Case Report

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Pathology Section

Undifferentiated Embryonal Sarcoma of Liver- A Rare Case Entity

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ABSTRACT

Undifferentiated Embryonal Sarcoma of the Liver (UESL) is a rare hepatic malignant mesenchymal neoplasm in the paediatric population, typically affecting children between 6-10 years of age without sex predilection. It accounts for 9-15% of paediatric liver malignancies, with an incidence of 0.6-1.2 cases per one million patients. Here, the authors present a case of an 11-year-old male, who presented with right upper quadrant pain, loss of appetite for the past one month, and high-grade fever for the past three days. On examination, a firm mass in the right hypochondrium and epigastrium, about 4 cm below the right costal margin, was noted, moving with respiration. Blood work showed normal values and normal alpha-fetoprotein levels. An ultrasonogram revealed a cystic lesion, while a contrast-enhanced Computed Tomography (CT) scan showed a large hepatic space-occupying lesion with cystic and solid architecture, with the following differential diagnosis as, embryonal sarcoma and hepatoblastoma. The patient underwent surgery for a hepatic hydatid cyst, and the procedure performed was percutaneous aspiration, irrigation and respiration. Gross examination revealed multiple grey-brown and grey-white fragments with a variegated appearance. Microscopic analysis showed a malignant neoplasm composed of spindle cells, stellate cells, multinucleated giant cells in a myxoid stroma, with many atypical mitoses present. Periodic Acid-Schiff (PAS) positive eosinophilic hyaline globules were observed in the tumour cell cytoplasm, along with extensive areas of haemorrhage and necrosis. The final diagnosis of embryonal sarcoma was made after a panel of Immunohistochemistry (IHC) markers. The present case is presented here due to its rarity and diagnostic challenge, arising from the lack of a characteristic clinical presentation, serological markers and inconclusive radiological findings.

Keywords: Hepatic hydatid cyst, Malignant mesenchymal neoplasm, Tumour cell cytoplasm

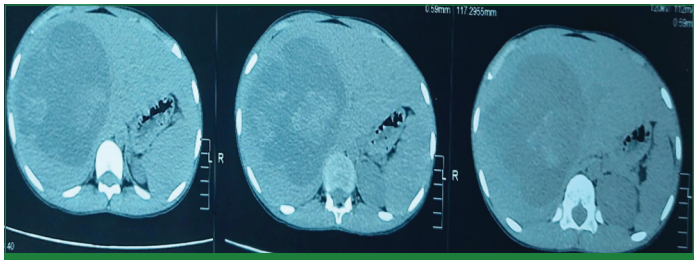
CASE REPORT

An 11-year-old male child presented with complaints of right upper quadrant pain, loss of appetite for the past month, and a high-grade fever for the past three days. The pain had an insidious onset, was gradually progressive, and described as a dull, aching pain without any specific aggravating or relieving factors. The child had a history of blunt abdominal trauma due to a handlebar injury during bicycle riding six months ago. However, there was no subsequent bleeding or swelling, so the child was not hospitalised for treatment at that time. There was no reported history of liver disease, drug allergies, or food allergies.

Laboratory findings have been summarised in [Table/Fig-1]. Serological studies for hepatitis B surface antigen and Hepatitis C virus antibody were negative. Ultrasonography of the abdomen and pelvis revealed hepatomegaly, with the liver measuring 16.2 cm and showing multiple solid and cystic areas. The impression given was a hydatid cyst. Plain X-rays of the chest and abdomen showed normal bilateral lung fields and cardiac shadow. A soft-tissue shadow was noted on the right side of the abdomen, displacing the bowel gas shadow to the left, with no visible calcification; the soft tissue appeared normal. A plain CT scan of the abdomen in the axial section displayed a large hypodense lesion in the right lobe of the liver, measuring 10×9 cm, with calcifications within it and no free fluid, as shown in [Table/Fig-2]. The contrast-enhanced CT scan of the abdomen in the arterial phase in the axial cut revealed a heterogeneous lesion measuring 10×9 cm with peripheral enhancement, displacing the portal vein and biliary tract to the left, as depicted in [Table/Fig-3]. The contrast-enhanced CT scan in the coronal section displayed similar findings as in the axial section, with the splenic shadow and bilateral kidney appearing normal, as seen in [Table/Fig-4]. The final impression was a large hepatic space-occupying lesion, and the following differential diagnoses were considered: 1) Embryonal sarcoma of the liver; 2) Hepatoblastoma. The clinical diagnosis was a hepatic hydatid cyst, and the patient underwent the Percutaneous Aspiration, Irrigation and Reaspiration (PAIR) procedure.

