Case Report

Undifferentiated embryonal sarcoma of liver in a 9-year-old: case report

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ABSTRACT

The embryonal sarcoma of the liver is an extremely malignant, aggressive and infrequent condition of the liver, predominantly affecting children in the age groups of four to ten. The disease manifests with fever, abdominal pain or mass, nausea and laboratory findings suggestive of liver cell injury. The diagnosis can be made using tumor markers, imaging, immunohistochemistry and histopathology. The multimodal management protocol focuses the use of surgical resection, chemotherapy and radiation to significantly improved survival rates and quality of life in these patients.

Keywords: Embryonal sarcoma, Undifferentiated embryonal sarcoma of the liver, Histopathology

INTRODUCTION

Undifferentiated Embryonal Sarcoma of the liver (UESL) is a highly aggressive, rare malignancy of mesenchymal origin. This mesenchymal tumor was first described by Stocker et al in his case series of 31 patients, to identify a group of mesenchymal liver tumors that do not show any signs of differentiation. This study recognizes UESL as a predominantly pediatric malignancy, where 51.6% of the patients are from the age group of six to ten years.1 It is the third most frequent primary liver malignancy, following hepatoblastoma and hepatocellular carcinoma in this patient population.2 Although, this disease may occur in adults, no more than 2 cases have been reported in any case series.3,4 There have been variable reports regarding its sex distribution, with some studies reporting a female predominance while others report an even pattern of distribution.1,3,5,6

The relatively low incidence of UESL is responsible for the limitation of observational studies to merely case reports and case series. UESL accounts for 5-15% of the liver tumors in children.7,9 The tumor sizes are highly variable from 10-30 cm, and this tumor has a predilection for the right lobe of the liver.10 The patient presents with abdominal mass, pain and some systemic symptoms such as anorexia, nausea, weight loss, lethargy and constipation.1,3,5,6 The diagnosis of this rare condition commences with clinical parameters and imaging. The imaging may establish a mass with both cystic and solid components.9,11 However, the clinical and radiologic diagnosis is often difficult and therefore relies on the use of histopathology and immunohistochemistry techniques.12,13 Cytogenetic studies have revealed a diversity of perturbations including gain of chromosome 1q, 5p, 6q, 8p, 12q, and losses of chromosomes 9p, 11p, and 14.13

The primary literature on this condition reports mortality with a year of occurrence, as shown by case series conducted by Stocker et al.1 However, with earlier detection, aggressive surgical resection and multidrug chemotherapy regimen, the expected life expectancy of these patients has been enhanced over the past few years.14,15 A retrospective study conducted by Mathias et al., shows a 100% event-free (EFS) and 100% overall survival (OS) with no recurrence or secondary malignancy over a median of eight years of follow-up.16
However, the mortality ensues from recurrent or metastatic disease.\textsuperscript{17,18} In the upcoming section, we discuss an interesting case of undifferentiated embryonal sarcoma of the liver in a seven-year-old male child.

**CASE REPORT**

A 9-year-old male child presented to the hospital with complaints of abdominal pain and nausea for two months. The abdominal pain was gradual, intermittent, non-radiating and of a dull aching character, localized to the right hypochondriac region. The pain was accompanied by reduced appetite and a significant weight loss of 8.5 kg over a period of two months. The vitals were stable during physical examination. The abdominal exam revealed an abdominal mass in right hypochondrium which was firm to hard in consistency with an irregular surface and smooth margins. The mass extended up to 15 cm below the right costal margin. The laboratory studies showed hemoglobin-9.3 g/dl, normal serum bilirubin level, elevated levels of aspartate aminotransferase (AST)-64 U/I, alanine transaminase (ALT)-59 U/I, alkaline phosphatase (ALP)-710 U/I, γ-glutamyl transpeptidase (GPT)-178 U/I and lactate dehydrogenase (LDH)-281 U/I (Normal range: 45-90 U/I).

The levels of tumor markers carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19-9, and cancer antigen 125 (CA125), alpha-fetoprotein, and protein induced by vitamin K absence-II (PIVKA-II) were within normal limits. The patient was referred to a tertiary care center where a CT scan was undertaken. The CT demonstrated a large expansive mass of solid-cystic complex aspect with gross septa (Figure 1), located in the right hepatic lobe topography. The mass. On post-contrast images, enhancing solid component with septae were noted. On arterial phase, a branch from the hepatic artery was supplying the lesion. On portal and venous, delayed phases, it is progressively enhancing. Inferiorly it is displacing the right kidney antero-inferiorly and medially. Medially it is displacing the gall bladder, celiac artery and SMA. Enlarged mesenteric lymph nodes were also seen (Figure-2).

