Soft tissue and bone tumors

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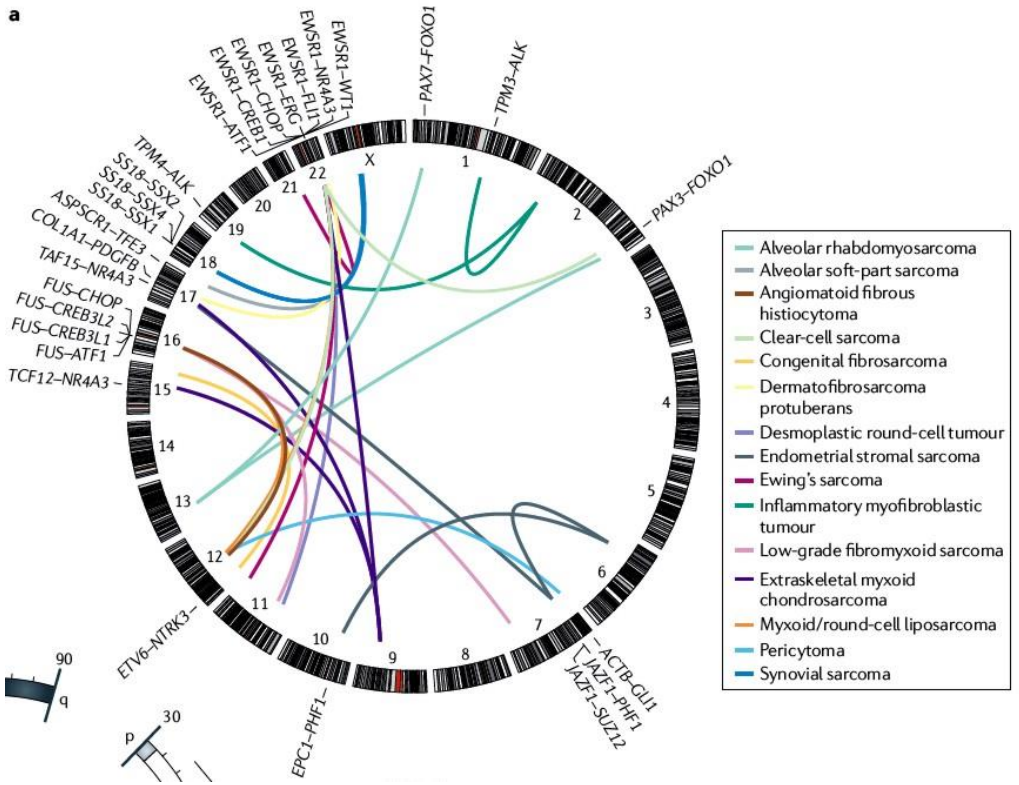
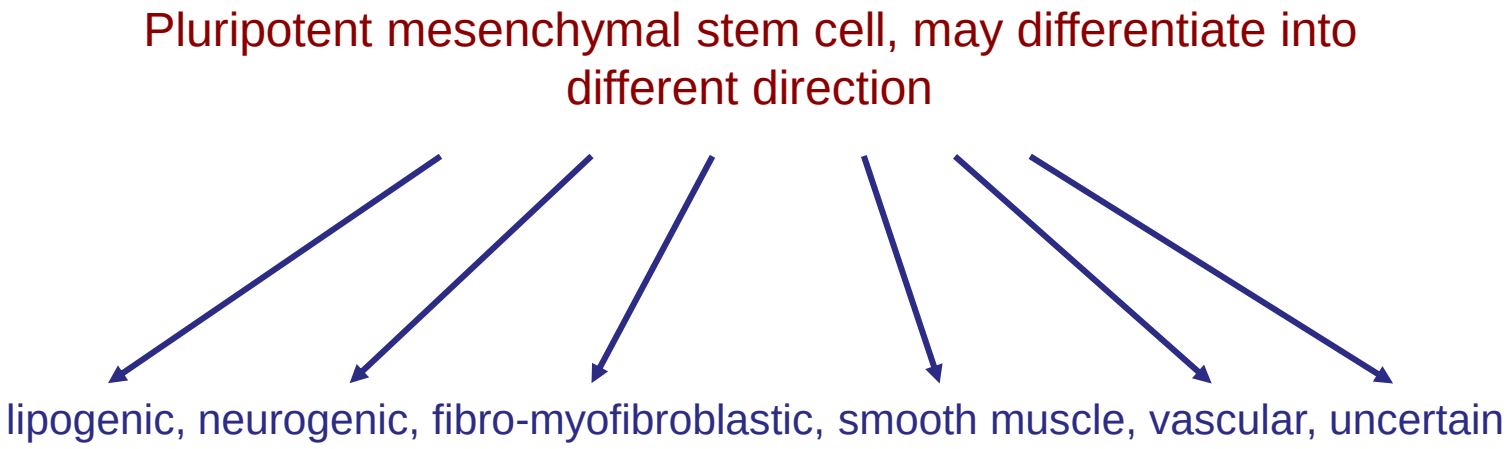


- Large and heterogeneous group with more than 200 entity and more than 50 sarcoma types
- Previously: classified according to a histogenetic concept (fibrosarcoma from fibroblast)
- Now: primitive multipotential stem cells differentiate along one or more lines



- Light microscopic evaluation (H&E) + many ancillary techniques

Principles

Characteristic morphology with corresponding biological behavior

Variants (with the same biological behavior)

Similar morphology but different biological behavior (MFS – LGFMS)

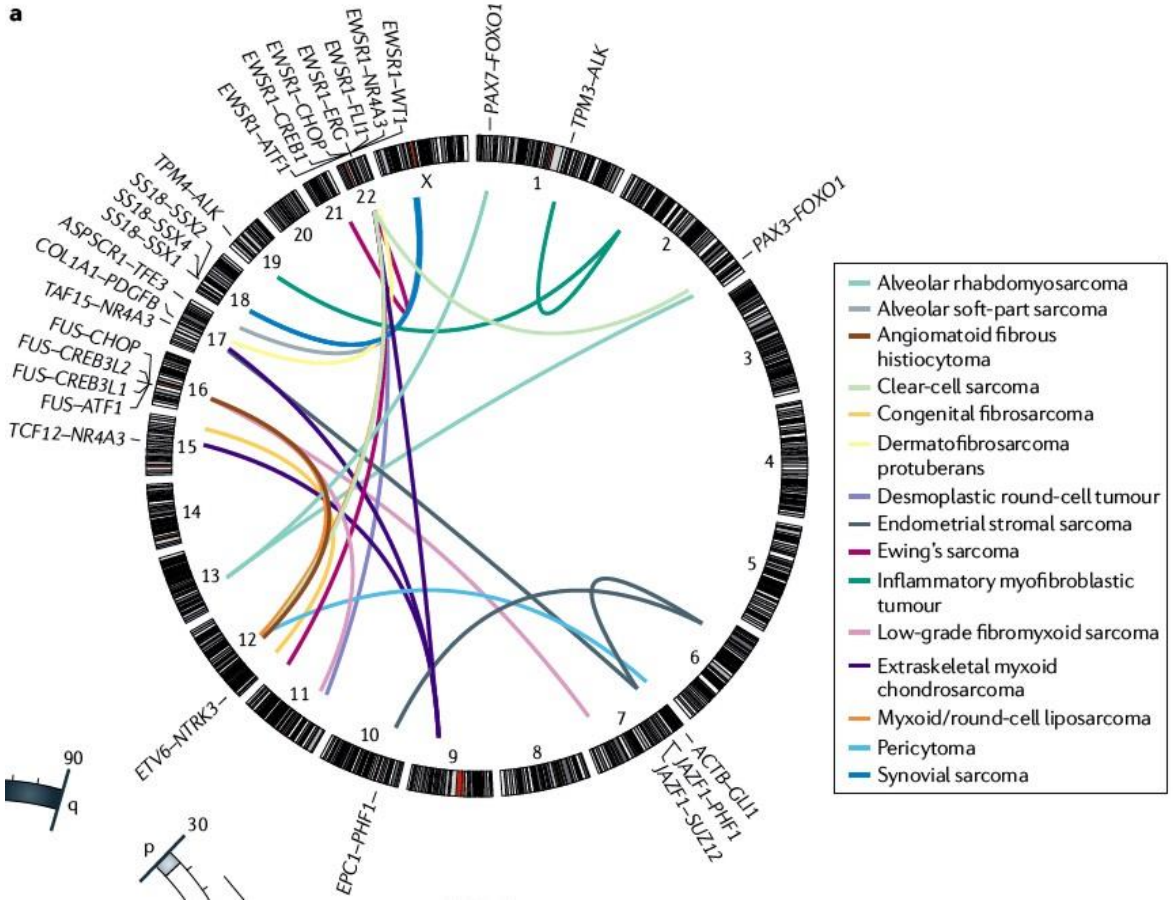
Different morphology but the same genetic background
(Giant cell fibroblastoma – DFSP)

Genetic promiscuity (partly or totally)

Molecular complexity

Recurrent cytogenetic alteration,
Translocations → fusion genes, proteins
de novo formation
fusion gene is the initial step/driving force
synovial sarcoma, myxoid liposarcoma

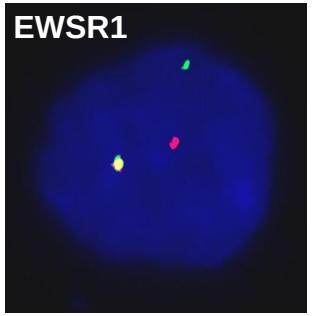
complex karyotype
genetic instability
no fusion gene
de novo formation, rarely
„dysplastic-precursors"
MPNST, leiomyosarcoma



FISH probes

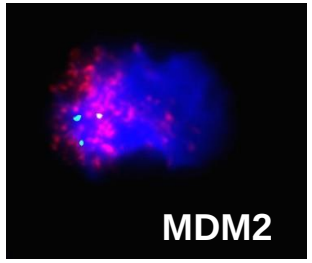
Break-apart

SS18 (SYT)	Synovial sarcoma
FOXO1	Alveolar rhabdomyosarcoma
DDIT3 (CHOP)	Myxoid liposarcoma
FUS	Myxoid liposarcoma, Angiomatoid fibrosus histiocytoma, LGFMS
EWSR1	Ewing sc, AFH, DSRCT, EMC, MC, Clear cell sc
COL1A1	Dermatofibrosarcoma protuberans
USP6	Nodular fasciitis, Aneurysmal bone cyst
ETV6	Infantile fibrosarcoma
NTRK3	Infantile fibrosarcoma
NTRK1	Lipofibromatosis like neural tumor
ALK1	Inflammatory myofibroblastic tumor
NR4A3	Extraskeletal myxoid chondrosarcoma



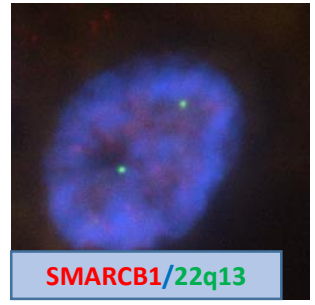
Amplification

MDM2	Atypical lipomatous tumor, Dedifferentiated liposarcoma
CDK4	Atypical lipomatous tumor, Dedifferentiated liposarcoma
cMYC	Secondary angiosarcoma



Deletion

SMARCB1 (INI1)	Rhabdoid tumor, Epithelioid sarcoma, Myoepith. cc

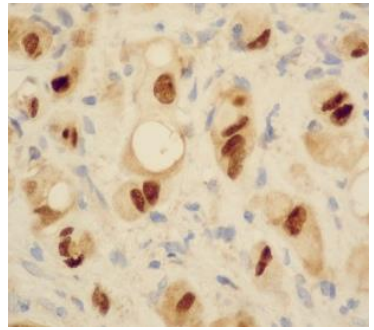


Immunohistochemical reaction

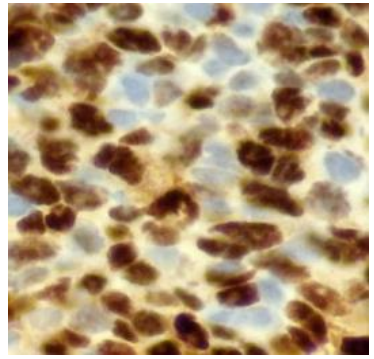
Special

CAMTA1	Epithelioid haemangioendothelioma
TFE3	Alveolar soft part sarcoma, EHE
STAT6	Solitary fibrous tumor
ERG	Angiosarcoma, Ewing sc
FLI1	Angiosarcoma, Ewing sc
MDM2	Atypical lipomatous tumor, Dedifferentiated liposarcoma
CDK4	Atypical lipomatous tumor, Dedifferentiated liposarcoma
ALK1	Inflammatory myofibroblastic tumor
ßCatenin	Fibromatosis, Nasopharyngeal angiofibroma, Intranod. pal. myofibrobl.
TLE1	Synovial sarcoma
Myf4	Rhabdomyosarcoma
MUC4	Epithelioid fibrosarcoma, LGFMS
HHV8	Kaposi sarcoma
DOG1	GIST
CD117	GIST

CAMTA1



fusion protein



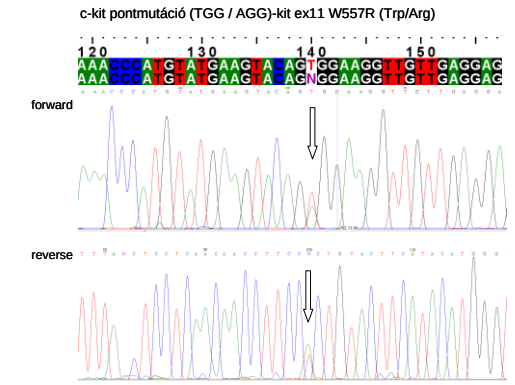
Myf4

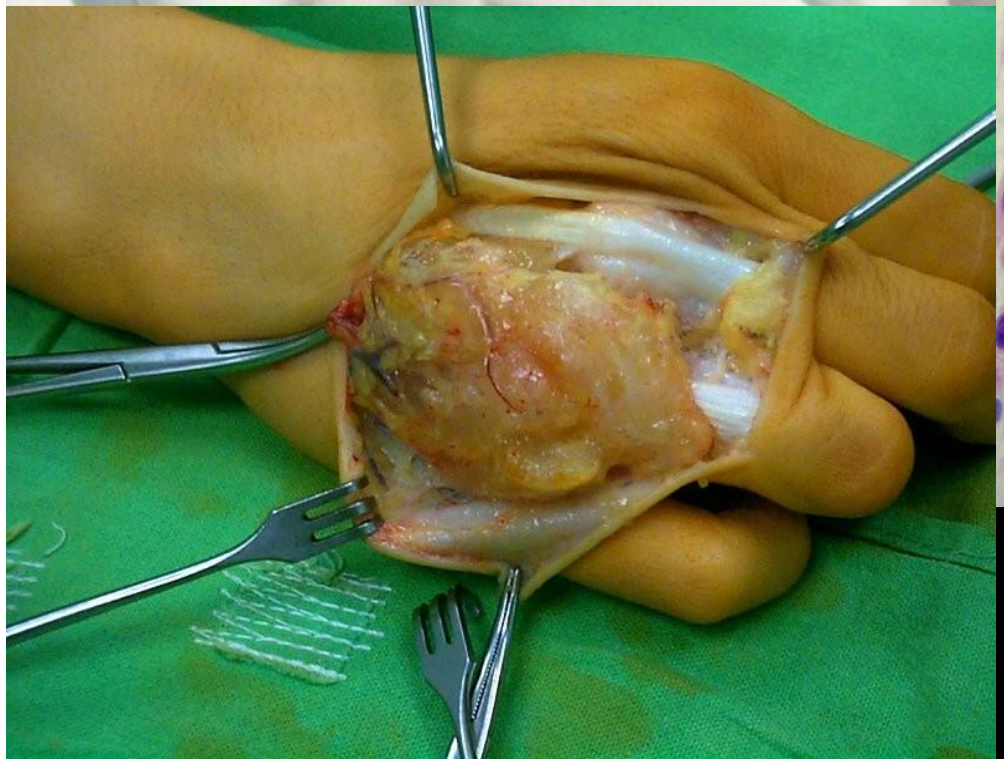
General

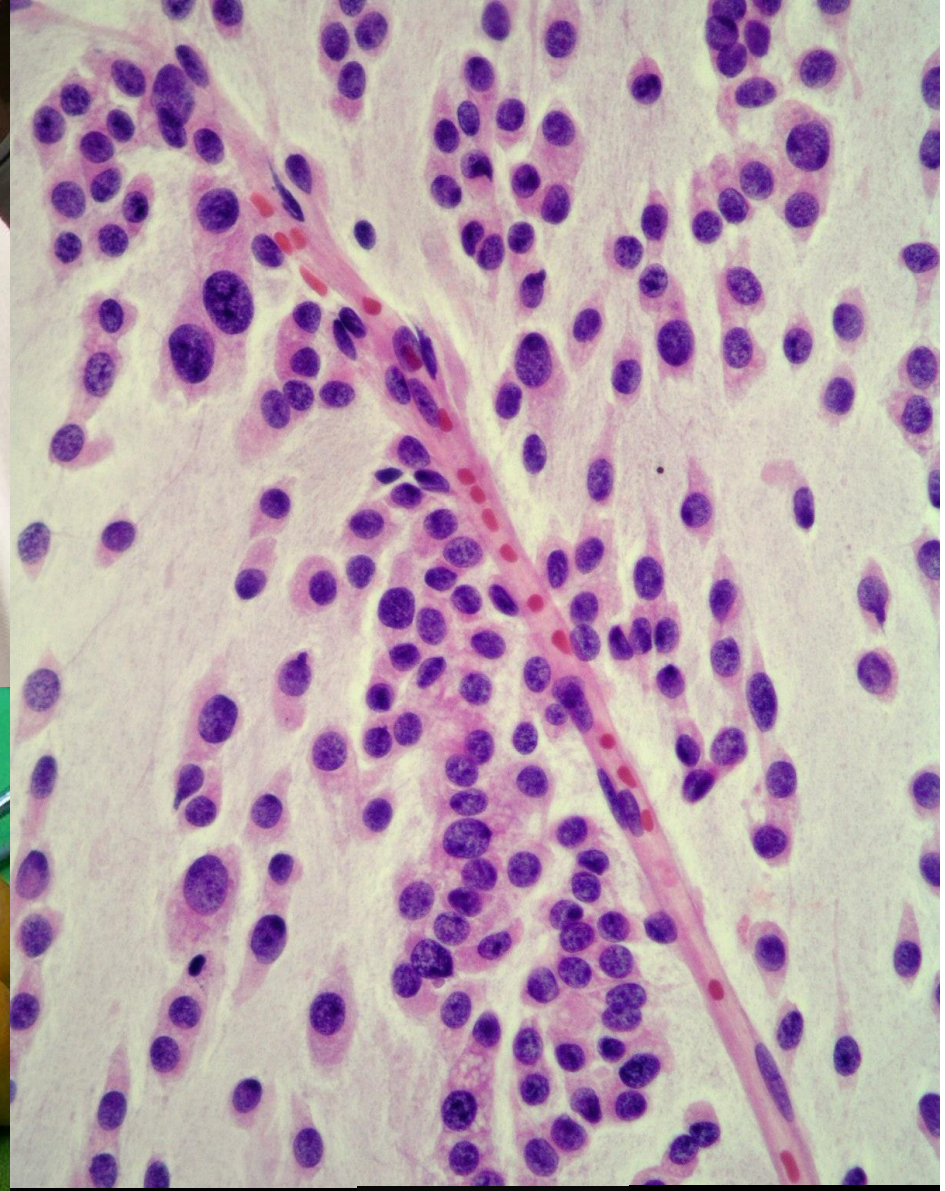
Vimentin, panKeratin, EMA, Claudin1, Desmin, SMA, H-Caldesmon, S100, Leu7, CD31, CD34,NKI-C3, Chromogranin, Synaptophysin, HMB45, MelanA

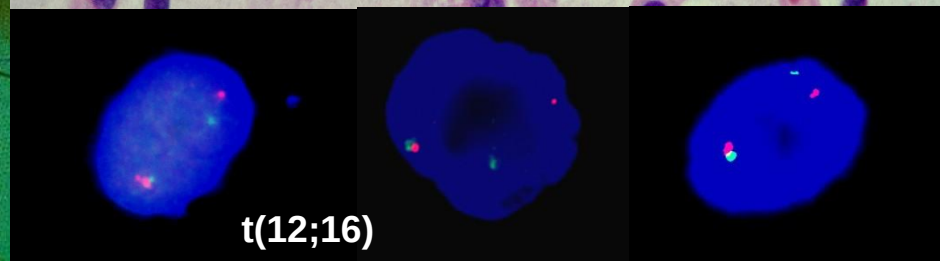
NGS; Sequencing

cKIT and PDGRFA gene exons of GIST





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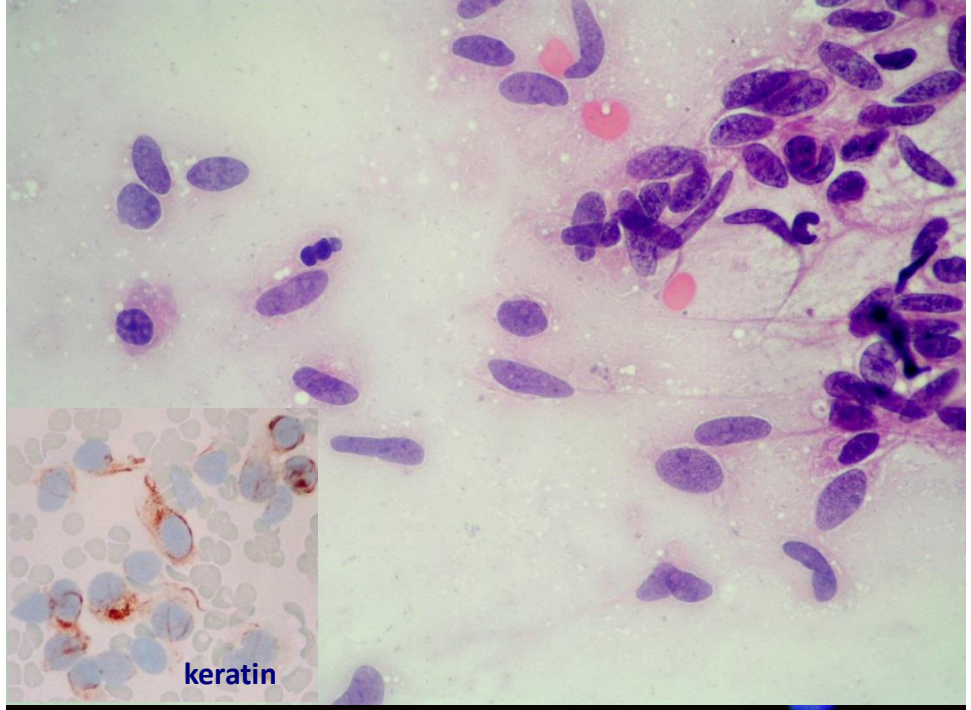
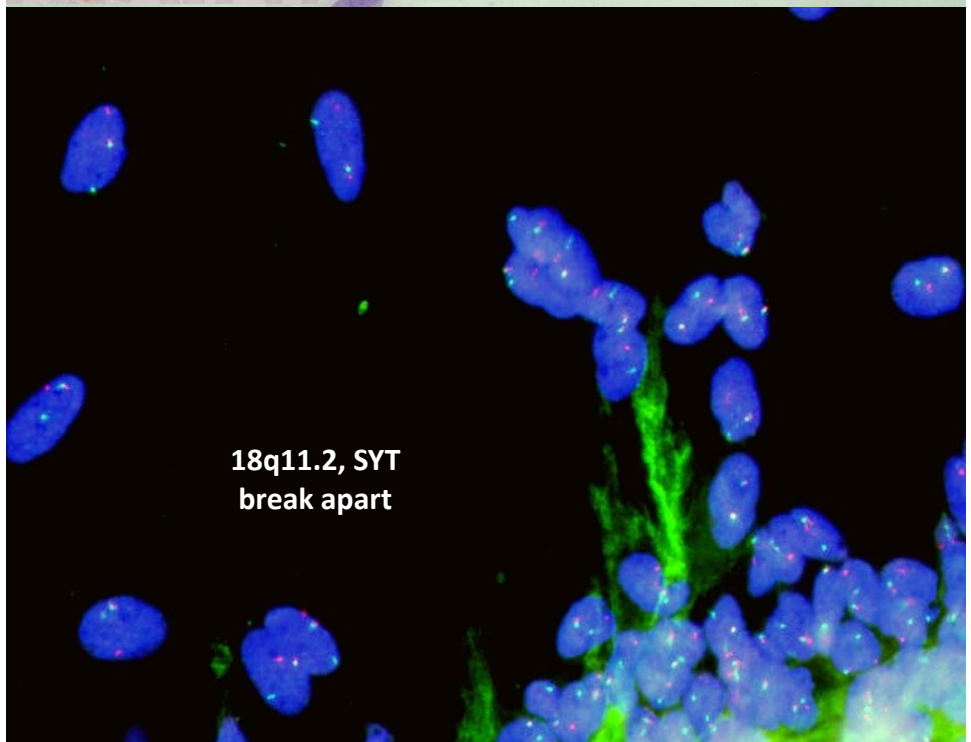




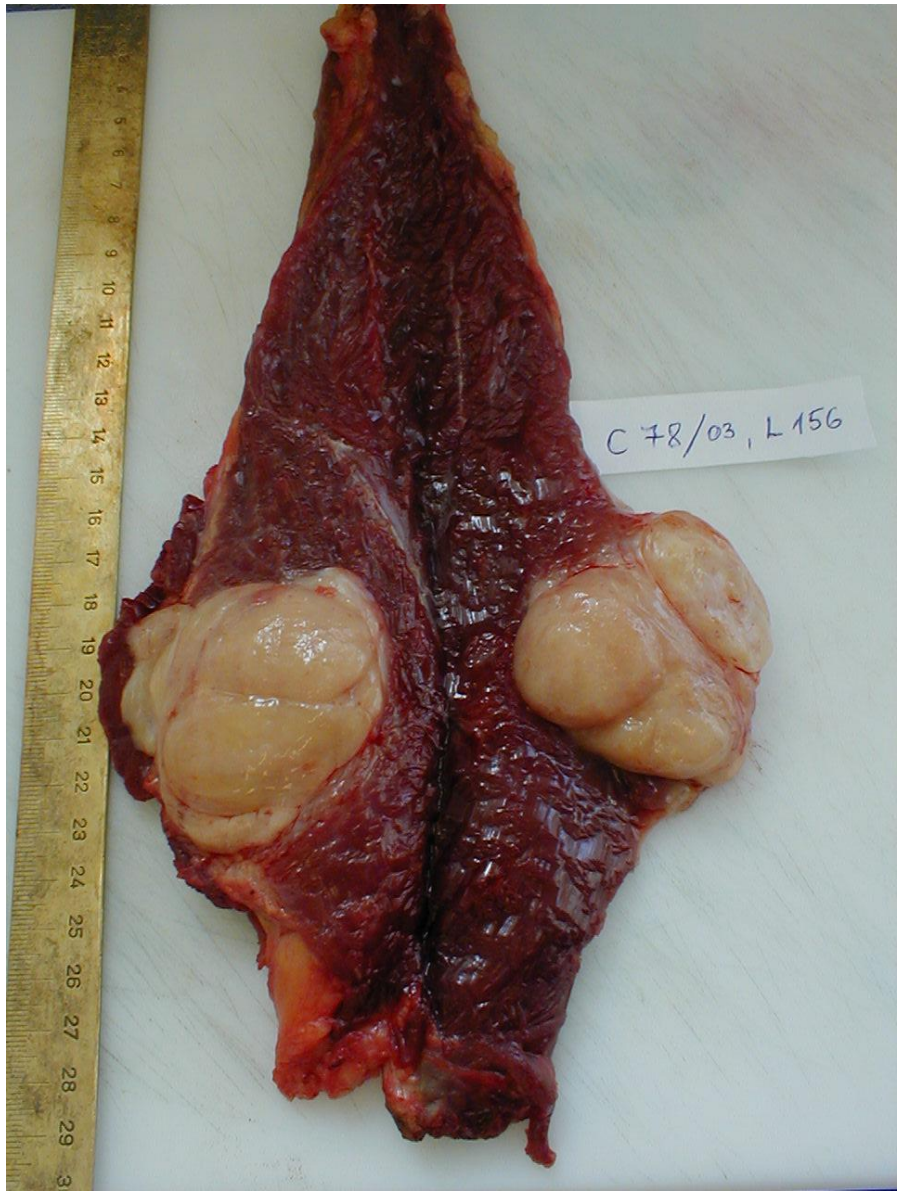
Preoperative cytology

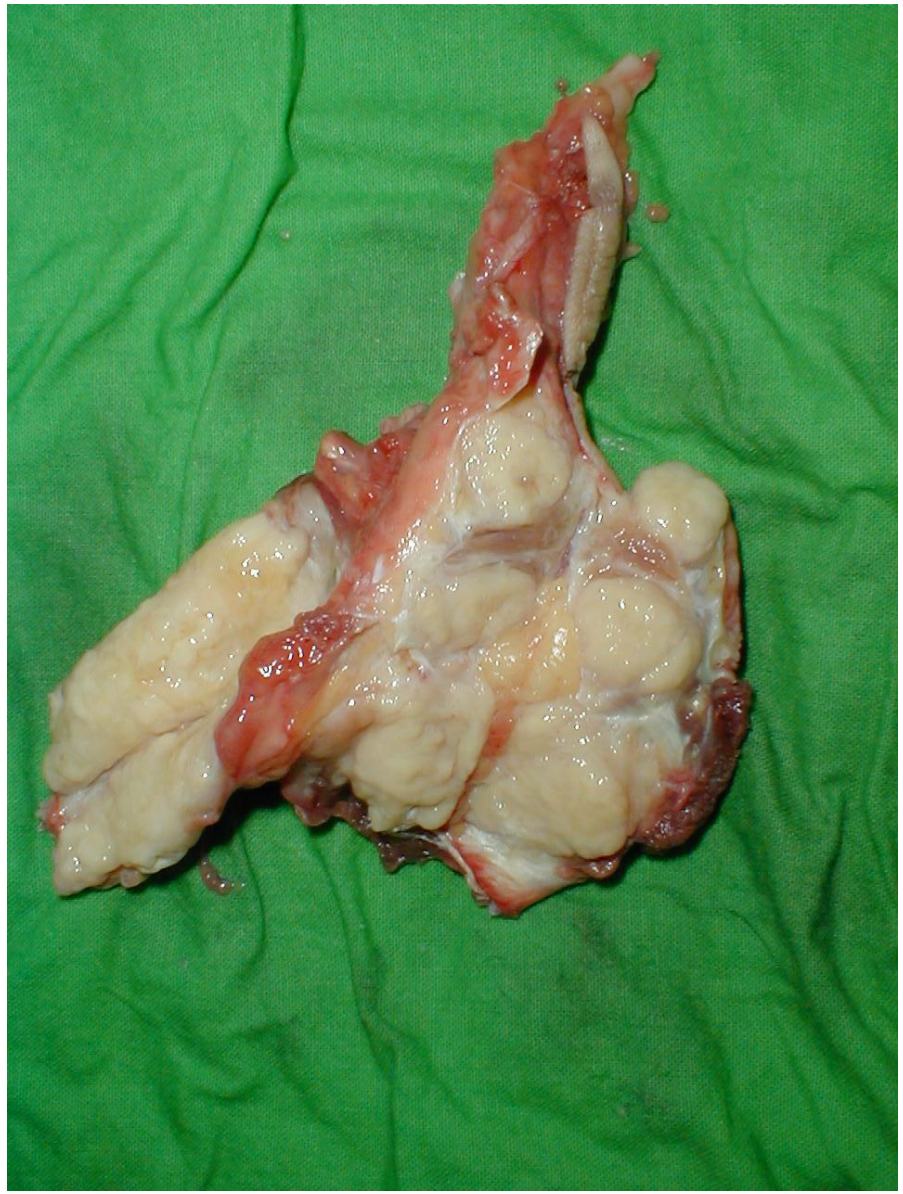
Useful, very fast

May yield definitive diagnosis

Grading is problematic

SS18-SSX2


C 78/03, L 156



SOFT TISSUE TUMORS; THERAPY

- **Small clearly benign STT (on clinical grounds) can be removed directly with a rim of uninvolved normal tissue**
- **If the tumor is benign by FNA, can be safely enucleated („shelling out" the tumor)**
- **If the tumor is intermediate and/or low grade malignant by FNA, a wide excision is recommended (often myectomy!), because of the existance of microsatellite tumor tissue**
- **If the tumor is high grade malignant by FNA, a combination of surgery, radiation therapy and multidrug chemotherapy is necessary**

