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ORIGINAL ARTICLE

# Liposarcoma of the extremities: MR imaging features and their correlation with pathologic data

F. El Ouni<sup>a,\*</sup>, H. Jemni<sup>a</sup>, A. Trabelsi<sup>b</sup>, M. Ben Maitig<sup>c</sup>, N. Arifa<sup>a</sup>,  
K. Ben Rhouma<sup>a</sup>, M. Ben Ayech<sup>c</sup>, K. Tlili<sup>a</sup>

<sup>a</sup> Department of Medical Imaging, Sahloul Teaching Medical Center, route Ceinture, 4054 Sousse, Tunisia

<sup>b</sup> Department of Pathology, Farhat Hached University Hospital Center, Sousse, Tunisia

<sup>c</sup> Orthopaedic surgery, Sahloul University Hospital Center, Sousse, Tunisia

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## KEYWORDS

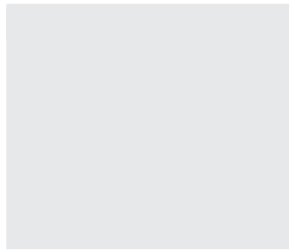
Soft tissues neoplasm;  
Lipomatous tumors;  
Liposarcomas;  
MRI;  
Pathology

## Summary

**Objective:** To describe the MRI features of liposarcomas of the extremities and correlate them with data from the histologic subtypes.

**Material and methods:** Retrospective study of 20 cases of liposarcoma of the extremities identified on MRI, surgically removed and confirmed at pathology. On MRI examination, T1- and T2-weighted fat-suppressed and non-fat-suppressed images were acquired then gadolinium-enhanced fat-suppressed T1-weighted images were obtained in at least two orthogonal planes. **Results:** Sixteen female and four male patients aged 12 to 77 years old at presentation, in 16 cases, with a slowly enlarging painless mass (demonstrating no associated local or general inflammatory components), located in the lower extremity (16 cases) and predominantly located in the thigh (13 cases). Pathologic examination revealed three cases of well-differentiated liposarcoma, 12 cases of myxoid liposarcoma one of which with round cells, three cases of pleomorphic liposarcoma, one case of dedifferentiated liposarcoma and one case of mixed-type liposarcoma. MR images mostly showed well-circumscribed tumors (19 cases). Well-differentiated liposarcomas typically demonstrated a very specific diagnostic appearance as a predominantly adipose mass containing nonlipomatous components seen as thick septa that may show nodularity. Other subtypes of liposarcoma demonstrated a small amount of adipose tissue thus producing a marbled textural pattern on T1-weighted images particularly in myxoid liposarcomas (9 cases), or even nonlipomatous elements in high-grade liposarcomas (in round cell liposarcoma and in two out of three pleomorphic liposarcomas). The myxoid subtype has also a relatively characteristic appearance as a low signal intensity noted on T1-weighted

\* Corresponding author. Tel.: +00 216 99 345 245; fax: +00 216 73367451.  
E-mail address: elounichedia@yahoo.fr (F. El Ouni).



images and a marked high signal intensity on T2. The dedifferentiated liposarcoma has a very specific radiologic appearance as a nonlipomatous component within a predominantly adipose mass, simulating that of well-differentiated liposarcomas.

*Conclusion:* MRI of extremity liposarcomas is a highly reliable and sensitive method to characterize liposarcomas. Besides its value in the diagnosis of liposarcoma and locoregional extension control, it allows proper identification of the specific histologic subtypes of liposarcoma.

*Level of evidence:* Level IV. Retrospective diagnostic study.

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## Introduction

Liposarcoma of the extremities (LPS) represents the second most common type of soft-tissue sarcoma, exceeded only by fibrous and fibrohistocytic malignancies. Liposarcoma accounts for 16 to 18% of all malignant soft-tissue sarcomas [1,2,3,4,5]. The World Health Organization (WHO) Committee for the Classification of Soft Tissue Tumors in 2002 has categorized soft-tissue liposarcomas into five distinct histologic subtypes: well-differentiated, myxoid, pleomorphic, dedifferentiated and mixed-type [1,6]. The diversity of these lesions is also reflected in their clinical behavior and radiographic assessment. Because of these variations in biologic behavior, a thorough clinical, radiologic and pathologic assessment is vital to direct appropriate therapy.

MRI examination is a highly reliable method in the diagnosis of these tumors. It helps provide accurate diagnosis in the majority of the cases since it demonstrates focal or diffuse areas of fat according to the histologic subtype of the lesion. The imaging appearance and amount of lipomatous or nonlipomatous components allows proper differentiation of the tumors and even identification of the histologic subtype of LPS [1,4,6].

