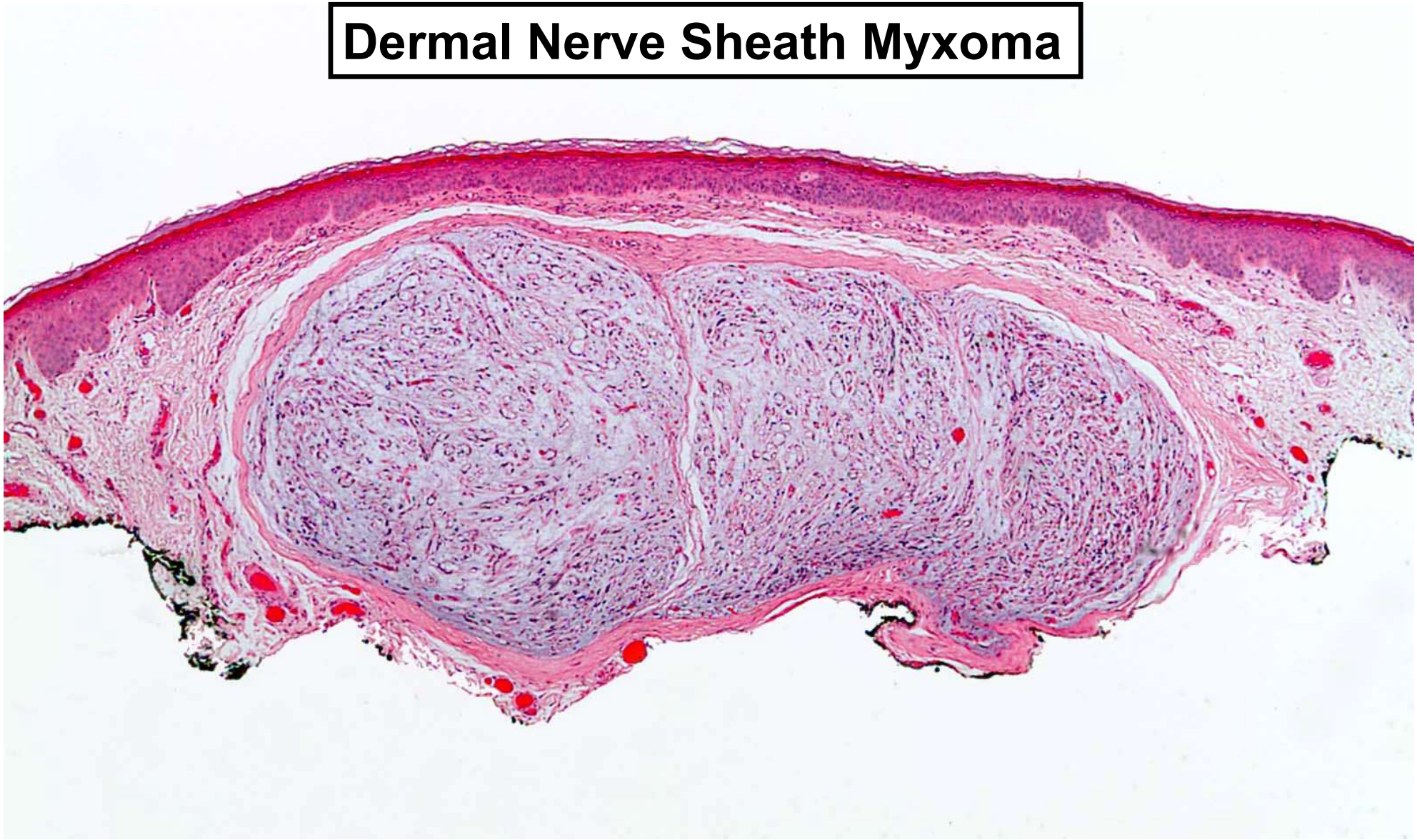
Dermal nerve sheath myxoma

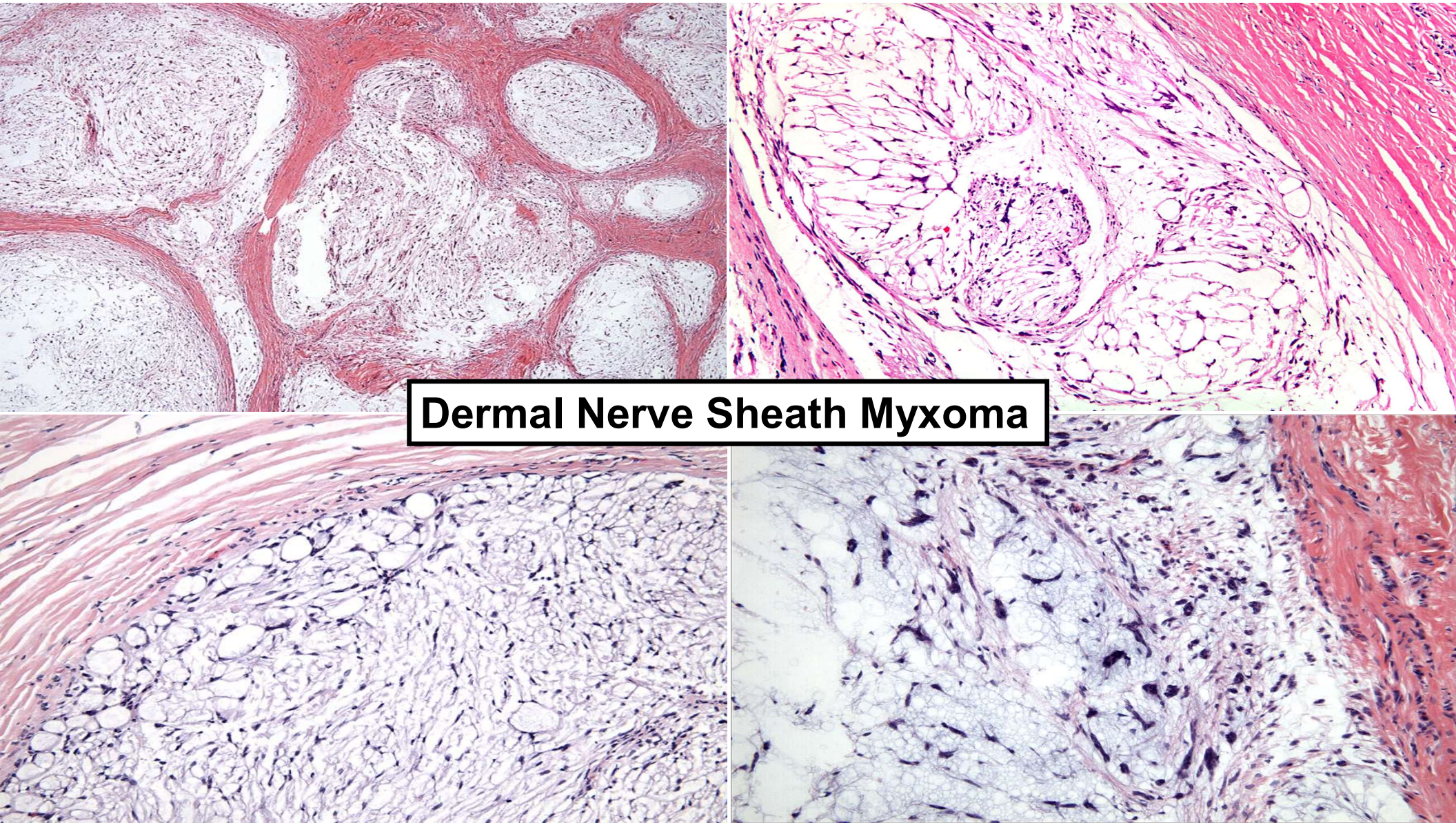
- Predilection for distal extremities, especially fingers
- Middle-aged adults
- Lobulated growth pattern; sharply demarcated
- Abundant myxoid stroma
- Spindle cell with hyperchromatic nuclei
- Positive for S100, GFAP
- High local recurrence rate (~50%)

