

Case Report

Liver transplantation for hepatic epithelioid hemangioendothelioma: a case report and literature review

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Abstract: Background: Hepatic epithelioid hemangioendothelioma (HEHE) is a rare tumor with incidence less than one per million. Due to low incidence of the disease, the risk factors, mechanism of the disease, treatment therapy and prognosis are not studied enough. Case presentation: Herein, we report a case of female patient who was diagnosed as HEHE and received liver transplantation in our center. She underwent the first deceased liver transplantation on 26th December 2013 in our center. Fifteen months later, she presented with yellow skin and sclera. She was diagnosed as intrahepatic biliary stricture. Both drug therapy and endoscopic nasobiliary drainage failed. She underwent retransplantation at last on 22nd August 2015. She recovered well and kept in good condition until now. Conclusion: Hepatic epithelioid hemangioendothelioma (HEHE) is an indication of liver transplantation. Long term survival after liver transplantation can be achieved.

Keywords: Hepatic epithelioid hemangioendothelioma, liver transplantation, outcome, incidence

Introduction

Epithelioid hemangioendothelioma is a rare tumor of vascular origin first described by Weiss and Enzinger in 1982 [1]. It can develop in lung, brain, spleen, bone, stomach, and most probably in liver. It's incidence is less than one per million [2]. Literature shows hepatic epithelioid hemangioendothelioma (HEHE) tend to occur in females, with a peak incidence in ages of 30 to 40 years [3]. Due to low incidence of the disease, knowledge of the risk factors, mechanism of the disease and prognosis is not adequate. Treatment therapy include chemotherapy, transarterial chemoembolization (TACE), radiotherapy, radiofrequency ablation (RFA) and surgery. For patients with unresectable HEHE, liver transplantation may be a choice. Herein, we report a case of female patient who was diagnosed as HEHE and received liver transplantation in our center.

Case presentation

A 33-year old woman found multiple hepatic masses when she received physical examina-

tion by ultrasound. Then she received positron emission computed tomography (PET-CT) examination and images showed multiple hepatic masses, liver carcinoma considered. However, she did not have any symptoms. Pathology of liver biopsy suggested hepatic epithelioid hemangioendothelioma. Then she received TACE therapy. 1 month later, she received computed tomography (CT) examination and majority of the liver masses were found to turn larger (shown in **Figure 1**). Then she underwent deceased liver transplantation on 26th December 2013 in our center. Pre-operative laboratory test showed liver function and tumor markers such as AFP, CEA, CA199 were normal. MELD score was 16. Immunosuppression therapy comprised tacrolimus and mycophenolate mofetil, without corticosteroid. She recovered well after transplantation.

Pathology after transplantation was consistent with hepatic epithelioid hemangioendothelioma (shown in **Figure 2A**). Immunohistochemical stains for CD31, CD34 and factor VIII-related antigen (FVIII-Rag) were positive (shown in **Figure 2B-D**).

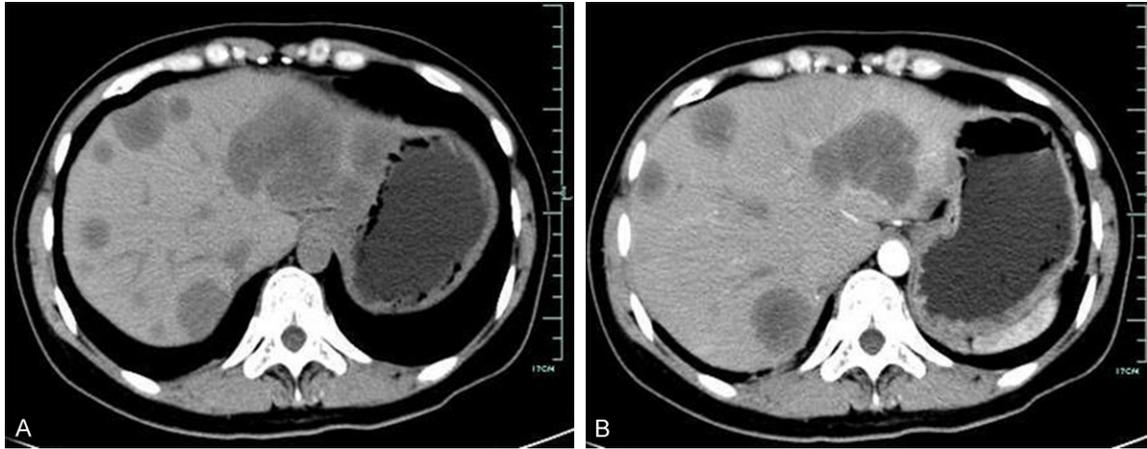


Figure 1. CT scan before liver transplantation. A. Multiple low density circular masses in liver, mostly near the edge of the liver. B. The edge of the tumor was slightly contrasted in artery phase.