The aim of that work was to analyze the MR imaging features of 20 cases of LPS by correlating the radiologic appearances with pathologic features.

## Material and methods

Twenty cases of liposarcomas of the extremities detected on MRI exploration, surgically removed and histologically confirmed between 1997 and 2008. The MRI scan was performed using a 1.5 Tesla apparatus (Signa General Electric). The typical MRI examination consisted of T1-weighted (pT1) and T2-weighted (pT2) fat-suppressed and non-fat suppressed images after injection of a gadolinium contrast agent. These sequences were performed in at least two orthogonal planes.

## Results

Sixteen females and four males, aged from 12 to 77 years (mean age 48 years) presenting with a mass lesion, underwent MRI of the thigh in 13 cases, of the buttocks in two, of the forearm in two, of the leg in one, of the shoulder in one and of the hand in one. Eighteen patients consulted for the first time with a tumor mass with no associated local inflammatory symptoms: this mass had been evolving from 4 months to 3 years, was asymptomatic and painless in 16 cases and had recently enlarged; in one case, the mass had

become painful associated with tightness (LPS of the back of the hand) while another patient became anorexic with a loss in weight of 3 kg. The other two patients consulted for recurrent LPS operated on 1 year and 4 years ago. The estimated tumor size varied from 5 to 25 cm with a mean size of 14 cm.

Histologic examination revealed three cases of well-differentiated liposarcoma, 12 cases of myxoid liposarcoma (one of which with round cells), three cases of pleomorphic liposarcoma, one case of dedifferentiated liposarcoma and one case of mixed liposarcoma.

At MR imaging, the three cases of well-differentiated liposarcoma demonstrated a predominantly adipose mass (of high-signal intensity with T1- and T2-weighting but decreasing after fat-suppression technique) with thick septa of low signal intensity and nodular foci thus producing a lobulated textural pattern. Gadolinium-enhancement of septa was regular, from moderate to high (Fig. 1).

In 10 cases of myxoid LPS, in one case of pleomorphic LPS and in our single case of mixed-type LPS, MRI revealed a lipomatous portion of linear and indented appearance of high-signal intensity on T1-weighted images, decreasing after fat-saturation, within an isointense tumor thus producing a marbled or nebulous textural pattern (Fig. 2). In four cases, two myxoid (one of which with round cells) and one pleomorphic LPS, the tumor was homogenous of iso-signal with T1-weighting and high-signal intensity with T2 weighting, with no lipomatous component thus producing a mass of pseudo-cystic radiologic appearance. Gadolinium-enhancement confirmed the solidity of the lesion (Fig. 3).

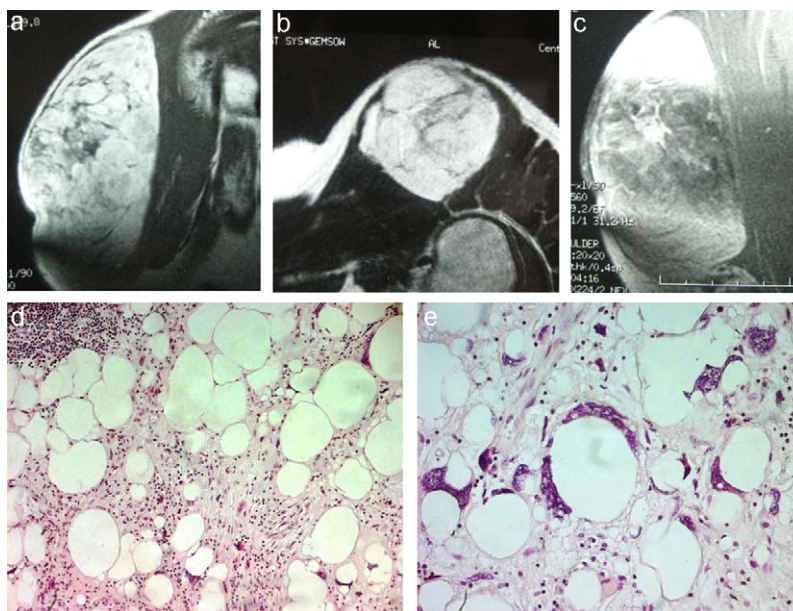
Dedifferentiated LPS demonstrated a largely lipomatous voluminous tissue component of lobulated appearance (simulating that of well-differentiated LPS) and a small non-lipomatous gadolinium-enhanced component (Fig. 4).

