Multifocal liposarcoma. Detection of *TLS-CHOP* translocation. A case report

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Liposarcoma muilticéntrico. Detección de la translocación *TLS-CHOP*. A propósito de un caso

Se dice que un sarcoma es multicéntrico cuando es detectado en dos o más localizaciones anatómicas diferentes antes de que se extienda a regiones donde es más frecuente encontrarlo como metástasis. Un aspecto controvertido y no demostrado de esta enfermedad es si este patrón de presentación se debe a un origen multicéntrico o, por el contrario, se trata de una forma rara de metástasis cuya causa se desconoce.
Nuestro objetivo es exponer un cuadro clínico compatible con un caso de liposarcoma multicéntrico. Se ha realizado además un estudio de la translocación *TLS-CHOP* para intentar verificar el origen metastásico o no de las masas.

Palabras clave: *liposarcoma, multicéntrico, multifocal, translocación.*

A sarcoma is said to be multicenter when it is detected in two or more different anatomical locations before it extends to regions to which it most frequently metastasizes. However it is not clear and still a matter of controversy whether this presentation of the disease is due to a multicenter origin or whether, on the other hand, it is a rare metastatic form whose cause is still unknown.
Our purpose is to present a clinical case that is compatible with the description of multicenter liposarcoma. In addition, a study of *TLS-CHOP* translocation was carried out to confirm the alleged metastasic origin of the disease.

Key words: *liposarcoma, multicenter, multifocal, translocation.*

INTRODUCTION

Multifocal soft tissue sarcomas (STS) are a rare pathological entity seen in approximately 1% of all STSs[1,2]. A STS is defined as multifocal when it appears in two or more different anatomical locations before extending to regions where it is more frequently found as a metastasis, such as lungs, liver and bones[1-3]. A controversial and not yet demonstrated issue is whether this presentation pattern is of true multifocal origin due to spontaneous transformation of cells in different locations into tumor cells or, on the contrary, if it is a rare form of metastasis of unknown cause[1-3].

CASE REPORT

We present a case of a 28 year old woman who came to the Urology Service of the hospital with a clinical condition of 6 months evolution, with a sensation of abdominal fullness, accompanied by great discomfort, early satiety and progressive loss of weight.

During physical examination a hard mass was found within the abdomen, on the right side. An abdominal CT of the abdomen was performed, amongst other tests. A large expansive lesion was seen in the right retroperitoneum. This tumor compressed the liver, the vena cava and the right kidney (Figure 1A). A fine needle aspiration biopsy (FNAB) of

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the mass was performed and was reported as compatible with sarcoma.

The patient was operated in September 2001 by the Urology Service of her referring center and a mass was removed that measured 32 x 22 x 16 cm. During this operation right kidney nephrectomy was performed due to tumor infiltration of the kidney. A biopsy of the tumor was reported as myxoid liposarcoma grade II.

During the second week of the postoperative period the patient presented neuropathic pain that progressed slowly until it became established in the left thigh, leg and foot. Within a few days there was a motor impairment of the limb compatible with a sciatic nerve lesion. On physical examination a large tumor was found in the posterior part of the left thigh and another 2.5 cm tumor was found at the base of the neck on the right and another 4 cm tumor was found in the left axilla.

A new CT was performed and a large mass was found to occupy the posterior compartment of the thigh and including the sciatic nerve (Figure 1B). The presence of the 2 masses at the base of the neck and in the axilla was also confirmed. The FNAB of these lesions were reported as compatible with sarcomas.

The patient was referred to our center for oncological treatment with a diagnosis of myxoid liposarcoma stage 4.

Neoadjuvant therapy was carried out with 6 cycles of adriamicine, a good response was achieved, and the volume of all masses was reduced.

In April 2002 a wide resection was carried out of the tumor in the posterior compartment of the thigh that included part of the left major sciatic nerve; it was necessary to partially resect this nerve. The histology report on the resected 15 x 13 x 8 cm specimen was of a well differentiated myxoid chondrosarcoma, with extensive areas of necrotic tissue and very few mitosis. Given her good response, we decided to continue administering chemotherapy to the patient, and when reviewed in January 2003 she presented remission of all masses; so controls were continued without treatment.

