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*Case Report*

# Primary Hepatic Leiomyosarcoma - A Rare Neoplasm with Diagnostic and Therapeutic Challenges

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**Abstract:** Primary hepatic leiomyosarcoma (PHL) is a rare malignant neoplasm, representing <0.1% of all primary liver tumors. Originating from the smooth muscle cells of the intrahepatic vessels or the round ligament, its diagnosis is complex and requires the exclusion of metastases and other sarcomas. This case and literature review summarizes current knowledge on the epidemiology, clinical presentation, diagnostic approach and therapeutic management of LHP based on published literature. The clinical presentation is non-specific, often with abdominal pain and a detectable mass. Radical surgical resection (R0) is the only potentially curative treatment, but the high rate of local and metastatic recurrence negatively impacts the prognosis. Chemotherapy and radiotherapy have a limited palliative or adjuvant role. Overall survival at 5 years is low (15-30%), emphasizing the need for early diagnosis and more effective multimodal therapeutic strategies.

**Keywords:** Sarcoma; Liver neoplasms; Leiomyoma.

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## 1. Introduction

Primary hepatic leiomyosarcoma (PHL) is an exceptionally rare malignant mesenchymal neoplasm derived from smooth muscle cells of the intrahepatic blood vessels, bile ducts or the round ligament of the liver [1]. Its incidence is estimated at less than one case per 1 million inhabitants/year, representing less than 0.1% of all primary liver tumors [2]. The rarity of LHP contrasts markedly with the frequency of hepatocellular carcinoma and leiomyosarcoma of gastrointestinal or uterine origin, whose liver metastases must be rigorously excluded for a definitive diagnosis of a primary lesion [3]. The differential diagnosis also includes other primary liver sarcomas (angiosarcoma, rhabdomyosarcoma, undifferentiated sarcoma and metastatic gastrointestinal stromal tumors (GIST).

This case report and review aims to: 1) Discuss the characteristic clinical, radiological and histopathological aspects of LHP; 2) Critically analyze the available therapeutic options and their results; 3) Evaluate prognostic factors and survival; and 4) Highlight gaps in knowledge and future directions for research.

