Primary extrarenal rhabdoid tumour of the liver: a case report and literature review

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Abstract

Background: **Extrarenal rhabdoid tumours (ERT) are highly aggressive tumours that are poorly responsive to standard cytotoxic chemotherapy and are associated with a grim prognosis. Primary ERT of the liver are most commonly observed in early childhood and exceptionally rare later in life.**

Case presentation: **We report the case of a 16-year-old male patient, presenting with flu-like symptoms after his second COVID-vaccination. During the work-up, a large solid liver lesion was incidentally discovered upon abdominal ultrasound examination. Pathological examination rendered the diagnosis of primary ERT of the liver, characterized by the loss of expression of INI-1 protein, encoded by the SMARCB1 gene. We summarized and discuss the existing literature by reviewing 53 pediatric and 6 adult cases, including the histological features treatment and outcomes of primary hepatic ERT.**

Conclusion: **Primary ERT of the liver are usually not associated with specific signs or symptoms, making the diagnosis very challenging. As ERT are associated with a high metastatic rate, delayed diagnoses lead to increased mortality, as complete resection is not possible in advanced-stage cases. Therefore, early diagnoses, enabling complete resection of the tumour are crucial to improve patient outcomes. Of interest, primary ERT of the liver, is associated with biallelic loss of the SMARCB1 (SWI/SNF Related, Matrix Associated, Actin Dependent Regulator Of Chromatin, Subfamily B, Member 1) gene, a potential target for cancer therapeutics. This is, to our knowledge, the first case of a hepatic rhabdoid tumour treated with liver transplantation.** (Acta gastroenterol. belg., **2023,** 86, **555-562**).

Keywords: rhabdoid tumour, liver tumour, SMARCB1, INI-1, liver transplantation.

Abbreviations

AFP :Alpha-fetoprotein; CA 125: Cancer antigen 125; CA 19.9: Carbohydrate antigen 19-; CBC: Complete blood count; CEA: Carci-noembryonic antigen; COVID: Coronavirus disease; CEUS: Contrast enhanced Ultrasonography; CEUS: Contrast enhanced Ultrasonography; CRP: C-reactive protein; CT :Computed tomography; DOX :Doxorubicin; EMA: Epithelial membrane antigen; ERT: Extra-renal rhabdoid tumour; ICE: Ifosfamide, Carboplatinum, Etoposide; INI-1: integrase interactor 1; MRI: Magnetic resonance imaging; MRT: Malignant rhabdoid tumour; PET: Positron emission tomography; SCUD: Small Cell Undifferentiated; US: Ultrasonography; VCA: Vincristine, Cyclophosphamide, Actinomycin-D.

1. Introduction

In 1978, Beckwith et al. were the first to describe a malignant rhabdoid tumour (MRT) located in the kidney as a variant of Wilms tumour (1). MRT have subsequently been diagnosed in extrarenal locations, e.g., the central nervous system, genitourinary tract, gastrointestinal tract, mediastinum and soft tissues, hence the name was changed to 'extrarenal rhabdoid tumour' (ERT). ERT have mainly been diagnosed in young children and infants.

Primary ERT of the liver is exceptionally rare and almost exclusively seen early in life, in children under 3 years old (2). The first case of ERT in the liver was described in 1982 by Gonzalez-Crussi et al. (3). To date, only a few cases of ERT have been described in the adult population (4-9). Histological origin, pathogenesis and best therapeutic strategies are still unclear.

We present the case of a 16-year-old patient who was diagnosed with hepatic ERT.

2. Patient concerns and investigations

2.1 Clinical presentation

A 16-year-old male without significant medical history was admitted to the emergency department with influenza-like symptoms, pyrexia up to 38.8 °C, a heart rate of 84 bpm, blood pressure of 124/88 mmHg, a saturation of 98% without oxygen supply and a respiration rate of 15 /min.

He complained about chills, headaches, and loss of appetite following his second COVID-vaccination.

He had also been experiencing generalized muscle weakness for several months.

He did not present any other symptoms, nor abdominal pain. The physical examination was normal. The patient had no relevant personal or familial medical history,

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other than a grandfather who smoked and died of lung cancer at the age of 83.

