TUMORS OF FAT, MUSCLE, BONE AND CARTILAGE

Soheil S. Dadras MD-PhD

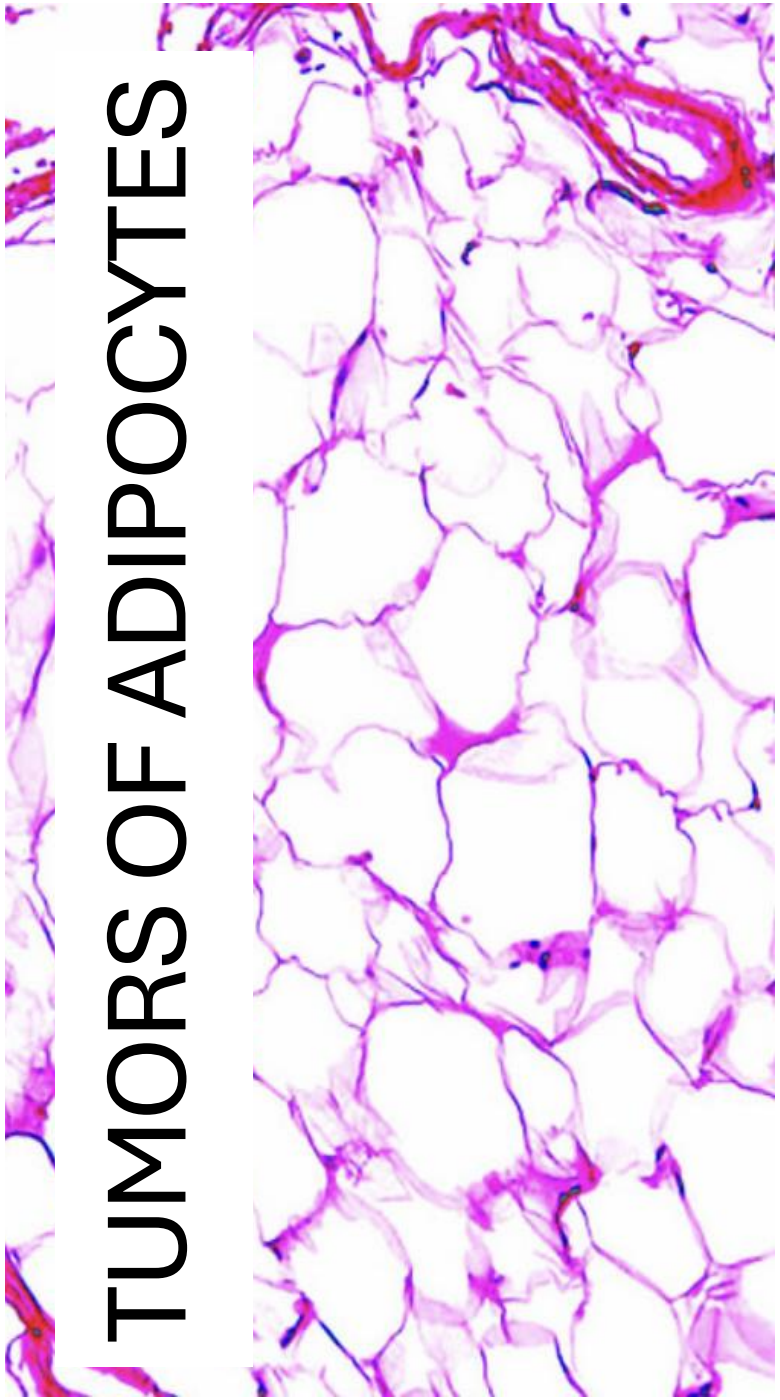
What are connective tissue tumors?

- **Tumors of mesenchymal tissue with multiple of lines of differentiation**
- **Subtypes**
  - Adipocytic tumors
  - Tumors of fibrous, fibroblastic, and myofibroblastic tissue
  - Fibrocystic tumors
  - Nerve sheath and neuroectodermal tumors and tumor-like lesions
  - Smooth muscle tumors
  - Skeletal muscle tumors
  - Tumors of vascular origin
  - Tumors of bone and cartilage-forming tissue

Overview: Connective Tissue (or Mesenchymal) Tumors

- Commonly found on the skin.
- Most are benign, often lacking distinct clinical characteristics, and are frequently missed by healthcare professionals.
- Histologically complex, with various differentiation pathways.
- Difficulty arises in distinguishing between benign and malignant lesions.
- Sarcomas are rare, constituting less than 1% of all malignant tumors.
- Atypical lesions are more challenging to categorize, if under sampled.
- Essential to have adequate tissue sampling for an accurate diagnosis.
- Molecular probes targeting specific gene arrangements may assist in accurately classifying histologically uncertain lesions.
- IHC markers developed based on these specific gene arrangements (first line).

TUMORS OF ADIPOCYTES

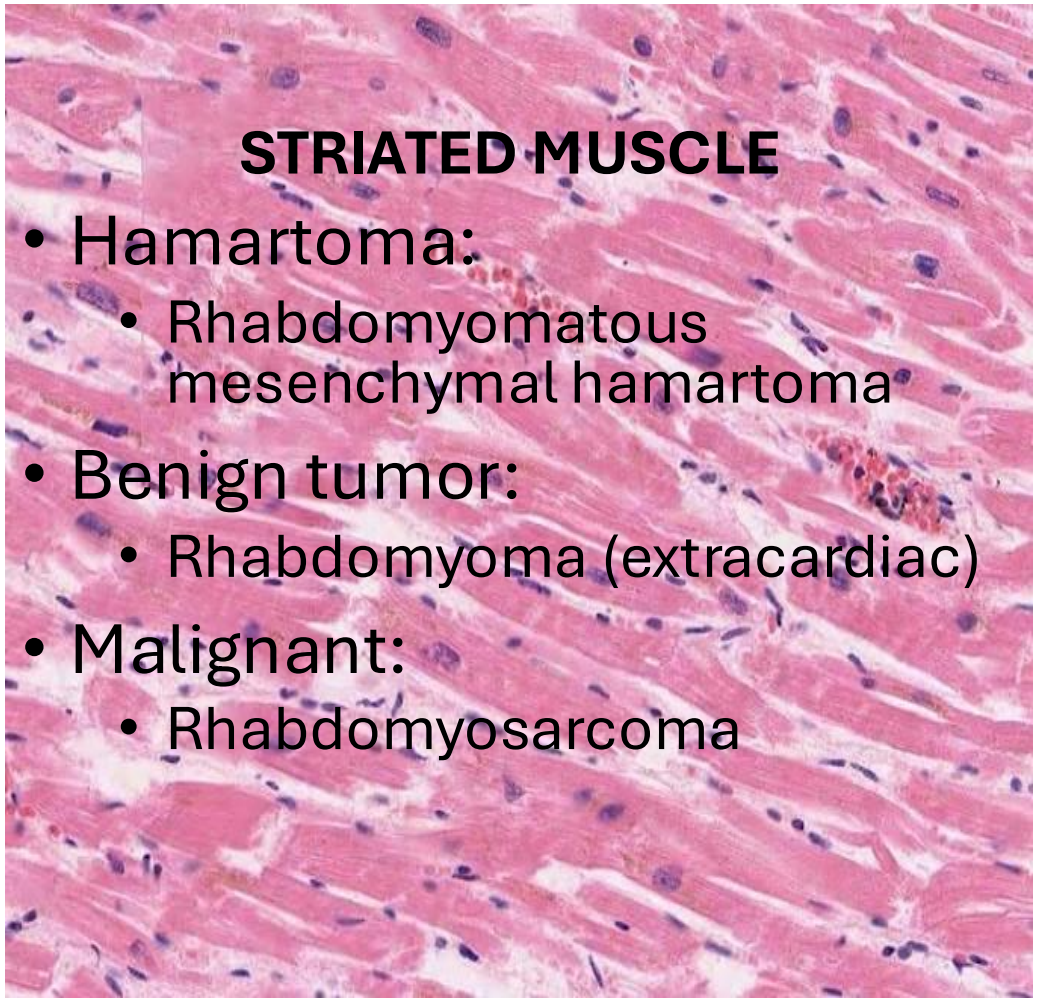


- Benign lipomatous tumors / conditions
  - Hibernoma
  - Lipoma
  - Nevus lipomatosus superficialis
  - (Lipomatosis)
  - (Adiposis dolorosa)
  - (Piezogenic pedal papules)
  - Lipomatosis of nerve
  - Lipoblastoma
  - Lipoblastoma-like tumor of the vulva
  - Angiolipoma
  - Myolipoma
  - Chondroid lipoma
  - Spindle cell lipoma / pleomorphic lipoma
- Atypical lipomatous tumor
  Atypical spindle cell lipomatous tumor
- Liposarcoma

TUMORS OF MUSCLE

SMOOTH MUSCLE

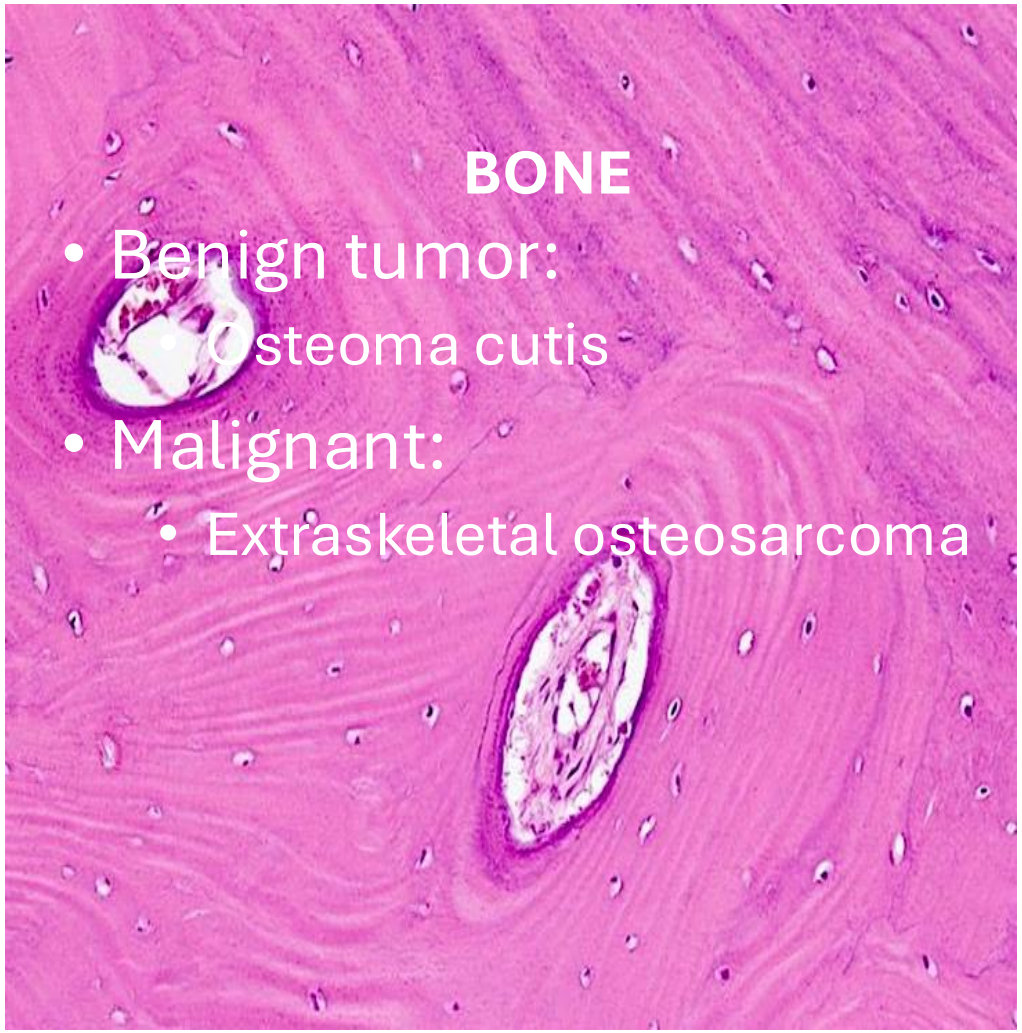
- Hamartoma:
  - Congenital smooth muscle hamartoma
- Benign tumor:
  - Pilar leiomyoma
  - Vascular leiomyoma
  - Genital leiomyoma
- Malignant:
  - Leiomyosarcoma



STRIATED MUSCLE

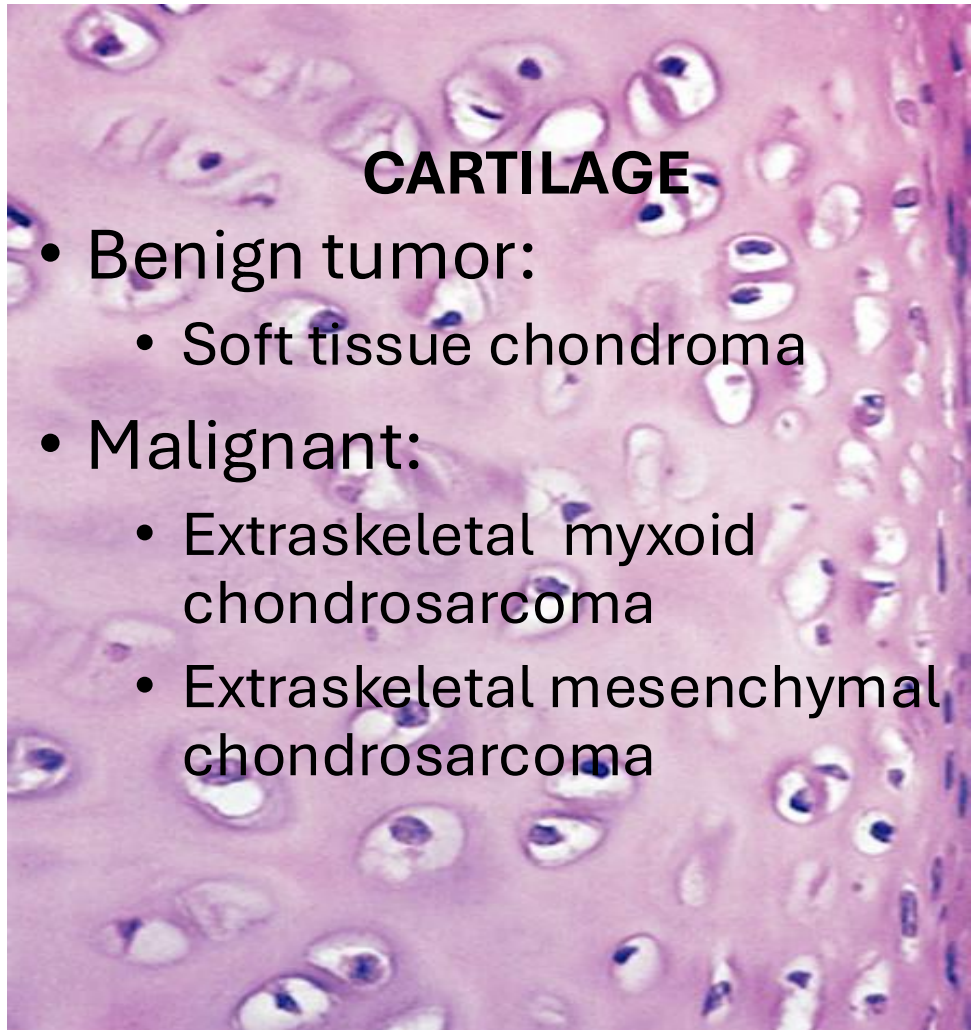
- Hamartoma:
  - Rhabdomyomatous mesenchymal hamartoma
- Benign tumor:
  - Rhabdomyoma (extracardiac)
- Malignant:
  - Rhabdomyosarcoma

TUMORS OF BONE AND CARTILAGE



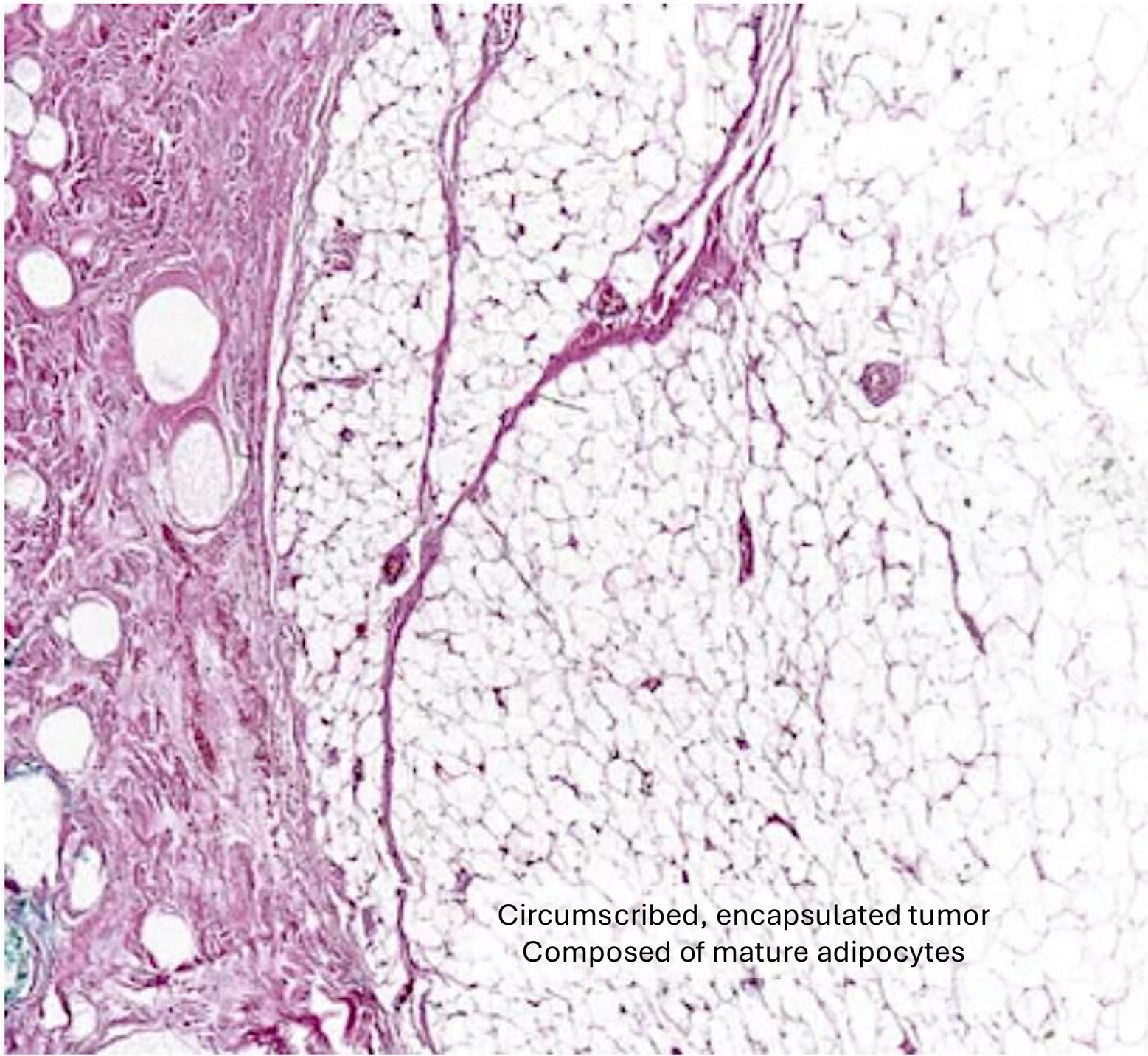
BONE

- Benign tumor:
  - Osteoma cutis
- Malignant:
  - Extraskeletal osteosarcoma



CARTILAGE

- Benign tumor:
  - Soft tissue chondroma
- Malignant:
  - Extraskeletal myxoid chondrosarcoma
  - Extraskeletal mesenchymal chondrosarcoma



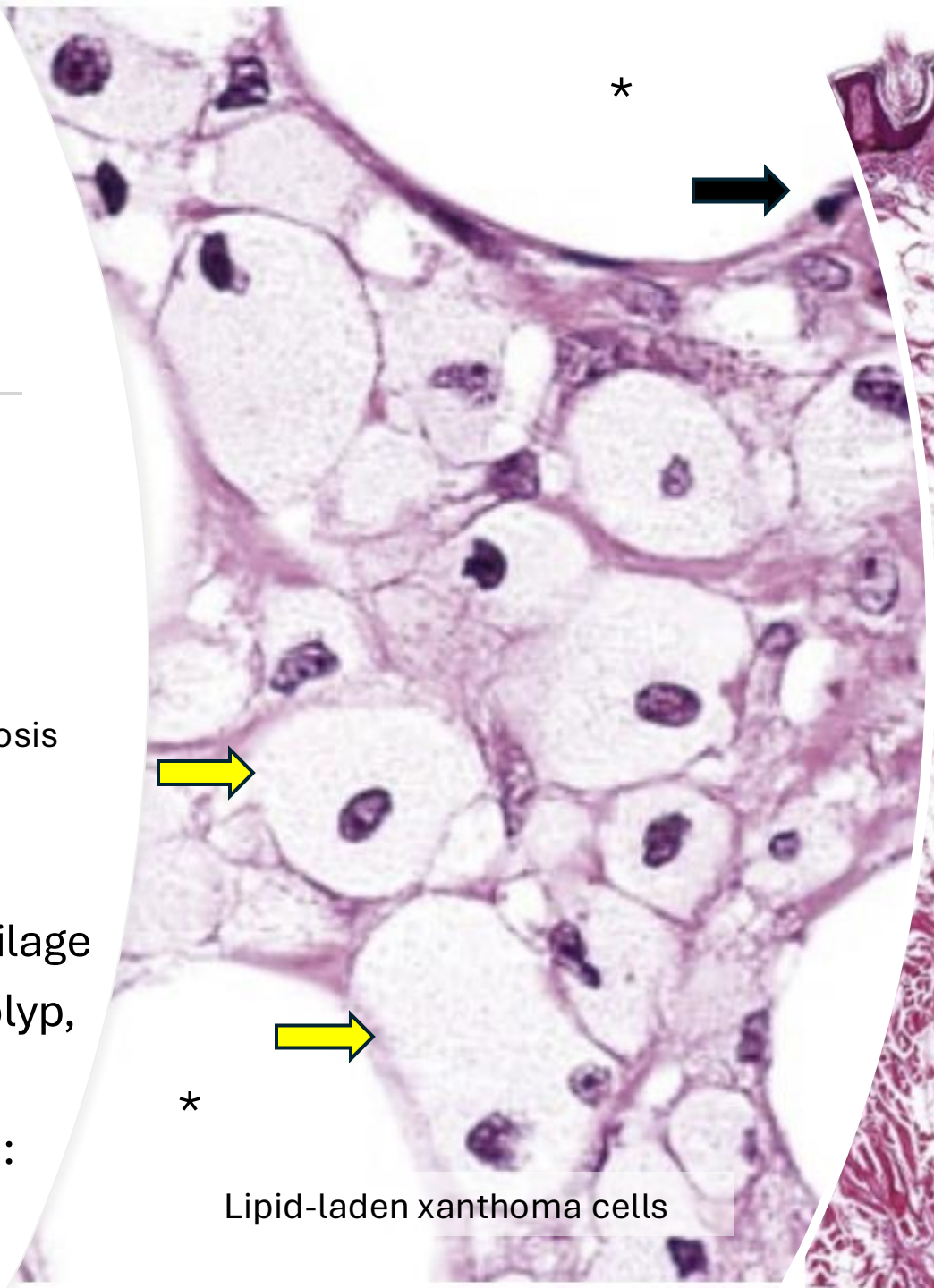
Circumscribed, encapsulated tumor
Composed of mature adipocytes