Dermal Nerve Sheath Myxoma

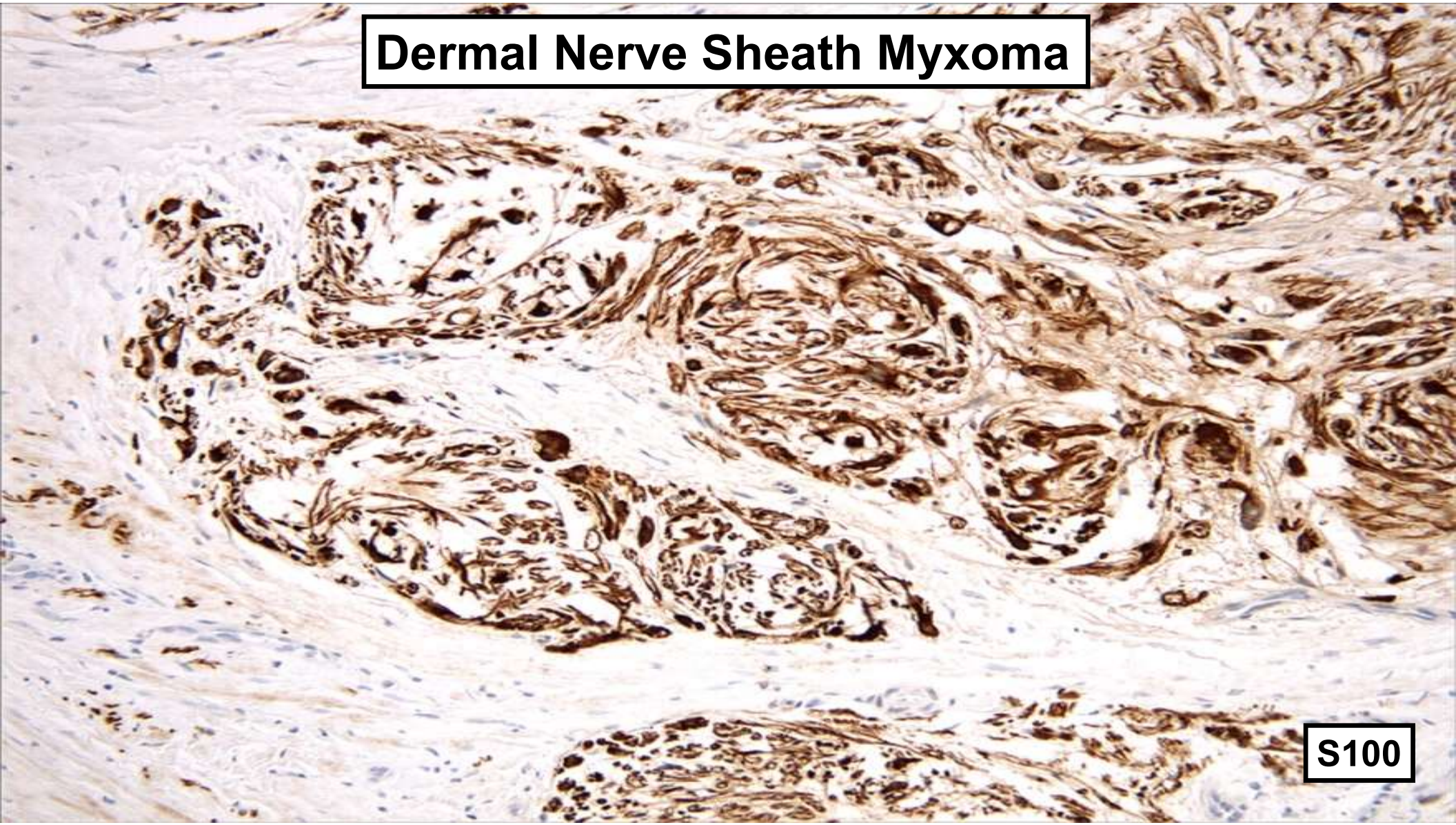


Dermal Nerve Sheath Myxoma





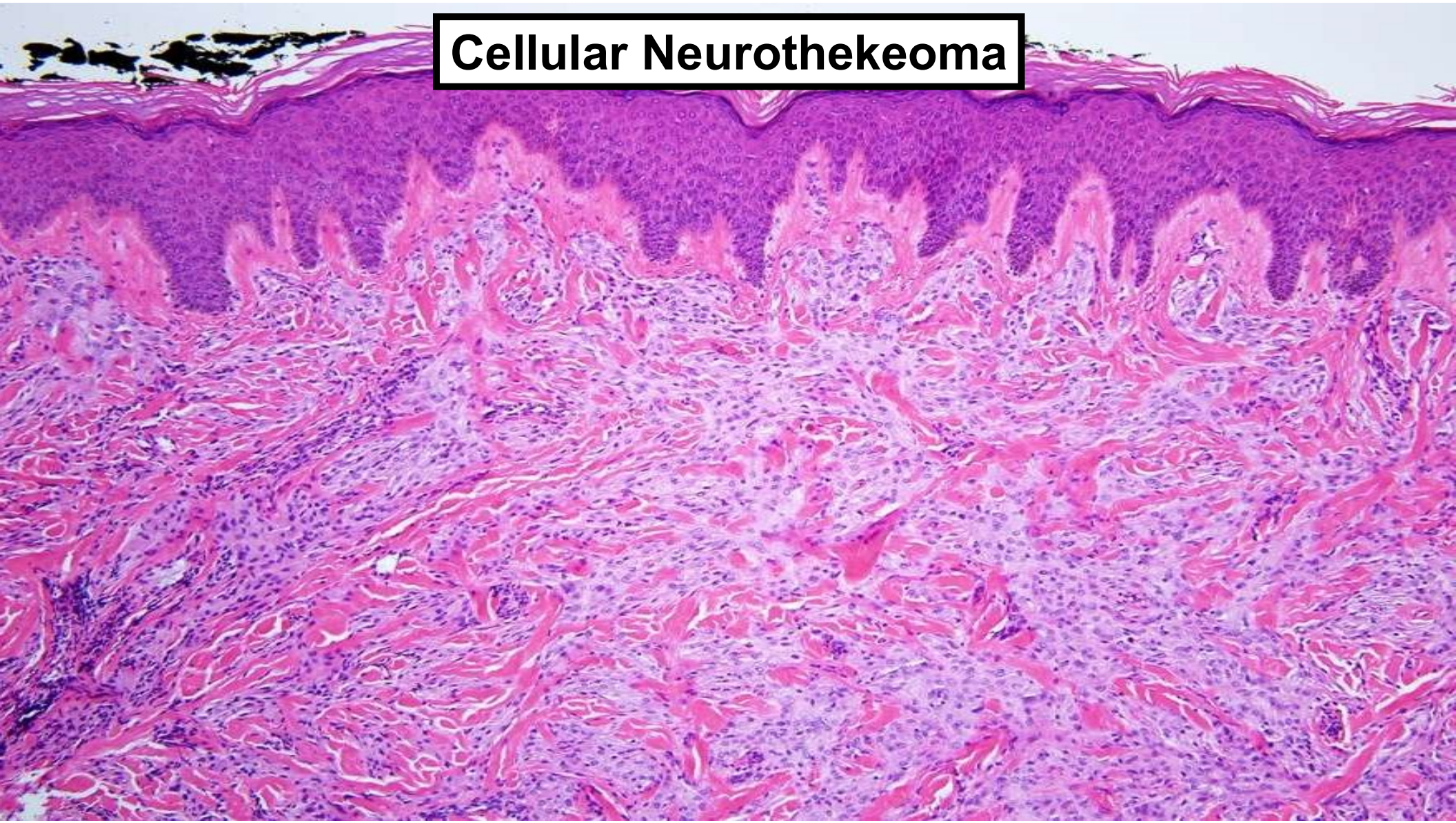
Dermal Nerve Sheath Myxoma

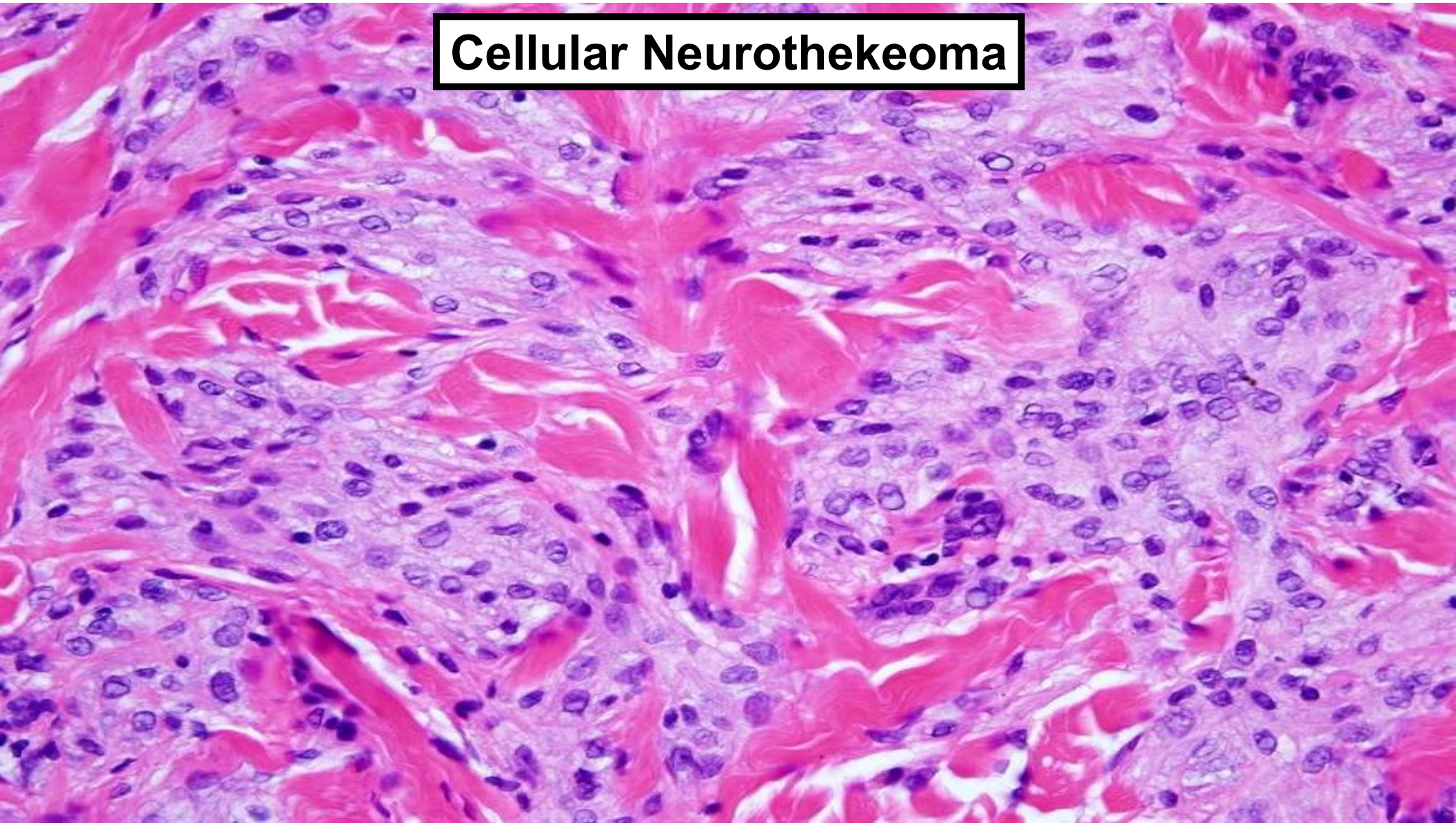

