SUBCLASSIFICATION OF PLEOMORPHIC SARCOMAS:
HOW AND WHY SHOULD WE CARE?

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Pleomorphic sarcomas: does subclassification matter?

Marked differences in metastatic potential!

Tumor type	Metastatic rate
Dedifferentiated liposarcoma	15-20%
Myxofibrosarcoma (high grade)	25-30%
Undifferentiated pleomorphic sarcoma	50%
Pleomorphic liposarcoma	50%
Extraskeletal osteosarcoma	60%
Pleomorphic leiomyosarcoma	70%
Pleomorphic rhabdomyosarcoma	90%

Approach to pleomorphic sarcomas

- Pay attention to anatomic site
- Know the relative incidence
- Careful sampling of resection specimen
- Look for subtle/focal histologic clues
- Apply immunohistochemistry judiciously

Somatic soft tissue (especially thigh)

Relatively common	Rare
Myxofibrosarcoma	Pleomorphic liposarcoma
Undifferentiated pleomorphic sarcoma	Pleomorphic rhabdomyosarcoma
Pleomorphic leiomyosarcoma	Extraskeletal osteosarcoma

Retroperitoneum

Relatively common	Rare
Dedifferentiated liposarcoma	Undifferentiated pleomorphic sarcoma
Pleomorphic leiomyosarcoma	Pleomorphic liposarcoma

What histologic features should we search for?

Myxoid stroma
Myxofibrosarcoma
Dedifferentiated liposarcoma
Pleomorphic liposarcoma
Undifferentiated pleomorphic sarcoma

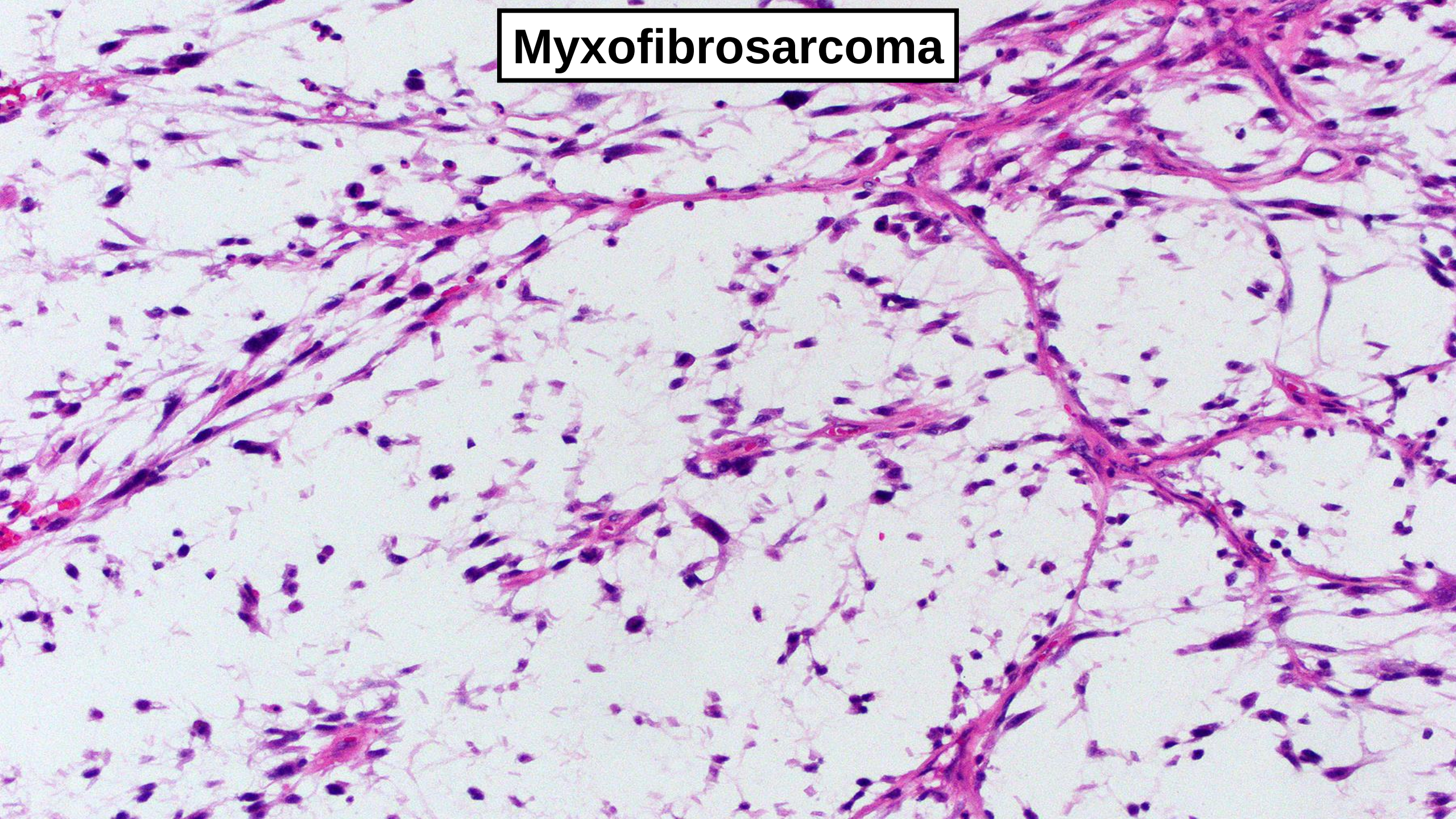
Lipoblasts
Pleomorphic liposarcoma
Dedifferentiated liposarcoma

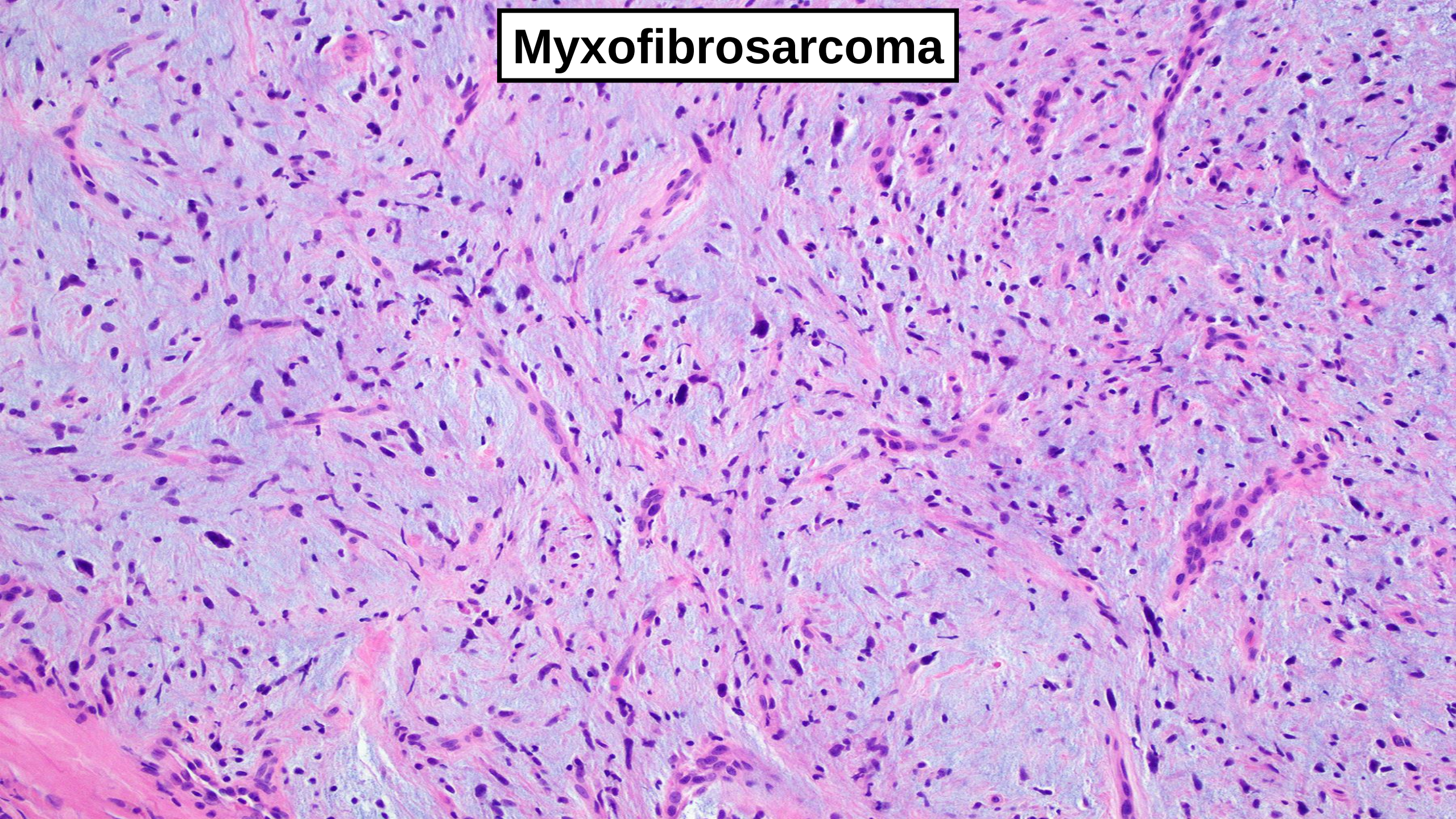
Osteoid
Extraskeletal osteosarcoma
Dedifferentiated liposarcoma

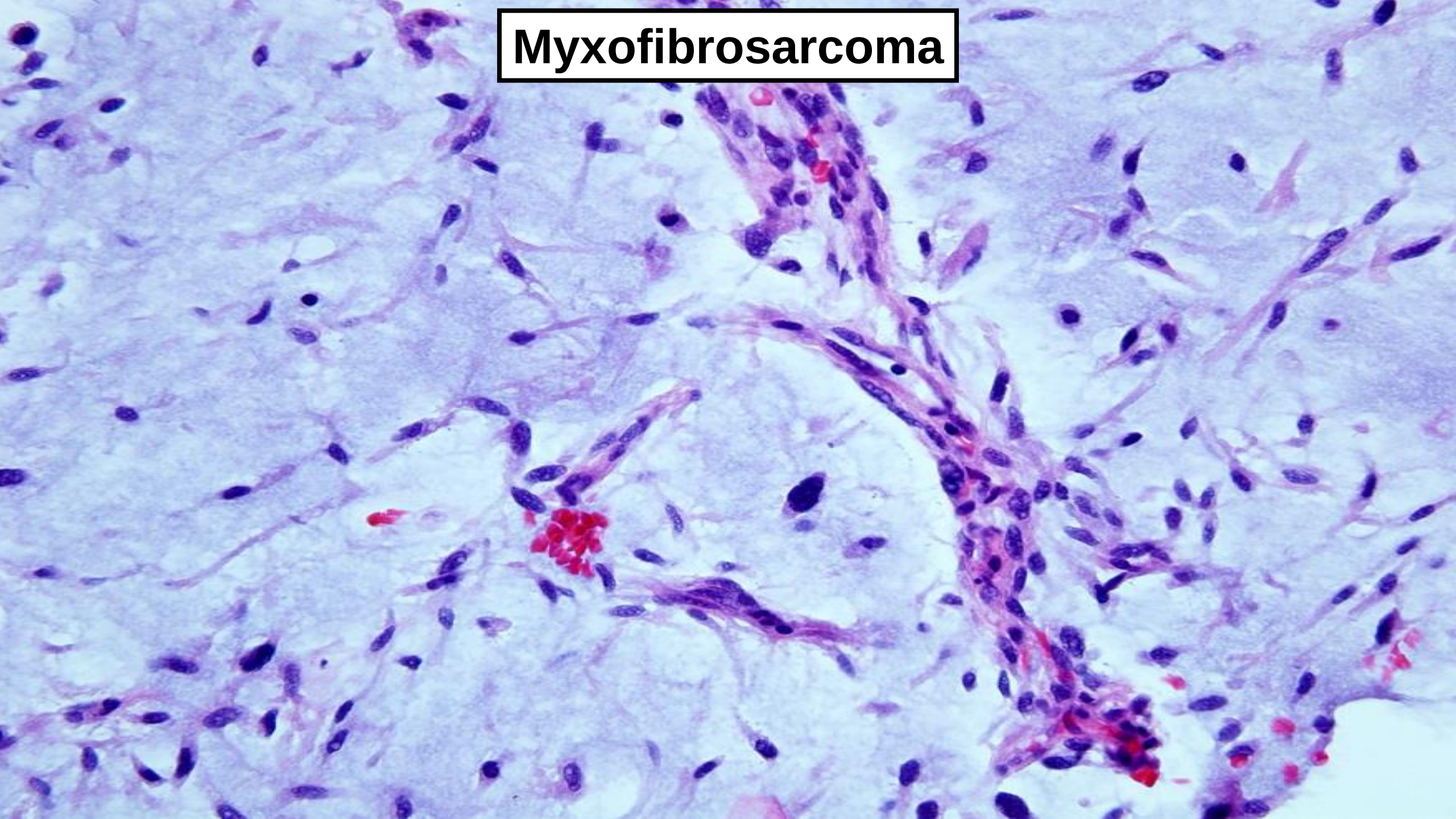
Myxofibrosarcoma

- Most common sarcoma of elderly
- Proximal extremities, trunk
- 70% superficial; 30% deep
- High rate of local recurrence
- Grade increases with recurrence
- Low grade: <5% metastasis
- High grade: 30% metastasis

Myxofibrosarcoma




Myxofibrosarcoma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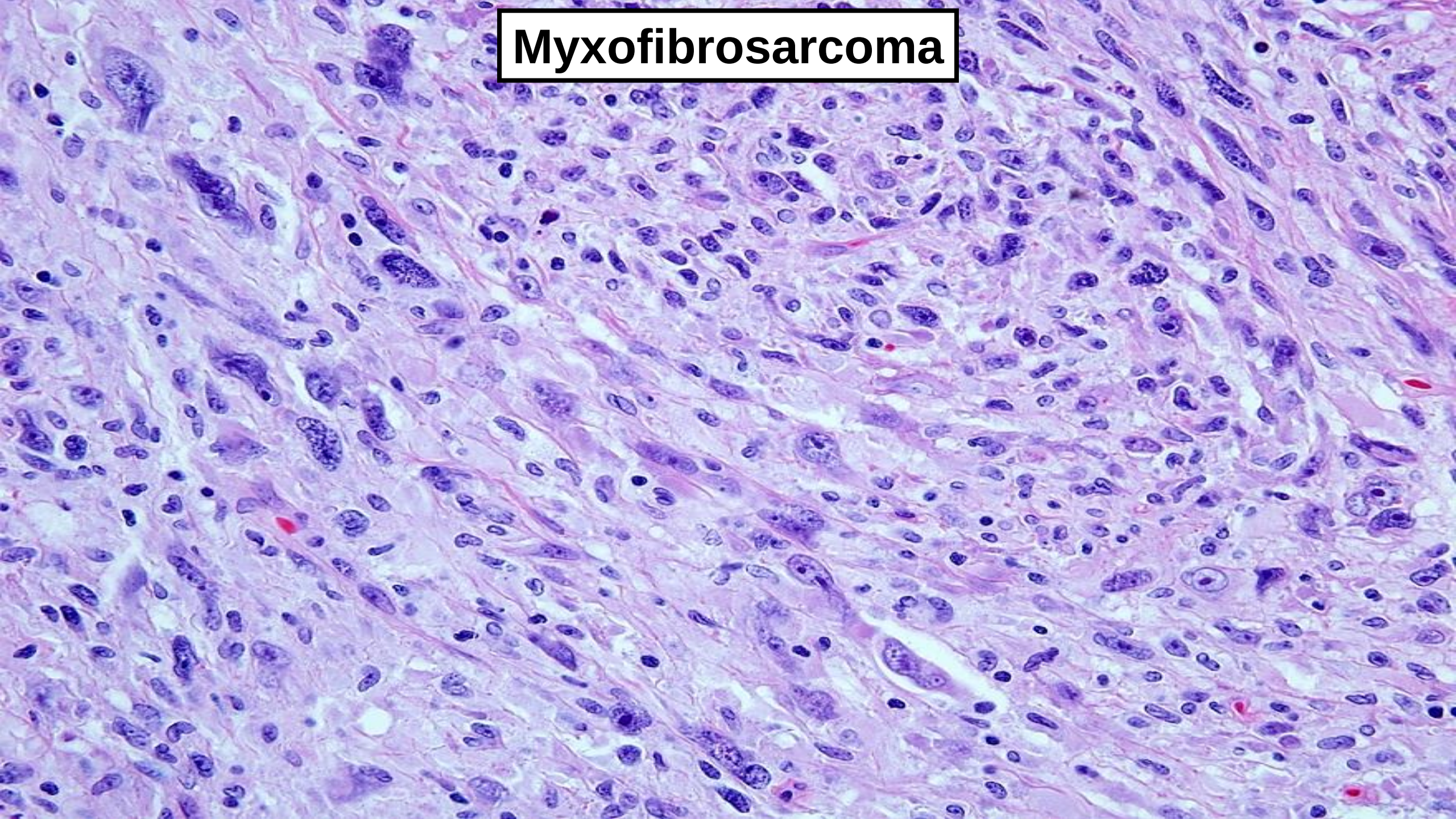
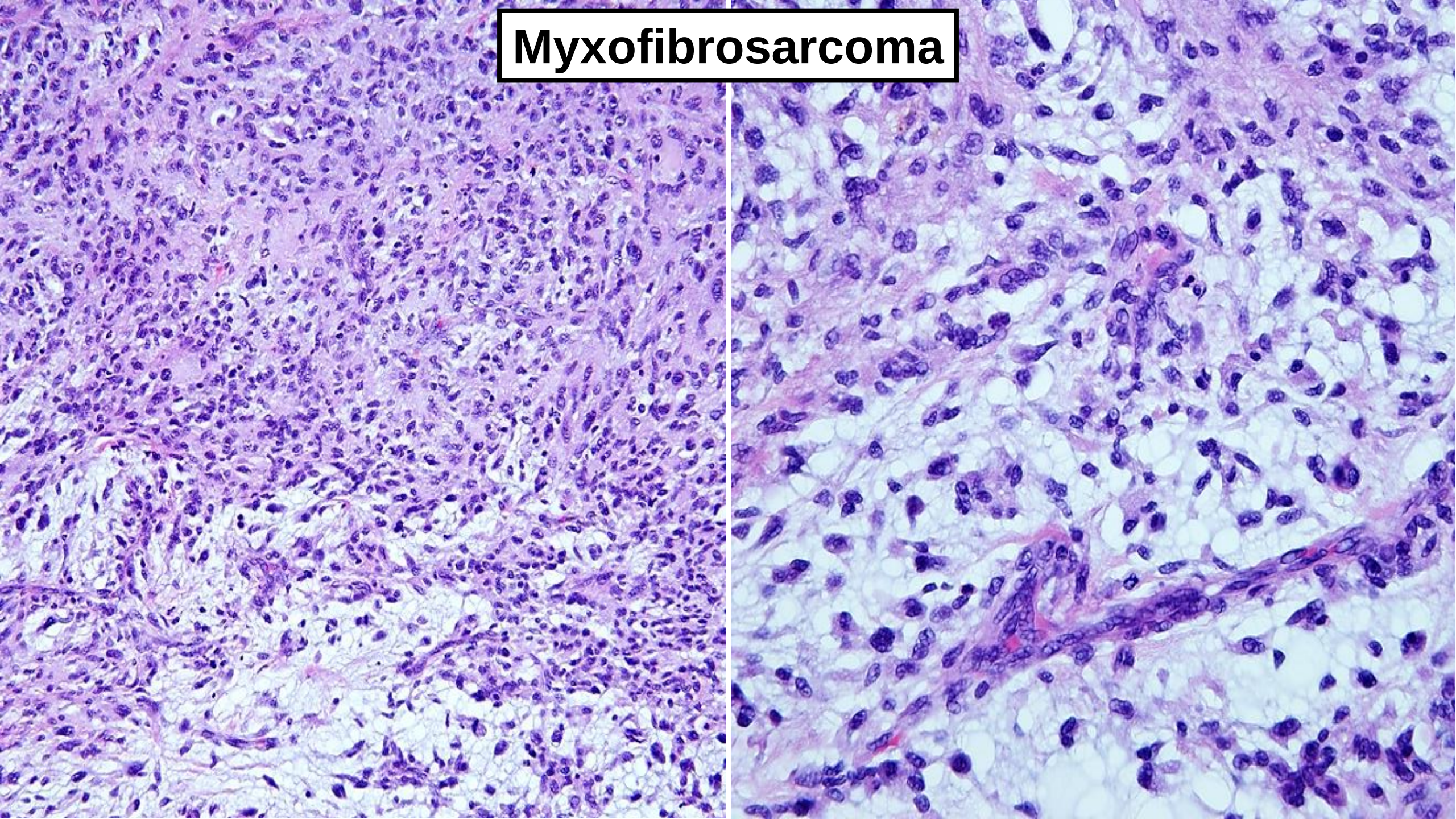
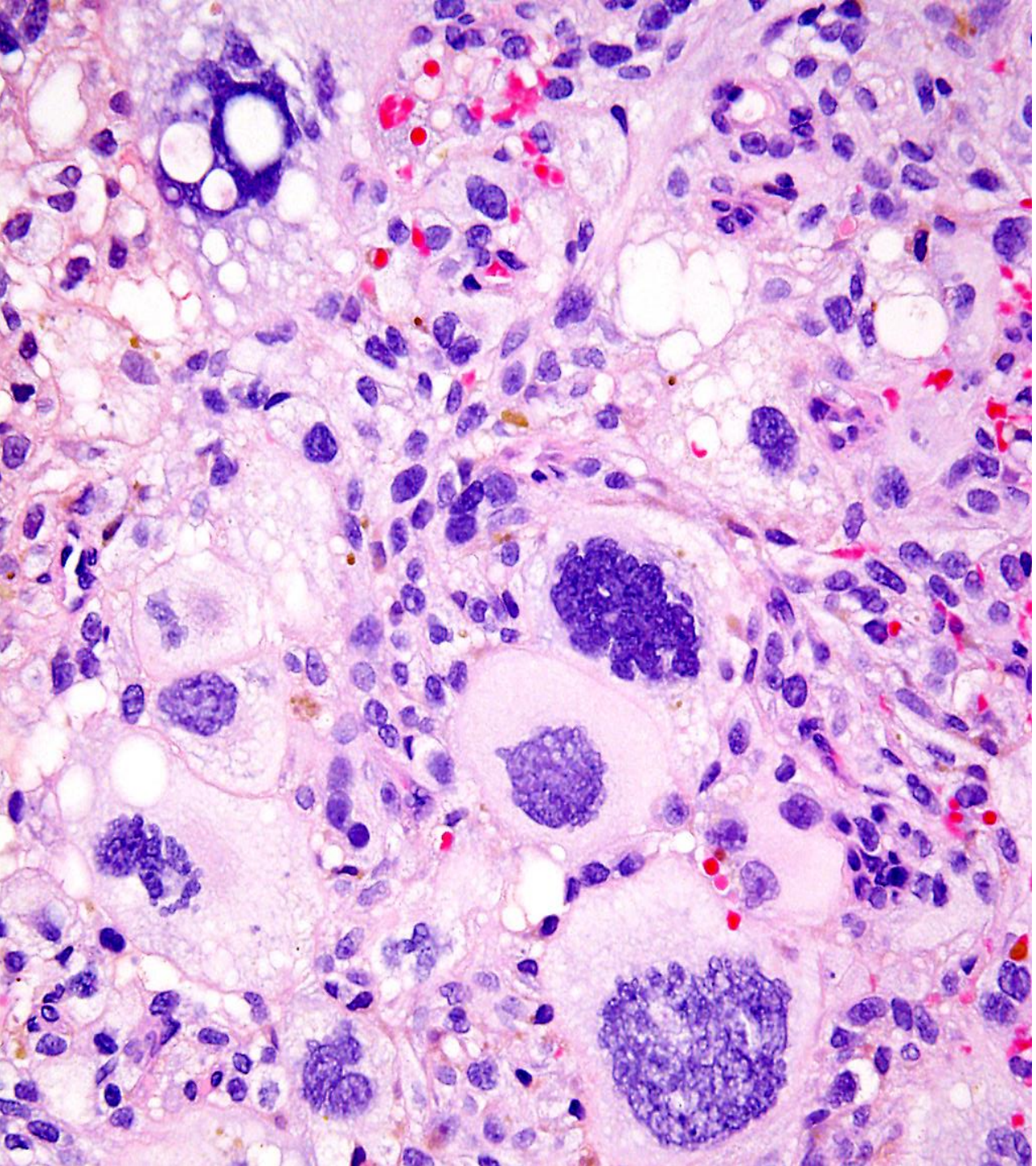

