

World Journal of *Clinical Cases*

World J Clin Cases 2020 October 26; 8(20): 4688-5069



MINIREVIEWS

- 4688 Relationship between non-alcoholic fatty liver disease and coronary heart disease
Arslan U, Yenercağ M

ORIGINAL ARTICLE**Retrospective Cohort Study**

- 4700 Remission of hepatotoxicity in chronic pulmonary aspergillosis patients after lowering trough concentration of voriconazole
Teng GJ, Bai XR, Zhang L, Liu HJ, Nie XH

Retrospective Study

- 4708 Endoscopic submucosal dissection as alternative to surgery for complicated gastric heterotopic pancreas
Noh JH, Kim DH, Kim SW, Park YS, Na HK, Ahn JY, Jung KW, Lee JH, Choi KD, Song HJ, Lee GH, Jung HY
- 4719 Observation of the effects of three methods for reducing perineal swelling in children with developmental hip dislocation
Wang L, Wang N, He M, Liu H, Wang XQ
- 4726 Predictive value of serum cystatin C for risk of mortality in severe and critically ill patients with COVID-19
Li Y, Yang S, Peng D, Zhu HM, Li BY, Yang X, Sun XL, Zhang M
- 4735 Sleep quality of patients with postoperative glioma at home
Huang Y, Jiang ZJ, Deng J, Qi YJ
- 4743 Early complications of preoperative external traction fixation in the staged treatment of tibial fractures: A series of 402 cases
Yang JZ, Zhu WB, Li LB, Dong QR
- 4753 Retroperitoneal vs transperitoneal laparoscopic lithotripsy of 20-40 mm renal stones within horseshoe kidneys
Chen X, Wang Y, Gao L, Song J, Wang JY, Wang DD, Ma JX, Zhang ZQ, Bi LK, Xie DD, Yu DX
- 4763 Undifferentiated embryonal sarcoma of the liver: Clinical characteristics and outcomes
Zhang C, Jia CJ, Xu C, Sheng QJ, Dou XG, Ding Y
- 4773 Cerebral infarct secondary to traumatic internal carotid artery dissection
Wang GM, Xue H, Guo ZJ, Yu JL
- 4785 Home-based nursing for improvement of quality of life and depression in patients with postpartum depression
Zhuang CY, Lin SY, Cheng CJ, Chen XJ, Shi HL, Sun H, Zhang HY, Fu MA

Observational Study

- 4793 Cost-effectiveness of lutetium (¹⁷⁷Lu) oxodotreotide *vs* everolimus in gastroenteropancreatic neuroendocrine tumors in Norway and Sweden
Palmer J, Leeuwenkamp OR
- 4807 Factors related to improved American Spinal Injury Association grade of acute traumatic spinal cord injury
Tian C, Lv Y, Li S, Wang DD, Bai Y, Zhou F, Ma QB
- 4816 Intraoperative systemic vascular resistance is associated with postoperative nausea and vomiting after laparoscopic hysterectomy
Qu MD, Zhang MY, Wang GM, Wang Z, Wang X

META-ANALYSIS

- 4826 Underwater *vs* conventional endoscopic mucosal resection in treatment of colorectal polyps: A meta-analysis
Ni DQ, Lu YP, Liu XQ, Gao LY, Huang X

CASE REPORT

- 4838 Dehydrated patient without clinically evident cause: A case report
Palladino F, Fedele MC, Casertano M, Liguori L, Esposito T, Guarino S, Miraglia del Giudice E, Marzuillo P
- 4844 Intracranial malignant solitary fibrous tumor metastasized to the chest wall: A case report and review of literature
Usuda D, Yamada S, Izumida T, Sangen R, Higashikawa T, Nakagawa K, Iguchi M, Kasamaki Y
- 4853 End-of-life home care of an interstitial pneumonia patient supported by high-flow nasal cannula therapy: A case report
Goda K, Kenzaka T, Kuriyama K, Hoshijima M, Akita H
- 4858 Rupture of carotid artery pseudoaneurysm in the modern era of definitive chemoradiation for head and neck cancer: Two case reports
Kim M, Hong JH, Park SK, Kim SJ, Lee JH, Byun J, Ko YH
- 4866 Unremitting diarrhoea in a girl diagnosed anti-N-methyl-D-aspartate-receptor encephalitis: A case report
Onpoaree N, Veeravigrom M, Sanpavat A, Suratannon N, Sintusek P
- 4876 Paliperidone palmitate-induced facial angioedema: A case report
Srifuengfung M, Sukakul T, Liangcheep C, Viravan N
- 4883 Improvement of lenvatinib-induced nephrotic syndrome after adaptation to sorafenib in thyroid cancer: A case report
Yang CH, Chen KT, Lin YS, Hsu CY, Ou YC, Tung MC
- 4895 Adult metaplastic hutch diverticulum with robotic-assisted diverticulectomy and reconstruction: A case report
Yang CH, Lin YS, Ou YC, Weng WC, Huang LH, Lu CH, Hsu CY, Tung MC

