Virchows Arch
DOI 10.1007/s00428-009-0815-x

REVIEW AND PERSPECTIVE

Well-differentiated and dedifferentiated liposarcomas

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Received: 4 March 2009 / Revised: 4 July 2009 / Accepted: 18 July 2009

Abstract Atypical lipomatous tumor or well-differentiated liposarcoma (ALT-WDLPS) and dedifferentiated liposarcoma (DDLPS) share the same basic genetic abnormality characterized by a simple genomic profile with a 12q14–15 amplification involving *MDM2* gene. These tumors are the most frequent LPS. This paper reviews the molecular pathology, general clinical and imaging features, histopathology, new diagnostic tools, and prognosis of ALT-WDLPS and DDLPS.

Keywords Well-differentiated liposarcoma · Dedifferentiated liposarcoma · MDM2 · CDK4

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Introduction

Liposarcoma (LPS) is one of the most frequent sarcoma of adult representing 25% of soft tissue sarcomas in a large European database (www.conticabase.org). According to its clinicopathological and molecular genetic characteristics, it can be subtyped in three categories [1]: atypical lipomatous tumor or well-differentiated LPS (ALT-WDLPS)/dedifferentiated LPS (DDLPS), myxoid/round cell LPS, and pleomorphic LPS. ALT-WDLPS/DDLPS is the most frequent LPS subtype and shows a simple genomic profile characterized by a 12q14–15 amplification involving the *MDM2* gene. Myxoid/round cell LPS is characterized by a specific reciprocal translocation t(12;16), leading to the fusion of *DDIT3* (*CHOP*) (12q13) and *FUS* (*TLS*) (16p11) genes. Pleomorphic LPS is the less frequent type and harbors a complex genomic profile with numerous gains and losses similar to the genomic profile seen in poorly differentiated sarcomas and particularly in myxofibrosarcomas [2].

During the last 10 years, the progressive identification of genomic abnormalities in DDLPS leads to a better understanding of these tumors as well as to the use of new criteria for the diagnosis. These genomic criteria are also very helpful for the diagnosis of ALT-WDLPS, which may be difficult to distinguish from benign adipocytic tumors. Moreover, a better knowledge of genomic aberrations seen in this category of LPS (ALT-WDLPS/DDLPS) suggests a multistep genetic process as recently reported in myxofibrosarcomas [3].

This paper reviews the cytogenetic and molecular genetic findings of ALT-WDLPS/DDLPS as well as their clinicopathological characteristics.

Published online: 18 August 2009

Genetics of atypical lipomatous tumor well-differentiated liposarcoma and dedifferentiated liposarcoma

Cytogenetics [4–6]

WDLPS and DDLPS show similar cytogenetic features. In most cases, there are one or two supernumerary rings or giant rod chromosomes. In most cases, these ring or giant chromosomes (also called "marker" chromosomes) are either the sole change, in addition of 46 apparently normal chromosomes, or may be associated with a few other numerical or structural abnormalities. Telomeric associations are frequently observed. Occasionally, especially in DDLPS, double minute chromosomes, multiple copies of the rings and giant markers, as well as genomic instability with random abnormalities from one cell to another can be observed (Fig. 1).

Molecular cytogenetics and genetics

Fluorescence in situ hybridization (FISH) and comparative genomic hybridization (CGH) studies have shown that these supernumerary chromosomes always contain amplified sequences of the region q14–15 of chromosome 12 [7] (Fig. 2). A large variety of other chromosomal regions, including 12q22 and 1q23 for the most frequently involved, have also been shown to be co-amplified in these supernumerary chromosomes. Surprisingly, there is usually no associated alteration on the corresponding chromosomes in the same cell. Molecular methods, such as Southern blotting and FISH analysis, showed that the *MDM2* gene, located at 12q15, was consistently amplified and could be considered as the target gene of this amplicon. More recently, it has been reported that the exons 1 and 2 of *HMGA2*, a gene located at 12q14.3 and known for being rearranged in ordinary lipomas, was consistently co-amplified with *MDM2* [8]. In addition, more centromeric genes, such as *CDK4* and *SAS/TSPAN31*, located at 12q14.1, belong to a separate amplicon that is co-amplified with *MDM2* and *HMGA2* in approximately 90% of cases. The *GLI* and *DDIT3* genes (12q13.3) are very rarely amplified. Another striking feature of the structure of supernumerary ring and giant chromosomes of ALT-WDLPS/DDLPS is that they most often lack alpha-satellite centromeric sequences [9, 10]. Instead, they contain a functional so-called neocentromere containing a high proportion of AT sequences and from variable chromosomal origin [11].

The detection of the amplification and overexpression of MDM2 in 100% of cases and of CDK4 in 90% of cases detected by FISH (Figs. 3 and 4) and immunohistochemistry (Fig. 5) represents nowadays an important tool for the diagnosis of ALT-WDLPS and DDLPS [12, 13].

In addition to the 12q14–15 amplicon, co-amplifications involving mainly 1p32 and 6q23 and also 2q14 (unpublished data) have been detected in DDLPS [14]. Co-amplifications of 1p32 and 6q23 are exclusive one of the other and never seen in WDLPS. Characterization by CGH array of the minimal region of amplification has shown that the target genes are *JUN* in the 1p32 band [15] and *ASK1* in the 6q23 band [16] (Fig. 6).

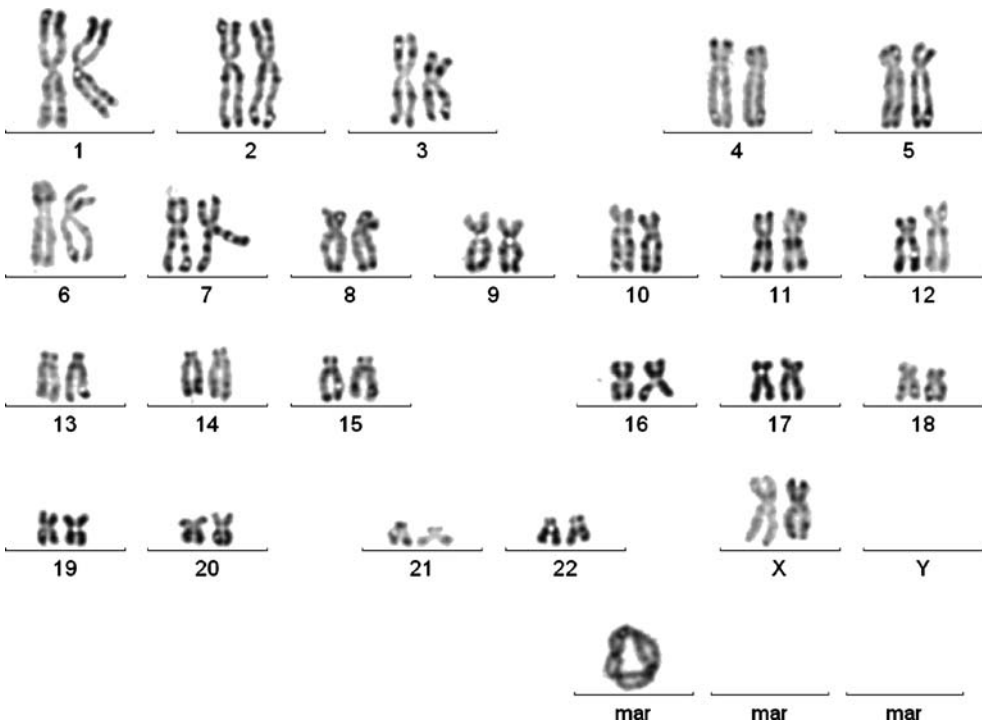

Fig. 1 Karyotype of an ALT-WDLPS in which the only rearrangement is a ring chromosome

