2022 CLASSIFICATION OF PEDIATRIC TUMORS: AN UPDATE ON SOFT TISSUE TUMORS

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WHO Classification of Pediatric Tumors

- **For the first time, the WHO published a comprehensive classification of tumors of children**
- **Includes all organ systems and lineages**
- **Emphasis on tumors with a predilection for (or relatively common presentation in) children and adolescents**
- **Also includes some tumor types that occasionally present in young patients**

WHO Classification of Pediatric Tumors

Hematolymphoid disorders	Female genital tumors
CNS tumors	Breast tumors
Peripheral neuroblastic tumors	Digestive system tumors
Eye tumors	Endocrine tumors
Soft tissue and bone tumors	Head and neck tumors
Germ cell tumors	Thoracic tumors
Renal and male genital tumors	Skin tumors
Genetic tumor syndromes	

Pediatric soft tissue tumors

- **Include a diverse arrange of benign, intermediate, and malignant mesenchymal neoplasms**
- **Incidence of soft tissue sarcomas <1 per 100,000 in children <10 yrs (18 per 100,000 in adults >70 yrs)**
- **Soft tissue sarcomas account for 7-8% of childhood cancers (compared to <1% of cancers in adults)**
- **Rhabdomyosarcomas most common sarcomas in children <15 yrs**
- **Non-rhabdomyosarcoma soft tissue sarcomas uncommon and heterogeneous**

Soft Tissue Tumors

Adipocytic tumors	Smooth muscle tumors
Fibroblastic and myofibroblastic tumors	Skeletal muscle tumors
So-called fibrohistiocytic tumors	Gastrointestinal stromal tumors
Vascular tumors	Peripheral nerve sheath tumors
Pericytic (perivascular) tumors	Tumors of uncertain derivation

Undifferentiated small round cell sarcomas of bone and soft tissue

Adipocytic tumors
Lipomatosis
Lipoblastoma/lipoblastomatosis
Liposarcomas

Types of liposarcoma	Pediatric population
Well-differentiated liposarcoma	Exceptionally rare
Dedifferentiated liposarcoma	Exceptionally rare
Myxoid liposarcoma	Over 70% of liposarcomas
Myxoid pleomorphic liposarcoma	Rare; over-represented in children
Pleomorphic liposarcoma	Exceptionally rare

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Pleomorphic liposarcoma	Exceptionally rare

Myxoid pleomorphic liposarcoma

- **Predilection for the mediastinum of children and young adults**
- **Some cases associated with Li-Fraumeni syndrome**
- **Histology: admixture of hypocellular zones with myxoid stroma, bland nuclei, and delicate branching vessels and areas with atypia and pleomorphism**
- **Lack *DDIT3* rearrangements and *MDM2* amplification**
- **Clinically aggressive with high rate of local recurrence and distant metastasis**

Liposarcomas in Young Patients

A Study of 82 Cases Occurring in Patients Younger Than 22 Years of Age

Rita Alaggio, MD, Cheryl M. Coffin, MD,† Sharon W. Weiss, MD,‡ Julia A. Bridge, MD,§ Josephine Issakov, MD,‖ Andre M. Oliveira, MD,¶ and Andrew L. Folpe, MD¶*

Am J Surg Pathol • Volume 33, Number 5, May 2009

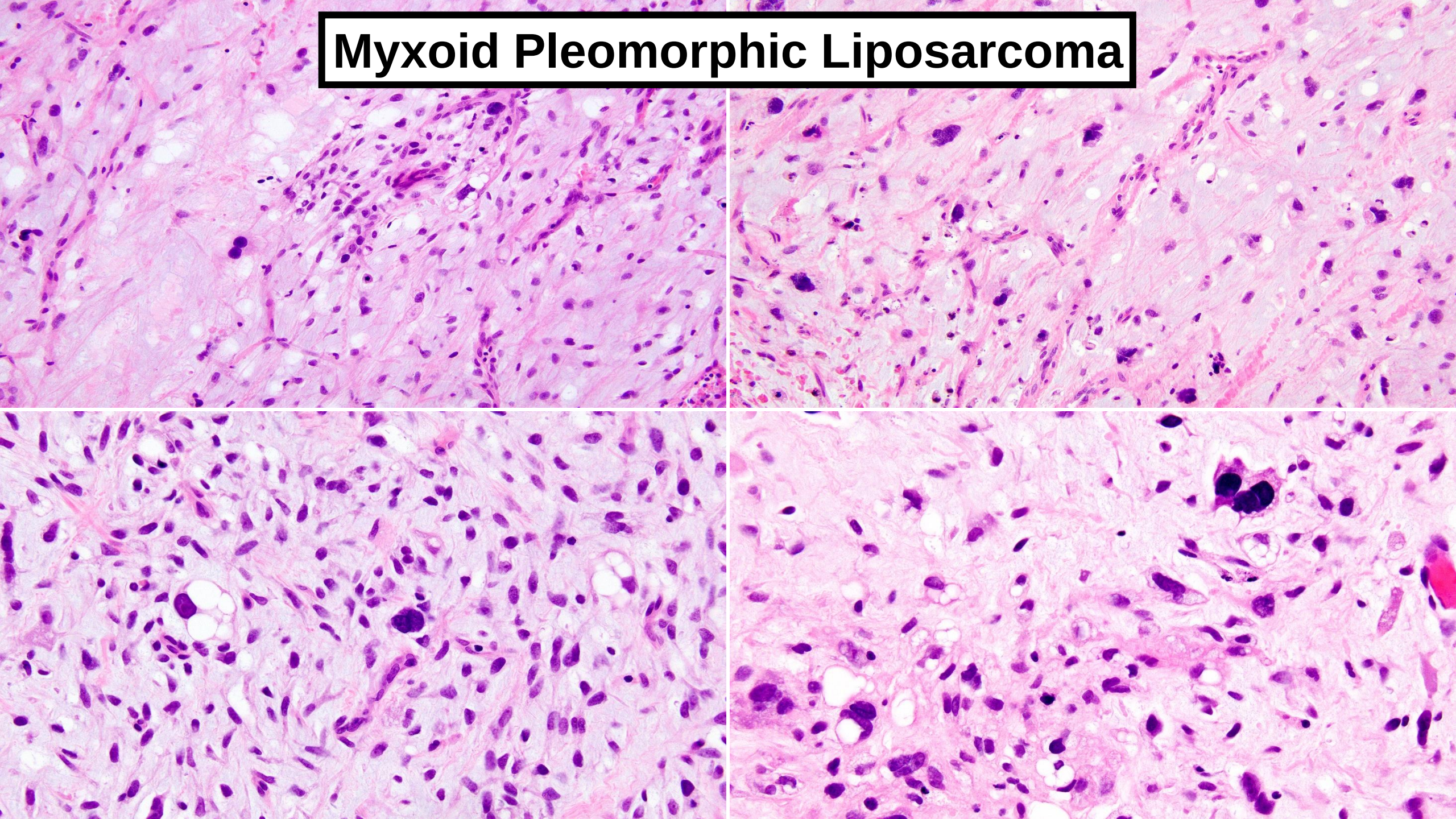
Liposarcomas of the Mediastinum and Thorax

A Clinicopathologic and Molecular Cytogenetic Study of 24 Cases, Emphasizing Unusual and Diverse Histologic Features

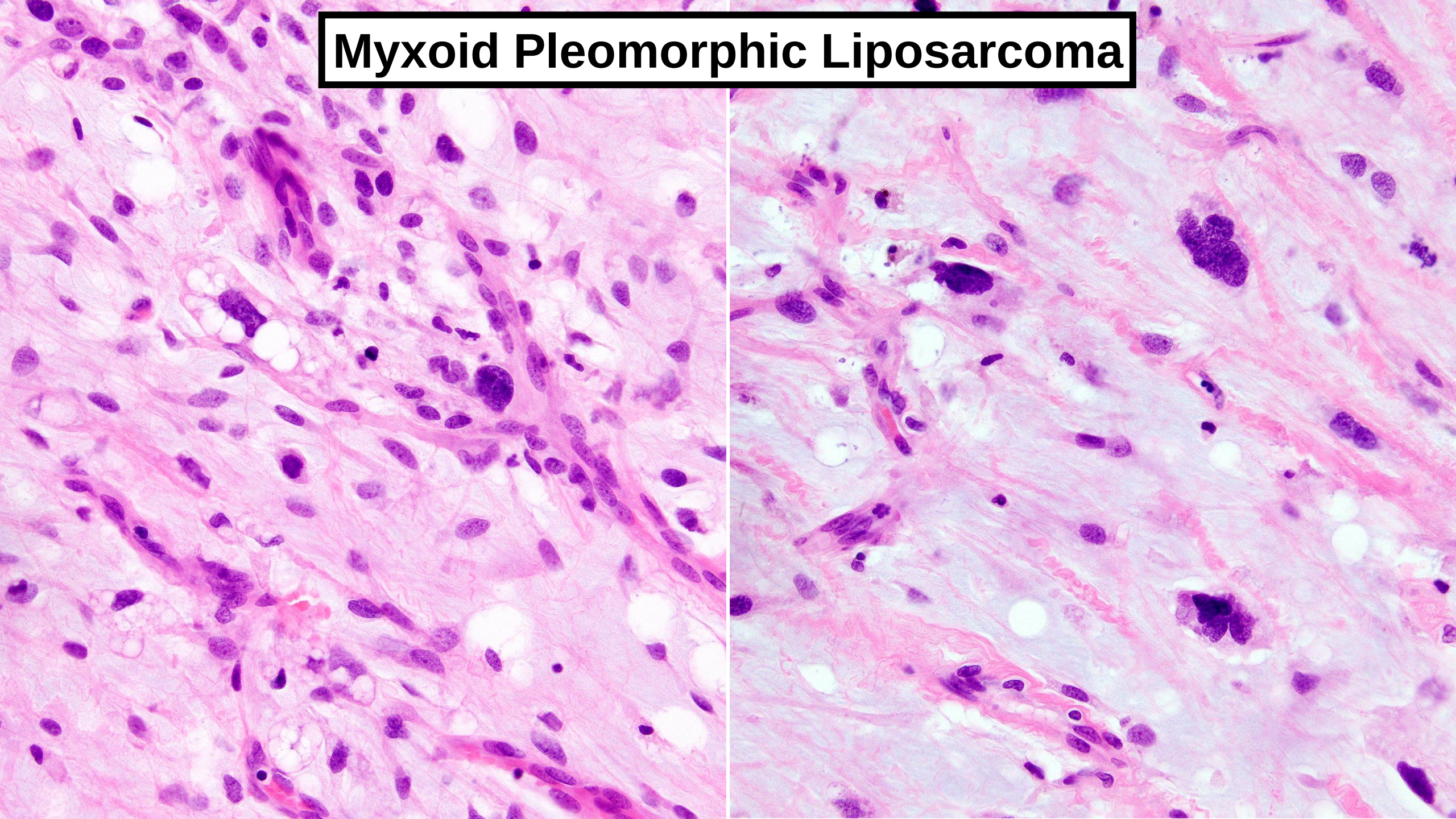
Jennifer M. Boland, MD, Thomas V. Colby, MD,† and Andrew L. Folpe, MD**

Am J Surg Pathol • Volume 36, Number 9, September 2012

Myxoid Pleomorphic Liposarcoma



Myxoid Pleomorphic Liposarcoma



Fibroblastic and myofibroblastic tumors

Fasciitis/myositis	Sinonasal angiofibroma
Fibroma of tendon sheath	Plantar/palmar fibromatosis
Gardner fibroma	Desmoid fibromatosis
Fibrous hamartoma of infancy	*EWSR1::SMAD3* fibroblastic tumor
Lipofibromatosis	Inflammatory myofibroblastic tumor
Inclusion body (digital) fibromatosis	*NTRK*-rearranged spindle cell neoplasm
Juvenile hyaline fibromatosis	Low-grade fibromyxoid sarcoma/ sclerosing epithelioid fibrosarcoma
Fibromatosis colli	Low-grade myofibroblastic sarcoma
Calcifying aponeurotic fibroma	Infantile fibrosarcoma

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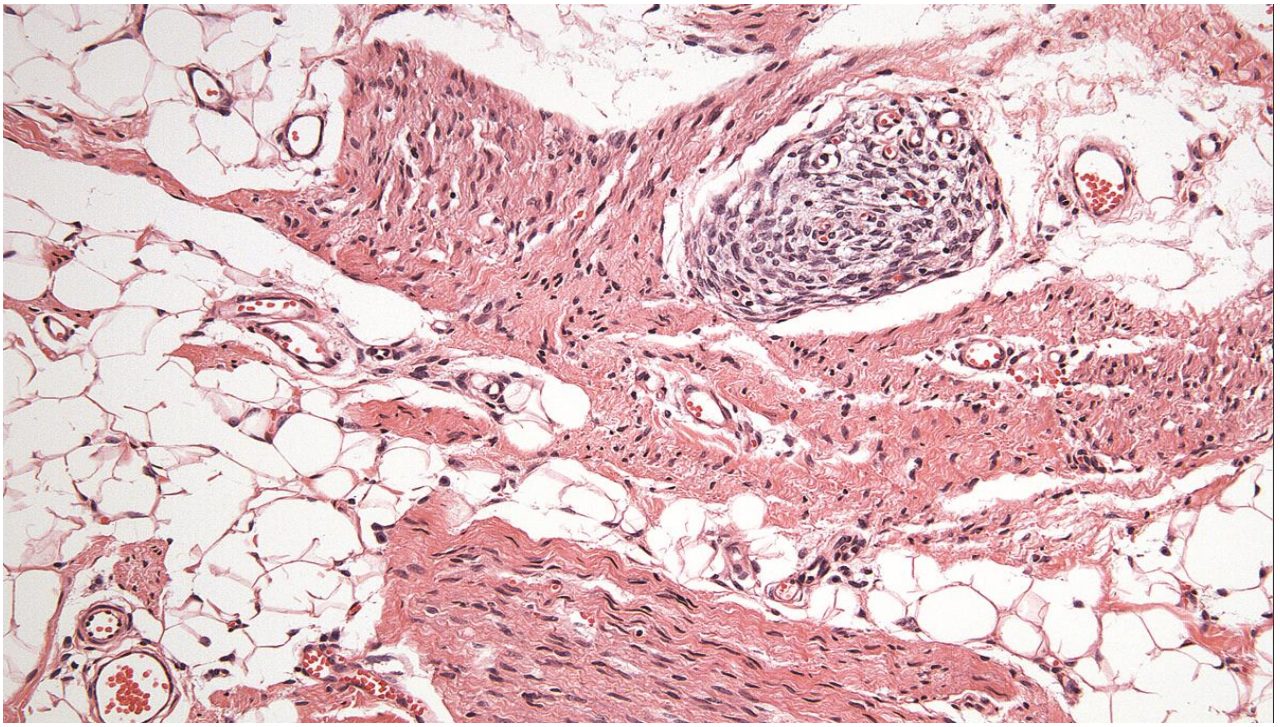
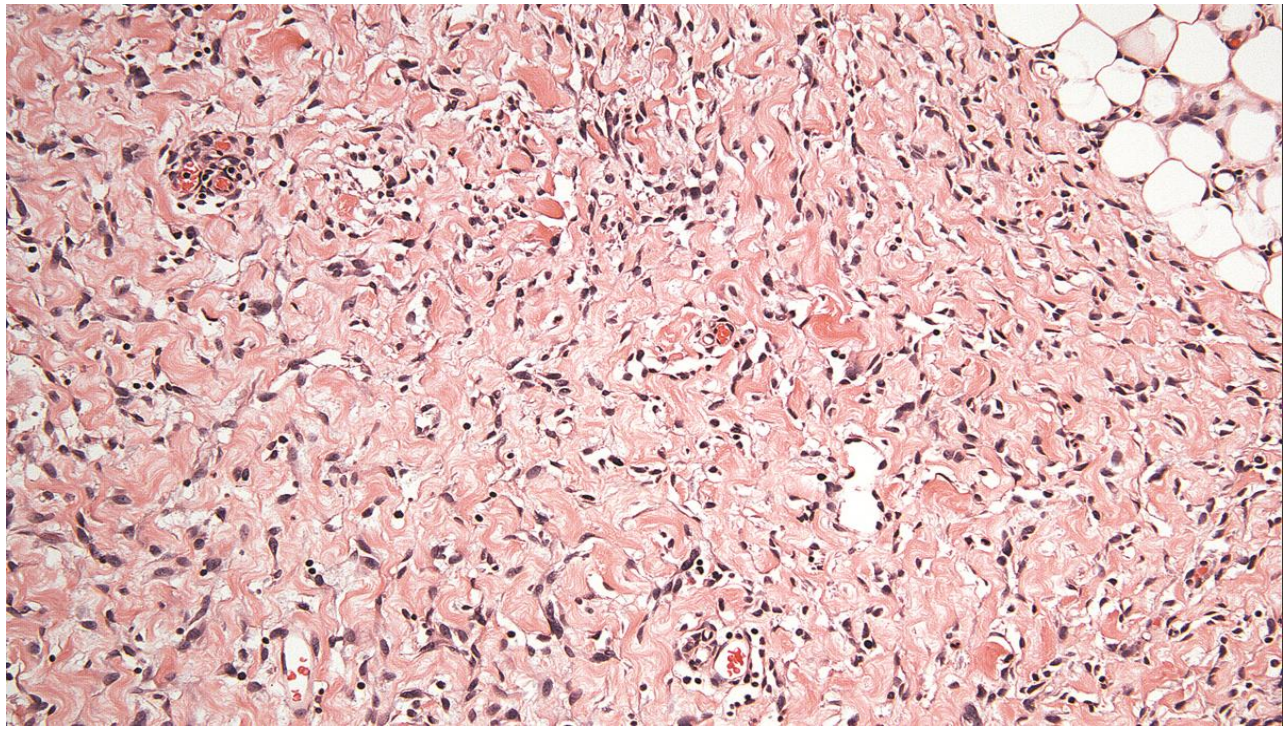
Fibrous Hamartoma of Infancy



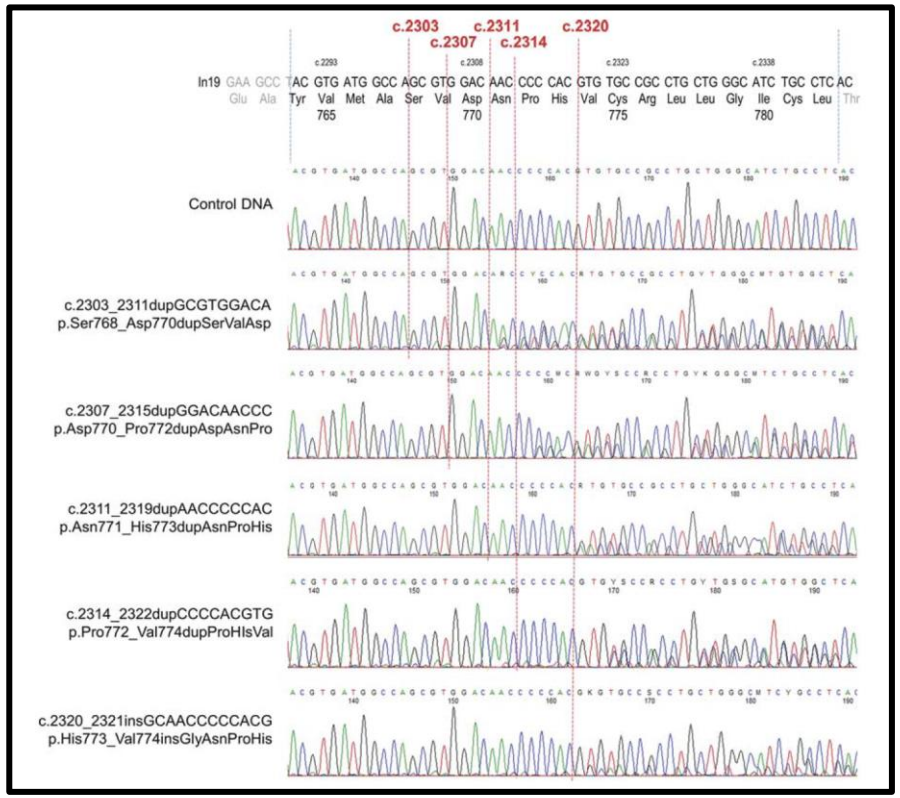


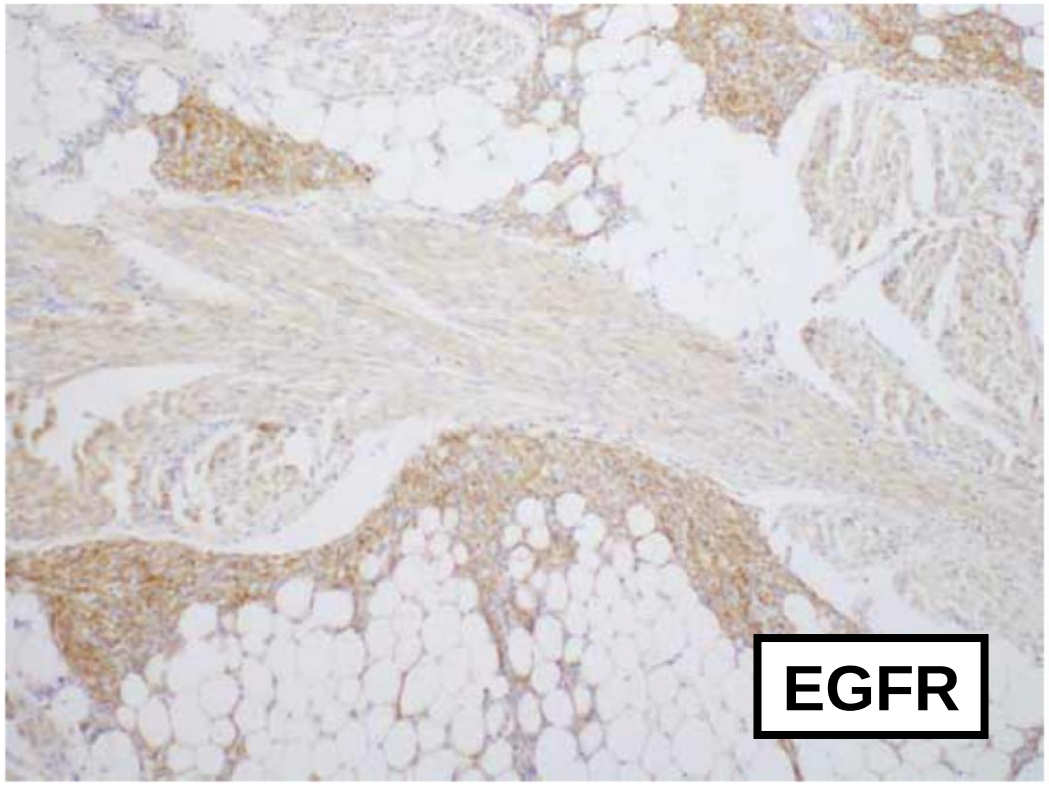
- Most children < 2 yrs; can be congenital (20%)
- Male predominance
- Axilla, trunk, upper extremities, genital region
- Local recurrence (non-destructive) in 15%

EGFR Exon 20 Insertion/Duplication Mutations Characterize Fibrous Hamartoma of Infancy

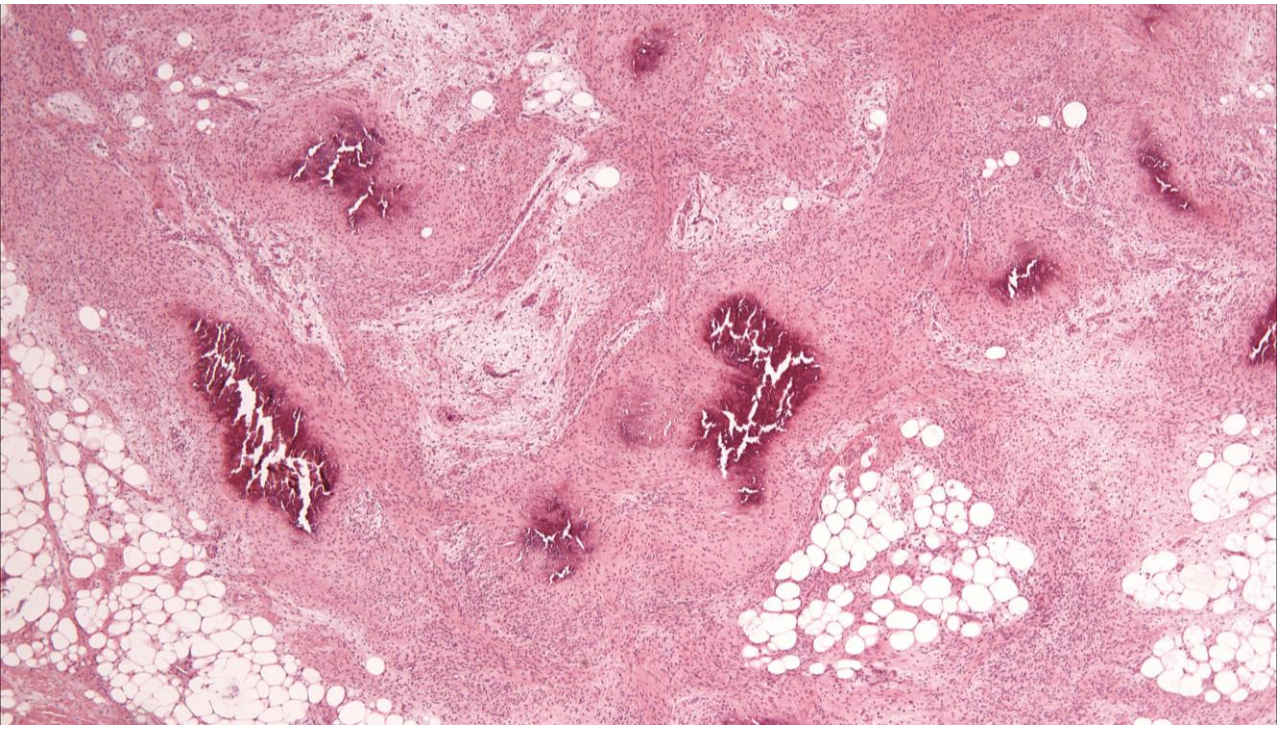
Jason Y. Park, MD, PhD,†‡ Cynthia Cohen, MD,§ Dania Lopez, BS,‡ Erica Ramos, BS,‡ Jennifer Wagenfuehr, BS,‡ and Dinesh Rakheja, MD*‡‖*

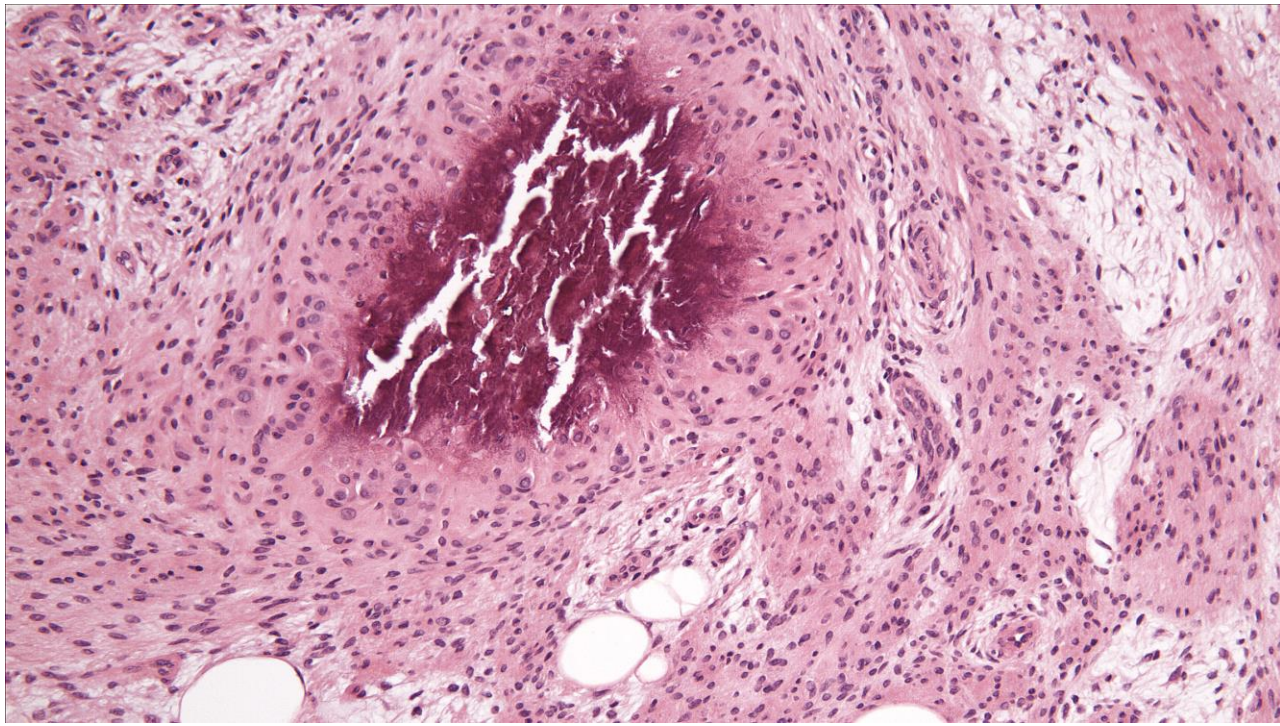
Am J Surg Pathol • Volume 40, Number 12, December 2016





Calcifying Aponeurotic Fibroma





- Peak in children 5 – 15 yrs; M > F
- Palmar hands/fingers >> plantar feet/toes >> wrists or ankles
- Local recurrence up to 50%, sometimes following prolonged interval; multiple recurrences rare

