

Pleomorphic cell tumors of soft tissue

Differential diagnosis

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I. Introduction

Pleomorphic cell tumors are characterized by variably sized and shaped cells (often including multinucleate giant cells), with atypical nuclei. They account for approximately 10-15% of soft tissue tumors.

Pleomorphism in a soft tissue neoplasm is usually regarded as suggestive of a sarcoma. However, this morphological group of tumors also includes benign pseudosarcomatous lesions and malignant non sarcomatous tumors, which must be recognized.

The correlation with clinical data is extremely important.

- Clinical history (previous cancer, ...)
- Tumor site:
 - Skin:
 - Benign fibrous histiocytoma
 - Carcinoma
 - Melanoma
 - Atypical fibroxanthoma
 - Limbs:
 - unclassified pleomorphic sarcomas ("MFH")
 - High-grade myxofibrosarcoma
 - Leiomyosarcoma
 - Liposarcoma (pleomorphic or dedifferentiated)
 - Rhabdomyosarcoma
 - Extremities:
 - Giant cell tumor of tendon sheath
 - Retroperitoneum
 - Dedifferentiated liposarcoma
 - leiomyosarcoma
- Tumor size: Most benign lesions are small. In contrast, pleomorphic sarcomas are often larger than 5 cm at the time of diagnosis.
- Age:
 - Children
 - Xanthogranuloma
 - Giant cell fibroblastoma
 - Young adults
 - Benign fibrous histiocytoma
 - Giant cell tumor of tendon sheath
 - Lymphomas
 - Elderly patients
 - Carcinoma
 - Melanoma
 - Unclassified pleomorphic sarcomas ("MFH")
 - High-grade myxofibrosarcoma
 - Leiomyosarcoma

Extensive sampling is mandatory, as most diagnosis of pleomorphic sarcomas will be based on the identification of small more differentiated areas.

Immunohistochemistry is required in most cases and molecular biology may be helpful, especially for retroperitoneal tumors.

Table 1. Immunohistochemical profile of pleomorphic sarcomas

	CK	S100	actin	desmin	caldesmon	myogenin	CD34	mdm2/ cdk4
LMS	+/-	-	+	+/-	+/-	-	+/-	-
RMS	-	-	+/-	+	-	+	-	-
LS, pleomorphic	+/-	+ /-	-	-	-	-	-	-
LS, WD/dediff.	-	-	+/-	+/-	-	-	+/-	+
Myxofibrosarcoma	-	-	+/-	-	-	-	+/-	-

II. Mimicks of pleomorphic sarcomas

II A. Benign pseudosarcomatous tumors

Benign lesions which may be mistaken for a pleomorphic sarcoma belong to almost all « histogenetic » categories. Their distinction from a sarcoma often rests on careful clinicopathologic correlation.

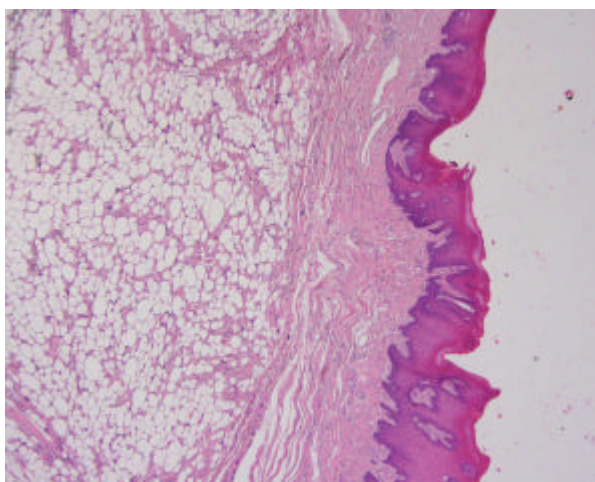
Table 2. Benign lesions which mimic pleomorphic sarcomas

Benign fibrous histiocytoma (atypical variant)
Pleomorphic lipoma
Diffuse-type giant cell tumor of tendon sheath
Atypical fibroxanthoma
Ancient schwannoma
'Bizarre' neurofibroma
Proliferative fasciitis / myositis
Ischaemic fasciitis
Pleomorphic hyalinizing angiectatic tumor
Giant cell tumor of soft tissue
Symplasmic hemangioma
Symplasmic glomus tumor

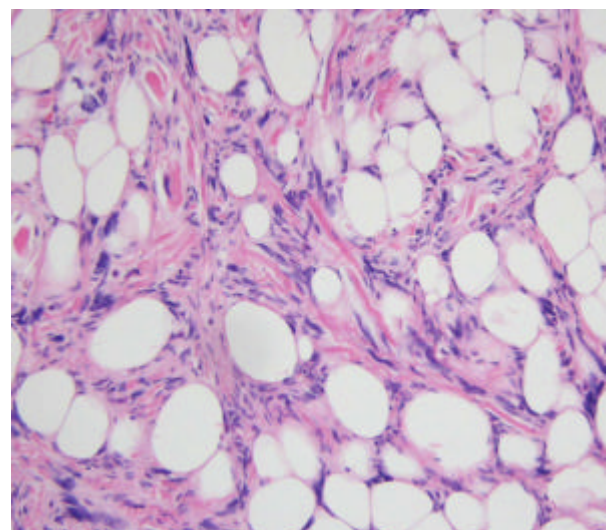
CASE 1

Clinical history : A 74 year-old female presenting with a small nodule in the tongue

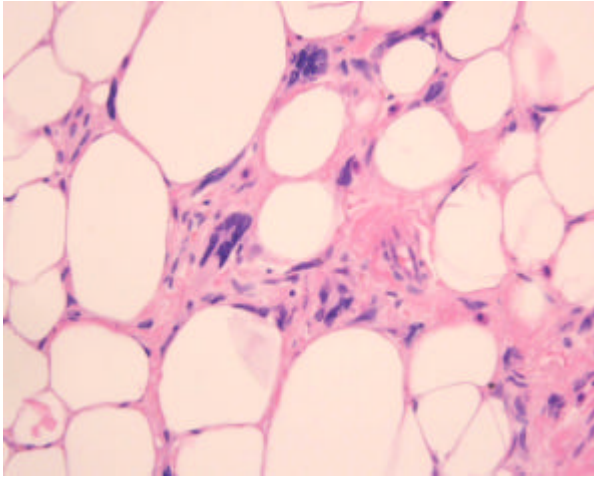
Microscopic findings : pictures 1A-1C



1A



1B



1C

Immunohistochemistry : CD34+, mdm2 -

Diagnosis : **Pleomorphic lipoma**

Spindle cell / Pleomorphic lipoma (13, 28)

Spindle cell and pleomorphic lipoma represent the ends of the morphological spectrum of a single entity, distinct from atypical lipomatous tumors. This relationship between spindle cell and pleomorphic lipoma, suggested by their clinicopathologic features, have been debated by some authors but is now widely accepted, and supported cytogenetic studies.

Spindle cell / pleomorphic lipoma occurs almost exclusively in the subcutaneous tissue of the posterior neck and shoulder area. Less common sites include the face, buccal cavity, scalp, forehead, and orbit. Only a few poorly documented cases have been reported in other locations. 90% of patients are males, usually of over 55 years. Most tumors are solitary, although very rare patients have multiple lesions and familial occurrence has been reported. Histologically, spindle cell/pleomorphic lipoma is a well circumscribed tumor, characterized by an admixture of mature adipocytes, bland spindle cells arranged in short fascicles, and thick, brightly eosinophilic collagen bundles. The relative proportion of these components may vary considerably. Abundant mast cells are usually present. Myxoid changes are not uncommon and may be prominent. The rare intradermal lesions are characterized by poorly defined margins.

In addition, pleomorphic lipoma contains a variable number of bizarre, commonly multinucleate cells with hyperchromatic nuclei. Lipoblasts may be present.

Spindle and pleomorphic cells are usually CD34 positive and S-100 negative. A non-specific Bcl-2 positivity has also been reported.

Spindle cell/pleomorphic lipoma shows consistent chromosomal aberrations of 13q and 16q, which are distinct from those seen in atypical lipomatous tumors.

Because of the morphological overlap between spindle cell/lipoma and atypical lipomatous tumor/well differentiated liposarcoma, the differential diagnosis is mainly based on the clinicopathologic correlation (anatomic site and location). It is currently widely accepted that the diagnosis of spindle cell/pleomorphic should be reserved for subcutaneous (or dermal) lesions, arising in the head and neck / upper back / shoulder region. Tumors arising in deep

soft tissues or in unusual locations should be regarded with caution and are probably best classified as atypical lipomatous tumors.

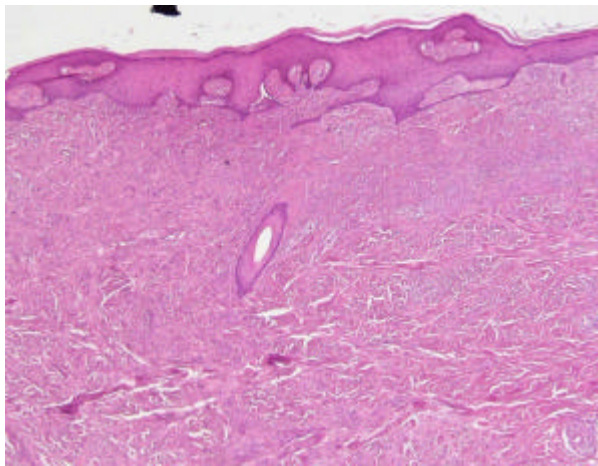
Occasionally, nuclear palisading may be reminiscent of schwannoma, which is encapsulated and is strongly and diffusely positive for S-100 protein. The differential diagnosis with solitary fibrous tumor and so-called lipomatous hemangiopericytoma (prominent branching vessels, alternance of hypocellular and hypercellular areas) may also be problematic.

