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REVIEW ARTICLE

Multicentric liposarcoma

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Liposarcoma is one of the most common malignant soft tissue tumours. It usually presents as a single mass, and the prognosis varies according to the degree of histological differentiation. Multicentric liposarcoma is an unusual presentation of this tumour in which several independent lesions develop and generally display an aggressive pattern. It may be difficult to establish a precise diagnosis because of the problems differentiating between recurrence or metastasis of a single liposarcoma and multicentric primary lesions. A systematic review was undertaken, assessing articles on multicentric liposarcoma, with emphasis on the diagnostic criteria and treatment for this condition. Illustrative cases of multicentric liposarcoma from our Institution are presented.

Keywords : liposarcoma ; multicentric ; multicentric liposarcoma.

INTRODUCTION

Liposarcoma is a common malignant soft-tissue tumour, accounting for 10% to 16% of all sarcomas. It typically affects patients between the fifth and seventh decade of life, and usually develops in the extremities or retroperitoneum (*16*). Liposarcoma has a clinically indolent course and is often diagnosed when it has reached a large size. The recommended treatment is surgical excision, which can be associated with radiotherapy or chemotherapy (*5,16*).

Several subtypes of liposarcoma have been described, depending on the degree of histological differentiation, including well-differentiated, myxoid, round cell, dedifferentiated, and pleomorphic liposarcoma (*6*). Well-differentiated liposarcomas are the most common, accounting for 40% to 60% of cases ; myxoid liposarcoma affects one third of patients with this condition, round cell liposarcoma (a myxoid type with more than 10% of round cells) affects around 10%, and pleomorphic liposarcoma represents 5% of cases (*5*). The myxoid and round cell types present the same chromosome translocation, t(12;16) (q13;p11), which determines formation of the CHOP fusion gene. This is not seen in the other subtypes, and for this reason, the World

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Health Organization (WHO) now considers these types to be a continuum of the same disease (*3,5,6,8*). Pure myxoid and pure round cell liposarcomas would represent the extremes of the spectrum of low- to high-grade tumours, with all possible degrees of transition. These tumours are considered high-grade when they show more than 5% of round cells (*6*).

The prognosis of liposarcoma depends on several factors, such as the histologic type, size of the tumour, areas of necrosis, and presence of metastasis or recurrences. Well-differentiated tumours do not present metastasis, and local recurrence is infrequent (10%). In high-grade liposarcoma, however, metastasis has been described in 20% to 36% of cases (*3,5,10*).

Multicentric liposarcoma is an unusual presentation form of this disease, in which several independent liposarcomas occur simultaneously or at different time points. Multicentric liposarcomas can have an aggressive pattern and require a different therapeutic approach (*1,4,13*).

METHODOLOGY

Literature search

A systematic review was done assessing the electronic database Medline (1960 to January 2010) for original articles, series and case reports of multicentric liposarcoma. The database was searched with the terms "Multicentric liposarcoma", "Multifocal liposarcoma" and "Multiple liposarcoma", with less than 50 references referring to this condition, and most in the form of case reports.

Definitions

– *Multicentric sarcoma :* This term is used to refer to malignant tumours occurring in two or more different anatomic locations, before affecting the usual regions where sarcoma metastasizes, mainly the lung (*5,8,10*).

– *Multicentric liposarcoma :* Sato *et al* (*12*) defined multicentric liposarcoma as a lesion that develops in any of the typical locations of primary liposarcoma, such as the thigh, retroperitoneum, arm or pleura, without metastasis to conventional areas (lung, liver, or bone), having a differentiated histologic type, and moreover, found in association with a lipoma.

Chronology

Many authors agree that if the lesions do not occur simultaneously, the time interval between their development must be long. Intervals of 5 to 10 years between the development of tumours have been cited as suggestive of multicentric liposarcoma, in contrast to the tendency of myxoid and high-grade liposarcomas to produce metastasis during the first 6 months after removal of the primary tumour (*7,11-13*).

Cytogenetics

The use of cytogenetic techniques enable the identification of characteristic markers for sarcomas, the most specific being the t(12;16) (q13;p11) translocation for liposarcomas, which is seen in the myxoid and round cell subtypes (*9*). These techniques can also be useful to recognize or rule out a clonal relationship between two lesions.