- 4902** Thrombus straddling a patent foramen ovale and pulmonary embolism: A case report
Huang YX, Chen Y, Cao Y, Qiu YG, Zheng JY, Li TC
- 4908** Therapeutic experience of an 89-year-old high-risk patient with incarcerated cholecystolithiasis: A case report and literature review
Zhang ZM, Zhang C, Liu Z, Liu LM, Zhu MW, Zhao Y, Wan BJ, Deng H, Yang HY, Liao JH, Zhu HY, Wen X, Liu LL, Wang M, Ma XT, Zhang MM, Liu JJ, Liu TT, Huang NN, Yuan PY, Gao YJ, Zhao J, Guo XA, Liao F, Li FY, Wang XT, Yuan RJ, Wu F
- 4917** Woven coronary artery: A case report
Wei W, Zhang Q, Gao LM
- 4922** Idiopathic multicentric Castleman disease with pulmonary and cutaneous lesions treated with tocilizumab: A case report
Han PY, Chi HH, Su YT
- 4930** Perianorectal abscesses and fistula due to ingested jujube pit in infant: Two case reports
Liu YH, Lv ZB, Liu JB, Sheng QF
- 4938** Forniceal deep brain stimulation in severe Alzheimer's disease: A case report
Lin W, Bao WQ, Ge JJ, Yang LK, Ling ZP, Xu X, Jiang JH, Zuo CT, Wang YH
- 4946** Systemic autoimmune abnormalities complicated by cytomegalovirus-induced hemophagocytic lymphohistiocytosis: A case report
Miao SX, Wu ZQ, Xu HG
- 4953** Nasal mucosa pyoderma vegetans associated with ulcerative colitis: A case report
Yu SX, Cheng XK, Li B, Hao JH
- 4958** Amiodarone-induced hepatotoxicity – quantitative measurement of iodine density in the liver using dual-energy computed tomography: Three case reports
Lv HJ, Zhao HW
- 4966** Multisystem involvement Langerhans cell histiocytosis in an adult: A case report
Wang BB, Ye JR, Li YL, Jin Y, Chen ZW, Li JM, Li YP
- 4975** New mutation in EPCAM for congenital tufting enteropathy: A case report
Zhou YQ, Wu GS, Kong YM, Zhang XY, Wang CL
- 4981** Catastrophic vertebral artery and subclavian artery pseudoaneurysms caused by a fishbone: A case report
Huang W, Zhang GQ, Wu JJ, Li B, Han SG, Chao M, Jin K
- 4986** Anastomosing hemangioma arising from the left renal vein: A case report
Zheng LP, Shen WA, Wang CH, Hu CD, Chen XJ, Shen YY, Wang J
- 4993** Bladder perforation caused by long-term catheterization misdiagnosed as digestive tract perforation: A case report
Wu B, Wang J, Chen XJ, Zhou ZC, Zhu MY, Shen YY, Zhong ZX

- 4999** Primary pulmonary plasmacytoma accompanied by overlap syndrome: A case report and review of the literature
Zhou Y, Wang XH, Meng SS, Wang HC, Li YX, Xu R, Lin XH
- 5007** Gastrointestinal stromal tumor metastasis at the site of a totally implantable venous access port insertion: A rare case report
Yin XN, Yin Y, Wang J, Shen CY, Chen X, Zhao Z, Cai ZL, Zhang B
- 5013** Massive gastrointestinal bleeding caused by a Dieulafoy's lesion in a duodenal diverticulum: A case report
He ZW, Zhong L, Xu H, Shi H, Wang YM, Liu XC
- 5019** Plastic bronchitis associated with *Botrytis cinerea* infection in a child: A case report
Liu YR, Ai T
- 5025** Chest, pericardium, abdomen, and thigh penetrating injury by a steel rebar: A case report
Yang XW, Wang WT
- 5030** Monocular posterior scleritis presenting as acute conjunctivitis: A case report
Li YZ, Qin XH, Lu JM, Wang YP
- 5036** Choriocarcinoma with lumbar muscle metastases: A case report
Pang L, Ma XX
- 5042** Primary chondrosarcoma of the liver: A case report
Liu ZY, Jin XM, Yan GH, Jin GY
- 5049** Successful management of a tooth with endodontic-periodontal lesion: A case report
Alshawwa H, Wang JF, Liu M, Sun SF
- 5057** Rare imaging findings of hypersensitivity pneumonitis: A case report
Wang HJ, Chen XJ, Fan LX, Qi QL, Chen QZ
- 5062** Effective administration of cranial drilling therapy in the treatment of fourth degree temporal, facial and upper limb burns at high altitude: A case report
Shen CM, Li Y, Liu Z, Qi YZ

ABOUT COVER

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Retrospective Study

Undifferentiated embryonal sarcoma of the liver: Clinical characteristics and outcomes

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Abstract

BACKGROUND

Undifferentiated embryonal sarcoma of the liver (UESL) is a rare liver malignancy originating from primary mesenchymal tissue. The clinical manifestations, laboratory tests, and imaging examinations of the disease lack specificity and the preoperative misdiagnosis rate is high. The overall prognosis is poor and survival rate is low.

