

CASO CLINICO

PERSPECTIVAS CLÍNICAS EN UN CASO SINGULAR DE LIPOSARCOMA DE PARED TORÁCICA: DIAGNÓSTICO Y ESTRATEGIAS TERAPÉUTICAS

CLINICAL PERSPECTIVES IN A SINGULAR CASE OF CHEST WALL LIPOSARCOMA: DIAGNOSIS AND THERAPEUTIC STRATEGIES

Marcel Leonardo Quintero Contreras¹, Mónica Kathalina Rodríguez Perdomo²,
Santiago Uzcátegui Parra³

Recibido: 15 de marzo de 2024.

Aprobado: 15 de mayo de 2024

RESUMEN:

Introducción: Los liposarcomas (LPS) son un tipo de cáncer que se desarrolla en los tejidos blandos y se caracteriza por derivar de células grasas. Principalmente se dividen en dos subtipos: bien diferenciado (WDLPS) y des diferenciado (DDLPS), ambos conocidos por su resistencia a los tratamientos convencionales. Se presenta el caso de una mujer de 57 años con historial médico de obesidad y hernia discal, quien experimentó un aumento progresivo en el tamaño de una masa en su hemitórax izquierdo, acompañado de disnea y dolor torácico. La evaluación diagnóstica, que incluyó ecografía, tomografía de tórax y resonancia magnética, fue esencial para tomar decisiones terapéuticas adecuadas. La paciente fue sometida a una cirugía exitosa para extirpar la masa, confirmándose luego el diagnóstico de liposarcoma bien diferenciado mediante análisis patológico. **Caso clínico:** Este caso clínico enfatiza el papel crucial de la cirugía en el tratamiento de liposarcomas localizados, con el objetivo de lograr una resección completa y mejorar la calidad de vida del paciente. La variabilidad en la respuesta a los tratamientos convencionales destaca la importancia de evaluar individualmente el perfil molecular de cada caso, y el seguimiento a largo plazo es fundamental para evaluar la efectividad del tratamiento y el pronóstico del paciente. Se destaca la necesidad de realizar más investigaciones para ampliar nuestro conocimiento y mejorar el manejo de estos tumores.

¹ Cirujano de Tórax, Instituto de Enfermedades del Tórax del Nororiente Colombiano INTÓRAX, Comité Departamental de Cáncer de Pulmón de Norte de Santander CDCP, Hospital Universitario Erasmo Meoz. <https://orcid.org/0000-0001-7394-8669>.

² Médico general, Instituto de Enfermedades del Tórax del Nororiente Colombiano INTÓRAX, Comité Departamental de Cáncer de Pulmón de Norte de Santander, CDCP. <https://orcid.org/0009-0008-8491-1309>.

³ Médico general, Instituto de Enfermedades del Tórax del Nororiente Colombiano INTÓRAX, Comité Departamental de Cáncer de Pulmón de Norte de Santander, CDCP. <https://orcid.org/0009-0005-8771-1394>.

PALABRAS CLAVE: Liposarcoma, liposarcoma bien diferenciado, tumor lipomatoso atípico

ABSTRACT:

Liposarcomas (LPS) are a type of cancer that develops in soft tissues and is characterized by deriving from fat cells. They are divided into two subtypes: well-differentiated (WDLPS) and dedifferentiated (DDLPS), both known for their resistance to conventional treatments. The case of a 57-year-old woman with a medical history of obesity and disc herniation is presented. She experienced a progressive increase in the size of a mass in her left hemithorax, accompanied by dyspnea and chest pain. Diagnostic evaluation, including ultrasound, chest tomography, and magnetic resonance imaging, was essential for appropriate therapeutic decisions. The patient underwent successful surgery to remove the mass, with subsequent confirmation of the diagnosis of well-differentiated liposarcoma through pathological analysis. This clinical case emphasizes surgery's crucial role in treating localized liposarcomas, aiming for complete resection to improve the patient's quality of life. The variability in response to conventional treatments highlights the importance of individually evaluating the molecular profile of each case, and long-term follow-up is essential to assess treatment effectiveness and patient prognosis. The need for further research to expand our knowledge and improve the management of these tumors is emphasized.

