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Hepatic epithelioid hemangioendothelioma: Clinical characteristics, diagnosis, treatment and prognosis

Zhao M² *et al.* Hepatic epithelioid hemangioendothelioma

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Abstract

BACKGROUND

⁶ Hepatic epithelioid hemangioendothelioma (HEHE) is a rare hepatic vascular tumor with unpredictable malignant potential. The etiology, characteristics, diagnosis, treatment, and prognosis of HEHE are not well-understood, and large-scale retrospective studies are required to better understand this disease.²⁸

AIM

To determine the characteristics of HEHE, and identify its optimal treatments and prognostic factors.

METHODS

The clinical data of 2¹³ patients diagnosed with HEHE at the Fourth Hospital of Hebei Medical University and 184¹ previously reported cases retrieved from the China National Knowledge Infrastructure and PubMed databases between 2010 and 2020 were combined and summarized. All cases were pathologically identified as HEHE. Information such as clinical features, laboratory examination findings, imaging findings, pathological characteristics, and treatment and survival periods were reviewed. Kaplan-Meier¹⁶ curves were used for survival analysis. Prognostic factors were identified by Cox regression analysis.

RESULTS

HEHE primarily affects middle-aged women. The typical manifestations included epigastric pain, hepatosplenomegaly, inappetence, distension, weight loss, and fatigue. Tumor markers were expressed normally. The incidence of extrahepatic metastasis was 31.7% at the time of diagnosis. The most common sites of extrahepatic involvement were the lungs (20.3%), lymph nodes (6.5%), peritoneum (3.3%), bones (4.1%), and spleen (3.3%). Furthermore, “capsular retraction”, “target sign”, and “lollipop sign” were the characteristic features of HEHE on imaging. The immunohistochemical profile for HEHE (expression of vascular markers, such as FVIII-RAg, CD31, and CD34; expression levels of D2-40 and CAMTA1) can facilitate and ensure an accurate diagnosis. The management options for patients with HEHE include liver resection (LR, 27.1%), liver transplantation (18.6%), palliative treatments (15.7%), transhepatic arterial chemotherapy and embolization (TACE, 8.6%), chemotherapy (10.0%), antiangiogenic therapy (11.4%), and other treatments (8.6%). The mean survival time was 170.4, 140.6, 4.0, 90.8, 69.6, 84.5, and 68.7 mo, respectively. The survival time of patients who underwent surgical treatment was longer than that of patients who did not undergo surgery. TACE and antiangiogenic therapy tended to prolong survival compared with other nonsurgical treatments. The 1-, 5-, and 10-year patient survival rates were 77%, 70%, and 63%, respectively. Multivariate analysis showed that liver function ($P = 0.033$), intrahepatic metastasis ($P = 0.037$), and treatment ($P = 0.022$) were independent prognostic factors. The presence of extrahepatic metastases was not an independent risk factor for poor prognosis ($P = 0.057$).

CONCLUSION

The clinical course of HEHE is rare and variable, and patients with intrahepatic metastases and liver dysfunction may have a poorer prognosis than those without. Surgical intervention, whether LR or transplantation, might be warranted regardless of extrahepatic metastasis. For patients without the option for surgery, clinicians should consider the use of TACE with antiangiogenic drugs in the treatment of HEHE.

Key Words: Hepatic epithelioid hemangioendothelioma; Clinical characteristics; Diagnosis; Treatment; Prognosis

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Core Tip: Hepatic epithelioid hemangioendothelioma (HEHE) is a rare hepatic vascular tumor with unpredictable malignant potential. Patients with intrahepatic metastases and liver dysfunction may have a poorer prognosis than those without. Surgical intervention, whether liver resection or transplantation, might be warranted regardless of extrahepatic metastasis. However, the therapeutic strategy for patients without the option for surgery is particularly controversial. Our experience highlights the efficacy of transhepatic arterial chemotherapy and embolization and antiangiogenic therapy in the management of HEHE.

INTRODUCTION

Hepatic epithelioid hemangioendothelioma (HEHE) is a rare neoplasm of vascular origin^[1]. The natural course of this neoplasm is variable, ranging from long-term survival without treatment to a rapidly progressive course with a fatal outcome^[2]. The etiology, characteristics, diagnosis, treatment, and prognosis of HEHE are not well-understood, and large-scale retrospective studies are required to better understand this disease.

MATERIALS AND METHODS

The clinical data of 2 patients diagnosed with HEHE at the Fourth Hospital of Hebei Medical University and previously reported cases retrieved from the literature were combined and summarized.

Data search

⁴¹ We searched the PubMed and China National Knowledge Infrastructure (CNKI) databases from January 2010 through December 2020 using search terms, including “HEHE” and “epithelioid hemangioendothelioma of liver”. The references of related studies and reviews were also retrieved, if necessary.

²⁰ *Study inclusion and exclusion criteria*

The studies that met the following criteria were included: (1) Tumor tissues obtained by liver biopsy or surgery were pathologically identified as HEHE; (2) accurate clinical statistical indicators were provided in the studies; ⁴³ (3) articles were published in English or Chinese.

Exclusion criteria: (1) Epithelioid hemangioendothelioma from other sites with liver metastasis; (2) duplicate publications; (3) studies without sufficient data; and (4) care reports, meeting abstracts, meta-analysis, and reviews.