S. No.	Biochemistry	Units	Patient values	Normal values (in range)
1.	Total bilirubin	mg/dL	0.6	(0.1-0.2)
2.	Direct bilirubin	mg/dL	0.3	Less than 0.3
3.	Aspartate aminotransferase	IU/L	18	(12-35)
4.	Alanine aminotransferase	IU/L	15	(6-40)
5.	Gamma-glutamyl transpeptidase	IU/L	60	(0-48)
6.	Alkaline phosphatase	IU/L	38	(115-359)
7.	Total protein	g/dL	6.5	(6.4-8.3)
8.	Albumin	g/dL	3.8	(3.8-5.2)
9.	Alpha-fetoprotein	ng/mL	5	(0-10)

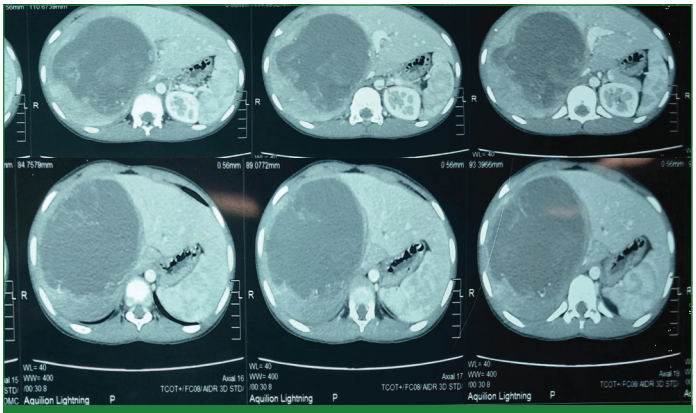
[Table/Fig-1]: Summary of laboratory data.



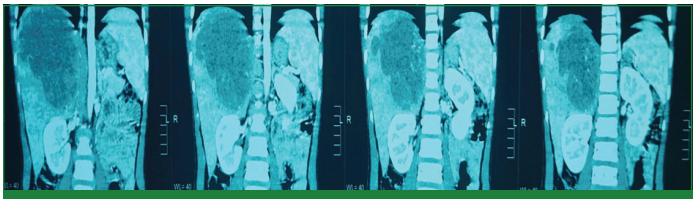
[Table/Fig-2]: Plain CT abdomen shows a hypodense lesion in right lobe of liver measuring 10×9 cm with calcification within it; no free fluid detected.

During the gross examination of the specimen received, multiple grey-brown and grey-white soft-tissue fragments were observed, with the largest measuring 7×4×2 cm and the smallest measuring 2×1×0.5 cm, as shown in [Table/Fig-5]. The external surface appeared grey-brown and congested, while the cut-surface displayed a variegated appearance with areas of necrosis and haemorrhage. Microscopic

