Case Report of Undifferentiated Hepatic Embryonal Sarcoma with Mesenchymal Hamartoma: A Rare Entity

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Abstract

Undifferentiated embryonal sarcoma (UES) is a highly malignant hepatic neoplasm, which occurs mostly in pediatric population. There is a link between embryonal sarcoma and mesenchymal hamartoma as evidenced by clinicopathological overlap and similar genetic abnormality. Here, we report a case of UES in a young female in a background of mesenchymal hamartoma of liver.

Keywords

- abdominal pain
- alpha-fetoprotein
- hepatomegaly
- mesenchymal hamartoma
- undifferentiated embryonal sarcoma

Introduction

Undifferentiated embryonal sarcoma (UES) of the liver is a rare tumor, with an estimated incidence of one case per million people per year.[1] It was first described as rhabdomyoblastic mixed tumor by Willis and as "malignant mesenchymoma" in 1973[2] by Stanley et al. Since the prognosis of UES is bad, timely detection and surgical resection along with neoadjuvant therapy is essential in achieving favorable outcomes. In pediatric patients, the 5-year survival is around 86%, with surgical resection being the most important aspect of treatment.[3]

Case Report

A 9-year-old female child presented with abdominal distension and a palpable mass. An ultrasound (USG) done from elsewhere showed a moderate-sized liver lesion. On examination, she had a firm palpable mass, 10 cm below the right costal margin.

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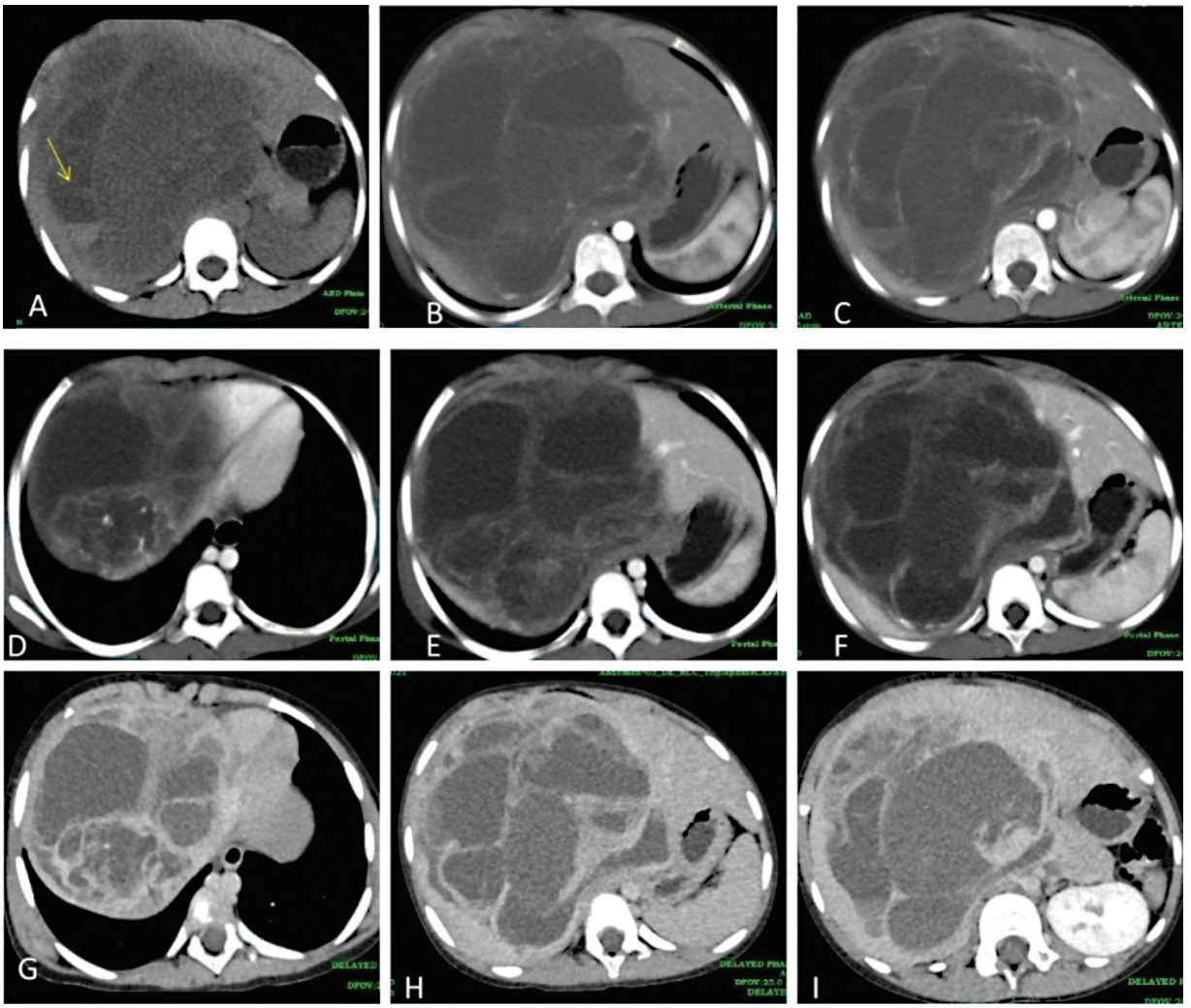

