Clinical Characteristic and Prognosis of Epithelioid Hemangioendothelioma: 35 Cases from Single Center in Recent Decade

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Research

Keywords: Epithelioid hemangioendothelioma, Ki-67, prognosis

Posted Date: October 15th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-91622/v1>

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Abstract

Backgrounds: Epithelioid hemangioendothelioma (EHE) is a rare carcinoma worldwide with low-grade malignancy. Few reports have evaluated large case series of EHE. And we tried to describe different treatment and the overall survival rate of EHE, exploring prognostic the factors of outcome.

Methods: This was a retrospective study enrolling patients diagnosed with EHE in our center from June 2009 to March 2020. Data including demographic characteristics, laboratory data, treatments, imaging data, immunohistochemical results, follow-up results were collected, and a retrospective database was constructed for analysis.

Results: This study enrolled 35 patients with EHE pathologically diagnosed in our center. We reported the mean onset age was 41 years old, ranging from 3 to 70. EHE was more common in female patients (60%). The most commonly affected organ was liver (63%). The 5-year survival rate was 62.86%. After we operated COX regression analyse to test the effect of age (≥ 55 years old or < 55 years old), sex, position (multiple organs or single organ involved), symptoms (symptomatic or asymptomatic) and Ki-67 ($\geq 10\%$ or $< 10\%$) on disease outcome, we only found that Ki-67 was the independent factor affecting the prognosis, with significant P value equal to 0.034 and hazard ratio equal to 5.809.

Conclusions: In conclusion, EHE has relatively low-grade malignancy and its 5-year survival rate is 62.86%. EHE patients whose Ki-67 $\geq 10\%$ tended to experience poor outcome.

Introduction

Epithelioid hemangioendothelioma (EHE) is a rare carcinoma worldwide with low-grade malignancy. The incidence of EHE is around one in a million and it represents less than 1% of all the vascular tumors[1]. As it is reported, the median age of onset is 36 years old, with a male to female ratio of 1:4. And there has also several reports about children and the elderly. Reported sites of EHE involves lung(12%), liver(21%), liver plus lung (18%), and bones(14%), although this kind of tumor may involve any site of body to be its target[2–4]. As for the prognosis, a survey of 264 EHE patients reported that the overall survival was 73% at 5 years[5].

Due to the rarity of EHE, there is still no optimal treatment strategy. Hence, we enrolled patients pathologically confirmed with EHE in our center in recent decade to describe different treatment and the overall survival rate. And we tried to explore the prognostic factors in outcome.

Material And Methods

This was a retrospective study enrolling patients diagnosed with EHE in our center from June 2009 to March 2020. All patients underwent lesion resect or puncture biopsy procedure and were confirmed EHE by pathological biopsy. If a patient had multiple lesions on several organs and was confirmed EHE on one

organ, after we reviewed the imaging data, we were able to conclude clinically that the lesions on the other organs were EHE.

We collected patients' demographic characteristics data like age, height, weight, body mass index (BMI), the duration of course and history of some underlying diseases such as hypertension and diabetes. Laboratory data like the concentration of hemoglobin was also recorded to determine if the patient had anemia, which is an indicator of general health condition. The imaging data like CT, PETCT or MRI scan was also retrieved if they had the examination. We recorded some lesion-related data, for example the position, the size, and the number. The immunohistochemical results of pathological biopsy were gathered to identify some specific markers like Ki-67 labeling index.

We completed the follow-up on the phone call or at our outpatient building and inquired about patients' health condition and some other subsequent treatment. The survival period started from the time at diagnosis to the date of death or last clinical follow-up. We defined endpoint event as death or discharge without medical order (usually in poor health condition) or lost to follow-up. Progressed disease was considered if a patient had recurrence of EHE on the same organ or we identified new metastatic lesion on distant positions after treatment.