AIM

To investigate the diagnosis, treatment, and prognosis of UESL.

METHODS

We performed a retrospective, single-center cohort study in Shengjing Hospital of China Medical University, which is a central hospital in northeast China. From 2005 to 2017, we recruited 14 patients with pathologically confirmed UESL. We analyzed the clinical manifestations, laboratory tests, imaging examinations, pathological examinations, therapy, and prognosis of these patients.

RESULTS

There were nine males and five females aged 2-60 years old included in the study. The major initial symptoms were abdominal pain (71.43%) and fever (57.14%). Preoperative laboratory tests revealed that seven patients had increased leukocyte levels, four showed a decrease in hemoglobin levels, seven patients had increased glutamyl transpeptidase levels, nine had increased lactate dehydrogenase levels, and three showed an increase in carbohydrate antigen 199. There was no

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difference in the rate of misdiagnosis in preoperative imaging examinations of UESL between adults and children (6/6 vs 5/8, $P = 0.091$). The survival rate after complete resection was 6/10, while that after incomplete resection was 0/4 ($P = 0.040$), suggesting that complete resection is important to improve survival rate. In total, five out of the eight children achieved survival. During the follow-up, the maximum survival time was shown to be 11 years and minimum survival time was 6 mo. Six adult patients relapsed late after surgery and all of them died.

CONCLUSION

Preoperative imaging examination for UESL has a high misdiagnosis rate. Multidisciplinary collaboration can improve the diagnostic accuracy of UESL. Complete surgical resection is the first choice for treatment of UESL.

Key Words: Undifferentiated embryonal sarcoma of the liver; Retrospective study; Clinical characteristics; Diagnosis; Treatment; Prognosis

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Core Tip: Undifferentiated embryonal sarcoma of the liver is rarely seen in clinical practice; it is difficult to diagnose and easily misdiagnosed before surgery. Comprehensive treatment based on complete surgical resection is the key for long-term survival. The methods for diagnosis, treatment, and prognosis evaluation of the disease should be further investigated.

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INTRODUCTION

Undifferentiated embryonal sarcoma of the liver (UESL) is a rare liver malignancy originating from primary mesenchymal tissue^[1]. The disease is more common in children but it can also occur in adults. The incidence of the disease ranks fourth in terms of liver malignancies in children, accounting for 9%-13% of cases^[2-4]. UESL has no sex predilection in children and a slight female predominance in adults^[5]. The clinical manifestations are non-specific, often include abdominal pain, fever, and hepatomegaly. The imaging examination usually shows a large, solitary nodule in the right liver lobe. Some cases are accompanied by extrahepatic spread^[5-6]. The clinical manifestations, laboratory tests, and imaging examinations of the disease lack specificity and the preoperative misdiagnosis rate is high. The definitive diagnosis of the disease depends on histopathology and immunohistochemistry. The overall prognosis is poor and survival rate is low^[7].

In this study, we retrospectively analyzed the clinical, imaging, and histopathological findings of 14 patients with UESL treated at the Shengjing Hospital of China Medical University between 2005 and 2017. This study is a single-center retrospective study with a large time span and wide age distribution among the enrolled patients. The clinical manifestations, laboratory and imaging examinations, and preoperative and postoperative diagnosis were comprehensively evaluated. And the patients were followed for a long time to investigate the impact of surgery and chemotherapy on prognosis. The results obtained will help to improve the clinician's understanding of the UESL.

MATERIALS AND METHODS

Patients

The following clinical data of 14 patients with UESL were collected and analyzed: General information including sex, age, and disease and treatment history; primary symptoms and positive signs; laboratory test results including routine blood tests, liver function, tumor biomarkers, and hepatitis virus markers; imaging examination results including ultrasonography and computed tomography (CT) examinations; postoperative histopathological and immunohistochemical examinations; preoperative and postoperative diagnosis; and surgery and postoperative chemotherapy. Ultrasonography or CT scan was performed every 3-6 mo during every year of follow-up to monitor tumor recurrence.

Patients were not required to give informed consent to the study because the analyses used anonymous clinical data that were obtained after each patient had agreed to treatment by written consent. This study was approved by The Ethical Committee of Shengjing Hospital.

Statistical analysis

Statistical software SPSS 21.0 (SPSS, Chicago, IL, United States) was used for statistical processing and analyses. The statistical review of the study was performed by a biomedical statistician (Li-Qiang Zheng, PhD, Department of Clinical Epidemiology, Shengjing Hospital of China Medical University). Categorical variables are presented as number and percentage and their inter-group comparison was performed by χ^2 test. Significant difference was deemed at $P < 0.05$.