Dermal Nerve Sheath Myxoma
S100

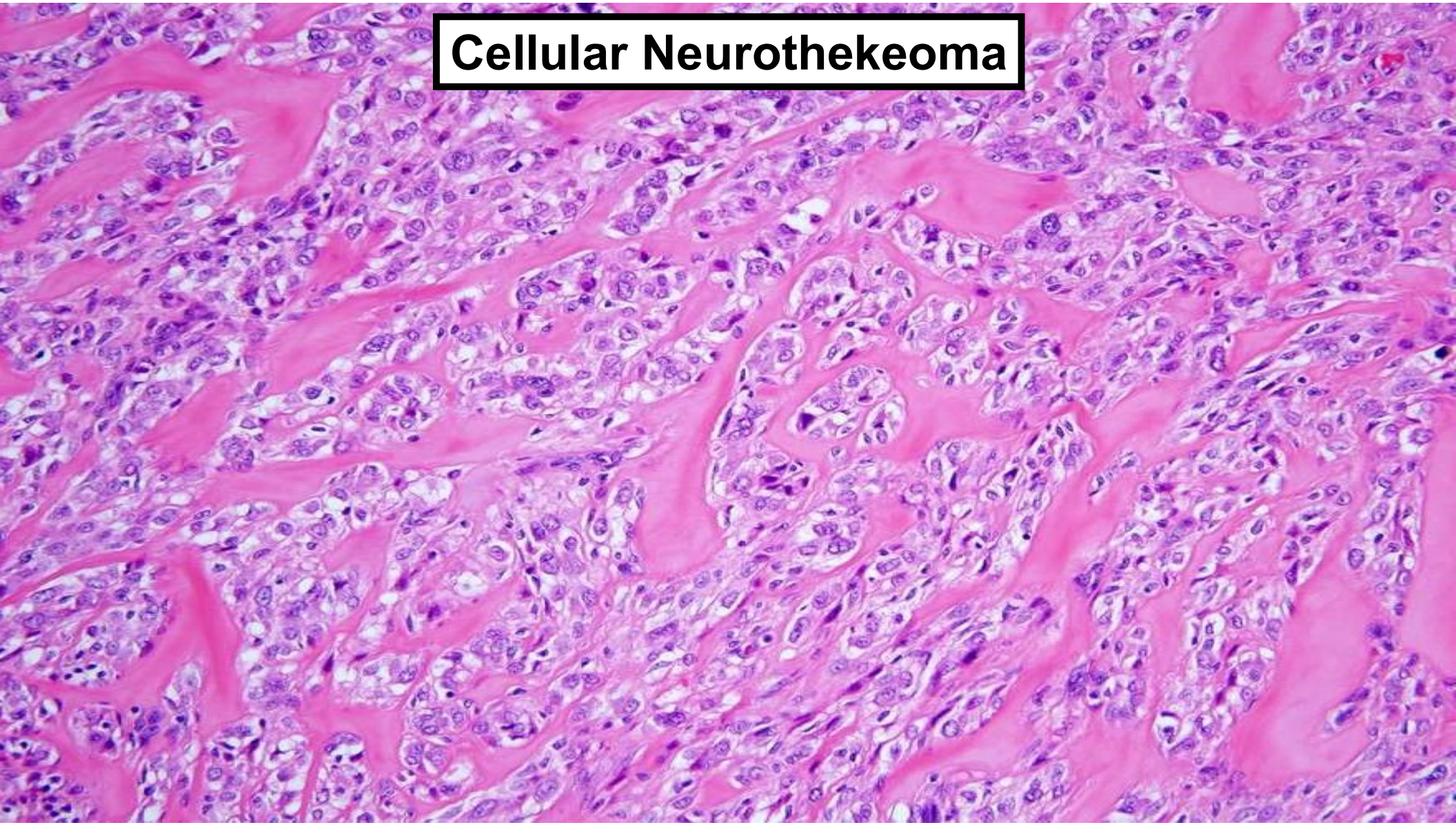
Cellular neurothekeoma

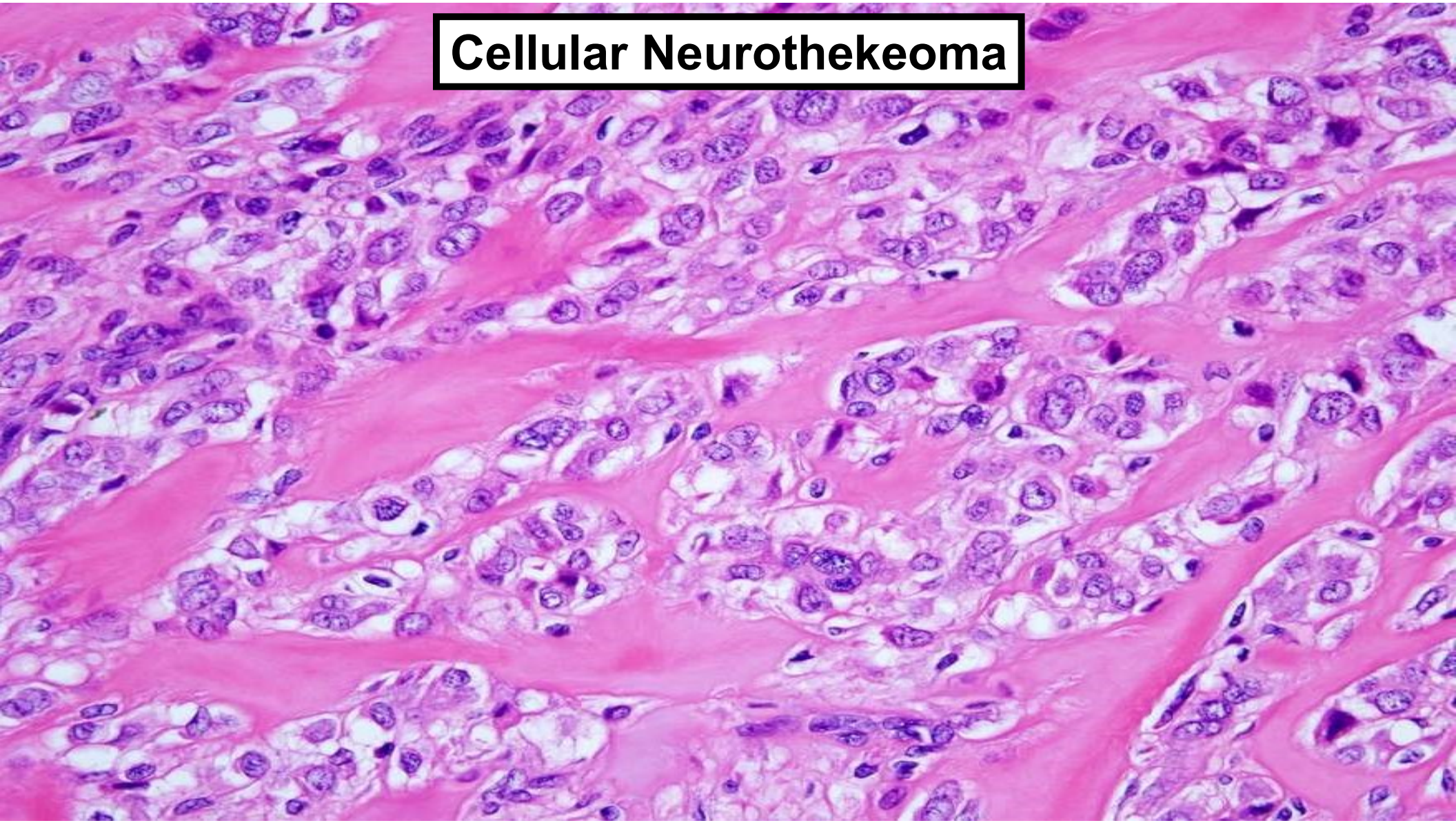
- **Not a nerve sheath tumor! No relationship to nerve sheath myxoma ("myxoid neurothekeoma")!**
- **2:1 female predominance**
- **Most patients 1st to 3rd decades**
- **Predilection for head and neck and upper limb (especially shoulder)**
- **Benign; occasionally recur if incompletely excised**