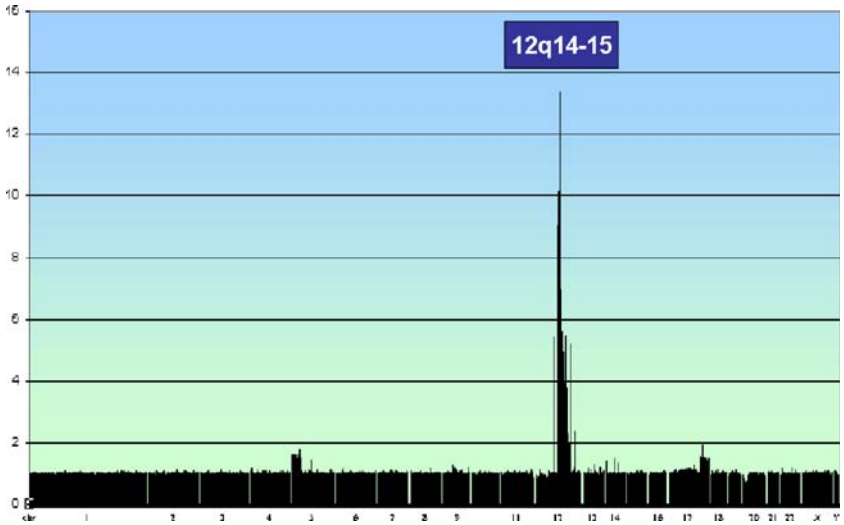

Fig. 2 Array CGH in an ALT-WDLPS showing an amplification of the 12q14–15 involving *MDM2* and *CDK4* genes

Mechanisms involved

MDM2 inhibits P53 and therefore decreases apoptosis and tends to increase cell survival [17]. CDK4 phosphorylates *Rb* gene product, which no longer interacts with E2F transcription factors, and the cell cycle proceeds through the G1-S checkpoint [18]. In summary, the biological consequence of the 12q14–15 amplicon is both to decrease apoptosis and to increase cell proliferation (Fig. 7).

ASK1 is a MAP3 kinase involved in the JNK signaling pathway [16]. Amplification and overexpression of *ASK1* activates JNK, which phosphorylates different target proteins, leading to the activation of some proteins, including JUN and inactivation of other proteins, in particular peroxisome proliferator-activated receptor (PPAR) gamma. It has been demonstrated that PPAR gamma plays a key role in adipocytic differentiation [19], and therefore, the amplification of *ASK1* inhibits adipocytic differentiation. *JUN* is an oncogene that also inhibits PPAR gamma via C/EBP beta [15]. Therefore, dedifferentiation in LPS might be explained by amplification and overexpression of *ASK1* or *JUN* genes. In summary, amplification of *MDM2* and *CDK4*, which are seen in both ALT-WDLPS and DDLPS, may be responsible for the malignant tumor process, whereas amplification of other genes such as *ASK1* and *JUN* may explain inhibition of adipocytic differentiation in DDLPS (Fig. 8).

Xenograft model on nude mice

The murine 3T3-L1 cell line is a highly relevant cellular model of human WDLPS and DDLPS. This cell line, which

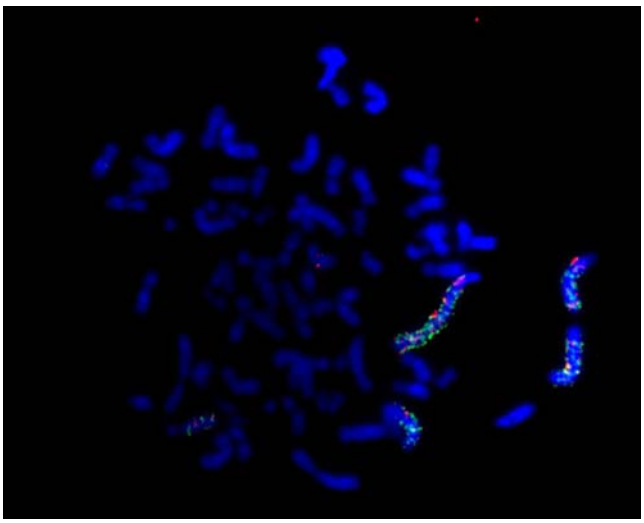

Fig. 3 FISH analysis on chromosomes showing that the ring chromosome is composed of *MDM2* genes copies

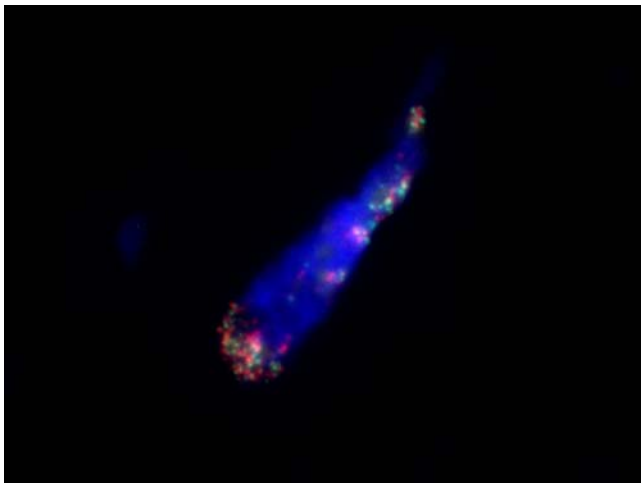

Fig. 4 FISH with MDM2 (red signal) and CDK4 (green signal) probes on formalin-fixed paraffin-embedded tissue from a DDLPS showing a high level amplification of both genes. Fluorescent signals are typically clustered

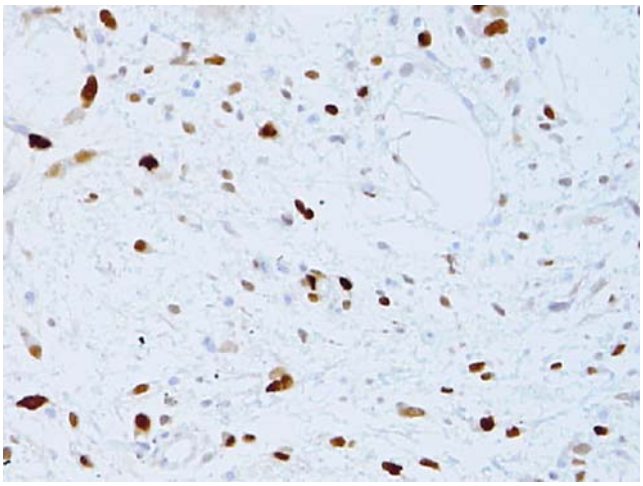

Fig. 5 Immunohistochemical staining for MDM2 (clone IF2) in a DDLPS. Many tumor cells show strong nuclear positivity

has often been used to define molecular events associated with adipogenesis, exhibits chromosomal features close to those of WDLPS and DDLPS with a high level MDM2 and CDK6 amplification in most cells associated with a high level amplification of the JUN locus in 1% of the cells [16]. CDK4 and CDK6 are closely related proteins, which play similar roles in cell-cycle progression.