RESULTS

General information

The sample consisted of 14 patients with UESL aged 2-60 years old, including nine males and five females. Eight patients were under 15 years of age, with average and median ages of 8 and 10 years, respectively. Six patients were older than 45 years old, and their average and median ages were 53 and 49 years. The duration of the disease among the patients ranged from 4 d to 1 mo. The major initial symptoms were abdominal pain (71.43%) and fever (57.14%). Most patients had a body temperature $< 38.5^\circ\text{C}$; only one patient had a maximum temperature of 40.5°C . Fever in the patients was generally not accompanied by chills. Nausea was described in 28.57% (4/14) of the patients. An abdominal mass was only found in children and accounted for 28.57% (4/14) of cases, and three of these children underwent emergency surgery due to tumor rupture. None of the 14 patients had a history of chronic hepatitis or cirrhosis, and only one female adult patient had a history of systemic lupus erythematosus and oral hormone therapy.

Laboratory tests

Preoperative laboratory tests showed that seven patients exhibited an increase in leukocyte levels ($11.2\text{-}25.5 \times 10^9/\text{L}$), four showed a decrease in hemoglobin levels (54-96 g/L), five had mild hypoalbuminemia (32-34.8 g/L), seven showed an increase in glutamyl transpeptidase (GGT; 87-419 U/L), nine showed an increase in lactate dehydrogenase (LDH; 253-4587 U/L), and three displayed an increase in carbohydrate antigen 199 (CA199; 54-131.5 U/L). All patients had normal alanine aminotransferase (ALT) and total bilirubin (TBil) levels, and hepatitis virus markers were all negative. The levels of α -fetoprotein (AFP) of the patients were also in normal ranges.

Imaging examinations

Ultrasound: Nine patients underwent an abdominal ultrasound examination. Cystic-solid mixed masses were found in six children. The masses were generally solid-dominant and separated by liquid components. The boundaries were unclear and internal echo was not uniform. In three adult patients, the masses were shown as having a heterogeneous moderately echoic and hypoechoic appearance with unclear edges on sonography.

CT examination: One child received an ultrasound examination, although this was only because of emergency surgery. All of the remaining 13 patients underwent CT examinations. In the plain scan, cystic-solid mixed hypodense masses were found in

seven children, and there were liquid areas in the masses. The solid components showed mild or significant enhancement in the arterial phase in contrast scans. The enhancement was strengthened in the venous phase. Plain scans in six adult patients showed irregular, slightly-hypodense masses. The enhancement of the masses was significantly lower than that of surrounding parenchyma in the arterial phase and increased gradually; however, until the delayed phase, the enhancement of the mass was still lower than that of the surrounding parenchyma (Figure 1 and 2).

Preoperative diagnosis

The rates of misdiagnosis in preoperative imaging examination of UESL in children and adults were 62.5% (5/8) and 100% (6/6), respectively. There was no difference in the rate of misdiagnosis between adults and children ($P = 0.091$). Among the eight cases of UESL in children, one patient was diagnosed as having liver cystadenocarcinoma, two were diagnosed as having hepatoblastoma complicated with rupture and hemorrhage, two were diagnosed as having a liver abscess, and in the remaining three cases there was a high suspicion of UESL. Among the six adult patients with UESL, three, two, and one patient were misdiagnosed as having primary hepatocellular carcinoma, a liver abscess, and a hepatic cyst, respectively.

Pathological examination

All of the 14 cases were confirmed as UESL by histopathological and immunohistochemical examinations of the resected specimens. The tumors were cystic-solid mixed or solid masses with a long diameter of 6–22 cm in gross anatomical analyses. The cystic part contained jelly-like or blood-like components; the texture of the solid part was soft, and sections showed a dark red or pink-white color; bleeding and necrosis could be observed. Microscopy showed that tumor tissue was composed of undifferentiated mesenchymal cells and a mucus matrix. Tumor cells displayed significant atypia and were of spindle or polygonal shape. Tumor giant cells could be found. Eosinophilic bodies were found between tumor cells, accompanied by bleeding and necrosis. Immunohistochemical staining revealed vimentin (+), $\alpha 1$ -antitrypsin (AAT) (+), AFP (-), epithelial membrane antigen (EMA) (-), smooth muscle actin (SMA) (-), cytokeratin (CK) (-), and hepatocyte (-) (Figure 3).

