Case Report

An acute progressing hepatic angiosarcoma in a young male diagnosed by contrast-enhanced ultrasound-guided liver needle biopsy: a case report

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Background: Primary hepatic angiosarcoma (PHA) is a rare hepatic malignancy primarily observed in the elderly. It carries a poor prognosis as a result of the characteristics of rapid progression, high aggressiveness, and resistance to traditional chemo- and radiotherapies. Its nonspecific clinical manifestations, along with the lack of laboratory features and various imaging findings, make it hard to recognize in clinic, especially among non-high-risk populations. Hence, pathological diagnosis is essential to establish an accurate diagnosis.

Case Description: In the present report, a young male presented with right upper quadrant abdominal pain and hemoperitoneum was eventually diagnosed as hepatic angiosarcoma based on the immunohistochemical staining results of a liver needle biopsy. Contrast-enhanced ultrasound (CEUS) effectively improved the accuracy of the liver needle biopsy in this case. This report describes the epidemiology, presentation, laboratory tests, imaging findings, and pathological features of a rare hepatic angiosarcoma seen in this young male. The patient rapidly developed severe abdominal hemorrhage. Transcatheter hepatic artery embolization, blood transfusions, and symptomatic treatments were administered. The family members abandoned treatment because the patient was in critical condition and could not receive antitumor therapy.

Conclusions: This case emphasizes the significance of pathological findings in the diagnosis of PHA especially in non-high-risk individuals, and the supportive role of CEUS in guiding the liver needle biopsy. Abdominal hemorrhage is one of the serious complications of PHA and transarterial embolization (TAE) should be considered for controlling life-threatening bleeding from ruptured tumor. Further investigation is required to early diagnosis and to improve the prognosis of patients with PHA.

Keywords: Contrast-enhanced ultrasound (CEUS); hepatic angiosarcoma; liver cancer; liver needle biopsy; case report

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Introduction

Primary hepatic angiosarcoma (PHA) is a rare malignancy originating from the hepatic vasculature with a poor prognosis, usually occurs in the elderly in their 60s (1,2). Most patients with PHA have no identifiable etiologic factors. In a small number of patients with clear etiology, the onset is thought to be related to exposure to environmental chemicals such as porphyrins, arsenic, and vinyl chloride (3). In patients with PHA, characteristic symptoms and laboratory findings are absent and/or nonspecific (3-5). The radiographic manifestations of PHA are complex (3,6). As a result, PHA is hard to diagnose clinically. Pathology results are needed to confirm the diagnosis. This report describes a rare case in a young male who was eventually diagnosed with PHA based on the biopsy results obtained from the guided of contrast-enhanced ultrasound (CEUS). This case emphasizes the challenge of the diagnosis and treatment of PHA. This case also highlights the potential of CEUS in assisting with the diagnosis by obtaining tumor pathology through liver needle biopsy in the complex condition of PHA. We present this case in accordance with the CARE reporting checklist (available at https://tgh.amegroups.com/article/view/10.21037/tgh-24-19/rc).

Highlight box

Key findings

- This report describes the epidemiology, presentation, laboratory tests, imaging findings, and pathological features of a rare hepatic angiosarcoma seen in a young male. This report also demonstrates the potential of using contrast-enhanced ultrasound (CEUS) guidance to improve the accuracy of liver needle biopsy and, consequently, assist in the diagnosis of hepatic angiosarcoma.

What is known and what is new?

- Primary hepatic angiosarcoma (PHA) is a rare hepatic malignancy mostly observed in elderly men. Its clinical symptoms are nonspecific, and diagnosis relies on pathology.
- The potential for PHA should be considered in non-high-risk populations. When facing the complexity of coexisting necrosis and hemorrhage in hepatic angiosarcoma tumors, CEUS can serve as an additional tool and assist in obtaining parenchymal pathology of the tumor through liver needle biopsy.

What is the implication, and what should change now?

- This report helps to raise awareness of rare cases of PHA occurring in young individuals. When conducting a liver needle biopsy to obtain pathology for diagnosing PHA, the use of CEUS guidance may be considered to enhance the accuracy.

