

Multiple cavernous hemangiomas of the lung and liver mimicking metastasis

A case report and literature review

Bo-wen Zhuang, MD^a, Wei Li, MD, PhD^a, Zhi-feng Chen, MD, PhD^b, Chuang-jie Cao, MD^c,
Xiao-yan Xie, MD, PhD^a, Xiao-hua Xie, MD, PhD^{a,*}

Abstract

Rationale: Cavernous hemangiomas are benign vascular malformations that usually involve the skin, subcutaneous tissue, and liver. Described herein was multiple masses in the lung and liver mimicking metastasis, which was proved to be cavernous hemangiomas histologically.

Patient concerns: A 78-year-old man with complaint of dizziness for 3 days was referred to the local hospital for medical attention.

Diagnoses: Multiple masses in the lung and liver was diagnosed pathologically as cavernous hemangioma.

Interventions: Because of the benign pathological characteristic and multiple distribution, no treatment except some symptomatic treatment for dizziness was administered.

Outcome: After more than 2 years of follow-up visits, the patient had no apparent symptoms and was healthy.

Lessons: Proper diagnosis of multiple cavernous hemangiomas is essential. The final diagnosis depends on the pathology results. The most appropriate management is follow-up. Surgical treatment is suitable for large or symptomatic lesions which can result in satisfactory prognoses.

Abbreviations: AFP = alpha-fetoprotein, CA = cancer antigen, CEA = carcinoembryonic antigen, CEUS = contrast-enhanced ultrasonography, HCHs = hepatic cavernous hemangiomas, PCHs = pulmonary cavernous hemangiomas, PET-CT = Positron emission tomography, SCCAg = squamous cell carcinoma antigen.

Keywords: contrast-enhanced ultrasonography, hemangiomatosis, hepatic cavernous hemangiomas, pulmonary cavernous hemangiomas, thoracoscopy

1. Introduction

Cavernous hemangiomas are benign diseases which are composed of large dilated vascular spaces lined by a single layer of endothelial cells and filled with blood.^[1] They frequently occur in various internal organs and the skin or subcutaneous tissues, but

they rarely occur in the lungs.^[2] According to a previous review of the international literature, only 10 cases of pulmonary cavernous hemangiomas (PCHs) were reported during the 60 years prior to 2010.^[3] Some literature reported cavernous hemangiomas not only occurring in the lung, but also appearing

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Written informed consent for publication of the case report was obtained from the patient.

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^a Department of Medical Ultrasonics, Institute of Diagnostic and Interventional Ultrasound, The First Affiliated Hospital of Sun Yat-Sen University, ^b Department of Nuclear Medicine, The First Affiliated Hospital of Sun Yat-Sen University, ^c Department of Pathology, The First Affiliated Hospital of Sun Yat-Sen University, No. 58 Zhongshan Road 2, Guangzhou, People's Republic of China.

* Correspondence: Xiao-hua Xie, Department of Medical Ultrasonics, Institute of Diagnostic and Interventional Ultrasound, The First Affiliated Hospital of Sun Yat-Sen University, No. 58 Zhongshan Road 2, Guangzhou 510080, People's Republic of China. (e-mail: 415610005@qq.com).

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in other organs of the body, such as the liver and pericardium.^[2,4,5] Severe bleeding caused by rupture of HCHs has been reported which leads to death.^[3] Therefore, it is important to identify reliable methods for the differential diagnosis of PCHs.^[3,6] Here, we describe rare multiple PCHs co-existing with HCHs and review cases reported worldwide in the literature for a better understanding of the clinical features of PCHs.

2. Case presentation

On December 12, 2014, a 78-year-old man with complaint of dizziness for 3 days was referred to the local hospital for medical attention. A brain MRI showed subcortical arteriosclerotic encephalopathy and cerebral atrophy. A chest X-ray displayed multiple nodules throughout both lung fields. The chest CT scan revealed multiple nodules throughout both lung fields. These nodules were mostly well circumscribed, ranging from a few millimeters to 1.5 cm in diameter. No prominent infiltration was observed at the periphery of the lesion (Fig. 1A). Abdominal CT revealed multiple low-density lesions up to 1.6 cm in diameter in the liver (Fig. 1B). On contrast-enhanced images, the tumors were hypo-enhanced in both arterial, and venous phases (Fig. 1C and D). The patient was treated with heteropathy to control blood pressure and improve circulation, and the symptom of dizziness was relieved 12 days later.

