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Undifferentiated Embryonal Sarcoma of Liver in a Young Female: A Case Report and Review of Literature

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Abstract

Undifferentiated embryonal sarcoma of liver is a rare mesenchymal malignancy, commonly occurring in children between 6 to 10 years of age. Here, we report a young female, who presented with a large liver inoperable liver mass and was clinically and radiologically a diagnostic challenge. She was histopathologically and immunohistochemically diagnosed as USEL and planned for neo- adjuvant chemotherapy, but unfortunately succumbed to toxicity in her first cycle of chemotherapy despite prudent management. Therefore, definitive diagnosis is dependent on histopathology post-biopsy or resection and prognosis on early accurate diagnosis along-with radical resection with clear margins whenever feasible. The treatment protocols are still under evaluation for standards and efficacy. Timely intervention and management of toxicities is crucial in all patients receiving chemotherapy.

Keywords: USEL; Rare; Ifosfamide; Toxicity; Undifferentiated; Embryonal; Sarcoma; Liver

Introduction

Undifferentiated Embryonal Sarcoma of Liver (USEL) is rare mesenchymal malignancy, which occur in children with peak incidence between ages of 6 to 10 years, with fewer than 60 cases reported in adults [1-3]. The term USEL was introduced in 1978 by Stocker and Ishaq [4]. There is a reported female predilection when it occurs in adults, which is not seen in children [5]. The behavior is generally highly aggressive, however diagnosis is rarely accurate in adults in view of overlapping clinical and radiological findings with other liver tumors [6-8]. It is potentially curable with multimodal management and supportive care, but the overall prognosis is poor [9].We report a young woman with a final diagnosis of undifferentiated embryonal sarcoma of liver, who succumbed during treatment.

Case Presentation

A 30 year old Kashmiri female, presented with right hypochondrial abdominal pain, fullness with anorexia and bloating, since three months. Abdominal examination revealed a bulky right abdominal mass, likely from the liver, measuring upto 15 cm below the right costal margin, as well as crossing the midline by 3 cm to left and 3 cm downwards (Figure 1).

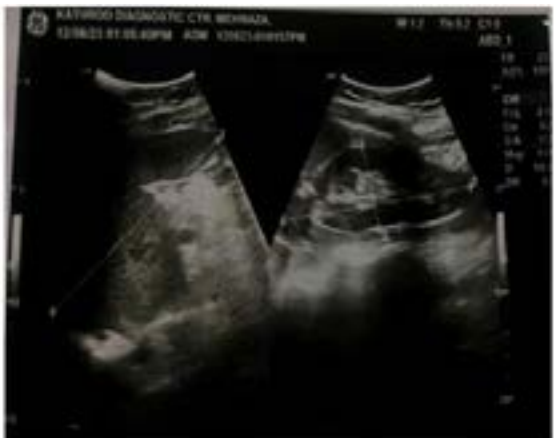

Figure 1. USG revealed hydatid cyst like lesions, as large well defined heterogeneously isodense hypoechoic lesions in right lobe of liver with multiple daughter cysts, however serology was negative for the same.

Routine laboratory test showed hemoglobin of 9.9 g/dL, WBC 9000/uL with neutrophil count 79%, lymphocyctes 15% and platelets 342000/uL. Liver function tests showed bilirubin 0.6 umol/L, SGPT 10 IU/L, SGOT 28 IU/L, ALP 381 IU/L, total protein 5.33 g/dL and albumin 2.26 g/dL, renal function were normal. Tumor markers LDH 1015 U/L, AFP 3.26 ng/mL. Hepatitis serology as well as hydatid serology was negative.

FNAC of liver lesion suggested occasional clusters of benign hepatocytic and a mixed inflammatory infiltrate in predominantly hemorrhagic background, with a few foci of fragments of eosinophilic homogenous material.

She developed rapid progression of abdominal distention with associated backache for which cross- sectional imaging was advised. CE-MRI (Fig 2A, 2B, 2C) liver revealed 17.4 x 17.5 x 16.5 cm mass replacing the entire right lobe of liver, heterogeneous solid cystic on T2 weighted images, with multiple areas of hyper intensity on T1 pre-contrast images, suggestive of hemorrhage. Multiple hypo enhancing areas along the superior and posterior wall. Plane with main portal vein, left portal vein, CBD and left hepatic duct appears maintained. Inferiorly the lesion abuts the upper pole of right kidney, with maintained fat planes. Differentials of the lesion were hepatic adenoma with hemorrhage, embryonal sarcoma or biliary cystadenoma (Figure 2a,2b,2c).

