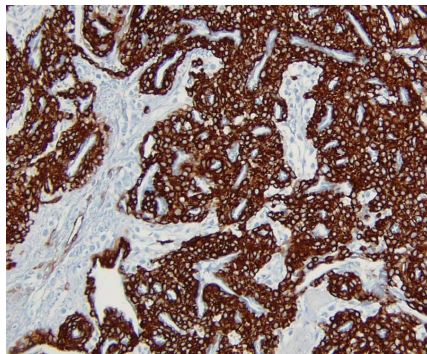


IMMUNOHISTOCHEMISTRY IN THE DIAGNOSIS OF SOFT TISSUE TUMORS



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I. Ancillary techniques in soft tissue tumors

A. Histochemistry

Since the introduction of immunohistochemistry, histochemistry has a very limited value in the diagnosis of soft tissue neoplasms.

Glycogen identification with PAS stain is not specific. Alcian blue stain with and without hyaluronidase, which has been used for the identification of cartilaginous matrix is not reliable. One of the rare potential applications is the demonstration of crystalloids in alveolar soft parts sarcoma, which has no specific immunohistochemical profile but shows a t(X;17) translocation which can be identified by molecular techniques.

B. Electron microscopy

Electron microscopy has also lost his value with the availability of immunohistochemical markers. As it is expensive and time consuming, it is only used in a limited number of specialized centres.

C. Immunohistochemistry

Immunohistochemistry has been introduced in the 80's. Because of its relatively low cost, simple technique and the availability of a large number of increasingly sensitive and / or specific antibodies, it has become the main diagnostic tool.

D. Cytogenetics and molecular biology

Specific translocations and chromosome rearrangements have been identified in an increasing number of sarcomas and benign neoplasms. Fusion products can be identified by RT-PCR and/or FISH in paraffin embedded tissue in most cases.

These translocations are summarized in Table 1.

Table 1

Ewing Sarcoma	t(11;22)(q24;q12) t(21;22)(q12;q12) t(2;22)(q33;q12) t(7;22)(p22;q12) t(17;22)(q12;q12)	<i>EWS-FLI-1</i> <i>EWS-ERG</i> <i>EWS-FEV</i> <i>EWS-ETV1</i> <i>EWS-EIAF</i>
Synovial sarcoma	t(X;18)(p11;q11)	<i>SYT-SSX1</i> <i>SYT-SSX2</i> <i>SYT-SSX-4</i>
Myxoid/round cell liposarcoma	t(12;16)(q13;p11) t(12;22)(q13;q12)	<i>TLS-CHOP</i> <i>EWS-CHOP</i>
Extraskelatal myxoid chondrosarcoma	t(9;22)(q31;q12) t(9;17)(q22;q11)	<i>EWS-NR4A3</i> <i>RBP56-NR4A3</i>
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14) t(1;13)(q35;q14)	<i>PAX3-FKHR</i> <i>PAX3-FKHR</i>
Desmoplastic round cell tumor	t(11;22)(p13;q12)	<i>EWS-WT1</i>
Clear cell sarcoma	t(12;22)(q13;q12)	<i>EWS-ATF1</i>
Alveolar soft parts sarcoma	Der(17)t(X;17)(p11;q25)	<i>ASPL-TFE3</i>
Infantile fibrosarcoma	t(12;15)(p13;q26)	<i>ETV6-NTRK3</i>
Dermatofibrosarcoma protuberans / giant cell fibroblastoma	t(17;22)(q21;q13)	<i>COL1A1-PDGFB</i>

Another application of molecular techniques is the identification of KIT or PDGF mutations, which provides important information regarding the potential response to Glivec in GISTs

As currently these techniques are only available in a few specialized laboratories, they will only be discussed briefly here.

II. Immunohistochemistry: introduction

As the interpretation of immunohistochemical results will strongly influence the final diagnosis in a significant amount of cases, a few general rules must be respected:

Technical quality and reproducibility must be controlled.

Immunohistochemistry should be used as complement of the morphological analysis.

Antibodies must always be chosen based on the histological differential diagnosis. Wide “random” panels can be misleading.

Panels of antibodies should be used.

Because of the lack of sensibility or specificity of markers, and of frequent “aberrant” immunoreactivities, the use of a single immunostain can lead to misdiagnoses.

For example, epithelioid angiosarcomas often express cytokeratins and will be regarded as carcinomas without a panel including a vascular marker.

A correct interpretation of immunohistochemical results is needed.

- Potential pitfalls (for example the positivity of entrapped non-neoplastic cells such as muscle fibres) must be avoided.

- “Aberrant positivities”, such as the frequent expression of cytokeratins in leiomyosarcomas, Ewing sarcomas or epithelioid angiosarcomas should be known.

- The type (nuclear, cytoplasmic, membranous...) and expected extent (diffuse/ focal) of positivity should also be known.

For example, in a monophasic synovial sarcoma, only scattered cells will be positive for CK and/or EMA.

III. Immunohistochemistry: antibodies

A. Most useful antibodies

Epithelial markers

Cytokeratins should be included in the immunohistochemical panel of most spindle and pleomorphic cell malignant tumors.

One of the most sensitive antibodies is CK AE1-AE3. When a carcinoma is suspected clinically (history of carcinoma, cutaneous and mucosal tumors, tumors located within the kidney, lung, breast... It is sometimes useful to test a second CK antibody such as KL1 or CAM5.2.

For the identification of sarcomatoid carcinomas of the skin, CK5-6 have been recommended.

Cytokeratins are also expressed by myoepithelial neoplasms, (90%), epithelioid sarcoma (90-100%), synovial sarcoma (70-90%), desmoplastic round cell tumor (80%), chordoma. "Unexpected" positivities include epithelioid vascular neoplasms (20-30%), leiomyosarcoma (40%), Ewing sarcoma / PNET (70%), rhabdomyosarcoma...

In addition to epithelial and myoepithelial neoplasms, epithelial membrane antigen (EMA) is expressed in epithelioid sarcoma (95%), synovial sarcoma (90%) and can be expressed by a large number of other soft tissue neoplasms: perineurioma, low-grade fibromyxoid sarcoma, epithelioid fibrosarcoma, superficial acral fibromyxoma...

Melanocytic / "neural" markers

S-100 protein is positive in more than 95% of melanomas and is useful in the distinction between benign peripheral nerve sheath tumors (strong and diffuse expression) and MPNSTs (focal positivity in 50-60% of cases).

It is also expressed by myoepithelial tumors (90-95%), clear cell sarcoma (which is regarded as a melanoma of soft tissue), extraskeletal myxoid chondrosarcoma (20%), myxoid and round cell sarcoma. "Unexpected" positivity has been reported in synovial sarcoma (30%).

Scattered dendritic S-100 positive cells are present in many tumors and should not be regarded as true positivity.

HMB-45 is expressed by melanoma, clear cell sarcoma and the vast majority of PEComas (which are usually negative for S-100 protein)

Lymphoid markers

Lymphoid markers will not be discussed in detail here.

They should be included in the differential diagnosis of round cell neoplasms (LCA, TdT...) and pleomorphic tumors (CD30).

Lymphoblastic lymphoma represents a potential pitfall as it is positive for CD99 in approximately 75% of cases and may be negative for LCA (but usually stains for TdT)

CD68 is useful in the identification of histiocytic proliferations or reactive lesions.

CD21, CD23 and CD31 are expressed by follicular dendritic cell sarcomas.

Muscle markers

Smooth muscle actin and desmin are usually included in basic panels. Smooth muscle actin is expressed by the vast majority of smooth muscle tumors and myofibroblastic lesions but is not very specific. It is also occasionally positive in rhabdomyosarcomas (1/3 of cases).

Desmin is positive in rhabdomyosarcomas and in 70-90% of smooth muscle tumors.

Myofibroblasts variably express smooth muscle actin and desmin but most myofibroblastic lesions such as fasciitis or fibromatosis will be focally positive for smooth muscle actin and negative for desmin.

Caldesmon is a protein combined with actin and tropomyosin that is thought to regulate cellular contraction. The high-molecular weight isoform (h-caldesmon) is relatively specific for smooth muscle differentiation. However its sensibility varies according to the degree and differentiation and the location of the tumor. Most smooth muscle tumors of the uterus are positive but only 40 to 70% of smooth muscle tumors of soft tissue express this marker. h-caldesmon also stains glomus tumors and GISTs. Myofibroblastic lesions and rhabdomyosarcomas are negative.

Myogenin (myf-4) is a myogenic regulatory protein playing a critical role in the differentiation of mesenchymal progenitor cells to the myogenic lineage and maintenance of the skeletal muscle phenotype. Myogenin is very specific and is expressed by more than 90% of rhabdomyosarcomas including virtually all embryonal and alveolar rhabdomyosarcomas. It can be positive in regenerative skeletal muscle at the periphery of infiltrating tumors. Myogenin immunostain may also provide information regarding the subtype of rhabdomyosarcoma as it is expressed in more than 50% of cells in alveolar RMS and in less than 25% of cells in embryonal RMS.

Table 2.

Muscle markers: summary				
	<i>SMA</i>	<i>desmin</i>	<i>caldesmon</i>	<i>myogenin</i>
Myofibroblastic lesions	foc. +	usually -	-	-
Smooth muscle tumors	+	+/- (50-70%)	+/- (40-70%)	-
Rhabdomyosarcoma	+/-	+	-	+

Vascular markers

The most sensitive and specific marker is CD31, which is expressed by 95-100% of benign and malignant vascular tumors. However, the expression of CD31 by macrophages is a potential pitfall.

CD34 is expressed by virtually all vascular neoplasms but also by a wide variety of mesenchymal tumors: dermatofibrosarcoma protuberans (100%), solitary fibrous tumor (90%), spindle cell / pleomorphic lipoma (100%), GISTs (70%), peripheral nerve sheath neoplasms, epithelioid sarcoma (50%),...

Occasional positivities have also been reported in leiomyosarcoma (+/- 10%), myxofibrosarcoma, myxomas...

The presence of non-tumoral CD34 positive dendritic cells is a potential pitfall in cutaneous tumors.

Other markers

- CD99 is expressed by most Ewing sarcomas, in a membranous fashion. However, it is expressed in a variety of other tumors: lymphoblastic leukemia (~100%), synovial sarcoma (80-90%), solitary fibrous tumor (90%), desmoplastic round cell tumor (30%), mesenchymal chondrosarcoma, thymoma, and in rare cases of rhabdomyosarcoma, carcinoma, MPNST...
- CD117 or KIT is a transmembranous tyrosine kinase receptor. It is normally expressed by interstitial cells of Cajal, mast cells, germ cells and melanocytes. It is expressed by more than 95% of gastrointestinal stromal tumors, focally or diffusely, with a cytoplasmic, membranous or dot-like pattern. Mast cells, which are virtually always present, represent a good internal control. Although recommended by Dako, it is now widely accepted that no antigen retrieval should be performed for CD117. Antigen retrieval does not improve the sensitivity but decreases the specificity of the antibody. This is responsible for the controversy regarding CD117 in fibromatosis, which is negative without antigen retrieval but consistently shows a non-specific positivity after microwave treatment. CD117 does not only stain GISTs. It may stain melanoma, some carcinomas, and a variety a sarcoma: Ewing sarcoma (20%), angiosarcoma (25%)...
- MDM-2 & CDK-4
Well-differentiated and dedifferentiated liposarcomas are characterized by amplifications of the 12q13-21 region resulting in ring and giant marker chromosomes. *MDM-2*, located in 12q14-15 and neighbouring gene *CDK-4* are consistently amplified and their product can be detected by immunohistochemistry. Although these markers are regarded y some authors as poorly specific, they can be useful in the distinction of lipoma / well-differentiated liposarcoma and in the diagnosis of dedifferentiated liposarcoma.
- FLI-1
Ewing sarcoma / PNET is characterized by a t(11;22)(q24;q12) translocation in approximately 90% of cases. The detection of the carboxy-terminus of FLI-1 by immunohistochemistry (nuclear staining) is more specific but less sensitive (70%) than CD99 in the diagnosis of Ewing Sarcoma / PNET. However, it is also expressed by a subset of normal lymphocytes, lymphoblastic lymphoma and by a few Merkel cell carcinomas, carcinomas and synovial sarcomas. FLI-1 also stains the majority of vascular neoplasms.
- WT-1

The product of *WT-1* gene, a suppressor gene normally expressed in some normal tissues including mesothelium, can be detected by immunohistochemistry. It is expressed in 75-95% of mesotheliomas (but also in 25% of carcinomas). WT1 may be also be useful in the diagnosis of desmoplastic small round cell tumor, which is characterized by a t(11;22)(*EWS-WT1*) translocation and is immunoreactive in 90% of cases. However WT1 is not very specific and also stains a variety of tumors including Wilm's tumor and has been reported occasionally in rhabdomyosarcoma, lymphomas ...