3T3-L1 cells induce LPS in nude mice and recapitulate tumor progression from WDLPS at early fat pad stage to DDLPS at later stage. In this tumor model, high level amplification of JUN was observed in large nuclei from the undifferentiated areas of the tumor but not in nuclei from the well-differentiated areas, which exhibited only MDM2 and CDK6 amplification [16].

Potential therapeutic targets

Several proteins involved in the mechanism of DDLPS are potential therapeutic targets [20] (Figs. 7 and 8).

Nutlins are MDM2 antagonists that stabilize TP53 and induce apoptosis in cell lines with *MDM2* amplification but which have no effect on apoptosis in cell lines with no *MDM2* amplification [21]. Phase 1 studies are ongoing (http://clinicaltrials.gov/ct2/show/NCT00559533?term=R7112&rank=2 and http://clinicaltrials.gov/ct2/show/NCT00623870?term=R7112&rank=1)

Flavoperidol is a CDK4 inhibitor used in phases 1 [22] and 2 (http://www.clinicaltrials.gov/ct2/results?term=Flavopiridol+) studies.

Thioredoxin is an ASK1 antagonist, which induces adipocytic differentiation in a dedifferentiated cell line exhibiting *ASK1* amplification [16].

Aplidin is a cyclic depsipeptide isolated from a Mediterranean tunicate, which leads to apoptosis by JNK pathway activation [23]. The constitutive activation of this pathway in DDLPS could make Aplidin more efficient in these tumors.

Atypical lipomatous tumor well-differentiated liposarcoma

Definition, terminology, and epidemiology

ALT-WDLPS is a mesenchymal neoplasm composed either entirely or in part of a mature adipocytic proliferation usually showing nuclear atypia in stroma cells [24] and associated with an amplification of MDM2 gene [5, 6].

Definition of ALT-WDLPS is classically based on histologic aspects alone, but on both conceptual and practical points of view, the presence of the molecular genetic alteration described above is of great help for delineating this tumor [25].

The fact that WDLPS shows no potential for metastasis unless it contains a dedifferentiated component led to the introduction of atypical lipomatous tumor, particularly for lesions located in the limbs or in the trunk wall, since wide resection is usually curative. ALT and WDLPS are synonyms describing lesions, which are identical both morphologically and genetically and in terms of biological potential. “The choice of terminology is therefore best determined by the degree of reciprocal comprehension between the surgeon and the pathologist to prevent either inadequate or excessive treatment” [24].

ALT-WDLPS accounts for about 30–40% of all LPS and is the second most frequent category of LPS after DDLPS. They mostly occur during the sixth and seventh decades of life with a predilection for men [26].

Clinical features [24, 27]

ALT-WDLPS occurs in the deep soft tissue of the limbs, particularly in the thigh, the retroperitoneum, the paratesticular area, and the groin. It rarely occurs in other sites, such as the mediastinum, subcutaneous tissue, and miscellaneous parenchymal sites.

Symptoms depend on the location of the tumor. In the extremities, it usually presents as a painless, slowly growing, and deep-seated mass present for months or even several years and which can attain very large size. In the retroperitoneum, it is associated with the usual symptoms of intra-abdominal mass or may be found by chance. In this location, the tumor is often more 20 cm in size.

Imaging and gross features

MRI in the extremities and CT scan in the retroperitoneum show that the tumor has a fat density with zones of higher

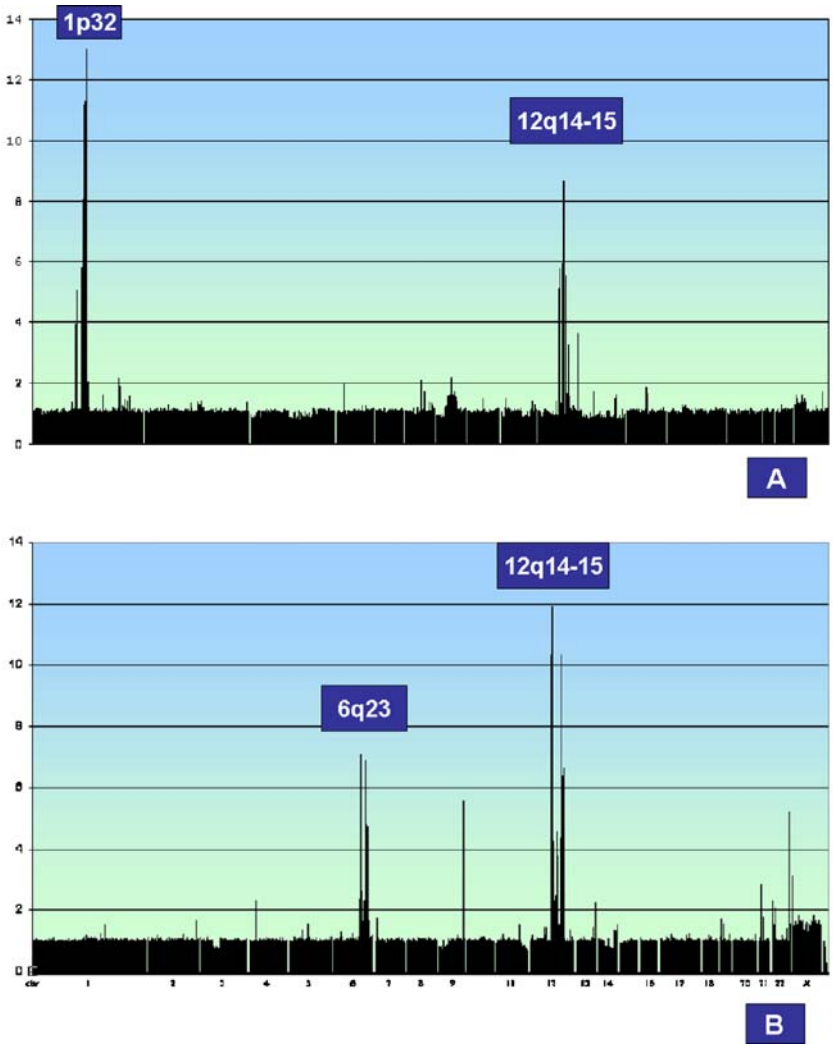

Fig. 6 Array CGH in two cases of DDLPS showing, in addition to the 12q14–15 amplification, a co-amplification of 1q32 in case A (**a**) and 6q23 in case B (**b**). These co-amplifications are exclusive one of the other and not seen in ALT-WDLPS

density corresponding to fibrous septa, sclerotic areas, or inflammatory component.

