

Clinical and radiological characteristics of Chinese patients with hepatic epithelioid hemangioendothelioma

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BACKGROUND AND OBJECTIVES: To study clinical features, imaging findings, and prognosis of hepatic epithelioid hemangioendothelioma (HEHE) in Eastern Hepatobiliary Surgical Hospital and to improve the level of recognition and preoperative diagnosis of HEHE.

DESIGN AND SETTINGS: This is a retrospective study. The study was conducted at Eastern Hepatobiliary Surgical Hospital in Shanghai, China from 1999 to 2012.

METHODS: Clinical data of 15 pathology-confirmed HEHE patients admitted in our hospital from 1999-2010 were collected and analyzed retrospectively.

RESULTS: Besides 7 cases of abdominal discomfort, this cohort of HEHE patients does not show common typical manifestations. Laboratory examinations found 8 low ALB/GLB cases, 3 mild anemia cases, and 1 high alanine aminotransferase case, but no abnormal α -fetoprotein, carcinoembryonic antigen, or CA19-9 cases. Plain computed tomography (CT) scanning found uneven multiple low-density lesions in most cases, dynamic enhanced CT scanning demonstrated peripheral enhancement in the hepatic arterial HA phase and more peripheral enhancement in the portal vein PV phase, and ring enhancement were detected in the delayed phase. Magnetic resonance imaging (MRI) demonstrated low signal intensity and even lower lesion centers in T1-weighted images, but slightly high signal intensity lesions and higher lesion centers in T2-weighted images. Enhanced MRI scanning showed ring enhancements but no obvious enhanced centers. Lesions were further enhanced in delayed MRI scanning. Prognosis of this cohort: 10 of these 15 patients were alive, including 4 cases with a tumor.

CONCLUSION: Comprehending the clinical and radiological characteristics of HEHE facilitates the level of recognition and preoperative diagnosis of this disease, and promotes surgeons to take active and appropriate surgeries.

Hepatic epithelioid hemangioendothelioma (HEHE) is a rare vascular tumor first named by Weiss¹ in 1982, and is common in middle-aged women with unknown cause. HEHE usually attacks soft tissue, lung, bone, brain, and small intestine, etc., but seldom onsets in liver. HEHE originates from mesenchymal tissue, whose degree of malignance is between hepatic hemangioma and angiosarcoma. Most patients were asymptomatic. Though there are certain imaging characteristics, the diagnosis is still difficult. In this study, we collected and analyzed clinical data and imaging findings of 15 HEHE cases from 1999-2010

in our hospital, and managed to draw some conclusions on its characteristics.

METHODS

In the cohort of 15 patients, 13 cases were confirmed HEHE by tumor paraffin biopsies after hepatectomies, and the other 2 cases were confirmed by liver biopsy under the guidance of ultrasound B-scans. All patients underwent routine ultrasound B-scans, computed tomography (CT), and/or magnetic resonance imaging (MRI) tests, and the clinical and imaging data of all patients were collected and reviewed. All patients were imaged

by 64-slice spiral CT and/or 1.5T MRI scanner, examining liver, gallbladder, pancreas, and spleen. Plain scanning was done first, followed by hepatic arterial (HA) phase and portal vein (PV) phase, and then delayed phase with layer thickness at 1 mm and layer spacing at 5 mm. All patients were followed up by telephone.

RESULTS

Clinical features

A total of 10 female patients and 5 male patients were included in this cohort, with the female-to-male ratio as 2:1. The mean and median ages were 56 and 40 years, respectively (range, 20-80 years). Seven (46.7%) patients had abdominal discomfort, including epigastric region pain or right hypochondriac region disorder. The other 8 (53.3%) patients were admitted in our hospital after discovering intrahepatic occupying lesions without obvious symptoms. Laboratory examination results did not show common specific features: 8 cases had low ALB/GLB (A/G ratio) (reference value is 1.5-2.5 in our hospital); 3 cases had mild anemia (reference value is 120-160 g/L in our hospital); 1 case had high alanine aminotransferase (ALT) level (reference value is 40 U/L in our hospital); and 1 case was HBsAg positive. α -fetoprotein (AFP), carcinoembryonic antigen (CEA), and CA19-9 levels in all patients were normal, and none of all patients had hepatitis C virus (HCV) infection.