Case presentation

An 18-year-old man who presented with chief complaints of right upper quadrant abdominal pain for 6 days was admitted to the Department of Gastroenterology of the Fifth Affiliated Hospital of Sun Yat-sen University in September 2022 (*Figure 1*). The patient experienced sudden intermittent right upper quadrant abdominal pain without obvious induction from 6 days ago and fever from 1 day ago. Ultrasound (US) at the local hospital revealed multiple solid-cystic space-occupying lesions in the liver.

The patient had no significant past medical history, and denied any relevant personal or family history except that his father tested positive for hepatitis B surface antigen, hepatitis B e-antibody, and hepatitis B core antibody test. Exposure to any of the known inciting agents of PHA was also denied.

Physical examination revealed abdominal distension, tenderness in the right upper quadrant of the abdomen, and shifting dullness.

Laboratory test results were suggestive of hepatic dysfunction, mild anemia, thrombocytopenia, and coagulation disorders: hemoglobin 11.0 g/dL, platelet count (PLT) 77×10^9/L, alanine aminotransferase 99.5 U/L, aspartate transaminase 61.2 U/L, total bilirubin 33.8 μmol/L, direct bilirubin 14.2 μmol/L, total bile acid 10.72 μmol/L, gamma-glutamyl transpeptidase 181 U/L, alkaline phosphatase 241 U/L, lactate dehydrogenase 545 U/L, prothrombin time 13.1 s, fibrinogen 1.39 g/L, D-dimer 175.72 μg/mL, carbohydrate antigen 19-9 (CA19-9) 52.00 U/mL, neuron-specific enolase 25.10 ng/mL, ferritin 725.00 ng/mL, and C-reactive protein 22.98 mg/dL. Procalcitonin and erythrocyte sedimentation rates were normal. Serology for hepatitis A, B, C, D, and E tested negative. The patient was positive for Clonorchis sinensis immunoglobulin G antibody, but no eggs were found in the feces. Immunoglobulin G4 2,691.0 mg/L, complement C3 1.75 g/L. There is no other significant finding in a series of tests in pathogen detection, biochemical test, and rheumatic diseases.

Peripheral blood smear and bone marrow puncture revealed a reduction in PLT, and that schistocyte account for approximately 1% of red blood cells. Contrast-enhanced computed tomography (CECT) and magnetic resonance imaging (MRI) revealed multiple nodules in the liver, considered to be malignant tumors with hemorrhage and cystic changes (*Figures 2,3*). Lesions within the right branch of the portal vein, spleen, and both lungs were considered

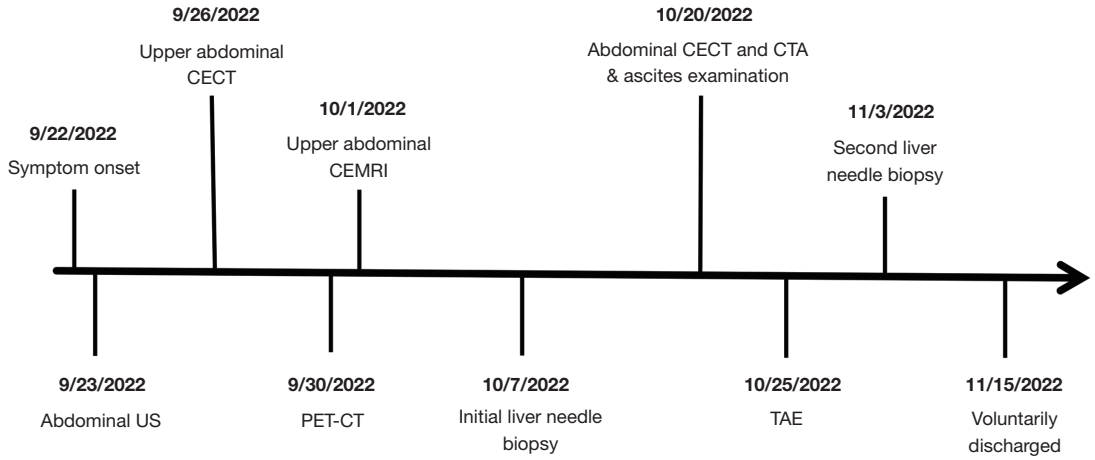

Figure 1 Timeline of the events. US, ultrasound; CECT, contrast-enhanced computed tomography; PET-CT, positron emission tomography-computed tomography; CEMRI, contrast-enhanced magnetic resonance imaging; CTA, computer tomography angiography; TAE, transarterial embolization.