Journal of Pathology
J Pathol 2016; **238:** 502–507
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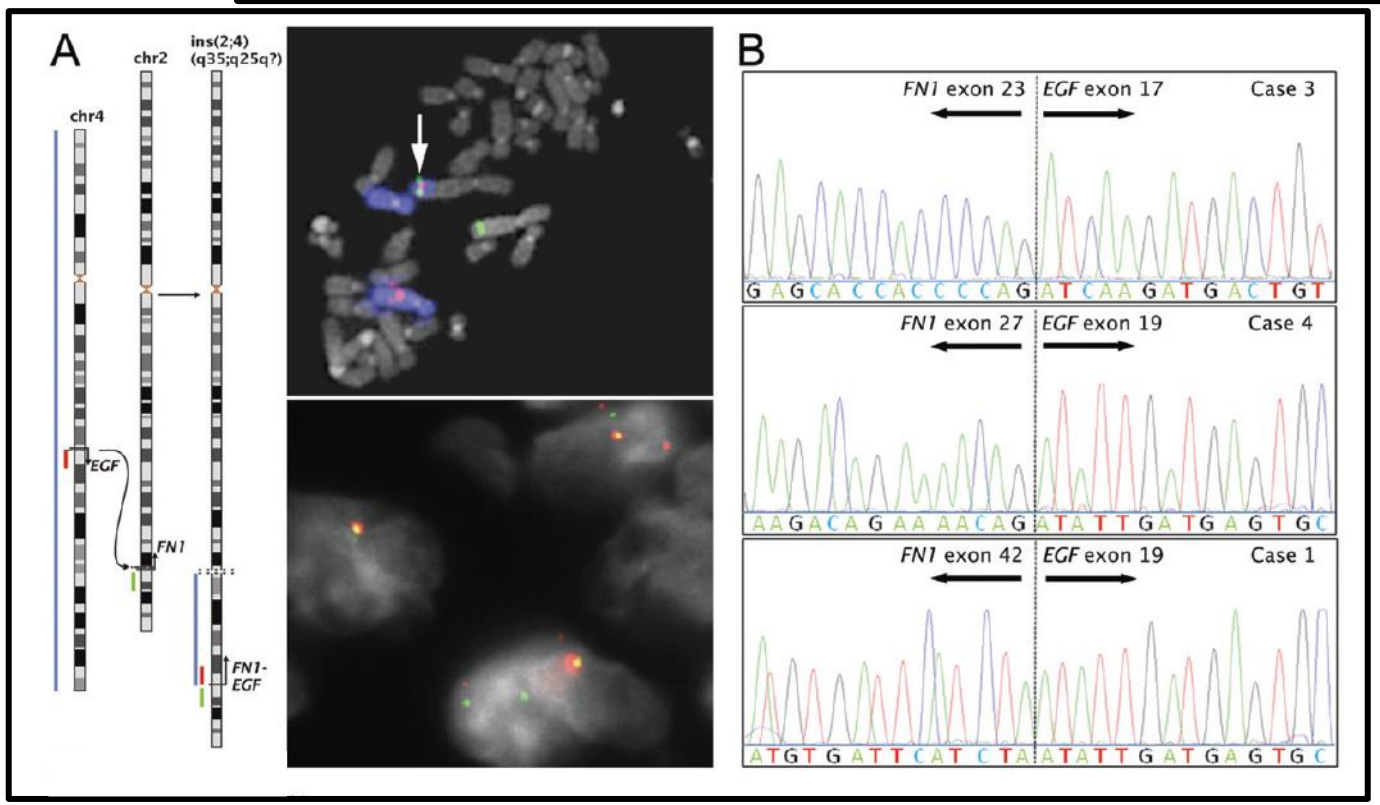
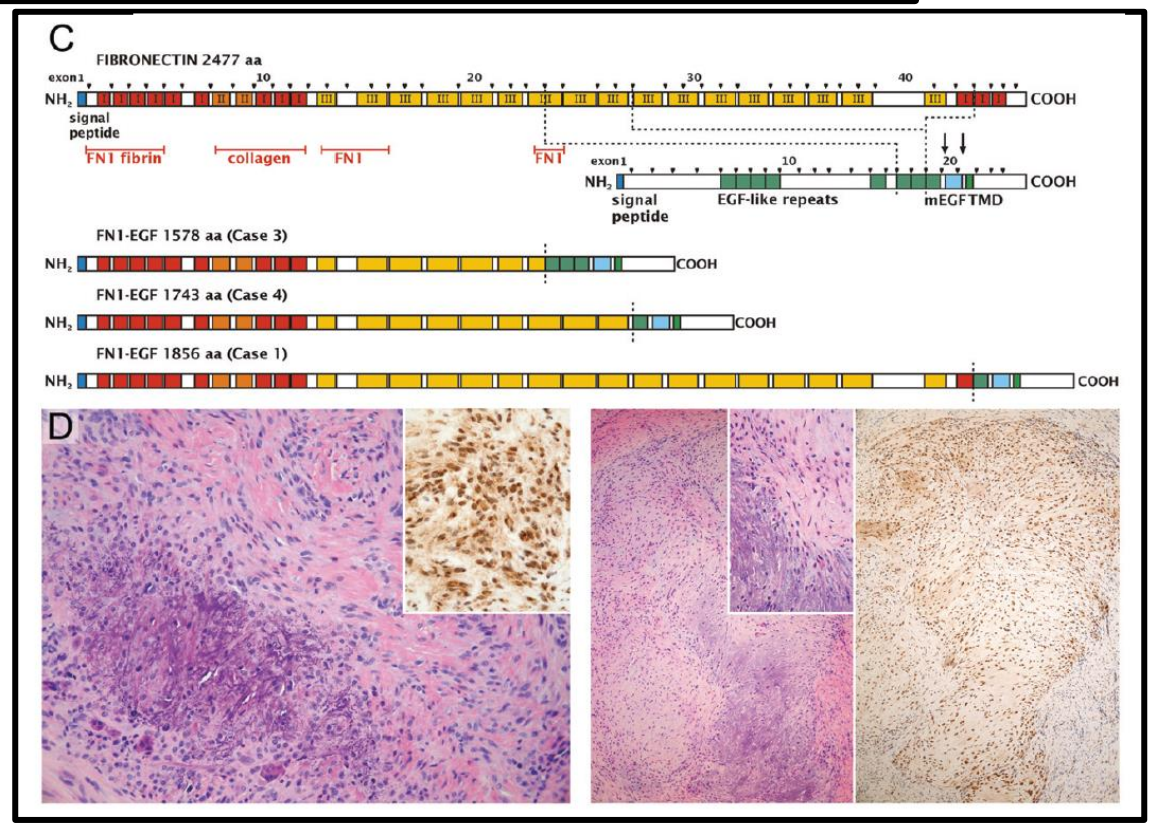
BRIEF DEFINITIVE REPORT

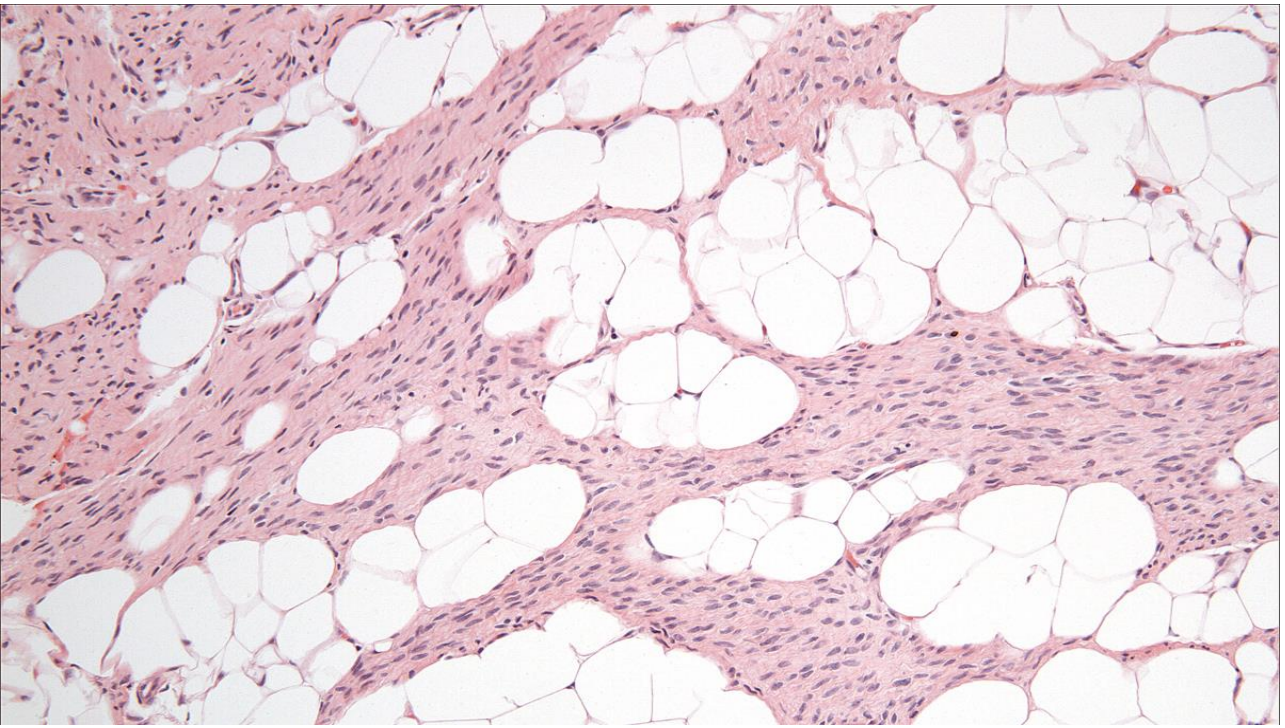
FN1–EGF gene fusions are recurrent in calcifying aponeurotic fibroma

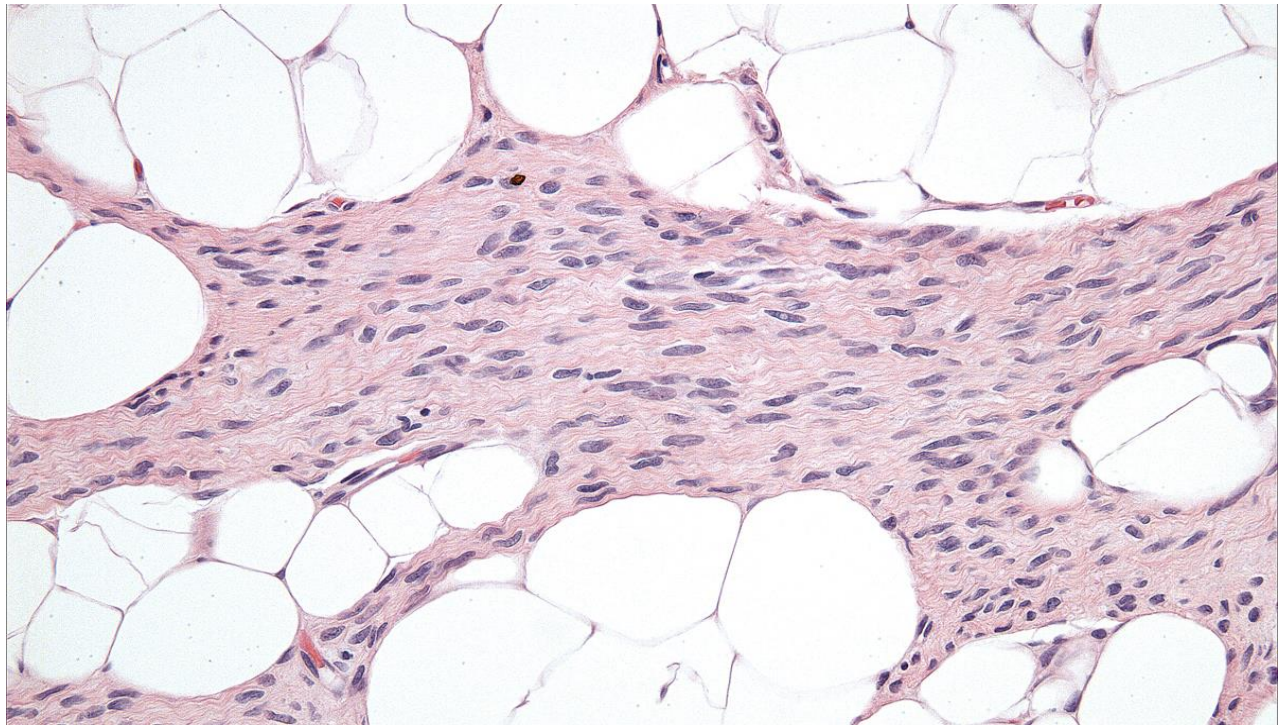
Florian Puls,[1†*] Jakob Hofvander,[2] Linda Magnusson,[2] Jenny Nilsson,[2] Elaine Haywood,[1] Vaiyapuri P Sumathi,[1] D Chas Mangham,[1,3] Lars-Gunnar Kindblom[1] and Fredrik Mertens[2]





Lipofibromatosis



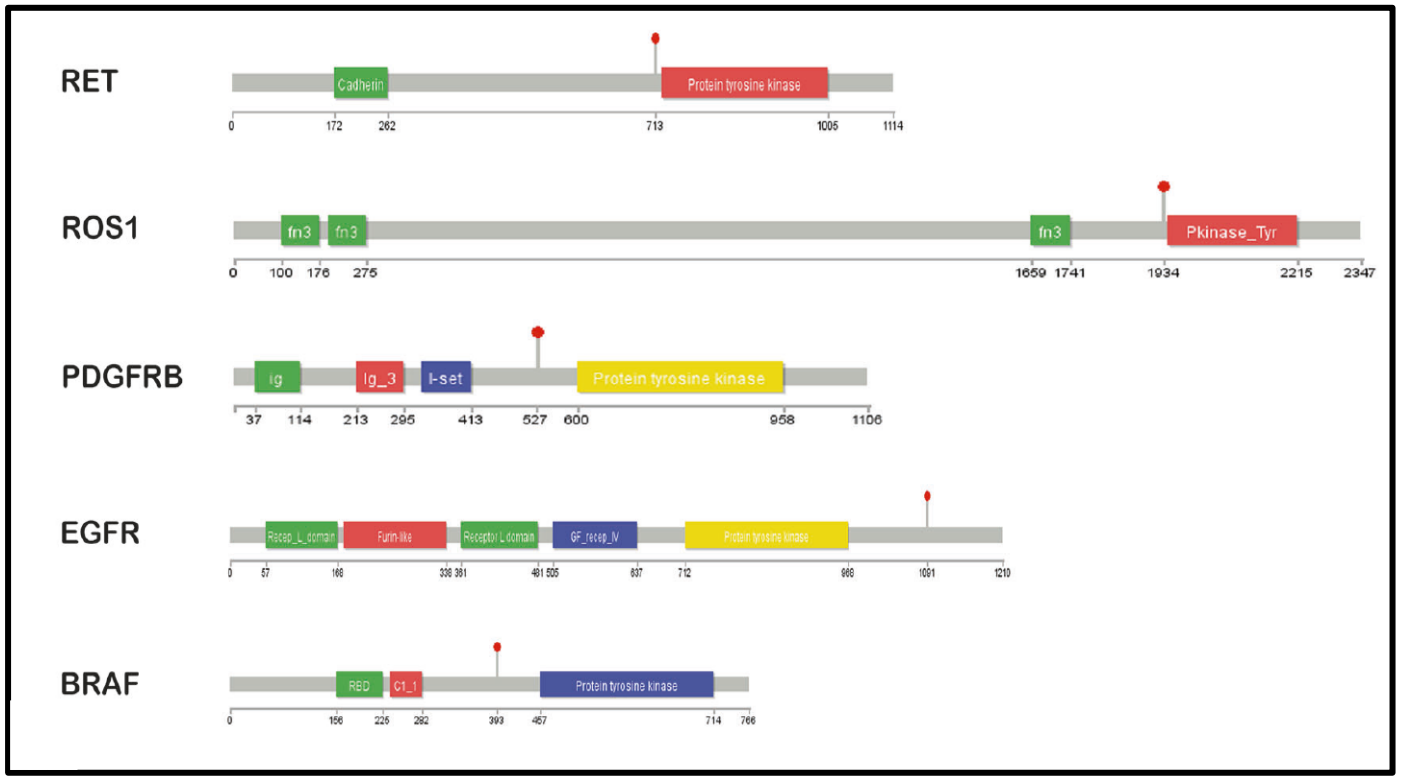


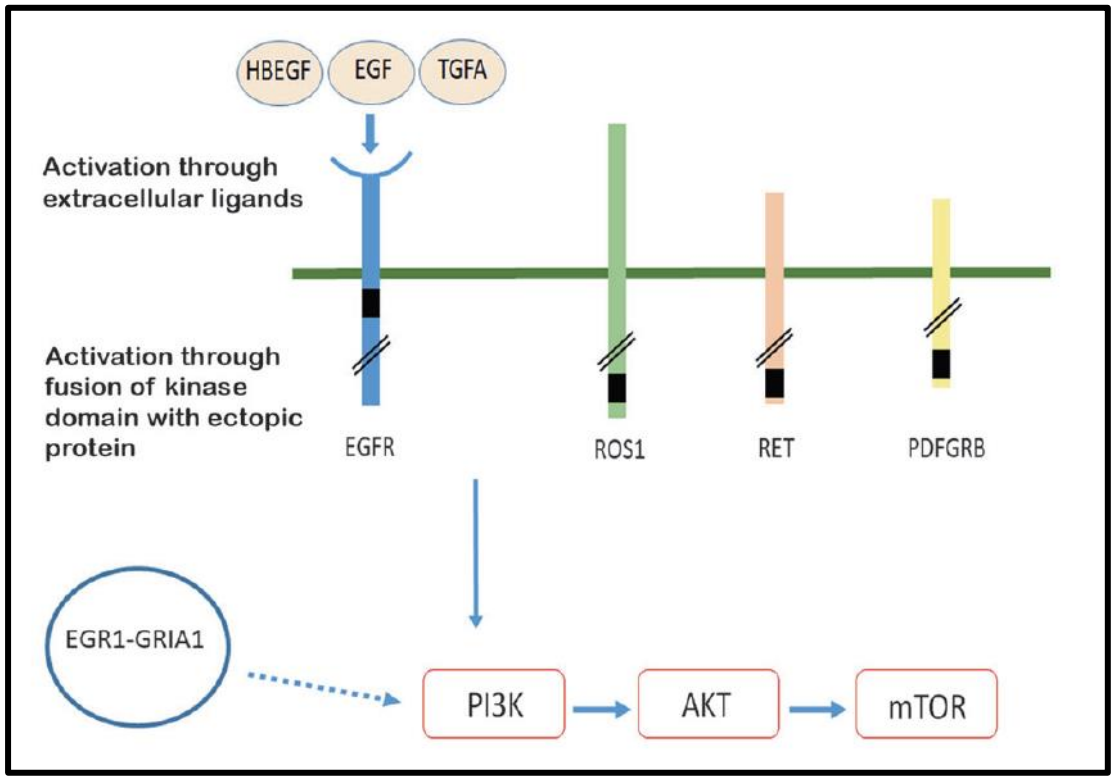
- Children; 50% < 1 yr; 20% congenital; M:F 2:1
- Hands and feet >> trunk and head and neck
- Slow-growing, poorly demarcated subcutaneous mass
- High local recurrence rate (70%)

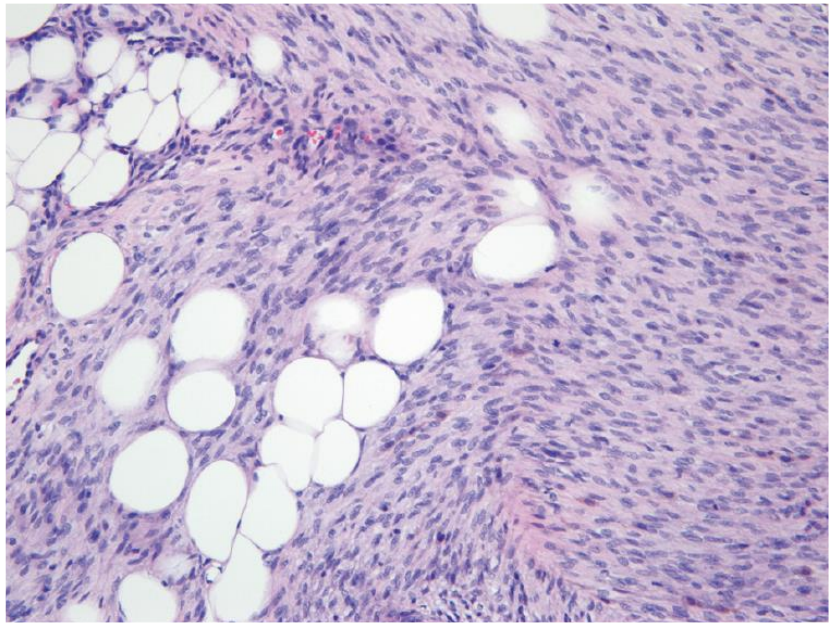
Aberrant receptor tyrosine kinase signaling in lipofibromatosis: a clinicopathological and molecular genetic study of 20 cases

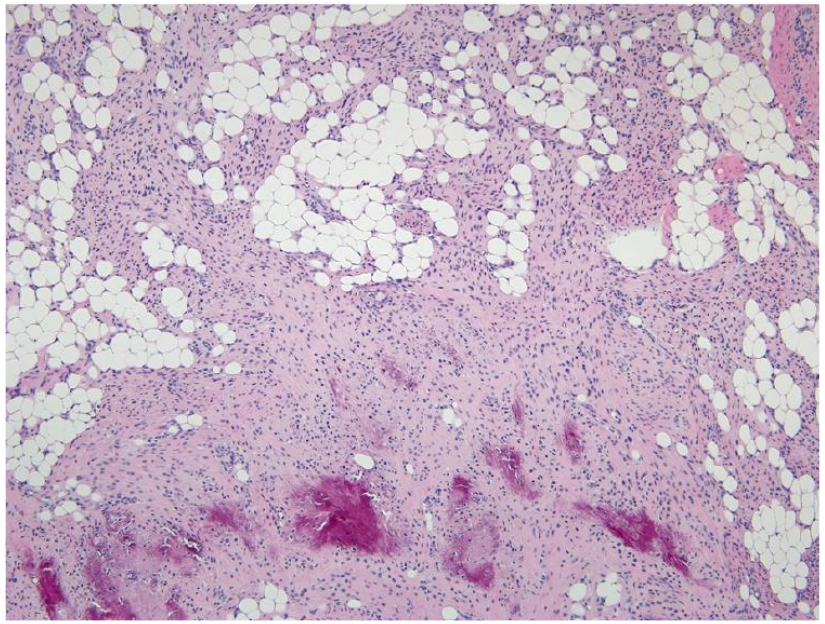
Alyaa Al-Ibraheemi[1] · Andrew L. Folpe[2] · Antonio R. Perez-Atayde[1] · Kyle Perry[3] · Jakob Hofvander[4] · Elsa Arbajian[4] · Linda Magnusson[4] · Jenny Nilsson[4] · Fredrik Mertens[4,5]

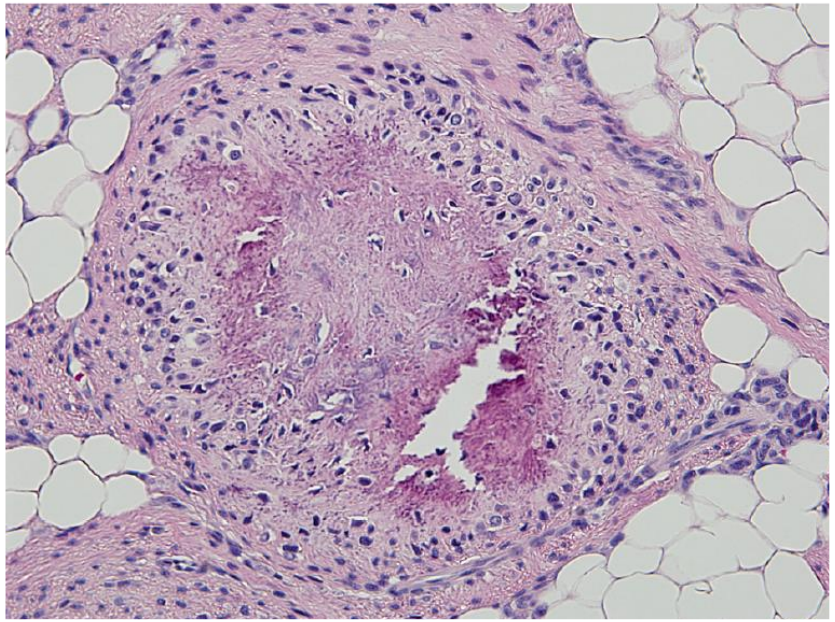
Modern Pathology (2019) 32:423–434



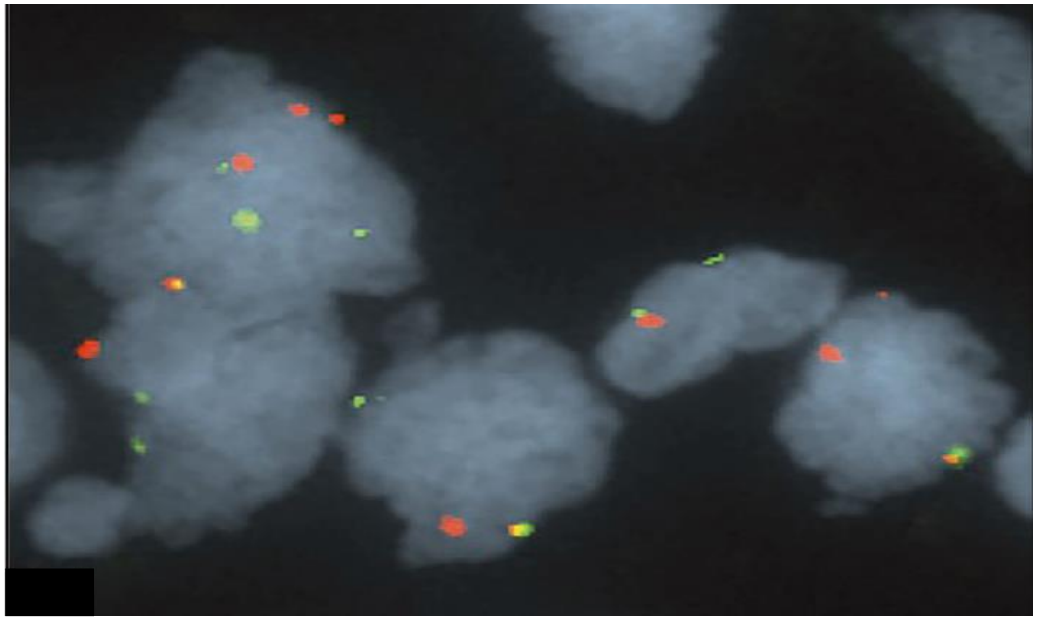








Primary tumor **Local recurrence (3 yr)**



- ***FN1::EGF* in 20%**
- **Some cases “early” calcifying aponeurotic fibroma?**

Al-Ibraheemi et al. *Mod Pathol* 2019

NTRK-rearranged Spindle Cell Neoplasms

Definition:

Emerging family of rare spindle cell tumors showing a wide morphologic spectrum, from lipofibromatosis-like to infantile fibrosarcoma-like lesions, and harboring *NTRK1/2/3* gene rearrangements or other gene alterations (such as *RAF1*, *BRAF*, or *RET*) implicated in receptor tyrosine kinase pathway activation. Our understanding of this category is rapidly evolving; additional genetic alterations may be discovered with further studies.

