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The clinical features of epithelioid hemangioendothelioma in a Han Chinese population

A retrospective analysis

Qinyue Guo, PhD[a], Jing Xue, PhD[b], Lin Xu, PhD[c], Zhihong Shi, PhD[b], Bo Zhou, PhD[b,*]

Abstract

Epithelioid hemangioendothelioma (EHE) is a rare indolent vascular tumor which occurs at liver, lung, bone, and so on. However, the etiology of EHE is evasive.

These patients were enrolled at the First Affiliated Hospital of Xi'an Jiaotong University from January 2011 to December 2015. Retrospective analysis is done by demographic data of clinical manifestations, laboratory parameters, CT imaging, histological, and immunohistochemical features in 9 cases in Shaanxi.

Of the patients, 8 were females (88.9%) and 1 were males (11.1%). The age ranged from 34 to 71 years (mean 49 years; median 49 years). Anatomical sites of primary lesions were as follows: liver (n = 6, 66.7%), upper extremities (n = 1, 11.1%), sublingual gland (n = 1, 11.1%), and spine (n = 1, 11.1%). Metastatic disease was diagnosed in 5 cases (55.6%) with occurrence in lung (n = 4, 44.4%), bone (n = 2, 22.2%), upper extremities (n = 1, 11.1%), pleura (n = 1, 11.1%), and spleen (n = 1, 11.1%). Tumor size ranged from 0.5 to 6.8 cm (mean 3 cm). The most tumors were composed of highly cellular areas with small and prominent nucleoli in vesicular nuclei, and ERG (100%) was the most frequently positive in these cases, followed by CD31 (88.9%) and CD34 (77.8%) via histology and immunohistochemistry techniques.

EHE is a very rare in Shaanxi. It is significant to find its clinical, radiological, and pathological characters, helping for EHE early diagnosis and treatment, reducing misdiagnosis and improving life quality.

Abbreviations: CT = computed tomography, EHE = epithelioid hemangioendothelioma.

Keywords: epithelioid hemangioendothelioma, immunohistochemical staining, retrospective analysis

1. Introduction

Epithelioid hemangioendothelioma (EHE) is a rare malignant vascular neoplasm with low-to-intermediate grade that usually occurs in liver, lung, bone, and skin.[1–3] The first case was described by Weiss and Enzinger in 1982.[4] Recent study in a cohort of 39 EHE cases in Europe showed that the primary sites were assessed including lung (17.9%), bone (15.4%), liver (5.1%), skin (5.1%), lymph node (2.6%), breast (2.6%), and the remainder in other soft tissue (head and neck [20.5%], trunk [12.8%], upper extremities [7.7%], lower extremities [5.1%], mediastinal [2.6%], and paratesticular [2.6%]).[5] Although considerable progress has been made in the diagnosis and treatment of EHE, retrospective analysis remains insufficient for EHE in a Han Chinese Population in Shaanxi.

It has been proven that EHE typically has more indolent behavior than angiosarcoma, and metastasis of EHE was found in about 30% of cases, and the 5-year survival rate was approximately 60%, but the EHE patients with hemoptysis and/or hemorrhagic pleural effusions had lower 5-year survival rate.[6] Additionally, pleural effusion, pulmonary symptoms, weight loss, and anemia are independent risk factors and predictors of survival in patients with pulmonary EHE.[6]

Histological findings showed that there were complicated and subtle epithelioid tumor cells in tissue slices of EHE patients. The cells contained intracytoplasmic vacuoles representing small vascular lumina.[2] Classically, the vacuolated cells are lined in short cords and primitive angiogenic cords.[7] Meanwhile, the bioptic tissues of all EHE cases were positive for ERG, FLI1, and CD31 by immunohistochemistry techniques, and CD34 and D2–40 positive rate were 81% and 71%, respectively.[6]

In the present study, retrospective analysis was used for 11 cases of EHE in a Han Chinese Population in Shaanxi, which were diagnosed and treated in the first affiliated hospital of Xi'an Jiaotong University. All the cases were observed with respect to the clinical manifestations, imaging findings, histopathological

Editor: Meixia Lu.