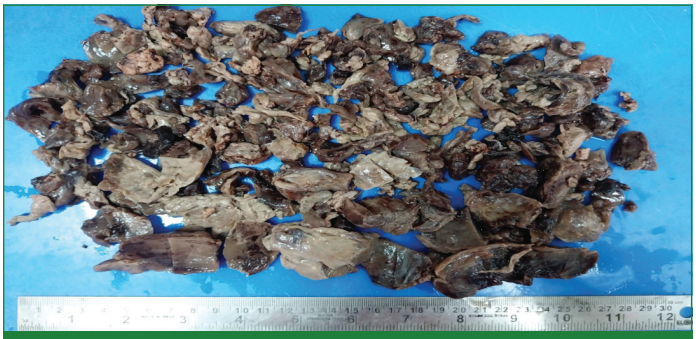
examination revealed a malignant neoplasm composed of spindle-shaped and stellate cells, along with pleomorphic multinucleated giant cells arranged in a myxoid stroma. The cells exhibited moderate cytoplasm and pleomorphic nuclei, with many atypical mitotic figures present, along with extensive areas of haemorrhage and necrosis, as depicted in [Table/Fig-6,7a]. Eosinophilic PAS positive hyaline globules were observed in the cytoplasm of tumour cells, as seen in [Table/Fig-7b]. To confirm the diagnosis, additional sections were taken, and a panel of IHC markers was utilised. Cluster Differentiation 10 (CD10) exhibited strong membranous positivity in 60-70% of tumour cells, as shown in [Table/Fig-8a]. Glypican displayed cytoplasmic positivity in 30-40% of tumour cells, as seen in [Table/Fig-8b]. Desmin showed cytoplasmic positivity in 50-60% of tumour cells, depicted in [Table/Fig-8c]. Ki67 demonstrated strong nuclear positivity in 70-80% of tumour cells, as seen in [Table/Fig-8d]. Vimentin exhibited positivity in 50-60% of tumour cells, as shown in [Table/Fig-8e]. Markers such as Smooth Muscle Actin (SMA), Pancytokeratin 2 (PanCK), B-cell Leukaemia/Lymphoma 2 (BCl-2), and myogenin were found to be negative, as presented in [Table/Fig-8f]. The patient underwent chemotherapy with doxorubicin and vincristine for four cycles over the past six months and is planned for a revision hepatectomy surgery later this year.



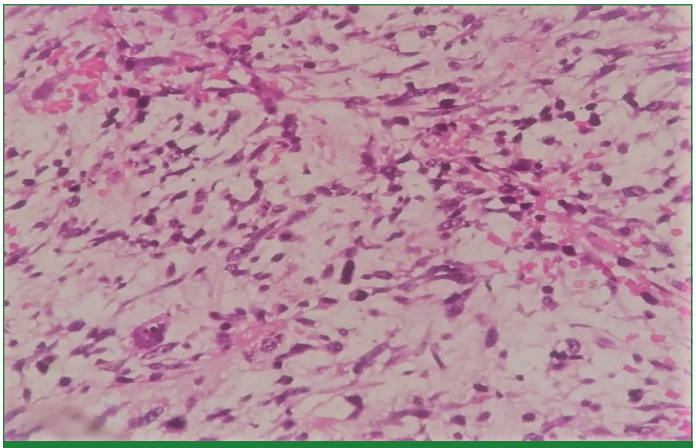
[Table/Fig-3]: Contrast enhanced CT scan-Axial section shows a heterogenous lesion measuring 10×9 cm with peripheral enhancement present, pushing biliary tract.



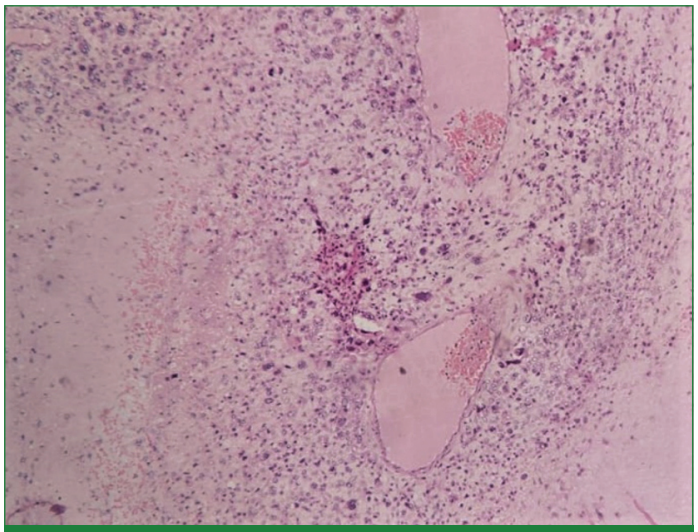
[Table/Fig-4]: Contrast enhanced CT scan coronal section shows a hypodense lesion measuring 10×9 cm with calcification in right lobe of liver, spleen and bilateral kidneys appear normal.