Myxofibrosarcoma

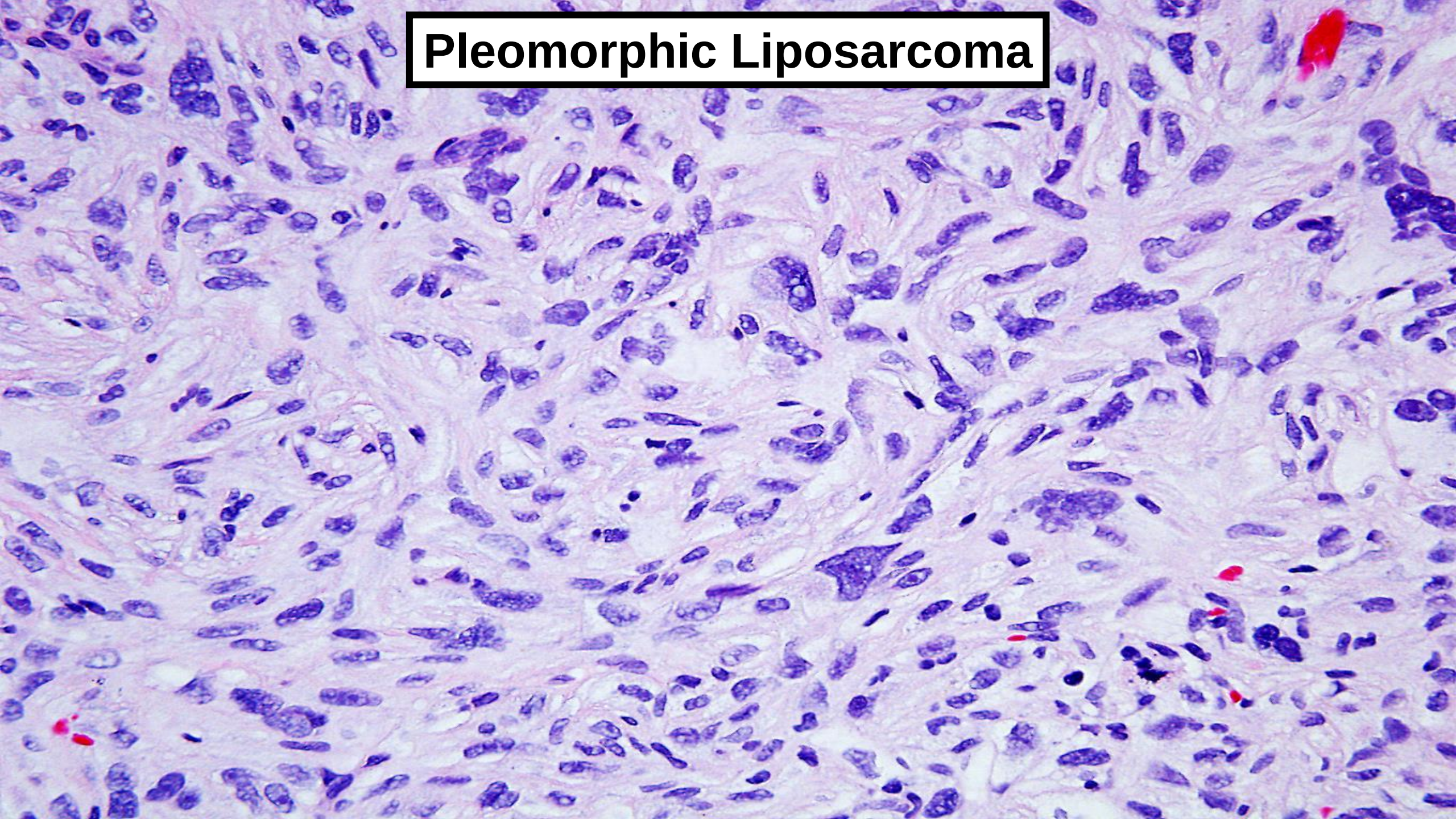
Myxofibrosarcoma



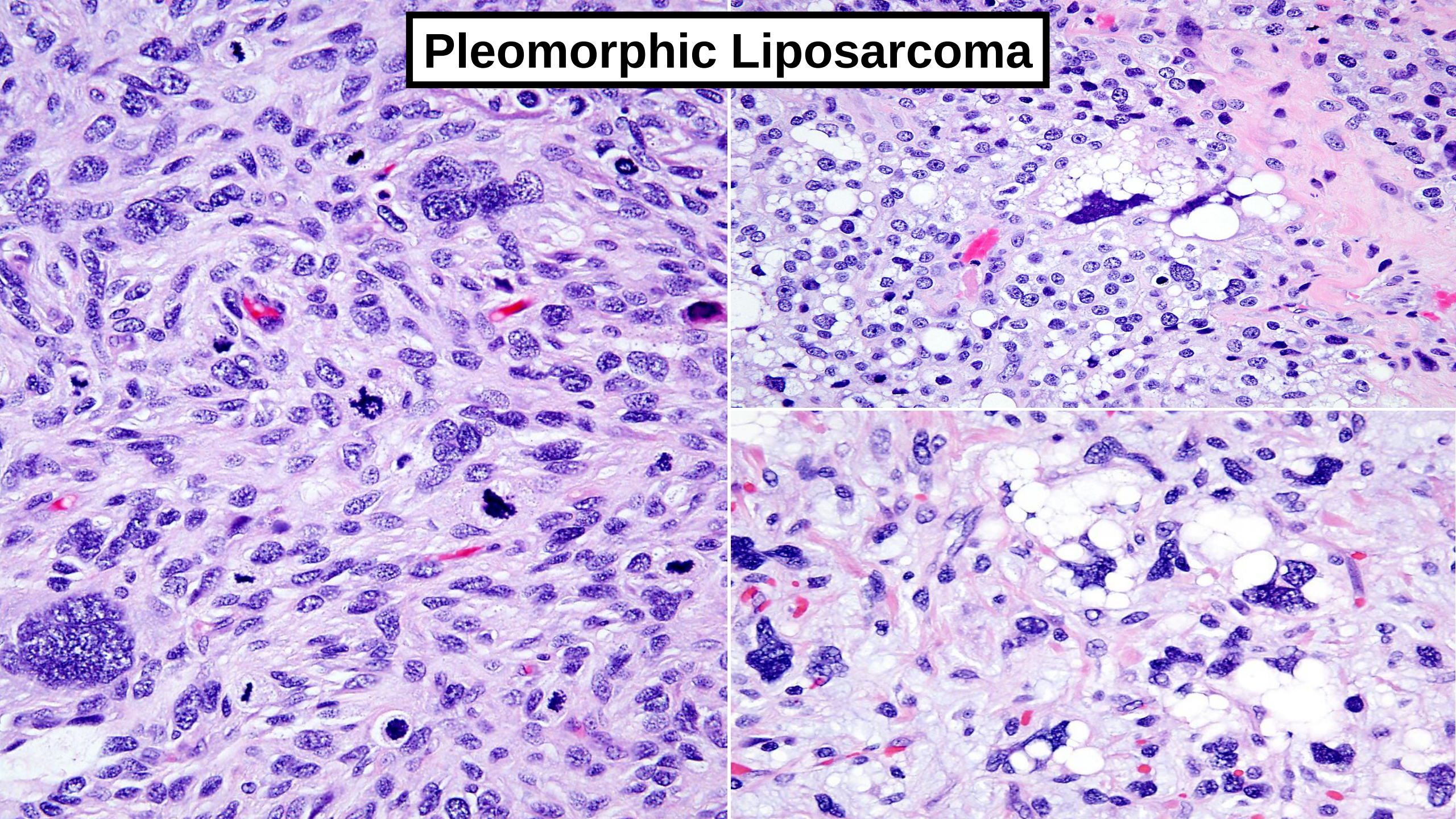


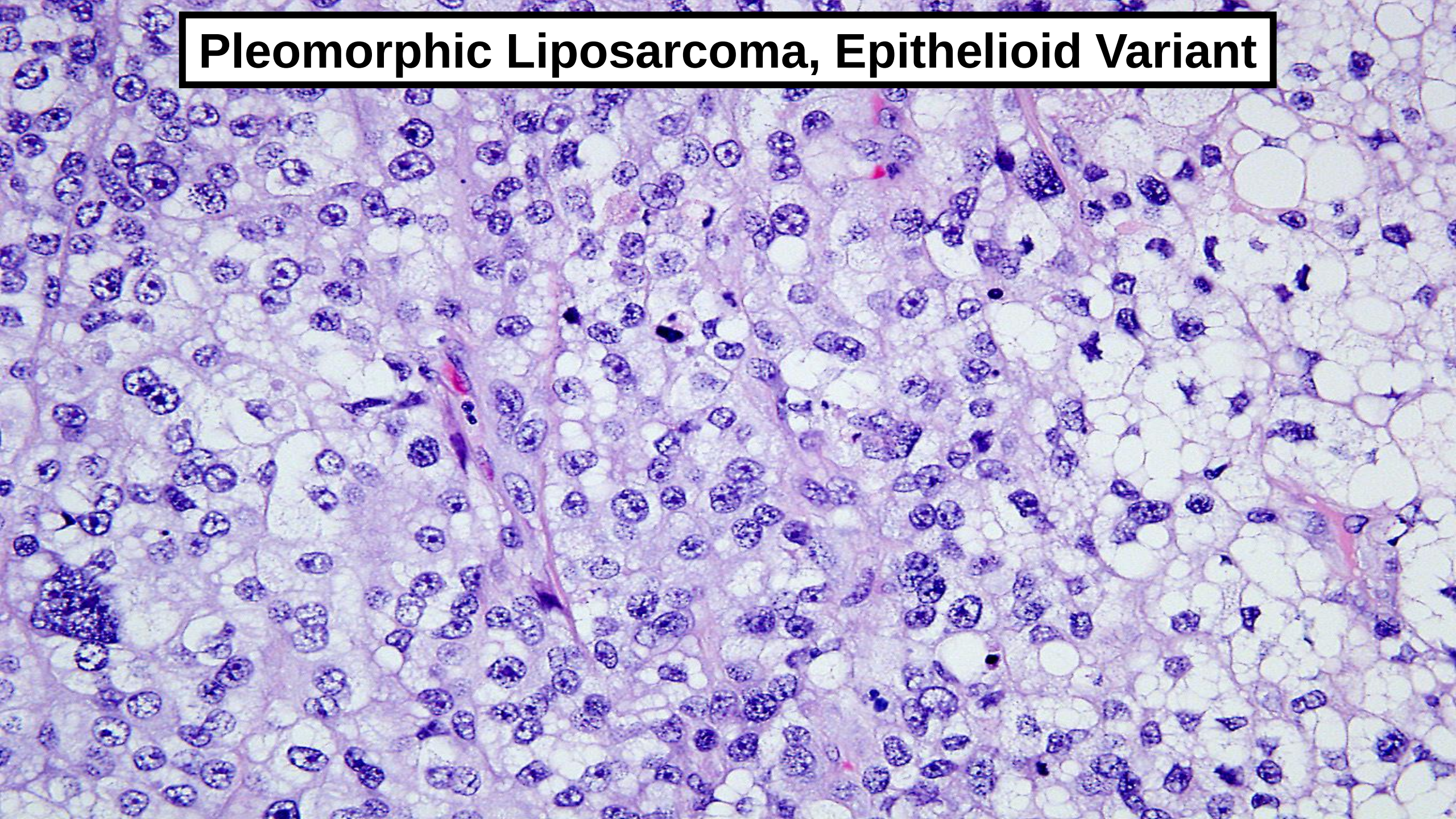
Pleomorphic liposarcoma

- 5% of liposarcomas
- Middle-aged to elderly adults
- Extremities >> retroperitoneum
- 90% deep; 10% superficial
- Metastatic rate 50%
- Wide histologic spectrum
- Lipoblasts must be identified!

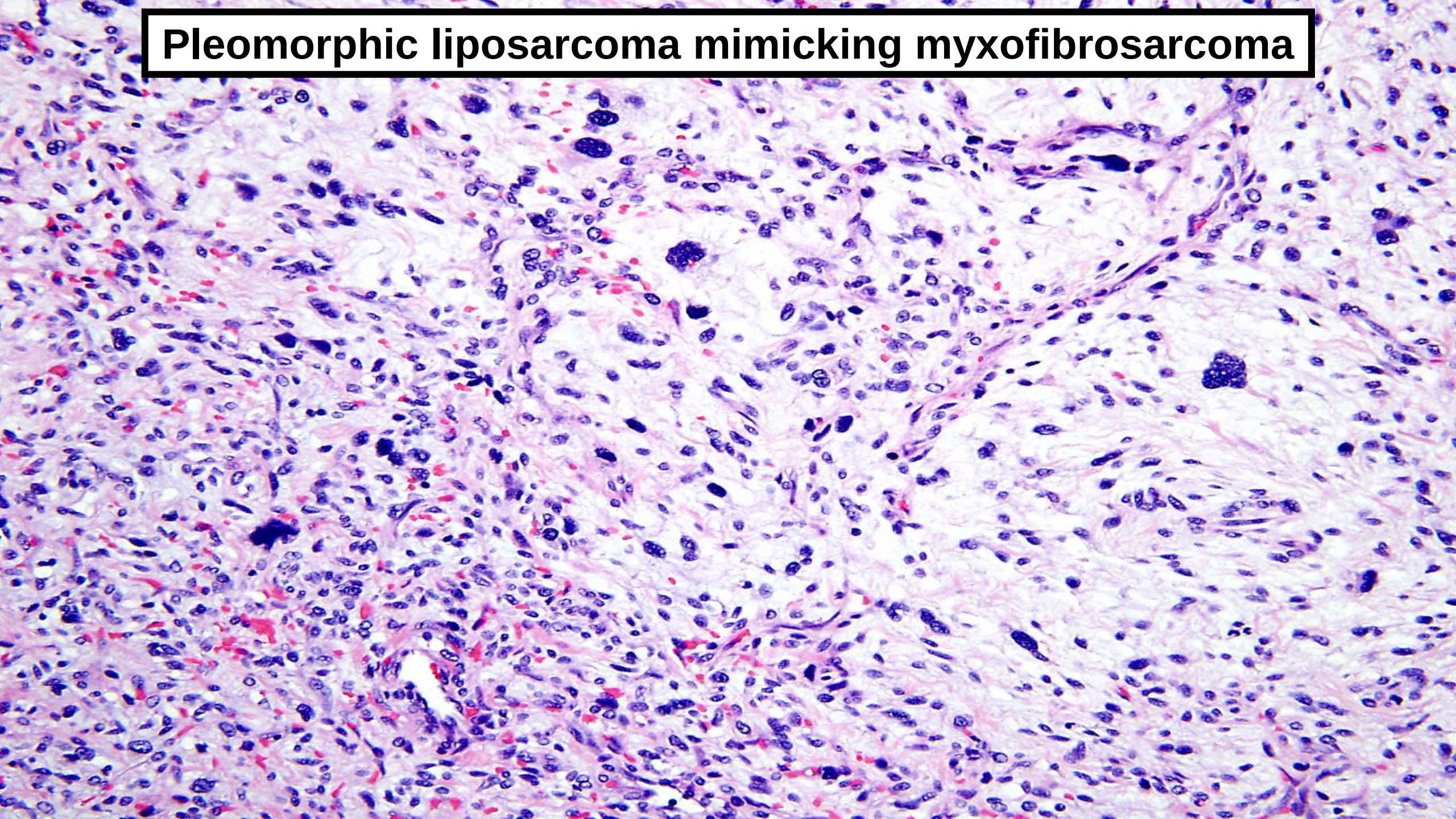

Pleomorphic Liposarcoma

Pleomorphic Liposarcoma

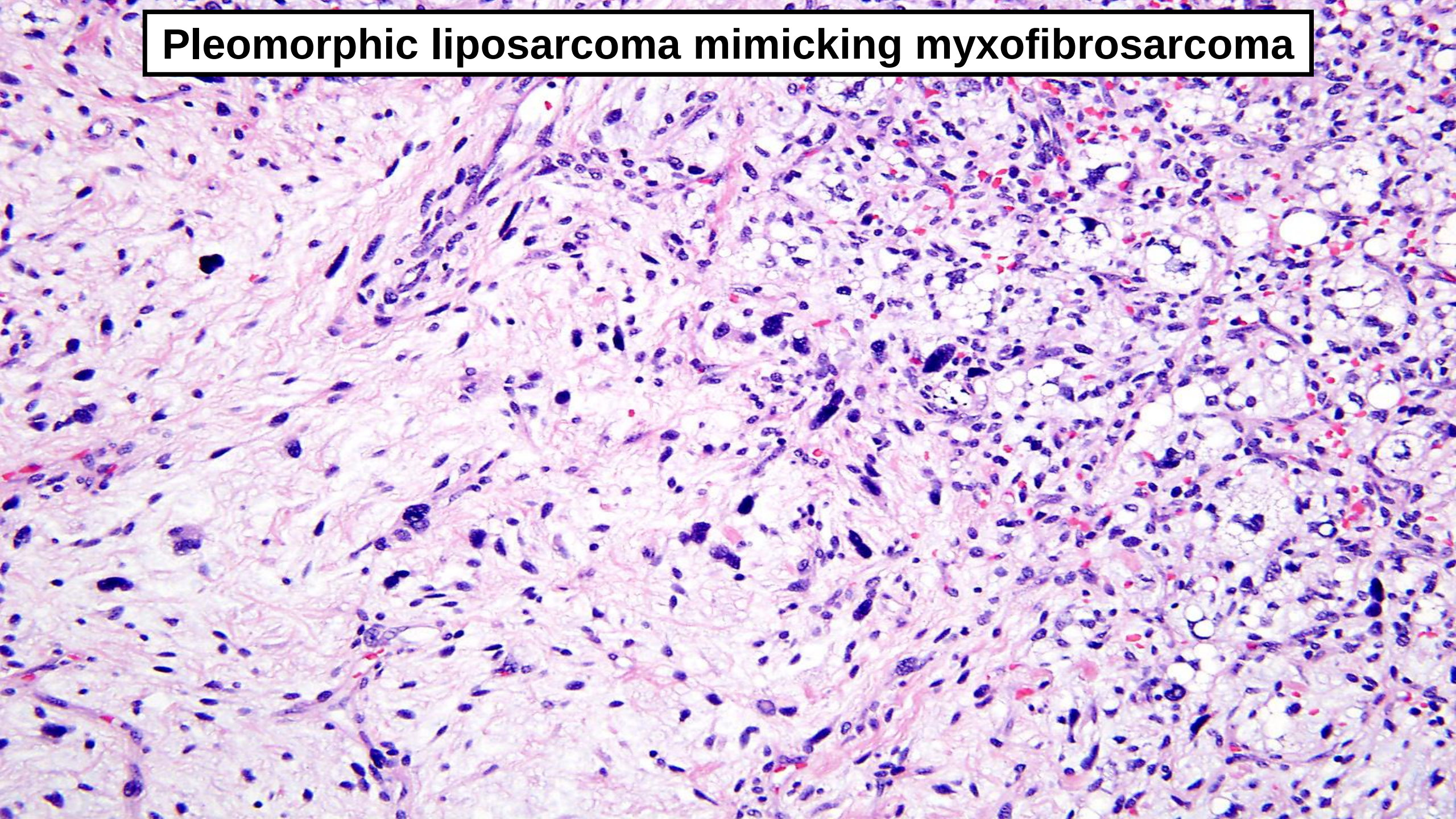



Pleomorphic Liposarcoma, Epithelioid Variant

Pleomorphic liposarcoma mimicking myxofibrosarcoma



Pleomorphic liposarcoma mimicking myxofibrosarcoma



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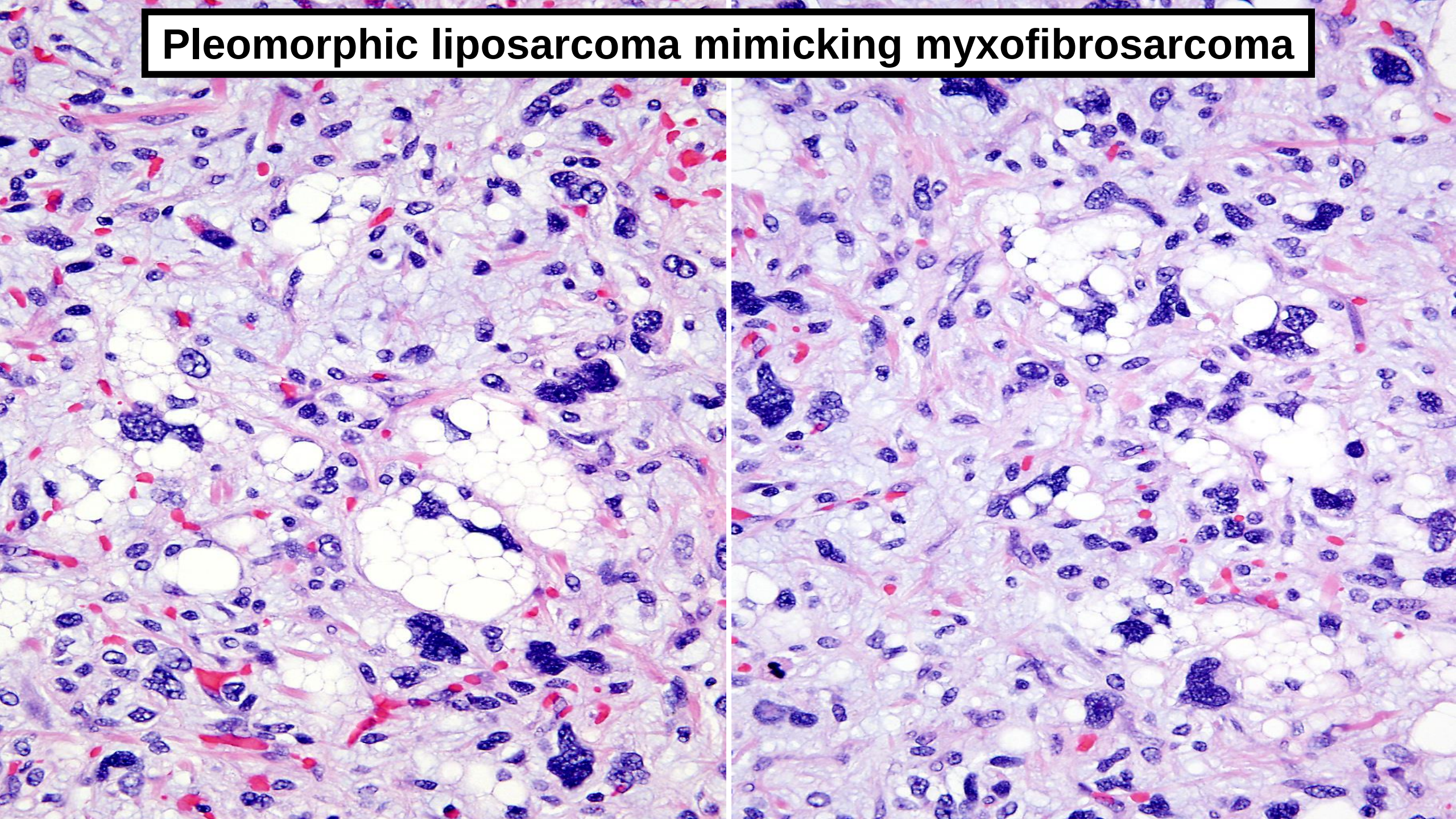
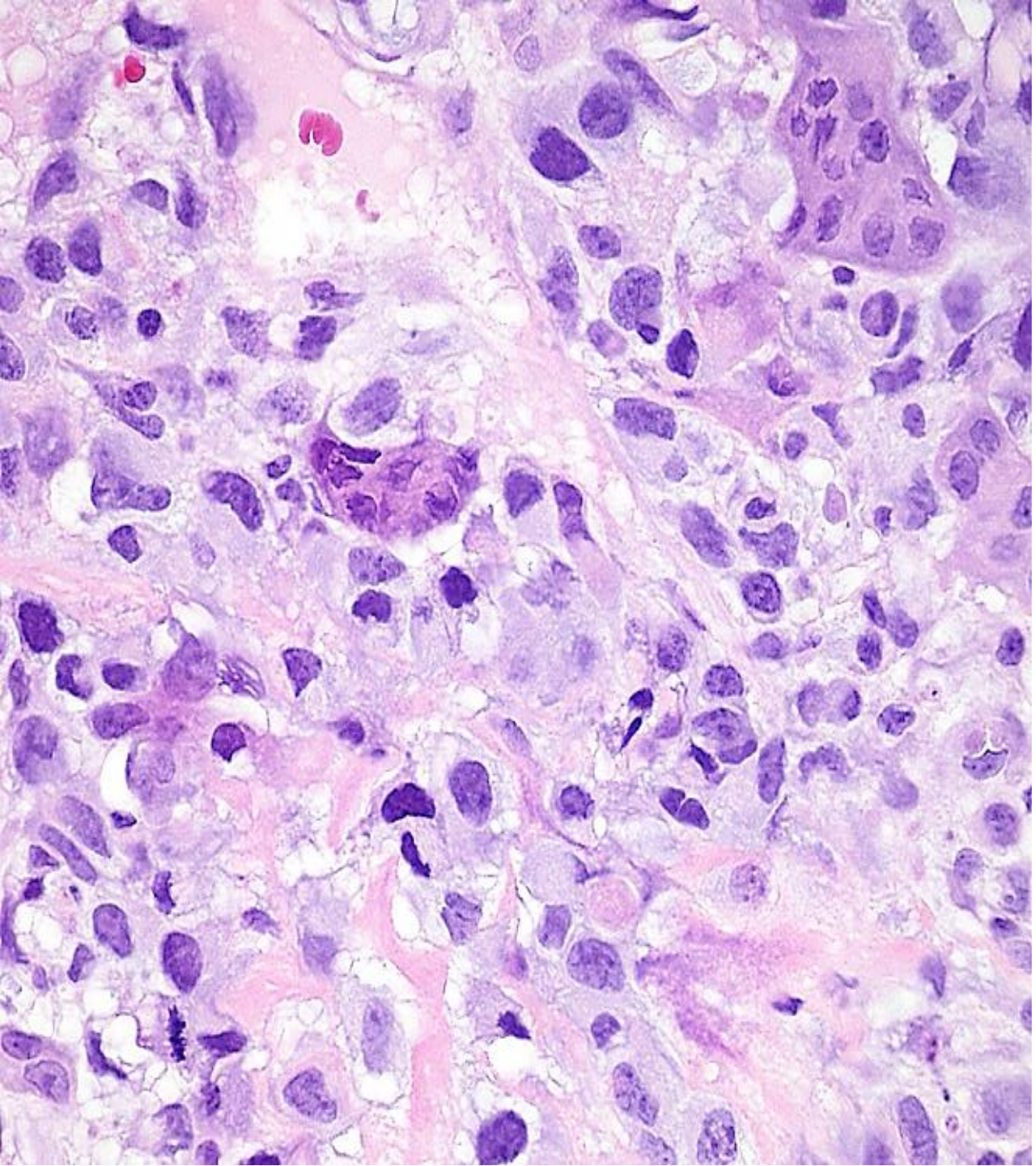
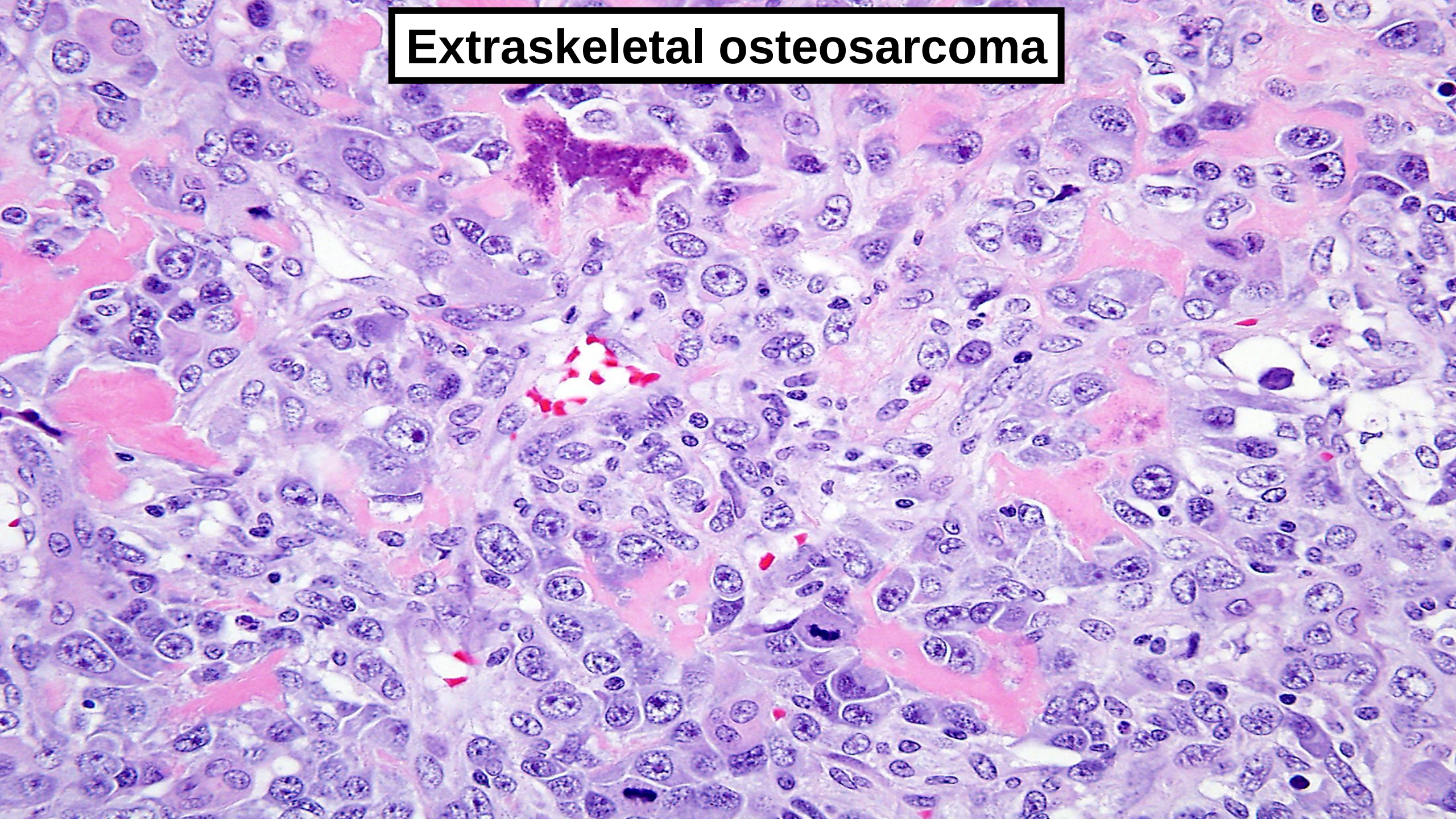