Fig 1 Plain (**A**) and dual-phase contrast-enhanced computed tomography (CECT) arterial phase (**B**, **C**), venous phase (**D**–**F**), and delayed phase (**G**–**I**) show multiseptated cystic lesion with varying density contents, high density areas with fluid-fluid level suggesting hemorrhage (arrow). Delayed phase (**G**–**I**) showing moderately enhancing thick septae and solid components.

Blood investigations including hemogram and liver function tests (liver enzymes, serum bilirubin, and albumin levels) were within normal limits.

Tumor markers like serum α-fetoprotein (AFP) and CA19–9 were also normal.

Triple-phase contrast-enhanced computed tomography (CECT) revealed a large well-circumscribed, hypodense, predominantly thick-walled multiloculated cystic lesion with septations and ill-defined enhancing solid components measuring 13 × 7.1 × 13 cm (anteroposterior × transverse × craniocaudal) involving segments 7, 8, and 4a (►**Fig. 1B–I**). Left branch of portal vein was splayed around the lesion with displacement of middle hepatic vein lateral to the mass in coronal CECT (►**Fig. 2A, C**). Right hepatic artery was displaced inferiorly (►**Fig. 2B**). Plain CT showed a few areas of hemorrhage (►**Fig. 1A**). The right diaphragm was elevated with basal lung atelectasis. There was no evidence of local or distant metastasis. A core needle biopsy was performed under USG guidance, using an 18-gauge automatic gun.

On histopathology, the lesion was composed of tortuous and elongated bile ducts lined by epithelium surrounded by abundant loose connective tissue. Highly cellular malignant tumor was also noted in a few areas adjacent to and intermingled with above lesion in a myxoid stroma, showing atypical mitotic figures and mitotic activity of approximately 30/10 high-power field (►**Fig. 3A–D**).

Immunohistochemistry confirmed foci of UES in a background of mesenchymal hamartoma (►**Fig. 4A–D**).

The tumor was large and hence neoadjuvant chemotherapy was given to downstage the tumor. The child was started on multidrug regimen with doxorubicin and ifosfamide. Follow-up CECT though revealed only mild reduction in tumor size, there was moderate to marked reduction in extent of enhancing soft tissue and septal thickening (►**Fig. 5A–D**).