Treatment

Surgery: There were ten cases in which the tumor lesions were in the right lobe, one case in which the tumor lesion was in the caudate lobe, and in three patients the tumor lesions were in the right lobe and left anterior lobe. According to the location and distribution of the tumor lesions, three-lobe resection of the right liver was performed in six cases, combined hepatic segmentectomy was performed in seven, and caudate lobe resection was performed in one. Complete tumor resection was performed in ten cases and incomplete tumor resection was performed in four (all were adult patients). Three patients who had anemia and were suspected of having tumor rupture and hemorrhage before operation had this confirmed by emergency surgery. Tumor invasion of the diaphragm occurred in three patients. Two children with intrahepatic recurrence underwent re-surgery.

Chemotherapy: None of patients received chemotherapy in addition to percutaneous transhepatic arterial chemoembolization before surgery. Six patients completed eight cycles of postoperative chemotherapy (vincristine + cyclophosphamide + epirubicin or vincristine + actinomycin D + cyclophosphamide). Three patients discontinued chemotherapy due to toxicity after one or two cycles of the treatment, and five patients declined chemotherapy.

Follow-up

Follow-up lasted until September 2017. The longest follow-up period was 11 years and the shortest was 6 mo; two patients (children) were lost to follow-up. Among the ten patients who had undergone complete resection (two patients were lost to follow-up), six survived. In contrast, all four patients who had undergone incomplete resection (all were adult patients) died. Complete resection is important to improve survival rate ($P = 0.040$; it was believed that the two patients lost to follow-up were dead). Five out of the eight children achieved survival. The maximum survival time to the end of follow-up was 11 years and minimum survival time was 6 mo. One child achieved tumor-free survival for 5 years. Three patients relapsed and there was no recurrence in the two cases after re-surgery; the postoperative tumor-free survival time of two patients was 24 mo and 30 mo, respectively. One case died because of rejecting re-surgery. Six adult

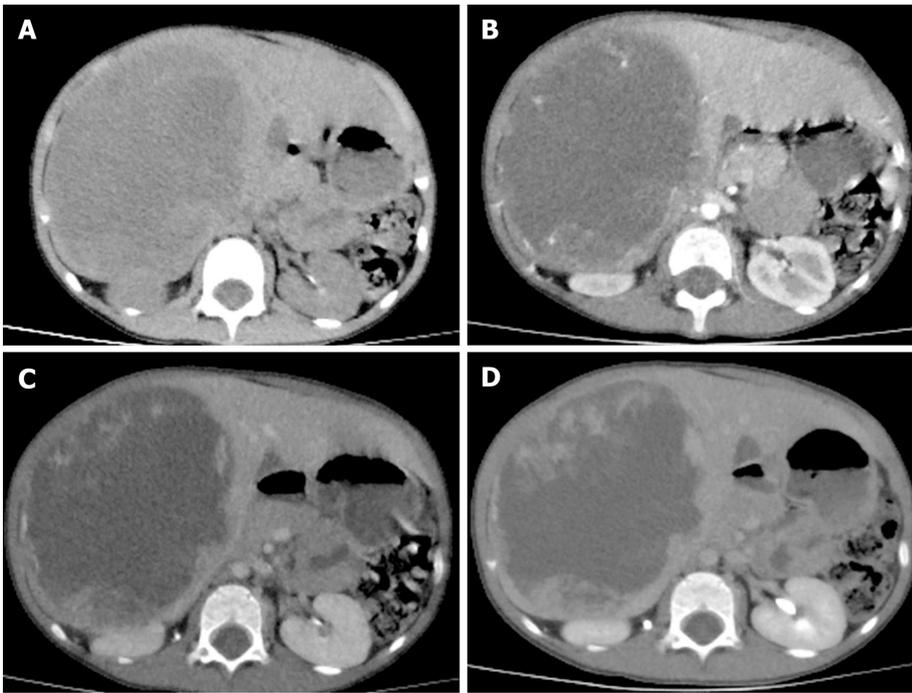


Figure 1 Computed tomography images of undifferentiated embryonal liver sarcoma. A: Plain CT scan revealed hepatomegaly. In the right lobe of the liver, there was a large oval cystic-solid mixed mass measuring 12.0 cm × 8.8 cm × 12.2 cm, with a clear boundary and non-homogeneous density; the solid part had multiple nodular soft tissue density shadows; B: In the arterial phase, the cystic components of the mass were not obviously strengthened; however, the solid components of the mass were obviously strengthened; C: In the portal venous phase, the enhanced extent of the masses was a little more obvious than that in the arterial phase; The enhancement of the masses was significantly lower than that of surrounding parenchyma; D: In the delayed phase, the enhanced extent of the masses was still a little more obvious than that in the arterial phase.