LIPOMA

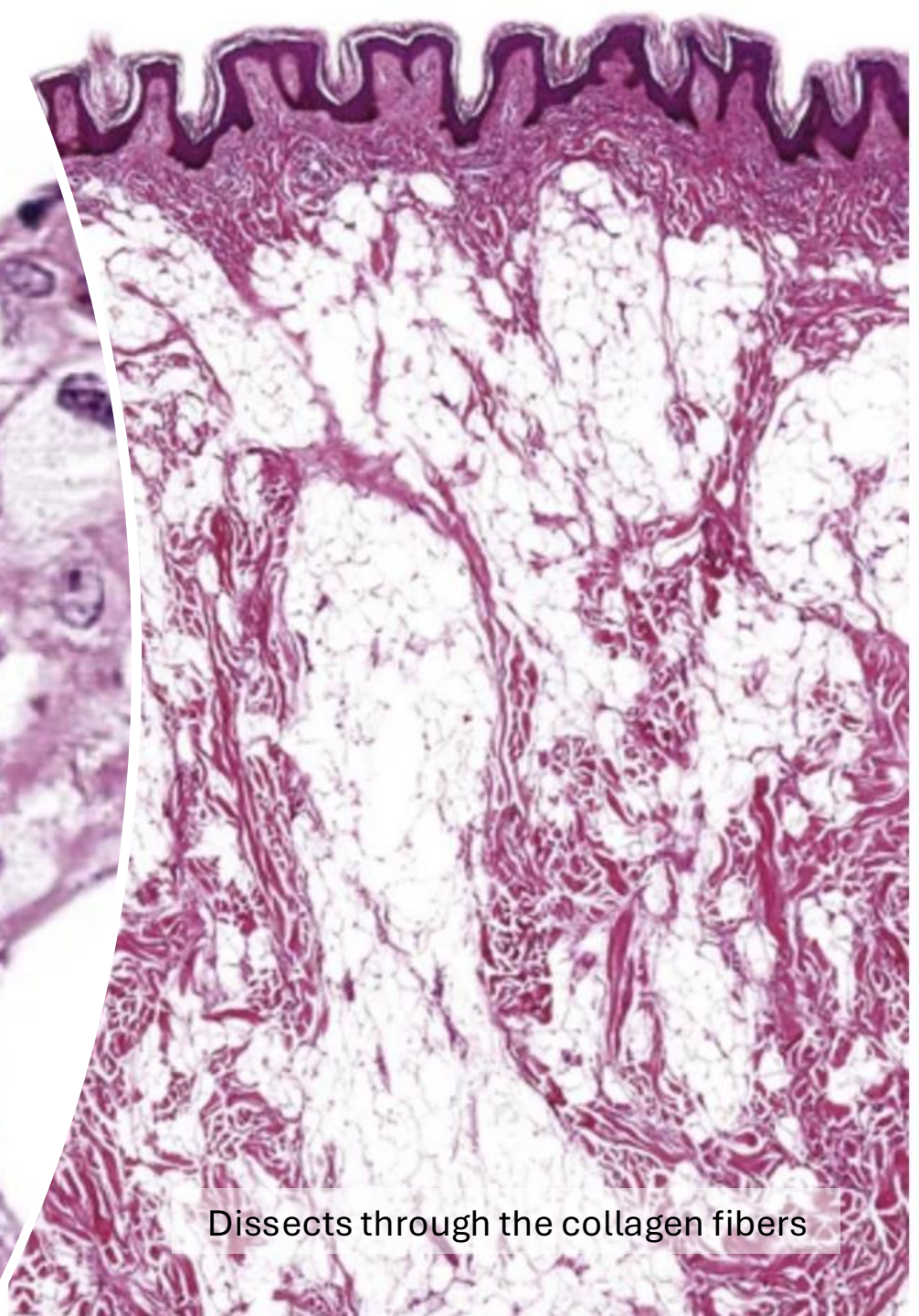
- Most common connective tissue tumor
- Uncommon in children (Bannayan-Riley-Ruvalcaba syndrome)
- Multiple lipomas in rosiglitazone, peroxisome proliferator activator gamma agonist
- Recurrence infrequent (<5%)
- t(3;12)(q27~28;q13~15) leading to a fusion gene *HMGA2-LPP*

DERMAL LIPOMA

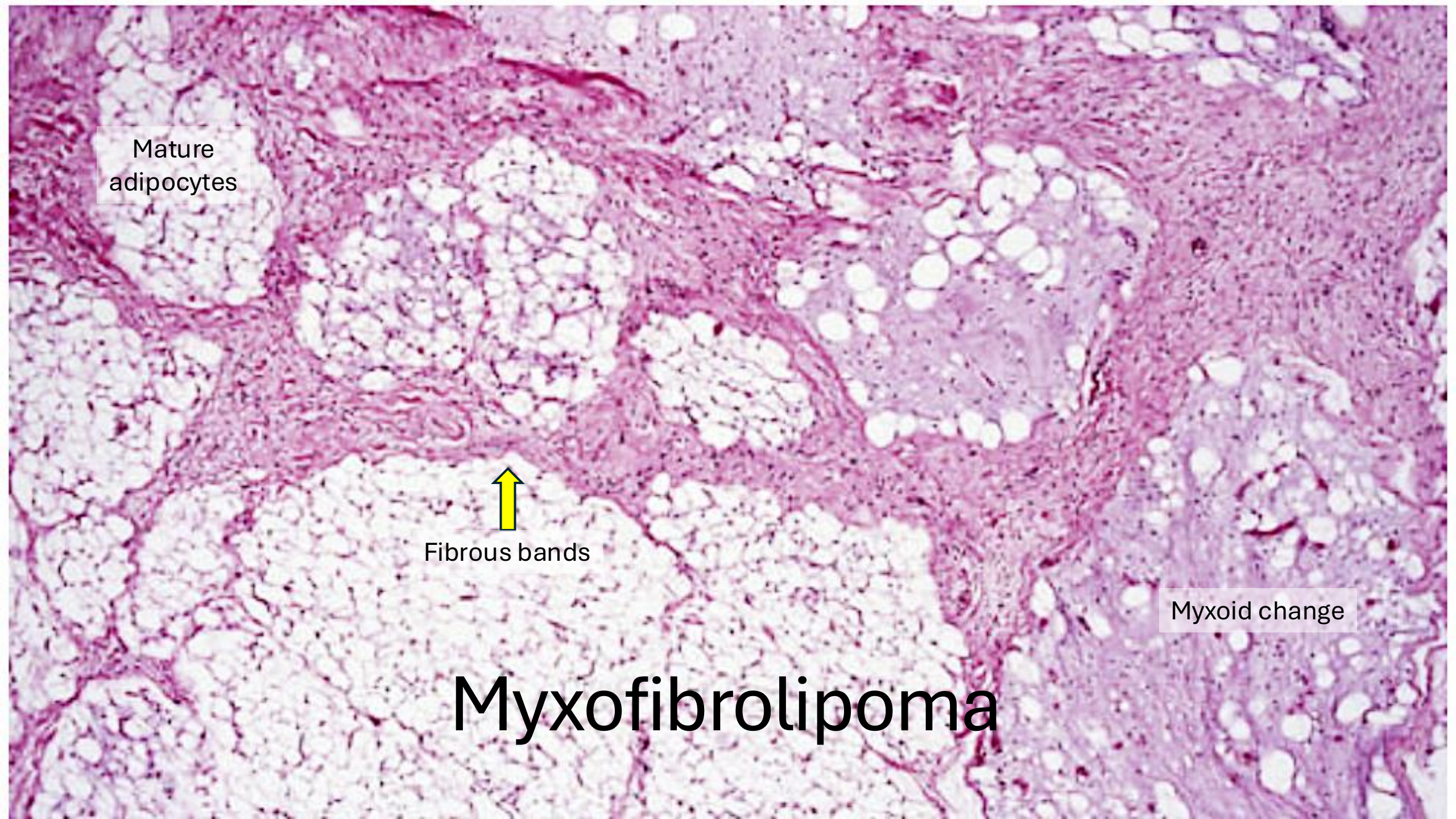
- Univacuolated, mature adipocytes
- Nucleus: compressed, pushed to the edge
- Degenerative changes:
  - Post-traumatic fat necrosis
  - Myxoid change
  - Fibrosis
- Other mesenchymal elements: bone or cartilage
- DDX: Fibroepithelial polyp, Nevus lipomatosus superficialis, Atypical lipomatous tumor (IHC: MDM2+, CDK4+)



Lipid-laden xanthoma cells



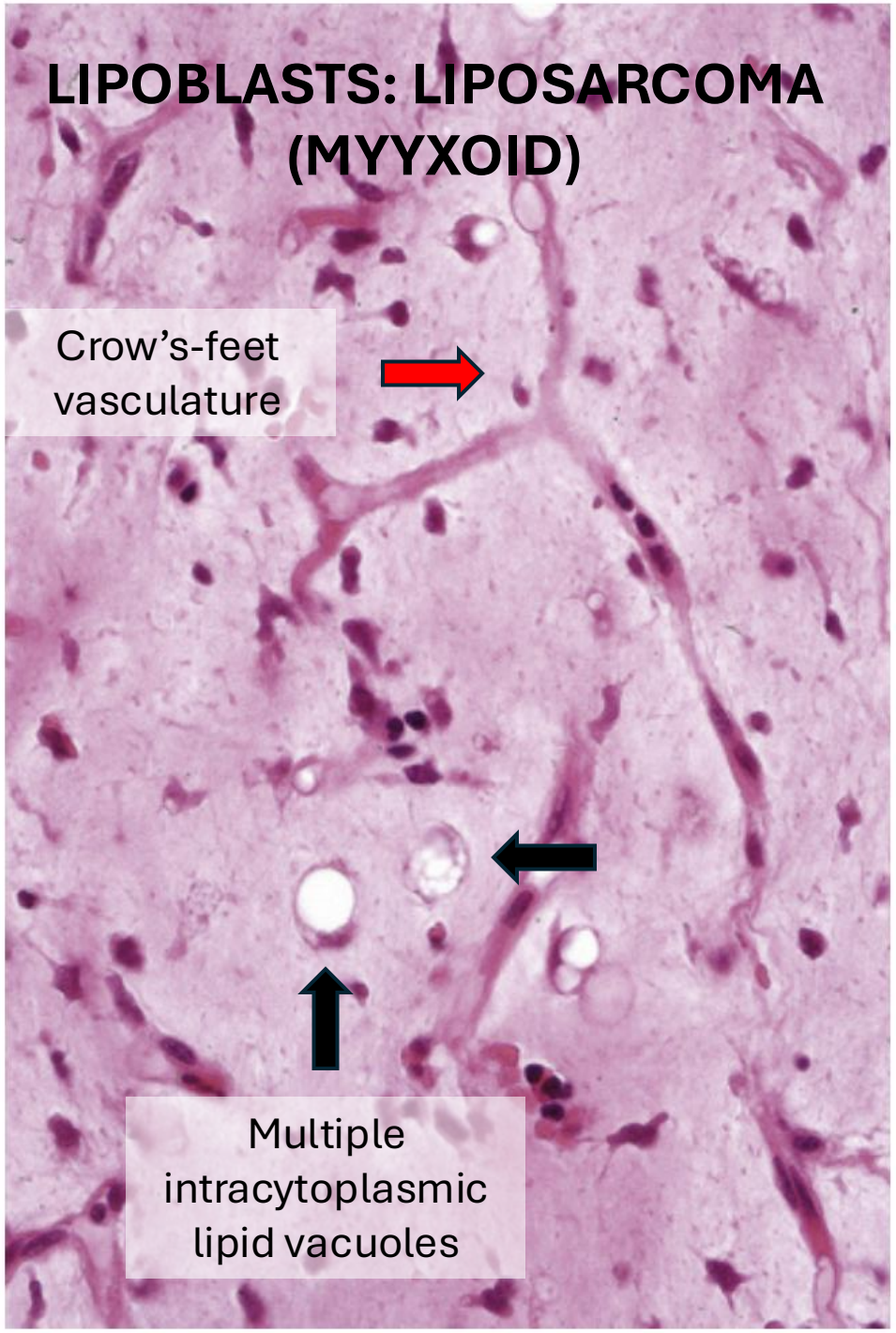
Dissects through the collagen fibers


Mature adipocytes
Fibrous bands
Myxoid change
Myxofibrolipoma

LOCHKERN CELLS: LIPOMA

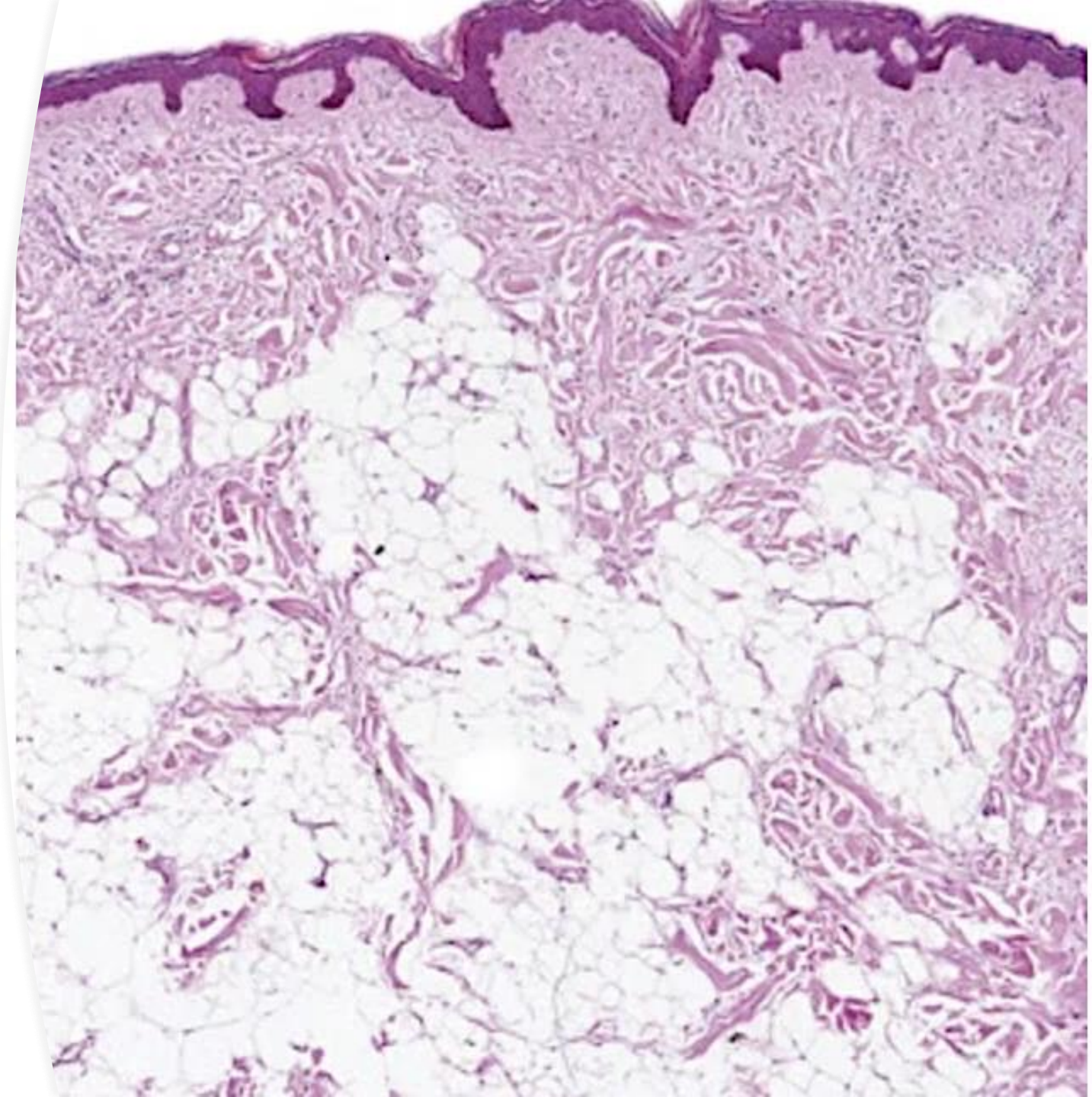
Intranuclear lipid “inclusion”

LIPOBLASTS: LIPOSARCOMA (MYYXOID)



NEVUS LIPOMATOSUS SUPERFICIALIS

- Uncommon connective tissue nevus
- Multiple papular, polypoid or plaques
- Buttocks, upper thigh or lower back

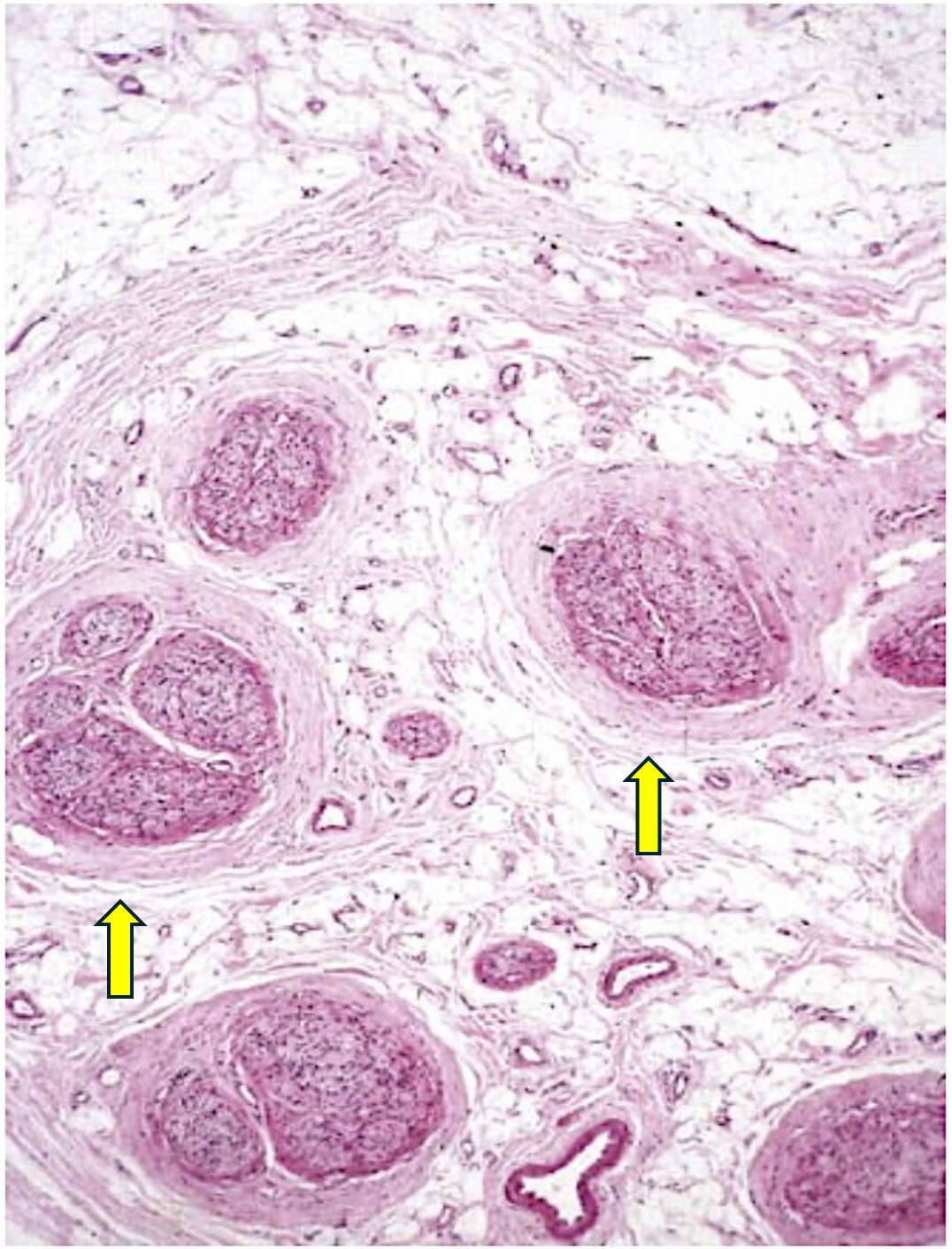


LIPOMATOSIS, ADIPOSIS DOLOROSA AND PIEZOGENIC PEDAL PAPULES

- CLINICAL:
  - Lipomatosis: symmetric/diffuse or asymmetric
    - Syndromic association
    - Etiology: HIV lipodystrophy, exogenous/endogenous production of steroids, or idiopathic
  - Adiposis dolorsa : increased fat in painful, plaque-like distribution
  - Piezogenic pedal papules: multiple skin-colored papules on the heels
- HISTOLOGY:
  - Normal, unencapsulated adipose tissue herniating into the dermis
- DDX: dermal lipoma

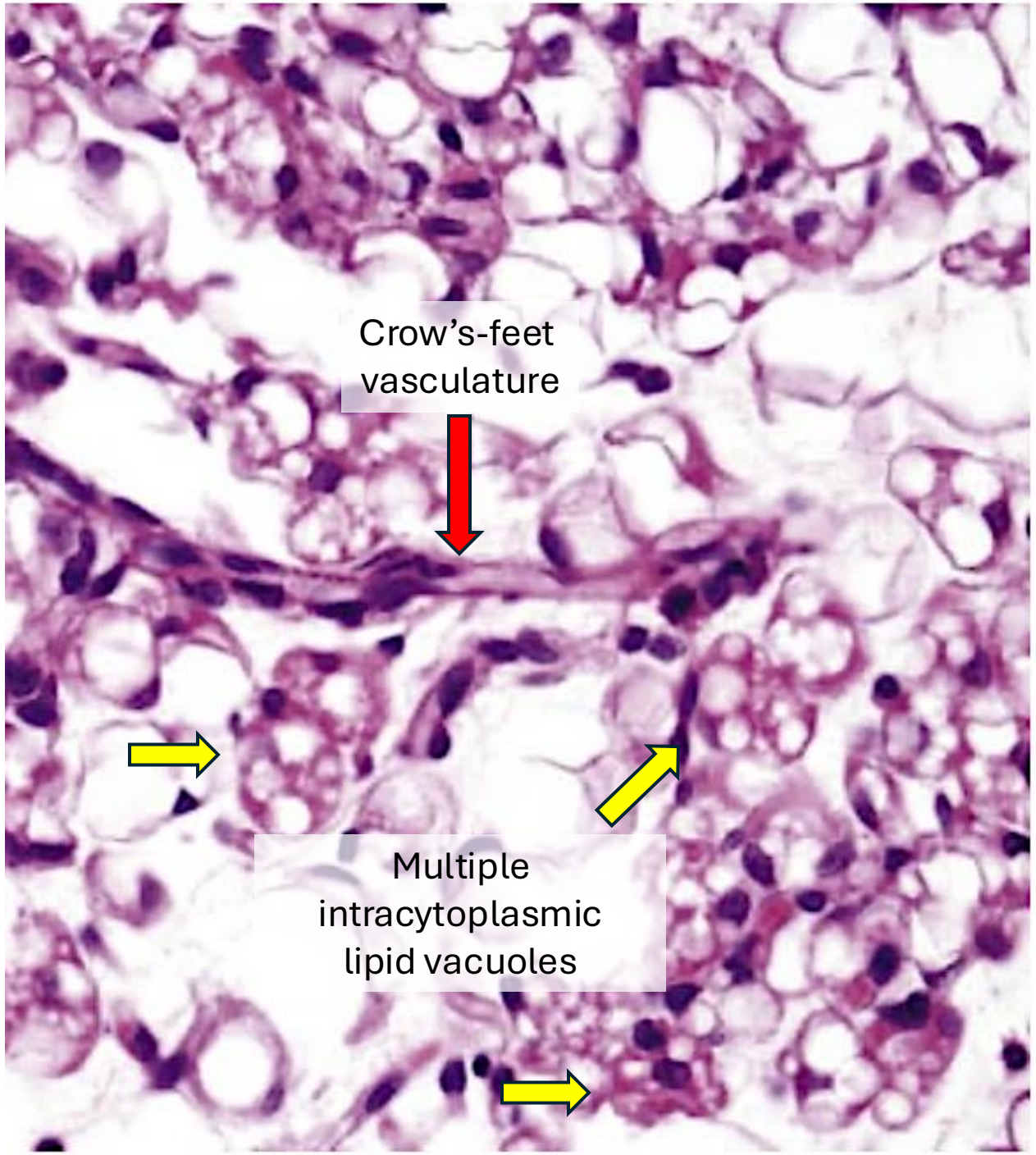
LIPOMATOSIS OF NERVE

- Hamartoma of nerve, adipose and fibrous tissue
- Located within epineurium of nerve
- Concentric perineural fibrosis
- Rare bone formation



LIPOBLASTOMA

- Counterpart of lipoma in infancy/childhood
- Resembles hemangioma
- Trunk > extremities > head and neck
- Rearrangement of 8q11~q13
  - Overexpression of *PLAG1* oncogene
- Recapitulates developing fat:
  - Mature adipocytes, lipoblasts and perilipoblats
- IHC: S100+, CD34+, PLAG1+, rare p16+