Triple phase CECT whole abdomen revealed similarly large 20.6 x 19.3 x 18.7 cm solid cystic hepatic lesion occupying the right hepatic lobe, with compression of right portal vein, and exophytic component of the lesion extending into the morrisons pouch. The lesion had mild

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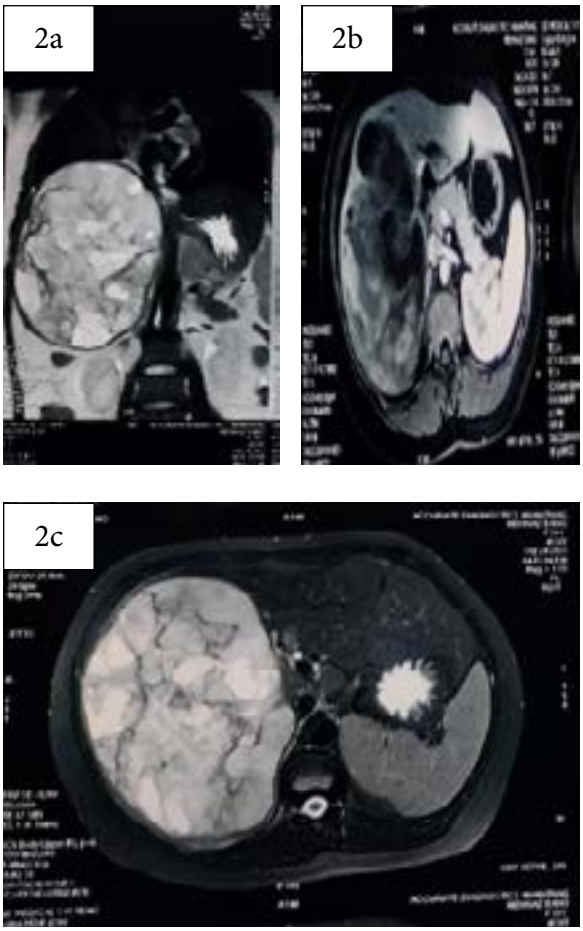

Figure 2. CE-MRI liver images (2a) Coronal section with T2 weighted image showing the large lesion replacing the entire right lobe of liver, (2b) Axial T1 post contrast fat saturated image of the same lesion, (2c) Axial T2 fat suppressed fast recovery sequence showing the heteroge-neity of the lesion

heterogenous enhancement in arterial phase with multiple traversing internal arterial channels. Heterogenous enhancement on portal venous phase predominantly, along the periphery of the lesion.

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The patient was referred to our centre with these reports and discussed in multidisciplinary tumour board. In view of huge unresectable lesion with fair performance status, she was planned for neo- adjuvant Adriamycin-Ifosphamide with MESNA chemotherapy. She was started at 70% dose of ifosphamide 2500 mg/m2 D1-3, Doxorubicin 50 mg/m2 D2 and MESNA 2000 mg/m2 D1-3 regimen, to assess the tolerability to the same. On day four of first cycle of chemotherapy she developed hemorrhagic cystitis grade III in the form of hematuria and small clots. Urine examination revealed 90-100 RBCS, 80-90 pus cells with albuminuria. 24 hour urine protein was 3.9 gm. Patient's MESNA dose was amped up, increased hydration and bladder irrigation.

On day 5, the patient developed hallucinations suggesting encephalopathy grade IV. Brain imaging in the form of CT and CEMRI were unremarkable. After ruling out all possible causes metabolic as well as infective, and opinion from the neurologist, drug related toxicity was considered as cause for encephalopathy. For encephalopathy, after reviewing literature, she was started on injection thiamine 100 mg intravenous 6 hourly for 5 days (Figure 3a,3b 3c).