Grossly, ALT-WDLPS is usually a large, well-demarcated, and lobulated mass. In the retroperitoneum, there may be several separated masses. Color varies from yellow to white

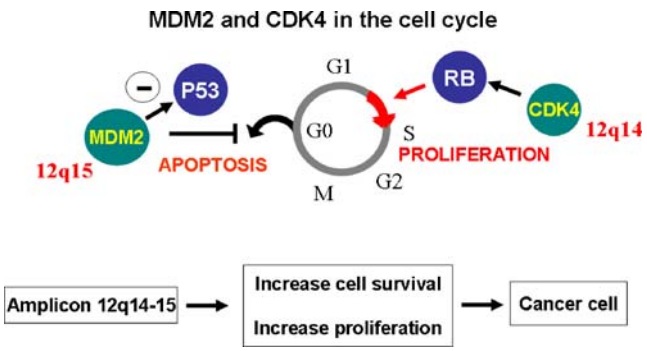

Fig. 7 Mechanism of action of *MDM2* and *CDK4* products on both cell survival and proliferation

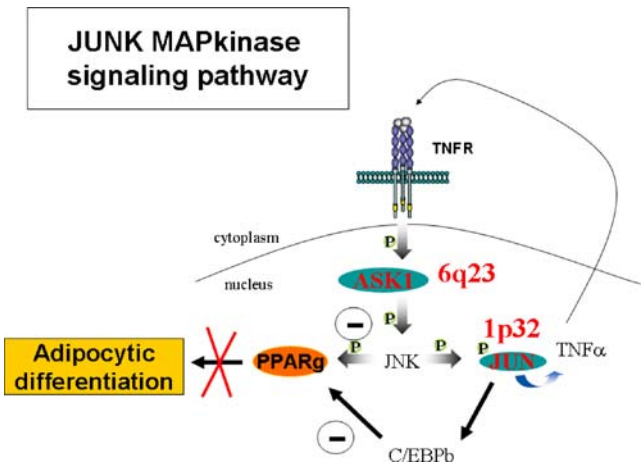

Fig. 8 Mechanism of dedifferentiation in LPS: amplification and overexpression of genes *ASK1* and *JUN* belonging to the JUN MAP kinase signaling pathway lead to inhibition of PPAR gamma, which plays a key role in adipocytic differentiation

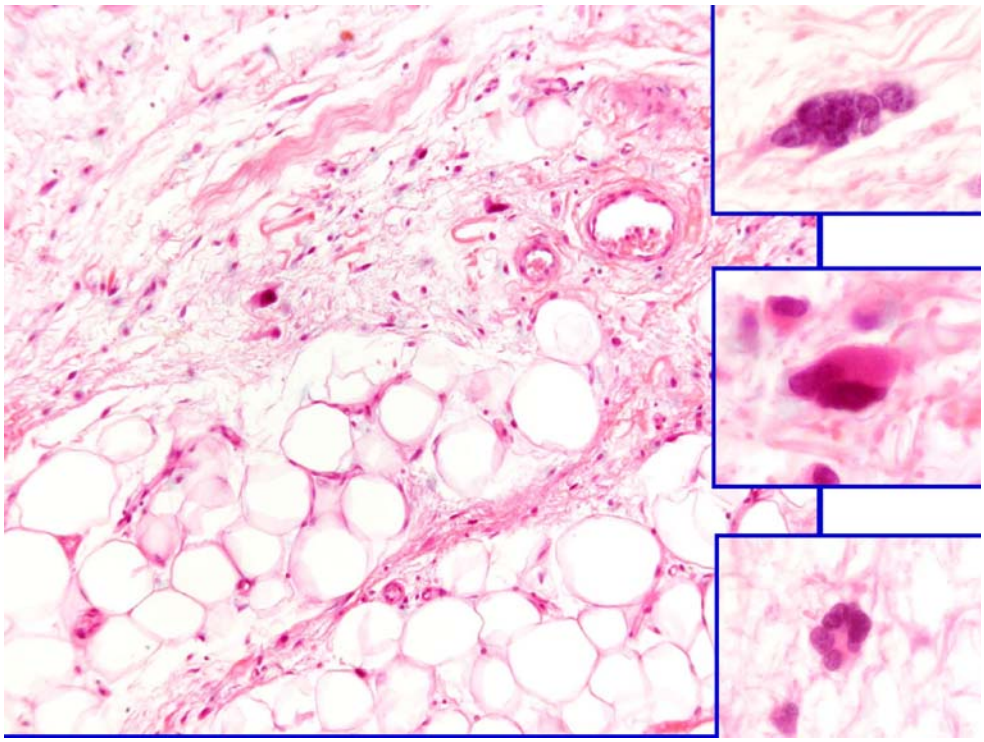

Fig. 9 ALT-WDLPS lipoma-like subtype is composed of mature adipocytic cells. The key for the diagnosis is the presence of atypical cells located in the fibrous septa

depending on the proportion adipocytic, fibrous, and myxoid component.

Histopathology [24, 27]

ALT-WDLPS can be subdivided into three main subtypes: lipoma-like, sclerosing, and inflammatory.

Many ALT-WDLPS combine areas of both lipoma-like and sclerosing subtypes in variable proportions. Therefore, the distinction between these two subtypes is often subjective and has no value in terms of diagnosis and prognosis.

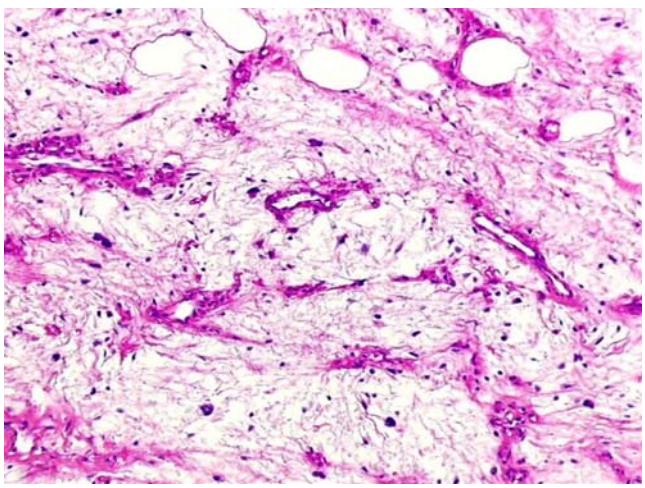

Fig. 10 ALT-WDLPS sclerosing subtype is composed of a myxofibrous background with scattered atypical cells and adipocytic cells

In the typical lipoma-like subtype, tumor is composed of mature adipocytic cells with a significant variation in size, associated with a variable number of atypical stromal cells, which constitute the key for the diagnosis of ALT-WDLPS. These cells tend to be more numerous in the fibrous septa where they should be looked for (Fig. 9). However, they could be so rare as to require extensive sampling. These atypical cells are spindle with hyperchromatic nuclear or multinucleated pleomorphic cells. Lipoblasts are rarely present and not required for the diagnosis of ALT-WDLPS.

The sclerosing subtype (Fig. 10) is most often seen in retroperitoneum or paratesticular region. It is composed of a fibrous or myxofibrous background with scattered stromal cells exhibiting nuclear hyperchromasia associated with multinuclear cells and sometimes rare multivacuolated lipoblasts. These sclerosing areas alternate with adipocytic areas, which can be limited in extent and sometimes missed particularly in small tissue samples. In this situation, analysis of *MDM2/CDK4* status is very helpful.

The inflammatory subtype is rare and occurs almost exclusively in the retroperitoneum [28]. It consists of a chronic inflammatory infiltrate superimposed on a lipoma-like or sclerosing form of ALT-WDLPS. This form may be easily confused with an inflammatory lesion or even a lymphoma. When dealing with a retroperitoneal lesion showing atypical stromal cells, we should always keep in mind the possibility of an ALT-WDLPS or DDLPS, and analysis of *MDM2/CDK4* status is regularly conclusive (Fig. 11).