Data extraction

⁷ We reviewed all titles and abstracts to identify potentially relevant articles. Two investigators reviewed all potentially relevant full texts for inclusion, with disagreements resolved through discussion and consensus. ⁷ We used standardized data extraction forms to collect the following items: First author’s name, geographical region and year of publication, study design, inclusion/exclusion criteria, size of the patient cohort, and clinical statistical indicators (age, sex, etiology, clinical features, laboratory tests, radiographic findings, pathological features, treatment, and survival).

⁴⁰ *Statistical analysis*

Statistical analyses were performed using SPSS 26.0. Distributions of patients’ characteristics (age, sex, clinical features, laboratory tests, radiographic findings, pathological features, treatment, and survival) were explored and summarized using descriptive statistics. Survival analysis was ⁴ performed using the Kaplan-Meier method. The differences between the survival curves were compared using the logrank test.

Multivariate Cox hazard regression analysis was performed on the factors shown to be significant on univariate analysis. All tests were two-sided, and P values of ≤ 0.05 were considered significant.

RESULTS

Two cases diagnosed with HEHE at the Fourth Hospital of Hebei Medical University

Case one: A 53-year-old female patient was admitted to the hospital because of intermittent right upper abdominal pain for > 10 d. Initial liver function tests indicated increased levels of alanine transaminase and alkaline phosphatase. Tumor markers were normal. Computed tomography (CT) revealed two round low-density nodules in the right lobe of the liver. The peripheral rims of the nodules were enhanced using a contrast media, giving the appearance of cancer metastases, but no tumors were found elsewhere (Figure 1). The preliminary diagnosis for the preoperative liver biopsy was HEHE. The patient subsequently underwent segmental hepatectomy of segments VIII and VI. Immunohistochemically, the tumor cells expressed CD34, vimentin, FVIII-Ag, Smooth muscle actin (SMA), S-100, and Ki-67 (Figure 2). Based on these histological and immunohistochemical findings, the tumor was pathologically diagnosed as HEHE, which was consistent with the preoperative biopsy results. After 4 years postoperatively, the patient was in good health and had no recurrence.

Case two: A 35-year-old woman was referred to our institution for the management of incidentally discovered nodules in the liver without symptoms. Laboratory examination findings were normal. CT showed multiple hypodense hepatic nodular formations, all of which were slightly enhanced in the arterial phase (Figure 3A). Immunohistochemical staining of the tumor tissue obtained via laparoscopic liver biopsy revealed tumor cells that were positive for CD34, FVIII-RAg, SM, CD68, and vimentin and negative for alpha fetoprotein (AFP), Cal, Me, CK, and S100. The final pathological diagnosis was HEHE, and the patient was diagnosed with unresectable hepatic disease with no distant metastases. Liver transplantation (LT) was

recommended, but the patient refused due to personal reasons. Transhepatic arterial chemotherapy and embolization (TACE) was performed using 1 g of fluorine glycosides, 10 mg of epirubicin, and 10 mL of lipiodol. Unfortunately, repeat CT indicated that the number of lesions had increased (Figure 3B). A decision was then made to change the treatment to interferon (IFN)- α 2b with a dose of 3 MU being administered every alternate day. The patient underwent clinical evaluation and laboratory tests every 3 wk and abdominal CT scans every 3.0 mo. As shown in Figure 3C-F, an evaluation of the tumor response using serial CT revealed a favorable response with a decrease in the number of lesions, which finally disappeared 18.0 mo after the initiation of treatment with IFN- α 2b. The patient remained tumor-free after 7 years and currently maintains a functional state of health.

Literature results

A total of 1199 related studies were screened out, which were eliminated according to the inclusion and exclusion criteria, and 96 studies with 184 cases were finally included (Supplementary reference) after quality evaluation. Reasons for exclusion at time of review are detailed in Figure 4. The total number of cases was 186, including 2 confirmed cases from the Fourth Hospital of Hebei Medical University.

Demographics

Among the patients with HEHE, 132 of 186 patients were women (71.0%), and the male-to-female ratio was 2:4.9. The mean age was 42.4 years (range, 3-80 years). Further, 21 patients had a history of viral hepatitis, including 2 cases of hepatitis A, 16 cases of hepatitis B, and 3 cases of hepatitis C. Three patients had a history of long-term oral contraceptive use, one patient had a silicone breast implant, and one patient was pregnant (Table 1).

Clinical features

The clinical manifestations were variable and nonspecific, and 30% of the patients were incidentally discovered without symptoms. Among symptomatic patients, the typical manifestations included epigastric pain (40%), hepatosplenomegaly (13.9%), inappetence (13.3%), distension (12.2%), weight loss (10.6%), and fatigue (10%) in addition to other manifestations like epigastric discomfort, hydrothorax, ascites, fever, and jaundice, with 33.9% of the patients with HEHE presenting with two or more symptoms simultaneously (Table 1).

Most of the patients presented with multiple lesions involving both hepatic lobes (65.9%). The incidence of extrahepatic metastases was 31.7% at the time of diagnosis. The most common sites of extrahepatic involvement were the lungs (20.3%), lymph nodes (6.5%), peritoneum (3.3%), bones (4.1%), and spleen (3.3%). The involvement of the pleura and omentum was also described, albeit relatively rarely (Table 1).