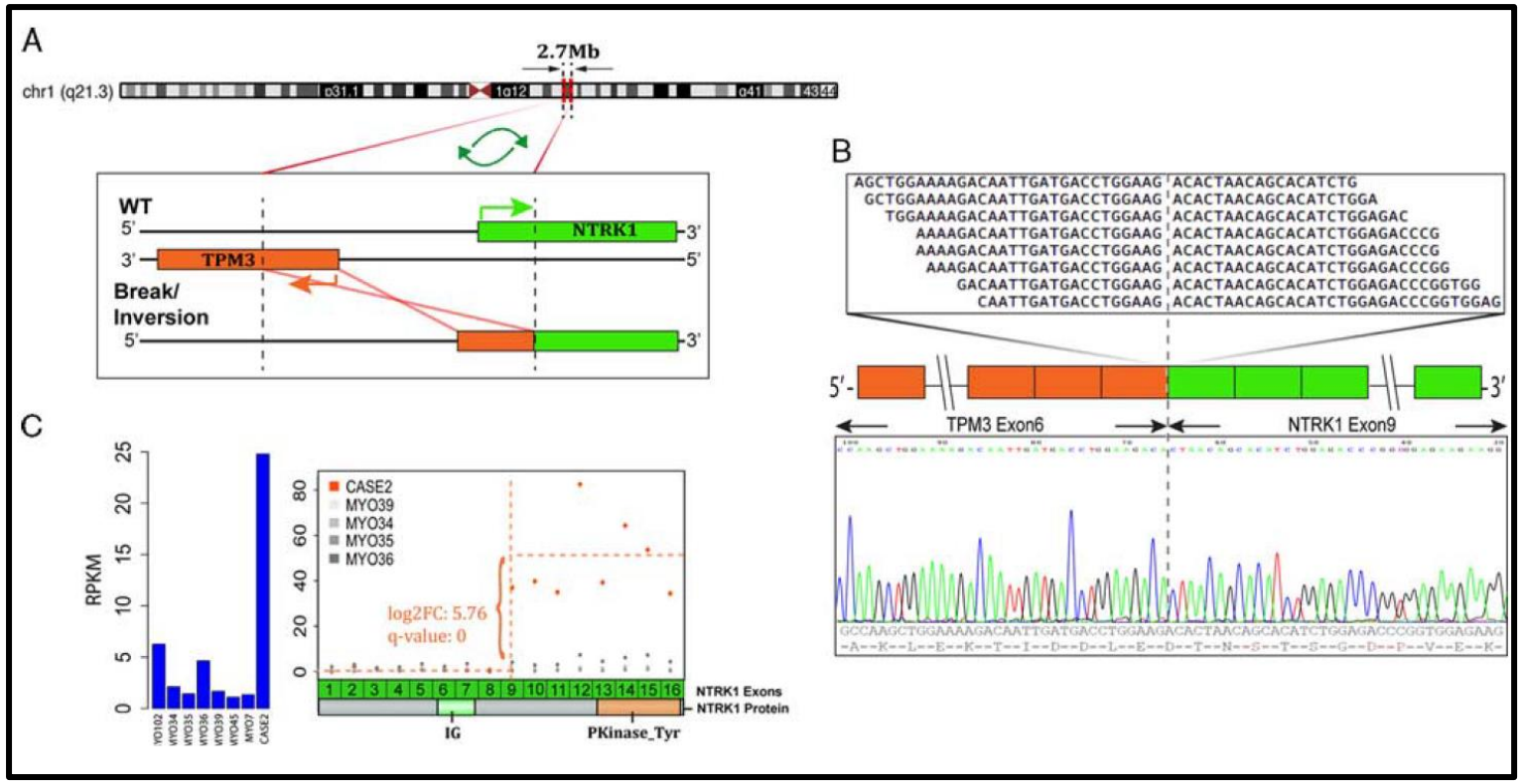
NTRK-rearranged Spindle Cell Neoplasms

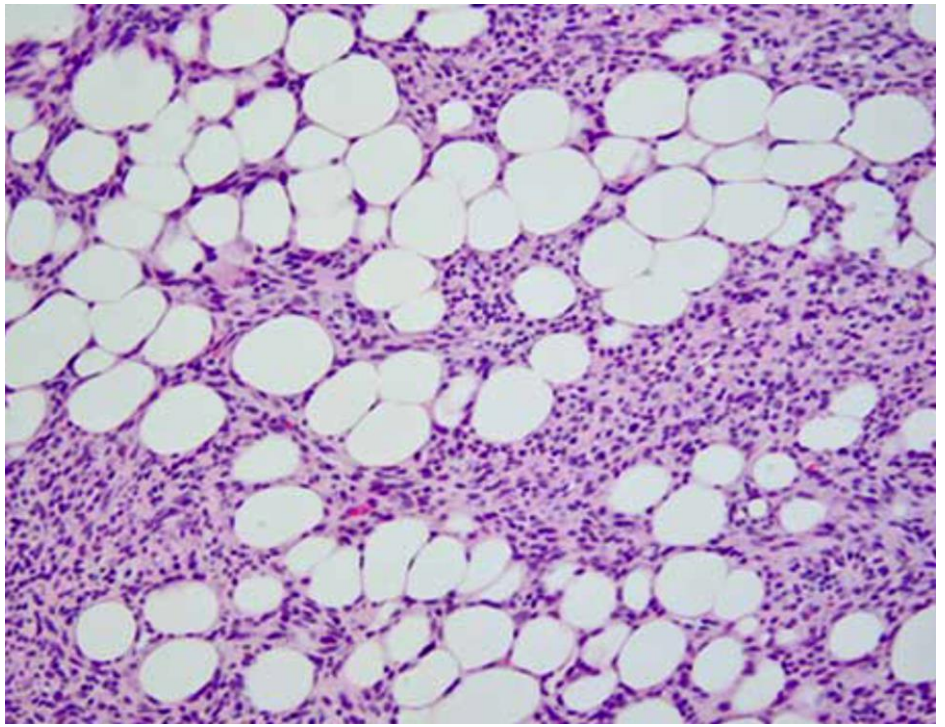
- **Majority occur in first two decades; rarely in adults**
- **Most common in extremities (superficial > deep); also trunk and GI tract**
- **May resemble lipofibromatosis, malignant peripheral nerve sheath tumor, infantile fibrosarcoma**
- **Co-expression of S100 protein and CD34 common**
- **Pediatric tumors can recur locally; metastasis rare**
- **Prognostic significance of histologic features (cellularity, mitotic rate, necrosis) not entirely clear**

Recurrent *NTRK1* Gene Fusions Define a Novel Subset of Locally Aggressive Lipofibromatosis-like Neural Tumors

Narasimhan P. Agaram, MBBS, Lei Zhang, MD,* Yun-Shao Sung, MS,* Chun-Liang Chen, MS,* Catherine T. Chung, MD,† Cristina R. Antonescu, MD,* and Christopher DM Fletcher, MD, FRCPath‡*

Am J Surg Pathol • Volume 40, Number 10, October 2016

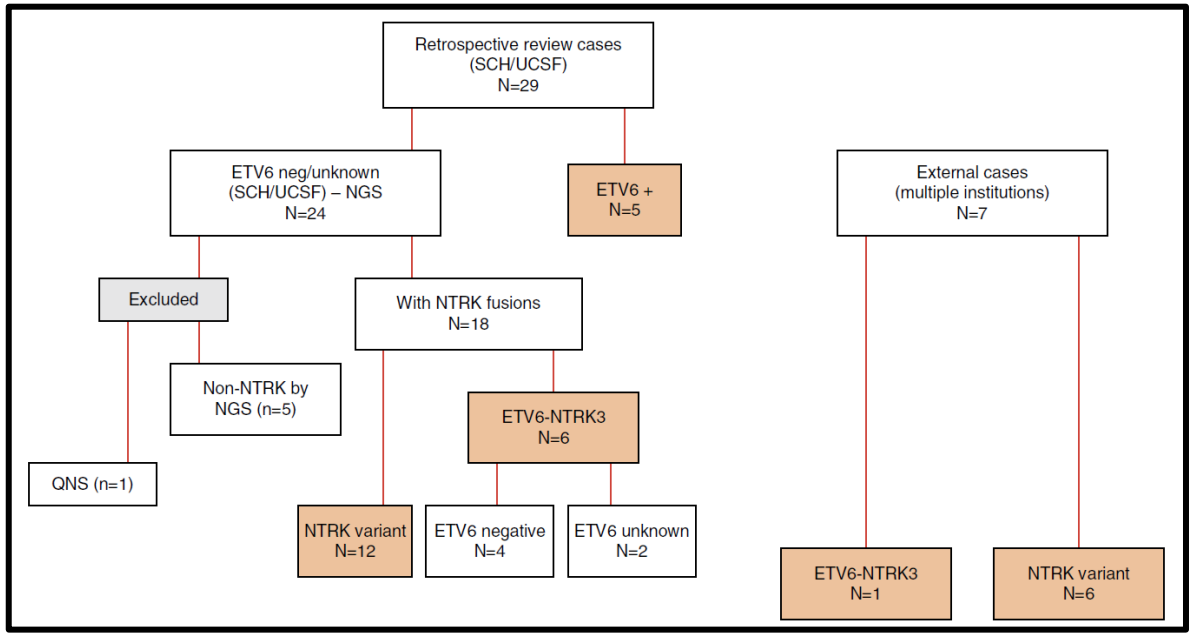




Expanding the Spectrum of Pediatric *NTRK*-rearranged Mesenchymal Tumors

Jessica L. Davis, MD,† Christina M. Lockwood, PhD,‡ Bradley Stohr, MD, PhD,† Carolin Boecking, MD,† Alyaa Al-Ibraheemi, MD,§ Steven G. DuBois, MD,‖ Sara O. Vargas, MD,§ Jennifer O. Black, MD,¶ Michael C. Cox, PharmD,# Mark Luquette, MD,** Brian Turpin, DO,†† Sara Szabo, MD,‡‡ Theodore W. Laetsch, MD,§§ Catherine M. Albert, MD,‖‖ David M. Parham, MD,¶¶ Douglas S. Hawkins, MD,‖‖ and Erin R. Rudzinski, MD##*

Am J Surg Pathol • Volume 43, Number 4, April 2019



NTRK variant fusions
TPM3::NTRK1
LMNA::NTRK1
MIR584F1::NTRK1
SQSTM1::NTRK1
TPR::NTRK1
STRN::NTRK2
EML4::NTRK3

Histopathology

Histopathology 2020, 76, 1032–1041. DOI: 10.1111/his.14082

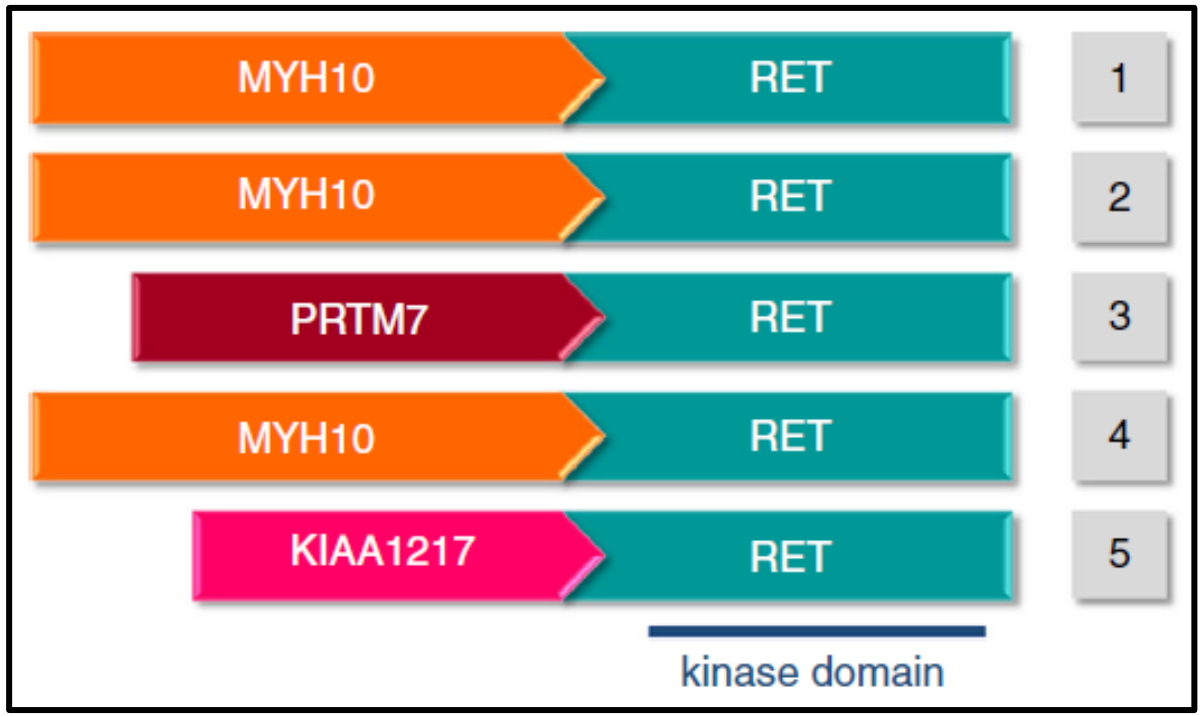
Recurrent *RET* gene fusions in paediatric spindle mesenchymal neoplasms*

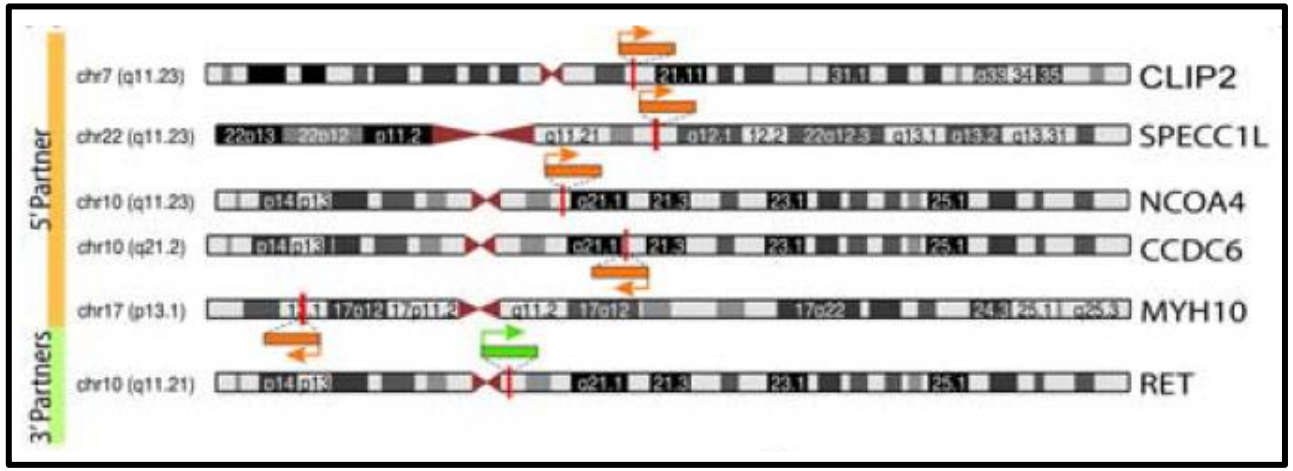
Jessica L Davis,[1] Sara O Vargas,[2] Erin R Rudzinski,[3] Jessica M López Marti,[4] Katherine Janeway,[5] Suzanne Forrest,[5] Katrina Winsnes,[6] Navin Pinto,[7] Sung E Yang,[1] Mandy VanSandt,[1] Theonia K Boyd,[2] Christopher L Corless,[1] Yajuan J Liu,[8] Lea F Surrey,[9] Marian H Harris,[2] Alanna Church[2] & Alyaa Al-Ibraheemi[2]

Spindle Cell Tumors With RET Gene Fusions Exhibit a Morphologic Spectrum Akin to Tumors With NTRK Gene Fusions

Cristina R. Antonescu, MD, Brendan C. Dickson, MD,† David Swanson, BSc,† Lei Zhang, MD,* Yun-Shao Sung, BSc,* Yu-Chien Kao, MD,‡ Wei-Chin Chang, MD,§ Leili Ran, PhD,‖ Alberto Pappo, MD,¶ Armita Bahrami, MD,# Ping Chi, MD, PhD,‖ and Christopher D. Fletcher, MD***

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





A novel group of spindle cell tumors defined by S100 and CD34 co-expression shows recurrent fusions involving RAF1, BRAF, and NTRK1/2 genes

Albert J. H. Suurmeijer[1] | Brendan C. Dickson[2] | David Swanson[2] | Lei Zhang[3] | Yun-Shao Sung[3] | Paolo Cotzia[3] | Christopher D. M. Fletcher[4] | Cristina R. Antonescu[3]

Genes Chromosomes Cancer. 2018;57:611–621.

Soft tissue tumors characterized by a wide spectrum of kinase fusions share a lipofibromatosis-like neural tumor pattern

Yu-Chien Kao[1,2] | Albert J. H. Suurmeijer[3] | Pedram Argani[4] | Brendan C. Dickson[5] | Lei Zhang[6] | Yun-Shao Sung[6] | Narasimhan P Agaram[6] | Christopher D. M. Fletcher[7] | Cristina R. Antonescu[6]

Genes Chromosomes Cancer. 2020;59:575–583.

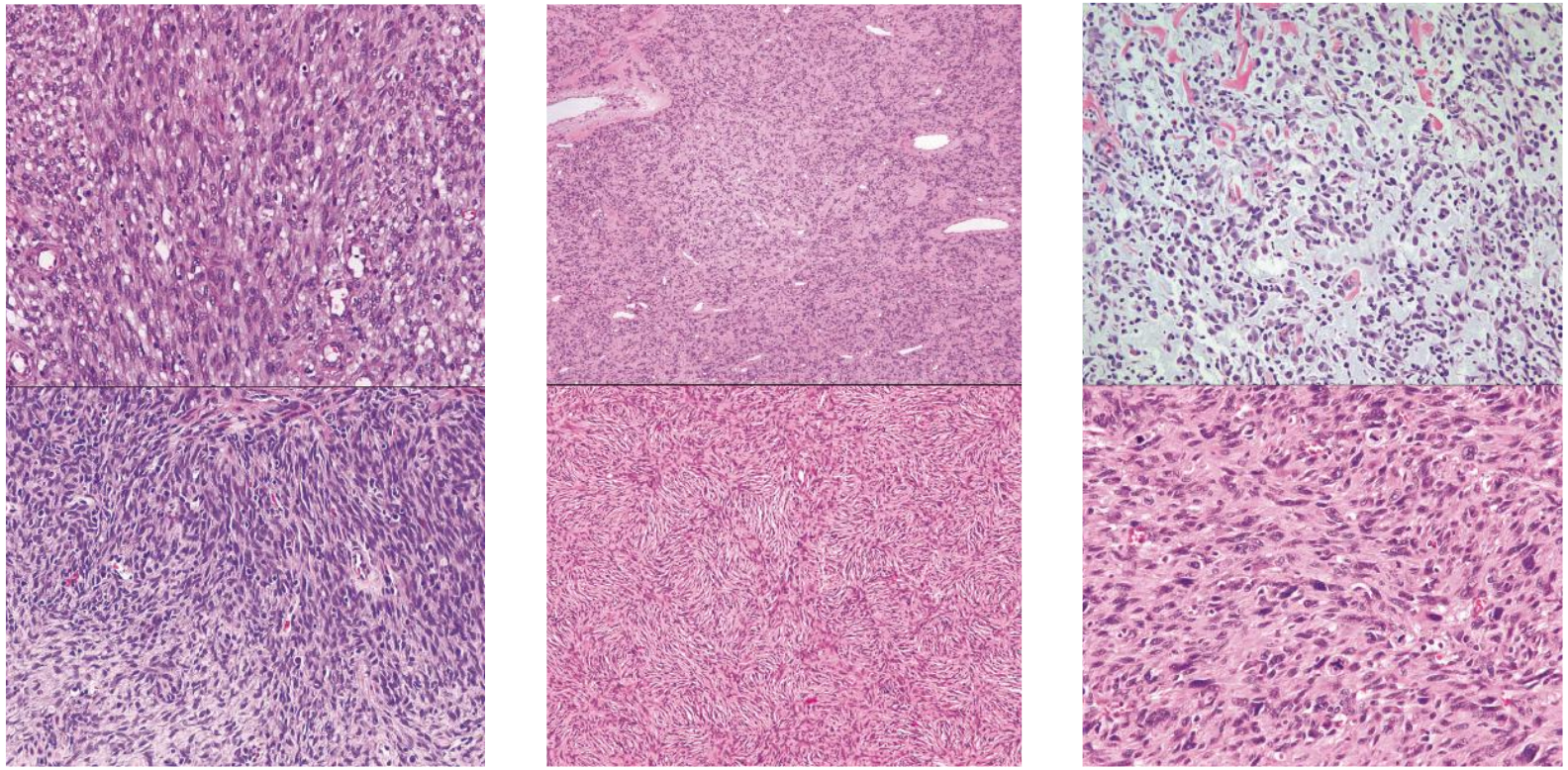
	NTRK1	*RET*	*ALK*	*NTRK3*	*NTRK2*	*ROS1*	*MET*	Total
Pure LPF-like	7	3	2	0	0	0	0	12
Hybrid	20	0	0	1	1	1	1	24
Subtotal (pure LPF-like+ hybrid)	27	3	2	1	1	1	1	36
No LPF area (denominator)	19	3	0	12	1	0	2	37
Total	46	6	2	13	2	1	3	73

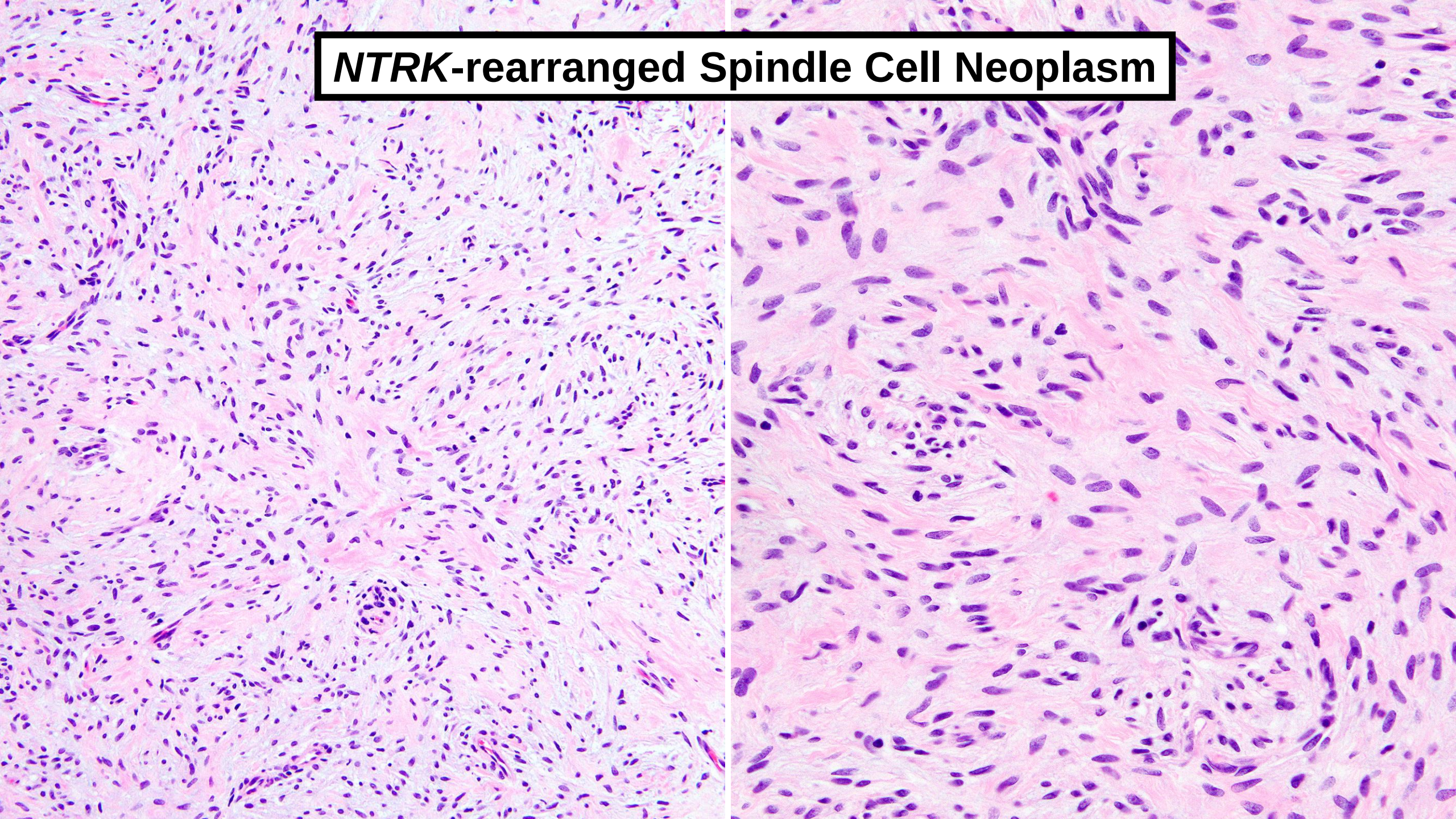
Mesenchymal tumors of the gastrointestinal tract with *NTRK* rearrangements: a clinicopathological, immunophenotypic, and molecular study of eight cases, emphasizing their distinction from gastrointestinal stromal tumor (GIST)

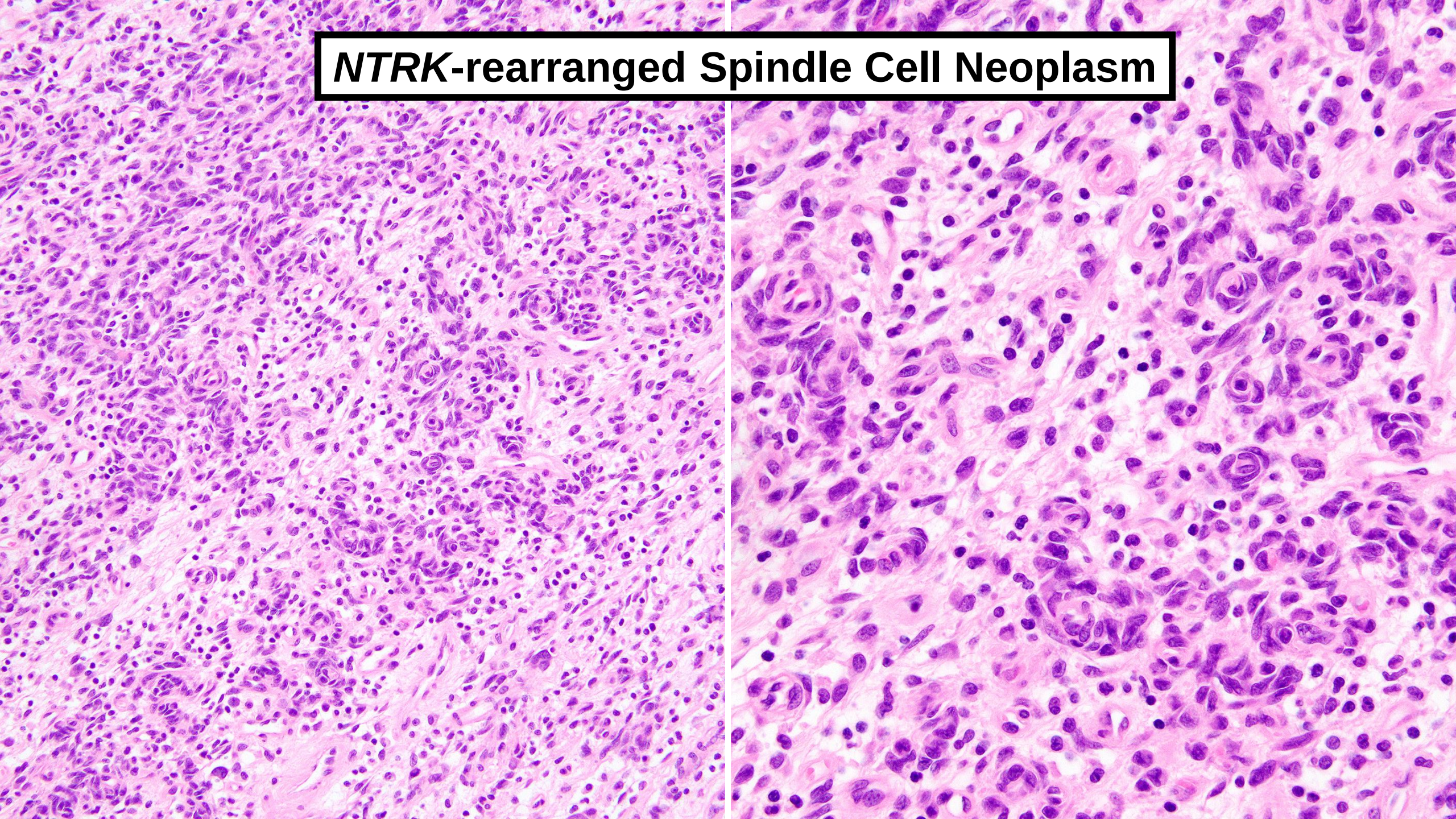
Mazen A. Atiq[1] · Jessica L. Davis[2] · Jason L. Hornick[3] · Brendan C. Dickson[4] · Christopher D. M. Fletcher[3] · Jonathan A. Fletcher[3] · Andrew L. Folpe[1] · Adrián Mariño-Enríquez[3]