KEYWORDS: Liposarcoma, Well-differentiated liposarcoma, Atypical Lipomatous Tumor

INTRODUCTION

Soft tissue sarcomas (STS) constitute a group of mesodermal malignancies that encompass a wide variety of histological entities. Within this group, liposarcomas (LPS) stand out as the most prevalent subtype of malignant tumors with adipocyte differentiation, representing approximately 15% to 20% of all STS cases.

Within this broad panorama we find a varied range of mesodermal

malignancies that encompass a variety of histological entities. This disease categorization is divided into four main subtypes: well-differentiated liposarcoma (WDLPS, also known as atypical lipomatous tumor), dedifferentiated liposarcoma (DDLPS), myxoid liposarcoma (MLPS), and pleomorphic liposarcoma (PLPS). Atypical lipomatous tumor/well-differentiated liposarcoma and dedifferentiated liposarcoma together constitute the largest subgroup of liposarcomas, being the

first responsible for approximately 40-45% of all the cases also represent a histological and behavioral spectrum of a single pathological entity.

WDLPS closely resembles mature adipose tissue but typically shows fibrous septation with nuclear atypia and enlargement within the adipose tissue and fibrous stroma. Although WDLPS can recur, it lacks metastatic capacity. However, up to 10% of WDLPS cases dedifferentiate into DDLPS, which exhibits a more aggressive behavior with local and subcutaneous recurrence rates potential metastatic significantly higher.

There is a wide variety of biological behavior among these subtypes, ranging from well-differentiated liposarcomas with low metastatic potential to high-risk pleomorphic or round cell types, which tend to be higher grade and are associated with a high rate of distant metastasis. 1,2,3,9

The typical clinical presentation of a soft tissue sarcoma is a painless mass that gradually increases in size, most prominent in areas such as the thigh and retroperitoneum. In some cases, patients may experience pain or symptoms related to compression from the mass, such as paresthesia or edema in an extremity. In situations exceptional, symptoms constitutional symptoms such as fever and weight loss may be present. 1,2,9

Soft tissue sarcomas can originate in various areas of the body, although most are located in the extremities, with 46% in the thigh, buttock, and groin, 13% in the upper extremity, 18% in the torso, 13% in the retroperitoneum, and 9% in the head and neck, according to studies conducted by the American College of Surgeons. 1,2,3,9

Liposarcoma presents as a well-circumscribed, palpable, and often painless, slowly growing mass. In cases of retroperitoneal involvement, diffuse abdominal enlargement may be observed. Fascial compartmentalization can give liposarcoma discoid and fusiform shapes, generating diverse morphologies and clinical manifestations. Pleomorphic liposarcoma, although uncommon, presents as a painless, pedunculated, pinkish papulonodular lesion, primarily located on the extremities, trunk, and head and neck. 1,2,3

Most patients with liposarcoma do not experience noticeable symptoms until the tumor reaches a considerable size and affects surrounding structures, causing tenderness, pain, or functional disturbances. In cases retroperitoneal, where detection is often late, the tumor may reach a significant size in the time of diagnosis. Liposarcoma generally

grows silently, and the clinical duration reported by patients is often unreliable. Additional symptoms may include painful swelling, decreased range of motion, numbness, enlarged varicose vein, fatigue, abdominal pain, weight loss, nausea, and vomiting. 1, 2, 3, 4

Well-differentiated liposarcoma, especially in the form of slow-growing masses in the retroperitoneum and proximal extremities, may be difficult to distinguish from benign adipocytic neoplasms.

WDLPS, without metastatic potential, show excellent results with complete resection, but local recurrence can be a challenge. The latter is more common when it arises in the retroperitoneum, mediastinum, or paratesticular region and is a cause of morbidity and mortality, as well as the appearance of undifferentiated diseases.

