

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.^{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 upto 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/l, alanine transaminase (ALT)-59 U/l, alkaline phosphatase (ALP)-710 U/l, γ -glutamyl transpeptidase γ (GPT)-178 U/l and lactate dehydrogenase (LDH)-281 U/l (Normal range: 45-90 U/l).

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.

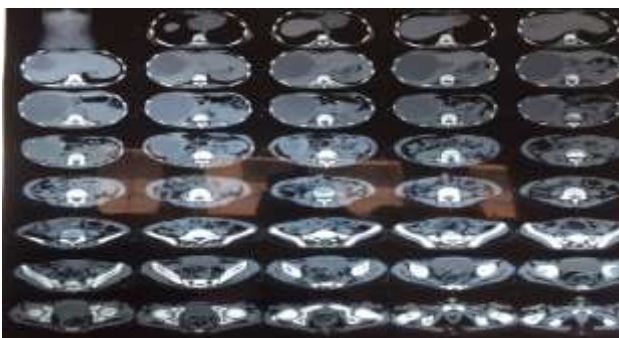


Figure 1: CT scan findings demonstrating undifferentiated embryonal sarcoma of right lobe of liver.

For further confirmation and details, an abdominopelvic contrast-enhanced CT was performed which revealed a relatively well-defined, smoothly marginated, large mass lesion measuring approximately 12.4×11.7×16 cm (APx MLxCC) along the right lobe of the liver. The lesion is predominantly exophytic. The lesion has a predominant solid than cystic component (confirmed with sonography correlation). No obvious calcification was noted within

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).



Figure 2: Abdominopelvic contrast-enhanced CT showing undifferentiated embryonal sarcoma of the liver.

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 12×10 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 12×10×7 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 mitosis. 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,

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.

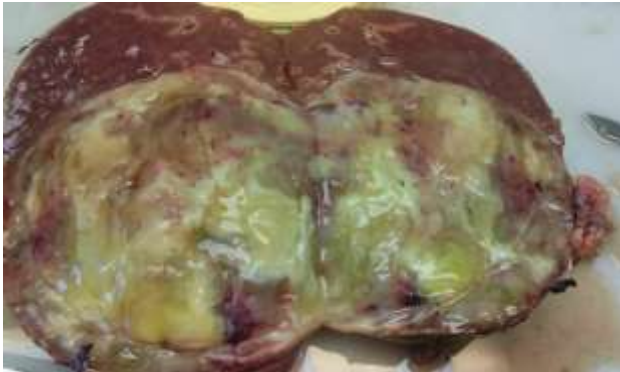


Figure 3: Cut surface of UESL showing grey white necrosis and hemorrhage.

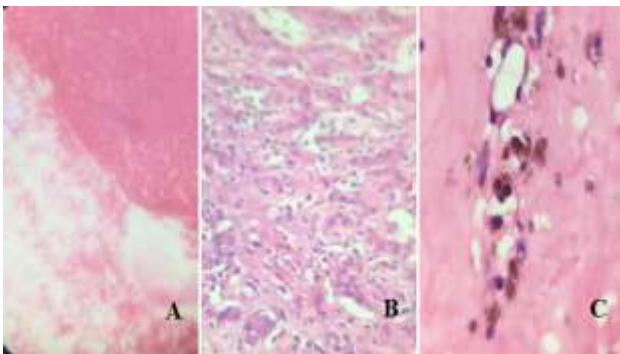


Figure 4: (A) Pseudocapsule separating the liver parenchyma from the tumor (B) malignant tumor cells in a myxoid stroma with eosinophilic globules in cytoplasm (C) shows hemosiderin laden macrophages.

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 UES 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 UES developing in association with MH.¹⁹⁻²¹ The DNA sequencing in a case of UES 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, diarrhoea, 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

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 nucleoli, 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 eosinophilic 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.^{1,29-32}

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 (ALK-1) (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 trails 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 Mathias et al report upto a median of eight years of survival after multimodal management.¹⁶ Similarly, May et al reported successful treatment of these patients using a chemotherapy regimen of vincristine, cyclophosphamide and actinomycin-D to encounter any residual tumor cells after surgical resection.³³ For unresectable cases, neoadjuvant chemotherapy may be used.^{29,33} In cases where the disease is refractory and recurrent, an orthotopic liver transplant may be an acceptable alternative to completely eliminate the malignant tissue.²⁹ 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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REFERENCES