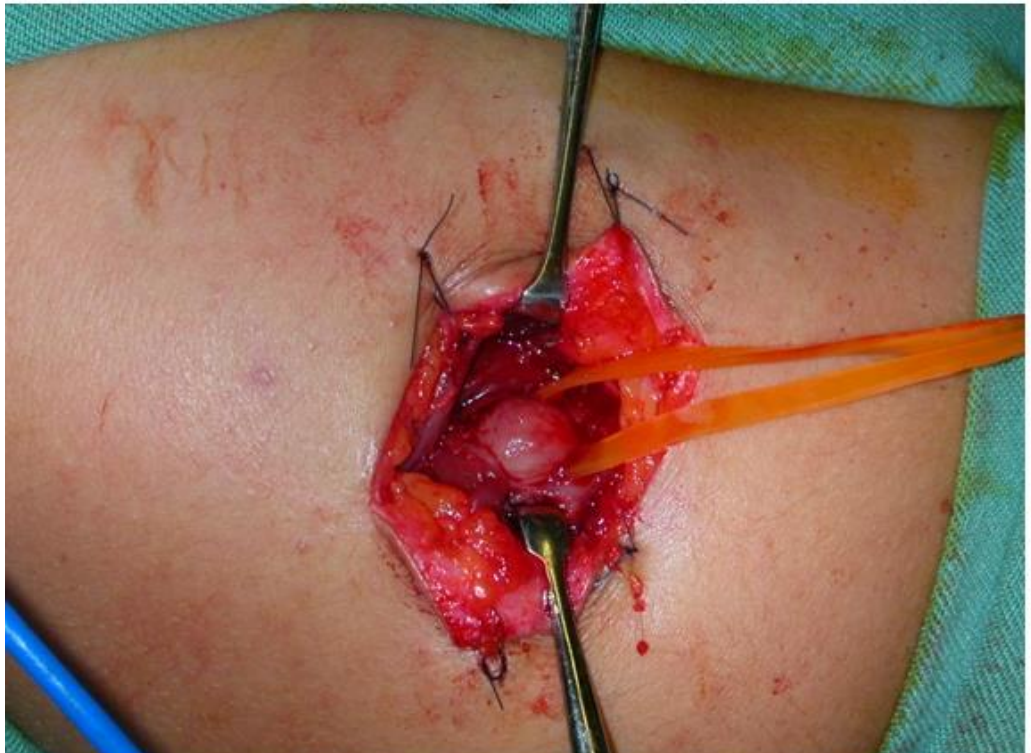
Fibroblastic/myofibroblastic tumours

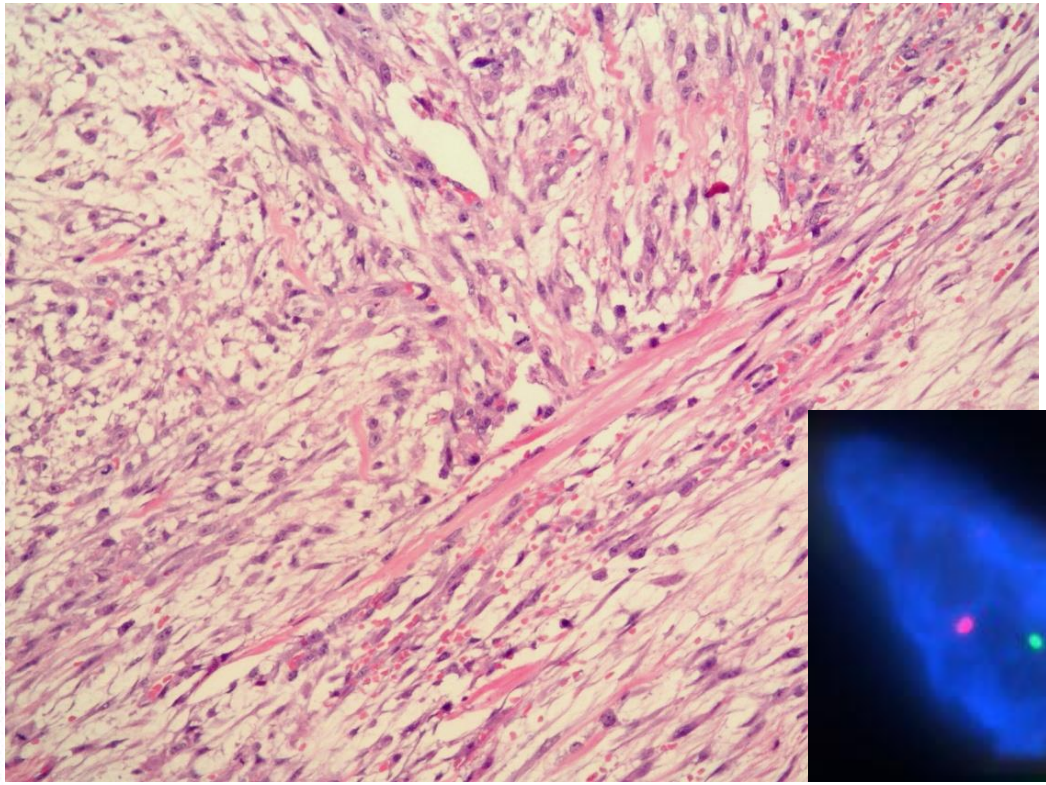
Nodular fasciitis
Proliferative fasciitis and proliferative myositis
Myositis ossificans and Fibro-osseous pseudotumour of digits
Ischaemic fasciitis
Elastofibroma
Fibrous hamartama of infancy
Fibromatosis col li
Juvenile hyaline fibromatosis
Inclusion body fibromatosis
Fibroma of tendon sheath
Desmoplastic fibroblastoma
Mammary-type myofibroblastoma
Calcifying aponeurotic fibroma
Angiomyofibroblastoma
Cellular angiofibroma
Nuchal-type fibroma
Gardner fibroma
Catcifyinq fibrous tumour
Palmar/plantar fibromatosis
Desmoid-type fibromatosis
Lipofibromatosis
Giant cell fibroblastoma

Dermatofibrosarcoma protuberans
Extrapleural solitary fibrous tumour
Inflammatory myofibroblastic tumour
Low-grade myofibroblastic sarcoma
Myxoinflammatory fibroblastic sarcoma
Infantile fibrosarcoma
Adult fibrosarcoma
Myxofibrosarcoma
Low-grade fibromyxoid sarcoma
Sclerosing epithelioid fibrosarcoma

NODULAR FASCIITIS

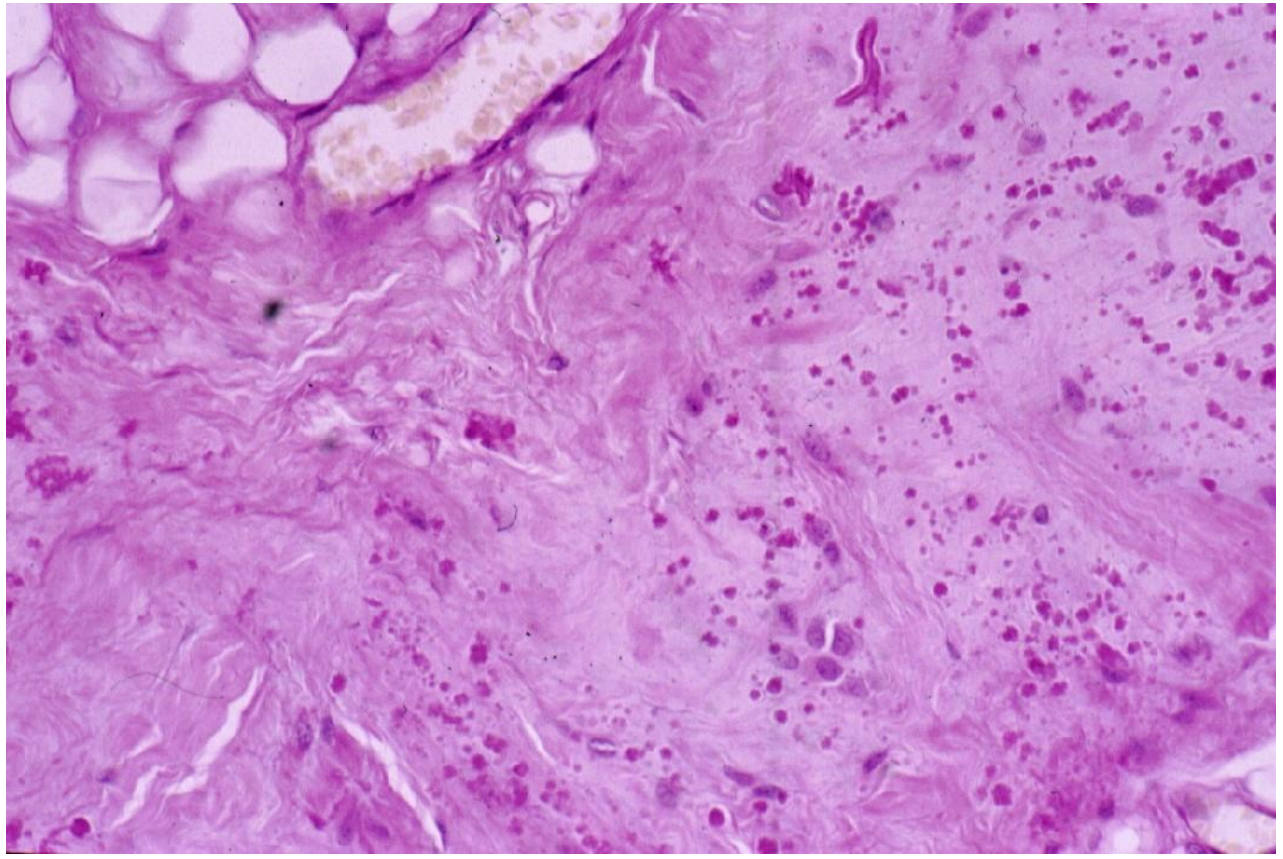
- SUBCUTANEOUS PSEUDOSARCOMATOUS TUMOR
- YOUNG ADULTS
- UPPER EXTREMITIES, TRUNK AND NECK/HEAD
- HISTORY OF RAPID GROWTH (USUALLY A FEW WEEKS)
- SMALL SIZE
- CELLULAR SPINDLE-CELL GROWTH SET IN A LOOSELY TEXTURED MUCOID MATRIX
- USP6 involvement, FISH!

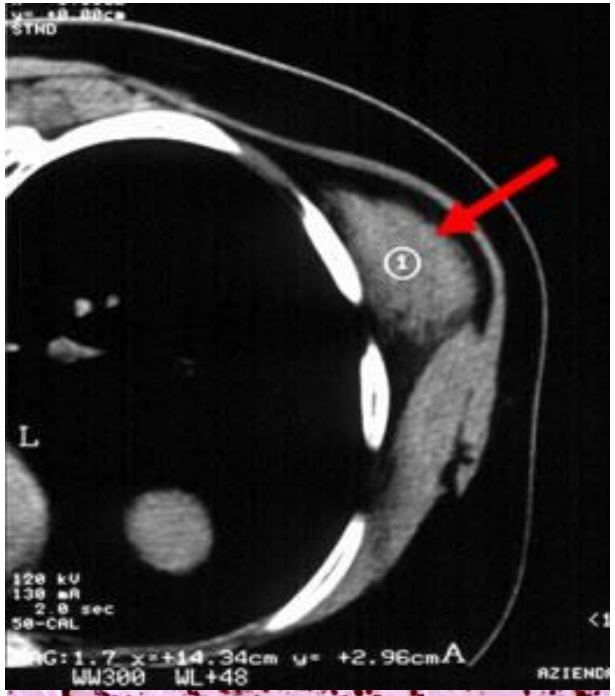


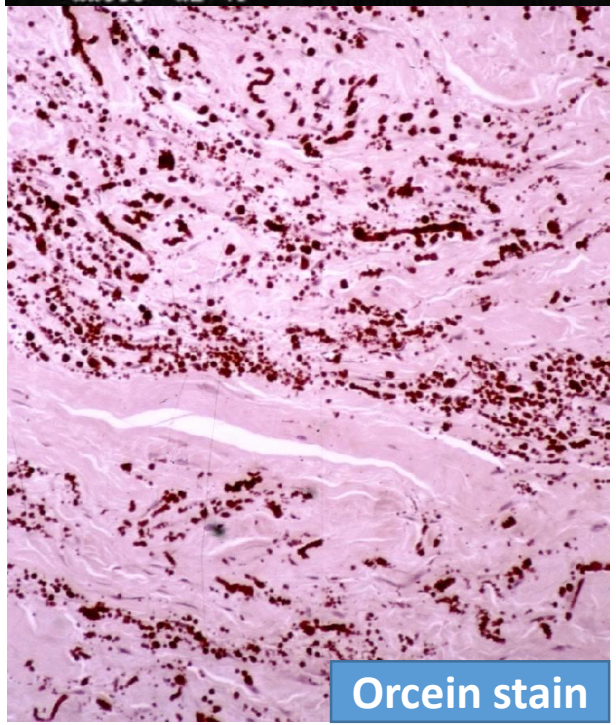


ELASTOFIBROMA

- **POORLY CIRCUMSCRIBED TUMOR OF SUBSCAPULAR REGION**
- **MAINLY SPORADIC BUT FAMILIAL CASES HAVE BEEN DESCRIBED**
- **COLLAGEN BUNDLES ALTERNATE WITH DEGENERATED ELASTIC FIBERS**
- **NOT TRUE NEOPLASM BUT RATHER REACTIVE HYPERPLASIA INVOLVING ABNORMAL ELASTOGENESIS**
- **ORCEIN STAIN**

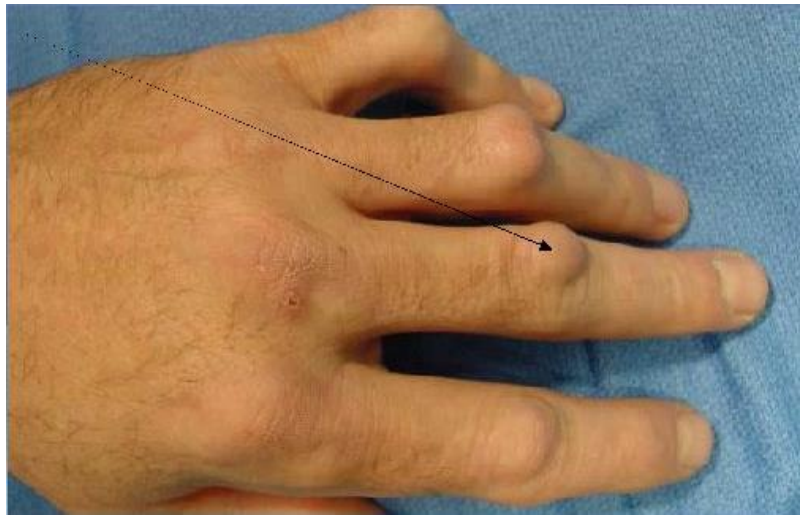






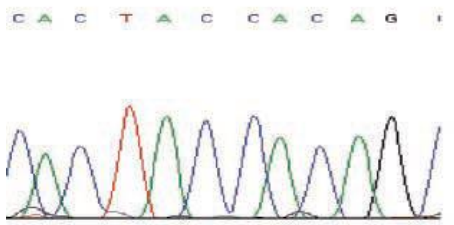
FIBROMATOSES

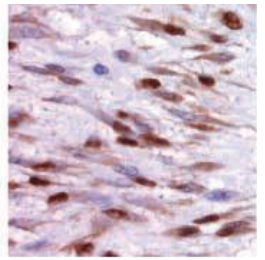
- **PROLIFERATION OF WELL-DIFFERENTIATED FIBROBLASTS, MYOFIBROBLASTS**
- **INFILTRATIVE GROWTH PATTERN**
- **LACK OF CYTOLOGIC FEATURES OF MALIGNANCY, SCANTY MITOSIS**
- **OFTEN ARISE IN MUSCULAR FASCIA**
- **FREQUENT LOCAL RECURRENCE BUT NO METASTASIZING POTENTIAL**
- **PROMPT RADICAL EXCISION WITH A WIDE MARGIN OF INVOLVED TISSUE**
- **TWO TYPES: SUPERFITIAL AND DESMOID TYPE**



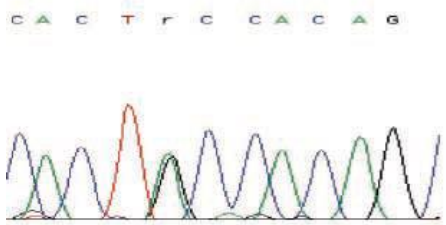
β katenin
mutation/accumulation

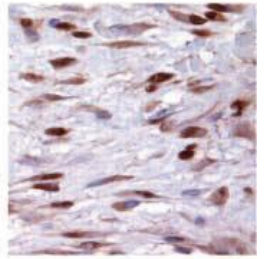
FAP
APC gene



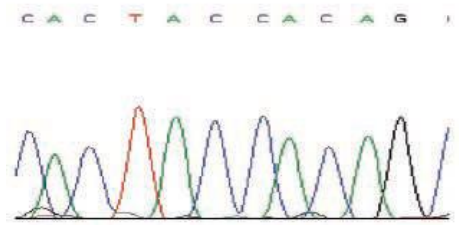


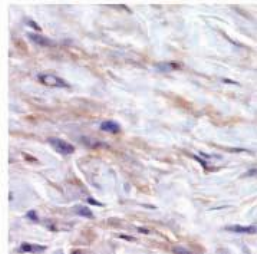
Sporadic
mutated

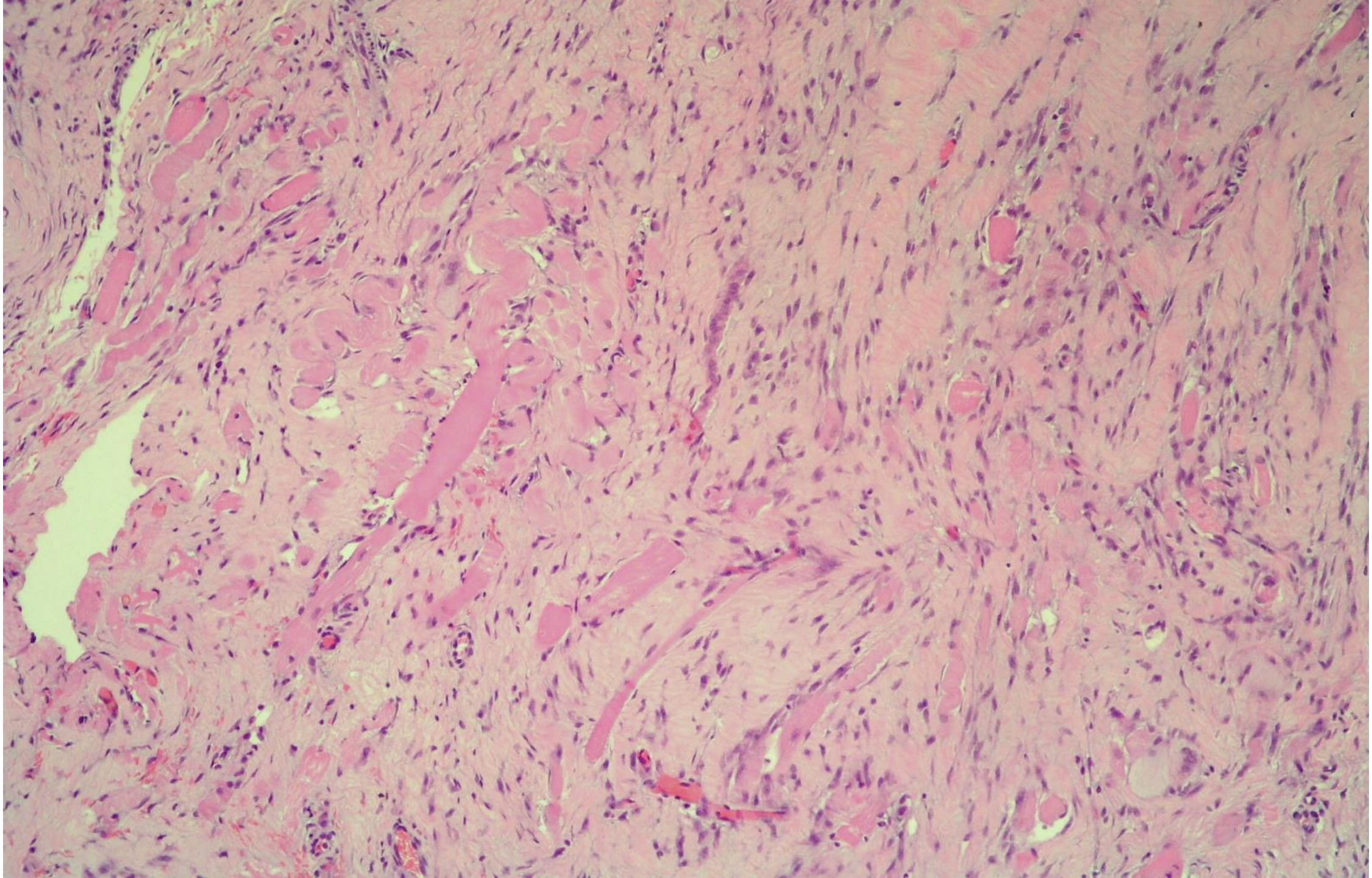




Sporadic
wild







DERMATOFIBROSARCOMA PROTUBERANS

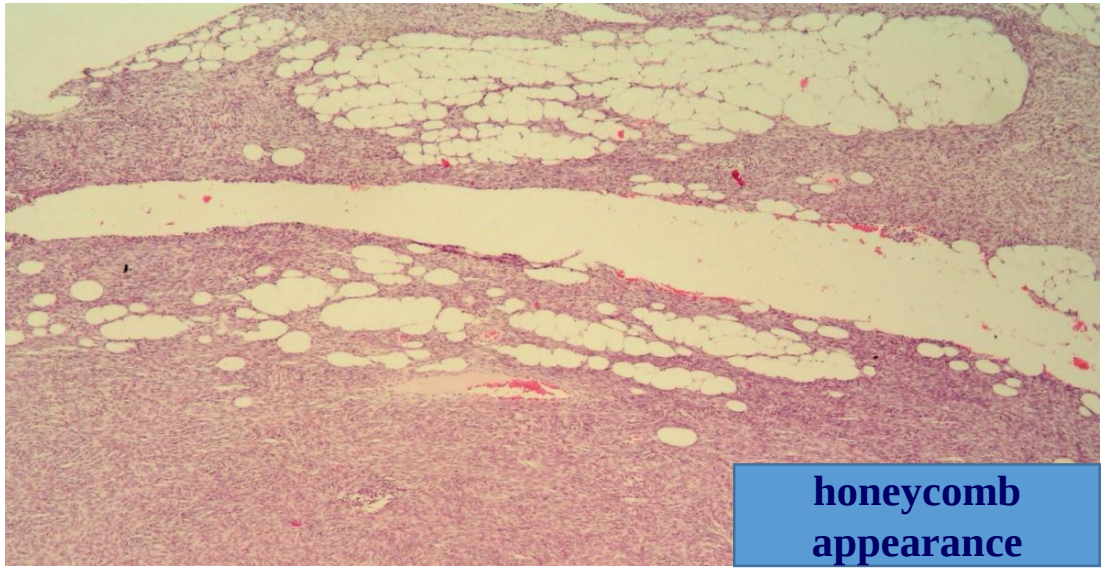
- Characteristic storiform pattern, monomorphic fibroblastic proliferation

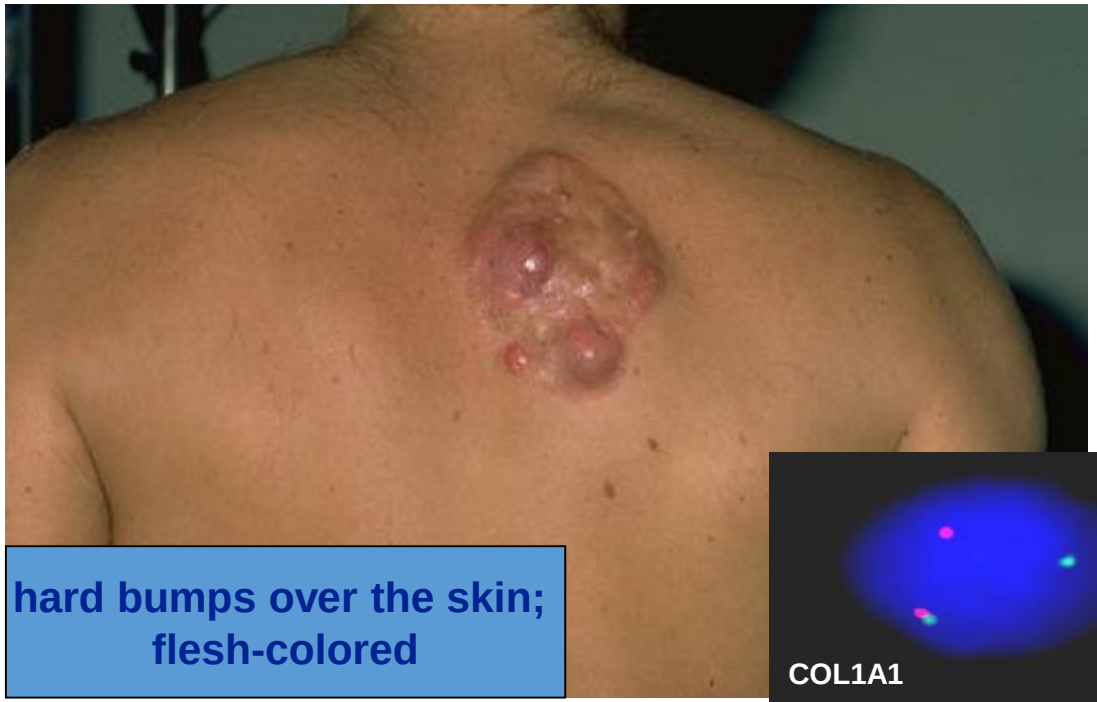
- Adipose tissue infiltration resulting in a typical honeycomb appearance

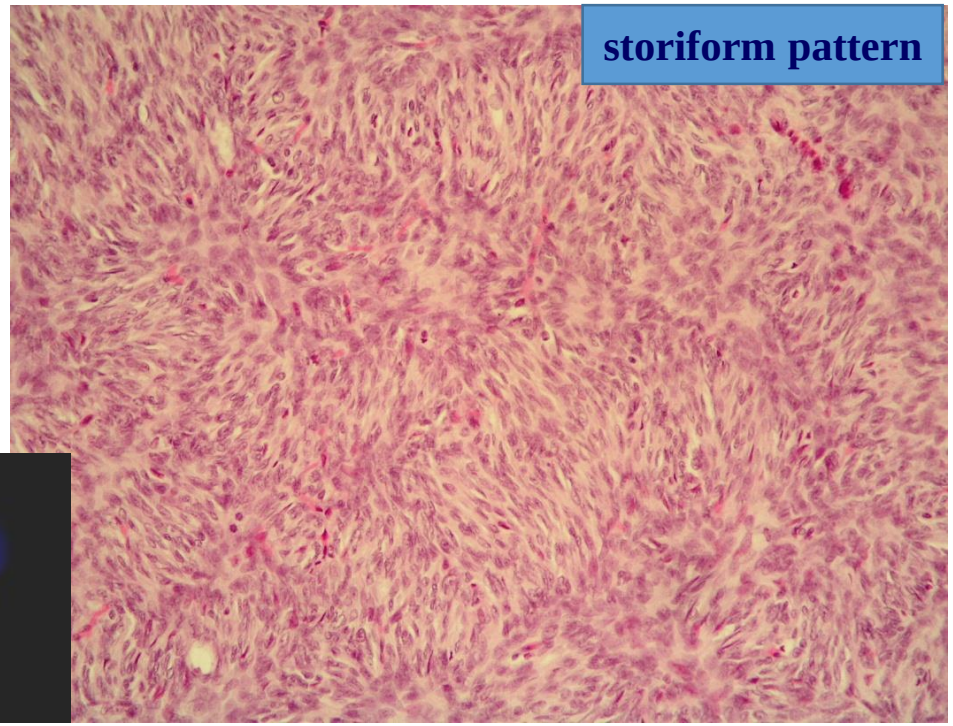
- *COL1A1- PDGFB fusion gene*

- Intermediate malignity

- Early adulthood; slowly growing tumor; can be large



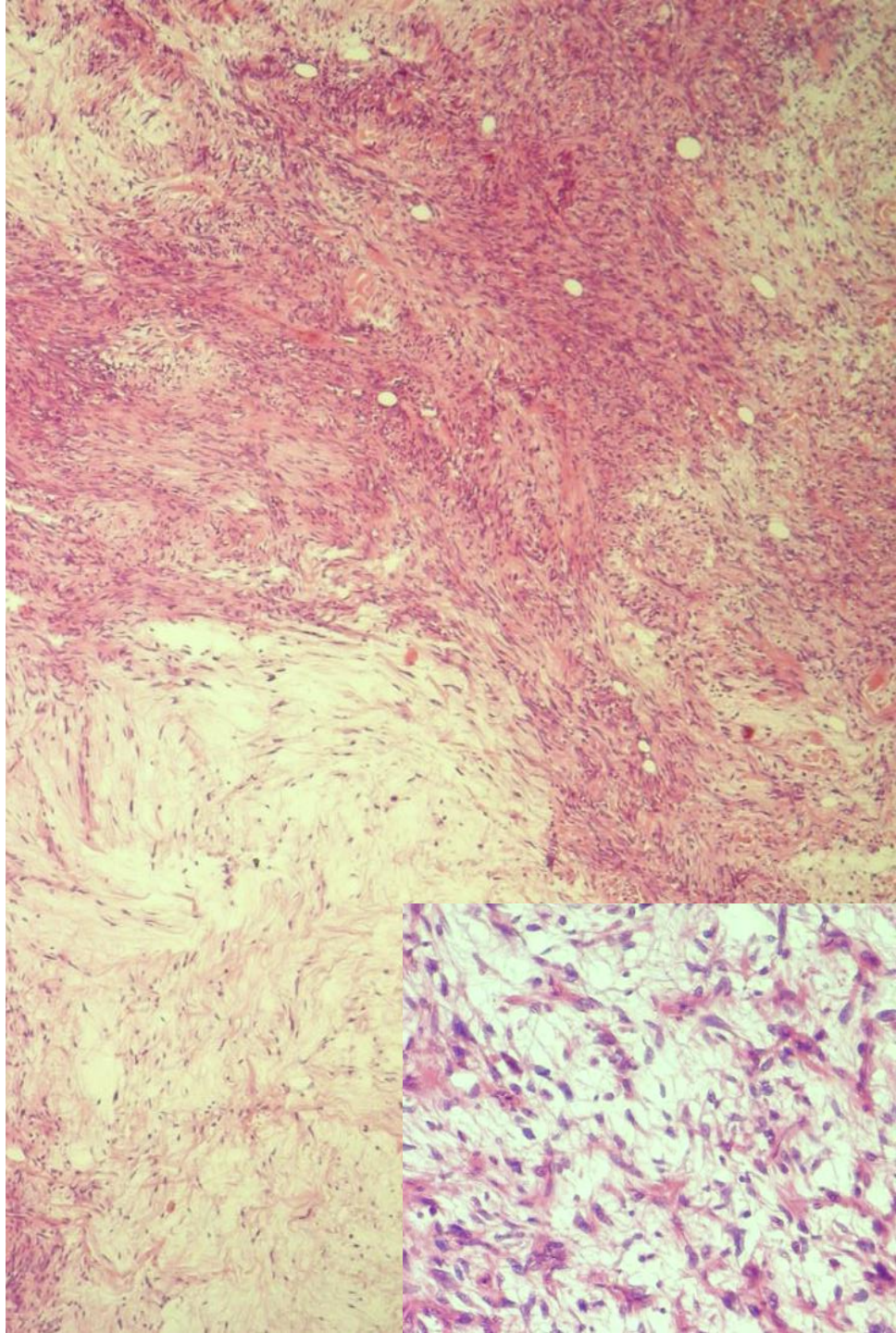




MYXOFIBROSARCOMA

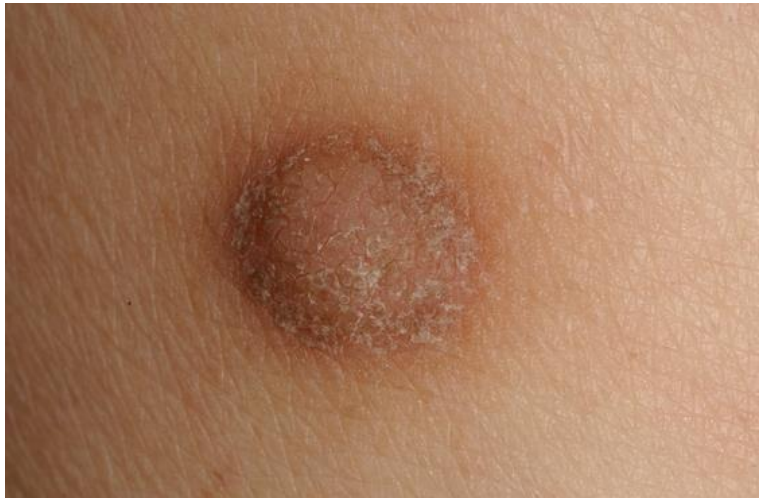
- **MOST COMMON TYPE OF SOFT TISSUE SARCOMA IN ELDERLY PATIENTS**
- **SLOWLY ENLARGING PAINLESS MASS WITH FREQUENT RECCURENCES**
- **BROAD SPECTRUM OF CELLULARITY; CURVILINEAR BLOOD VESSELS;**