ZS and BZ contributed equally to this work.

Funding/support: This study was supported by the programs from the National Natural Science Foundation of China (81270094 and 81500016), and the Young Innovators Awards of the First Affiliated Hospital of Xi'an Jiaotong University (2014YK3 and 2015YK6).

The authors have no conflicts of interests to disclose.

[a] Critical Care Medicine, [b] Department of Respiratory, the First Affiliated Hospital of Xi'an Jiaotong University, [c] Department of Endocrinology, the Affiliated Guangren Hospital, Xi'an Jiaotong University, Xi'an, Shaanxi, China.

[*] Correspondence: Bo Zhou, Department of Respiratory, the First Affiliated Hospital of Xi'an Jiaotong University, 277 Yanta West Road, Xi'an, Shaanxi 710061, China (e-mail: zb_bob@stu.xjtu.edu.cn).

Medicine (2017) 96:26(e7345)

Received: 21 June 2016 / Received in final form: 4 June 2017 / Accepted: 6 June 2017

http://dx.doi.org/10.1097/MD.0000000000007345

characteristics, immunohistochemical phenotypes, and prognosis, helping for EHE early diagnosis and treatment, reducing misdiagnosis and improving life quality.

2. Methods

These patients were enrolled at the First Affiliated Hospital of Xi'an Jiaotong University (Xi'an, Shaanxi, China) from January 2011 to December 2015, who were of Han Chinese ethnicity from Shaanxi, China. All subjects in the study have been diagnosed as EHE through histopathological analysis. This study was performed according to the Declaration of Helsinki and was approved the ethics committee of the First Affiliated Hospital of Xi'an Jiaotong University. Written informed consent was obtained from all patients.

In all cases, the tissue was fixed in 4% buffered formalin, routinely processed and embedded in paraffin; 2 to 4 μm thick sections were stained with hematoxylin and eosin and immunohistochemically using commercially available antibodies (ERG, CD31, CD34, Vim, F8, panCK, HSP70, SMA, S100, and EMA). Appropriate positive and negative controls were used throughout.

3. Results

3.1. Demographic data

Demographic data are presented in Table 1. Of the 9 patients, 8 were females (88.9%) and 1 were males (11.1%). The age ranged from 34 to 71 years (mean 49 years; median 49 years). Anatomical sites of primary lesions were as follows: liver (n = 6, 66.7%), upper extremities (n = 1, 11.1%), sublingual gland (n = 1, 11.1%), and spine (n = 1, 11.1%). Metastatic disease was diagnosed in 5 cases (55.6%) with occurrence in lung (n = 4, 44.4%), bone (n = 2, 22.2%), upper extremities (n = 1, 11.1%), pleura (n = 1, 11.1%), and spleen (n = 1, 11.1%). Two of them had metastases to more than 2 sites (22.2%). The primary lesions were treated by surgery with excision in 4 cases (44.4%). Four patients received chemotherapy (44.4%). Another patient voluntarily abandoned treatment. Follow-up information was available for all 9 patients. Seven patients were alive, and 2 patients died of the disease after 2 and 1.5 years, respectively.

3.2. Clinical manifestations

The clinical manifestation of EHE was heterogeneous and varied because of different primary and metastatic lesions. At the time of diagnosis, 3 patients were asymptomatic (33.3%), and 6 patients were symptomatic (66.7%). The most common clinical manifestations were pain of the primary site, weakness, and weight loss.

3.3. Laboratory parameters

The laboratory data on all patients were available. Six patients (66.7%) did not show any abnormality, and 3 patients (33.3%) had abnormal findings, including increased aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase. However, tumor markers (alpha fetoprotein, carcinoembryonic antigen, CA125, CA153, CA 199, and CA724) were normal.

