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CASE REPORT

Undifferentiated Embryonal Sarcoma of the Liver: a Great Masquerader

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Introduction

Undifferentiated embryonal sarcoma of the liver (UESL) is a rare primary tumor in adults. Misdiagnosis is largely due to its infrequency in adult patients, the absence of specific diagnostic blood tests, and lack of classic radiologic findings. This is a case of a 33-year-old Asian male who presented with a painful hepatic mass and fevers thought initially to be infectious, but later diagnosed as UESL which was successfully resected.

Case

A 33-year-old male with known glucose-6-phosphate dehydrogenase deficiency was admitted for worsening right upper quadrant abdominal pain, nausea, and vomiting of 1 day duration in the setting of subacute weight loss, malaise, and intermittent fevers as high as 103.7 °F at home. Three weeks prior to admission, in addition to these symptoms, he developed new right scapular pain which he treated with ibuprofen and acetaminophen. One day prior to admission, he experienced sharp, right upper quadrant pain as well as an episode of non-bilious, non-bloody emesis which prompted him to come to the emergency department. The patient was born in Hong Kong and emigrated to Canada as an infant. During the past year, the patient traveled to Southeast Asia and the Middle East. Vital signs on presentation were initially within normal limits. Physical examination showed anicteric sclera, abdominal distention, and tender hepatomegaly. Initial white blood cell count was 18×10^9/L and liver tests were within normal limits. Computed tomography showed a large predominantly cystic lesion containing multiple thickened septations and ill-defined soft tissue within the right hepatic lobe measuring approximately $16.5 \times 13.3 \times 18.6$ cm in AP transverse and craniocaudal dimension (Fig. 1); this was redemonstrated on magnetic resonance imaging (Fig. 2). That night, the patient developed a fever of 102 °F and became hypotensive, tachypneic, and tachycardic. The patient was moved to the medical intensive care unit for closer monitoring and started on piperacillin-tazobactam for presumed sepsis from superinfected hepatic mass/abscess. A liver biopsy revealed acute and chronic inflammation with no malignant cells seen. The biopsy cultures were sterile for bacterial, fungal, and mycobacterial pathogens. Additional blood tests include normal sera alpha fetoprotein, carcinoembryonic antigen, carbohydrate antigen 19-9, and non-reactive *Entamoeba histolytica* antigen and echinococcal antibody. Procalcitonin value was 0.07 mg/ml. The patient continued to have intermittent fever, tachycardia, and tachypnea and complained of right scapular and right upper quadrant pain. Blood cultures remained sterile. Voriconazole was added to his antibacterial therapy for possible fungal

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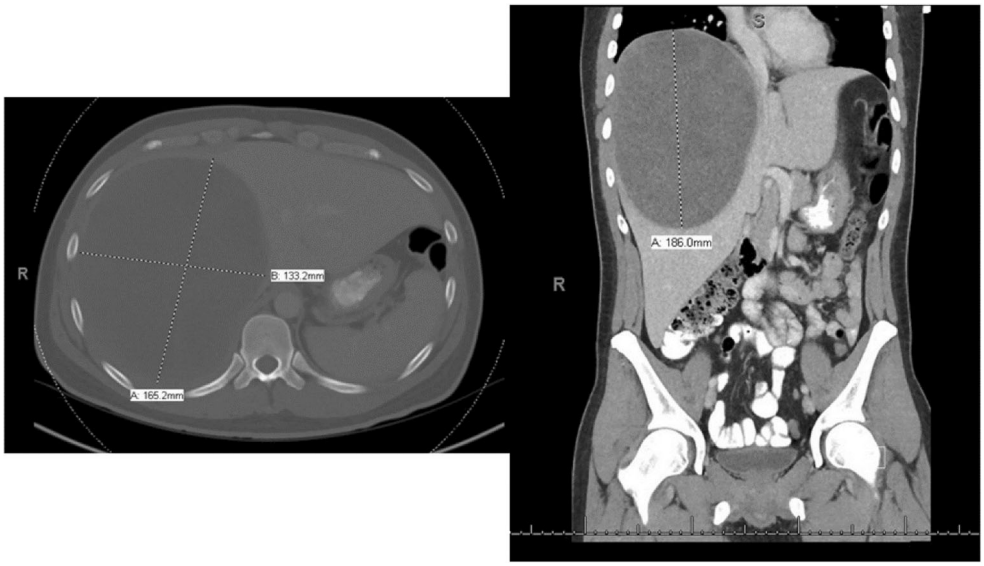