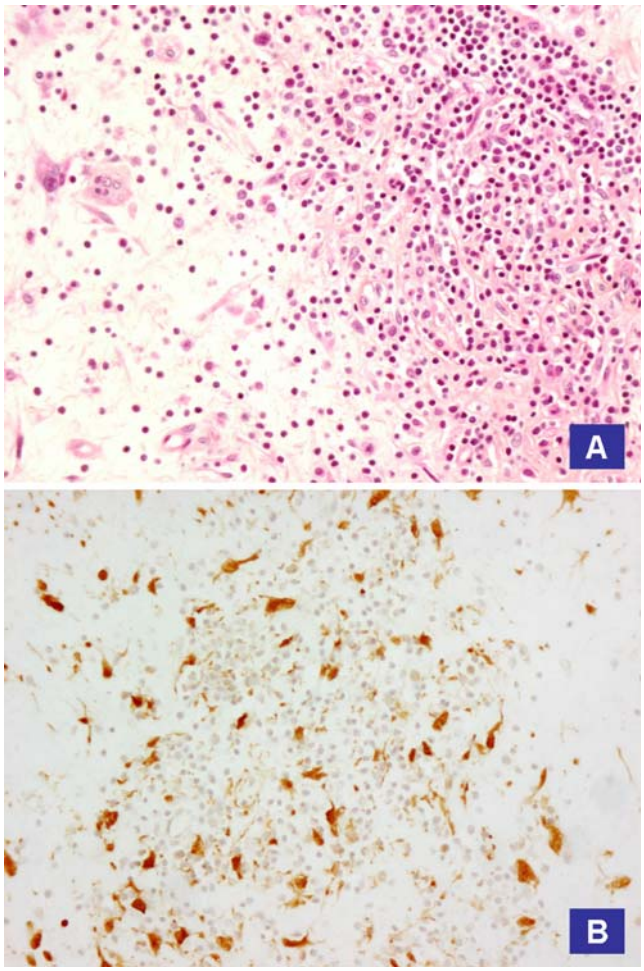

Fig. 11 ALT-WDLPS inflammatory subtype. Retroperitoneal tumor showing a chronic inflammatory infiltrate with a few atypical cells (**a**). Immunohistochemistry shows numerous cells positive for MDM2 and CDK4 (**b**)

Ancillary techniques

With the identification of 12q13–15 amplicon involving *MDM2*, *HMGA2*, and often *CDK4* genes in ALT-WDLPS, ancillary diagnostic tools can now be utilized to distinguish these tumors from benign lipomatous tumors. Immunohistochemistry showing overexpression of MDM2 and/or CDK4 may be used on first line to detect tumors with potential amplification of these genes. Clones IF2 for MDM2 and DCS-31 for CDK4 were respectively positive in 100% and 91% in ALT-WDLPS and also in 4% and 2% in benign lipomatous tumors [13]. Moreover, these antibodies may also stain the nuclei of histiocytes and reactive giant cells, which are often present in lipomas displaying inflammatory or necrotic changes. On the other hand, FISH showing amplification of *MDM2*, *HMGA2*, and *CDK4* is sensitive and specific for identifying ALT-WDLPS [12, 29].

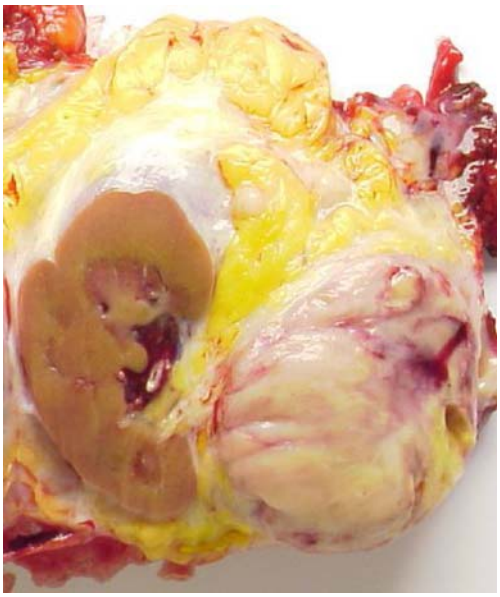

Fig. 12 Gross appearance of a retroperitoneal DDLPS showing areas of ALT-WDLPS and of DDLPS

Differential diagnosis [30–32]

One of the most frequent diagnostic problems revealed by second opinion practice is the distinction of ALT-WDLPS from benign lipomatous tumors. Deep lipomas with secondary changes may show irregular adipocytic size due to atrophic adipocytes admixed with inflammatory cells and histiocytes and reactive fibrous tissue with spindle cells mistaken for atypical cells and lipoblasts. Careful sampling, immunohistochemistry, and FISH for MDM2 and CDK4 are the keys for diagnosis. Normal fat with *Lochkern* (hole in the adipocyte nucleus), intramuscular lipoma with atrophic muscle, some spindle and pleomorphic cell lipomas, fat necrosis, atrophy of fat secondary to malnutrition or local trauma, silicone reaction due to injection of silicone for therapeutic or cosmetic purposes, and rare localized massive lymphoedema seen in morbid obesity can be mistaken for an ALT-WDLPS. In these situations, the use of immunohistochemistry and/or FISH for the detection of *MDM2* and *CDK4* amplification is frequently conclusive.

Prognosis

ALT-WDLPS are nonmetastasizing tumors for which the local recurrence rate is mainly dependant on their location. Tumors in the extremities have significantly lower rates of local recurrence than those in the retroperitoneum, which recur in almost 100% of cases and often cause the patient's death. The risk of dedifferentiation is time dependent and is probably more than 20% in retroperitoneum and less than 5% in extremities. Overall mortality ranges from 0% in the