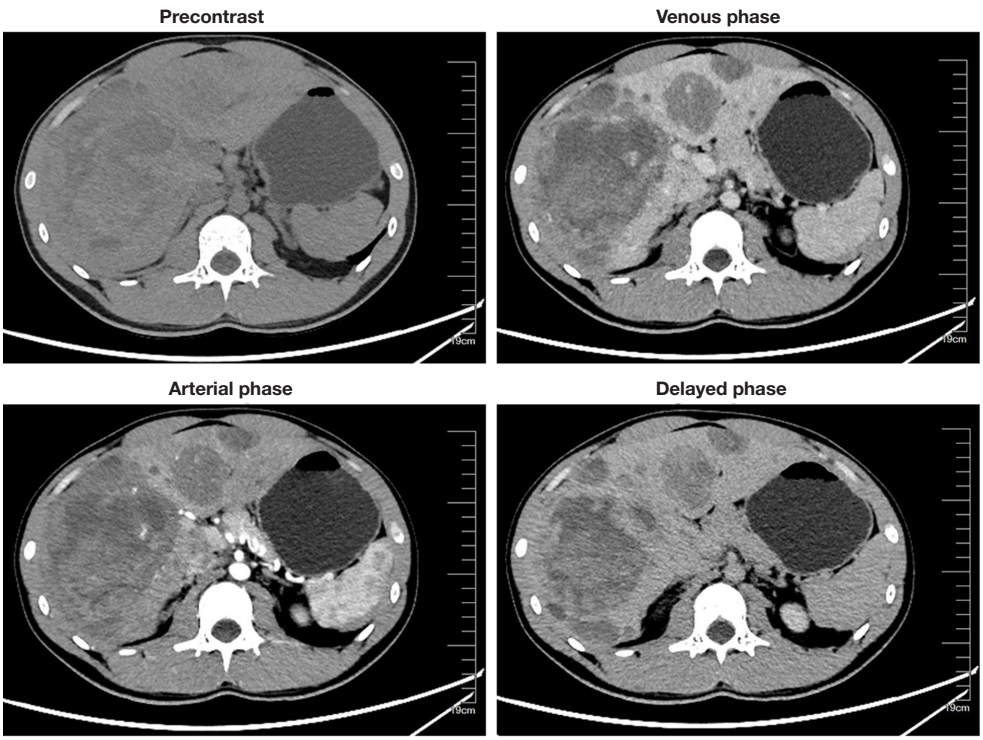

Figure 2 CECT scan of the upper abdomen. CECT, contrast-enhanced computed tomography.

metastasized. Positron emission tomography-computed tomography (PET-CT) showed most of the nodules were hemorrhagic, necrotic, and decreased uptake of ^{18}F-fluorodeoxyglucose (^{18}F-FDG), while the rest of nodules were hypermetabolic. Hemoperitoneum was also seen.

Based on these findings, the lesions were strongly suspected to be malignant tumors. Therefore, the patient underwent liver needle biopsy. No clear evidence of malignancy was found in the liver tissue examined and no pathogens were detected by the next-generation sequencing