Fig. 1 Computed tomography of the abdomen showed a large predominantly cystic lesion containing multiple thickened septations and ill-defined soft tissue within the right hepatic lobe measuring approximately 16.5 × 13.3 × 18.6 cm in AP transverse and craniocaudal dimension

infection. Testicular ultrasound and serum beta human chorionic gonadotropin were normal. Serologic testing for aspergillus and T2 candida testing were negative. It was suspected that the ongoing fevers may be secondary to malignancy and necrosis. A repeat liver biopsy was performed which revealed a high grade malignancy with very pleomorphic, often spindle-shaped cells, growing in edematous ground substance/matrix (Fig. 3a). There were intra- and extracellular hyaline globules throughout the tumor and an immunostain confirmed it to be alpha-1-antitrypsin. Other positive immunostains include CD56, glypican-3, and desmin (Fig. 3b). The immunostain for myoglobin was equivocal and the immunostains for erg-1, myogenin, and HMB45 were negative, thus excluding angiosarcoma, embryonal rhabdomyosarcoma, and melanoma. These results indicate a poorly differentiated malignant neoplasm with features suggestive of embryonal sarcoma in the sampled tissue. The patient underwent right hepatectomy: Intra-operatively, the large right hepatic lobe tumor was seen involving the right diaphragm thus requiring a median sternotomy for proper mobilization, exposure, and subsequent en bloc resection of the involved portions of diaphragm (Fig. 4a–d). Patient did well post-operatively and his fever subsided. He was discharged 10 days post-operatively. The final pathology was undifferentiated embryonal sarcoma of the liver with tumor dimension of 21 cm. The resection margins, diaphragm, gall bladder, and xiphoid process were negative for tumor (Fig. 5a–d). He is scheduled to receive chemotherapy with cyclophosphamide, vincristine, and doxorubicin.

Discussion

Primary sarcomas are extremely rare and represent less than 1% of all primary liver tumors in adults [1]. They include angiosarcoma, epithelioid hemangioendothelioma,

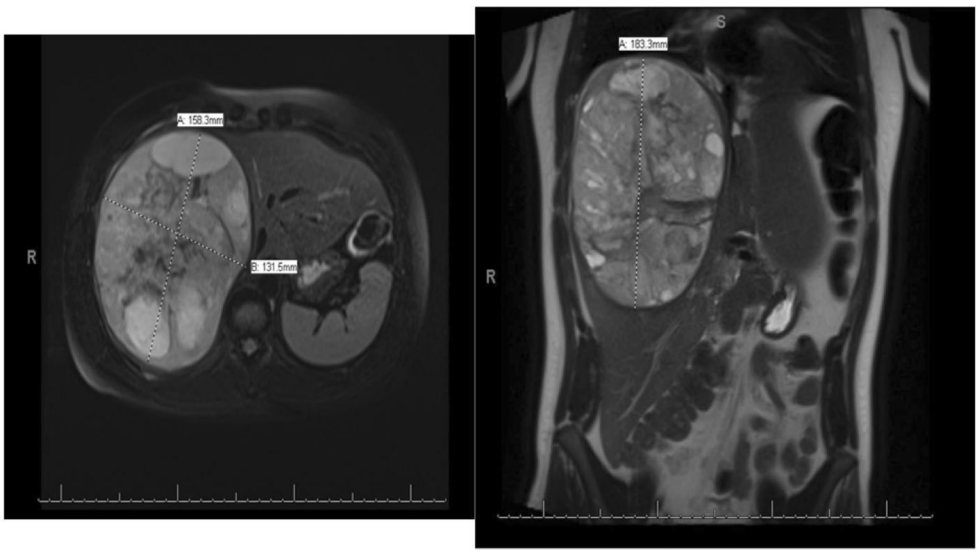

Fig. 2 Magnetic resonance imaging of the abdomen revealed an enlarged liver with normal contour and a 15.8 × 13.2 × 18.3 cm right lobe lesion that is cystic with progressive low-level confluent internal thickened septal and nodular solid enhancement