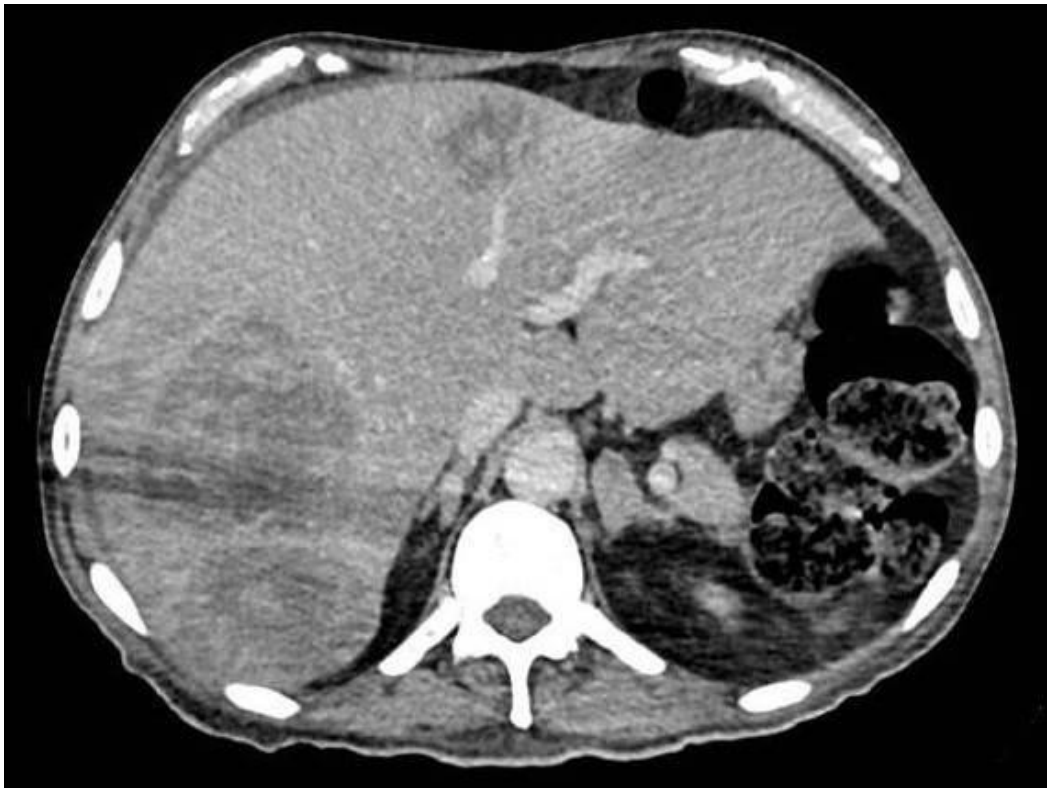
## 2. Case Report

A 59-year-old man who had been carrying the human immunodeficiency virus (HIV) since 2002 and had been diagnosed with treated pulmonary tuberculosis came to the emergency department of the Emilio Ribas Institute of Infectious Diseases (IIER) due to

weight loss and inappetence for a month, with a loss of approximately 10 kg despite taking antiretroviral therapy. He reported that his general condition had worsened in the last 20 days, with a reduction in motor strength. He denied any complaints related to type B symptoms. The initial physical examination revealed a painful abdomen in the right hypochondrium with a palpable mass in the same topography 5 cm from the right costal margin with no signs of peritoneal irritation, and the rest of the physical examination was normal. The patient was hemodynamically stable on admission.

Laboratory tests on admission were Hb: 7.8 mg/dL, Ht: 25%, Leukocytes: 8,900 cells/mm$^3$, platelets: 574,000/mm$^3$, AST: 33, ALT: 14, HIV viral load: 128 copy/mL, CD4+: 26 cel/mm$^3$, C-reactive protein: 187.2 with normal electrolytes and renal function. The patient underwent an abdominal computed tomography scan with intravenous contrast using the liver protocol, which showed an enlarged liver with regular contours and heterogeneous density due to various hepatic nodules with heterogeneous contrast enhancement in both hepatic lobes, some confluent, measuring 15.0 cm X 9.4 cm X 9.3 cm in segment VII. The gallbladder and bile ducts were normal at the time of the study (Figure 1).

**Figure 1.** Computed Tomography (CT) of the abdomen with intravenous contrast with liver protocol showing an enlarged liver with regular contours and heterogeneous density at the expense of several hepatic nodules with heterogeneous contrast enhancement in both hepatic lobes, some confluent, measuring 15.0 cm X 9.4 cm X 9.3 cm at in segment VII.



After the imaging tests, serologies for hepatitis B and C were requested, as well as tumor markers (alpha-fetoprotein, CEA and CA 19-9), all of which were normal. Together with the infectology and general surgery teams, the decision was made to carry out a liver biopsy using a 14G tru-cut needle puncture with the acquisition of 3 relevant samples, and the procedure was carried out under general anesthesia without any complications. The result of the liver biopsy was a sarcomatous neoplasm with a fusocellular pattern (Figure 2). The complementary immunohistochemical study showed focal positivity for

pancytokeratins (AE1/AE3) (Figure 3), smooth muscle actin (AML) and h-caldesmon (Figure 4), favoring smooth muscle differentiation of the neoplasm.

**Figure 2.** A fusocellular neoplasm with moderate to intense atypia and pleomorphism. There are also some figures of mitoses (Hematoxylin-eosin, 400x magnification).