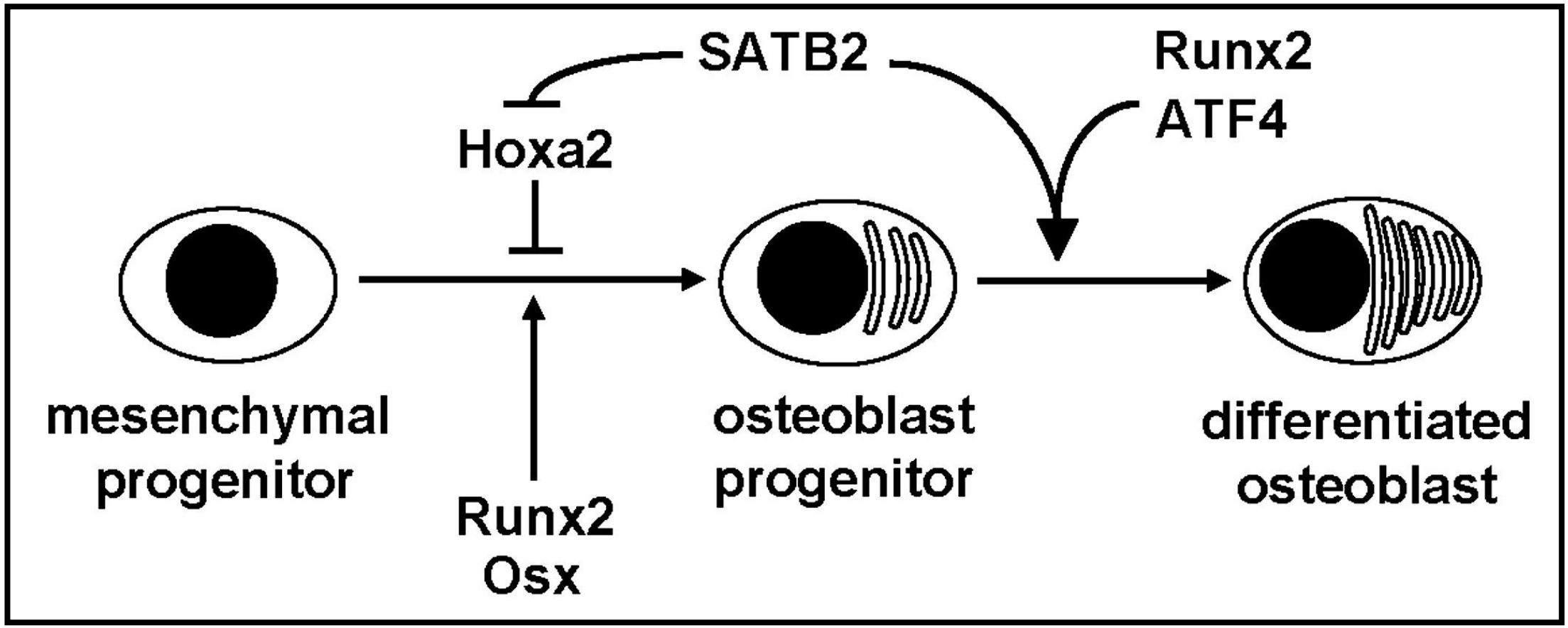


Extraskeletal osteosarcoma

- Middle-aged to elderly adults
- Men > women
- Proximal extremities (50% thigh), trunk, shoulder, pelvic girdle
- Nearly all deep
- Local recurrence 40%
- Distant metastasis 60%


Extraskeletal osteosarcoma

SATB2: Osteoblast transcription factor

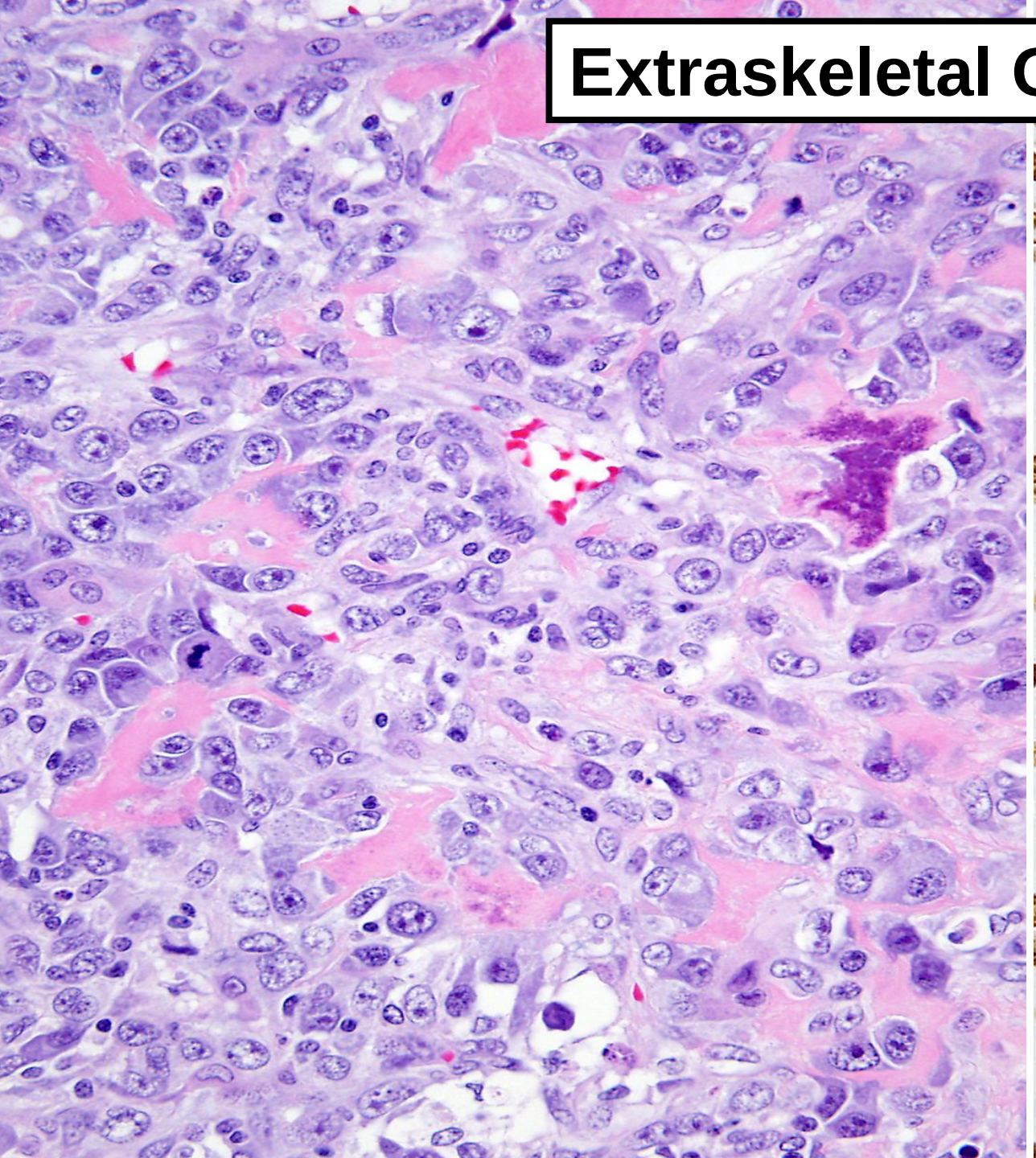


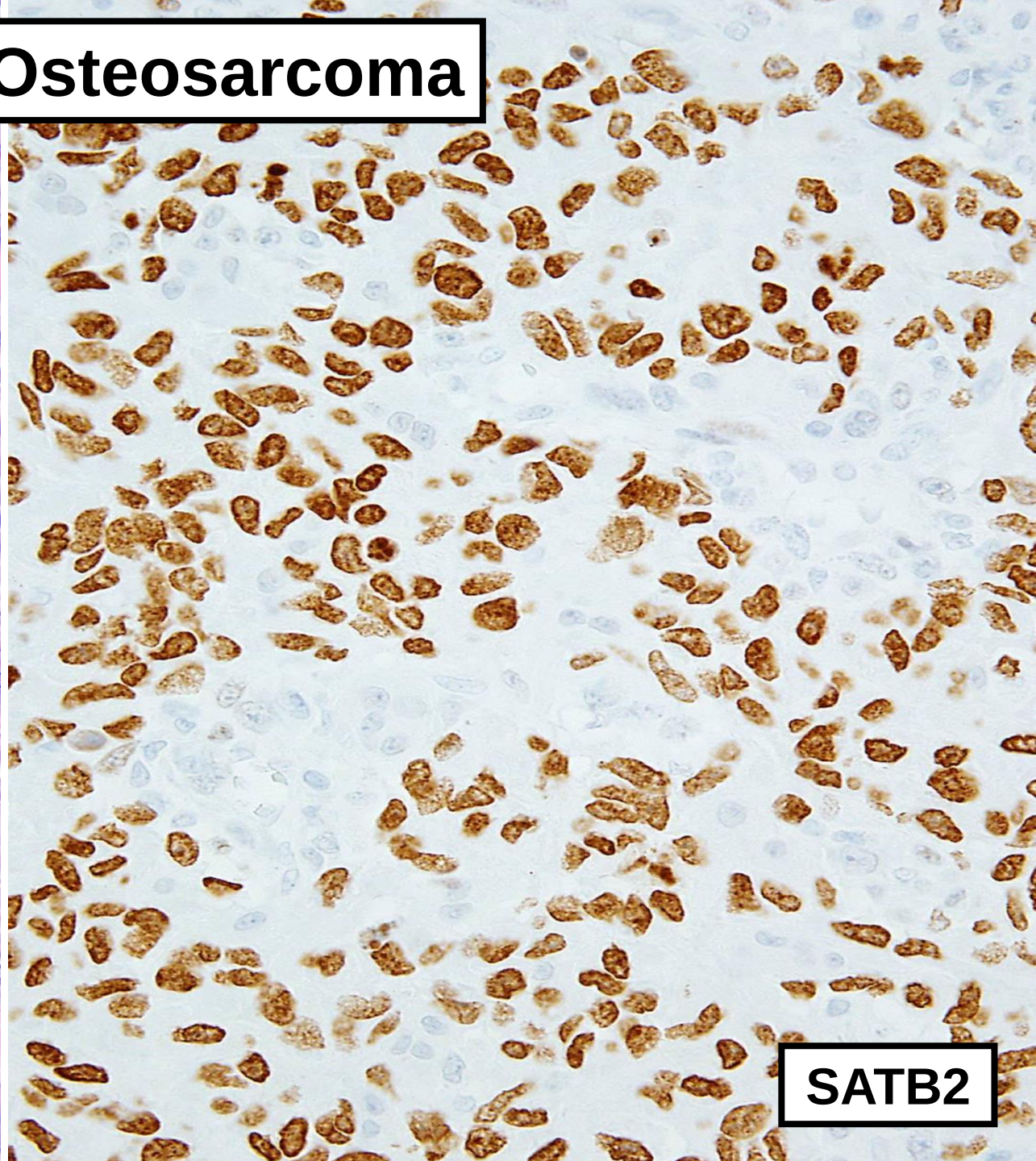
Dobreva et al. Cell 2006

SATB2: Osteoblast transcription factor

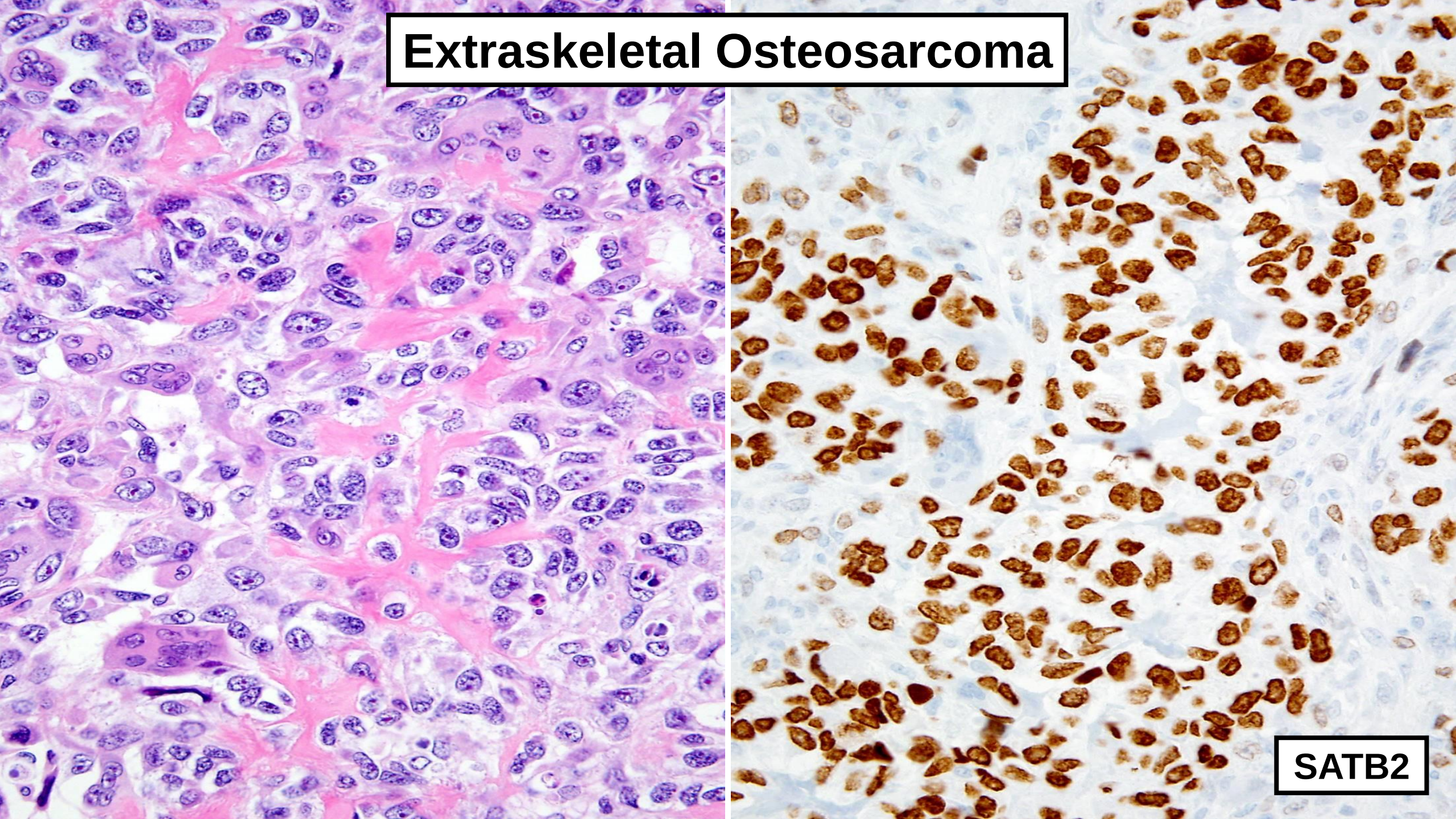
- **Strong nuclear staining – sensitive and moderately specific marker for osteoblastic differentiation**
- **Can be used as a diagnostic adjunct in selected cases**
- **When histologic features of matrix are equivocal (is it sclerotic collagen or osteoid?)**
- **NOT specific for osteosarcoma – the cells adjacent to metaplastic bone are positive!**

Extraskeletal Osteosarcoma





Extraskeletal Osteosarcoma



Which IHC are helpful for pleomorphic sarcomas?

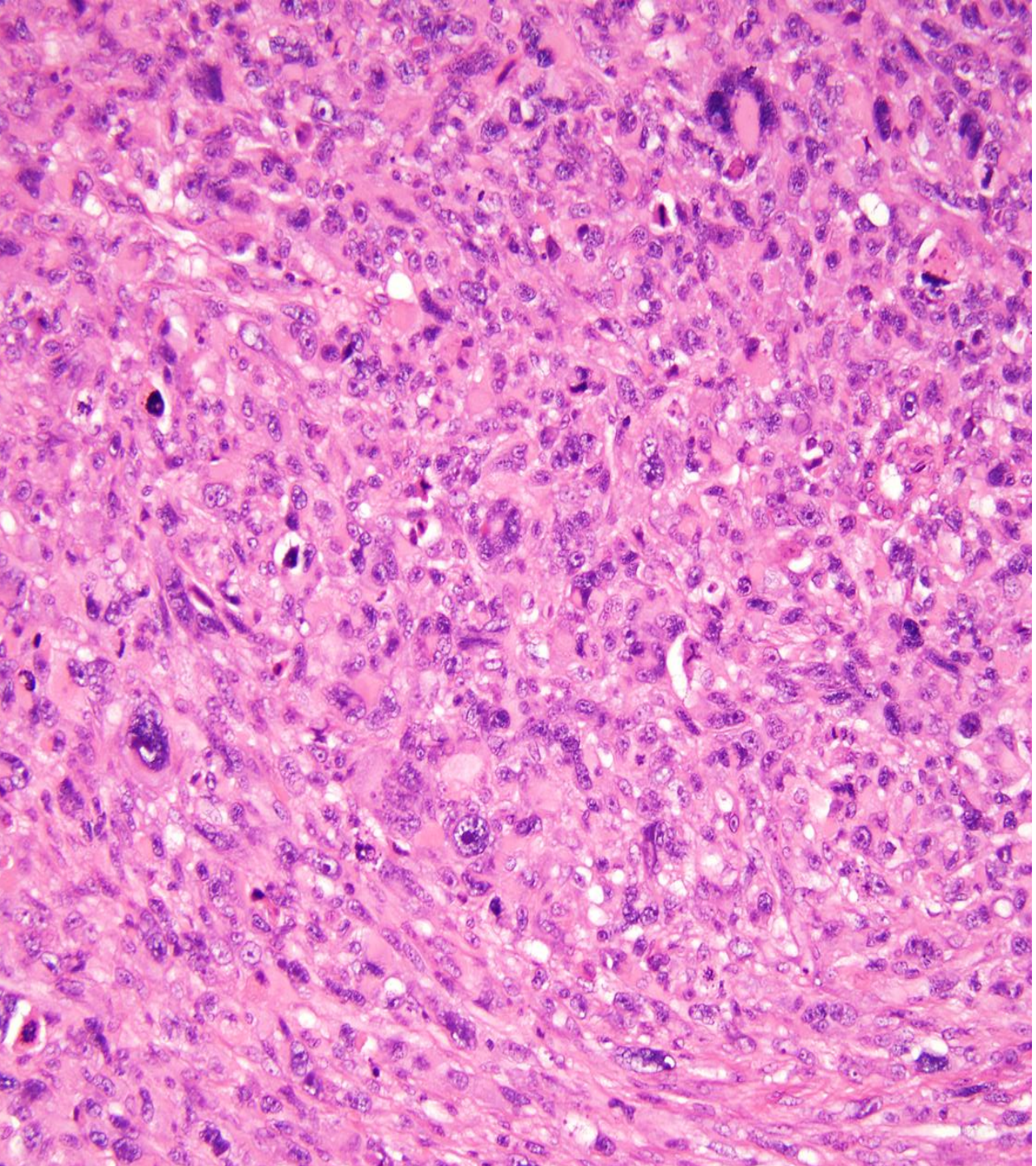
Smooth muscle markers
SMA
Desmin
Caldesmon

Skeletal muscle markers
Desmin
Myogenin
MyoD1

Osteoblast marker
SATB2

Dedifferentiated liposarcoma markers
MDM2
CDK4

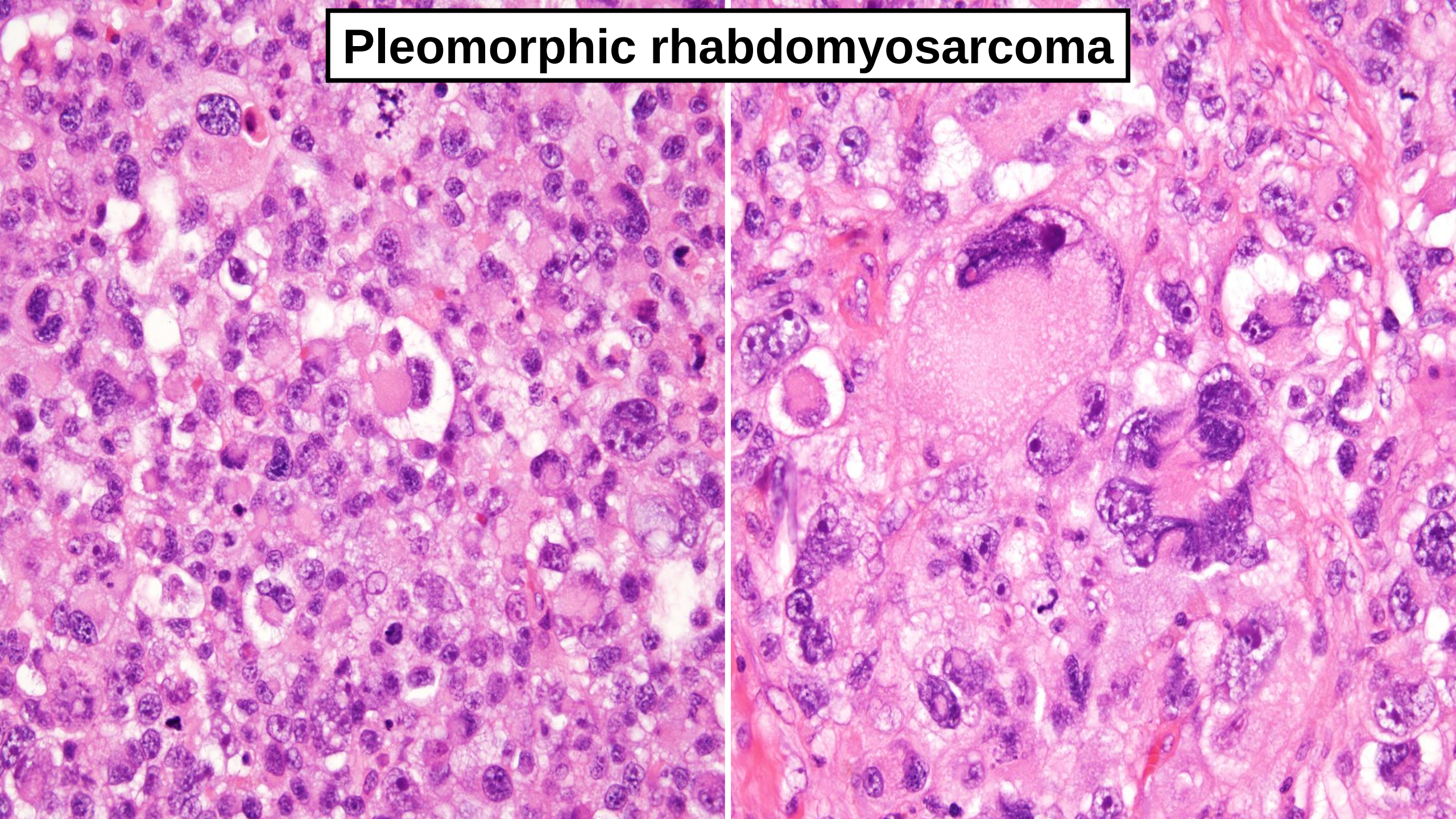
Exclude metastatic sarcomatoid carcinoma and melanoma!
Keratins
S100
SOX10



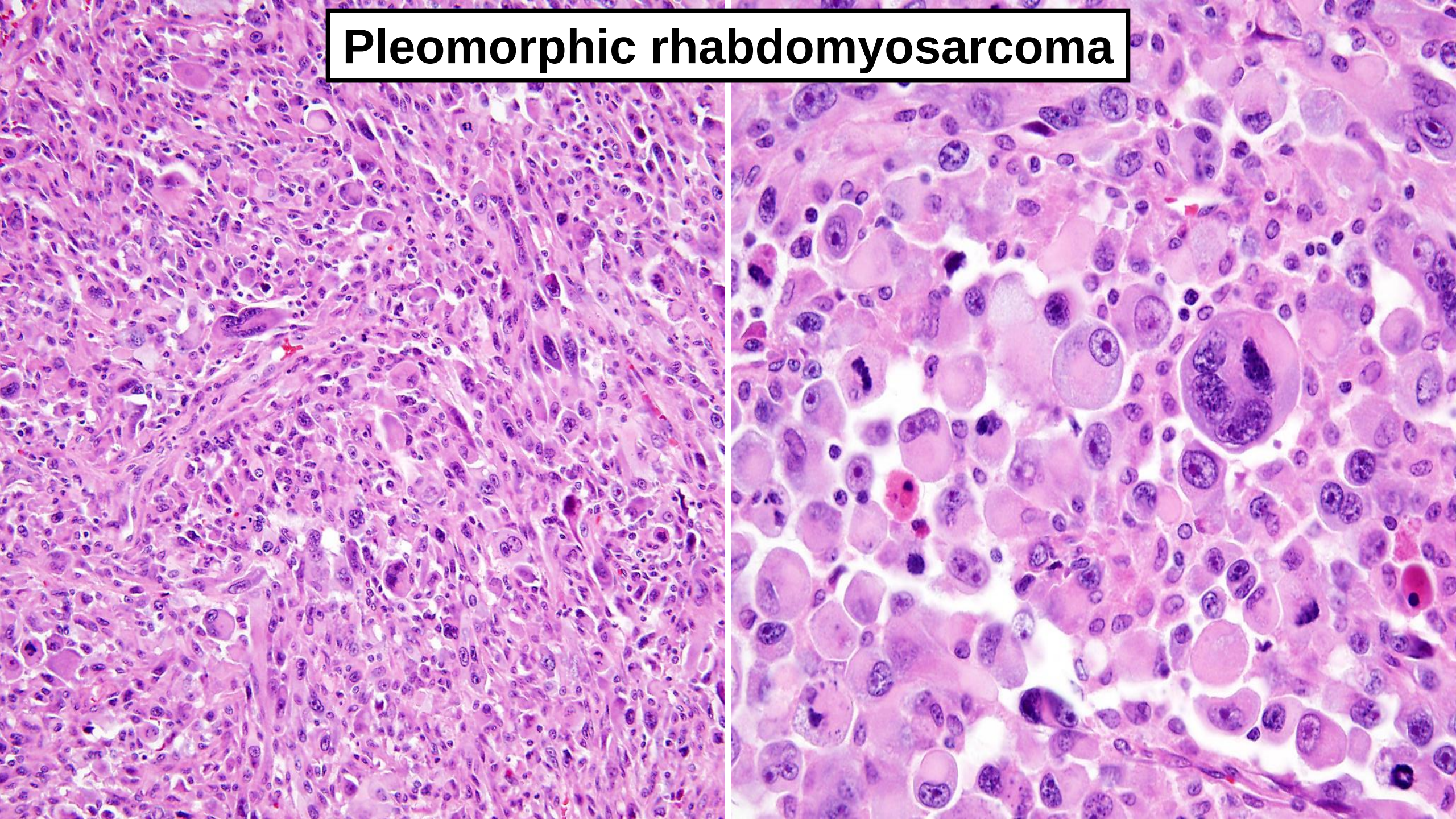
Pleomorphic rhabdomyosarcoma

- Elderly > middle-aged adults
- Men > women
- Predilection for lower extremities
- Usually in deep soft tissue
- Highest metastatic rate among pleomorphic sarcomas: 90%