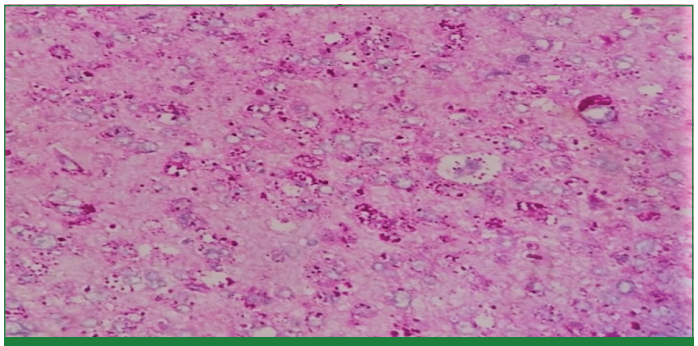
[Table/Fig-5]: Gross specimen showing multiple grey white-grey brown fragments with variegated appearance on cut surface.



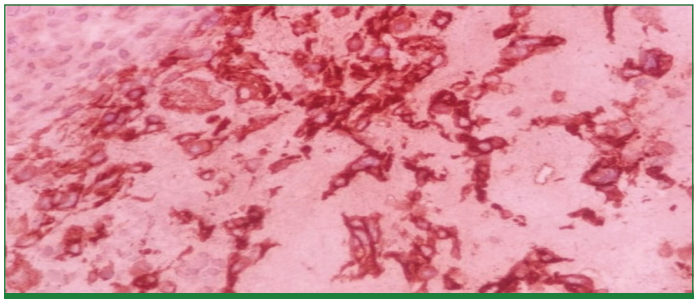
[Table/Fig-6]: Microphotograph showing spindle-shaped cells and stellate cells in myxoid background (H&E, 40x).



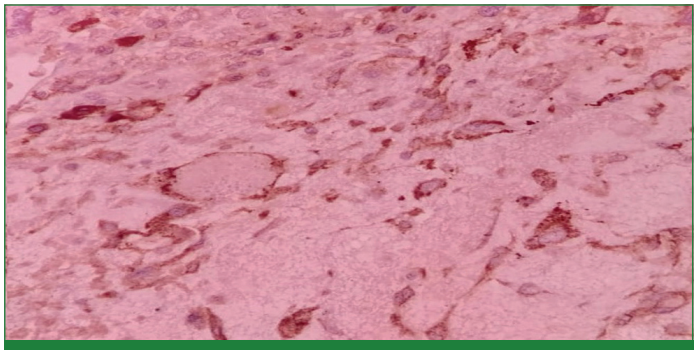
[Table/Fig-7a]: Microphotograph showing extensive areas of haemorrhage and necrosis along with pleomorphic cells and multinucleated giant cells (H&E, 10x).



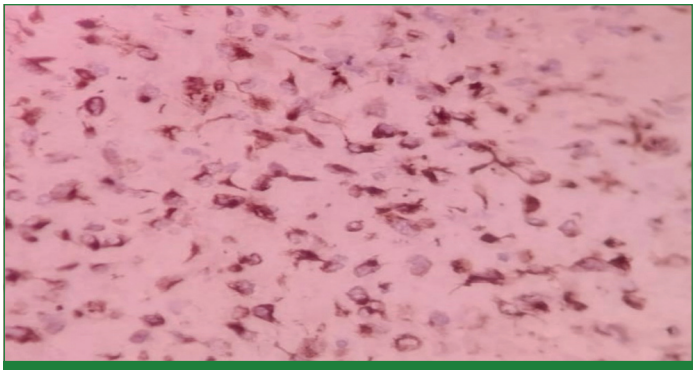
[Table/Fig-7b]: Shows PAS positive eosinophilic hyaline globules within tumour cell cytoplasm (PAS, 40x).



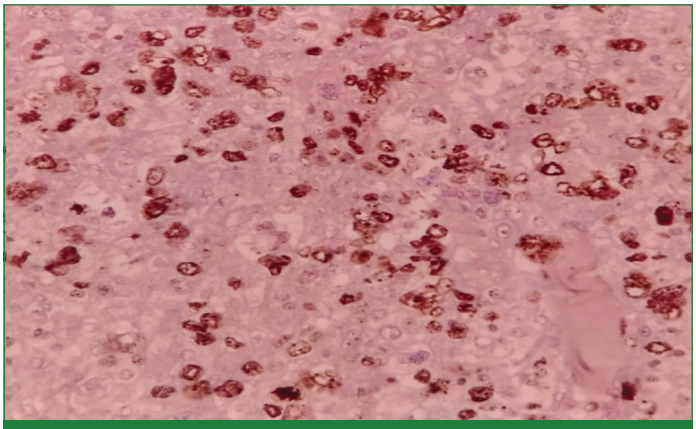
[Table/Fig-8a]: CD10 showed strong membranous positivity in 60-70% of tumour cells.