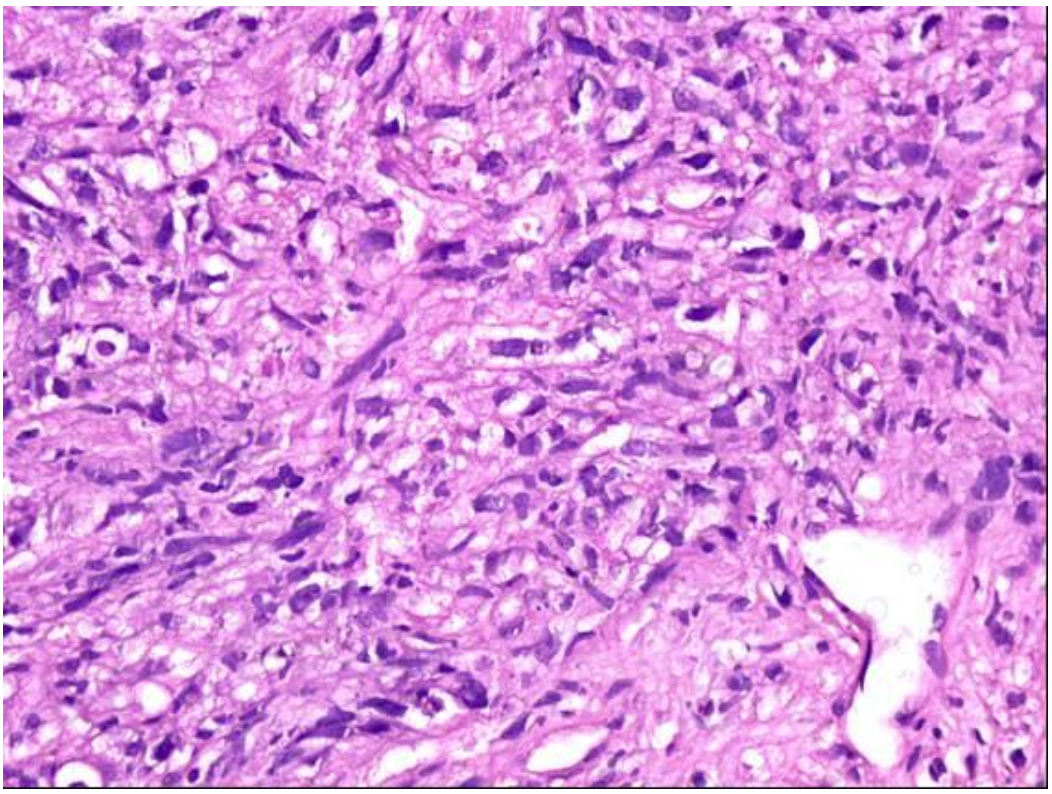


**Figure 2.** Immunoexpression of AE1/AE3 in the neoplasm and highlighting bile ducts interspersed in the neoplasm. Immunoexpression of pancytokeratins is an expected event in leiomyosarcomas and does not invalidate this diagnosis.