Morphologically, only one patient (subcutaneous pleomorphic LPS of the buttocks with no adipose component) had a badly limited even infiltrative mass (Fig. 5); the other 19 cases demonstrated a well-encapsulated mass with no tumor infiltration or invasion of the adjacent structures. In one of these cases (pleomorphic LPS), the tumor had recurred in three independent points of the same thigh (Fig. 6).

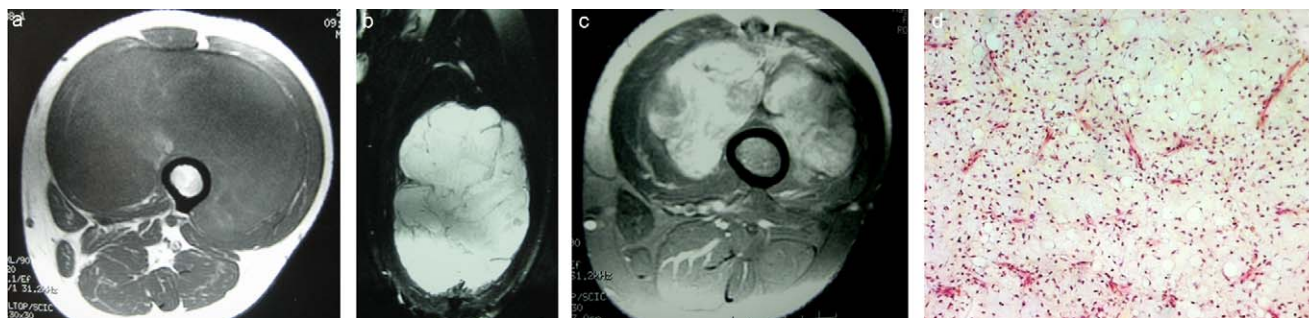
The lipomatous component was identified on MRI in nine myxoid LPS, one pleomorphic LPS, the single mixed-type LPS and in all 3 well-differentiated LPS and 1 dedifferentiated LPS.

Moreover, the tumor was deep-seated (intra- or inter-muscular space) in 17 cases and involved the subcutaneous tissues in three cases.

Table 1 reports the clinical and topographic data, the diagnosis of histologic subtypes as well as the presence and extent of lipomatous components.



**Figure 1** Well-differentiated intramuscular LPS of the shoulder: 47-year-old male with a painless slowly enlarging tumor (case n° 1). Signal of fat mass (hypersignal on pT1– [a] and pT2– [b] weighted images) with well-enhanced thickened or nodular septa of low signal intensity as shown on combined gadolinium-enhanced and fat-saturated T1-weighted images (c). Histological section (magnifications of 200 × [d]): lobules of mature adipocytes with atypical cells and lipoblasts (high magnification × 400 [e]) separated by thick septa.



**Figure 2** Myxoid intermuscular LPS of the thigh: a 41-year old male with a 4-year history of painless slowly enlarging mass (case n° 5); well-circumscribed tumor of low signal intensity on T1-weighted images with subtle area of adipose tissue of high signal intensity thus producing a marbled textural pattern (a). Marked high signal intensity on T2-weighted images (b) related to the myxoid contingent. Marked heterogeneous enhancement of the tumor after gadolinium injection and fat-saturation (c). Histological section (magnification × 100) (d): proliferation of fusiform cells associated with adipocytes within an abundant myxoid stroma of plexiform capillary pattern corresponding to the water signal on MRI (marked low signal intensity of T1-weighted images and high signal intensity on T2-weighted images).

The initial examination regarding tumor extension included a bone scintigraphy, an abdominal echography and a thoracic CT in all cases. It was negative in 18 cases but revealed a secondary hepatic localization in one case of myxoid LPS and secondary pulmonary localization in one case of pleomorphic LPS.

Treatment included excision of the tumor in all cases followed by a 6-week local radiation therapy. In two cases, an adjuvant chemotherapy was associated after metastases were found. Examination of the resected tumor tissues revealed a wide surgical excision in 12 cases and a marginal excision in eight cases.