- HHV-8 is present in all clinical forms of Kaposi sarcoma (and also in primary effusion lymphoma)
- GFAP is expressed by 40-60% of myoepithelial neoplasms and occasionally in peripheral nerve sheath tumors
- Beta-catenin has been proposed as a marker for desmoid fibromatosis. (nuclear staining)
- Claudin-1 has been recommended as a marker of perineurial differentiation

B. Antibodies of debatable usefulness

A few antibodies that have been used commonly in the past have been replaced with most reliable markers or are now regarded as poorly specific, without any diagnostic value.

- vimentin

The best example is vimentin that is still widely used, although it does not provide any reliable diagnostic information. Vimentin was originally regarded as a marker of mesenchymal differentiation but is now known to be positive in a wide variety of neoplasms including melanoma and some carcinomas.

- myoglobin

Myoglobin is poorly specific and has been replaced by other markers. Myogenin (*myf-4*) is now regarded as the best marker of striated muscle differentiation.

- Bcl-2

The use of Bcl-2 has been advocated in the diagnosis of synovial sarcoma, solitary fibrous tumor... However, this marker has a very poor specificity and is expressed in many other spindle cell neoplasms.

- Calponin

Calponin has been introduced as a maker of myoepithelial differentiation but is poorly specific. It is expressed by the majority of smooth muscle tumors, glomus tumors, GISTs, myofibroblastic lesions, synovial sarcoma...

- FXIII, FVIII, alpha 1 antitrypsin, alpha 1 antichymotrypsin, ...

C. immunohistochemical panels

It is difficult to recommend panels as the choice of antibodies will change according to the specific clinicopathological differential diagnosis. However, a few “basic” panels can be suggested, depending on the morphological category of the tumor:

Spindle cell tumors

- Smooth muscle actin
- Desmin
- S100
- Cytokeratins
- (CD34)
- (EMA)

Pleomorphic cell tumors

- CK
- S100
- Actin
- Desmin
- (CD30)

Epithelioid tumors

- CK
- S100
- CD34

Round cell tumors:

- CK
- LCA
- Desmin and/or myf-4
- CD99
- (S100)

These suggested panels should of course be modified on the basis of the histological features of the tumor and the clinical presentation.

For example, CD117 should be added to the panel of any spindle cell / epithelioid tumor of the GI tract or abdominal cavity; mdm-2 / cdk-4 can be useful in the differential diagnosis of pleomorphic neoplasms of the retroperitoneum / abdominal cavity.

IV. Immunohistochemistry: Interpretation

A. Technical quality

The technical quality of the slide should always be evaluated. Intense background staining should be avoided. Internal controls are available for most antibodies (for example mast cells for CD117). For markers such as myogenin, mdm-2, control tissue should be used.

B. Pitfalls

Pitfalls include the presence of areas of false positivity, the presence of intratumoral pigment (melanocytic tumors, Bednar tumor...) which could be regarded as positivity, the presence of normal tissue entrapped by the tumor (muscle fibres, epithelial structures...), or the presence of intratumoral non-neoplastic cells (S100 positive dendritic cells, actin + myofibroblasts...)

C. Type / Extent of positivity

The type of positivity expected with the antibody must be known. For example, nuclear positivity for mdm-2, myf4; membranous staining for CD99 in Ewing sarcoma...

The extent of the immunoreactivity is also important. S100 will be diffusely positive in benign nerve sheath tumors but only focally positive in MPNSTs. In monophasic synovial sarcomas, EMA and CKs will only stain scattered cells.

D. Expected / unexpected positivity

Most antibodies are not entirely specific and can occasionally be expressed by various neoplasms. For example, the "expected" and "unexpected" positivity of cytokeratins is summarized in table 3.

Table 3

Cytokeratins	
Expected positivity	Unexpected positivity
Carcinoma	Ewing sarcoma / PNET (70%)
Mesothelioma	Leiomyosarcoma (40%)
Myoepithelioma	Epithelioid vascular tumors
Epithelioid sarcoma	(Pleomorphic liposarcoma)
Chordoma	(Rhabdomyosarcoma)
Desmoplastic round cell tumor	(MPNST)
Rhabdoid tumor	

V. Immunohistochemistry: Applications

The applications of immunohistochemistry fall into 3 main categories:

- The identification of rare or “atypical” benign pseudosarcomatous tumors
- The exclusion of non-sarcomatous neoplasms
- The classification of sarcomas

A. Identification of rare or atypical benign lesions

1. Benign nerve sheath tumors with pseudosarcomatous features

- Cellular schwannoma
- Neurofibroma with atypia
- “Ancient” schwannoma
- Diffuse neurofibroma
- Plexiform neurofibroma or schwannoma
- Granular cell tumors

Benign nerve sheath tumors show a strong and diffuse expression of S-100 protein, whereas MPNSTs stain only focally, in 50-60% of cases.

2. Reactive myofibroblastic lesions

The immunophenotype of myofibroblasts is variable (sma +/-, desmin +/-) but the vast majority of benign pseudosarcomatous proliferations (fasciitis) focally express smooth muscle actin.

3. Histiocytic neoplasms

Histiocytic neoplasms such as diffuse-type giant cell tumor or reactive infiltrates can occasionally mimic a sarcoma.

4. Identification of unusual benign lesions

- paragangliomas express chromogranin, NSE and their “sustentacular” component is positive for S100 protein
- glomus tumors and myopericytomas express smooth muscle actin and caldesmon
- solitary fibrous tumor and spindle cell lipoma express CD34
- PEComas express HMB45 and muscle markers
- myoepitheliomas express CK/EMA, S100 and variably actin, desmin, GFAP...

B. Identification of non-sarcomatous malignant neoplasms

As the treatment is different, it is extremely important to always rule out a non-sarcomatous tumor: carcinoma, melanoma, and lymphoma using adequate immunostains.

This is particularly true in the following situations:

- Previous history of cancer
- Cutaneous or mucosal tumors
- Tumors located in lymphoid area (axilla, inguinal region, neck)
- Tumors located within or near the lung, kidney, breast, pancreas...
- Tumors with a non-specific histology (such as "MFH-like" pleomorphic neoplasms)

C. Classification of sarcomas

Immunohistochemistry is required for the diagnosis of a variety of sarcomas, including synovial sarcoma (EMA, CK), epithelioid sarcoma (EMA, CK), clear cell sarcoma (S100, HMB45), GIST (CD117), rhabdomyosarcoma (desmin, myf4), desmoplastic small round cell (CK, desmin, NSE), epithelioid angiosarcoma (CD31, CD34)...

It is also useful in the diagnosis of leiomyosarcoma (actin +, desmin +/-, caldesmon +/-), MPNST (S100 + in 50-60% of cases), dermatofibrosarcoma protuberans (CD34 +), dedifferentiated liposarcoma (mdm2 +, cdk4 +)

CD99 and FLI-1 are useful in the diagnosis of Ewing sarcoma / PNET but as they are their specificity (CD99 may be positive in a large variety of tumors including poorly differentiated synovial sarcoma, desmoplastic small round cell tumor, lymphoblastic leukemia) or sensitivity (FLI-1 is only positive in 70% of cases of Ewing sarcoma), molecular proof of the translocation is increasingly required.

VI. Slide seminar

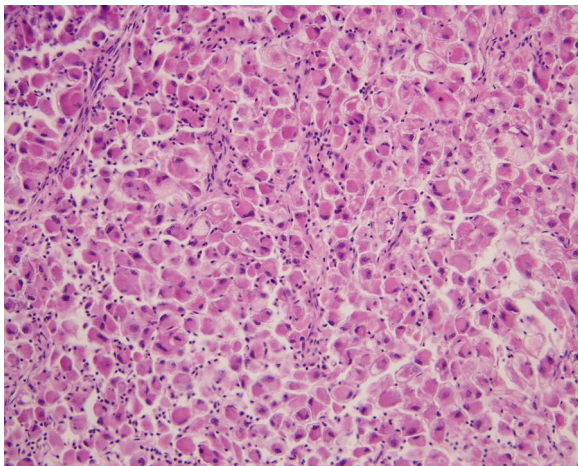
Case 1

Clinical history :

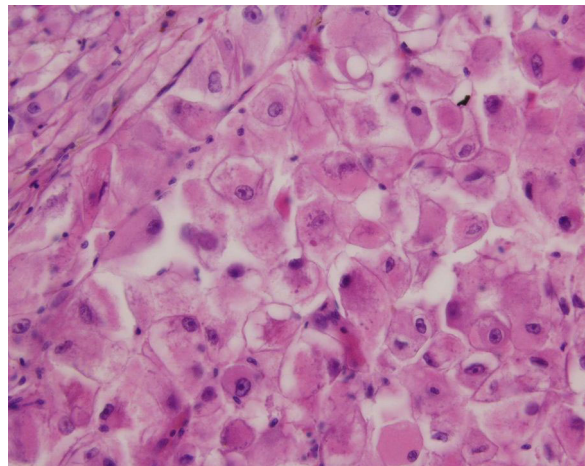
65 year-old female with tuberous sclerosis.
Large pararenal tumor, 4.5 kg.

Histological features:

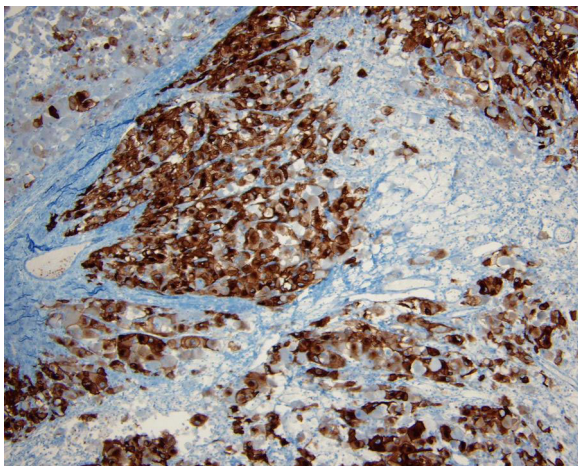
The tumor is composed of large epithelioid cells characterized by abundant granular cytoplasm. The stroma is highly vascularized.