To identify the nature of the tumors in the lung and liver, the patient was admitted to our hospital on December 24, 2014. The patient had no family history, and the physical examination was normal. Tumor markers such as alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), cancer antigen (CA) 19-9, and squamous cell carcinoma antigen (SCCAg) were negative. Conventional ultrasound showed multiple high-echo nodules in the liver (Fig. 2A), and contrast-enhanced ultrasonography (CEUS) showed hypo-enhancement of the nodules compared with surrounding normal liver parenchyma throughout the arterial, portal venous and late phases (Fig. 2B and C). Positron emission tomography (PET-CT) was then performed on the patient. PET-CT showed that none of the pulmonary or hepatic neoplasms exhibited high uptake of fluorodeoxyglucose. Due to the atypical characteristic of the tumors, a thorascopic tumor biopsy was performed to identify the nature of the tumors. Multiple smooth, medium-hard, dark-red masses measuring 0.5 to 1.0 cm were identified in the apicoposterior and anterior segments of the lung (Fig. 3). A thorascopic surgical lung biopsy was performed on one of the tumors in the right middle lobe to reveal the lung masses. The ultrasound-guided percutaneous biopsy for liver lesions was later performed.

Microscopically, multiple irregular dilated vascular spaces lined by a single layer of endothelial cells were observed in the

