PRIMARY HEPATIC LEIOMYOSARCOMA. A CASE REPORT

Palabras clave: Leiomiosarcoma; Sarcoma; Neoplasias hepáticas; Hepatectomía; Actina de músculo liso.
Keywords: Leiomyosarcoma; Sarcoma; Hepatic neoplasms; Hepatectomy; Smooth muscle actin.

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ABSTRACT

Primary hepatic leiomyosarcoma is extremely rare among cases of liver tumors in adults, with an incidence of 0.1 and 1%. This paper describes the case of a 55 year-old man with a clinical evolution of five months consisting of abdominal pain, a large hard lump, weight loss, shortness of breath and fever.

A three-phase computed tomography (CT) showed a hypercaptive mass at its periphery during hypodense arterial phase at its center, located in segments V and VI, without a plane of separation of the liver. Due to the symptoms, the patient underwent an exploratory laparotomy, finding a cerebroid mass of 40 x 40 cm; a lumpectomy without hepatectomy was performed, leaving free surgical margins.

The diagnosis was largely made through a histopathological assessment, finding stromal multinucleated pleomorphic forms, desmin (+), SMA (smooth muscle actin) and MSA (muscle specific actin) (+), Ki67 (+) and negative for S100 (protein S100) and CD117 antibody, which confirmed the high grade pleomorphic leiomyosarcoma diagnosis. The patient was discharged 16 days after admission once his condition improved, and was referred to the oncology department for adjuvant chemotherapy.

Given the size of the mass, the prognosis was bleak, which left surgery as the only option to offer survival expectations through regulated or "atypical" hepatectomies along with safety margins and liver transplantation. With this in mind, the first option was chosen; six months after surgery, with clinical improvement and adjuvant therapy, the patient, still with unfavorable prognosis, remained stable attending multidisciplinary medical management controls.

INTRODUCTION

Primary hepatic leiomyosarcoma (PHL) is an extremely rare tumor. In 2011, the English literature reported less than 50 patients with this type of tumor **(1,2)**. To date, in the context of this study, there are no reports of similar cases in Ecuador, and by 2014, there were very few cases reported in Latin America **(3)**.

In adults, primary liver sarcomas are a group of rare tumors, representing between 0.1 and 1% of all existing malignant liver tumors in this population **(4)**. Usually, they develop in the uterus, the retroperitoneum, genital organs, lungs, liver and large vessels **(5)**; on the other hand, PHL generate in the smooth muscle cells of intrahepatic, bile ducts or round ligament vascular structures **(6)**.

Their unusualness, image manifestations and non-specific clinical presentation make early diagnosis difficult **(7)**. Currently, diagnosis can be made before surgery through cytology or image-guided percutaneous biopsy or after surgery **(8-12)**. However, the differential diagnosis between primitive or metastatic liver sarcoma may present difficulties sometimes **(9)**, reason why the anatomopathological study is fundamental. The histopathological diagnosis is characterized by the presence of diffuse infiltrates and uniform spindle-shaped cells with hyperchromatic nuclei **(8,9)**, while a positive reaction for desmin, SMA, MSA, Ki67 and a negative reaction for S100 and CD117 are observed in immunohistochemistry.

Resective surgery is the best treatment option for this condition; the same surgical principles of soft tissue sarcoma surgery should be kept, with margin cancer liver resection as the most appropriate choice or gold standard. Nevertheless, due to the advanced stage of the disease at diagnosis, lumpectomy or enucleation,

followed by treatment with adjuvant chemotherapy, may be another therapeutic approach to consider, even in cases with metastases **(10)**, leaving liver transplant as the last resort.

CLINICAL CASE

Male patient, 55 years old, professional working at an office with no relevant medical history, who denied using or consuming alcohol and tobacco, and reported a family history of diabetes *mellitus*, esophageal cancer and ocular melanoma. The clinical picture of the patient presented five months of evolution characterized by oppressive abdominal pain of moderate intensity, located in the right upper quadrant and umbilical region, accompanied by a rigid, hard abdominal mass of about 20 cm in diameter, painful on palpation (Figure 1), hyporexia and weight loss of about 45 pounds in 100 days, dyspnea on moderate efforts, afternoon fever one month prior to hospitalization, and stable vital signs.