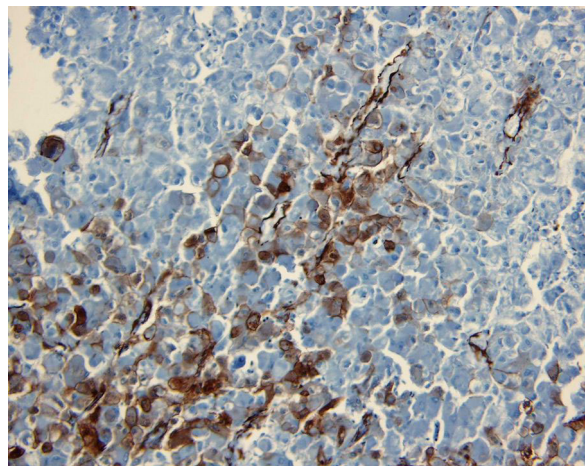
1.



2.



3. HMB45



4. actin

Differential diagnosis:

Because of the clinical setting of tuberous sclerosis and the pararenal location, an epithelioid angiomyolipoma must be considered. The differential diagnosis includes carcinoma and, less likely, paraganglioma, epithelioid GIST or metastatic melanoma.

Immunohistochemistry:

Suggested panel:

- HMB-45: positive
- Smooth muscle actin: positive
- S-100 protein: negative
- CytoK: negative
- (CD117: negative)
- (chromogranin)

Diagnosis: **Epithelioid angiomyolipoma**

Discussion:

Angiomyolipoma is a renal or hepatic tumor that may also present as a retroperitoneal mass and simulate a sarcoma. Angiomyolipoma can occur sporadically or in association with tuberous sclerosis. There is a predilection for middle-aged females.

Tumors have 3 components: myoid spindle or epithelioid cells, with granular eosinophilic or clear cytoplasm, mature adipocytes, and thick-walled vessels. Tumors with a predominant spindle cell component may simulate leiomyosarcoma; predominantly adipocytic tumors may be misdiagnosed as well-differentiated liposarcoma.

Diagnostic clues are the clinical data (tuberous sclerosis ?), imaging (attachment to the kidney ?) and a careful sampling for the 3 components.

The diagnosis is confirmed by the co-expression of myogenic (smooth muscle actin +, desmin +/-) and melanocytic (HMB45 +, melan-A +, S100 usually -) markers.

Epithelioid Angiomyolipoma is a rare variant, which associated with tuberous sclerosis in more than half of the cases. Tumors are usually large and are composed of sheets of large round or polygonal cells with abundant granular eosinophilic cytoplasm. Nuclei are large, with prominent nucleoli. Tumors may display high mitotic activity. The immunophenotype is similar to “classical” angiomyolipoma.

Epithelioid angiomyolipoma must be distinguished from renal cell carcinoma, oncocytoma or metastatic melanoma.

“Classical” angiomyolipoma is benign. Epithelioid angiomyolipoma metastasize in up to 1/3 of cases.

Angiomyolipoma shares its peculiar myo-melanocytic phenotype with a few other tumors: clear cell “sugar” tumor of the lung, lymphangioliomyoma(tosis), and myomelanocytic tumor of the ligamentum teres, for which the term perivascular epithelioid tumor (PEComa) have been introduced by Bonetti et al.

Recently, tumors showing morphological features of myomelanocytic tumor, clear cell “sugar” tumor or epithelioid angiomyolipoma have been reported in an increasing number of

locations including the uterine corpus, skin, bladder, prostate, pancreas, breast and in soft tissue (3 cases).

Histological features suggestive of a PEComa include a rich vascularization and the presence of clear to granular eosinophilic cytoplasm, which often shows a paranuclear condensation.

PEComas must be distinguished from granular cell tumors, melanoma, granular cell smooth muscle tumors...Immunohistochemistry is essential.

Most PEComas behave in a benign fashion but cases with aggressive behavior have been reported.

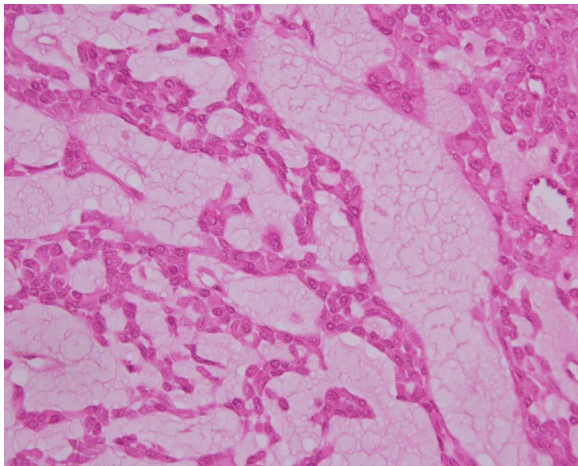
Case 2

Clinical history :

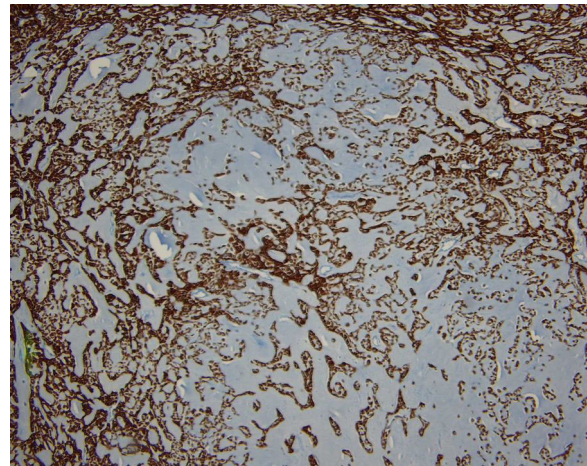
Male, 21.
1.5 cm tumor in the eyelid.

Histological features:

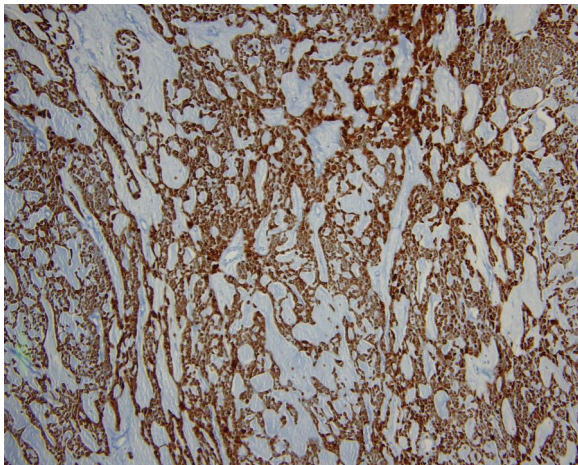
A well-circumscribed tumor composed of large uniform epithelioid cells arranged in interlacing cords. Tumor cells have abundant brightly eosinophilic cytoplasm and uniform vesicular nuclei.



1.



2. CK



3. S100

Differential diagnosis:

This appearance is suggestive of myoepithelioma.

A mucinous carcinoma is unlikely at this age and with this morphology. In soft tissues of the limb, the differential would have included extraskeletal myxoid chondrosarcoma.

Immunohistochemistry:

Cytokeratins: +

EMA: +

S100: +

Smooth muscle actin: -

Desmin: -

GFAP: -

(Calponin)

(p63: -)

Diagnosis: **Myoepithelioma**

Discussion:

Mixed tumors / myoepitheliomas similar to their salivary gland counterparts were well documented in the skin and the vulvo-vaginal region but have only been described in soft tissue in 1997. Since the publication of this series, an increasing number of cases have been reported in a variety of locations and myoepithelioma have been included in the WHO classification.

Myoepithelioma affects predominantly young adults but may occur at any age, including in children. The majority of cases involve the superficial or deep soft tissue of the limbs, but cases have been reported in the head and neck region, trunk, and in bone.

As their salivary gland counterparts, myoepitheliomas / mixed tumors show a wide morphological spectrum. They are composed of variable proportions of epithelial structures and myoepithelial cells embedded in a myxoid, chondroid or hyaline stroma. Myoepithelial cells may have a spindled, epithelioid, or plasmocytoid appearance. They are arranged in anastomosed nests and cords. Cytoplasm is eosinophilic or clear.

The diagnosis is based on the resemblance with their salivary glands counterparts and on the immunophenotype. Tumors usually co-express at least epithelial markers and S-100 protein. Muscle markers (smooth muscle actin and desmin) and GFAP are variably positive. Calponin is often expressed but is not specific. P63 is often negative in myoepithelial tumors of soft tissue.

Table 4

Myoepithelioma: immunohistochemistry	
Cytokeratins	90-95%
S100	85-90%
Calponin	85%
EMA	45%
GFAP	35%
Smooth muscle actin	25%
Desmin	15%
P63	15%

The majority of myoepitheliomas / mixed tumors are benign but rare cases showing high grade atypia should be regarded as malignant as they often behave very aggressively.

Case 3

Clinical history :

34 years-old male, with a 5 cm retroperitoneal tumor

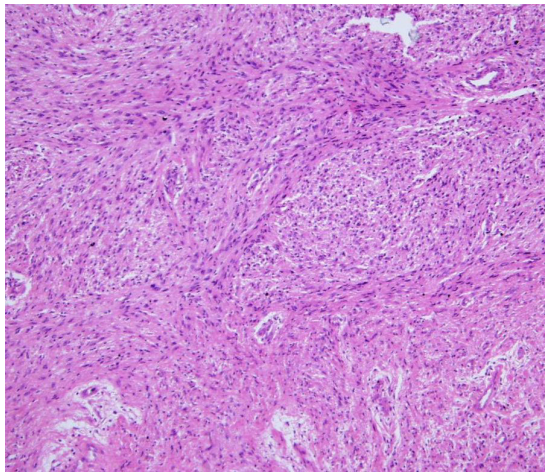
Histological features:

A thick fibrous capsule with lymphoid nodules surrounds the tumor.

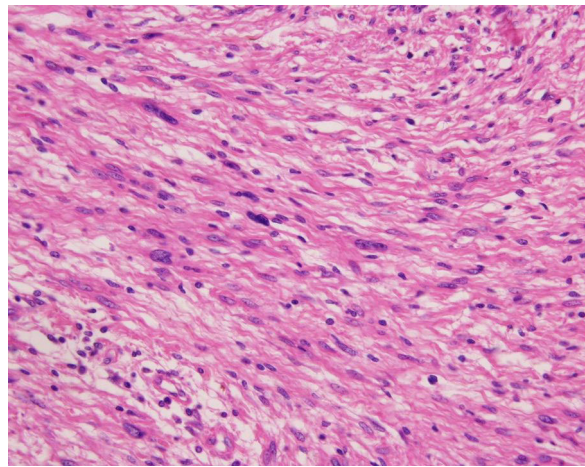
Spindle cells, with pale cytoplasm, are arranged in fascicles.

Rare cells show enlarged hyperchromatic nuclei. Mitotic activity is low (2/10 HPF)

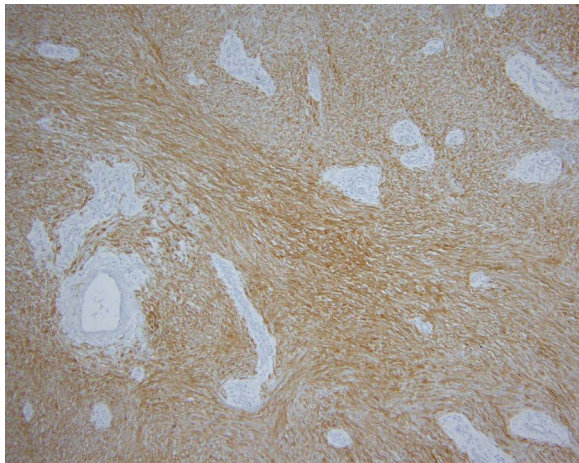
The tumor contains lymphocytic and histiocytic aggregates.



