Improved Survival with Surgery and Systemic Chemotherapy for Undifferentiated Embryonal Sarcoma of the Liver

Gidon Almogy MD[1], Orit Pappo MD[2], Maya Gips MD[3], Sivan Lieberman MD[4], Yair Edden MD[1] and Ahmed Eid MD[1]

Departments of [1]Surgery, [2]Pathology, [3]Oncology and [4]Radiology, Hadassah Medical Center and Hebrew University–Hadassah Medical School, Jerusalem, Israel

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Stocker and Ishak in 1978 [1] were the first to describe undifferentiated embryonal sarcoma of the liver as a clinopathologic entity. The tumor typically presents in late childhood (between 6 and 10 years of age) as a painful right upper quadrant mass, fever and weight loss. The tumor is composed of primitive spindle cells with myxoid stroma and has no recognizable sarcomatous differentiation. Electron microscopic studies suggest several possibilities for its origin, most notably a myogenous component. Cytokeratins, which are usually identified in cells of epithelial origin, have been found in pediatric embryonal sarcomas.

The sonographic findings in USL range from predominantly echogenic solid areas to multi-septated hypoechoic cystic areas. Computed tomography scan reveals a well-demarcated, low attenuation mass with hyperdense septations of variable shapes, and peripheral solid portions. This misleading cyst-like appearance on CT and the discordance with the sonographic findings is typical of USL. Magnetic resonance imaging with gadolinium has been shown to reveal peripheral enhancement, corresponding to the pseudocapsule of the tumor [2]. The angiographic appearance of USL is usually described as hypovascular to avascular. Neoplastic vasculature such as macro-aneurysms, arteriovenous shunting and vascular encasement can be found in the solid portions of the tumor. Macro-aneurysms have not been reported in other liver tumors.

USL = undifferentiated embryonal sarcoma of the liver
CA = carcinoembryonic antigen

Surgery is the treatment of choice for USL, and several chemotherapeutic regimens have been added to improve outcome in the pediatric population. Only sporadic cases have been reported in adults, the majority with a dismal prognosis. We report a case of a 21 year old female with USL who was treated at our institution with a combined approach consisting of repeated cycles of hepatic resection and systemic chemotherapy. We discuss presenting symptoms and signs, imaging findings, treatment and outcome.

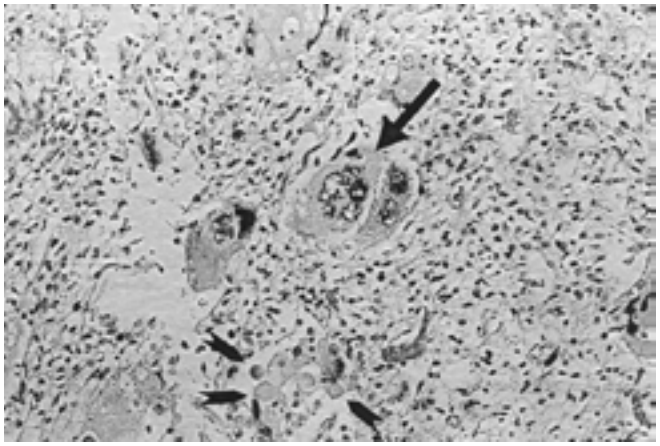
Patient Description

A 21 year-old female was admitted for a 2 month history of right upper quadrant pain, weight loss, fever and night sweats. Her blood count was relevant for hemoglobin of 8.7 g/dl. Liver enzymes were moderately elevated and coagulation tests were within the normal range. Tumor markers including alpha-fetoprotein and carcinoembryonic antigen were normal, except for CA-125 that was elevated to 140 U/ml (normal range 0–30 U/ml).

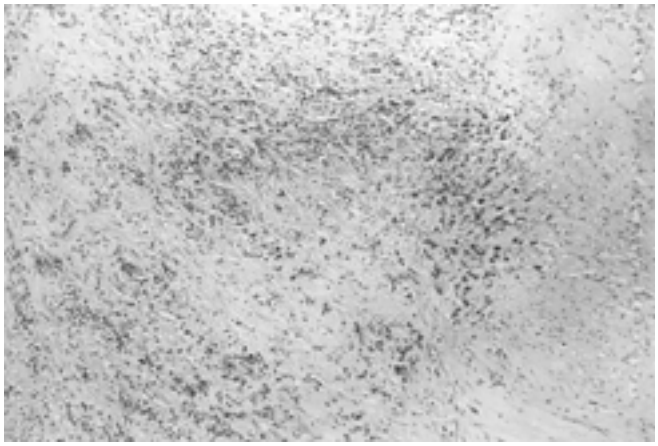
Abdominal ultrasound showed a solid hypoechoic mass with cystic components. Abdominal CT revealed a 15 x 15 cm cystic mass confined to the right lobe of the liver. The mass was hypovascular on angiography and compressed the right hepatic artery and right portal vein. CT-guided percutaneous fine-needle aspiration and core biopsy were performed. Tumor cytology and histopathology showed round and elongated malignant cells of mesenchymal origin, but a definite histopathologic diagnosis could not be established.