2.2 Laboratory investigations:

Laboratory investigations revealed a normal complete blood count (CBC). Tumour markers were negative: alpha-fetoprotein (AFP) <3.0 µg/L, carbohydrate antigen 19-9 (CA 19-9) of 14 kU/L, cancer antigen 125 (CA 125 of 9.2 kU/L and carcinoembryonic antigen (CEA) <1.8 µg/L. Inflammation markers were elevated: Creactive protein (CRP) of 150 mg/L and sedimentation rate of 83 mm/H. Tests for viral hepatitis (B and C) and Human immunodeficiency Virus (HIV) were negative. There was no coagulation disorder. Renal function was normal, and there were no electrolyte disturbances (table 1).

2.3 Radiological investigations

After identifying an anicteric cholestasis, we proceeded with further investigation through imaging. Radiological work-up included ultrasonography (US) (Figure 1), computerized tomography (CT) (Figure 2), and magnetic resonance imaging (MRI) (Figure 3). A large heterogenous mass was found in the right liver, no extrahepatic metastasis were observed, which was corroborated subsequently by positron emission tomography (PET) scan.

2.4 Histological investigations

Biopsies were taken from the liver tumour and from the healthy liver parenchyma. The latter did not show any abnormalities. The tumour was highly cellular, lacking hepatocellular differentiation, confirmed by the lack of hepar and glypican-3 expression upon immunohistochemical staining. The tumour cells had cleared, atypical nuclei with prominent nucleoli. They showed scant cytoplasm, which was clear or eosinophilic, sometimes vacuolated, with indistinct cell borders. Only rare tumour cells with eccentric nuclei (i.e., with a rhabdoid aspect) were found. (Figure 4 A)

Further immunohistochemical investigation showed the absence of pan-cytokeratin (CK AE1/3), focal membranous, but not nuclear, staining of beta-catenin, (*Figure 4 B*) and loss of nuclear INI-1 (integrase interactor 1) expression (Fig. 4). Based upon morphological findings and the characteristic loss of nuclear INI-1 expression, the diagnosis of ERT was made.

Further molecular analysis was conducted using methylation profiling (in collaboration with the Genome Diagnostics section of the Department of Biomedical Genetics and *the Deutsches Krebsforschungszentrum in Heidelberg*, EPIC 800k array, v12.2). This analysis confirmed the diagnosis of ERT, with a calibrated score for the array of 0.95 (scores more than 0.90 are deemed reliable). In addition, homozygous loss of INI -1, duplication of chromosomes 1q, 7, and 12 and heterozygous loss of chromosome 16q were found using whole genome sequencing (*Figure 4 C*).

Table 1. — **Laboratory investigations**

Hemostasis		
APTT Actin FS	25.4	21.6-28.7 s
Actin FS ratio	1.08	0.80-1.20
PT	99.0	70-130 %
I.N.R	1.02	0.95-1.31
PT secondes	10.7	9.8-12.5 s
Hematologie		
Hemoglobine	12.6	13-18 g/dL
Plaquettes	318	150-440 x10^3/mm³
Leucocyte	9.34	3.5-11 x10^3/mm³
Lymphocytes absolu	1.38	1.2-3.5 x10^3/mm³
Monocytes absolus	0.71	0.1-1 x10^3/mm³
Eosinophiles absolus	0.04	0.1-0.5 x10^3/mm³
Leukocyte classification		
No lymphocytosis or B or T lymphopenia.		
No detectable T phenotypic anomaly.		
Chemistry		
Sedimentation rate	83	<15 mm/H
C-reactive Protein	55	<5.0 mg/L
Conjugated bilirubin	0.48	<0.20 mg/dL
Total bilirubin	0.93	<1.2 mg/dL
Alkaline phosphatases	681	82-331 U/L
Gamma-glutamyl transferase	716	10-71 U/L
Alanine aminotransferase	41	<18 U/L
Aspartate aminotransferase	27	<32 U/L
Lactate dehydrogenase	432	<240 U/L
Albumin	40	40-49 g/L
Humoral immunity		
IgG g/L	10.81	7.36-15.04 g/L
IgA g/L	1.68	0.70-3.21 g/L
IgM g/L	0.82	0.51-1.94 g/L
Viral serology		
HIV 1+2 (Ac + Ag p24)	Negative	Negative
Antibody anti HCV	Negative	Negative
Antibody anti HBcore	Negative	Negative
Antigene HBs	Negative	Negative
Tumour markers		
Alpha-fetoprotein	<3.0	<14 µg/L
CA 19-9	14	<27 kU/L
CA 125	9.2	<35 kU/L
CEA	<1.8	<5,2 µg/L