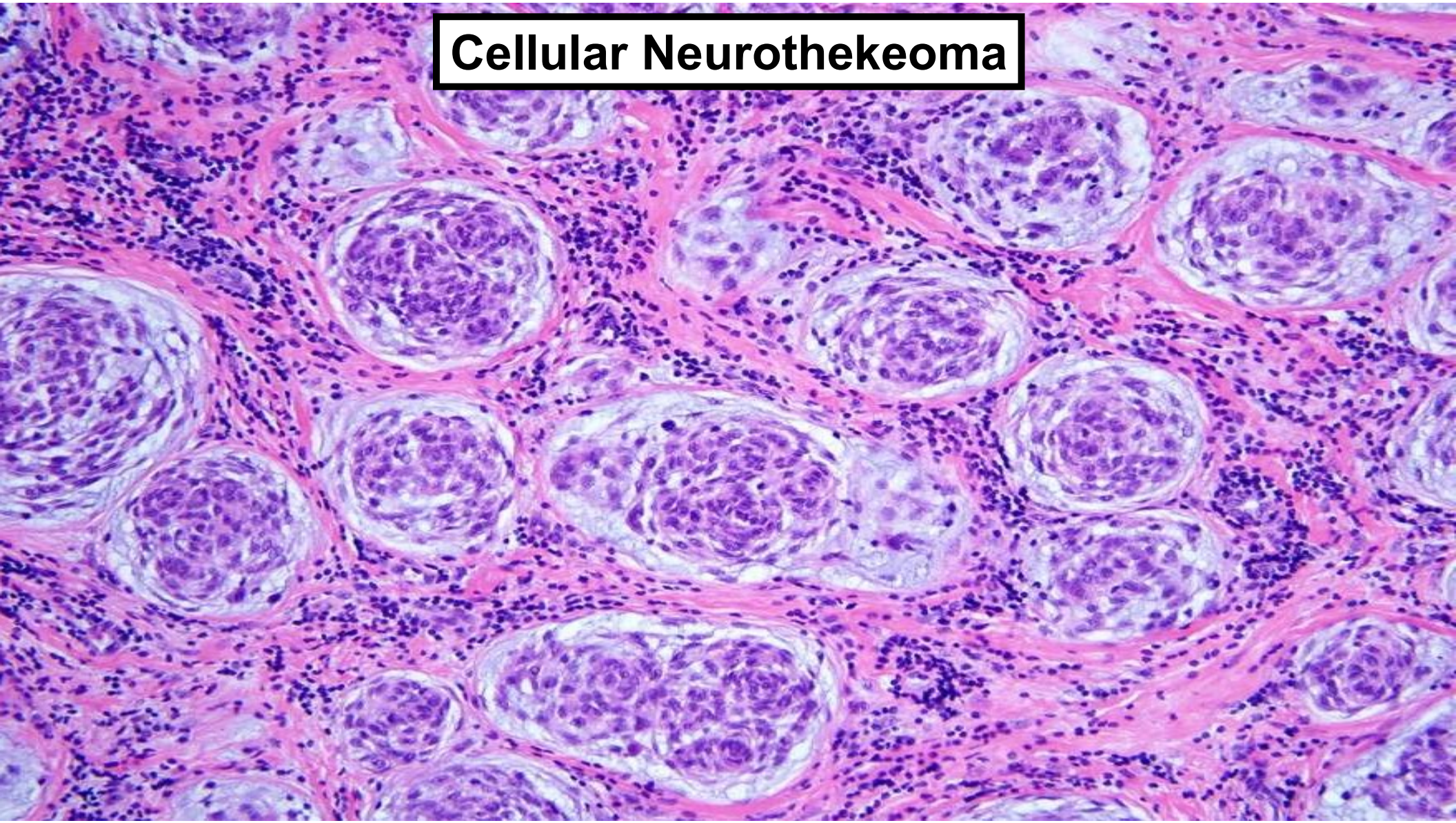
Cellular Neurothekeoma




Cellular Neurothekeoma


Cellular Neurothekeoma


Cellular Neurothekeoma