3.4. Computed tomography (CT) imaging

All patients who had CT scans are available. As shown in Figure 1A to D, tumor size ranged from 0.5 to 6.8 cm (mean 3 cm). The common radiological features are low-density pattern (multiple nodular lesions and/or large masses), capsular retraction, and calcifications. The majority of enhanced CT scanning showed the pattern of circular or peripheral enhancement. However, enhanced CT imaging of some patients with liver involvement also showed no obvious enhancements. Thus, the radiological characteristics are relatively nonspecific.

3.5. Histological findings

As shown in Figure 2A to F, all tumors were made up of epithelioid cells, which were arranged in strands, cords, and nests with potential invasive growth. Additionally, histiocytoid and/or fusiform cells were found in these cases. The most tumors were composed of highly cellular areas with small and prominent nucleoli in vesicular nuclei. Some cases showed nuclear atypia, accompanied by occasional intranuclear pseudoinclusions. All lesions exhibited abundant clear cytoplasm with intracytoplasmic vacuoles. There are some prominent features in the cases, such as well-formed multicellular vascular access, hyaline thrombus forming, ischemic necrosis, and desmoplastic reaction.

3.6. Immunohistochemical findings

The results of immunohistochemical staining are summarized in Table 2. ERG (100%) was the most frequently positive in these cases, followed by CD31 (88.9%) and CD34 (77.8%). The epithelioid cells were positive for Vim (37.5%), F8 (33.3%), and panCK (28.6%). HSP70 was focally expressed in 1/7 lesions (10%). Moreover, the epithelioid cells were negative for SMA, S100, and EMA.

Table 1

Clinical data.

Case	Sex/age	Site	Size, mm	Therapy	Metastases	Follow-up
1	f/52 y	Sublingual Gland	45 × 40 × 10	Excision	–	NED, 0.5 y
2	f/71 y	Liver	68 × 43	Chemotherapy	Bone	AWD, 0.5 y
3	f/34 y	Thoracic Vertebra	30 × 30 × 15	Excision	–	AWD, 1 y
4	f/41 y	Hand	22 × 18 × 15	Excision	–	NED, 1 y
5	f/42 y	Liver	40 × 40	Chemotherapy	Lung, pleura, and spleen	DOD, 1.5 y
6	f/49 y	Liver	20 × 20	Chemotherapy	Lung	AWD, 1.5 y
7	f/59 y	Liver	60 × 45 × 28	Excision	–	NED, 1.5 y
8	m/51 y	Liver	50 × 45	Chemotherapy	Lung, bone, and arm	DOD, 2 y
9	f/42 y	Liver	10 × 5	–	Lung	AWD, 1 y

AWD = alive with disease, DOD = death of disease, f = female, m = male, NED = no evidence of disease, y = year(s).