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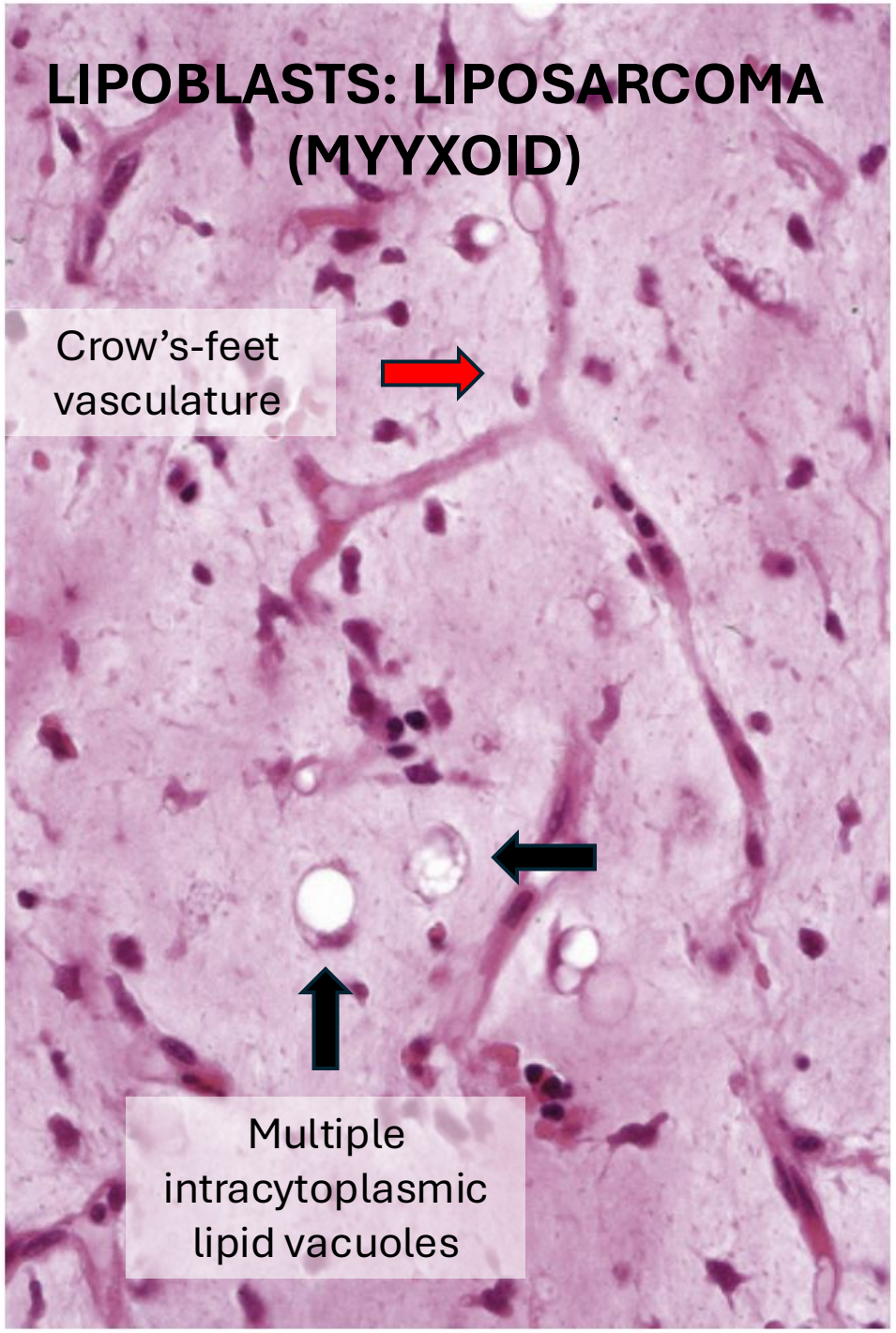
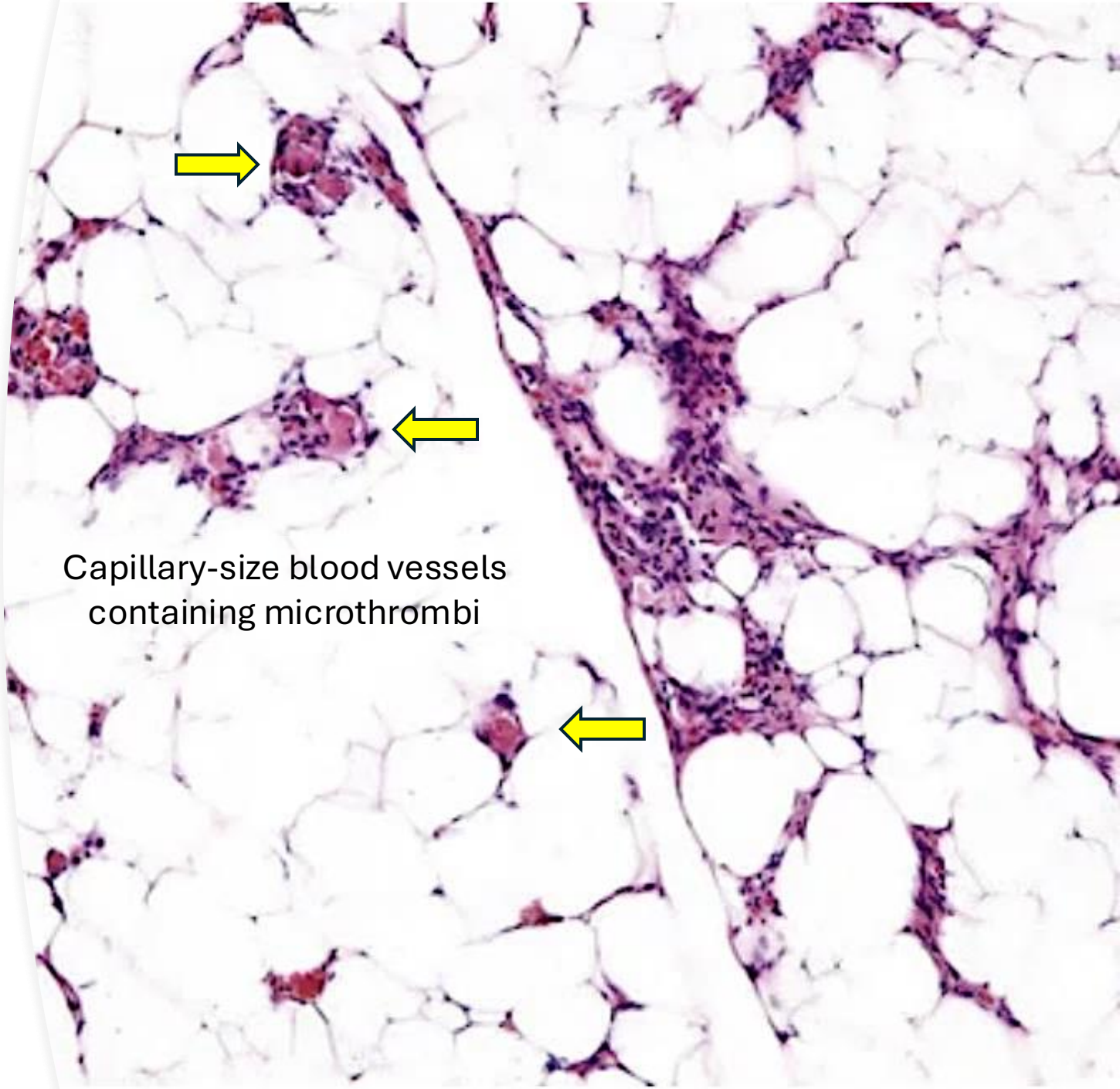
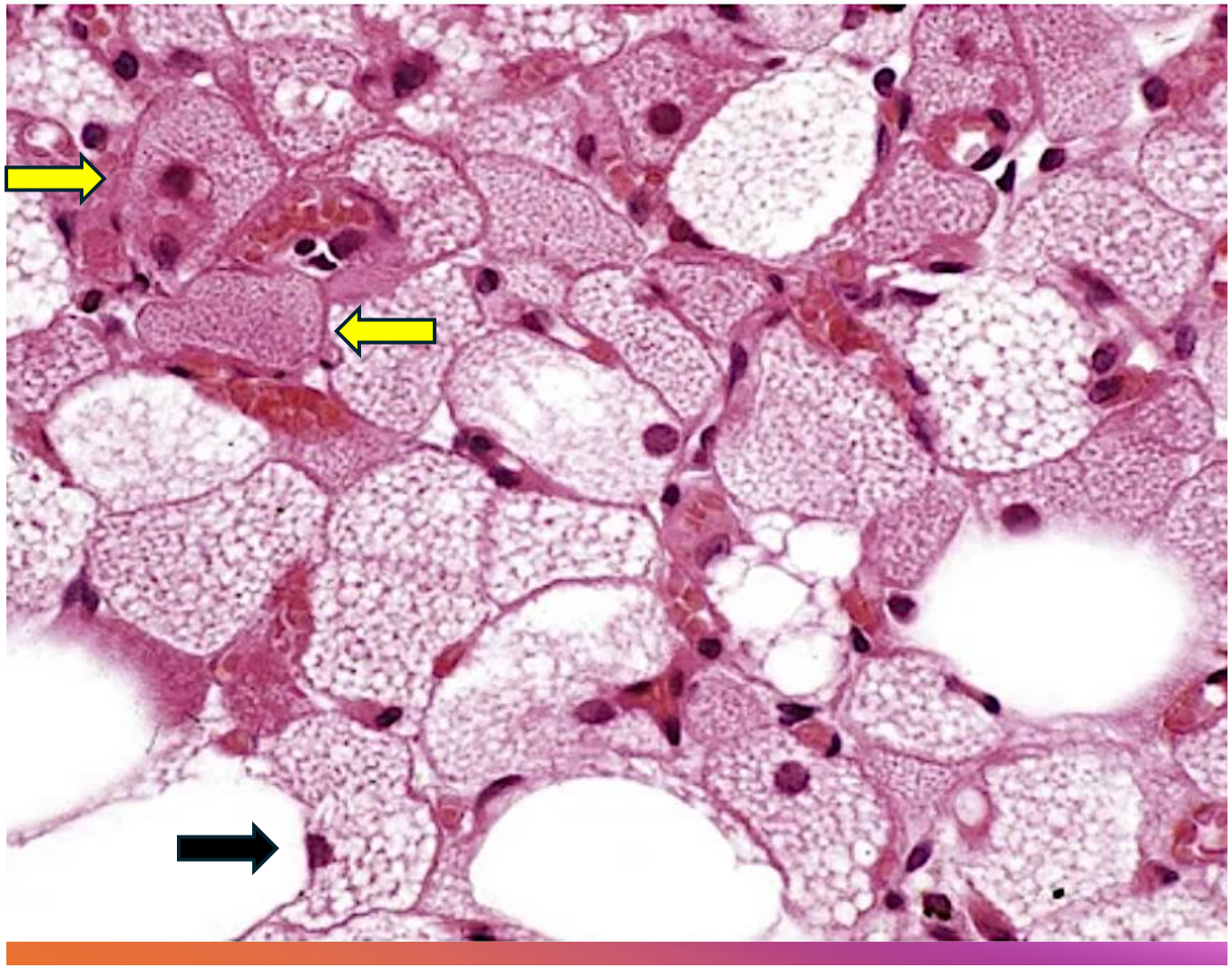


ANGIOLIPOMA

- Young adults, the subcutis of forearm and trunk
- Tender, painful, red-blue discoloration
- Multiple indinavir and saquinavir
- Aberrant structure of chromosome 13, expression of protein kinase D2 and HMGA2
- DDX: capillary hemangioma and KHE





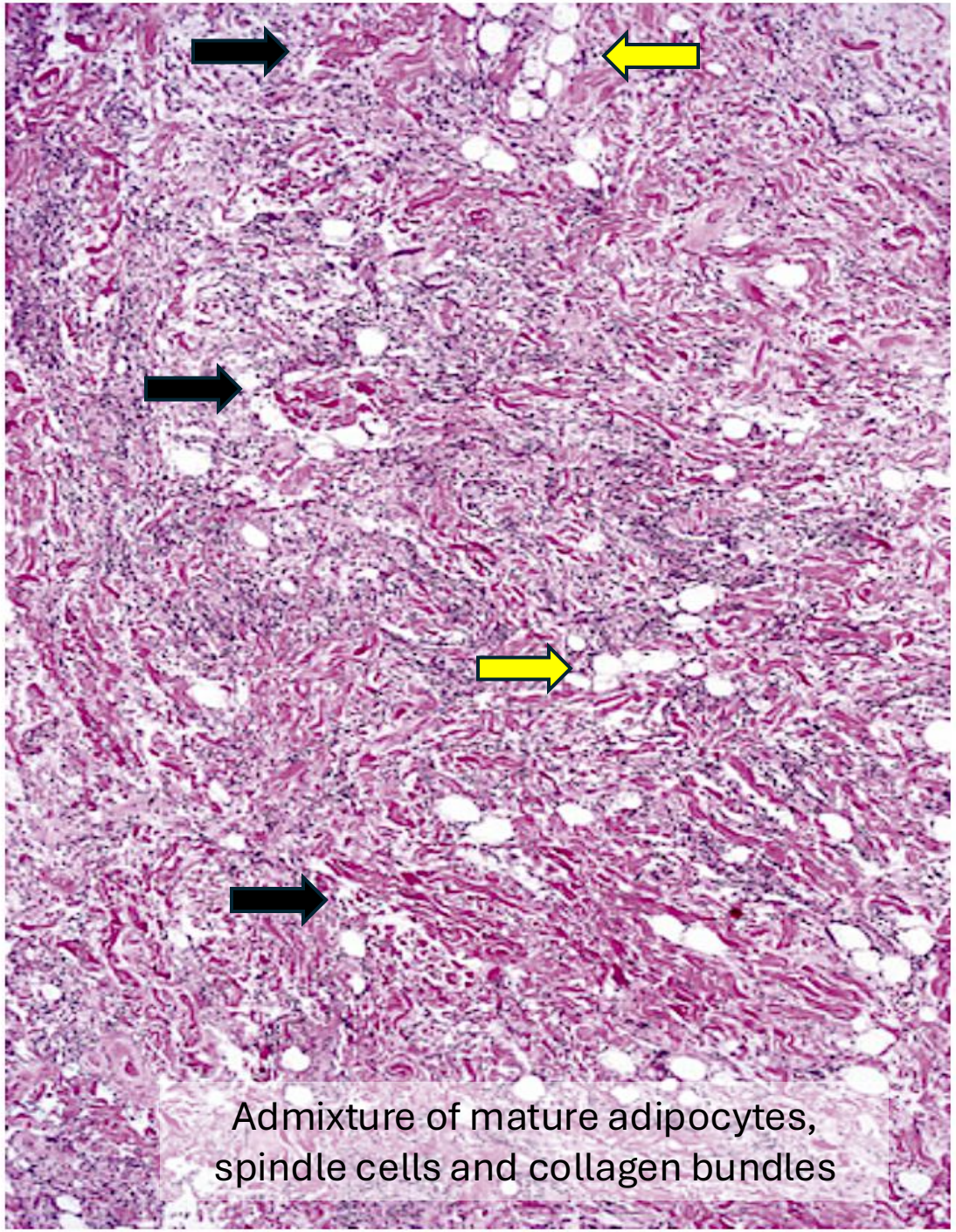
Mixed mature adipocytes and multivacuolated adipocytes with granular eosinophilic cytoplasm

HIBERNOMA

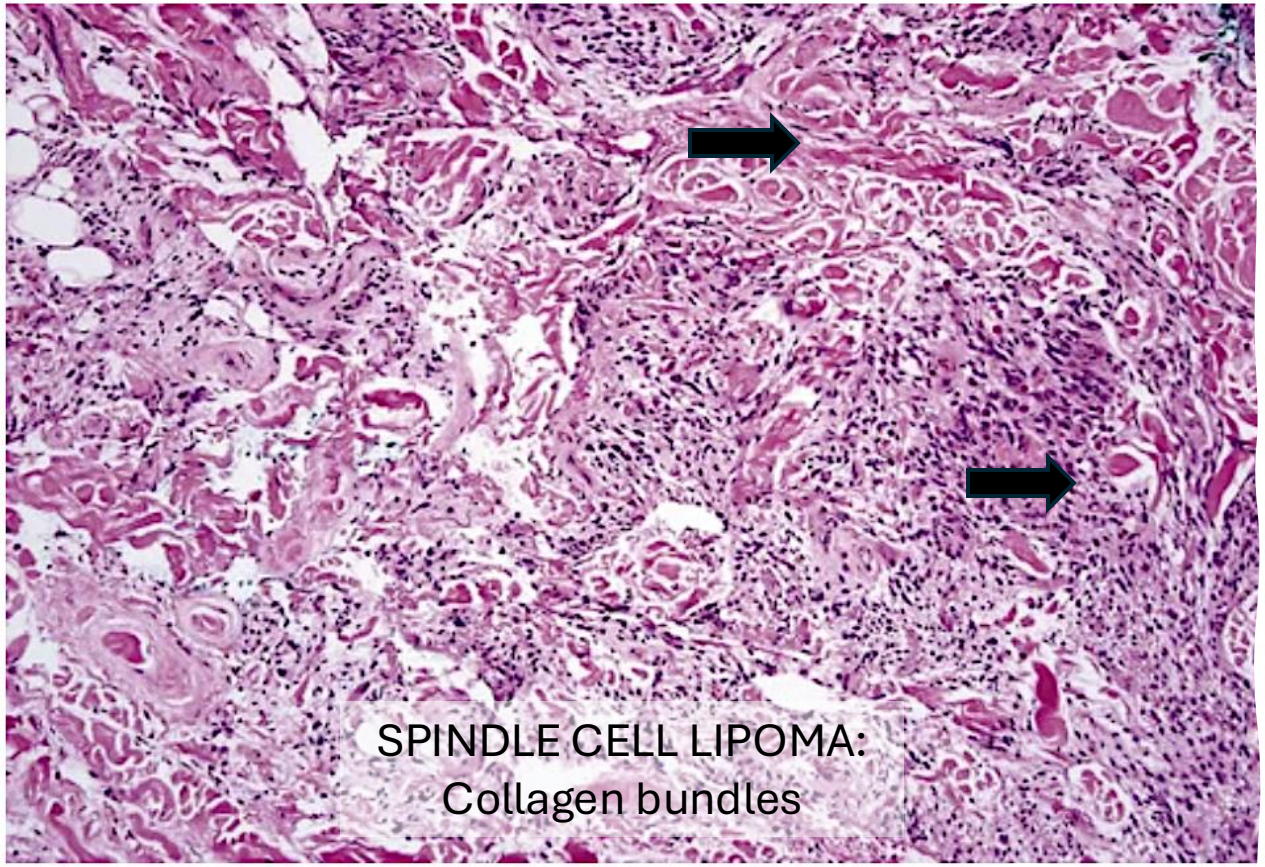
- Rare, benign brown fat in young adults
- Interscapular space, axillae, chest wall and head and neck
- Rearrangement of 11q13
- *MEN1* and/or *AIP* loss
- Encapsulated, lobulated mass
- ± Lipoblast-like cells
- IHC: MDM2-, CDK4-

SPINDLE CELL LIPOMA/ PLEOMORPHIC LIPOMA

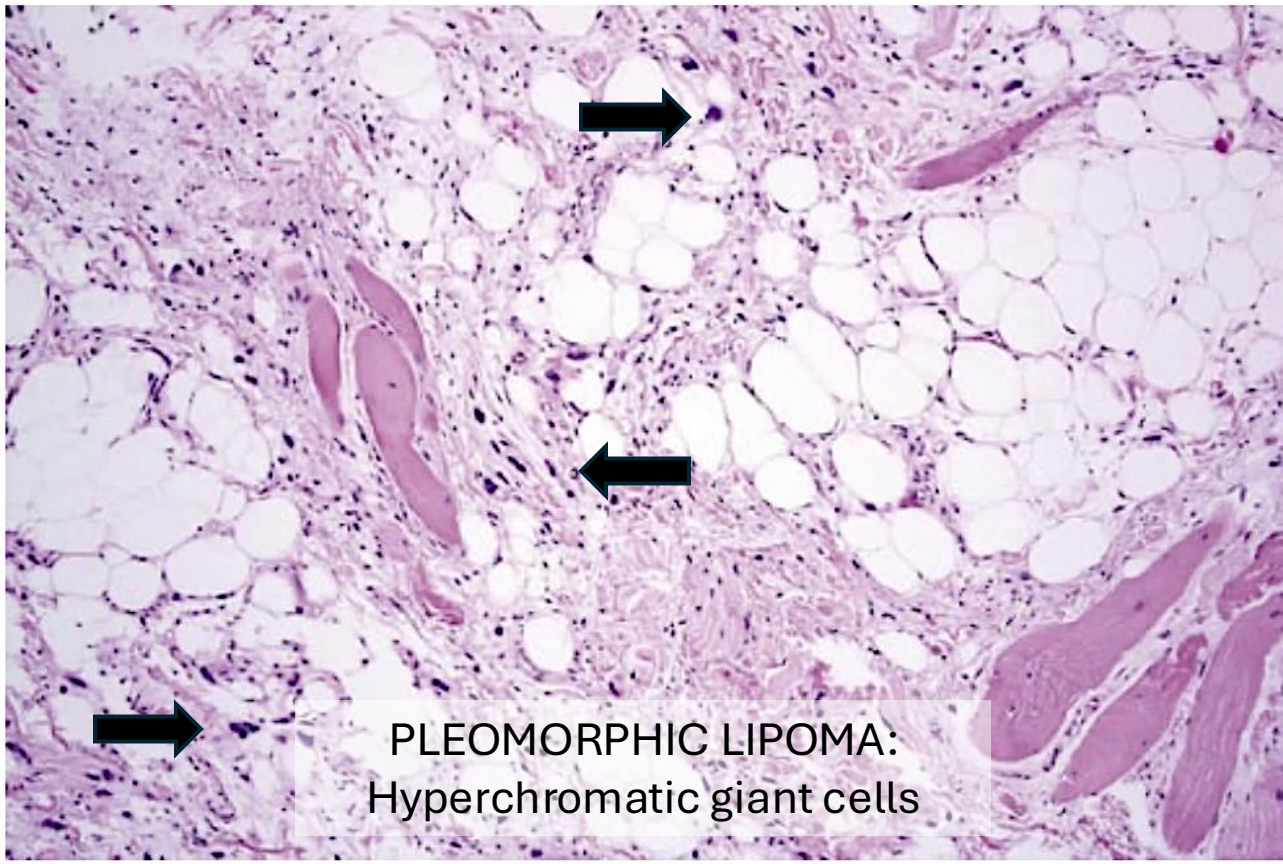
- Uncommon variants of lipoma (benign)
- Histologically concerning to the novice
- Posterior neck, shoulder or upper back of adult males
- Aberrant structure of chromosomes 13 and 16
- DDX: liposarcoma, soft tissue neoplasm NOS
- IHC: spindle cells CD34+, S100-



Admixture of mature adipocytes, spindle cells and collagen bundles



SPINDLE CELL LIPOMA:
Collagen bundles

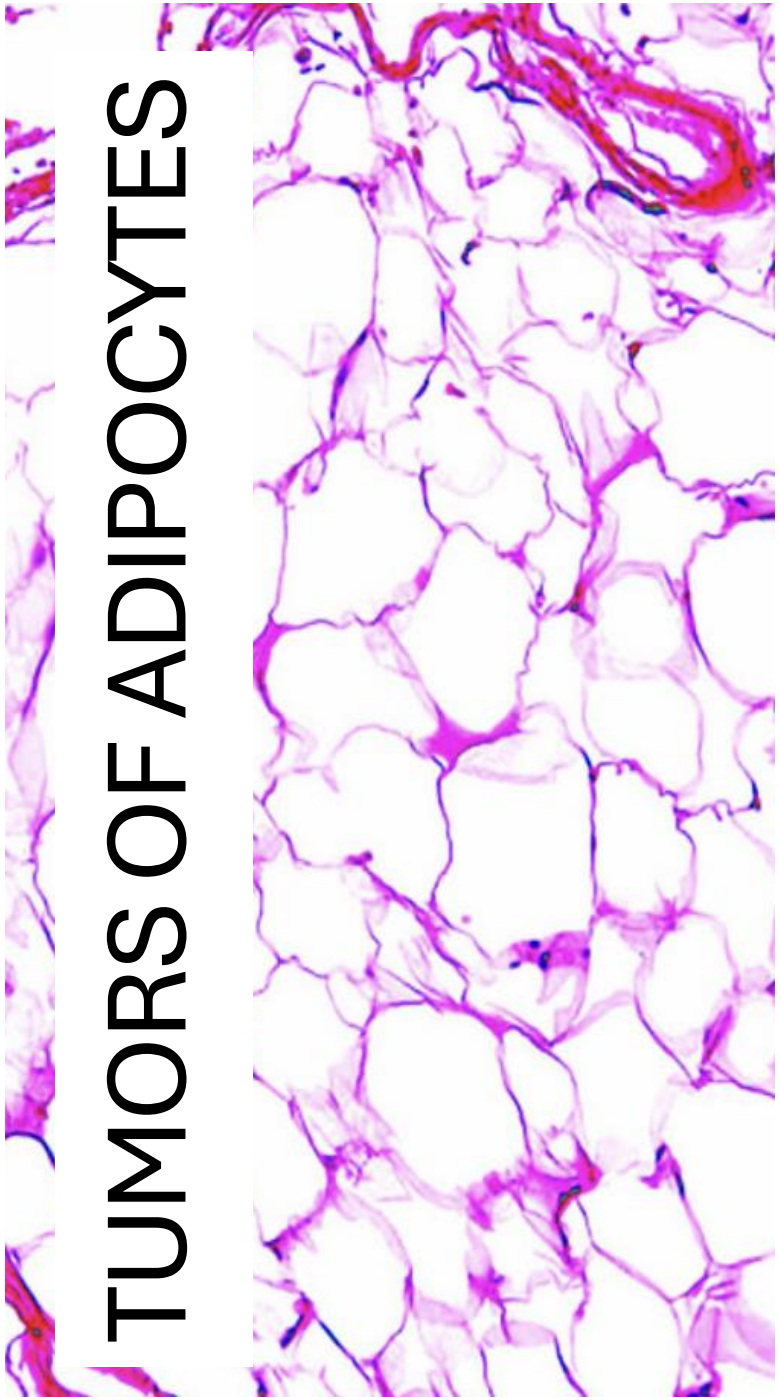


PLEOMORPHIC LIPOMA:
Hyperchromatic giant cells

Morphologic continuum

- Ill-defined subcutaneous mass
- Univacuolated adipocytes and slender spindled cells
- Collagen bundles
- Myxoid degeneration (pseudovascular spaces)
- Fat and vascular components may vary
- Mast cells