Spindle cell / pleomorphic lipoma is a benign lesion; recurrences are very uncommon.

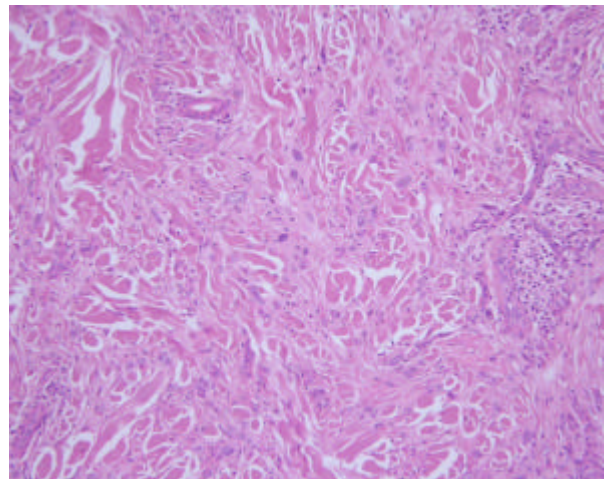
CASE 2

Clinical history : 48 year-old female with a 1 cm nodule in the back

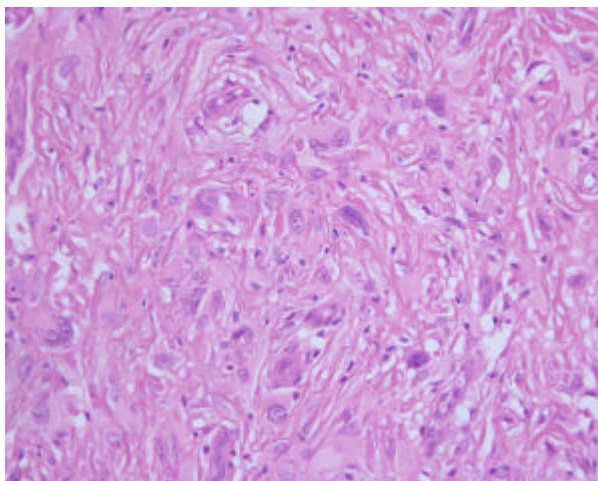
Microscopic findings : pictures 2A-2D



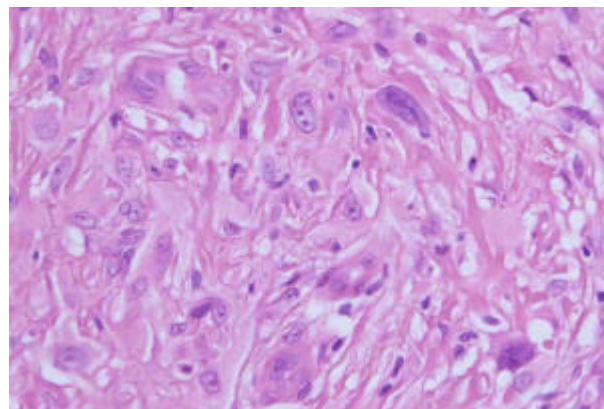
2A



2B



2C



2D

Diagnosis : **Benign fibrous histiocyoma, atypical variant**

Benign fibrous histiocyoma, atypical variant (4,20)

Benign fibrous histiocyoma or dermatofibroma is one of the commonest soft tissue tumors. Over the years, several clinico-pathologic variants have been delineated : cellular, aneurysmal, atypical, lipidized, epithelioid, palisading, FH with giant cells... Although the recognition of some of those variants is purely academic, the identification of cellular, aneurysmal and atypical FH is clinically relevant because they mimic malignant tumors and show a higher tendency to recur locally than ordinary dermatofibroma.

Atypical FH ('pseudosarcomatous' FH, dermatofibroma with monster cells...) represents less than 2% of benign FHs and clinically does not differ significantly from common FH. The lesions affect middle-aged adults with a predilection for the limbs.

Histologically, tumors show the classic features of FH : hyperplasia of the overlying epidermis, presence of thickened collagen bundles at the lesional periphery, admixture of spindle cells / foam cells / giant cells. In addition, they contain variable numbers of large atypical cells, characterized abundant foamy or deeply eosinophilic cytoplasm, and enlarged, irregular, hyperchromatic nuclei. Mitotic activity is usually low but may reach up to 15 mitoses / 10 HPF and include atypical forms. Other occasional worrisome features include large lesional size, involvement of subcutaneous adipose tissue (commonly), and geographic necrosis (10-15% of cases). The diagnosis of atypical FH is based on the identification, at low magnification, of features of classic FH (epidermal hyperplasia, deeply eosinophilic collagen bundles in the periphery, mixed cellularity...).

The differential diagnosis includes :

- atypical fibroxanthoma, which occurs in a completely different clinical setting (rapidly enlarging exophytic lesion on sun-damaged areas, in elderly patients), and shows more diffuse atypia
- Dermatofibrosarcoma protuberans, which does not show significant atypia, is composed of monomorphic spindle cells, and is CD34 positive
- Leiomyoma and leiomyosarcoma, which are composed of brightly eosinophilic spindle cells and are positive for desmin and h-caldesmon
- Spindle cell carcinoma and melanoma (clinical information, immunohistochemistry)
- Pleomorphic fibroma, which is a polypoid lesion containing scattered atypical multinucleate cells

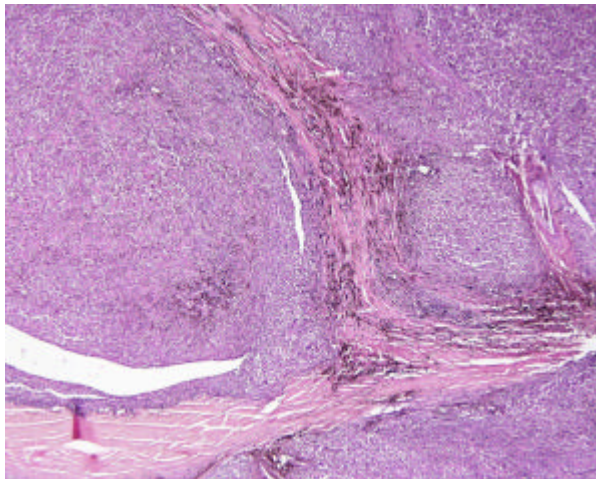
Atypical FH shows a recurrence rate of 10-15%, which is similar to that of cellular and aneurysmal FH but higher than in ordinary FH (~ 1%). A complete excision with clear margins is recommended.

Distant metastases (lymph nodes, lung, ...) have been reported in very few cases of atypical, cellular and aneurysmal FH. This phenomenon, which remains enigmatic and cannot be predicted histologically, is so rare – particularly when compared with the large numbers of FHs seen in daily practice - that it could be disregarded for practical purposes

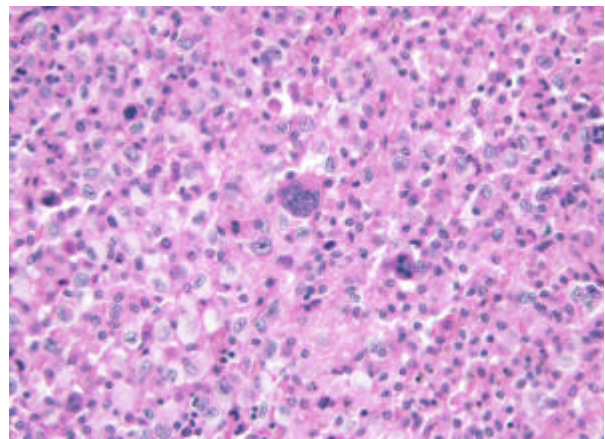
*****CASE 3*****

Clinical history : Female, 55 y.o. Third recurrence of a "synovial sarcoma" of the ankle.

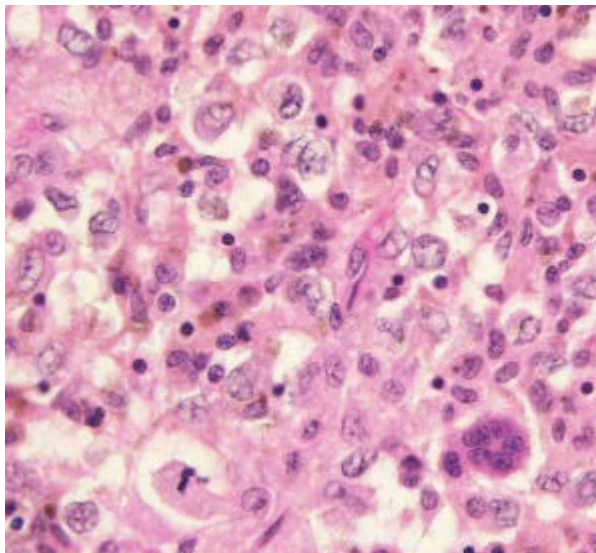
Microscopic findings : pictures 3A-3C



3A



3B



3C

Immunohistochemistry: CD68 +

Diagnosis : **Diffuse-type giant cell tumor of tendon sheath**

Diffuse-type giant cell tumor of tendon sheath (9)

Tenosynovial giant cell tumors are classically separated according to their intra- or extra-articular location and their localized or diffuse growth pattern.

Extra-articular lesions (“pigmented villo-nodular synovitis”), and localized tumors (“nodular tenosynovitis”) are usually easily recognized. In contrast, diffuse-type giant cell tumors are not uncommonly misdiagnosed as a sarcoma.