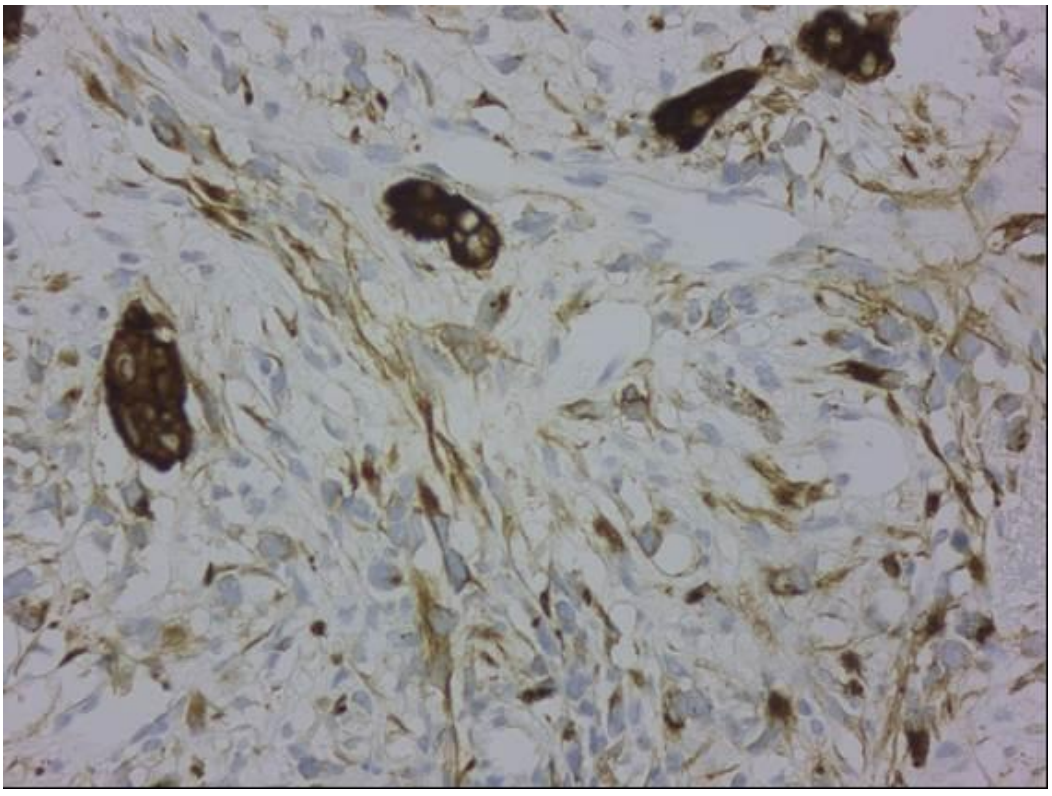
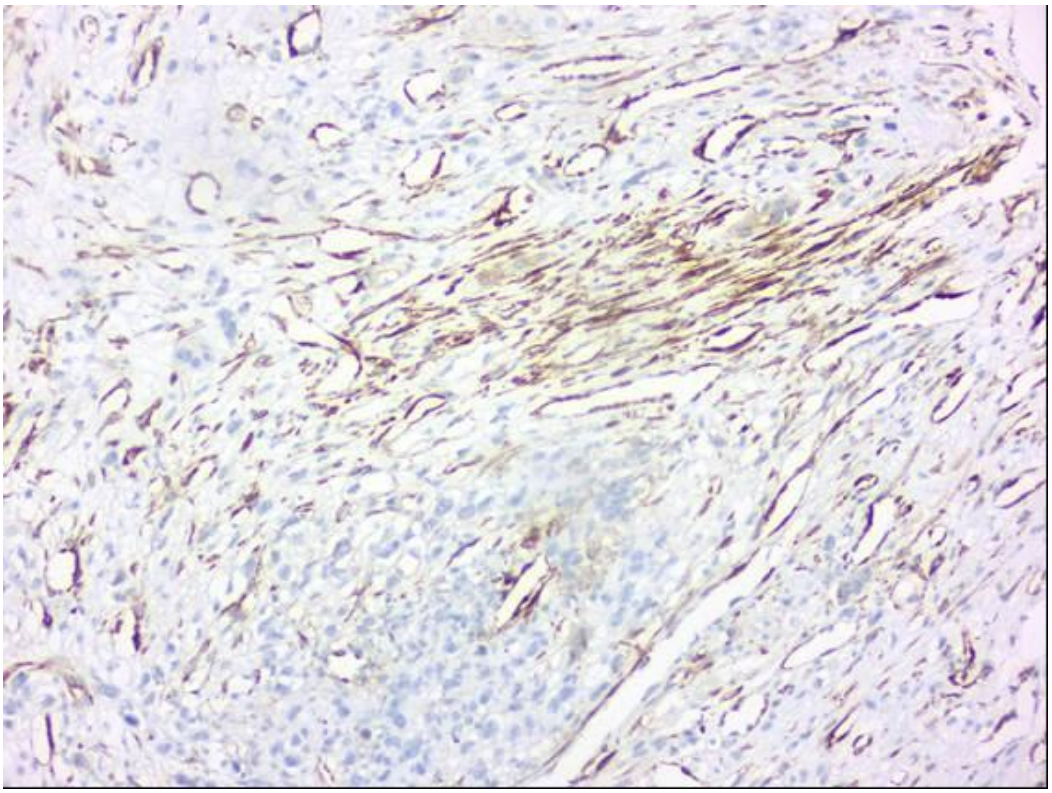


**Figure 3.** Focal positive for caldesmon.



The proliferative index measured by ki67% was high, indicating that it was a high-grade sarcoma. Despite the focal positivity for C-KIT, there was no immunoexpression of CD34 and DOG-1, thus disfavoring the diagnosis of gastrointestinal stromal tumor (GIST) and EBV was investigated but was not present in tissue. The diagnosis of rhabdomyosarcoma was disfavored due to the negativity of desmin. The patient was referred to for surgical treatment with resection of the liver tumor, and a segmental hepatectomy was performed. The patient is undergoing post-surgical follow-up and is progressing well, with no perioperative complications to date.