ILLUSTRATIVE CASES

Case 1

A 37-year-old man consulted for a mass of several months' evolution in the anterior aspect of the left thigh. Magnetic resonance imaging (MRI) showed a 5 × 7 cm lesion consistent with low-grade liposarcoma and malignant fibrohistiocytoma. Complete surgical removal and subsequent adjuvant radiotherapy was carried out. Histologic study diagnosed a round-cell liposarcoma (high-grade myxoid type with 40% of round cells) with free margins. The follow-up studies, including computed tomography (CT) scanning to investigate bone involvement, chest radiographs, and MRI of the thigh region, did not detect other disease foci. Seven years after surgery, the patient presented symptoms of radiculopathy, and MRI showed a lytic lesion at S2 with extension into the spinal canal. Biopsy study identified a

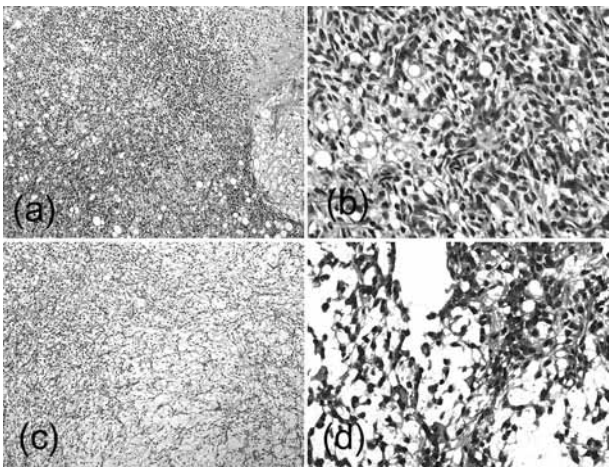

Fig. 1. — Case 1.
(a) Pattern of myxoid liposarcoma with increased cellular density and scarce lipoblasts (HE 40×).
(b) Detail of the round cell component, with some atypical mixed lipoblasts (HE 250×).
(c) Panoramic view of the recurrent lesion showing a lax myxoid pattern with slight increase of the cellular density (above, left) (HE 40×).
(d) S-100 stain shows the adipocytic nature of the cells. S100 250×.

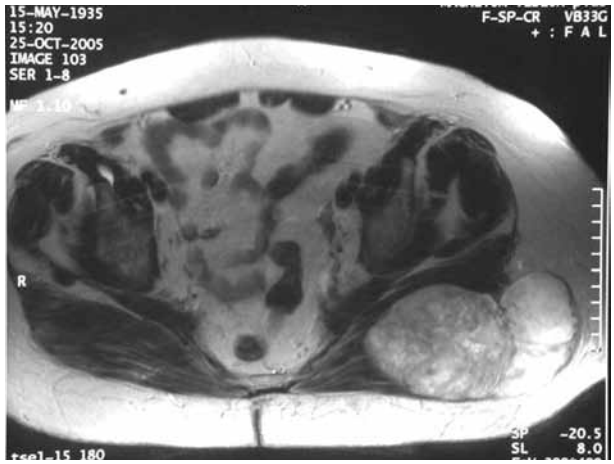

Fig. 2. — MRI image showing a mass in the medial area of the left thigh of 3 months' evolution (Case 2).

round-cell liposarcoma (40% round cells) (Fig. 1). Laminectomy with tumour excision was performed, and later, radiotherapy (DT 63 Gy/35 Fr) and chemotherapy (6 cycles of epirubicin-ifosfamide). Eighteen months after the second surgery, follow-up study disclosed several lesions at the sternum, ribs, and base of the skull, the latter causing symptoms of ocular paralysis. The patient was treated with radiotherapy (DT 30 Gy/10 Fr) and chemotherapy (4 cycles of trabectedin). Two years after the second surgery, he presented weakness of the lower limbs suggestive of cord compression. A mass was found at the second thoracic vertebra that required urgent decompression and radiotherapy (DT 30 Gy/10 Fr). Despite this treatment, the patient died one month later.

Case 2

A 59-year-old woman consulted for a 15-cm diameter mass in the medial area of the left thigh of 3 months' evolution (Fig. 2). Imaging studies and arteriography of the thigh were negative and surgical removal was carried out based on a suspected diagnosis of liposarcoma (Fig. 3). Histology identified round cell liposarcoma (myxoid with 50% round cells) with free resection margins (Fig. 4) ; adjuvant radiotherapy and chemotherapy were performed. Ten years after surgery, a 15 cm mass was detected in the ipsilateral gluteal area and biopsy was undertaken. Histological study again identified round cell liposarcoma (20% round cells and 15% necrosis), which was surgically removed with subsequent radiotherapy (45 Gy/25 Fr and 63 Gy/35 Fr). Two years after the second surgery, a 3 cm subcutaneous lesion appeared in the inframammary area, which proved to be round cell liposarcoma on biopsy study (70% round cells). Surgical removal of the mass confirmed the diagnosis and adjuvant radiotherapy was carried out (DT 63 Gy/35 Fr). One year after the last surgery, follow-up studies showed no signs of disease.