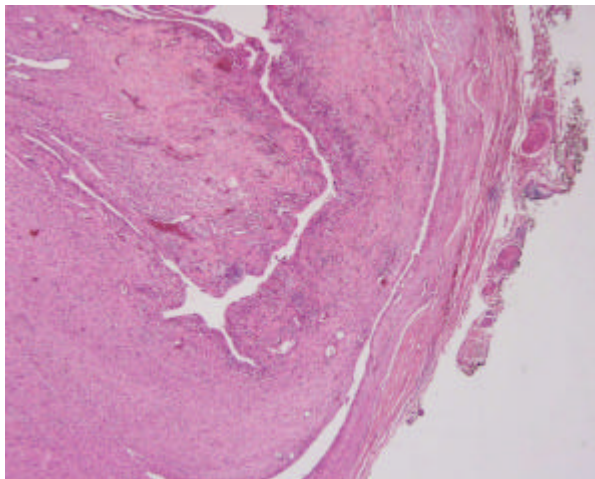
Extra-articular diffuse-type giant cell tumors (DT-GCT) tend to affect young adults, with a predilection for the knee area. Some cases can be purely intramuscular (with a predilection for the thigh).

DT-GCT is usually large and is composed of sheets of mono- and multinuclear giant cells, associated with clusters of foam cells. The mononuclear component comprises two types of cells: small histiocyte-like cells with ovoid nuclei (which often display nuclear grooves), and larger cells. The latter frequently show a dendritic appearance and often contain a peripheral rim of haemosiderin. Their nuclei are larger and vesicular. The occasional predominance of these larger cells may obscure the typical features of giant-cell tumours and lead to a diagnosis of sarcoma. Another worrisome feature is the presence of a significant mitotic activity, which is quite common. Osteoclast giant cells tend to be less abundant than in localized GCT and may be absent or extremely rare in approximately 20% of cases. GCTs stain for CD68 and large mononuclear cells express desmin in up to 40% of cases. DT-GCT is a benign locally aggressive tumor, which recurs in 30 to 50% of cases. Malignant forms of GCT are extremely uncommon.

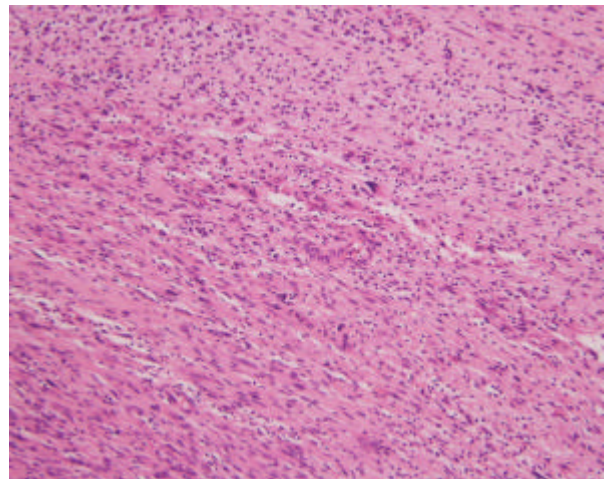
*** CASE 4***

Clinical history : 45 year-old male presenting with a 2 cm tumor in the paravertebral area

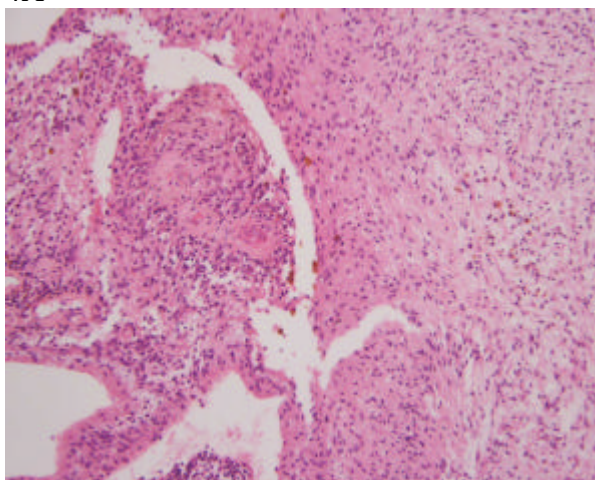
Microscopic findings : pictures 4A-4D



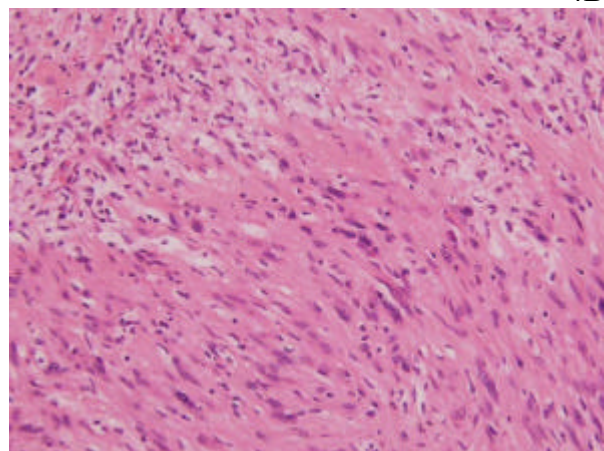
4A



4B



4C



4D

Immunohistochemistry : S100 +

Diagnosis : « **Ancient** » schwannoma

“Ancient” schwannoma (3)

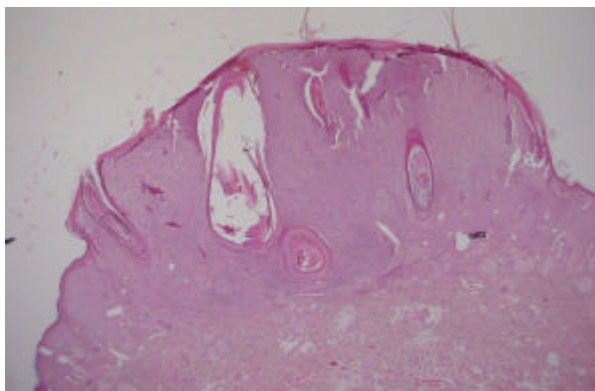
Schwannoma is a rather common and ubiquitous tumor, and typical cases are usually easily diagnosed. In contrast, histological variants such as “ancient” schwannoma and cellular schwannoma show some worrisome features which can lead to diagnosis of malignancy. So-called « ancient » schwannoma tend to be larger and of longer duration. They are more common in deep soft tissues such as the retroperitoneum. They display degenerative changes including cystic degeneration, hemorrhagic foci, haemosiderin deposits, hyalinization of the stroma, and the presence of sheets of histiocytes and lymphoid aggregates, which may obscure the diagnostic features of the lesion. In addition they often display some degree of nuclear atypia (enlarged, hyperchromatic, vacuolated nuclei) which can be misleading. Atypical cells should be scattered within bland Schwann cells, and the mitotic activity is usually low. Other diagnostic clues include the presence of a capsule, hyalinized vessel walls and clusters of histiocytes. S100 immunostaining is diffuse, in contrast with MPNST, which is only focally positive (in 50-60% of cases). Malignant changes in benign schwannomas is extremely unusual.

Focal degenerative atypia can also be seen in neurofibromas. Malignant changes in a neurofibroma are characterized by more diffuse atypia, increased cellularity and the presence of mitotic figures

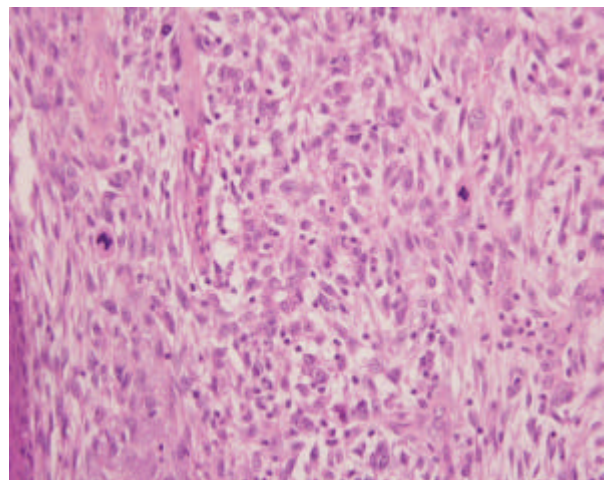
*** CASE 5***

Clinical history : 1 cm ulcerated lesion on the forehead of a 79 year-old male

Microscopic findings : pictures 5A-5B



5A



5B

Immunohistochemistry: CK -, S100 -

Diagnosis : **Atypical fibroxanthoma**

Atypical fibroxanthoma (15, 21)

Atypical fibroxanthoma (AFX) is a controversial pleomorphic tumor, which is variably regarded as a cutaneous variant of so-called “malignant fibrous histiocytoma” or as a benign UV-related pseudosarcomatous lesion.

The clinical presentation of AFX is typical and of diagnostic value. AFXs are rapidly growing, ulcerated exophytic or polypoid lesions occurring almost exclusively in the sun-exposed areas (mostly the head and neck area) of elderly patients.

A second group lesions involving the extremities of younger patients is sometimes mentioned but most likely correspond to atypical benign fibrous histiocytomas.

The diagnosis of AFX requires strict criteria and the use of immunostains to rule out alternative diagnoses such as spindle cell carcinoma or melanoma.

AFX are exophytic, superficial lesions and only very limited involvement of the subcutis can be accepted. Tumors show a smooth deep margin, and tend to push down degenerate elastic fibers and adnexal structures. Perineurial or vascular invasion should not be present.

Tumors are classically composed of pleomorphic cells but a spindle-cell variant has been described. Abnormal mitotic figures are usually easily found.