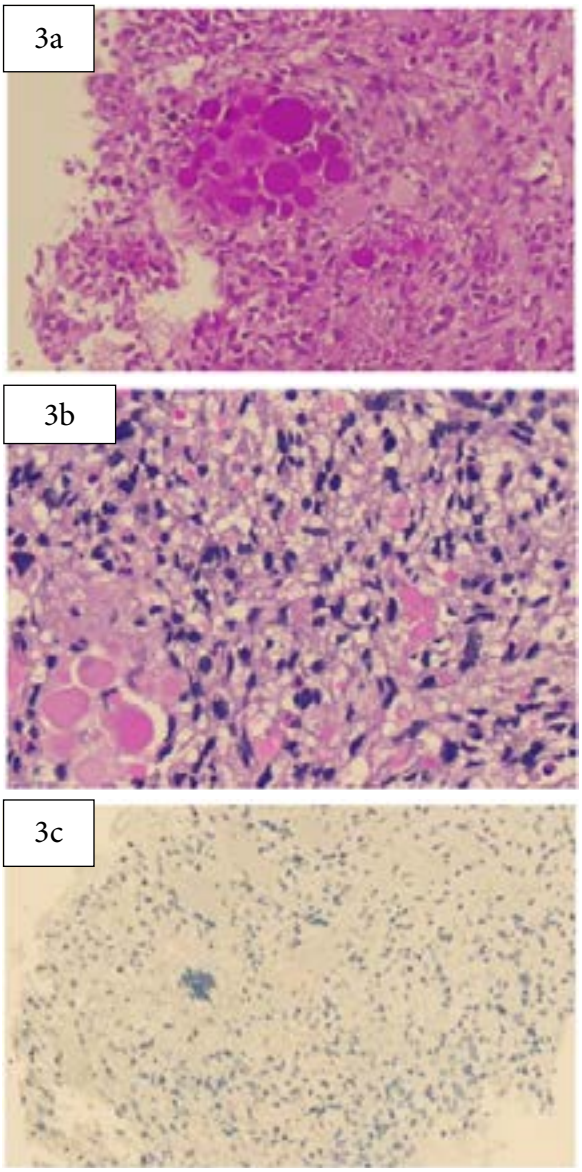

Figure 3. Histopathology and IHC images (3a) Tumor showing short fascicles of cells with hyperchromatic nuclei, multinucleated forms and abundant mitosis,(3b) PAS positive eosinophilic hyaline globules in the cytoplasm,(3c) Negative IHC staining

She also developed febrile neutropenia with grade IV neutrophil counts and thrombocytopenia grade IV with platelet counts 8000 on day 8 of chemotherapy and was started on injection GCSF and Romiplostim support. Her neurological status started to improve on day 11th of chemotherapy. Repeat urine routine was unremarkable. Patient became fully conscious on day 14 of chemotherapy. She was afebrile in 3 days with antibiotics but had persistent thrombocytopenia grade IV. Unfortunately, she succumbed to a massive pulmonary thromboembolism on day 16 with D-dimer of 1568 ug/ml.

Discussion

USEL is rare liver malignancy in clinical practice, which is infrequent in adults, accounting for fewer than 1% of primary liver neoplasm in this age group [9]. The etio-pathogenesis are not fully understood,

and are in general not associated with liver disease like hepatitis and cirrhosis but are associated with few cytogenetic abnormalities like amplification or deletion in chromosomes 6, 1q, 5p, 8p and 12q and translocation 19q13.4 [10]. A few studies have suggested involvement of p53 pathway in the carcinogenesis in the form of TP53 mutations or overexpression [11,12].

There are no specific clinical features or laboratory markers and image findings on CT, USG, MRI are often inconclusive. The delay in diagnosis are usually due to presentation in the form of large cystic hepatic lesions suggesting benign nature like hydatid disease, hemorrhage cystic tumor or abscess [13-18]. Pachera et al reported delay in 23.5% cases in view of benign lesion in imaging studies [19].

USEL commonly presents as palpable upper abdominal masses with varying degree of tenderness on examination. Although, it can occur in any part of the liver, a single rapidly growing mass in the right lobe is a common presentation [4,20]. The advanced tumors are known to grow at faster rates and are complicated with spontaneous rupture and bleed [21]. Large tumor volume may result in abnormal liver function tests. Mild leukocytosis, low albumin, anemia, elevated LDH and normal or mild increased liver enzymes may be seen. AFP may occasionally be elevated, one case has reported increased CA-125 levels [13,21]. Zaheer et al reported an adult patient with peripheral eosinophilia and suggested that USEL should be considered as differential diagnosis in cases with hepatic cysts with accompanying eosinophilia [13]. Our patient had low albumin, elevated LDH and anemia but had normal liver enzymes, AFP and CA125. Rarely, erythropoietin secretion and paraneoplastic manifestations are seen [22,23].

Often diagnosis is made through multidisciplinary participation. Microscopically, neoplasm may have round, stellate and spindle cells with inconspicuous nucleoli, and indistinct cellular borders in myxoid matrix. Scattered cells with hyperchromatic and bizzare nuclei and multinucleated giant cells are seen. They have typically high mitotic index and frequent atypical mitioses. PAS-positive, diastase resistant, variably sized eosinophilic globular inclusions in cytoplasm as well as extracellular matrix are seen [24-25].