CT and MRI findings

Tumor number: Multiple intrahepatic nodular were found in 9 out of 15 (60%) HEHE cases; and single nodular were found in the other 6 cases (40%). **Tumor appearance:** Twelve ovals and 3 irregular shaped. All lesions were in low density under plain CT scanning without local calcification. Dynamic enhanced CT scanning demonstrated peripheral enhancement in the HA phase and even more peripheral enhancement in the PV phase, and ring enhancement were detected under delayed scanning (**Figure 1**). MRI demonstrated low-density lesions and even lower density lesion centers in T1-weighted images (T1WI), but slightly high signal intensity lesions and higher intensity lesion centers in T2WI. Enhanced MRI scanning showed ring enhancements but no obvious enhanced centers. Lesions were further enhanced in delayed MRI scanning (**Figure 2**) There is a characteristic image call "capsular retraction" due to the fact that the fiber matrix components of a tumor produce fiber contractile response in the surrounding liver parenchyma. In this cohort, 5 cases were initially diagnosed with metastatic liver cancer, 3 cases with cholangiocellular carcinoma, 1 case with he-

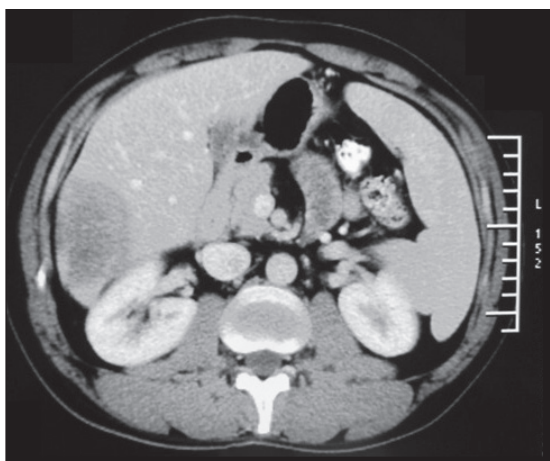


Figure 1. CT PV phase image.

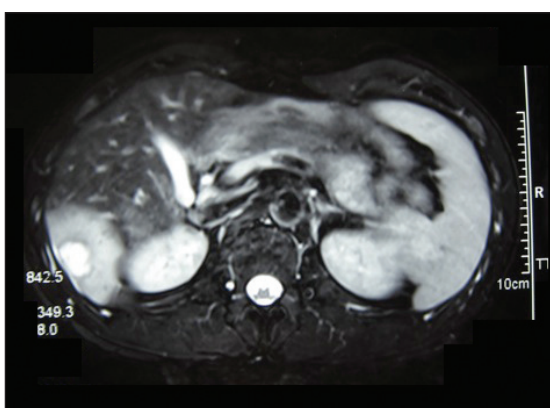


Figure 2. MRI T2WI image.

patic cavernous hemangioma, 1 case with intrahepatic diffused hepatocellular carcinoma, 1 case with hepatic cystadenoma, 1 case with primary liver cancer and 1 case with intrahepatic uneven fatty infiltration.

Treatment and follow-up

Thirteen patients underwent surgical procedures, including 4 orthotopic liver transplantation (OLT) cases, and 3 of them received transcatheter arterial chemoembolization (TACE) treatment after surgeries. The other 2 patients underwent TACE treatment after final diagnosed as HEHE. Twelve out of 15 patients survived at the last follow-up (**Table 1**).

DISCUSSION

HEHE is a kind of rare hepatic primary tumor, with an incidence lower than 1/1000000.² Its degree of malignance is between hepatic hemangioma and angiosarcoma. Although the etiology of HEHE is unknown,

Table 1. Treatment and follow-up of 15 HEHE cases (by April 2012).