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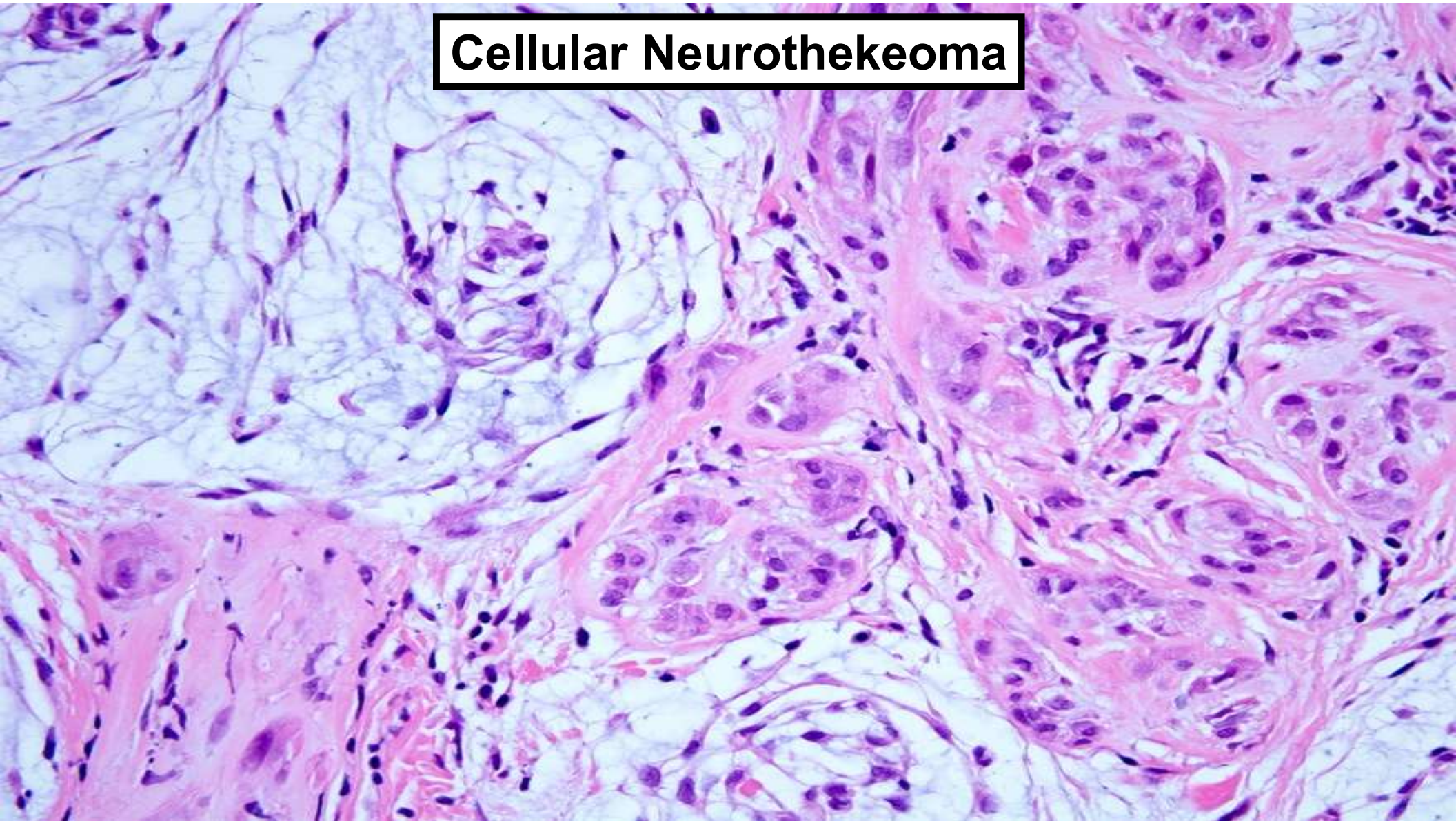
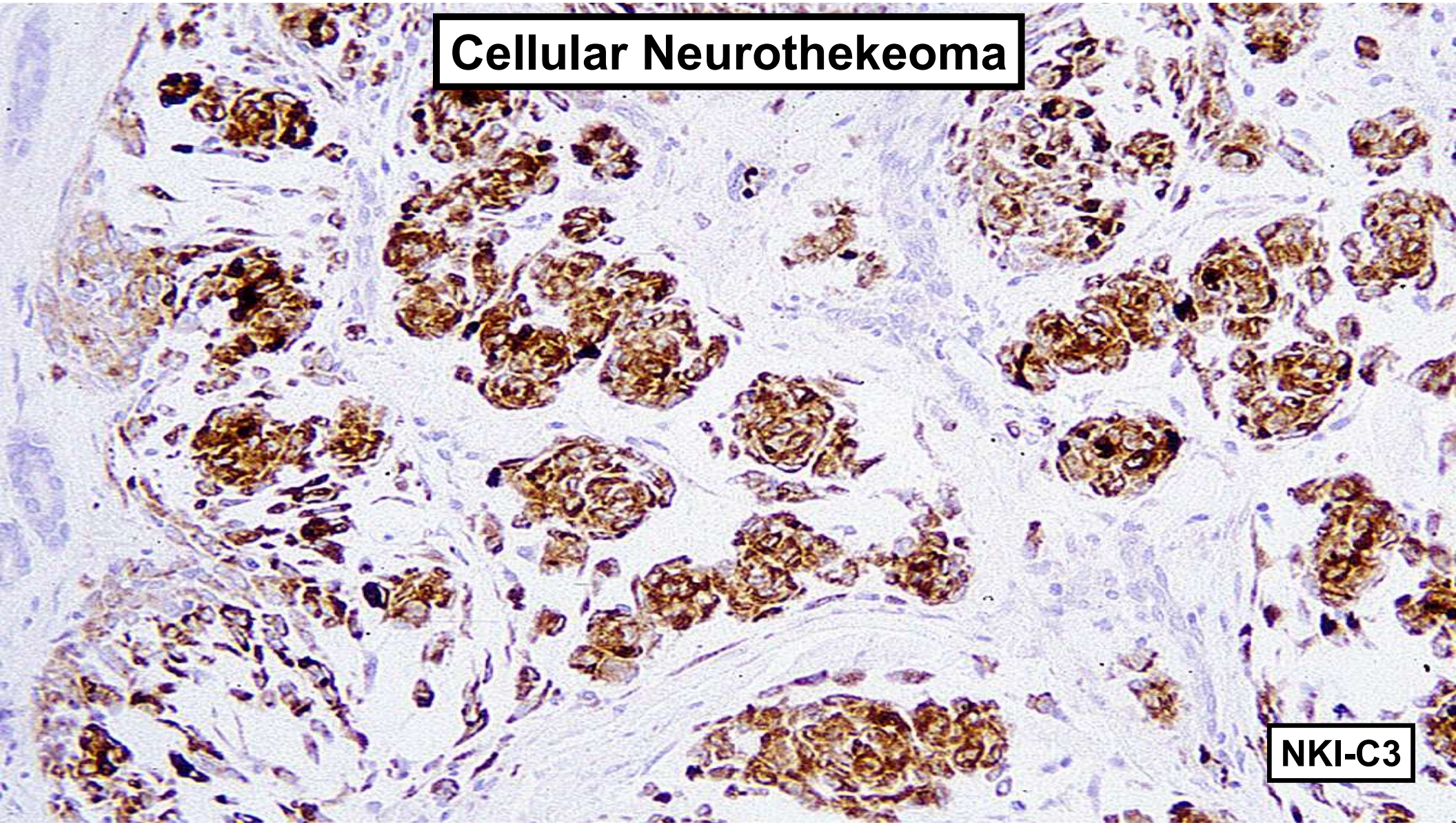
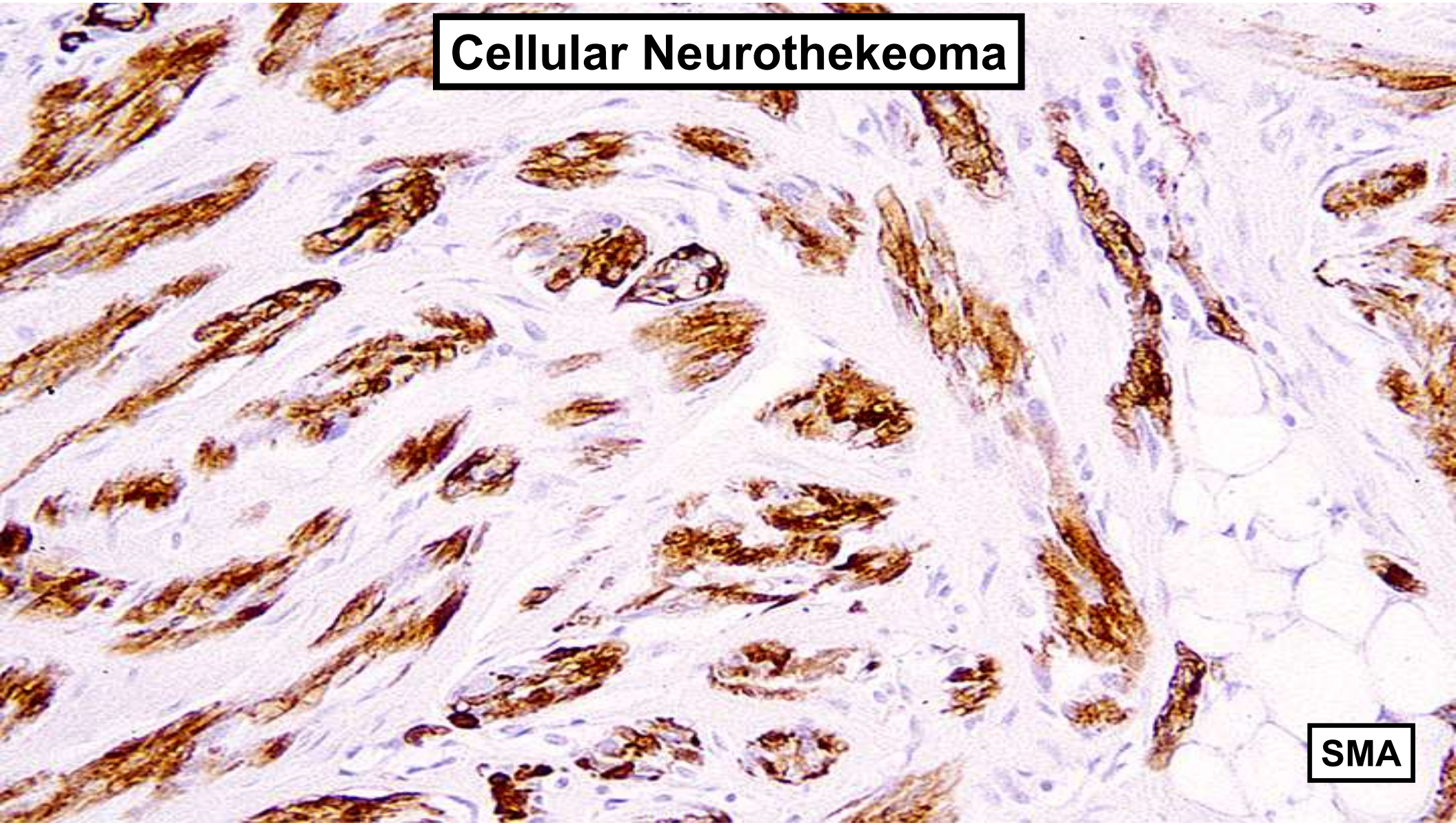