Case 3

A 44-year-old man underwent surgical removal of a 20-cm tumour of several months' evolution in the posterior area of the thigh, with no signs of extension on abdominal/pelvic CT. Histology reported high-degree myxoid liposarcoma with 40% round cells (Fig. 5), and local radiotherapy (63 Gy/35 Fr) was performed. Two years after

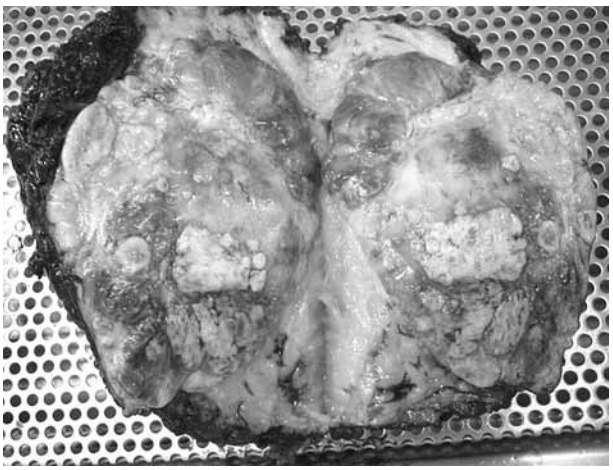

Fig. 3. — Macroscopic view of the tumour after the surgical procedure (Case 2).

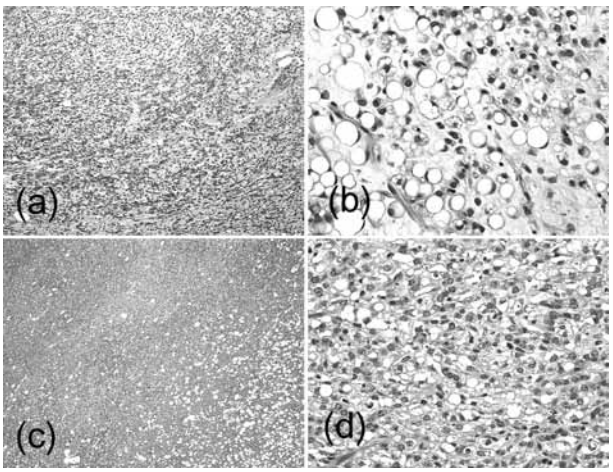

Fig. 4. — Case 2
(a) Pattern of myxoid liposarcoma with diffuse round cellularity (HE 40×).
(b) Presence of atypical lipoblasts and lipocytes with some round cells (HE 250×).
(c) In the recurrent lesion, the pattern is similar to that of the first tumor (HE 25×).
(d) At higher magnification, similar pattern, with atypical lipoblasts and lipocytes (HE 100×).

surgery, a tumour appeared in the lateral aspect of the arm, which proved to be round cell liposarcoma (50% round cells) on biopsy study. Multiple intramuscular lesions were found in the area of the pelvis, as well as a hepatic mass. Chemotherapy

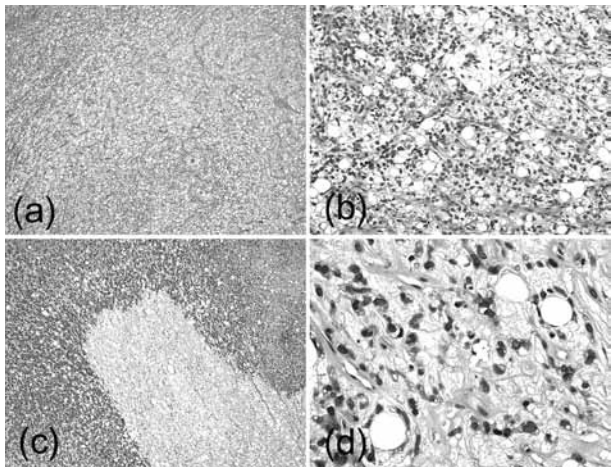

Fig. 5. — Case 3
(a) Panoramic view of the first lesion ; myxoid type with scarce increase of cellular density (HE 25×).
(b) Presence of atypical lipoblasts and lipocytes (HE 100×).
(c) In the recurrent lesion an area of predominantly round cells is seen (HE 25×).
(d) Detail of round cells with atypical lipoblasts (HE 250×).

and radiotherapy were started, but the patient died a few months later.

In all 3 patients, t(12;16) (q12;p11) translocation was proven by fluorescence *in situ* hybridization (FISH), which detected the CHOP fusion gene (Table I).

DISCUSSION

The first description of multicentric liposarcoma was made by Siegmund in 1934 (*14*) ; since that time, less than 50 cases have been described, mainly in clinical case studies. Because of the low incidence of this condition, the aetiopathogenesis is controversial, with disagreement regarding whether it is a condition involving multiple primary tumours or a single liposarcoma with an unconventional pattern of metastasis (*1,4,8,12,13*).