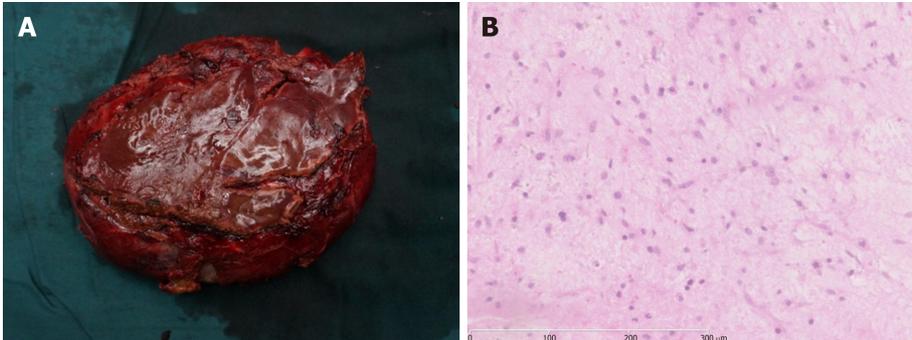


Figure 2 Pathological findings of undifferentiated embryonal liver sarcoma. A: Macroscopically, the large cystic mass with an amount of dark red blood clots in the lumen was observed; B: Microscopically, the tumor was composed of pleomorphic and polynuclear dysplastic cells, and mesenchymal hamartoma-like lesions were partially seen (hematoxylin and eosin staining).

cases had a late relapse 6–30 mo after operation and all of them died. The causes of death were intrahepatic recurrence and distant metastasis.

DISCUSSION

UESL was first reported and named by Stocher and Ishak in 1978^[1]. It is a malignant liver tumor composed of undifferentiated malignant mesenchymal cells. UESL is rarely seen in clinical practice and accounts for only 0.1% of surgically-resected primary liver lesions^[7]. The peak onset of the disease occurs between 6 and 15 years of age^[8]. The disease is a common liver malignancy in children, only behind hepatoblastoma, hepatic epithelioid hemangioendothelioma, and hepatocellular carcinoma in terms of frequency^[2]. UESL is rarely reported in adults^[9]. The reported oldest patient was 86 years old^[10]. UESL accounts for fewer than 1% of all primary liver neoplasms in adults^[11]. In this study, we retrospectively analyzed 14 cases of UESL in

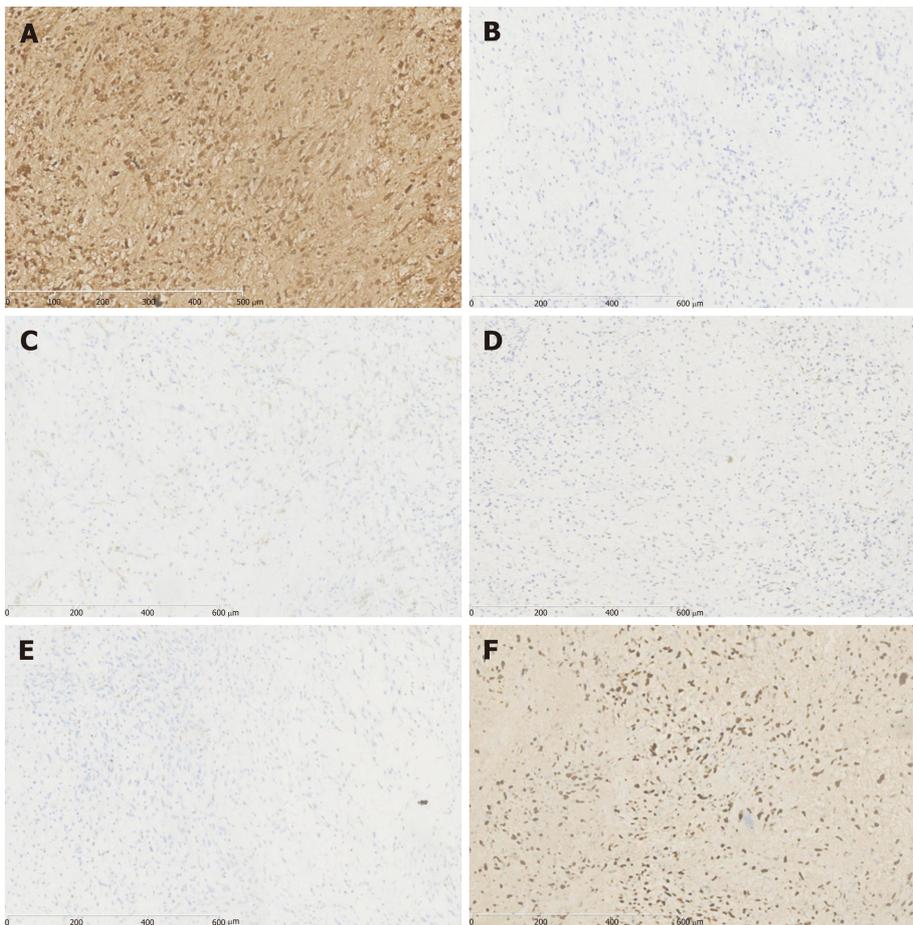


Figure 3 Immunohistochemical examinations of undifferentiated embryonal liver sarcoma. Immunohistochemical analysis showed that the tumor stained positively for α 1-antitrypsin (+) (A), α -fetoprotein (-) (B), smooth muscle actin (-) (C), cytokeratin (-) (D), Desmin (-) (E), and Ki67 (F). (+): The test is positive; (-): The test is negative.

our hospital over the last 12 years. There were eight patients under 15 years of age. Of note, adult patients were not uncommon in this cohort; six (42.86%) out of 14 patients were older than 45 years of age.