2.5 Neoadjuvant chemotherapy

The patient was treated with the EU-RHAB-V5 2016 protocol more than 18 months for MRT consisting of a chemotherapy regiment with Doxorubicin, (DOX) Ifosfamide, Carboplatinum, Etoposide, (ICE) Vincristine,

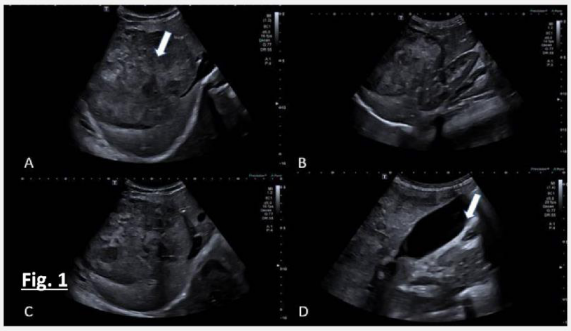

Fig. 1

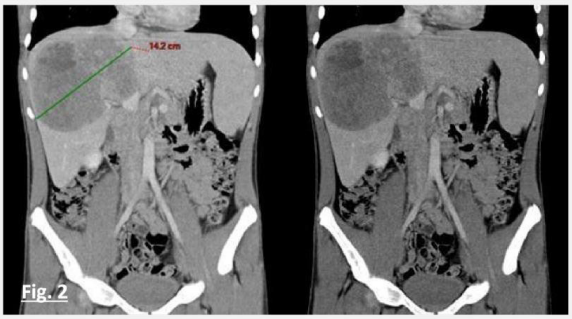

Fig. 2

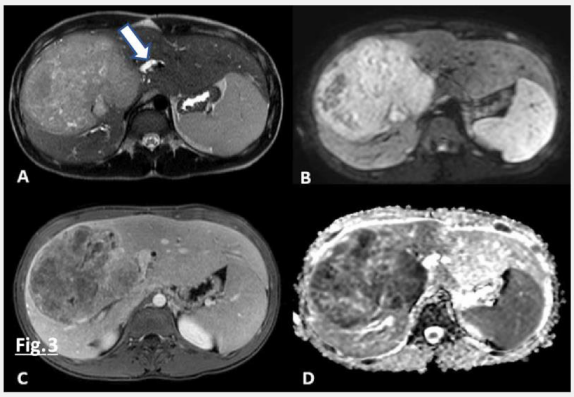

Fig.3

Fig. 1: Ultrasonography (US):

A+C: Large heterogenous mass (arrow) measuring 12,5 cm x 10,9 cm x 12,7 cm, compressing the hepatic vessels without invading them.

B: Mass causing dilating of the biliary ducts.

D: No signs of cholecystitis or gallstones. (arrow)

Fig. 2: Computerized tomography (CT): in the portal venous phase, coronal plane shows a well-defined hypo-attenuating heterogeneous mass in the right liver, without calcifications. No extrahepatic metastases can be seen which was confirmed subsequently by positron emission tomography (PET) scan.

Fig. 3: Magnetic resonance imaging (MRI)

A: T2 image in the axial plane showing the hyperintense mass in the right liver causing compression on the biliary bifurcation with left duct dilation (arrow)

B: Diffusion weighted imaging shows a hyperintense lesion, with a high b value (b800)

C: Axial T1 weighted image after gadolinium-based intravenous contrast injection in the portal venous phase shows a heterogeneous enhancement of the mass with perilesional capsule and no vascular invasion.

D: Apparent diffusion coefficient (ADC) map showing diffusion restriction.

Cyclophosphamide and actinomycin-D (VCA). (10) The chemotherapy was initiated in January 2022. After the first 2 cycles of chemotherapy, a reduction in size of the tumour was confirmed by an abdominal ultrasound. However, the tumour was still considered unresectable due to its vascular contact with the vessels of the left liver (Figure *5*), therefore a liver transplantation was performed.