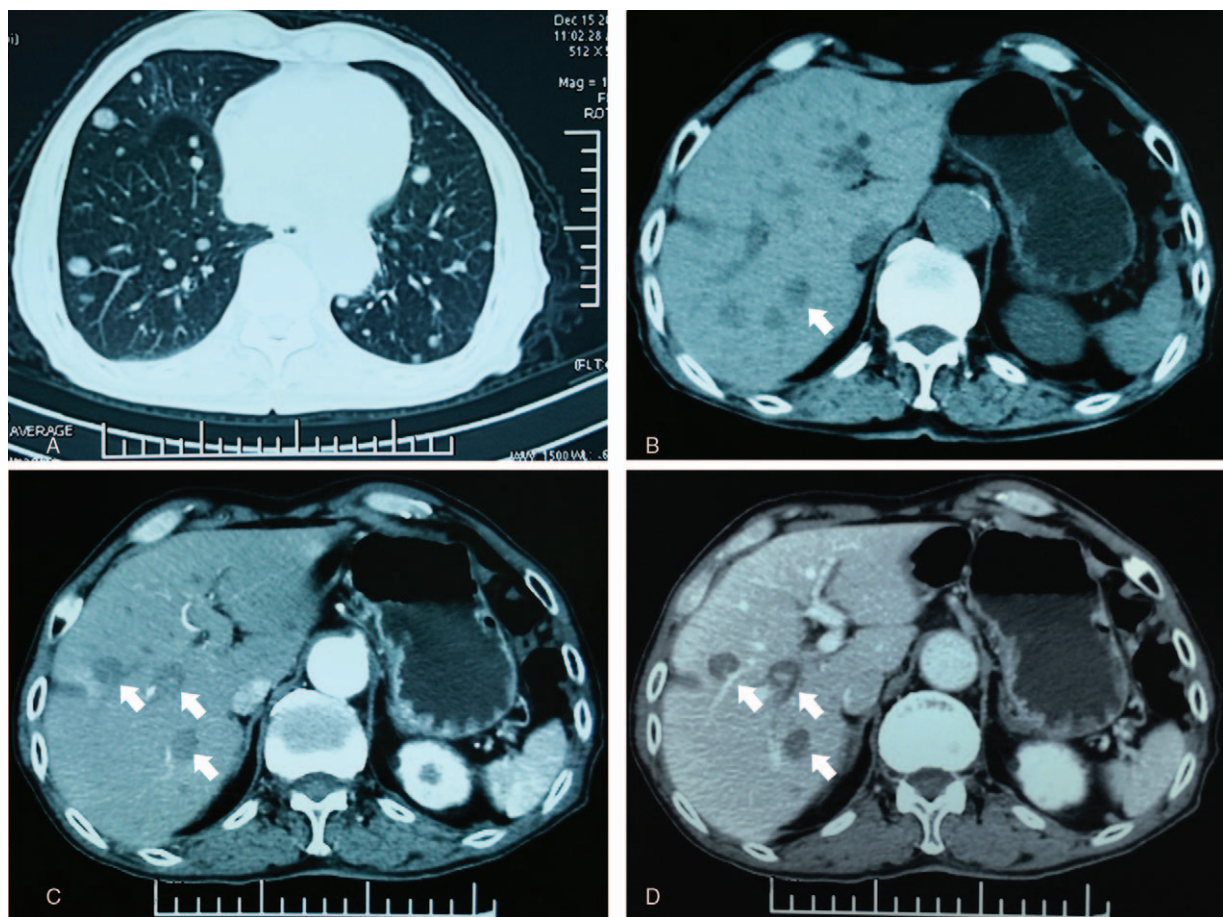


Figure 1. Chest and abdominal CT scan. Chest CT scan showed multiple nodules scattered in the bilateral lungs and right pneumothorax due to the thoracoscope. These lesions were well circumscribed, ranging from a few millimeters to 1.0 cm in diameter. They had a relatively uniform density and no calcified spots (Fig. 1A). The abdominal CT scan showed multiple hepatic low-density masses (arrows, Fig. 1B). Contrast-enhanced CT scan revealed that hepatic masses presented as hypo-enhanced in both the arterial and portal venous phases (Fig. 1C and D).