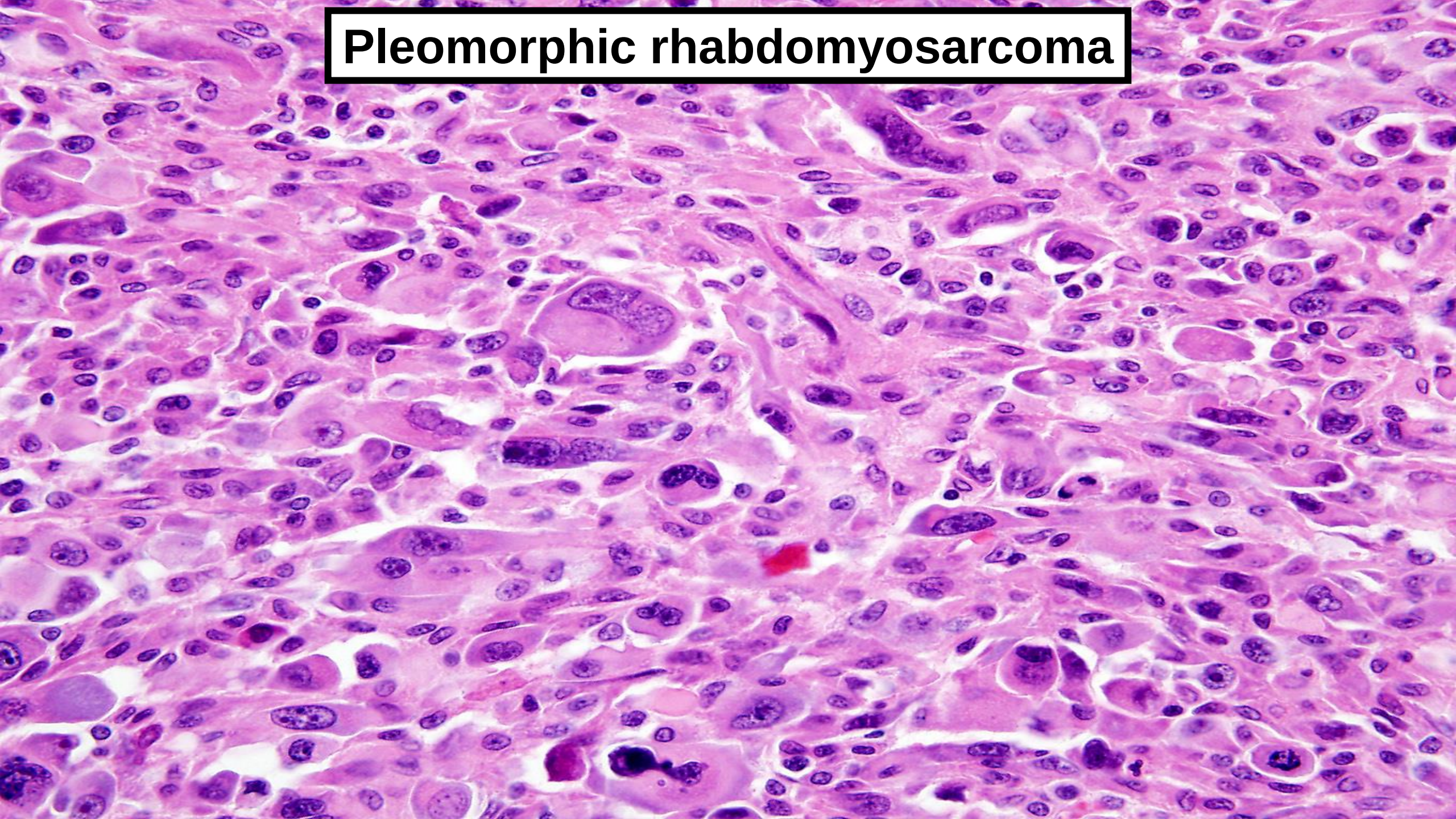
Pleomorphic rhabdomyosarcoma



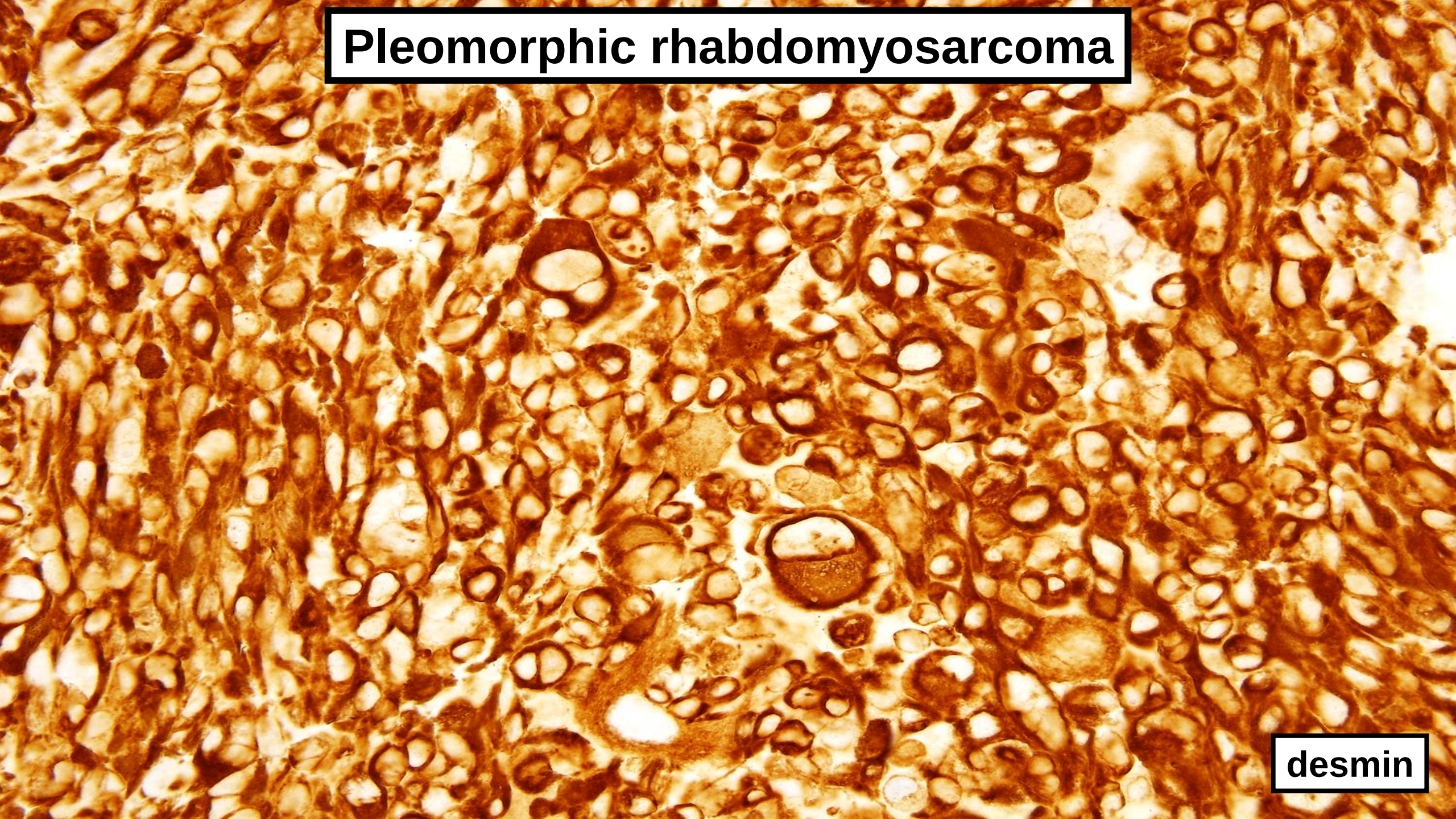
Pleomorphic rhabdomyosarcoma



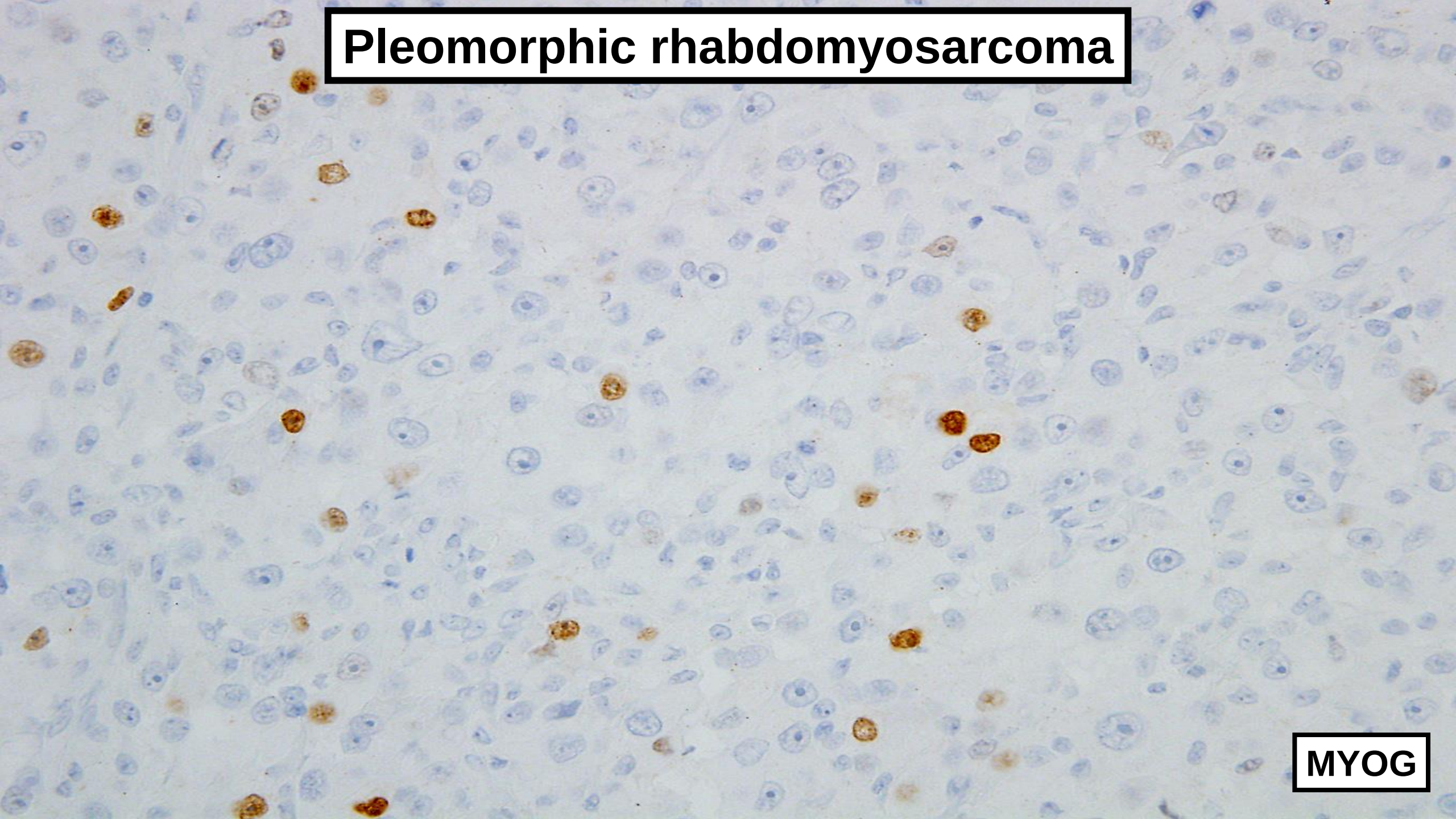
Pleomorphic rhabdomyosarcoma

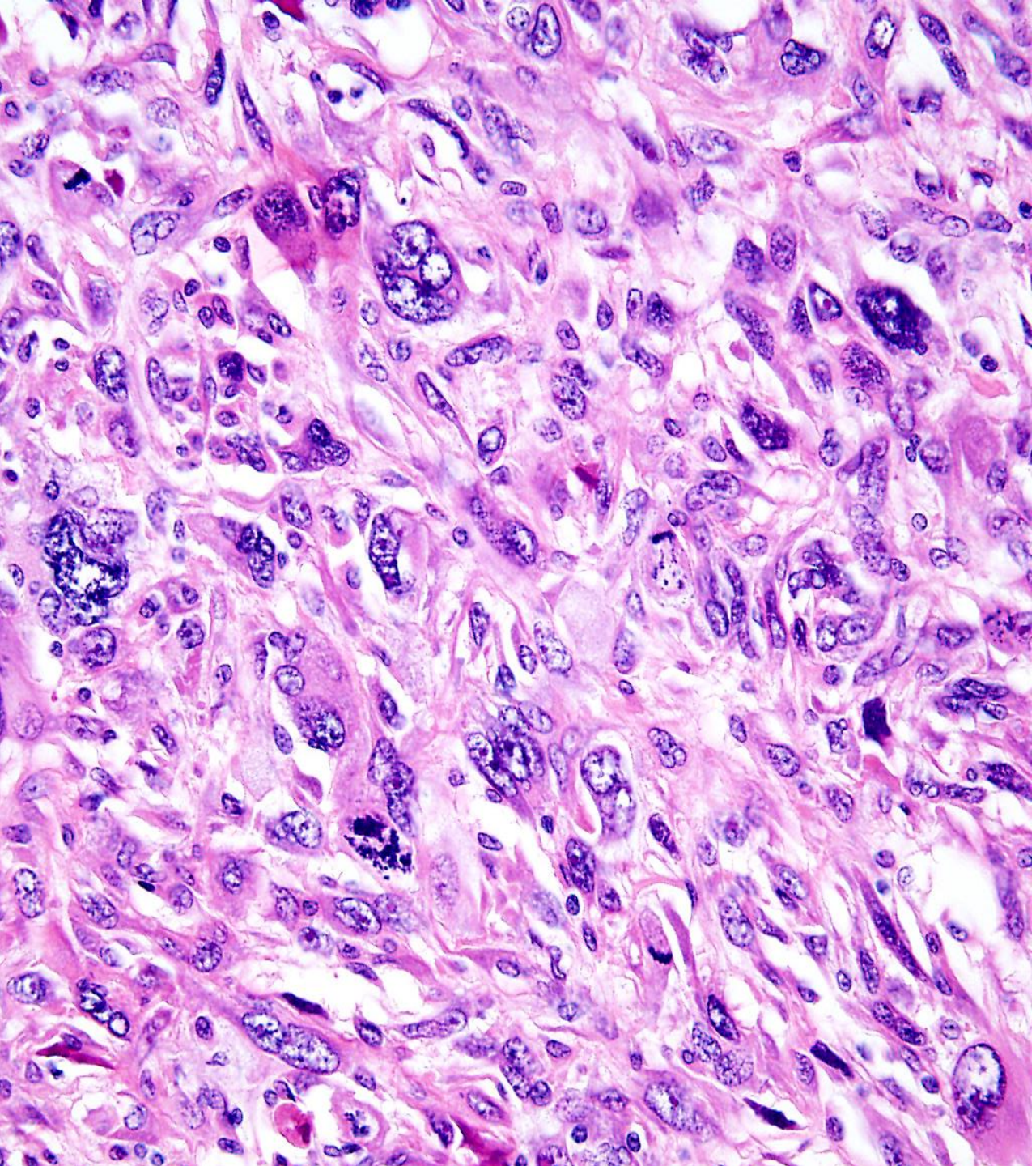


Pleomorphic rhabdomyosarcoma



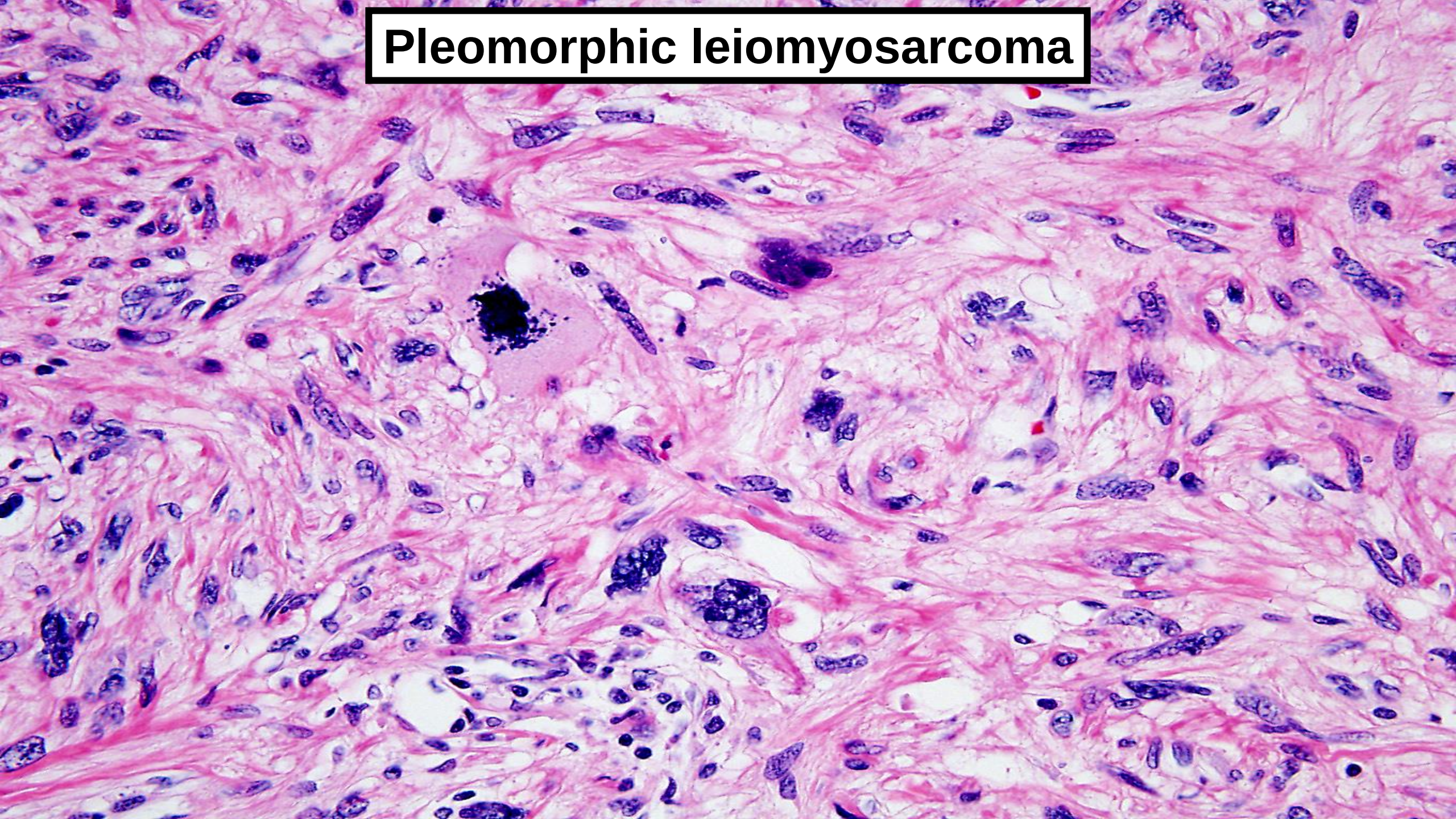
Pleomorphic rhabdomyosarcoma

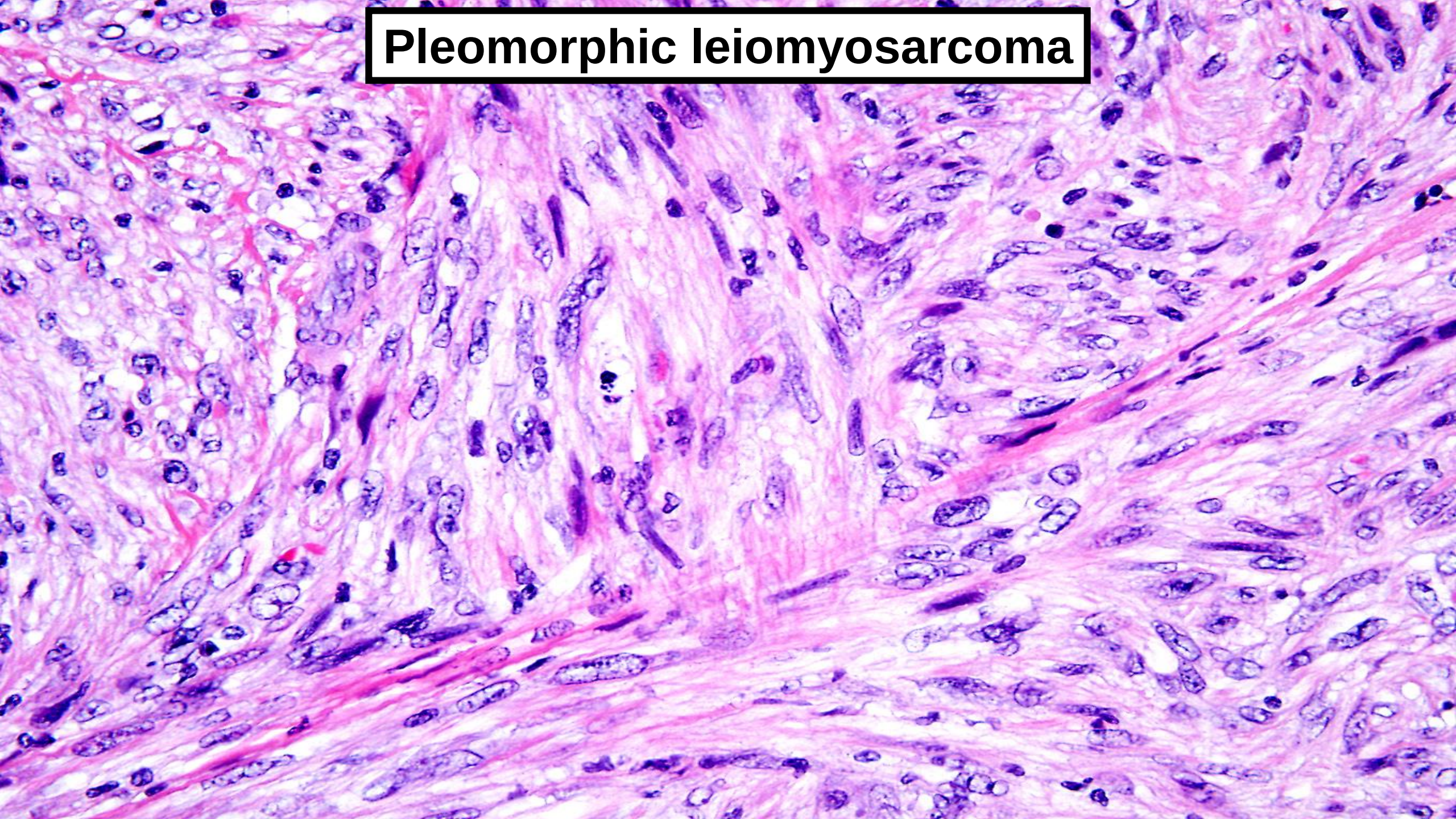




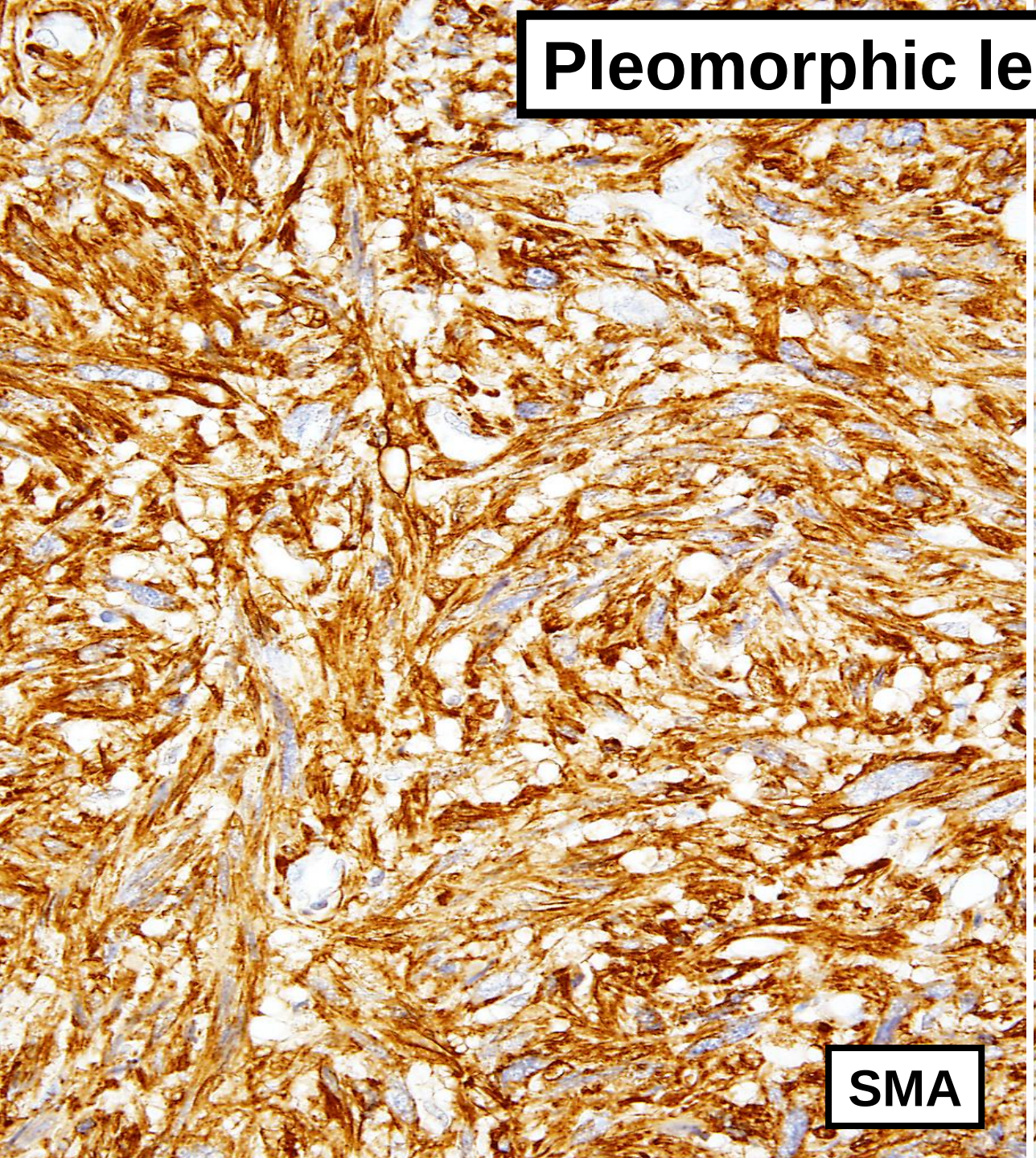
Pleomorphic leiomyosarcoma

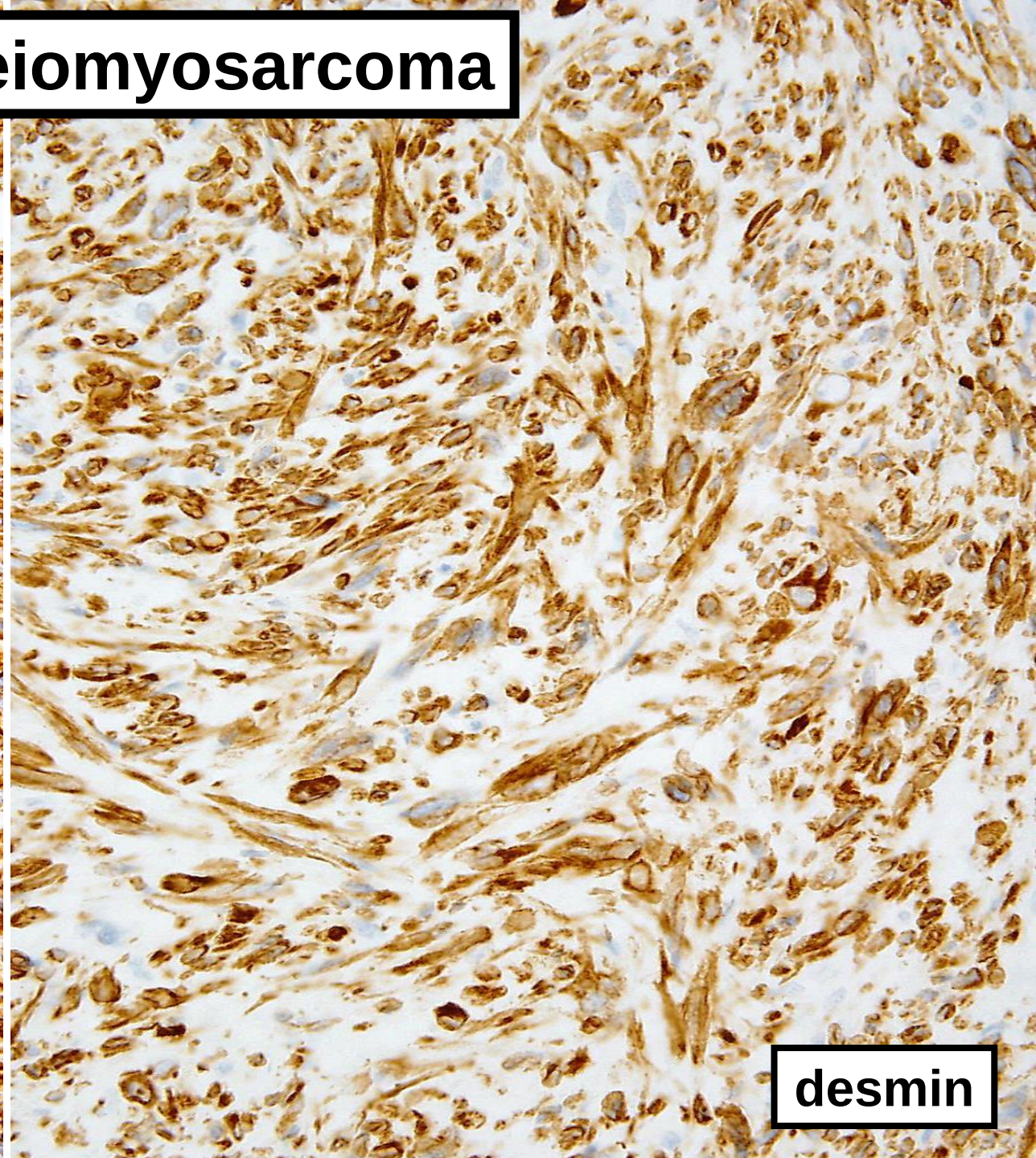
- Middle-aged to elderly adults
- Pleomorphic variant most often in extremities, retroperitoneum
- Deep >> subcutaneous
- 70% metastatic risk
- Lungs, bone, liver, skin

