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Sclerosing Hemangioma of the Liver. Unusual and Benign Hepatic Neoplasm

Hemangioma Esclerosante del Hígado. Neoplasia Hepática Inusual y Benigna

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SUMMARY: Hemangiomas are the most common non-cystic benign liver tumors. Typically, they are incidentally discovered through routine radiological imaging. These tumors can become complicated and develop fibrosis, with the extreme presentation being hepatic sclerosing hemangioma (HSH), a very rare, atypical benign tumor. Initial diagnosis of HSH is often erroneous, as it can be confused with primary or secondary malignant liver neoplasms. Consequently, HSH are frequently resected, and the diagnosis is confirmed through histological and immunohistochemical studies of the resected specimen. The aim of this manuscript was to report a surgically treated case of HSH and review the existing evidence regarding its clinical and morphological characteristics. The case of a 79-year-old male patient, who underwent surgical intervention for HSH at RedSalud Mayor Temuco Clinic in October 2023, was examined. A solid tumor situated Segment VI, measuring 4 cm in its largest dimension was identified. MRI demonstrated a mass with low-signal intensity mass on T1-weighted images and areas of high-signal intensity on T2-weighted images and a hypointense mass in the hepatobiliary phase. The tumor was completely excised. Subsequent to histopathological analysis, immunohistochemical staining was performed for WT1, CD31, ERG, CD34, and Pancitoqueratina AE3 & AE1. The patient experienced an uneventful postoperative course and was discharged on the third day after the surgery. During follow-up assessments, the patient's overall condition remains satisfactory. HSH is an exceedingly rare tumor. Clinical features and imaging findings associated with this type of lesion are non-specific. It should be included in the differential diagnosis of solid liver lesions. Complete surgical resection with clear margins is the treatment of choice, and it prognosis is favorable.

KEY WORDS: Hemangioma; Cavernous hemangioma; Sclerosing hemangioma; Liver.

INTRODUCTION

Hepatic cavernous hemangioma represents one of the most frequently encountered benign hepatic neoplasms; however, hepatic sclerosing hemangioma (HSH) is exceedingly rare (Yugawa *et al*., 2018; Xu *et al*., 2019). The degeneration of hemangioma may occur through an escalation in fibrosis and thrombosis within its vascular channels, a condition known as sclerosing or hyalinizing hemangioma. This process may lead to the final stage or involution, during which the hemangioma undergoes complete sclerosis or hyalinization (Yamada *et al*., 2012).

The first report of a HSH dates back to 1983, documenting four individuals with solitary necrotic liver nodules that mimicked metastases: two diagnosed during surgery and the other two through post-mortem examination (Shepherd & Lee, 1983). Furthermore, there is evidence suggesting that by December 2022, only 78 cases had been documented in the literature (Poras *et al*., 2022). Nevertheless, as of October 2023, our records indicate the publication of slightly over 100 cases (Makhlouf & Ishak, 2002; Ridge *et al*., 2014; Hwang *et al*., 2019; Kim *et al*., 2021; Poras *et al*., 2022).

The differential diagnosis of HSH includes considerations for intrahepatic cholangiocarcinoma, hepatocellular carcinoma, hepatic metastases, cystadenocarcinoma, and gallbladder carcinoma (Yamada *et al*., 2012; Wakasugi *et al*., 2015; Sugo *et al*., 2018; Yugawa *et al*., 2018; Koyama *et al*., 2019; Zhan *et al*., 2023). In the majority of cases, the definitive diagnosis is achieved through the histopathological examination of the surgical specimen (Miyamoto *et al*., 2015; Yugawa *et al*., 2018).

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Macroscopically, HSH presents as whitish solid masses, often with a yellowish area, featuring an elastic, soft, and homogeneous surface (Sugo *et al*., 2018). Microscopically, fibrotic areas with hyalinization and a predominance of sclerosed regions are typically observed (Miyamoto *et al*., 2015; Sugo *et al*., 2018). Despite the benign nature of HSH, the differential diagnosis guides towards the complete excision of the lesion as a curative treatment (Xu *et al*., 2019).

The aim of this manuscript was to report a surgically treated case of HSH and review the existing evidence regarding its clinical and morphological characteristics.

CASE PRESENTATION

This report was written according to the Case Report Guidelines (CARE) (Gagnier *et al*., 2014).