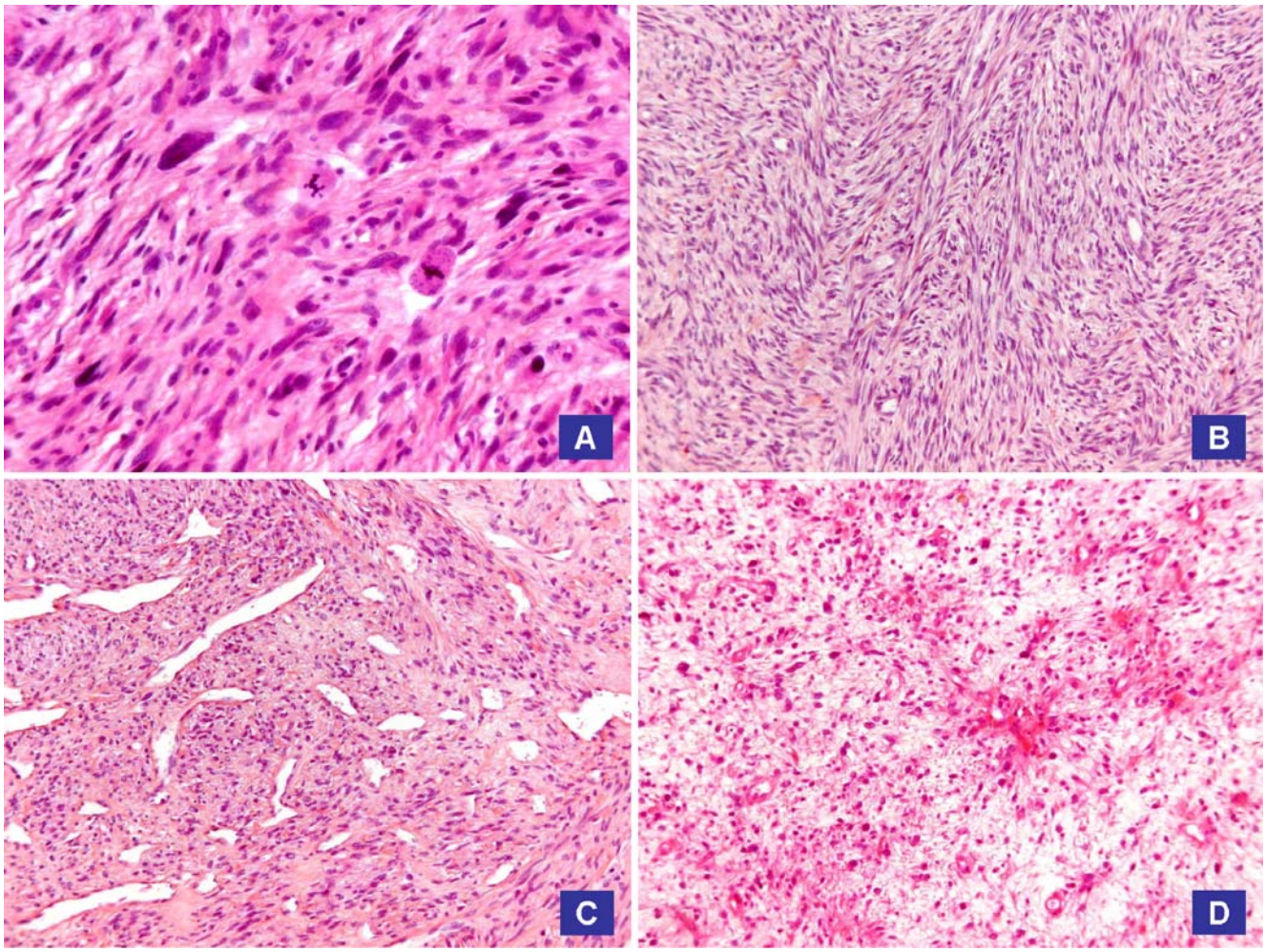

Fig. 13 Dedifferentiated component of DDLPS is usually composed of pleomorphic malignant fibrous histiocytoma (**a**), fibrosarcoma (**b**), malignant hemangiopericytoma (**c**) or high-grade myxofibrosarcoma-like areas (**d**)

limbs to more than 80% for cases occurring in the retroperitoneum for patients with a long follow-up.

Dedifferentiated liposarcoma

Definition, terminology, and epidemiology

DDLPS is a term first introduced by Evans in 1979 [33] to describe LPS containing ALT-WDLPS juxtaposed to areas of high-grade nonlipogenic sarcoma, usually resembling either high-grade pleomorphic sarcoma NOS or fibrosarcoma. DDLPS was believed to occur from ALT-WDLPS after several years. These traditional views have been modified by the description of exclusively low-grade dedifferentiated component and by the fact that most DDLPS arise in fact de novo and are diagnosed on the original excision [34]. Moreover, thanks to its specific genomic profile, DDLPS can now be identified in the absence of ALT-WDLPS areas [14]. Absence of ALT/WDLPS component may be explained by inappropriate sampling, disappearance of the ALT-WDLPS component, or even by absence of the well differentiated component in the initial tumor. The latter situation corresponds to undifferentiated LPS rather than to dedifferentiated LPS. Genomic abnormalities described in DDLPS support the fact that this tumor corresponds to a malignant adipocytic tumor showing progression from ALT-WDLPS to non-lipogenic sarcoma of variable aspect and grade [14–16]. About 90% of DDLPS arises de novo, while 10% occurs in recurrence. The risk of dedifferentiation is higher in deep-seated tumors, particularly in the retroperitoneum and is probably a time-dependent phenomenon. Numerous reports have supported the concept of DDLPS with two histological series of 32 [35] and 155 cases [34]. It represented 18% of LPS in a large series reported in 2006 [36], but we suspect a much more frequency due to the recent genomic criteria used for diagnosing cases without any ALT-WDLPS areas.

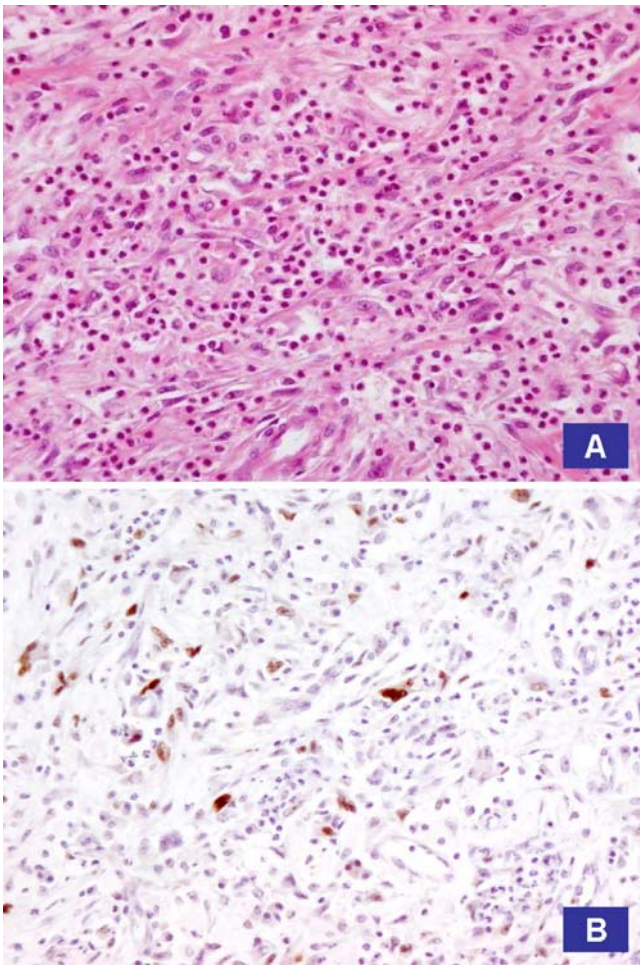

Fig. 14 Most so-called inflammatory malignant fibrous histiocytomas are in fact DDLPS. Typical aspect in **a** and strong nuclear positivity of tumor cells for MDM2 antibody in **b**

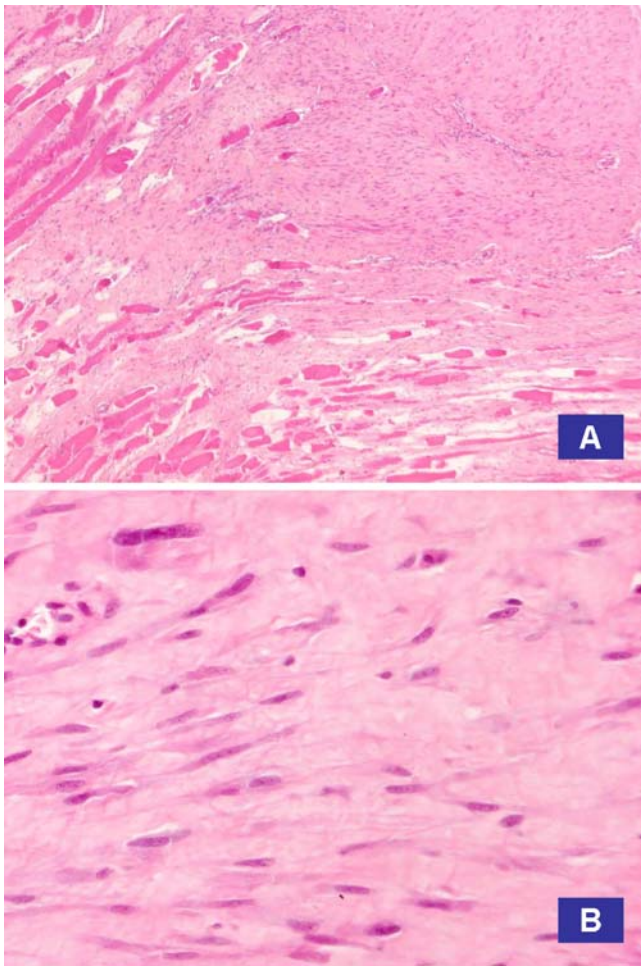

Fig. 15 Example of a low-grade dedifferentiated component in a DDLPS simulating a desmoid tumor with infiltration of the adjacent muscles in **a**. The tumor shows a fibrous background with moderately atypical spindle cells in **b**

Clinical features

DDLPS occur in late adult life with no sex predilection, most commonly in the retroperitoneum (more than 80% of cases), extremities, spermatic cord, and other sites of internal trunk. Occurrence in head and neck may be seen but is rare in subcutaneous tissue. In our experience, 60% of retroperitoneal sarcomas are LPS, two thirds of which are DDLPS. It usually presents as a large painless mass, which may be found by chance, particularly in the retroperitoneum.