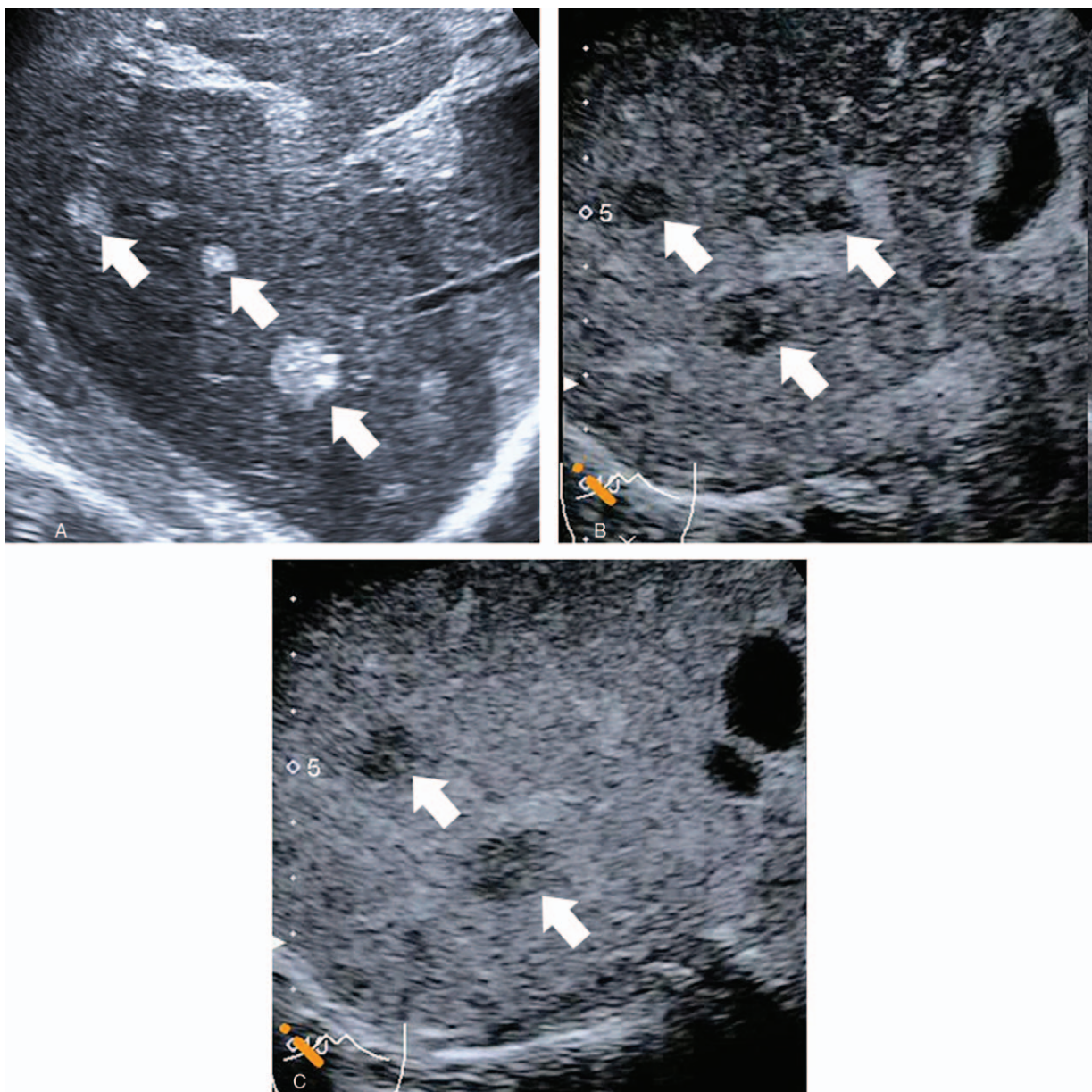


Figure 2. Conventional ultrasound examination exhibited multiple high-echo nodules in the liver (arrows, Fig. 2A). CEUS showed homogeneous hypo-enhancement during the arterial and venous phases (arrows, Fig. 2B and C).

liver biopsy tissue (Fig. 4A). Similarly, several nodules composed of large dilated vascular spaces, variably filled with blood, were scattered in the lung tissue (Fig. 4B). The spaces were each lined with a single layer of thin endothelial cells. Based on the observed histological features, the diagnoses of HCHs and PCHs were made.

Because of the benign pathological characteristic and multiple distribution, no treatment except for some symptomatic treatment for dizziness was administered. The patient was discharged on the ninth postoperative day without complications. After more than 2 years of follow-up visits, the patient had no apparent symptoms and was healthy.

3. Discussion

Cavernous hemangiomas can occur throughout the body. They can be superficial, deep, or visceral, and are predominantly found

in the skin. The most common internal organ in which cavernous hemangiomas occur is the liver, and they are mostly found there by chance. The etiology of cavernous hemangiomas is not completely understood, however, they are considered to be congenital vascular malformations, which may be due to genetic loss-of-function mutations.^[7] Pulmonary cavernous hemangioma is an extremely rare disease, and only 15 cases have been reported in the database of PubMed, Embase and Web of Science from 1996 to 2017 (Table 1). The age of PCH patients in the literature ranges widely between 7 and 84 years old. Cavernous hemangiomas affect both sexes equally. Most of patients are asymptomatic, but the most frequent and severe symptom related to PCHs is minor to massive hemoptysis. The main symptoms related to PCHs are hemoptysis (4 patients), dyspnea (3 patients), chest pain (2 patients), and pleural effusion (1 patient). Multiple nodular hemangiomas were seen in 9 cases (9/16, 56%).

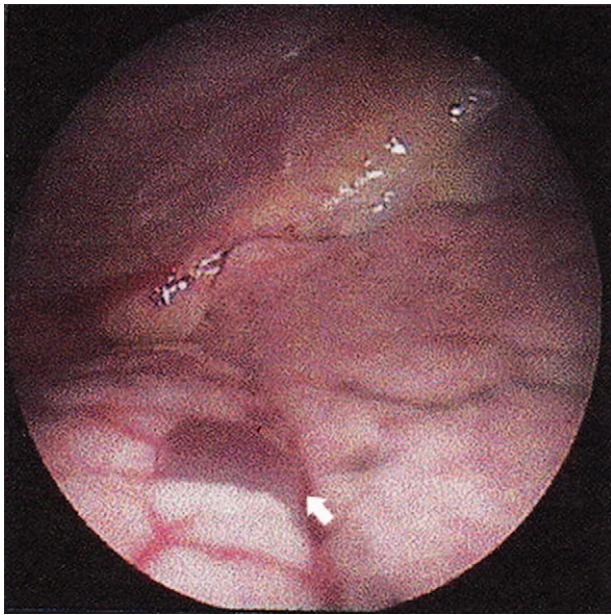


Figure 3. Thoracoscope showed a small dark-red nodule on surface of the lung (arrows).

Although the PCHs were benign in pathology, one case reported a 7-year-old boy with diffuse hemangiomatous tissue studded over the mediastinum, pleura, chest wall, and pericardium,^[8] with a manifestation of malignant biological behavior. Both pulmonary and hepatic cavernous hemangiomas are benign lesions, and their natural clinical course advances toward regression, therefore, it is essential to establish an accurate diagnosis and not to regard them as malignant neoplasms, which may lead to unnecessary treatment.