The main outcome of this study was to identify the effect of some factors on prognostic outcome and to describe the overall survival rate of EHE. All the data analysis is operated on SPSS 25.0. Continue variables are described as mean $\pm$ standard deviation (SD) and category variables as composition. Kaplan-Meier survival curve is utilized to represent the overall survival rate of EHE in the whole cases and in subgroup patients. The difference of overall survival rate between subgroups is examined by Log-Rank Test. We also operate COX regression analyse to identify independent factors affecting the prognostic outcome of EHE.

Results

We collected 35 patients confirmed EHE eligible for our study. The mean age was 41 years old, ranging from 3 to 70. Male and female incidence ratio was 1:1.5. At the time of the last follow-up, the lesion was mainly located at liver (n = 22) and lung (n = 14). Thirteen patients were found the lesions at multiple places, with lung and liver (n = 7) accounting for the most part. Even for the lesion at only single place, there could be multiple nodules. Nearly half of the patients were conscious of the disease when they underwent physical examination, which meant they did not present with any symptom or discomfort. Clinical and laboratory data were detailed in Table 1.

Table 1
Clinical and laboratory characteristics of enrolled patients

Item	
Cases, n	35
Mean Height, cm	161.19 ± 7.55
Mean Weight, kg	56.73 ± 12.04
Mean BMI, kg/m ²	22.25 ± 3.26
Male/Female	14/21
Mean Age, year	41 ± 14
Mean Hemoglobin, g/L	131.94 ± 20.09
Underlying disease, n	
Hypertension	2
Diabetes	1
Chronic Hepatitis B	3
Liver Cirrhosis	1
Moderate Anemia	1
Hyperthyroidism	1
Pleural Effusion	11
Position, n	
Liver	22
Lung	14
Thoracic Vertebra	2
Lumbar Vertebra	1
Pleura	2
Peritoneum	1
Mediastinum	2
Adrenal Gland	1
Bone	3
BMI: body mass index	

Item	
Other	3
Chief Complaint, n	
Chest and Back Pain	5
Cough	3
Hemoptysis	1
Abdominal and Lumbar Pain	8
Asymptom	14
BMI: body mass index	

We tested the main pathological diagnosis features of EHE, including CD31, CD34, factor-VIII, ERG, TFE3 gene fracture, CAMTA1 showed in Fig. 1. The pathological data we collected showed that the positive rate of CAMTA1 and TFE3 were 66.6% (8/12) and 18.2%(2/11) respectively.

Among the 35 cases, 6 underwent observation treatment. Three of them lost to follow-up and another 2 patients, who were not in good condition and refused to receive any further therapy, finally discharged from our hospital without medical order. Nine of the whole 35 patients received palliative treatment, with 2 patients experiencing systematic chemotherapy, 1 taking Chinese traditional medicine and 1 receiving combination therapy of radiotherapy and chemotherapy. Ultimately, 1 lost to follow-up, 1 died as a result of disease recurrence on liver, 1 discharged from hospital without medical order and 1 had progressed disease. The rest of the 35 patients underwent curative treatment. All the details of treatment were explained in Table 2.

Table 2
Therapeutic regime of all the 35 patients.

Treatment	Outcome
Observation treatment (n = 6)	
	Lost to follow-up (n = 3)
	Discharged without medical order (n = 2)
Palliative treatment (n = 9)	
Palliative operation (n = 8)	Lost to follow-up (n = 1)
Systematic chemotherapy (n = 2)	Discharged without medical order (n = 1)
Chinese traditional medicine (n = 1)	Died as a result of disease recurrence on liver (n = 1)
Combination of radiotherapy and chemotherapy (n = 1)	Progressed disease (n = 1)
TACE (n = 1)	
Curative treatment (n = 20)	
Curative operation (n = 19)	Lost to follow-up (n = 5)
Systematic chemotherapy (n = 2)	Progressed disease (n = 3)
Radiotherapy (n = 2)	
Combination of radiotherapy and chemotherapy (n = 2)	
Combination of Chinese traditional medicine and chemotherapy (n = 1)	
Liver transplantation (n = 1)	
TACE: transcatheter arterial chemoembolization	