Laboratory parameters

Approximately 40.2% of the patients had abnormal liver function. The most common changes were increased levels of alanine transaminase (24.7%), aspartate transaminase (23.7%), total bilirubin (10.3%), γ -glutamyl transpeptidase (16.5%), and alkaline phosphatase (24.7%). The levels of the tumor markers AFP, carcinoembryonic antigen (CEA), and carbohydrate antigen 19-9 (CA-199) were normal (Table 1).

Imaging studies

CT was performed in 138 patients. Low-density patterns were the most common abnormal features (98.6%). High-density and heterogeneous mixed-density lesions were observed in 1.4% of the patients with HEHE. Information on enhancement patterns was available for 103 patients. Enhancements were observed in 86.4% of the patients. Most of the lesions were found along the liver periphery, which tended to occur in groups and coalesce over time, forming large, confluent masses (19.6%). Additional findings included calcification (15.9%), capsular retraction (18.1%), "target sign" (26.2%), and "lollipop sign" (11.7%) (Figure 5 and Table 1).

Histopathological findings

The immunohistochemical factors detected in patients with HEHE were varied. FVIII-RAg (98.9%), CD34 (99.4%), CD31 (99.1%), Vimentin (98.8%), VEGF (100%), and D2-40 (80%) were positive in majority of the patients, whereas CK (41.5%), SMA (44.4%), hepatocytes (16.3%), epithelial membrane antigen (EMA, 11.5%), Ki-67 (20%), CD117 (25%), and S-100 (3.6%) were positive only in a small group of patients. Some markers, such as AFP, CEA, and desmin, were consistently negative. Moreover, strong and diffuse CAMTA1 expression was observed in one patient (Table 1).

Treatment and survival rates

The management options for patients with HEHE included liver resection (LR), LT, palliative treatments, TACE, chemotherapy or radiotherapy, antiangiogenic therapy, and other treatments, such as traditional Chinese medications and radiofrequency ablation. A number of patients (27.1%) underwent LR, and their mean survival time was 170.4 mo. Some patients (18.6%) underwent LT, and their mean survival time was 140.6 mo. Other patients (15.7%) opted for follow-up without any therapy, and their mean survival time was 4.0 mo. Some patients (8.6%) underwent TACE, and their mean survival time was 90.8 mo. Some patients (10.0%) chose chemotherapy, and their mean survival time was 69.6 mo. Additionally, some patients (11.4%) opted for antiangiogenic therapy, and their mean survival time was 84.5 mo. Further, some patients (8.6%) chose other treatments, and their mean survival time was 68.7 mo. For surgically treated patients, the 1-, 5-, and 10-year survival rates were 86%, 82%, and 82%, respectively. However, for patients who underwent nonsurgical treatment, the 1-, 5-, and 10-year survival rates were 73%, 62%, 53%, respectively. Not considering the type of treatment provided, the 1-, 5-, and 10-year survival rates were 77%, 70%, and 63%, respectively. The survival time of patients who underwent surgical treatment was longer than that of patients who did not. Similarly, the survival time of treated patients was longer than that of untreated patients (Table 2).

Prognostic analysis

We collected nine possible factors from other studies that influenced the survival of these patients. Based on univariate analysis, sex, age, AFP, maximum tumor diameter, and extrahepatic metastasis had no significant prognostic value ($P > 0.05$); however, symptoms, liver function, treatment, and intrahepatic metastasis significantly affected the prognosis ($P < 0.05$). Based on multiplicity analysis, liver function ($P = 0.033$), intrahepatic metastasis ($P = 0.037$), and treatment ($P = 0.022$) were independent prognostic factors (Figure 6 and Table 3).

DISCUSSION

Epithelioid hemangioendothelioma is a rare tumor of vascular origin with low-to-moderate grade malignant properties. It arises preferentially in the soft tissues, lungs, and bones, and rarely in the liver (with a global incidence of < 1 in 1000000)^[3].

Demographics

HEHE occurs in all age groups, but it primarily affects middle-aged women^[4]. The pathogenesis of HEHE remains unclear, and it is speculated that it is related to oral contraceptive use^[5], pregnancy and hormone therapy^[6], vinyl chloride pollution^[7], asbestos^[8], colloidal thorium oxide^[9], trauma repair^[10], and viral hepatitis^[11].

Clinical features

The clinical manifestations of HEHE were variable and nonspecific. Approximately half of the patients had abnormal liver function. Tumor markers were normal in most patients. The incidence of extrahepatic metastasis was 31.7% at the time of diagnosis. The most common sites of extrahepatic involvement were the lungs. The radiologic features of HEHE can vary, it can present in diffuse, multifocal, or solitary nodular forms. The “target sign”, “capsule retraction sign”, and “lollipop sign”^[12,13] support the diagnosis of the disease, but the specificity is not high, and the final diagnosis must rely

on pathological examination. Immunohistochemical staining can provide the evidence of endothelial differentiation for the definitive diagnosis of HEHE. Neoplastic cells are positive for endothelial markers (FVIII-RAg, CD31, and CD34)^[14]. The lymphatic endothelial marker D2-40 is specifically expressed in 78% of epithelioid hemangioendotheliomas^[15]. On a genetic level, approximately 90% of all patients with HEHE have a t(1;3)(p36;q25) translocation, resulting in the fusion gene *WWTR1-CAMTA1* with high *CAMTA1* activity. Moreover, this gene fusion has not been observed in other vascular tumors, making it a genetic and diagnostic hallmark^[16,17].