At the time of the December 2003 follow-up visit, tumor growth was observed in the left groin (at the base of the *Scarpa triangle*), in the left hemithorax (rib cage, below the *pectoralis major*) and in the right hemithorax (rib cage, below the angle of the scapula and below the *latissimus dorsi*). In view of the circumstances we decided to once more administer chemotherapy and consider the possibility of surgery according to the patient's evolution. As before, the patient responded very favorably to treatment and there was volume reduction of all tumors.

From January to August 2004 we lost track of the patient and she was neither treated nor controlled by the Medical Oncology Service.

Up to that time the patient had shown a very good response to chemotherapy and we were assessing the possibility of performing a resection of the tumor in the left *Scarpa* triangle.

In August 2004 the patient returned to the Medical Oncology Service for a clinical exam. New CTs were taken and significant growth was seen of all tumor masses known to be present during previous exams (left groin, left pectoral and right subscapular region), the most marked being that of the left groin (Figure 1C). Examination was completed with an extension study that showed the patient was still free of metastasis in lung, liver, bones and other structures.

A new chemotherapy cycle was administered and the response was once more favorable with volume reduction of all masses.

In October 2004 the mass in the left groin was removed, it measured 14 x 10 x 8 cm.

The biopsy was reported as a round cell liposarcoma grade II. The patient continued to undergo chemotherapy, and this controlled the growth of the tumor masses until May 2006; at that time we decided to remove the right subscapular mass (Figure 1D). The histological diagnosis of the specimen (15 x 11 x 5 cm) was dedifferentiated liposarcoma with areas of chondroid degeneration grade 3, compatible with round cell liposarcoma. Chemotherapy was continued after this operation.

During a new CT control in June 2006 a new mass was found in the gluteal region of the right thigh, immediately behind the trochanteric area of the femur (Figure 2A). The patient was operated again in October 2006 and a 12 x 12 x 5 cm tumor was removed (Figure 2B). On pathological exam the tumor was seen to have the histology of a dedifferentiated liposarcoma compatible with round cell sarcoma.

In June 2007 the patient once more underwent surgery and a tumor of 8 x 7 x 6 was removed from the left pectoral region. The diagnosis of this tumor specimen was myxoid liposarcoma.

Currently (October 2007) there has been no recurrence at the operated sites nor any further metastasis. The patient comes to periodic controls at the Oncology Service and leads a normal life, taking into account the sequelae due to tumor growth, chemotherapy and operations performed: right kidney nephrectomy (although currently of no clinical significance but which may condition future therapy it the patient's renal function is impaired), and the paralysis of the sciatic nerve, which was infiltrated by the left thigh tumor and had to be partially resected.

Detection of *TLS-CHOP* translocations

The genetic hallmark of myxoid liposarcomas (MLS) is t(12;16)(q13;p11) translocation, it seems to be highly specific for this type of tumors and is present in more than 85% of cases. This translocation causes rearrangement of