IHC is required for definitive diagnosis, even though a specific immune-phenotype has still not been identified. No marker is diagnostic alone.Vimentin,desmin,CD68,BCL2,alpha1 antitrypsine,CD10 are usually positive and Myogenin,CD 34,CD117,Hep-par1,ALK,S-100 are found to be negative. Focal expression of cytokeratins and positivity for Glypican 3 are reported [26-28]. These help in differentiating it from other differential diagnosis in adults like GIST,HCC with sarcomatoid aspects, other high-grade sarcomas like leiomyosarcoma and angiosarcoma,and melanoma [29,19].

Prognosis of this malignant condition has improved considerably with multimodality treatment with radical surgery, chemotherapy and in some cases, radiotherapy. There is an improvement in long term survival rates from lower than 37% with surgery alone to about 70% with multimodality treatment [4,7,10,20,30,31]. Standardized treatment protocol for this malignancy in adults does not exist due to rarity ,and most treatments are based on extrapolation from pediatric case series. R0 resection is the most important prognostic factor, both in children and adults [32]. TACE has been preoperatively used in children for unresectable tumors and some studies have suggested liver transplantation as an option for chemo-intolerant or unresectable or recurrent tumors [33,34]. Chemotherapy combinations suggested have developed based on pediatric soft tissue and liver malignancies including drugs like vincristine, actinomycin D, doxorubicin, cyclophosphamide, ifosphamide and cisplatin. Combination of carboplatin and etoposide has also been used [3]. Neo- adjuvant chemotherapy has been seen to downstage bulky unresectable tumors in children [20]. Adjuvant chemotherapy is offered to all patients, and is especially necessary in the setting of positive margins and tumor rupture [2,4]. Radical resection is also recommended in recurrence [32].

Overall incidence of ifosphamide induced hemorrhagic cystitis are seen in 18% to 40% patientswithout MESNA and ,and in <5% patients with MESNA [35,36]. Management includes assessment of hemodynamic stability, paraentral hydration, blood transfusions, encouraging bladder emptying, bladder irrigation with saline and anticholinergics for painful bladder spasms [37,38]. Incidence of ifosfamide induced CNS toxicity is seen in 10-40% patients and this is usually associated with protein malnutrition [39]. Concomitant aprepitant use has been implicated in few reports as well along with hyponatremia, elevated serum creatinine, bulky pelvic diseases, history of nephrectomy or cisplatin usage, and poor performance status [40]. Our patient had hypoalbuminemia and aprepitant was also used as premedication for emesis. Pharmacological remedies for this has been suggested in literature as injection methylene blue and thiamine [41,42]. Buesa et al have published case series which showed dramatic results with I.V thiamine in ifosfamide induced encephalopathy [43].

In summary, we report a case of USEL,in a young female who had this uncommon disease for her age. Clinically and radiologically, she had non-specific features .Needle biopsy helped in her definitive diagnosis. In view of un-resectable disease was decided for neo-adjuvant chemotherapy but could not tolerate her first chemotherapy cycle, despite prudent toxicity management. The results would have been different if she was diagnosed early as a resectable case or involvement of liver volume was lesser, which would have helped to tolerate chemotherapy better.

Conclusion

A definitive diagnosis is dependent on histopathology post-biopsy or resection and prognosis on early accurate diagnosis along-with radical resection with clear margins whenever feasible. The treatment protocols are still under evaluation for standards and efficacy. Timely intervention and management of toxicities is crucial in all patients receiving chemotherapy. Continued research, collaboration among health care professionals and development of standardized treatment approaches needs to be encouraged.

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Abbrevations

(USEL) Undifferentiated Embryonal Sarcoma of Liver, (USG) Ultrasonography , (WBC) White Blood Cells, (SGPT) Serum Glutamic Pyruvic Transaminase, (SGOT) Serum Glutamic Oxaloacetic Transaminase, (ALP) Alkaline Phosphatase, (LDH) Lactate dehydrogenase, (AFP) Alpha Fetoprotein, (FNAC) Fine Needle Aspiration Cytology, (CE-MRI) Contrast-Enhanced Magnetic Resonance Imaging (CECT) Contrast-Enhanced Computed Tomography, (SMA) Smooth Muscle Actin, (CD) Cluster of Differentiation, (CK) Cytokeratin, (EMA) Epithelial Membrane Anitigen, (DOG-1) Discovered on GIST-1, (MESNA) Sodium 2-mercaptoethane sulphonate, (GCSF) Granulocyte-Colony Stimulating Factor, (CA 125) Cancer Antigen 125, (Bcl-2) B-cell lymphoma 2, (ALK) Anaplastic Lymphoma Kinase, (GIST) Gastro-intestinal Stromal Tumor, (HCC) Hepatocellular Carcinoma,(TACE) Trans-arterial chemoembolisation and (CNS) Central Nervous System.

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