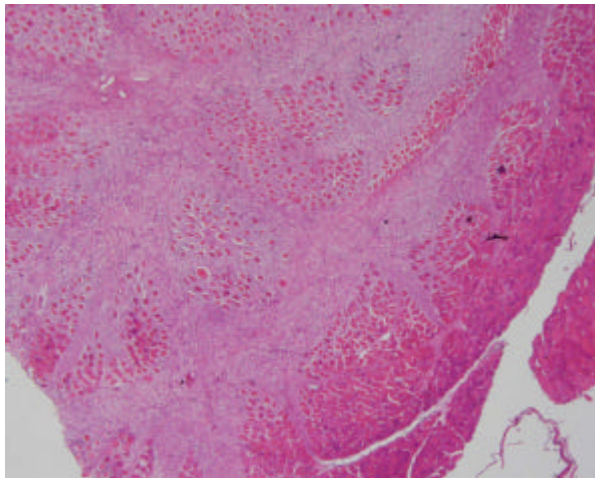
Immunohistochemistry for cytokeratins and S-100 protein is required to rule out carcinoma and melanoma. A recent study showed a common positivity for CD99 (usually negative in carcinoma and melanoma) but the diagnostic value of this immunostain has to be confirmed. In addition to carcinoma, and melanoma, the differential diagnosis included atypical benign fibrous histiocytoma which shows more focal atypia and a completely different clinical setting.

When diagnostic criteria are strictly respected, the clinical course is benign. In a large study of 140 cases by Fretzin and Helwig, only 9 cases recurred and none metastasized

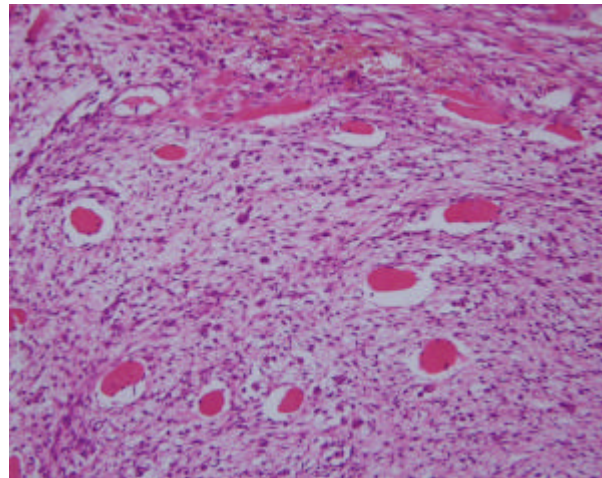
***** CASE 6*****

Clinical history : 38 year-old female with a 3 cm rapidly growing nodule in the back

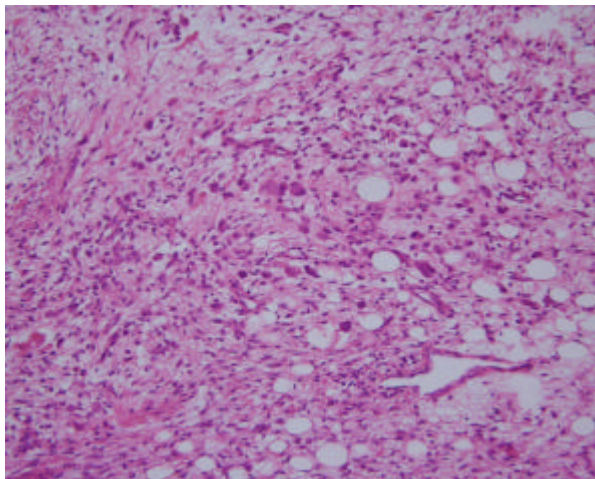
Microscopic findings : pictures 6A-6D



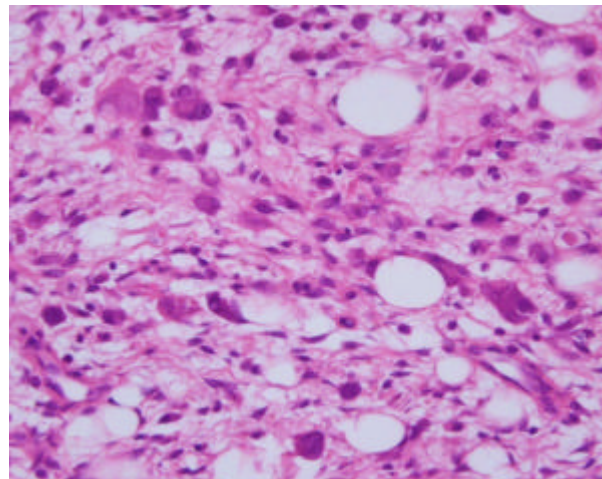
6A



6B



6C



6D

Immunohistochemistry : actin focally +

Diagnosis : **proliferative myositis**

Proliferative fasciitis / myositis (1,2)

Proliferative fasciitis is a subcutaneous lesion characterized by the presence of scattered large ganglion-like cells within a fibroblastic/myofibroblastic background.

Proliferative myositis has the same cellular composition but occurs within skeletal muscle and usually displays a typical “checkerboard” pattern.

Proliferative fasciitis and myositis are less common than nodular fasciitis and usually affect older patients. There is predilection for the upper extremity and the trunk.

There is characteristically a rapid growth history and most tumors measure less than 3 cm. Histologically, the spindle cell proliferation is similar to that seen in nodular fasciitis. Large ganglion-like cells are characterized by abundant amphophilic cytoplasm and one or more

large vesicular nuclei. In proliferative myositis, the extension of the lesion between individual skeletal muscle cells is responsible for the “checkerboard” pattern.

Smooth-muscle actin is focally expressed.

Recurrences are very uncommon.

Ischaemic fasciitis, which virtually always occur over the bony prominences (sacrum, shoulders, trochanters) of immobilized patients, also contains atypical ganglion-like cells which can lead to confusion with a sarcoma. The diagnosis is based on the clinical history and the “zonal” pattern at low-power examination.

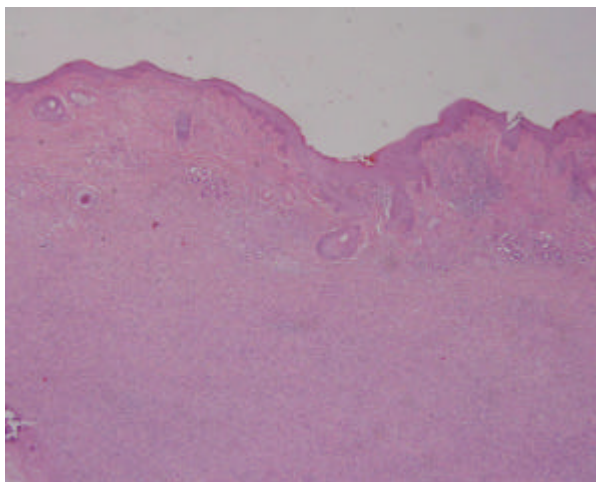
II B. Non sarcomatous malignant tumors

Carcinoma, melanoma and lymphoma may occasionally mimick pleomorphic sarcomas. Their recognition, which is crucial for adequate therapy, is based on the tumor location, clinical history, adequate sampling and immunohistochemistry.

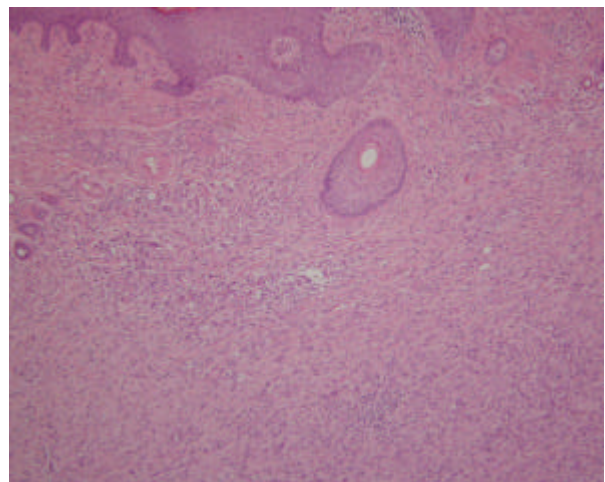
*** Case 7 ***

Clinical history : tumor on the forehead of a 82 year-old male

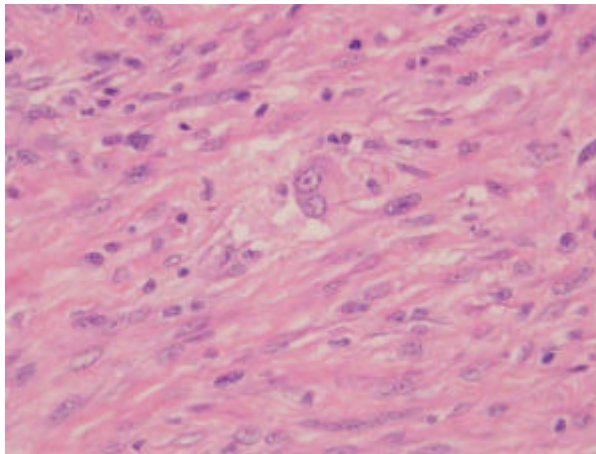
Microscopic findings : pictures 7A-7C



7A



7B



7C

Immunohistochemistry: CK5/6 +, CK AE1-AE3 +, S100 -

Diagnosis : **Sarcomatoid carcinoma**

In adult patients, carcinoma, melanoma and lymphoma are more common than sarcomas and should be considered in the differential diagnosis of pleomorphic tumors, especially when :

- **there is a history of previous cancer**
- **the tumor is located in the the skin or mucosa**
- **the tumor is located in a lymphoid area**
- **the tumor is located within or near the kidney, lung, breast, thyroid...**

Spindle cell carcinoma (7, 11, 12, 19, 29)

As a rule, carcinoma and melanoma should be ruled out before making any diagnosis of atypical fibroxanthoma or cutaneous high-grade sarcoma.

Spindle cell carcinoma of the skin is composed of spindle or pleomorphic associated or not with epithelial structures. Overlying dysplasia / carcinoma in situ is only identified in approximately 50% of cases. Rarely, tumors may exhibit foci of osteosarcomatous, chondrosarcomatous or rhabdomyosarcomatous differentiation (so-called « carcinosarcomas »).

As epithelial elements or epidermal dysplasia are inconstant, the diagnosis will usually require immunohistochemistry. Cytokeratins are often only focally positive and the use of several antibodies may be required. The most sensitive antibody seems to be CK 5/6. Vimentin is usually positive and smooth muscle actin may be focally expressed.