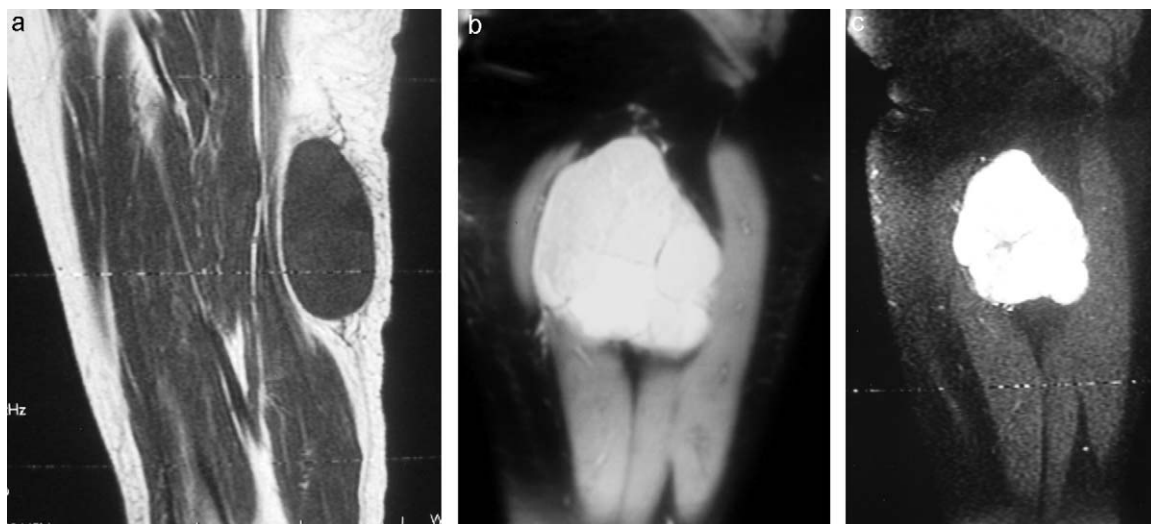
Locoregional tumor recurrence was noted in three cases after one to three postoperative years demonstrat-

ing parotidian metastases in one case (a patient with synchronous hepatic metastases) and calvarial metastases in one case of pleomorphic LPS. Recurrences involved marginal resections of liposarcomas. These patients were managed with wide excision in two cases and in one case of recurring pleomorphic type LPS, limb disarticulation was not accepted by the female patient.

## Discussion

Liposarcoma represents the second most common type of soft-tissue sarcoma after malignant fibrous histiocytoma, and accounts for 16 to 18% of all soft-tissue sarcomas.





**Figure 3** Myxoid LPS of the thigh with round cells predominance: 48-year-old female with a 3-year history of slowly enlarging painless mass (case n° 15). Well-circumscribed lesion located in the intermuscular space, of intermediate signal intensity on pT1-weighted images (a) and high signal intensity on pT2-weighted images but less intense than that of typical myxoid subtype, related to its prominent cellular region. The prominent cellular feature is confirmed on gadolinium contrast-enhanced fat-saturation pT1-weighted images (c). No lipomatous component was observed.

Liposarcomas in children is a rare tumors and occurs almost exclusively in adults with the peak prevalence between 40 and 60 years of age [1,2].

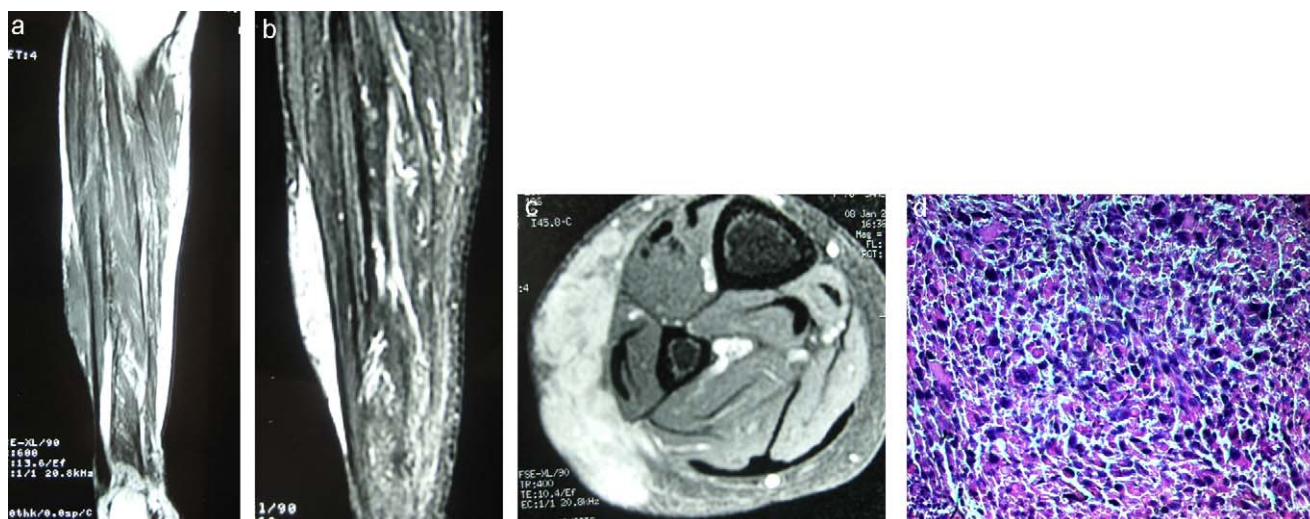
Clinically, as in other types of soft-tissue sarcomas, LPS frequently reveals as a painless soft-tissue mass. However, painful liposarcomas account for 10 to 15% of the cases [1,2,3].