TUMORS OF ADIPOCYTES



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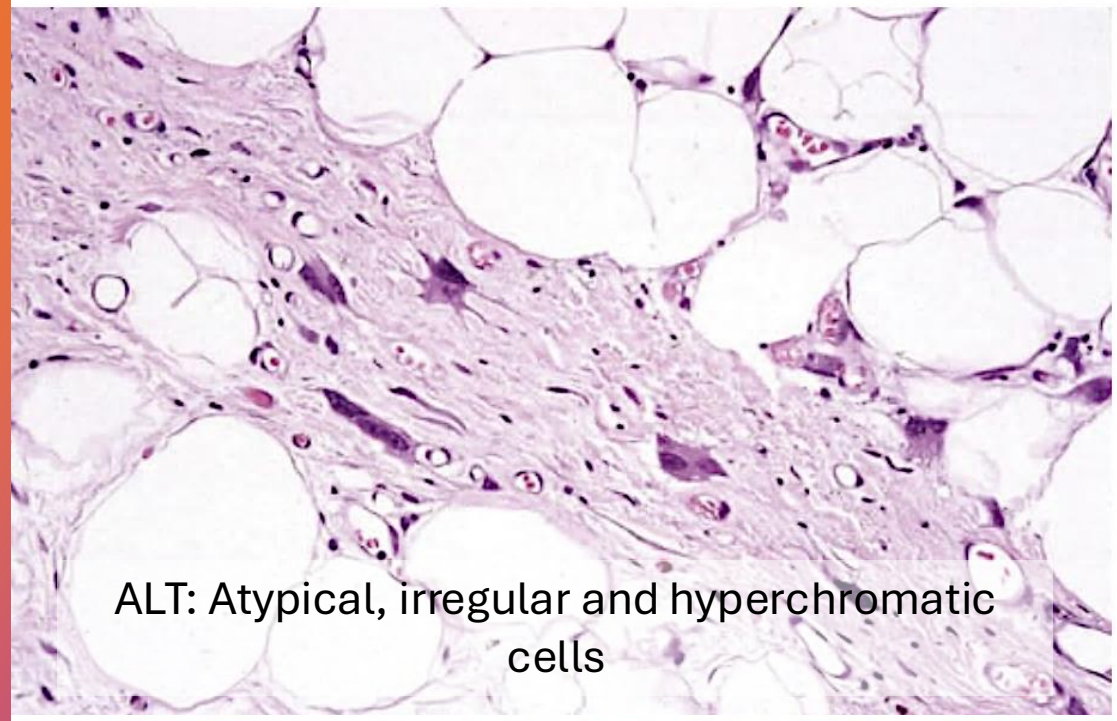
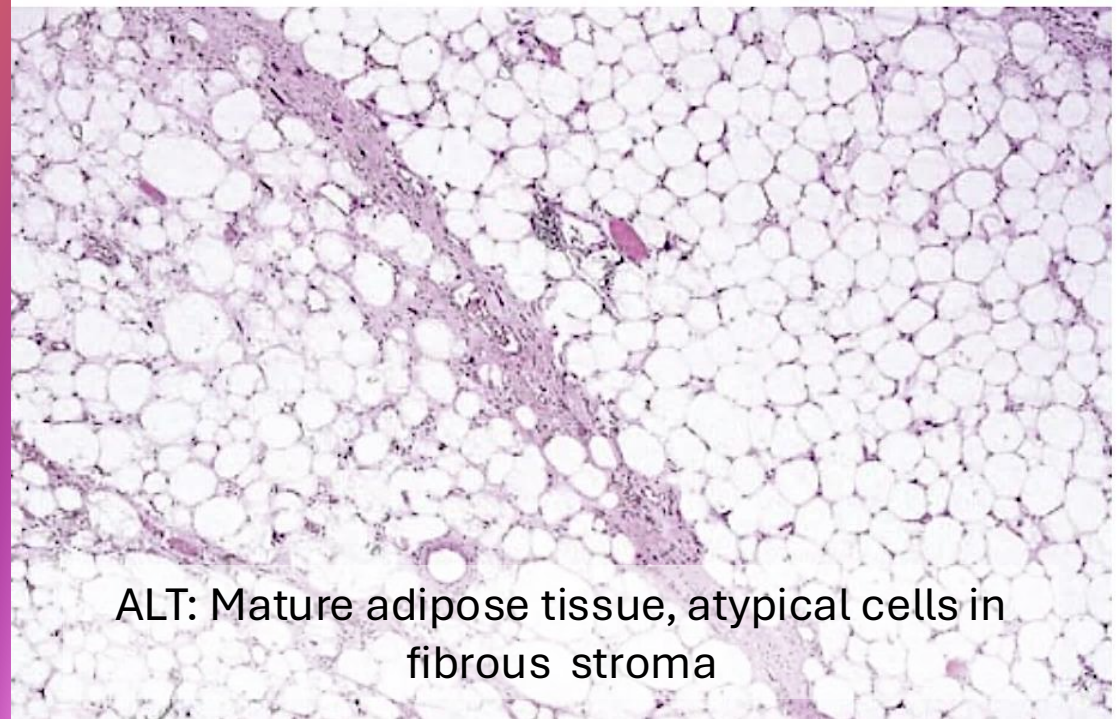
- Atypical lipomatous tumor
  Atypical spindle cell lipomatous tumor
- Liposarcoma



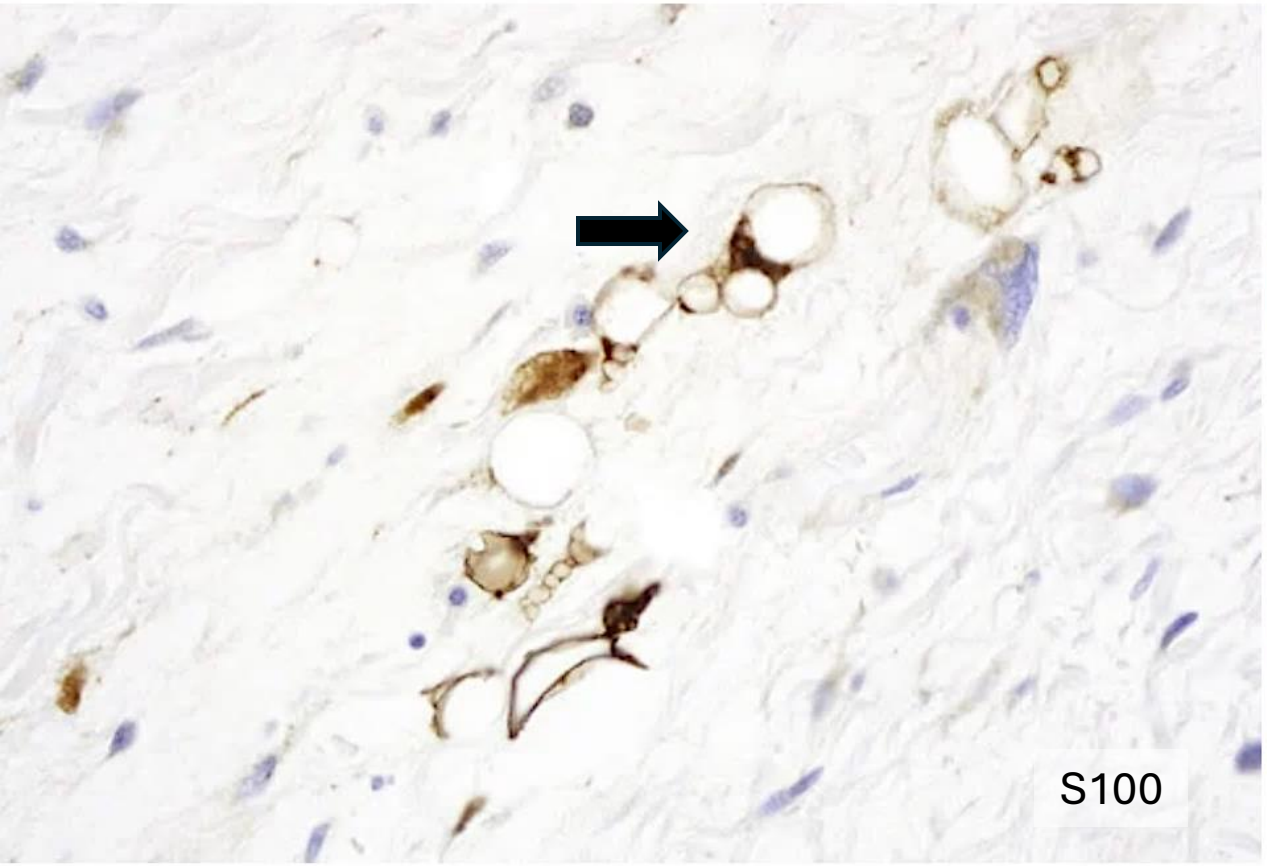
ALT: Atypical, irregular and hyperchromatic cells

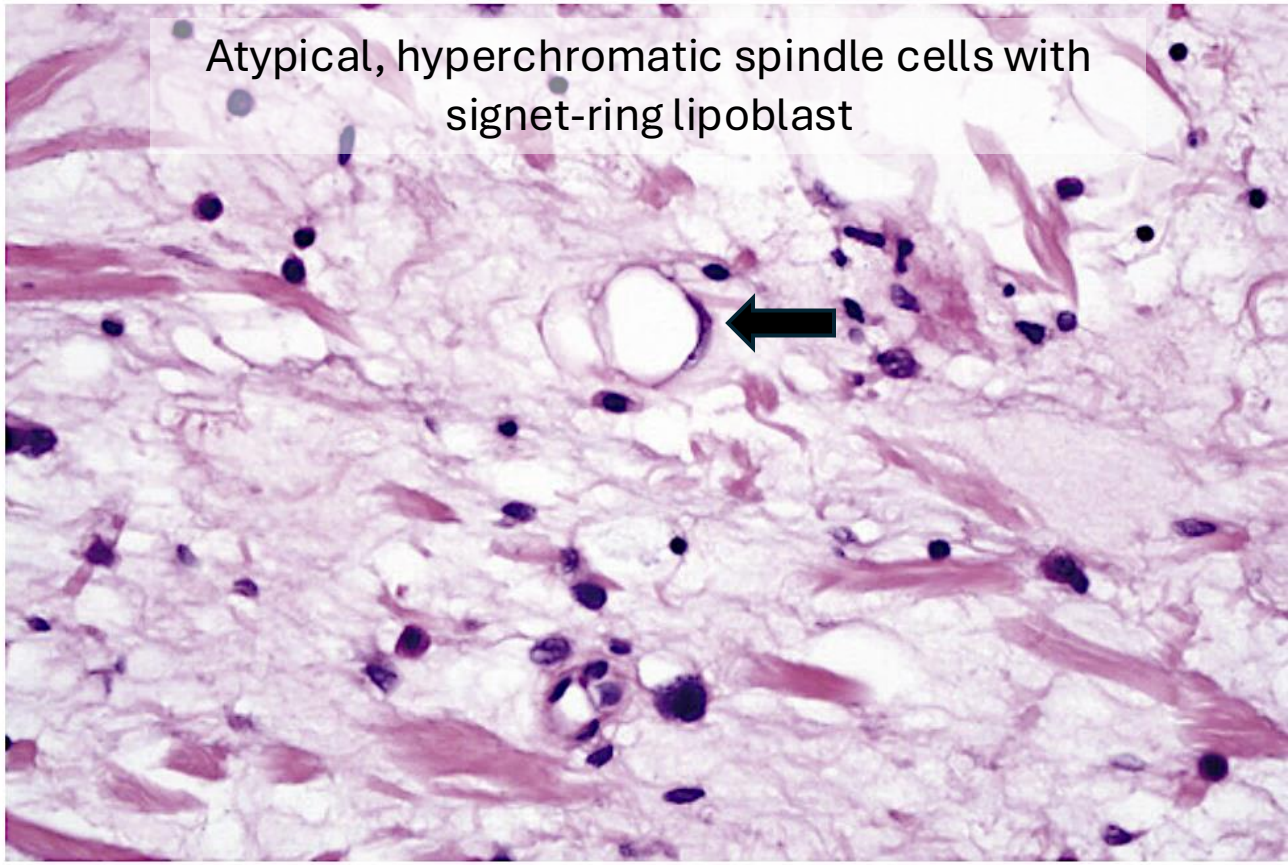


ALT: Mature adipose tissue, atypical cells in fibrous stroma

ADIPOCYTIC TUMORS OF INTERMEDIATE MALIGNANCY

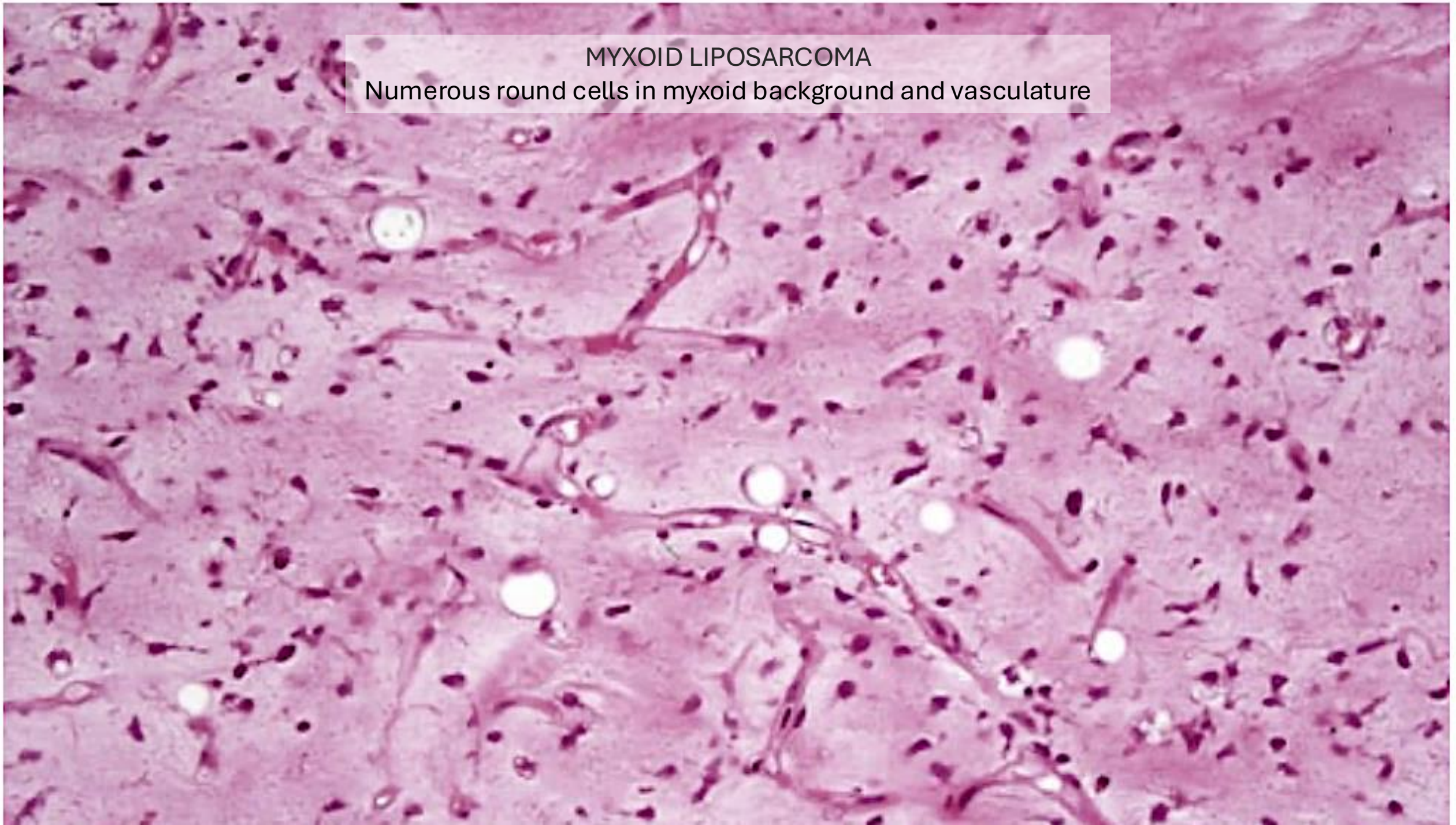
- Locally aggressive, no metastatic potential
  - Atypical lipomatous tumor (ALT)
  - Atypical spindle cell lipomatous tumor
- Local recurrence, if incompletely excised
- Deep seated: subcutis, skeletal muscle, retroperitoneum, mediastinum, and spermatic cord
- Older males, trunk
- Ring 12q13~15, amplified *MDM2* and *CDK4* (IHC+)
- DDX: Lipoma (lochkorn cells)

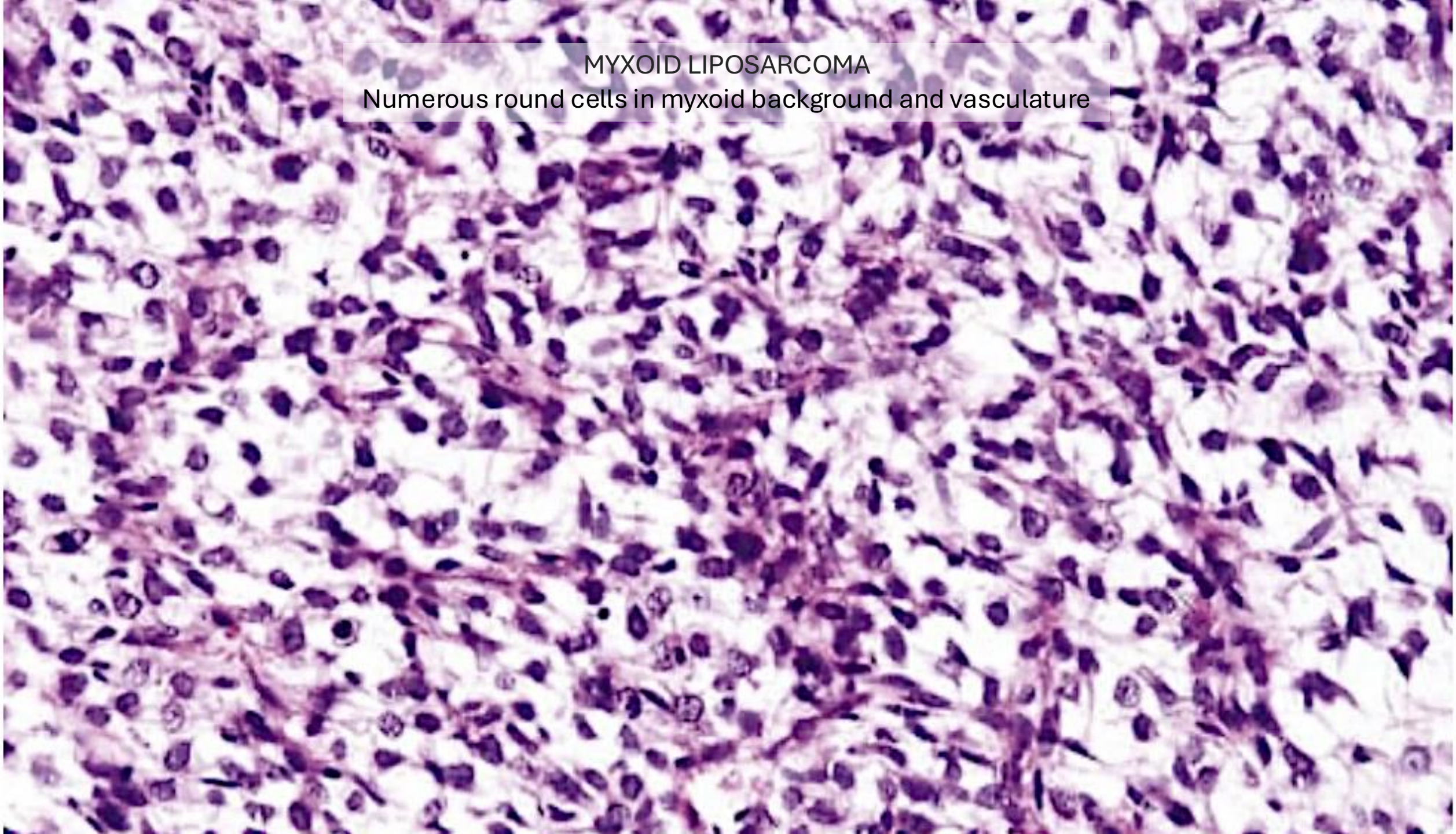




ATYPICAL SPINDLE CELL LIPOMATOUS TUMOR

- Middle-aged males: hands, feet and limb girdles
- Local recurrence: 12%, no metastatic potential
- Heterozygous deletion of *RB1* (loss of expression by IHC)
- IHC: RB1-, CD34+, S100+, MDM2 ±, CDK4±
- DDX: pleomorphic lipoma, DFSP, low-grade malignant peripheral nerve sheath tumor, low-grade dedifferentiated liposarcoma


MYXOID LIPOSARCOMA
Numerous round cells in myxoid background and vasculature



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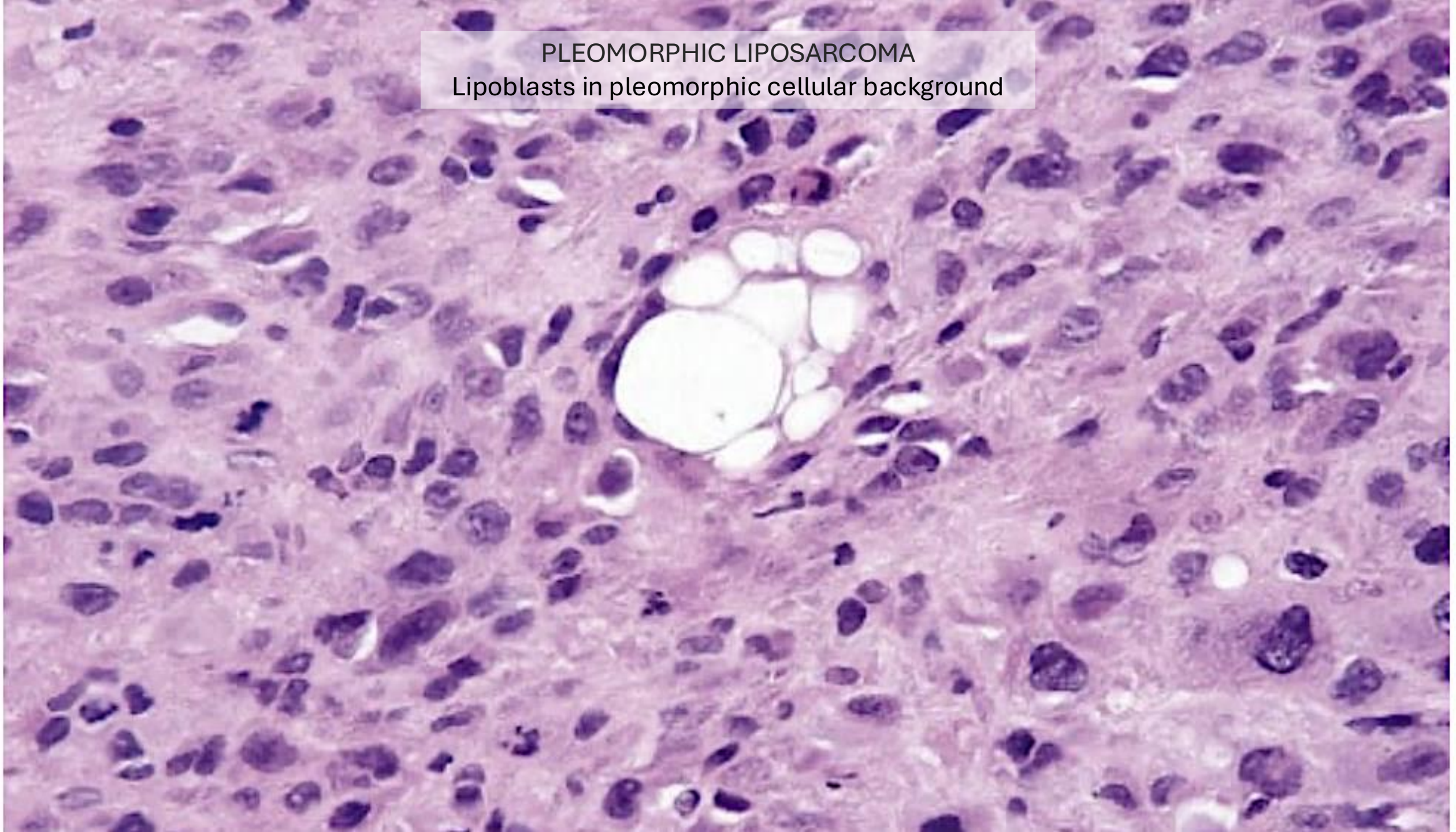

PLEOMORPHIC LIPOSARCOMA
Lipoblasts in pleomorphic cellular background

LIPOSARCOMA VARIANTS

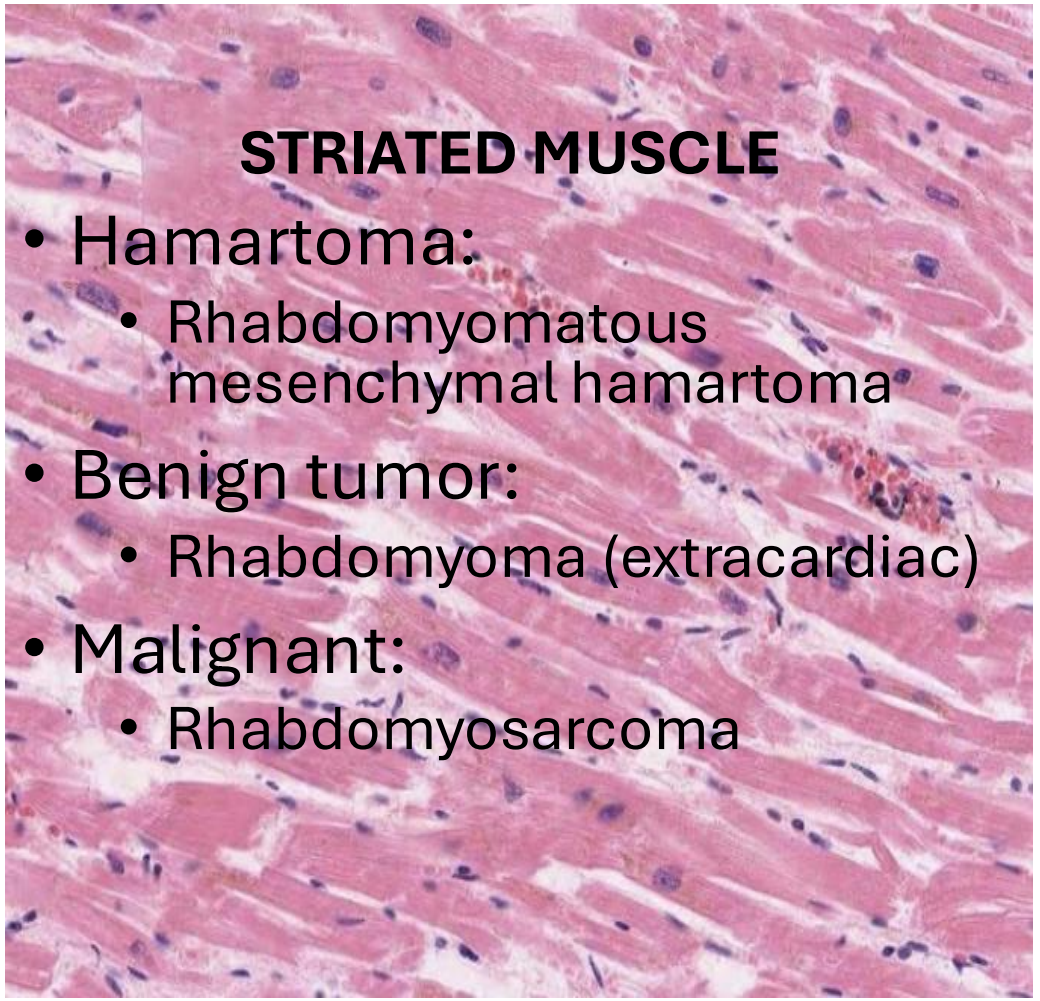
- ALT/Dedifferentiated/Well-differentiated
  - Abrupt transition to high-grade, nonlipogenic sarcoma
  - IHC: MDM2+, CDK4+
- Myxoid
  - Middle-aged adults, rare in children
  - Lower limb, thigh
  - ‘Crows-feet’ pattern small thin-walled capillaries
  - Local recurrence
  - 30% metastasize
  - Poor prognosis: p53 overexpression, necrosis
- Pleomorphic
  - Elderly, deep-seated, limbs
  - Rapid growth, high local recurrence and metastasis