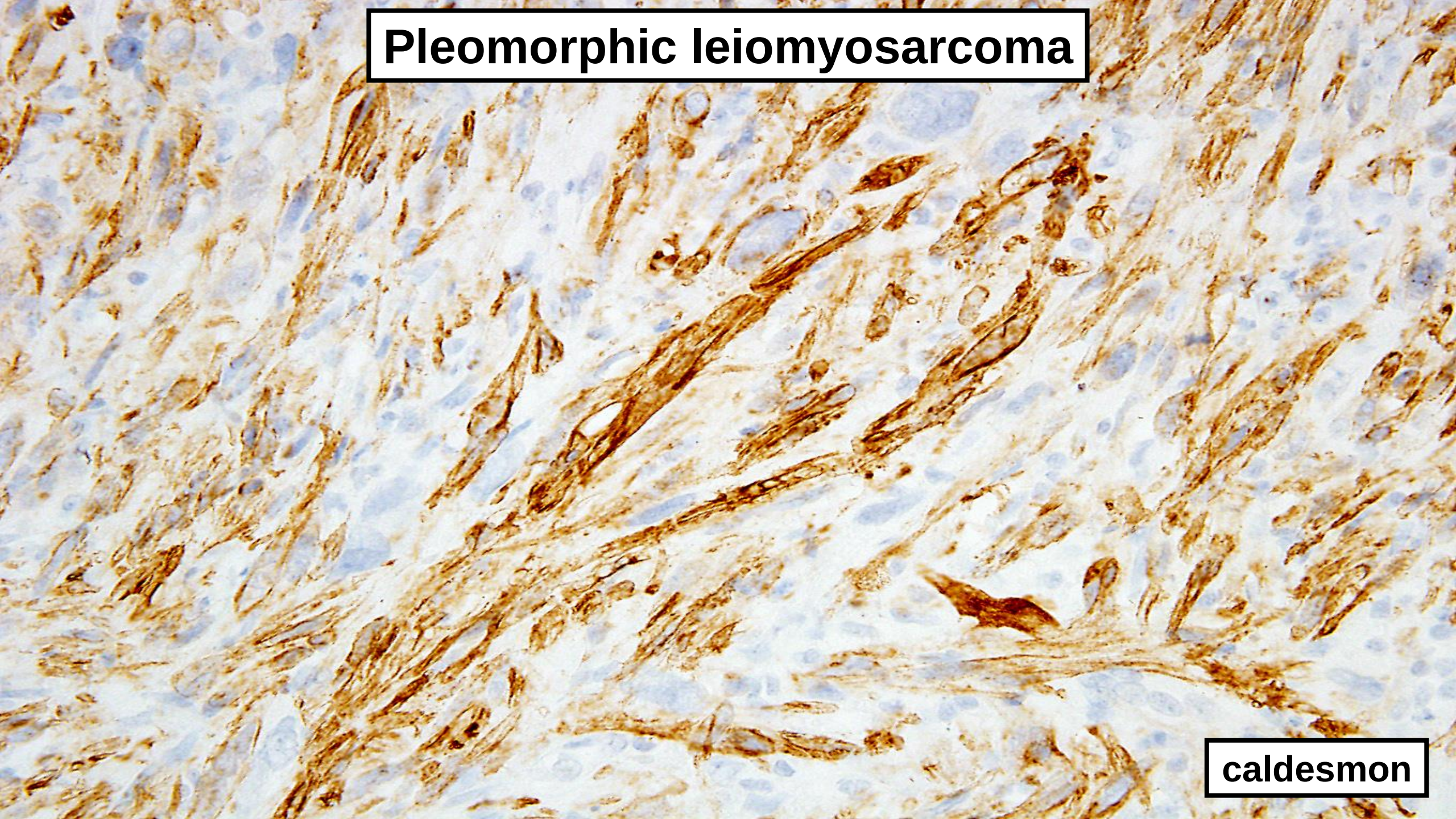

Pleomorphic leiomyosarcoma


Pleomorphic leiomyosarcoma

Pleomorphic leiomyosarcoma






Pleomorphic leiomyosarcoma
caldesmon

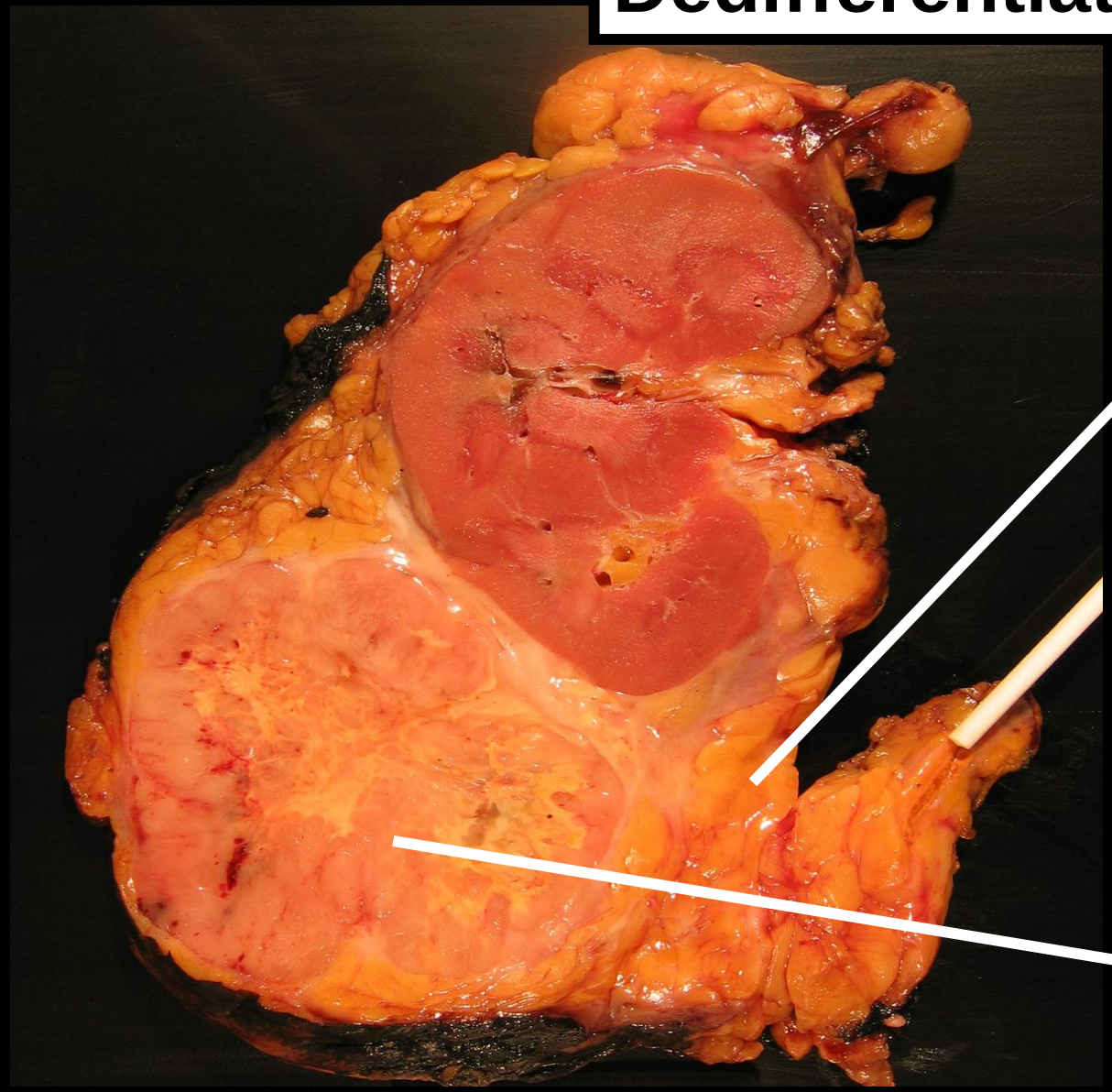
Dedifferentiated liposarcoma

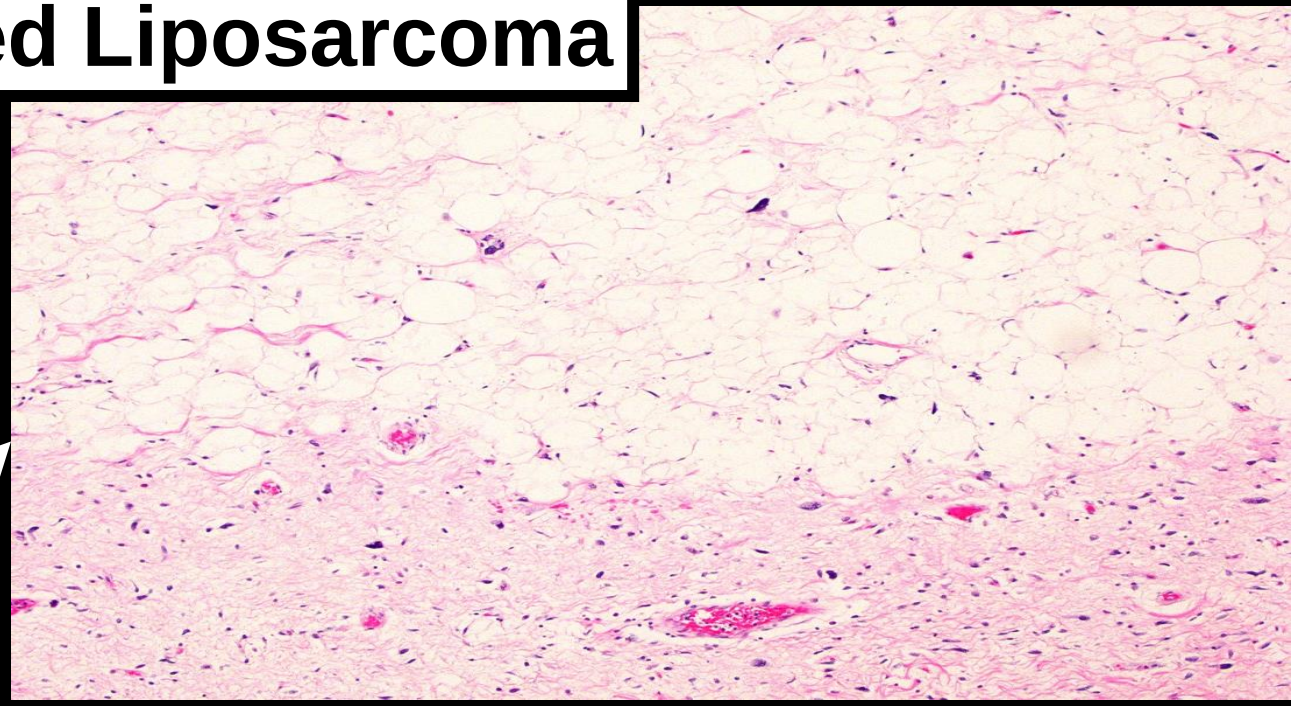
- Middle-aged to elderly adults
- Retroperitoneum >> abdominal cavity, pelvis, paratesticular
- Rare in extremities, trunk
- Very high local recurrence rate
- Metastasis in 15-20%
- Most patients die in 5-20 years

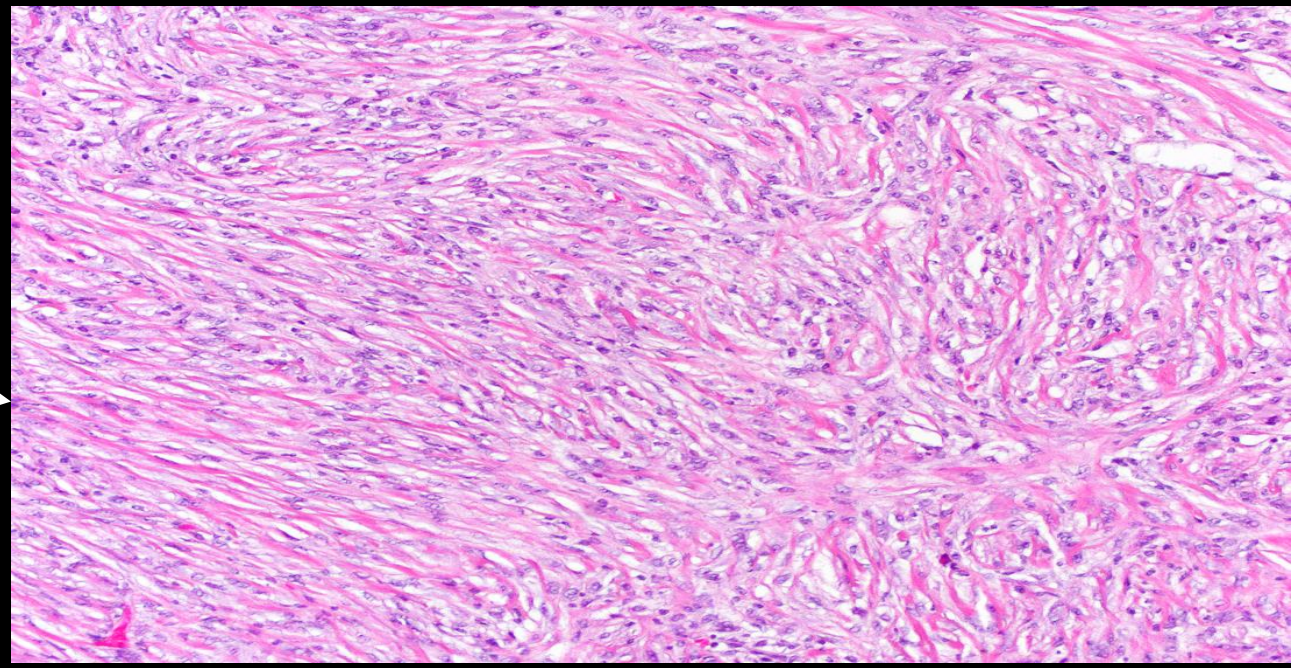
Dedifferentiated liposarcoma

- Classically, abrupt transition from well-differentiated liposarcoma to a non-lipogenic sarcoma
- Highly variable morphology: pleomorphic, spindle cell, myxoid stroma
- 10% heterologous differentiation (skeletal muscle, bone, cartilage)
- May rarely show “homologous” lipoblastic differentiation in higher grade component (mimicking pleomorphic LPS)
- Now that we understand molecular genetics, can make diagnosis without finding well-differentiated LPS