The patient underwent hepatic lobectomy for resection of the mass and was given chemotherapy (ifosamide 4 cycles and doxorubicin 2 cycles) followed by primary site radiotherapy at week four followed by chemotherapy (ifosamide 2 cycles and doxorubicin 3 cycles) followed by primary site radiotherapy at week 16 for gross or microscopic residual tumor after surgery followed by surgery/radiotherapy to metastatic sites at completion of treatment and observation. Samples were sent for histopathological analysis.

The macroscopic examination of the surgical specimen showed a large mass involving the right lobe of the liver. The mass weighs approximately 890 grams. The external surface shows wrinkling in most of the parts along with a raw area measuring 12x10 cm. The mass is both solid and cystic in consistency. On cutting open the mass, a single tumor, multi-lobulated, well-circumscribed, solid and cystic mass is noted measuring 12x10x7 cm. The cut surface showing a greyish-yellow soft mass with cystic degeneration, together with areas of hemorrhage and necrosis (Figure-3).

Histopathological analysis by periodic acid-schiff (pas) stain revealed a tumor surrounded peripherally by normal liver parenchyma with a thickened capsule outside (Figure 4). Pleomorphic spindle-shaped cells, oval cells and stellate-shaped cells are dispersed singly in the myxoid stroma which shows necrosis. The cells show nuclear hyperchromatism, coarse chromatin and easily identifiable miosis. Many acinar structures which are signs of bile ducts are seen entrapped within the tumor. Many hemosiderin laden macrophages were seen. The overall interpretation was of a sarcomatous, high-grade tumor with myxoid background, high mitotic activity,

![Figure 1: CT scan findings demonstrating undifferentiated embryonal sarcoma of right lobe of liver.](image1)

![Figure 2: Abdominopelvic contrast-enhanced CT showing undifferentiated embryonal sarcoma of the liver.](image2)
characteristic eosinophilic globules. Furthermore, the immunohistochemistry showed focally positive desmin, positive vimentin, CD34- positive in supporting blood vessels and negative in tumor cells. Additionally, myogenin, hep par 1 were found to be negative.

Figure 3: Cut surface of UESL showing grey white necrosis and hemorrhage.

Figure 4: (A) Pseudocapsule separating the liver parenchyma from the tumor (B) malignant tumor cells in a myxoid stroma with eosinophilic globules in cytoplasm (C) shows hemosiderin laden macrophages.

The diagnosis of embryonal sarcoma of the liver was confirmed using histopathology, imaging and immune histochemistry. Furthermore, the patient underwent a whole-body PET CT Scan after 4 cycles of chemo therapy and after surgery which showed a marked reduction in the tumor size (14 cm) and reduction in the size and metabolic resolution of the mesenteric Lymph nodes consistent with partial treatment response.

DISCUSSION

UESL previously referred to as fibromyxoid sarcoma, malignant mesenchymoma, is a destructive, highly malignant tumor of mesenchymal origin.¹

The pathologic evaluation reveals a mesenchymal hamartoma (MH) of the liver in association with several malignant sarcomatous elements, which raises the likelihood of it being a precursor lesion for UESL.¹ The morphologic and histologic resemblances between UESL and MH are the foundation for this proposed linkage. Some case reports support this linkage, signifying a mutual breakpoint, 19q.¹³,¹⁴ in lesions with UESL developing in association with MH.¹⁹-²¹ The DNA sequencing in a case of UESL arising in MH harboring t (11;19) (q11;q13.4) established the breakpoint at the MALAT1 (metastasis-associated lung adenocarcinoma transcript 1) gene on chromosome 11 and the MHLB1 (mesenchymal hamartoma of the liver breakpoint 1) locus on chromosome 19.²² Furthermore, both the liver tumors occur predominantly in the right lobe of the liver and share mutual microscopic components, such as the presence of cystic changes, benign ductular elements, loose myxoid stroma, and immature mesenchymal cells, supports the concept of a malignant transformation.²³ Additionally, TP53 mutations were recognized in UESL, suggesting a contribution towards the malignant change.²⁴ Finally, the clinical presentation of patients affected with both UES and MH were analogous to the patients with UES alone, including abdominal pain, distention, and/or abdominal mass.