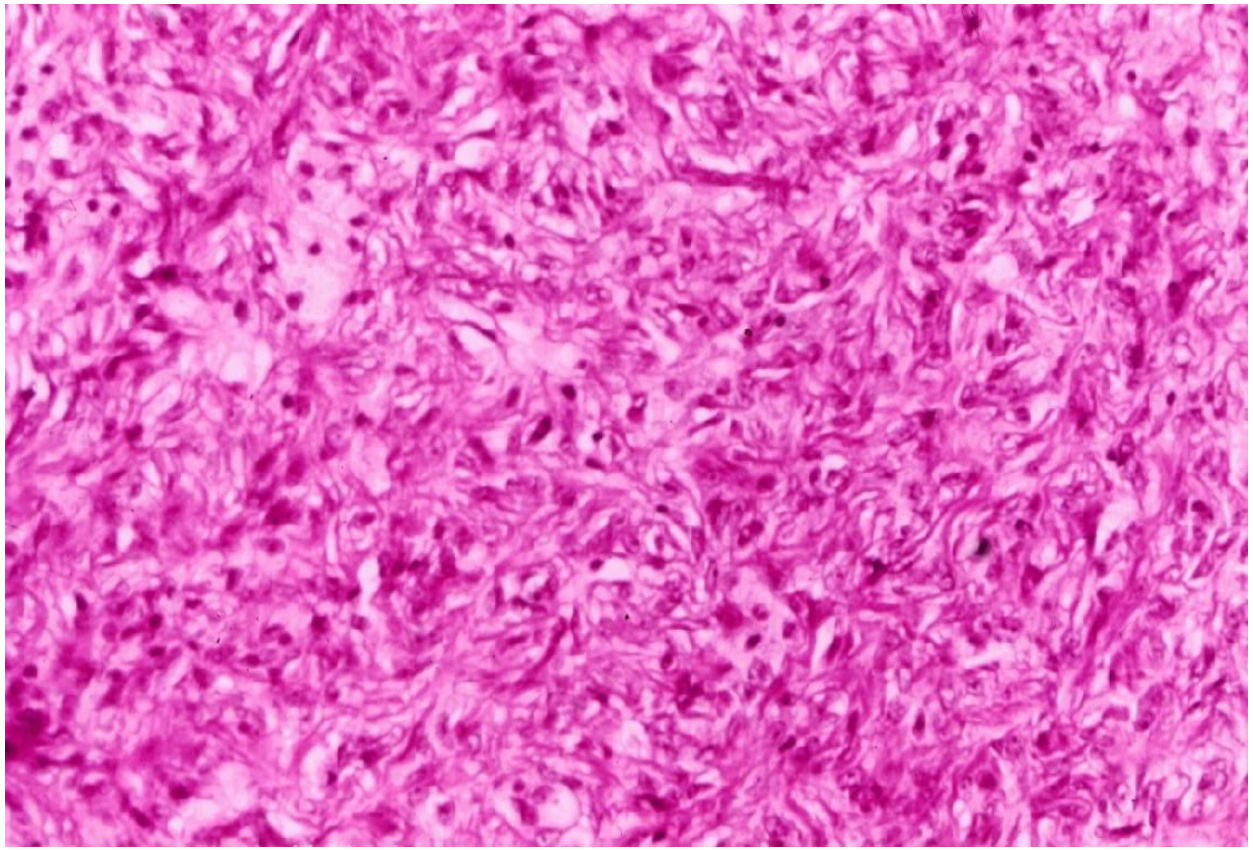
  LOW, INTERMEDIATE AND HIGH GRADE
- **ONLY VIMENTIN POSITIVITY, NO SPECIFIC GENETICS**
- **DIFF. DG.: CELLULAR MYXOMA, LOW GRADE FIBROMYXOID SARCOMA, MYXOID LIPOSARCOMA, MYXOID VARIANTS OF DIFFERENT SOFT TISSUE SARCOMAS**



FIBROUS HISTIOCYTOMA (DERMATOFIBROMA)

- VERY COMMON
- VARIABLE MIXTURE OF FIBROBLASTIC AND HISTIOCYTE-LIKE CELLS (FOAMY, MULTINUCLEATED CELLS), HEMOSIDERIN
- MAINLY SUBCUTANEUS





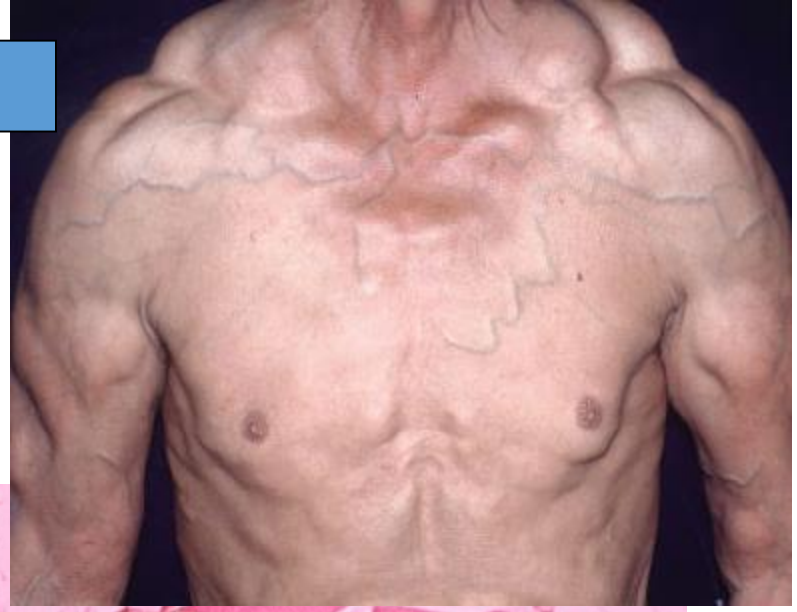
Adipocytic tumours

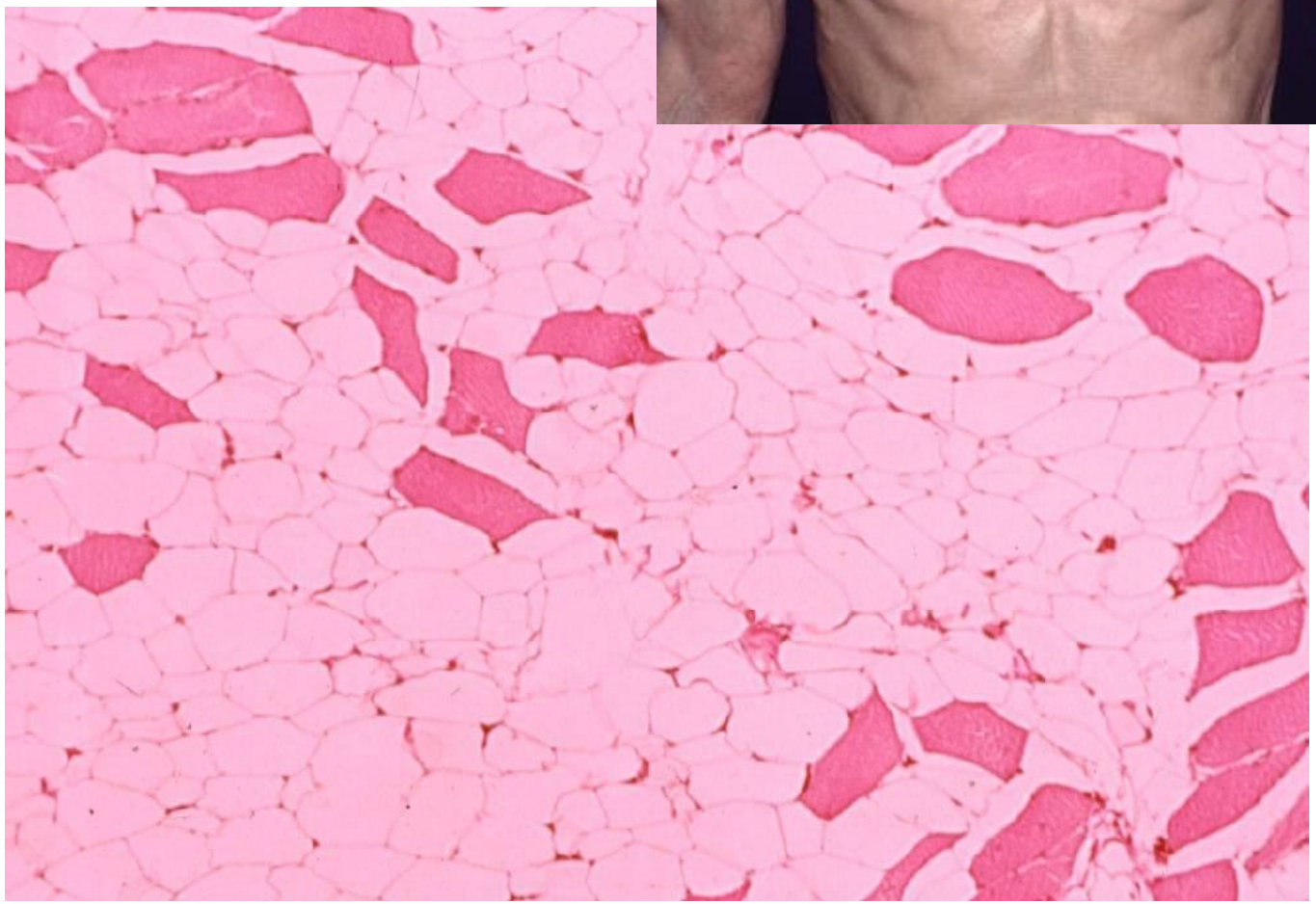
Lipoma
Lipomatosis
Lipomatosis of nerve
Lipoblastoma
Angiolipoma
Myolipoma of soft tissue
Chondroid lipoma
Spindie cell/pleomorphic lipoma
Hibernoma
Atypical lipomatous tumour
Dedifferentiated liposarcoma
Myxoid liposarcoma
Pleomorphic liposarcoma

LIPOMA

* BENIGN FATTY TUMOR WHICH CAN ARISE IN ANY LOCATION, VERY COMMON
* MAINLY SUPERFICIAL RARELY DEEP-SEATED
* OFTEN GROW TO A LARGE SIZE AND ARE USUALLY ENCAPSULATED
* MAY BE SINGLE OF MULTIPLE
* MATURE FATTY TISSUE; OFTEN MIXED WITH VESSELS, SMOOTH MUSCLE (ANGIOMYOLIPOMA IN KIDNEY)
* CHROMOSOMAL ABBERATION OF 12q, 6p BUT NOT RING OR GIANT CHROMOSOMES

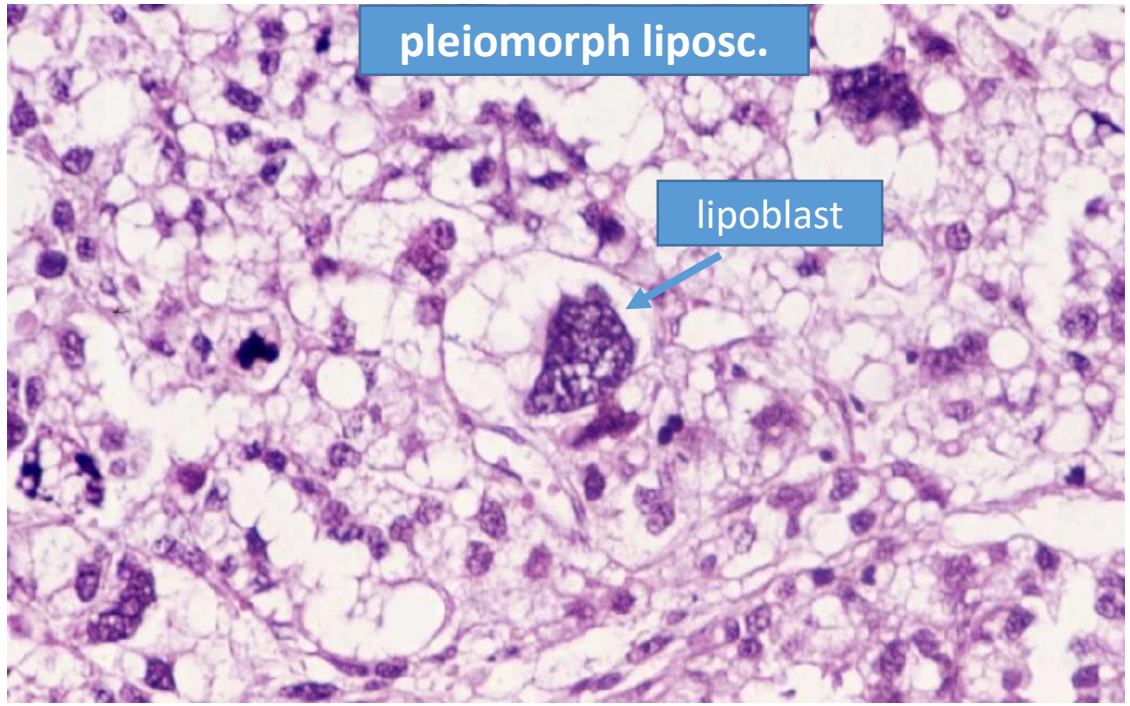
pseudoathletic appearance

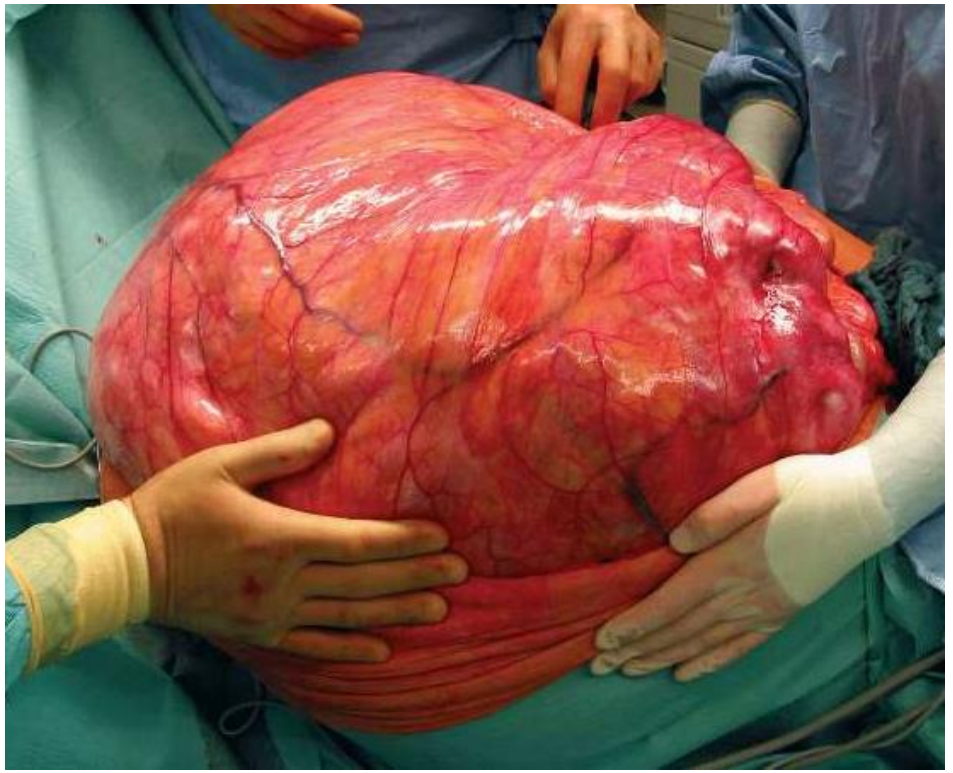




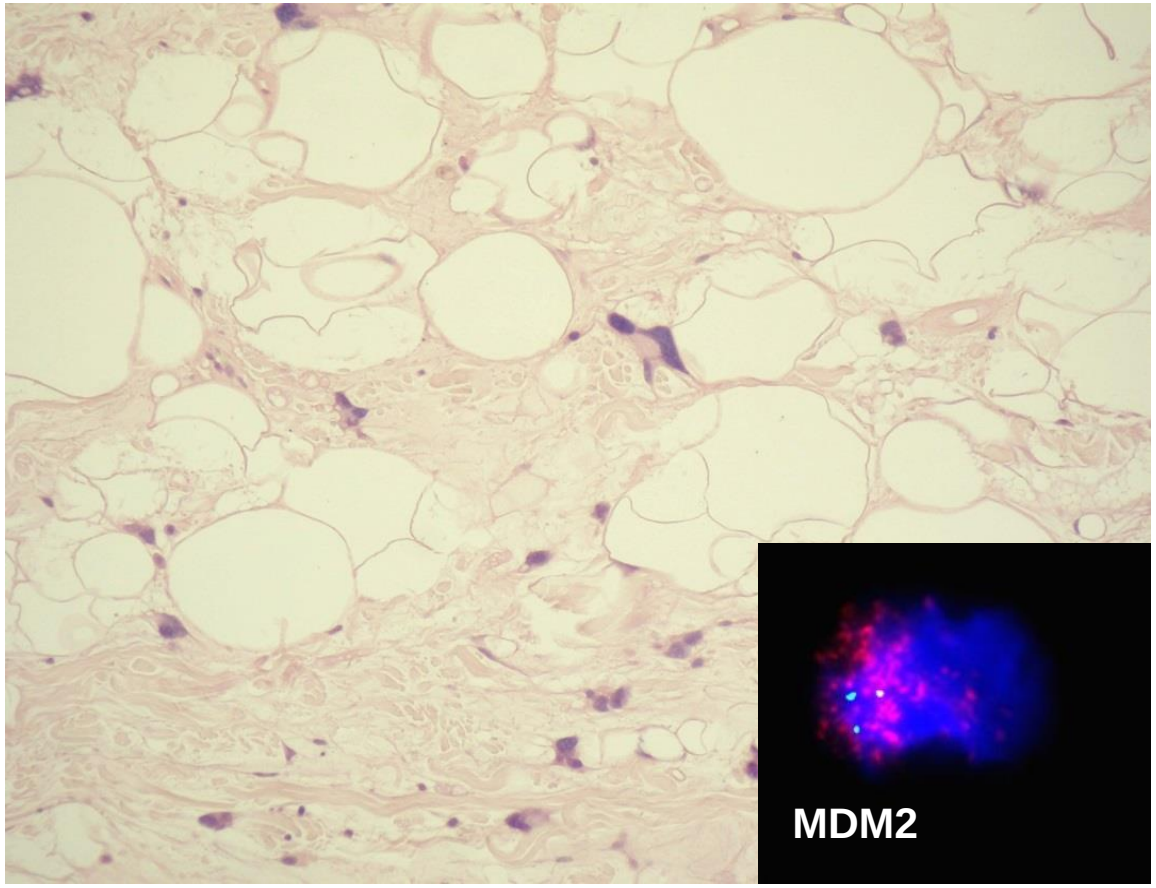
LIPOSARCOMA

- **SECOND MOST FREQUENT SOFT TISSUE SARCOMA IN ADULTS**
- **USUALLY LARGE AND OCCUR MOST FREQUENTLY IN THE LOWER EXTREMITIES**
- **DIFFERENT SUBTYPES BUT THE CLUE IS THE LIPOBLAST**
- ***MYXOID LIPOSARCOMA*: t(12;16)(q13;p11), *ATYPICAL LIPOMATOUS TUMOR* AND *DEDIFFERENTIATED LIPOSARCOMA*: MDM2 AND CDK4 AMPLIFICATION, *PLEIOMORPHIC LIPOSARCOMA*: COMPLEX KARYOTYPE**