Case Description: A 79-year-old male patient with a history of arterial hypertension and type II diabetes mellitus, under treatment with olmesartan, amlodipine, bisoprolol, and metformin, presented with an entirely asymptomatic hepatic focal lesion. The lesion was diagnosed through abdominal computed tomography in 2022, revealing a focal lesion in segment VI measuring 3.6 x 3.3 x 2.9 cm with irregular margins, symmetry, and hypovascularity. Progressive enhancement with intravenous contrast was noted, displaying irregular capsular enhancement, associated with small focal dilations of the adjacent intrahepatic bile duct, as well as retraction of the hepatic capsule, suggesting neoplastic characteristics. In September 2023, Magnetic Resonance Imaging (MRI) confirmed the presence of a focal lesion that was hyperintense in T2 and hypointense in T1, located in segment VI, with a diameter of 4.2 cm. The lesion exhibited hepatic capsule retraction, diffusion restriction, progressive enhancement with intravenous contrast, peripheral enhancement in the late phase, and a non-enhancing component, indicative of a neoplastic lesion, secondary implant, or primary lesion resembling cholangiocarcinoma (Fig. 1). As for surgical history, the patient had only undergone a cholecystectomy.

Laboratory findings indicated an elevated erythrocyte sedimentation rate, uremia, and glycemia; however, tumor markers were negative (Table I). Due to the growth of the lesion, diagnostic uncertainty, and the patient's preference, patient was admitted for surgical exploration. A syndromic

Table I. Preoperative laboratory tests.

Variables	Our case	Normal values
Hemoglobin (g/dL)	14.5	13 - 17
Hematocrit (%)	41.4	40 - 54
Leukocytes (10^3/ul)	7.32	4 - 10
Platelets (10^3/ul)	224	150 - 400
ESR (mm/h)	**14.0**	0 - 13
C-Reactive Protein (mg/dL)	15.1	0 - 10
Blood glucose (mg/dL)	**119**	74 - 99
Uremia (mg/dL)	**47.1**	19.3 - 42.8
Creatinine (mg/dL)	1.1	0.6 - 1.2
Total proteins (g/dL)	7.6	6.4 - 8.3
Albumin (g/dL)	4.1	3.5 - 5.0
Total bilirubin (mg/dL)	0.8	0.2 - 1.3
Alkaline phosphatases (U/L)	74	38 - 126
AST (U/L)	24	17 - 59
ALT (U/L)	21	21 - 72
GGTP (U/L)	36	15 - 73
Prothrombin (%)	97.9	70 - 100
PTTK (s)	26.2	21 - 32
INR	1.01	---
Alpha-fetoprotein (UI/mL)	2.6	0 - 7.5
Carcinoembryonic Antigen (ng/mL)	0.6	0 - 7.5
Ca 19-9 (Um/L)	13.4	0 - 37

ESR: Erythrocyte sedimentation rate; AST: Aspartate aminotransferase; AST: Alanine aminotransferase; GGTP: Gamma-glutamyl transpeptidase PTTK: Partial thromboplastin time; INR: International Normalized Ratio.