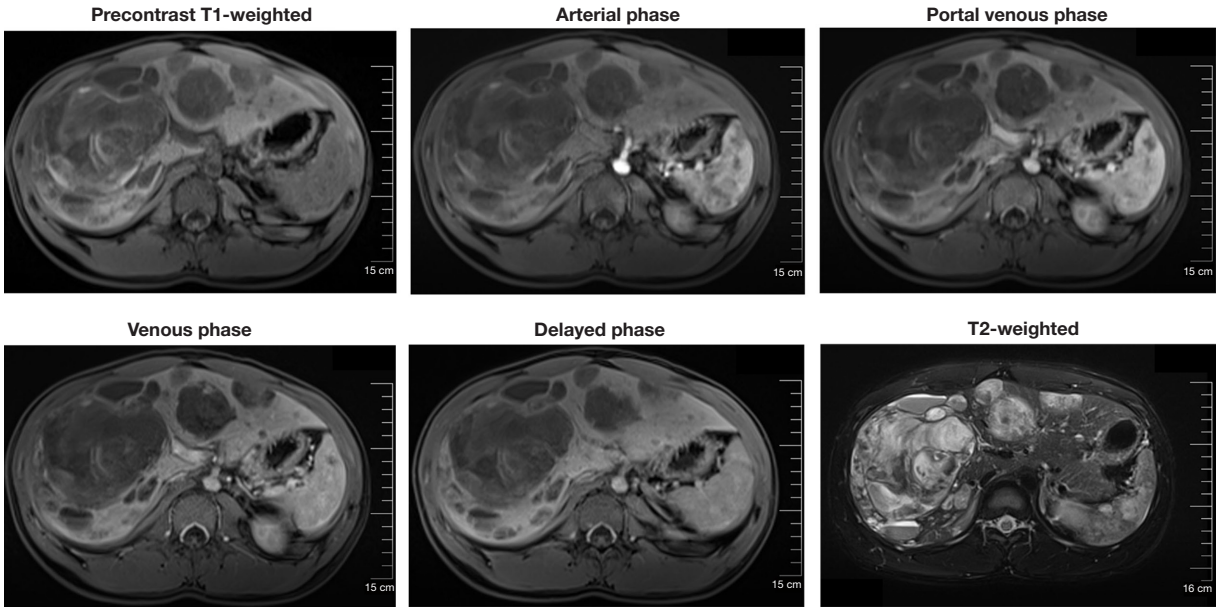

Figure 3 Contrast-enhanced MRI scan of the upper abdomen. MRI, magnetic resonance imaging.

method.

As the diagnosis was not definitive, the patient received symptomatic treatments including protecting the liver, lowering the body temperature, and blood transfusions. Empirical antibiotic therapy was also initiated after multidisciplinary consultation because infection by specific pathogens could not be completely excluded. The patient's hepatic function had improved but the hemoglobin and PLT kept decreasing and empiric antibiotic regimens failed to control the body temperature.

Therefore, the patient was admitted to Sun Yat-sen Memorial Hospital of Sun Yat-sen University for further diagnosis and treatment. The patient underwent CECT and computer tomography angiography, which revealed multiple masses of variable size in the liver, lung, spleen, kidney, and bone, showing mixed density on computed tomography (CT) scanning. On enhanced scanning, there were strips of enhancement at the edges of the masses in the liver, with persistent increase in the venous phase and delayed phase. The masses were strongly suspected as angiogenic malignant tumors with systemic metastasis to lung, spleen, kidney, and bone. The levels of CA19-9 (54.5 U/mL; normal range, ≤34 U/mL), carbohydrate antigen 125 (CA125) (102.0 U/mL; normal range, ≤35 U/mL), lactate dehydrogenase (936 U/L; normal range, 108–252 U/L), and creatine kinase (223 U/L; normal range, 26–174 U/L) were elevated. Natural killer cell activity assay and lymphocyte subgroups analysis were normal. Echocardiography disclosed mild mitral and tricuspid regurgitation, and the ejection fraction of the left ventricular was within normal range.

After being admitted to the Department of Gastroenterology, the patient continued receiving symptomatic treatments. Gradually, blood transfusions could hardly alleviate anemia. The patient then underwent transcatheter hepatic artery embolization for hemostasis, but with limited success (Figure S1).

Abdominocentesis was performed several times to ease the patient's bloating. The ascites was bloody, and no cancer cell was found in the fluid sample. Since the results of the examinations above could not exclude the possibility of angiogenic malignant tumors, a second liver needle biopsy guided by CEUS was performed. CEUS showed necrosis in the center of most of the lesions without enhancement. In order to obtain liver tissue that was still viable, enhanced areas at the portal stage such as the edge of the lesions in the left lobe of the liver were selected for biopsy (*Figure 4*).

Three liver biopsy samples were obtained, fixed in a 10% formalin solution, embedded in paraffin, and sliced into 4 μm thickness. Sections were stained with hematoxylin and eosin for histopathological examination. Sections for immunohistochemistry were staining with CD20 (clone L26; Ventana Medical Systems, Tucson, AZ, USA; dilution 1:150), CD30 (OTI1C6; ZSGB-BIO, Beijing, China; dilution 1:150), PAX5 (OTI3A7;