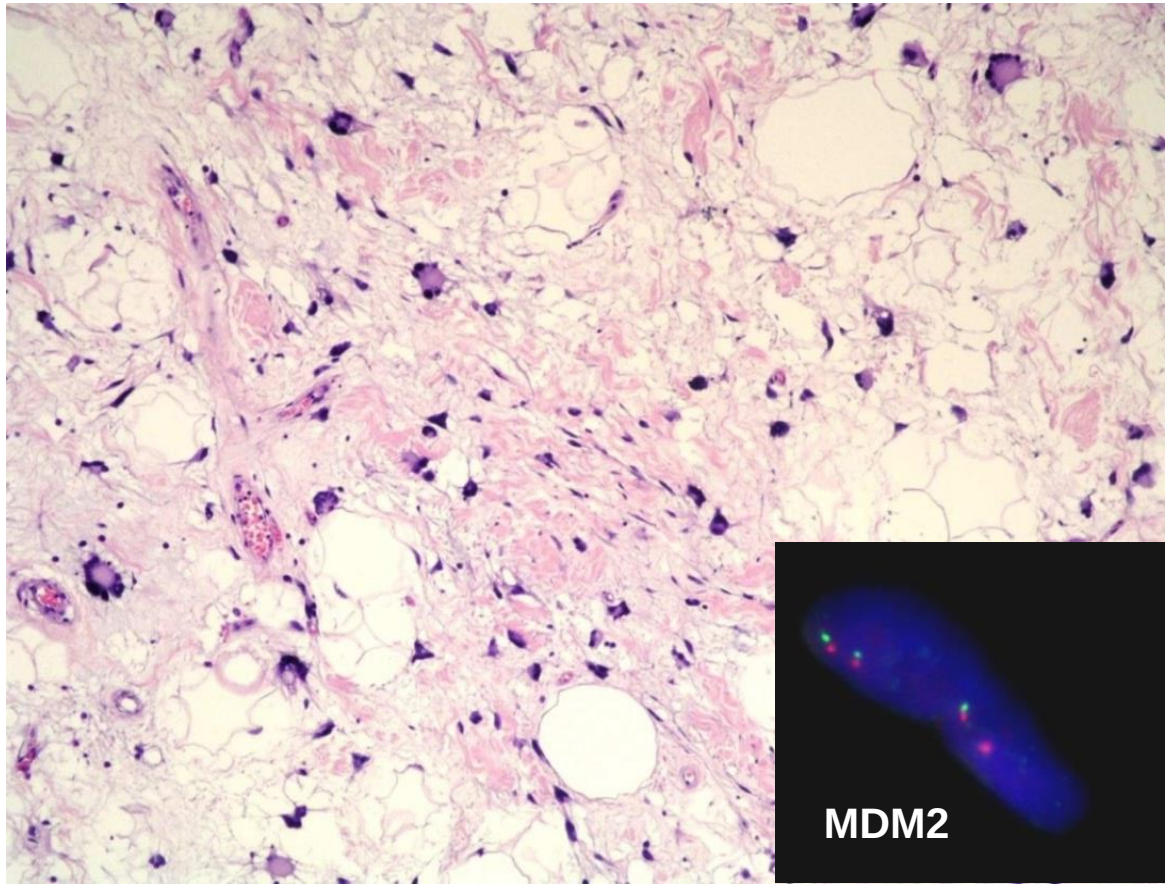




Atypical lipomatous tumor/well diff. liposarcoma

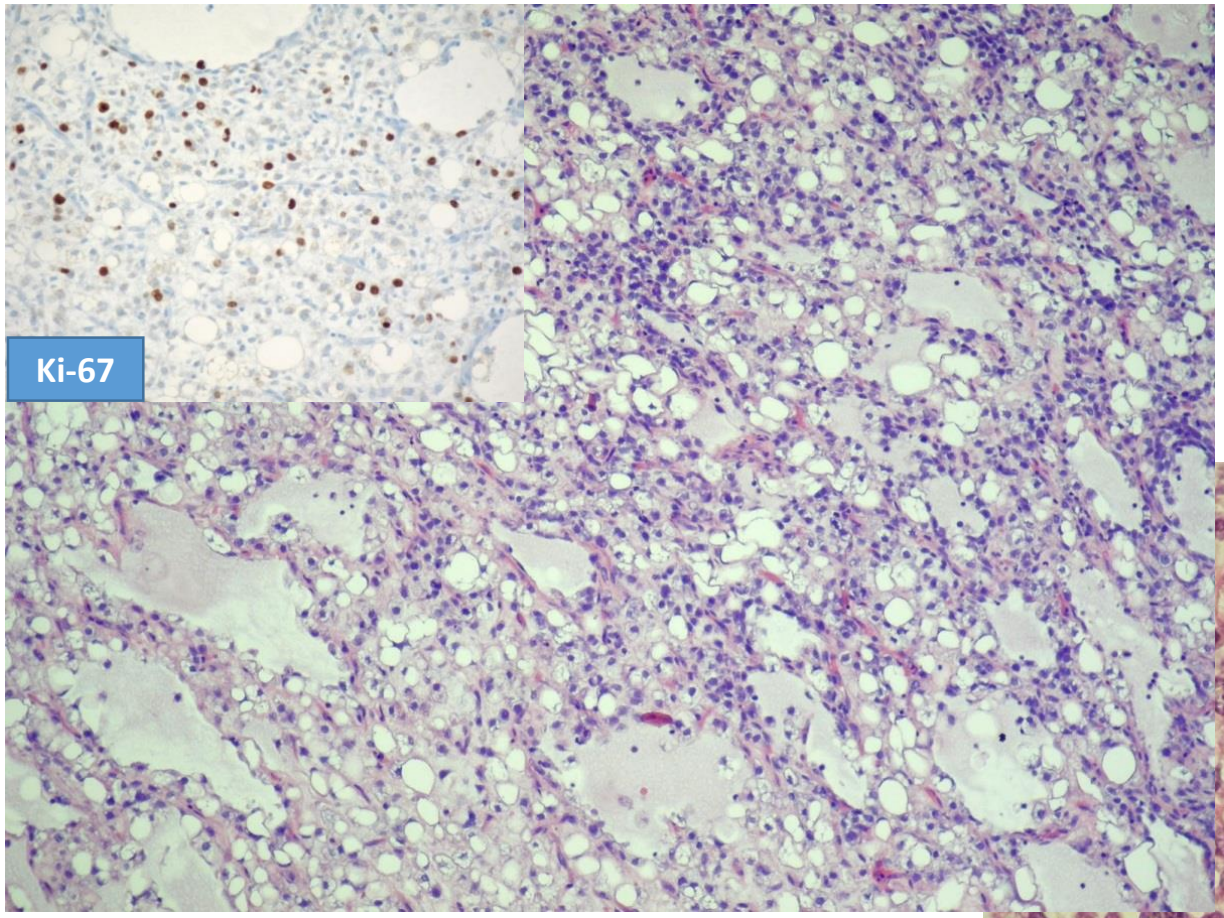


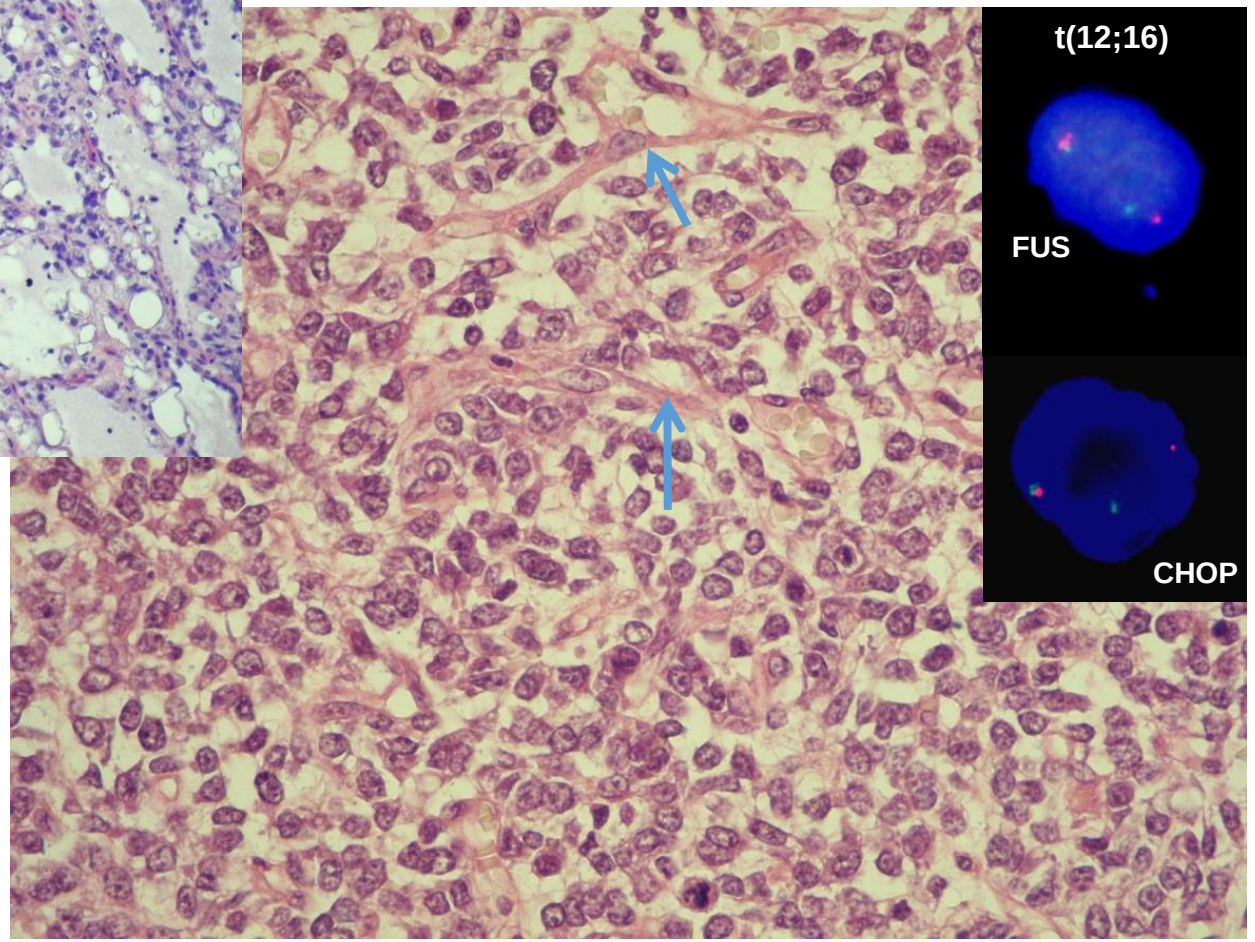
Atypical lipomatous tumor



Pleomorphic lipoma

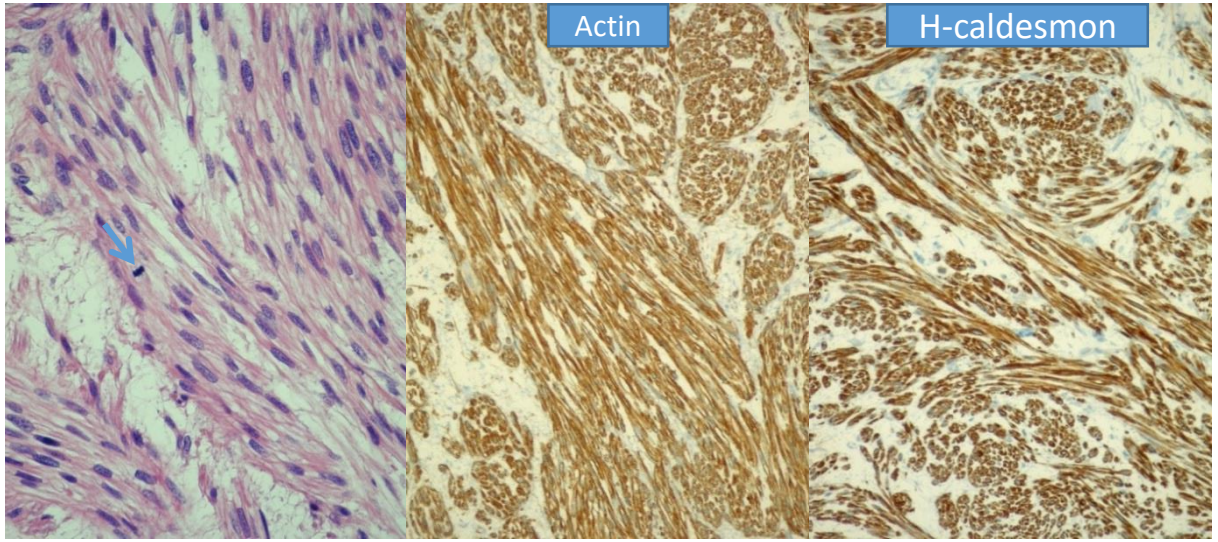
Myxoid liposarcoma





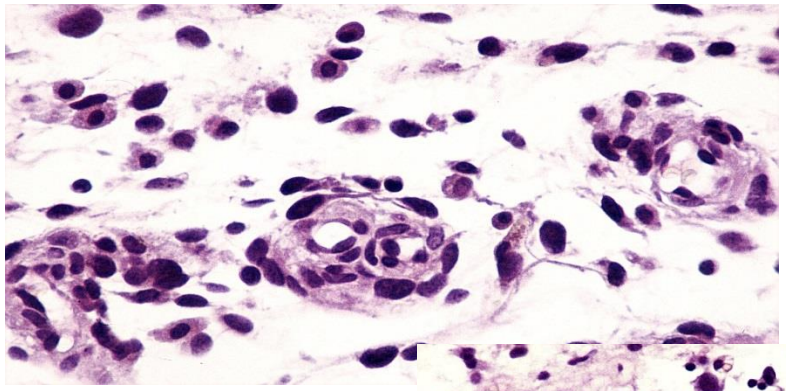
Smooth-muscle tumors

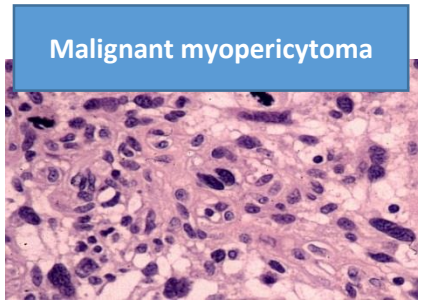
Leiomyosarcoma

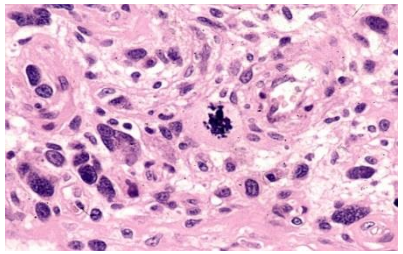


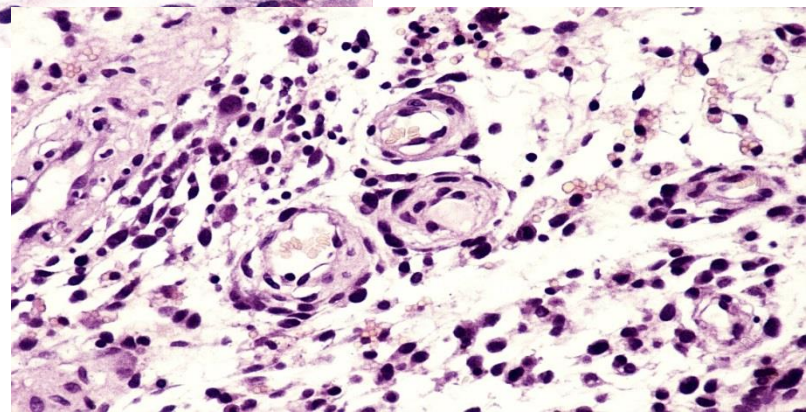
Pericytic (perivascular) tumors

Glomus tumours
Myopericytoma and myofibroma
Angioleiomyoma









No haemangiopericytoma!

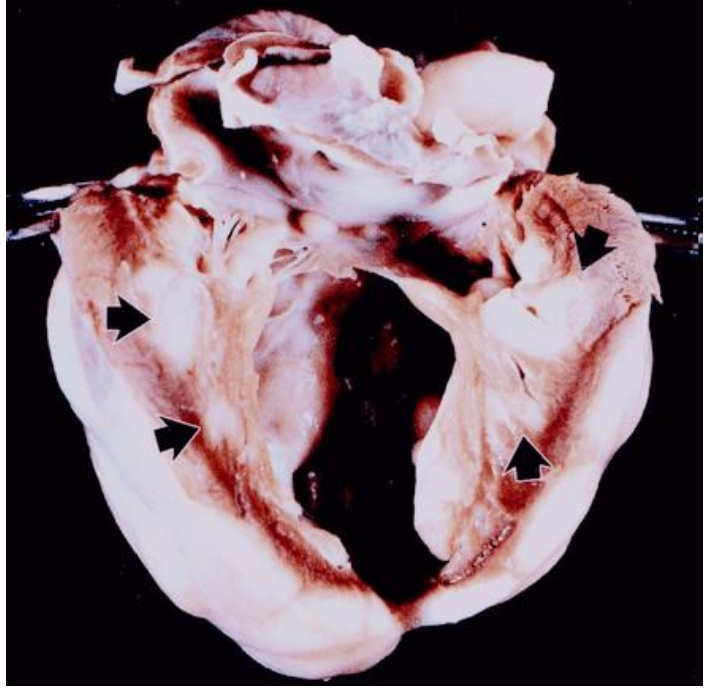
Skeletal-muscle tumours

Rhabdomyoma
Embryonal rhabdomyosarcoma
Alveolar rhabdomyosarcoma
Pleomorphic rhabdomyosarcoma
Spindie cell/sclerosing rhabdomyosarcoma

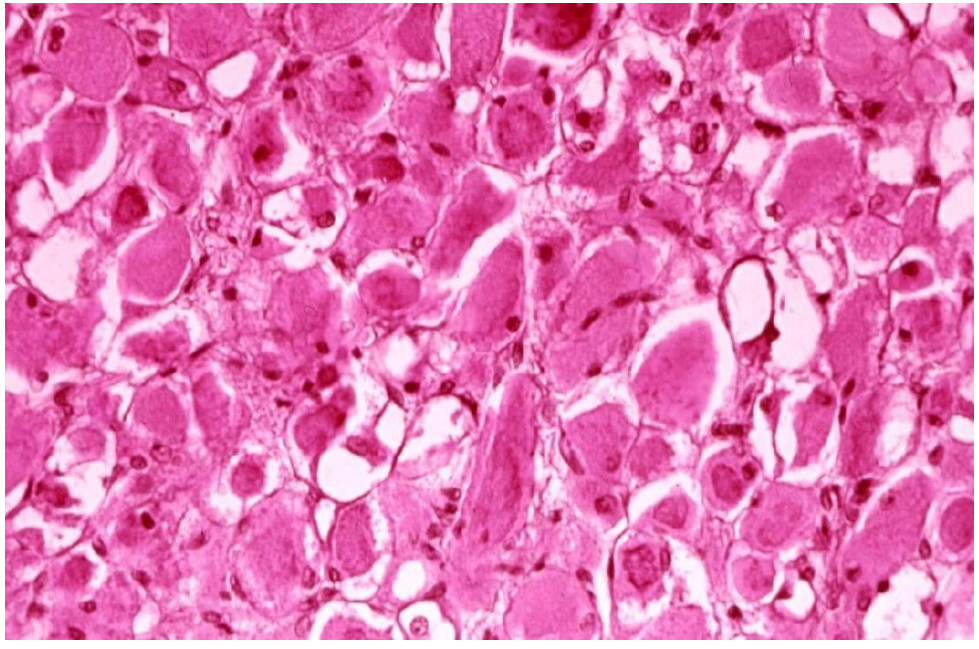
RHABDOMYOMA

- **ADULT TYPE (IN THE ORAL CAVITY), FETAL FORM (HEAD AND NECK AREA AND HEART) AND GENITAL TYPE (VULVOVAGINAL REGION); VERY RARE, BENIGN; SCLEROSIS TUBEROSA**

- **WELL DIFFERENTIATED LARGE, ROUNDED OR POLYGONAL TUMOR CELLS WITH ABUNDANT ACIDOPHILIC CYTOPLASM; CROSS STRIATION**



Rhabdomyoma in a 3-month-old boy with tachycardia.



RHABDOMYOSARCOMA

Mainly in the first 10 years; most common soft tissue sarcoma of childhood

Four regions: head and neck, genito-urinary, retroperitoneal and limbs

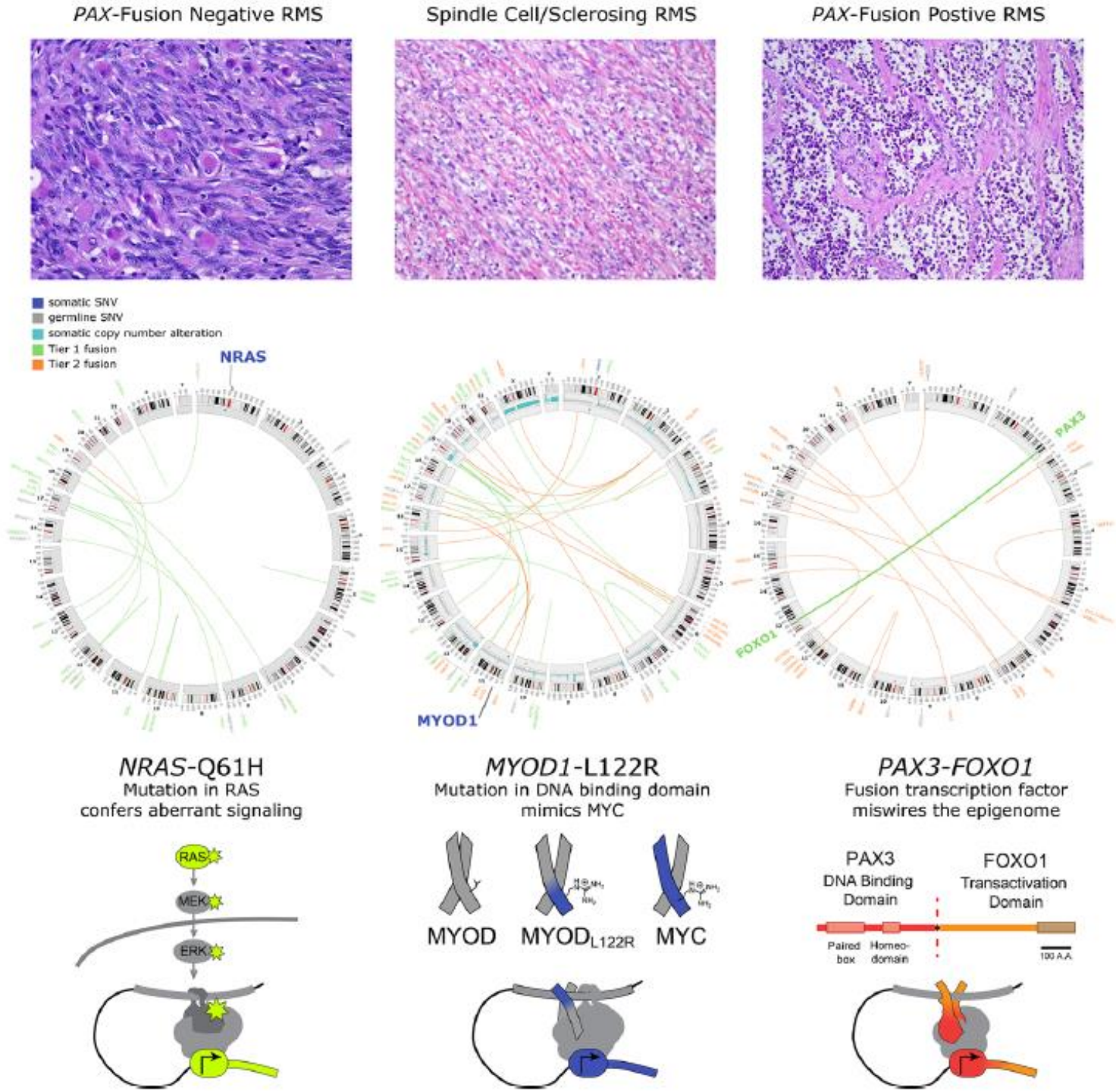
Embryonal type: primitive mesenchymal cells in various stages of myogenesis; rhabdomyoblast
Alveolar type: small round cell tumor with alveolar or solid pattern; mainly in adolescents and young adults; characteristic translocation: t(2;13) resulting FOXO1-PAX3/7 fusion gene

Spindle cell type: MyoD1 mutation – *bad prognosis*; VGLL2 mutation (congenital/infant), – *very good prognosis*;
no mutation – *good prognosis*

Pleomorphic type: older age or adults; pleomorphic tumor cells with abundant eosinophilic cytoplasm but usually no cross-striation

Immunostaining: desmin, Myf4/myogenin

All types are highly malignant, but the alveolar type has the worst prognosis



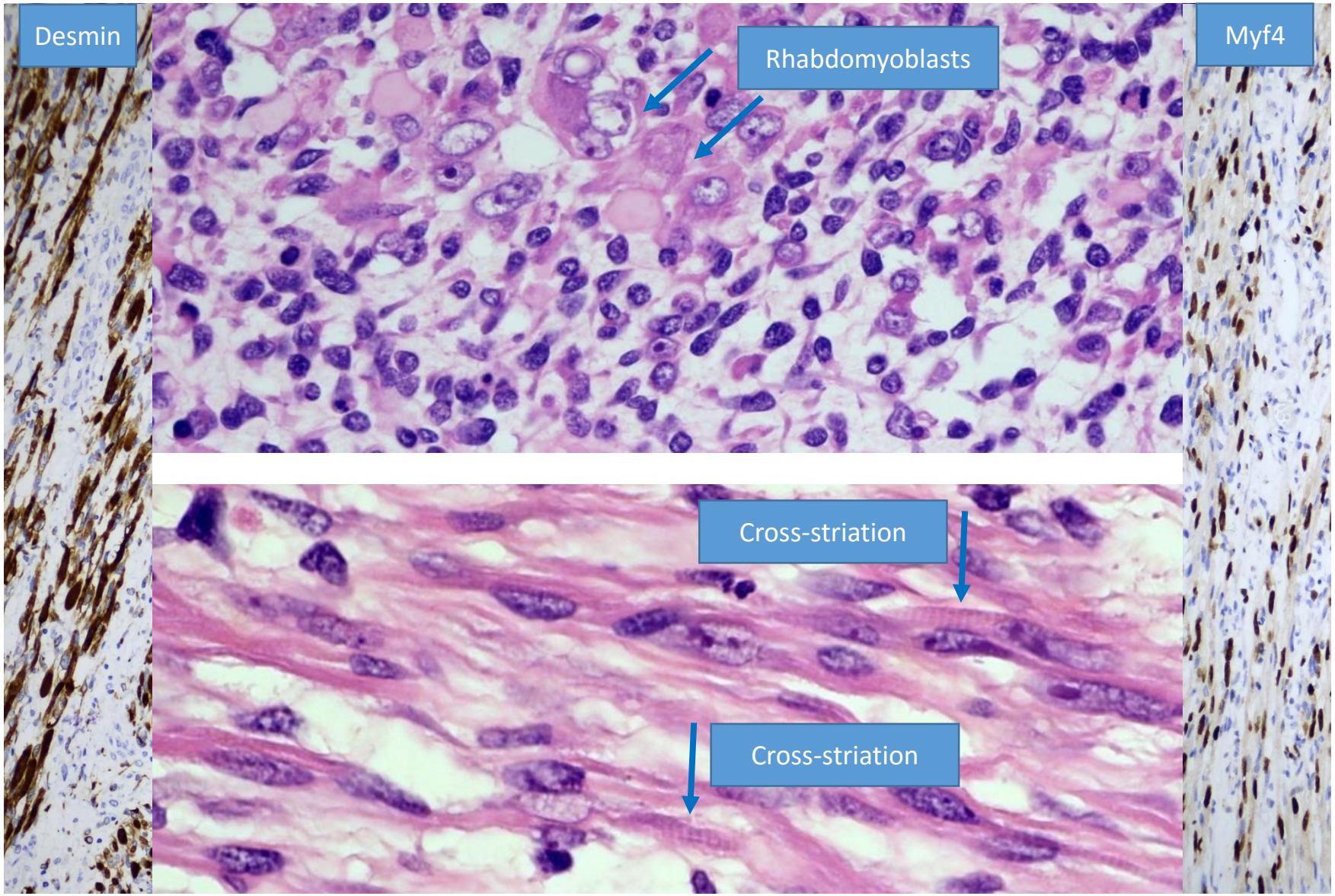
Insights into pediatric rhabdomyosarcoma research: Challenges and goals.
Yohe ME,, Tapscott SJ, Vakoc CR, Langenau DM.
Pediatr Blood Cancer. 2019 Oct;66(10):e27869.

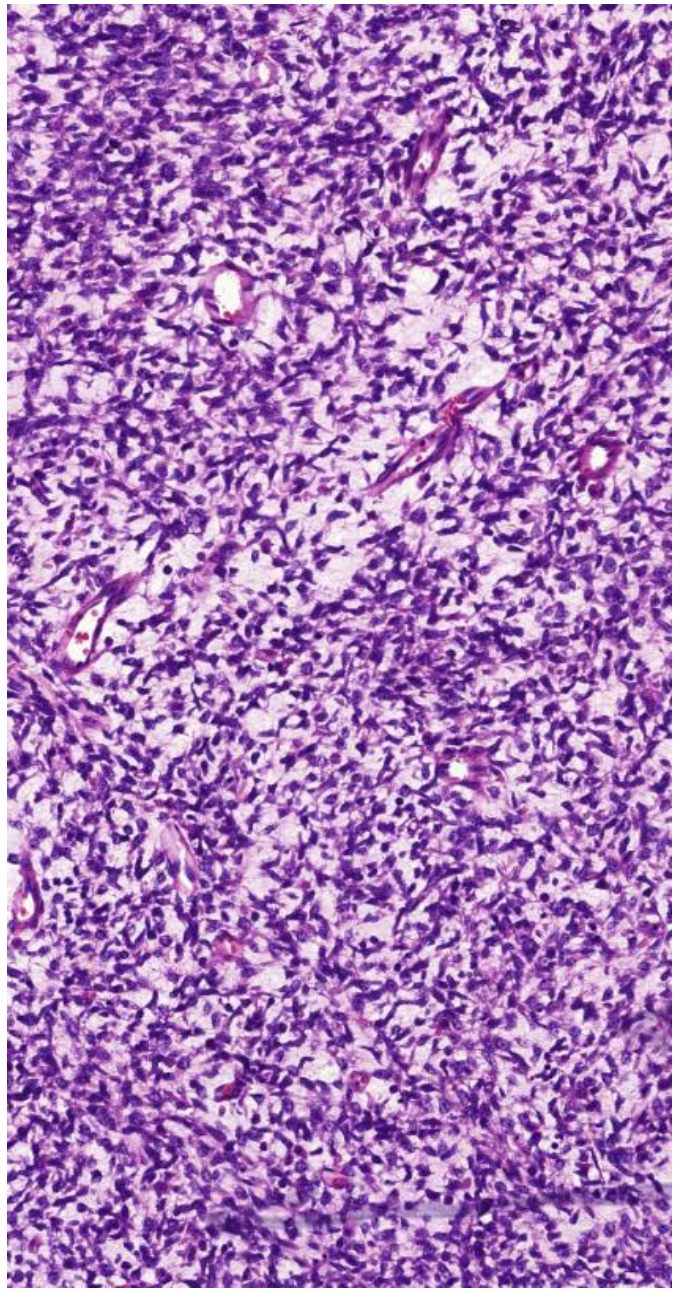
TABLE 1 Preclinical targets in pediatric RMS

Target	Potential agent
Asparagine metabolism	PEG-asparaginase
Aurora kinases	Alisertib
BRD4 inhibitor	OTX015
CDK4/6	Palbociclib
DNA methyltransferases	5-Azacytidine
Histone deacetylases	Entinostat
IGF-1R	Ganitumab
MEK 1/2	Trametinib
NOTCH	RO4929097
PARP	Olaparib
PI3 kinase/ mTOR	Buparlisib
SMO	Vismodegib
VANGL	N/A
WEE1	AZD1775

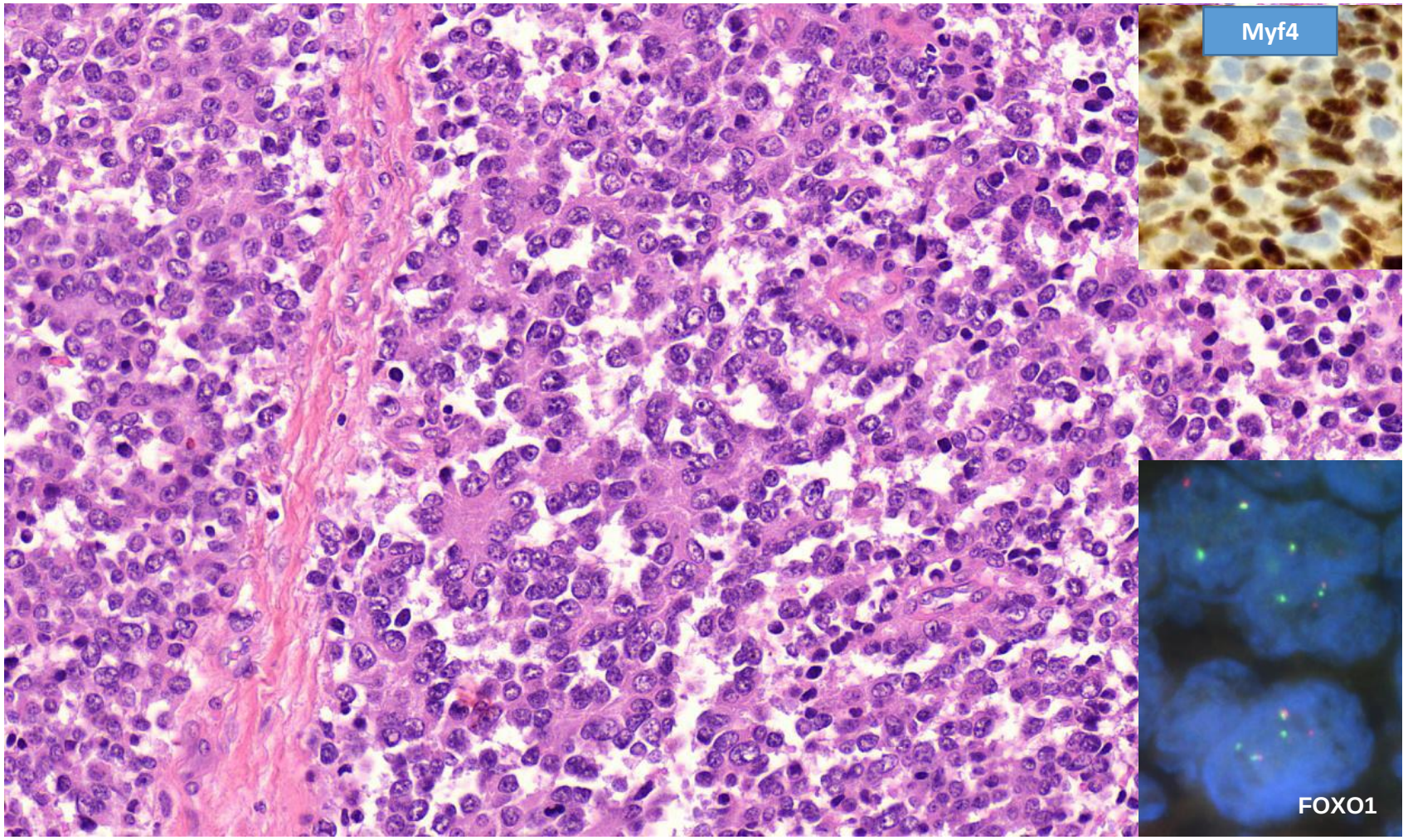
Embryonal rhabdomyosarcoma

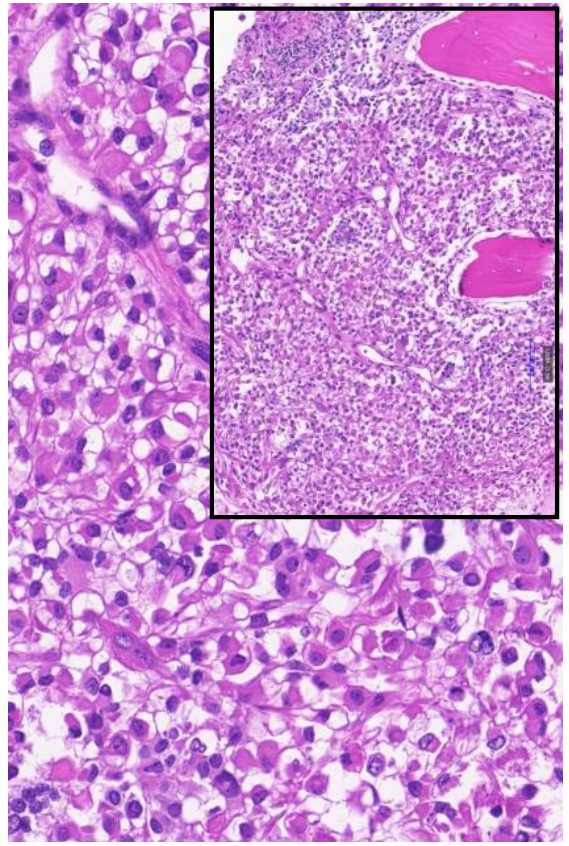
Botryoid variant: epithelial-lined viscera (bladder, pharynx, vagina), polypoid masses





Alveolar rhabdomyosarcoma

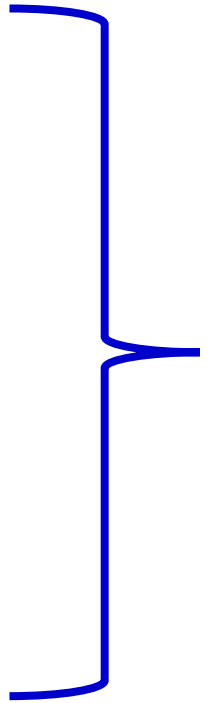




Balogh P, Bánusz R, Csóka M, Váradi Z, Varga E, Sápi Z.
Primary alveolar rhabdomyosarcoma of the bone: two cases and review of the literature.
Diagn Pathol. 2016 Oct 18;11(1):99.