1. Stocker JT, Ishak KG. Undifferentiated (embryonal) sarcoma of the liver. Report of 31 cases. *Canc.* 1978;42(1):336-48.
2. Weinberg AG, Finegold MJ. Primary hepatic tumors of childhood. *Huma Pathol.* 1983;14(6):512-37.
3. Bisogno G, Pilz T, Perilongo G, Ferrari A, Harms D, Ninfo V, et al. Undifferentiated sarcoma of the liver in childhood: a curable disease. *Canc.* 2002;94(1):252-7.
4. Almogy G, Lieberman S, Gips M, Pappo O, Edden Y, Jurim O, et al. Clinical outcomes of surgical resections for primary liver sarcoma in adults: results from a single centre. *Europea J Surg Oncol.* 2004;30(4):421-7.
5. Pachera S, Nishio H, Takahashi Y, Yokoyama Y, Oda K, Ebata T, et al. Undifferentiated embryonal sarcoma of the liver: case report and literature survey. *J Hepat-Bilia-Pancrea Surg.* 2008;15(5): 536-44.
6. Lenze F, Birkfellner T, Lenz P, Hussein K, Länger F, Kreipe H, et al. Undifferentiated embryonal sarcoma of the liver in adults. *Cancer.* 2008;112(10):2274-82.
7. Ismail H, Dembowska, Bagińska B, Broniszczak D, Kaliciński P, Maruszewski P, Treatment of undifferentiated embryonal sarcoma of the liver in children-single center experience. *J Pediat Surg.* 2013;48(11):2202-6.
8. Lack EE, Schloo BL, Azumi N, Travis WD, Grier HE, Kozakewich HP. Undifferentiated (embryonal) sarcoma of the liver. Clinical and pathologic study of 16 cases with emphasis on immunohistochemical features. *Americ J Surg Pathol.* 1991;15(1):1-16.
9. Joshi SW, Merchant NH, Jambhekar NA. Primary multilocular cystic undifferentiated (embryonal) sarcoma of the liver in childhood resembling hydatid cyst of the liver. *Briti J Radiol.* 1997;70(831):314-6.
10. Chung EM, Lattin Jr GE, Cube R, Lewis RB, Marichal-Hernández C, Shawhan R, Conran RM. From the archives of the AFIP: pediatric liver masses: radiologic-pathologic correlation part 2. Malignant tumors. *Radiograph.* 2011;31(2):483-507.