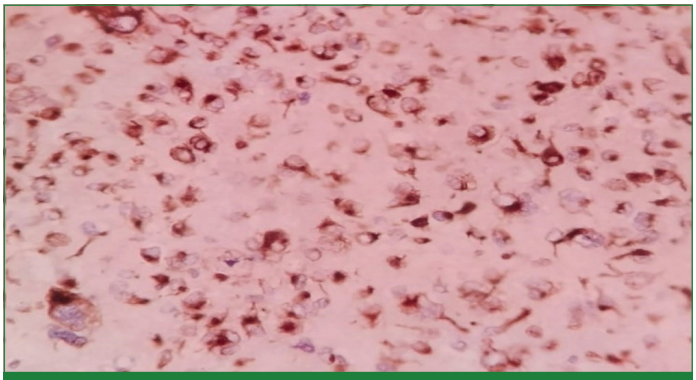
[Table/Fig-8b]: Glypican showed cytoplasmic positivity in 30-40% of tumour cells.



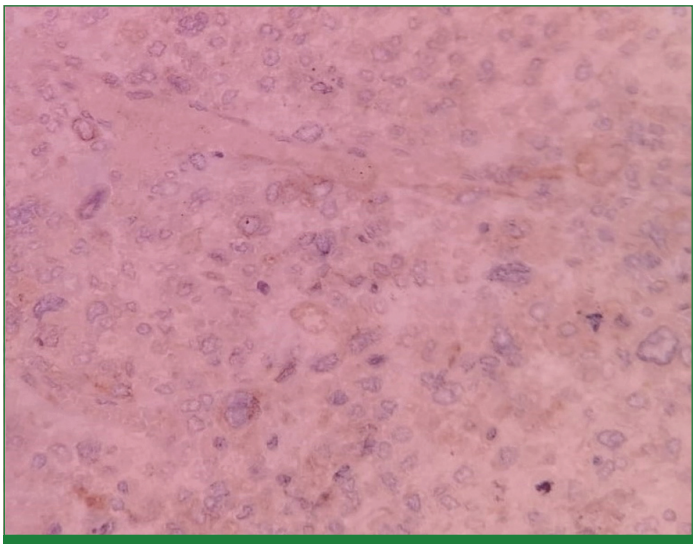
[Table/Fig-8c]: Desmin showed cytoplasmic positivity in 50-60% of tumour cells.



[Table/Fig-8d]: Ki67 showed strong nuclear positivity in 70-80% of tumour cells.



[Table/Fig-8e]: Vimentin showed positivity in tumour cells.



[Table/Fig-8f]: Myogenin was found to be negative.

DISCUSSION

Willis first described the pathology of UESL in 1962 as a rhabdomyoblastic mixed tumour. In 1973, Stanley classified it as a malignant mesenchymoma due to the presence of focal chondroid-appearing cells. In 1978, Stocker and Ishak definitively described the pathology and adopted the term "undifferentiated embryonal sarcoma of the liver" to describe a mesenchymal hepatic tumour without any sign of specific differentiation based on the Armed Forces of Pathology (AFIP) series [1,2]. There were only 26 reported adult cases in the literature from 1977 to 2015, with sarcomas accounting for less than 1% of primary liver tumours and 13% of primary hepatic malignancies. It has non-specific clinical features with varied symptoms ranging from sharp abdominal pain, fever, anorexia, diarrhoea, or a solitary liver cyst, resulting in a diagnostic dilemma [1]. Only 150 to 200 cases were reported in the literature, with an annual incidence of one per million cases. The prognosis is significantly worse in adult patients compared to paediatric cases [3-5].

It is the first case reported in the present Institution. Jaundice is usually absent. Typical ultrasound findings show a large mass with solid and cystic components, mostly mistaken for an abscess or an echinococcal cyst [5]. Usually, there are no abnormal liver function tests, normal alpha fetoprotein levels, non specific laboratory findings, and no specific serum markers. Increased C-reactive protein, erythrocyte sedimentation rate, and leucocytosis are usually seen in cases of haemorrhage or necrosis in the tumour [3,6]. Metastasis sites include the lung, pleura and peritoneum [6]. UESL is a malignant mesenchymal neoplasm and the third most common type of liver malignancy in the paediatric population, following hepatoblastoma and hepatocellular carcinoma, accounting for 16% of primary hepatic sarcoma [7,8].