After the first medical diagnosis and treatment about EHE, patients were followed up for a period of time ranging from 2 months to about 11 years. The 1-year, 3-year and 5-year survival rate was 80.00%, 68.57% and 62.86%, respectively. (Fig. 2) According to the main complaint at the diagnosis of EHE, we found that the survival curve was poorer in symptomatic patients than that in asymptomatic ones. However, the difference was not significant. ($P = 0.252$) (Fig. 3A) The situation was similar when we divided patients into male and female. (Fig. 3B) As for the pathological biopsy, 26 samples had Immunohistochemistry results about Ki-67 and we classified them into two groups, $\geq 10\%$ and $<10\%$. After we utilize Kaplan-Meier Survival Curve to calculate the overall survival rate, we found patients with $Ki-67 \geq 10\%$ experienced worse consequence than that with $Ki-67 < 10\%$. P value was 0.016 and the difference is statistically significant. (Fig. 3C) Finally, we operated COX regression analyse to test the effect of age (≥ 55 years old or <55 years old), sex, position (multiple organs or single organ involved), symptoms (symptomatic or

asymptomatic) and Ki-67 ($\geq 10\%$ or $<10\%$) on disease outcome. We only found that Ki-67 was the independent factor affecting the prognosis, with significant P value equal to 0.034 and hazard ratio equal to 5.809.

Discussion

In this study, we collected 35 pathologically confirmed EHE patients and analyzed the impact of several factors on outcome. EHE was initially described by Dail and Liebow in 1975 as intravascular sclerosing bronchioalveolar tumor [6]. In 1982, Weiss and Enzinger proposed the name of EHE, whose malignant degree is between hemangioma and angiosarcoma[7]. EHE is prone to occur in soft tissue and multiple organs, and originates from vascular endothelial or pre-endothelial cells.

The etiology is still unclear. In 2013 WHO classification of sarcomas, EHE is identified with pathognomonic WWTR1-CAMTA1 which results from t(1;3)(p36.3;q25) translocation, as well as with the less common YAP1-TFE3 fusion gene[1, 2, 4, 8, 9]. In our study, CAMTA1 and TFE3 positive rate among detected patients was 66.6% (8/12) and 18.2% (2/11), respectively. As for the diagnosis of disease, CD31, CD34 and FLI-1 should be taken into comprehensive consideration in the immunohistochemical identification of EHE[2].

EHE has characteristic radiological features on contrast-enhanced CT and MR imaging, for instance, "Target Sign" (Fig. 4A) and "Lollipop Sign" (Fig. 4B). And the tumor near the periphery of liver usually causes the hepatic capsular retraction (Fig. 4C)[10, 11].

Studies had reported several factors affecting prognosis: multiple organs involvement, disease progression, more than 55 years old, male patients, patients with obvious symptoms of vessels invaded (for example: hemoptysis and anemia), pleural involvement with pleural effusion and Ki67 greater than 10%[12, 13]. EHE has no specific clinical manifestations. All symptoms are related to the sites of tumor. Of the cases we collected, 22 patients had corresponding clinical manifestations, including cough, chest pain, backache abdominal pain and some other symptoms. The study showed that patients with clinical manifestations had poorer prognostic outcome than those without. Although there was no statistical difference in the p value, there was a tendency for symptomatic patients to be worse than asymptomatic patients. This was similar with the study by Satoshi Shiba[14], however, the author found the difference to be significant. We suggest that larger samples of EHE are needed to analyze the relationship between the main complaint and the overall survival rate.

Previous study considered Ki-67 $\geq 10\%$ to be an important factor with poorer prognosis in angiosarcoma, which originates from vascular endothelial cell and is similar with EHE[15]. We also compared the overall survival rate between EHE with Ki-67 $\geq 10\%$ and Ki-67 $<10\%$, and we found that the difference was statistically significant, which meant EHE patients with Ki-67 $\geq 10\%$ had worse outcome than those with Ki-67 $<10\%$. It was frustrating that only 26 samples had Ki-67 labeling index, and as a consequence, the role of Ki-67 needed to be further explored.