Mild normocytic hypochromic anemia (hemoglobin: 10.1mg / dl), normal hepatic and cholestatic function, normal coagulation times and acute phase reactants without alterations were observed through tests. Also, normal results of tumor markers such as CEA, alpha-fetoprotein, CA 125, CA 15-3, CA 19-9 and CA 72-4 were obtained. Abdominal ultrasound showed a hypoechoic and vascularized tumor mass in the liver bottom of approximately 30 x 20 cm (Figure 2). Moreover, plain abdominal radiograph showed a radiopaque image in the hypochondria and right flank. Three-phase computed tomography angiography of the

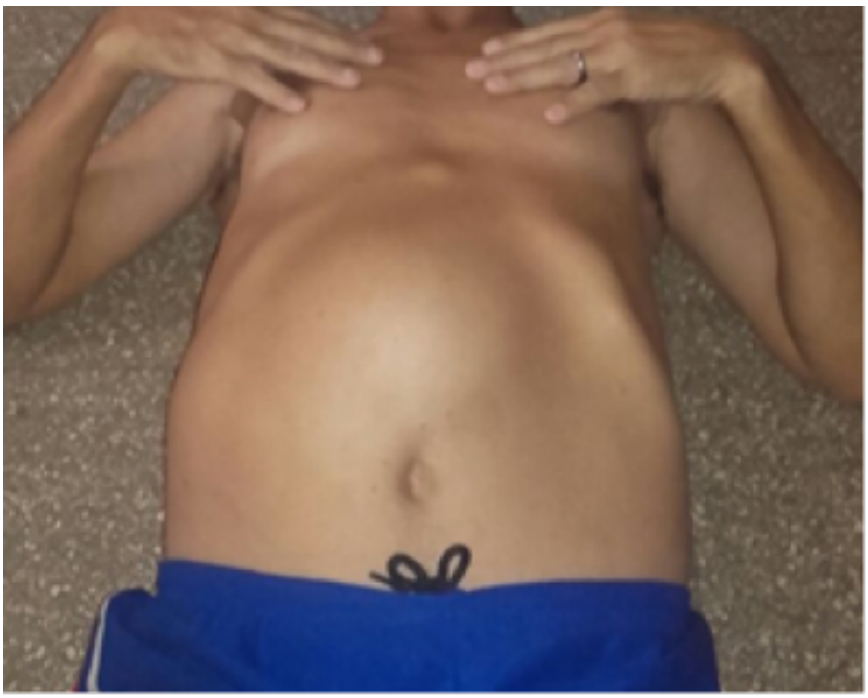

Fig 1. Patient's morphology. Large tumor mass in the right abdomen.
Source: Own elaboration based on the data obtained in the study.

abdomen showed a hypercaptive mass on its periphery, hypodense center in heterogeneous portal and late arterial phase, located in liver segments V and VI, without a plane of separation of the liver, in addition to retroperitoneal adenomegaly (Figure 3).