Vascular tumours

Haemangiomas
Epithelioid haemangioma
Angiomatosis
Lymphangioma
Kaposiform haemangioendothelioma
Retiform haemangioendothelioma
Papillary intralymphatic angioendothelioma
Composite haemangioendothelioma
Kaposi sarcoma
Pseudomyogenic haemangioendothelioma
Other intermediate vascular neoplasms
Epithelioid haemangioendothelioma
Angiosarcoma of soft tissue



intermediate malignancy

Infantile haemangioma

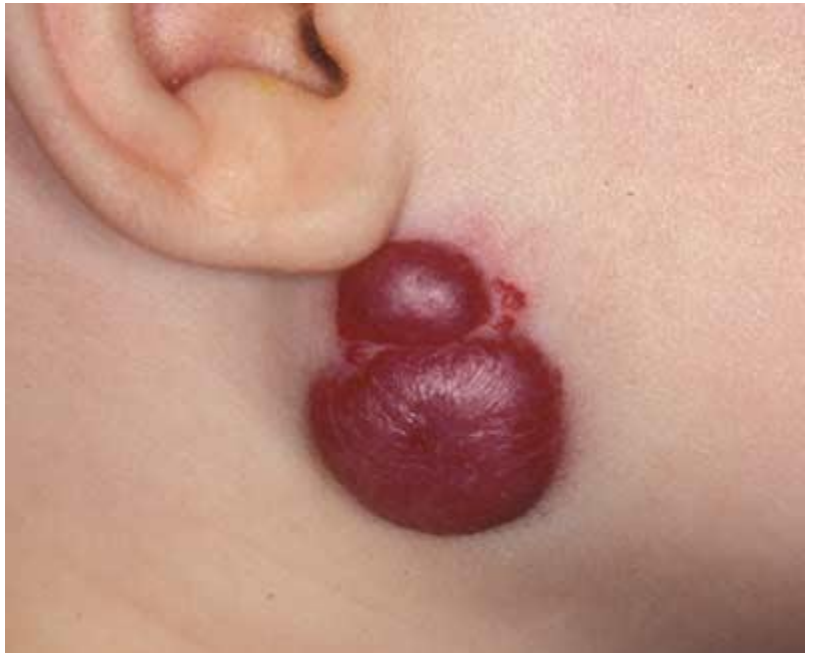
First 1-4 weeks after birth

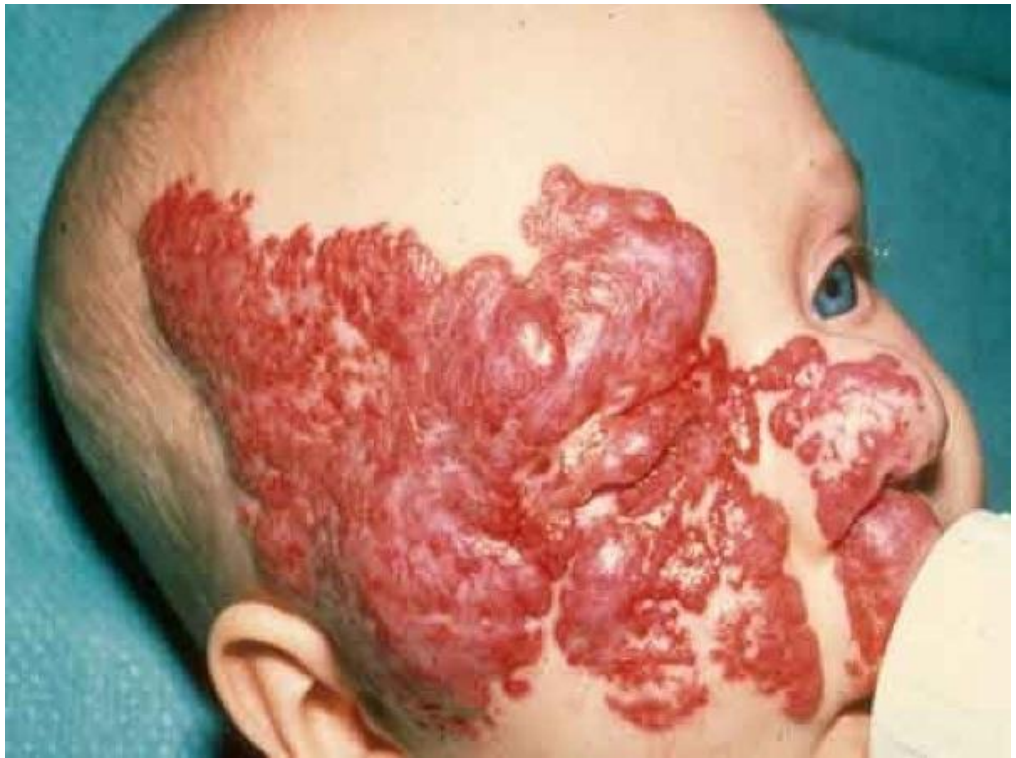
Duration: 5-8 years

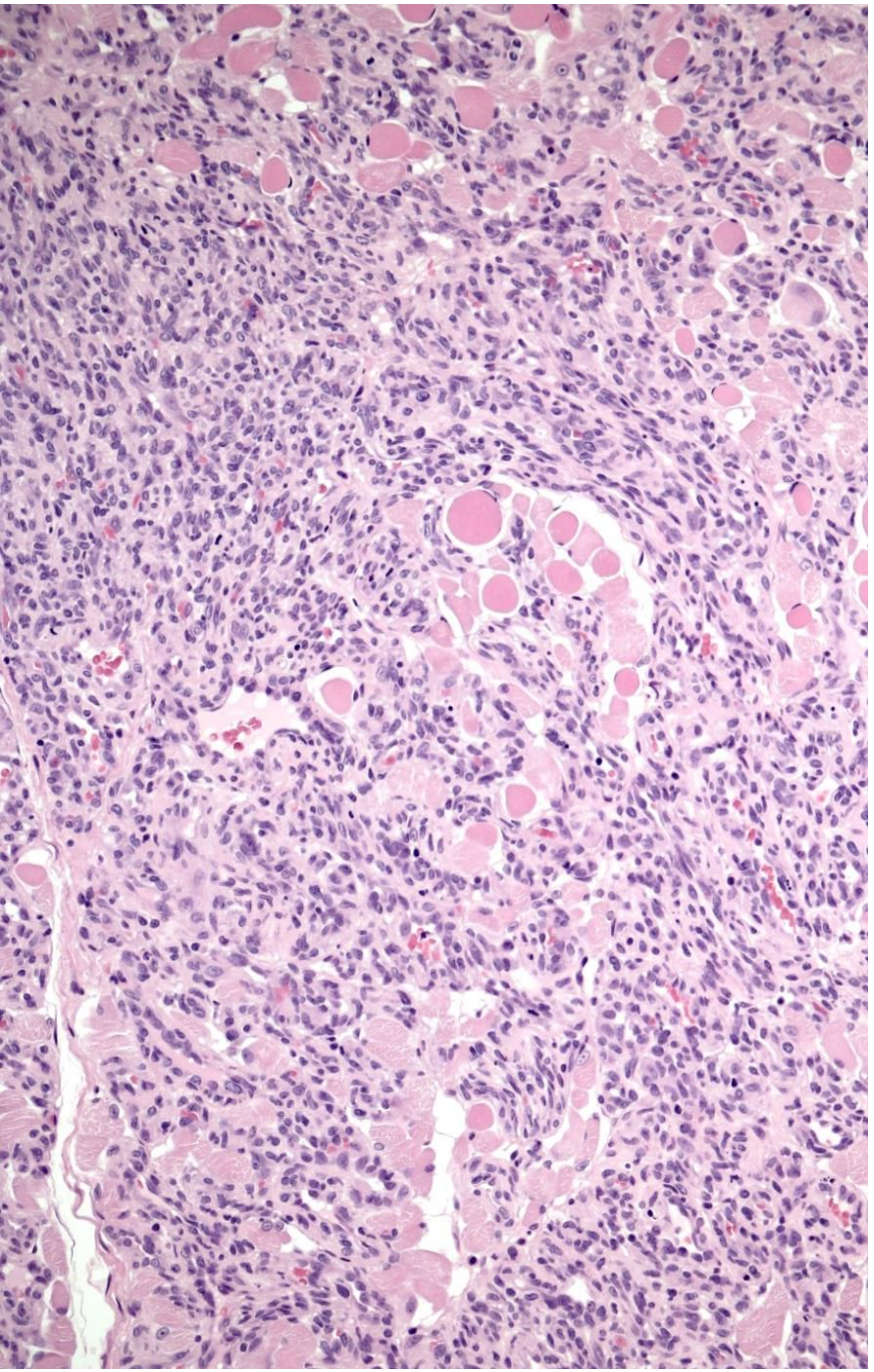
Special regression

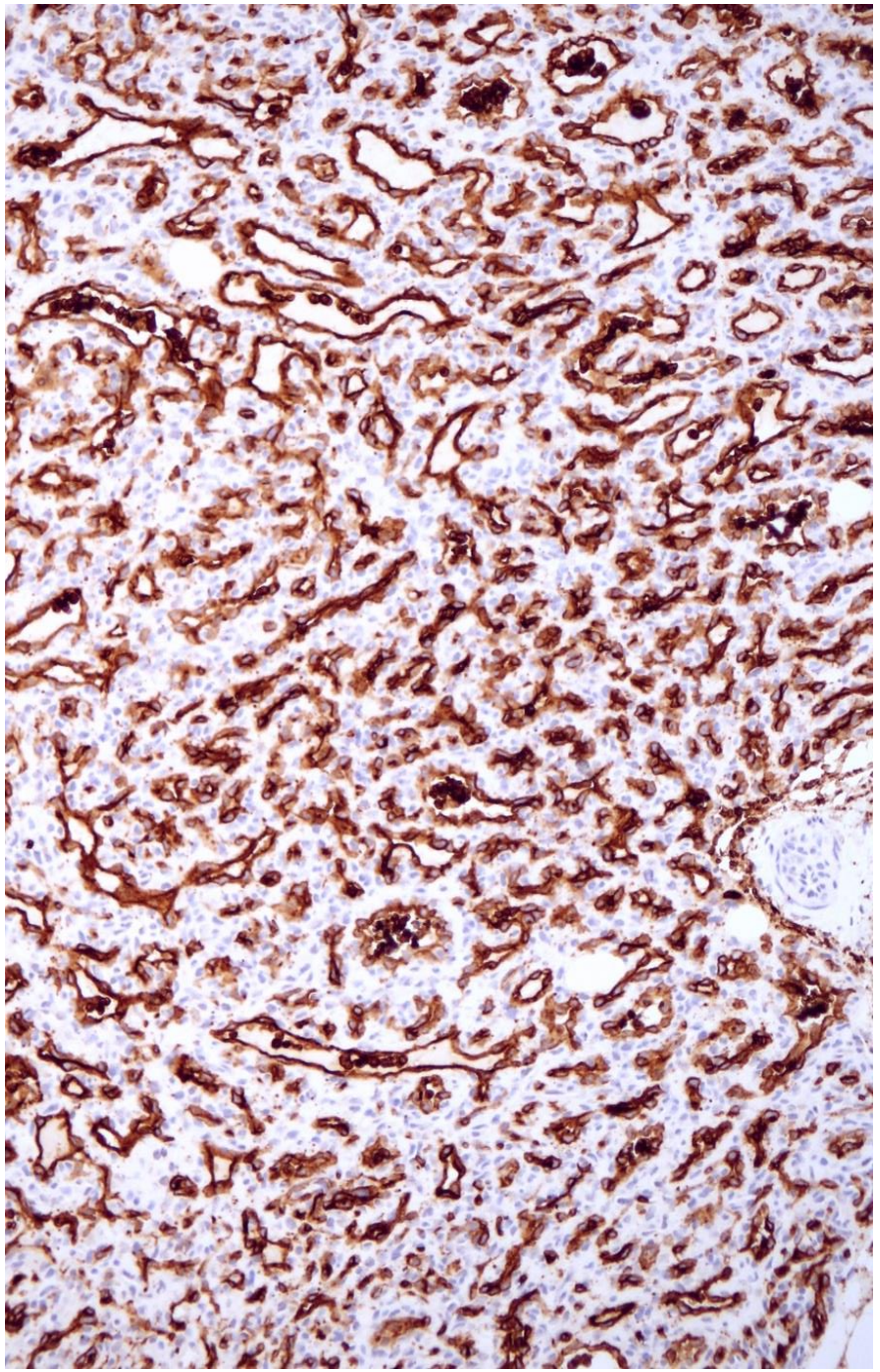
Usually no treatment, except Glut1 negative tumors

Treatment: corticosteroid, interferon, propranolol or surgical









Immunostaining: **Glut1**

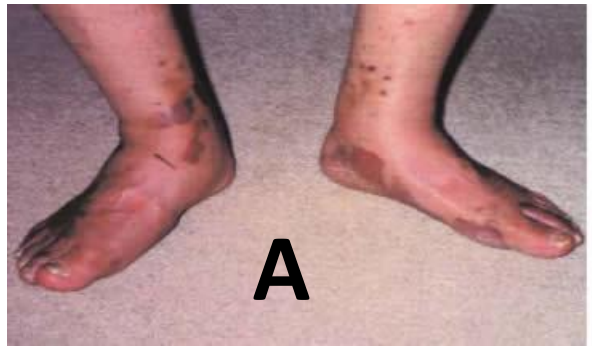
If there is Glut1+ :
haemangioma

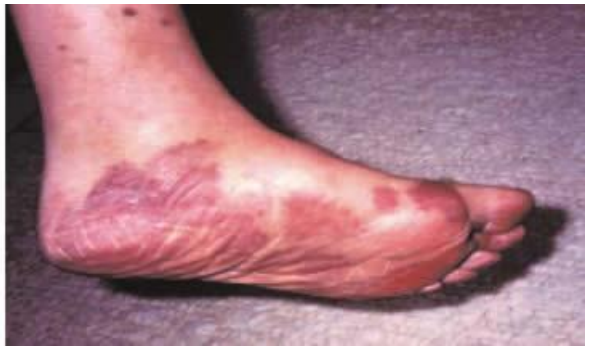
If there is no Glut1+ :
vascular malformation

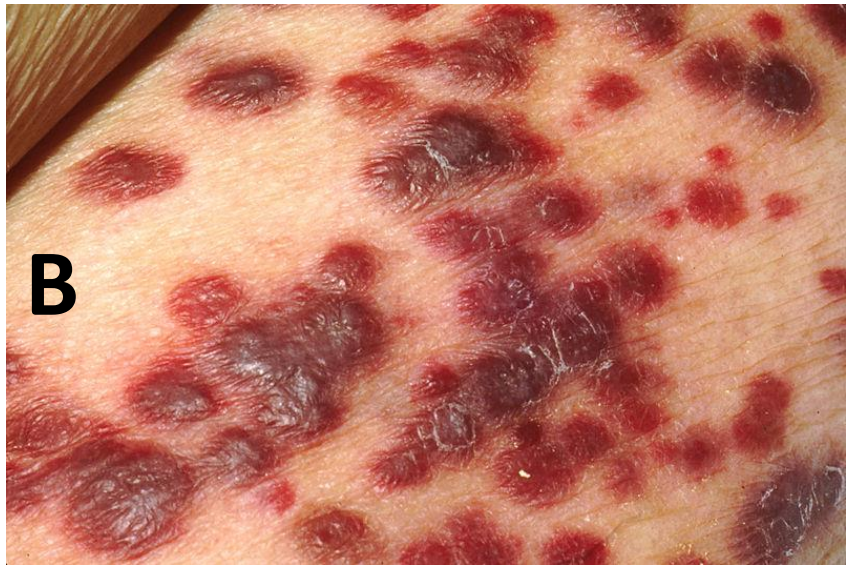
KAPOSI SARCOMA

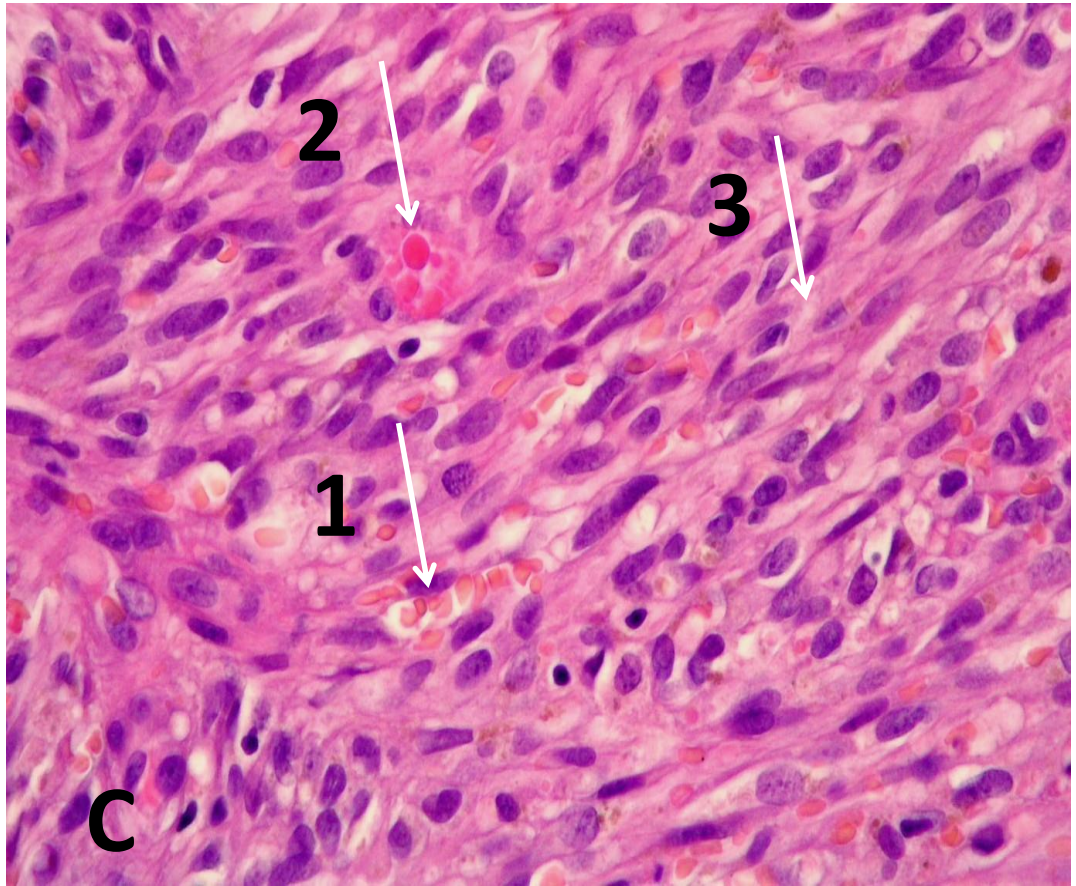
- Classical KS (sporadic); KS in Africa (endemic); HIV associated KS (epidemic); KS associated with immunosuppressive treatment (iatrogenic)
- Male, multiplex cutaneous lesions, typically on leg
- Early phase: vascular proliferation, extravasated erythrocytes, hemosiderin pigment
- Late phase: fibrosarcoma-like picture; hyaline globules in the cytoplasm
- CD-34 +, CD-31+, HHV8+
- Prognosis: much better comparing with angiosarcoma

Kaposi sarcoma

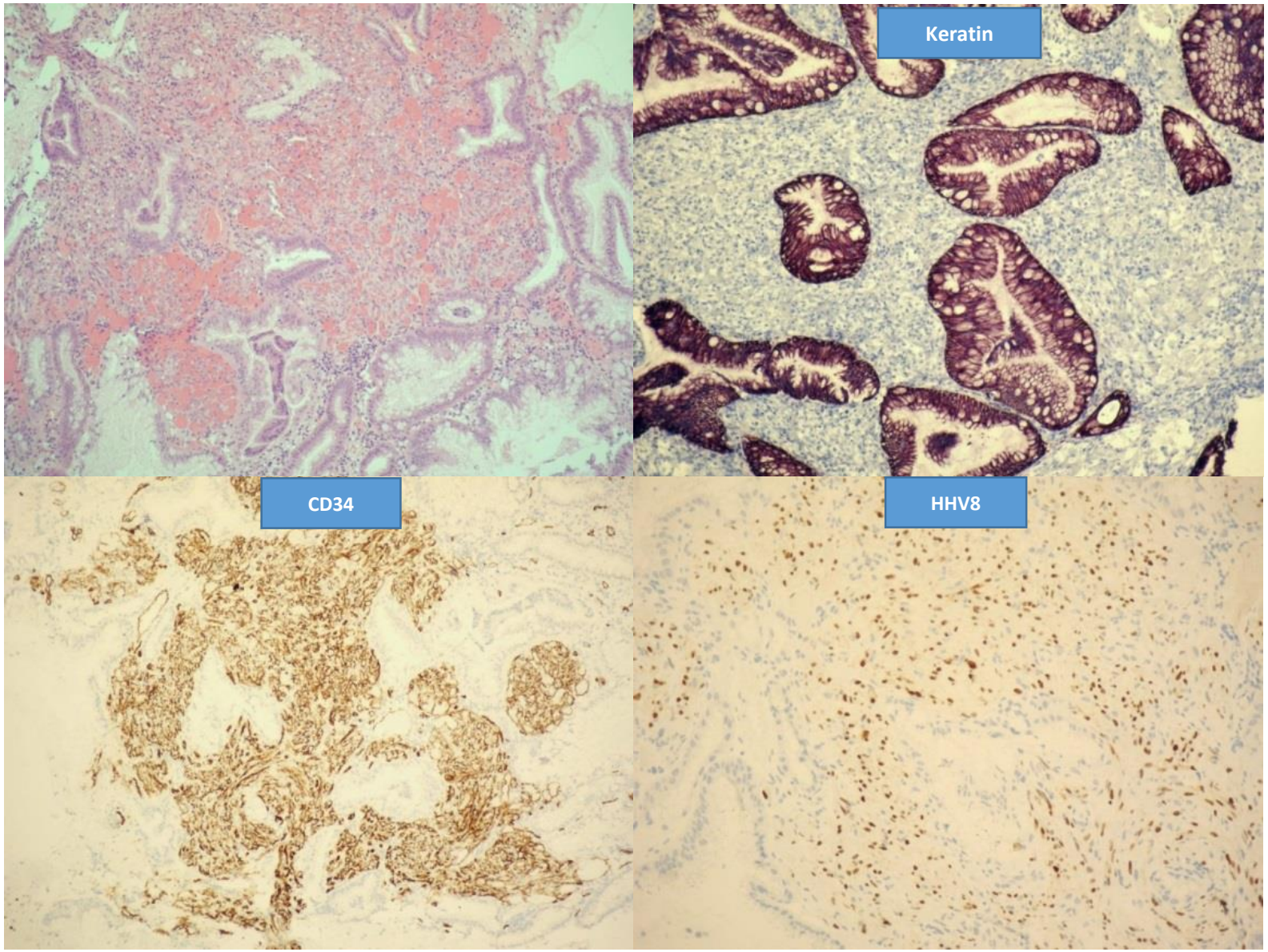








Gastric biopsy



EPITHELIOID HAEMANGIOENDOTHELIOMA

- **Adults, arise from venous walls**

- **Spindle endothelial cells with large vacuolated cytoplasm (primitive luminal forming)**

- **Mimics carcinoma**

- **Special places: lung, liver**

- **Multifocal!**

- **Intermediate malignancy,**

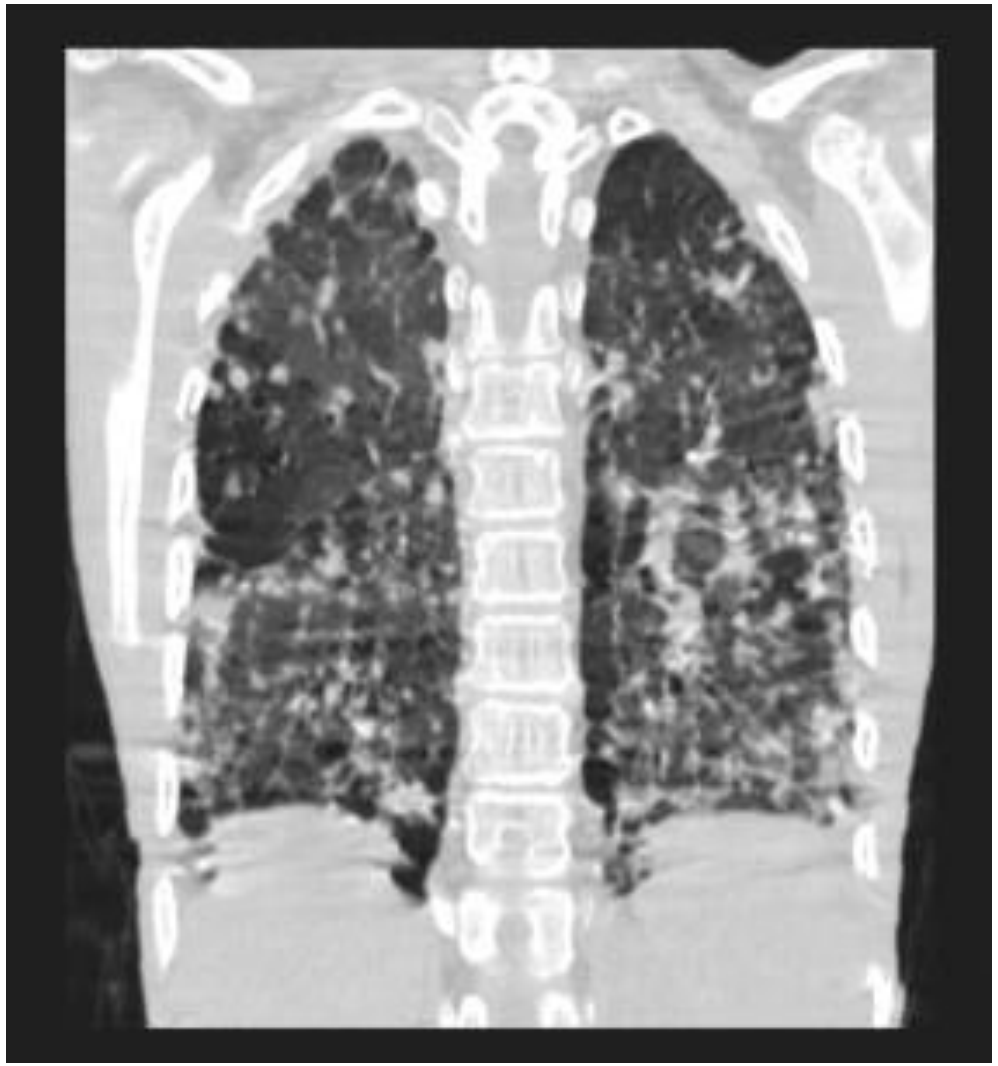
  low grade sarcoma

- **Immun: CD31, CD34, FLi1, ERG,**

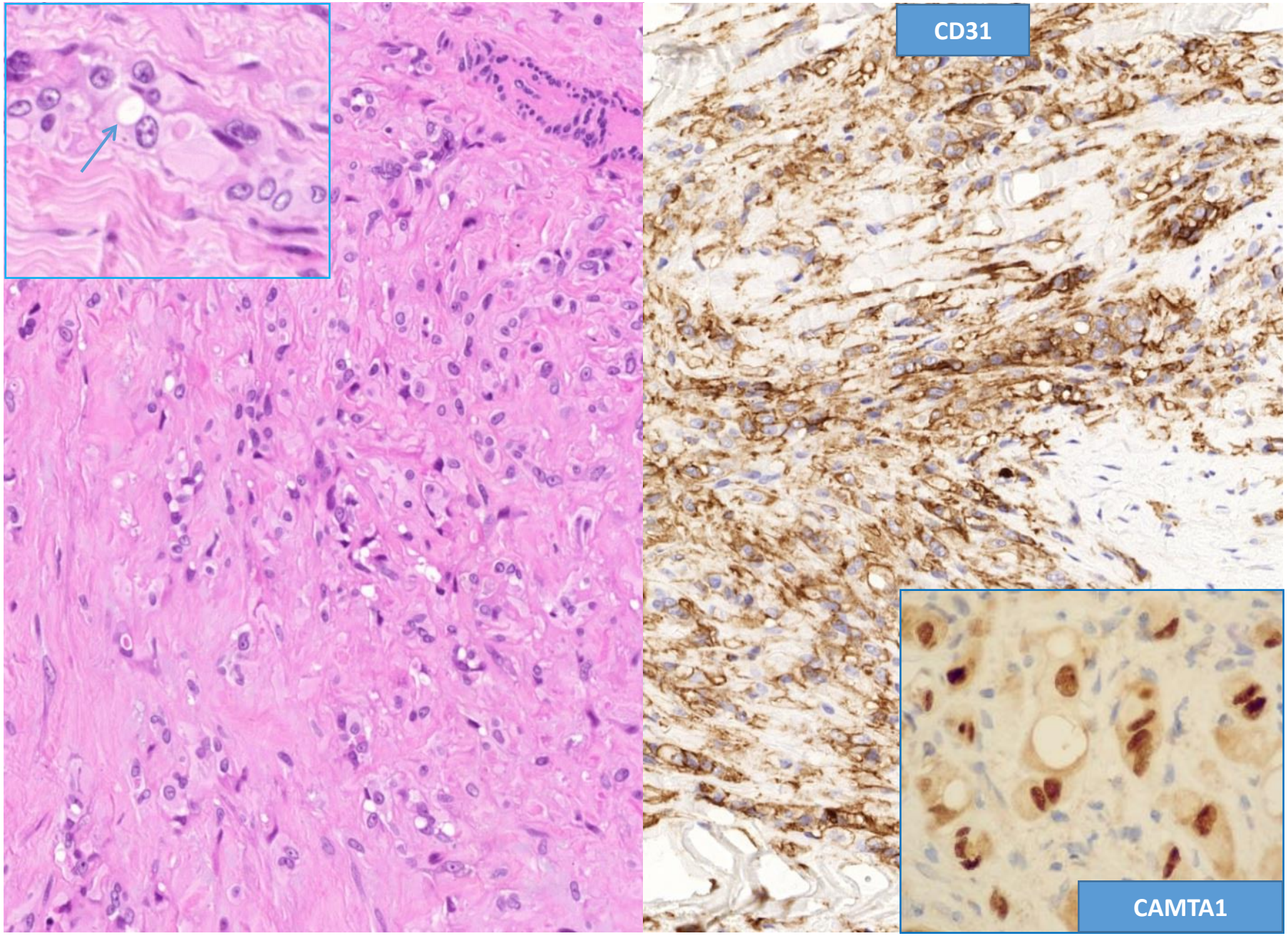
  Keratin, EMA!

- **Genetics: t(1;3)(p36;q23-25)**

  WWTR1-CAMTA1

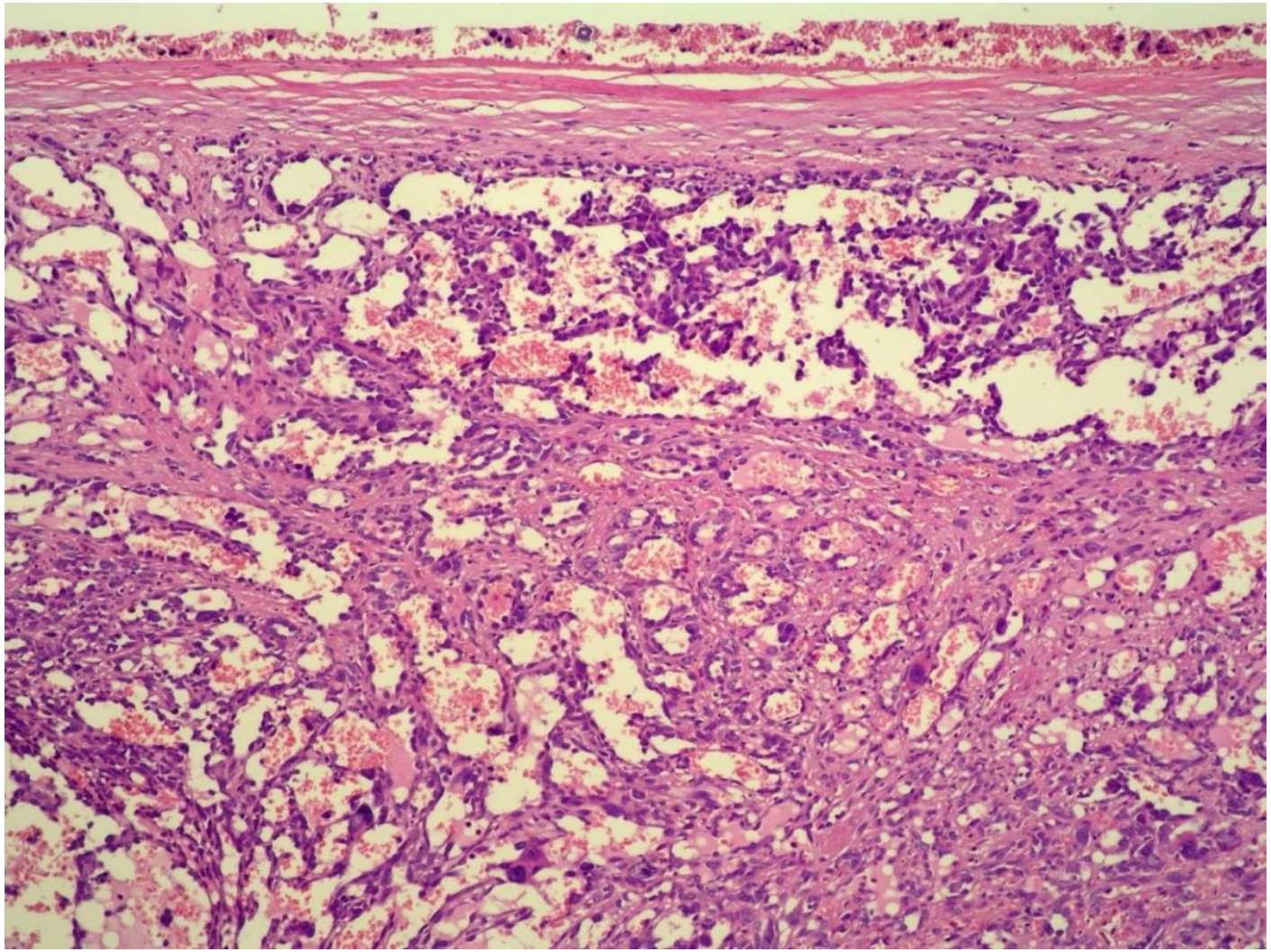


Epithelioid haemangioendothelioma



ANGIOSARCOMA

- Atypical endothelial cell forming irregular spaces or solid fascicles
- Highly vascular tumors are not angiosarcomas!
- Highly malignant tumors, multiplicity
- Very rare
- It is lethal within one year
- CD31, ERG positivity and Keratin, EMA also can be positive!