Treatments and prognosis

A standard treatment for HEHE has not been established owing to its low incidence. The management of patients with HEHE includes LR, LT, palliative treatments, TACE, chemotherapy or radiotherapy, antiangiogenic therapy, and other treatments, such as traditional Chinese medications and radiofrequency ablation.

For localized disease, complete resection of the tumor is preferred to reduce the chances of recurrence. Palliative resection is not suggested because these tumors tend to behave aggressively after LR^[18]. In this study, case one had no recurrence 4 years after LR. The mean survival time of patients after LR was better than that after other treatments. The 5-year survival rate after resection was 86%^[19]. Radical hepatic resection with negative margins was the best curative approach if feasible and was associated with the best prognosis.

However, in majority of the patients, oncologic resection is impossible because of the multicentricity of the lesions or anatomic difficulties. LT had been proposed as the treatment of choice in patients with unresectable and diffuse HEHE. In this study, after LT, the mean survival time was lower than that after LR but better than that after other nonsurgical treatments. Notably, unlike other malignant hepatic tumors, limited extrahepatic disease should not be considered an absolute contraindication to LT as the life expectancy of patients with HEHE is potentially favorable^[20]. Zamparelli *et al*^[21] described a patient who showed a good outcome following LT despite lung metastasis.

¹⁹ The 5-year survival rate after LT was 54%-88% (superior to the overall survival of other indications for LT)^[22].

¹⁸ The optimal treatment for patients who do not undergo surgical treatment remains uncertain. There is still controversy about the effectiveness of traditional chemotherapeutic drugs. Doxorubicin, 5-fluorouracil, cyclophosphamide, and platinum are the most commonly used drugs for chemotherapy^[23]. In this study, one patient with HEHE who had lung metastasis was treated with adriamycin liposomes and was alive after 9 years^[24]. Patients ¹¹ who received chemotherapy had significantly ¹⁵ better survival ¹⁵ than those who did not receive treatment. However, another ¹⁵ study suggested that ¹⁵ chemotherapy in patients who do not undergo surgical treatment decreased their 5-year survival rate (43.6%) compared with patients who did not receive treatment (82.9%)^[25]. These differences in survival can be explained by the very different levels of HEHE aggressiveness and the diversity of chemotherapy regimens in addition to selection biases resulting from the small sample size of the investigated studies. Hence, the effectiveness of traditional chemotherapy drugs for HEHE warrants further investigation.

In this study, 8.6% of the patients underwent TACE and their mean survival time was 90.8 mo, which showed a trend of prolonged survival compared with other nonsurgical treatments. In this study, one patient was treated with the combination of TACE and the administration of cisplatin, pirarubicin, and hydroxyamptothecin. This patient survived for 112.0 mo^[26]. However, another patient died of hepatic failure 4.0 mo after treatment with TACE^[27]. ²⁷ Clinicians should be aware of the potential adverse effects of ² hepatic decompensation that are induced by TACE, particularly in cases of widespread tumor involvement and poorly preserved hepatic function. TACE may be a valid treatment for patients with HEHE who have advanced hepatic lesions and good liver reserve.

Because HEHE originates from vascular endothelial cells, antiangiogenesis drugs, such as IFN, sunitinib, thalidomide, sorafenib, and bevacizumab, have attracted the attention of researchers. ²⁴ In this study, the mean survival time of patients treated with

antiangiogenesis drugs was similar to those treated with TACE. One patient with pulmonary metastasis was treated with sunitinib for 6 years, which resulted in a substantial regression of extrahepatic disease^[28]. The French Sarcoma Group previously reported the outcome of sorafenib treatment in a series of 15 patients with HEHE, and the Eastern Cooperative Oncology Group reported the results of bevacizumab treatment in a series of 7 patients with HEHE. Both studies were phase II trials including patients with advanced, unresectable, metastatic diseases. Both drugs could stabilize the disease up to 10.0 mo in 20%-40% of the patients; approximately 10% of the patients showed partial response up to 6.0 mo^[29,30]. IFN therapy for HEHE has also been proposed for tumor reduction and metastasis prevention^[31]. IFN has been reported to inhibit cancer cell growth, activate immune cells, inhibit vascularization, and induce cytokines^[32,33]. In this study, case two underwent TACE, but the disease was not controlled, and she was subsequently treated with IFN- α 2b. The lesion gradually shrank and the disease was in complete remission for 7 years. TACE can cause ischemia and necrosis of the cancer tissue and control tumor growth. However, hypoxia after treatment can upregulate angiogenic factors, stimulate the proliferation of residual tumor cells, and lead to tumor survival or recurrence^[34]. The combination of IFN with TACE can be synergistic for the treatment of HEHE by reducing the stimulation of tumor cells by angiogenic factors and inhibiting tumor angiogenesis. This proved to be an effective, tolerable regimen for a patient with metastatic hepatic hemangioendothelioma. Although LT and LR may be the best options for improved survival, clinicians should consider the use of TACE with antiangiogenic drugs in the treatment of HEHE, particularly in those awaiting LT or nonsurgical candidates.