Extended right hepatectomy was performed. Gross specimen showed extensive necrosis, hemorrhage, and infarction (►**Fig. 6A** and **B**). Histopathology showed scanty residual

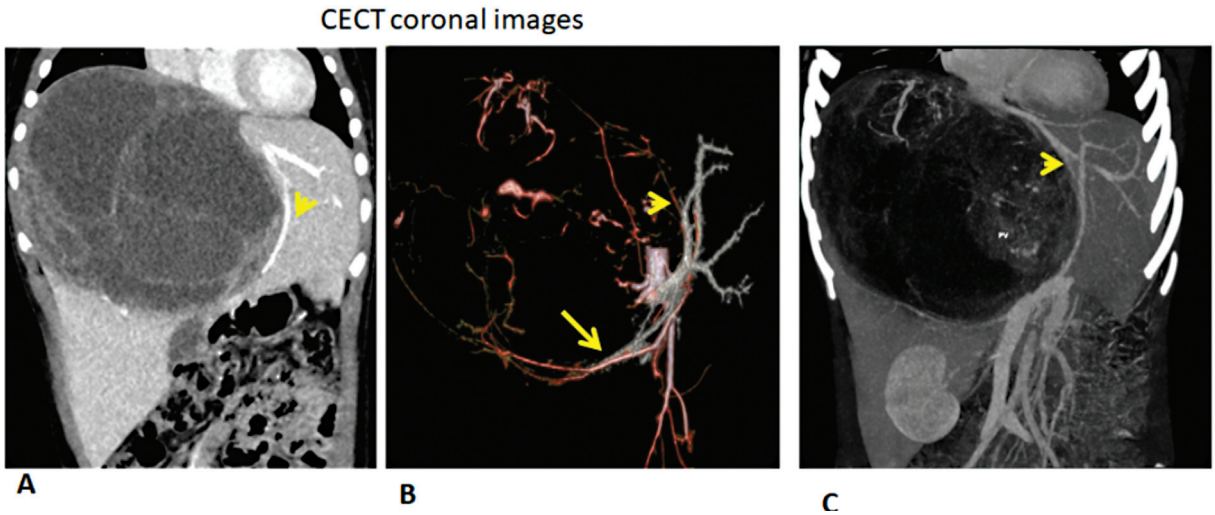

Fig. 2 (A) Contrast-enhanced computed tomography (CECT) coronal images showing predominantly cystic tumor displacing the middle hepatic vein (arrowhead). (B) Volume rendered image showing displacement of hepatic artery (arrow) and portal vein (arrowhead) around the lesion. (C) Coronal oblique multiplanar reconstruction (MPR) images showing tumor displacing portal vein radicles (arrowhead).