If feasible, surgical removal is the best curative strategy. For pulmonary EHE, surgery can be proposed in cases of unilateral single or multiple nodules. Lung transplantation should be evaluated in patients with vascular aggressivity and pleural effusion. Besides, unresectable hepatic EHE without extrahepatic metastases is an excellent indication for liver transplantation[16]. We had a special patient. She was diagnosed as multiple hepatic EHE with main complaint of epigastric pain at her age of 34 and had the first liver transplantation in December 2013. After 64 months, tumor recurred and she had a second liver transplantation. Now she is having a regular follow-up, and taking immunosuppressants such as Sirolimus, and Everolimus. These pills are the mTOR inhibitors which have been proved to inhibit the growth of tumor cells[17]. Previous studies had described the use of the mTOR inhibitor Everolimus in combination with Sirolimus after transplantation, which not only suppressed the immune response, but also effectively prevented tumor recurrence and improved survival after liver transplantation[18–21]. This case explains that repeated liver transplantation is a feasible and effective treatment strategy for liver-confined EHE[17, 22–24]. On the other hand, follow-up is also considered a reasonable strategy for asymptomatic patients with diffuse lesions due to the low degree of malignancy of EHE, as spontaneous degeneration of EHE has also been reported[25].

Conclusions

In conclusion, EHE has relatively low-grade malignancy and its 5-year survival rate is 62.86%. EHE patients whose Ki-67 $\geq$ 10% tended to experience poor outcome.

Abbreviations

EHE: Epithelioid hemangioendothelioma

BMI: body mass index

Declarations

Ethics approval and consent to participate

Not applicable. This study was approved by the West China Hospital of Sichuan University Institutional Review Board, and the need for informed consent was waived due to the retrospective nature of the study.

Consent for publication

Written informed consent for publication was obtained from all participants.

Availability of data and materials

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

Not applicable. There have no competing interests to declare.

Funding

Not applicable. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

Guarantor of integrity of the entire study: Qiaoqi Li

Study concepts and design: Qiaoqi Li, Lede Lin

Literature research: Qiaoqi Li

Clinical studies: Qiaoqi Li, Jielang Li

Experimental studies / data analysis: N/A

Statistical analysis: Qiaoqi Li, Lede Lin

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Acknowledgement

None.

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Figures

Figure 1

Microscopic immunohistochemistry findings immunohistochemical features of EHE A. Microscopic immunohistochemistry findings of EHE with hematoxylin and eosin (magnification $\times 400$). B. Microscopic immunohistochemistry findings of EHE with hematoxylin and eosin (magnification $\times 200$) C. The cells stain positively for CD 31 D. The cells stain positively for CD 34 E. The cells stain positively for ERG F. The

cells stain positively for Factor-VIII G. The cells stain positively for CAMTA1 EHE: epithelioid hemangioendothelioma

Figure 2

Overall Survival of the 35 Patients with EHE

Figure 3

Survival Curve according to Different Factors A. Survival Curve according to Main Complaint at the Time of Diagnosis B. Survival Curve according to Sex C. Survival Curve according to Ki-67 from Pathological Biopsy

Figure 4

"Target Sign", "Lollipop Sign" and hepatic capsular retraction A. Target Sign, Magnetic resonance imaging (MRI) demonstrated a hypermetabolic peripheral rim reflecting hyperactivity tumor regions and a relatively hypometabolic central area reflecting fiber stroma (white arrow). B. Lollipop Sign, hepatic nodules with hepatic or portal vein in the periphery of the lesion (white circle). This configuration

resembled a lollipop. C. Hepatic capsular retraction, the lesion near periphery caused hepatic capsular restriction (black arrow).