Nerve sheath tumors

Malignant peripheal nerve sheath tumor (MPNST)
Malignant granular cell tumor

Ectomesenchymoma

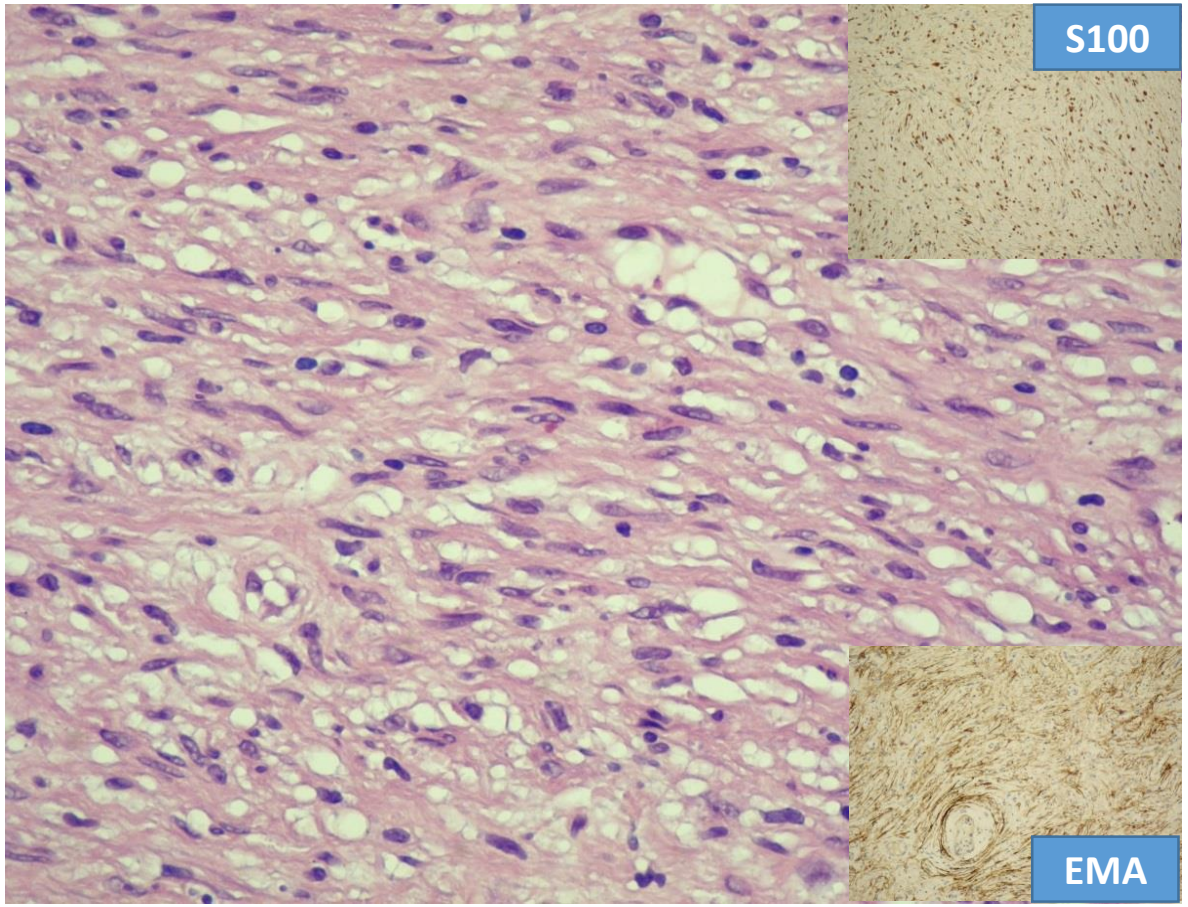
Schwannoma
Perineurioma

Hybrid nerve sheath tumors

↓

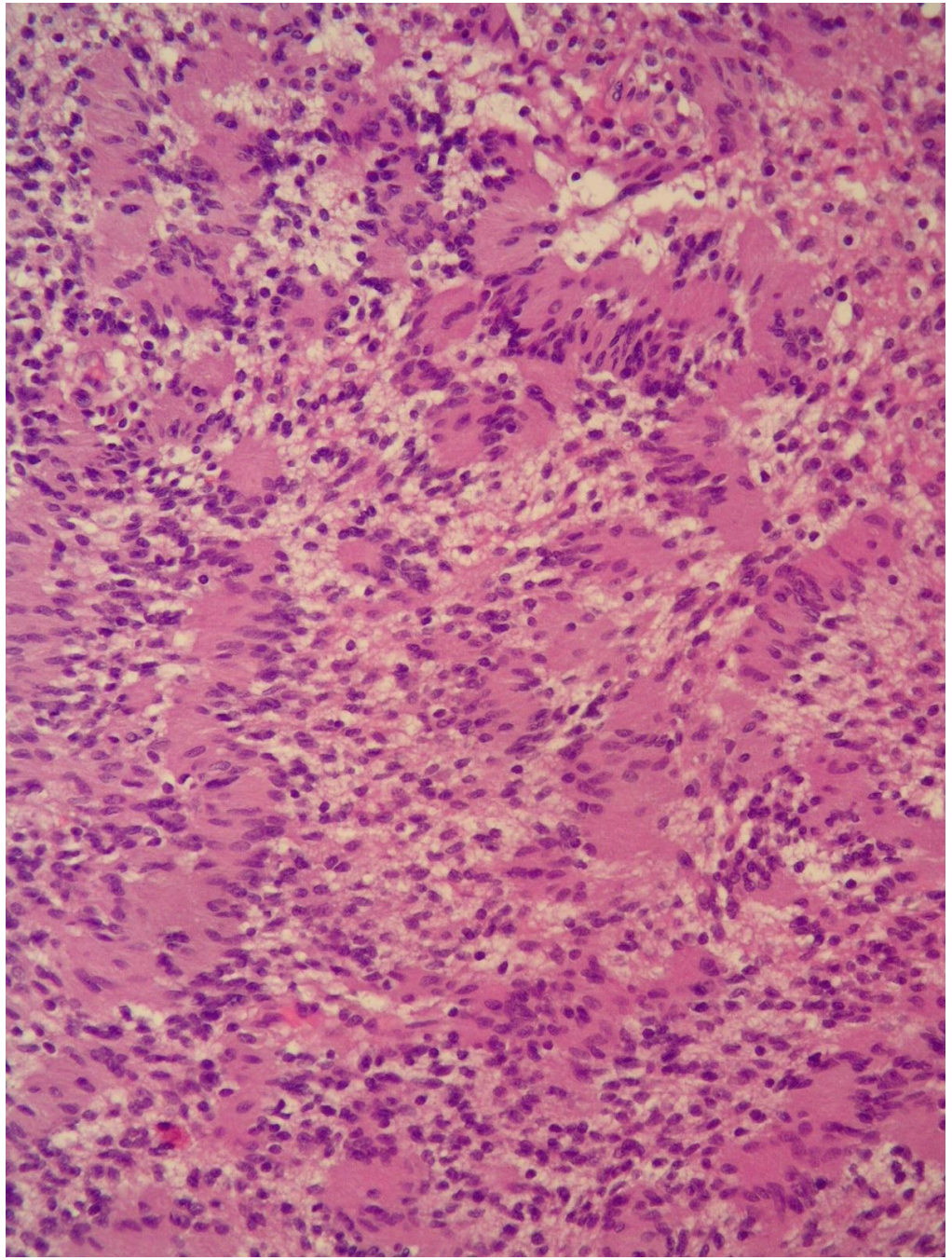
new entity

Hybrid schwannoma/perineurioma



Schwannoma

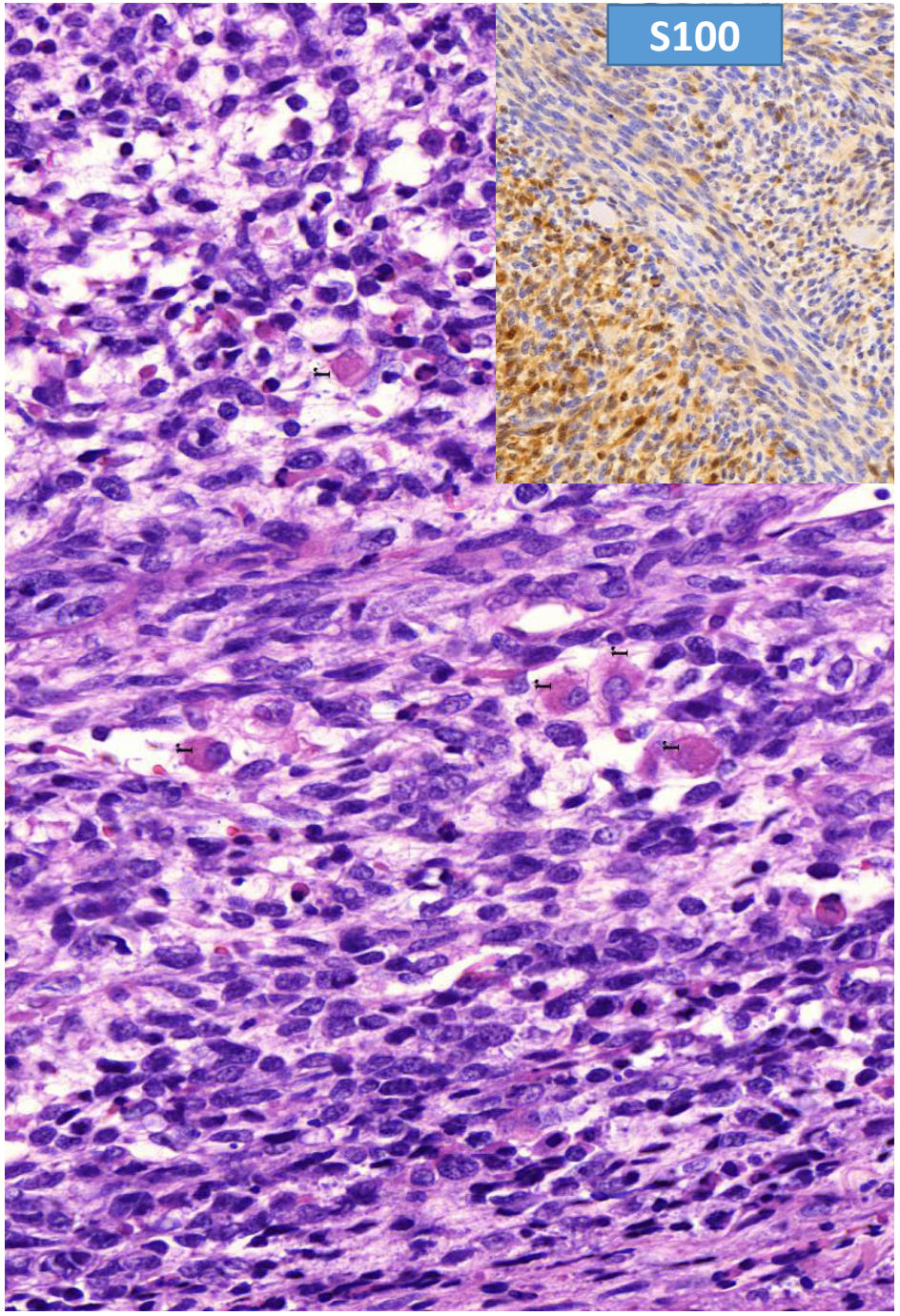
- Solitary, encapsulated tumor
- Extremities, neck, mediastinum, retroperitoneum,
- Antoni-A (cellular type) palisaded-organoid cell proliferation (Verocay-body)
- Antoni-B, myxous, less cellular
- Benign, no recurrences

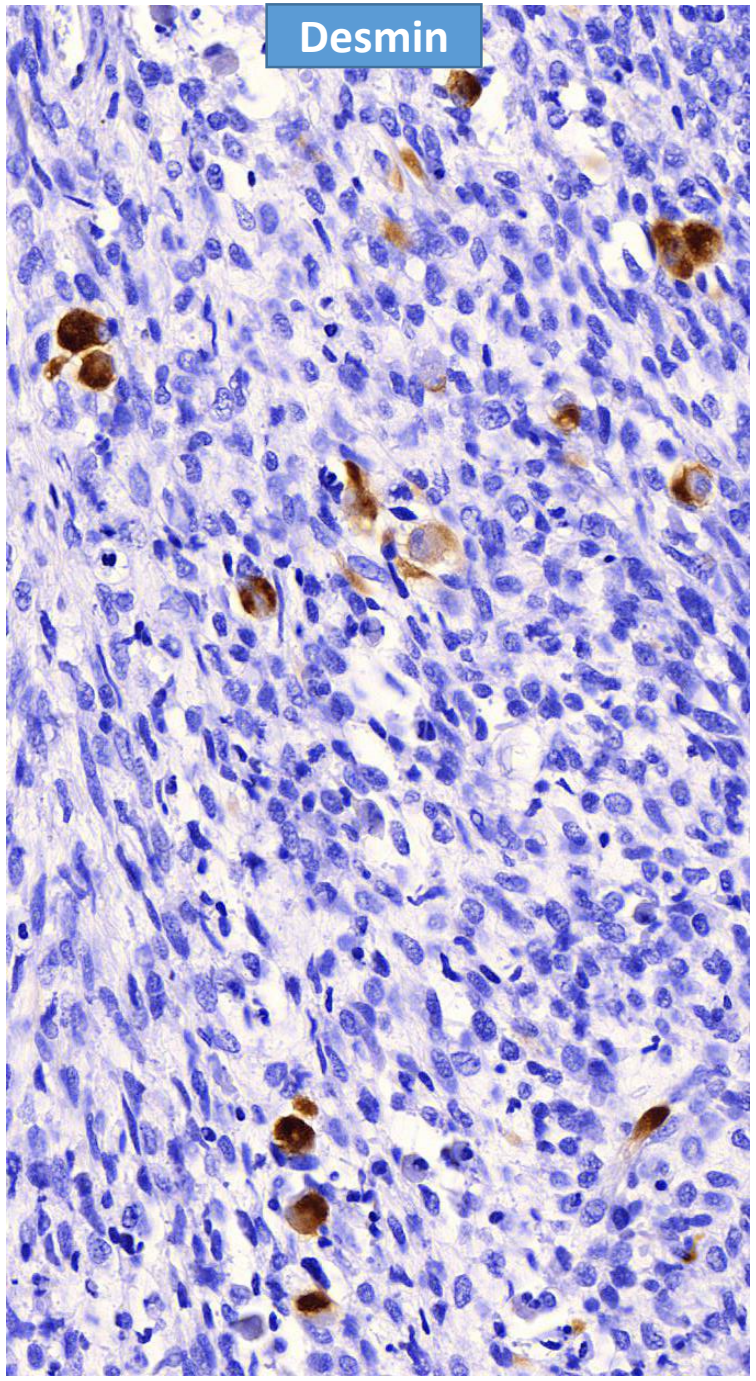


Malignant Peripheral Nerve Sheath Tumor (MPNST)

- Adulthood, any places, sometimes connected to larger nerve
- Fibrosarcoma-like picture, but nuclei are twisted; many mitoses
- S-100, Leu7 +, Histon (H3K27) nuclear negativity
- Malignant MPNST with rhabdomyoblastic differentiation = malignant Triton tumor
- Epithelioid variant,
- Highly malignant

Malignant Triton tumor





Tumours of uncertain differentiation

Acral fibromyxoma
Intramuscular myxoma
Juxta-articular myxoma
Deep ('aggressive') angiomyxoma
Pleomorphic hyalinizing angiectatic tumour of sof t parts
Ectopic hamartomatous thymoma
Atypical fibroxanthoma
Angiomataid fibrous histiocytoma
Ossifying fibromyxoid tum ou r
Myoepithelioma/myoepithelial carcinoma/mixed tumour
Haemosiderotic fibrolipomatous tumour
Phosphaturic mesenchymal tumour
Synovial sarcoma
Epithelioid sarcoma
Alveolar soft part sarcoma
Clear cell sarcoma of soft tissue
Extraskeletal myxoid chondrosarcoma
Malignant mesenchymoma
Desmoplastic small round cell tumour
Extrarenal rhabdoid tumour
PEComa
Intimal sarcoma

Alveolar soft part sarcoma

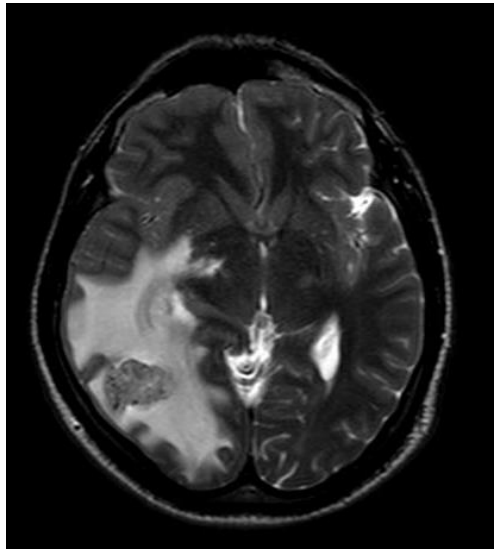
Rare; any age, but young adults

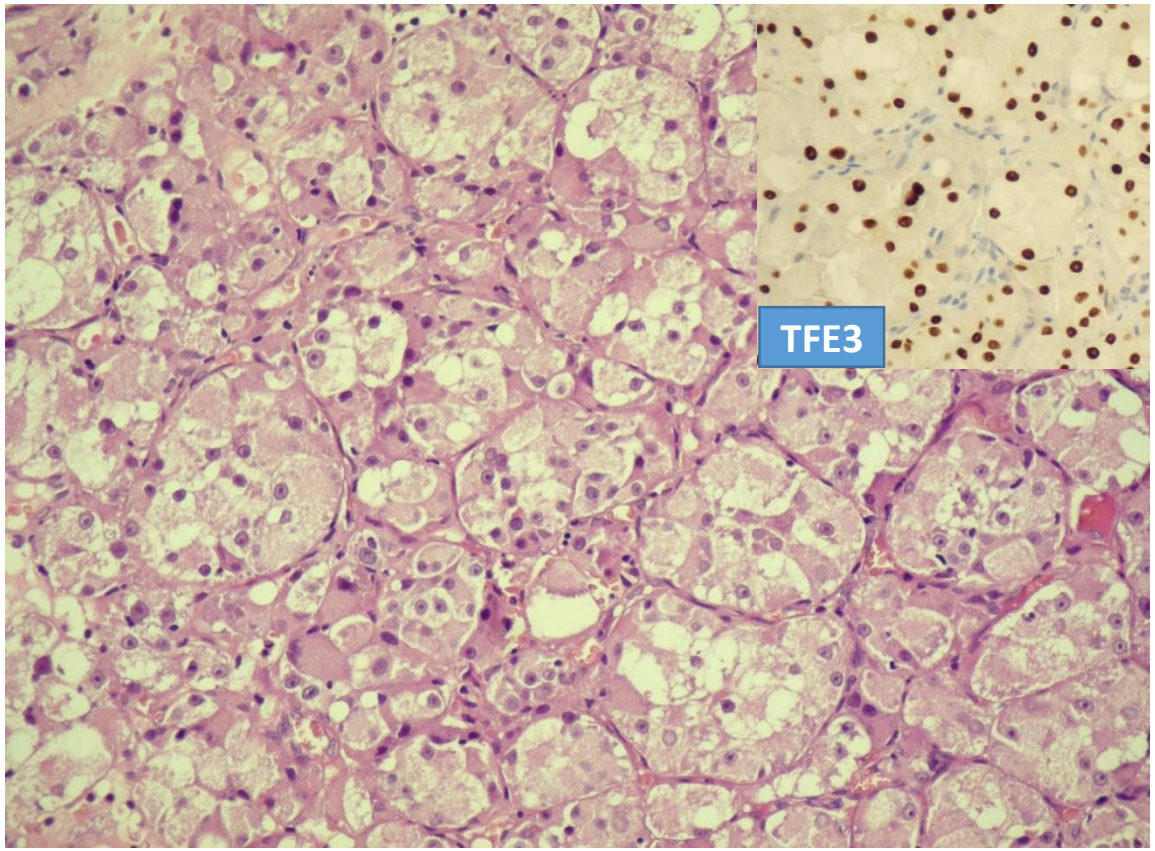
Slowly growing mass of deep soft tissues

Early metastases into brain
(first manifestation of the disease)

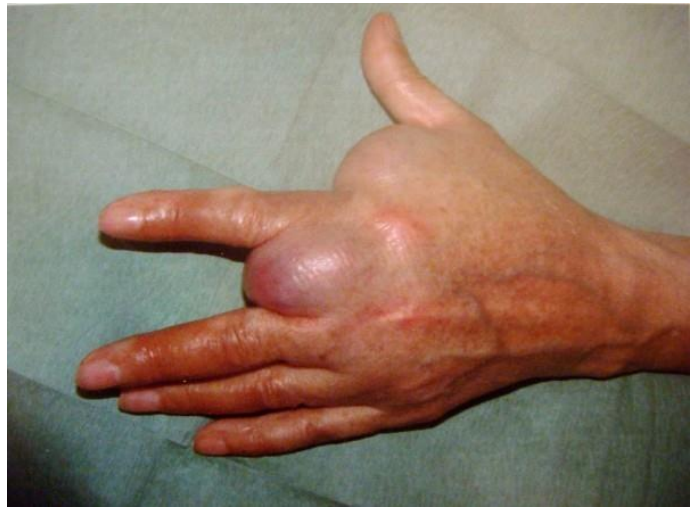
Distinctive organoid, nesting pattern
vesicular nucleus, prominent nucleolus
abundant, clear cytoplasm

No special immunostaining except TFE3
TFE3-ASPSCR1 fusion gene

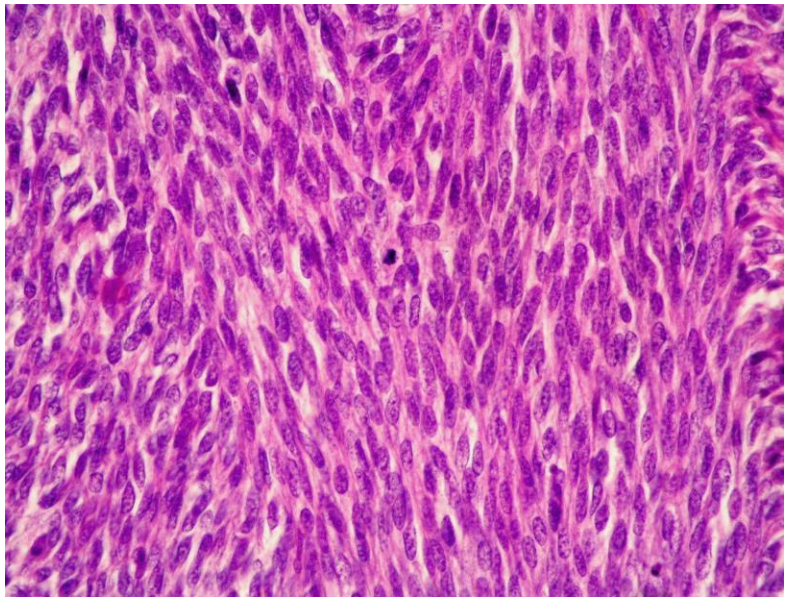


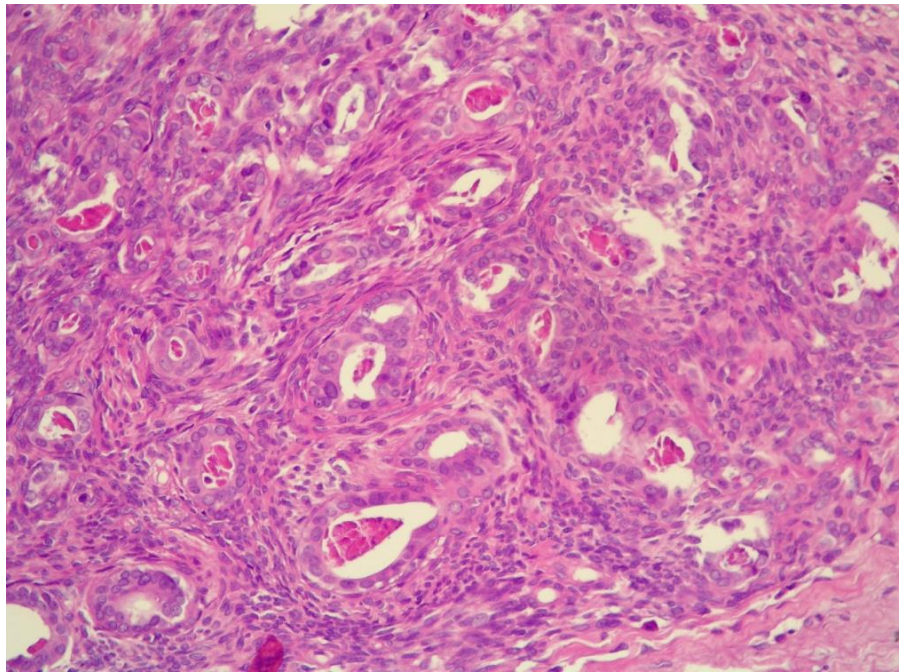


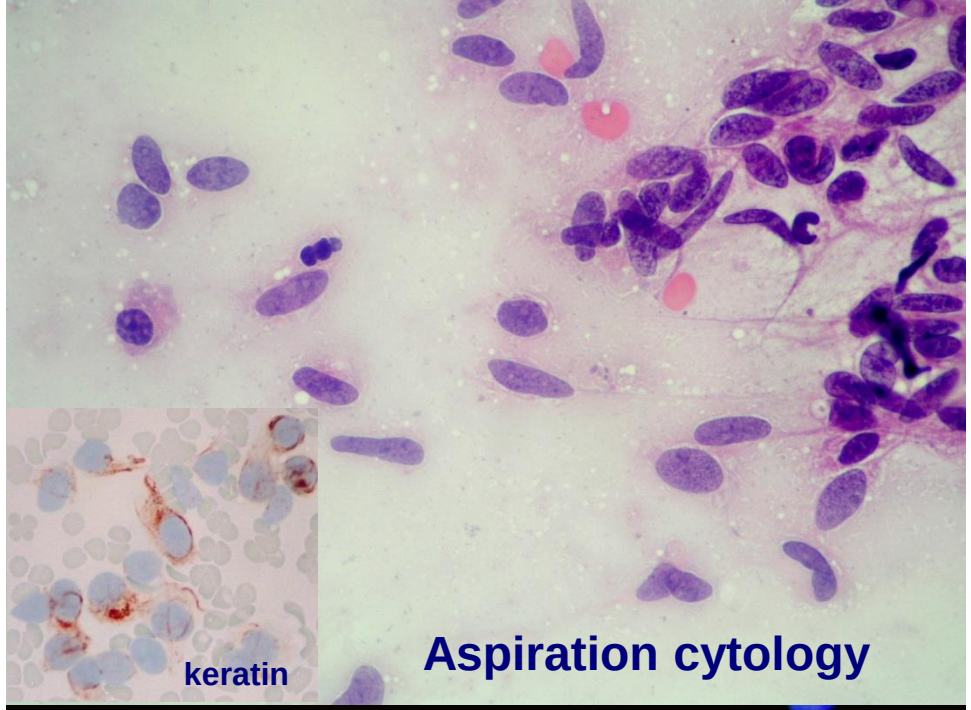
Synovial sarcoma

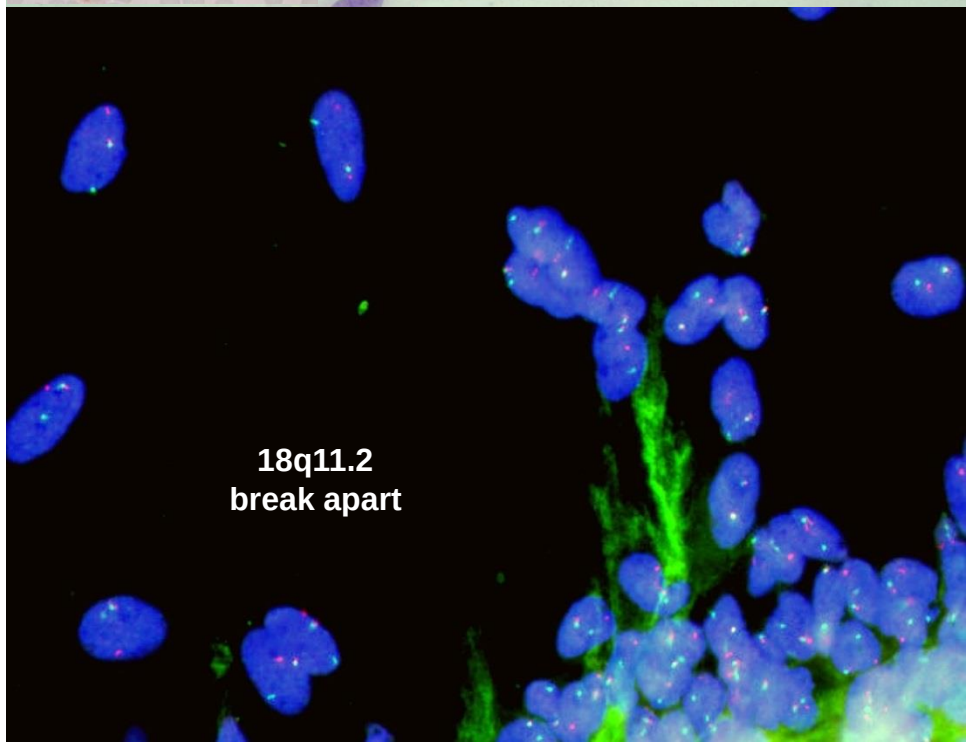


- Usually a deep seated mass present for years around large joints (80% in knee and ankle) in young adults (age 20-40); only 10% actually involve the joint
- Represent 10% of adult soft-tissue tumors (third most common)
- 5 year survival is 50-70%; 10 year survival 40%; recurs locally, 10-15% metastasize to lung and pleura, bone, regional nodes
- **Treatment:** wide local excision plus radiation
- **Gross:** well circumscribed, firm, gray-pink; focal calcifications on Xray
- **Micro:** biphasic or monophasic or undifferentiated;
  Spindle cells are arranged in plump fascicles ; biphasic have spindle cells and plump epithelial cells forming glands/cords









Genetic findings

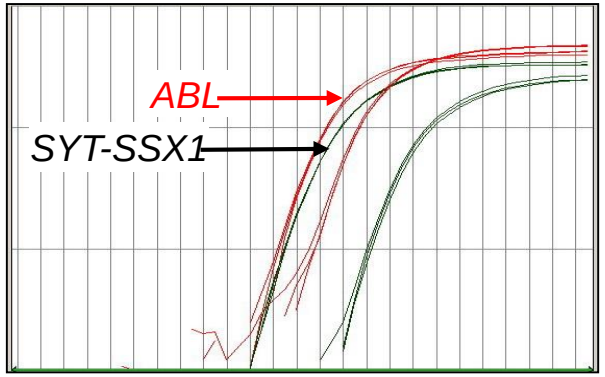
t(X;18)(p11.2;q11.2)