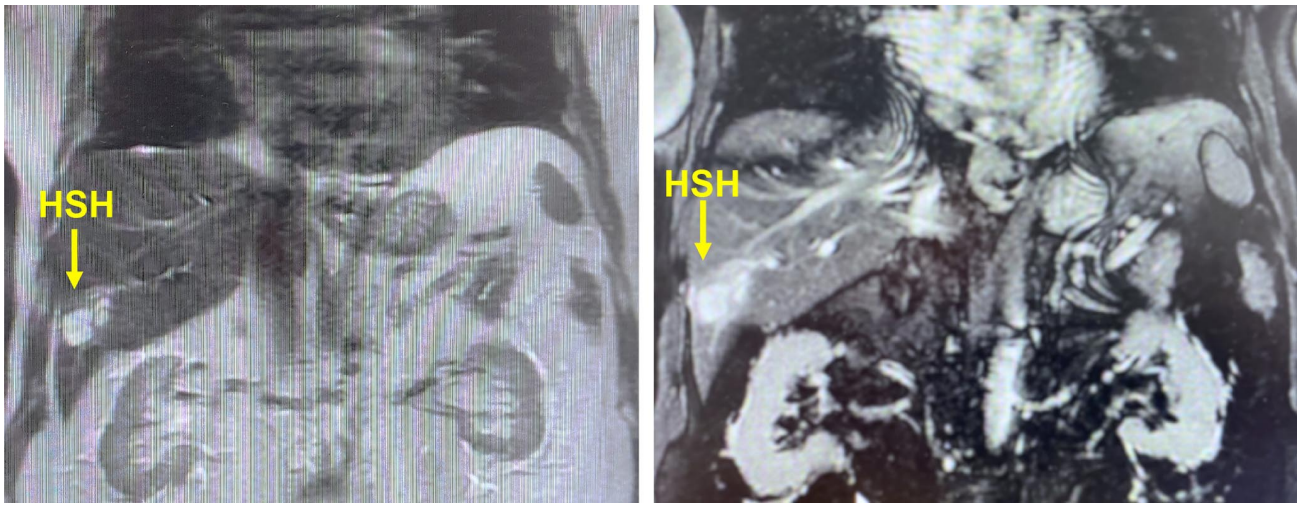

Fig. 1. Image of the patient's lesion by MRI. A localized lesion is observed in segment VI, measuring 4 x 4 x 4 cm. Contrast enhancement reveals wall enhancement, with high signal intensity on T2-weighted images.

diagnosis of a hepatic tumor of unspecified origin, possibly peripheral cholangiocarcinoma, was established.

Surgical findings: Upon laparotomy, the presence of a solid hepatic mass was confirmed in the patient, localized in segment VI, measuring approximately 5 cm in the greater diameter, with retraction of the hepatic capsule. Notably, there was an absence of ascites, enlargement of local lymph nodes, any additional lesions within the liver or peritoneal cavity. Intraoperative ultrasonography facilitated the precise localization of the lesion, assessment of capsular retraction, and evaluation of the lesion's relationship with tributaries of the right hepatic and portal veins (Fig. 2).

Surgery performed: After performing a midline supraumbilical laparotomy with a right-sided in J-shaped extension, the abdominal cavity was systematically explored in quadrants. The round, suspensory, coronary, and right triangular ligaments were sequentially ligated using Ligasure Impact®. Following the aforementioned ultrasonographic exploration, a segmental hepatectomy was performed with safety margins, employing total clamping of the hepatic pedicle with ischemia time of 21 minutes and blood loss of 320 cc. Parenchymal transection was achieved using Ligasure Impact®. Subsequently, a drain was placed in the tumor bed, exteriorized through a counter-opening, and the abdominal wall was closed in layers, utilizing continuous Vycril-0 sutures for the peritoneum, continuous PDS-1 sutures for the aponeurosis, and staples for the skin.

Pathological study: In the macroscopic analysis of the specimen, a piece of hepatic tissue measuring 6 x 6 cm was observed, containing a moderate amount of adipose tissue. Upon sectioning, an indurated nodular formation with irregular margins, whitish-pink in color, measuring 2.7 x 2.5 x 2.5 cm, was identified, situated 3 mm from the surgical margin and 2 cm from the hepatic capsule (Fig. 3). Microscopic analysis revealed a specimen composed of fragments of hepatic tissue with focal architectural distortion, characterized by nodular areas of acellular fibrosis, partly hyalinized, with accumulations of lymphocytes, macrophages containing hemosiderin-type pigment, and foci of dystrophic calcification. In the periphery of these areas, dilated vascular structures with normotypic endothelium were recognized. Focally, vascular structures with irregular, dilated lumens and fibrous septa measuring up to 1 mm were identified. The surrounding hepatic tissue exhibited microfoci of hemorrhagic infiltration, mild steatosis, and micro and macrovesicular vacuolation. Focal lymphocytic and lobular inflammatory infiltration was present, with some eosinophils. Additionally, bile ducts with cholestasis were observed (Fig. 4). The final pathology report concluded the specimen to be a 'sclerosing hemangioma with foci of dystrophic calcification, without atypical features.