Imaging and macroscopy

Radiological imaging may suggest the diagnosis by showing the coexistence of a fatty component with a non-fatty solid one.

The gross appearance of DDLPS is often helpful for the diagnosis. It usually consists of multinodular yellow (fatty) masses containing firm tan-gray areas corresponding to dedifferentiated foci (Fig. 12). Necrosis is often observed.

Histopathology [27, 37]

Histologically, DDLPS is traditionally defined by the association of ALT-WDLPS areas and a non-lipogenic sarcoma, usually with an abrupt transition, although in some cases, it can be gradual, and rarely the two components appear to be intermingled.

Dedifferentiated areas exhibit a wide morphological spectrum. Most cases show areas of high-grade poorly differentiated sarcoma resembling pleomorphic malignant fibrous histiocytoma, fibrosarcoma, malignant hemangiopericytoma, or high-grade myxofibrosarcoma (Fig. 13). It has been shown that most sarcomas diagnosed as poorly differentiated sarcoma and arising in the retroperitoneum are in fact dedifferentiated LPSs [38]. The keys of diagnosis are the presence of an ALT-WDLPS component easily

demonstrated by extensive sampling of the surrounding fat tissues and the positivity of immunohistochemistry for MDM2 and CDK4. Nowadays, these poorly differentiated sarcomas represent less than 10% of all sarcomas arising in retroperitoneum as well as in paratesticular areas and other internal trunk areas. Dedifferentiated areas resembling inflammatory malignant fibrous histiocytoma, characterized by numerous benign xanthomatous cells admixed with acute and chronic inflammatory cells and a variable number of atypical cells, have been associated with fever, weight loss, leukocytosis, eosinophilia, and leukemoid reaction. In fact, based on a combination of a careful histological review, *MDM2* and *CDK4* status, and genomic profiling, it has been showed that most so-called inflammatory malignant fibrous histiocytoma were, in fact, DDLPS [39] (Fig. 14).

The concept of low-grade dedifferentiation has increasingly been recognized [34]. Usually, low-grade areas coexist with areas of high-grade sarcomas, but in about 10% of cases, only low-grade areas are present [40–42]. These areas resemble low-grade myxofibrosarcoma, fibromatosis (Fig. 15), well-differentiated fibrosarcoma, and even dermatofibrosarcoma protuberans.

In about 5–10% of cases, the dedifferentiated component shows divergent differentiation featuring myogenic or osteochondromatous elements. An angiosarcomatous component has also been reported. Myosarcomatous differentiation is the most frequent but must be established with both morphological features and immunohistochemical profile, and specific muscle markers such as h-caldesmon and myogenin should be used given the non-specificity of markers such as smooth muscle actin and desmin and their frequent positivity in conventional DDLPS (Fig. 16). It has been recently reported that most tumors developed in the internal trunk and diagnosed as pleomorphic rhabdomyosarcoma or malignant mesenchymoma are actually DDLPS with a divergent differentiation. In this report, the presence of a divergent differentiation does not affect the clinical outcome [42].

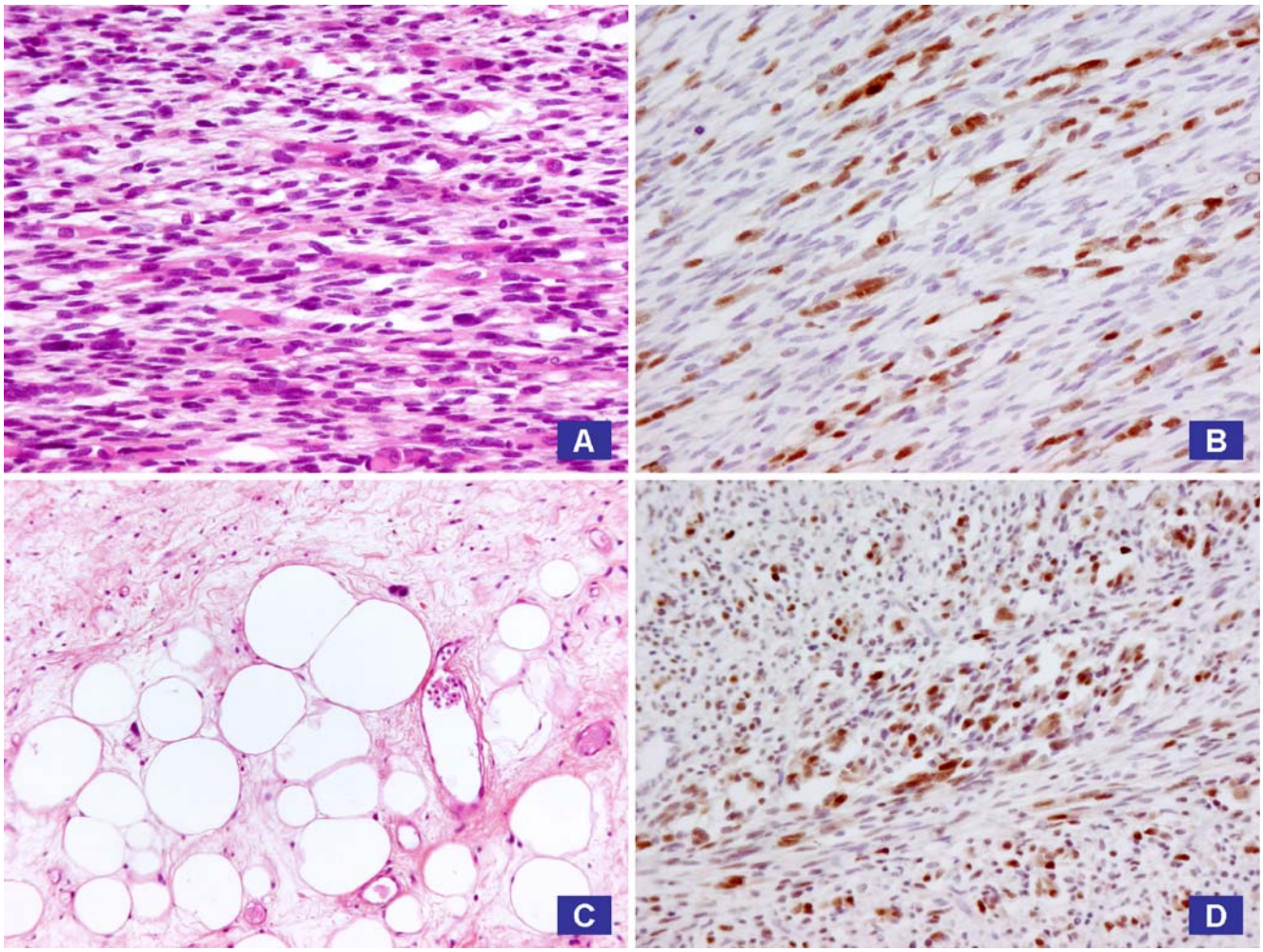

Fig. 16 DDLPS with a divergent differentiation. Histological aspect of a rhabdomyosarcoma (**a**) with a strong positivity for myogenin (**b**). Careful sampling shows an ALT-WDLPS component (**c**), and heterologous component is positive for MDM2 (**d**)

A number of unusual patterns are seen in DDLPS. A "neural-like" or "meningothelial-like" whorling pattern of differentiation often associated with ossification has been described [43, 44] (Fig. 17). Epithelial-like pattern composed of undifferentiated large round cells resembling a carcinoma or a melanoma, areas with dense amianthoid-like fibers, and areas composed of hibernoma-like cells have also been described [34].