The etiology and pathogenesis of UESL are not fully understood. Mesenchymal hamartoma and UESL share the same cytogenetic abnormality, and they are often considered to be the entities of the same spectrum of diseases^[12,13]. It has been reported that UESL cases can be accompanied by the amplification or deletion in chromosomes 1q, 5p, 8p, and 12q, and the translocation of 19q13.4^[8]. Aberrations in chromosomes 6, 11, 12, 14, and X, and mutations in p53 have also been reported^[14,15]. UESL is generally not complicated with initial liver diseases such as hepatitis B and hepatitis C; however, adult UESL cases complicated with multiple sclerosis or with a chemotherapy history have been reported^[16,17]. In our patients, only one female adult patient had a history of systemic lupus erythematosus and long-term use of oral hormone therapy; it is not clear whether the situation was associated with UESL pathogenesis. Hepatitis or other special disease history was not found in other patients. The detection of molecular genetics could be beneficial for the differential diagnosis of UESL.

UESL usually lacks specific clinical manifestations. In children, the disease can present with abdominal pain and fever, which may be caused by intratumoral hemorrhage, necrosis, and infection^[18]. A palpable upper abdominal mass, accompanied by varying degrees of tenderness, can be detected on physical examination. The advanced tumor grows at a faster rate and is often complicated with intratumoral hemorrhage or spontaneous rupture. A few patients are admitted as a result of acute abdominal syndrome due to tumor rupture and bleeding^[19]. In our 14 UESL patients, ten had abdominal pain and eight had fever. A palpable upper abdominal mass was only found in four patients (children), of whom three underwent emergency surgery because of tumor rupture and bleeding. Adult patients only had mild upper abdominal pain and discomfort; the tumor was relatively small and no palpable upper abdominal mass was found in adult patients.

There are no specific laboratory tests for UESL. Although UESL patients generally do not have initial liver diseases such as hepatitis and cirrhosis, because the tumor has a large volume and squeezes the surrounding normal liver tissue, liver function may be abnormal. For example, the elevation of ALT and TBil can be seen. The increase in leukocytes can be detected in cases complicated with intratumoral hemorrhage, necrosis, and infection^[18]. The serum tumor biomarkers in UESL patients are usually negative, although in adults increases in AFP, CA125, and CA199 have been reported^[20-22]. Among the 14 patients in our study, seven were misdiagnosed as having a liver abscess because of the leukocyte increase in preoperative blood tests. Anti-infective therapy was ineffective in these patients. A decrease in hemoglobin was detected in four patients, three of which subsequently underwent emergency surgery due to tumor rupture and bleeding. ALT and TBil levels were normal in all patients, and increases of GGT and CA199 were found in seven and three patients, respectively. Nine patients displayed a significant increase in LDH. A previous study reported that 71.43% of children with UESL had increased LDH levels^[23]; however, the reason is still unclear.

On ultrasound examination, UESL often shows solid-dominant mixed echogenic masses; in CT images, tumors are displayed as a cystic-solid mixed (cystic-dominant) space-occupying lesions with characterized delayed enhancement. The lesions are dominantly cystic because part of the gel-like component in the tumor is shown as having a region with water-like density on CT^[24]. Such an inconsistency in ultrasound and CT examination is a diagnostic feature of the disease and the misdiagnosis rate of imaging examination is 23.5%^[25]. Due to insufficient understanding of the disease, the misdiagnosis rates of preoperative imaging examination in our children and adult patients were 62.5% and 100%, respectively. The clinical manifestations and examination of UESL lack specificity, and preoperative diagnosis of UESL is difficult, particularly for adult patients. Definitive diagnosis is often made through multidisciplinary collaboration. Surgical histopathology and immunohistochemistry tests are the main measures to confirm diagnosis of UESL. Only three pediatric patients in this study were diagnosed with UESL preoperatively. Four cases were misdiagnosed as having a liver abscess due to fever, leukocyte increase, and liver lesions. They had a poor response to anti-infective treatment and were finally diagnosed by surgical histopathology after multidisciplinary collaboration. The UESL lesions are generally in the right lobe of the liver and measure about 10–30 cm in diameter. However, it was reported that postoperative recurrent lesions were located in the left lobe^[22]. Among our patients, ten had lesions in the right lobe, which was consistent with previous reports. In gross anatomy examinations, the tumors had a dark red section with cystic degeneration, bleeding, and necrosis. Under the microscope, spindle-shaped undifferentiated mesenchymal cells could be found in a loose mucus matrix. The tumor cells were mononuclear or multinuclear, and nuclear deformity and mitotic figures could also be observed. Immunohistochemical staining demonstrated that vimentin and AAT were diffusely expressed in most UESL lesions. The most characteristic pathological evidence is the presence of eosinophilic bodies with varying sizes found in the cytoplasm of large tumor cells or in the extracellular matrix; periodic acid–Schiff (PAS) staining of these structures is positive^[26]. Moreover, CK, SMA, myoglobin, S-100, and CD34 can be expressed locally in parts of the lesions^[27]. In our patients, immunohistochemical staining showed all were positive in the expression of vimentin and AAT, one patient had focal expression of SMA, and CK, and other antigens were negative, suggesting that the tumor cells originated from primitive mesenchymal cells, with a few of the tumor cells differentiating toward smooth muscle cells. The pathological diagnosis of UESL is difficult in some cases but is of great importance. Three of our patients were definitively diagnosed by a group of experienced pathologists from multiple hospitals.