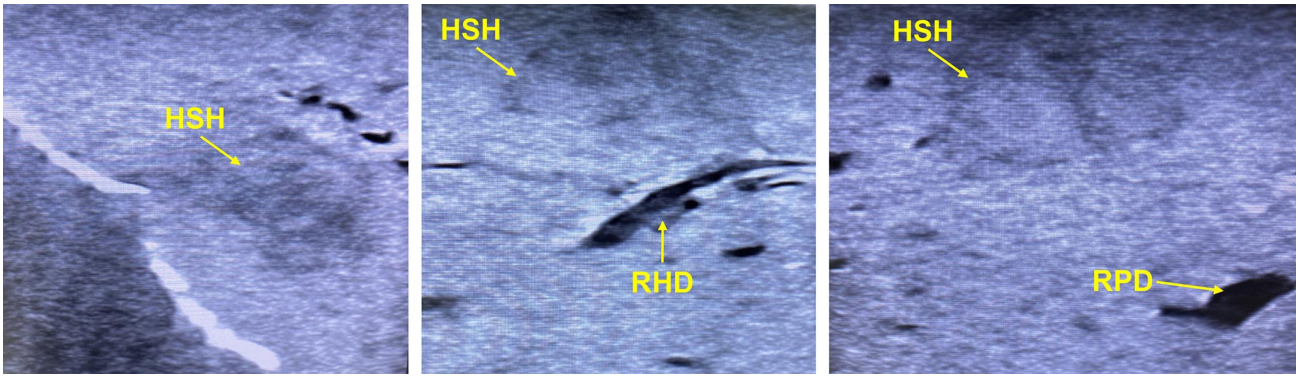

Fig. 2. Intraoperative ultrasound images. RHD: Right Hepatic Vein. RPD: Right Portal Vein. HSH: Hepatic Sclerosing Hemangioma.

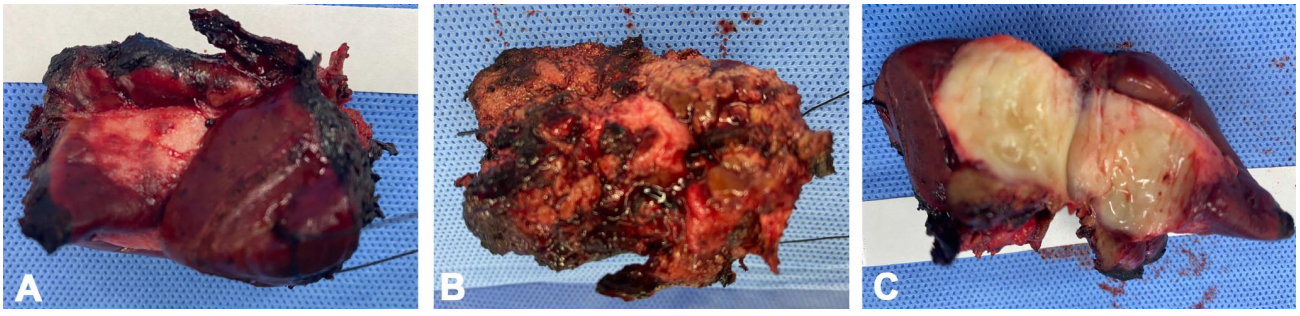

Fig. 3. Fresh surgical specimen. A) Lateral view of segment VI and the HSH. B) Surgical specimen's bloody aspect. C) Cross-section of the specimen. Lesion exposed and extended.