Ancillary techniques

Immunohistochemistry for MDM2 and CDK4 is currently used for the diagnosis of DDLPS. Analysis of immunohistochemistry on a large number of sarcomas reported a sensitivity of 95% and 92% and a specificity of 81% and 95% for, respectively, MDM2 and CDK4 for the diagnosis of DDLPS [13]. In this report, 18.9% of various sarcomas, including malignant peripheral nerve sheath tumor, myxofibrosarcoma, embryonal rhabdomyosarcoma, poorly differentiated sarcoma leiomyosarcoma, and myxoid LPS, were also positive for MDM2. However, 90.2% of DDLPS were positive for both MDM2 and CDK4 as opposed to only 3.7% of other sarcomas. Moreover, due to the fact that there is no internal positive control for these antibodies, we should keep in mind that a non-immunoreactivity could correspond to a false negativity. These findings underline the importance of the clinical and morphological context as well as the need to use a panel of antibodies for achieving the right diagnosis.

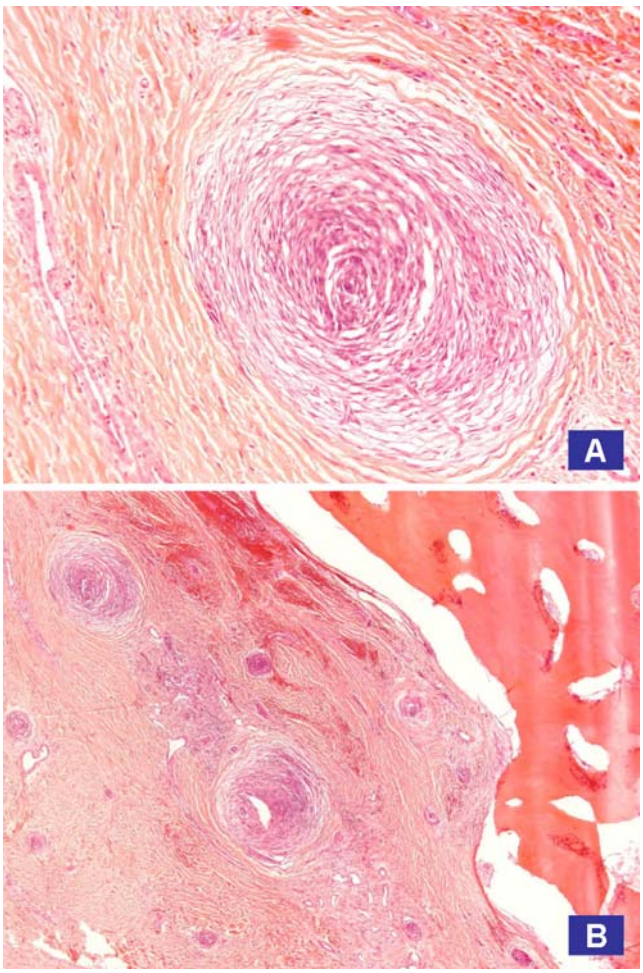

Fig. 17 DDLPS with a meningothelial-like-dedifferentiated component showing a whorling pattern (**a**) often associated with ossification (**b**)

Detection of *MDM2* and *CDK4* amplification by FISH or quantitative PCR is more efficient than immunohistochemistry for the diagnosis of DDLPS. FISH and quantitative PCR [12] gave concordant results but FISH was more powerful than quantitative PCR when tumor cells represented a minor component such as with inflammatory tumors and is more and more often use in the daily practice. In our experience, FISH is a powerful tool for the diagnosis of DDLPS, since it shows a true amplification with clustering of the signal. In addition, when a moderate gain of MDM2/CDK4 is detected, a complementary analysis with a centromeric probe for chromosome 12 can be performed. This helps to identify a polysomy 12 that has to be distinguished from a genuine amplification. As previously reported, a gain of *MDM2* or a polysomy can be seen in other sarcomas, particularly those with a complex genetics such as pleomorphic poorly differentiated sarcomas [29]. In these cases, fluorescent signals are not clustered, and the number of copies of centromere 12 is usually the same than the number of copies of *MDM2*/*CDK4*.

Multicolor FISH like COBRA has been reported to be helpful for difficult cases [45].

For difficult cases, the gold standard is array CGH, which shows a simple genomic profile with only a few amplicons, one in the 12q14.15 and usually another in the 1p32 or 6q23 chromosomal regions.

Differential diagnosis

Due to the histological complexity of DDLPS, many differential diagnoses may be raised on the morphological aspect alone: poorly differentiated sarcomas such as malignant fibrous histiocytoma, fibrosarcoma and malignant hemangiopericytoma, myxofibrosarcoma, pleomorphic rhabdomyosarcoma, and malignant mesenchymoma. In internal trunk areas, these diagnoses can be retained only after exclusion of a DDLPS, and in this situation, an extensive sampling should be performed in order to demonstrate an ALT-WDLPS component, and the MDM2-CDK4 status should be evaluated.

A DDLPS can be mistaken for an ALT-WDLPS because of minimal areas of dedifferentiation, which can be missed in case of insufficient sampling. According to Weiss and Goldblum, the presence of a macroscopically visible nodule

of dedifferentiation (>1.0 cm) should be demonstrated in an ALT-WDLPS for diagnosing a DDLPS [27].

Prognosis

Prognosis is mainly dominated by local recurrences (40–60%), particularly in the retroperitoneum, with a quite low metastatic potential (15–20%) [34, 35]. In fact, almost all retroperitoneal cases seem to locally recur if patients are followed for at least 10–20 years. Overall mortality range from 30% to 40% at 5 years. The most important prognostic factor is anatomic location with a poor prognosis for retroperitoneal tumors. Traditionally, neither histological grade nor extent of dedifferentiation is of prognostic value. However, a recent study on retroperitoneal LPSs suggested that grade and extent of dedifferentiation are predictors for event-free survival [46].

Conclusions

Advances in our knowledge about genetics of the ALT-WDLPS/DDLPS have led to significant improvements in the diagnostic approach of LPSs, especially by detection of MDM2 and CDK4 overexpression and/or amplification. Thanks to these new criteria, the distinction of ALT-WDLPS from challenging benign adipocytic tumors on one hand and identification of DDLPS among histologically poorly differentiated sarcomas on the other hand has become easier. More importantly, better understanding of the mechanisms involved in the development of DDLPS has led to the identification of new potential therapeutic targets.

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