Cellular Neurothekeoma


Cellular Neurothekeoma
NKI-C3


Cellular Neurothekeoma
SMA

Cutaneous Syncytial Myoepithelioma

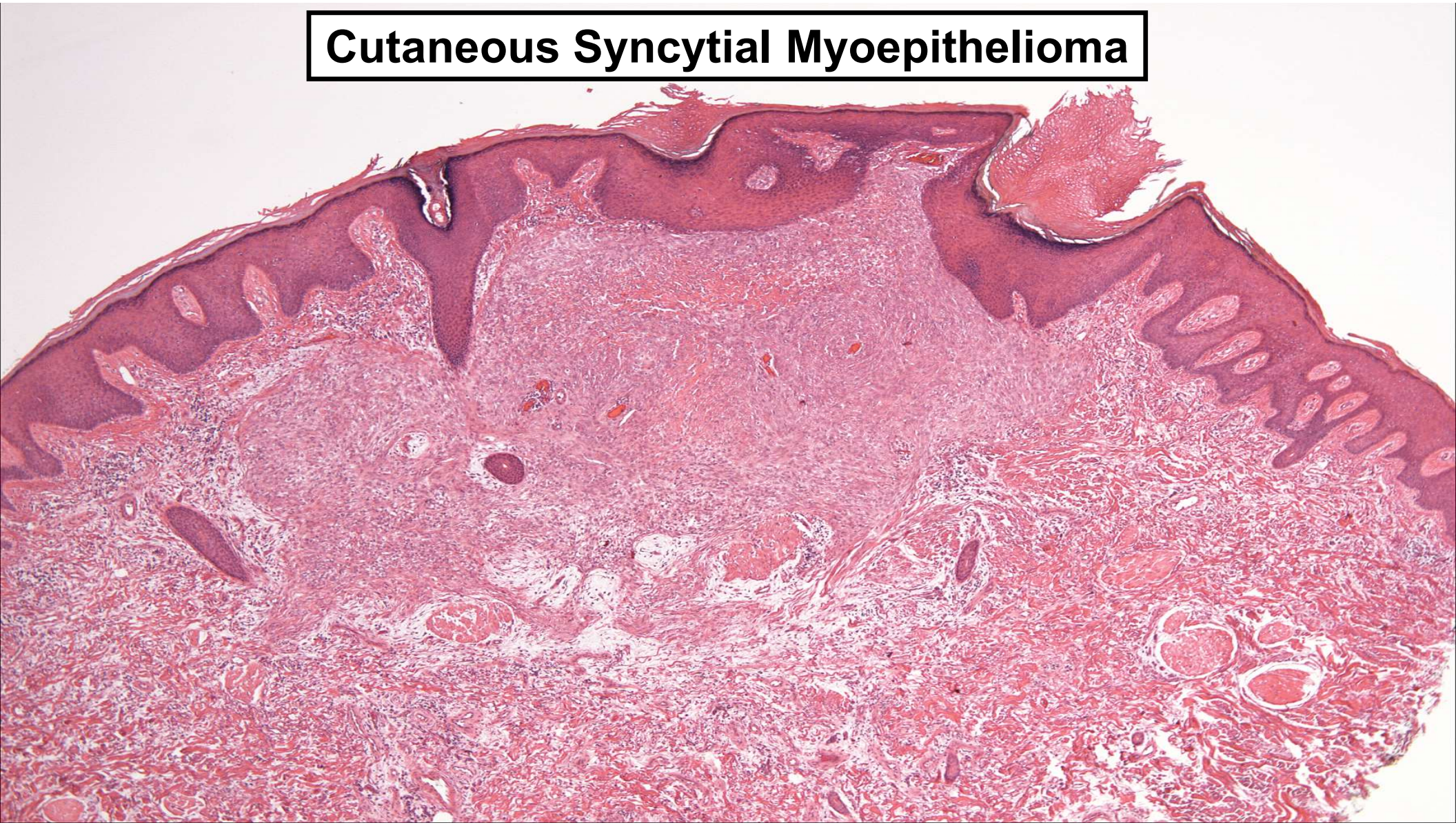
Clinicopathologic Characterization in a Series of 38 Cases

Vickie Y. Jo, MD, Cristina R. Antonescu, MD,† Lei Zhang, MD,† Paola Dal Cin, PhD,* Jason L. Hornick, MD, PhD,* and Christopher D.M. Fletcher, MD, FRCPath**

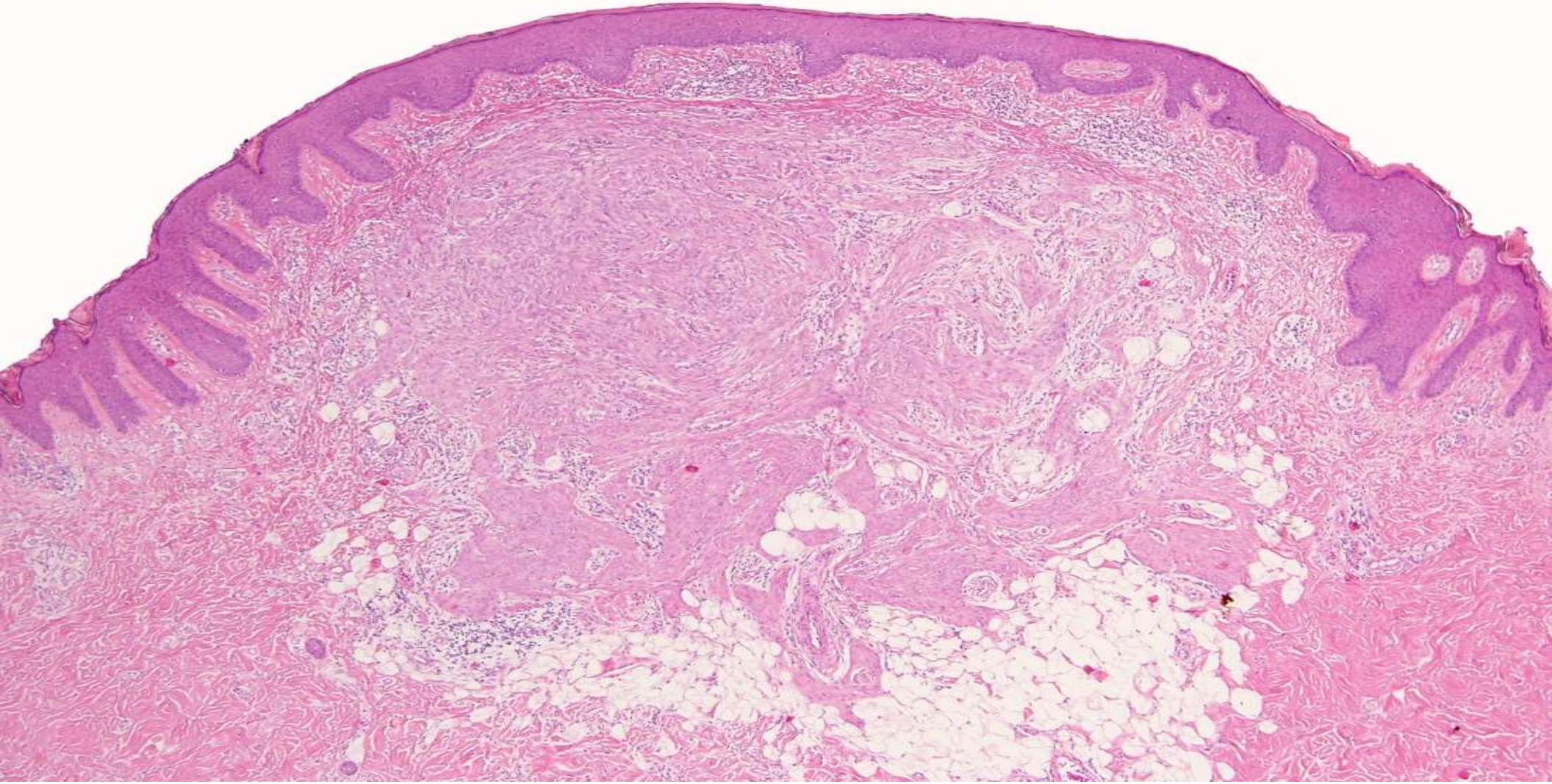
Am J Surg Pathol • Volume 37, Number 5, May 2013