Case No.	Treatment	Postoperative recurrence or metastasis (mo)	Postoperative survival time (mo); survival status
1	RL tumor resection and liver nodules excavation, with postoperative TACE	RL recurrence 2 mo after operation, re-perform resection	45; dead
2	LL and RL VIII segment resection, cholecystectomy, with postoperative TACE	Extensive metastasis 8 mo after operation, poor liver function	9; dead
3	RL (VI, VII, partial VIII segment) resection, LL inferior segment resection, cholecystectomy	No recurrence or metastasis	60; tumor-free survival
4	RL tumor resection	Intrahepatic recurrence and thoracic vertebrae metastasis 38 mo after operation	42; survival with tumor
5	Right subphrenic tumor resection	No recurrence	38; tumor-free survival
6	Left external lobe resection, left internal lobe tumor resection, right posterior lobe tumor resection, liver cyst drainage	RL recurrence 12 mo after resection	16; dead
7	RL resection, liver cyst drainage	No recurrence or metastasis	28; tumor-free survival
8	RL tumor resection, RL tumor biopsy, cholecystectomy	No recurrence or metastasis	24; tumor-free survival
9	Right posterior lobe tumor resection, cholecystectomy	No recurrence or metastasis	23; tumor-free survival
10	LL tumor resection	RL recurrence 20 mo after operation	22; survival with tumor
11	Ultrasound B-guided liver biopsy, TACE treatment 1 and 2 mo later	Multiple metastasis 31 mo after treatment	34; dead
12	Ultrasound B-guided liver biopsy, TACE treatment 1 and 2 mo later	Spleen and lung metastasis 54 mo after treatment	58; survival with tumor
13	RL multiple tumor resections	No recurrence or metastasis	40; survival with tumor
14	RL tumor resection	No recurrence or metastasis	63; tumor-free survival
15	RL multiple tumor resections, TACE 1 and 2 and 3 mo after operation	Spleen and lumbar metastasis 26 mo after operation	30; dead

LL: Left liver lobe, RL: right liver lobe, HEHE: hepatic epithelioid hemangiioendothelioma, TACE: transcatheter arterial chemoembolization.

it may associate with oral contraceptives, liver trauma history, long-term inhalation, and exposure to vinyl chloride. HEHE usually occurs in adults, especially in women, with a young onset age between 30 and 40 years old.³⁻⁵ Min-Shu et al⁶ reported that the female-to-male ratio was 5:1, and the onset age was from 25 to 86 years old—mostly between 30 and 40 years old. In the 15 cases we collected in our hospital, there were 10 female and 5 male patients, with the female-to-male ratio as 2:1, and the onset age was from 20 to 80 years old, while 8 of them (53.3%) were between 33 and 48 years old, which is similar to the data in Min-Shu Hsieh's report. Most HEHE patients are asymptomatic. In this study, 8 patients (53.3%) were discovered in regular health examinations without obvious discomfort, and the other 7 patients had epigastric region pain or their right-side hepatic region was unwell. No typical specificity was

observed in laboratory examinations: routine tumor markers such as AFP, CEA, CA19-9, etc., were all in the normal range; only the ALT level was abnormally increased.⁷ Min-Shu Hsieh et al⁶ reported that 1 out of 6 HEHE patients had elevated ALT and aspartate aminotransferase levels, and 2 HEHE had mild anemia. In our study, there were 8 low A/G ratio cases, 3 mild anemia cases, 1 high ALT level case, and 1 HBsAg positive case. AFP, CEA, and CA19-9 levels in all patients were normal, and none of the patients had HCV infection.

HEHE patients usually have multiple nodular. Min-Shu Hsieh⁶ reported 6 cases, in which 4 cases had multiple nodular and 2 cases had single nodular. In this cohort, 9 out of 15 (60%) patients had multiple nodular, presenting intrahepatic low echo under ultrasound B-scans, with a low blood flow signal and sometimes a slightly flow signal at the edge, showing characteris-