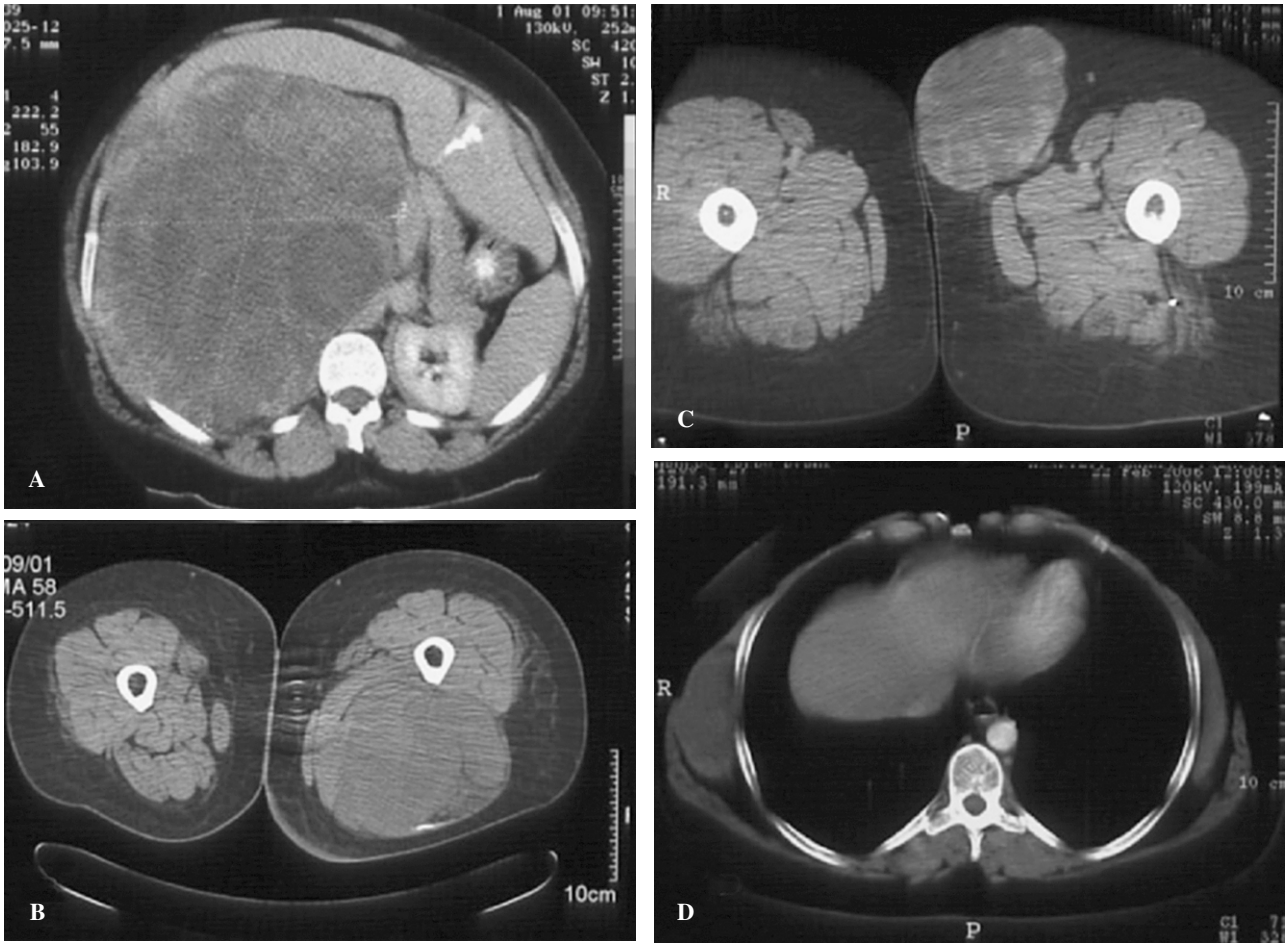

Figura 1. *(A) Abdominal computed tomography in which it is possible to see the first tumor diagnosed in the patient that was located in the retroperitoneum on the right side and that caused compression and displacement of all viscera to the opposite side. (B) CT image of the tumor located in the posterior region of the left thigh that includes part of the sciatic nerve. (C) CT of the proximal third of the thigh in which it is possible to see the tumor located at the base of the Scarpa triangle on the left side. (D) CT of the chest in which it is possible to see the tumor located in the right hemithorax immediately below the latissimus dorsi.*

the *CHOP* and *TLS* genes (also known as *FUS*) at 12q13 and 16p11, respectively, generating a hybrid gene *TLSCHOP* that encodes an aberrant transcriptional regulator[3,4].

It has recently been confirmed that there is a strong specificity of TLS-CHOP genetic rearrangement for myxoid and round cell liposarcoma[4].

As in other translocations, the genome rupture points for the t(12;16) translocation are spread out in specific introns of the TLS and CHOP genes, and determine the genetic differences between tumors. Therefore, it has been suggested that if the clone origin of the cells of each multifocal liposarcoma in a patient is determined, it would be possible, if the cell clone were the same[3,5], to know if they are of metastatic origin.

In the Molecular Oncology Laboratory of the Central University Hospital of Asturias a molecular study was performed of the tumors removed from the patient described above. For this study samples of frozen tissue from the Tumor Bank and the Pathology Service of our center were used. The aim of the study was to determine if all the tumors presented a t(12;16) translocation, since in the histological studies of the specimens it was not possible to determine with certainty if all were liposarcomas. We also wished to determine if the location of the translocation in the DNA was the same in all the tumors, so as to consider the possibility that the origin of all tumors was one single cell clone. We were not able to use material from the first tumor removed, because the operation had taken place in another hospital.

The result of this study was that all specimens analyzed showed the same *TLS-CHOP* translocation in the same DNA segment, we therefore think that the most probable origin of the patient's tumors is monoclonal, therefore: in all cases the tumors were myxoid liposarcomas and derived from the same cell clone.