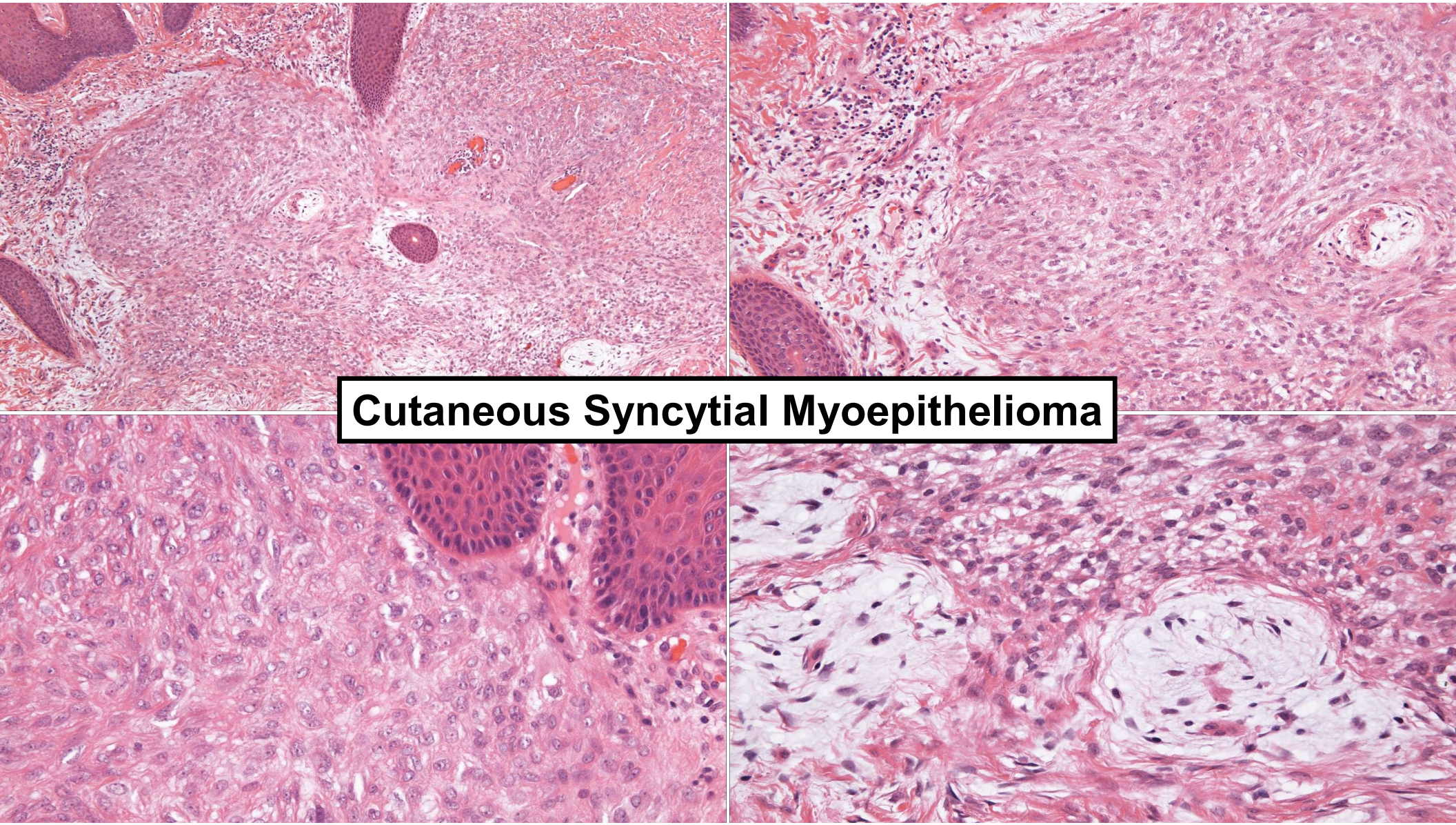
- **Variant exclusive to the skin**
- **Unique histologic features**
- **Positive for S100 and EMA**
- **Lack keratin expression**

Cutaneous Syncytial Myoepithelioma



Cutaneous Syncytial Myoepithelioma



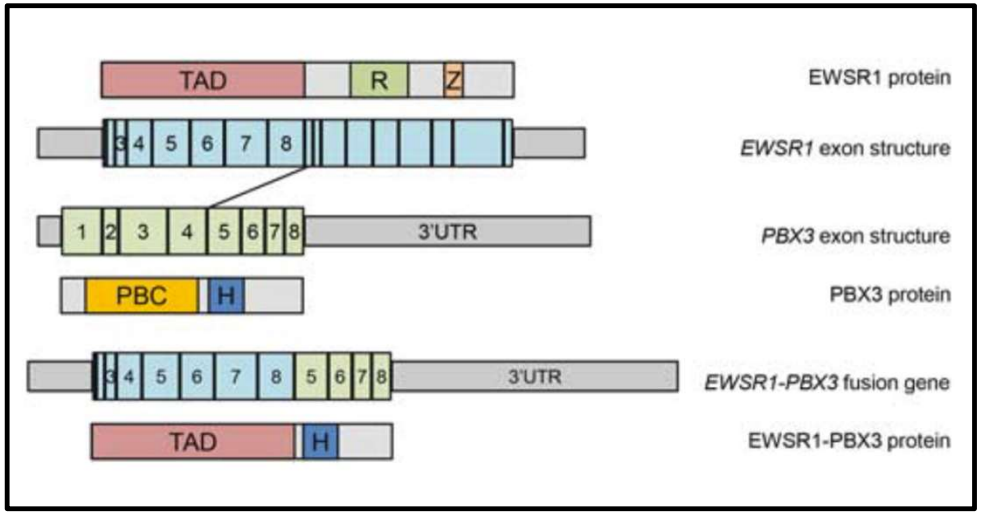


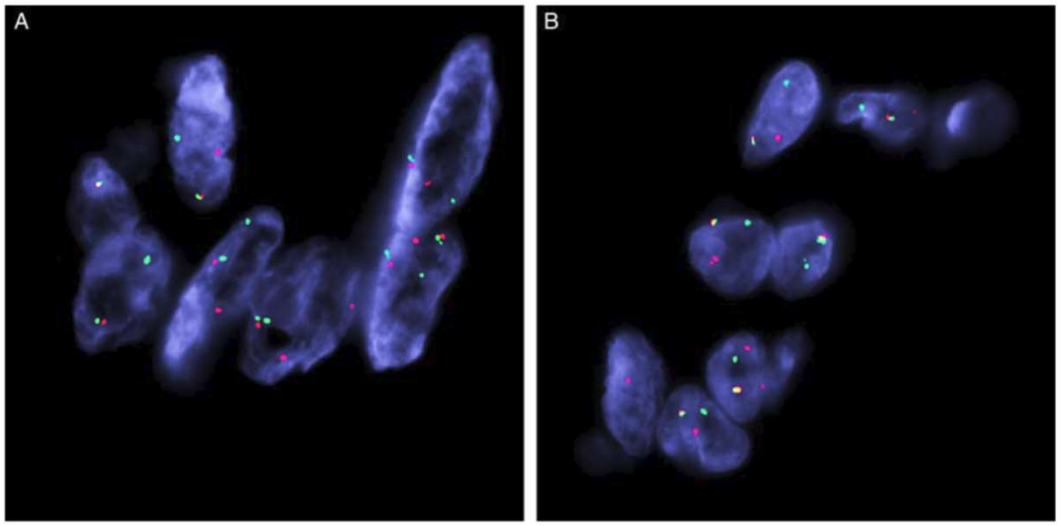
Cutaneous Syncytial Myoepithelioma

Cutaneous Syncytial Myoepithelioma Is Characterized by Recurrent *EWSR1-PBX3* Fusions

Vickie Y. Jo, MD, Cristina R. Antonescu, MD,† Brendan C. Dickson, MSc, MD,‡ David Swanson, BSc,‡ Lei Zhang, MD,† Christopher D.M. Fletcher, MD, FRCPath,* and Elizabeth G. Demicco, MD, PhD‡*

Am J Surg Pathol • Volume 43, Number 10, October 2019





Practice Points

- **“Fibrohistiocytic” is a misnomer – most tumors in this category are fibroblastic/myofibroblastic**
- **Epithelioid fibrous histiocytoma is unrelated to dermatofibromas**
- **Dermal nerve sheath myxoma is not related to cellular neurothekeoma**
- **Cutaneous syncytial myoepithelioma is a distinctive translocation-associated neoplasm**

@JLHornick

THANK YOU!