These tumors most frequently affect the extremities (approximately 66 to 75% of the cases) and occur in the

lower limb about four times more than in the upper limb, with the thigh being predominantly affected in 40 to 65% of the cases. These lesions are usually deep-seated, involving the intra- or intermuscular space. In our series, the tumor occurred in the lower limb in 16 cases, 13 out of which were located in the thigh, and was deep-seated in 17 cases. Myxoid LPS most frequently affects the intermuscular space (70 to 80% of the cases) rather than the intramuscular space or subcutaneous tissues whereas the



**Figure 4** Dedifferentiated LPS of the thigh: a 69-year-old female with a 4-year history of painless slowly enlarging tumor having recently rapidly increased in volume (case n° 19). This well-circumscribed tumor is located in the intermuscular space and demonstrates a large lobulated component of fat-signal on pT1- (a and b), on pT2-weighted images (c) and on fat-saturated sequences (d) with thick septa thus suggesting a well-differentiated LPS. A central area of non adipose tissue of gadolinium-enhanced low signal intensity on T1-weighted images and high signal intensity on T2-weighted images (e) demonstrating the dedifferentiate component of the tumor, confirmed after pathologic analysis.



**Figure 5** Pleomorphic LPS of the leg: a 77-year-old female with a 6-month history of painless tumor (case n° 17). Subcutaneous, poorly limited even infiltrative mass of muscle isosignal on pT1-weighted images (a), of high signal intensity and marked heterogeneous enhancement on gadolinium-enhanced (c) fat-saturated T2-weighted images, with no lipomatous component detected. Histologic section (magnification of  $\times 400$ ): sarcoma cells proliferation of small differentiation with some lipoblasts allowing a positive diagnosis.

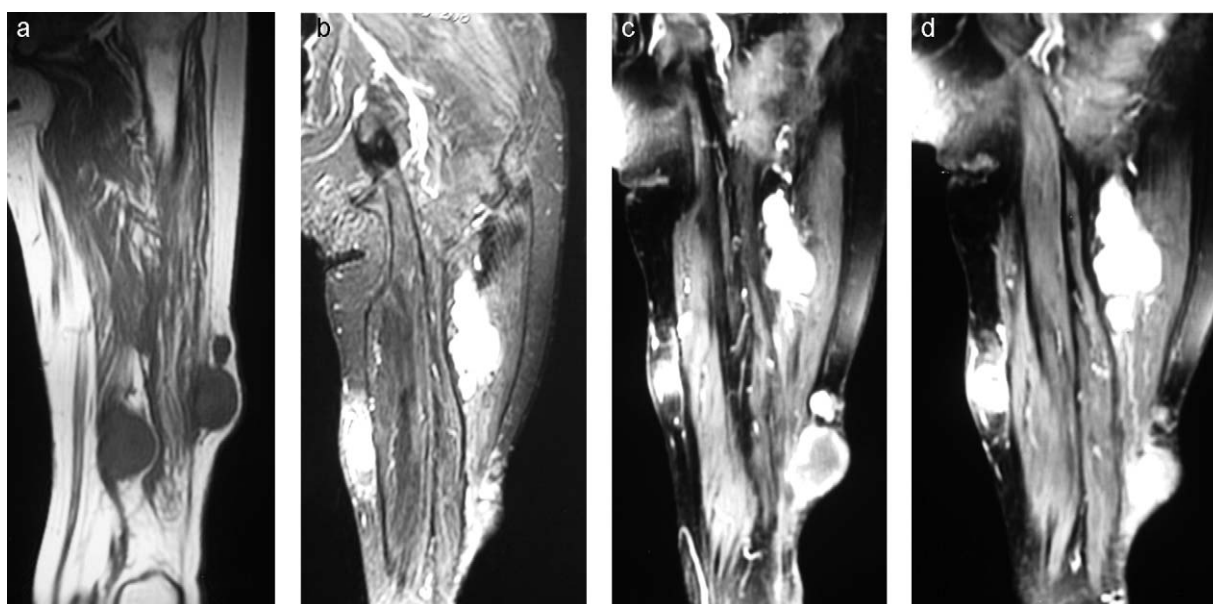
pleomorphic LPS most commonly occurs in the intramuscular space [1,2,3,4,5,6].