## 3. Discussion and Conclusion

LHP occurs predominantly in adults, with a peak incidence in the 5th and 6th decades of life, with no clear gender predilection [4]. The etiology remains unclear, although rare cases have been associated with immunodepression (especially in transplant recipients and HIV/AIDS patients), suggesting possible involvement of the Epstein-Barr virus (EBV) in the pathogenesis in these subgroups [5]. Although its etiology is not well explained, there is no established association with liver cirrhosis or chronic viral hepatitis, which are well-known risk factors for hepatocellular carcinoma [2]. Symptoms are often nonspecific and delayed, with pain in the right upper quadrant, a palpable abdominal mass, weight loss and fatigue being the most common findings [3]. Laboratory tests may reveal nonspecific elevation of alkaline phosphatase or DHL, while conventional liver tumor markers (alpha-fetoprotein, CEA, CA19-9) are typically normal [6].

On imaging, LHP usually presents as a large solitary mass, well circumscribed but not encapsulated, with a heterogeneous enhancement pattern on CT and magnetic resonance imaging (MRI) and areas of central necrosis and hemorrhage are frequent in larger lesions with peripheral enhancement in the arterial phase with progressive filling may occur but is not pathognomonic [7]. PET-FDG usually shows high uptake, useful for staging and detecting recurrence [8].

Definitive diagnosis requires histological and immunohistochemical (IHC) analysis of a biopsy sample or surgical specimen. Microscopically, the tumor shows interlaced

bundles of spindle-shaped cells, "cigaroid" nuclei, varied nuclear pleormofism and eosinophilic cytoplasm, as well as a high mitotic index [9]. Tumor necrosis is common and the IHQ profile is crucial: the tumor cells consistently express smooth muscle actin (SMA), desmin and h-caldesmon, confirming smooth muscle differentiation [9]. Positivity for vimentin is frequent, while negativity for CD117 (c-KIT), DOG1, CD34, S100, HMB-45 and cytokeratins helps to exclude GIST, schwannoma, melanoma and sarcomatoid carcinoma, respectively [10]. Positivity for EBV-encoded RNA (EBER) should be investigated in immunosuppressed patients [5].

The therapeutic approach to hepatic angiosarcoma involves multiple strategies. Radical hepatectomy (R0) remains the cornerstone of curative treatment and is the only factor consistently associated with improved overall survival [3,11]. Both anatomical (such as lobectomies and segmentectomies) and non-anatomical resections are performed, depending on tumor location and size. However, achieving R0 resection is often challenging due to the large tumor size at diagnosis. Systemic chemotherapy plays a limited role, with regimens based on anthracyclines (e.g., doxorubicin) and ifosfamide being used in neoadjuvant settings (to shrink the tumor and allow resection), adjuvantly, or palliatively in advanced or inoperable cases. Response rates are low (15–25%) and intra-arterial hepatic chemotherapy has been attempted with variable outcomes [8,12].

External radiotherapy may be considered as an adjuvant treatment in cases with compromised or microscopically positive margins (R1), or as palliative therapy for pain or bleeding control in inoperable disease [8]. Stereotactic body radiotherapy (SBRT) is an emerging option for inoperable lesions or oligometastatic disease. Regarding targeted therapies and immunotherapy, data are extremely limited and mostly derived from case reports or extrapolated from other soft tissue sarcomas. Molecular studies reveal complex and heterogeneous genetic alterations, with no established therapeutic targets to date [5,12].