11. Buetow PC, Buck JL, Pantongrag-Brown L, Marshall WH, Ros PR, Levine MS, et al. Undifferentiated (embryonal) sarcoma of the liver: pathologic basis of imaging findings in 28 cases. *Radiolo.* 1997;203(3):779-83.
12. Putra J, Ornvold K. Undifferentiated embryonal sarcoma of the liver: a concise review. *Archiv Pathol Laborat Medic.* 2015;139(2):269-73.
13. Sowery RD, Jensen C, Morrison KB, Horsman DE, Sorensen PH, Webber EM. Comparative genomic hybridization detects multiple chromosomal amplifications and deletions in undifferentiated embryonal sarcoma of the liver. *Canc Geneti Cytogenet.* 2001;126(2):128-33.
14. Weitz J, Klimstra DS, Cymes K, Jarnagin WR, D'Angelica M, La Quaglia MP, et al. Management of primary liver sarcomas. *Cancer: Interdisciplinary International J Americ Canc Soc.* 2007;109(7): 1391-6.
15. Kim DY, Kim KH, Jung SE, Lee SC, Park KW, Kim WK. Undifferentiated (embryonal) sarcoma of the liver: combination treatment by surgery and chemotherapy. *J Pediatr Surg.* 2002;37(10):1419-23.
16. Mathias MD, Ambati SR, Chou AJ, Slotkin EK, Wexler LH, Meyers PA, et al. A single-center experience with undifferentiated embryonal sarcoma of the liver. *Pediatr Bloo & Canc.* 2016;63(12): 2246-8.
17. Nicol K, Savell Jr V, Moore J, Teot L, Spunt SL, Qualman S. Children's Oncology Group, Soft Tissue Sarcoma Committee. Distinguishing undifferentiated embryonal sarcoma of the liver from biliary tract rhabdomyosarcoma: a Children's Oncology Group study. *Pediatr Developmen Pathol.* 2007;10(2):89-97.
18. Horowitz ME, Etcubanas E, Webber BL, Kun LE, Rao BN, Vogel RJ, et al. Hepatic undifferentiated (embryonal) sarcoma and rhabdomyosarcoma in children. Results of therapy. *Cancer.* 1987;59(3): 396-402.
19. Speleman F, De Telder V, De Potter KR, Dal Cin P, Van Daele S, Benoit Y, et al. Cytogenetic analysis of a mesenchymal hamartoma of the liver. *Canc Geneti Cytogenet.* 1989;40(1):29-32.
20. Mascarello JT, Krous HF. Second report of a translocation involving 19q13.4 in a mesenchymal hamartoma of the liver. *Canc Genet Cytogeneti.* 1992;58(2):141-2.
21. Bove KE, Blough RI, Soukup S. Third report of t (19q) (13.4) in mesenchymal hamartoma of liver with comments on link to embryonal sarcoma. *Pediatr Developmen Pathol.* 1998;1(5):438-42.
22. Rajaram V, Knezevich S, Bove KE, Perry A, Pfeifer JD. DNA sequence of the translocation breakpoints in undifferentiated embryonal sarcoma arising in mesenchymal hamartoma of the liver harboring the t (11; 19)(q11; q13.4) translocation. *Gene, Chromo som Canc.* 2007;46(5):508-13.
23. Rakheja D, Margraf LR, Tomlinson GE, Schneider NR. Hepatic mesenchymal hamartoma with translocation involving chromosome band 19q13.4: a recurrent abnormality. *Canc Genet Cytogenet.* 2004;153(1):60-3.
24. Lepreux S, Rebouissou S, Le Bail B, Saric J, Balabaud C, Bloch B, et al. Mutation of TP53 gene is involved in carcinogenesis of hepatic undifferentiated (embryonal) sarcoma of the adult, in contrast with Wnt or telomerase pathways: an immunohistochemical study of three cases with genomic relation in two cases. *J Hepatol.* 2005; 42(3):424-9.
25. Wei ZG, Tang LF, Chen ZM, Tang HF, Li MJ. Childhood undifferentiated embryonal liver sarcoma: clinical features and immunohistochemistry analysis. *J Pediatr Surg.* 2008;43(10): 1912-9.
26. Sakellaridis T, Panagiotou I, Georgantas T, Micros G, Rontogianni D, Antiochos C. Undifferentiated embryonal sarcoma of the liver mimicking acute appendicitis. Case report and review of the literature. *World J Surg Oncol.* 2006;4(1):9.
27. Lashkari HP, Khan SU, Ali K, Sashikumar P, Mukherjee S. Diagnosis of undifferentiated embryonal sarcoma of the liver-importance of combined studies of ultrasound and CT scan. *J Pediat Hematol/Oncol.* 2009;31(10):797-8.
28. Massani M, Caratozzolo E, Baldessin M, Bonariol L, Bassi N. Hepatic cystic lesion in adult: a challenging diagnosis of undifferentiated primary embryonal sarcoma. *J Surg.* 2010;31(5):225-8.
29. Plant AS, Busuttill RW, Rana A, Nelson SD, Auerbach M, Federman NC. A single-institution retrospective cases series of childhood undifferentiated embryonal liver sarcoma (UELS): success of combined therapy and the use of orthotopic liver transplant. *J Pediat Hematol/Oncol.* 2013;35(6):451-5.
30. Baron PW, Majlessipour F, Bedros AA, Zuppan CW, Ben-Youssef R, Yanni G, et al. Undifferentiated embryonal sarcoma of the liver successfully treated with chemotherapy and liver resection. *J Gastrointest Surg.* 2007;11(1):73-5.
31. Kiani B, Ferrell LD, Qualman S, Frankel WL. Immunohistochemical analysis of embryonal sarcoma of the liver. *Appl Immunohistochemis Molecul Morphol.* 2006;14(2):193-7.
32. Levy M, Trivedi A, Zhang J, Miles L, Mattis AN, Kim GE, et al. Expression of glypican-3 in undifferentiated embryonal sarcoma and mesenchymal hamartoma of the liver. *Hum Pathol.* 2012;43(5):695-701.
33. May LT, Wang M, Albano E, Garrington T, Dishop M, Macy ME. Undifferentiated sarcoma of the liver: a single institution experience using a uniform treatment approach. *J Pediat Hematol/Oncol.* 2012;34(3):e114.

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