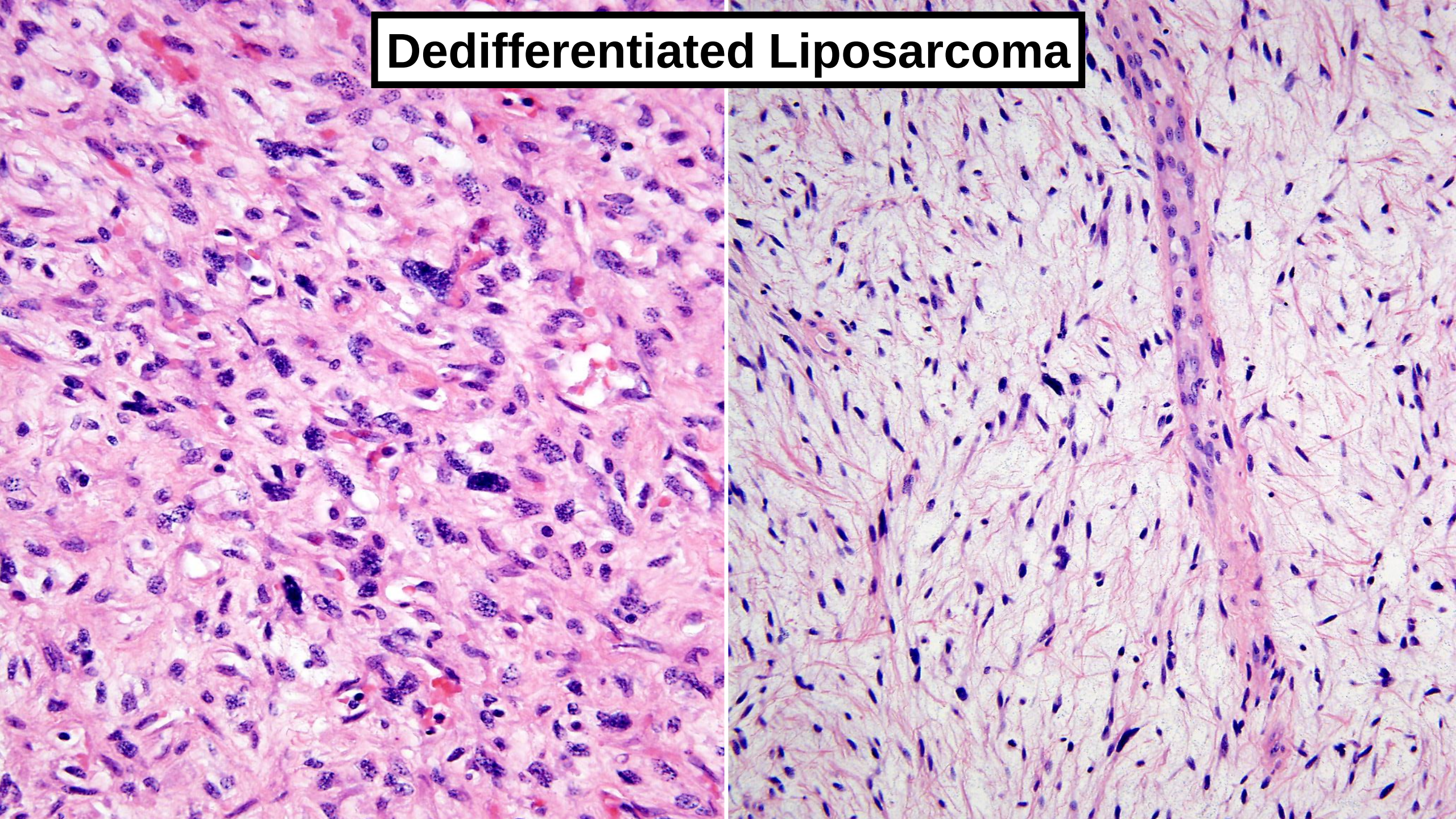
Dedifferentiated Liposarcoma



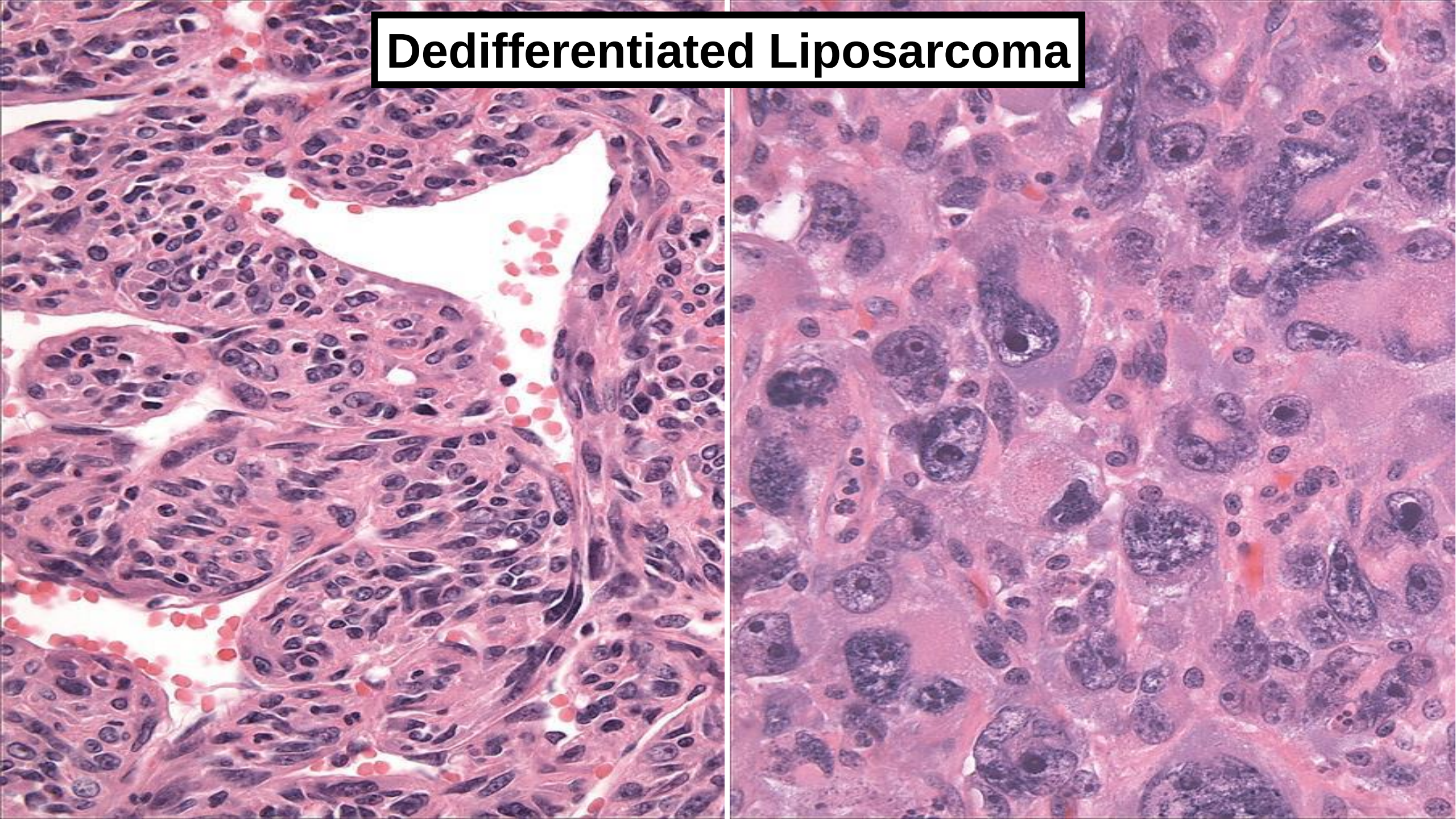




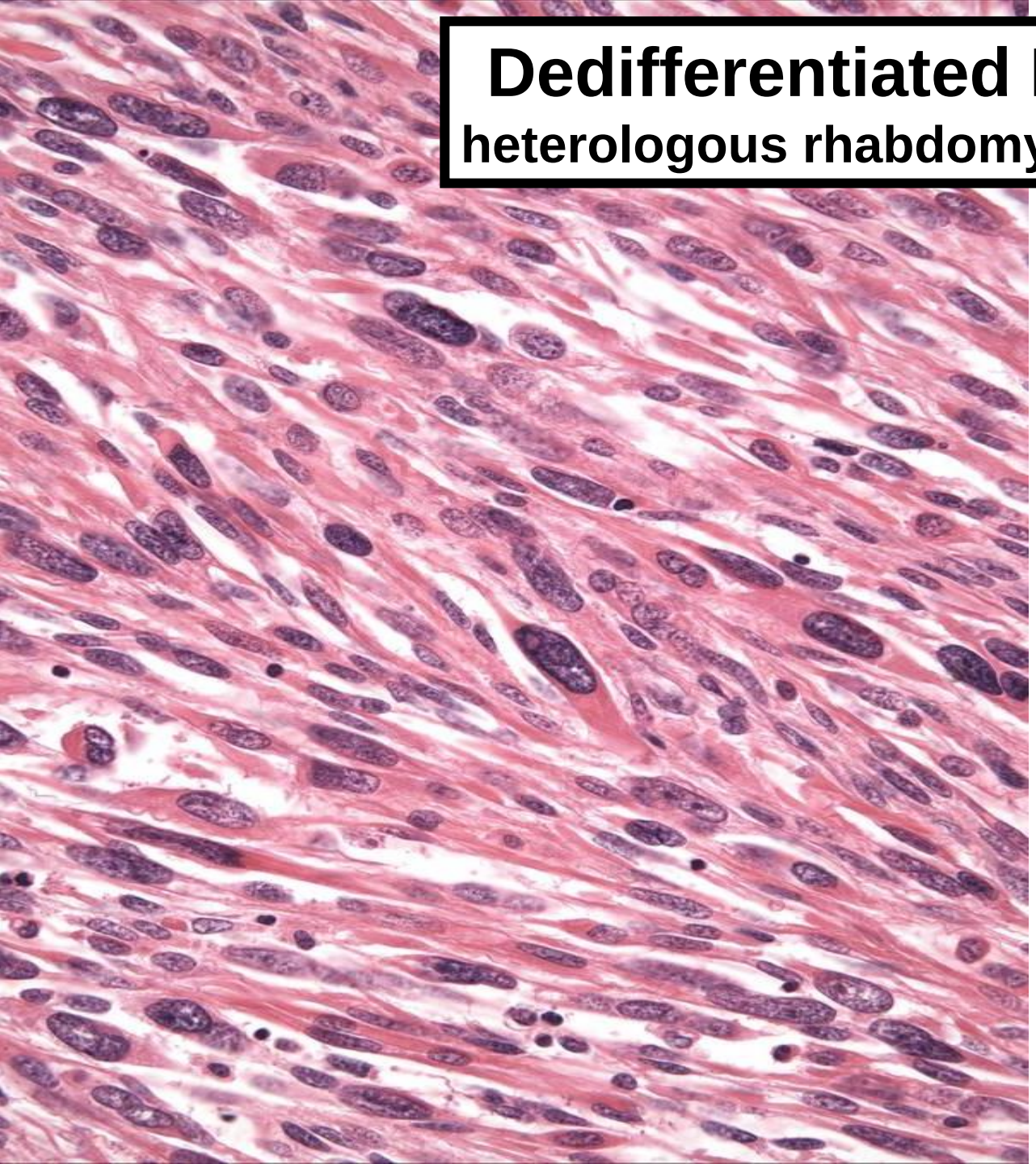
Dedifferentiated Liposarcoma

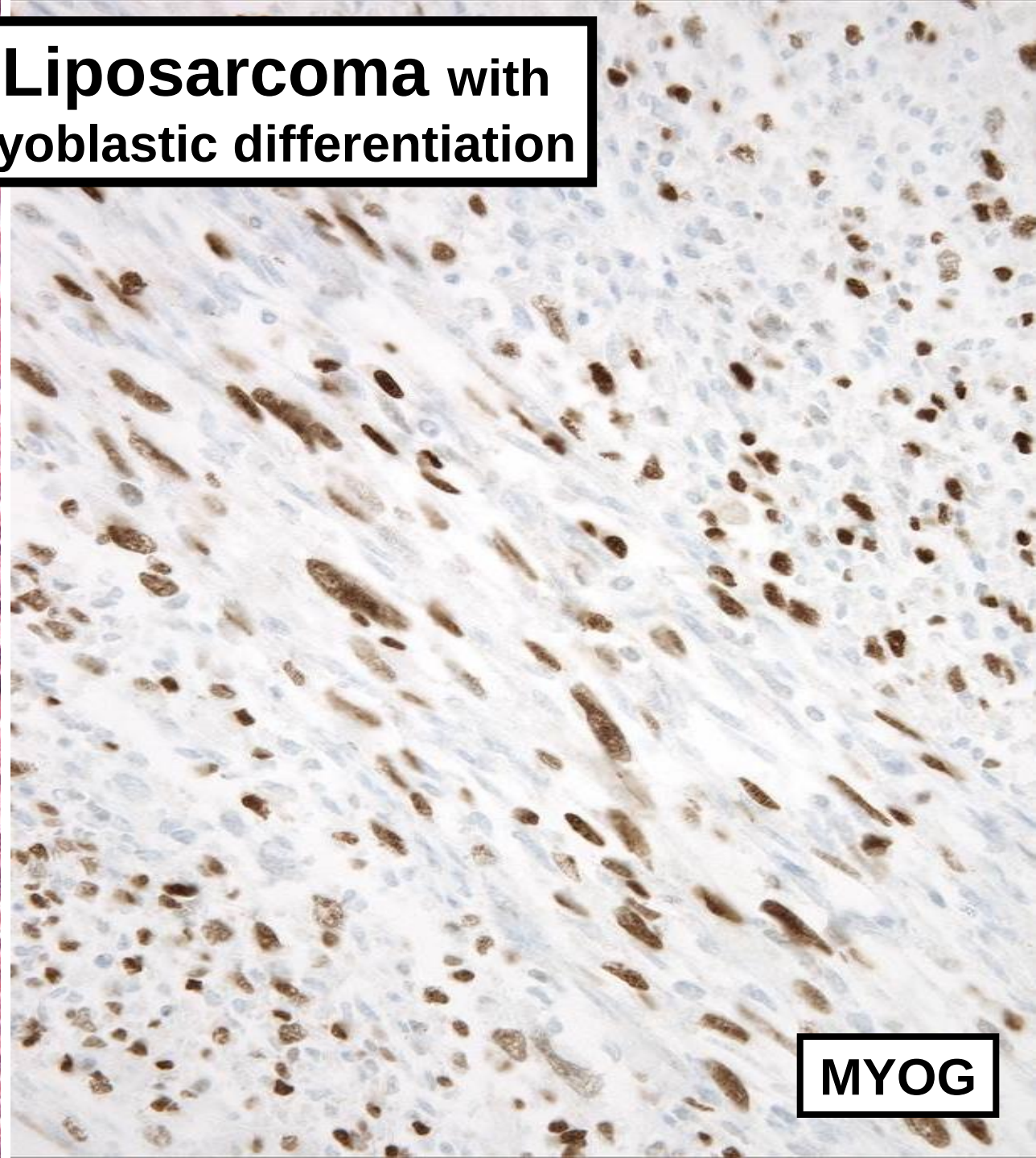


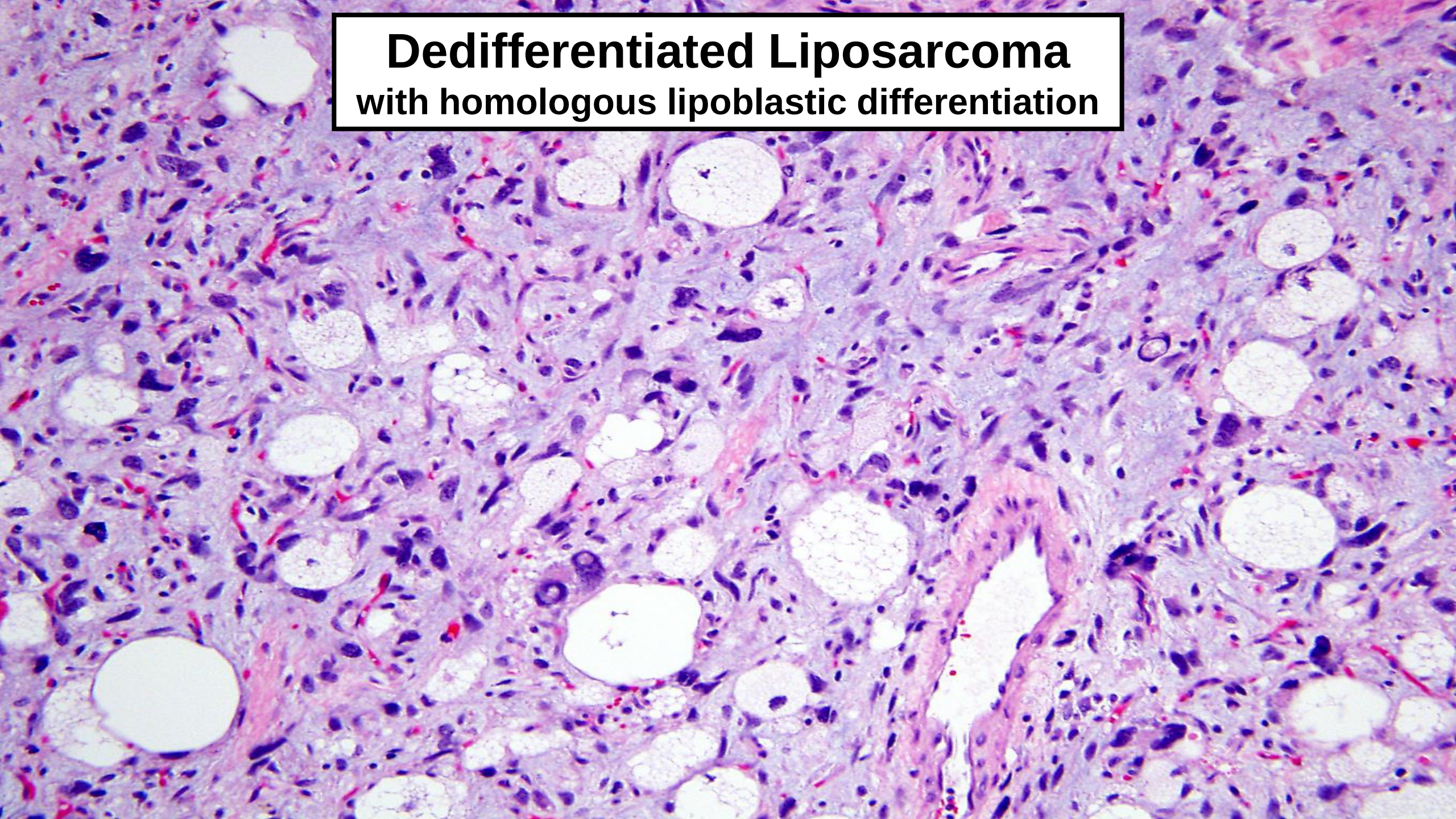
Dedifferentiated Liposarcoma

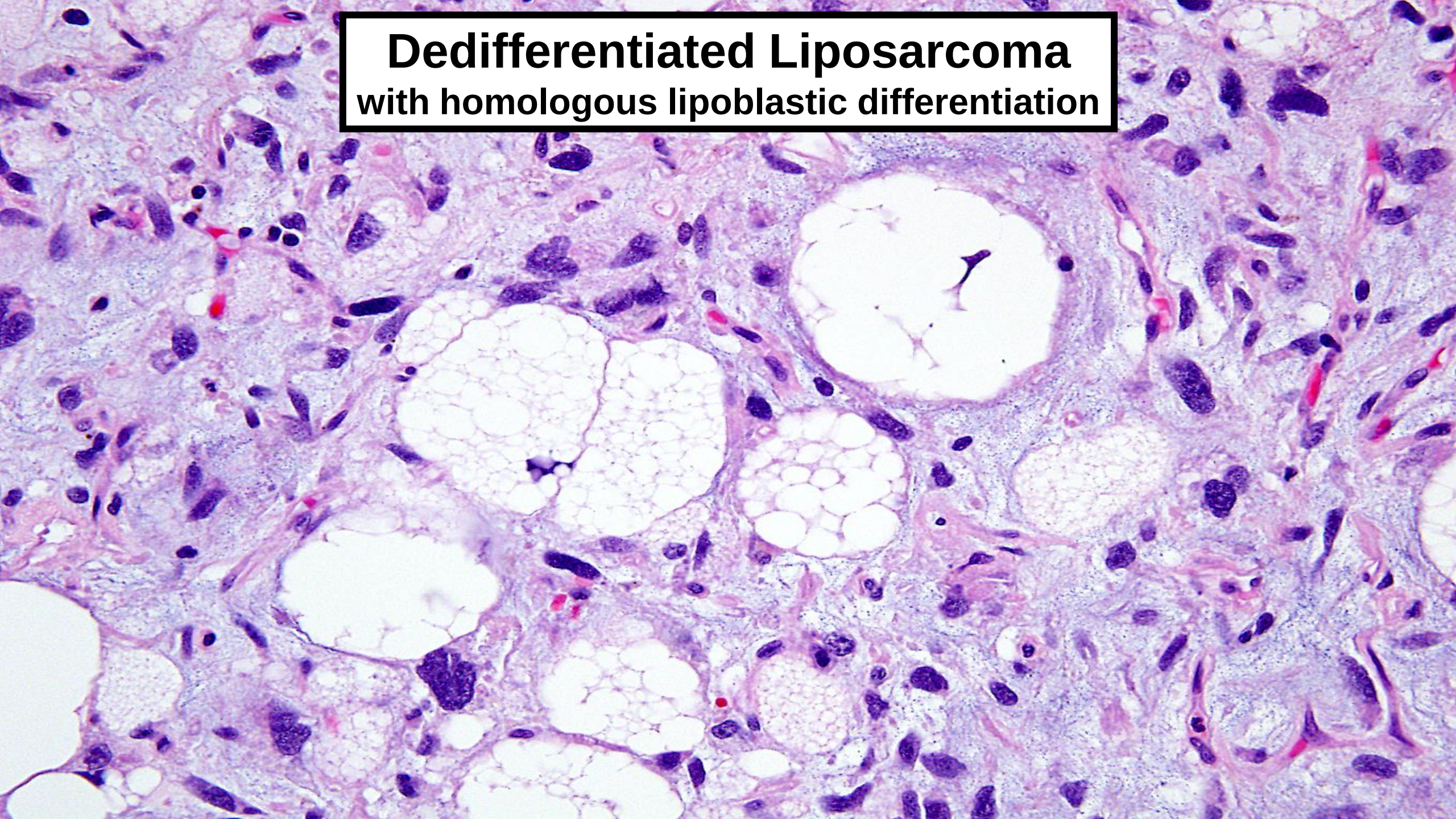


Dedifferentiated Liposarcoma with heterologous rhabdomyoblastic differentiation






Dedifferentiated Liposarcoma
with homologous lipoblastic differentiation

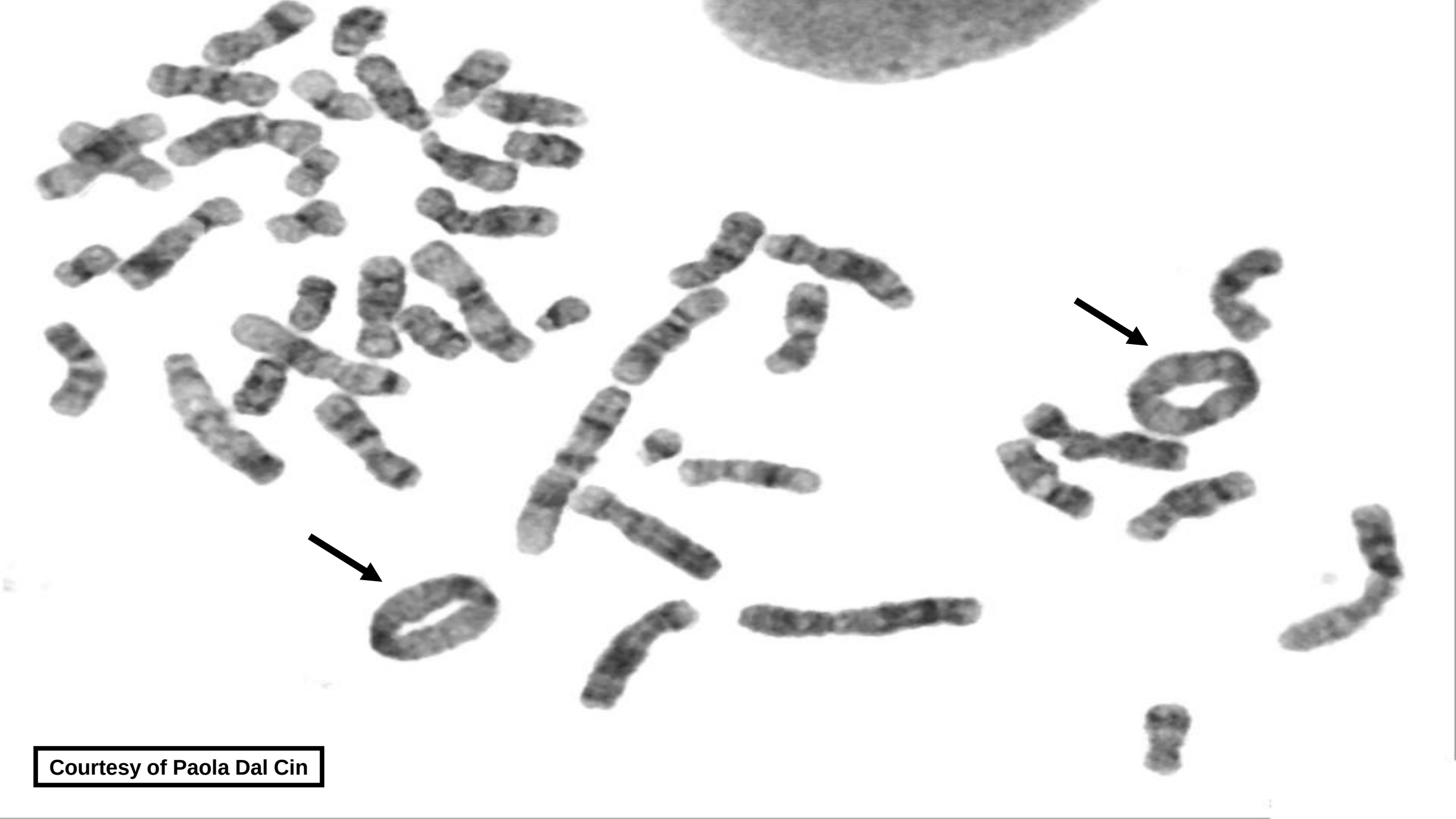

Dedifferentiated Liposarcoma
with homologous lipoblastic differentiation

MDM2 and CDK4

- **Chromosome 12q13~15; role in cell cycle regulation**
- **Amplified in nearly all cases of well-differentiated and dedifferentiated liposarcomas**

MDM2	**~98%**
CDK4	**~92%**

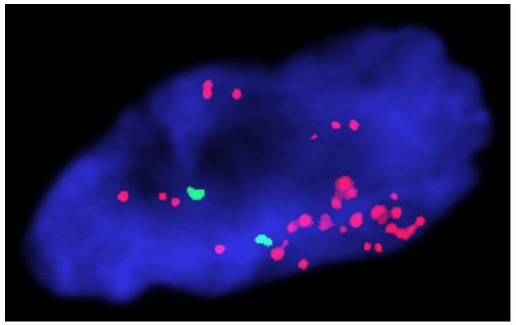
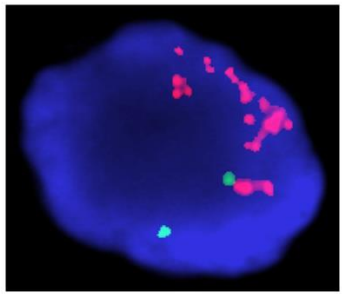
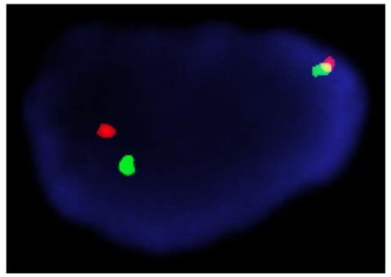
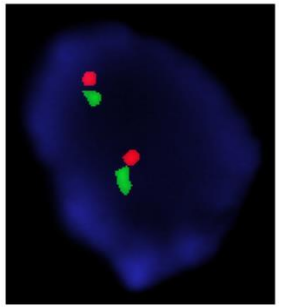
- **Ring and giant marker chromosomes**



Courtesy of Paola Dal Cin

FISH

Dedifferentiated Liposarcoma

12q15 - MDM2

CEP12

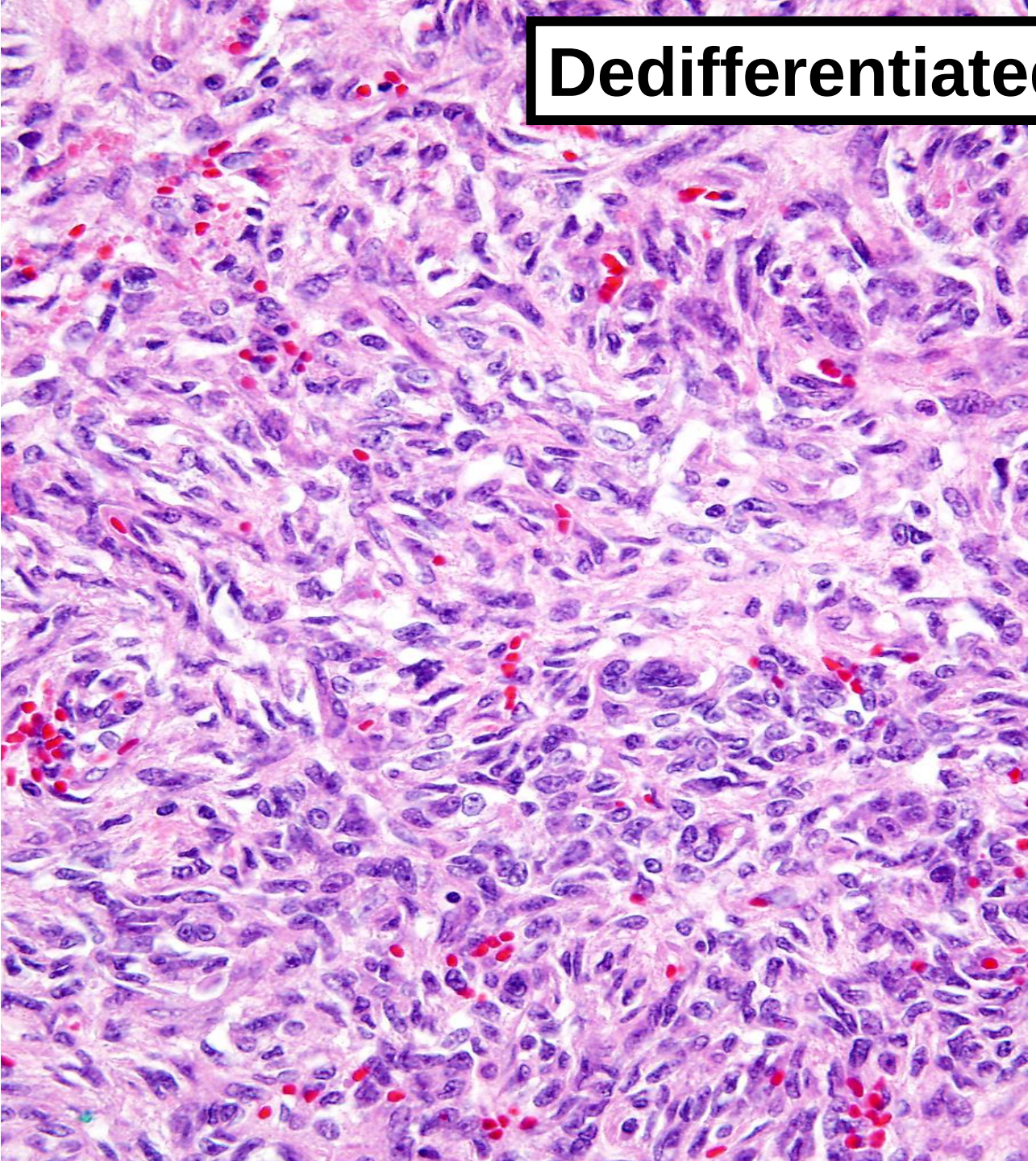
Immunohistochemistry for MDM2/CDK4

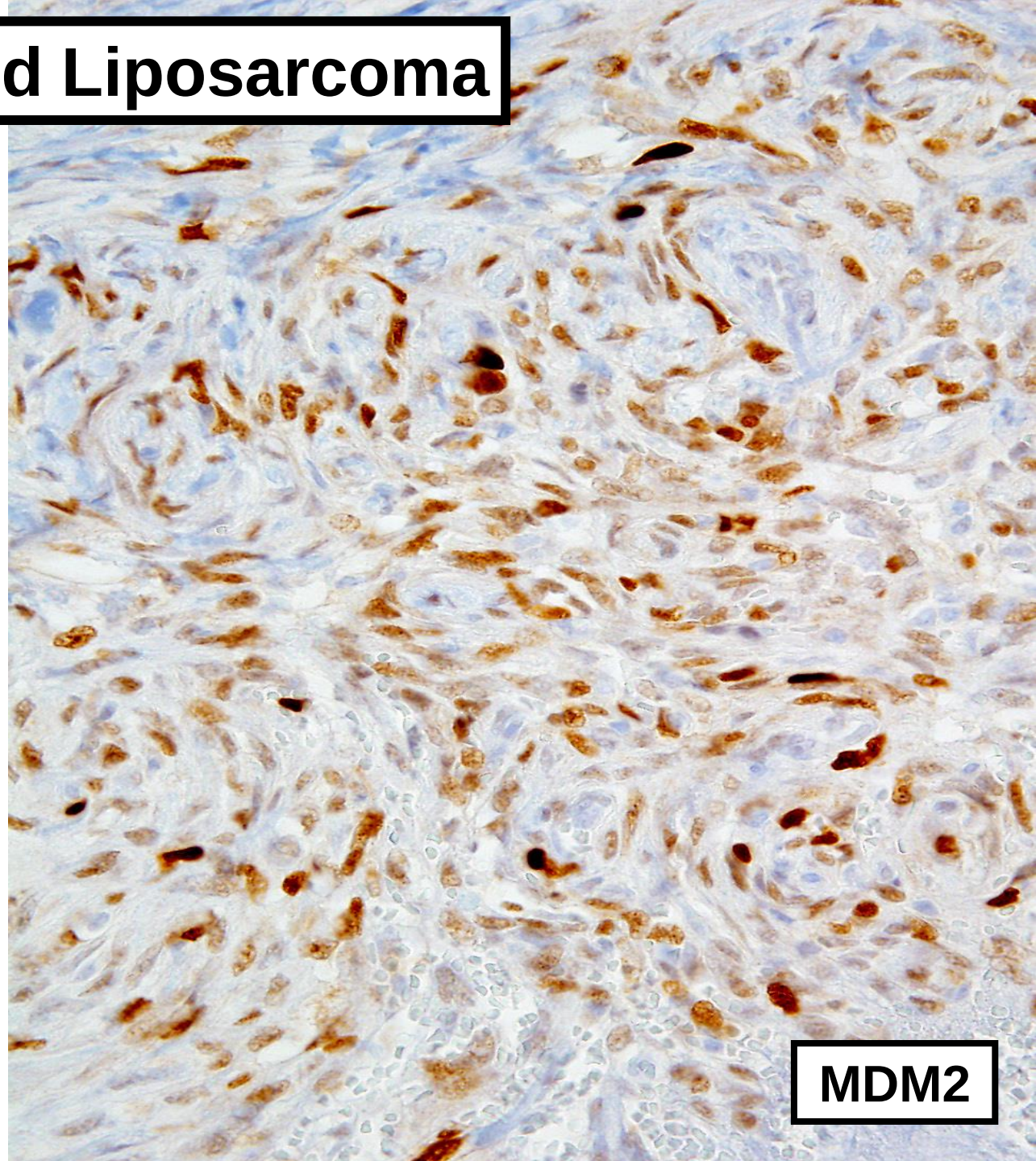
- **Highly sensitive for DDLPS, but not entirely specific**
- **FISH more specific**
- **In proper clinical context, can be helpful in differential diagnosis: DDLPS vs other pleomorphic/spindle cell sarcomas**
- **Especially in small biopsy or when well-differentiated LPS component is absent**

Immunohistochemistry

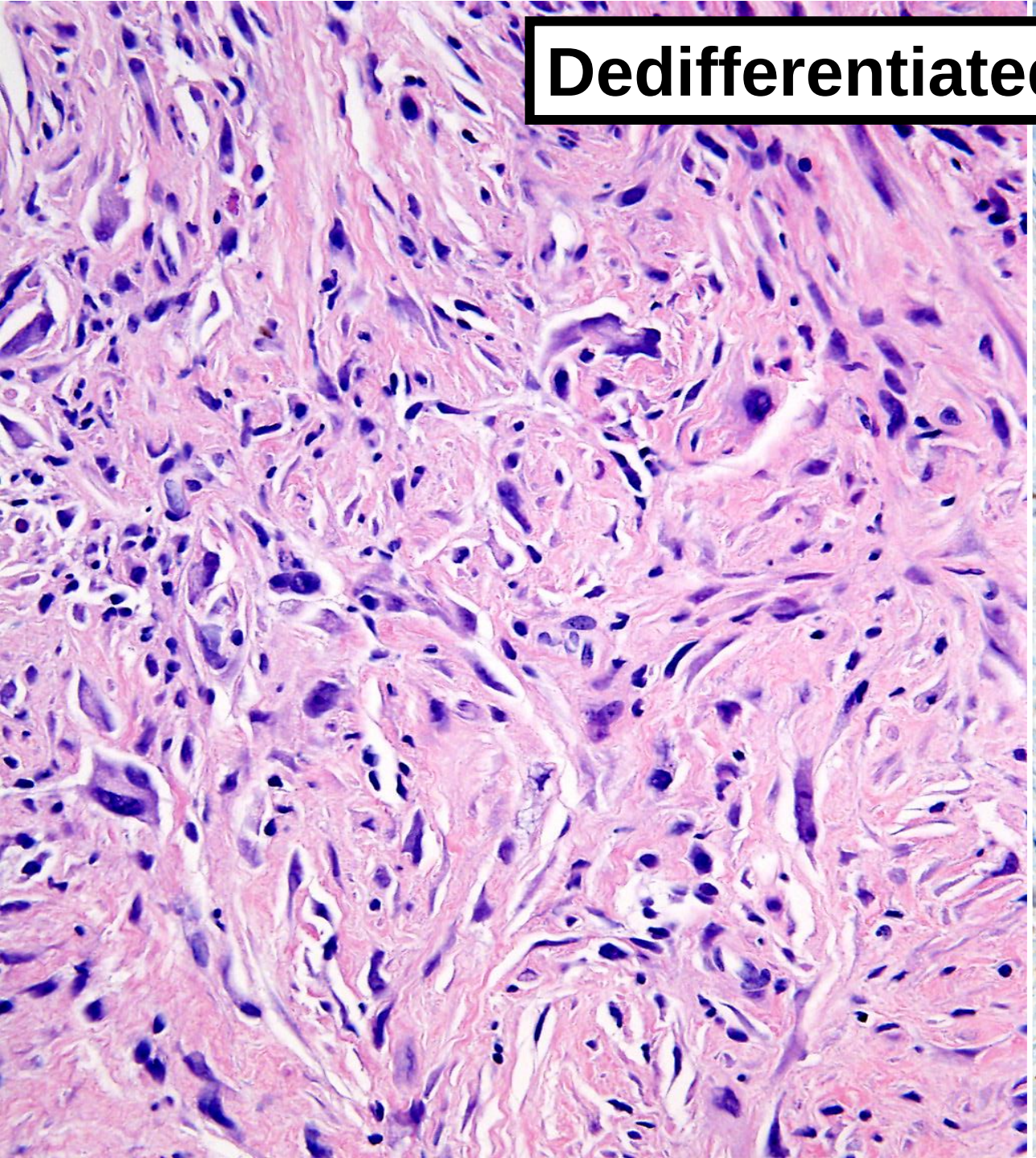
Tumor type	MDM2	CDK4
Dedifferentiated liposarcoma	98%	92%
Malignant peripheral nerve sheath tumor	65%	10%
Myxofibrosarcoma	40%	15%
Leiomyosarcoma	5%	1%
Gastrointestinal stromal tumor	0%	0%