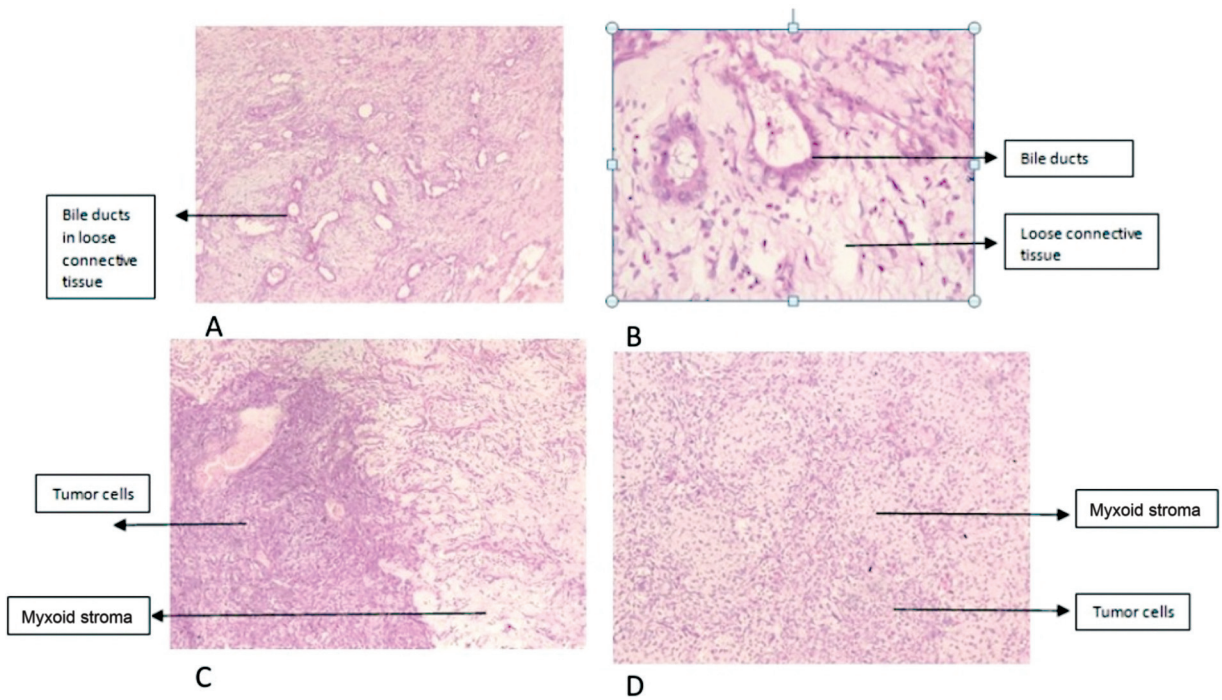

Fig. 3 (A, B) Hematoxylin and eosin (H&E) sections from liver showed a lesion composed of tortuous and elongated bile ducts lined by epithelium without atypia in varying configuration and surrounded by abundant loose connective tissue. (C) Also noted in few sections is a highly cellular malignant tumor adjacent to and intermingled with above lesion composed of pleomorphic cells arranged in sheets, short fascicles, and focal vague storiform pattern in a myxoid stroma. (D) Tumor cells in myxoid stroma.

viable tumor with features consistent with mesenchymal hamartoma and a small focus of UES (0.6 cm).

Discussion

UES is an aggressive childhood mesenchymal tumor. Though rare, UES is the most common sarcoma and the third most common hepatic malignancy in the pediatric population after hepatoblastoma and hepatocellular carcinoma (HCC). Most cases of UES are diagnosed in the first decade of life, between 6 and 10 years of age, but few case reports have been described in adults and even elderly patients. UES shows no sex predilection in children and a slight female predominance in adults.[4,5]

Patients with UES usually have variable and nonspecific symptoms, with abdominal pain and abdominal mass reported to be the most common presenting complaints. Other symptoms are fever, nausea, vomiting, weight loss, fatigue, anorexia, and jaundice. Few patients are asymptomatic at diagnosis. Fever is usually associated with hemorrhage

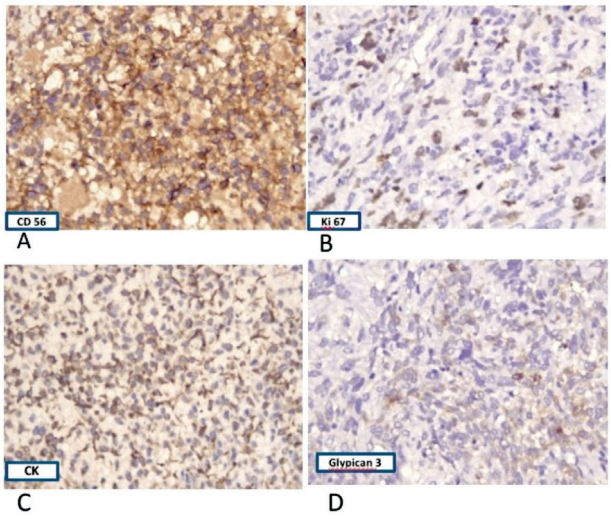

Fig. 4 (**A**, **B**) Immunohistochemistry (IHC). The malignant cells were positive for CD56 with a high proliferation index of 40 to 50%. (**C**, **D**) The cells show patchy positivity for CK and Glypican-3.