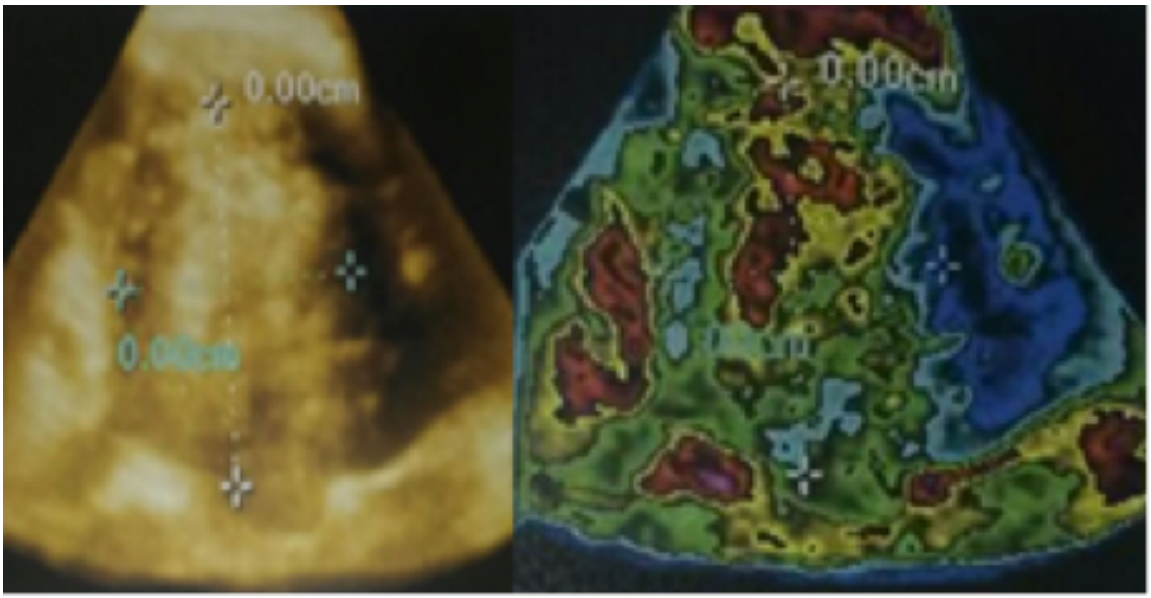

Fig 2. 2D abdominal ultrasound. Large, hypoechoic liver mass with vascularization.
Source: Own elaboration based on the data obtained in the study.

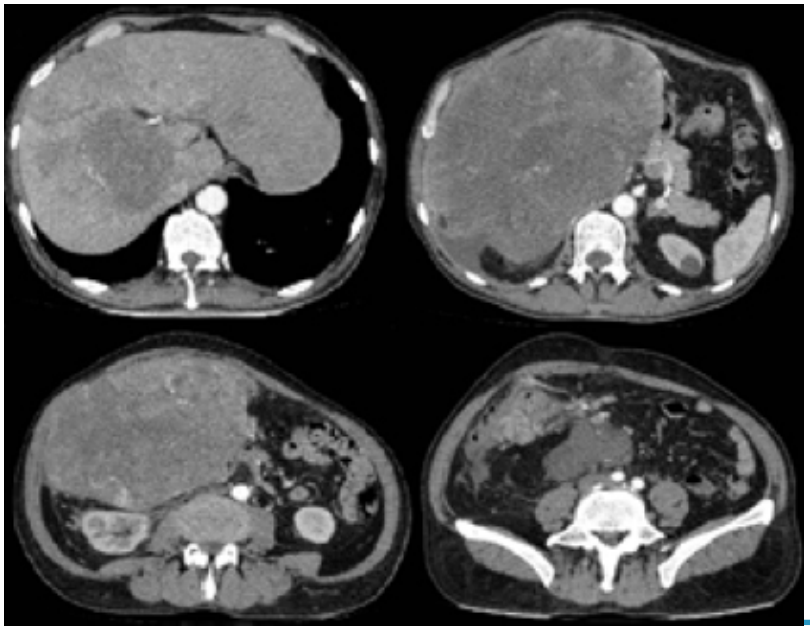

Fig 3. Three-phase tomography angiography. Large tumor mass in the right hepatic lobe, segments V and VI, which moves intra-abdominal organs.
Source: Own elaboration based on the data obtained in the study.

Finally, colonoscopy revealed normal-looking mucosa and decreased light at the ascending colon due to an apparent extrinsic compression. Exploratory laparotomy was performed to improve the clinical condition of the patient, finding a large, encapsulated, cerebroid tumor in liver bed, segments V and VI, of about 40x40 cm, displacing the right diaphragm and surrounding abdominal structures. A lumpectomy without hepatectomy was performed, with free surgical margins in sample freeze; also, neighboring structures were released and no masses, lymph nodes or metastatic seeding were identified with the naked eye. No intraoperative surgical complications occurred (Figure 4).