2.6 Liver transplantation

The liver transplantation was performed 3 months after the initiation of chemotherapy. After a modified Mercedes-Benz subcostal incision, the muscular, fascial layer and peritoneum were dissected, revealing yellow-brownish ascites that did not contain any neoplastic cells upon extemporaneous examination. No peritoneal carcinomatosis was demonstrated during the intervention. The right liver contained a large mass. A classical hepatectomy was done with implantation of an entire cadaveric liver transplant. Vascularization of the graft was controlled with ultrasonography. Empirical antibiotics (temocillin and ampicillin) were administered as well as immunosuppression (tacrolimus and basiliximab).

2.7 Anatomopathological examination of the resected liver

Macroscopic and microscopic examination of the resected liver are seen in figure 6.

2.8 Post-operative treatment and follow-up

One month after the transplantation, the patient began adjuvant chemotherapy according to the EU-RHAB V5 2016 protocol. He completed his ninth cycle of VCA in September 2022. The follow-up consisted of thoracic radiography and abdominal ultrasound.

In May 2023, the patient experienced a relapse characterized by the presence of multiple perihilar

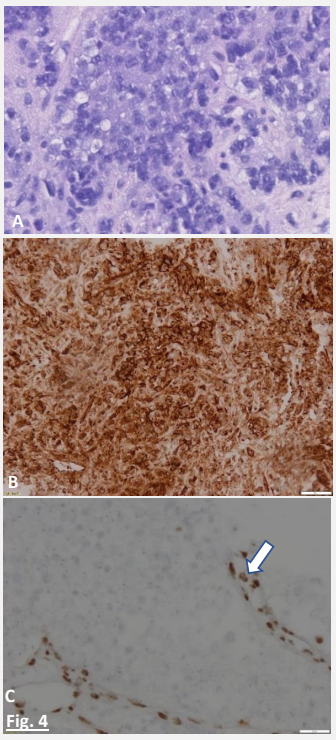

Fig. 4:
A: Hematoxylin and eosin-stained slide of highly cellular liver tumour with pleomorphic nuclei, some with prominent nucleoli. (Hematoxylin and eosin-stained slide. Magnification:100x)

B: Immunohistochemistry stains showed focal membranous, but not nuclear, staining of beta-catenin. (Magnification : 100x)

C: Immunohistochemical staining of the same tumour INI-1, the protein product of the SMARCB1 gene, showing absence of staining in tumour cells, while normal intervening cells have retained immunoreactivity,(arrow) supportive of a diagnosis of malignant rhabdoid tumour. (Magnification 100x)

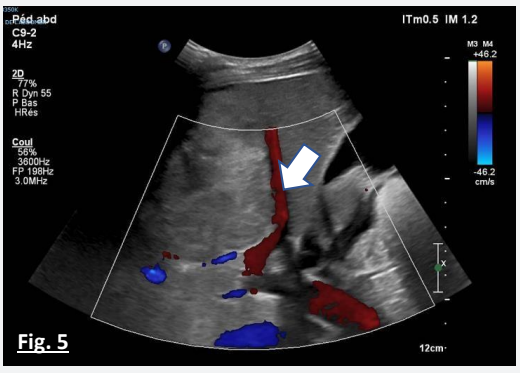

Fig 5.: Contact between the tumour and the right hepatic artery confirmed by ultrasonography (arrow)

nodules in the transplanted liver, which was confirmed through an ultrasound-guided biopsy. We performed DNA NGS analysis a 73-gene panel for sarcoma, including fusions and splice variants in 55 genes, as well as CNV sequencing. We identified a pathogenic variant in the CTNNB1 gene.

In July 2023, a TOTEM chemotherapy regimen was initiated with palliative intent. It involved the administration of topotecan and temozolomide on days 1-5, along with ribociclib on day 1. During the last medical assessment in August 2023, the patient is still alive.

3. Review of literature and discussion

Primary ERT of the liver is a rare and highly aggressive malignancy, most frequently encountered before the age of 3 years old, with a median age of 8 months at presentation, associated with a poor prognosis (2). Its pathogenesis is poorly understood, and the histopathological origin is still unknown. The best treatment modality remains unclear (11). In patients older than 16 years old, it is exceptionally rare, with only 6 cases being published to date, with a mean age of 45 years. In contrast, 53 paediatrics cases have been published, leading to a child-to-adult ratio of approximately 9:1.