The clinical course of HEHE is variable, ranging from spontaneous regression and long-term survival without any treatment to a rapidly progressive and deadly course. Makhoul *et al*^[6] reported one patient who was alive after 27 years without any treatment. However, in this study, the mean survival time of untreated patients was only 4.0 mo. Compared with the untreated patients, the survival time of the treated patients was significantly longer. This may be because most of the untreated patients

had poor prognostic factors, 75% had obvious symptoms, and 58% had abnormal liver function and intrahepatic metastases. Notably, ²⁵ there are some reports of long-term survival in the presence of stable HEHE without any treatment. However, until the reliable identification of patients with nonaggressive stable disease is possible, a wait-and-see approach is not recommended.

The ³⁶ prognosis for HEHE was much better than that for other hepatic malignant tumors. The 1-, 5-, and 10-year survival rates of all patients were 77%, 70%, and 63%, respectively. The prognostic factors of HEHE remain mostly undetermined till date. This study found that patients with intrahepatic metastasis (diffuse type) and liver dysfunction have poor prognosis. Unlike other liver malignancies, the ⁵ presence of extrahepatic metastases was not an independent risk factor for poor prognosis. Active treatment should be considered in cases of liver ⁴² decompensation or radiological evidence of diffuse or progressive disease.

CONCLUSION

The clinical course of HEHE is rare and variable, and patients with intrahepatic metastases and liver dysfunction may have a poorer prognosis than those without. Surgical intervention, whether LR or transplantation, might be warranted regardless of extrahepatic metastasis. For patients without the option for surgery, ³ clinicians should consider the use of TACE with antiangiogenic drugs in the treatment of HEHE.

ARTICLE HIGHLIGHTS

Research background

²⁹ Hepatic epithelioid hemangioendothelioma (HEHE) is a rare hepatic vascular tumor with unpredictable malignant potential.

Research motivation

The etiology, characteristics, diagnosis, treatment, and prognosis of HEHE are not well-understood, and large-scale retrospective studies are required to better understand this disease.

Research objectives

To determine the characteristics of HEHE and identify its optimal treatments and prognostic factors.

Research methods

The clinical data of 2 patients diagnosed with HEHE at the Fourth Hospital of Hebei Medical University and 184 previously reported cases retrieved from the China National Knowledge Infrastructure and PubMed databases between 2010 and 2020 were combined and summarized. Information such as clinical features, laboratory examination findings, imaging findings, pathological characteristics, and treatment and survival periods were reviewed. Kaplan-Meier curves were used for survival analysis. Prognostic factors were identified by Cox regression analysis.

Research results

The management options for patients with HEHE include liver resection (LR, 27.1%), liver transplantation (18.6%), palliative treatments (15.7%), transhepatic arterial chemotherapy and embolization (8.6%), chemotherapy (10.0%), antiangiogenic therapy (11.4%), and other treatments (8.6%). The mean survival time was 170.4, 140.6, 4.0, 90.8, 69.6, 84.5, and 68.7 mo, respectively. Multivariate analysis showed that liver function ($P = 0.033$), intrahepatic metastasis ($P = 0.037$), and treatment ($P = 0.022$) were independent prognostic factors.

Research conclusions

The clinical course of HEHE is rare and variable, and patients with intrahepatic metastases and liver dysfunction may have a poorer prognosis than those without.

Surgical intervention, whether LR or transplantation, might be warranted regardless of extrahepatic metastasis. For patients without the option for surgery, clinicians should consider the use of transhepatic arterial chemotherapy and embolization with antiangiogenic drugs in the treatment of HEHE.

Research perspectives

Large prospective studies are needed to determine the best nonsurgical treatment options.

Figure Legends

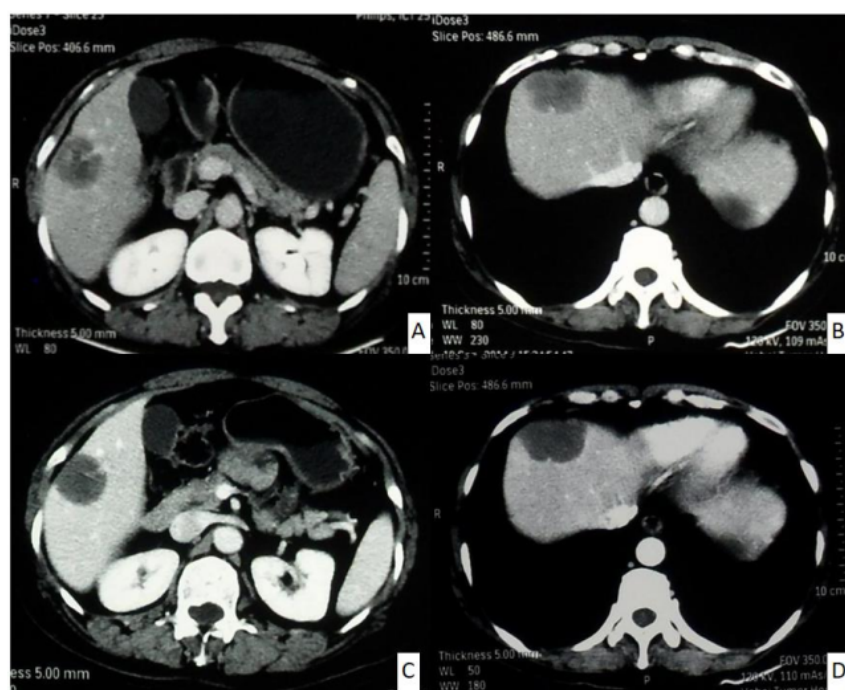


Figure 1 Abdominal computed tomography of case one. A and B: Computed tomography (CT) scan showed two round low-density nodules in the right lobe of the liver; C and D: Contrast-enhanced CT showed the peripheral rim of the nodules are enhanced.