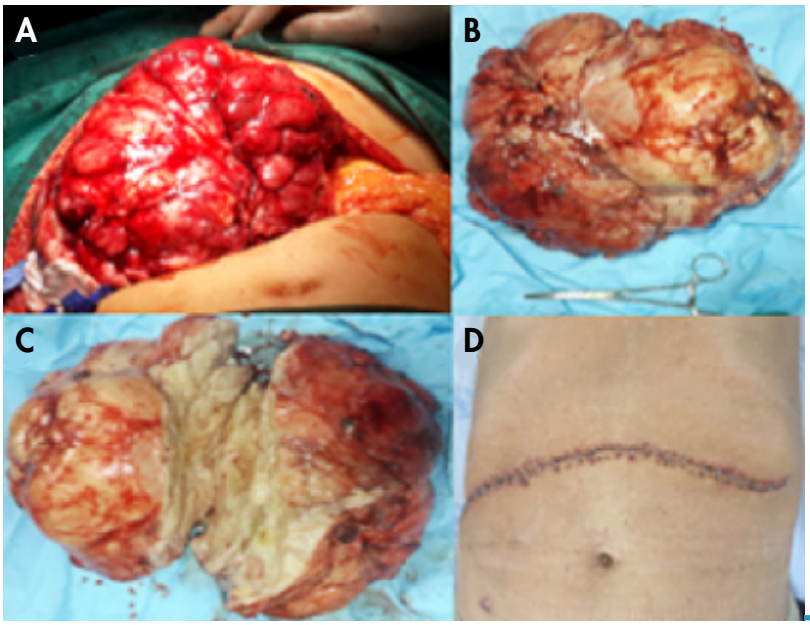

Fig 4. Visualization during exploratory laparotomy of primary, multilobulated, cerebroid, encapsulated hepatic leiomyosarcoma located in the right hepatic lobe.
Figure 4a. Tumoration dependent on hepatic segments V and VI.
Figure 4b. Tumor exposed once extracted from the liver.
Figure 4c. Longitudinal section of the tumor showing the macroscopic structure.
Figure 4d. Extended subcostal wound closure used in this surgical procedure.

Anatomopathological study (Figure 5) reported a malignant multilobulated tumor with the following characteristics: weight 4341 g; size 38 x 35 x 20cm; encapsulated, with irregular edges and cavitated; mesenchymal strain composed of spindle cells; with elongated core and numerous mitoses. Meanwhile, the immunohistochemical study showed positive desmin, positive SMA and MSA, positive Ki67 in 80% of cells and negative for S100 and CD117, confirming the diagnosis of high-grade pleomorphic leiomyosarcoma.

The patient was hospitalized for 16 days; after showing a favorable evolution, he was discharged and ordered monthly outpatient follow-up. He was also referred to the oncology department to initiate adjuvant chemotherapy every 25 days in three cycles, observing the clinical course and conforming to the requirements, with the possibility of subsequent radiotherapy to control clinical, imaging and laboratory parameters, which is currently pending. Six months after surgery, still with unfavorable prognosis, the patient was stable and attending multidisciplinary medical controls.

DISCUSSION

Clinical manifestations of PHL are not specific and, usually, tumors are asymptomatic

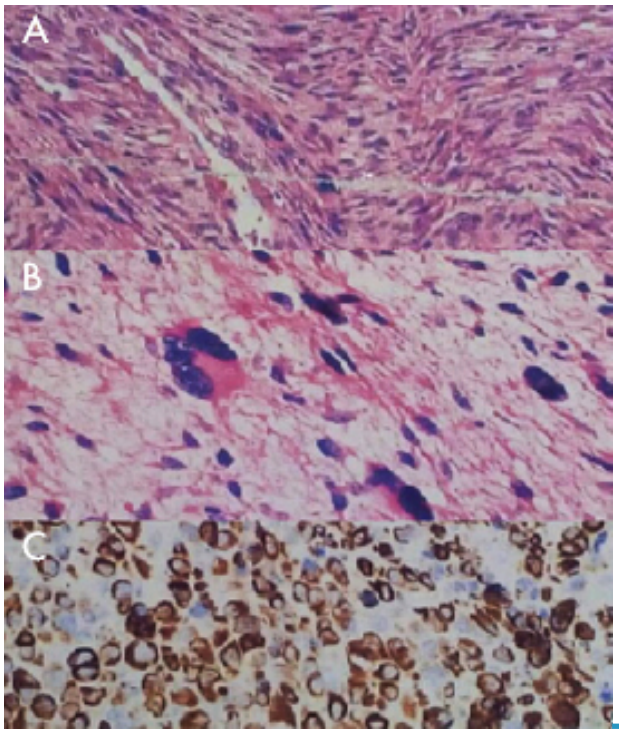

Fig 5. Histological and immunohistochemical study.
5.a. Fusiform muscle malignant cells with elongated core and necrosis areas, typical in this kind of tumor, are observed (staining with hematoxylin-eosin x100).
5.b. Presence of numerous mitosis, interwoven fascicles and pink cytoplasm with numerous pleomorphic multinucleated forms (staining with H&E x400).
5.c Immunohistochemistry reveals positive desmin sample with presence of typical smooth muscle cells (original magnification: x50).

before enlargement **(11,12)**. The average age of onset is between 40 and 50, with extreme ages of 22 and 77 **(13)**. The most common symptom is mild to severe pain in the upper abdomen, accompanied by weight loss, afternoon fever and asthenia **(14)**. Clinical examination allows identifying palpable abdominal mass or hepatomegaly in right-epigastric hypochondriac region. In general, non-specific increases in some biochemical function/liver damage parameters can be observed (bilirubin, alkaline phosphatase or transaminases) unlike specific tumor markers, as in this case, which does occur in sarcomas in other parts of the body.