- DDX: atypical lipomatous tumor, other soft tissue neoplasms (fat-free) myxofibrosarcoma

TUMORS OF MUSCLE

SMOOTH MUSCLE

- Hamartoma:
  - Congenital smooth muscle hamartoma
- Benign tumor:
  - Pilar leiomyoma
  - Vascular leiomyoma
  - Genital leiomyoma
- Malignant:
  - Leiomyosarcoma

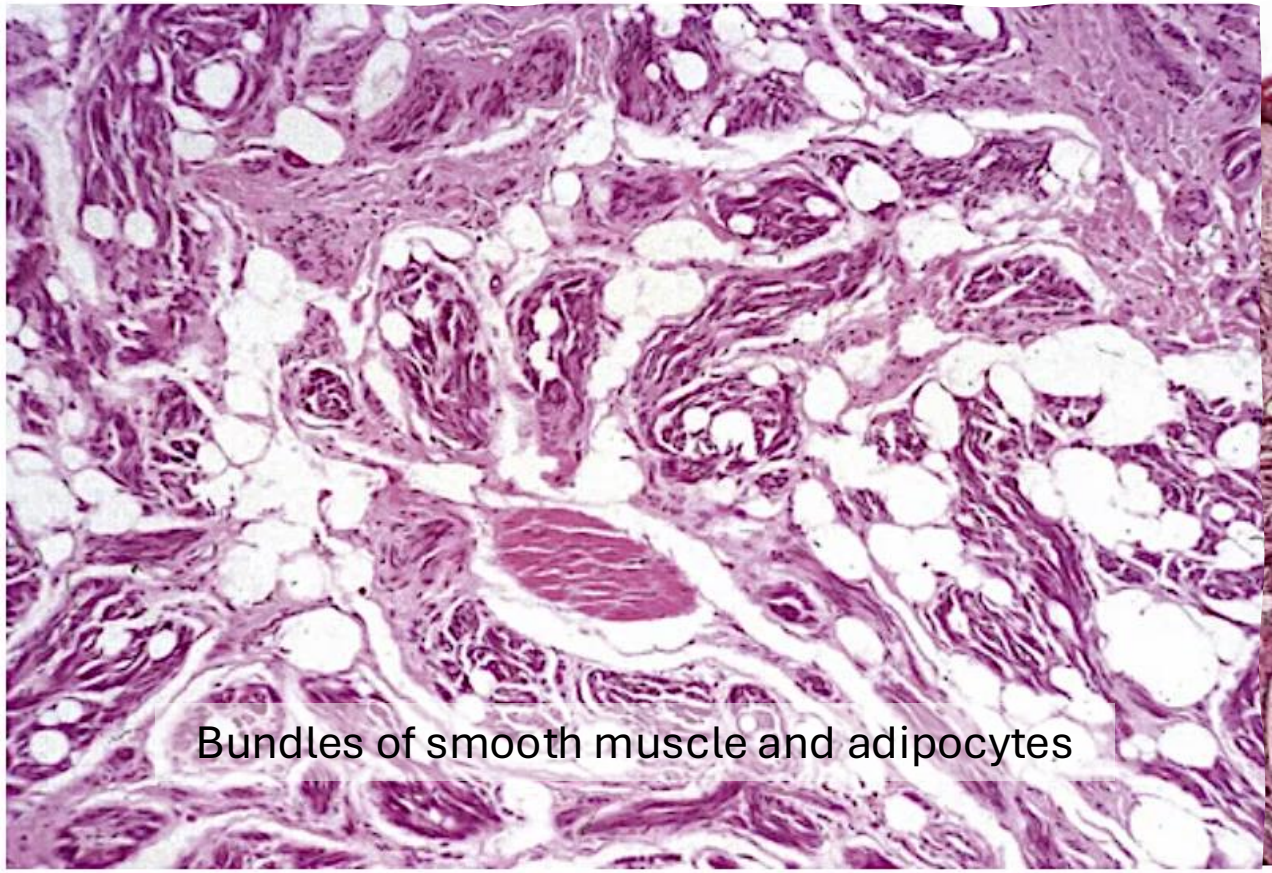


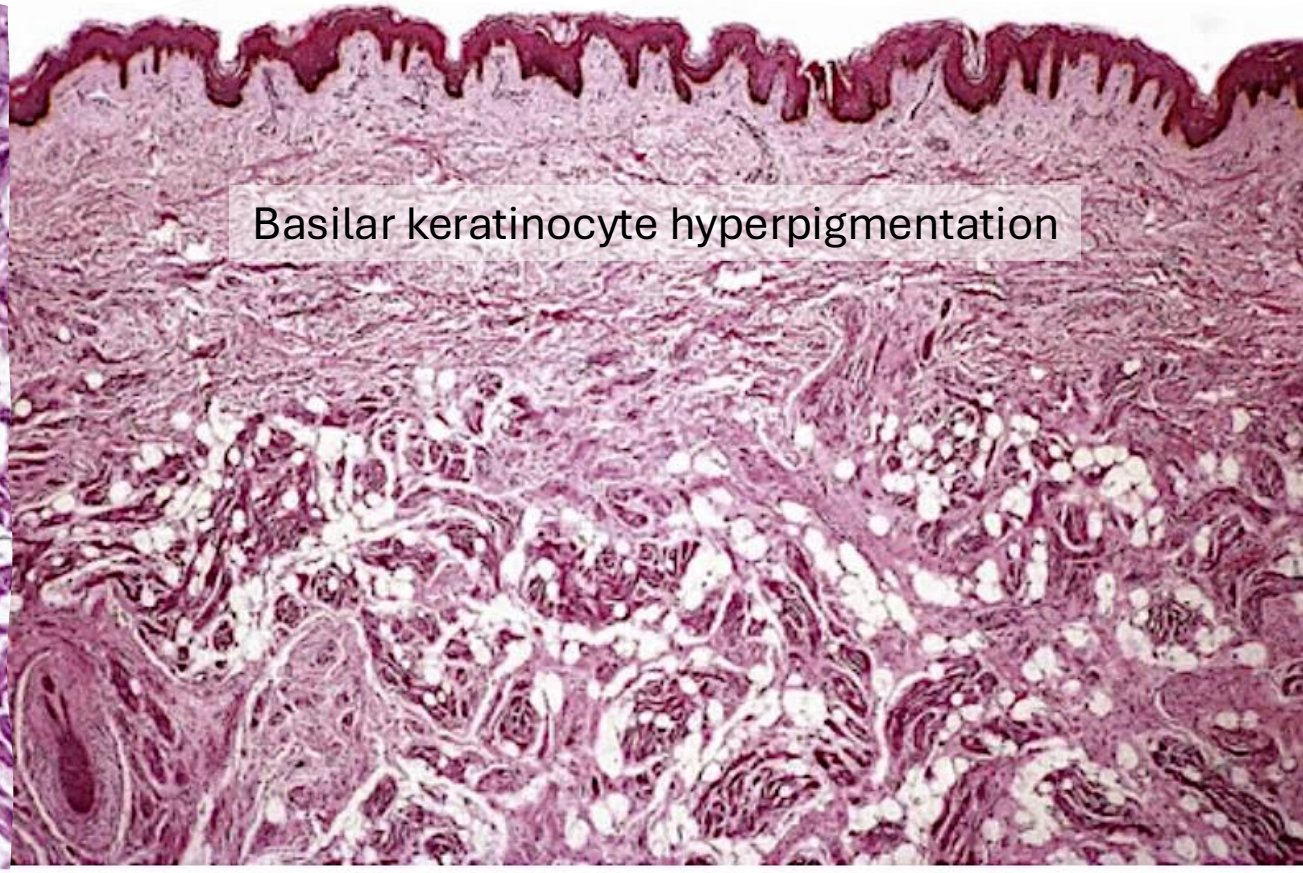
STRIATED MUSCLE

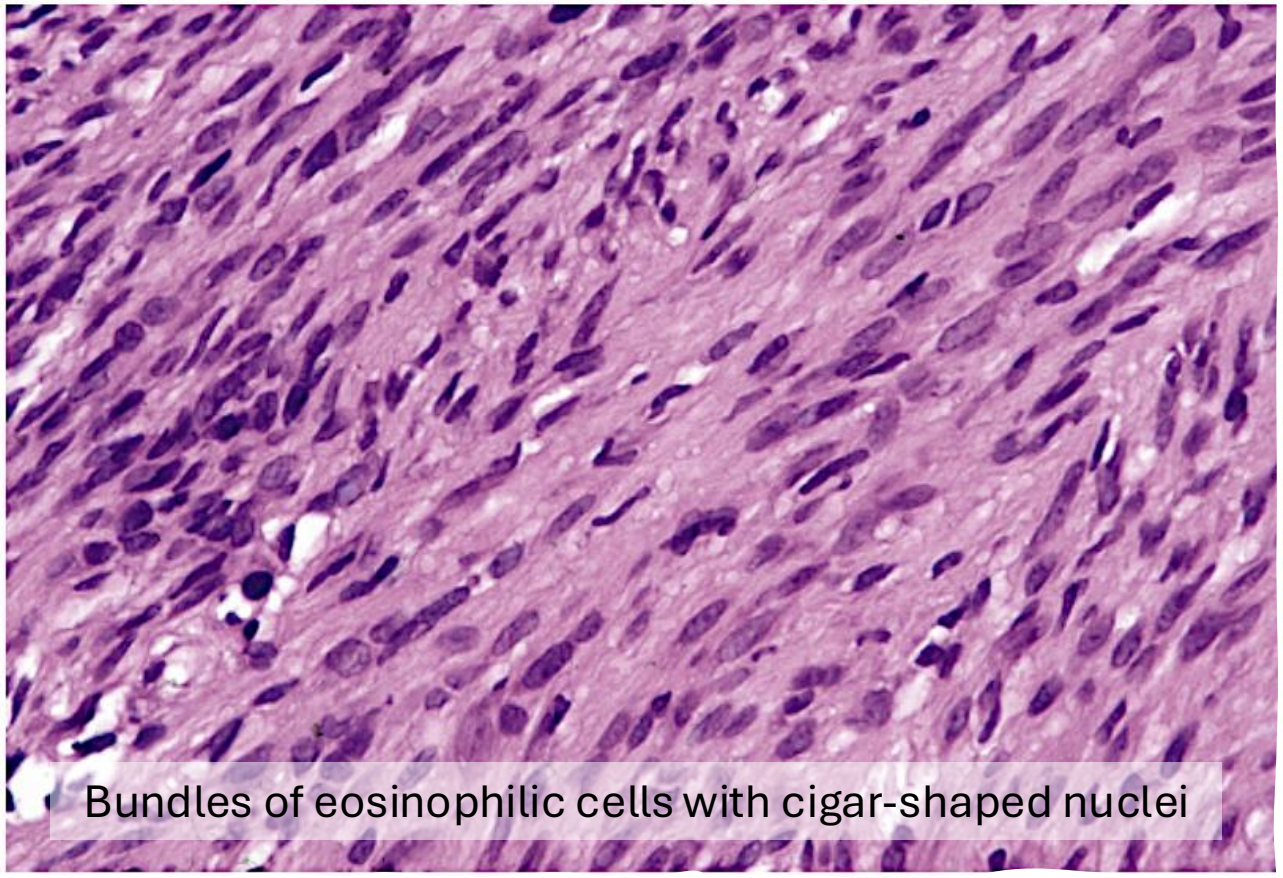
- Hamartoma:
  - Rhabdomyomatous mesenchymal hamartoma
- Benign tumor:
  - Rhabdomyoma (extracardiac)
- Malignant:
  - Rhabdomyosarcoma

CONGNEITAL SMOOTH MUSCLE HAMARTOMA

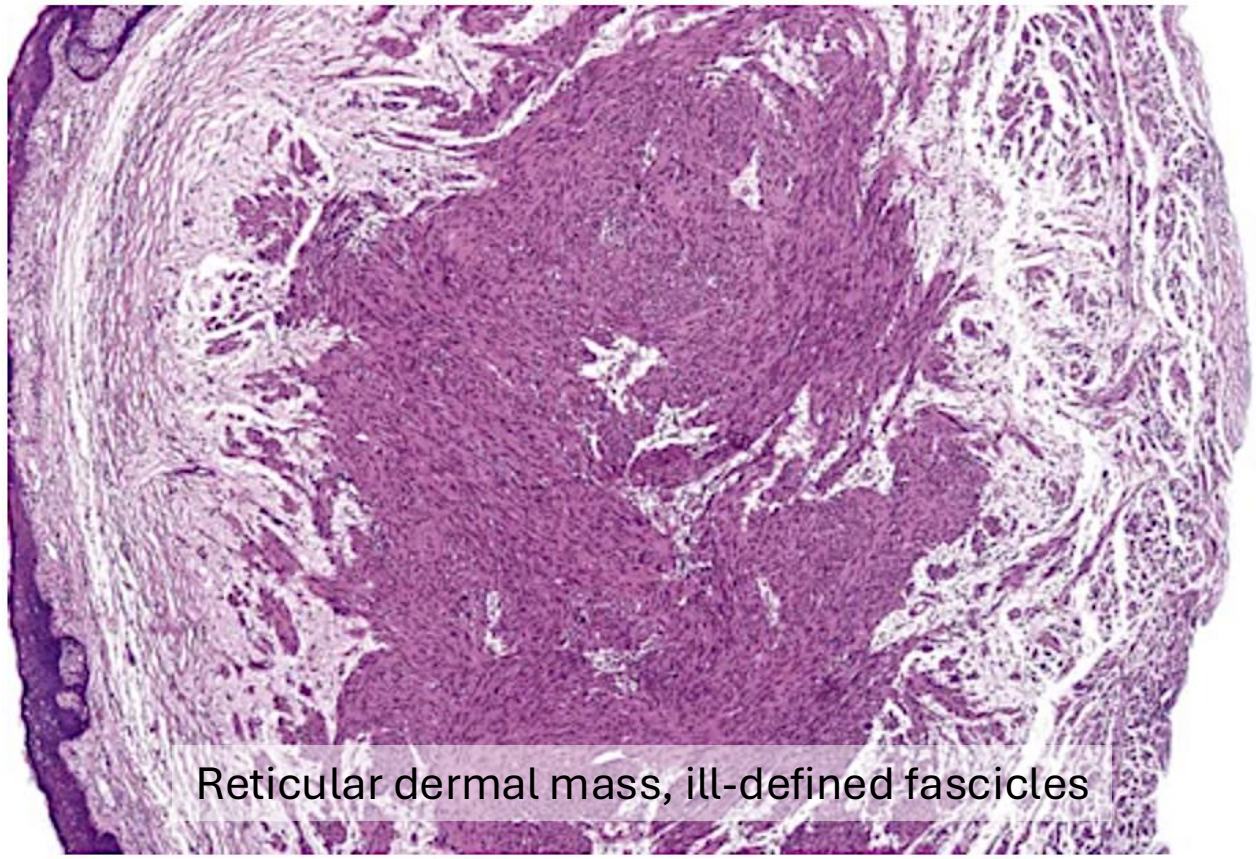
- Male infants
- Lumbosacral, proximal thighs
- Indurated, hyperpigmented macule/plaque with coarse hairs
- DDX: Becker nevus (acquired, hypertrichosis, subtle histology)
- IHC: SMA+, desmin+, and h-caldesmon+ (smooth muscle)







Bundles of eosinophilic cells with cigar-shaped nuclei

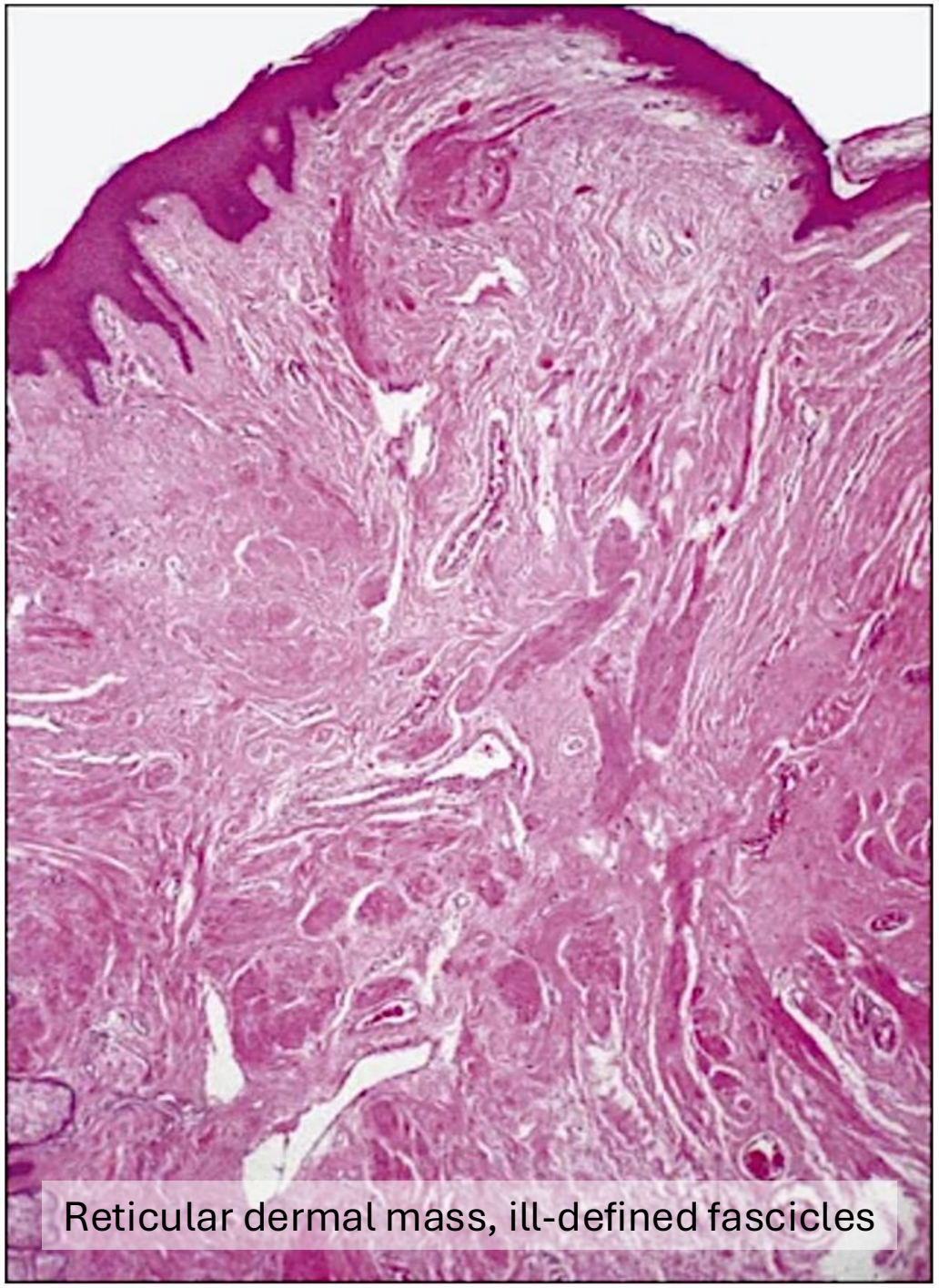


Reticular dermal mass, ill-defined fascicles

PILAR LEIOMYOMA

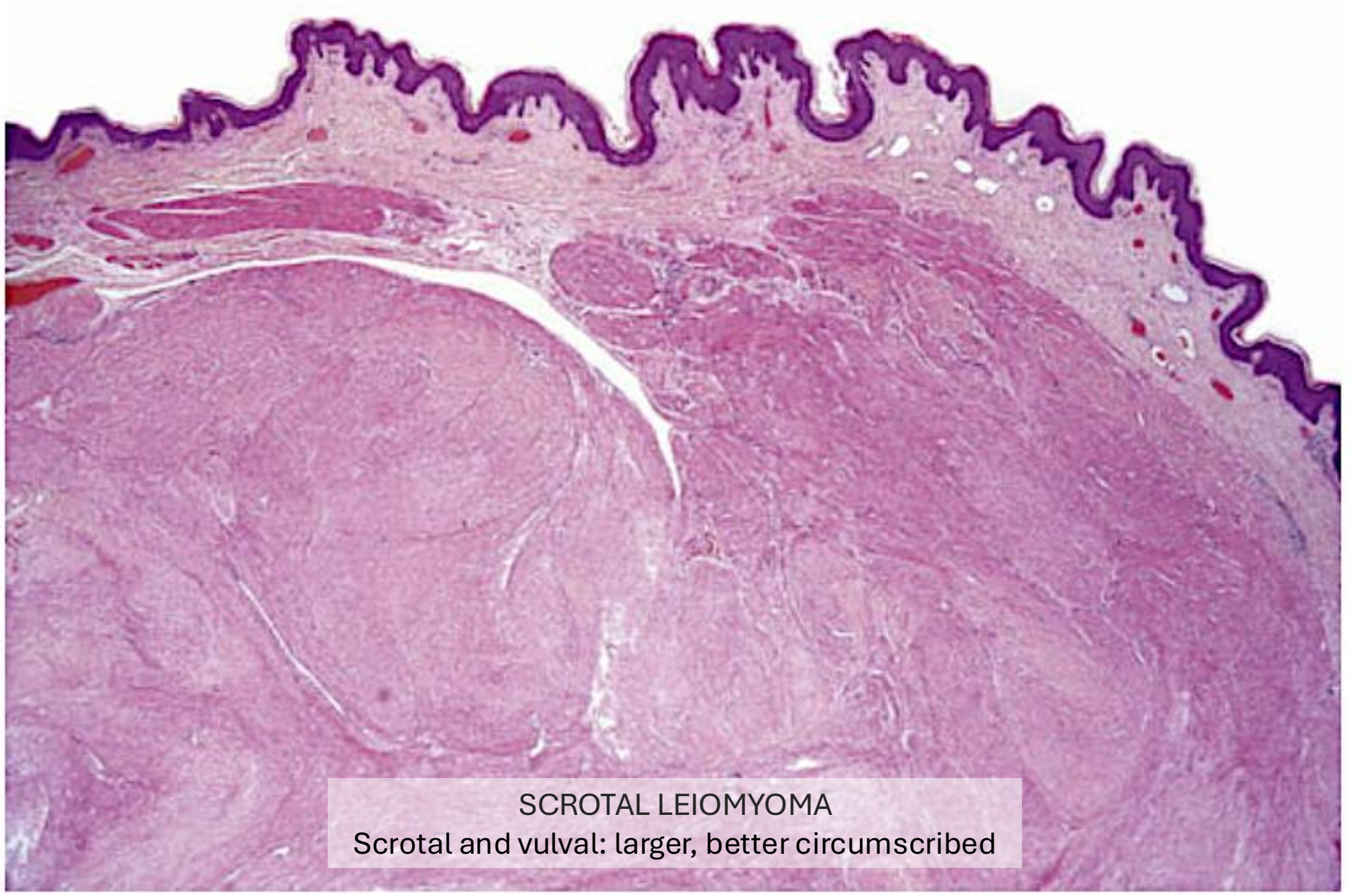
IHC: SMA+, desmin+, and h-caldesmon+, S100A6-

- Young adults, limbs or trunk
- Can present as multiple papules, painful/tender (cold or compressed)
- Hereditary leiomyomatosis and renal cell cancer (HLRCC), *FH* (1q42.3~q43):
  - Cutaneous and uterine leiomyomas, renal cell carcinoma
- Fumarate hydratase deficiency (tricarboxylic acid cycle):
  - TS gene and DNA damage response
- DDX: DF, dermatomyofibroma, cellular neurofibroma, leiomyosarcoma (atypical intradermal smooth muscle neoplasm: less mitoses and nuclear pleomorphism)