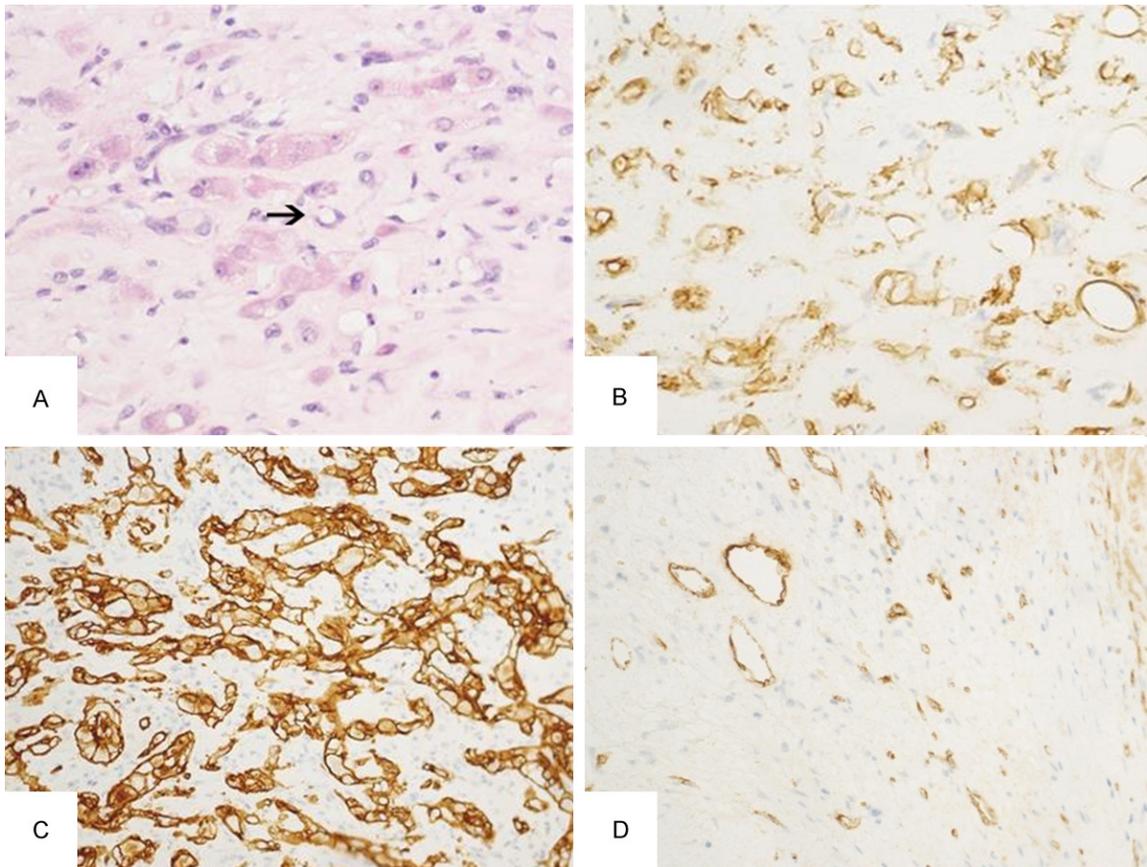


Figure 2. Hematoxylin-eosin and Immunohistochemistry staining. A. Epithelioid hemangioendothelioma cells in liver (HE×20) (arrow). Nucleus of tumor cell migrated to one side, with cytoplasmic vacuole. B. Tumor cells positive for CD31; C. Tumor cells positive for CD34; D. Tumor cells positive for FVIII-Rag.