On the other hand, dedifferentiated liposarcoma, a highly aggressive disease that predominantly occurs in the retroperitoneum has significant rates of local recurrence, metastasis and specific mortality that are six times higher than WDLPS.

Both types are generally resistant to radiotherapy and chemotherapy, and share similarities morphological and molecular characteristics, suggesting thatDDLPS arises as a focal projection within WDLPS precursor

lesions. 2,3,4

Histologically, well-differentiated liposarcoma (WDLPS) presents as a proliferation of mature, pleomorphic adipocytes, crossed by fibrous septa and with single, large, hyperchromatic nuclei. On the other hand, dedifferentiated liposarcoma (DDLPS) is characterized by higher cellular areas of high-grade undifferentiated sarcoma, which generally appears abruptly into a WDLPS background. 2,3,4

Both types of liposarcoma show supernumerary ring or giant rod chromosomes, which contain amplified segments of 12q13-15, where cancer-related genes involved in tumorigenesis are located.

Among them, MDM2 and CDK4 are key, co-amplifying in most patients. Other commonly co-amplified genes within this amplicon include HMG2A, TSPAN31, and YEATS4 and CPM, which play roles in cellular dedifferentiation and transformation. YEATS4, a transcription factor, has been associated with the suppression of p53 function, while CPM encodes a proteolytic enzyme involved in growth factor activation. 2, 3, 4

In cell line and xenograft studies, YEATS4 inhibition has demonstrated a greater antiproliferative effect than loss of MDM2 expression in DDLPS cells.

Furthermore, CPM knockout resulted in inhibition of growth, migration, and invasion, associated with downregulation of the MAPK and PI3K pathways. These findings underscore the molecular complexity and involvement of several genes in liposarcoma progression and dedifferentiation.^{2,3,4}

Myxoid pleomorphic liposarcoma (MLPS) accounts for approximately 30% of liposarcomas (LPS) and is clinically and pathologically distinct from well-differentiated or dedifferentiated liposarcomas (WD/DDLPS). More than 90% of MLPS have a t(12;16)(q13;p11) translocation resulting in the expression of the FUS-DDIT3 fusion protein, while a smaller proportion carry gene fusions. EWSR1-DDIT3. Microscopically, MLPS shows small, round to oval, nonadipocytic mesenchymal tumor cells, along with variable numbers of immature lipoblasts in a background of prominent myxoid stroma.^{2,3,4}

Round cell liposarcoma is now recognized as a more cellular, high-grade variant of MLPS, associated with less severe outcomes. favorable.

MLPS usually develops in the proximal extremities, with two-thirds of cases originating in the thigh. Local recurrence and metastasis to atypical sites such as bone,

retroperitoneum, serous surfaces, and/or contralateral limbs are commonly found.

In addition to a larger round cell component, higher histological grade, multifocality, and p53 overexpression have been associated with an adverse prognosis. Unlike WD/DDLPS, MLPS demonstrates marked sensitivity to chemotherapy and radiotherapy.^{2,3,4}

Pleomorphic liposarcoma is a rare and clinically aggressive subtype of liposarcoma (PLS). It usually develops in the extremities or, less commonly, in the trunk or retroperitoneum. Histologically, PLPS presents as a high-grade, undifferentiated sarcoma of no recognizable lineage, containing a variable number of pleomorphic lipoblasts. Distant metastases develop in 30% to 50% of patients, usually involving the lungs and showing poor response to chemotherapy or radiation therapy. Tumor-associated mortality occurs in up to 50% of patients.^{2,3,4}

Current understanding of the molecular pathology of PLPS is limited. PLPS typically have complex karyotypes with losses and multiple chromosomal gains, indicating a pathogenesis driven by complex and variable molecular events. Deletion of 13q14.2-5 (containing RB1) has been observed in up to 50% of

patients.