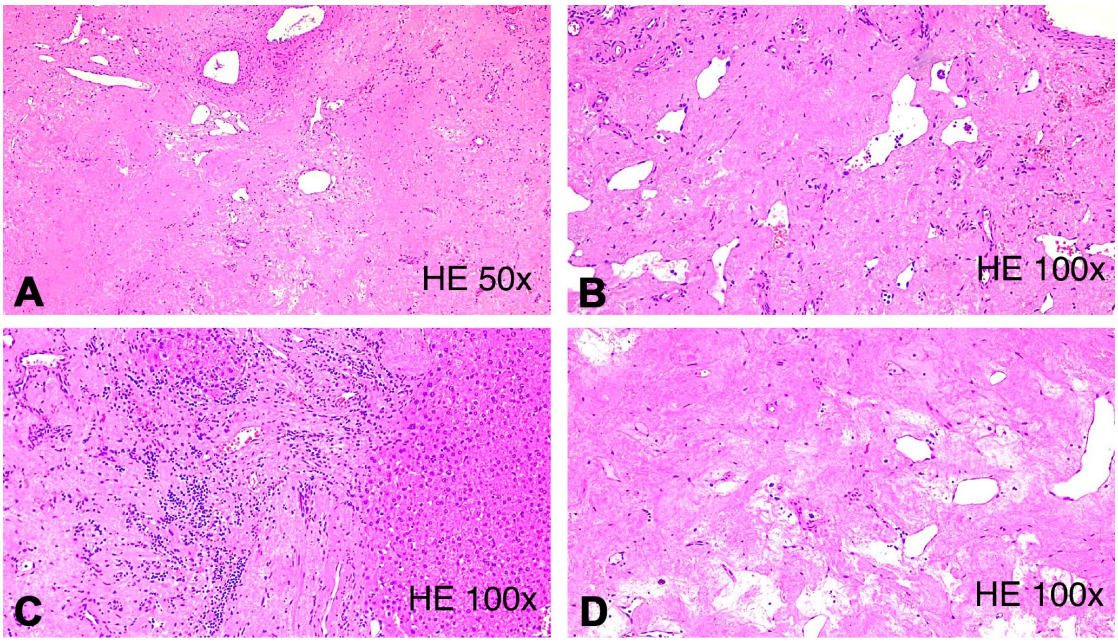

Fig. 4. Microscopy images. H&E staining reveals a lesion composed of vessels of various sizes, dilated, with hyalinized, sclerotic, and fibrous stroma. A) 50x. B) 100x. C) 100x. D) 100x.

Immunohistochemical study: The immunohistochemical analysis, performed using the Roche BenchMark Ultra system, revealed positive staining for WT1 (mouse monoclonal, 6F-H2, Cell Marque), CD31 (mouse monoclonal, JC70, Cell Marque), ERG (rabbit monoclonal, EP111, Cell Marque), and CD34 (mouse monoclonal, QBEND/10, Cell Marque). Conversely, it showed negative results for Pan-cytokeratin AE3 & AE1 (AE/AE/PCK26, Ventana). This comprehensive profile led to the conclusive identification of a «vascular lineage proliferation» (Fig. 5). Postoperative Course: The patient experienced an uneventful postoperative course, with mobilization and oral intake initiated on the first postoperative day, leading to discharge on the third day. During the subsequent follow-up, it was confirmed that the patient was in good overall condition and had resumed normal activities.

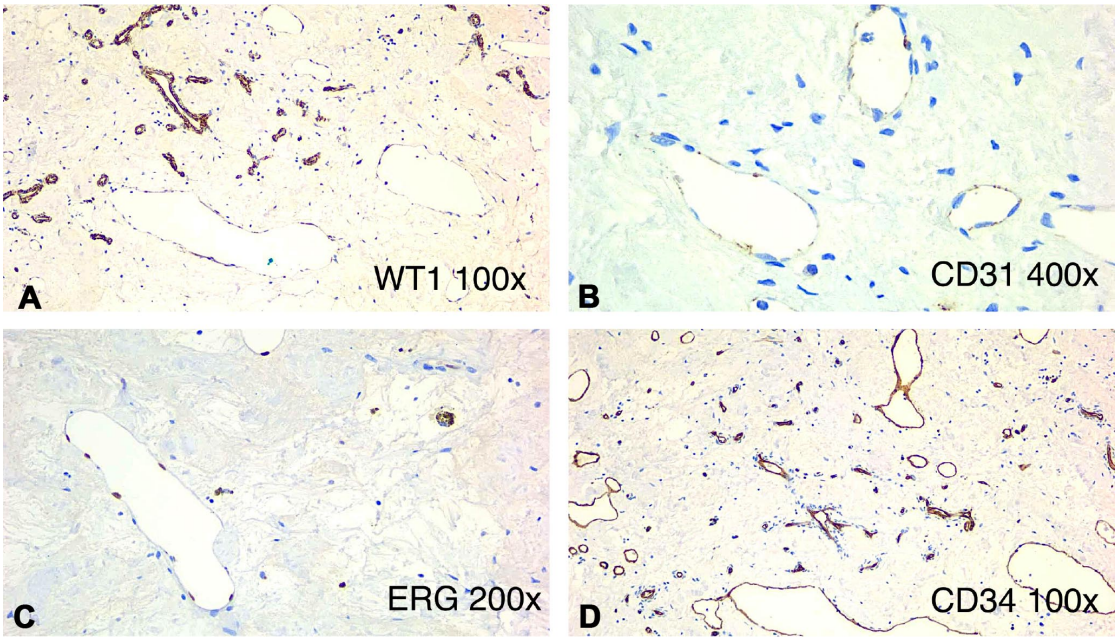

Fig. 5. Immunohistochemistry staining images. Vascular components with positive staining for: A) WT1 in 100x. B) CD31 in 400x. C) ERG in 200x. D) CD34 in 100x.