Modern Pathology (2021) 34:95–103

ETV6–NTRK3
ETV6–NTRK3
TPM3–NTRK1
SPECC1L–NTRK3
TPM3–NTRK1
LMNA–NTRK1
TPM3–NTRK1
TPR–NTRK1




NTRK-rearranged Spindle Cell Neoplasm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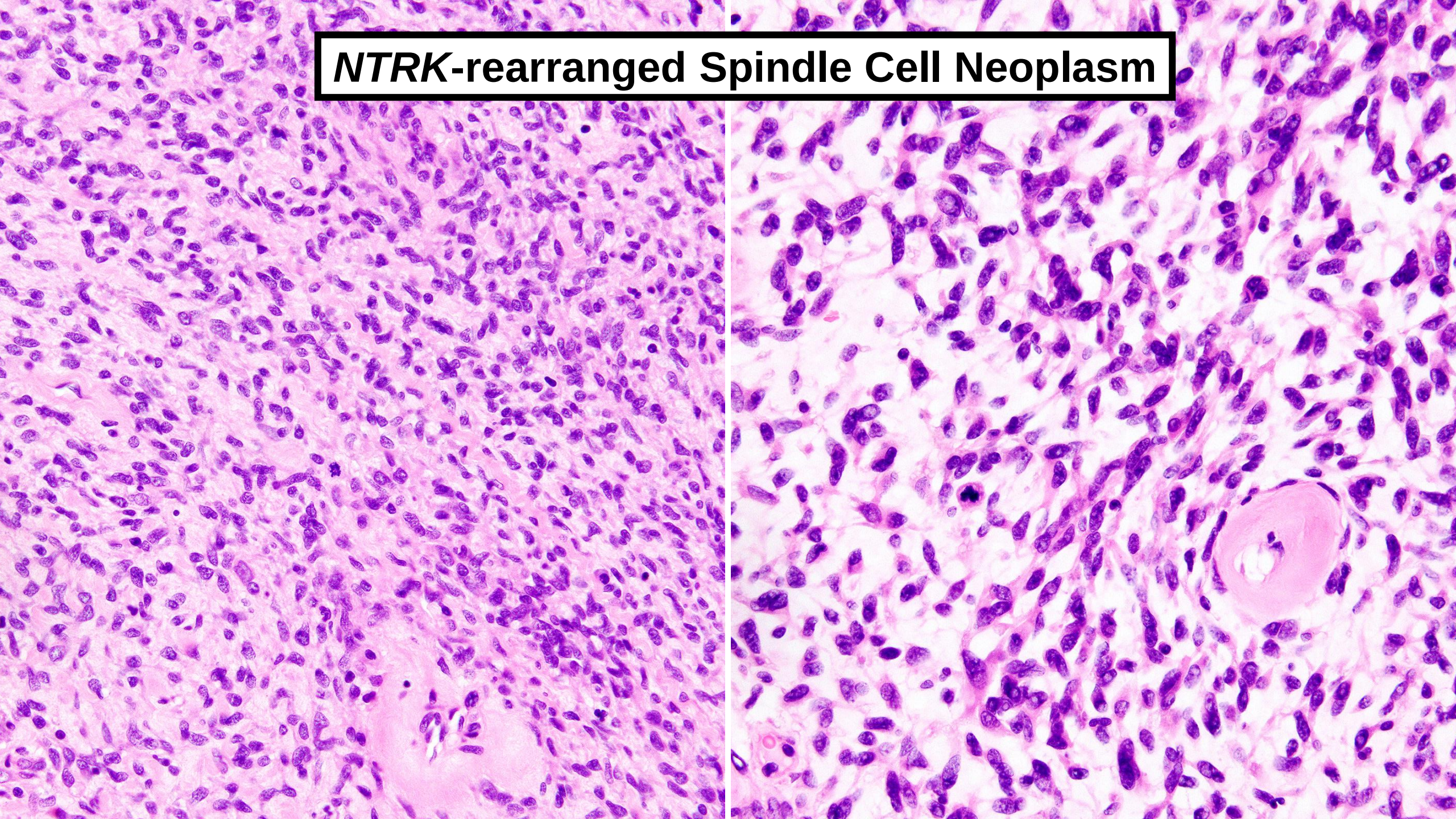
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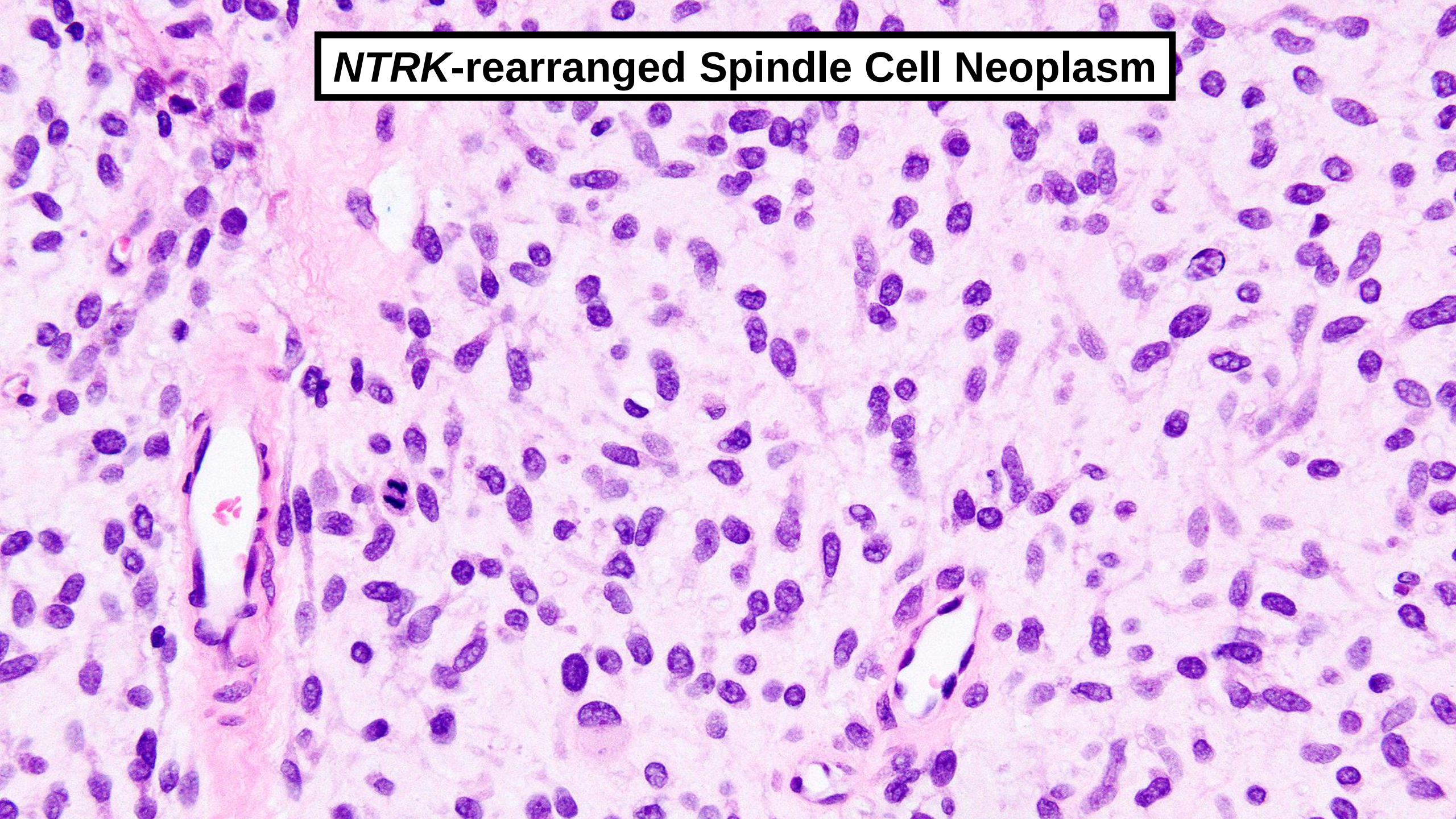
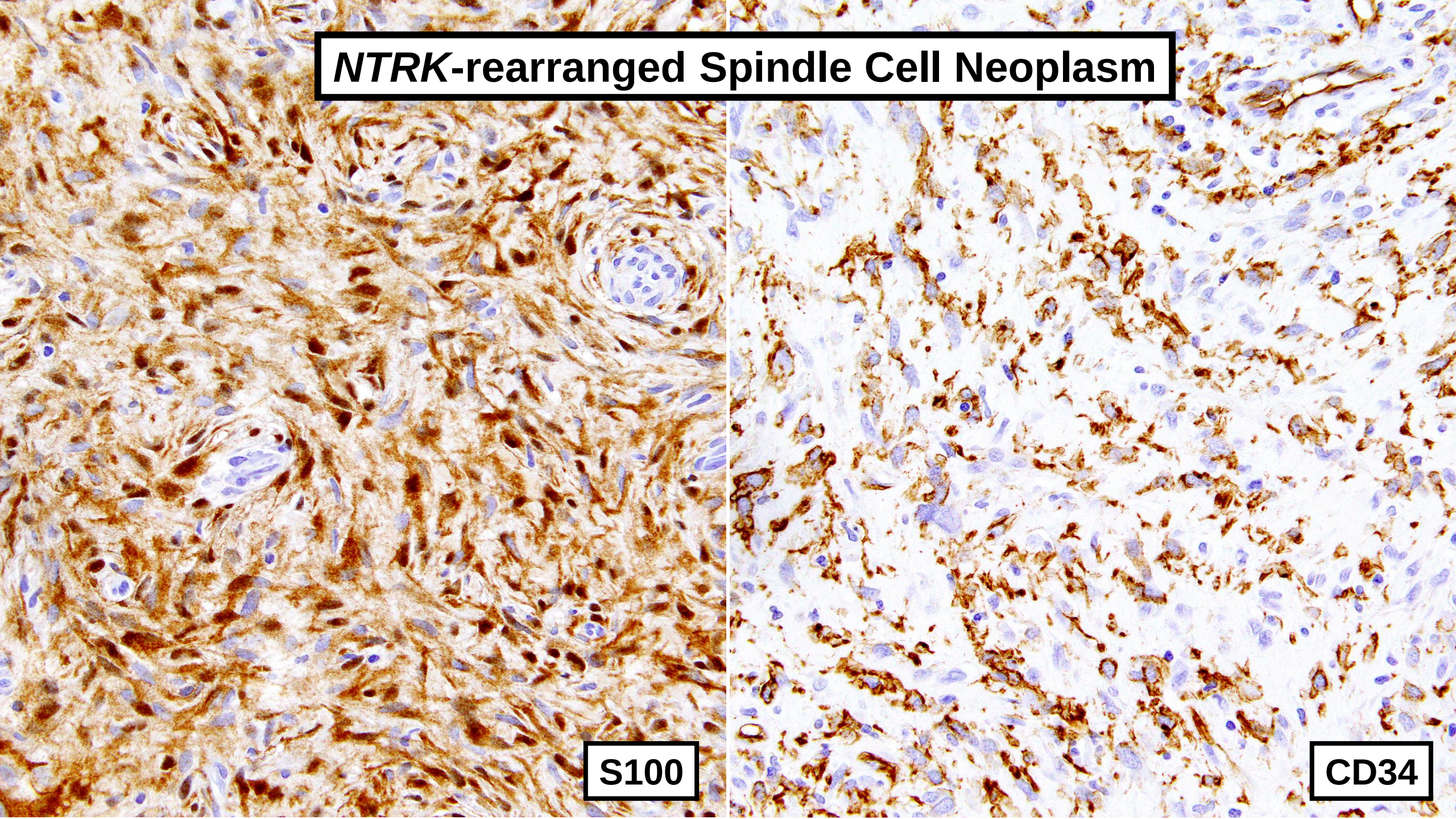
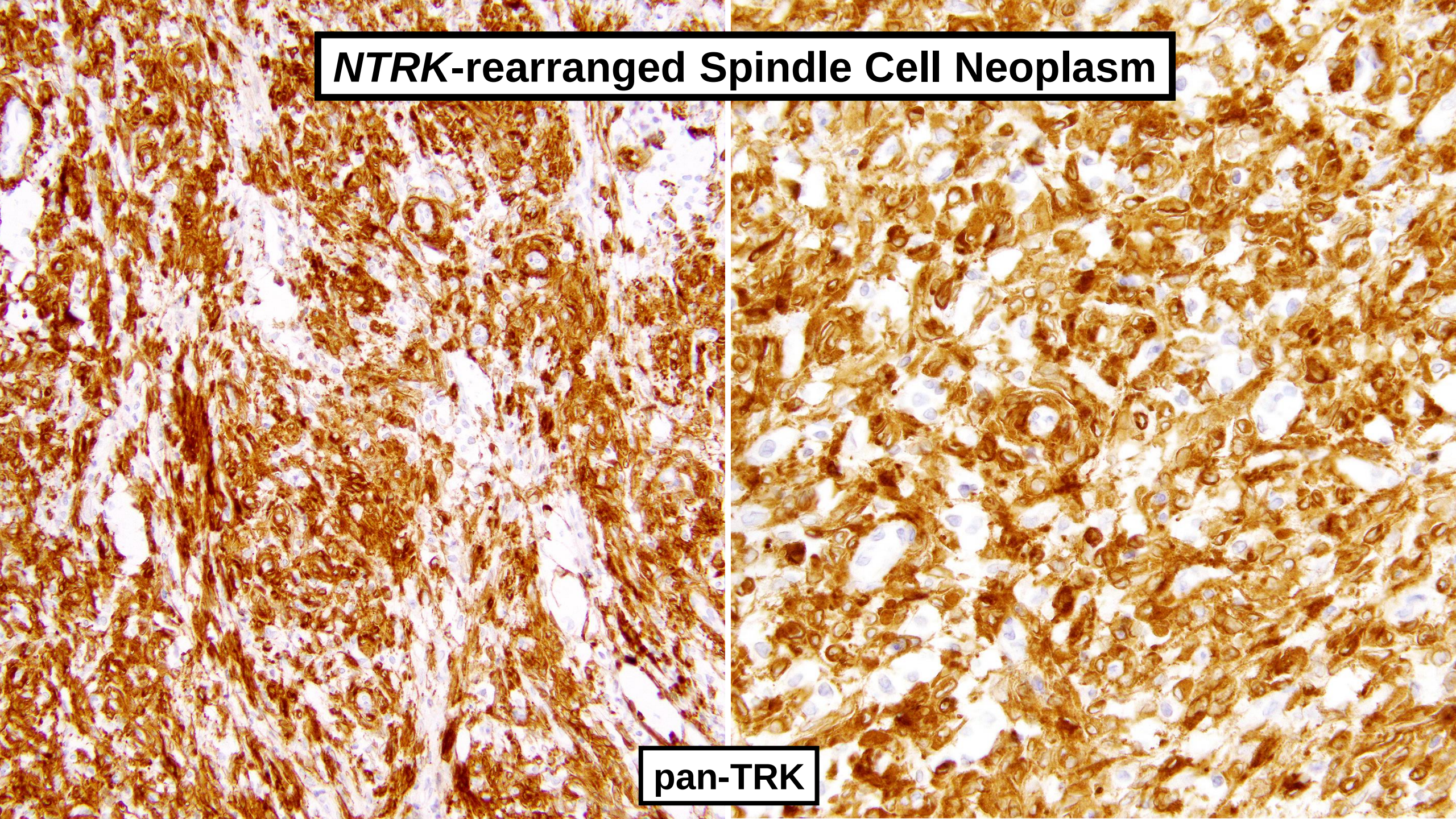

NTRK-rearranged Spindle Cell Neoplasm


NTRK-rearranged Spindle Cell Neoplasm
S100
CD34


NTRK-rearranged Spindle Cell Neoplasm
pan-TRK

So-called Fibrohistiocytic Tumors
Fibrous histiocytoma
Plexiform fibrohistiocytic tumor
Giant cell fibroblastoma / dermatofibrosarcoma protuberans
Tenosynovial giant cell tumor

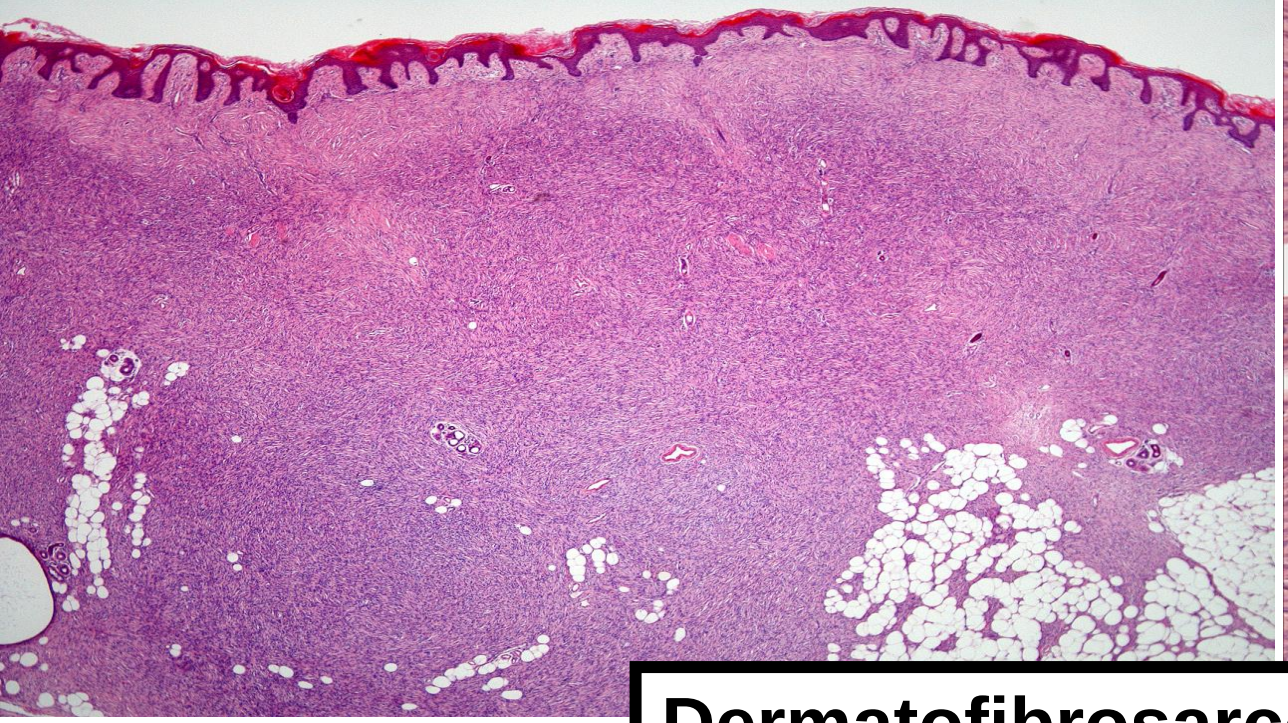
So-called Fibrohistiocytic Tumors

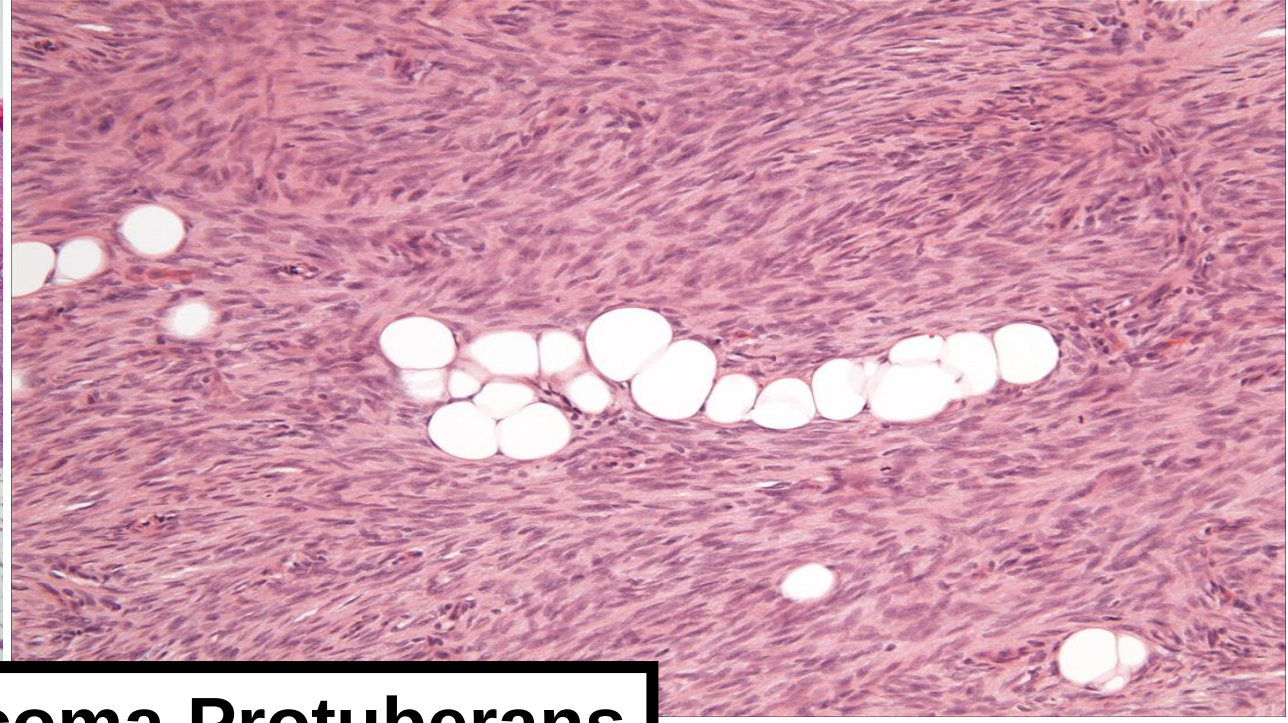
Fibrous histiocytoma

Plexiform fibrohistiocytic tumor

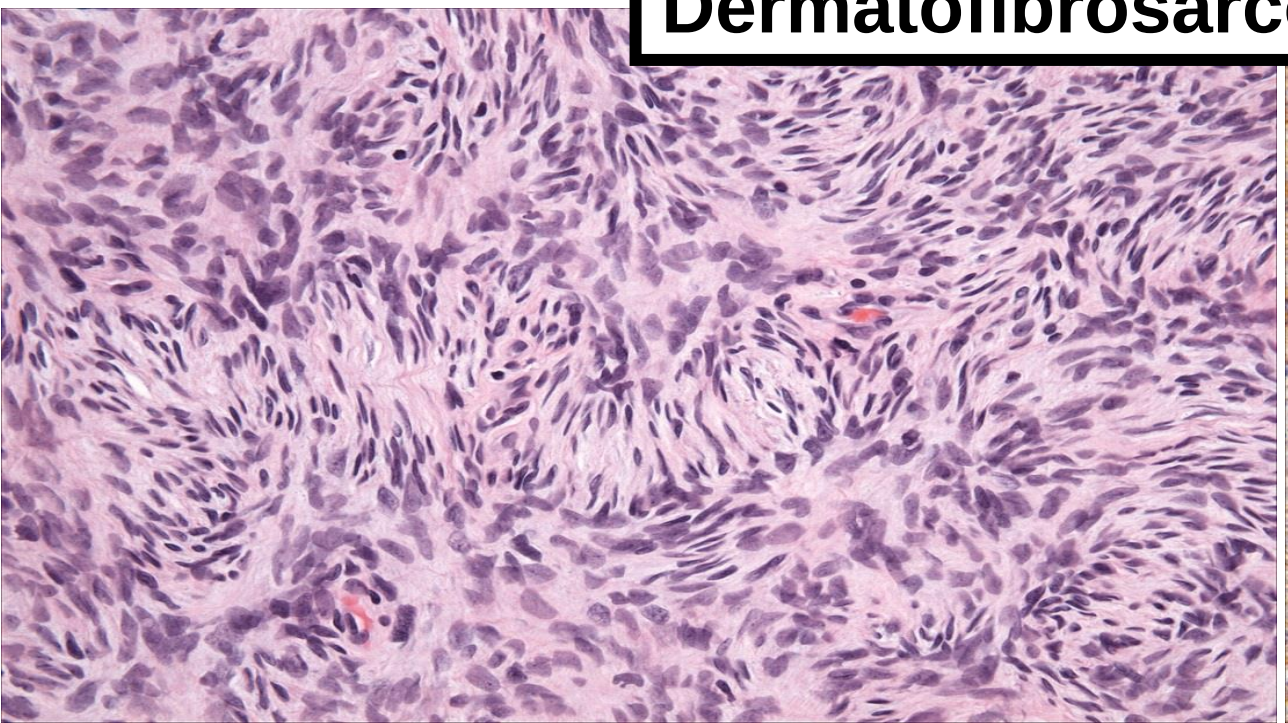
Giant cell fibroblastoma / **dermatofibrosarcoma protuberans**

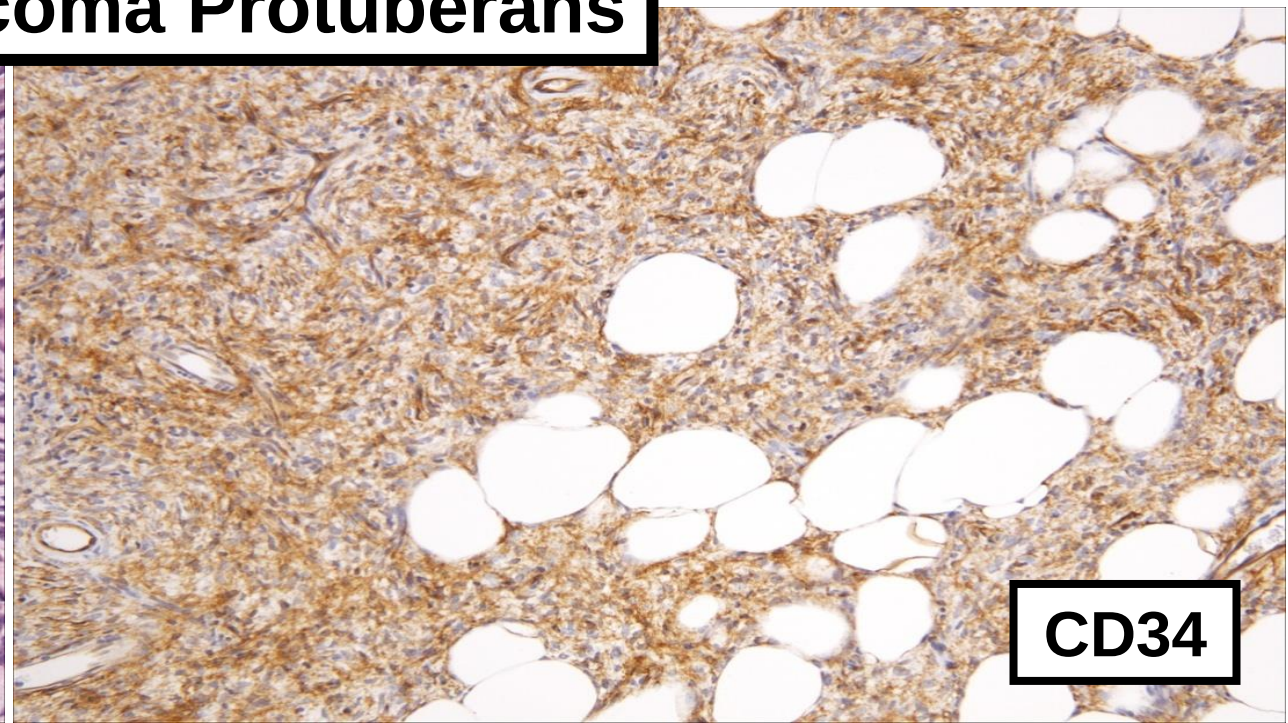
Tenosynovial giant cell tumor





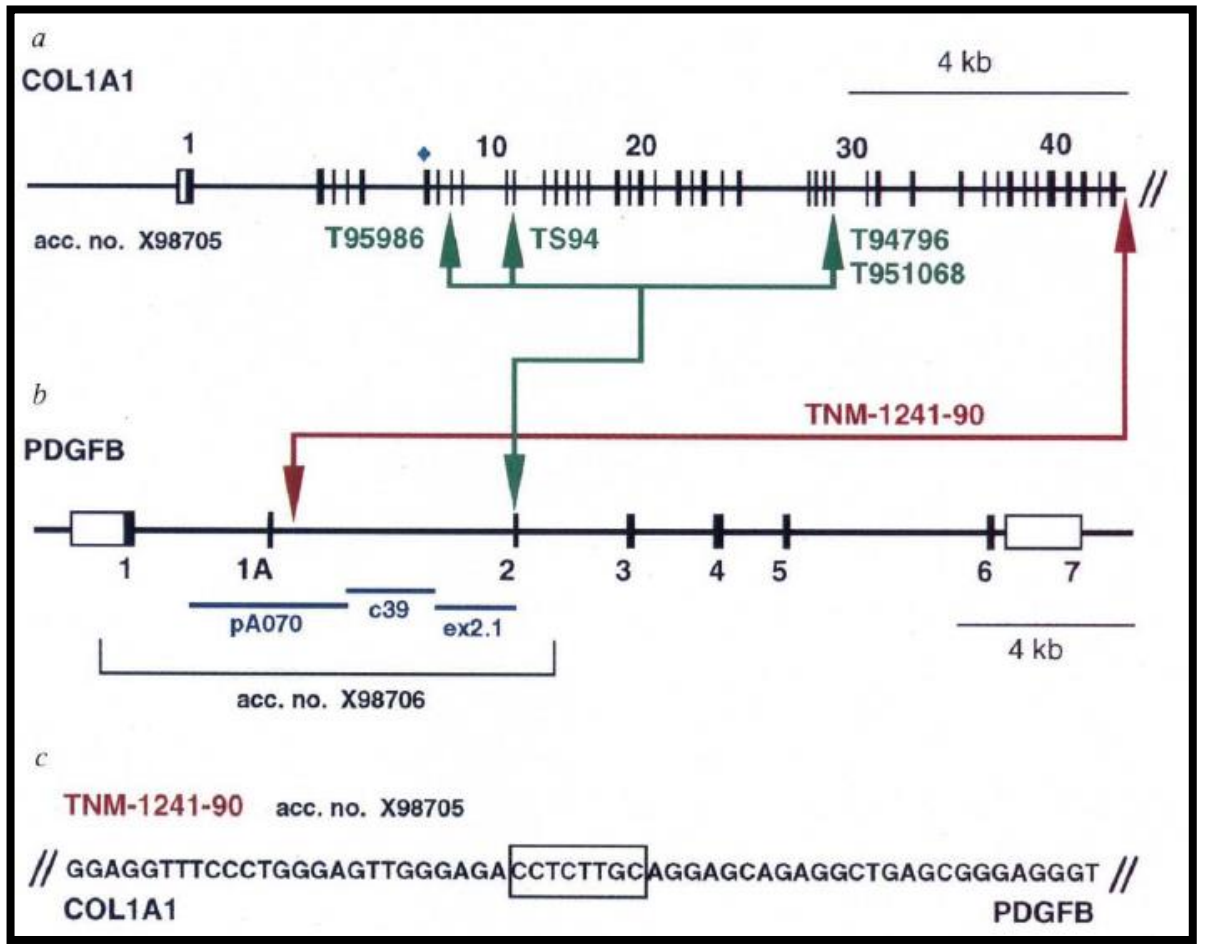
Dermatofibrosarcoma Protuberans





Dermatofibrosarcoma Protuberans Genetics

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



Simon et al. *Nat Genet* 1997

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

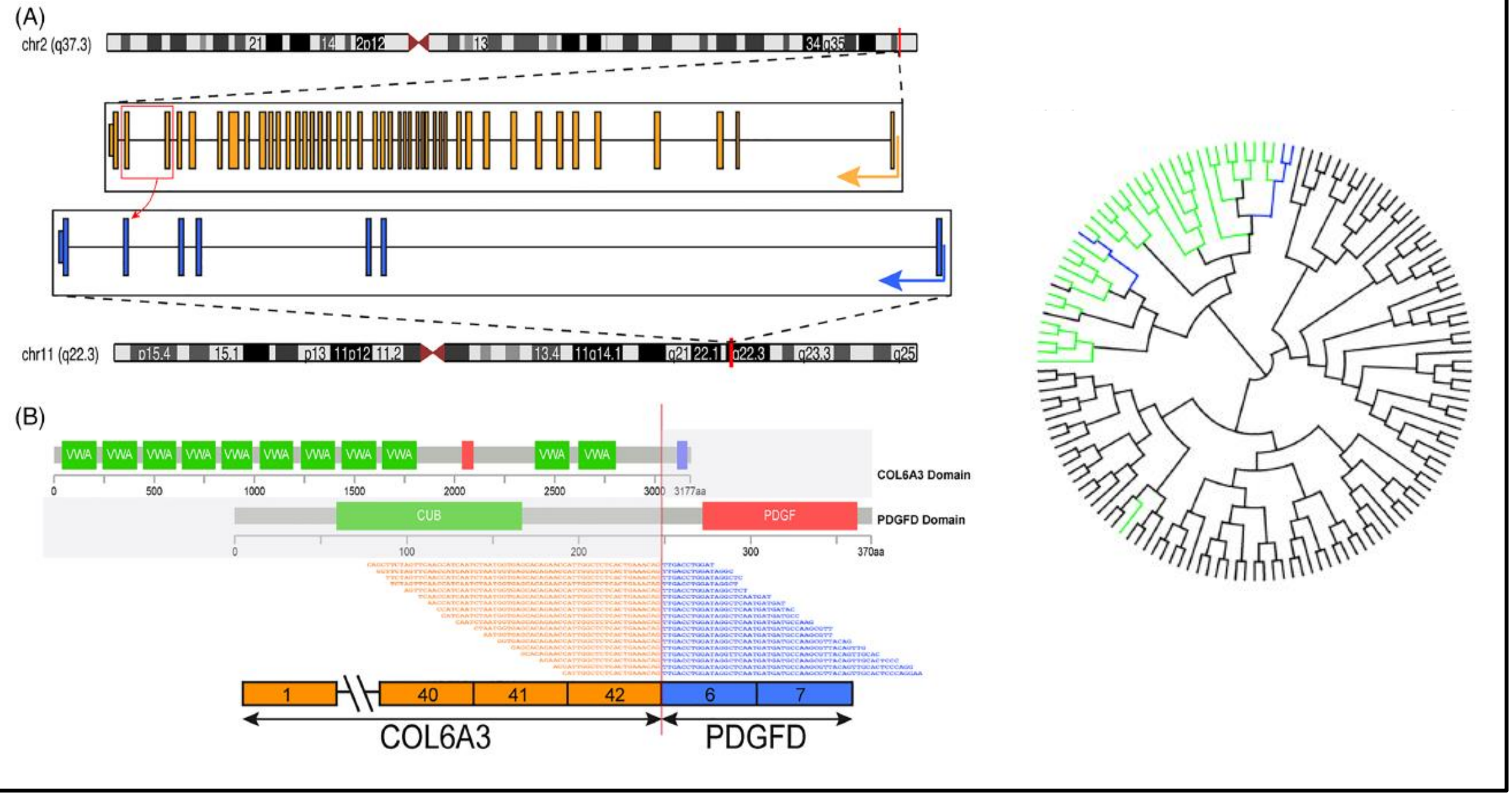
DFSP More Genetics

- **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



Dickson et al. *Genes Chromosomes Cancer* 2018

Vascular tumors

Capillary malformations	Pyogenic granuloma
Venous malformations	Epithelioid hemangioma
Arteriovenous malformations	Tufted hemangioma / kaposiform hemangioendothelioma
Intramuscular vascular anomalies	Papillary intralymphatic angioendothelioma and retiform hemangioendothelioma
Lymphatic anomalies	Pseudomyogenic hemangioendothelioma
Congenital hemangioma	Kaposi sarcoma
Infantile hemangioma	Epithelioid hemangioendothelioma
Hemangioma of placenta	Angiosarcoma