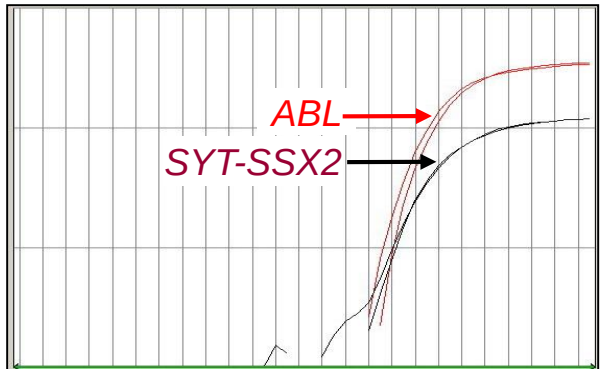
SYT on chromosome 18

SSX1,SSX2 and SSX4 on chromosome X

SYT-SSX chimeric protein

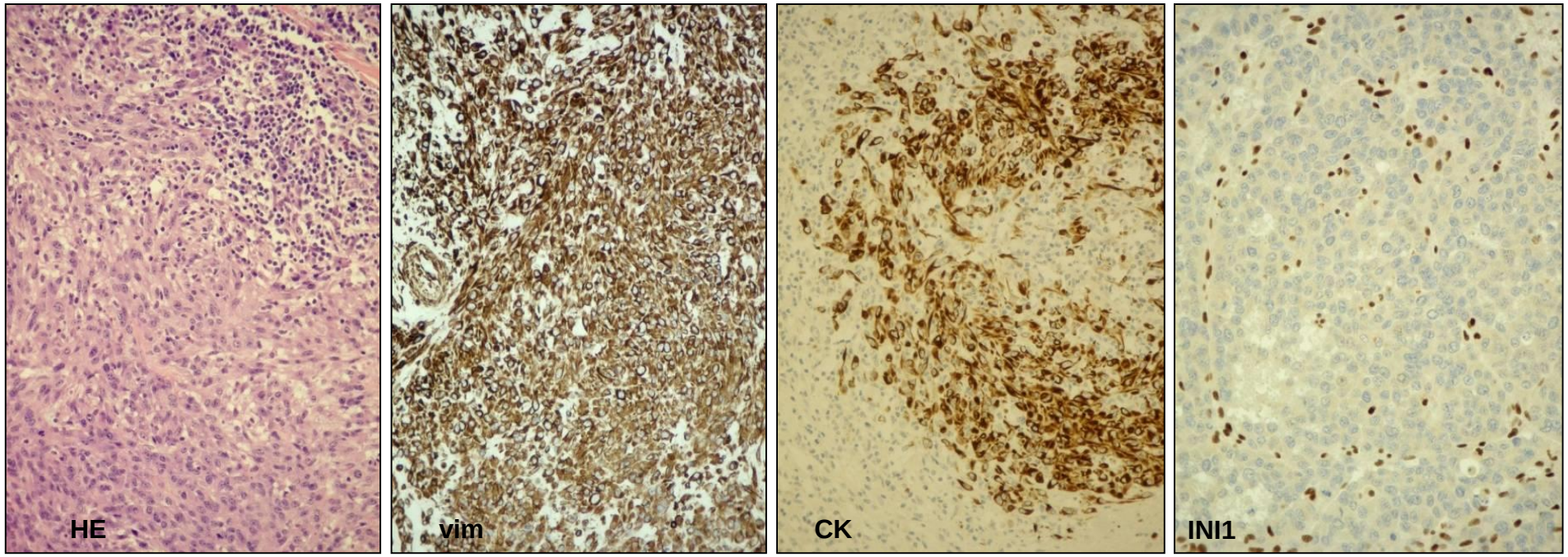
oncogenic effect



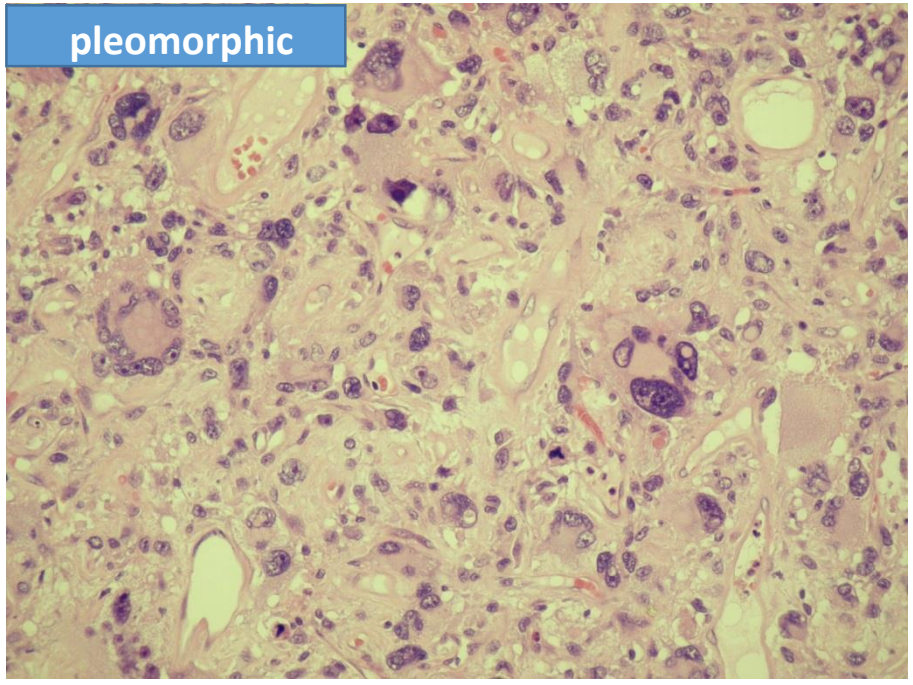


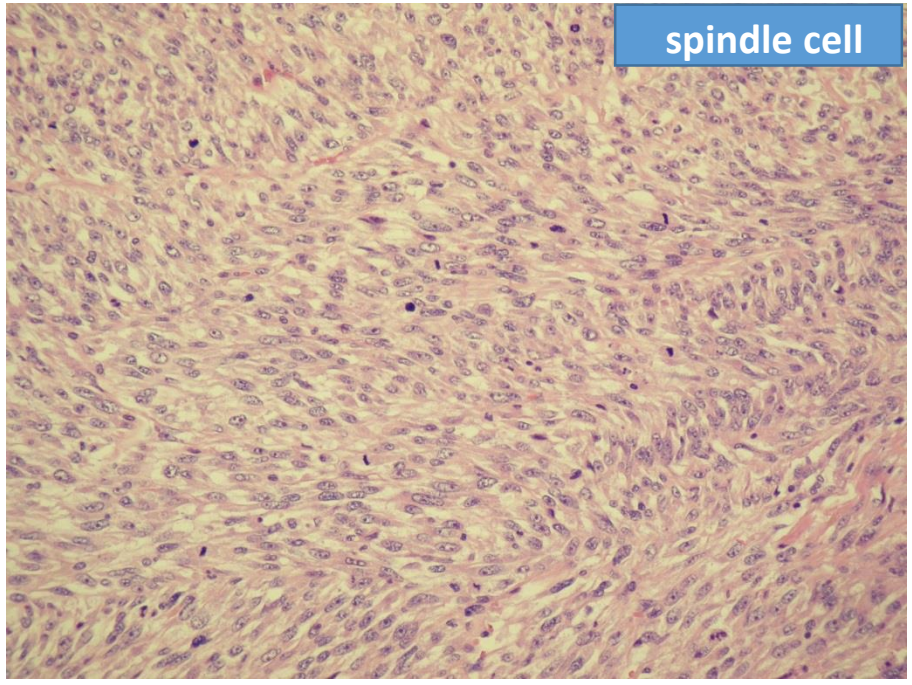
Epithelioid sarcoma

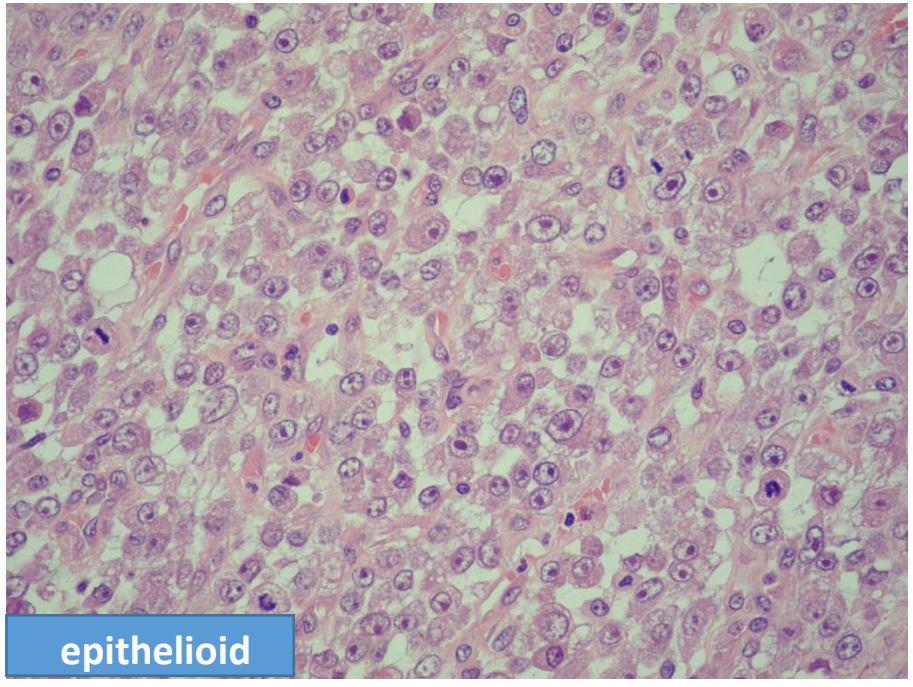
- Rare, 1% of soft tissue sarcomas; young adults (proximal and distal type)
- Tumors of uncertain differentiation
- Prognosis: aggressive tumor, recurrence: 34-77%, metastatic capacity: 40%
- Immunophenotype: vimentin, cytokeratin, EMA co-expression; CD34 (50%) positivity, and SMARCB1/INI1 negativity
- **Genetic and/or epigenetic regulation?** (majority of ESs have no biallelic mutation on SMARCB1/INI1)

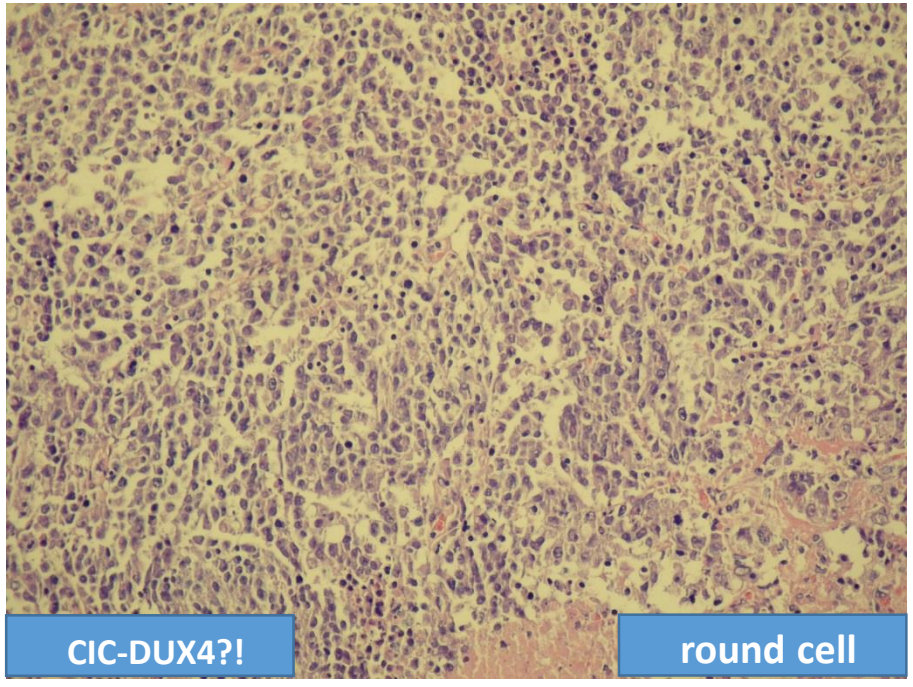


Undifferentiated/unclassified sarcomas



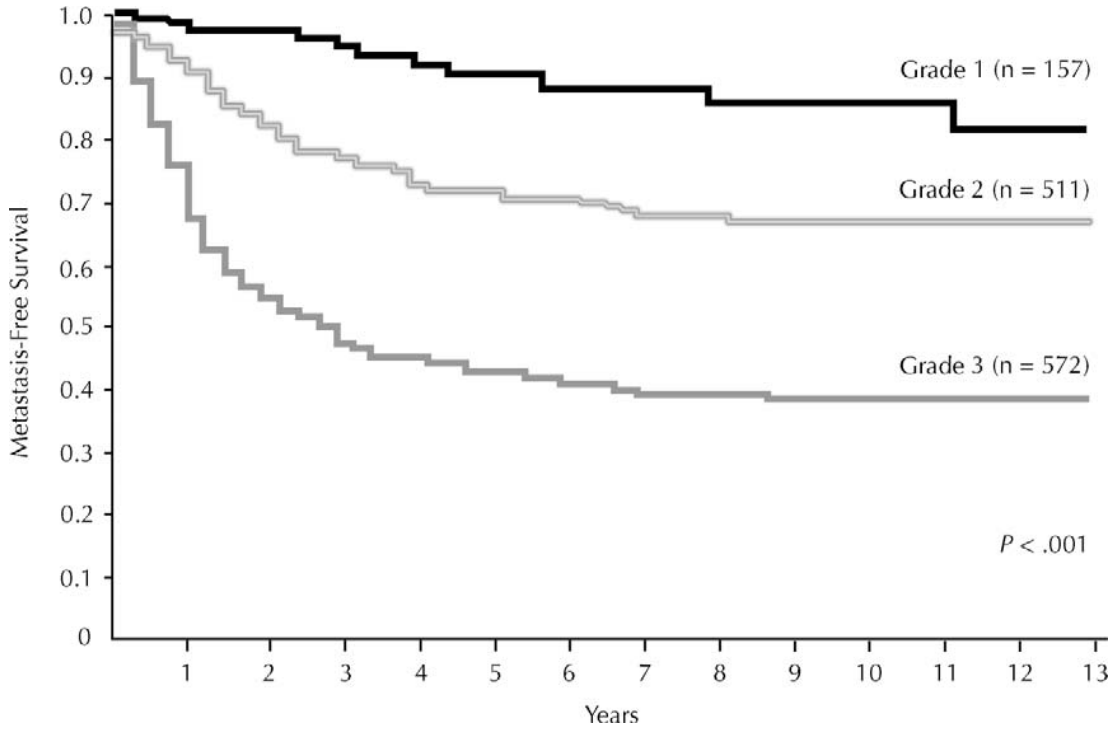






Grade

- In many soft tissue sarcomas the best prognostic factor
- For stage, it is inevitable
- Concerning the modern oncological treatment, the grade is very important



Jean-Michel Coindre: Grading of Soft Tissue Sarcomas; Review and Update, Arch Pathol Lab Med. 2006;130:1448–1453

FNCLCC Grading System

Fe´de´ration Nationale des Centres de Lutte le Cancer

Tumor differentiation (see Table 2)	
Score 1:	Sarcomas closely resembling normal adult mesenchymal tissue (eg, well-differentiated liposarcoma)
Score 2:	Sarcomas for which histologic typing is certain (eg, myxoid liposarcoma)
Score 3:	Embryonal and undifferentiated sarcomas, sarcomas of doubtful type, synovial sarcomas, osteosarcomas, PNET
Mitotic count	
Score 1:	0–9 mitoses per 10 HPF†
Score 2:	10–19 mitoses per 10 HPF
Score 3:	≥20 mitoses per 10 HPF
Tumor necrosis	
Score 0:	No necrosis
Score 1:	<50% tumor necrosis
Score 2:	≥50% tumor necrosis
Histologic grade	
Grade 1:	Total score 2, 3
Grade 2:	Total score 4, 5
Grade 3:	Total score 6, 7, 8

* Modified from Trojani et al[18] with permission from John Wiley and Sons, Inc. FNCLCC indicates Fédération Nationale des Centres de Lutte le Cancer; PNET, primitive neuroectodermal tumor.
† A high-power field (HPF) measures 0.1734 mm².

Histologic Type	Tumor Differentiation Score
Well-differentiated liposarcoma	1
Myxoid liposarcoma	2
Round cell liposarcoma	3
Pleomorphic liposarcoma	3
Well-differentiated fibrosarcoma	1
Conventional fibrosarcoma	2
Poorly-differentiated fibrosarcoma	3
Myxofibrosarcoma	2
Pleomorphic MFH with storiform pattern	2
Pleomorphic MFH with no storiform pattern	3
Giant cell MFH	3
Well-differentiated leiomyosarcoma	1
Conventional leiomyosarcoma	2
Poorly-differentiated/pleomorphic/epithelioid leiomyosarcoma	3
Embryonal/alveolar/pleomorphic rhabdomyosarcoma	3
Mesenchymal chondrosarcoma	3
Osteosarcoma	3
PNET	3
Malignant triton tumor	3
Synovial sarcoma	3
Well-differentiated/conventional angiosarcoma	2
Poorly-differentiated/epithelioid angiosarcoma	3
Epithelioid sarcoma	3
Clear cell sarcoma	3

* Modified from Guillou et al[23] with permission from the American Society of Clinical Oncology. FNCLCC indicates Fédération Nationale des Centres de Lutte le Cancer; MFH, malignant fibrous histiocytoma; PNET, primitive neuroectodermal tumor.

Jean-Michel Coindre: Grading of Soft Tissue Sarcomas; Review and Update, Arch Pathol Lab Med. 2006;130:1448–1453

Bone Tumors

WHO classification

Osteogenic tumors
Osteoid osteoma
Osteoblastoma
Osteosarcoma

Cartilage tumors
Osteochondroma
Chondromas
Chondromyxoid fibroma
Synovial chondromatosis
Chondrosarcoma

Giant cell tumors
Giant cell tumor
Malignancy in giant cell tumor

Ewing sarcoma/PNET
Ewing sarcoma

Notochordal tumors
Chordoma

Tumors of undefined neoplastic nature
Aneurismal bone cyst
Simple bone cyst
Fibrous dysplasia
Osteofibrous dysplasia
Langerhans cell histiocytosis

Hematopoietic tumors
Plasma cell myeloma
Malignant lymphoma

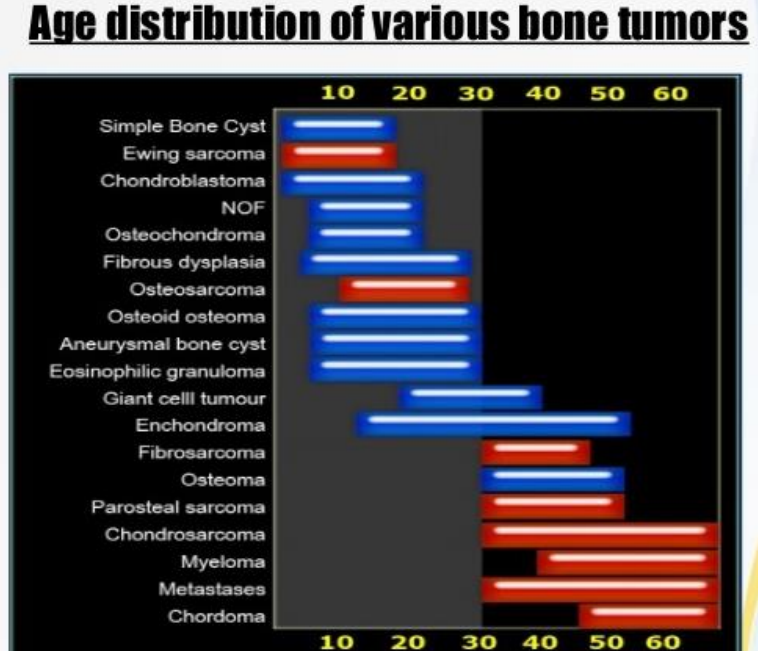
Malignant bone tumors – 0.5-1%

Genetic background:
Familiar retinoblastoma syndrome
Ly-Fraumeni syndrome

General symptoms: pain, swelling, pathological fracture, can be incidental

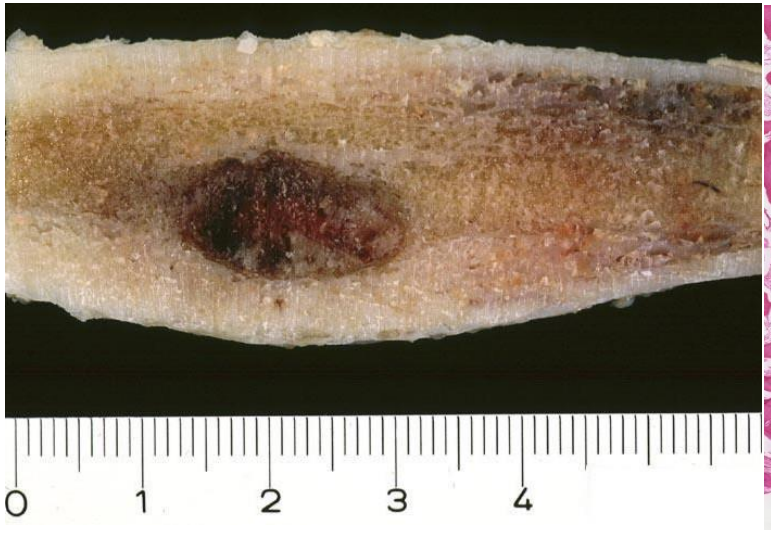
Metastasis is more frequent than primary bone tumors in adults!

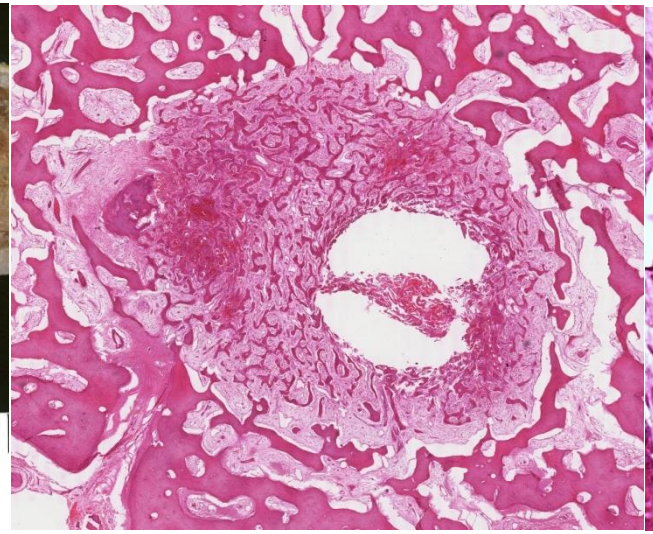
Radiology is very important for proper diagnosis!

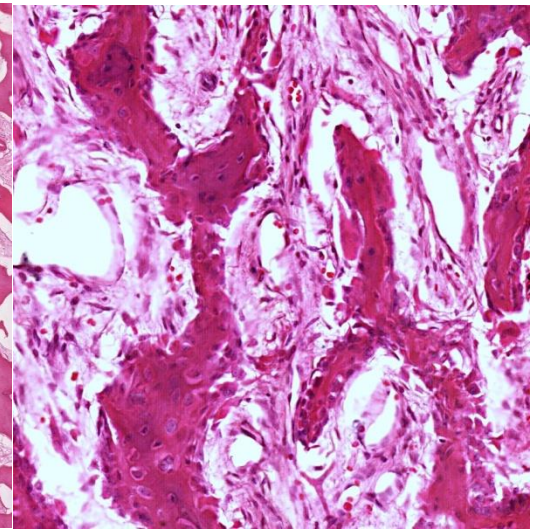


Osteoid osteoma

Rare; benign tumor, nidus measures 1.5-2.0 cm or less
75% under age 25; 2/3 male; 50% in femur/tibia;
Intense localized pain, particularly at night, due to production of prostaglandin E2 or nerve fibers in reactive zone; pain relieved dramatically by aspirin
Xray: small, round lucency with variable mineralization surrounded by extensive sclerosis
Micro: central nidus is sharply circumscribed, anastomosing bony trabeculae with variable mineralization, plump osteoblasts, vascularized connective tissue
Treatment: CT localization of nidus and excision or radiofrequency ablation; recurrence is unusual







Osteosarcoma

Most common primary bone tumor after myeloma

Definition: malignant bone tumor that produces osteoid directly from tumor cells and unconnected with cartilage

60% male; usually ages 10-25 years, associated with Paget's disease after age 40

Not associated with trauma, although trauma may lead to discovery of tumor

Sites: metaphysis of long bones

Xray: large, destructive, lytic or blastic mass with permeative margins

Codman's triangle: shadow between cortex and raised ends of periosteum (due to reactive bone formation), non-specific

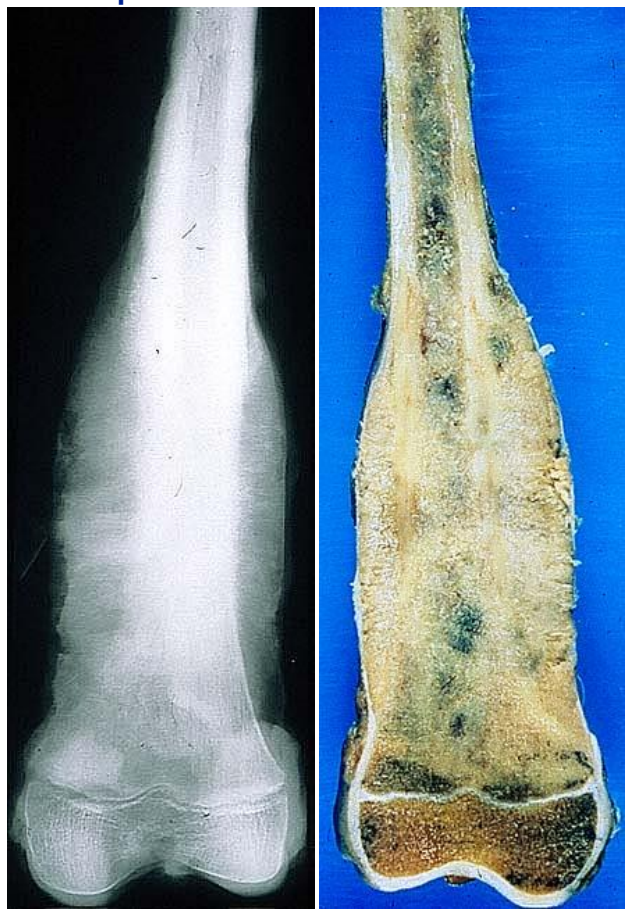
Sites of metastasis: lung (98%, 20-80% at diagnosis)

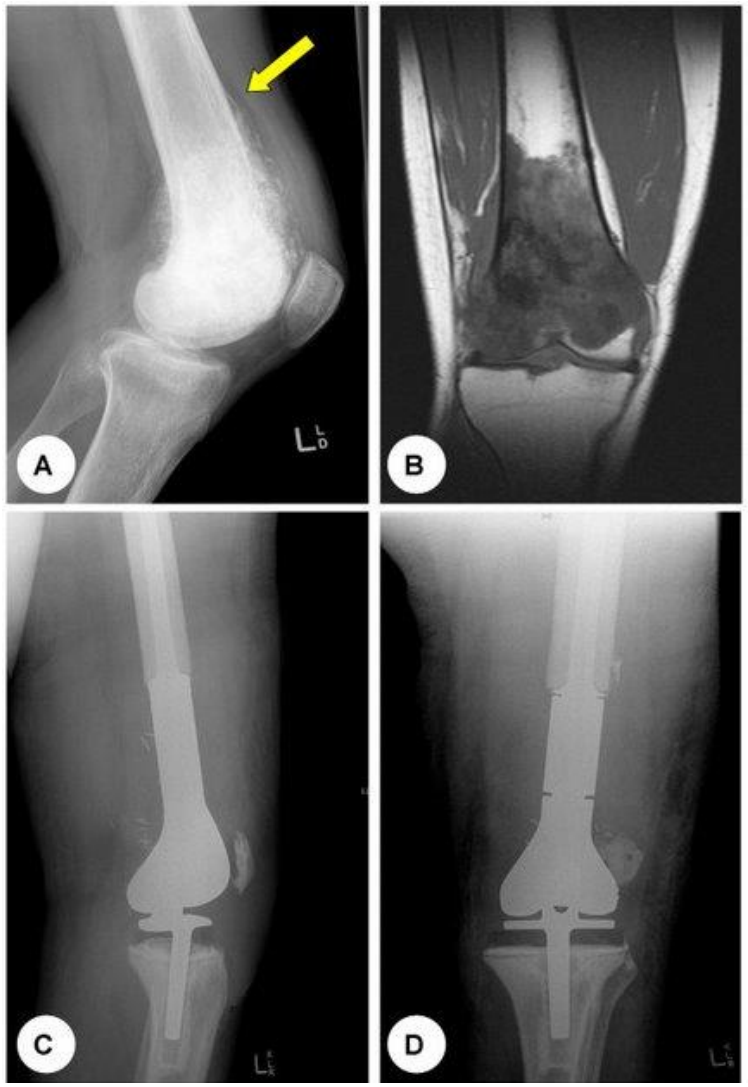
Note: excision of metastatic lung nodules may prolong survival

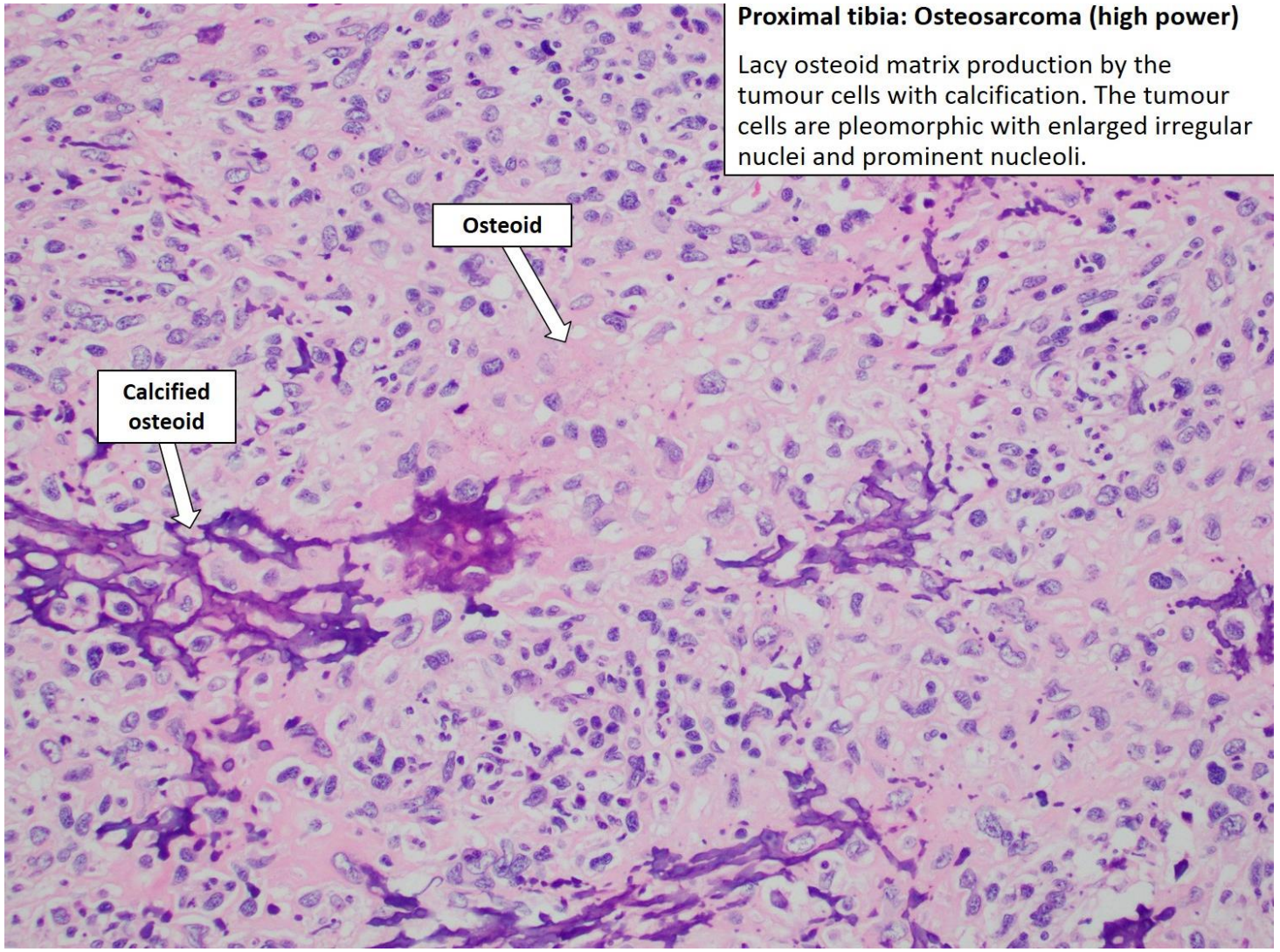
5 year survival: 70%

Treatment: preoperative chemotherapy is helpful to spare limbs

Micro: high grade spindle cell tumor that produces osteoid matrix





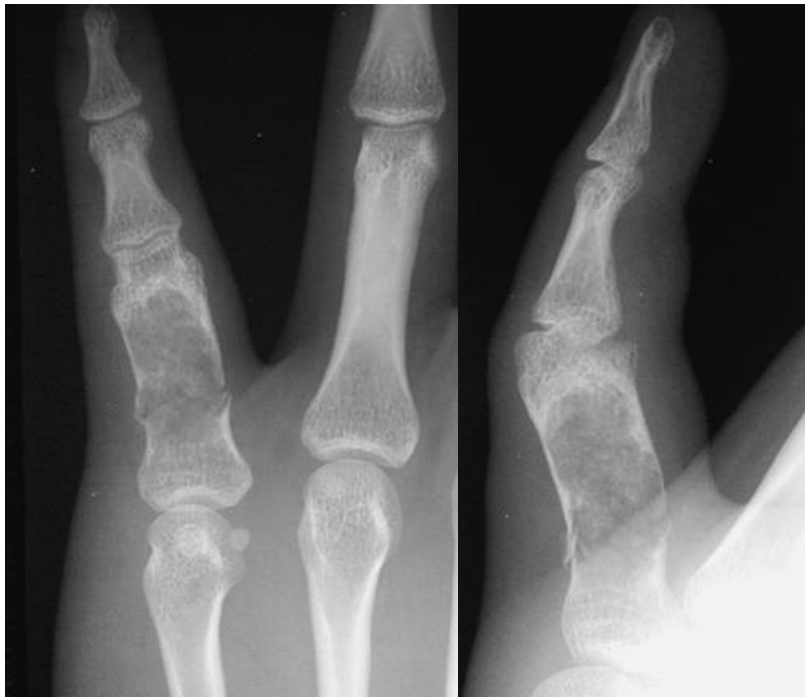


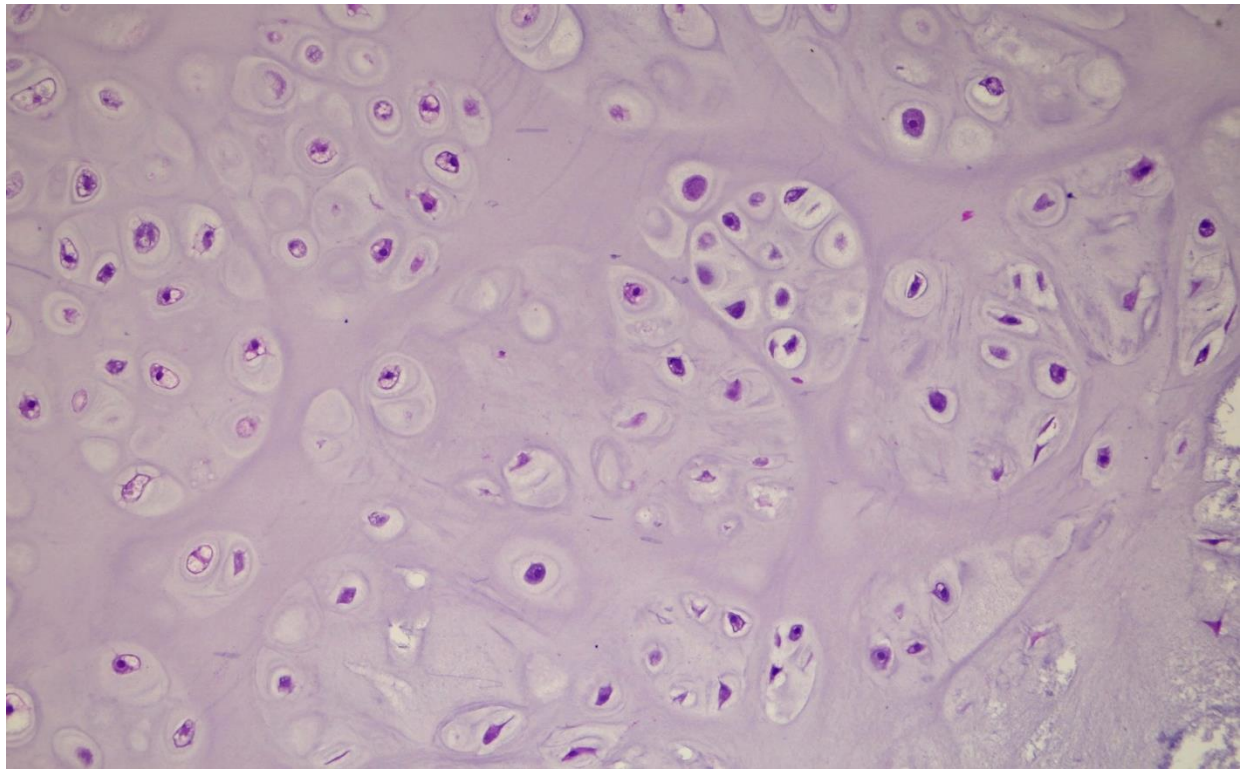
Proximal tibia: Osteosarcoma (high power)

Lacy osteoid matrix production by the tumour cells with calcification. The tumour cells are pleomorphic with enlarged irregular nuclei and prominent nucleoli.