Computed tomography usually shows a well-circumscribed huge cystic/solid mass with few internal septations and a dense peripheral rim corresponding to the fibrous pseudocapsule, which is hypodense in the pre-contrast phase and slightly enhanced in the contrast phase. Central foci of high attenuation representing acute haemorrhage may be present. The presence of serpiginous vessels within the tumour has been recently reported in the literature as an important finding for diagnosis [6,9].

The prognosis is generally poor due to delayed diagnosis caused by the lack of initial symptoms, rapid tumour growth and early invasion of adjacent tissue. However, the outcome of treatment has improved with primary surgical resection followed by chemotherapy [9]. Macroscopically, usually large, unencapsulated well-circumscribed tumours are commonly seen in the right lobe of the liver, with an average diameter of 10-30 cm and a variegated appearance: cystic and solid components of grey-white gelatinous areas with or without red and yellow haemorrhagic and necrotic parts [6,9].

Microscopically, UES is composed of primitive, high-grade undifferentiated spindle cells, with numerous mitotic figures and myxoid stroma with varying degrees of spindling and myxoid change. It is histologically heterogeneous with a variable but distinctively sarcomatous appearance [10,11]. The morphology will vary considerably depending on the area of examination. Some areas may appear to be composed of a relatively uniform sheet of undifferentiated cells, while other areas demonstrate wildly pleomorphic anaplastic cells, some with multinucleation and a myxosarcomatous background. Considerable areas of necrosis with abundant mitoses are easily identified. Areas of cystic change can often be seen histologically corresponding to this tumour's cystic appearance on both gross and radiology.

Despite the presence of a pseudocapsule, cords of normal hepatocytes and bile ducts are commonly entrapped along the periphery of this tumour, suggesting malignant transformation of mesenchymal hamartoma. Periodic Acid-Schiff positive Diastase (PASD)-resistant eosinophilic globules are often seen in the tumour stroma or within the cytoplasm of some of the tumour cells [12]. There is no immunohistochemistry that is specific for UESL, as the markers are usually variable and non specific. In fact, the key role of immunohistochemistry is to rule out other possible tumours in the differential diagnosis. Variable expression of SMA, vimentin, CD68, BCL-2, desmin, and CD10 is commonly seen in

UESL. Alpha-1-antitrypsin and alpha-1-antichymotrypsin positivity within the eosinophilic globules are commonly encountered. Weak cytokeratin staining has also been reported, and a minority of UESLs have positivity for glypican 3 and nuclear positivity for CD117. UESL is usually negative for S100, myogenin, ALK-1, Beta-catenin, and HepPar1, and hence important differential diagnoses include hepatoblastoma, embryonal rhabdomyosarcoma and mesenchymal hamartoma [Table/Fig-9].

S. No.	Diagnosis	Age and sex	Clinical history	Microscopy	Immunohis-tochemistry
1.	Hepatoblastoma	M:F=3:2, age 0-19 months	Hepatomegaly elevated alpha-fetoprotein levels with thrombocytosis	Different subtypes resembles various stages of liver development	Beta catenin, glypican 3, Hep par-1 (variable in different subtypes)
2.	Embryonal rhabdomyosarcoma	F>M, age <5 years	Fever, icterus	Small round blue cells underneath cambium	Myogenin, desmin, Myo-D1
3.	Mesenchymal hamartoma	M>F, age <2 years	Enlarged liver mass, respiratory distress	Clustered hepatocytes, lobular growth, elongated branched bile ducts with stromal component	Non contributory
4.	Hepatocellular carcinoma	M=F, history of chronic liver injury, Adults	Abdominal mass mostly in the setting of chronic liver disease	Pleomorphic hepatocytes arranged as thickened trabeculae	Hep par-1, glypican 3, arginase, alpha-fetoprotein, CD10, pCEA
5.	Gastrointestinal stromal tumour	M=F, Adults	Intra-abdominal mass	Spindle cells with eosinophilic fibrillary cytoplasm	CD34, c-KIT, DOG1