Signs and symptoms associated with ERT are often nonspecific and include fatigue, anorexia, chronic epigastric pain, fever, and vomiting. Acute signs and symptoms can be seen in case of tumour rupture with haemorrhage (table 2).

In our case, imaging played a crucial role in the diagnostic work-up. In the literature, ERT of the liver in the adult population are described as solid heterogenous single or multiple masses on CT scan with edge enhancement and as cystic or solid heterogenous masses on ultrasound. The largest series of 14 cases including all age groups describes ERT of the liver as large and

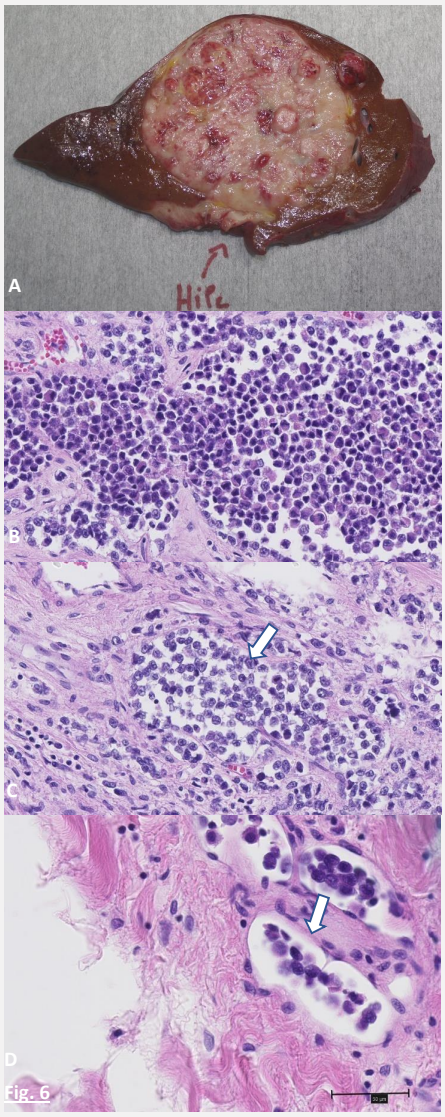

Fig. 6:
A: Macroscopically, the right lobe presented a well - defined mass of 8 x 7 × 14 cm,limited by a thin capsule. It was characterised by a necrotic haemorrhagic parenchyma interspersed with fibrotic and fatty areas. Necrosis was estimated macroscopically at 15%. The lesion involved all segments of the right lobe. (hile=hilum)

B: Microscopically, the lesion was relatively well circumscribed and consisted of nodules of tumour cells, forming small islands, cords and glandular structures. These were interspersed by a fibrous or loose and myxoid stroma. Some lakes of intratumoural red cells were noted as well as small foci of foamy macrophages, cholesterol clefts, giant cells and necrosis, which could either represent non -specific changes related to the prior biopsy, true tumour necrosis or a mild therapeutic effect (post-chemotherapy). The tumour was composed of a homogeneous cell population, of small and round cells, with either a clear and nucleolated nucleus or a hyperchromatic one. (Hematoxylin and eosin-stained slide Magnification 40x)

C: Some reniform nuclei were also noted, as well as rare cells with a rhabdoid appearance, (arrow) i.e., cells characterized by an eosinophilic cytoplasm and an eccentric nucleus.(Hematoxylin and eosin-stained slide Magnification 40x)

Mitotic activity was estimated at 10 mitotic figures per 10 high power fields.

D: Lymphovascular invasion (arrow) was present at the hepatic hilum.

All analysed lymph nodes were free of metastasis. Surgical resection was complete. All margins were healthy. Stade TNM : ypTI NO Mx. (Hematoxylin and eosin-stained slide Magnification 40x)

heterogeneous masses with a medial long axis size of 10.6 cm. Calcifications and cystic changes are occasionally described (12). However, no pathognomonic imaging features have yet been identified to make the diagnosis of hepatic ERT. The diagnosis indispensably requires histological examination of the tumour.