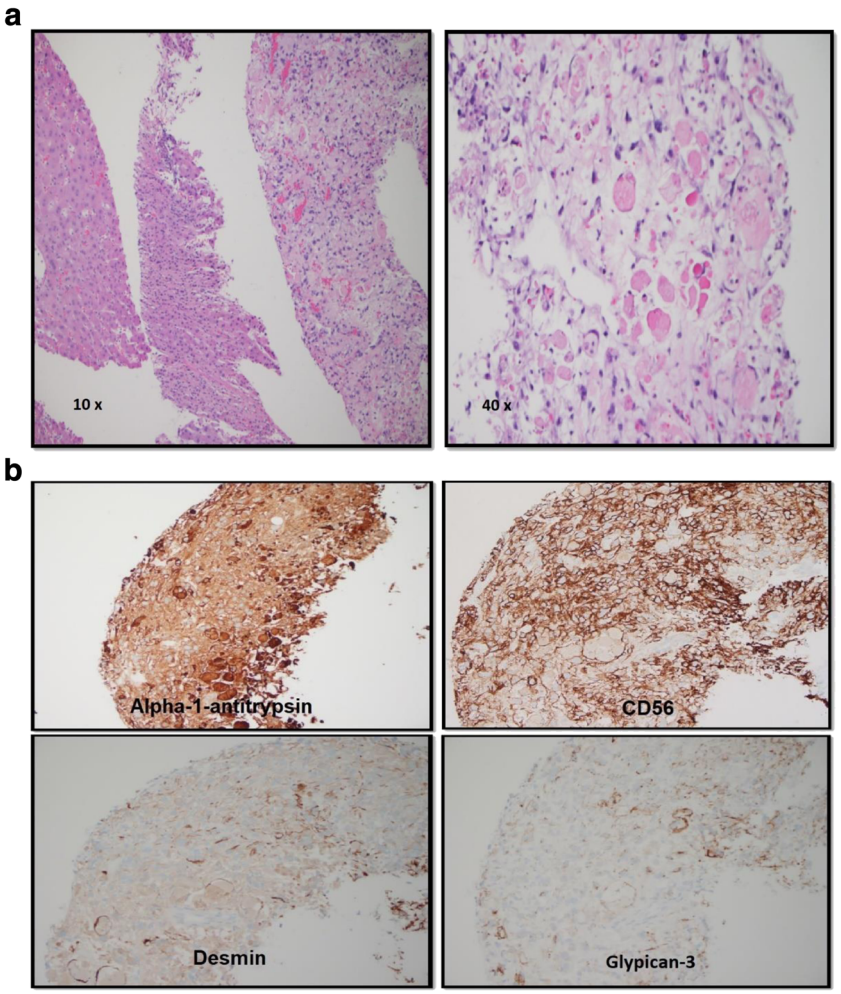

Fig. 3 **a**: Liver biopsy × 10 and × 40 magnification showing a very pleomorphic, often spindle shaped cells, growing in edematous ground substance/ matrix. **b**: immunohistochemical stain at × 20 magnification showing positive for alpha-1-antitrypsin, CD56, desmin and glypican-3

leiomyosarcoma, fibrosarcoma, malignant fibrous histiocytoma, and the UESL.

UESL, alternatively referred to as malignant mesenchymoma or undifferentiated sarcoma of the liver, was first described by Stocker and Ishak in 1978 [2]. While this malignancy occurs more frequently in pediatric patients between ages 6 and 10 years, it is a very rare primary hepatic sarcoma in adults where it accounts for less than 1% of all primary liver neoplasms [3]. The histogenesis of tumor growth is unclear. One hypothesis is that it may arise from a benign mesenchymal hamartoma of the liver (MHL) which is the second most common benign liver tumor in children. Other hypotheses for origination include alterations of TP53, allelic imbalances of 1p, 80, and 20q, loss of heterozygosity of 7p, 11p, 17p, and 22q. [4].