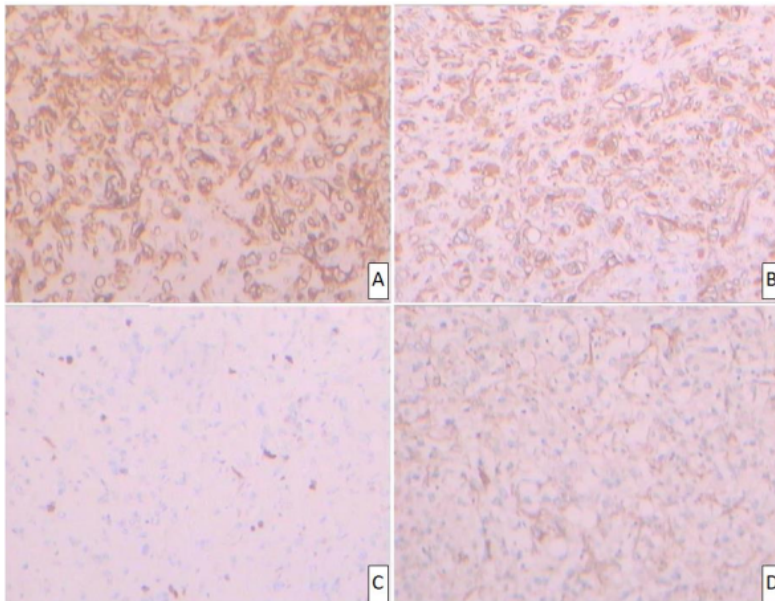


Figure 2 Immunohistochemical staining of case one. A: Positive of CD34 in case one (magnification $\times 200$); B: Positive of vimentin in case one (magnification $\times 200$); C: Positive of Ki-67 in case one (magnification $\times 200$); D: Positive of SMA in case one (magnification $\times 200$).

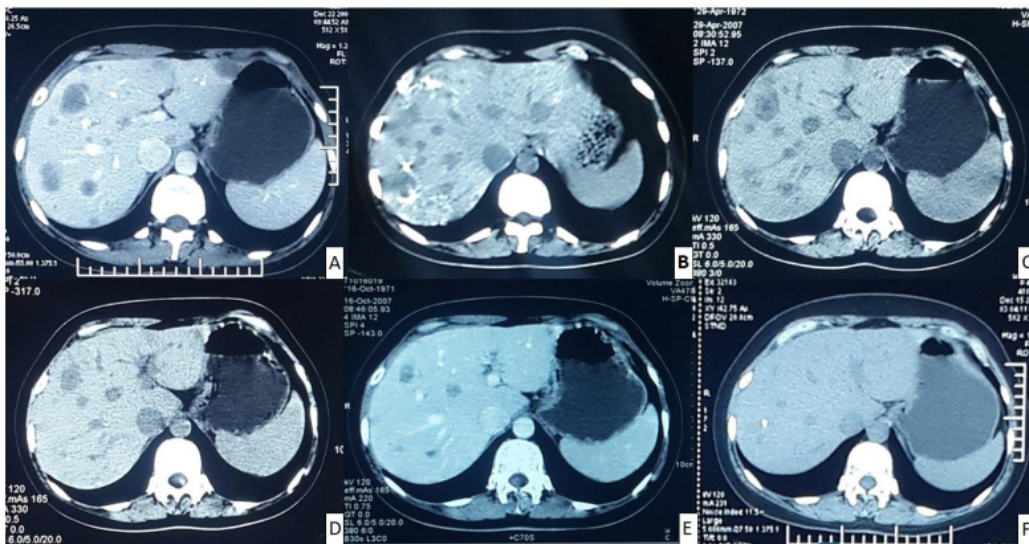


Figure 3 Abdominal computed tomography of case two. A: Computed tomography scan showed multiple hypodense hepatic nodular formations, all of which are slightly enhanced during the arterial phase; B: After four cycles of transhepatic arterial

chemotherapy and embolization, the number of lesions were increased; C-F: After 18 mo of interferon treatment, all lesions were gradually reduced and disappeared.