The diagnosis of HCHs is relatively easy; typical contrast-enhanced ultrasound (CEUS) and contrast enhancement CT (CECT) patterns of hepatic hemangiomas are observed as peripheral globular enhancement progressing toward the center of the nodule in the arterial and portal phases and on persistent enhancement in the late phase.^[19] However, in our case, the liver lesions had atypical CEUS and CECT features, which were

hypo-enhanced in both arterial and venous phases. We then performed a biopsy and histological examination. There are extremely rare cases reported in which HCHs with a CEUS feature are hypo-enhanced in 3 phases. The reasoning for hypo-enhancement of those uncommon cases of hemangiomas is not clearly understood. This probably occurred due to microbubble rupture caused by continuous ultrasound scanning that was not adequately compensated for due to very slow blood flow in the nodules.^[20,21] The other reason is probably because the lesions undergo thrombosis with scarring.^[22]

Despite the advances in imaging technologies, accurately diagnosing PCHs could be challenging because the clinical presentation and radiological appearances are nonspecific and cannot be distinguished with certainty from other malignant neoplastic processes. Radiologically, PCHs may largely mimic other granulomatous lesions (such as sarcoidosis and tuberculosis) or malignant lesions (such as metastatic tumors, lung cancer, and lymphoma). PCHs can display as single or multiple masses with non-specific radiological appearances. The nature of the tumors cannot be clearly diagnosed by preoperative diagnoses in many cases. All cases that have been reported in the literature were diagnosed by intraoperative or postoperative examination or at autopsy. Additionally, PET-CT scans may be valuable for identifying new primary lung cancer, loco-regional relapses, and distant metastatic foci from benign pulmonary disease. PET-CT was performed in our case and showed no high uptake of 18F-FDG as in the previous case,^[17] and this might resemble benign disease.

Despite the nonspecific radiological appearances, it can be concluded that various clinical features and imaging modalities may offer valuable clues for diagnosing PCHs in patients with the following characteristics:

- (1) clinically asymptomatic or symptoms of minor to massive hemoptysis;
- (2) normal serum tumor markers such as CEA, CA 19-9, SCCAg and AFP;
- (3) evidence of single or multiple mass-occupying pulmonary lesions on imaging, well circumscribed, no prominent infiltration was observed at the periphery of the lesion; and
- (4) low uptake of 18F-FDG on PET-CT scans. Radiological techniques provide complementary data on the differential diagnosis of hemangioma.

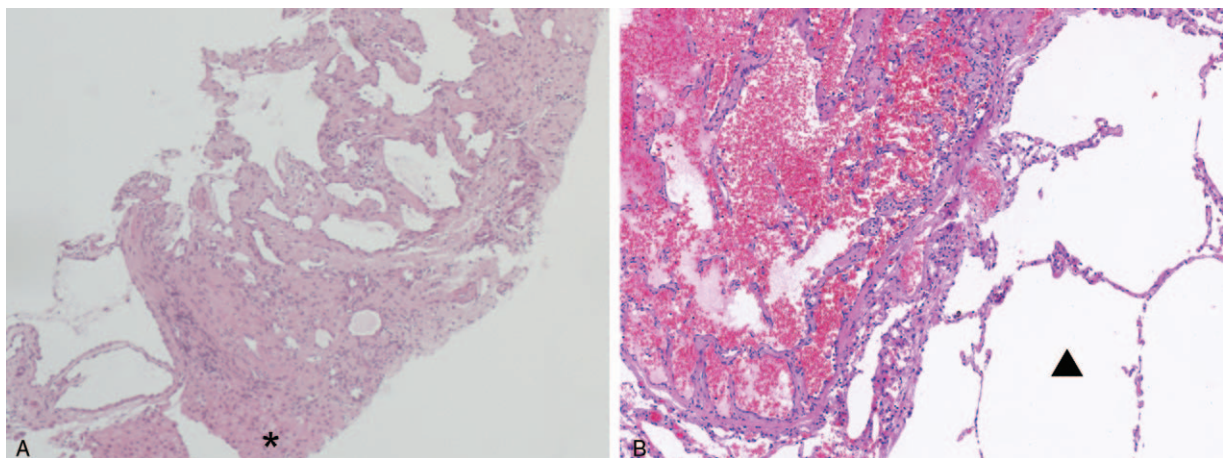


Figure 4. Micropathologic views. Hepatic mass (Fig. 4A) and pulmonary nodule (Fig. 4B) showing dilated, blood-filled vascular spaces with thin connective tissue stroma (hematoxylin-eosin, original magnification, 10 \times).