At laparotomy the tumor appeared soft and fragile with imminent rupture. Intraoperative ultrasound of the liver revealed a second smaller lesion in the left lateral segment of the liver. Due to inadequate liver reserve, a decision was made to resect the right-sided lesion only, and hepatic tri-segmentectomy was performed without complications. The tumor was well circumscribed, measuring 20 cm in the largest diameter, located 0.3 cm from the resection margins. The cut surface was variegated with solid gray tissue alternating with soft hemorrhagic areas. Microscopically, the tumor was composed of spindle cells, with occasional bizarre giant nuclei and no differentiation. Some of the cells contained periodic acid Schiff-positive diastase-resistant hyaline inclusions in the cytoplasm. The tumor cells were separated by a myxoid matrix [Figure A]. Tumor cells stained with vimentin and alpha-antitrypsin. Desmin, epithelial markers, and endothelial markers were negative. The surgical margins were free of tumor. Electron microscopic examination revealed giant multinucleated cells with phagocytic activity. Intercellular bridges were not found and there was no evidence of cellular differentiation. The diagnosis of USL was based on the above findings.

The patient was treated postoperatively with five cycles of intravenous ifosfamide, doxorubicin and mesna – at doses of 2,500 mg/m^2 (days 1–3), 50 mg/m^2 (day 2) and 2,000 mg/m^2 (days 1–3), respectively – at 3 week intervals with good tolerance and significant regression in the size of the left-sided lesion. The patient was then brought back to the operating room for re-exploration. Significant liver regeneration coupled with marked tumor regression allowed complete resection of



[A]. The tumor is composed of small stellate cells in a loose myxoid stroma. Multinucleated giant tumor cells are seen (arrow). Characteristic periodic acid Schiff-positive diastase-resistant eosinophilic globules are seen (arrowhead).



[B]. Section from the resected specimen after chemotherapy. There is fibrosis, chronic inflammation and hemosiderin deposition. No viable tumor cells are seen.

the left-sided lesion. Tumor size was 3.4 cm, located 0.2 cm from the resection margins. Histologic examination revealed scar tissue with chronic inflammation accompanied by hemosiderin-laden macrophages. Only rare atypical giant cells were noted [Figure B]. Resection margins were free of tumor. Postoperatively the patient received two additional cycles of the above chemotherapeutic regimen and is currently well with no evidence of disease 71 months after her second hepatic resection.

Comment

USL is a rare tumor of mesenchymal origin and accounts for less than 1% of all primary liver neoplasms in the adult. Symptoms are non-specific, tumor markers such as alpha-fetoprotein and carcinoembryonic antigen are normal, and imaging studies are often non-conclusive. These factors make diagnosis difficult to establish and treatment is often delayed. Radical resection is the treatment of choice for USL; the relatively large size of these tumors does not seem to influence survival [3]. Our experience, though limited, shows that repeated cycles of surgical resection coupled with systemic chemotherapy consisting of ifosfamide and doxorubicin can achieve cure in adults with large USL.

Adjuvant chemotherapy is used routinely in many cancer centers to treat high grade extremity sarcomas in order to improve local control and disease-free survival, even though the majority of clinical trials have failed to show improvement in overall survival [4]. The routine use of ifosfamide and/or doxorubicin-based neoadjuvant and adjuvant chemotherapy has improved survival in the pediatric population with USL [5]. Various chemotherapeutic protocols have been used, usually in a small number of patients. It is therefore difficult to recommend one protocol over another. Our decision to administer adjuvant chemotherapy was based on the poor prognosis of USL in adults and the literature regarding high grade sarcoma. Similar to experience acquired in the pediatric population, our limited experience adds to the growing body of evidence favoring administration of ifosfamide and doxorubicin-based systemic chemotherapy as an adjunct to surgery for patients with USL. Longer follow-up in more patients is necessary to better assess the efficacy of adjuvant therapy in the treatment of USL in adults.

Hepatocellular carcinoma is the most common primary hepatic neoplasm and is usually associated with cirrhosis of the liver. Imaging findings cannot reliably differentiate the rare USL from the much more common hepatocellular carcinoma. Tissue diagnosis may aid in directing treatment in non-cirrhotic patients and liver biopsy should therefore be performed in these selected cases. Patients with resectable tumors should be referred for surgery with the obvious goal of achieving clear margins. Patients with seemingly non-resectable tumors and those with residual disease should be offered the potential benefit of systemic chemotherapy to downstage the tumor and facilitate resection.

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Correspondence: Dr. G. Almogy, Dept. of Surgery, Hadassah Medical Center, P.O. Box 12000, Jerusalem 91120, Israel.
Phone: (972-2) 677-7111
Fax: (972-2) 644-9412
email: galmogy@hadassah.org.il