1.



2.



3. S100

Differential diagnosis:

The differential diagnosis includes spindle cell tumors of the abdomen / retroperitoneum. Because of the young age of the patient, the thick capsule with lymphoid nodules and the presence of histiocytes, a cellular schwannoma must be suspected. The most important differential diagnoses are sarcomas: malignant peripheral nerve sheath tumor (MPNST) and leiomyosarcoma (which would appear more eosinophilic). GIST could also be considered. Synovial sarcoma is very uncommon in such location.

Immunohistochemistry:

Suggested panel:

S100: diffusely positive

SMA: negative

Desmin: negative

CytoK: negative

(CD117: negative)

Diagnosis: **Cellular schwannoma**

Comments:

This case illustrates the importance of S-100 protein in the recognition of benign nerve sheath tumors. Schwannomas and neurofibromas diffusely express S-100 protein, whereas MPNST shows focal positivity in only 50-60% of cases. This is particularly important in cellular or atypical variants of benign nerve sheath tumors such as cellular schwannoma, “atypical” neurofibromas and schwannomas, “ancient” schwannoma.

Cellular schwannoma is a rare clinically and histologically distinctive variant of benign schwannoma, which is misdiagnosed as a sarcoma in up to 25% of cases.

These tumors affect young adults, in the retroperitoneum (60% of cases), mediastinum, or less commonly the limbs. Tumors can be very large at the diagnosis (up to 20 cm). They are composed of Antoni A fascicular tissue; Verocay bodies are usually absent. Worrisome histological features include a high cellularity, mitotic activity (usually less than 5/10 HPF), and the occasional presence of necrosis (5-10% of cases).

Diagnostic clues are the presence of a thick fibrous capsule, lymphoid nodules, clusters of foamy macrophages, hyalinized vessels and the strong and diffuse positivity for S-100 protein.

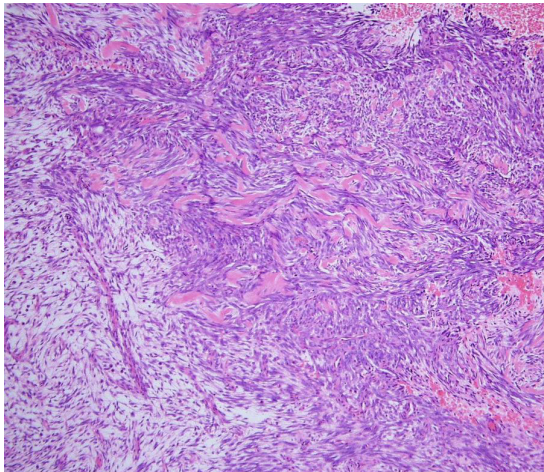
Case 4

Clinical history :

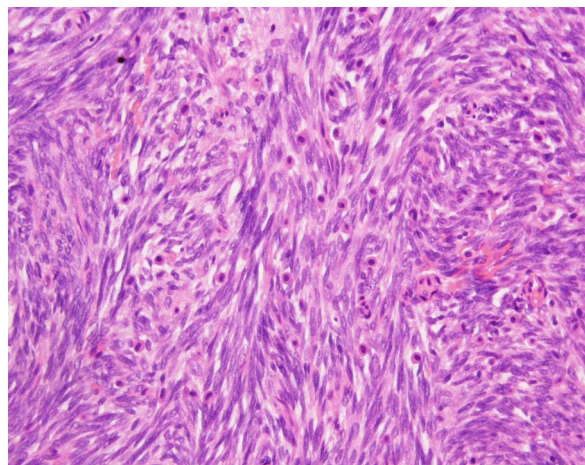
28 years-old female with a 4 cm tumor in the foot.

Histological features:

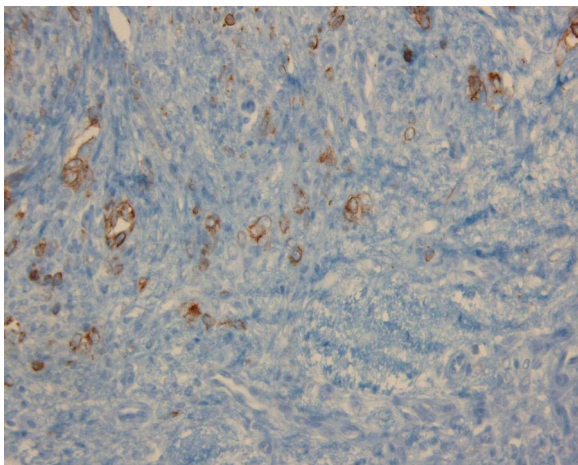
A spindle cell neoplasm with a basophilic appearance and a fascicular “herringbone” architecture. Spindle cells display monotonous ovoid nuclei.



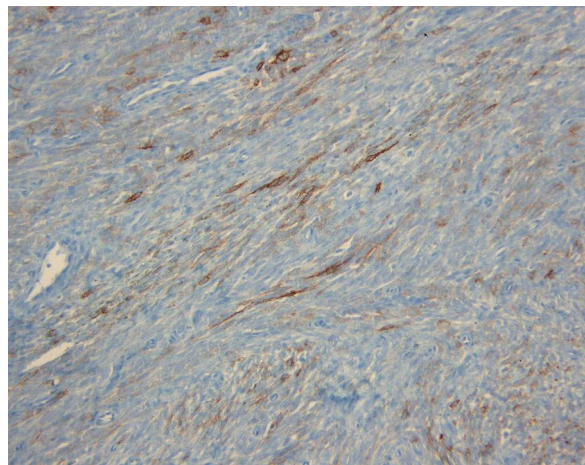
1.



2.



3. CK



4. EMA

Differential diagnosis:

This tumor shows a “herringbone” fibrosarcoma-like fascicular architecture. This pattern is not specific. Conventional fibrosarcoma is now regarded, at best, as a diagnosis of exclusion. In the skin/ subcutis, such tumors correspond to fibrosarcomatous dermatofibrosarcoma protuberans. In deep soft tissue, there is a differential diagnosis between MPNST and synovial sarcoma.

In this case, the location and the monotonous appearance of the spindle cells are in favor of synovial sarcoma.

Immunohistochemistry:

CytoK: focally positive

EMA: focally positive

CD34: negative

S-100 protein: negative

Molecular biology:

t(X:18) SYT/SSX (demonstrated by FISH analysis)

Diagnosis: **Synovial sarcoma (monophasic spindle cell variant)**

Comments:

Synovial sarcoma accounts for approximately 10% of soft tissue sarcomas. There is a predilection for young patients (15-35 years). Tumors frequently arise in deep soft tissue, in the vicinity of joints or tendon sheaths, and there is a predilection for the knee. An increasing number of cases are reported in the thoracic wall and the thoracic cavity.

Biphasic tumors are usually easily recognized. Monophasic synovial sarcoma is composed of uniform spindle cells arranged in a fascicular “herringbone” pattern. Cytoplasm is sparse. Nuclei are uniform, with fine chromatin and inconspicuous nucleoli. A prominent hemangiopericytoma-like vascularization is commonly seen. Abundant mast cells are usually present. Some cases display abundant calcifications. Poorly differentiated synovial sarcoma is uncommon (less than 20% of synovial sarcomas). It is characterized by increased cellularity, high mitotic activity and is composed of round cells showing more pleomorphism.

EMA and cytokeratins are expressed in more than 90% of cases, in the epithelial component (if present) and in spindle cells (singly or in clusters). Positivity of spindle cells may be very focal and require careful screening of the slides. CD34 is usually negative which may be helpful in the differential diagnosis with solitary fibrous tumor (positive for CD34 in more than 90% of cases) and MPNST (+/- 40%). S-100 protein is expressed in up to 30% of cases. A non-specific positivity for CD99 and Bcl-2 is common.

Synovial sarcoma is characterized by a translocation t(X;18) *SYT-SSX* which can be detected by RT-PCR or FISH in paraffin-embedded tissue.

Case 5

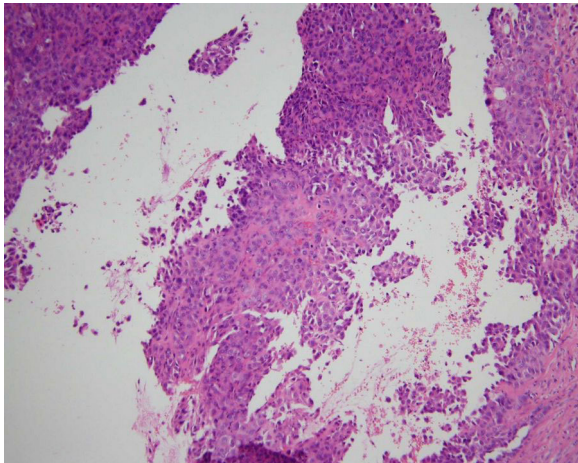
Clinical history:

Female, 32.

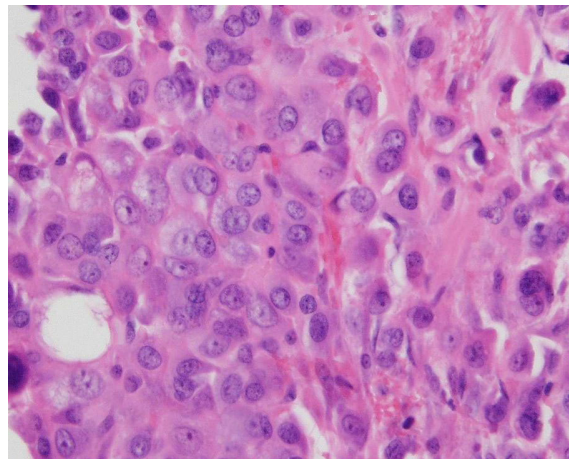
Recurrent paravaginal mass

Histological features:

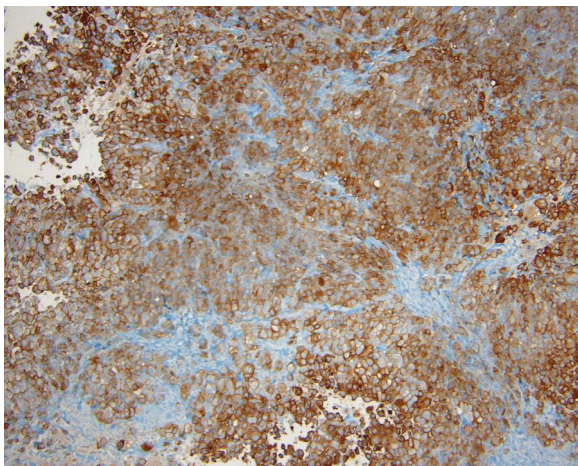
In the biopsy, the tumor was composed of sheets of large epithelioid cells with abundant eosinophilic cytoplasm and uniform vesicular nuclei.



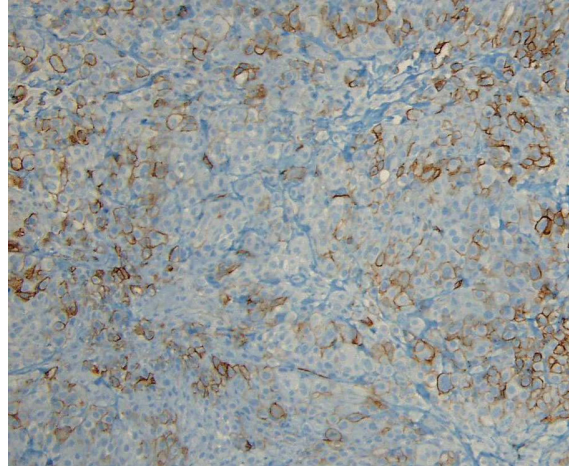
1.