The term "Liposarcoma" does not imply that the tumor is derived from the fat but merely because of its lipomatous differentiation. The WHO has categorized soft-tissue liposarcomas into five distinct histologic subtypes: well-differentiated, myxoid, pleomorphic, dedifferentiated and mixed type. The round cell liposarcoma belongs to the myxoid subtype [1,6].

MR imaging is a valuable method for the detection of LPS. Besides MRI interest in the control of locoregional extension

(bone, soft-tissues and neurovascular involvement), its improved contrast-resolution allows proper differentiation of the tumor and identification of the specific histologic subtypes in some cases; such data are essential in establishing accurate therapeutic management and prognosis of these tumors.

Accurate diagnosis of these tumors is based on histologic data using biopsy guided by MRI findings, which should be performed prior to any therapeutic management. New immunohistochemistry techniques improve the accuracy of the therapeutic analysis thus providing a better diagnostic



**Figure 6** Multifocal recurrence of a pleomorphic LPS of the thigh in a 67-year-old female patient (case n° 18) of subcutaneous and intramuscular location. Well-delimited lobulated, heterogeneous lesions of low signal intensity on pT1-weighted images (a) and high signal intensity on pT2-weighted images (b) heterogeneously enhanced after injection of contrast agents (c and d) with no evidence of lipomatous component.

**Table 1** Clinical and topographic data, histologic diagnosis and extent of lipomatous component in 20 cases of LPS.

Case n°	Gender	Age (years)	Size (cm)	Location	Fat on MRI	Histologic diagnosis
1	M	47	20	Shoulder, intramuscular	+++	Well-differentiated LPS
2	F	47	5	Thigh, subcutaneous	+++	Well-differentiated LPS
3	F	68	10	Thigh, intramuscular	+++	Well-differentiated LPS
4	F	70	14	Thigh, intermuscular	+	Myxoid LPS
5	M	41	9	Thigh, intermuscular	+	Myxoid LPS
6	F	22	20	Thigh, intramuscular	+	Myxoid LPS
7	M	42	15	Thigh, intermuscular	+	Myxoid LPS
8	F	26	10	Thigh, intermuscular	+	Myxoid LPS
9	F	47	20	Thigh, intermuscular	+	Myxoid LPS
10	F	12	8	Thigh, subcutaneous	-	Myxoid LPS
11	F	24	12	Buttock, intermuscular	-	Myxoid LPS
12	F	30	8	Forearm, intramuscular	+	Myxoid LPS
13	M	49	8	Forearm, intermuscular	+	Myxoid LPS
14	F	61	10	Hand, intermuscular	+	Myxoid LPS
15	F	48	10	Thigh, intermuscular	-	Round cell liposarcoma
16	F	74	18	Thigh, intramuscular	+	Pleomorphic LPS
17	F	77	18	Leg, subcutaneous	-	Pleomorphic LPS
18	F	67	7; 6 and 6	Thigh, intramuscular and subcutaneous	-	Pleomorphic LPS
19	F	69	20	Thigh, intermuscular	++	Dedifferentiated liposarcoma
20	F	47	25	Buttock, intramuscular	+	Mixed-type LPS

of well-differentiated LPS, which, unlike lipoma, expresses MDM2 and CDK4 markers [7].

### Well-differentiated liposarcoma

Well-differentiated liposarcoma represents the most common type of soft-tissue liposarcoma, accounting for approximately 40 to 50% of all liposarcomas [1,6,8,9]. The rarity of well-differentiated liposarcoma in our series is explained by the fact that a great number of benign lipomatous lesions are operated on after echographic assessment without any MRI examination. This histologic subtype corresponds to a low-grade LPS with a predominantly adipose mass (over 75% of the lesion) with no metastatic potential and should be distinguished from lipoma [1,6,8,9]. According to Evans [10], well-differentiated LPS and atypical lipomatous tumor are identical in histologic, biologic and karyotype behavior. Any large lipomatous lesion is best considered a "well-differentiated" liposarcoma when located in areas which prevent any wide resection (in the mediastinum and retroperitoneum) while in other locations, the tumor is considered an "atypical lipoma" whether it occurs in the cutaneous tissues or within the intramuscular space.