Fifteen months later, however, she presented with yellow skin and sclera. Laboratory test showed total bilirubin was 124 $\mu\text{mol/l}$. She

received drug therapy which comprised of ademetionine, magnesium isoglycyrrhizinate, reduced glutathione hormone, ursodeoxycholic

acid, but total bilirubin continued rising, reaching to 428 $\mu\text{mol/l}$. Endoscopic retrograde cholangio-pancreatography (ERCP) showed multiple intrahepatic biliary stricture, without stricture of biliary anastomosis. Ultrasound showed the blood flow of portal vein and hepatic artery was normal. She received endoscopic nasobiliary drainage, but only a little amount of bile was drained out. Liver biopsy suggested intrahepatic cholestasis, without acute rejection. She underwent the second deceased liver transplantation at last on 22nd August 2015. Post transplantation immunosuppression comprised tacrolimus, mycophenolate mofetil and corticosteroid (early withdrawn). She recovered well and was still at good condition on the last follow up date of 21st February 2017.

Discussion

HEHE is a rare tumor with very low incidence. Its clinical presentation varies from asymptomatic to vague abdominal pain, weight loss, jaundice, hepatosplenomegaly and even progressive ascites [4, 5]. The levels of tumor markers such as Alpha-fetoprotein (AFP), Carbohydrate antigen 199 (CA199) were often normal, but carcinoembryonic antigen (CEA) level was reported to be elevated in some cases [3]. Immunohistochemical stains for CD31, CD34 and factor VIII-related antigen were positive in HEHE patients. FVIII-Rag was reported to be positive in 98% of cases [4], been suggested as a diagnostic marker for HEHE. This female patient in our center was asymptomatic, with normal level of AFP, CEA and CA199. Immunohistochemical stains for CD31, CD34 and factor FVIII-Rag were positive.

Spontaneous complete regression of HEHE was reported in one case [6], however, no treatment for HEHE was proven to have poor prognosis, with 1-year survival rate less than 50% [7]. Treatment therapy for HEHE include chemotherapy, radiotherapy, RFA, TACE and surgery. Mehrabi et al reported a 5-year survival rate of 30% for patients receiving chemotherapy or radiotherapy [7]. Due to low incidence of the tumor, there were not enough data to evaluate the efficacy of chemotherapy, radiotherapy, RFA and TACE. Radical liver resection should be considered if possible, however, palliative resection was not recommended due to poor prognosis after surgery [8]. HEHE is usually multifocal, and radical resection is often impos-

sible in many patients. Liver transplantation may be a good choice for these patients. 1-year survival rate reported after liver transplantation ranges from 80% to 93%, and 5-year survival rate was 64% to 83% [9-11]. However, HEHE can have rapid recurrence after transplantation. Qusay A. Abdoh et al reported a 40-year-old female with diffuse disease recurrence just 4 months after liver transplantation, and died 2 weeks later [12]. The longest interval between liver transplantation and tumor recurrence was reported to be thirteen years [13]. Limited extrahepatic lesions should not be a contraindication to surgical resection or liver transplantation. Local recurrence in the liver was also recommended resection or RFA [11]. Vascular endothelial growth factor (VEGF) was considered playing an important role in the generation of HEHE. There were also research suggested anti-VEGF therapy can be an option to reduce tumor volume, treat unresectable HEHE, or as an adjuvant therapy for liver transplantation [14].

This female patient in our center received TACE first but the effect was poor. Then she underwent liver transplantation and twenty months later received retransplantation because of severe biliary complication. During the first transplantation we did not give steroids therapy for her for fear of the recurrence of the tumor. However, steroids was added in the immunosuppression therapy during her second transplantation, but early withdrawn. She recovered well and kept in good condition on the last follow up date of 21st February 2017. No tumor recurrence was detected.

Conclusion

HEHE is a rare tumor and treatment efficacy of chemotherapy, radiotherapy, RFA, TACE should be further assessed and improved. New therapy such as molecular targeted drugs should also be developed. HEHE can be an indication for liver transplantation and the outcome is excellent.

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Written informed consent was obtained from the patient for publication of this manuscript.

Disclosure of conflict of interest

None.

Authors' contribution

Cheng Fang collected and analysed the data. Cheng Fang, Wei Zhang wrote the manuscript. Shusen Zheng revised the manuscript.

Abbreviations

PET-CT, positron emission computed tomography; TACE, transcatheter arterial chemoembolization; CT, computed tomography; ERCP, Endoscopic retrograde cholangio-pancreatography; RFA, radiofrequency ablation; AFP, Alpha-feto-protein; CEA, Carcinoembryonic antigen; CA-199, Carbohydrate antigen 199; VEGF, Vascular endothelial growth factor; MELD, Model for end-stage liver disease.

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