Mutation or loss of TP53 is also present, unlike other types of LPS where alteration of TP53 is uncommon. Loss of the tumor suppressor gene NF1 is observed in a proportion of patients, while epigenetic inhibition of the p53 target gene, p14ARF, has been implicated in tumorigenesis. 2, 3, 4

The diagnosis of liposarcoma involves a comprehensive approach that includes clinical evaluation, imaging studies, and pathological confirmation. Initially, a detailed clinical history and physical examination are performed to assess symptoms and the characteristics of the mass.

Imaging studies, such as magnetic resonance imaging (MRI) and computed tomography (CT), are essential for visualizing the extent and planning surgical intervention. 4, 5, 6, 7

The atypical component demonstrates high signal intensity on T1- and T2-weighted images, consistent with a lipomatous tumor.

The portion undifferentiated generally has a larger size 3 cm and typically presents nonspecific features on magnetic resonance imaging (MRI), with prolonged T1 and T2 relaxation times. Occasionally, signs of hemorrhage and necrosis can be identified within this high-grade

portion. In our limited experience, gadolinium contrast enhancement in the dedifferentiated component shows variability. 7,8,9

Pathological confirmation is achieved through a biopsy, either by fine needle or surgical procedure, where the sample is histologically analyzed for lipoblastic cells and specific patterns. In addition, genetic and molecular studies can be performed to evaluate the amplification of genes such as MDM2 and CDK4, which are common in liposarcomas. Subtyping and tumor grading help characterize tumor aggressiveness.4,5,6,7

The evaluation of the extent of liposarcoma is performed to determine the stage of the cancer, using techniques such as positron emission tomography (PET-CT) to detect possible metastasis. The importance of this diagnostic process is emphasized in guiding treatment and providing an accurate understanding of liposarcoma and its potential impact on the patient.4,5,6,7

Regarding the management of this type of tumor, surgery is the fundamental treatment for tissue sarcomas soft localized in adults, performed by specialized surgeons in sarcoma centers. En bloc excision with R0 margins is the standard practice, with the option of R1 excision in specific cases, especially for atypical lipomatous tumors. 9,10

Radiotherapy, typically integrated with surgery for high-grade lesions, has shifted from preferably postoperative to slight Preoperative radiotherapy. Not recommended for compartmental resections.

Neoadjuvant radiotherapy can be combined with chemotherapy. Surgery is scheduled 4–8 weeks after the last chemotherapy or radiotherapy. In R2 surgeries, re-excision is required at referral centers, possibly after preoperative treatments if adequate margins are not achieved. 9,10

When re-excision is not possible after R1-R2, postoperative radiation therapy is considered, tailoring the decision based on additional considerations, including the impact on future surgeries. In exceptional cases, amputation may be the only option.

It is vital to distinguish regional lymph node metastases from soft tissue metastases in lymph node regions, as the former are rare and have a poor prognosis. Appropriate management, tailored to the complexity of the case, is crucial to improving outcomes. 9,10

In advanced stages of the disease, when soft tissue liposarcoma is locally unresectable or has metastasized, the prognosis tends to be poor. The conventional therapeutic approach involves the use of anthracycline-based regimens. However, the results of

the EORTC 62012 clinical trial, which compared the combination of doxorubicin and ifosfamide with doxorubicin alone, did not show significant improvements in either response rates or overall survival. 2,10

It is important to note that the specific efficacy of olaratumab, a drug used in certain types of sarcomas, has not yet been conclusively established for the liposarcoma subtype. This fact underscores the need for additional research and dedicated clinical trials to determine the usefulness of olaratumab in the treatment of LPS. 2,10

It is important to note that there is clinical evidence suggesting a possible differential sensitivity of liposarcoma subtypes to various available systemic therapies. This variability in response to different treatments highlights the importance of conducting an individualized and accurate assessment of the genetic and molecular profile of each case of LPS. The research continued in this area is essential to identify more effective therapeutic strategies and improve the outlook for patients with advanced liposarcoma. 2,10