- **Chondroma**

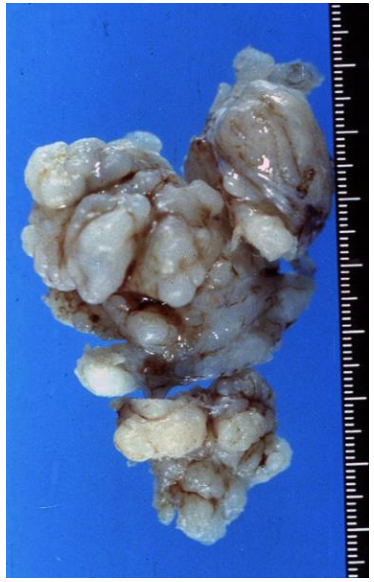
- Benign cartilaginous tumor
- Enchondroma (arise from diaphyseal medullary cavity), subperiosteal/juxtacortical chondroma or soft tissue chondroma
- Usually asymptomatic or pain due to pathologic fracture
- Age 20-49 years, no gender preference; may be due to displaced growth plate
- **Sites:** small bones of hands and feet; 70% solitary; 30% multiple
- **Molecular:** 12q13-15 (HMGA2 / HMGI-C)
- ***Maffuci's syndrome:*** multiple enchondromas and soft tissue hemangiomas;
- ***Ollier's disease:*** nonhereditary disease of multiple enchondromas of long and flat bones
- **Treatment:** excision, may recur if incompletely excised; often leave alone

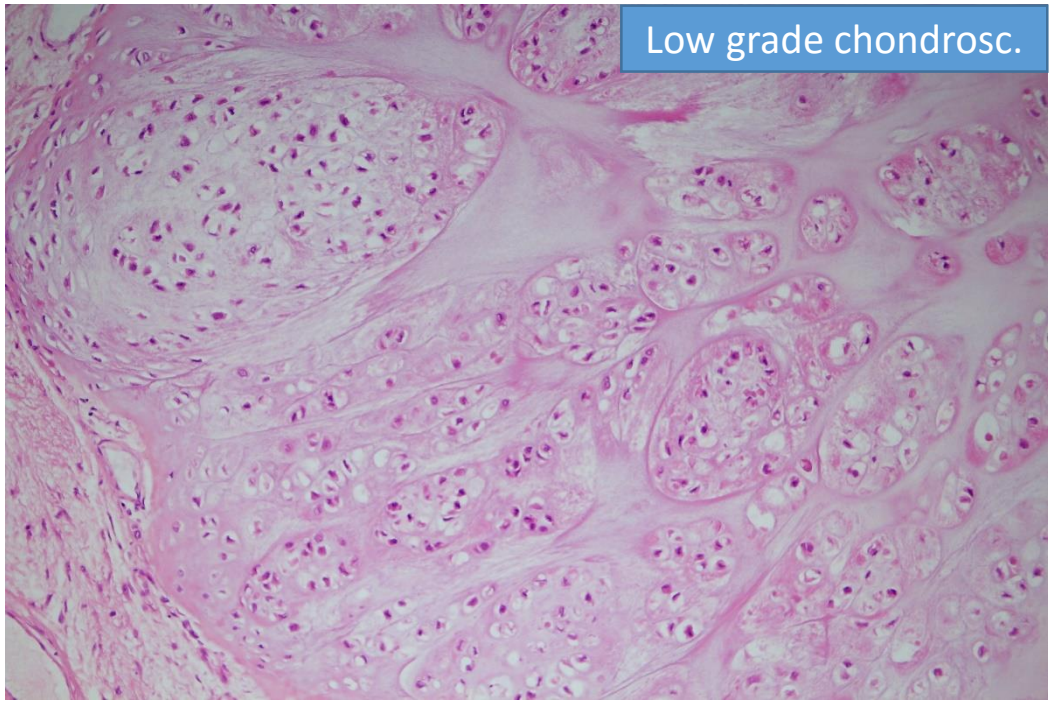


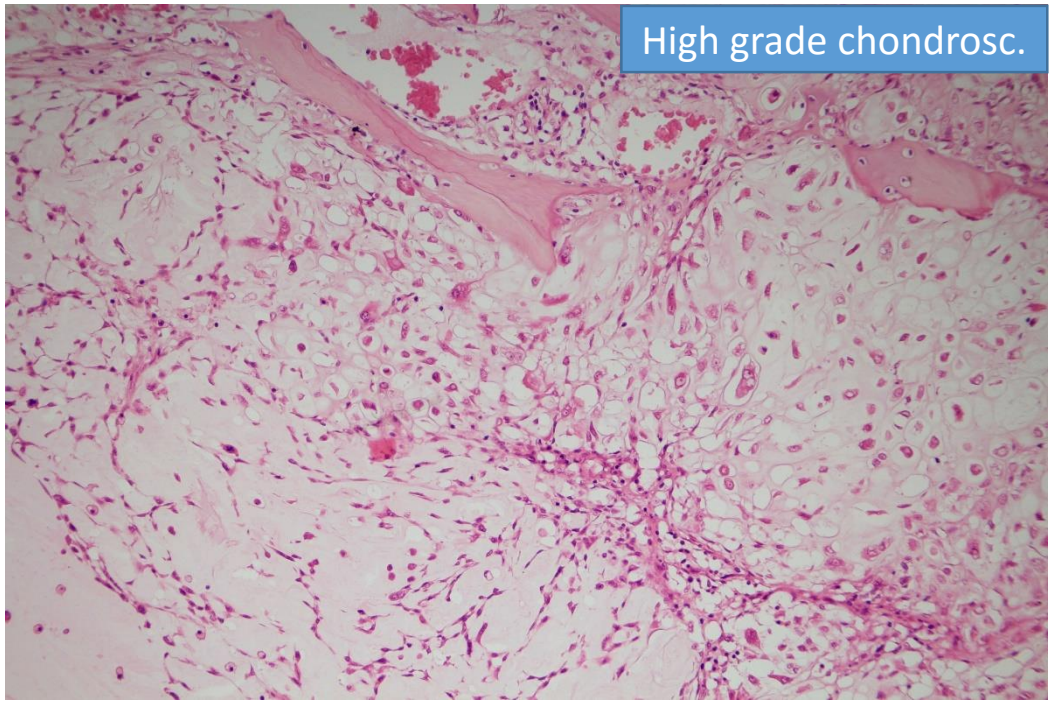


Chondrosarcoma

- Malignant cartilage forming tumor that does not produce osteoid
- May arise from osteochondroma
- Third most common bone malignancy after myeloma and osteosarcoma
- Usually ages 30-60 years, 75% males
- Often large painful tumors of long bones or ribs that grow rapidly
- **Grading:** based on cellularity and nuclear changes in chondrocytes; well, moderate or poorly differentiated correspond to grades 1-3
- **Prognostic features:** grading important for 5 year survival: well differentiated-78%, moderate-53%, poorly differentiated-22%
- **Gross:** pearly white or light blue, often with focal calcification
- **Micro:** tumor cells produce cartilaginous matrix, may have only minor or focal atypia, but consider malignant if malignant radiologic features





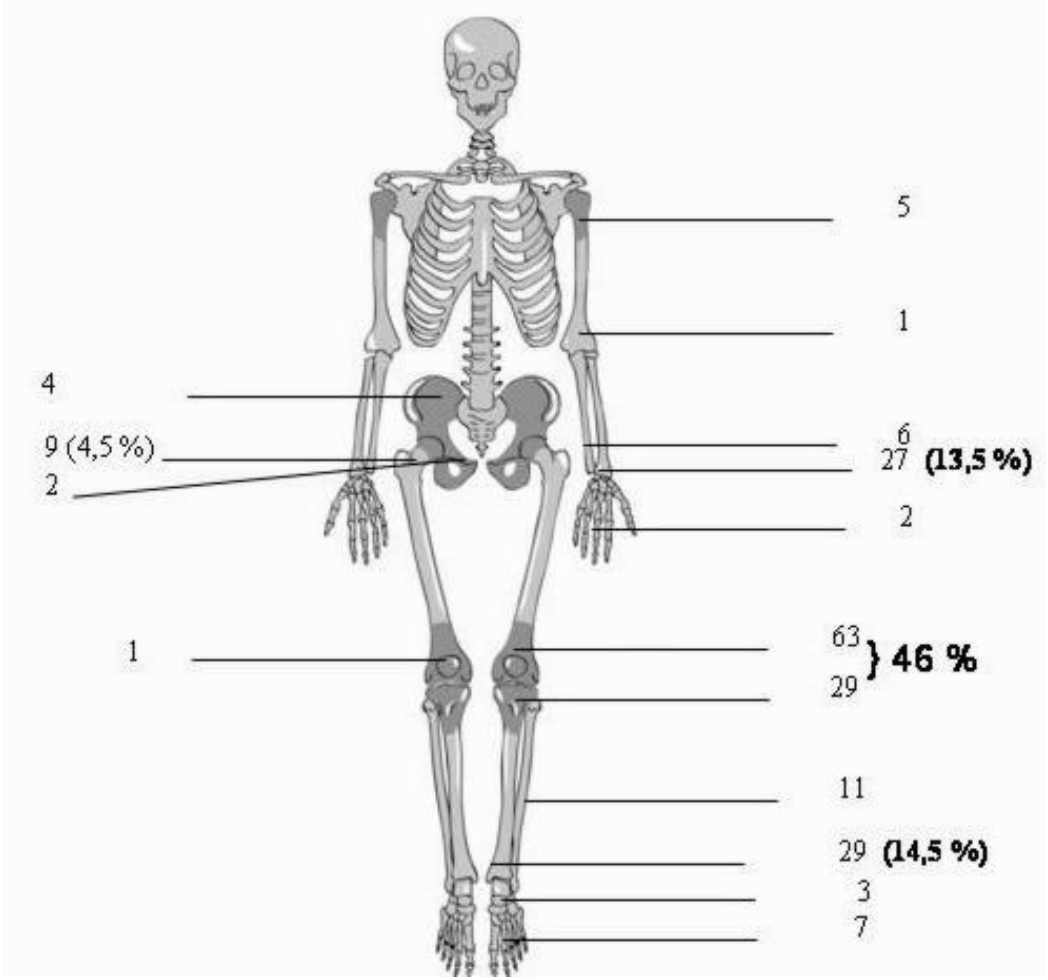


Giant cell tumour of bone

Definition

Giant cell tumour of bone is an intermediate, locally aggressive neoplasm which is composed of sheets of neoplastic ovoid mononuclear cells interspersed with uniformly distributed, large osteoclast-like giant cells

Clinical feature



4-5% primary bone tumors

peak: 20-45 years

very rare below 10 years

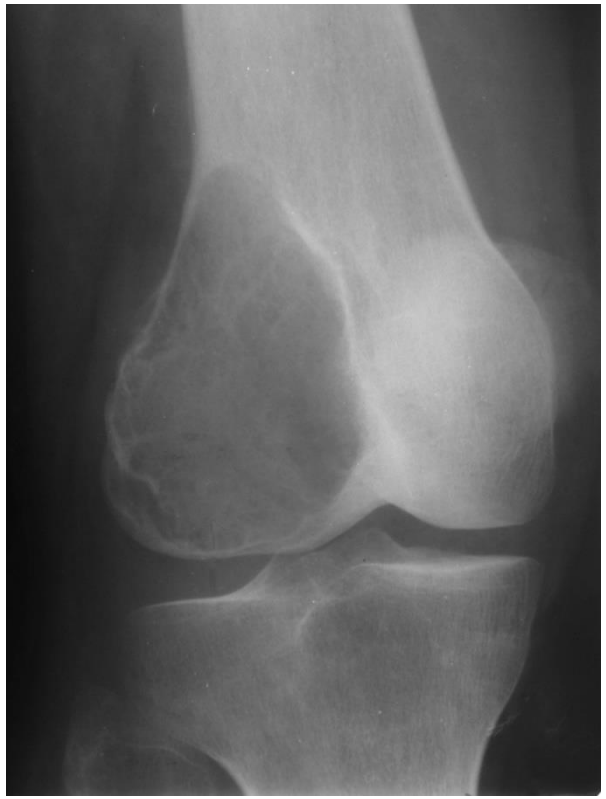
female predominance (slight)

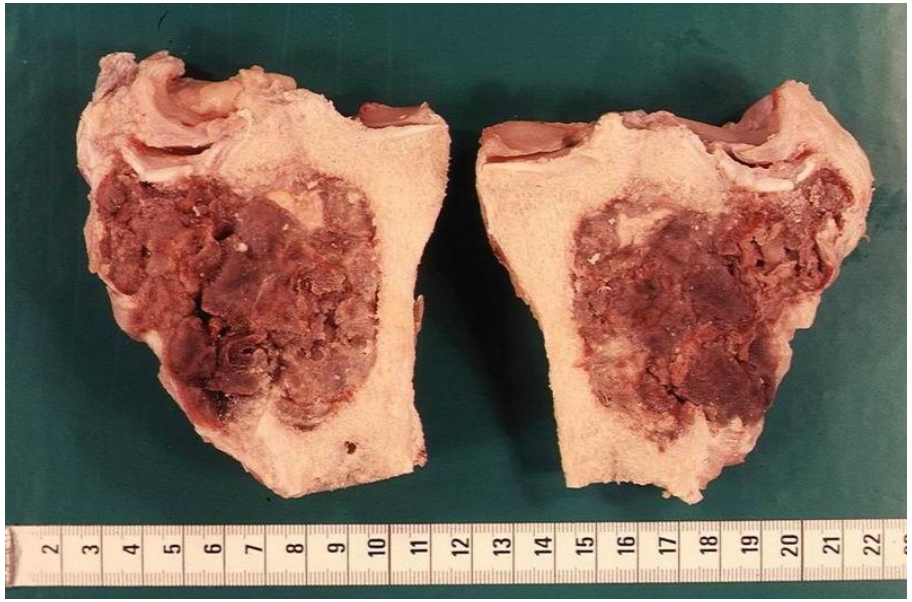
end of long bones – typical

5% flat bones

pain, swelling, lim. joint movement

path. fracture: 5-10%





Imaging/macro

expanding, eccentric, lytic area

epiphysis and adjacent metaphysis

well-defined margin with sclerosis
well-defined margin without sclerosis
ill defined margin with cort. destr.

soft and reddish brown

blood filled spaces

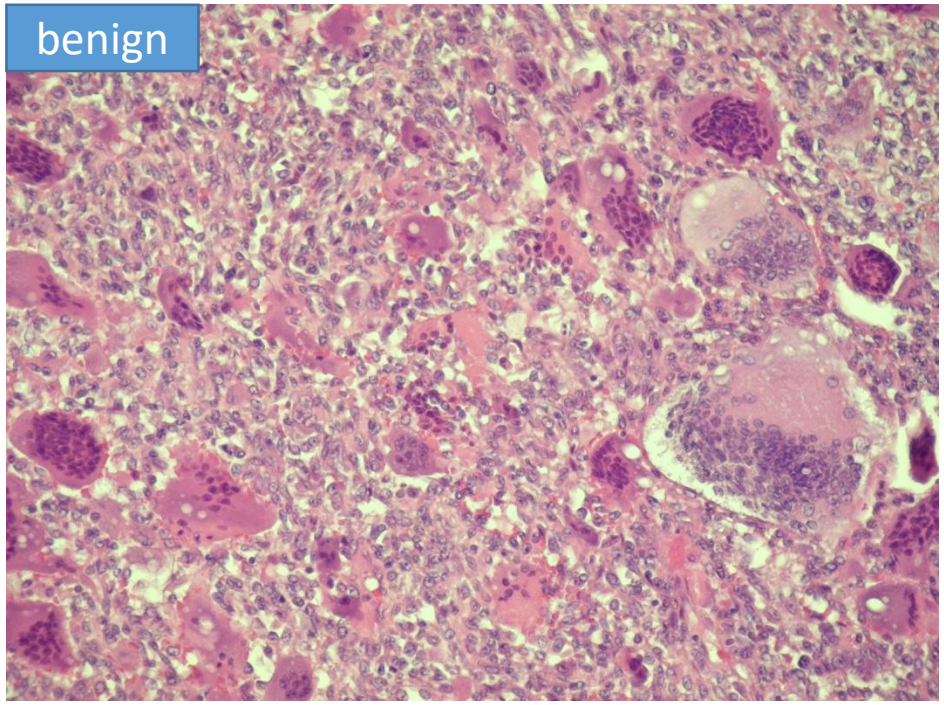
Classification of GCTB - WHO

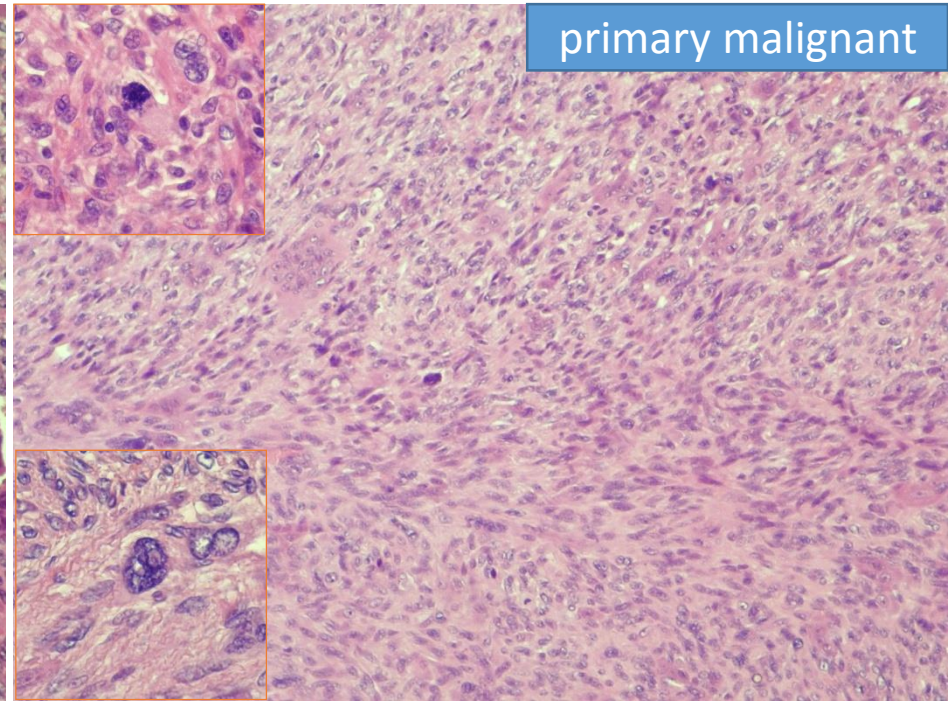
GCTB with benign histological appearance: sheets of mononuclear Cells admixed with numerous osteoclastic giant cells

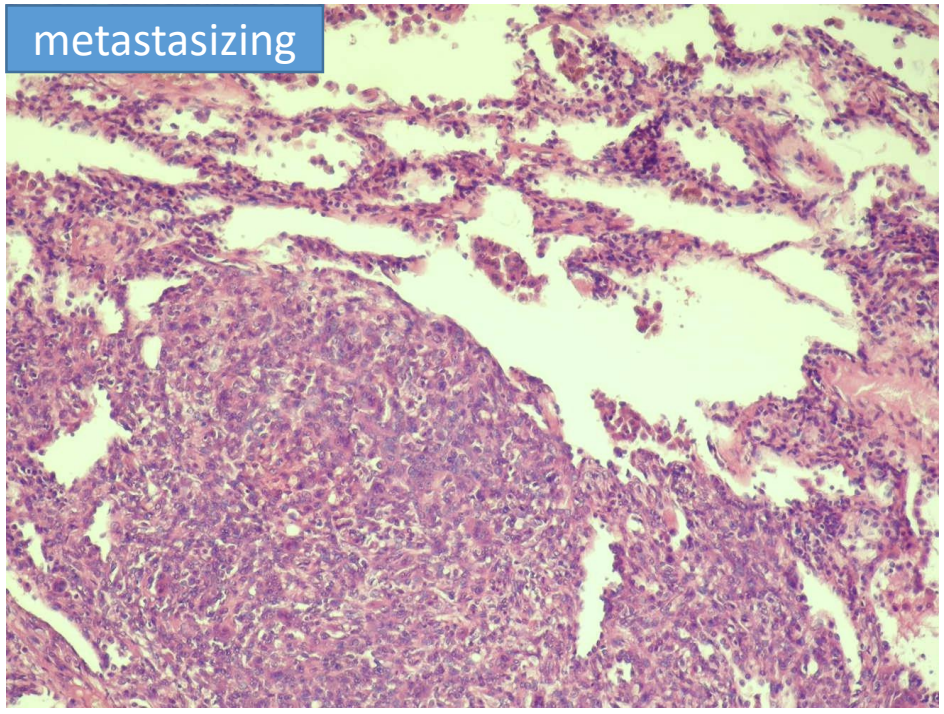
Metastasizing GCTB: the same as above, but distant metastasis

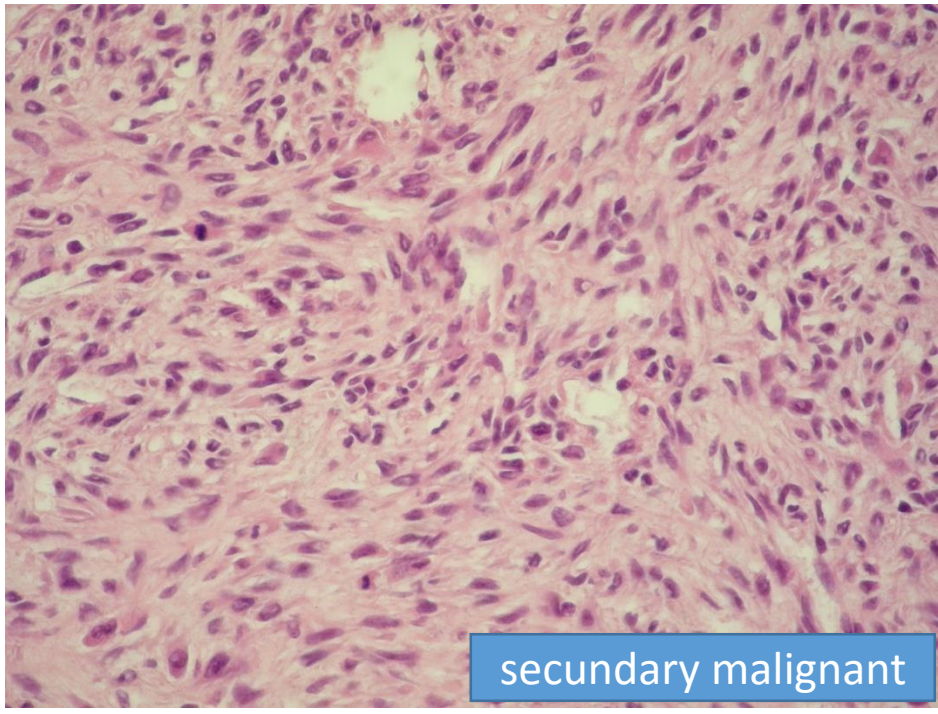
Malignancy in GCTB: a sarcoma appears at the site of previously documented GCTB; progression in the same tumor

Malignant GCTB/giant-cell rich MFH: a high grade sarcoma arises within the GCTB





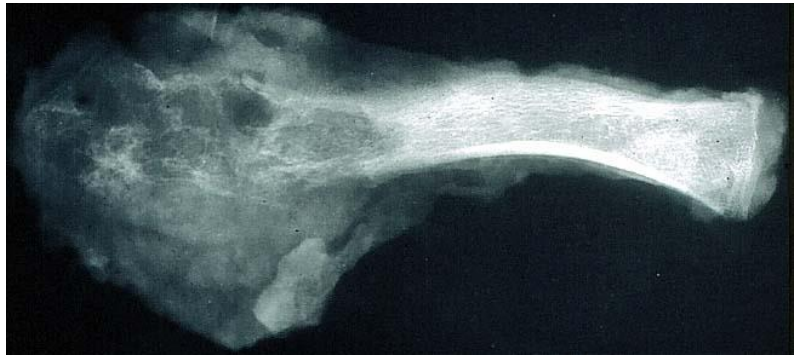


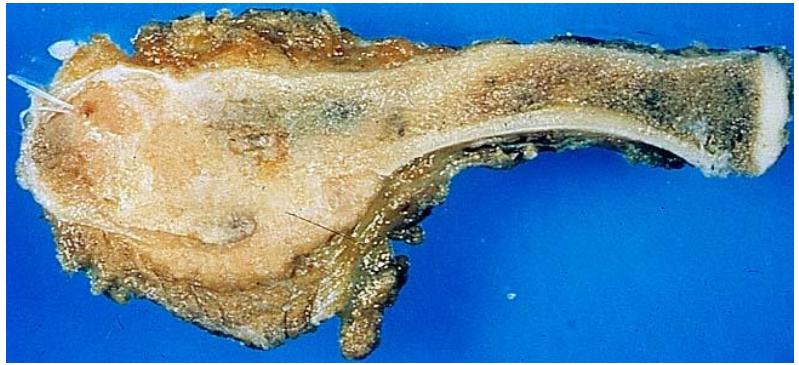


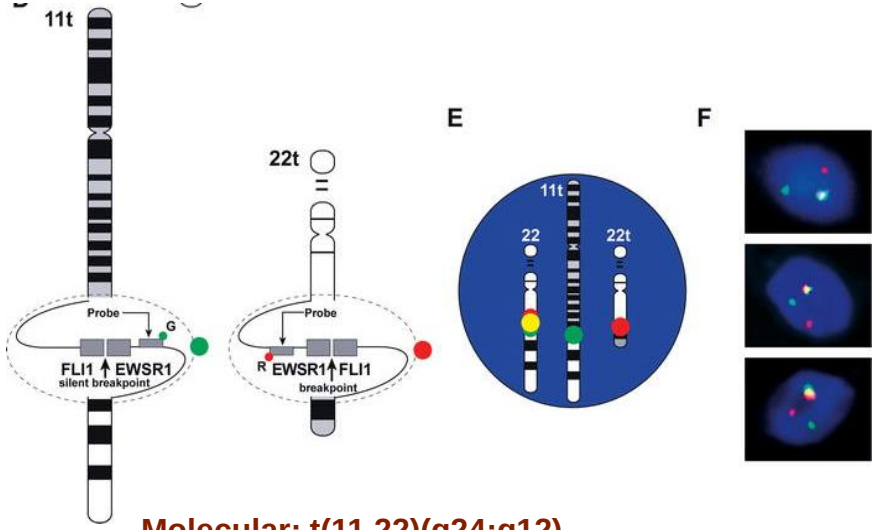
Ewing's sarcoma / primitive neuroectodermal tumor (PNET)

Terms usually used interchangeably; some suggest to call PNET if neural diff.

- Second most common bone sarcoma in children
- May present with pain, fever, weight loss, leukocytosis and increased erythrocyte sedimentation rate mimicking osteomyelitis
- **Sites:** marrow of femur, tibia, humerus, fibula, pelvis, ribs, vertebra
- **Xray:** destructive, lytic tumor with reactive periosteal bone resembling onion skin
- **Treatment:** preoperative chemotherapy, surgery, radiation therapy
- **5 year survival:** 75%; 50% are cured; metastases to lung, skull, pleura
- **Poor prognostic factors:** high stage, direct extension into soft tissue, aneuploidy







Molecular: t(11,22)(q24;q12)
22q12 is EWS, a transcription factor;
11q24 is FL-1;
EWS-FL1 is a transactivator of the c-myc promoter

Micro: sheets of small, round, uniform cells 10-15 microns with scant clear cytoplasm, divided into irregular lobules by fibrous strands; indistinct cell membranes; round nuclei with indentations, small nucleoli