The gross pathologic appearance of well-differentiated liposarcoma is that of a large well-circumscribed multi-lobulated mass with five histologic variants of which the lipoma-like is the most common [1,6,8]. Some sections of the tumor are composed of abundant mature adipose tissue that can appear identical to classic lipoma. However, other regions are focally punctuated by scattered lipoblasts

or cells with enlarged hyperchromatic nuclei representing lipocytic atypia (Fig. 1d). Moreover, immunohistochemistry techniques help distinguish lipoma from well-differentiated LPS, which expresses MDM2 and CDK4 markers unlike lipoma, which does not contain these genetic markers [1,6,7,10].

On MRI, well-differentiated LPS typically demonstrates a largely lipomatous mass representing over 75% of the lesion and nonlipomatous components in thick septa (> 2 mm) of irregular aspect or nodular foci. Nonlipomatous components may be larger but do not exceed 2 cm. The nonlipomatous component is MRI explored mainly on T1-weighted images. After gadolinium-enhancement on fat-saturated T1-weighted images, these areas are enhanced in a variable manner [1,6,8,9,11]. Due to this feature, well-differentiated LPS may appear identical to classic lipoma, which demonstrates abundant and homogenous adipose tissue in 48 to 71% of the cases, with thin septa (< 2 mm) and enhancement of lower signal intensity than in well-differentiated LPS.

In our three cases of well-differentiated LPS, MRI revealed within the lipomatous mass, thick linear nonlipomatous and sometimes nodular components thus providing diagnosis of this histologic subtype (Fig. 1).

### Myxoid liposarcoma

Myxoid liposarcoma is the second most common type of liposarcoma and represents 20 to 50% of all liposarcomas and 10% of all soft-tissue sarcomas [1,3,4,6].



The WHO classification of Soft Tissue Tumors has now combined myxoid and round cell liposarcomas. Myxoid liposarcomas are considered intermediate grade lesions if predominantly composed of myxoid tissue but high-grade lesions if they contain a substantial round cell component [1,6].

Regarding pathologic features, myxoid liposarcomas are well-circumscribed, multinodular masses whose gross histologic appearance varies depending on the degree of myxoid and round cell components. Predominantly myxoid lesions are gelatinous, composed of an abundant myxoid matrix with variable degrees of differentiation and a thin plexiform vascular network. The lipomatous component of relatively mature adipose tissue is not predominant (less than 10% of the whole tumor) and may be even absent [2,3,4,6,12].

Round cell tumors are hypocellular containing opaque white nodules made of round cells (which replace the myxoid stroma) and typically hyper-vascularized, which mimics the appearance of other soft-tissue sarcomas [6].

On MRI examination, myxoid liposarcoma consists of well-delineated lobules located in the intermuscular space, of low signal intensity with T1 weighting and marked high signal intensity with T2 weighting in relation to the adjacent muscle and corresponding to the predominant myxoid containing. The presence of linear, edented and even nodular areas of high signal intensity with T1 weighting produces a marbled and slight heterogeneous textural pattern. The mass was of high signal intensity on T2-weighted MRI images whereas the linear areas were of low signal intensity. These areas disappear after fat-saturation and correspond to the lipomatous component of the lesion. Fat also typically constitutes only a small volume of the overall mass size (<10% of the lesion) and identification of this subtle fat is aided by the careful comparison of T1- and T2-weighted images in the same plane (usually axial is optimal) and by use of fat-suppression techniques [1,3,5,6,12,13]. Among our 11 cases of pure myxoid LPS, a lipomatous component was observed in nine cases thus producing a characteristic marbled appearance on T1-weighted sequences. This appearance combined with a high signal intensity on T2-weighted images, contrast-enhanced images and tumor location in the intermuscular plane are very suggestive of myxoid LPS.

In about 20% of the cases, myxoid LPS may simulate a cystic mass with homogeneous signal on T1- and T2-weighted images. The presence of an abundant myxoid tissue increases the T1 and T2 relaxation times thus producing a water textural pattern. Gadolinium-enhanced T1-weighted images help confirm the solidity of the mass by demonstrating tumor enhancement which degree depends on cell density, tumor vascular pattern and the presence or not of necrosis. This diffuse or nodular, central or peripheral enhancement helps distinguish these tumors from other cystic masses [1,3,5,6,12]. Only two out of 11 cases from our series demonstrated such a pseudocystic appearance with no adipose tissue detected on MRI.

On the other hand, intratumoral calcifications are rare and should be analyzed with CT scan [1,5,13].