Vascular tumors

Capillary malformations	Pyogenic granuloma
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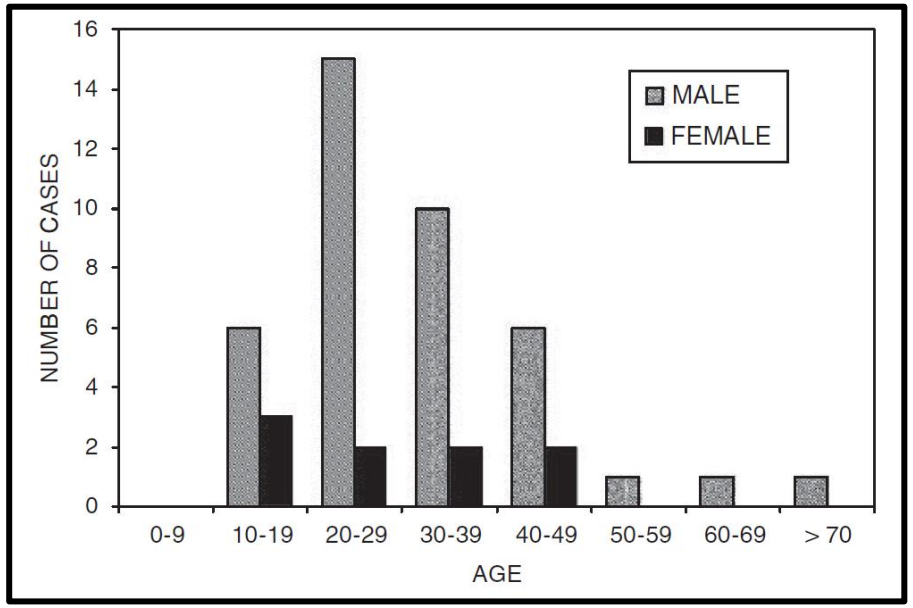
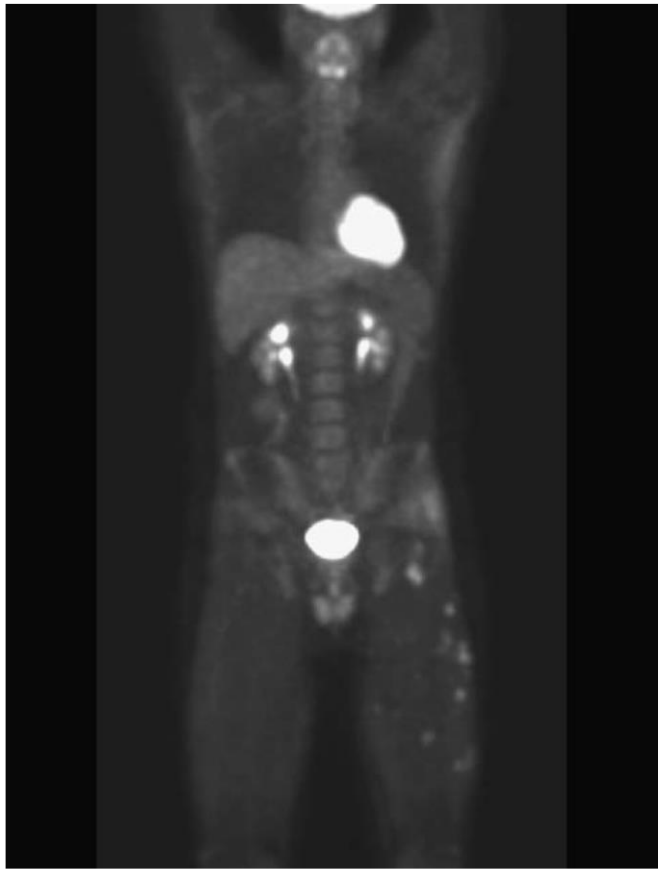
Infantile hemangioma	Epithelioid hemangioendothelioma
Hemangioma of placenta	Angiosarcoma

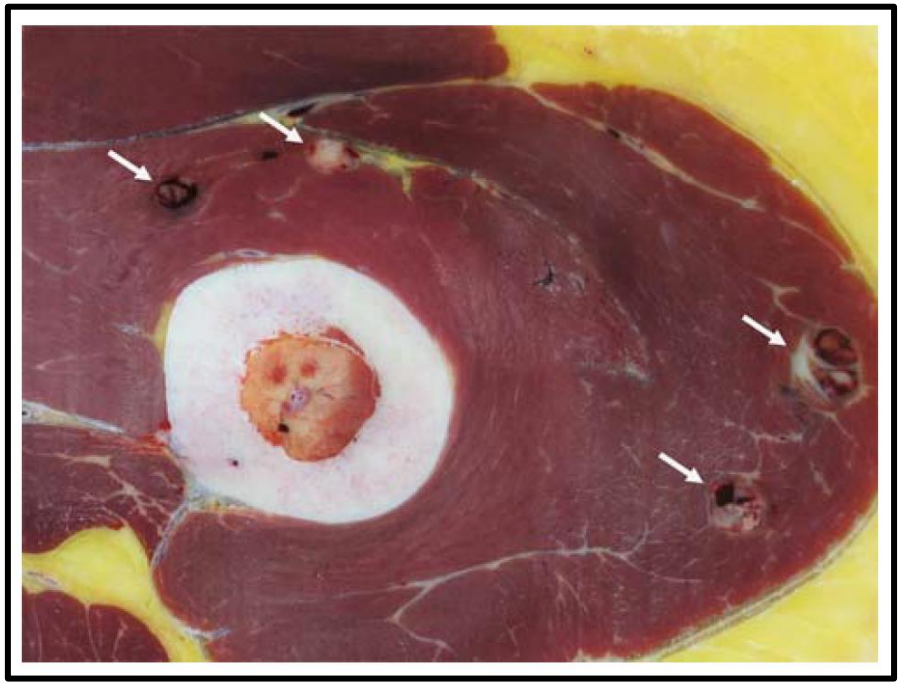
Pseudomyogenic Hemangioendothelioma: A Distinctive, Often Multicentric Tumor With Indolent Behavior

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

Am J Surg Pathol • Volume 35, Number 2, February 2011





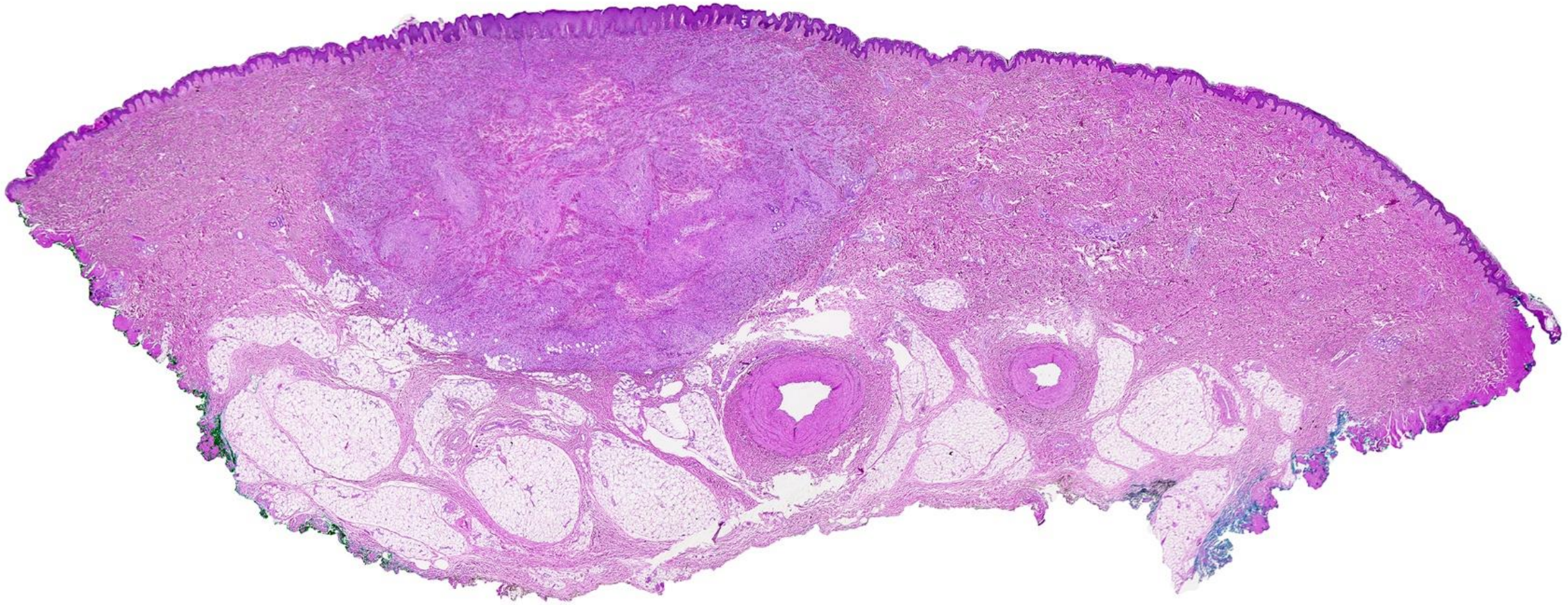


Courtesy of G. Petur Nielsen

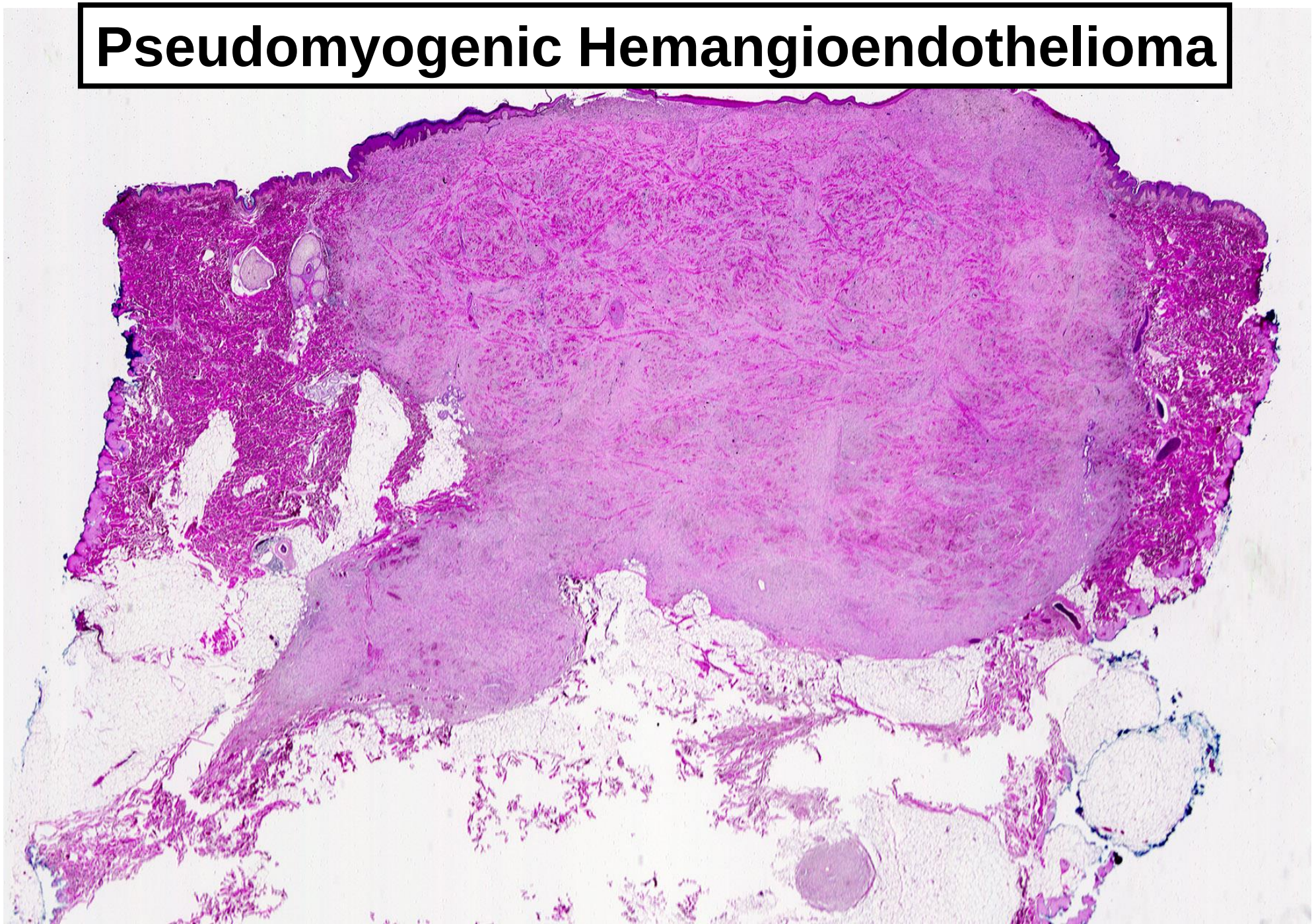
Clinical Features (200 cases)	
Age	Mean: 30 years
M : F	4 : 1
Multifocal	>50%
Anatomic distribution	Lower extremities: 60% Upper extremities: 20% Trunk: 15% Head and neck: 5%
Depth	Skin: 75% Muscle: 50% Bone: 20%

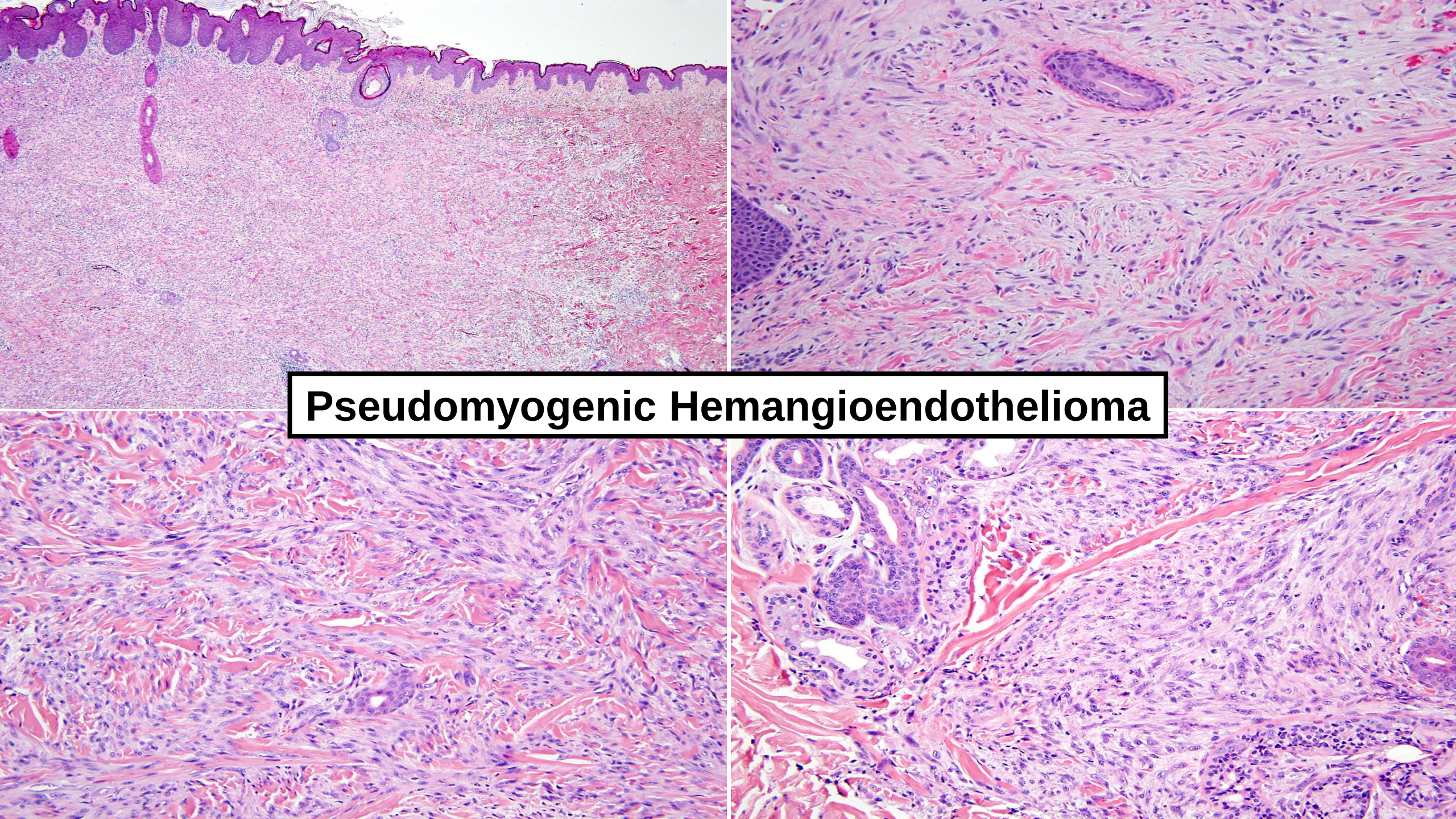
Despite ominous clinical presentation, distant metastasis rare

Pseudomyogenic Hemangioendothelioma

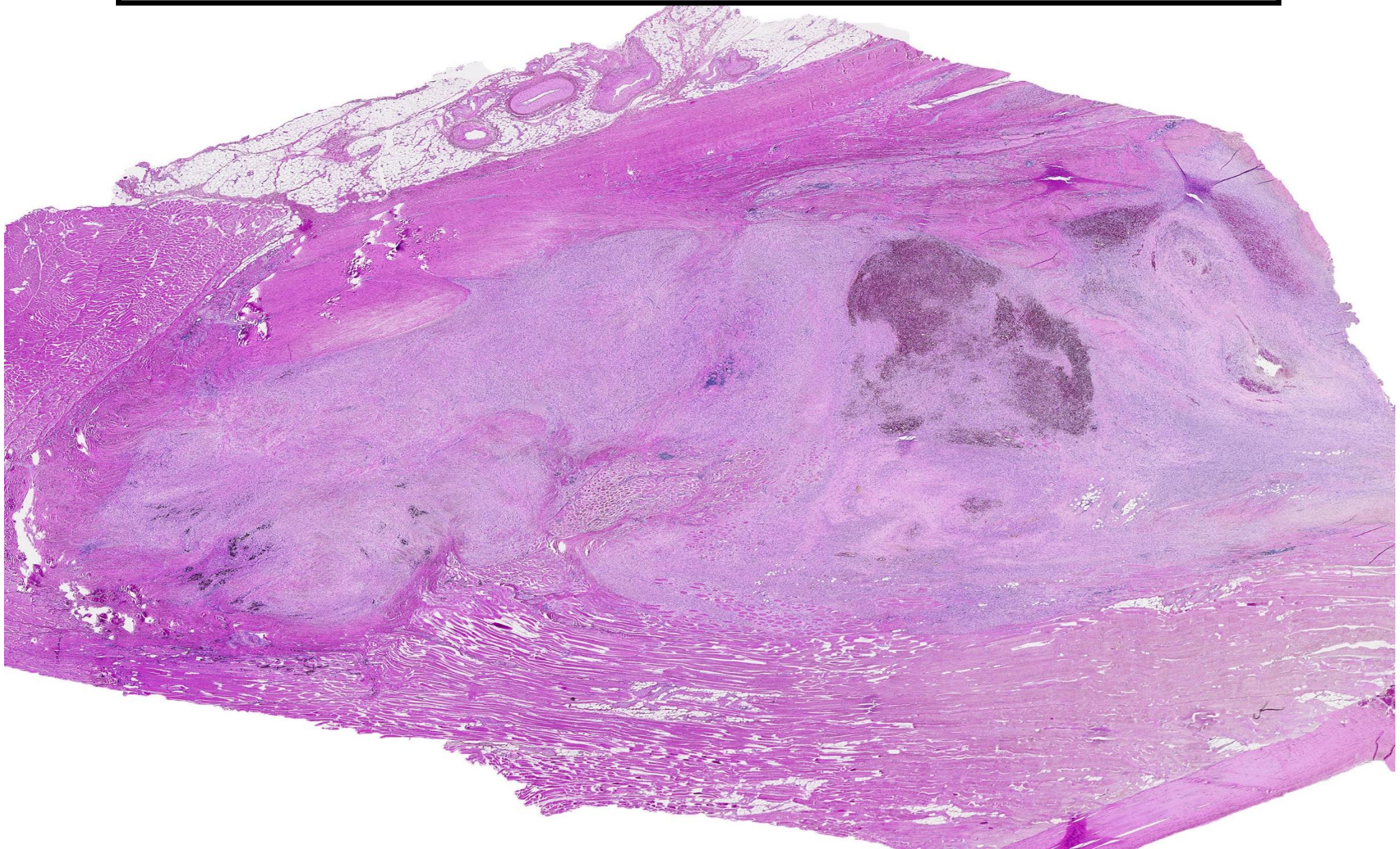


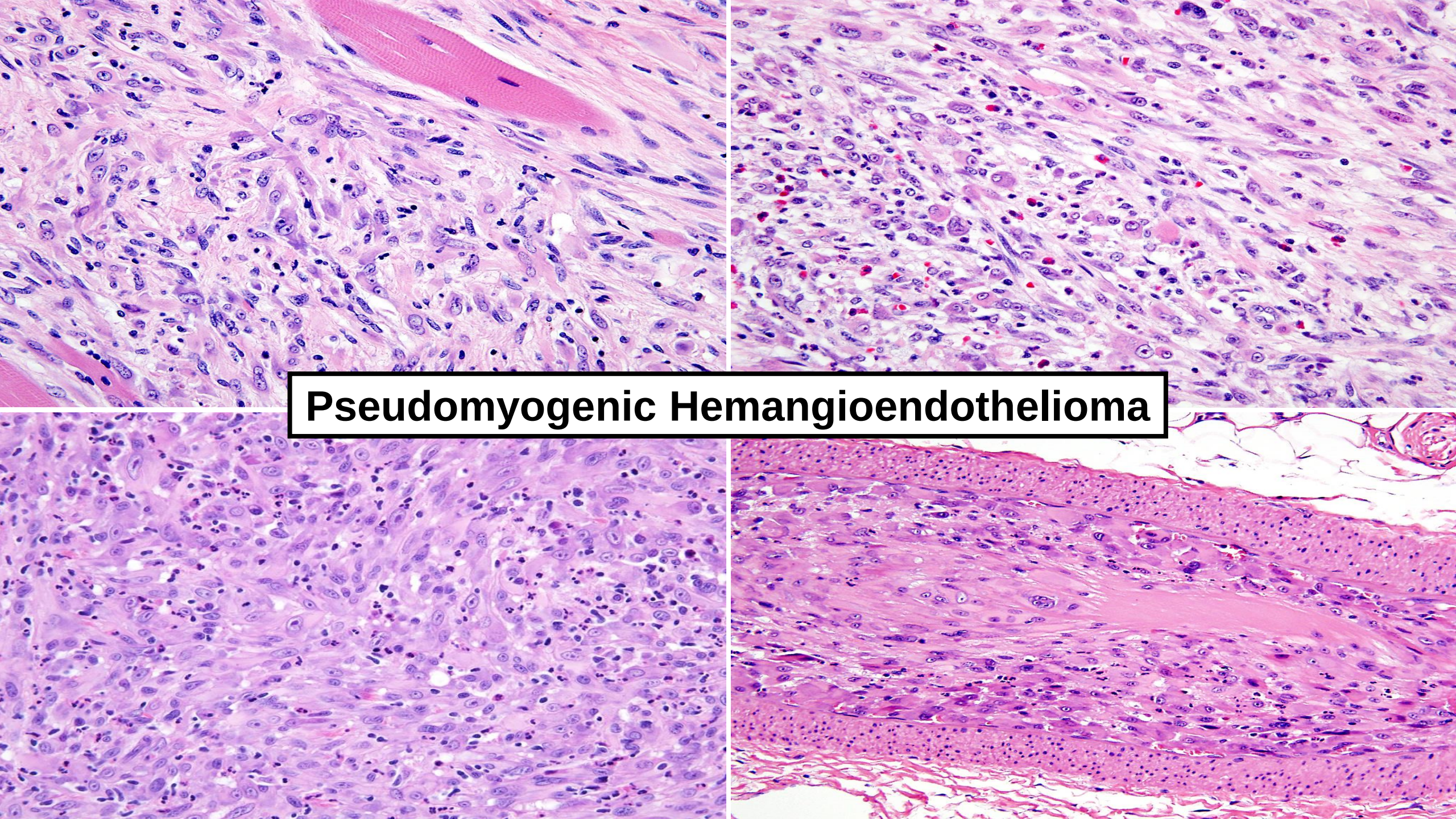
Pseudomyogenic Hemangioendothelioma




Pseudomyogenic Hemangioendothelioma

Pseudomyogenic Hemangioendothelioma

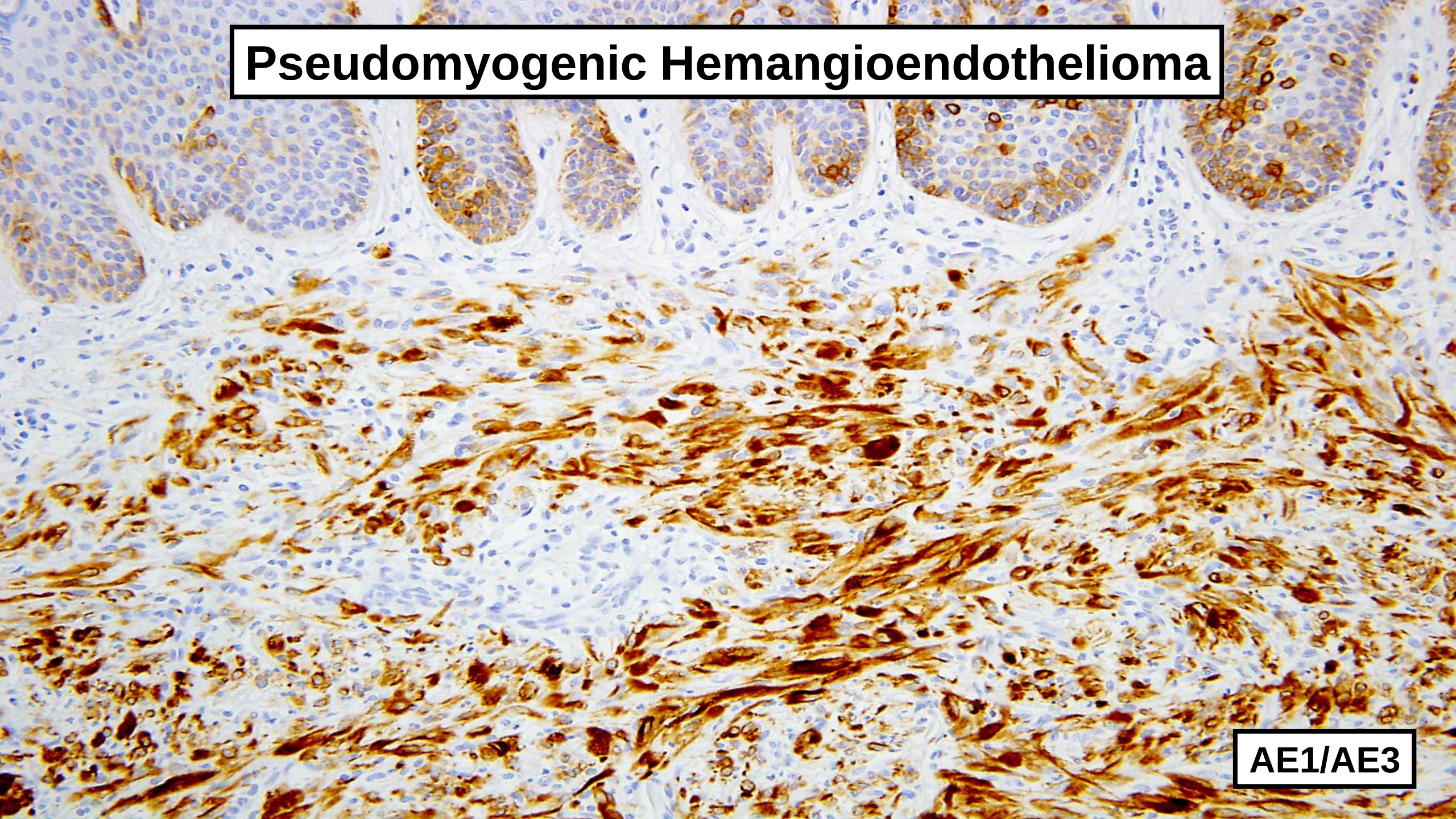



Pseudomyogenic Hemangioendothelioma

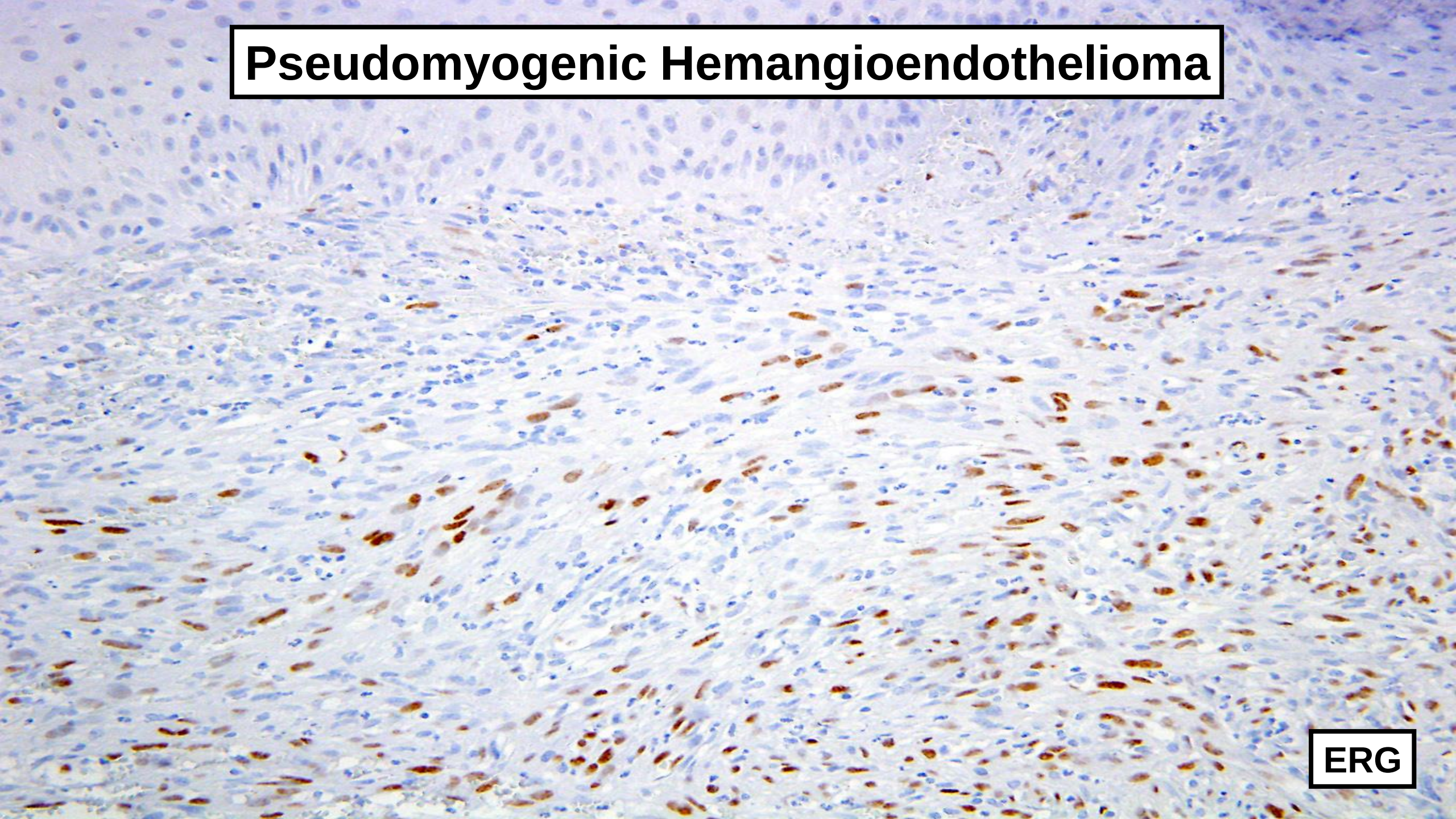
Immunohistochemistry

Positive	Negative
Keratins AE1/AE3	Keratins MNF116
ERG	EMA
FLI1	CD34
CD31 (often)	S100 protein
INI1 (retained)	Desmin