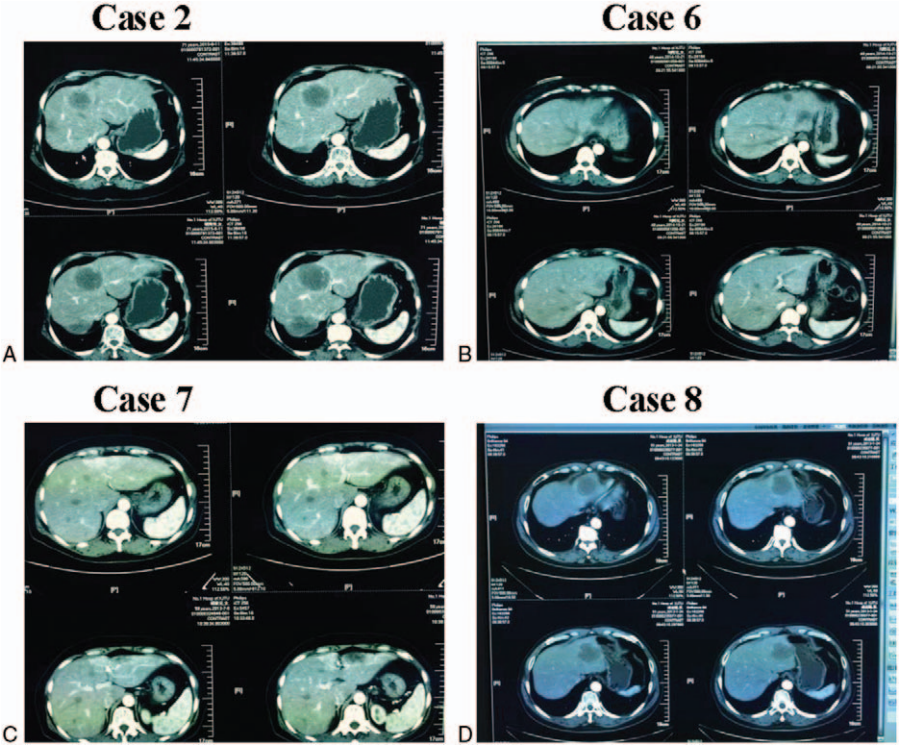

Figure 1. Abdominal computed tomography (CT). (A) Circular enhancements (case 2); (B) multiple nodular lesions (case 6); (C) peripheral enhancements (case 7); and (D) no obvious enhancements (case 8).

4. Discussion

EHE is a rare neoplasm of vascular origin that involves soft tissue and visceral organs. To date, more than 100 cases have been reported in the world, but the etiology of EHE remains unknown. Retrospective analysis based on clinical findings and tests is very rare in China. In the present study, retrospective analysis is done by demographic data of clinical manifestations, laboratory parameters, CT imaging, histological, and immunohistochemical features in 9 cases in Shaanxi.

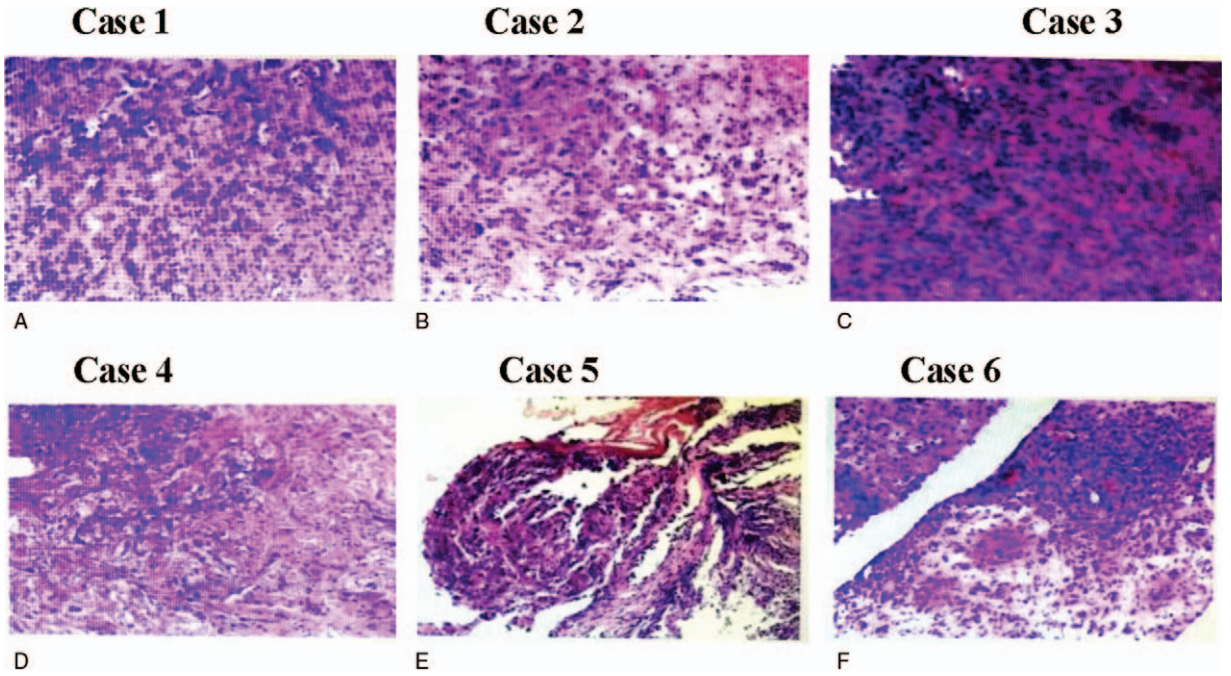

Figure 2. Hematoxylin-eosin staining (×10). (A) Epithelioid cells were arranged in cords (case 1); (B) epithelioid cells were arranged in strands (case 2); (C) mild nuclear atypia (case 3); (D) in strands (case 4); (E) in cords (case 5); and (F) in nests (case 6).