Metastatic carcinoma may also occur in soft tissues, where it is often regarded as so-called « MFH ». In one series of 159 cases of « pleomorphic sarcomas », reviewed with immunohistochemistry and electron microscopy, Fletcher identified as much as 13% of non-sarcomatous neoplasms.

III. Pleomorphic sarcomas

The group of pleomorphic sarcomas represent common types of sarcoma in adult patients. Pleomorphic sarcomas tend to affect patients older than 60 y.o., with a predilection for the deep soft tissue of the lower limbs, at the exception of well-differentiated and dedifferentiated liposarcoma, which occur predominantly in the retroperitoneum.

III A. The concept of « pleomorphic MFH » (5,6,8,12,14,31)

The concept of “MFH” has been introduced in the late 60’s, based on morphology and cell cultures. For many years “MFH” has been regarded as the most common sarcoma in adult, and represented as much as 40-45% of all sarcomas in some series.

The introduction of ancillary techniques, which failed to show any evidence for a histiocytic differentiation, and the fact that some poorly differentiated neoplasms could show areas indistinguishable from MFH led some pathologist to question MFH as a discrete entity.

In a famous paper, Fletcher could identify a specific subtype of sarcoma in 63% of 159 cases diagnosed as MFH. In the same series, 20 cases proved to be non-sarcomatous neoplasms.

Recently, comparative genomic hybridization studies demonstrating that subsets of MFH were sharing the genomic abnormalities of leiomyosarcoma or dedifferentiated liposarcoma have supported the hypothesis that MFH was a morphological pattern rather than a true entity. Despite the loss of credibility of MFH, the concept have been maintained because of the presumed absence of influence of the histologic type on therapy or prognosis.

However, some recent series have demonstrated significant differences in terms of metastatic rate and survival between pleomorphic sarcomas, justifying attempts to subclassify them.

For example, the metastatic rate of dedifferentiated liposarcoma (around 10-15%), and high-grade myxofibrosarcoma (20-30%) are relatively low compared to sarcomas with myogenic differentiation, which also have a shorter relapse-free interval.

Critical reviews of the inflammatory and giant-cell subtypes have also shown that they corresponded to non-specific patterns rather than specific entities.

Table 3. Subtypes of “MFH”

◆ Storiform-pleomorphic MFH: non-specific pattern

- carcinoma ? melanoma ?
- retroperitoneum: liposarcoma ?
- limbs: specific subtype of sarcoma ?
- Unclassified sarcomas

◆ Myxoid MFH: “true entity”

- Myxofibrosarcoma

◆ Giant-cell MFH: non-specific pattern

- Osteosarcoma
- GC-rich leiomyosarcoma
- Osteoclastoma of soft tissue

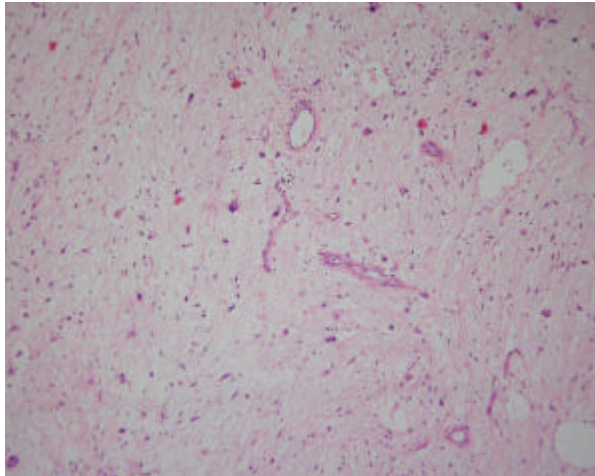
-	Unclassified sarcomas
◆	Inflammatory MFH: non-specific pattern
-	Liposarcoma ?
-	Lymphoma ?
-	Carcinoma ? melanoma ?
◆	Angiomatoid MFH: “true” entity
-	Angiomatoid FH

III B. Pleomorphic sarcomas of the retroperitoneum

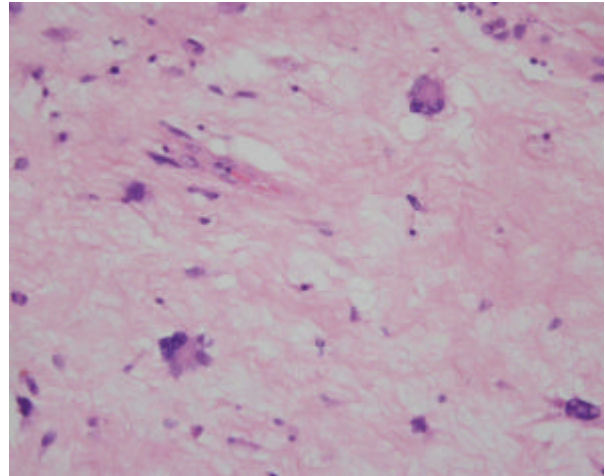
*** CASE 8 ***

Clinical history : 56 year-old male. 7 cm tumor located in the kidney area

Microscopic findings : pictures 8A-8B



8A



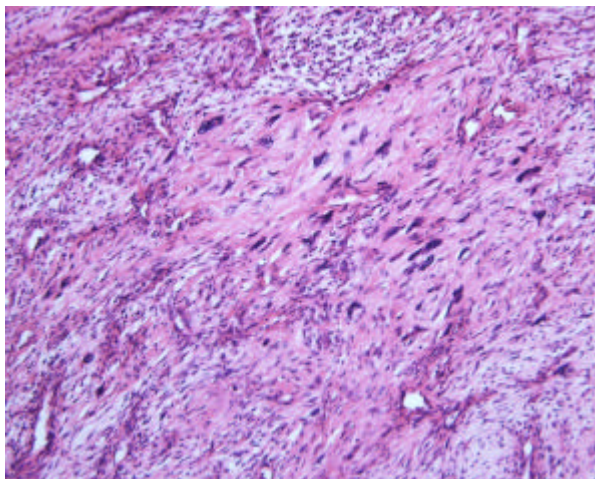
8B

Diagnosis : **Well-differentiated (sclerosing) liposarcoma**

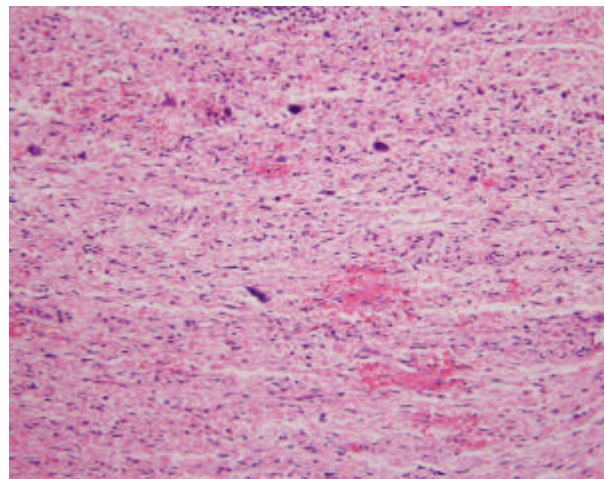
*** CASE 9 ***

Clinical history : 75 year-old female. 17 cm retroperitoneal tumor

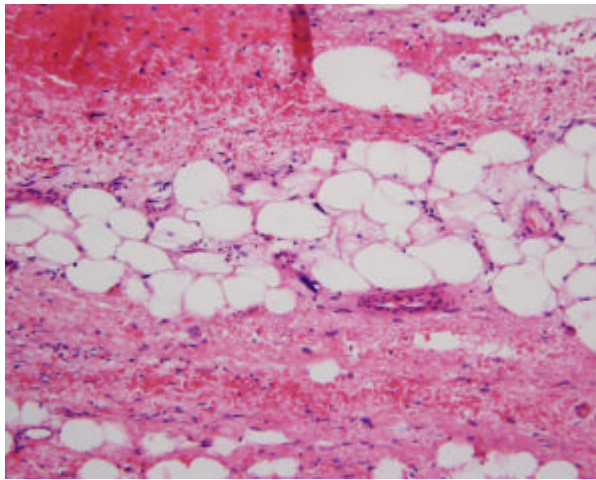
Microscopic findings : pictures 9A-9D



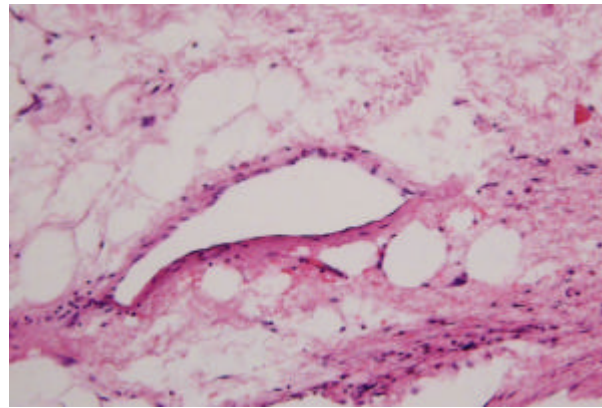
9A



9B



9C



9D

Immunohistochemistry: mdm2 +

Diagnosis : **Dedifferentiated liposarcoma**

Well-differentiated and dedifferentiated liposarcoma (5,6,1018,23,24,27)

Atypical lipomatous tumor/well differentiated liposarcoma (WDLs) represent a single entity, with common genetic changes. The use of the terms is determined by the location and resectability of the tumors.

WDLs are locally aggressive sarcomas composed entirely or partially of mature fat showing nuclear atypia and associated with atypical stromal cells.

They account for 50% of all liposarcomas. Tumors tend to affect adults around 60 y.o., with a predilection for the retroperitoneum (where it is the most common sarcoma), the thighs and the paratesticular area.