Pseudomyogenic Hemangioendothelioma



Pseudomyogenic Hemangioendothelioma

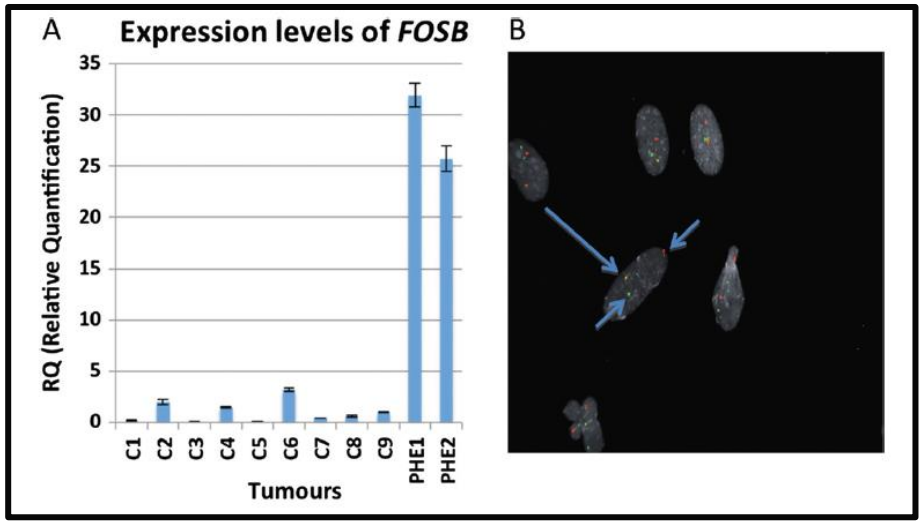


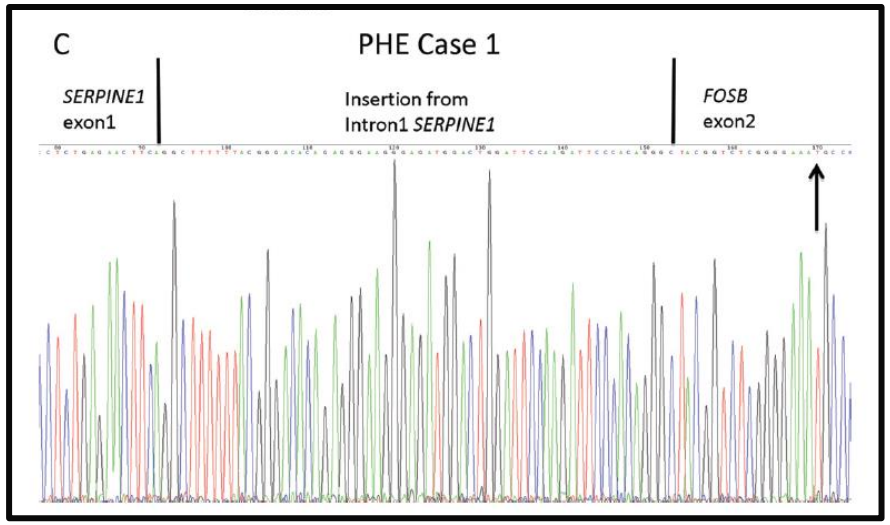
Journal of Pathology
J Pathol 2014; **232:** 534–540
Published online 29 January 2014 in Wiley Online Library
(wileyonlinelibrary.com) DOI: 10.1002/path.4322

ORIGINAL PAPER

A novel *SERPINE1–FOSB* fusion gene results in transcriptional up-regulation of *FOSB* in pseudomyogenic haemangioendothelioma

Charles Walther,[1,2]* Johnbosco Tayebwa,[1] Henrik Lilljebjörn,[1] Linda Magnusson,[1] Jenny Nilsson,[1] Fredrik Vult von Steyern,[3] Ingrid Øra,[4] Henryk A Domanski,[2] Thoas Fioretos,[1] Karolin H Nord,[1] Christopher DM Fletcher[5] and Fredrik Mertens[1]





RESEARCH Open Access

Diagnostic utility of FOSB immunohistochemistry in pseudomyogenic hemangioendothelioma and its histological mimics

Shintaro Sugita[1], Hiroshi Hirano[1], Noriaki Kikuchi[1], Terufumi Kubo[1], Hiroko Asanuma[1], Tomoyuki Aoyama[1], Makoto Emori[2] and Tadashi Hasegawa[1*]

Diagnostic Pathology (2016) 11:75

FOSB is a Useful Diagnostic Marker for Pseudomyogenic Hemangioendothelioma

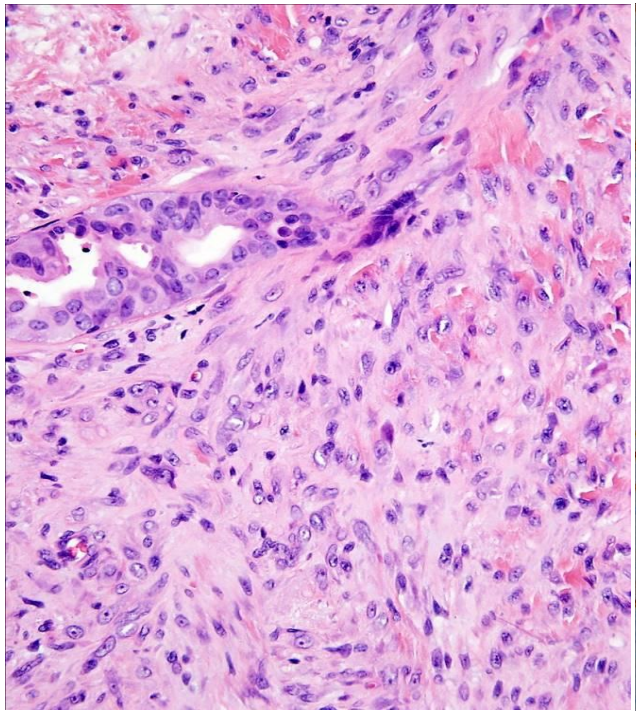
Yin P. Hung, MD, PhD, Christopher D.M. Fletcher, MD, FRCPath, and Jason L. Hornick, MD, PhD

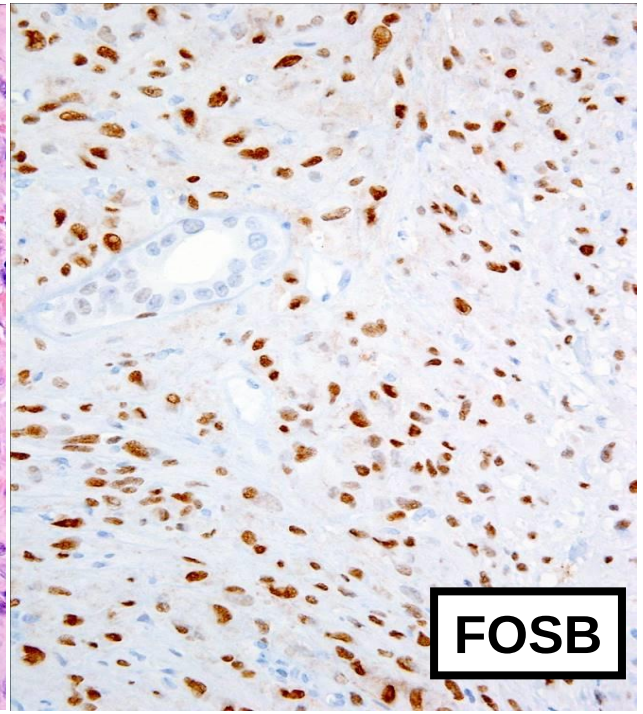
Am J Surg Pathol • Volume 41, Number 5, May 2017

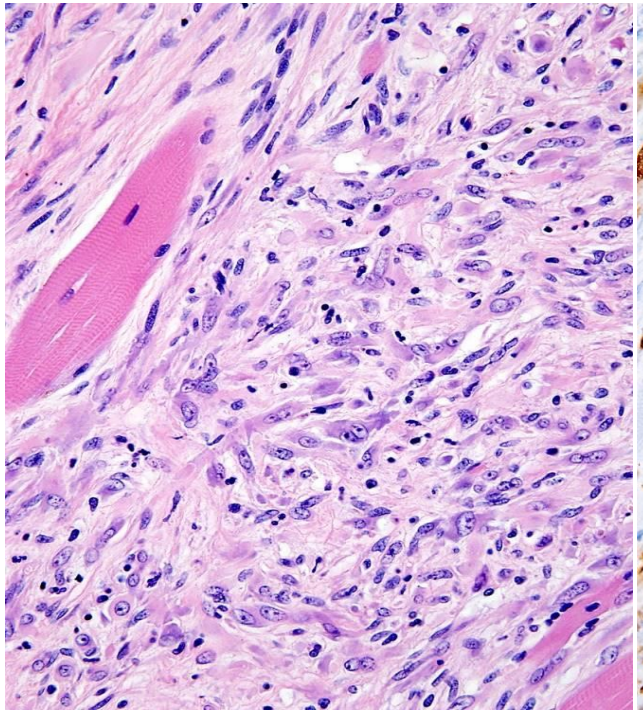
Pseudomyogenic Hemangioendothelioma

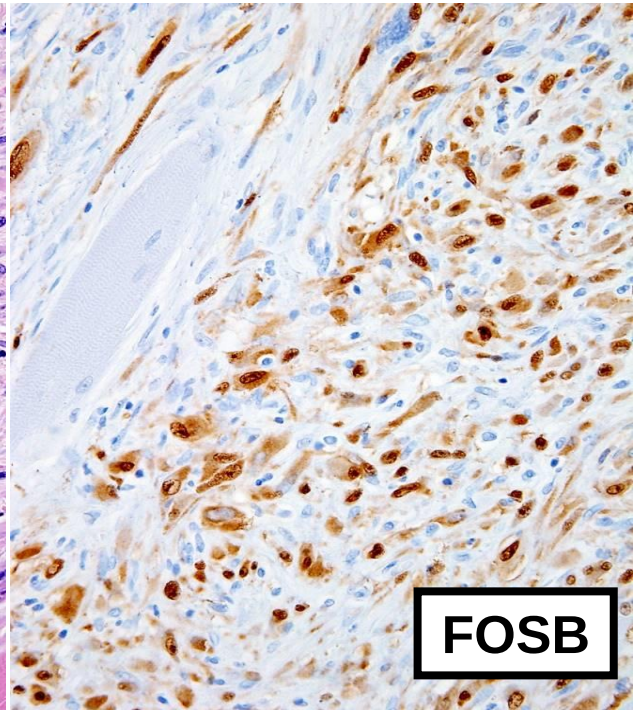
TABLE 1. Summary of Immunohistochemical Staining for FOSB

Tumor Type	Total Cases	FOSB Positive (%)*	0	1+	2+	3+	4+
Pseudomyogenic hemangioendothelioma	50	48 (96)	2	0	0	1	47
Epithelioid hemangioma	24	13 (54)	6	4	1	6	7
Conventional	8	6 (75)	0	1	1	4	2
Cellular	10	1 (10)	6	3	0	0	1
Angiolymphoid hyperplasia with eosinophilia	6	6 (100)	0	0	0	2	4
Other endothelial neoplasms and histologic mimics	200	7 (4)	142	42	9	4	3



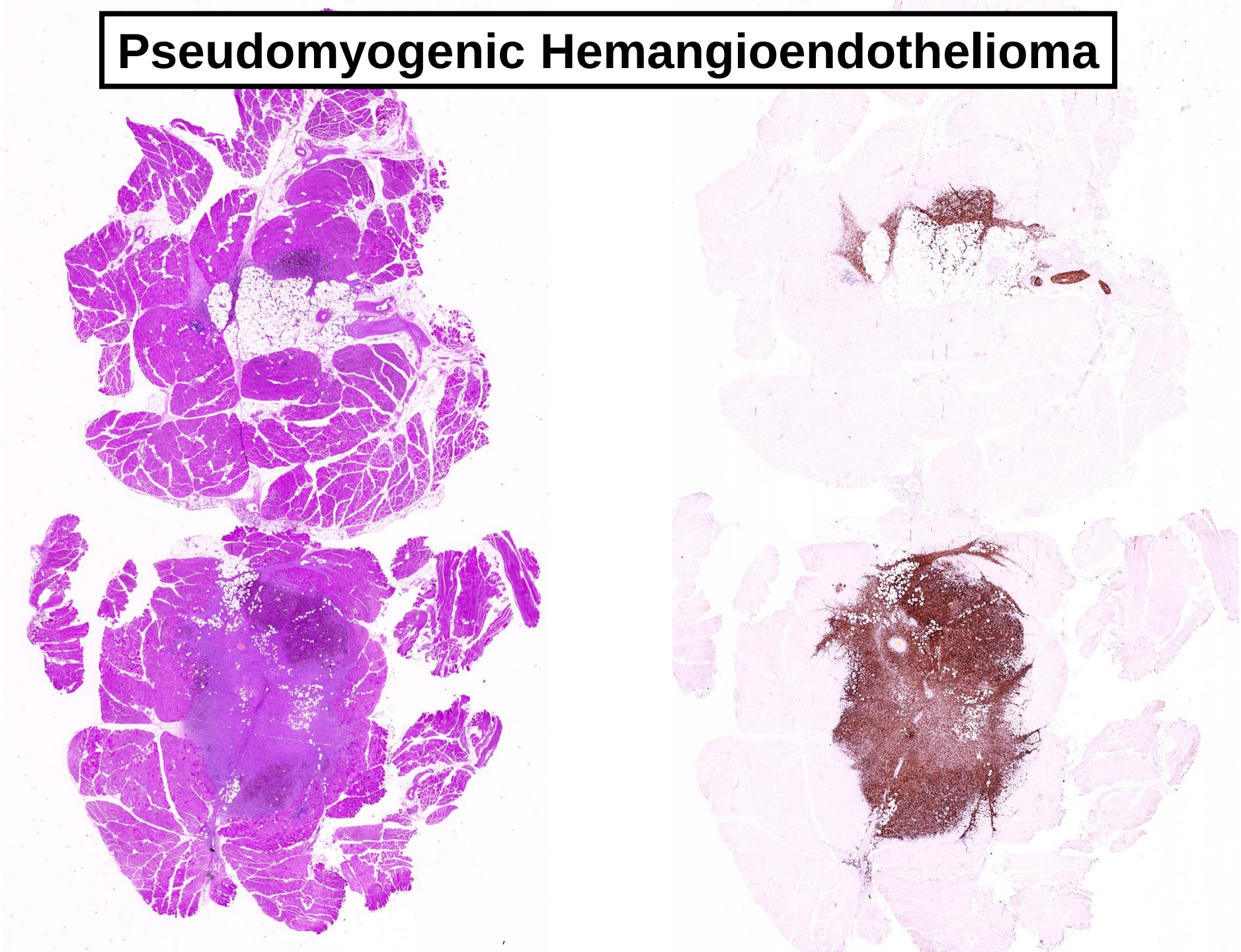






Hung et al. *Am J Surg Pathol* 2017

Pseudomyogenic Hemangioendothelioma



FOSB

Expanding the Spectrum of Genetic Alterations in Pseudomyogenic Hemangioendothelioma With Recurrent Novel *ACTB-FOSB* Gene Fusions

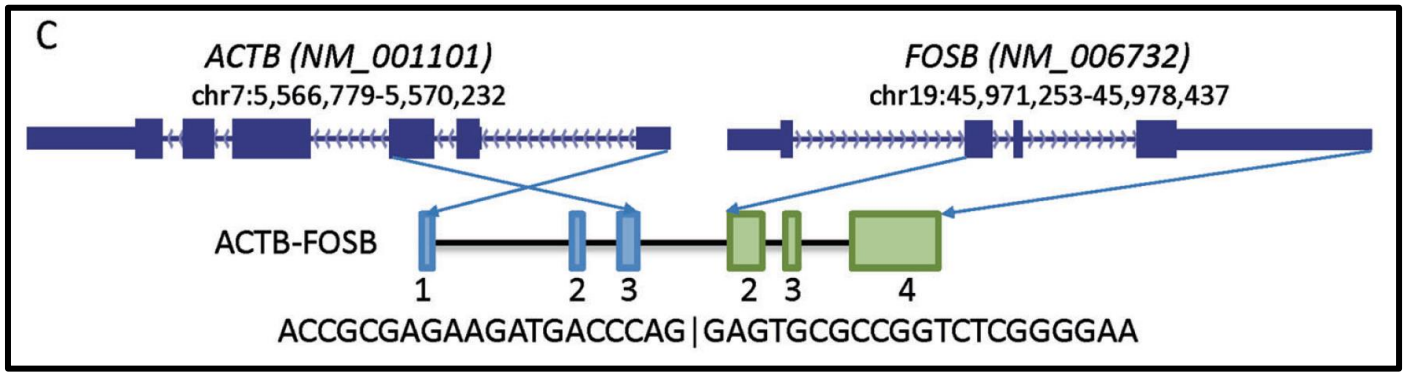
Narasimhan P. Agaram, MBBS, Lei Zhang, MD, Paolo Cotzia, MD, and Cristina R. Antonescu, MD

Am J Surg Pathol • Volume 42, Number 12, December 2018

Diagnosis of known sarcoma fusions and novel fusion partners by targeted RNA sequencing with identification of a recurrent *ACTB-FOSB* fusion in pseudomyogenic hemangioendothelioma

Guo Zhu[1] · Ryma Benayed[1] · Caleb Ho[1] · Kerry Mullaney[1] · Purvil Sukhadia[1] · Kelly Rios[1] · Ryan Berry[2] · Brian P. Rubin[2] · Khedoudja Nafa[1] · Lu Wang[1] · David S. Klimstra[1] · Marc Ladanyi[1] · Meera R. Hameed[1]

Modern Pathology Published online: 21 November 2018



Pericytic (perivascular) tumors

Myofibroma and myopericytoma

Glomus tumor and glomuvenous malformation

Smooth muscle tumors

EBV-associated smooth muscle tumor

Skeletal muscle tumors

Rhabdomyoma

Rhabdomyosarcoma family

Ectomesenchymoma

Gastrointestinal stromal tumors

Pediatric gastrointestinal stromal tumor

Pericytic (perivascular) tumors

Myofibroma and myopericytoma

Glomus tumor and glomuvenous malformation

Smooth muscle tumors

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Skeletal muscle tumors

Rhabdomyoma

Rhabdomyosarcoma family

Ectomesenchymoma

Gastrointestinal stromal tumors

Pediatric gastrointestinal stromal tumor

Classification of Rhabdomyosarcomas

Type	Age	Sites
Embryonal	Children	Head and neck, GU, retroperitoneum, biliary
Alveolar	Adolescents or young adults	Extremities, head and neck, trunk, pelvis
Pleomorphic	Older adults	Extremities
Spindle cell/sclerosing	Children or adults	Head and neck, paratesticular

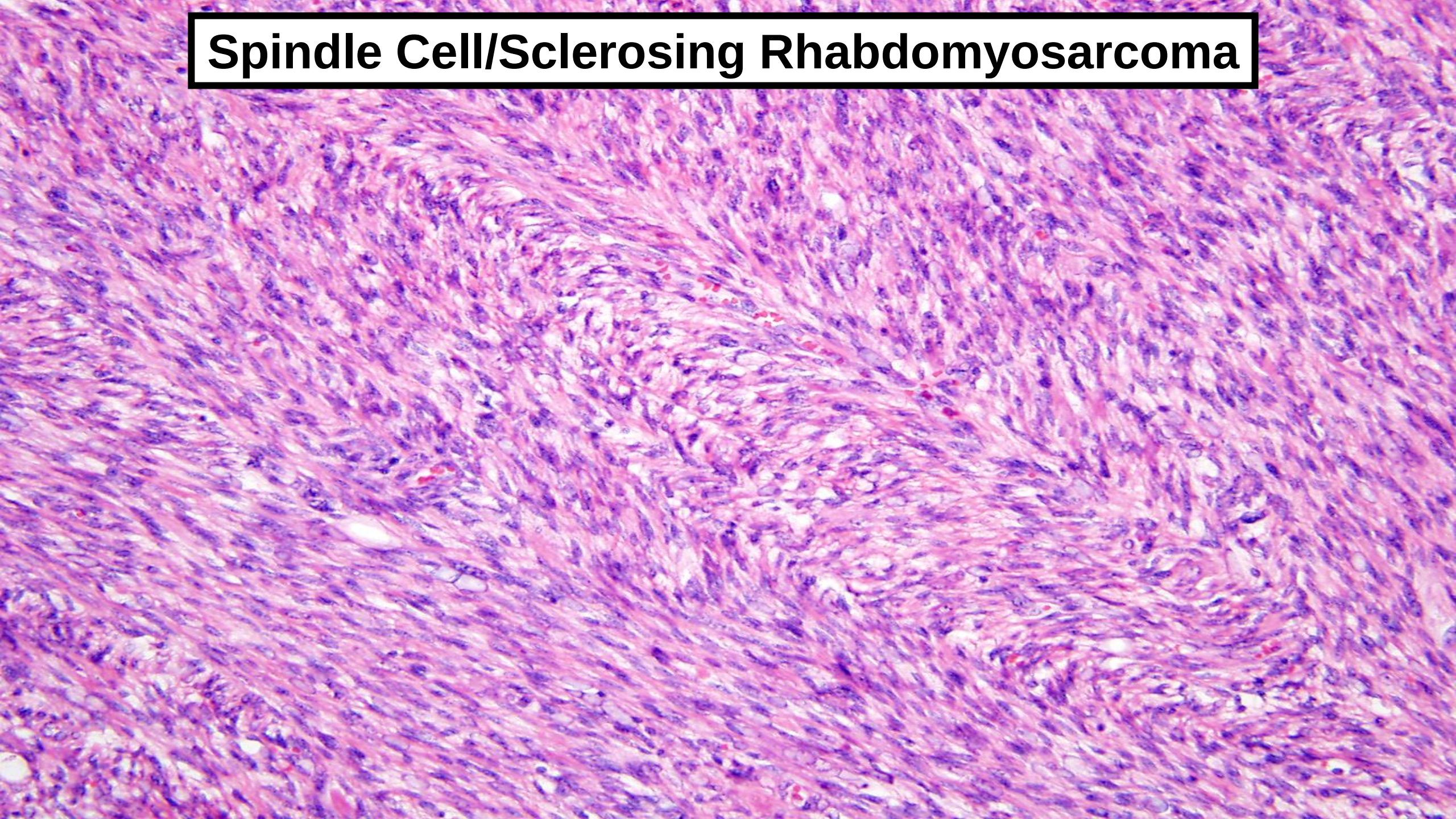
Genetics of Rhabdomyosarcomas

Type	Alterations
Embryonal	**RAS pathway mutations (<50%)**
Alveolar	**t(2;13) *PAX3::FOXO1* (80%)** **t(1;13) *PAX7::FOXO1* (20%)**
Pleomorphic	**Complex karyotypes**
Spindle cell/sclerosing	**Adolescents/adults:** ***MYOD1* mutations**
	Congenital/infantile: ***VGLL2/NCOA2/CITED2* rearrangements**

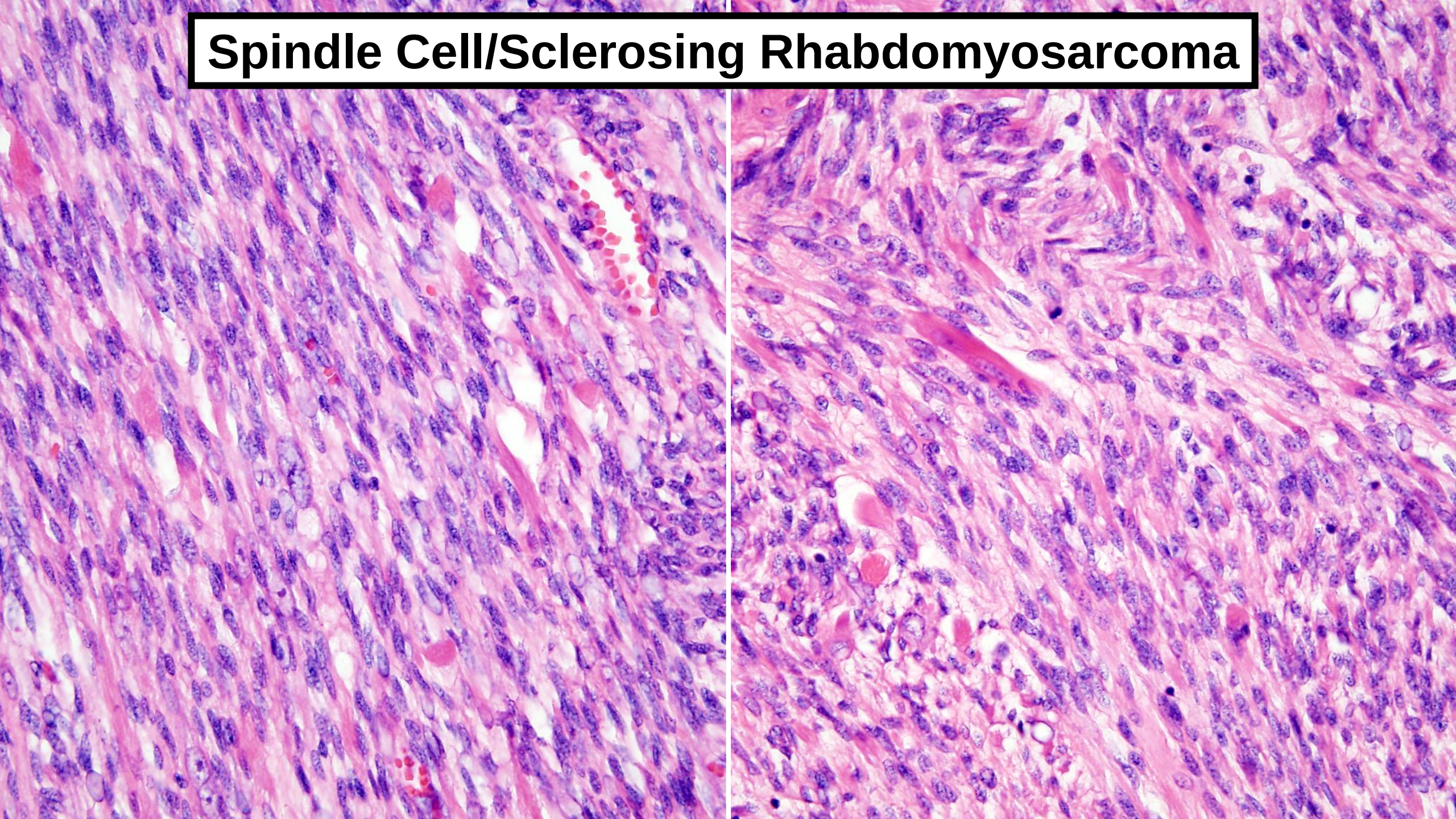
Spindle Cell/Sclerosing Rhabdomyosarcoma

- **Most common in head and neck >> extremities**
- **Pediatric: paratesticular more common**
- **Female predominance for *MYOD1*-mutant cases**
- **Rapidly growing mass; symptoms related to local compression**
- **Congenital/infantile with fusions: favorable prognosis**
- ***MYOD1*-mutant: poor prognosis (5-year survival <20%)**

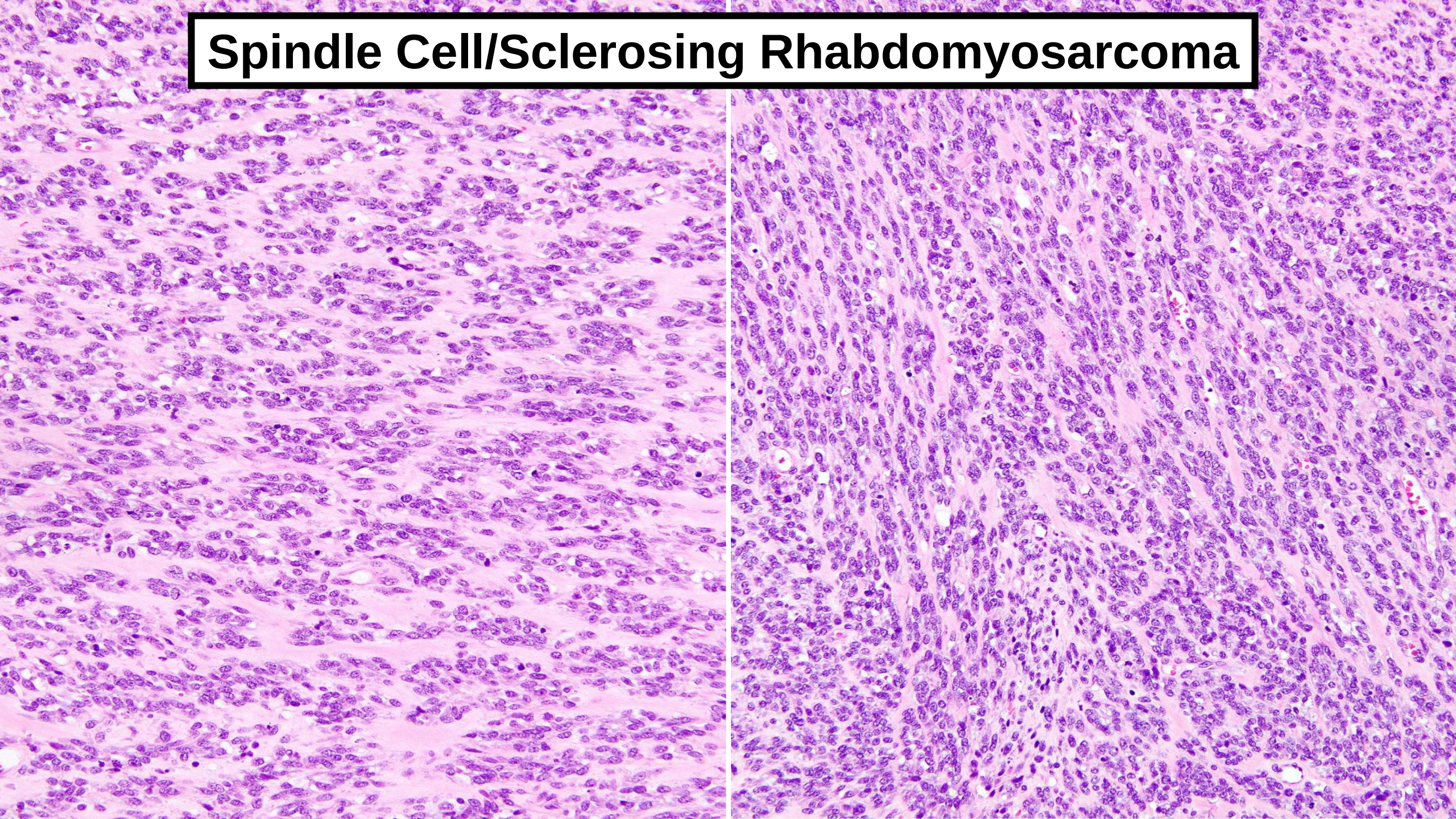
Spindle Cell/Sclerosing Rhabdomyosarcoma