Histopathological diagnosis is challenging, due to the overlap with several other entities like rhabdomyosarcoma, epithelioid sarcoma, rhabdoid melanoma and Small Cell Undifferentiated (SCUD) Hepatoblastoma (13-15). Furthermore, ERT of the liver can be either mixed or pure and is thought to be misclassified in one-third of the cases as SCUD Hepatoblastoma (14, 15). Therefore it is not surprising that three out of the first reported 20 cases of ERT of the liver were initially misdiagnosed as hepatoblastoma (16-18).

Laboratory investigation can help to differentiate between hepatoblastoma and other neoplasms of the liver in young children, but specificity and sensitivity are low. Oita and al. (2) reported elevated AFP levels, relative to age-matched standard values, in 26.7% of 53 cases of paediatric hepatic ERT. In our literature review, 1 of 6 cases presented elevated AFP and CEA levels.

Microscopically, ERT typically show a rhabdoid morphology, but in the liver, they are often composed of rather undifferentiated cells, with only focal rhabdoid features, as was true for our case. ERT cells are polyphenotypic, expressing a wide range of immunohistochemical markers, including epithelial markers such as cytokeratins and epithelial membrane antigen (EMA), and often also neuroectodermal markers such as CD99 and synaptophysin. However, the diagnosis is mostly based on the characteristic loss of nuclear INI-1 expression (encoded by *SMARCB1*), or, more rarely, loss of BRG1 protein expression (the protein product of the SMARCA4 gene, mutations of which account for 5% of ERT cases).

In our literature review, nuclear INI-1 expression was lost in all examined adult (5 out of 5, the 6th adult case not being examined) and pediatric cases (32 out of 32 tested cases), making deletion of the *SMARCB1* gene, a presumed tumour suppressor gene located in

Table 2. — **Literature review of liver ERT > 16 years**

Author	Age (years)	Sexe	Inaugural symptoms	Laboratory investigations	INI-1	Radiological investigations	Treatment	Metastasis	Outcome
Marzano (2009) (4)	27	male	Acute epigastric pain	AFP (1.3 ng/mL), CA 19.9 (15.2U/mL) were within normal range. No alterations of biological examinations.	NA	**US**: heterogeneous (15 × 7 cm) mass with intratumoral arterial vascularization **CEUS**: precocious hypervascularisation of the lesion with hypoechogenic spots and late wash-out. **CT-scan and MRI** confirmed the ultrasound report and moreover showed a nodule of 1.5 cm on the segment VIII. The signal and the vascular kinetic were in favour of a fibrolamellar hepatocarcinoma or of a cholangiocarcinoma.	Left hepatectomy	NA	Still alive after diagnosis 25 months
Sibilieau (2011) (5)	27	male	Fatigue, acute epigastric pain	Normal liver function test, AFP, CEA and CA 19.9 within normal range	loss	**US:** heterogenous mass **CT:** low-density mass with edge enhancement **MRI:** low signal on T1, heterogeneous high signal on T2	Left hepatectomy chemotherapy	Without	Still alive after diagnosis 41 months
Kang (2013) (6)	50	male	Weight loss	AST/ALT/alkaline phosphatases elevated, AFP and CEA elevated CA19.9 within normal range	loss	**CT:** large hypoattenuating hepatic mass with rim enhancement in the left lobe of the liver **Positron emission tomography** shows a very large hypermetabolic hepatic mass	NA	NA	NA
Basir (2017) (7)	51	male	Weight loss, dysphagia	CEA and AFP within normal range	loss	**CT:** hepatomegaly with multiple irregular hypoechoic necrotic lesions	NA	Left adrenal wide-spread lymphad-enopathies	NA
Ye (2020) (8)	40	female	Chronic epigastric pain, followed by acute epigastric pain due to tumour rupture	Hemoglobin 8,2 g/dL, normal liver function test, normal coagulation, AFP, CEA and CA19.9 within normal range	loss	**US:** heterogenous mass **CT:** Subcapsular mass shadow with regular shape, clear boundary and uneven density, suggesting haematoma (Hu between 20 and 45) **MRI:** irregular mass with mixed short T1-weigh	Right hemihepa-tectomy no chemo-therapy	Metastasis: is it really "paraoesophaesophageal" or rather "paraoesophageal"	Alive 18 month after surgery
Pasricha (2020) (9)	60	male	Chronic abdominal pain, nausea, vomiting, weight loss, fatigue	Total bilirubin at 3,8 mg/dl, ALT 185 U/L, AST 411 U/L, CEA and AFP within normal range, but CA19.9 elevated at 256 U/mL	loss	US: heterogenous mass CT: multiple discrete and conglomerate heterogeneously enhancing nodular lesions in the right lobe	1 cycle of chemo-therapy followed by supportive care	FDG avid lesions in the paraoesophaesophageal and supraclvicular region and shaft of femur bone	Died one month after initiation of chemotherapy
	Mean: 42,5	F:M (1:6)	*AFP Alpha-fetoprotein, ALT alanine transaminase, AST aspartate transaminase, CA 125 Cancer antigen, CA 19.9 Carbohydrate antigen 19-9, CEA Carcinoembryonic antigen, CEUS Contrast enhanced Ultrasonography, MRI Magnetic resonance imaging, US Ultrasonography*						