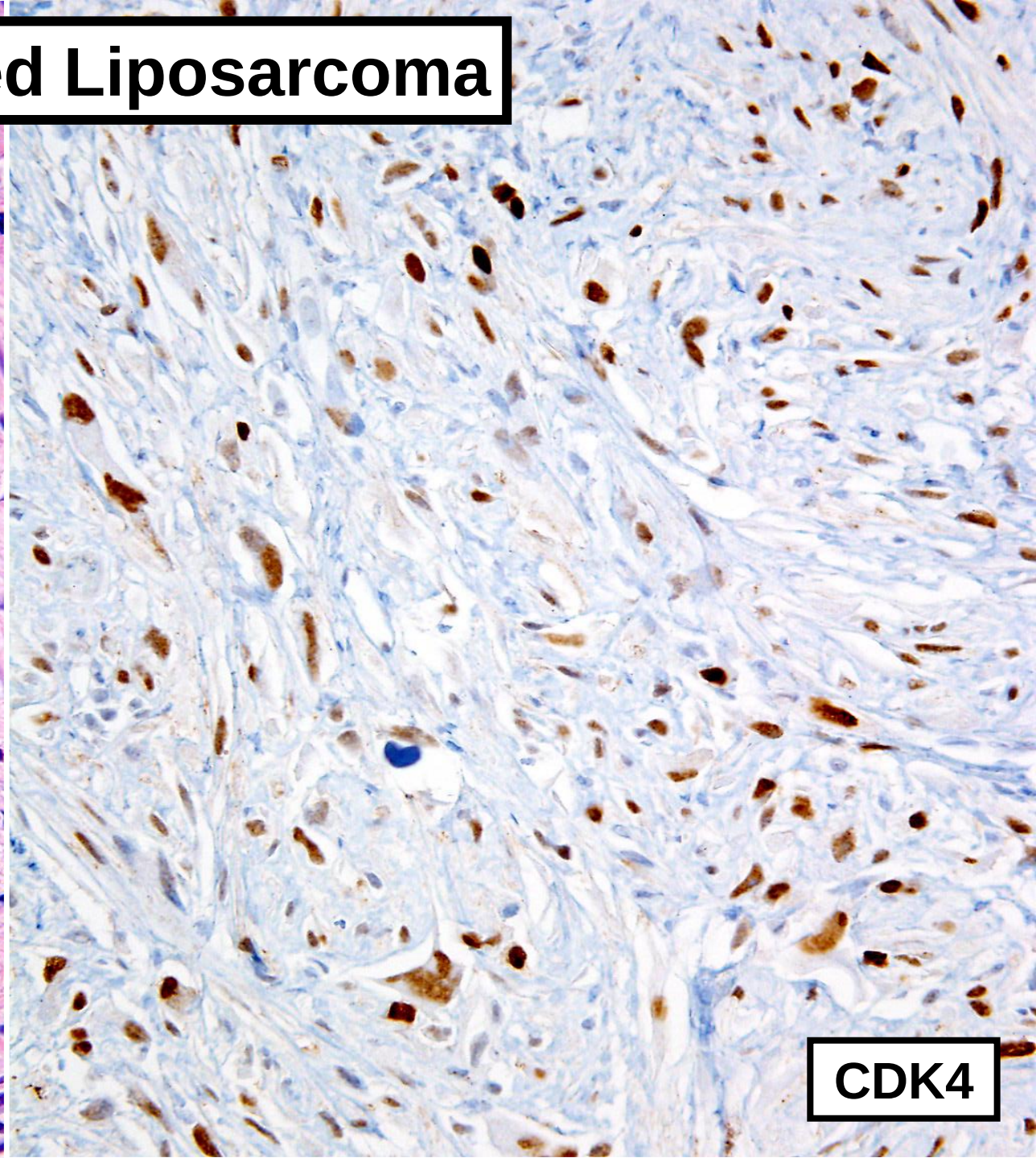
Dedifferentiated Liposarcoma





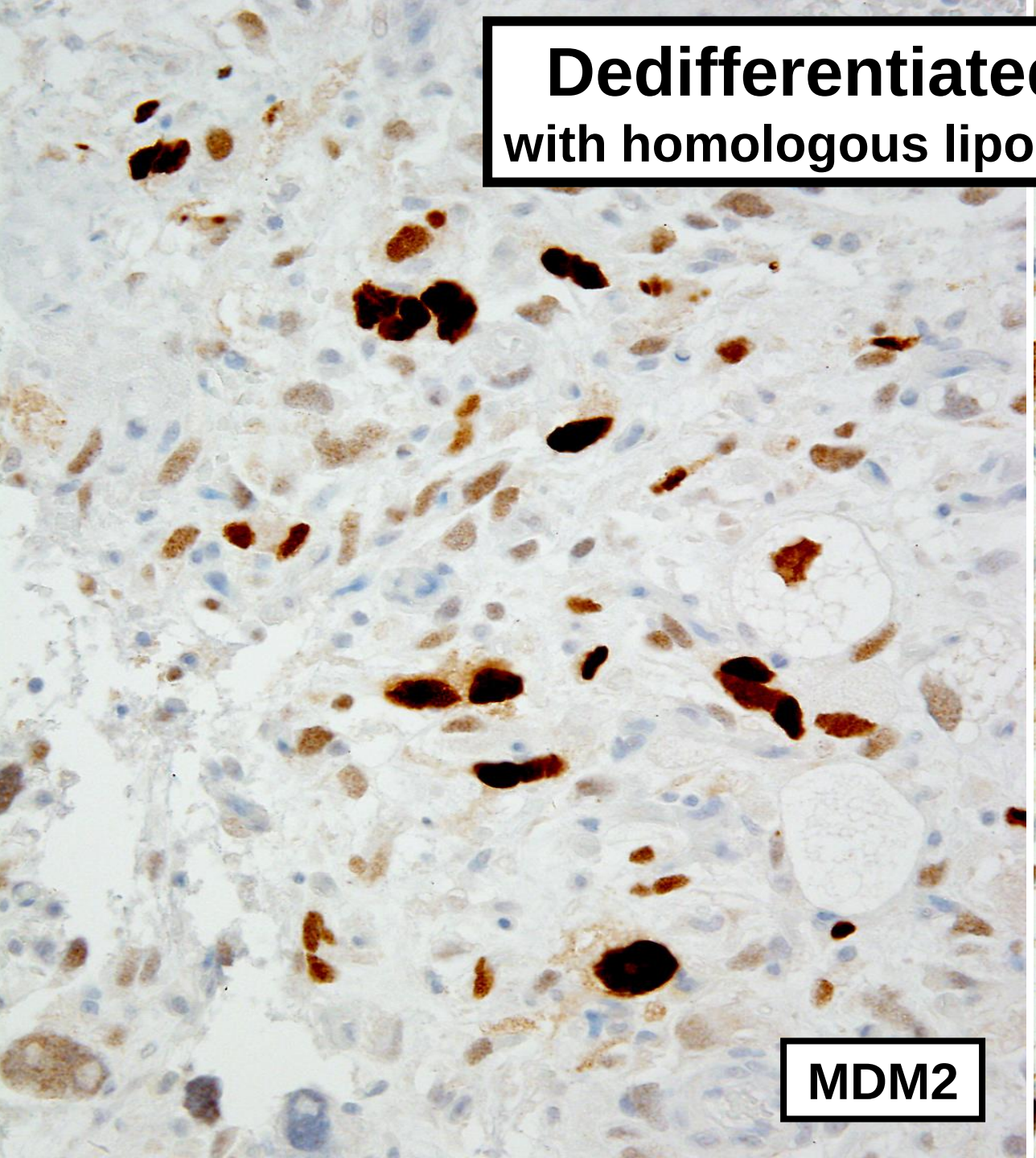
Dedifferentiated Liposarcoma

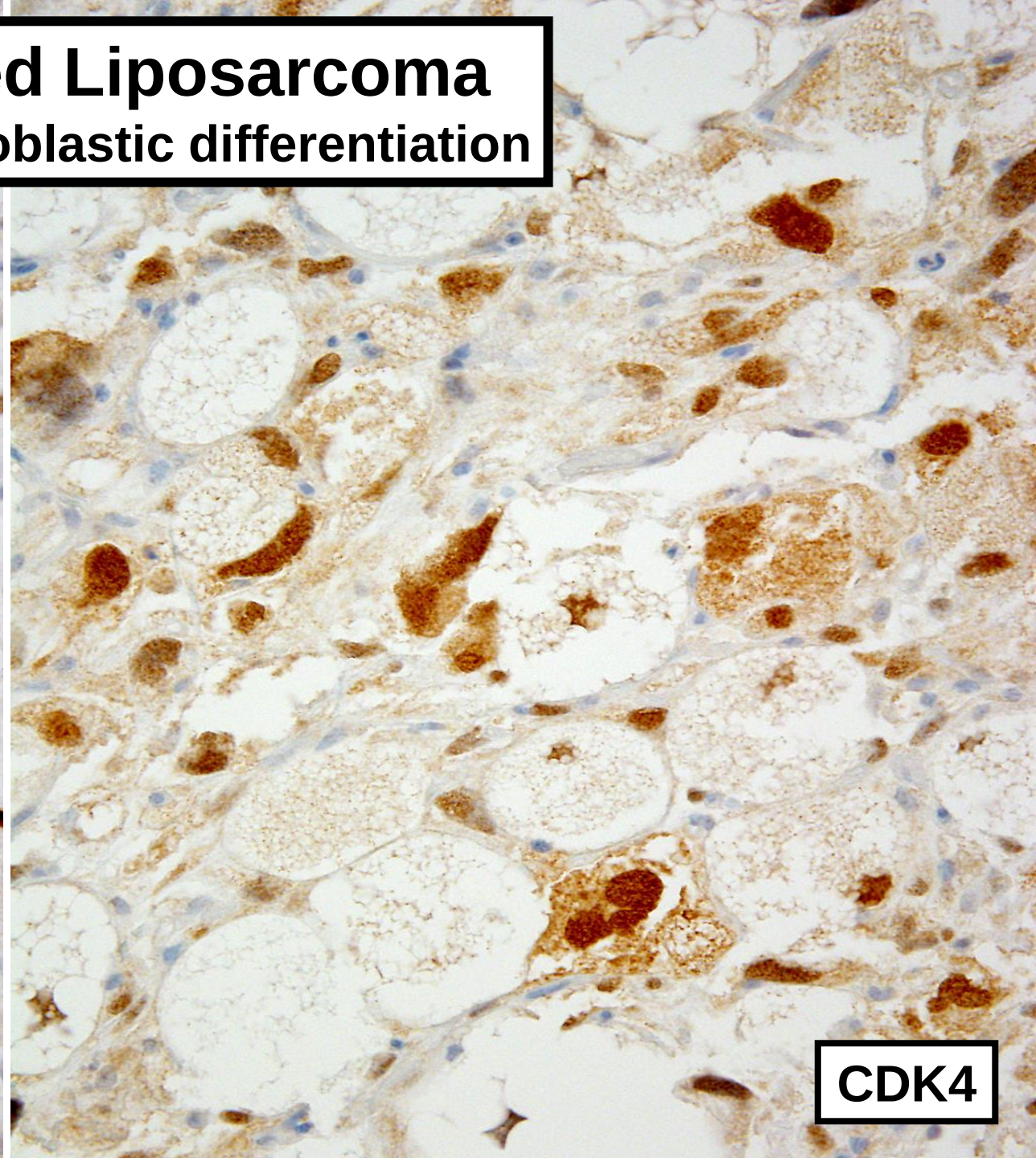




Dedifferentiated Liposarcoma

with homologous lipoblastic differentiation



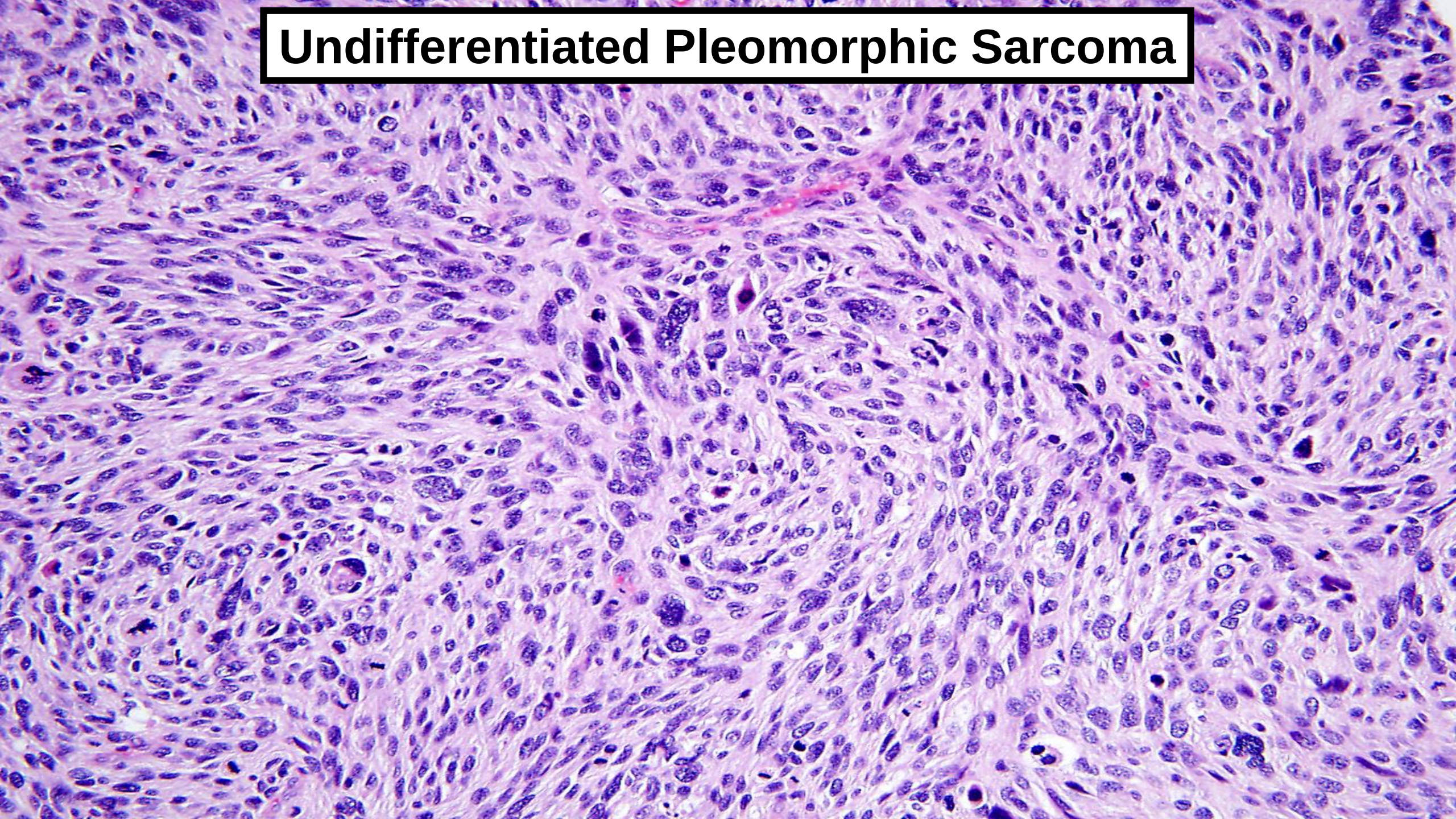


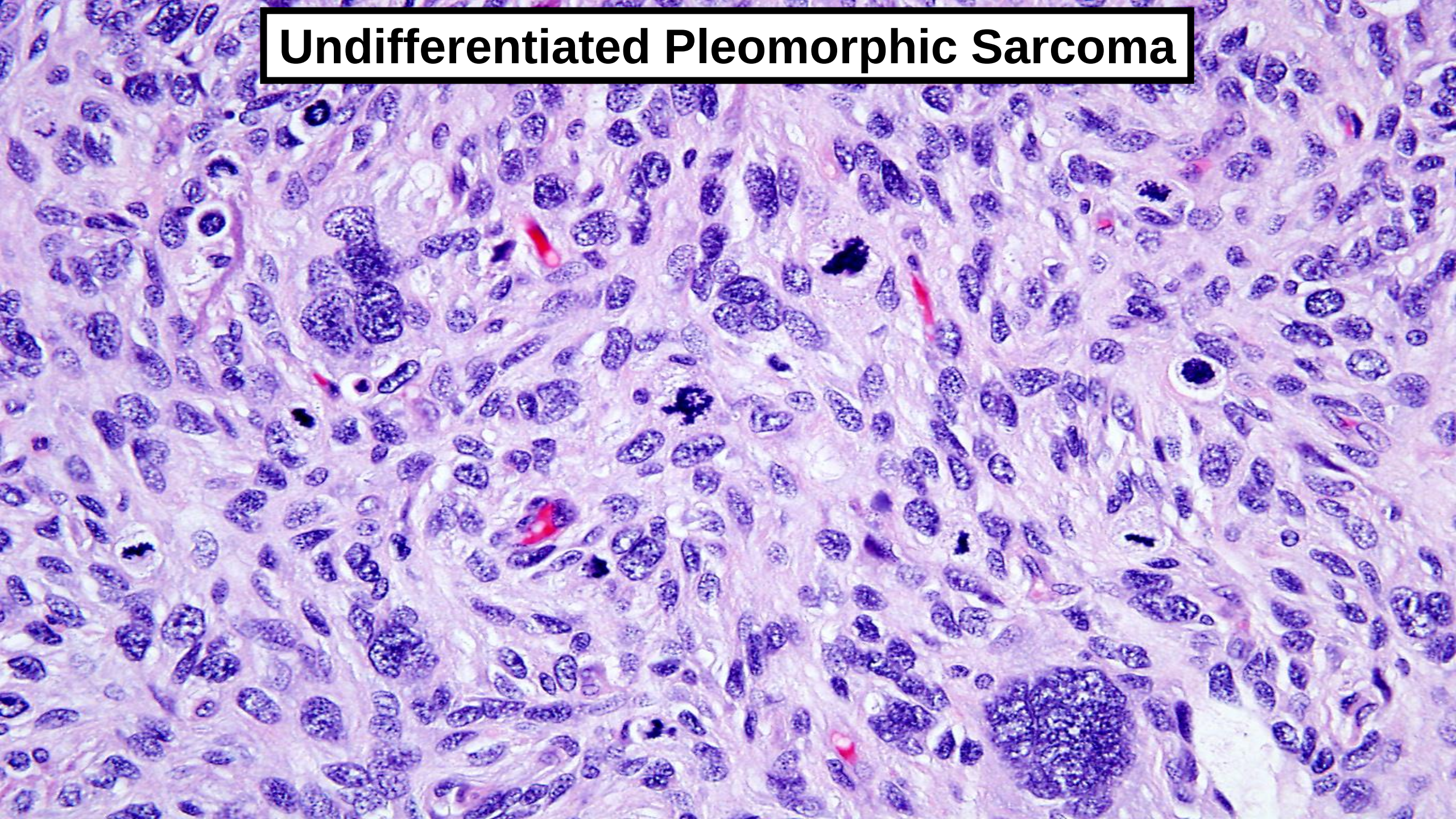
When should we consider dedifferentiated liposarcoma?

- **At central body cavity sites: retroperitoneum, abdominal cavity, pelvis, mediastinum**
- **When there is marked intratumoral heterogeneity: spindle cell, pleomorphic, and/or epithelioid; variably myxoid stroma**
- **Search for an adjacent well-differentiated component!**

When should we diagnose undifferentiated pleomorphic sarcoma?

- Diagnosis of exclusion
- Sample extensively
- Search for well-differentiated liposarcoma
- Search for myxoid stroma
- Search for lipoblasts
- Search for osteoid
- Perform IHC: SMA/desmin, S100/SOX10, keratins, +/- MDM2


Undifferentiated Pleomorphic Sarcoma


Undifferentiated Pleomorphic Sarcoma

WARNING: PITFALL!!

pleomorphic

Superficial CD34-positive fibroblastic tumor: report of 18 cases of a distinctive low-grade mesenchymal neoplasm of intermediate (borderline) malignancy

Jodi M Carter[1], Sharon W Weiss[2], Konstantinos Linos[2], David J DiCaudo[3] and Andrew L Folpe[1]

MODERN PATHOLOGY (2014) 27, 294–302

- **Involves skin and subcutaneous tissue**
- **Predilection for lower extremities (70%)**
- **Local recurrence: 1/13**
- **Lymph node metastasis: 1/13**

Recurrent *PRDM10* Gene Fusions in Undifferentiated Pleomorphic Sarcoma

Jakob Hofvander[1], Johnbosco Tayebwa[1], Jenny Nilsson[1], Linda Magnusson[1], Otte Brosjö[2], Olle Larsson[3], Fredrik Vult von Steyern[4], Nils Mandahl[1], Christopher D.M. Fletcher[5], and Fredrik Mertens[1]

Clin Cancer Res; 21(4) February 15, 2015

Undifferentiated pleomorphic sarcomas with *PRDM10* fusions have a distinct gene expression profile

Jakob Hofvander[1]*, Florian Puls[2], Nischalan Pillay[3], Christopher D Steele[4], Adrienne M Flanagan[3,4], Linda Magnusson[1], Jenny Nilsson[1] and Fredrik Mertens[1,5]

J Pathol 2019; **249:** 425–434

Pleomorphic

Superficial CD34-Positive Fibroblastic Tumor

A Clinicopathologic, Immunohistochemical, and Molecular Study of 59 Cases

William J. Anderson, MBChB, Fredrik Mertens, MD, PhD,†‡ Adrián Mariño-Enríquez, MD, PhD,* Jason L. Hornick, MD, PhD,* and Christopher D.M. Fletcher, MD, FRCPath**

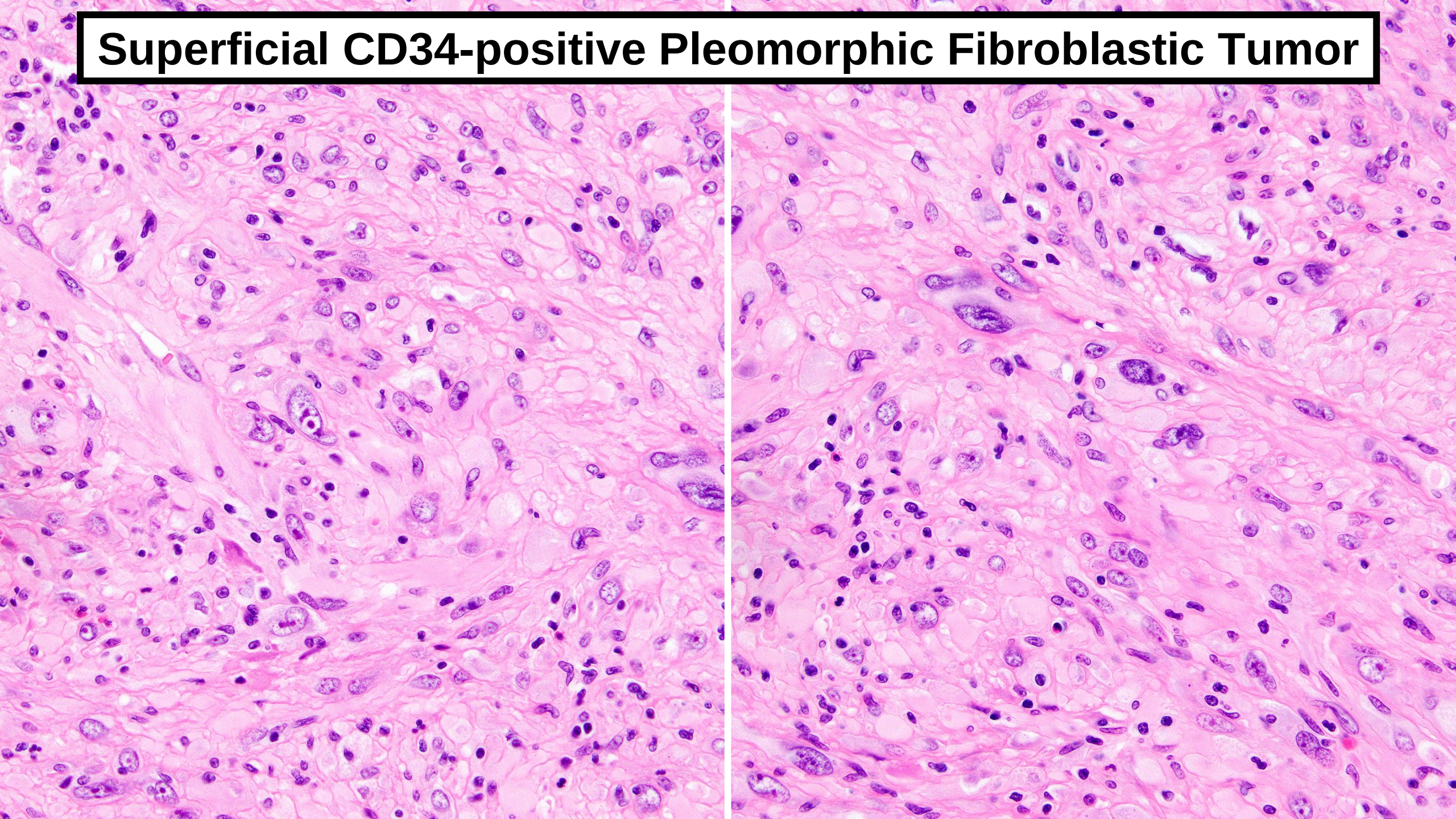
Am J Surg Pathol • Volume 46, Number 10, October 2022

- ***PRDM10* rearrangement in 3/8**
- **Local recurrence: 2/32**
- **Lymph node metastasis: 1/32**