Given the frequency and apparent oncogenic role of MDM2 and CDK4 overexpression in WD/DDLPs, significant efforts have been made to therapeutically target these proteins. 2,10

CLINICAL CASE

A 57-year-old female patient with a history of obesity and a herniated disk presented with a three-year history of a mass in the left lateral hemithorax between the midclavicular line and the left breast. Two years earlier, she had undergone surgery to remove a lipoma in the same area, for which no further information was provided. She attended due to the growth of the mass, progressive dyspnea on minimal exertion, and intermittent oppressive chest pain. Other medical history included second-degree relatives with pancreatic, breast, and gastric cancer.

The patient brought to the consultation a soft tissue ultrasound that reported a large subcutaneous mass of heterogeneous adipose tissue in the left anterolateral pectoral region measuring 15 x 8 x 13 cm, highly suspicious of liposarcoma due to large size and growth. Given the above, a chest computed tomography was

requested (Figure 1) which showed a mass of homogeneous fat density and well-defined contours at the level of the left chest wall, centered in the axilla and retropectoral region, measuring 246 x 129 x 86 mm, which had thin septa inside. Its most caudal aspect extends between the latissimus dorsi muscle and the intercostals muscles to the base of the hemithorax, in the posterolateral region of the same.

For its part, magnetic resonance imaging of the thorax (Figure 2), one of the key studies for the diagnosis, showed a deep, anterior, left soft tissue mass located between the pectoral, latissimus dorsi, serratus and subscapularis muscles; isointense to fat in all sequences with some linear septa of low signal intensity, measuring approximately 70 x 130 x 170 mm anteroposterior, transverse and cephalocaudal, due to its characteristics it suggested low-grade liposarcoma as the first diagnostic possibility.

THERAPEUTIC MANAGEMENT

After pre-anesthetic assessment, a left anterolateral thoracic incision was made in layers to the chest wall with evidence of a giant 30x30 cm lobulated tumor, with a fatty appearance in the left anterolateral subpectoral region with extension to the chest wall and axillary fossa without compromising them, a parietal pleurectomy was performed,

revealed thickened left parietal pleura without pleuropulmonary involvement. The thoracic lesion was identified with subsequent capsule-preserving resection and excision with vascular pedicle ligation (Figure 3). The cavity was finally lavage with hemostasis, a hemovac drain was installed, and the lesion was closed in layers.

Finally, the pathological study of the resected lesion (Figure 4) reported adipose tissue composed of adipocytes of different sizes with occasional and scattered hyperchromatic stromal cells, whose Immunohistochemistry showed reactivity in nucleoli with CDK4 and MDM2, without reactivity for P16. This confirmed the final pathological diagnosis of well-differentiated liposarcoma. The removed lymph node was negative for tumor involvement.

Currently, five years after the surgical procedure, the patient presents no related symptoms, is fully functional in her daily activities, and is being monitored and followed up by clinical oncology at six-month intervals.

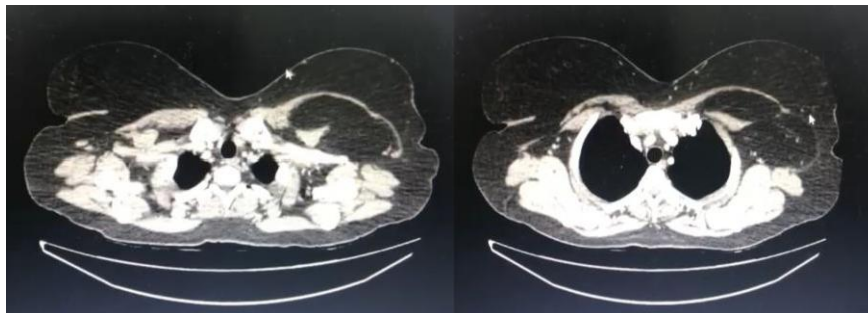


FIGURE 1. Axial section of chest computed tomography showing a mass in the left chest wall.