[Table/Fig-9]: Differential diagnoses [1].
Hep par-1: Hepatocyte paraffin-1; Myo-D1: Myogenic regulatory protein; pCEA: Polyclonal carcinoembryonic antigen; C-kit: A type of receptor tyrosine kinase; DOG1: Discovered on gastrointestinal stromal tumors (a transmembrane protein)

Pathogenesis

Comparative Genomic Hybridisation (CGH) studies suggest a role for chromosomal instability and show that copy number alterations are common in UESL [1]. Although the exact mechanism of tumourigenesis has not been identified, MHL cases harbour recurring chromosomal rearrangements involving 19q13 [1]. There are gains in chromosomes 1q, 5p, 6q, and losses in chromosomes 14, 9p, and 11p [1,13]. Even though the precise histogenesis and its cell of origin are still to be defined [1], UESL is considered the malignant counterpart of mesenchymal hamartoma, so the mesenchymal origin of this tumour is accepted by many authors [2,6]. A translocation of the long arm of chromosome 19 has been reported (19q13.4) [13]. The synchronous or metachronous occurrence of mesenchymal hamartoma and UES suggests they share a common genetic link.

Based on imaging, the differential diagnoses include abscess, mesenchymal hamartoma of the liver, hydatid cyst, cystic degeneration in hepatoblastoma, or hepatocellular carcinoma, and cystic metastasis in adults. Published cases are tabulated in [Table/Fig-10] [1,6,7,12,14]. Various differential diagnoses have been documented in the literature based on the overlapping clinical and histopathological features, so it is important to rule out those tumours [Table/Fig-10].

S. No.	Articles	Age/ Sex	Clinical features	Size and site of lesion	Radiology findings	Immunohis-tochemistry
1.	Manabe Y et al., 2020 [1]	50-year-old male	Incidental cystic liver lesion	5.4×4.6×5.37 cm in liver	Cystic lesion without solid lesion	CD31, CD34, S100, SMA-negative
2.	Gomes F et al., 2021 [6]	Six-year-old female	Recurrent urinary tract infection-incidental finding	8.2×7.3×7.3 cm in right lobe of liver	Complex hypoechoic mass with solid isoechoic mass	-
3.	Kinjo S et al., 2010 [7]	31-year-old female	Upper abdominal pain, back pain	14.5×10.4 cm in anterior and medial segment of liver	Multicystic and solid lesion	Positive for vimentin, desmin, Smooth Muscle Actin (SMA) Negative for p53, S100p, HMB-45, caldesmon
4.	He B et al., 2014 [12]	9-year-old female	Abdominal pain, fever	11.5×8.3×6.7 cm	Cystic and solid mass with well-defined border	Caldesmon, CD68, Ki67, Vimentin-positive; Cytokeratin, Desmin, Myo-D1, SMA, Alphafetoprotein-negative
5.	Iqbal K et al., 2008 [14]	14-year-old boy	Five day history of non specific right hypochondriac pain	14×15×15 cm in right lobe of liver	Large hypodense mass	Positive for phospho-enolpyruvate carboxykinase, vimentin, alpha 1 antitrypsin . Negative for Epithelial Membrane Antigen (EMA)
6.	Present case	11-year-old boy	Right hypochondriac pain, loss of appetite and fever	10×9 cm involving right lobe of liver	Large heterogenous lesion with peripheral enhancement	Positive for CD10, glypican, desmin, vimentin, Ki67. Negative for SMA, PanCK, BCl-2, myogenin

[Table/Fig-10]: Comparison of published literature with present case [1,6,7,12,14].

CONCLUSION(S)

Undifferentiated embryonal sarcoma is a diagnosis of exclusion in paediatric liver tumours. Usually, in imaging, it shows a paradoxical appearance of solid and cystic features on ultrasound and CT scans, which is peculiar due to the high water content of the myxoid stroma. This can lead to confusion with cystic liver lesions. The present case is presented here for its rarity and diagnostic challenge, as the patient was clinically diagnosed and imaged as having a hydatid cyst, which was then curetted, and the specimen was sent for histopathological examination. It was only discovered to be a malignant neoplasm on microscopic examination by pathologists. A high index of clinical suspicion, along with a panel of immunohistochemical markers, can enable a peroperative frozen section, which can help in the diagnosis and early initiation of treatment.

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