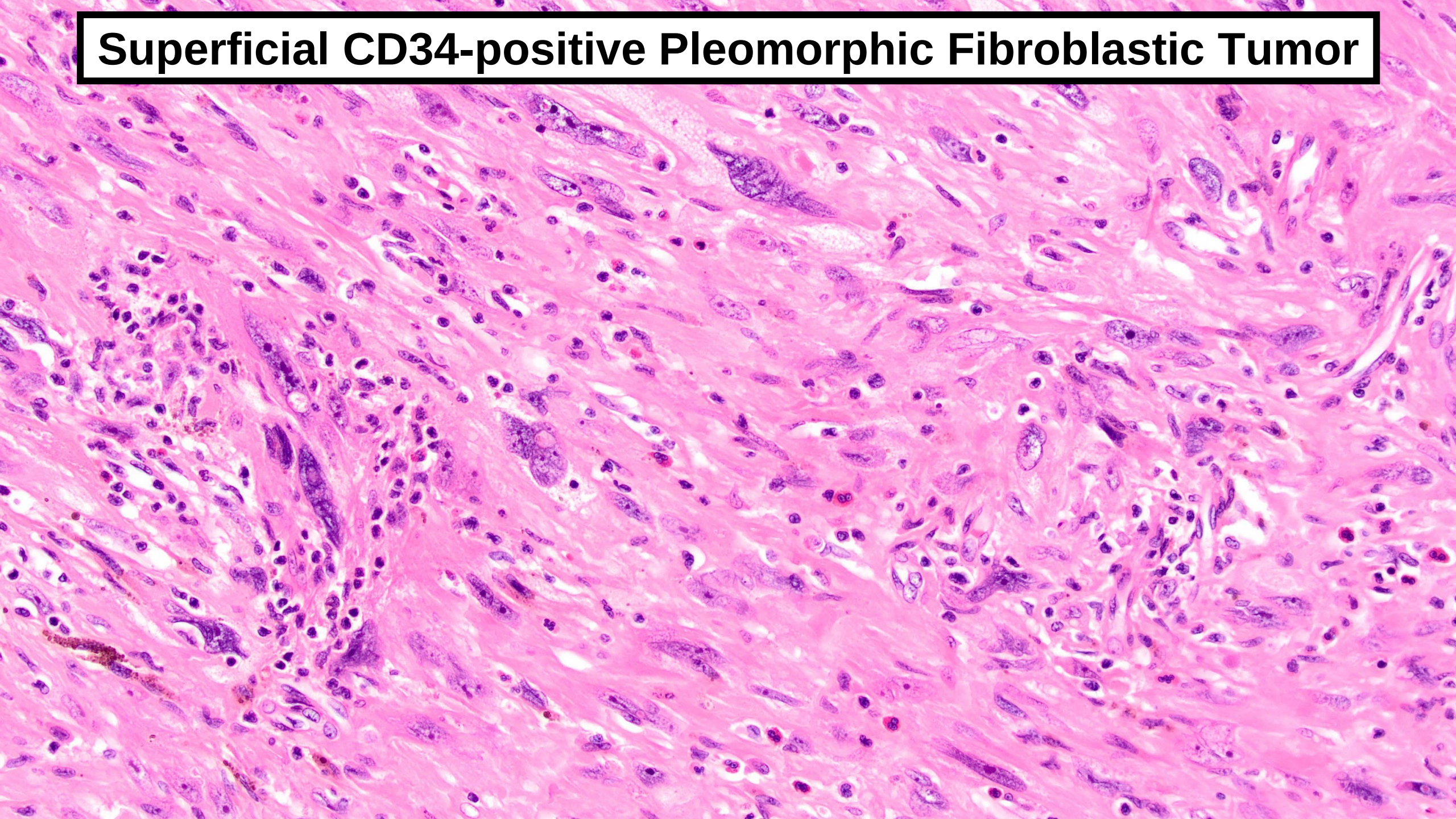
TABLE 1. Clinical Characteristics of 59 Superficial CD34-Positive Fibroblastic Tumors

Age	
Median (range)	42 (14-85) years
Sex	
Male	33
Female	26
Male-to-female ratio	1.3 : 1
Anatomic site (%)	
Lower limb	43 (73)
Thigh	25 (42)
Leg	14 (24)
Gluteal region	2 (3)
Ankle	1
Foot	1
Upper limb	5 (8)
Arm	4
Forearm	1
Other	11 (19)
Back	4
Supraclavicular region	2
Neck	1
Chest	1
Axilla	1
Abdominal wall	1
Breast	1
Tumor size (cm)	
Median (range)	3.0 (1.0-9.0)

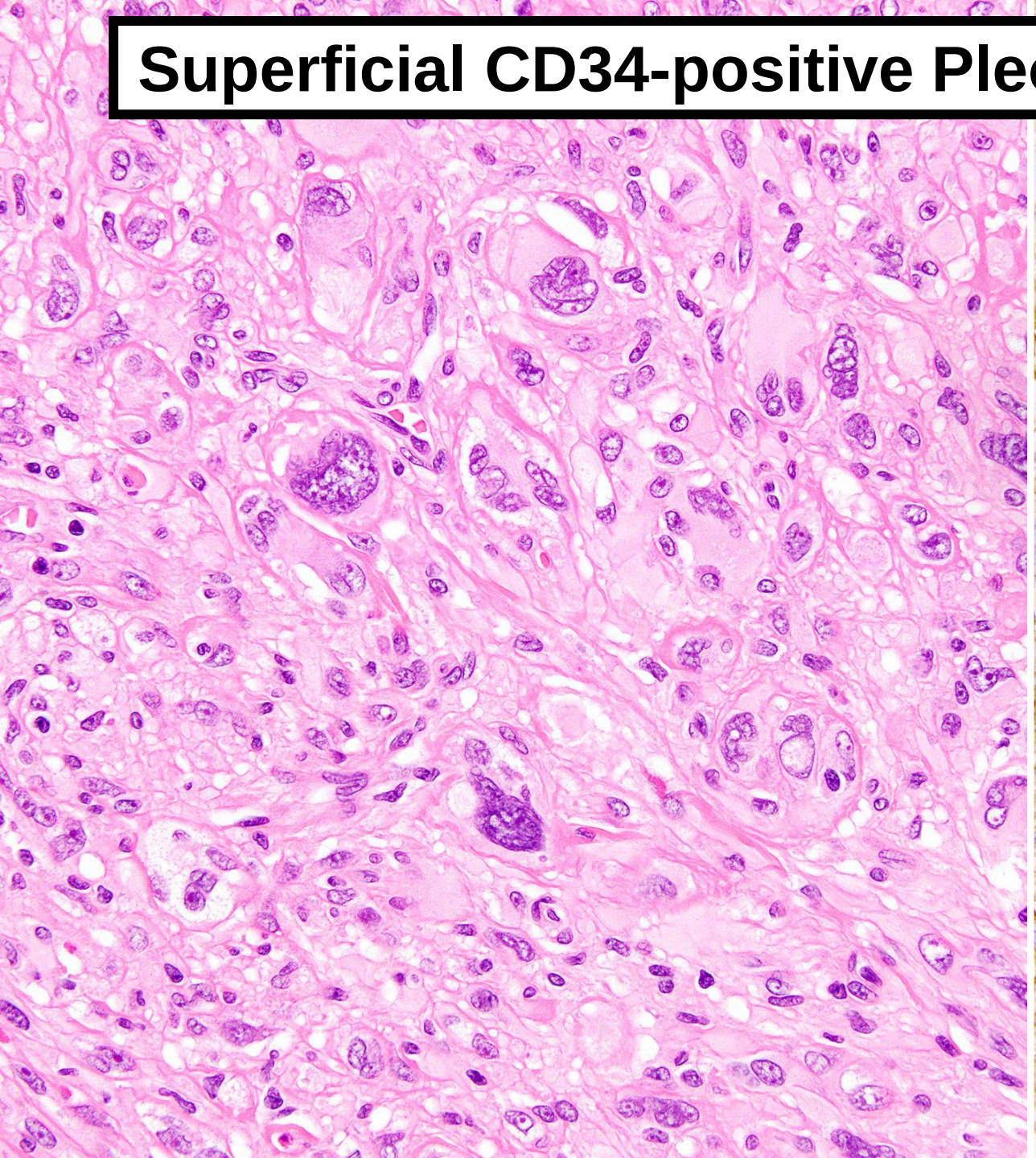
Superficial CD34-positive Pleomorphic Fibroblastic Tumor

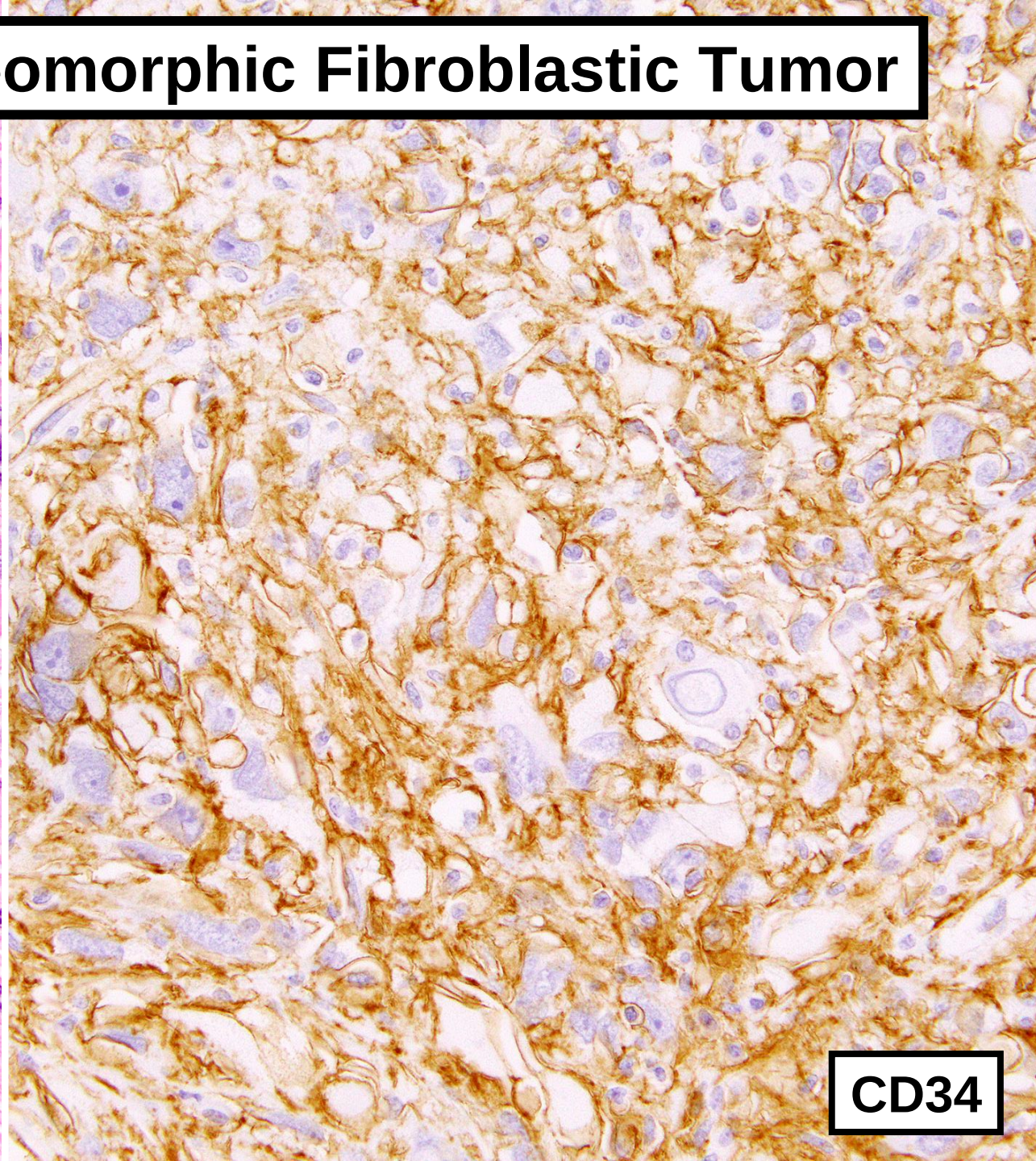


Superficial CD34-positive Pleomorphic Fibroblastic Tumor



Superficial CD34-positive Pleomorphic Fibroblastic Tumor





CD34-positive pleomorphic fibroblastic tumor

Marker	Positive
CD34	100%
AE1/AE3	70%
Desmin	35%
CADM3	95%
WT1	75%

Carter et al. *Mod Pathol* 2014

Anderson et al. *Am J Surg Pathol* 2022

Superficial CD34-positive Pleomorphic Fibroblastic Tumor

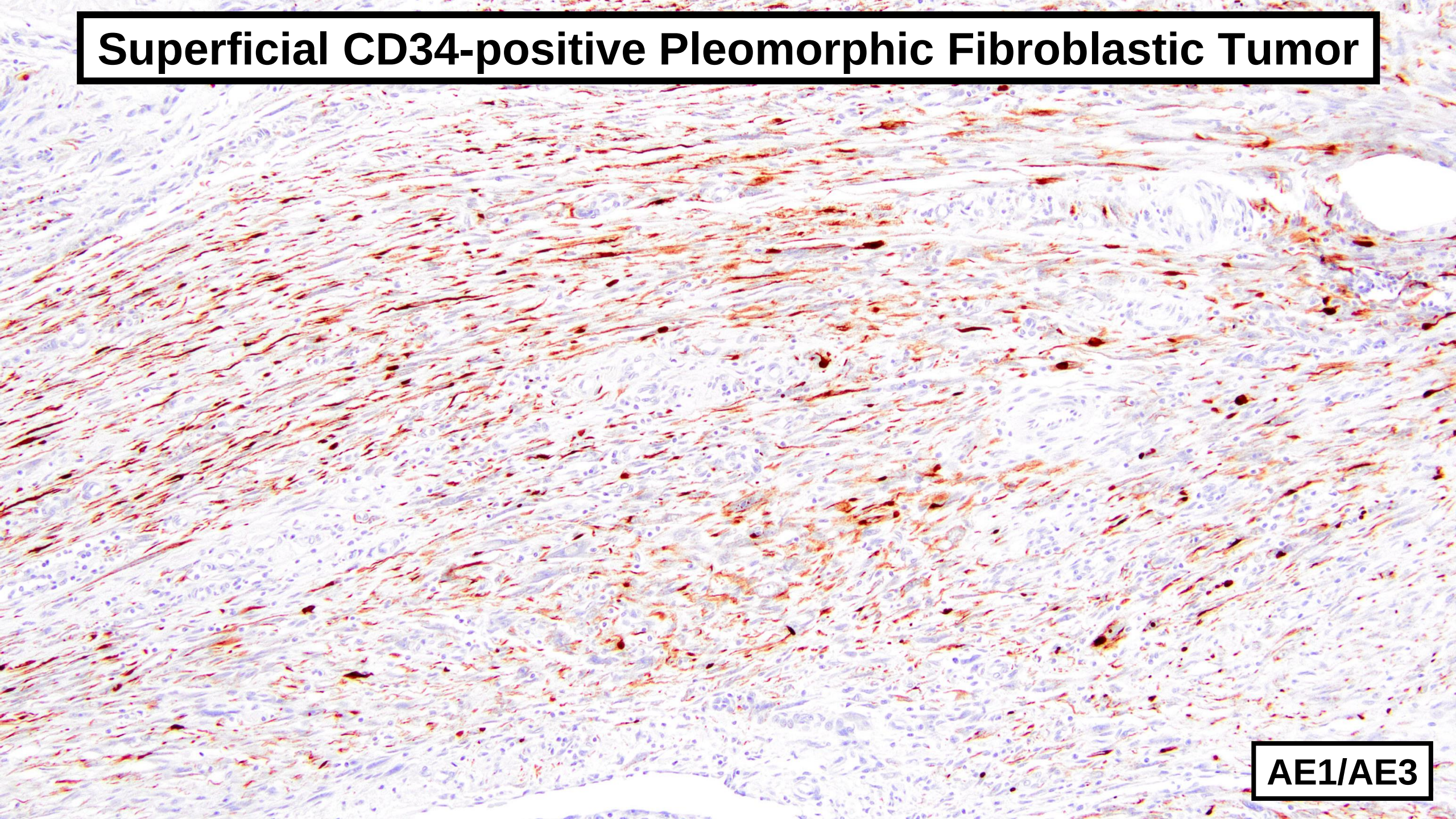


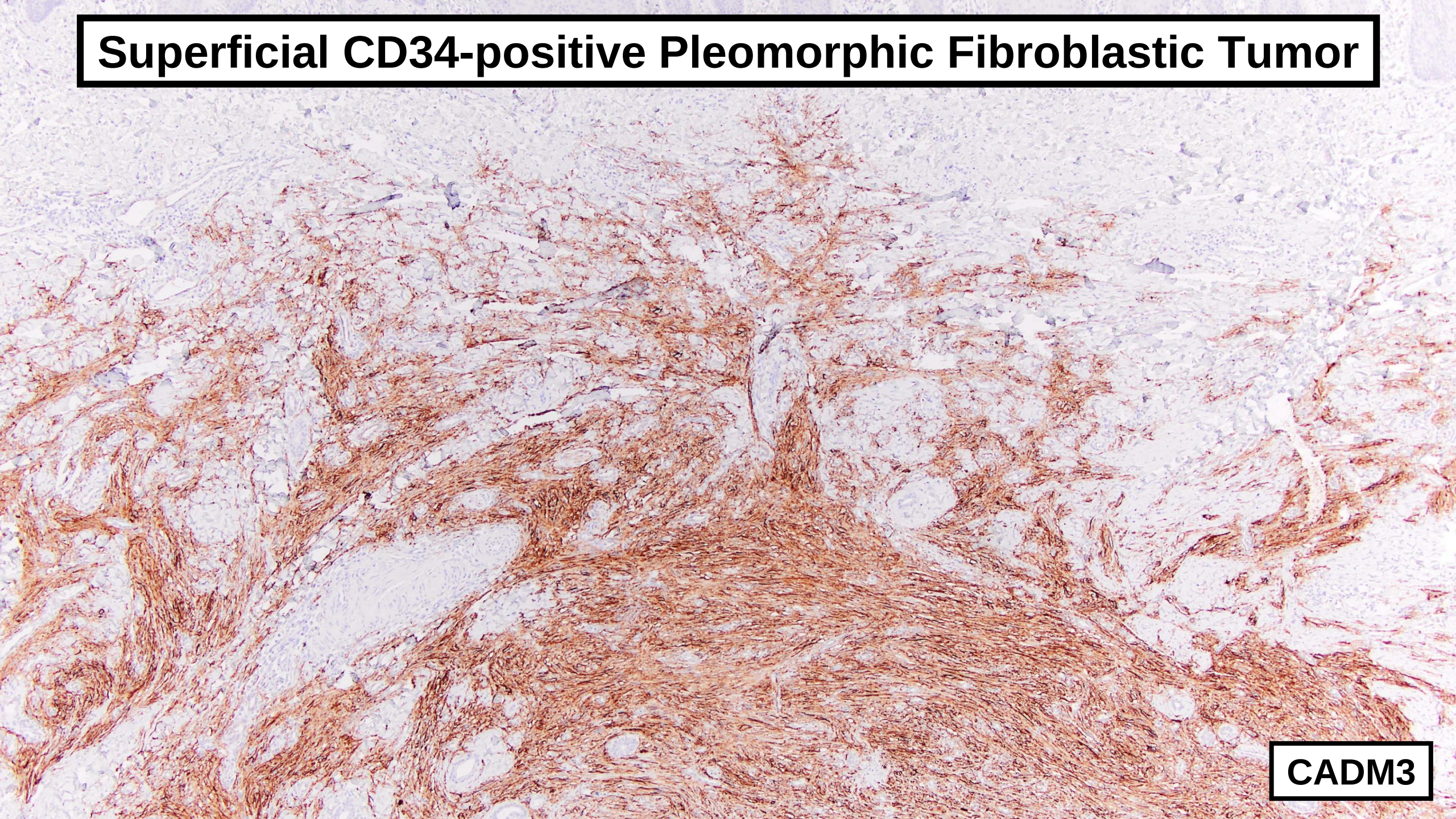
TABLE 2. Immunohistochemistry for CADM3 in Superficial CD34-Positive Fibroblastic Tumor and Histologic Mimics

Tumor Type	Total Cases	Positive, n (%)	0	1+	2+	3+	4+	5+
Superficial CD34-positive fibroblastic tumor	59	56 (95)	3	0	0	1	1	54
Histologic mimics								
Undifferentiated pleomorphic sarcoma	20	2 (10)	18	1	0	1	0	0
Pleomorphic liposarcoma	20	4 (20)	16	0	1	2	1	0
Cellular benign fibrous histiocytoma	20	0	20	0	0	0	0	0
Atypical fibrous histiocytoma	5	0	5	0	0	0	0	0
Pleomorphic hyalinizing angiectatic tumor	10	4 (40)	6	1	1	2	0	0
Dermatofibrosarcoma protuberans	10	0	10	0	0	0	0	0

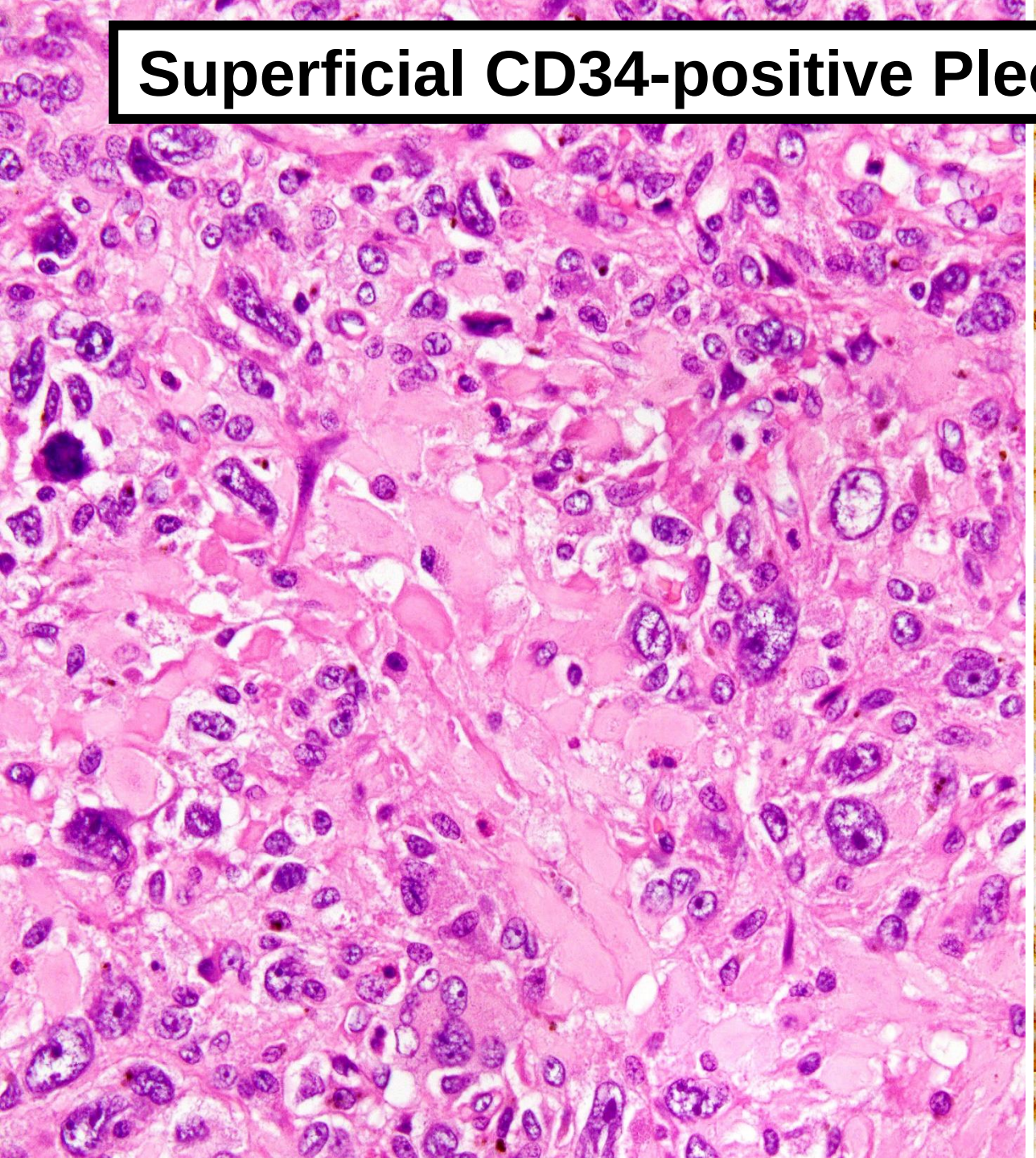
0; 1+ (< 5%); 2+ (5%-25%); 3+ (26%-50%); 4+ (51%-75%); 5+ (76%-100%).

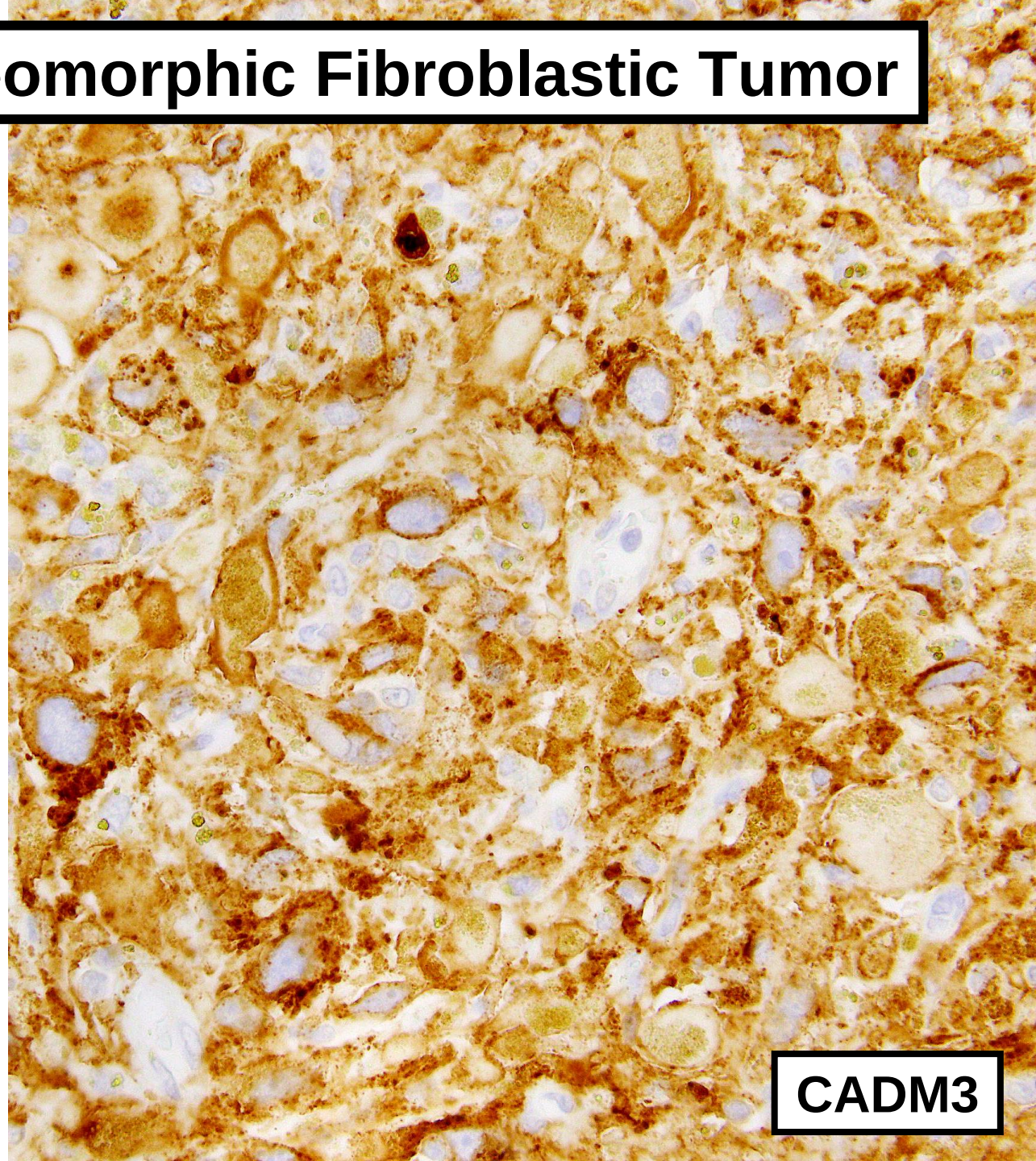
Anderson et al. *Am J Surg Pathol* 2022

Superficial CD34-positive Pleomorphic Fibroblastic Tumor



Superficial CD34-positive Pleomorphic Fibroblastic Tumor

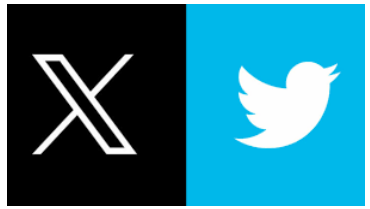




Practice points

- **Subclassification of pleomorphic sarcomas clinically significant**
- **Sample thoroughly; search for histologic clues**
- **Pleomorphic sarcomas with myogenic differentiation particularly high metastatic potential**
- **IHC plays important role identify/confirm myogenic sarcomas, dedifferentiated liposarcoma**

jhornick@bwh.harvard.edu



@JLHornick

THANK YOU!