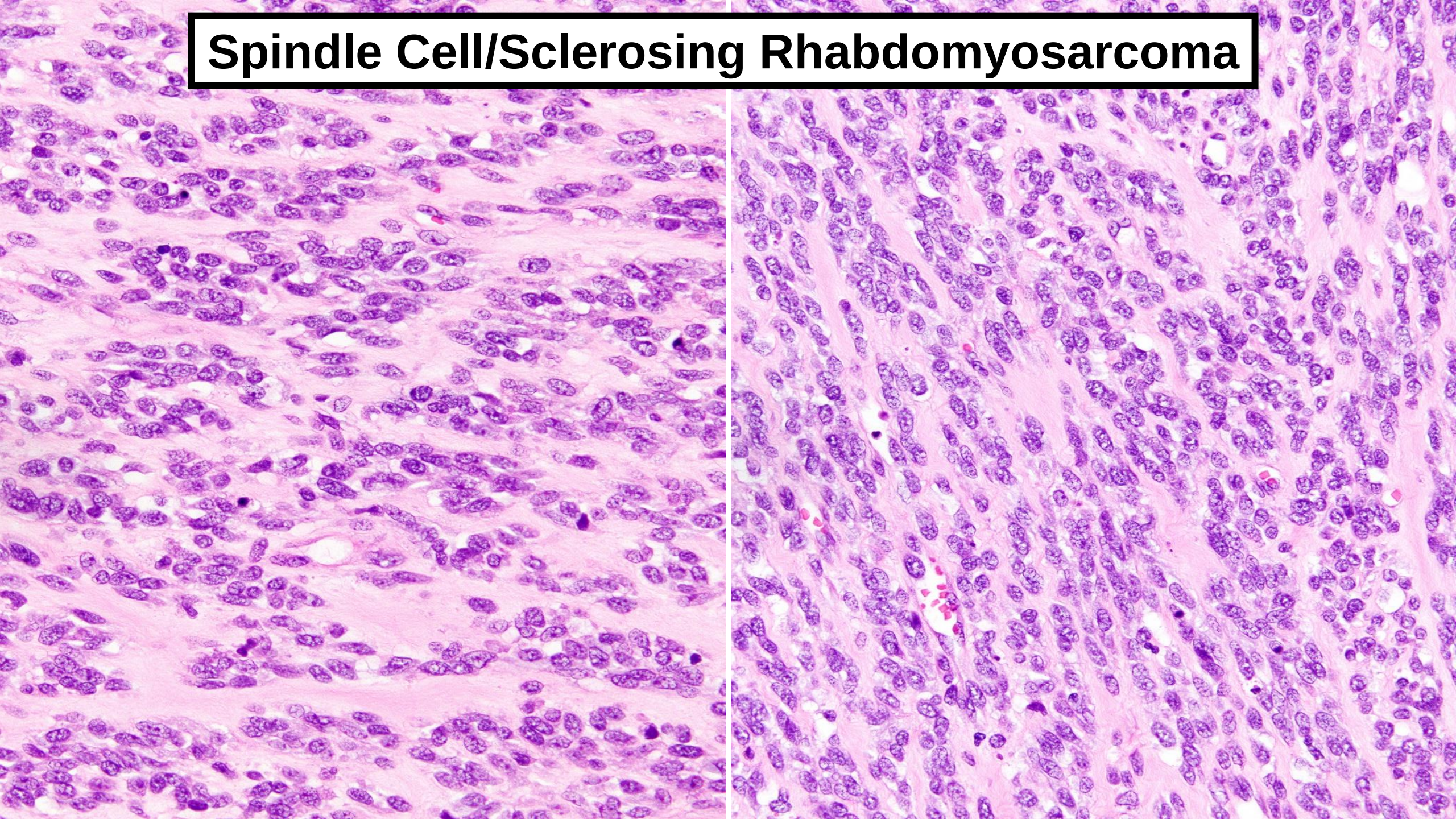
Spindle Cell/Sclerosing Rhabdomyosarcoma



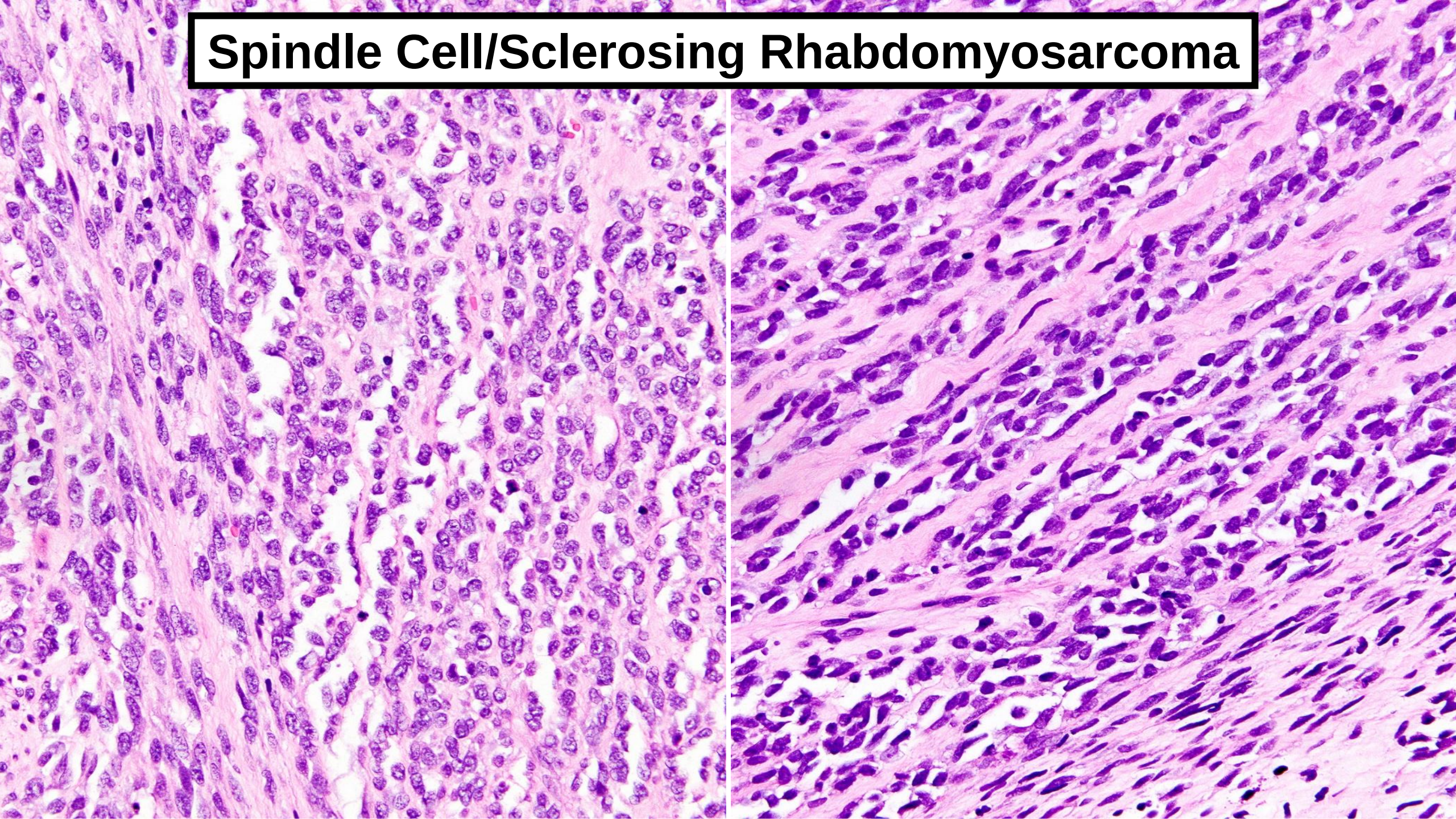
Spindle Cell/Sclerosing Rhabdomyosarcoma



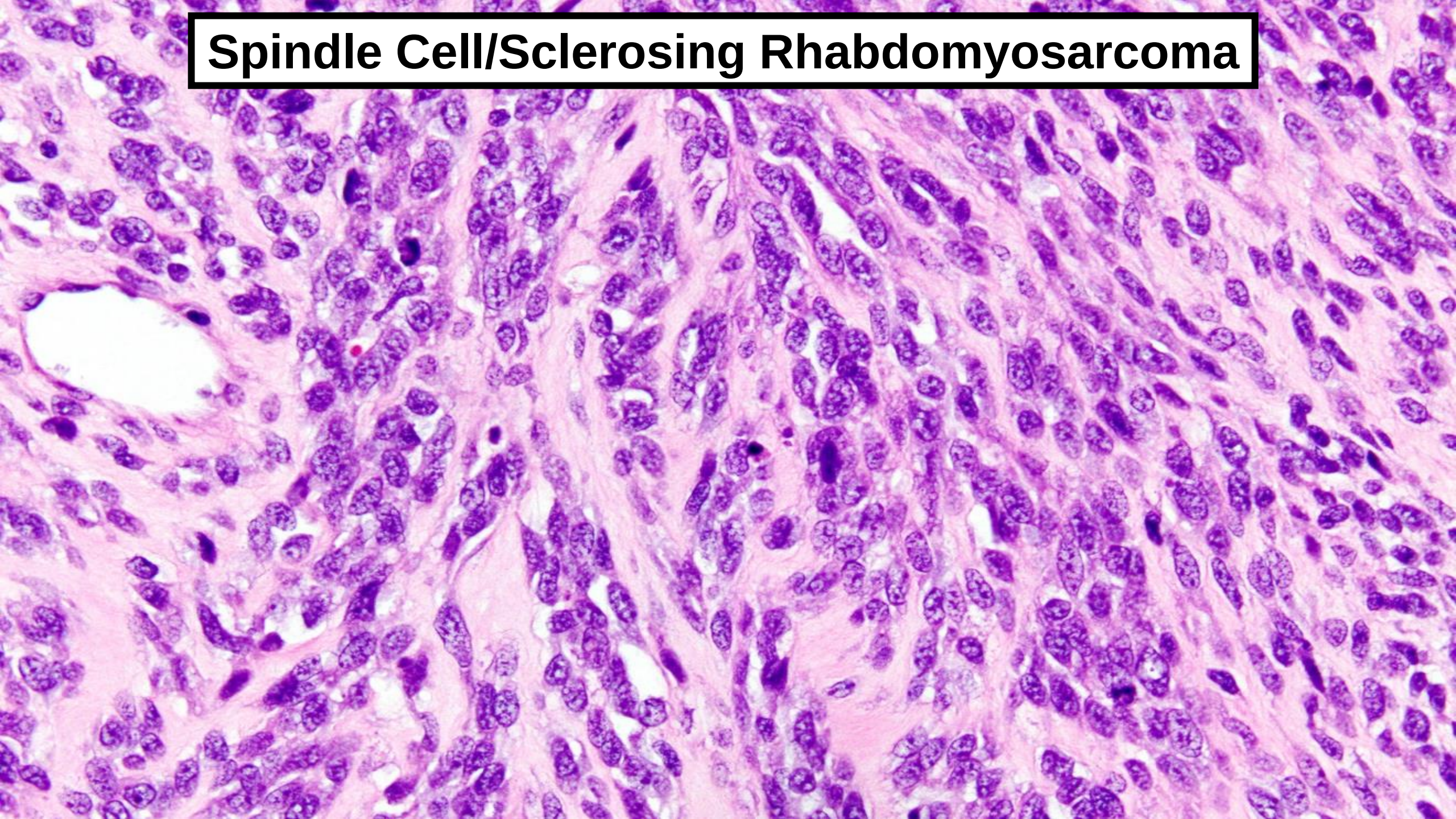
Spindle Cell/Sclerosing Rhabdomyosarcoma



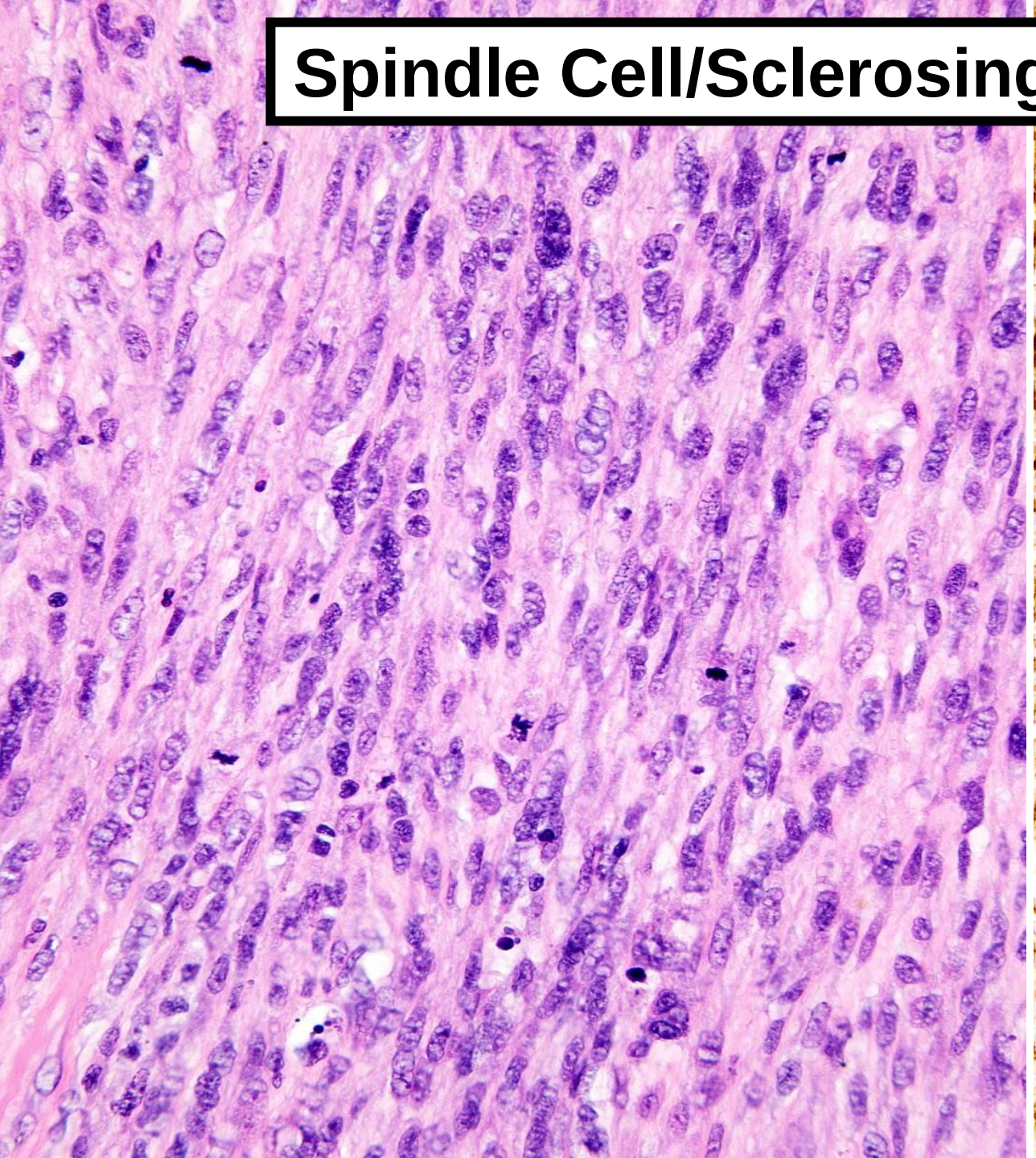
Spindle Cell/Sclerosing Rhabdomyosarcoma

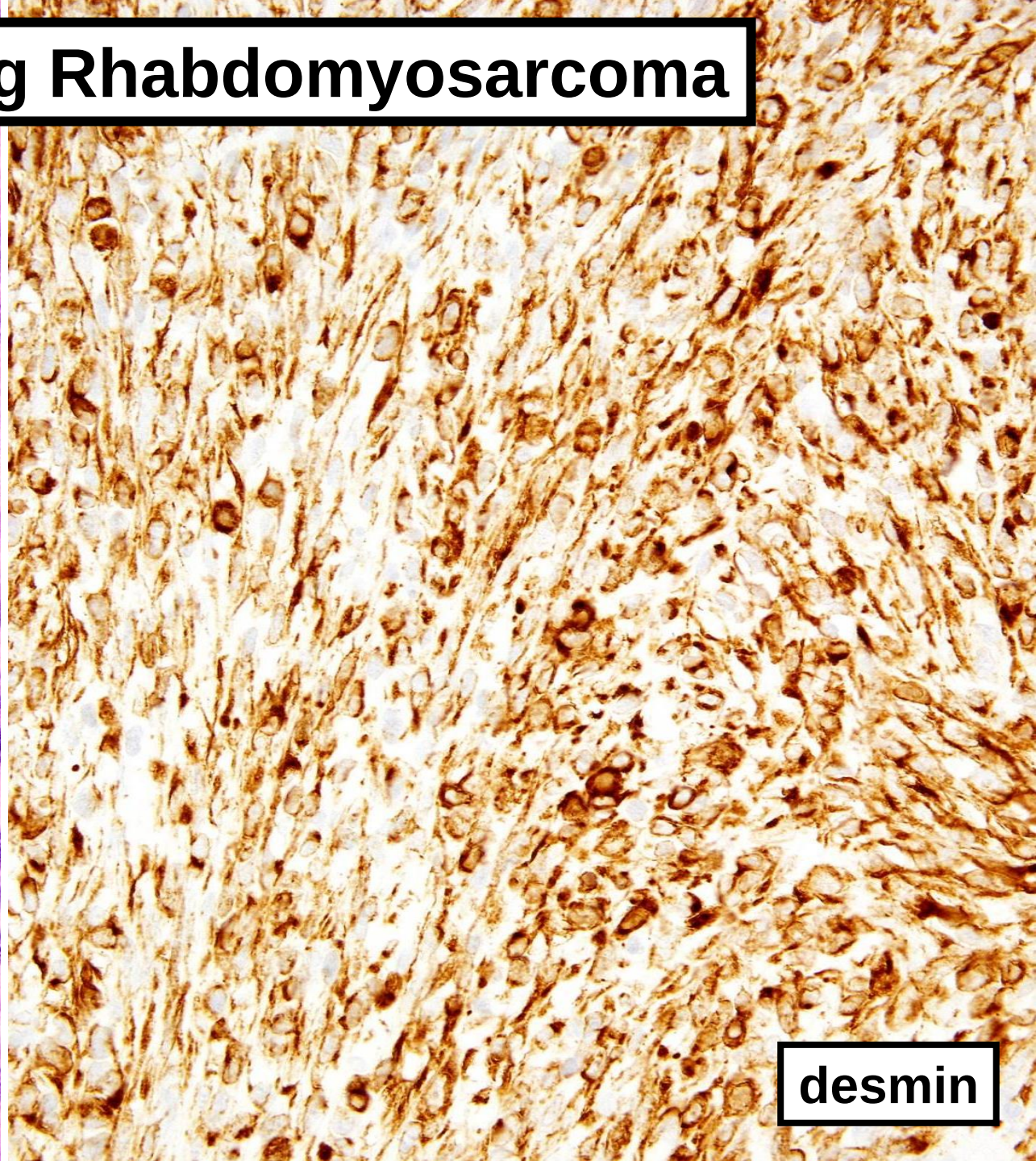


Spindle Cell/Sclerosing Rhabdomyosarcoma

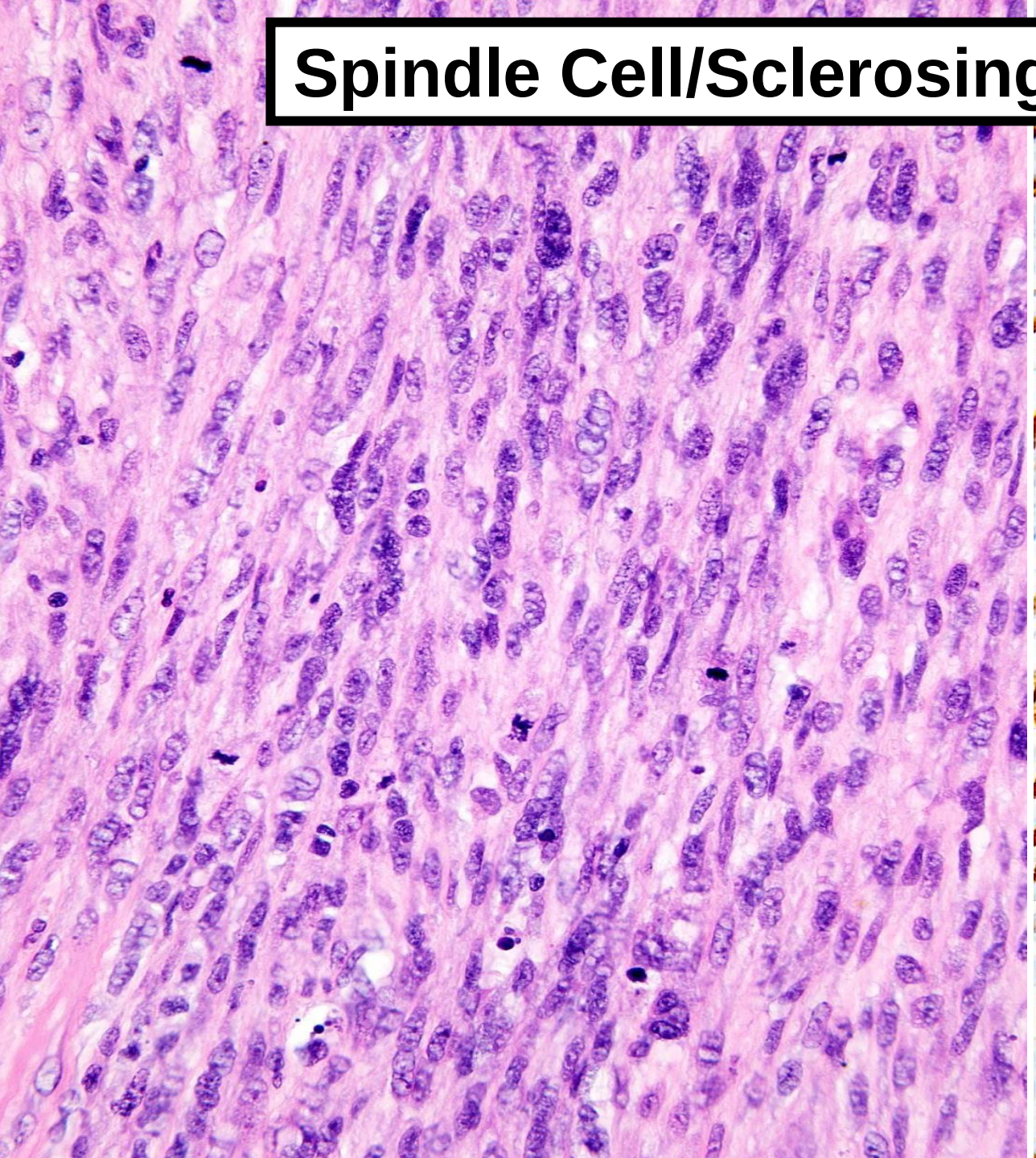


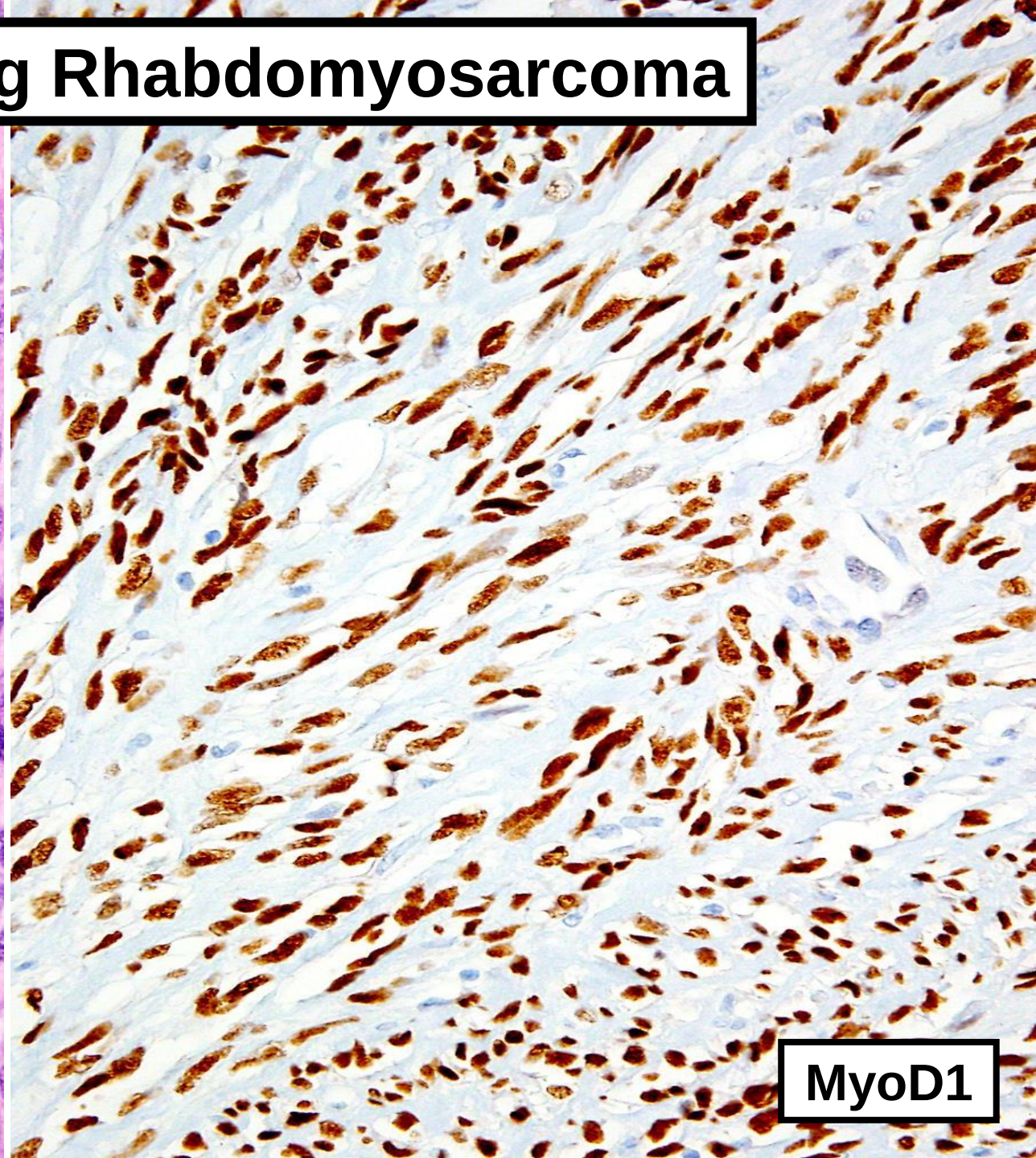
Spindle Cell/Sclerosing Rhabdomyosarcoma





Spindle Cell/Sclerosing Rhabdomyosarcoma





Peripheral nerve sheath tumors
Schwannoma
Neurofibroma
Perineurioma
Hybrid nerve sheath tumors
Granular cell tumor
Solitary circumscribed neuroma
Ectopic meningioma and meningothelial hamartoma
Benign triton tumor / neuromuscular choristoma
Malignant peripheral nerve sheath tumor

Peripheral nerve sheath tumors

Schwannoma

Neurofibroma

Perineurioma

Hybrid nerve sheath tumors

Granular cell tumor

Solitary circumscribed neuroma

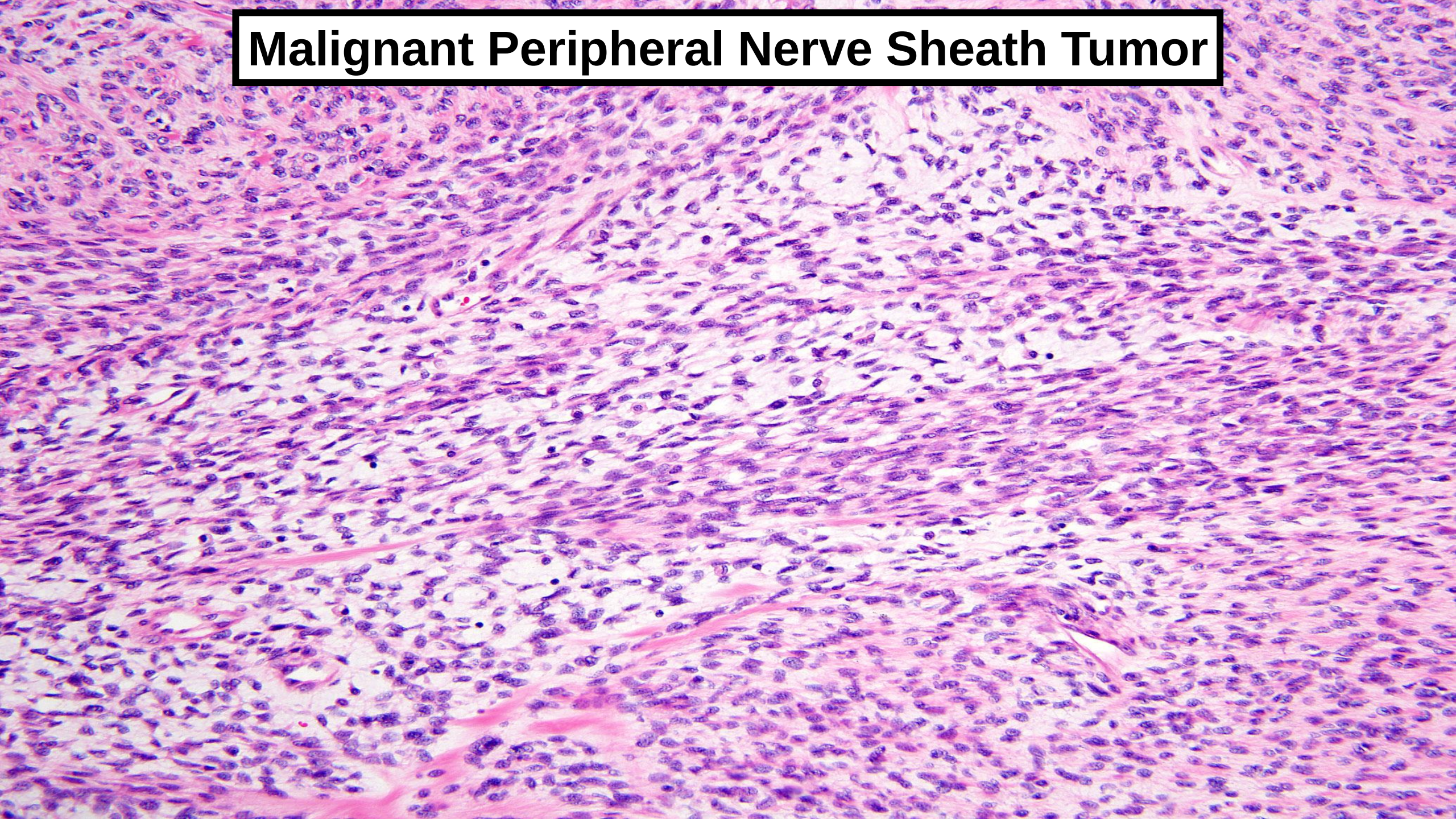
Ectopic meningioma and meningothelial hamartoma