Reticular dermal mass, ill-defined fascicles

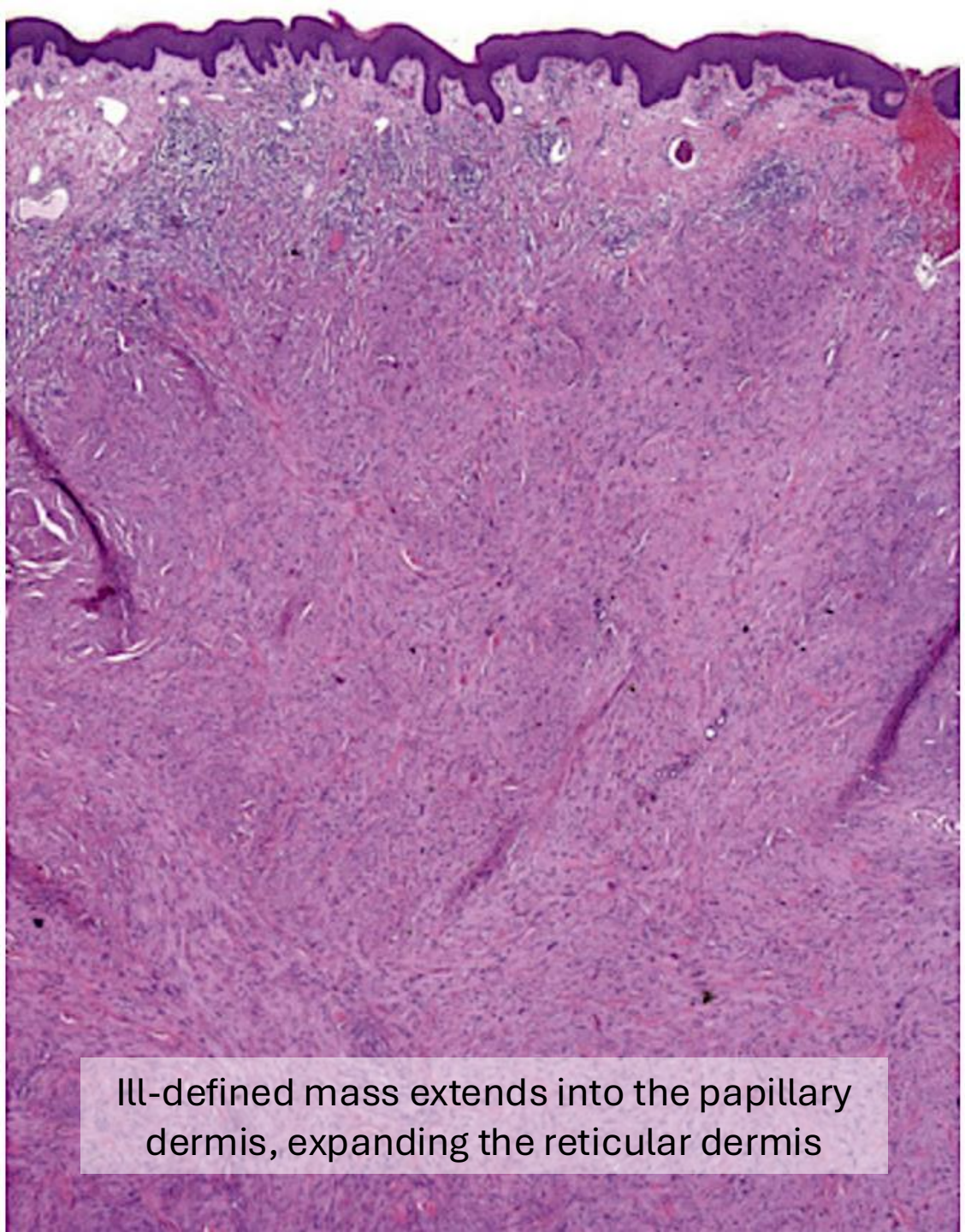
GENITAL LEIOMYOMA

- Originates from the smooth muscle:
  - scrotum (dartos muscle)
  - vulva (labia majora) or
  - nipple
- Middle-aged adults
- Multiple leiomyomas of the vulva (Alport syndrome)



SCROTAL LEIOMYOMA

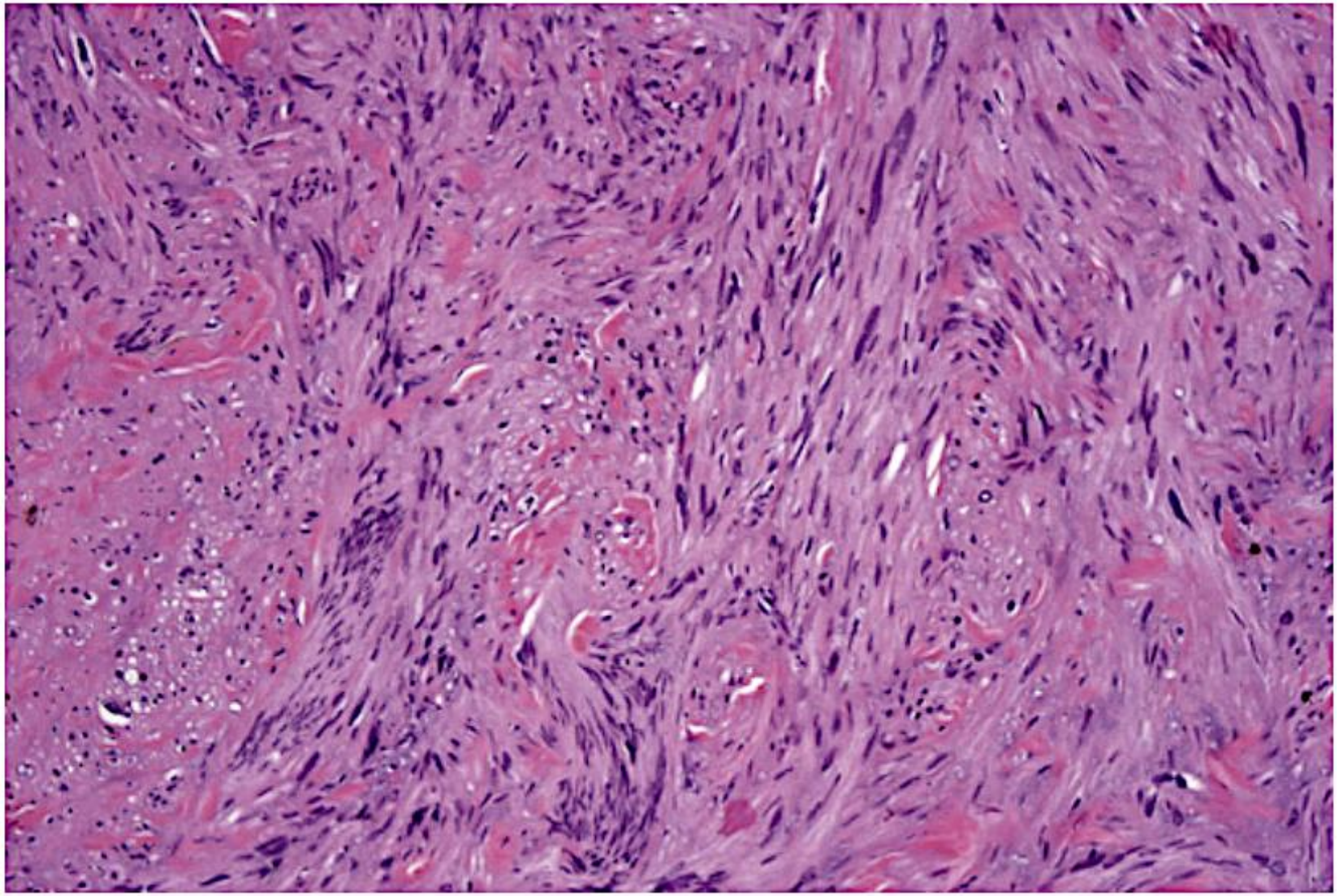
Scrotal and vulval: larger, better circumscribed



Ill-defined mass extends into the papillary dermis, expanding the reticular dermis

LEIOMYOSARCOMA

- **Deep**: abdomen and retroperitoneum
- **Superficial**:
  - Cutaneous: leiomyosarcoma of the nipple
    - Arrector pili origin
    - Middle-aged males
    - Trunk and limbs
    - Local recurrence common
      - Margin status critical (> 1 cm)
      - Mohs with follow-up
  - Subcutaneous: scrotal and vulval variants related to deep
    - Vein wall origin
    - Older adult males, thighs
    - Larger than cutaneous lesions
    - Local recurrence common
    - 50% metastasize (mortality 30-50%)
- Metastasis rare (to skin)



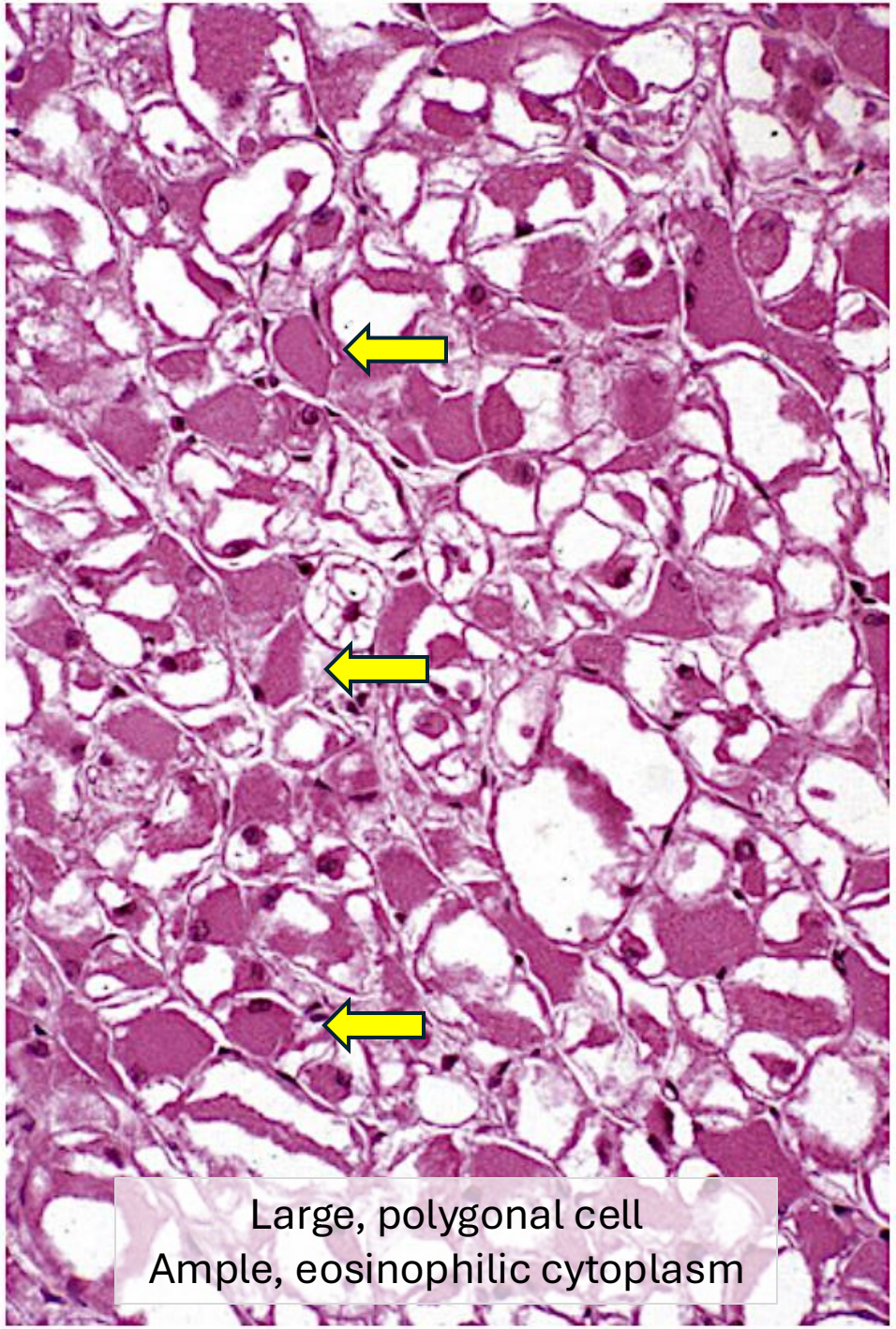
Eosinophilic spindled cells with hyperchromatic and pleomorphic nuclei
Mitotic activity
Shares eosinophilia with leiomyoma

LEIOMYOSARCOMA

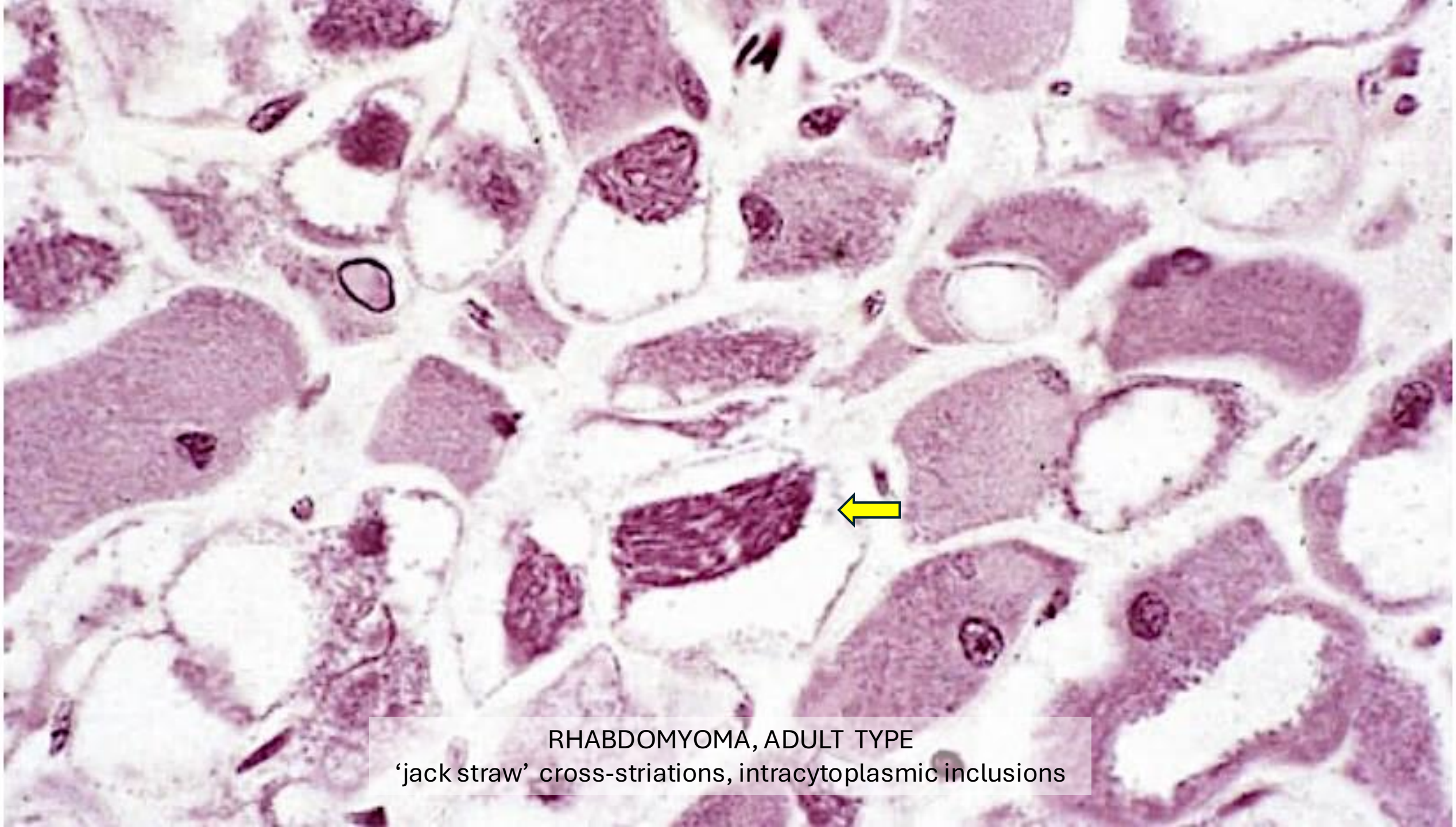
- IHC: SMA+, desmin+, and h-caldesmon+
  - PTEN- (loss)
  - P53+, S100A6+
  - ki-67 increased proliferative index
- Epithelioid variant exists
- Malignant features: necrosis and hemorrhage
- DDX: spindle cell melanoma (S100+, SOX-10+), metastatic leiomyosarcoma (needs CPC)

RHABDOMYOMA (EXTRACARDIAC)

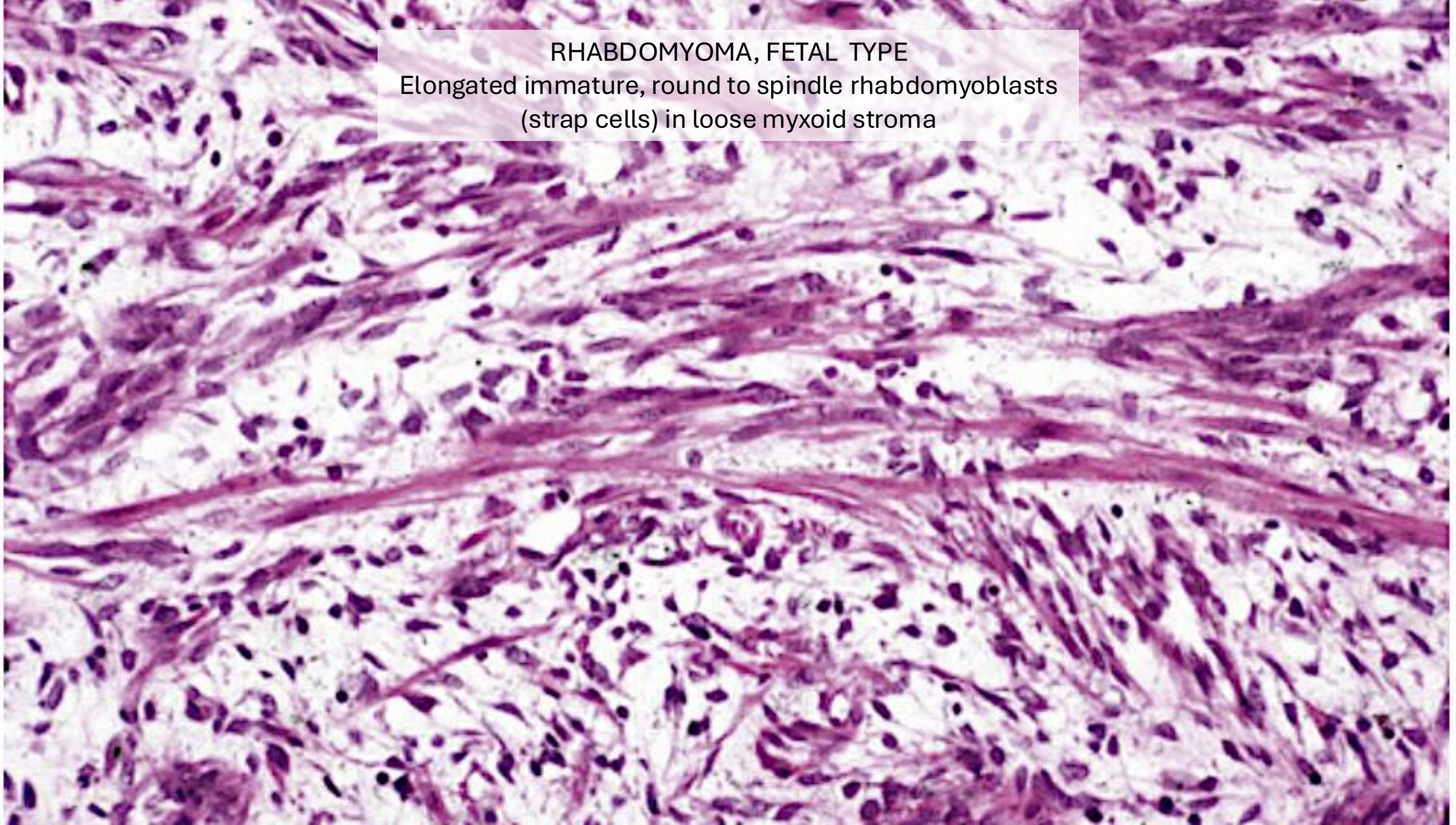
- Rare, deep-seated mass
- Genital type:
  - Middle-aged women
  - Vagina, cervix > vulva
  - Males: paratesticular soft tissue
- Adult type:
  - Older adult males
  - Head and neck, oral cavity
- Fetal type:
  - Male infants
  - Face, neck
- IHC: muscle-specific actin+, myoglobin+, desmin+
- DDX: rhabdomyosarcoma



Adult type rhabdomyoma

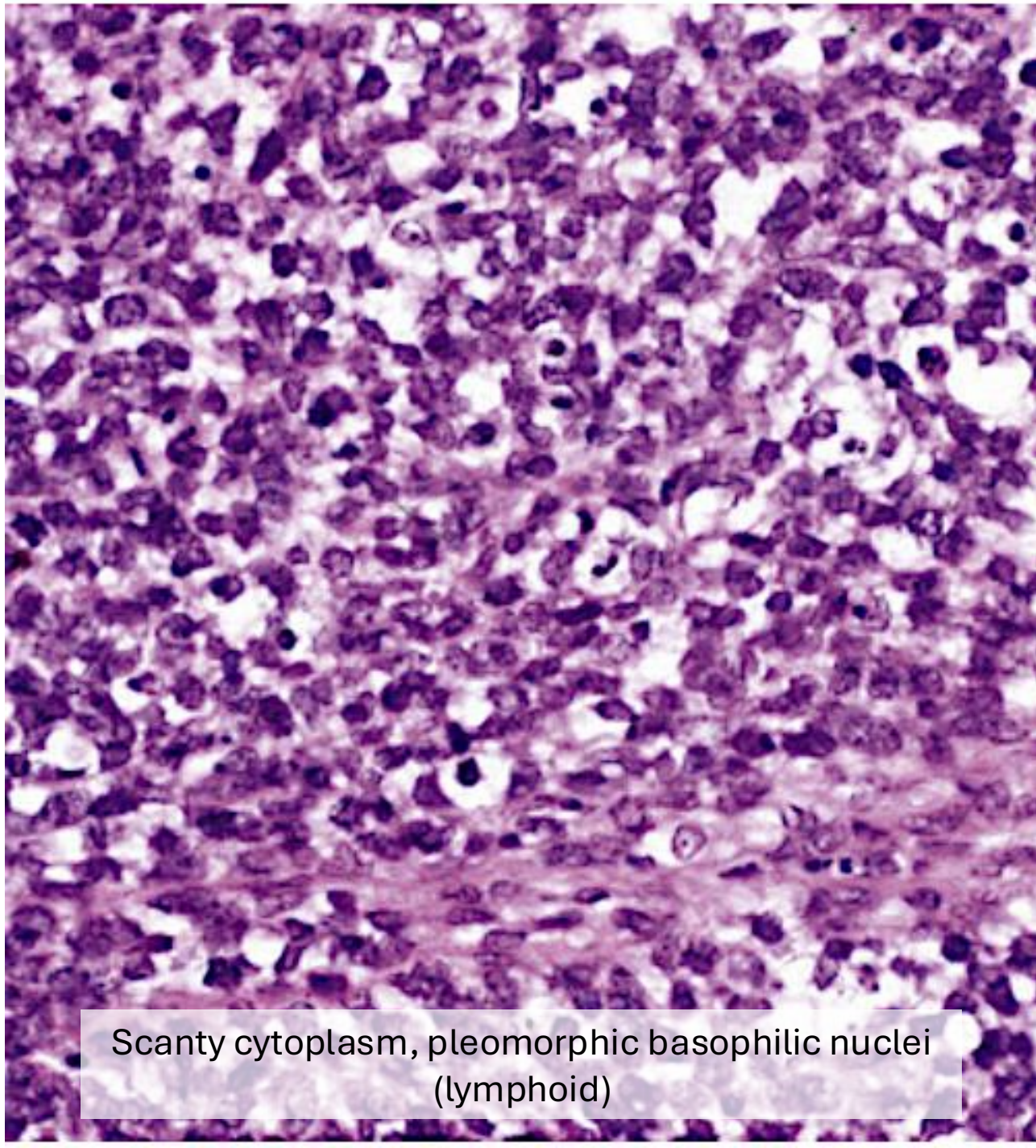


RHABDOMYOMA, ADULT TYPE
‘jack straw’ cross-striations, intracytoplasmic inclusions


RHABDOMYOMA, FETAL TYPE
Elongated immature, round to spindle rhabdomyoblasts
(strap cells) in loose myxoid stroma