The adipocytic (lipoma-like) subtype is characterized by variation in size and shape of adipocytes, which show some degree of nuclear enlargement and hyperchromatism. Atypical stromal cells are usually found in fibrous septae and vessel walls. Lipoblasts are usually found but are not required.

The sclerosing subtype, which is more common in the retroperitoneum and spermatic cord area, is characterized by scattered bizarre multinucleate “floret” cells in a fibrous or fibromyxoid background.

The inflammatory and spindle cell subtypes are much less common.

WDLs consistently show supernumerary ring and giant marker chromosomes composed of amplified sequences of the 12q14-15 region. Amplifications of the *mdm2* and *cdk4* genes can be demonstrated by FISH or more recently by immunohistochemistry.

The more important prognostic factor is tumor location with a long-term mortality from essentially 0% in the extremities to more than 80% in the retroperitoneum.

Dedifferentiated liposarcoma is defined by the association of areas of well-differentiated liposarcoma and areas of high-grade non-lipogenic sarcoma.

Dedifferentiation is rather uncommon superficial tumors (less than 2% of cases) but occurs in 20 to 50% of cases in the retroperitoneum.

The transition between WD and dedifferentiated areas is abrupt or gradual, and in rare cases both component can be intermingled. The dedifferentiated component most commonly

resembles so-called MFH or high-grade myxofibrosarcoma but can show variable appearances, including that of a low-grade sarcoma. A heterologous component (myogenic, osteosarcomatous, chondrosarcomatous...) is present in 10% of cases and does not seem to affect the clinical outcome. A peculiar “meningotheelial-like” whorling pattern has also been described.

Cytogenetic and molecular studies have shown amplification of 12q13-21 region, as observed in WDLS.

Dedifferentiated liposarcoma is characterized by a tendency to recur locally in approximately 40% of cases and in almost all cases when the tumor is located in the retroperitoneum. Distant metastases are observed in about 15% of cases. The most important prognostic factor is the tumor location.

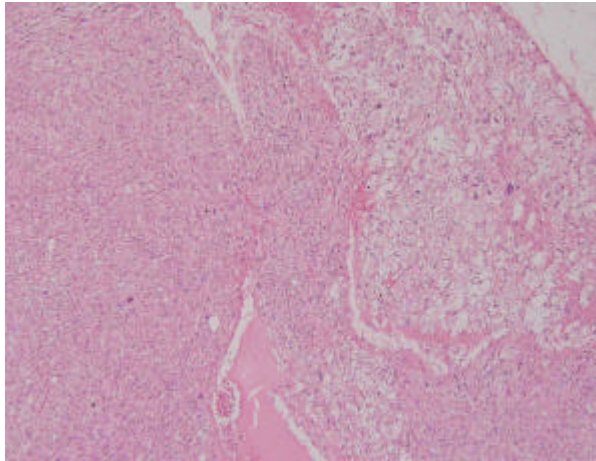
A recent reappraisal of 25 cases initially diagnosed as so-called MFH of the retroperitoneum, correlated with evaluation of mdm2 and cdk4 amplification by immunohistochemistry and comparative genomic hybridization have shown that in most cases areas of WDLS could be identified, leading to the hypothesis that virtually all so-called MFHs in this location represent dedifferentiated liposarcoma. The significant difference in terms of prognosis between dedifferentiated and other pleomorphic sarcomas justifies a careful sampling of the peripheral fat of all retroperitoneal sarcomas, and if possible immunohistochemical or cytogenetic analysis.

III C. Other pleomorphic sarcomas

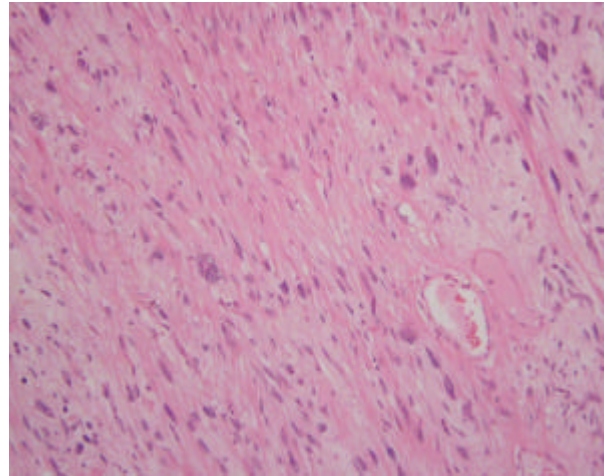
*** CASE 10 ***

Clinical history : 70 year-old female. 7 cm tumor in the thigh

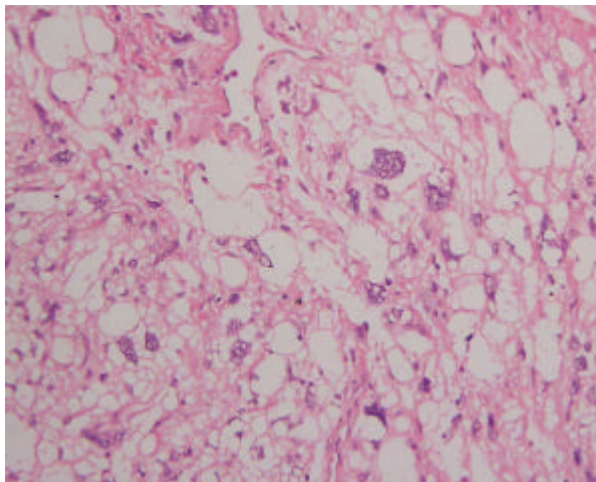
Microscopic findings : pictures 10A-10C



10A



10B



10C

Immunohistochemistry: S100 +

Diagnosis : **Pleomorphic Liposarcoma**

Pleomorphic liposarcoma (17)

Pleomorphic liposarcoma is defined as a high-grade pleomorphic sarcoma, containing a variable number of lipoblasts. No areas of well-differentiated liposarcoma should be present. It is the less common subtype of liposarcoma, accounting for only 5% of all liposarcomas.

Pleomorphic liposarcoma usually presents as a rapidly enlarging mass and shows a predilection for the lower limbs. Most cases are larger than 10 cm at the time of diagnosis. Histologically, most cases contain sheets of pleomorphic lipoblasts with enlarged, hyperchromatic, scalloped nuclei. However, some tumors only contain scattered lipoblasts, and the diagnosis rests on a careful sampling. Non-lipogenic areas show a variable appearance. The most common pattern is a “MFH-like” storiform growth pattern, but epithelioid and round cell variants have recently been described.

Immunohistochemically, about 50% of cases show S-100 positivity. Epithelioid variants occasionally stain for cytokeratins.

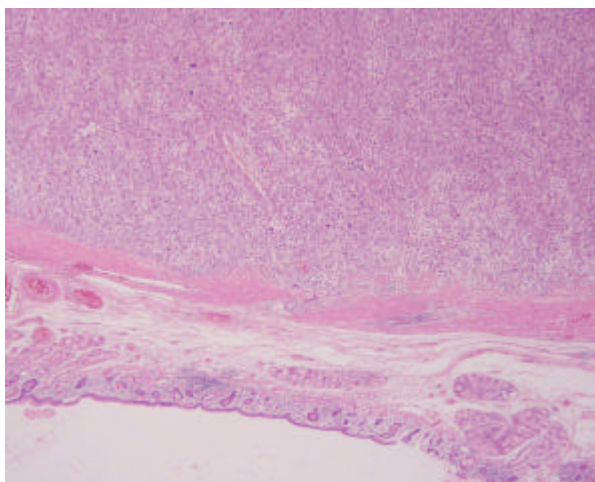
Pleomorphic liposarcoma have complex cytogenetic abnormalities. In contrast with well-differentiated/dedifferentiated liposarcoma, amplification of the 12q14-15 region are not consistently found.

Pleomorphic liposarcoma is an aggressive neoplasm with a 40-50% metastasis rate and a 5-year survival of about 50%

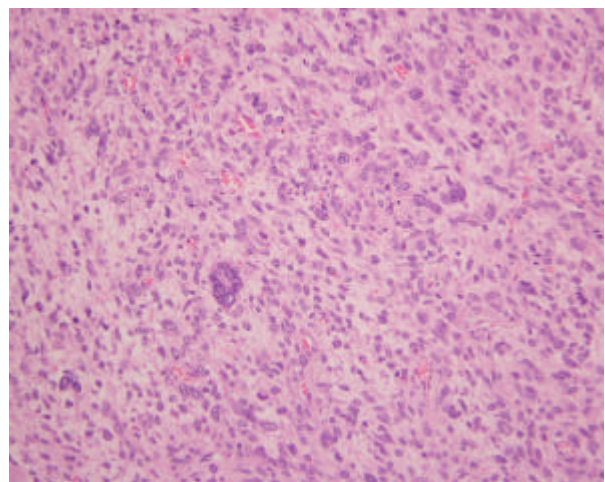
*** CASE 11 ***

Clinical history : 63 year-old female with a small bowel mass

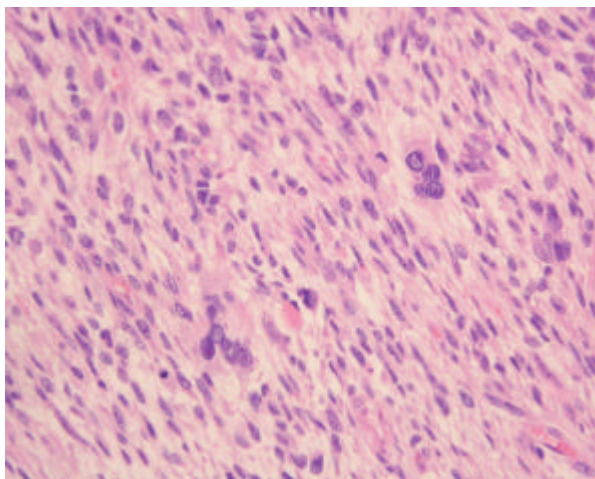
Microscopic findings : pictures 11A-11C



11A



11B



11C

Immunohistochemistry: actin +, desmin +, CD117 -

Diagnosis : **Pleomorphic leiomyosarcoma**

Pleomorphic leiomyosarcoma (8, 26, 30)

Leiomyosarcoma is rather common in the retroperitoneum and is the most common sarcoma arising from large vessels.