The prognosis of LHP is generally poor. Overall survival for 5 years ranges from 15% to 30% in most series [4,11]. Consistent negative prognostic factors include large tumor size (>10 cm), presence of metastases at diagnosis (pulmonary and peritoneal are the most common), positive surgical margins (R1/R2), high histological grade (Fédération Nationale des Centres de Lutte Contre le Cancer - FNCLCC grade 3) and high proliferative index (Ki-67 >30%) [3,11]. Local recurrence and distant metastasization are frequent even after apparently complete resection, occurring in more than 50% of cases, often within 2 years [2]. In 2021, Saikia et al. reviewed 118 cases of leiomyosarcoma, addressing clinical features, management strategies and prognosis. Aggressive surgical resection with negative margins was identified as crucial for long-term survival. Median overall survival was 60 months, with disease-free survival of 28 months [13].

Primary hepatic leiomyosarcoma remains a rare and challenging oncological entity, and its diagnosis requires a high level of clinical suspicion, careful integration of radiological findings and rigorous histopathological and immunohistochemical confirmation to exclude critical differential diagnoses, especially metastases from other primary leiomyosarcomas. Some 19 cases like the one reported in this article have been found in the literature and are listed in Table 1.

**Table 1.** Management outcomes of published case series of primary hepatic leiomyosarcoma.

| Reference | Age in years | Sex | Risk factors | Management | Follow up/outcome |
|---|---|---|---|---|---|
| [14] | 49 | F | | Wedge ressection | Died at 18 mo |
| [15] | 62 | M | | Died at 18 mo | Died at 20 mo |
| [16] | 69 | M | | Alive at 24 mo | Alive at 24 mo |

| | | | | | |
|---|---|---|---|---|---|
| [17] | 69 | F | | Surgery | Recurrence after 10 years |
| [18] | 62 | F | | Recurrence after 10 yr | Diagnosis at autopsy |
| [19] | 25 | M | | Diagnosis at autopsy | Death at three mo |
| [20] | 64 | F | | Surgery | No evidence of desease at 24 mo |
| [21] | 78 | M | Chemotherapy, radiation | | Death at 10 mo |
| [22] | 62 | M | Gastric GIST post resection | Right lobectomy + wedge resection of the left lobe | No evidence of disease |
| [23] | 62 | M | | Chemotherapy, radiation | No evidence of disease at 5 mo |
| [24] | 78 | M | | Left hepatectomy | No evidence of disease at 18 mo |
| [25] | 58 | F | | Right posterior segmentectomy | Death in 11th postoperative day |
| [26] | 12 | F | Trisegmentectomy, chemotherapy | Surgery | No evidence of disease at 6 yr |
| [27] | 86 | F | Surgery | Liver transplant | No evidence of disease at 5 mo |
| [28] | 63 | M | Conservative | Right extended hepatectomy | No evidence of disease |
| [29] | 67 | M | | Hepatectomy | Recurrence at 18 mo |
| [30] | 38 | M | Hepatitis C | Surgery | Death at 37 mo |
| [31] | 33 | F | Prior renal transplant | No evidence of disease | No evidence of disease at 82 mo |
| [32] | 26 | M | Hodgkin's lymphoma | Death at 25 mo | No evidence of disease at 8 mo |

Radical surgical resection (R0) offers the only chance of a cure or prolonged survival, highlighting the importance of early diagnosis. Unfortunately, the overall prognosis is unfavorable due to late diagnosis, large tumor size, high recurrence rate and limited options for effective systemic treatment. Chemotherapy and radiotherapy have mainly palliative or adjuvant utility in selected scenarios. Future advances depend on a better understanding of the molecular biology underlying LHP, which can identify actionable therapeutic targets, and the development of international collaborative clinical trials focused on rare sarcomas. The registration of cases in multicenter databases is essential to generate more robust evidence to guide the management of this devastating disease.

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**Research Ethics Committee Approval:** Written informed consent was obtained from the patient for the publication of anonymized clinical data and images. The study followed the ethical guidelines established by the Declaration of Helsinki.

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**Conflicts of Interest:** None.

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