2.



3. EMA



4. CD34

Differential diagnosis:

The differential diagnosis includes carcinoma, melanoma, and less likely epithelioid sarcoma. Clinicopathological correlation is very important.

Immunohistochemistry:

CK AE1-AE3: +

EMA: +

CD34: +

S100: -

Diagnosis: **Epithelioid sarcoma (proximal type ?)**

Comments:

In this case, the clinical presentation is unusual and a carcinoma must be ruled out clinically. However, CD34 positivity is in favor of epithelioid sarcoma, as it is positive in 50% of cases but is negative in the vast majority of epithelial tumors.

Epithelioid sarcoma is a rare tumor affecting mainly young adults, with a very strong predilection for the fingers, hand, wrist or forearm.

Most cases show a pseudogranulomatous appearance, with mildly atypical epithelioid and spindle cells arranged around central necrotic areas.

Immunohistochemically, more than 95% of cases express cytokeratins and EMA. CD34 is positive in 50% of cases, which may be useful in the differential diagnosis with carcinoma.

Occasional reactivity for actin and S100 protein as been reported.

In “usual” locations, the main differential diagnosis is a granulomatous process such as granuloma annulare or rheumatoid nodule; CK and CD68 stains should be performed on any unequivocal case.

Proximal type ES is a variant that tends to present in the pelvis, perineum or genital tract. It often lacks the “pseudogranulomatous” pattern of ES and is composed of larger cells with marked nuclear atypia and predominant nuclei. This variant seems to be associated with a more aggressive course.

This case shows intermediate morphological features. The primary tumor showed only mild atypia and a pseudogranulomatous architecture, which is the appearance of classical ES. In recurrences, tumor cells were larger, more atypical, and arranged in sheets, which is more consistent with the proximal type variant.

Case 6

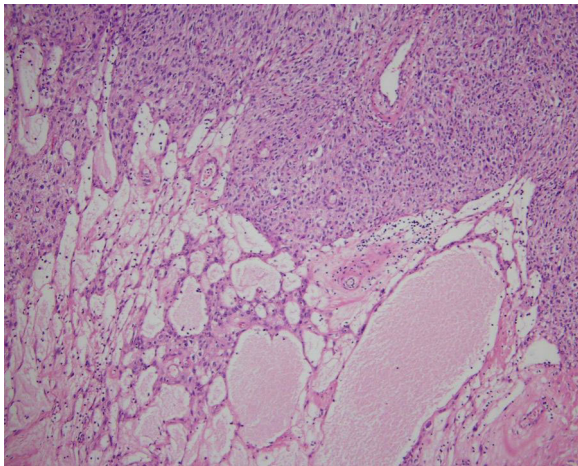
Clinical history :

Male, 57

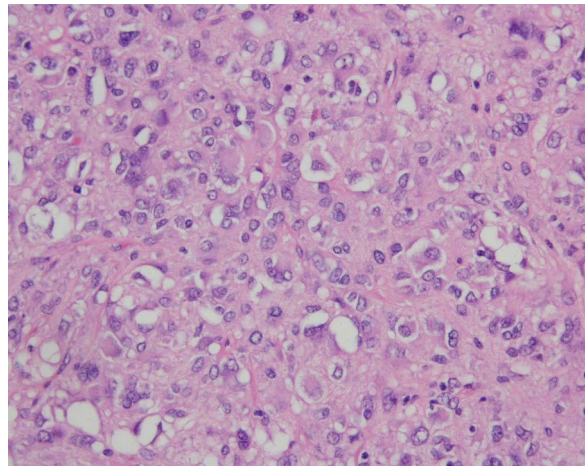
19 cm tumor in the gastric wall.

Histological features:

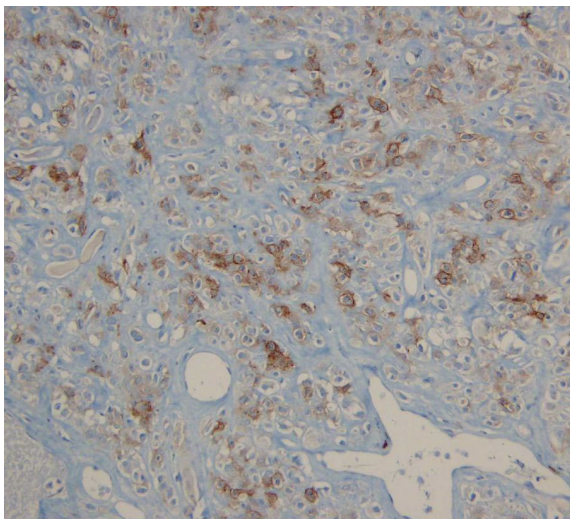
The tumor is composed of sheets of large monomorphic epithelioid cells with pale eosinophilic cytoplasm and ovoid nuclei showing mild pleomorphism. A large number of cells contain a paranuclear inclusion. Mitotic activity is minimal.



1.



2.



3. CD117

Differential diagnosis:

The most common mesenchymal tumor of the GI tract is GIST. As GIST can benefit from Glivec treatment, their identification is crucial and CD117 stain should be performed on virtually every intraabdominal spindle cell / epithelioid neoplasm of the GI tract and the abdominal cavity.

Immunohistochemistry:

Suggested panel:

CD117: positive
S-100 protein: negative
CytoK: negative
Actin: positive
Desmin: positive
(CD34 : positive)

Diagnosis: **Gastro-intestinal stromal tumor (GIST)**

Discussion:

GISTs will not be discussed in detail here. Spindle cell and epithelioid tumors of the GI tract were initially regarded as smooth muscle neoplasms. The term gastro-intestinal stromal tumor has been introduced by Mazur and Clark in 1984, following immunohistochemical studies that showed the absence of muscle markers in a significant number of tumors, and the presence of a neural phenotype in some cases. However, the spectrum of GISTs has only been well defined and delineated from other mesenchymal neoplasms of the GI tract recently.

GISTs are located within the gastric or small bowel wall and less commonly in the colon, mesentery or peritoneum. Histologically, they are composed of rather monotonous spindle cells (2/3 of cases) or epithelioid cells (1/3) with pale cytoplasm. Pleomorphism is usually minimal.

Immunohistochemically, GISTs are characterized by the expression of CD117 (KIT) in the majority of cases. Positivity may be focal or diffuse, and cytoplasmic, membranous or dot-like. CD34 is positive in approximately 70% of cases. Muscle markers actin and h-caldesmon are variably expressed (40-70%) but desmin expression is very uncommon (<5%).

KIT is a receptor tyrosine kinase that is involved in the development and maintenance of interstitial cells of Cajal, mast cells, germ cells and melanocytes. Mutations that result in ligand independent activation of KIT are identified in 85-90% of cases. Approximately 5% of GISTs have mutations within the *PDGFRA* gene. Identification of the KIT or PDGFRA mutations can be extremely useful in CD117 negative cases. The location of the mutations within the KIT gene is also predictive of the response to Glivec.

The differential diagnosis of spindle cell GISTs include spindle cell carcinoma, metastatic melanoma (which is not uncommon in the GI tract and can be CD117 positive), leiomyoma / leiomyosarcoma (desmin +, CD117 -), schwannoma, desmoid fibromatosis. The differential diagnosis of epithelioid GISTs is broad: carcinoma, melanoma, paraganglioma...

The correct identification of GISTs is crucial, as patients may benefit from tyrosine kinase inhibitor STI-571 (Glivec) treatment.

It is important to remember that:

- GISTs are not always KIT positive

Approximately 5% of GISTs are KIT negative. These tumors are more likely to have epithelioid morphology, have PDGFRA mutations and arise in the omentum or peritoneum. KIT negative GISTs may contain imatinib-sensitive KIT or PDGFRA mutations; therefore, patients with KIT-negative GISTs should not be denied imatinib therapy.

- KIT stains other tumors

A potential pitfall is the common expression of KI by metastatic melanoma.

Many grading schemes have been proposed but currently, GISTs are regarded as malignant, and it is the risk evaluation is based on the size of the tumor and mitotic index.

Very low risk:	< 5 mitoses / 50 HPF	< 2 cm
Low risk:	< 5 mitoses / 50 HPF	2-5 cm
Intermediate risk:	< 5 mitoses / 50 HPF	5-10 cm
	6-10 mitoses / 50 HPF	< 5 cm
High risk	> 5 mitoses / 50 HPF	> 5 cm
	Any mitotic index	> 10 cm
	> 10 mitoses / 50 HPF	Any size

Case 7

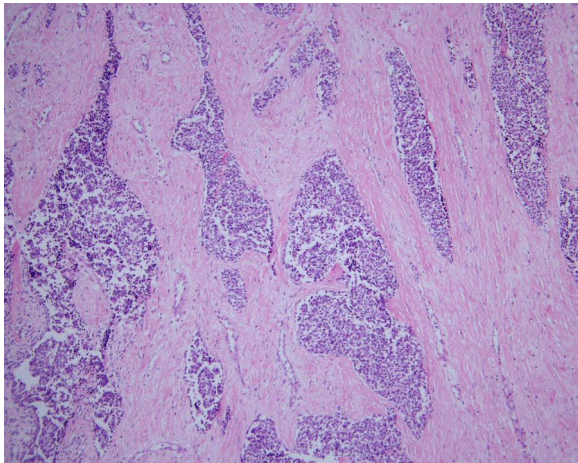
Clinical history :

Male, 19.

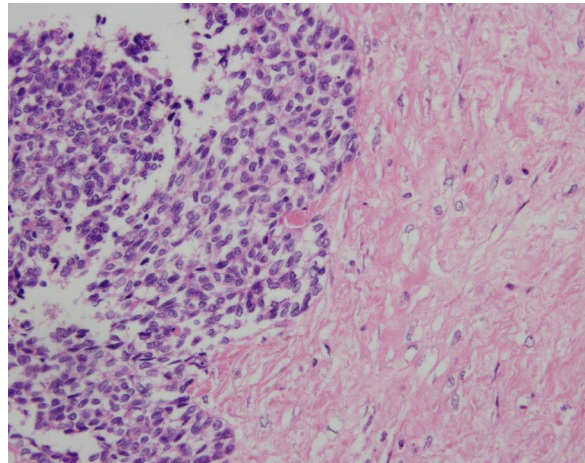
Clinically: “peritoneal carcinomatosis”

Histological features:

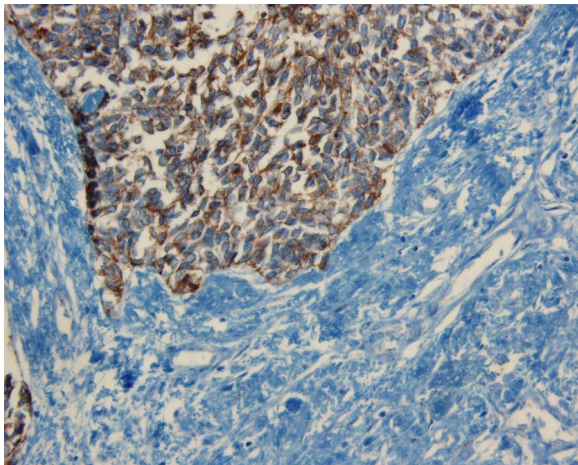
The tumor is composed of sheets of medium-sized rounded cells, with pale cytoplasm, embedded in a desmoplastic fibrous stroma.