Patients can present with non-specific signs and symptoms such as abdominal pain, weight loss, palpable liver mass, or fever. Radiographically, the tumor appears as a solid mass with extensive cystic or necrotic changes. These cystic changes and the rarity in adults often lead to misdiagnosis with the most commonly reported differential diagnoses of hepatic abscess, hydatid cyst, hemorrhage cystic tumor, mucinous cystic neoplasms, and Klatskin tumor. In general, the tumor does not produce alpha-fetoprotein, carbohydrate antigen 19-9, carcinoembryonic antigen, or cancer antigen 125. However, a case of erythropoietin-secreting UESL has been reported [5]. Most lesions are seen in the right lobe of the liver, although the tumor can also grow in the left lobe of the liver or even bilaterally. Macroscopically, the tumor consists of both solid and cystic components with areas of necrosis. Histologically, the cells are spindle or stellate shaped with inconspicuous nucleoli and ill-defined cell borders in a myxoid background. The multiple intracellular or extracellular eosinophilic globules which are positive for Periodic acid-Schiff (PAS) stain and resistant to diastase, are characteristic of UESL. Immunohistochemically, vimentin is consistently expressed in the tumor cells. There is variable expression with desmin, keratin, α-smooth muscle actin, α-1-antichymotrypsin, CD10, CD68, and α1-AT. The individual markers are often not helpful in differentiating UESL from other liver tumors. Therefore, multiple immunostains are usually performed to help with the diagnosis. Due to its rarity, metastatic sarcoma and sarcomatoid carcinoma should be excluded first.

Tumor complications include local recurrence after surgical resection, distant metastasis, intrahepatic bleeding [6],