FIGURE 2. Coronal magnetic resonance imaging showing a deep, anterior, left soft tissue mass located between the pectoral, latissimus dorsi, serratus, and subscapularis muscles.



FIGURE 3. Intraoperative images showing the tumor extraction process and vascular pedicle.



FIGURE 4. Surgical specimen.

CONCLUSIONS

In this case, in accordance with the literature, surgery proves to be the fundamental pillar in the management of localized liposarcomas, seeking complete removal with R0 margins to improve the patient's quality of life.

The variability in response to conventional treatments highlights the need to individually assess the genetic and molecular profile of each case, underscoring the importance of ongoing research to identify more targeted therapies.

The management of advanced liposarcomas remains a challenge, with inconclusive results for specific therapies such as olaratumab. Future research is essential to develop more effective therapeutic approaches and improve the outlook for advanced stages of the disease.

REFERENCES:

1. Thway, Khin "Well-differentiated liposarcoma and dedifferentiated liposarcoma: An updated review." *Seminars in diagnostic pathology* vol. 36,2 (2019): 112-121. doi:10.1053/j.semdp.2019.02.006
2. Lee, Alex Thomas John et al. "Clinical and Molecular Spectrum of Liposarcoma." *Journal of clinical oncology*: official journal of the American Society of Clinical Oncology vol. 36,2 (2018): 151-159. doi:10.1200/JCO.2017.74.9598
3. Lawrence, W Jr et al. "Adult soft tissue sarcomas. A pattern of care survey of the American College of Surgeons." *Annals of surgery* vol. 205,4 (1987): 349-59. doi:10.1097/00000658-198704000-00003
4. Jo, Vickie Y, and Christopher D M Fletcher. "WHO classification of soft tissue tumours: an update based on the 2013 (4th) edition." *Pathology* vol. 46,2 (2014): 95-104. doi:10.1097/PAT.0000000000000050
5. Singer, Samuel et al. "Histologic subtype and margin of resection predict pattern of recurrence and survival for retroperitoneal liposarcoma." *Annals of surgery* vol. 238,3 (2003): 358-70; discussion 370-1. Doi: 10.1097/01.sla.0000086542.11899.38
6. ESMO/European Sarcoma Network Working Group. "Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up." *Annals of oncology: official journal of the European Society for Medical Oncology* vol. 25 Suppl 3 (2014): iii102-12. doi:10.1093/annonc/mdu254
7. Mashima, Emi et al. "Recent

- Advancement in Atypical Lipomatous Tumor Research." International journal of molecular sciences vol. 22,3 994. 20 Jan. 2021, doi:10.3390/ijms22030994
8. Haddox, Candace L, and Richard Riedel. "Recent advances in the understanding and management of liposarcoma." Faculty reviews vol. 10 1. 4 Jan. 2021, doi:10.12703/r/10-1
 9. Nishio, Jun, et al. "Biology and management of dedifferentiated liposarcoma: state of the art and perspectives." Journal of Clinical Medicine 10.15 (2021): 3230.
 10. Gronchi, A., et al. "Soft tissue and visceral sarcomas: ESMO–EURACAN–GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow- up☆." Annals of Oncology 32.11 (2021): 1348-1365.
 11. Muratori, Francesco, et al. "Liposarcoma: Clinico- pathological analysis, prognostic factors and survival in a series of 307 patients treated at a single institution." Journal of Orthopaedic Science 23.6 (2018): 1038-1044.
 12. Suarez-Kelly, Lorena P., Giacomo G. Baldi, and Alessandro Gronchi. "Pharmacotherapy for liposarcoma: current state of the art and emerging systemic treatments." Expert Opinion on Pharmacotherapy 20.12 (2019): 1503-1515.
 13. Tyler, Robert, et al. "A review of retroperitoneal liposarcoma genomics." Cancer treatment reviews 86 (2020): 102013.