Pleomorphic leiomyosarcoma is a morphologic variant rather than a distinctive subtype. It is usually defined by the association of areas of undifferentiated pleomorphic sarcoma and areas showing morphological, immunohistochemical or ultrastructural evidence of smooth muscle differentiation.

However, there is no agreement on the minimal criteria for smooth muscle differentiation and the distinction from poorly differentiated sarcomas with myofibroblastic features is somewhat arbitrary.

Morphological features in favor of a smooth muscle differentiation include: intersecting fascicles of spindle cells, eosinophilic cytoplasm, paranuclear vacuoles, blunt-ended nuclei. Smooth-muscle actin is usually positive but not specific. Desmin is more specific but is only positive in approximately 50% of cases. H-caldesmon, a novel marker, is highly specific for smooth muscle differentiation but is expressed in only 40% of cases. Cytokeratins are expressed in about 40% of cases.

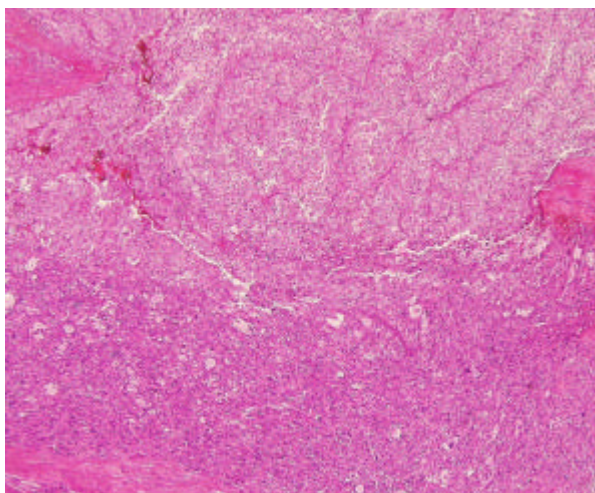
Leiomyosarcoma is an aggressive neoplasm with a 5-year survival of less than 50%.

Prognosis is mainly related to tumor size and stage.

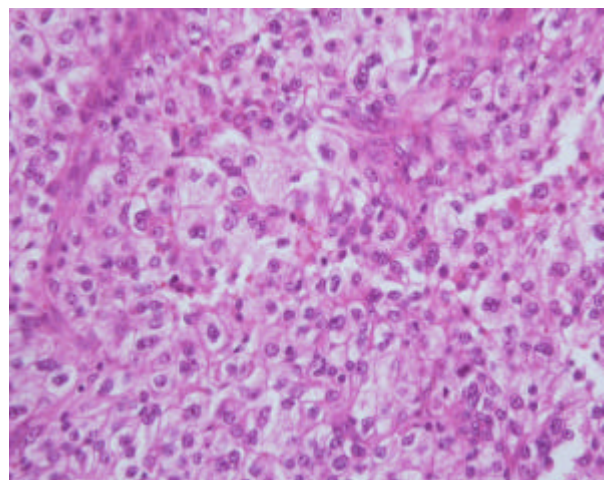
***** CASE 12 *****

Clinical history : 43 year-old male presenting with a large tumor in the deep soft tissues of the right arm

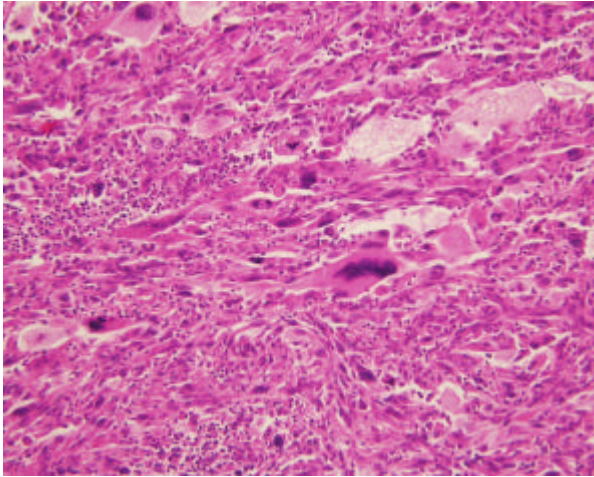
Microscopic findings : pictures 12A-12C



12A



12B



12C

Immunohistochemistry: desmin + , myogenin +

Diagnosis : **Pleomorphic rhabdomyosarcoma**

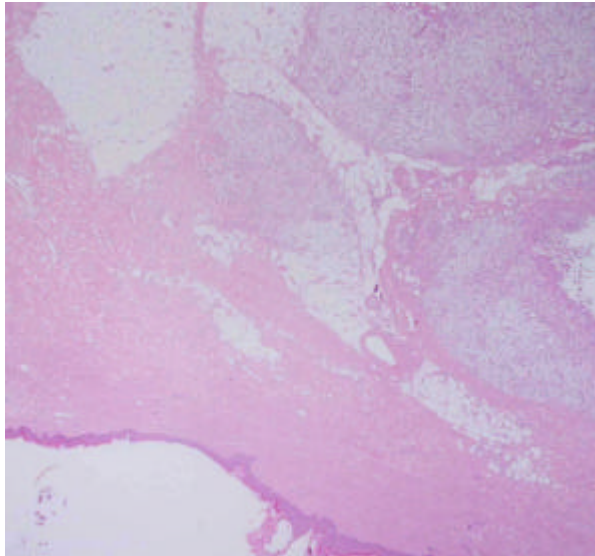
Pleomorphic rhabdomyosarcoma (16,22)

Pleomorphic rhabdomyosarcoma is defined as a high-grade sarcoma containing large polygonal eosinophilic cells showing immunohistochemical and/or ultrastructural features of skeletal muscle differentiation. No embryonal or alveolar component should be identified. Tumors are usually large and affect adult patients, with a predilection for the lower limbs. Cross-striations are rarely identified in H&E sections and the diagnosis requires immunohistochemistry. Pleiomorphic rhabddomyosarcoma expresses desmin and occasionally smooth-muscle actin. The most specific antibodies are myoD1 and myogenin but they usually show very limited positivity. Pleomorphic rhabdomyosarcoma is a very agressive tumor ; up to 75% of patients die of disease.

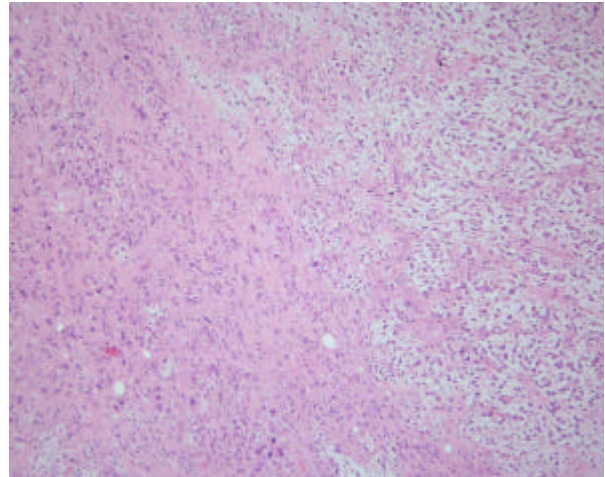
*** CASE 13 ***

Clinical history : 74 year-old female with a 4 superficial tumor in the thigh

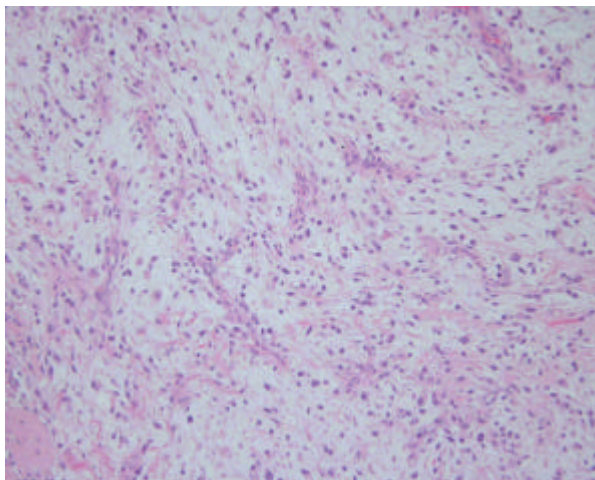
Microscopic findings : pictures 13A-13D



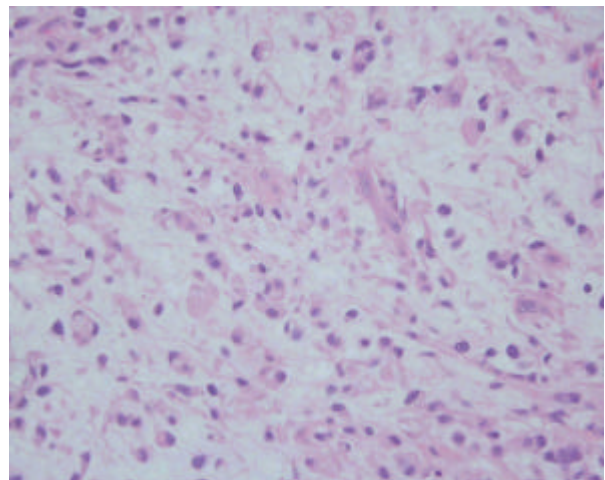
13A



13B



13C



13D

Diagnosis : **high-grade myxofibrosarcoma**

Myxofibrosarcoma (25)

Myxofibrosarcoma has been described simultaneously by Angervall et al. and by Weiss and Enzinger (“myxoid MFH”). Myxofibrosarcoma covers a wide morphological spectrum ranging from low-grade lesions resembling myxoma to high-grade pleomorphic sarcomas. The diagnostic criteria for high-grade tumors are still debated. Although for Goldblum and Weiss, 50% of myxoid areas are required, most authors include in the spectrum of

myxofibrosarcoma pleomorphic tumors containing no more than 10% of typical myxoid areas.