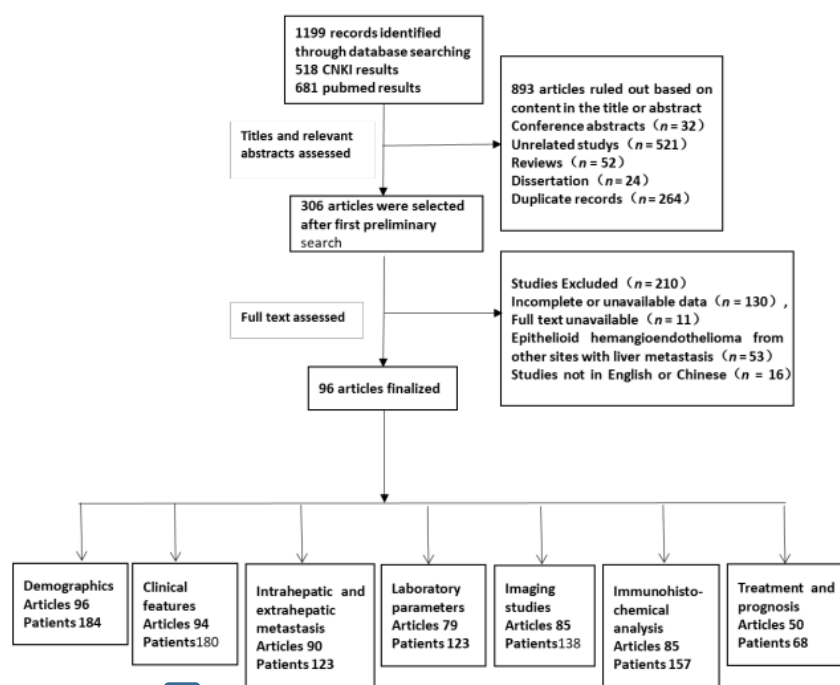


Figure 4 Search and selection process. CNKI: China National Knowledge Infrastructure.

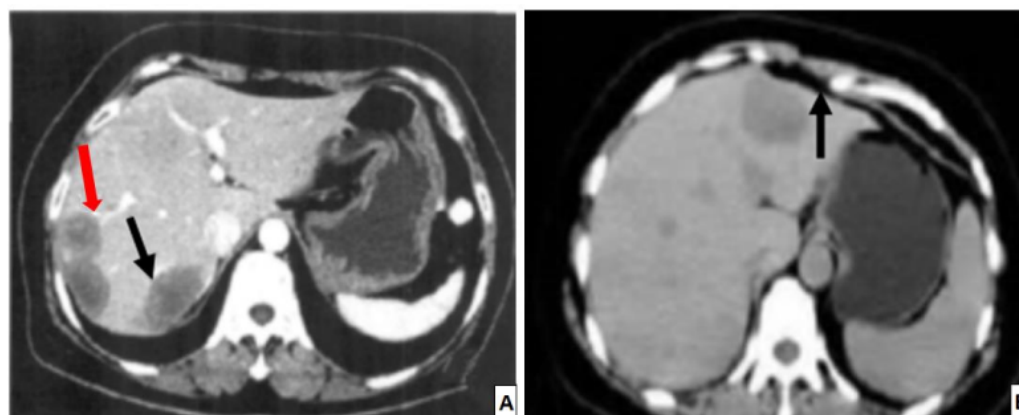


Figure 5 Abdominal computed tomography of hepatic epithelioid hemangioendothelioma. A: Target sign (the black arrow), Lollipop sign (the red arrow); B: Capsular retraction (the black arrow).

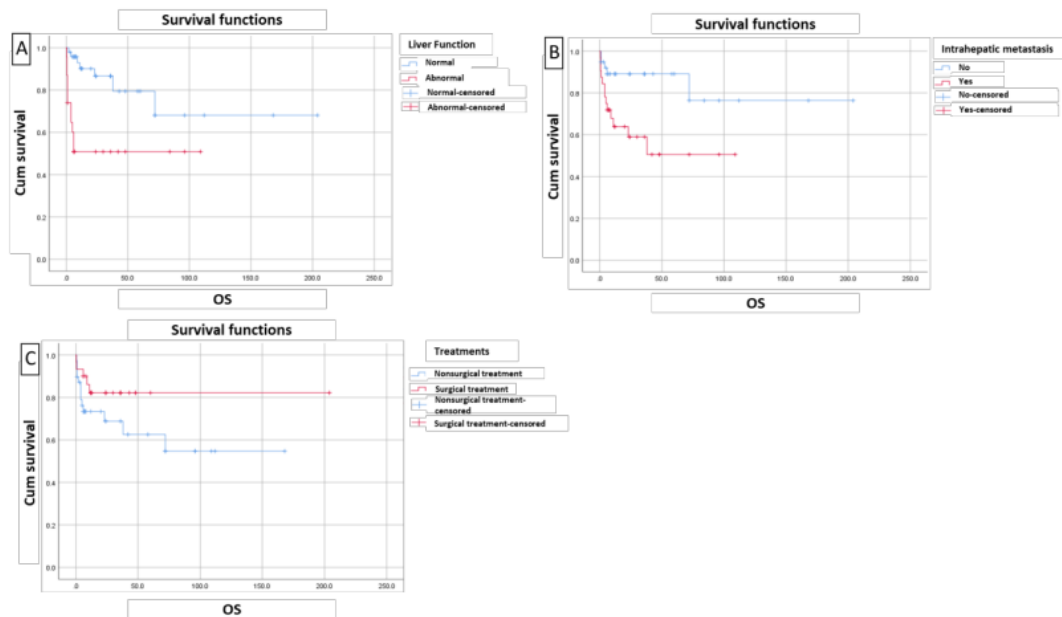


Figure 6 Overall survival of patients with hepatic epithelioid hemangioendothelioma.
A: According to liver function; B: According to intrahepatic metastasis; C: According to treatment. OS: Overall survival.