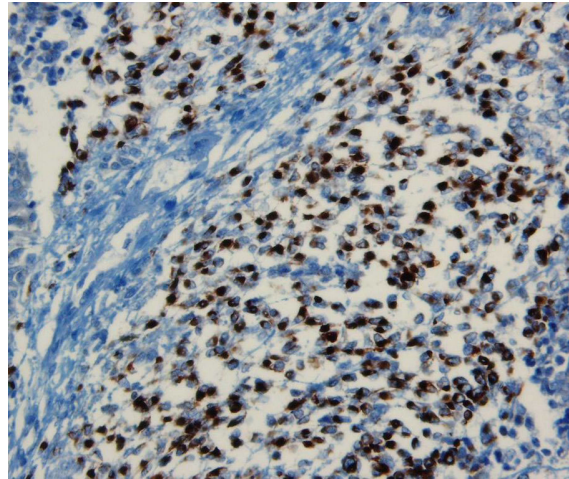
1.



2.



3. CK



4. desmin

Differential diagnosis:

The differential diagnosis includes Ewing sarcoma, desmoplastic round cell sarcoma, and lymphoma. Small cell carcinoma is unlikely at that age. Rhabdomyosarcoma is uncommon in adults and in the abdominal cavity.

Immunohistochemistry:

Suggested panel:

Cytok: positive
Desmin: positive
(NSE: positive)
CD99: negative
LCA: negative
(WT1)

cytogenetics / molecular biology were not performed in this case.

Diagnosis: **(Intraabdominal) desmoplastic small round cell tumor**

Comments:

Desmoplastic small round cell tumor shows a strong predilection for the peritoneum of young males, but rarely involve other locations. Multiple serosal implants are common. Tumors are very aggressive and prognosis is poor despite aggressive therapy. DSRCT is characterized histologically by variably sized nests of small to medium-sized round cells, surrounded by a prominent desmoplastic stroma. A glandular or rosette growth pattern may be seen. Mitoses are frequent and necrosis is common.

Immunohistochemically, tumors are characterized by the co-expression of cytokeratins (>90%), EMA (>90%), desmin (>90%), often with a dot-like pattern, and NSE. WT1 is positive in all cases but is not very specific. S100 protein and CD99 may be positive.

DSRCT is characterized by a translocation t(11;22) *EWS-WT1* but clinico-pathological features and the immunohistochemical profile are sufficient to establish the diagnosis.

Case 8

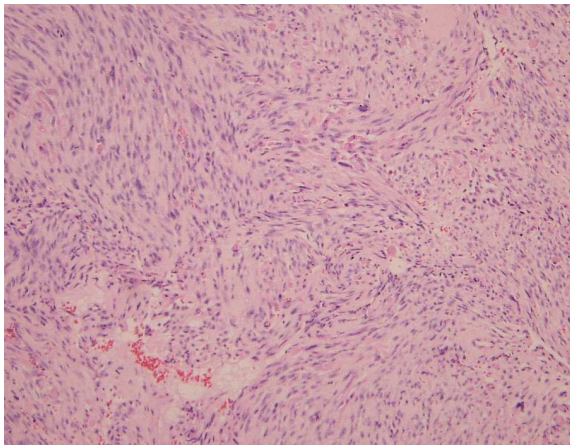
Clinical history :

Male, 45.

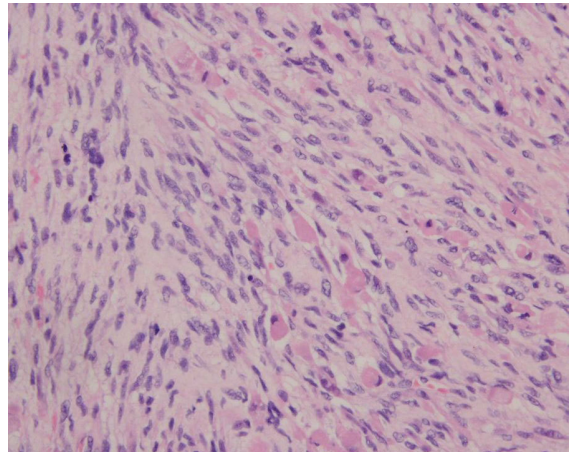
Parapharyngeal mass, 5 cm.

Histological features:

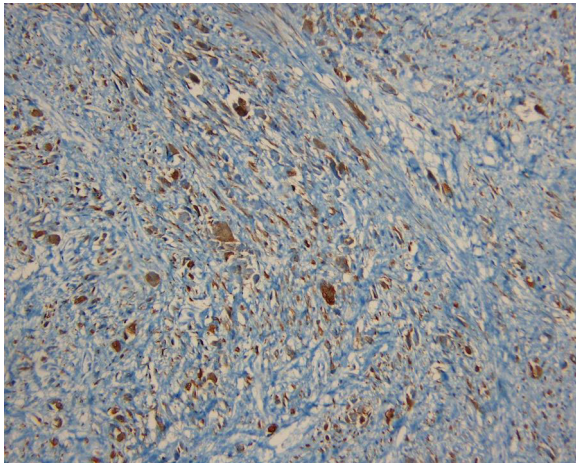
The tumor is composed of spindle cells admixed by scattered larger pleomorphic cells with abundant brightly eosinophilic cytoplasm. .



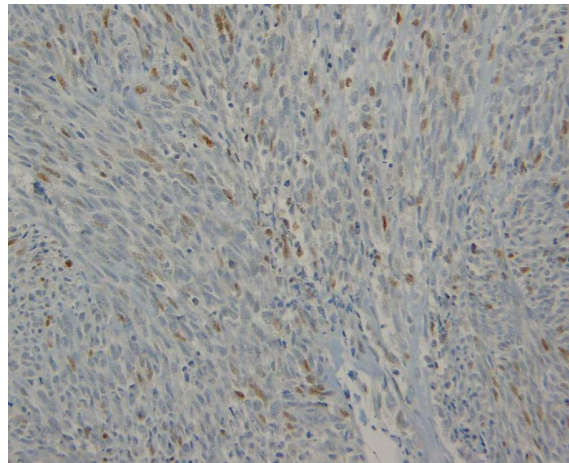
1.



2.



3. desmin



4. myogenin

Differential diagnosis:

The differential diagnosis includes myogenic sarcomas: leiomyosarcoma and rhabdomyosarcoma. In this parapharyngeal location, a carcinoma should also be ruled out.

Immunohistochemistry:

Desmin: diffusely +
Smooth muscle actin: focally +
Myogenin: +
CK AE1-AE3: -

Diagnosis: **Rhabdomyosarcoma (pleomorphic ?)**

Comments:

This case illustrates the role of myogenin (myf4) in the differential diagnosis of myogenic sarcomas. Myogenin is currently regarded as the more sensitive and specific marker for smooth muscle differentiation, as discussed above.

Pleomorphic rhabdomyosarcoma is a rare, aggressive sarcoma, which occur almost exclusively in adults. Sampling for the identification of polygonal rhabdomyoblasts is required, but the identification of cross striations is exceedingly rare. The diagnosis requires immunohistochemistry.

Case 9

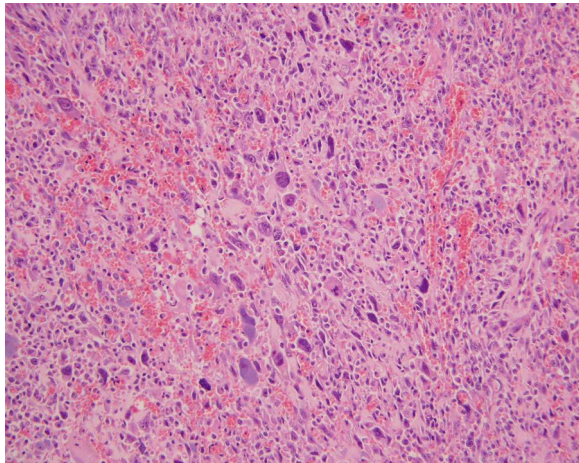
Clinical history :

Female, 73.

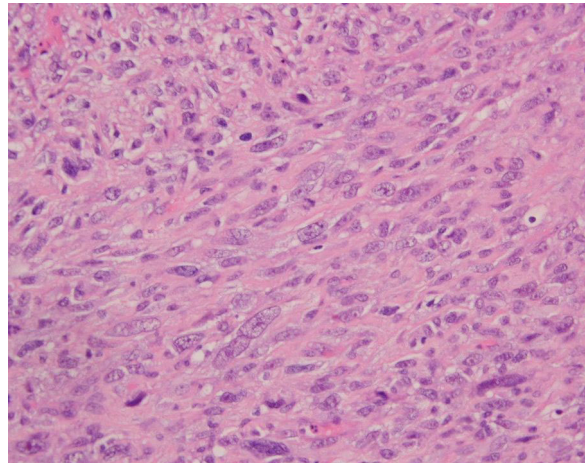
6 cm tumor in the duodenal wall

Histological features:

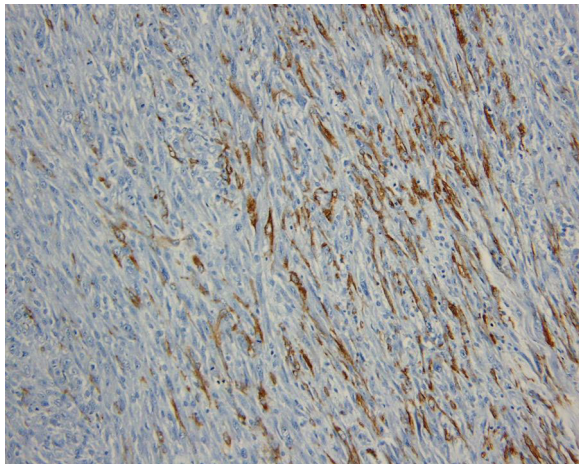
A poorly differentiated spindle and pleomorphic cell sarcoma, with a non-specific “MFH-like” appearance.



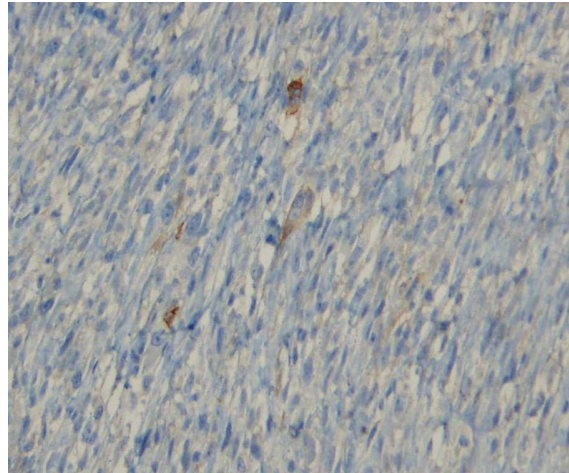
1.



2.



3. actin



4. caldesmon

Differential diagnosis:

The most important step with pleomorphic cell tumors is to rule out non-sarcomatous tumors: metastatic carcinoma or melanoma, or anaplastic lymphoma.

The second step will be to try to classify the sarcoma, which is important as the prognosis of myogenic sarcomas (LMS and RMS) is worse (with a metastatic risk of approximately 60-70%) than the prognosis of high-grade myxofibrosarcoma or dedifferentiated liposarcoma.

Immunohistochemistry:

Suggested panel:

Cytokeratins: negative

S-100 protein: negative

Actin: positive

Desmin:

Caldesmon:

(CD30: negative)

Diagnosis: **Pleomorphic leiomyosarcoma**

Comments:

Although the subclassification of pleomorphic sarcomas has for long been regarded as meaningless during the “MFH” years, a few studies have now demonstrated that there are significant differences in terms of survival. Myogenic sarcomas (rhabdomyosarcoma and leiomyosarcoma) are very aggressive, with a metastasis rate approaching 70%. Pleomorphic liposarcoma shows a 50% metastasis rate. High-grade myxofibrosarcoma is very aggressive locally but metastasize in only 20-35% of cases. In dedifferentiated liposarcoma, metastases occur in approximately 15% of cases.