UESL is a highly malignant tumor; at diagnosis, most patients have already progressed to the advanced stages. The postoperative recurrence rate of the disease is high and survival rate is only 37%^[28]. Multimodal therapies in patients with UESL have improved survival rates, ranging from 70% to 100%^[29,30]. Therefore, it is accepted that the comprehensive treatment based on complete resection of the tumor is the key for long-term survival. For example, a combination with systemic chemotherapy can shrink the tumor, improve the radical resection rate, and prolong postoperative survival^[31-33]. May *et al*^[34] reported on five pediatric UESL patients treated by surgical resection combined with chemotherapy; the average postoperative tumor-free survival time reached 53 mo. Another study also suggested that the efficacy of surgery in combination with postoperative chemotherapy was better than that of surgery alone^[35]. Transcatheter arterial chemoembolization (TACE) may be applied as a preoperative therapy for children with unresectable UESL. The size of the tumors was

reduced after TACE. The tumors were completely removed by surgical procedures after TACE^[35]. For those who were chemotherapy-intolerant, did not undergo surgery, or relapsed after operation, some studies suggested that liver transplantation was an option. Overall survival in these five patients was 100%, with a follow-up period ranging from 21 mo to 68 mo. Disease-free survival ranged from 8 mo to 46 mo, and no patients had residual disease^[30]. In our patients, tumors were completely resected in ten cases. Pediatric patients had a relatively good prognosis and longer tumor-free survival. The patients with intrahepatic recurrence who had undergone re-surgery also had a good prognosis. On the contrary, the adult patients all died due to incomplete resection of the tumors. Our study showed that postoperative chemotherapy could reduce recurrence and improve survival.

Our study has some limitations. First, this is a single-center study, and the disease is a rare disease. Although the time span is large, the relatively small number of cases would lead to biases in the observation of clinical manifestations and laboratory/imaging examinations. Second, retrospective research usually has intrinsic bias. In this study, patients came from the same center with complete clinical data and uniform diagnostic criteria, which can minimize such bias.

CONCLUSION

In conclusion, the clinical manifestations and tests of the UESL have low specificity, resulting in the difficulty in preoperative diagnosis and high possibility of misdiagnosis. Multidisciplinary collaboration is recommended for suspected cases. Comprehensive treatment based on complete resection of the tumor is the key for long-term survival. The standards and efficacy of comprehensive treatment need to be further investigated.

ARTICLE HIGHLIGHTS

Research background

Undifferentiated embryonal sarcoma of the liver (UESL) is a rare liver malignancy originating from primary mesenchymal tissue. The clinical manifestations, laboratory tests, and imaging examinations of the UESL lack specificity and the preoperative misdiagnosis rate is high.

Research motivation

Analyzing the clinical characteristics of UESL, summarizing the diagnostic criteria, and discussing the best treatment scheme are of great significance for the diagnosis and treatment of this malignancy.

Research objectives

The aim of this study was to investigate the diagnosis, treatment, and prognosis of UESL.

Research methods

This study is a single-center retrospective study with a large time span and wide age distribution among the enrolled patients. From 2005 to 2017, we recruited 14 patients with pathologically confirmed UESL. We analyzed the clinical manifestations, laboratory tests, imaging examinations, pathological examinations, therapy, and prognosis of these patients.

Research results

There were nine males and five females aged 2–60 years old included in the study. The major initial symptoms were abdominal pain (71.43%) and fever (57.14%). Preoperative misdiagnosis rate was high, and there was no difference between adults and children. Complete resection was important to improve survival rate.

Research conclusions

Preoperative imaging examination for UESL has a high misdiagnosis rate. Multidisciplinary collaboration can improve the diagnostic accuracy of UESL. Complete surgical resection is the first choice for treatment of UESL.

Research perspectives

The standards and efficacy of comprehensive treatment need to be further investigated.

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