Table 1 General features of ² patients with hepatic epithelioid hemangioendothelioma

Presence of symptoms (<i>n</i> = 180)	No. of patients	%
Asymptomatic	54	30
Symptomatic	126	70
Epigastric pain	72	40
Hepatosplenomegaly	25	13.9
Inappetence	24	13.3
Abdominal distension	22	12.2
Weight loss	19	10.6
Fatigue	18	10
Epigastric discomfort	17	9.4
Hydrothorax and ascite	11	6.1
Fever	9	5
Jaundice	8	4.4
Thoracalgia and humeral back pain	8	4.4
Nausea and vomiting	6	3.3
Edema	5	2.8
Cough and expectoration	4	2.2
Abdominal mass	2	1.1
Hematemesis and melena	2	1.1
Intrahepatic involvement type (<i>n</i> = 123)		
Multinodular type (including diffuse type)	104	84.6

Mononodular type	19	15.4
Type of involvement (<i>n</i> = 123)		
Intrahepatic involvement	84	68.3
Extrahepatic involvement	39	31.7
Lung	25	20.3
Lymph node	8	6.5
Bone	5	4.1
Peritoneum	4	3.3
Spleen	4	3.3
Pleura	3	2.4
Omentum	2	1.6
Liver function (<i>n</i> = 97)		
Normality of liver function	58	59.8
Abnormality of liver function	39	40.2
Elevated ALT (u/L)	24	24.7
Elevated AST (u/L)	23	23.7
Elevated TBIL (μmol/L)	10	10.3
Elevated ALP (u/L)	24	24.7
Elevated GGT (u/L)	16	16.5
Decreased albumin (g/L)	6	6.2
Tumor markers		
Elevated AFP (ng/mL)	4/123	3.3

Elevated CEA (ng/mL)	3/85	3.5
Elevated CA19-9 (U/mL)	5/88	5.7
Elevated CA125 (U/mL)	8/29	27.6
CT		
Plain CT scan (<i>n</i> = 138)		
Low density lesions	136/138	98.6
High density or uneven density lesions	2/138	1.4
Calcification	22/138	15.9
Capsular retraction	25/138	18.1
Confluent masses	27/138	19.6
Contrast-enhanced CT (<i>n</i> = 103)		
Tumor edge enhancement	89/103	86.4
Tumor edge without enhancement	14/103	13.6
Target sign	27/103	26.2
Lollipop sign	12/103	11.7
Immunohistopathological markers		
FVIII-rag	92/93	98.9
CD34	156/157	99.4
CD31	116/117	99.1
VEGF	14/14	100
Vimentin	79/80	98.8
SMA	8/18	44.4

CD117	1/4	25
Desimin	0/13	NA
Hepatocyte	7/43	16.3
CK	22/53	41.5
EMA	3/26	11.5
AFP	0/29	NA
CEA	0/9	NA
S-100	1/28	3.6
KI-67	3/15	20
D2-40	4/5	80

HEHE: Hepatic epithelioid hemangioendothelioma; CT: Computed tomography; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CEA: Carcinoembryonic antigen; VEGF: Vascular endothelial growth factor; AFP: Alpha fetoprotein; CK: Cytokeratin; SMA: Smooth muscle actin; EMA: Epithelial membrane antigen.

Table 2 Treatments and prognosis of patients with hepatic epithelioid hemangioendothelioma

Treatment and outcome, <i>n</i> = 70	<i>n</i> (%)	Mean survival time (mean ± SD, mo)
LR	19 (27.1)	170.4 ± 17.8
LT	13 (18.6)	140.6 ± 17.7
Palliative treatment	11 (15.7)	4.0 ± 0.9
TACE	6 (8.6)	90.8 ± 19.0
Chemotherapy	7 (10.0)	69.6 ± 22.4
Other treatments	6 (8.6)	68.7 ± 13.7
Antiangiogenic therapy	8 (11.4)	84.5 ± 10.8

LR: Liver resection; LT: Liver transplantation; TACE: Transhepatic arterial chemotherapy and embolization.

Table 3 The results of univariable and multivariate analysis

Parameters	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Gender (male/female)	1.696 (0.663-4.342)	0.270		
Age (> 45 yr/≤ 45 yr)	1.656 (0.640-4.281)	0.298		
Symptoms (symptomatic/asymptomatic)	7.843 (1.027-59.876)	0.047	6.573 (0.862-50.139)	0.069
AFP (elevated/normal)	1.839 (0.654-5.171)	0.248		
Liver function (abnormal/normal)	3.208 (1.260-8.166)	0.014	2.834 (1.087-7.393)	0.033
Maximum diameter of tumor (≥ 5 cm/< 5cm)	1.891 (0.470-7.612)	0.370		
Intrahepatic metastasis (Yes/No)	3.540 (1.259-9.956)	0.017	3.178 (1.073-9.413)	0.037
Extrahepatic metastasis (Yes/No)	2.518 (0.974-6.507)	0.057		
Treatments (nonsurgical treatment/surgical treatment)	1.273 (1.024-1.583)	0.03	1.327 (1.042-1.688)	0.022

HR: Hazard ratio; CI: Confidence interval; AFP: Alpha fetoprotein.

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