UESL may arise in any region of the liver, but frequently originates in the right lobe as a solitary, rapidly expanding mass. The symptoms are directly correlated with the extent of spread, size and progress of the tumor. These include abdominal pain and swelling, weight loss, anorexia, vomiting, diarrhea, lethargy, constipation, and respiratory distress.¹,³,¹⁴ Fever may additionally develop in cases of hemorrhage or necrosis within the tumor.²⁵ A case report by Sakellaridis et al. demonstrates an atypical presentation of embryonal sarcoma, mimicking acute appendicitis, due to the rupture of the tumor into the peritoneal cavity.²⁶

The diagnosis of embryonal sarcoma in children commences with nonspecific tumor markers such as CA-125, CA-199, ALP and LDH. The ALP and LDH are usually elevated in cases of UESL in children. This is followed by imaging studies where ultrasonography scan (US) shows hepatomegaly and a heterogeneous mass containing some echoless areas, and CT scan demonstrates a lesion occupying a large space with cystic areas, hypodense areas that do not enhance in an enhanced scan, compression or displacement around the tissue.²⁷,²⁸ The US is limited by its inability to differentiate UESL from a benign lesion. Magnetic resonance imaging is helpful in surgical planning because it may detect vascular invasion, biliary obstruction, and hilar adenopathy.²⁵

Following imaging, the diagnosis can be confirmed with histopathological examination of the tumor. The gross examination shows a large tumor, usually greater than 10 cm, with solid areas admixed with areas of cystic degeneration, necrosis and hemorrhage within the tumor. In some cases, tumor may be as large as 30 cm associated with massive necrosis and degeneration.²⁹,³⁰ On histologic examination of the specimen, the tumor is

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distinguished from normal hepatic parenchyma by a pseudocapsule, which comprises of cords and clusters of hepatocytes. The tumor consists of proliferation of mesenchymal spindle or stellate shaped cells with ill-defined borders and inconspicuous nuclei, which makes the tumor appear sarcomatous, with an interspersed myxoid background. Additionally, multinucleated giant cells and bizarre cells with hyperchromatic nuclei are seen in between these sarcomatous cells. The cytoplasm of the tumor cells demonstrates cosinophilic globules, which are positive for periodic acid Schiff staining and impervious to elastase digestion. Furthermore, hemorrhage and necrotic tissue is also seen in these lesions.12,32

The immunohistochemistry panel, due to its objectivity, specificity and reproducibility, supplements the histopathological diagnosis. Since no single marker is particularly diagnostic, a panel of multiple markers can be used to establish diagnosis. The commonly used markers such as vimentin, desmin, CD10, CD 68, alpha-1 antitrypsin (a1-AT) and B-cell lymphoma 2 are positive in majority of the cases of embryonal sarcoma.25,31,32 Glypican 3 (GP 3), a marker for hepatoblastoma and hepatocellular carcinoma, has also been found to be positive in UESL.32 However, negative markers such as hepatocyte paraffin 1 (hepatoblastoma and Hepatocellular carcinoma), myogenin (embryonal rhabdomyosarcoma), CD34 (solitary fibrous tumors and vascular lesions), C-kit (gastrointestinal stromal tumors), anaplastic lymphoma kinase 1 (ALK1) (anaplastic large cell lymphoma), and S100 (melanoma) aid with the diagnostic process by ruling out other differential diagnoses.25,31 Therefore, the use of multiple markers collectively contributes to the diagnosis of the origin of tumor cells in embryonal sarcoma.

There are no standard treatment guidelines reported for the management of embryonal sarcoma of the liver, due to the paucity of randomized controlled trials and prospective studies to support any particular treatment approach. Historically, embryonal sarcoma was managed only with surgical resection leading to poor long-term outcomes in these patients. However, with the onset of the multimodal approach of chemoradiation and surgical resection, the prognosis is better for the affected patients.3 The survival rates have improved to 70-100% with the use of multimodal strategies for the management of embryonal sarcoma.14,33

CONCLUSION
UESL is a common pediatric malignancy of the liver, which generally presents with fever, nausea, weight loss, and abdominal mass. This condition requires imaging along with histopathology and immunohistochemistry for the diagnosis. The management depends on a multimodal approach of surgical excision, chemotherapy, and radiation therapy to improve survival in these patients.

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