The diagnosis of multicentric liposarcoma is not well established, the main problem being differentiation between multiple primary lesions and metastasis of a single liposarcoma. One criterion used to define multicentric liposarcoma is the presence of tumours in areas where metastasis does not usually occur ; hence, it is important to be familiar with the

Table I. — Locations, histological types, and chronology of the tumours occurring in each patient

	CASE 1	CASE 2	CASE 3
Primary location	Thigh	Thigh	Thigh
Primary histology	MX/RC	MX/RC	MX/RC
Secondary location	Vertebra	Gluteus	Arm
Secondary histology	MX/RC	MX/RC	MX/RC
Latency time	7 years	10 years	2 years
Other locations	Skull base Sternum Ribs	Inframammary	Intrapelvic Liver

Abbreviations : MX/RC = myxoid/round cell.

pattern of extension of liposarcoma. The most common site of sarcoma metastasis is to the lung. However, myxoid liposarcoma often produces lesions in other regions, such as in the retroperitoneum, mesentery, bone, and soft tissue of the trunk and glutei. This unconventional extension pattern of myxoid liposarcoma adds difficulty to the diagnosis of multicentric tumour because primary and metastatic locations can coincide (*2,5,8,10*). Thus, when investigating extension of liposarcomas, particularly the myxoid type, the retroperitoneum and trunk should be examined in addition to the thorax. Furthermore, when retroperitoneal liposarcoma is detected, the presence of sarcomatosis lesions in the extremities should be ruled out.

The most common histologic subtypes presentations of multicentric liposarcoma are myxoid and round cell. These subtypes are also known to produce local and distant recurrence most frequently (*3-5,8,16*). As mentioned above, the WHO considers the myxoid and round cell types as a spectrum of the same disease ; different histological subtypes are indeed sometimes found in distant anatomic locations (*1,13*).

Advances in cytogenetic techniques have enabled identification of the characteristic markers for liposarcoma, the most specific being the t(12;16) (q13;p11) translocation, which is seen in the myxoid and round cell subtypes (*9*). The presence of abnormalities in this translocation is unusual, and its identification in a primary liposarcoma and in other coexistent lesions has been used by several authors as an indication of the multicentric origin of the tumour (*1,13*). Detection of the same cytogenetic anomalies in different sarcomas is not considered indicative of metastatic spread by some authors ; instead they propose that this finding could be related with a common aetiologic factor, such as a systemic illness or toxicity (*4,10,13,15*).

The treatment of choice for liposarcoma is surgical removal, which can be combined with radiotherapy and chemotherapy depending on the histological type, the surgical margins obtained in the resection, and the presence of other concomitant lesions (*4*).

The prognosis of liposarcoma is mainly related to the histological subtype. Ten-year survival in well-differentiated and myxoid tumours is greater than 95% whereas in high-grade tumours (round cell and pleomorphic), it is around 60% (*3*). Multicentric liposarcomas are described to have a more aggressive progression pattern ; hence the newer and more intensive radiotherapies and chemotherapies may be more appropriate to use with surgery (*4,5,8*).

In the illustrative cases, Patient 1 presented a new bone lesion 7 years after the initial treatment. The histological subtype coincided with the first liposarcoma, and within a few months, several lesions had developed in various locations, with a fatal outcome. Although the disease features in this patient are in keeping with the definition of multicentric liposarcoma, they could also fit with recurrence of the primary tumour some years after the initial treatment and metastasis in the most aggressive form of this disease. In Patient 2, the second liposarcoma was detected 10 years after the initial tumour and it had an apparently less aggressive morphological pattern than that of the first lesion. However, the third presentation disclosed a harmful nature. In Patient 3, several lesions in the typical locations of primary liposarcoma were diagnosed two years after the initial treatment. These were more aggressive and had affected the liver, a typical site of sarcoma metastasis. In all three cases, the

diagnosis of myxoid/round cell liposarcoma was confirmed by molecular biology.

CONCLUSIONS

Multicentric liposarcoma is an uncommon condition with a controversial diagnosis. Differentiation between several primary tumours and metastasis of a single liposarcoma represents the main difficulty in diagnosis. The metastatic pattern of the myxoid subtype, the most common form seen in multicentric liposarcoma, differs from that of other sarcomas, with lesions occurring at unusual distant locations, several years after the initial diagnosis. Because the myxoid and round cell forms constitute a spectrum of the same condition, various histological forms of liposarcoma may be found in metastasis of a tumour. For this reason, the criteria currently used to define a liposarcoma as multicentric can be explained by the special features inherent to liposarcoma and not by the fact that it is a different clinical entity.

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