DISCUSSION

Cavernous hemangioma is the most common benign tumor of the liver, with a prevalence of up to 20 % in autopsy studies, and it is five times more common in women (Papafragkakis *et al*., 2011; Yamada *et al*., 2012; Behbahani *et al*., 2016; Navale *et al*., 2018; Sugo *et al*., 2018; Yugawa *et al*., 2018). However, HSH is an exceedingly rare condition, described in up to 2 out of every 1000 autopsies (Yamada *et al*., 2012; Xu *et al*., 2019).

Sclerosing hemangiomas arise from degenerative changes such as recent hemorrhages, hemosiderin deposits, thrombus formation, necrosis, and scar formation in cavernous hepatic hemangiomas (Xu *et al*., 2019; Takinoshita *et al*., 2022; Ibrahim *et al*., 2023). This can lead to the final stage, where the hemangioma undergoes complete sclerosis or hyalinization. Coexistence of an HSH with a cavernous hemangioma has been documented (Shimada *et al*., 2013; Andeen *et al*., 2015; Yuki *et al*., 2015), as well as the evolution of a cavernous hemangioma into HSH (Jia *et al*., 2021), or the development of pericapillary smooth muscle proliferation (Choi *et al*., 2008). In this case, we observed the synchronous coexistence of an HSH with a cavernous hemangioma.

Imaging techniques play a crucial role in the diagnostic process: Ultrasound (Wang *et al*., 2022), computed tomography (CT) and MRI may exhibit evidence of irregular margins in addition to associated enhancement (peripheral on CT and central on MRI) without contrast uptake (including fluorine-18 fludesoxyglucose and gadoxetic acid), as well as changes during follow-up, related to decreased lesion volume and loss of enhancement regions. Such findings may suggest HSH (Hida *et al*., 2010; Ozaki *et al*., 2018; Hwang *et al*., 2019; Jia *et al*., 2021; Kim *et al*., 2021; Poras *et al*., 2022; Renzulli *et al*., 2022). However, it is common for an HSH to be misdiagnosed as a primary or secondary malignant neoplasm of the liver, often resulting in hepatectomy in such cases (Shin, 2011; Song *et al*., 2013; Sugo *et al*., 2018; Navale *et al*., 2018). In the current case,

Table II. HSH. Evidence 2002-2023.

Author	Age	Sex	LS	Diameter (cm)	Dynamic TC	MRI (T1/T2)	Preoperative Dg.
Makhlouf & Ishak, 2002 (n=18)	63	M:12	RL=12	6.0	NR	NR	NR
Choi *et al*., 2008	63	M	6-7	14.0	No enhancement	Low/intermediate	CC
Hida *et al*., 2010	75	F	5-6	3.0	Ring enhancement	Low/High	LM
Papafragkakis *et al*., 2011	52	F	7	6.2	NR	NR	NR
Shin, 2011	50	M	RL	10.0	Ring enhancement	Low/High	HSH
Yamada *et al*., 2012	75	M	8	1.1	Ring enhancement	Low/High	LM
Yamada *et al*., 2012	75	M	8	1.1	Ring enhancement	Low/High	LM
Song *et al*., 2013	63	F	2-3	9.1	Ring enhancement	NR	Undetermined
Shimada *et al*., 2013	63	M	8	1.0	Ring enhancement	Low/High	Hemangioma
Ridge *et al*., 2014 (n=12)	63.3	F10	NR	4.2	NR	Low/High-5	NR
Andeen *et al*., 2015	60	F	4	3.5	No enhancement	Low/intermediate	CC
Miyamoto *et al*., 2015	76	M	6-7	5.9	Ring enhancement	Low/High	CC
Wakasugi *et al*., 2015	67	F	7	2.8	Ring enhancement	High/High	LM
Yuki *et al*., 2015	81	M	RL	7.0	NR	NR	LM
Behbahani *et al*., 2016	67	M	8	3.8	Ring enhancement	High/High	LM
Navale *et al*., 2018	69	F	4-5	4.0	No enhancement	Low/Low	Gallbladder Cancer
Ozaki *et al*., 2018	57	M	2-3	4.5	Ring enhancement	High/High	CC
Sugo *et al*., 2018	39	F	RL	17.0	Ring enhancement	Low/High	Cystadenocarcinoma
Yugawa *et al*., 2018	48	M	RL	6.7	Ring enhancement	Low/High	HCC
Hwang *et al*., 2019 (n=9)	57.5	M=5	NR	NR	NR	Low8/Low6	Malignant neoplasm
Koyama *et al*., 2019	68	M	5	2.2	Ring enhancement	Low/High	LM
Xu *et al*., 2019	65	M	RL	16.7	No enhancement	NR	Hemangioma
Jia *et al*., 2021	56	F	6-7	3.9	Ring enhancement	Low/High	LM
Jia *et al*., 2021	63	M	7	3.8	Ring enhancement	Low/High	CC
Kim *et al*., 2021 (n=18)	64.5	F10	NR	NR	Ring enhancement	High/High	NR
Takinoshita *et al*., 2022	60	F	8	3.5	Ring enhancement	Low/High	CC
Poras *et al*., 2022	85	F	3-4	3.0	Ring enhancement	Low/High	CC
Zhan *et al*., 2023	52	F	6-7-8	9.7	NR	High/High	HCC
Ibrahim *et al*., 2023	36	F	RL	15.7	Ring enhancement	NR	NR
Our case	79	M	6	4.5	Ring enhancement	Low/High	CC