On the other hand, imaging does not provide specific data **(16,17)**, because ultrasound shows a hypoechoic liver tumor, while three-phase CT shows a well-defined, heterogeneous, hypodense or isodense mass through central necrosis areas and peripheral enhancement, or as a thick wall cystic mass **(18)**, with an angiographic pattern of peripheral avascular mass or important pathological neovascularization **(19)**, superimposed on any liver tumor. Finally, through nuclear magnetic resonance, a heterogeneous area with hypointense lesion on T1 and hyperintense lesion on T2, with possible encapsulation, is observed **(2)**.

The most common site of tumor is the right lobe and metastases of about 40% at the time of diagnosis are common **(6)**, which is consistent with data reported here. Therefore, the differential diagnosis must be made between various types of benign and malignant hepatic solid tumors **(20,21)** such as hepatocarcinomas of different strain **(22)**, primitive or metastatic sarcoma **(8)**, and even sarcomas of the retrohepatic vena cava **(23)**.

Today, and in most case series **(20,24,25)**, the diagnosis of hepatic sarcoma can be established preoperatively, through image-guided percutaneous biopsy or cytology; however, if the liver damage appears to be malignant and

is considered resectable, diagnosis is made postoperatively, as in this case. Histopathological diagnosis shows four types of leiomyosarcomas: well differentiated, moderately differentiated, poorly differentiated and myxoid leiomyosarcoma **(26)**. In this case, the patient was classified as type 1, since immunohistochemical study showed positive desmin and SMA, but negative S-100, CD117 and NSE **(18,19)**, which is consistent with the parameters of this type of tumor and confirms PHL diagnosis.

As this was a large liver mass that generated large compression of neighboring structures and dyspnea, as well as peripheral vascularization, the possibility of image-guided percutaneous biopsy was discarded due to high risk of bleeding. Regulated or atypical hepatectomy with safety margins was the selected treatment. However, and due to the advanced evolutionary stage of the disease at diagnosis, enucleation followed by chemotherapy was an alternative treatment, which can also be used in metastases cases **(8)**; for this patient, this was the best option *a priori*, thus constituting an exceptional case with apparent absence of metastasis and free surgical margins.

Since this is the only treatment that allows prolonged survival expectations, its analysis reveals the main favorable prognostic factors: being younger than 50 years of age, early diagnosis with a size below 5 cm, tumor location, radical surgery with safety margins, adjuvant treatment with chemotherapy and, as a last resort, liver transplantation **(9)**. King *et al.* **(27)** describe cases with large tumors, which after five years had a survival rate of 18%, as well as cases with about 80% of survival at five years in the presence smaller tumors with clear margins. Also, Gates *et al.* **(28)** indicate that the combination of surgery with chemotherapy offers a median survival of 3.3 years.

PHL can present hematogenous metastases, mainly in the lung, followed by lymphatic and peritoneal paths. In this regard, Shivathirthan *et al.* **(29)** describe that the intermediate range in the identification of metastases between primary leiomyosarcoma and PHL was 29 months (range: 6-58 months). They also note that inoperability criteria may include extrahepatic spread of tumor, diffuse intrahepatic tumor and impaired liver function **(29)**.

The patient in this case has received three cycles of chemotherapy with ifosfamide and doxorubicin; he has also attended monthly clinical, laboratory and imaging follow-ups. However, the role of adjuvant therapy with chemotherapy/radiotherapy is not well defined yet because, despite the fact that chemotherapy with doxorubicin and ifosfamide shows a slow course of the disease and may prolong survival in resections with R1 stage, there is not sufficient evidence in unresectable tumors and metastases by PHL **(30)**.

The role of liver transplantation is still controversial, since it has low rates of survival and recurrence 95% before six months **(31)**.

CONCLUSIONS

PHL is an extremely rare tumor that, in most cases, is diagnosed in advanced stages, delaying treatment and worsening prognosis. Its finding should be suspected in patients with large tumor masses. However, despite having many advanced imaging studies, diagnosis is completely histopathological, whereas treatment is surgical, in most cases, depending on several factors. This case highlights surgical therapy and the rare diagnosis of this tumor.

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CONFLICTS OF INTEREST

None stated by the authors

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