Benign triton tumor / neuromuscular choristoma

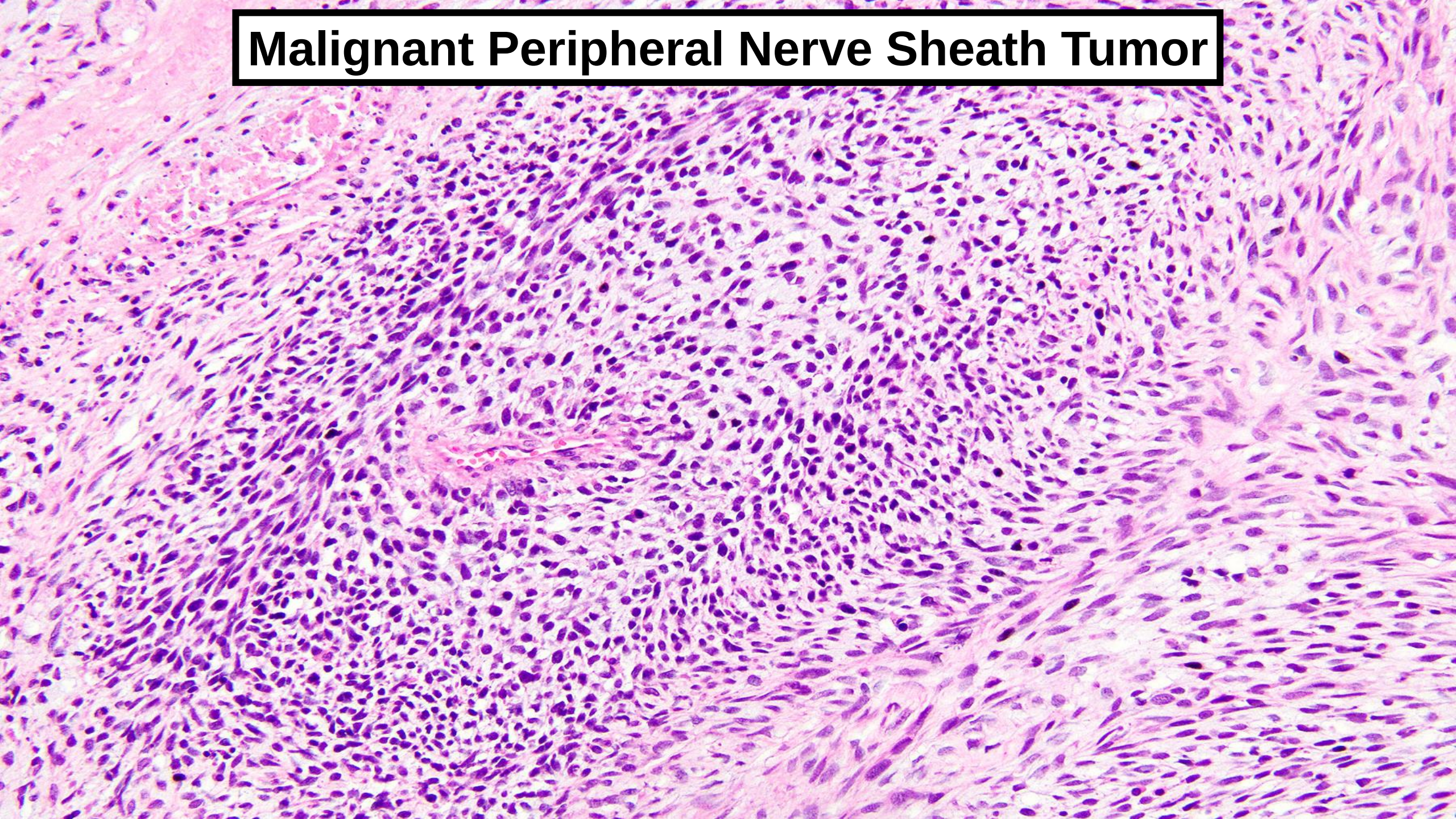
Malignant peripheral nerve sheath tumor

Malignant peripheral nerve sheath tumor

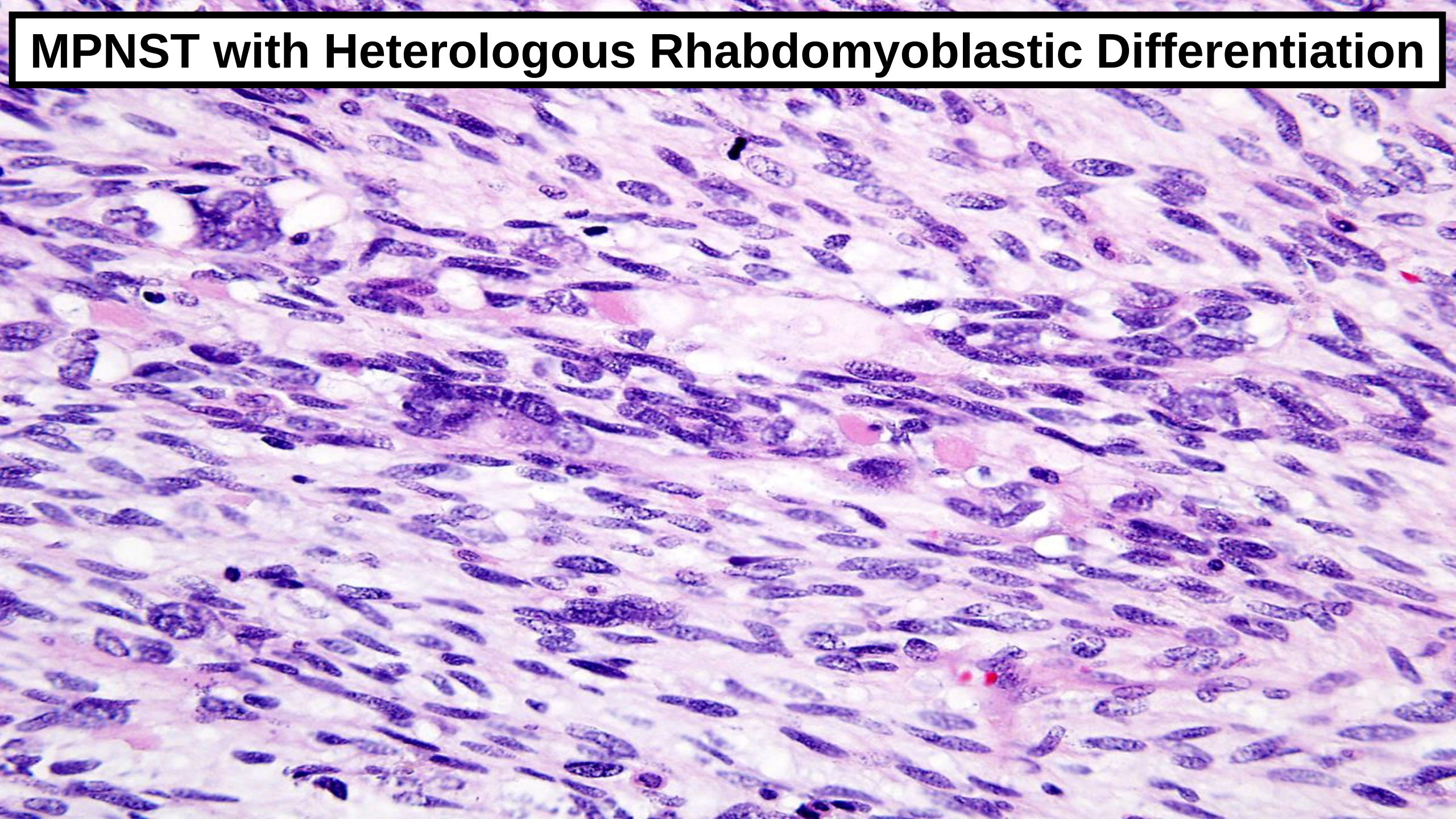
- **Arise in patients with NF1 (50%), sporadically (40%), or following radiation therapy (10%)**
- **Challenging diagnosis**
- **Diagnostic criteria:**
  1. **Origin from a nerve or a neurofibroma**
  2. **Spindle cell sarcoma in a patient with NF1**
  3. **Evidence of Schwann cell differentiation by IHC**
     - **S100 protein and SOX10 only 30-50% sensitivity**
- **Diagnosis in sporadic setting relies on distinctive histology and exclusion of mimics**


Malignant Peripheral Nerve Sheath Tumor

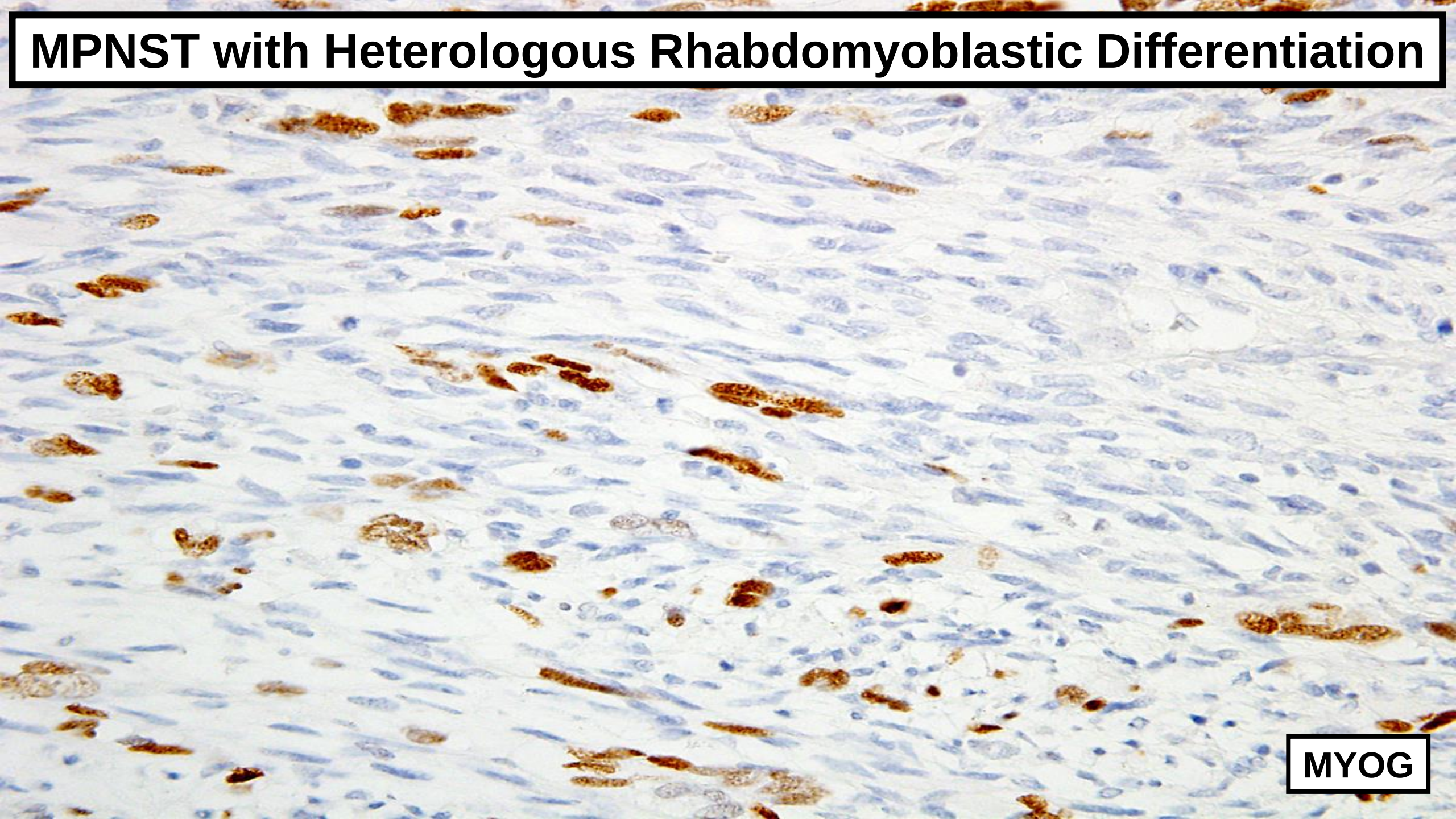
Malignant Peripheral Nerve Sheath Tumor



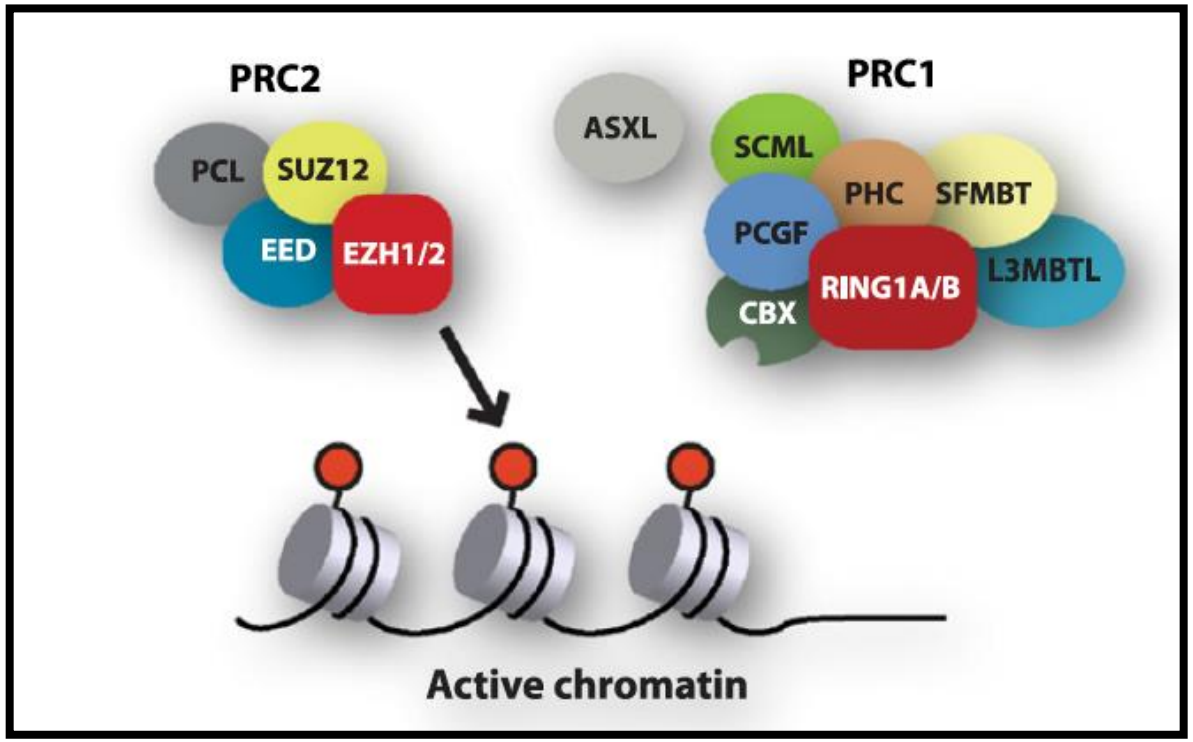
MPNST with Heterologous Rhabdomyoblastic Differentiation



MPNST with Heterologous Rhabdomyoblastic Differentiation



Polycomb repressive complex



H3K27me3

Epigenetic modification of chromatin:

- **PRC2 recruits to chromatin and trimethylates histone H3 at lysine 27**

Physiologic regulation of cell fate and stem cell differentiation

Deregulation → cancer development

Modified from Sauvageau et al. *Cell Stem Cell* 2010

LETTER NATURE

doi:10.1038/nature13561

PRC2 loss amplifies Ras-driven transcription and confers sensitivity to BRD4-based therapies

Thomas De Raedt[1,2,3], Eline Beert[4]*†, Eric Pasmant[5,6]*, Armelle Luscan[5,6], Hilde Brems[4], Nicolas Ortonne[5,6], Kristian Helin[7,8,9], Jason L. Hornick[10], Victor Mautner[11], Hildegard Kehrer-Sawatzki[12], Wade Clapp[13], James Bradner[2,14], Michel Vidaud[5,6], Meena Upadhyaya[15], Eric Legius[4,16] & Karen Cichowski[1,2,3]

Oct 2014

LETTERS

nature genetics

PRC2 is recurrently inactivated through *EED* or *SUZ12* loss in malignant peripheral nerve sheath tumors

William Lee[1,2,17], Sewit Teckie[2,3,17], Thomas Wiesner[3,17], Leili Ran[3,17], Carlos N Prieto Granada[4], Mingyan Lin[5], Sinan Zhu[3], Zhen Cao[3], Yupu Liang[3], Andrea Sboner[6–8], William D Tap[9,10], Jonathan A Fletcher[11], Kety H Huberman[12], Li-Xuan Qin[13], Agnes Viale[12], Samuel Singer[14], Deyou Zheng[5,15,16], Michael F Berger[3,4], Yu Chen[3,9,10], Cristina R Antonescu[4] & Ping Chi[3,9,10]

Nov 2014

BRIEF COMMUNICATIONS

nature genetics

Somatic mutations of *SUZ12* in malignant peripheral nerve sheath tumors

Ming Zhang[1,2], Yuxuan Wang[1,2], Sian Jones[3], Mark Sausen[3], Kevin McMahon[1,2], Rajni Sharma[4], Qing Wang[1,2], Allan J Belzberg[5], Kaisorn Chaichana[5], Gary L Gallia[5], Ziya L Gokaslan[5], Greg J Riggins[5], Jean-Paul Wolinksy[5], Laura D Wood[4], Elizabeth A Montgomery[4], Ralph H Hruban[4], Kenneth W Kinzler[1,2], Nickolas Papadopoulos[1,2], Bert Vogelstein[1,2] & Chetan Bettegowda[1,2,5]

Nov 2014

PRC2 and MPNST

- **PRC2 alterations (*SUZ12* or *EED* mutations) in 90% of MPNST**
- **Homozygous mutations result in loss of H3K27me3 (histone H3 lysine 27 trimethylation) in 70% of MPNST**
- **Rate of H3K27me3 loss depends on grade**
- **IHC for H3K27me3 highly specific diagnostic marker**

Schaefer et al. *Mod Pathol* 2016

Prieto-Granada et al. *Am J Surg Pathol* 2016

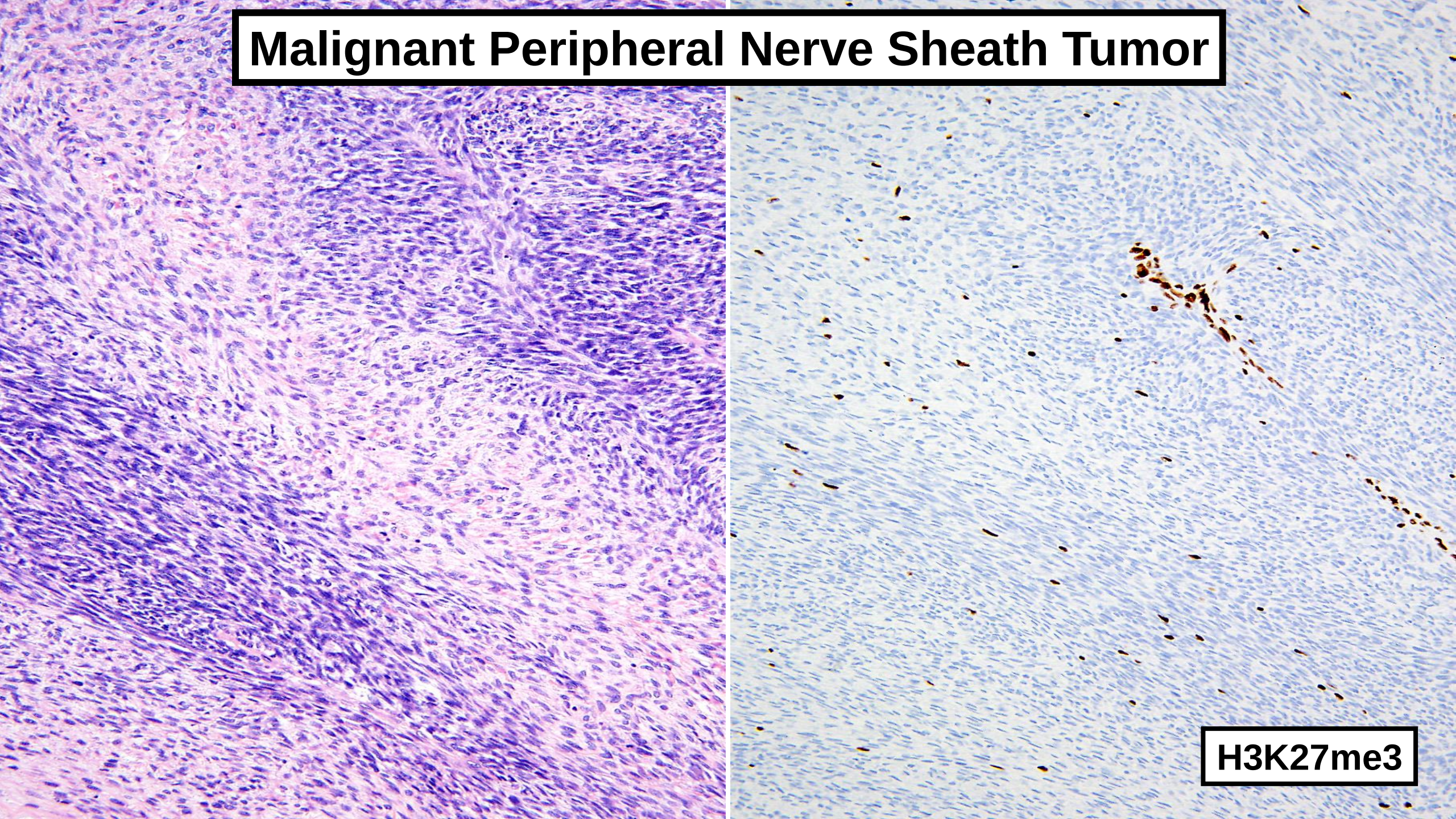
IHC for H3K27me3 in MPNST

MPNST grade	H3K27me3 loss
Low grade	30%
Intermediate grade	60%
High grade	80%

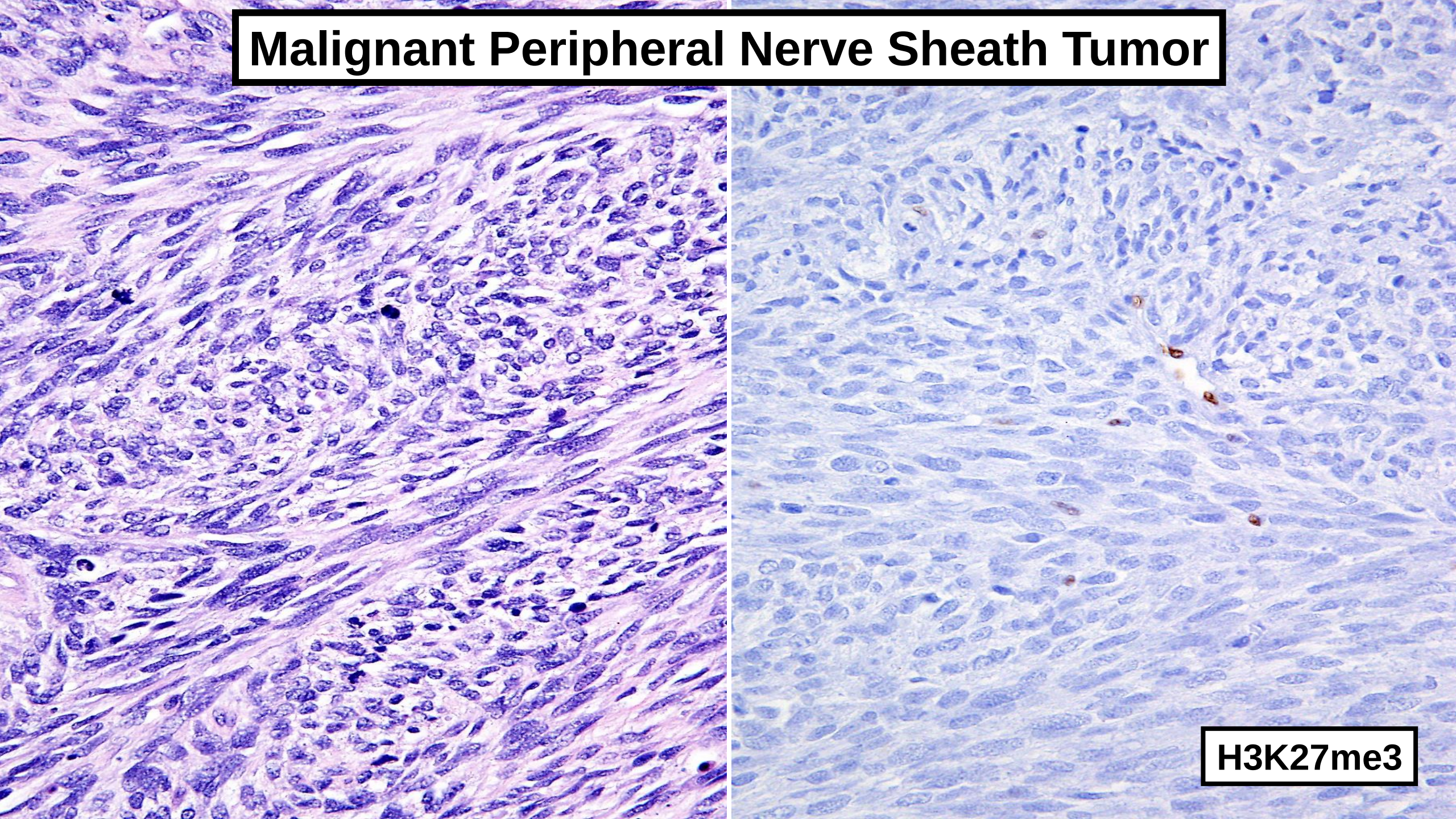
Schaefer et al. *Mod Pathol* 2016

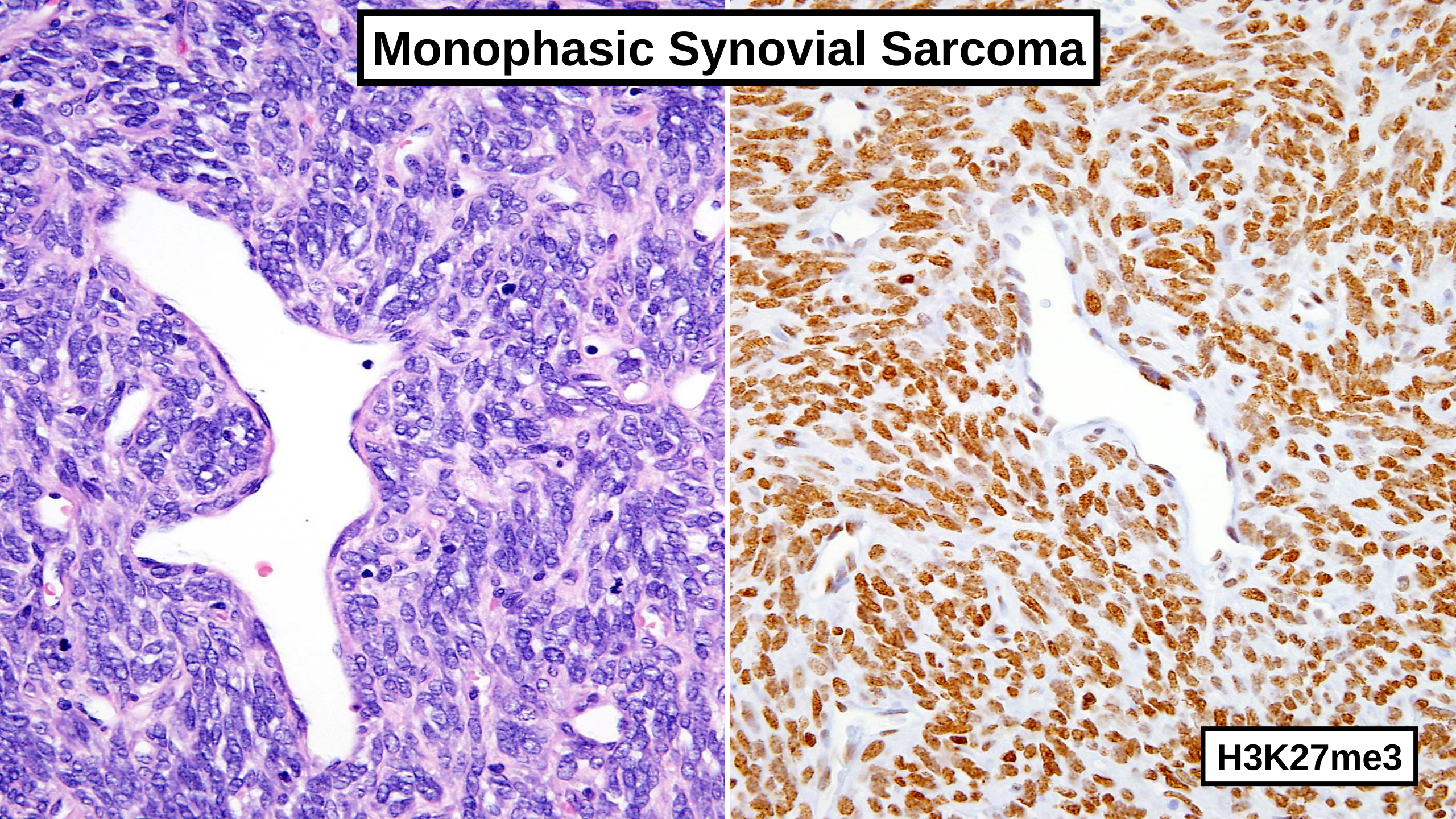
Prieto-Granada et al. *Am J Surg Pathol* 2016

Malignant Peripheral Nerve Sheath Tumor



Malignant Peripheral Nerve Sheath Tumor




Monophasic Synovial Sarcoma
H3K27me3

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THANK YOU!