Table 2

Immunohistochemical analyses.

Case	ERG	CD31	CD34	Vim	F8	panCK	HSP70	SMA	S100	EMA
1	+	+	+	+	+	−	−	−	−	ND
2	+	+	+	+	−	+	−	−	−	−
3	+	−	+	−	−	+	−	−	ND	−
4	+	+	+	+	−	−	−	−	−	−
5	+	+	−	−	−	−	−	−	−	ND
6	+	+	−	ND	−	−	ND	ND	−	−
7	+	+	+	−	−	ND	ND	ND	−	−
8	+	+	+	−	+	ND	+	ND	ND	−
9	+	+	+	−	+	−	−	−	−	−

ND = not done.

Our results showed that the highest incidence of EHE was in the age 40 to 50 years range, female over male. The most common primary lesion was liver, and lung is the most common site suffering from tumor metastasis. When the patients with EHE did not initially appear to have metastasis, surgery treatment is recommended for them. However, the tumor does not respond to chemotherapy and/or radiotherapy, so the patients with metastasis have a low 3-year survival rate, and alive patients still need long-term follow-up in our study.

Some patients were asymptomatic, and physical abnormality was found only by a regular medical checkup. Moreover, the clinical manifestations of EHE are usually nonspecific including pain of the primary site, weakness, and weight loss. However, some studies found that some patients may present with liver failure, the Budd–Chiari syndrome, or portal hypertension.[8] Thus, the clinical development of EHE is variable and unpredictable.

EHE with low-to-intermediate grade progresses slowly, so laboratory parameters of most patients did not show any abnormality. Even if the patients had abnormal findings about liver function, tumor markers such as alpha fetoprotein, carcinoembryonic antigen, CA125, and so on were still normal. Therefore, specific markers of EHE in the serum still need to explore in the future.

The common radiological features are usually nonspecific, but CT scan is necessary to discover tumors early. Some results showed the following criteria in the liver: approximately 4 to 5 cm slow-growing tumor, often located in the periphery, without liver capsule invasion; peripheral enhancement, some nodules integrating into the group and no obvious marker of the portal vein and hepatic veins; and portal hypertension and calcifications.[9–11] Because EHE has the variable patterns similar with other lesions, the pathologist's awareness is an essential content of EHE diagnosis.[12] Approximately 60% of patients with EHE were initially misdiagnosed in China. The common misdiagnoses include metastatic carcinoma, angiosarcoma, hepatocellular carcinoma, and sclerosing hemangioma.[13] If several following criteria are present, EHE should be considered for differential diagnosis. These features include the infiltrative growth with preservation of the hepatic acinar zones; the vascular invasion such as portal vein branches; the identification of epithelioid and dendritic tumor cells; and immunohistochemical staining for epithelial differentiation markers, especially CD31, CD34, and ERG.

EHE is a very rare in Shaanxi. It is important to summarize its clinical, radiological, and pathological characters. In the present study, retrospective analysis is done by demographic data of clinical manifestations, laboratory parameters, CT imaging, histological, and immunohistochemical features in 9 cases in Shaanxi, helping for EHE early diagnosis and treatment, reducing misdiagnosis and improving life quality in Shaanxi.

Acknowledgments

The authors thank the technical support and materials from the Department of Pathology, the First Affiliated Hospital of Xi'an Jiaotong University. The authors also thank the programs from the National Natural Science Foundation of China (81270094 and 81500016), and the Young Innovators Awards of the First Affiliated Hospital of Xi'an Jiaotong University (2014YK3 and 2015YK6) for the support.

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