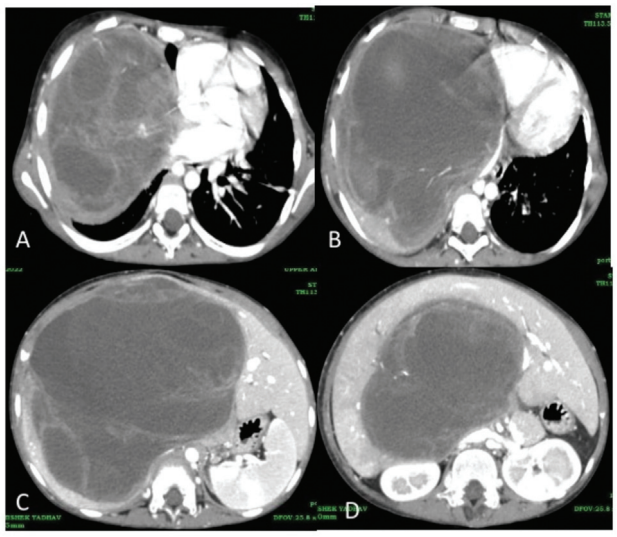

Fig. 5 (**A**–**D**) Post-chemotherapy contrast-enhanced computed tomography (CECT) axial sections in venous phase shows marked reduction in septal enhancement and solid components.

and necrosis within the tumor. Spontaneous rupture resulting in intraperitoneal hemorrhage due to rapid tumor growth has also been reported.[6]

The usual presentation of the lesion is large (10 cm), solitary mass in the right lobe of liver. Multifocal disease and involvement of the left lobe are less frequent.[7] Extrahepatic spread is observed in 5 to 15% of all the patients and common metastatic site include the lung, diaphragm, heart, and peritoneum. Distant metastases are more common in adults than in pediatric patients.[6]

There are no specific laboratory features to suggest UES. Mild leukocytosis or leukopenia, low albumin, anemia, slightly elevated transaminase levels, and erythrocyte sedimentation rates may be seen. Evaluation of tumor markers including AFP, CA19–9, and carcinoembryonic antigen often

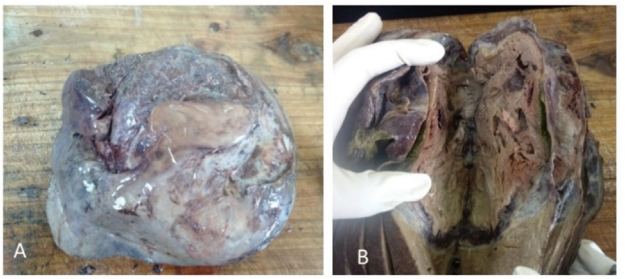

Fig. 6 (**A**) Extended right hepatectomy specimen comprising of right lobe and caudate lobe measuring 26 × 20 × 5 cm and weighing 1.908 kg. (**B**) Cut surface shows a solid-cystic tumor with variegated cut surface comprising of necrotic and hemorrhagic area measuring 20 × 16.5 × 6.5 cm. The periphery of the tumor showed viable cystic area.

yields normal results, but rare cases with increased levels of AFP and CA-125 have been reported. Sometimes lactate dehydrogenase levels can be elevated due to unknown reasons.[8]

The imaging appearance of UES are nonspecific, varies from solid-to-solid cystic lesions with variable cystic contents. The lesion can have a paradoxical appearance in USG and CT. On USG, UES is mostly a solid-dominant mixed echogenic mass with variable cystic areas and septation; however, it often appears as a cystic lesion with low attenuation on CT and magnetic resonance. This discrepancy is due to hyperechoic appearance of myxoid tissue on USG. The cystic appearance in CT is due to the high water content of the abundant myxoidstroma.[9,10] Sometimes, lesions are predominantly cystic with multiple septa, simulating benign tumors. Intralesional hemorrhage is a common feature of UES. Hyperintense signal on T1-weighted images with fluid-fluid levels can occur because of internal hemorrhage and necrosis. Hemorrhagic ascites or perihepatic fluid may be seen in cases of tumor rupture.[8]

UES can coexist with mesenchymal hamartoma or can arise from preexisting mesenchymal hamartoma when these two entities are seen together on histopathology as in our case.