Immunohistochemistry is often needed for the diagnosis of high-grade leiomyosarcoma. Smooth muscle actin is not specific and may be positive in rhabdomyosarcoma, myxofibrosarcoma, unclassified sarcoma / so-called “MFH” ... Desmin is not always expressed (50-70% of cases). H-caldesmon is relatively specific, and is positive in the majority of uterine smooth muscle tumors but in only 40-70% of soft tissue leiomyosarcomas. The minimal criteria for smooth muscle tumors are not well defined. Tumors which show morphological features of smooth muscle differentiation (intersected fascicles, eosinophilic cytoplasm with apparent cell membranes, blunt-ended nuclei) and positivity for actin, and poorly differentiated sarcomas showing reactivity for at least 2 of these markers can probably be regarded confidently as smooth muscle neoplasms. A negative myogenin may be required, as rhabdomyosarcomas may express smooth muscle actin.

Leiomyosarcoma can occasionally stain for cytokeratins (40%), CD34, EMA.

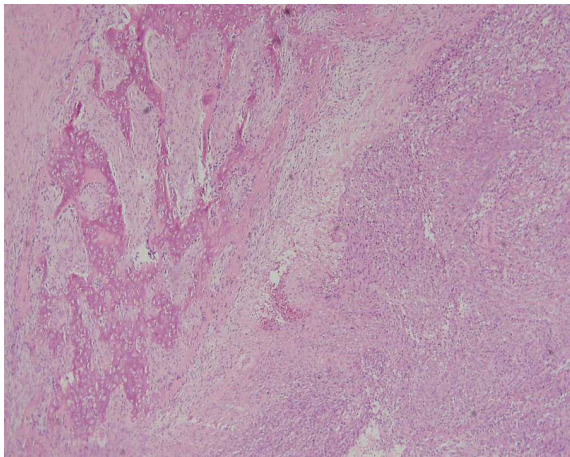
Case 10

Clinical history :

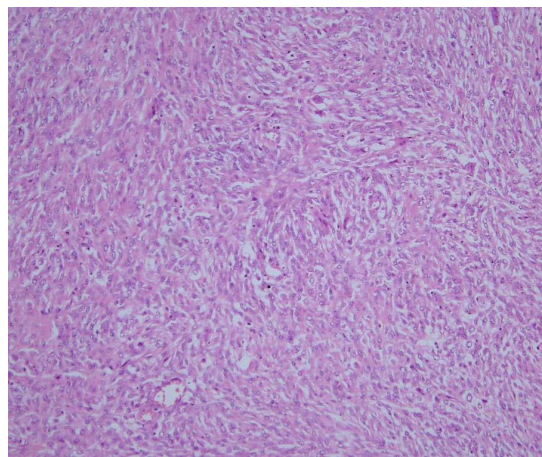
Male, 72.
12 cm retroperitoneal tumor

Histological features:

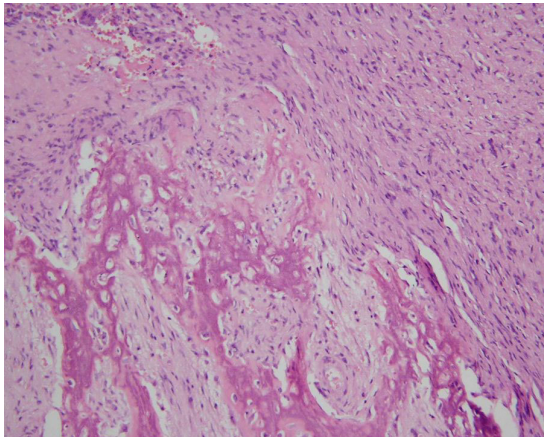
The tumor is composed of spindle and pleomorphic cells and has 2 components: an osteosarcomatous component and a spindle cell component with a vague storiform architecture.



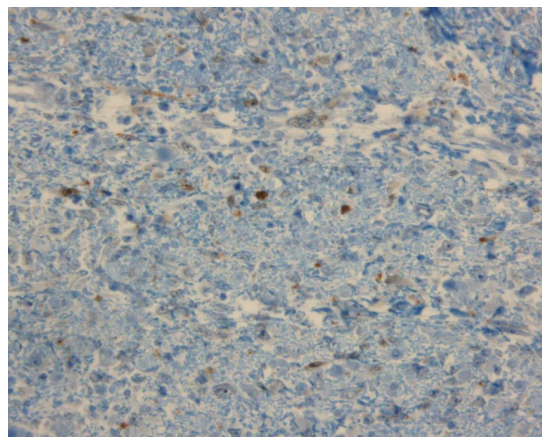
1.



2.



3.



4. mdm2

Differential diagnosis:

Dedifferentiated liposarcoma should always be considered in the differential diagnosis of pleomorphic sarcomas of the retroperitoneum as it has been shown that most so-called “MFH” in this location show the molecular signature of dedifferentiated liposarcoma (ring and marker chromosomes resulting from amplifications of chromosome 12). The presence of heterologous elements (with osteosarcomatous, chondrosarcomatous or myogenic differentiation) is common in dedifferentiated liposarcoma and most cases previously regarded as “malignant mesenchymomas” of the retroperitoneum are probably unrecognized dedifferentiated liposarcomas.

Other diagnostic considerations include: metastatic carcinoma, metastatic melanoma, anaplastic lymphoma and pleiomorphic leiomyosarcoma. GISTs usually do not display significant pleomorphism.

Immunohistochemistry:

Suggested panel:

- mdm-2: positive
- (cdK-4)
- cytoK: negative
- S-100 protein: negative
- Desmin: negative
- (actin: focally positive)
- (CD30: negative)
- (CD 117: negative)

Diagnosis: **Dedifferentiated liposarcoma**

Comments:

Dedifferentiated liposarcoma is usually defined by the coexistence of a well-differentiated liposarcoma component and a non-lipogenic sarcoma. However, the well-differentiated component may be minimal and require extensive sampling.

Dedifferentiation occurs in approximately 10% of well-differentiated liposarcoma. It is extremely uncommon with superficial tumors and relatively uncommon in deep situated tumors of the limbs but is more frequent in the retroperitoneum (20-40%) and the paratesticular area (10-20%). Approximately 70% of all dedifferentiated liposarcoma occur in the retroperitoneum.

Dedifferentiated liposarcoma usually present as large painless masses, in adults, with a peak in the 7th decade.

Histologically, the transition between the well-differentiated and dedifferentiated component may be abrupt or gradual or, less frequently, both components may be intermingled. The extent of the dedifferentiation is highly variable and does not seem to influence the prognosis. The dedifferentiated component may show a variable histological picture but in most cases is pleomorphic and resemble so-called “MFH” or high-grade myxofibrosarcoma. Low-grade dedifferentiated areas may resemble low-grade myxofibrosarcoma or “low-grade fibrosarcoma”. A peculiar “meningothelial-like” whorling pattern of dedifferentiation, often associated with ossification, has been reported. In 10% of cases, liposarcoma contain

heterologous elements, which does not seem to have any prognostic impact. Heterologous elements may show leiomyosarcomatous (65%), rhabdomyosarcomatous (20%), osteochondromatous (10%) or even angiosarcomatous differentiation.

Dedifferentiated liposarcoma is characterized, as well-differentiated liposarcoma, by amplification of the 12q13-21 region, including *mdm-2*, *cdk-4*, *SAS*, *HMGI-Cs* genes. This amplification of *mdm-2* and *cdk-4* proteins can be demonstrated by immunohistochemistry. Although still regarded by some as poorly specific, these immunostains can be extremely useful in the appropriate clinicopathological setting. A recent study by Binh et al. showed a good correlation between molecular analysis and immunohistochemistry with only a few benign adipocytic tumors or other sarcomas positive for these markers.

Case 11

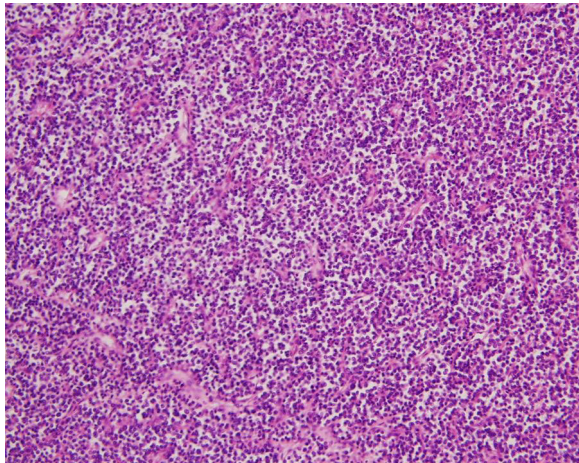
Clinical history :

Female, 18.

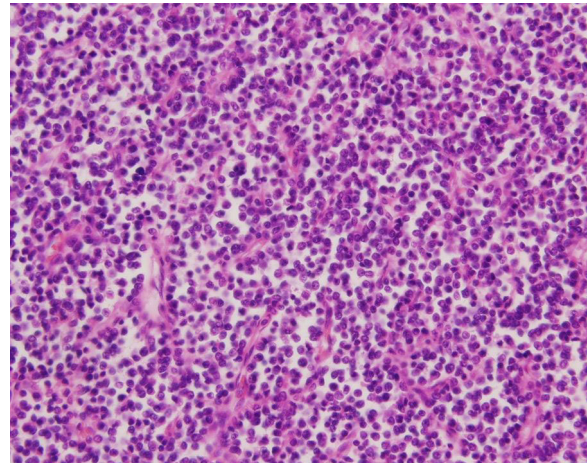
Multiple superficial and deep-seated nodules in the lower limb.

Histological features:

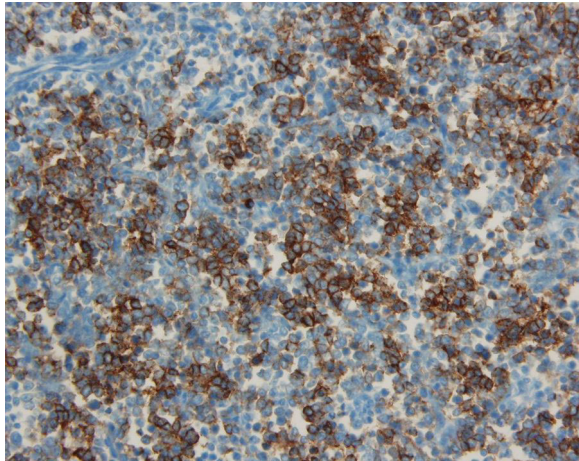
The tumors are composed of rather monotonous rounded cells with rounded nuclei, arranged in a vaguely alveolar pattern.



1.



2.



3. CD99

Differential diagnosis:

This case illustrates the diagnosis of round cell neoplasms in young patients. The rather monotonous nuclei with rounded nuclei are in favor of Ewing sarcoma but the architectural features might suggest an alveolar rhabdomyosarcoma. Lymphoma, round cell synovial sarcoma, mesenchymal chondrosarcoma could also be considered.

Immunohistochemistry:

Suggested panel:

CD99: positive (membranous pattern)
Desmin: negative
LCA: negative
CytoK: negative
(FLI-1)

Molecular analysis:

Rearrangements of the EWS gene have been demonstrated by FISH, confirming the diagnosis.

Diagnosis: **Ewing sarcoma**

Comments:

Ewing sarcoma / primitive neuroectodermal tumor (PNET) is a round cell sarcoma showing varying degrees of neuroectodermal differentiation. The term Ewing sarcoma is usually used for poorly differentiated tumors lacking morphological features of morphological differentiation. PNET are more differentiated and display rosettes.