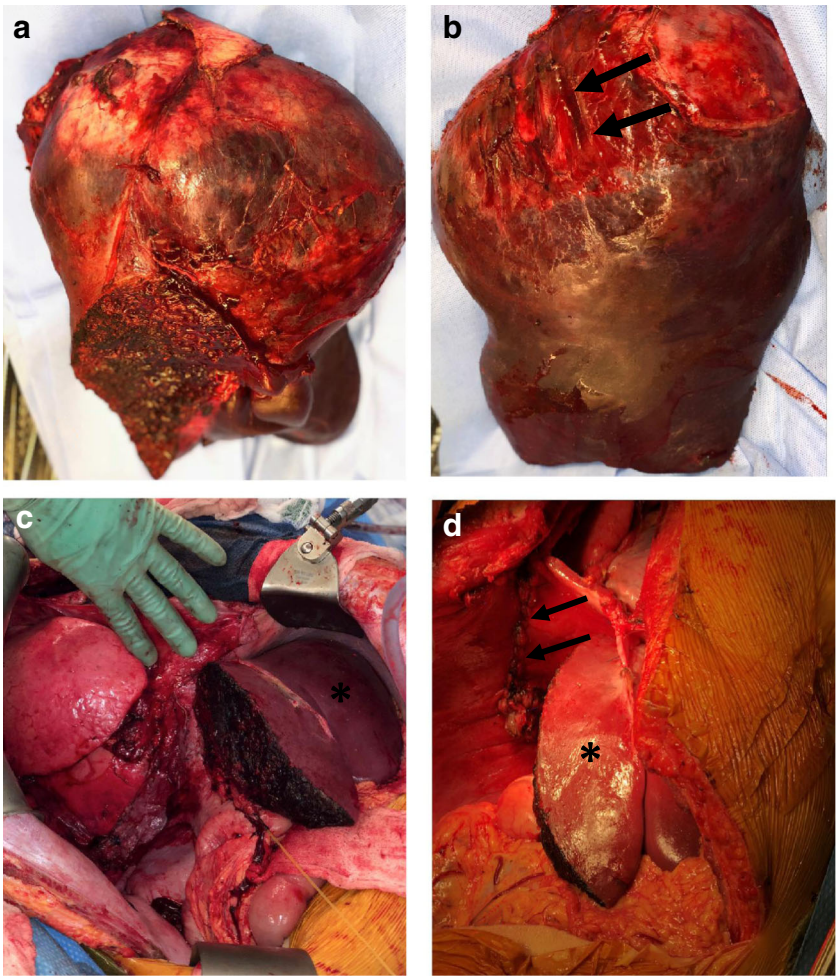

Fig. 4 Intra-operative images and specimen: **a** and **b**: resection specimen, right lobe with tumor and involved diaphragm (arrow). **c**: status post right hepatectomy with en bloc resection of tumor and involved diaphragm through bilateral subcostal incision and median sternotomy. **d**. primary right diaphragm repair (arrow) and remnant left lobe (*)

spontaneous rupture into the peritoneal cavity and tumor thrombus extending into the right atrium [7]. Because of the infrequency of this tumor type in adults, most treatment plans and survival data are from pediatric studies where, in the past, UESL prognosis has been very poor, with a median survival of less than 1 year following diagnosis as reported in a study by Stocker and Ishak [2]. However, the long-term survival rate in pediatric patients has improved significantly after the

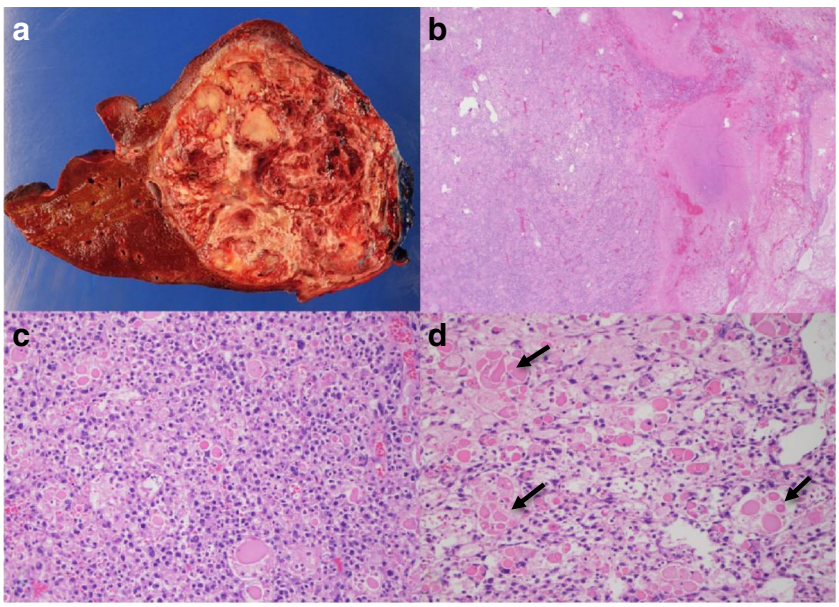

Fig. 5 **a**: Gross cut section revealed tumor is cystic and solid with hemorrhage, infarction and necrosis including abscess-like foci. The tumor has a pseudo capsule that encircles and permeates the tumor with foci of entrapped liver parenchyma. **b**, **c**, and **d** at × 10, × 20, and × 40 magnification showing pleomorphic, spindled and undifferentiated round cells with variable nuclear morphology. Among and within the cells, there are hyaline and eosinophilic globules (arrows)

introduction of multimodal therapy, including surgery and neoadjuvant or adjuvant chemotherapy [8].

In a retrospective study of PubMed searches of adults with UESL by Lenze et al. [9], improved survival rates were also seen in adults receiving adjuvant chemotherapy after complete tumor resection as compared to radical tumor resection alone. However, even with complete resection of the tumor, tumor recurrence is not uncommon. Currently, other modalities have been explored including interventional radiological techniques to decrease tumor size preoperatively and reduce the burden of potentially toxic chemotherapy; orthotopic hepatic transplantation as an alternative therapeutic method for non-resectable tumors or tumor recurrence isolated to the liver [10]; and novel treatments like stem cell transplantation providing the potential opportunity to cure [3].

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Informed Consent Informed consent was taken from the patient.

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