F: Feminine; M: Masculine; LS: Liver segment ; RL: Right Lobe; LL: Left Lobe; CT: Computed Tomography; NR: Not Reported; MRI: Magnetic Resonance Imaging; HSH: Hepatic Sclerosing Hemangioma; CC: Cholangiocarcinoma; LM: Liver Metastasis; HCC: Hepatocellular Carcinoma.

MRI suggested the possibility of the lesion being a cholangiocarcinoma or a secondary neoplasm; hence, the decision was made to perform the excision of the lesion along with the adjacent hepatic segment.

From the available evidence spanning from the year 2000 to the present, a bibliographic record revealed somewhat over 100 cases of HSH. These cases are predominantly observed in females (55.7 %), with an average age and lesion diameter of 64 years and 5.6 cm, respectively (Table II).

In conclusion, it can be asserted that HSH represents a rare benign entity, occurring in association with the degeneration and sclerosis of cavernous hepatic hemangiomas. Surgical resection stands as the treatment of choice for HSH.

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MANTEROLA, C.;RIVADENEIRA, J. & BENDEL, S. Hemangioma esclerosante del hígado. Neoplasia hepática inusual y benigna. *Int. J. Morphol., 42(3)*:728-734, 2024.

RESUMEN: Los hemangiomas son los tumores hepáticos no quísticos benignos más comunes. Lo habitual es que se descubran de forma incidental con imágenes radiológicas de rutina. Estos pueden complicarse y desarrollar fibrosis, cuya presentación extrema es el hemangioma esclerosante hepático (HEH); un tumor benigno atípico muy poco frecuente, cuyo diagnóstico inicial suele ser erróneo, confundiéndose con neoplasias malignas primarias o secundarias del hígado. Por ello, es frecuente que sean resecadas y que el diagnóstico se establezca mediante estudios histológicos y de inmunohistoquímica del espécimen resecado. El objetivo de este manuscrito fue reportar un caso de HEH, que fue intervenido quirúrgicamente; y revisar la evidencia existente respecto de sus características morfológicas y clínicas. Caso clínico: Hombre de 79 años, con HEH intervenido quirúrgicamente en Clínica RedSalud Mayor Temuco en octubre de 2023. Se verificó un tumor sólido de 4 cm de diámetro mayor, localizado en el segmento VI del hígado. La resonancia magnética demostró una masa con baja intensidad de señal en T1 y áreas de alta intensidad de señal en T2. El tumor fue extirpado por completo. Después del estudio histopatológico, se realizaron tinciones inmunohistoquímicas complementarias para WT1, CD31, ERG, CD34 y Pancitoqueratina AE3 & AE1. El paciente tuvo un curso postoperatorio sin incidentes, siendo dado de alta al tercer día postoperatorio. En el control alejado, se encuentra en buenas condiciones generales. El HEH es un tumor muy poco frecuente. Las características clínicas e imágenes de este tipo de lesiones son inespecíficas. Debe de las lesiones sólidas del hígado. La resección considerarse en el diagnóstico diferencial quirúrgica completa con bordes libres es el tratamiento de elección; y su pronóstico es favorable.

PALABRAS CLAVE: Hemangioma; Hemangioma cavernoso; Hemangioma esclerosante; Tumor hepático.

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