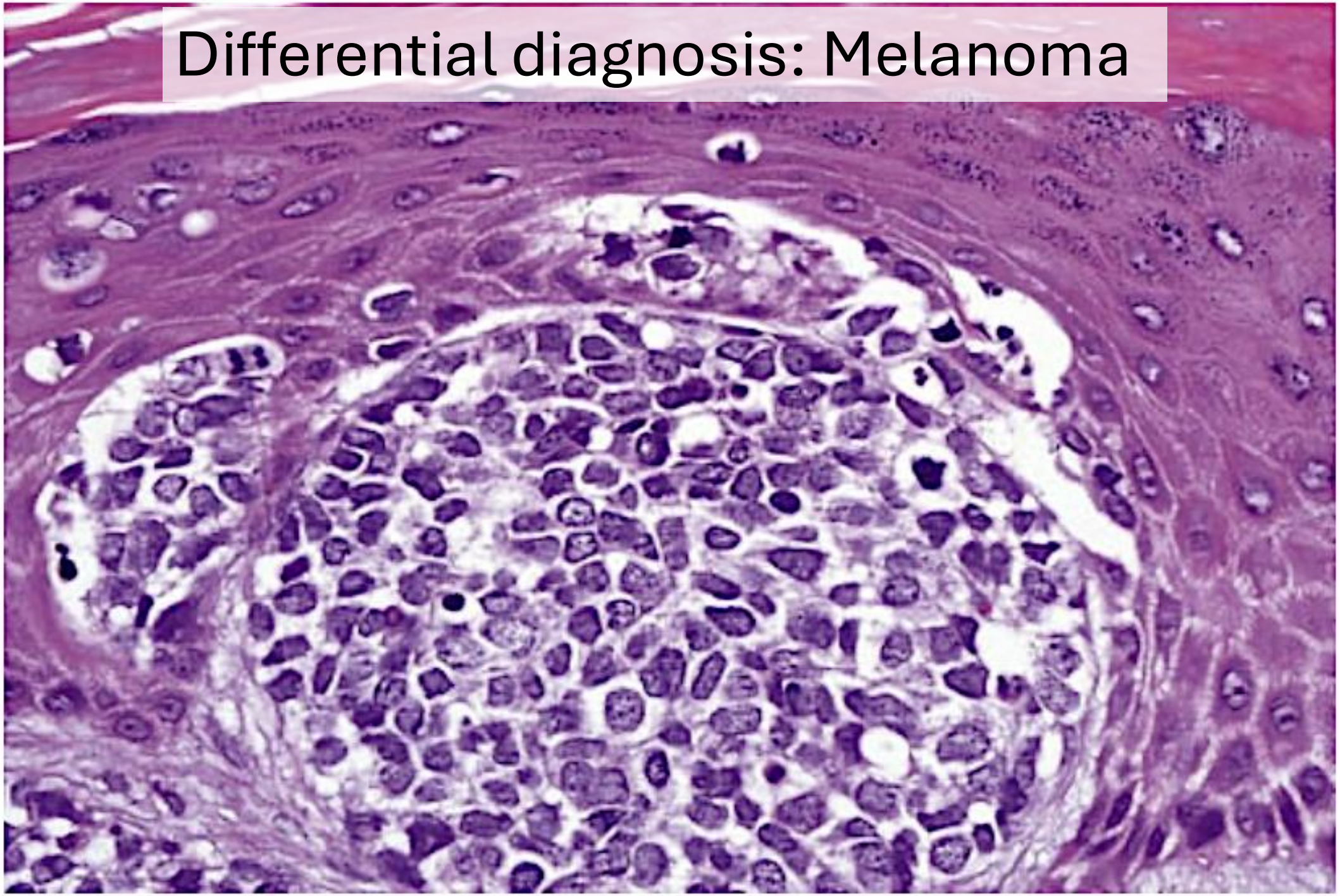
RHABDOMYOSARCOMA

- Very rare
- Bimodal age (mean): 10 and 74 years
- 4 histologic types:
  - Alveolar and embryonal (peds)
  - Pleomorphic and spindle cell/sclerosing (adults)
- Variable genetic alterations
- IHC: desmin+, MSA+, myogenin+, MyoD1
- DDX (small round cell tumor): neuroblastoma, primitive neuroectodermal tumor, MCC, lymphoma, melanoma



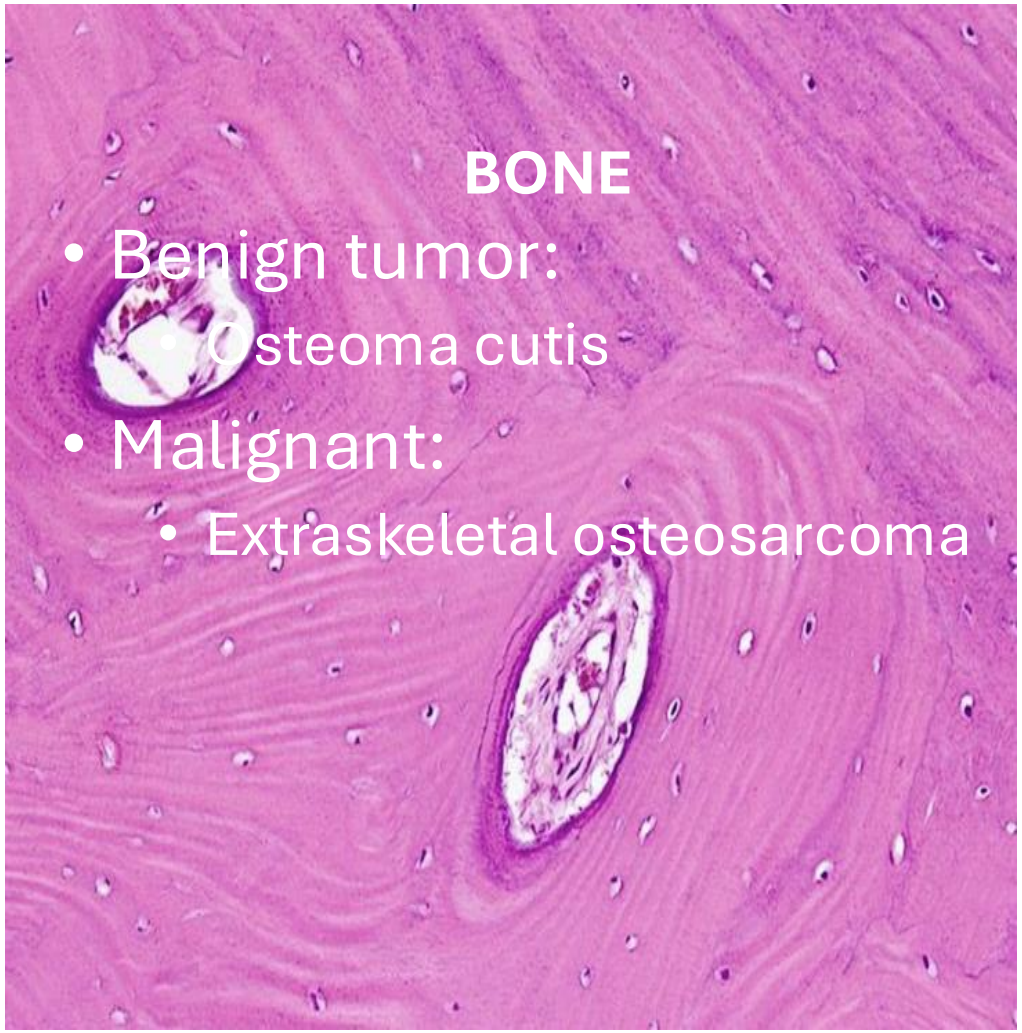
Scanty cytoplasm, pleomorphic basophilic nuclei (lymphoid)

Differential diagnosis: Melanoma



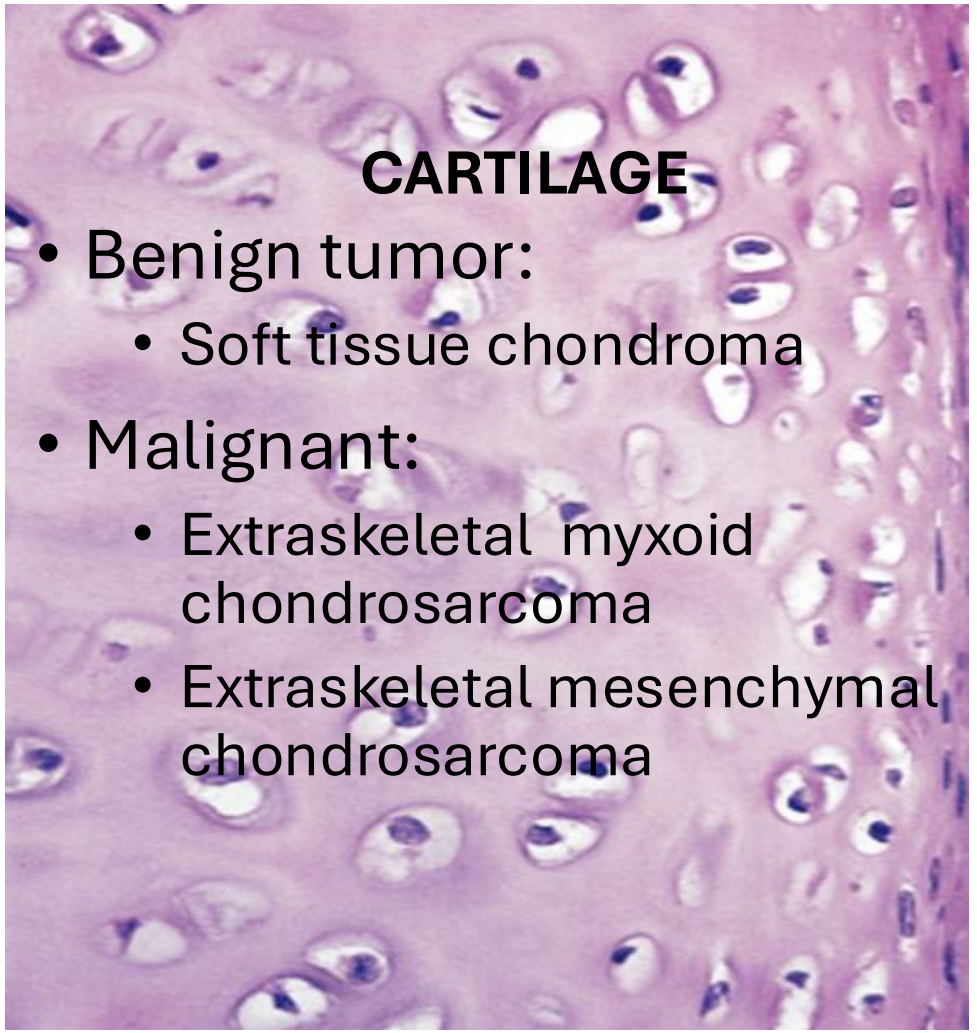
Alveola rhabdomyosarcoma

TUMORS OF BONE AND CARTILAGE



BONE

- Benign tumor:
  - Osteoma cutis
- Malignant:
  - Extraskeletal osteosarcoma

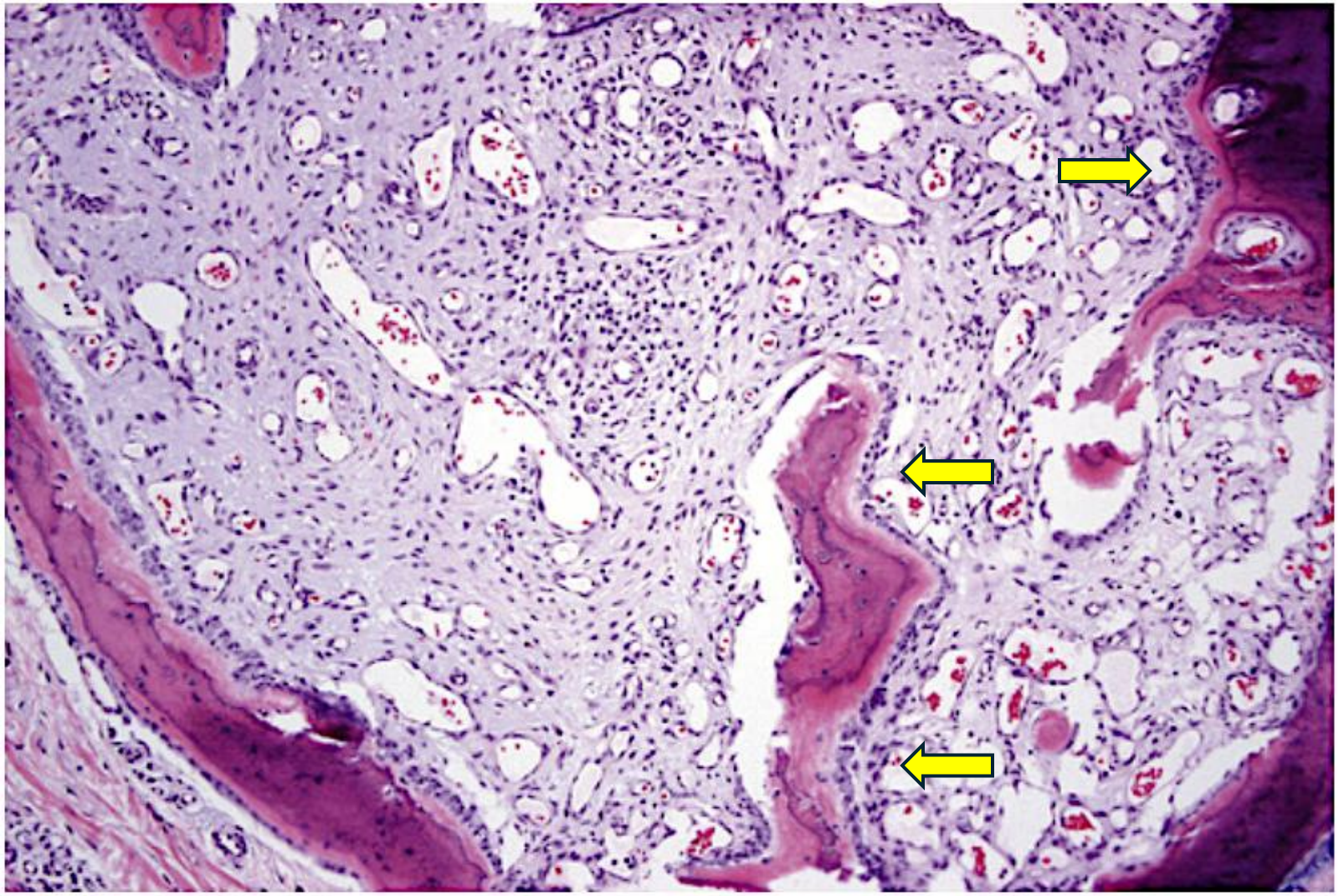


CARTILAGE

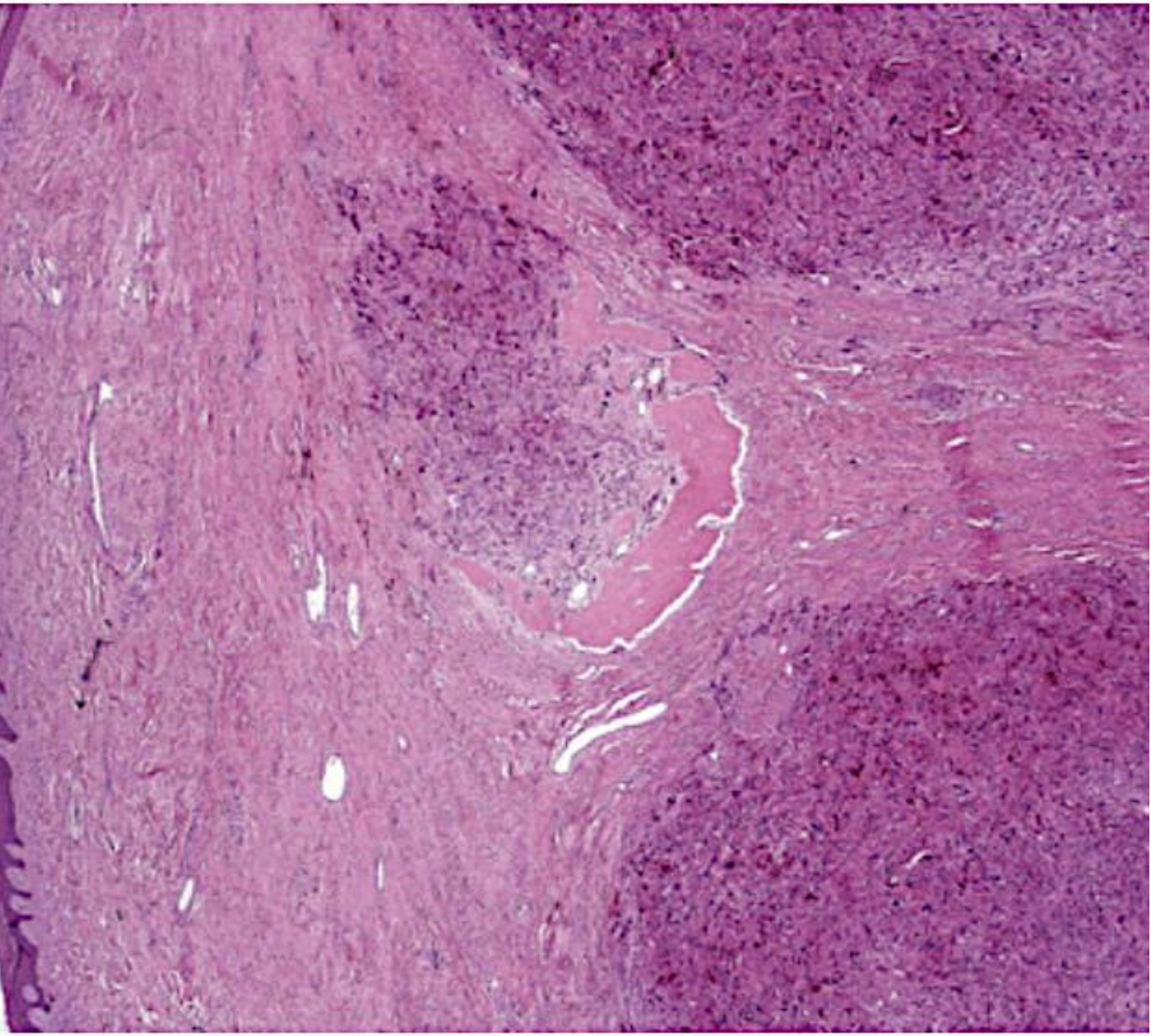
- Benign tumor:
  - Soft tissue chondroma
- Malignant:
  - Extraskeletal myxoid chondrosarcoma
  - Extraskeletal mesenchymal chondrosarcoma

TUMORS OF BONE AND CARTILAGE

- Majority of ossification in skin:
  - Secondary degenerative, e.g., osteoma cutis
  - Metaplastic process in
    - Melanocytic nevi
    - Pilomatrixoma
- Primary lesions are very rare
- Osteoma cutis-
  - Dystrophic ossification in acne and folliculitis
  - Syndromes: e.g., Albright hereditary osteodystrophy
- DDX: benign cartilaginous exostosis (osteochondroma)

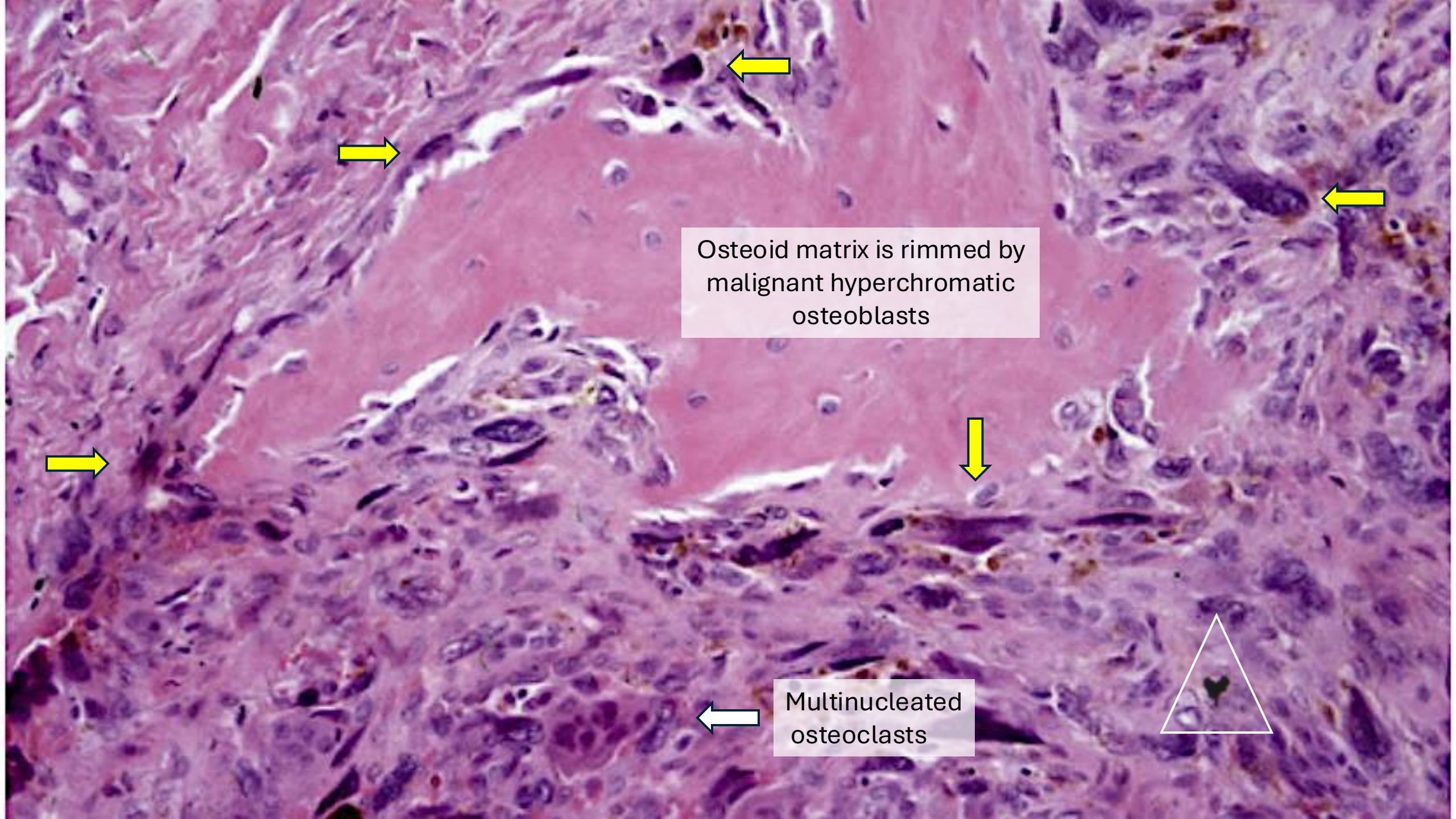


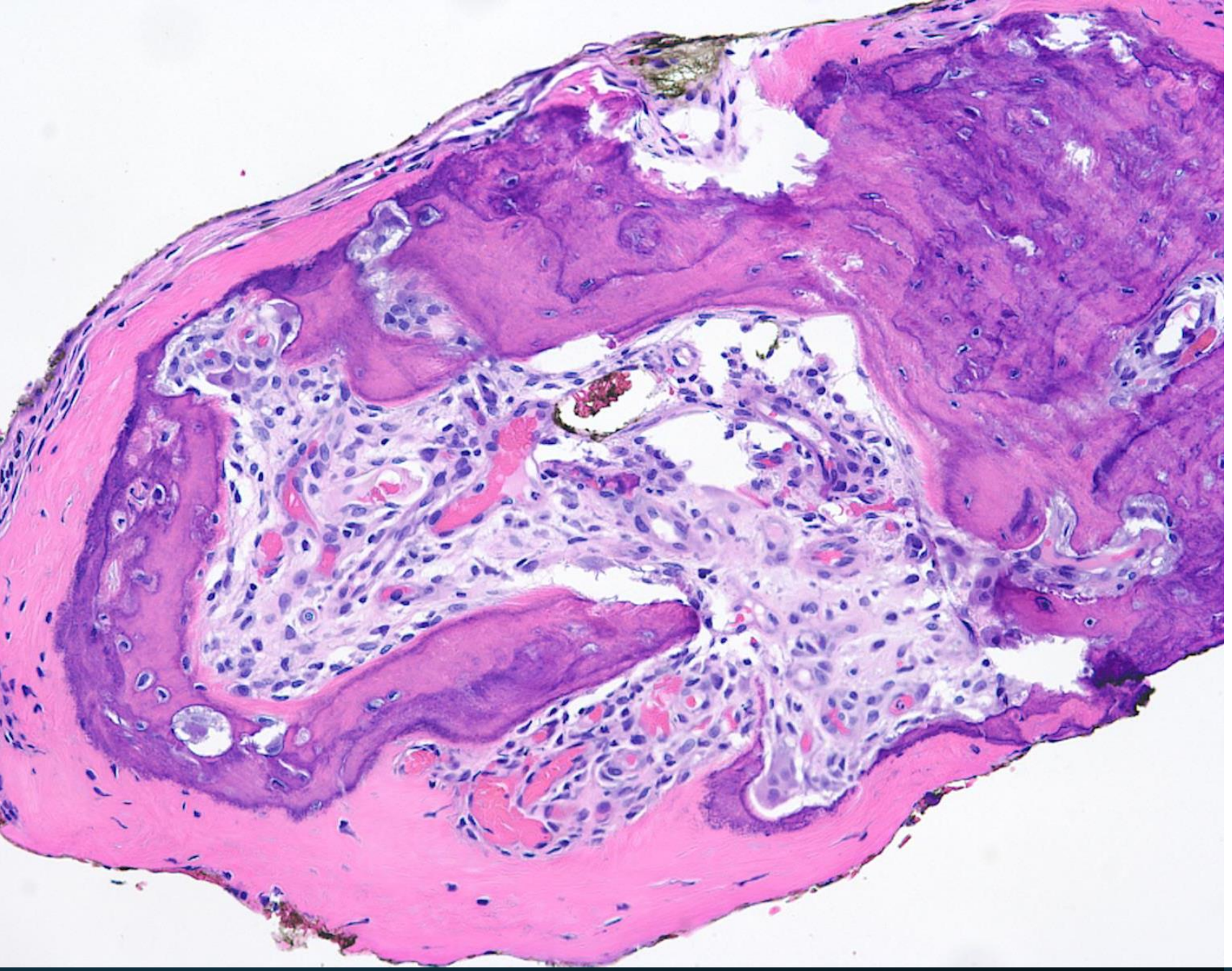
Bone formation, osteoid area rimmed by osteoblasts (ant trails), scarred medullary cavity