DISCUSSION

Multifocal STS has been intermittently described in the literature since the first years of the XX century, the first known report was that of Siegmund in 1934[6]. The first references are based on data from autopsies, so there is little information on the clinical aspects of the disease[1,6,7]. The largest series in the literature is one of 20 cases published by Enzinger and Winslow in 1962 based on data from the *Armed Forces Institute of Pathology*, but without clinical follow-up[7]. More recently, data of clinical cases has been published that makes it possible to clarify some controversial aspects of this condition[1,8,9]. Up to the year 2000 there were less than 50 cases described in the literature[1,3].

Liposarcoma is the most frequent histology identified in multifocal STSs, and within these, the most frequent variety seen are myxoid liposarcomas (Figure 2C)[3,7].

Myxoid liposarcomas are also the most frequent subtype of liposarcoma, and, according to different series, constitute 50% of cases[3]. These tumors have a tendency to recur locally and approximately in a third of cases develop distant metastasis[3]. Amongst this type of tumors it is frequent to observe progression to histologically less differentiated tissue: round cell sarcoma (Figure 2D). This type of histology is associated with a much worse prognosis than that of a myxoid, which is already poor[10,11].

According to published data solitary STSs have an incidence of pulmonary metastasis of 21% and a survival rate at 5 years of 75%[1,12-14]. Patients with multifocal STSs have an incidence of lung metastasis of 63% and a survival rate at 5 years of 36%[1]. Therefore, we can state that patients with multifocal STSs clearly have a worse prognosis than patients with solitary lesions, as was to be expected.

One thing that is striking about the patient we have presented here is that it is now 5 years since the first tumor was detected. Since then up to 5 large sized masses were detected that have been removed (posterior compartment of the