In our experience myxofibrosarcoma is one of the most common sarcomas, accounting for as much as 20 to 25% of all adult soft tissue sarcomas. Patients are usually older than 60 y.o. and there is a predilection for the thigh. As much as 2/3 of the cases involve the superficial soft tissues (hypodermis and dermis).

Histologically, myxofibrosarcoma is characterized by a lobulated, infiltrative growth pattern. Myxoid areas contain abundant thick walled curvilinear capillaries, spindle or stellate cells with hyperchromatic nuclei and vacuolated cells ("pseudolipoblasts"). An inflammatory infiltrate is often present.

Myxofibrosarcoma is characterized clinically by a very high recurrence rate (more than 50% of cases). Low-grade purely myxoid tumors have virtually no metastatic potential. Tumors containing high-grade areas metastasize in approximately 20 to 30% of cases, according to the depth of the tumor.

Low-grade tumors must be distinguished from myxomas. High-grade lesions must be differentiated from other pleomorphic sarcomas.

IV. CONCLUSIONS

1. A pleomorphic cell tumor is not always a sarcoma

Rule out :

- **benign pseudosarcomatous lesions**
 - **clinico-pathologic correlation**
- **malignant non-sarcomatous tumors**
 - **clinical history**
 - **sampling**
 - **immunohistochemical stains**

2. Most pleomorphic sarcomas of the retroperitoneum are dedifferentiated liposarcomas

- **Sample the fat**
- **mdm2 /CDK4 amplifications**
 - **FISH**
 - **Immunohistochemistry**

3. The subclassification of pleomorphic sarcomas is meaningful due to significant differences in terms of prognosis. Myogenic sarcomas seems to behave more aggressively. A specific diagnosis requires:

- **Ssampling**
- **Immunohistochemical stains**

References

1. WHO classification of tumours. Tumours of soft tissue and bone. CDM Fletcher, KK Unni, F Mertens Eds. IARCPress, Lyon, 2002
2. Weiss SW, Goldblum JR: Enzinger and Weiss's soft tissue tumors. 4th edition, Mosby, 2001
3. Scheithauer BW, Woodruff JM, Erlandson RA. Tumors of the peripheral nervous system. Atlas of tumor pathology, 3rd series, AFIP, 1999
4. Calonje E, Fletcher CDM. Cutaneous fibrohistiocytic tumors: an update. *Advances in Anatomic Pathology* 1994;1:2-15.
5. Chibon F, Mariani O, Derre J, Malinge S, Coindre JM, Guillou L, Lagace R, Aurias A. A subgroup of malignant fibrous histiocytomas is associated with genetic changes similar to those of well-differentiated liposarcomas. *Cancer Genet Cytogenet.* 2002;139:24-9.
6. Coindre JM, Mariani O, Chibon F, Mairal A, De Saint Aubain Somerhausen N, Favre-Guillevin E, Bui NB, Stoeckle E, Hostein I, Aurias A. Most malignant fibrous histiocytomas developed in the retroperitoneum are dedifferentiated liposarcomas: a review of 25 cases initially diagnosed as malignant fibrous histiocytoma. *Mod Pathol.* 2003;16:256-62.
7. Damron TA, Heiner J. Distant soft tissue metastases : a series of 30 new patients and 91 cases from the literature. *Ann Surg Oncol* 2000;7:526-34
8. Derre J, Lagace R, Nicolas A, Mairal A, Chibon F, Coindre JM, Terrier P, Sastre X, Aurias A. Leiomyosarcomas and most malignant fibrous histiocytomas share very similar comparative genomic hybridization imbalances: an analysis of a series of 27 leiomyosarcomas. *Lab Invest.* 2001;81:211-5.
9. de Saint Aubain Somerhausen N, Fletcher CD. Diffuse-type giant cell tumor: clinicopathologic and immunohistochemical analysis of 50 cases with extraarticular disease. *Am J Surg Pathol* 2000;24:479-92.
10. Evans HL, Khurana KK, Kemp BL, Ayala AG. Heterologous elements in the dedifferentiated component of dedifferentiated liposarcoma. *Am J Surg Pathol.* 1994;18:1150-7.
11. Evans HL, Smith JL. Spindle cell squamous carcinomas and sarcoma-like tumors of the skin: a comparative study of 38 cases. *Cancer* 1980;45:2687-97.

12. Fletcher CD. Pleomorphic malignant fibrous histiocytoma: fact or fiction? A critical reappraisal based on 159 tumors diagnosed as pleomorphic sarcoma. *Am J Surg Pathol* 1992;16:216-28
13. Fletcher CD, Akerman M, Dal Cin P, de Wever I, Mandahl N, Mertens F, Mitelman F, Rosai J, Rydholm A, Sciort R, Tallini G, van den Berghe H, van de Ven W, Vanni R, Willen H. Correlation between clinicopathological features and karyotype in lipomatous tumors. A report of 178 cases from the Chromosomes and Morphology (CHAMP) Collaborative Study Group. *Am J Pathol* 1996;148:623-30.
14. Fletcher CD, Gustafson P, Rydholm A, Willen H, Akerman M. Clinicopathologic re-evaluation of 100 malignant fibrous histiocytomas: prognostic relevance of subclassification. *J Clin Oncol*. 2001;19:3045-50.
15. Fretzin DF, Helwig EB. Atypical fibroxanthoma of the skin. *Cancer* 1973;31:1541-52.
16. Furlong MA, Mentzel T, Fanburg-Smith JC. Pleomorphic rhabdomyosarcoma in adults: a clinicopathologic study of 38 cases with emphasis on morphologic variants and recent skeletal muscle-specific markers. *Mod Pathol*. 2001;14:595-603.
17. Gebhard S, Coindre JM, Michels JJ, Terrier P, Bertrand G, Trassard M, Taylor S, Chateau MC, Marques B, Picot V, Guillou L. Pleomorphic liposarcoma: clinicopathologic, immunohistochemical, and follow-up analysis of 63 cases: a study from the French Federation of Cancer Centers Sarcoma Group. *Am J Surg Pathol*. 2002;26:601-16.
18. Henricks WH, Chu YC, Goldblum JR, Weiss SW. Dedifferentiated liposarcoma: a clinicopathological analysis of 155 cases with a proposal for an expanded definition of dedifferentiation. *Am J Surg Pathol*. 1997;21:271-81.
19. Herring CL Jr, Harrelson JM, Scully SP. Metastatic carcinoma to skeletal muscle. A report of 15 patients. *Clin Orthop* 1998;355:272-81.
20. Kaddu S, McMenamin ME, Fletcher CDM. Atypical fibrous histiocytoma of the skin : clinicopathologic analysis of 59 cases with evidence of infrequent metastasis. *Am J Surg Pathol* 2002 ;26 :35-46
21. Kempson RL, McGavran MH. Atypical fibroxanthomas of the skin. *Cancer* 1964;17:1463-8
22. Kumar S, Perlman E, Harris CA, Raffeld M, Tsokos M. Myogenin is a specific marker for rhabdomyosarcoma: an immunohistochemical study in paraffin-embedded tissues. *Mod Pathol*. 2000;13:988-93.
23. Laurino L, Furlanetto A, Orvieto E, Del Tos AP. Well-differentiated liposarcoma (atypical lipomatous tumors). *Semin Diagn Pathol*. 2001;18: 258-62.

24. McCormick D, Mentzel T, Beham A, Fletcher CD. Dedifferentiated liposarcoma. Clinicopathologic analysis of 32 cases suggesting a better prognostic subgroup among pleomorphic sarcomas. *Am J Surg Pathol*. 1994;18:1213-23.

25. Mentzel T, Calonje E, Wadden C, Camplejohn RS, Beham A, Smith MA, Fletcher CDM. Myxofibrosarcoma. Clinicopathologic analysis of 75 cases with emphasis on the low-grade variant. *Am J Surg Pathol* 1996;20:391-405.

26. Miyajima K, Oda Y, Oshiro Y, Tamiya S, Kinukawa N, Masuda K, Tsuneyoshi M. Clinicopathological prognostic factors in soft tissue leiomyosarcoma: a multivariate analysis. *Histopathology*. 2002;40:353-9.

27. Pilotti S, Della Torre G, Mezzelani A, Tamborini E, Azzarelli A, Sozzi G, Pierotti MA. The expression of MDM2/CDK4 gene product in the differential diagnosis of well differentiated liposarcoma and large deep-seated lipoma. *Br J Cancer*. 2000;82:1271-5.

28. Shmookler BM, Enzinger FM. Pleomorphic lipoma : a benign tumor simulating liposarcoma. A clinicopathologic analysis of 48 cases. *Cancer* 1981;47:126-33.

29. Sigel JE, Skacel M, Bergfeld WF, HouseNS, Rabkin MS, Goldblum JR. The utility of cytokeratin 5/6 in the recognition of cutaneous spindle cell carcinoma. *J Cutan Pathol* 2001;28:520-4.

- 30 .Watanabe K, Kusakabe T, Hoshi N, Saito A, Suzuki. h-Caldesmon in leiomyosarcoma and tumors with smooth muscle cell-like differentiation: its specific expression in the smooth muscle cell tumor. *Hum Pathol* 1999;30:392-6

31. Weiss SW, Enzinger FM. Malignant fibrous histiocytoma: an analysis of 200 cases. *Cancer*. 1978;41:2250-66.