EXTRASKELETAL OSTEOSARCOMA

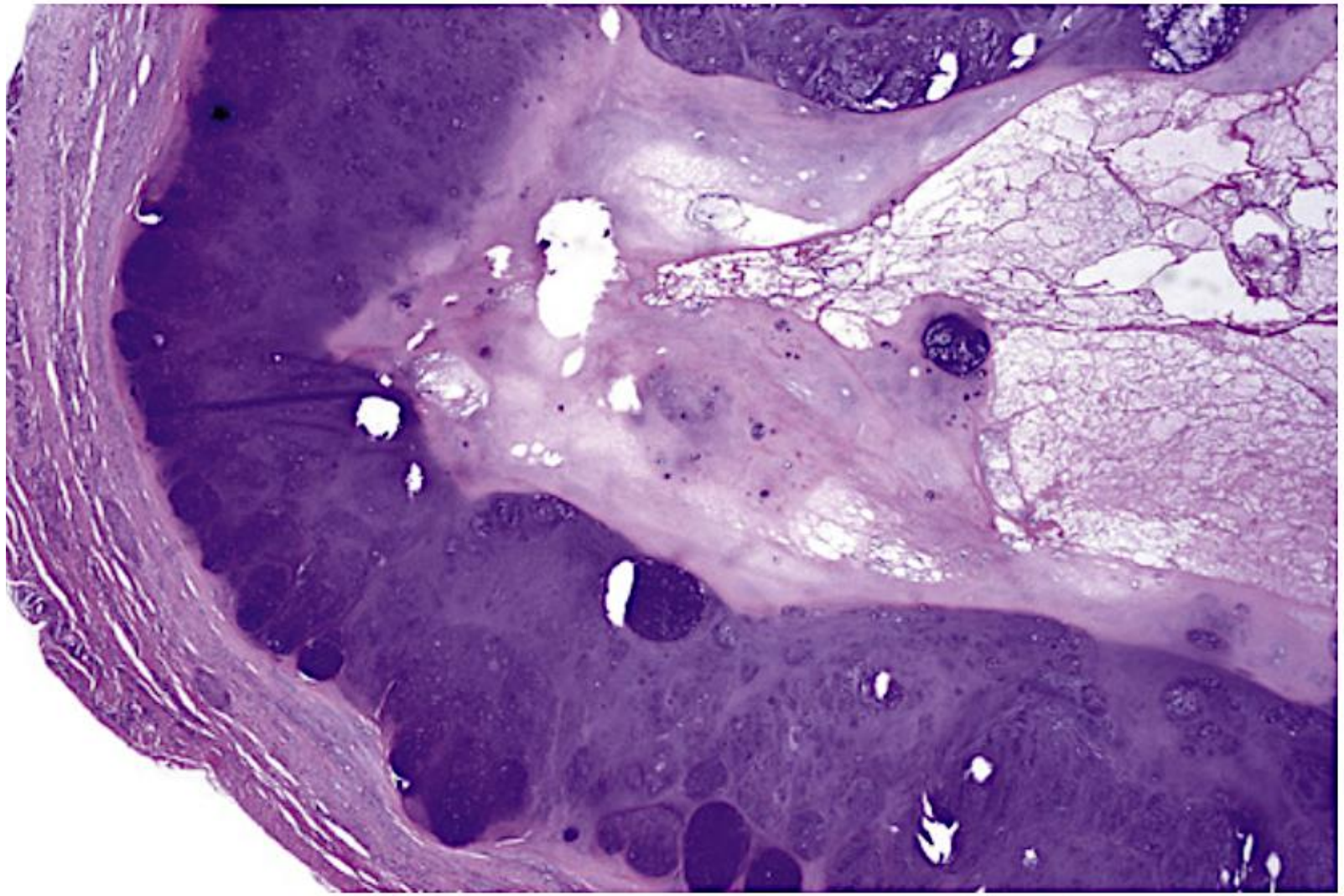
- Rare, in older adults
- Unusual in children
- Deep soft tissue, subcutis or dermis of the limbs (legs)
- 10% associated with XRT
- Rapid local recurrence, widespread metastasis with 75% mortality
- 12q amplification better prognosis
- Loss of CDKN2A biallelic simultaneous losses of RB1 and TP53
- IHC: Osteocalcin+, SATB2+, ERG (cartilaginous area)


Osteoid matrix is rimmed by malignant hyperchromatic osteoblasts
Multinucleated osteoclasts



OSTEOCHONDROMA (EXOSTOSIS)

- Solitary, under the nail, hard and painful tumor
- Mature cartilage overlying a layer of lamellar bone
- Arises from the underlying phalanx

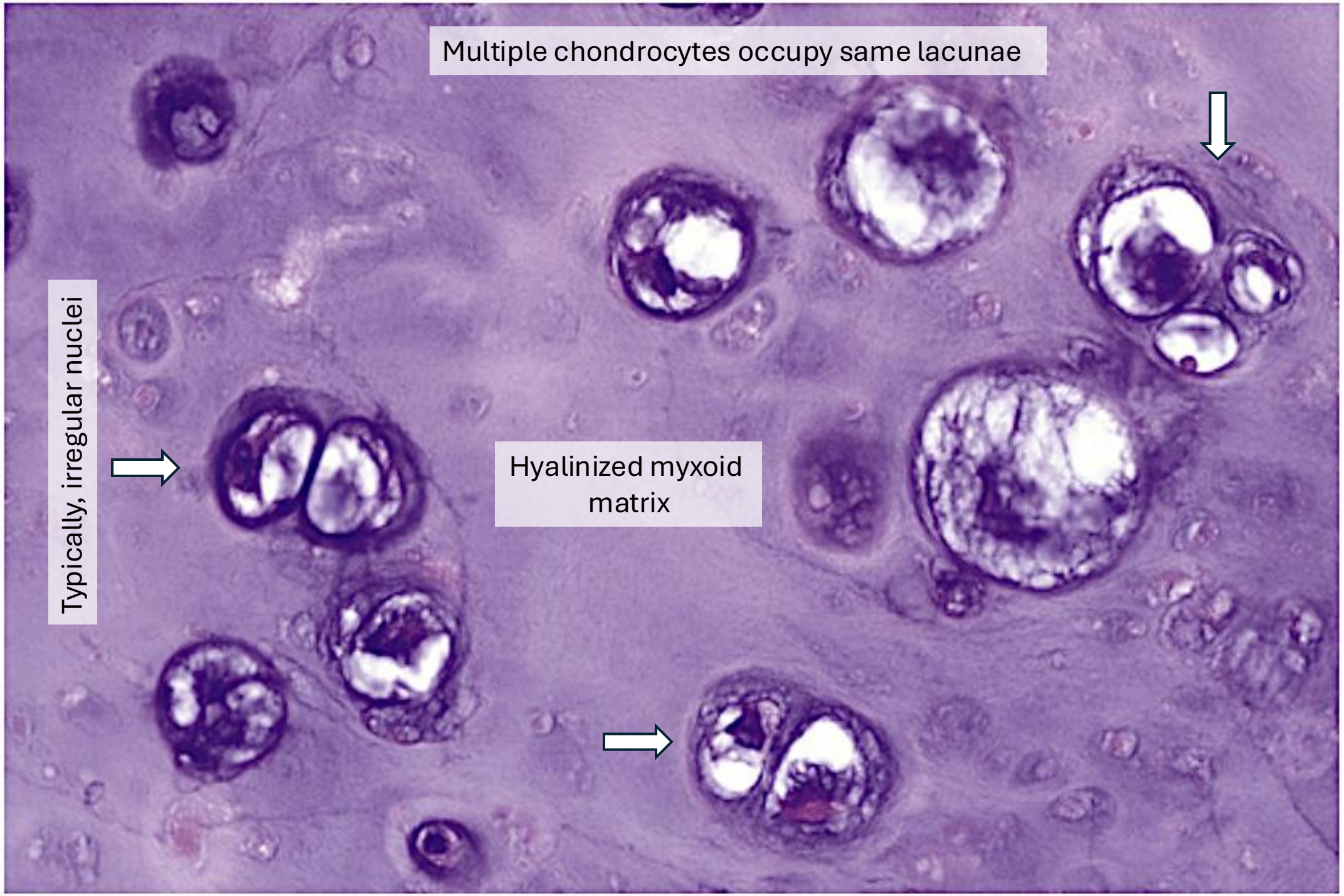


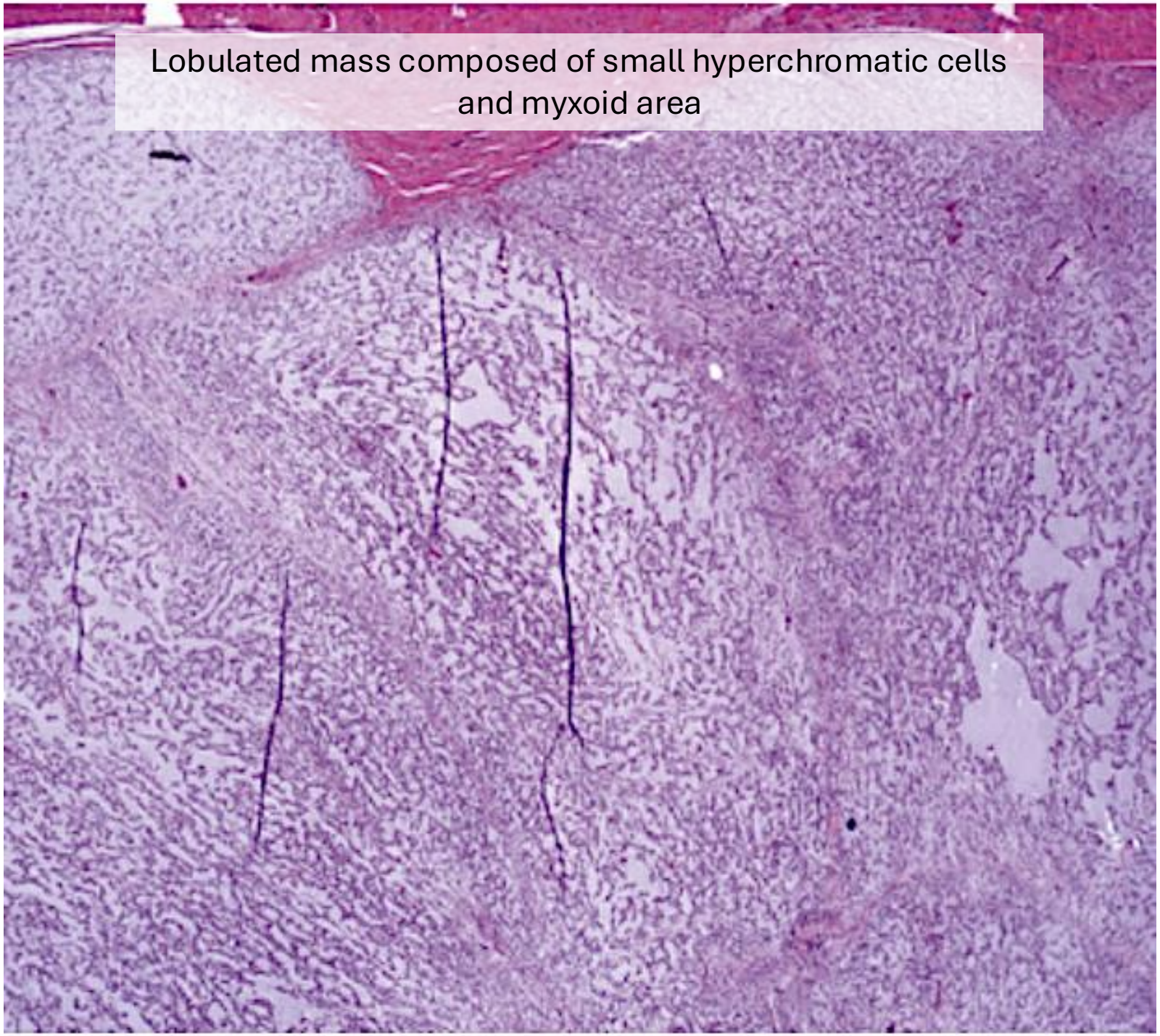
Intradermal, well-circumscribed, lobulated mass of mature hyaline cartilage

SOFT TISSUE CHONDROMA

- Uncommon, middle-aged males on hands or feet
- 10% recurrence, no malignant change
- 12q 13-15 rearrangements, expression of *HMGA2*
- Monosomy 5, trisomy 6
- Histology: degenerative changes: myxoid, hemorrhage, calcification or ossification
  - Reactive osteoclastic giant cells
- IHC: ERG (cartilaginous area)
- DDX: mixed tumor of skin

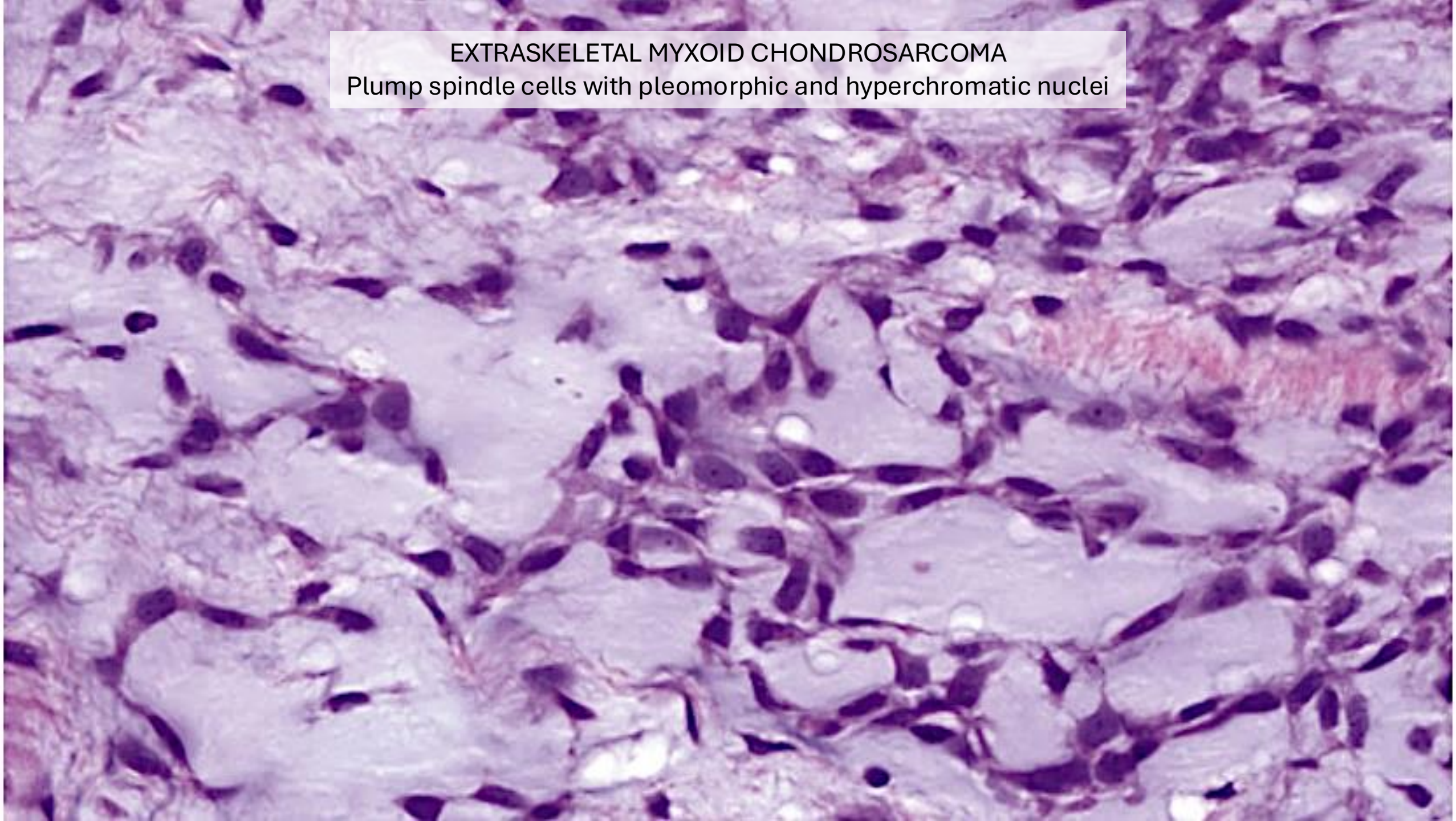
SOFT TISSUE CHONDROMA





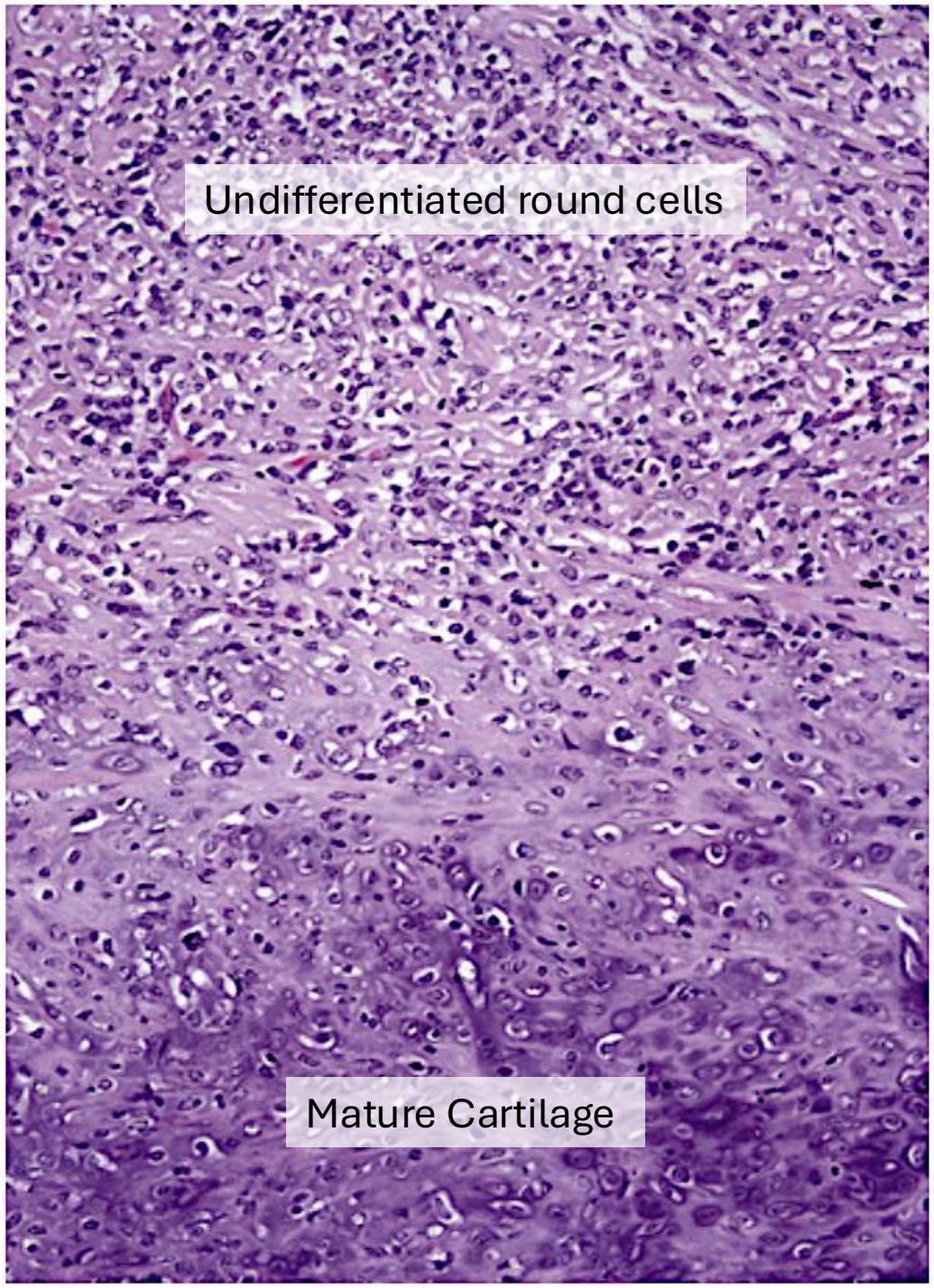
EXTRASKELETAL MYXOID CHONDROSARCOMA

- Uncommon, adult males (legs)
- Deep origin, 20% subcutaneous
- Recurs and metastasizes
  - 5-, 10- & 15-year survival: 82%, 65% and 58%
- t(9;22) (q22;q12) fusing *NR4A3* and *EWSR1*
- IHC: INI1 loss, S100+, SOX10+, rare EMA+, Keratin+
- DDX: myxoid liposarcoma and malignant mixed tumors


EXTRASKELETAL MYXOID CHONDROSARCOMA
Plump spindle cells with pleomorphic and hyperchromatic nuclei

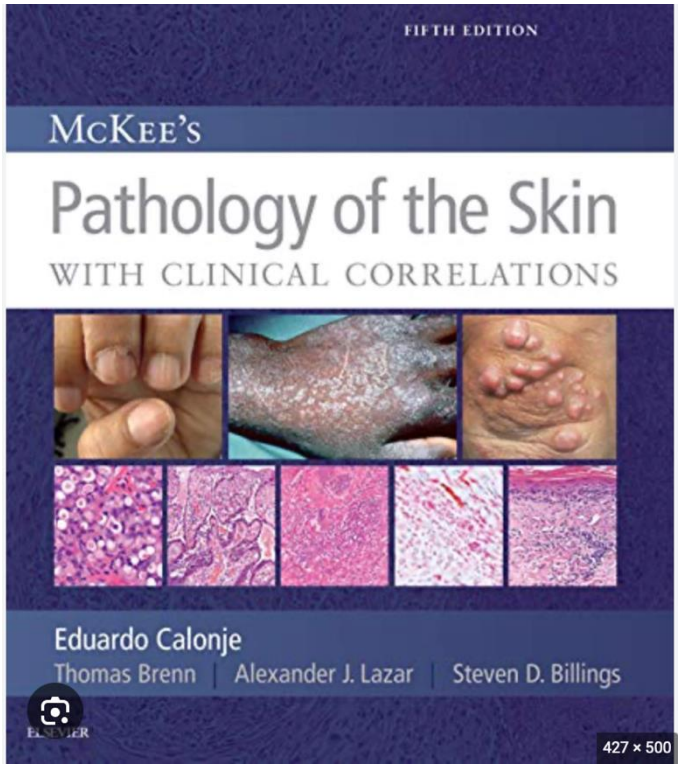
EXTRASKELETAL MESENCHYMAL CHONDROSARCOMA

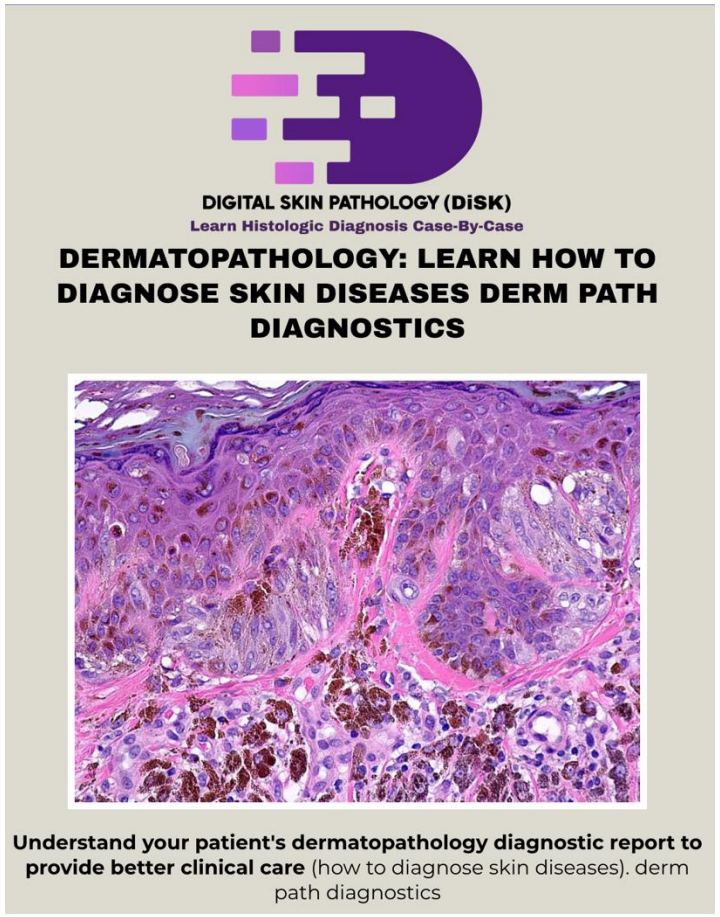
- Very rare, deep tumor in young adults, children (females)
- Head and neck, upper trunk > limbs
- Prognosis worse than the myxoid variant
- Inv(8) (q13q210), *HEY1-NCOA2* fusion
- IHC: CD99+, BCL-2+, S100+, ERG+, SOX-9+
- Biphasic Histology: hypercellular tumor with undifferentiated round or spindled mesenchymal cells AND mature cartilage



References

- *McKee's Pathology of the Skin* Eduardo Calonje
- Digital Skin Pathology https://digitalskinpathology.com
  - Current lecture
  - Examples of cases
  - Quizzes






QUIZZ CASES
Digital Skin Pathology
https://digitalskinpathology.com