Myxoid LPS with round cells predominance has a less gelatinous appearance, with an intermediate signal intensity both on pT1 and pT2 sequences, demonstrating no septa or peripheral capsule while showing a pronounced

contrast enhancement. These areas may have non-specific features of solid tissue since the lipomatous component has rarely been described in this histologic subtype and diagnosis must only be confirmed by thorough histologic assessment [1,5,13]. Since our single case of round cell LPS demonstrated no lipomatous component at MRI, diagnosis was challenging.

### Pleomorphic liposarcoma

This is the least common subtype of LPS accounting for about 5 to 15% of all liposarcomatous lesions, arising in patients older than 50 years of age. These lesions are considered high-grade malignant tumors with a high degree of pleomorphic cells and less frequently containing adipose tissue. The gross pathologic appearance of pleomorphic liposarcoma is a large (>10cm), multinodular, white to yellow mass containing myxoid and necrotic areas [1,6,10,13].

The radiographic appearance of pleomorphic LPS is typically that of a nonspecific soft-tissue mass. MR imaging usually reveals a relatively well-defined mass, although infiltrative margins may also be seen on adjacent soft-tissues. Areas of necrosis and hemorrhage are frequent and account for the prominent heterogeneity seen in these lesions. Compared with other types of liposarcoma, pleomorphic liposarcoma less frequently contains adipose tissue, (in our series only one out of three cases presented a small amount of adipose tissue). This feature also makes the imaging diagnosis more difficult [1,6,9,12,13]. On the other hand, the signal intensity of the adipose component – if present – may be slightly less than that of subcutaneous fat, which allows differentiation with intra tumoral hemorrhage after using a fat-suppression technique [6].

Pleomorphic liposarcoma has a marked propensity for tumor recurrence and metastatic disease. Among the three cases of our series, one recurred 3 years after excision, one presented with pulmonary metastases at the time of diagnosis and the 3rd one was discovered after multifocal recurrence associated with metachrone bone metastases.

### Dedifferentiated liposarcoma

Dedifferentiated liposarcoma is a rare subtype of liposarcoma of high-grade malignancy, representing a biphasic neoplasm combining well-differentiated components with dedifferentiated ones. This LPS has a delayed occurrence in the evolution of a well-differentiated LPS.

A dedifferentiated liposarcoma shares radiologic features with a well-differentiated LPS associated with or juxtaposed on a nonlipomatous mass. This latter has a typically non-specific appearance frequently containing areas of hemorrhage and necrosis whereas the lipomatous component is of small abundance (<25% of the whole mass volume) [1,4,6,12,14]. In our series, only one case of dedifferentiated liposarcoma was identified, the MRI data correlated those published in the literature thus allowing diagnosis of this subtype of liposarcoma.

### Mixed-type liposarcoma

The mixed-type liposarcoma represents a combination of two histologic subtypes of liposarcoma within the same

tumor. It accounts for 5 to 12% of all liposarcomas and most frequently affects older patients. The extremities are rarely involved, common sites of involvement being the retroperitoneum, abdominal cavity and mediastinum. The pathologic and imaging features are a combination of the specific components of the lesion [1,6,13,15].

Whatever the subtype, LPS treatment depends on its grade of histologic malignancy, its location and the presence of metastases. It consists of a surgical excision of the tumor including a cuff of surrounding healthy tissue beyond the margin of the lesion indicated by MRI, which could appear wrongly reassuring. Healthy resection margins are a vital condition for prognosis and should be pathologically confirmed. In low grade LPS, surgical excision is sufficient in case of subcutaneous location of the tumor. However, adjuvant radiation therapy should be implemented in deep-seated lesions according to the degree of tumoral extent and where wide excision is compromised due the proximity of the adjacent neurovascular structures, to prevent the risk of any local recurrence. High grade LPS, due to their metastatic potential, should be treated with wide surgical excision associated with adjuvant chemotherapy and local radiation therapy [16,17,18].

## Conclusion

The MRI features of soft-tissue liposarcomas vary according to the wide spectrum of pathologic appearances. MRI, with fat-saturated T1-weighted images and gadolinium-enhanced sequences, is a valuable method which helps distinguish LPS from other types of soft-tissue lesions by detection of an adipose component commonly reported in these tumors. These data may be sufficiently characteristic to provide specific diagnosis of the subtypes of liposarcomas (well-differentiated, myxoid, dedifferentiated). Imaging findings contribute to the final histologic diagnosis of these tumors and can be used to orientate the biopsy, which should be performed on both the lipomatous and nonlipomatous components. The histologic analysis should be combined with recent immunohistochemistry techniques which are now nearly mandatory, to confirm the diagnosis of LPS, particularly in the well-differentiated subtype through the research of MDM2 and CDK4 markers.

## Conflict of interest statement

No conflict of interests.

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