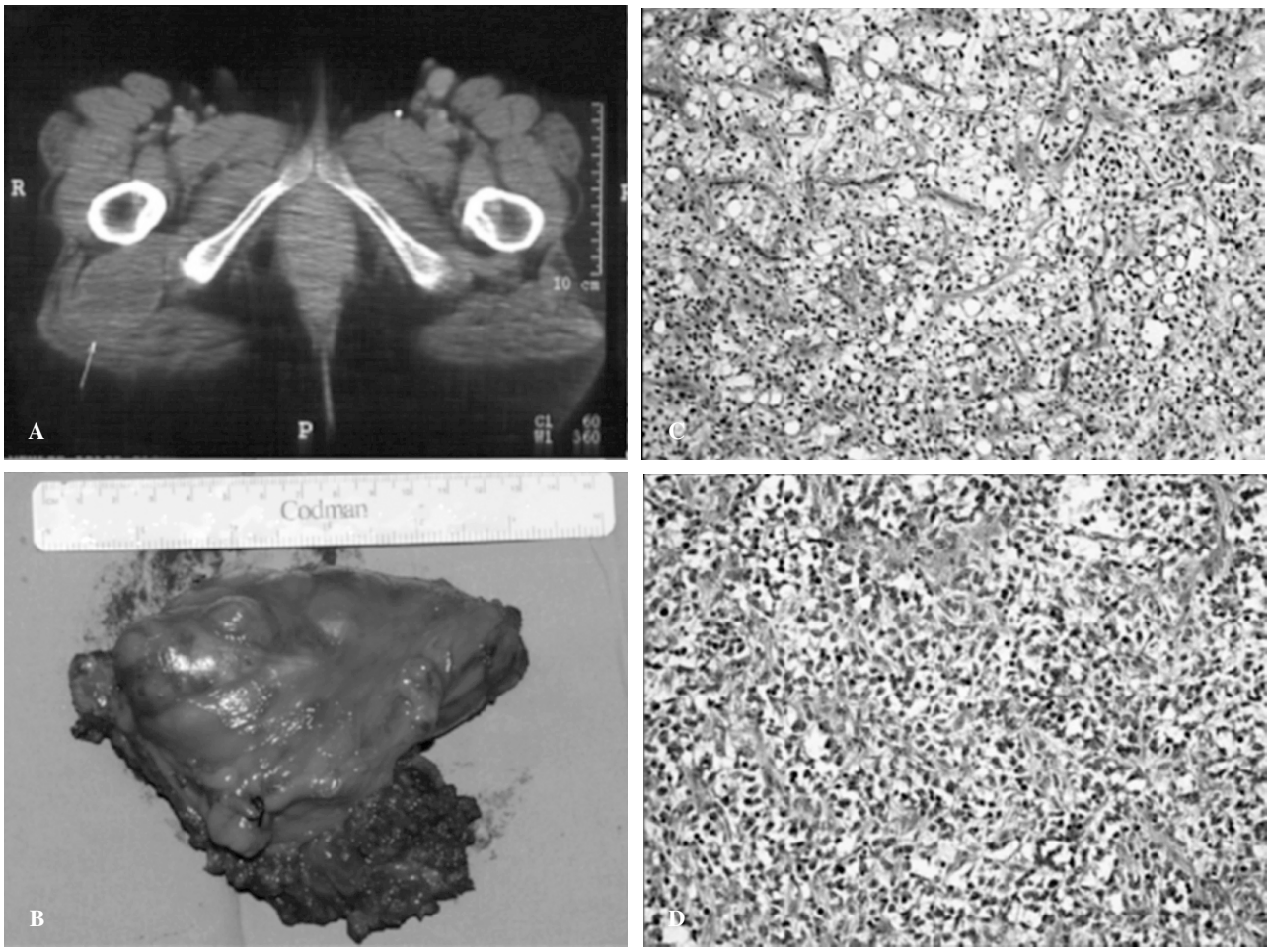

Figure 2. *(A) Computed tomography (CT) of the pelvis in which it is possible to see the tumor located in the patient's right gluteal region. (B) Image of the specimen removed by surgery from this lesion. (C) Histology of the myxoid liposarcoma (x20). (C) Histology of the round cell liposarcoma (x20).*

left thigh, left groin, right hemithorax, right gluteal region, left pectoral region), with a histology in all cases compatible with high grade liposarcoma. With the exception of the complications caused by chemotherapy and the sequelae due to local tumor growth, the patient is in an optimum general condition and can lead a normal life.

We attribute the prolonged survival of this patient to her good tolerance of and response to the chemotherapy she underwent (adriamicine, caelyx and gemitaline) and to the fact that she did not develop bone or visceral metastasis.

Furthermore, the operations performed made it possible to eradicate the tumor from different locations.

Based on clinical and pathological data alone it is difficult to determine in each specific case if a tumor located in an unusual place for a metastasis, but usual for a primary tumor, is a metastasis or a second primary. In the case of this disease, the only way to differentiate a multifocal from a metastatic origin is to carry out molecular and genetic studies[3].

The study carried out by Antonescu et al[3] established the monoclonal origin of the tumors found in each patient in 6 cases of multifocal STSs, which were in all cases myxoid liposarcomas. In our study we used a different laboratory strategy, but which led us to the same conclusion as Antonescu et al[3] who considered metastasis the most probable option.

All the tumors removed from the patient in our center provided us with specimens that had the same genetic translocation in the same DNA segment. On one hand, therefore, it was confirmed that tumor cell genetic material from all the resections was that of a myxoid liposarcoma.

The explanation of why the pathologists did not in all cases diagnose myxoid liposarcoma is due to the fact that the tumor in this case was aggressive in behavior and progressed rapidly to histological types with greater cellularity; from a myxoid liposarcoma it progressed to a round cell liposarcoma[10]. On the other hand, the second tumor treated at our center was identified as a chondrosarcaoma due to the fact that it contained extensive areas of cartilage.

A review of the histological sections of this specimen carried out by the pathologists at our center led to the conclusion that chemotherapy had caused cartilage metaplasm within a myxoid liposarcoma, which led to an initial misleading diagnosis.

The fact that in all the tumors analyzed the translocation was in the same DNA segment leads us to think that we are in the presence of the same cell clone, that is to say, that metastasis originated from a primary tumor, in the same way as has been described by other authors who studied similar cases[3].

The difficulty in proving the true pathophysiology of multifocal sarcomas lies in their low frequency, which makes it impossible to study series of patients in sufficient numbers. Recent studies based on molecular biology analysis show that the most likely process is metastasis from a primary tumor[3].

However, it is still necessary to determine the property that causes this strange metastasis pattern in which tumors spread throughout the body without affecting the organs which are theoretically most susceptible. It is likely that the tumor cells have a lower affinity for lung tissue for some reason unknown to us, but we must not rule out mere chance. We consider further future studies are necessary.

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Conflict of interests

The authors have declared that they have no conflict of interests.