Table 1**Review of case reports detailing pulmonary cavernous hemangiomas over the past 20 years.**

Authors	Gender/ Age (yr)	Chief clinical symptoms	Pulmonary lesions number	Extra-pulmonary lesions	Treatment and outcome
Wu et al ^[8]	M/7	Chest pain, hemoptysis and dyspnea	Multiple	Mediastinum, left pleura, chest wall, and pericardium, thymus	Interferon alfa-2a injection and the tumor gradually resolved at the 2-year follow-up
Ienaga et al ^[9]	M/45	Asymptomatic	Single	Not provided	Thoracoscopic surgery
Kase et al ^[10]	F/29	Asymptomatic	Single	Not provided	Thoracoscopic surgery
Kobayashi et al ^[5]	F/15	Asymptomatic	Multiple	Liver	No remarkable progression under observation for more than 2 years
Sirmali et al ^[6]	M/54	Massive hemoptysis	Single	Not provided	Lobectomy
Fine et al ^[11]	M/84	Repeated falls unrelated to PCHs	Multiple	Not provided	Dead due to cardiovascular disease
Maeda et al ^[12]	M/54	Asymptomatic	Single	Not provided	Thoracotomy
Basile et al ^[13]	M/73	Haemoptysis and dyspnoea	Single	Not provided	Lobectomy
Ishikawa et al ^[3]	F/73	Coughing and spitting blood	Single	Not provided	Dead due to massive blood aspiration.
Lovrenski et al ^[14]	M/67	Pneumonia	Single	Not provided	Thoracotomy
Matsubara et al ^[4]	F/29	Vaginal hemorrhage unrelated to PCHs	Multiple	Liver	Follow-up
Chen et al ^[15]	F/19	Dyspnea and fatigue	Multiple	Not provided	Thoracoscopic Biopsy and follow-up with no apparent symptoms
Yang et al ^[2]	M/36	Pleural effusion	Multiple	Pericardium	Dead because of heart and respiratory failure 2 months later
Jia et al ^[16]	F/54	Intermittent cough and sputum	Single	Not provided	Thoracotomy
Miyamoto et al ^[17]	M/61	Asymptomatic	Multiple	Not provided	Follow-up
Wang et al ^[18]	F/35	Chest pain	Multiple	Liver and pericardium	Liver transplant for hepatic hemangioma and surgically removed for cardiac hemangioma
Our case	M/78	Dizziness unrelated to PCHs	Multiple	Liver	Follow-up

However, when radiological findings are inconclusive, performing a biopsy and/or surgical resection is essential for making a definite diagnosis.

The management of PCHs remains a topic of dispute. The most effective treatment for a solitary PCH is considered to be surgical resection. If a tumor is diagnosed as PCH during operation, wedge resection or enucleation is feasible because of its benign behavior. Recurrences after complete surgical resection have not been reported thus far, but for multiple lesions, complete resection is not realistic. Interferon alfa has been reported to be effective in treating intractable life-threatening angiomatous disease. Wu et al^[8] successfully treated PCHs with interferon alfa-2 α , however, this method had not been widely used. Due to the characteristics of benign lesions, it is a good choice to follow-up closely in cases with asymptomatic, stable, small lesions. In our case, the patient's symptoms were not related to PCHs and HCHs, and we did not perform a surgery or other treatments. Cavernous hemangiomas of the lungs and liver have made no remarkable progression under observation for more than 2 years. However, there is a possibility that the lesions will enlarge and become symptomatic. Therefore, the clinical course should be carefully followed up.

In conclusion, diagnosis of HCHs can be so difficult when imaging findings are atypical. Accurately diagnosing PCHs can be challenging because the clinical presentation and radiological appearances are nonspecific and cannot be certainly distinguished from malignant neoplastic processes. The consensus regarding management includes conservative treatment unless surgical resection is needed. Histopathological analysis of the lung lesion will yield a definitive diagnosis.

Author contributions

ZBW collected the data and references, followed up the patient, performed the literature review, and drafted the manuscript. LW and XXH critically revised the manuscript and assisted in the literature review. CZF and CCJ contributed to the acquisition, analysis, and interpretation of data. All authors have read and approved the final manuscript.

Data curation: Bo-wen Zhuang.

Funding acquisition: Wei Li.

Methodology: Wei Li.

Project administration: Xiao-yan Xie, Xiao-hua Xie.

Resources: Zhi-feng Chen, Chuang-jie Cao.

Writing – original draft: Bo-wen Zhuang, Wei Li.

Writing – review & editing: Bo-wen Zhuang, Wei Li.

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