chromosome 22q11.2, the most specific characteristic of liver ERT.

In the study of Oita et al. (2), 76.1% of 53 paediatrics cases had already metastasized at the time of diagnosis. The most common metastatic sites were lung (65.6%) and lymph nodes (34.4%). This series comprised a patient who demonstrated survival despite the presence of residual tumour following an incomplete resection. This individual had received an adjuvant treatment regimen comprising five cycles of vincristine/adriamycin/cyclophosphamide, followed by an additional seven months of ifosfamide/etoposide chemotherapy (16). Positive predictive factors for survival included older age, female gender, absence of metastasis at the time of diagnosis and the ability to undergo complete tumour resection.

In our literature review, half of the tumours had metastasized at the time of diagnosis. For two patients, this piece of information was missing, and only one patient did not present any metastasis at the time of diagnosis. Interestingly, in our case report, lymphovascular invasion was seen in the resection specimen, but no metastasis were observed at the time of diagnosis.

Currently, no effective chemoradiotherapy regimen has been formulated for ERT. ERT of the liver respond to chemotherapy regimens directed against soft tissue sarcoma, different from hepatoblastoma directed chemotherapy (14), making this diagnostic distinction of utmost importance. It is not known whether patients would benefit from neoadjuvant or adjuvant chemotherapy. Chemotherapy is the only option in the advanced stage, and it seems that ifosfamide and platinum-based chemotherapy are effective in MRT of various locations (2,10). Radical surgical resection with meticulous dissection of all relevant lymph node stations, remains the treatment of choice, whenever feasible. Due to the rarity of the disease, large randomized controlled trials are missing. Therefore, the European Rhabdoid Registry (EU-RHAB) aims to build a database of rhabdoid tumours with standardized registration of epidemiologic, molecular, and clinical data of patients with rhabdoid tumours of any anatomical localization, building a basis for future therapeutic trials (10).

Of note, there are ongoing studies investigating Tazemetostat, a novel small molecule enhancer of zeste homolog 2 (EZH2) inhibitor and a first-in-class agent, adult subjects affected by either INI1-Negative Tumours or those experiencing relapsed/refractory synovial sarcoma (20). Tazemetostat already obtained accelerated approval in the USA in January 2020 for its use in treating adults and adolescents aged ≥ 16 years old who suffer from locally advanced or metastatic epithelioid sarcoma, and are not eligible for complete surgical resection (21).

To the best of our knowledge, we described the seventh case of ERT of the liver in the ≥ 16 years old population, and it is the first time that hepatic ERT has been treated with neoadjuvant chemotherapy followed by liver transplantation and adjuvant chemotherapy. With this new approach, we have proposed a new therapeutic strategy for the management of these neoplasms. Given the rarity of this neoplasia, this review of case reports offers the most reliable evidence-based management approach for this specific type of tumour.

Compliance with Ethical Standards: The patient has given his written consent to publish this manuscript. The samples originated from patient material obtained during routine care and were excluded from research regulations requiring informed consent.

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Contributions: M.M. wrote the article and performed the review of the literature, D.P., D.R.A.K. and D.K.R.R performed morphology and immunohistochemistry analyses of the tissues, P.M. performed imaging investigations, D.M.C. performed the transplantation, provided patient material and clinical data, B.B. and V.G. provided patient material and clinical data. All authors discussed the different results together, proposing their modifications at all stages. The final version of the manuscript has been approved by all authors.

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