tics similar to hepatic metastases without specificity. However, there were certain features in CT and MRI examinations. Jiang and Yuan reported 79 intrahepatic nodular in 9 patients and found low-density in all nodular, and even lower signal inside nodular; except 1 single-nodular patient, among the other 78 nodular in 8 patients, there were 26 nodular made by nodule combinations, and only 2 calcified nodular; 7 patients had capsular retractions; most patients had slight enhancement around lesions in the enhanced HA phase imaging, and all patients had different levels of enhancement, mainly in the peripheral lesions in the PV phase, showing the “bull’s eye” sign, leading to clinical misdiagnosis. Sejal et al⁹ studied 3 cases of HEHE patients with MRI findings, and reported that most nodular were in low density in T1WI, and in relatively high density in T2WI under plain scanning, while the center of lesions had low signal, which may be related to tissue hemorrhage, coagulative necrosis, or calcification; “bull’s eye” signs were seen in strengthened scanning without intrahepatic bile duct dilatation. Features on CT and MRI have also been reported as “lollipop” signs, describing the tumor lesion as candy, and the vein as rod.¹⁰ In this study, lesions were in low density under plain CT scanning, without local calcifications, and the liver tissue near capsule contractions were commonly seen in 10 patients (66.7%), which, as we considered, were caused by the contraction of abundant collagen fibrous tissues. Dynamic enhanced CT scanning demonstrated peripheral enhancement in the HA phase and even more peripheral enhancement in the PV phase, and ring enhancement were detected under delayed scanning. MRI demonstrated low-density lesions and even lower signal intensity lesion centers in T1WI, but slightly high-intensity lesions and higher signal intensity lesion centers in T2WI. Enhanced MRI scanning showed ring enhancements but no obvious enhanced centers, presenting as “bull’s eye” signs. Lesions were further enhanced in delayed MRI scanning. Therefore, 13 out of 15 HEHE cases in our hospital were initially diagnosed with other primary or metastatic liver tumors. However, we still can exclude primary hepatocellular carcinoma, hepatic cavernous hemangioma, and even hepatocholangiocarcinoma and other metastatic hepatic carcinoma and perform positive treatments according to the conclusions drawn from imaging findings, such as lower signal in the tumor center than in the peripheral part under plain scanning, slight enhancement around a tumor in the HA phase, further enhancement in the PV phase, retraction of the tumor

surrounding near liver capsule, local calcification, and large feeding vessels inside lesions, etc.

Due to the low malignancy of HEHE, the treatment effectiveness and prognosis are quite inspiring, despite its multiple-nodular onset. The main treatments for HEHE patients nowadays include hepatectomy, live transplantation, minimally invasive surgery, chemotherapy, and radiotherapy, etc. Which therapy is more effective is still under debate because of the lacking of prospective study with large capacity. Kpodonu et al¹¹ advocated an individualized treatment. Zhu and Li¹² considered that hepatectomy should be done in patients with single or localized tumor, chemotherapy in postoperative patients or patients with no chance of operation (patients with multiple lesions), and radiotherapy only in patients with osseous metastasis to release pain. Other surgeons demonstrated that radical excisions for HEHE patients with lesions limited in 1 lobe can achieve better survivals,¹³ even in patients with extrahepatic metastasis.⁷

Zhang et al¹⁴ investigated 7 HEHE patients and pointed out that OLT could be a potential trend in treating a tumor confined to liver. In this study, we performed 13 cases of surgeries (including 4 cases of OLT), among which 7 cases were multiple HEHE and 6 cases were single HEHE, and 3 cases received TACE treatment 1 month after surgeries; the other 2 cases underwent TACE treatment directly after diagnosing HEHE by liver biopsy. Twelve cases in this study survived at the last follow-up. According to our experience, single HEHE patients can be nearly cured after radical resections and multiple HEHE patients can obtain long-term survival time after positive radical resections adjunctive with interventional chemotherapies, which may be related to its low malignant biological behavior.

In conclusion, although there are some imaging features of HEHE, it still lacks typical clinical manifestations and specific iconographic characteristics and presents negative routine tumor marker results, thus causing misdiagnosis. The final diagnosis of HEHE should be confirmed by pathological examinations. Radical resections and even OLT should be considered in single and multiple nodular HEHE, and combining with chemotherapy or radiofrequency ablation, if necessary, good therapeutic effect can be obtained.

Acknowledgments

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