The most common differential of UES is mesenchymal hamartoma and both share common imaging findings. Mesenchymal hamartoma is a developmental anomaly, usually have cystic predominance with internal septa, or mesenchymal predominance with multiple small cysts, thick septa, and variable solid areas.

Differentiating mesenchymal hamartoma from UES is difficult based on imaging alone. Age less than 2 years usually favors mesenchymal hamartoma and age more than 5 years favors UES. Lack of necrosis, calcification, and hemorrhage also favors mesenchymal hamartoma. However, because of the risk of recurrence and malignant transformation, the gold standard for the treatment of mesenchymal hamartoma is complete surgical excision.[11] Based on imaging, the other common differentials are abscess, hydatid cyst, cystic degeneration in hepatoblastoma, and HCC. On CT, liver abscess show predominant peripheral enhancement with no internal solid components. Hepatoblastoma occurs mostly below

4 years of age with raised AFP and show heterogeneous enhancement on CT, coarse calcification is seen in 40 to 50% of cases.

Pathology

Grossly, UES typically presents as a large, spherical, and well-demarcated mass with a fibrous pseudocapsule. It reveals a yellow to tan, heterogeneous tumor with glistening solid regions, alternating cystic areas with necrotic and hemorrhagic tissue, clotted blood, and gelatinous material on cut surface. Histologically, UES shows hypercellular sheets of highly pleomorphic tumor cells, necrosis, high mitotic index, frequent atypical mitoses, and apoptotic bodies. These important microscopic features of this tumor indicate fast cellular turnover and the proliferative index of UES by immunohistochemistry is usually high (Ki67 index 30%). On immunohistochemistry, there is no specific marker for the diagnosis and broad immunohistochemical panels are often necessary to rule out differential diagnoses. Most cases of UES are positive for vimentin, α-1 antitrypsin, and CD68. Study by Habibzadeh et al[12] reveals two markers Bcl-2 and CD34 show strong immunoreactivity in different components of the mesenchymal hamartoma case found in association with UES. The development of UES after incomplete excision of mesenchymal hamartoma reported in the literature corroborates this hypothesis.[12]

UES may also arise within mesenchymal hamartoma or demonstrate focal regions of mesenchymal hamartoma-like histology. Study by Lauwers et al[13], suggests a potential evolutive continuum between mesenchymal hamartoma and UES revealing the cytogenetic analogy on chromosome 19 (19q13.4 alteration) between UES and mesenchymal hamartoma components, but a different DNA-ploidy (UES DNA-triploid/mesenchymal hamartoma DNA-diploid).[12,14,15] Studies have shown chromosomal instability like copy number alterations and point mutations in UES.

Treatment

There is no definite treatment protocol for UES. The prognosis of UES is very poor, with a median reported survival time of less than 1 year.[16] Due to the widespread use of multimodal therapy, including primary resection, neoadjuvant or adjuvant chemotherapy, and radiation, the long-term survival rate of UES patients has improved significantly and is currently reported to be more than 70%. Our patient underwent multiagent chemotherapy following complete resection with negative margins and is on follow-up.

Conclusion

UES coexisting with mesenchymal hamartoma is a rarity. The preoperative diagnosis of complex cystic hepatic mass in pediatric population is always challenging due to the lack of characteristic clinical manifestations and tumor markers and nonspecific radiological imaging. Although none of the findings are specific to differentiate between mesenchymal hamartoma and embryonal sarcoma, the diagnosis of UES should be suspected in a young child in the age group 6 to 10 years with a rapidly growing liver mass, especially if the AFP is normal. Definitive diagnosis relies on postoperative thorough pathological examination and immunohistochemistry. Long-term follow-up is also important to rule out early recurrence.

Conflict of Interest
None declared.

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