Tumors affect bone or soft tissue of young patients, with a peak incidence in the second decade. The morphology is variable. Most tumors are composed of uniform round cells with uniform round nuclei containing fine chromatin. The more differentiated tumors display Homer-Wright rosettes. Necrosis is common. Rare cases show marked nuclear atypia ("atypical" Ewing sarcoma) or are composed of more spindled cells.

Ewing sarcoma is positive for CD99 in more than 90% of cases, with a membranous pattern. CD99 positivity is positive in many other tumors including desmoplastic small round cell, lymphoblastic leukemia, poorly differentiated synovial sarcoma, mesenchymal chondrosarcoma. FLI-1 seems more specific but is only expressed in 70% of cases. It also stains lymphoblastic leukemia and some cases of synovial sarcoma, desmoplastic round cell sarcoma. . . Ewing sarcoma / PNET often expresses cytokeratins (20-70% of cases).

Approximately 85% of cases are characterized by a t(11;22) *EWS-FLI1* translocation that can be detected by conventional cytogenetics, RT-PCR or FISH. Other translocations are summarized in Table 1.

Because of the variability of histological features and the relative lack of sensitivity / specificity of CD99 and FLI-1, molecular biology is increasingly regarded as the gold standard.

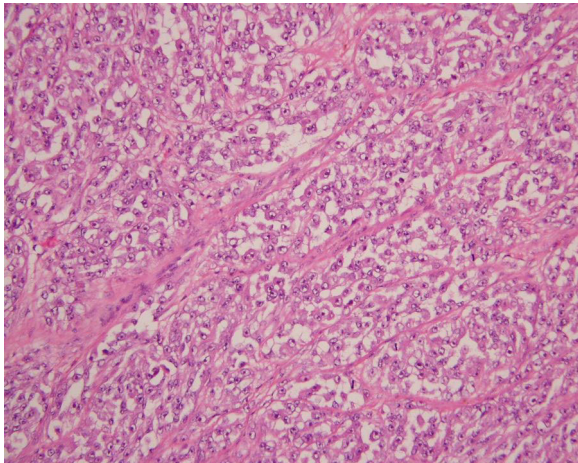
Case 12

Clinical history:

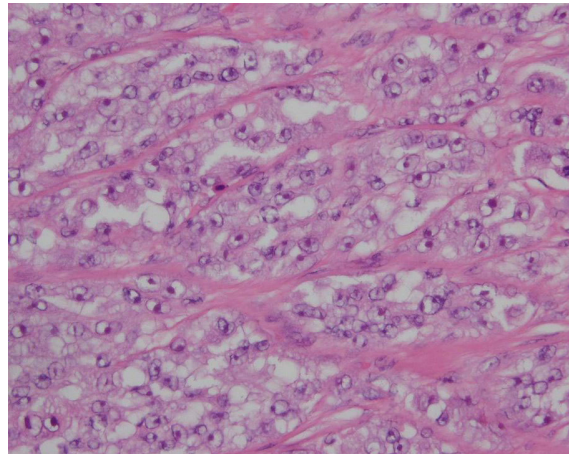
Female, 46.
4 cm ankle tumor.

Histological features:

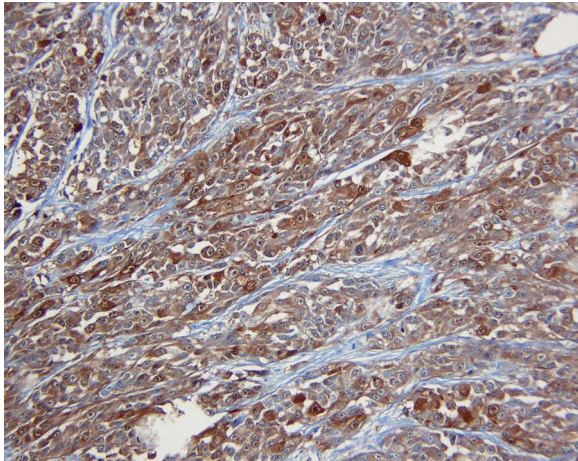
The tumor is composed of nests of spindle or ovoid cells, embedded in a hyalinized stroma. Cells have abundant eosinophilic or clear cytoplasm and large nuclei with prominent nucleoli.



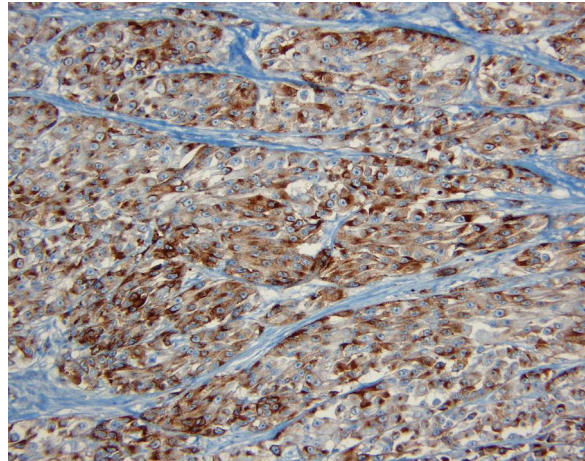
1.



2.



3. S100



4. HMB45

Differential diagnosis:

This appearance is highly suggestive of clear cell sarcoma.

Immunohistochemistry:

S-100 protein: +
HMB-45: +

Diagnosis: **Clear cell sarcoma**

Comments:

Clear cell sarcoma is regarded as a melanoma of soft tissue. Although it produces melanin and shows a melanocytic immunophenotype, it differs significantly from conventional melanoma. Tumors are usually deep-seated, unrelated to the epidermis, and there is usually a translocation t(12;22)(q13;q12) EWS-ATF-1 which has never been identified in cutaneous melanoma.

Clear cell sarcoma affects young adults (20-40 years), with a predilection for the foot and ankle. Since the availability of molecular techniques, a few cases have been reported in unusual locations such as the stomach. Tumors are located in deep soft tissue, in association with tendons and aponeuroses. Histologically, the tumor is subdivided in nests by thick hyalinized fibrous bands. Within the nests, spindle or ovoid cells are arranged in fascicles.

Melanin is rarely identified on H&E but is detected in half of the cases with histochemical stains. Immunohistochemically, S-100 protein and HMB-45 are expressed in the vast majority of cases.

Case 13

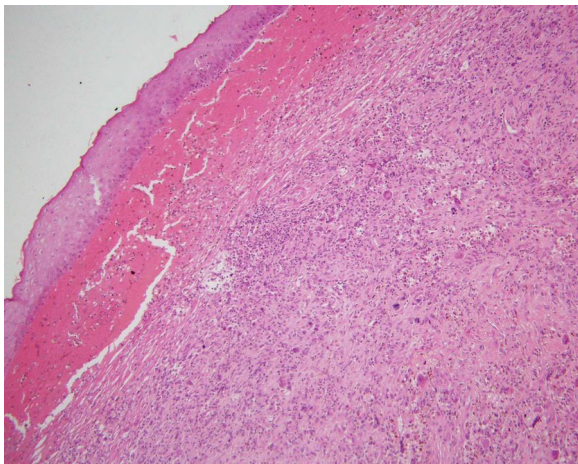
Clinical history :

Female, 85.

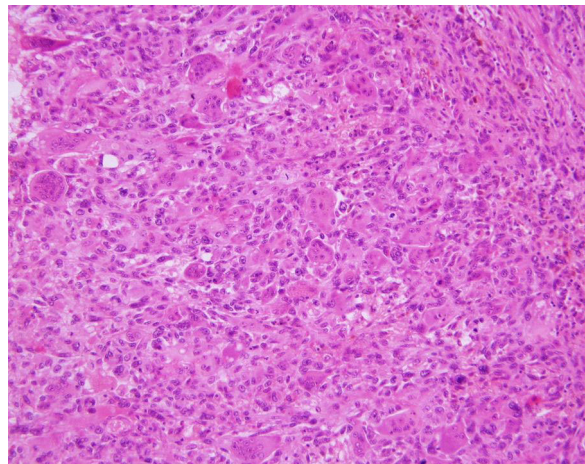
Ulcerated occipital tumor.

Histological features:

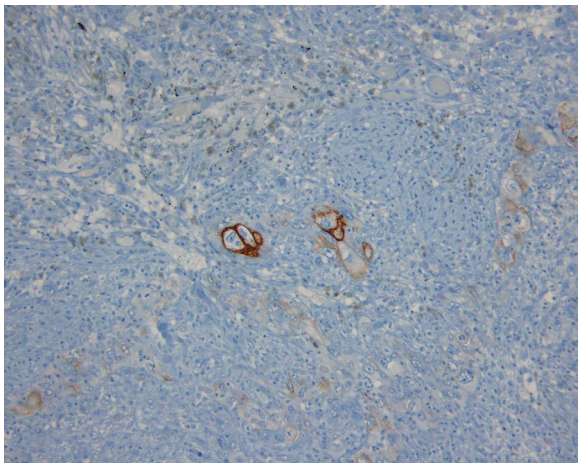
The epidermis is ulcerated. Focally, in the periphery of the specimen, it shows severe dysplasia. The dermis contains a nodular tumor, composed of dyscohesive pleomorphic cells associated with osteoclastic giant cells. There are frequent mitoses, including atypical forms.



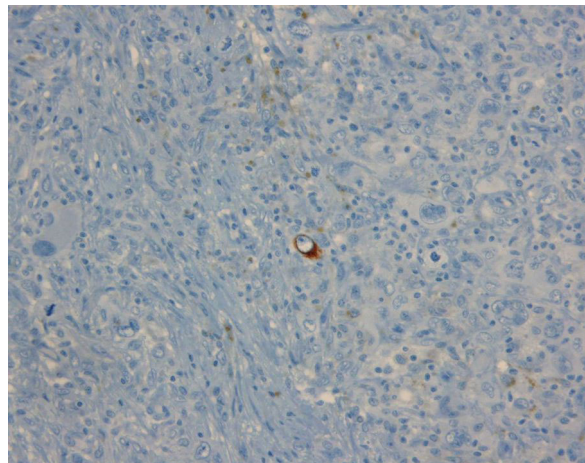
1.



2.



3a. CK



3b. CK

Differential diagnosis:

The differential diagnosis of a “histologically malignant” cutaneous tumor on sun-exposed surfaces sun includes sarcomatoid carcinoma, melanoma and atypical fibroxanthoma. Atypical fibroxanthoma can be ruled out in this case as the lesion is endophytic. To identify spindle cell carcinomas of the skin / mucosal surfaces, the most sensitive cytokeratin antibody seems to be CK5/6. p16 has also been reported to be positive in most cases of spindle cell carcinomas of the skin. Spindle cell melanomas are usually strongly positive for S-100 protein but tend to be negative for HMB-45 and melan-A.

Immunohistochemistry:

CytoK 5/6: focally positive

CytoK AE1-AE3: focally positive

S-100 protein: negative

Diagnosis: **Spindle cell carcinoma**

Comments:

Sarcomatoid carcinoma must always be included in the differential diagnosis of spindle cell or pleomorphic tumors in elderly patients, particularly if the tumors occurs on sun-exposed skin (scalp and face), or near the breast, kidney, lung, thyroid...

Sampling is essential and immunohistochemistry is needed. Positivity for cytokeratins may be very focal and it is often necessary to use several antibodies.

Spindle cell carcinoma of the sun-exposed skin is usually clinically indolent, with rare recurrences and metastases, while radiation-induced spindle cell carcinomas behave more aggressively.