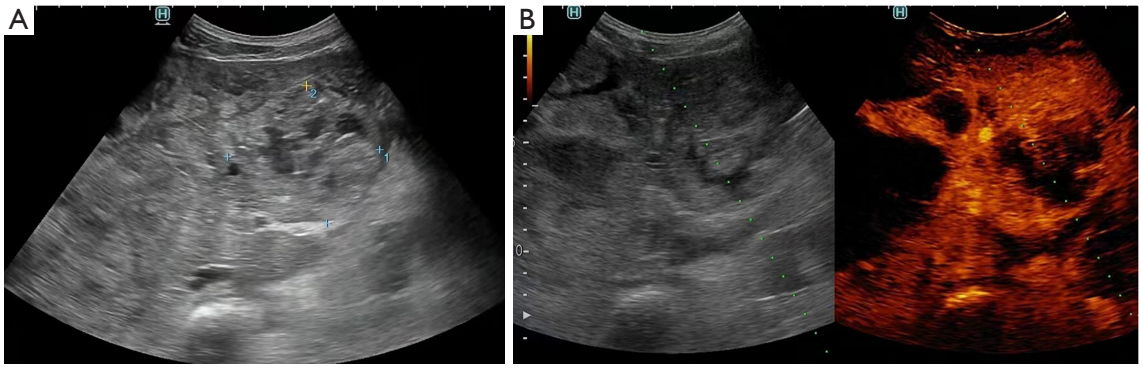

Figure 4 CEUS-guided liver needle biopsy images. (A) Routine US showed a slightly hyperechoic, roughly round lesion in the liver, with a patchy anechoic area in the center. (B) CEUS-guided liver needle biopsy images. CEUS, contrast-enhanced ultrasound; US, ultrasound.

ZSGB-BIO; dilution 1:150), and CD15 (MMA; Maixin Biotech., Fuzhou, China; dilution 1:150) using the EnVision method. The liver biopsy of the patient showed that some hepatic sinusoidal cells were enlarged and exhibited obvious atypia. Immunohistochemistry demonstrated the tumor cells to be positive for CD31, CD34, ERG, P53, Ki67 (positive rate of 70%), INI-1 (SMARCB1), BRG1 (SMARCA4), and CD99 (*Figure 5*). Staining negative for LEF-1, LCA, CK, and SALL4. These findings were consistent with the diagnosis of hepatic angiosarcoma. A final diagnosis of PHA was established based on the needle biopsy and immunohistochemical staining results. However, the patient was in a critical condition and not suitable for chemotherapy, radiotherapy, and surgery. Finally, the family members gave up treatment and voluntarily discharged from the hospital.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Although PHA is the most common primary malignant mesenchymal tumor of the liver in adults, it accounts for only 2% of all primary hepatic malignancies, frequently observed in the elderly in their 60s (1,2). The ratio of male to female patients is approximately 3–4:1 (1). PHA is more common in the white population compared to other racial groups (7). It is rapidly progressing, highly invasive and resist to traditional chemo- and radiotherapies (2,8). Thus, patients with PHA show poor long-term survival that most of them have dead within 6 months of liver failure or hemorrhage after diagnosis (1,2,9).

The clinical manifestations of PHA are not typical, such as abdominal pain, fatigue, weight loss, fever, hepatomegaly, ascites, and jaundice (3-5). Some patients may present with symptoms of hemoperitoneum as a result of tumor rupture, as in the present case, which may be life-threatening. Most patients have metastatic lesions at the time of presentation. Metastatic spread occurs usually in the lung, followed by the spleen (6).

The absence of specific tumor markers compounds the diagnostic difficulty. The levels of alpha-fetoprotein, CA199, or CA125 were mostly within the normal range. However, in this case, mild elevation was observed in the levels of CA199 and CA125. In some cases, patients were concomitant with anemia and thrombocytopenia (6,10).

Imaging can provide clues to the initial diagnosis of PHA. The radiographic appearances of PHA can be various, typically manifesting as aggressive multifocal tumors and lack of vascular invasion. Growth patterns of multiple cystic or solid masses, a dominant mass, or a mixed pattern of them have been reported. Compared with the normal hepatic parenchyma, lesions commonly appear as heterogeneous hypoattenuating on unenhanced and CECT images, but some can be with enhanced foci on CECT, showing irregularity, central enhancement or ring enhancement. Features of hemorrhage, heterogeneity, and hypervascularity of the lesions can be seen on MRI findings. Dynamic enhancement at CT or MRI imaging can show a delayed progressive enhancement pattern.

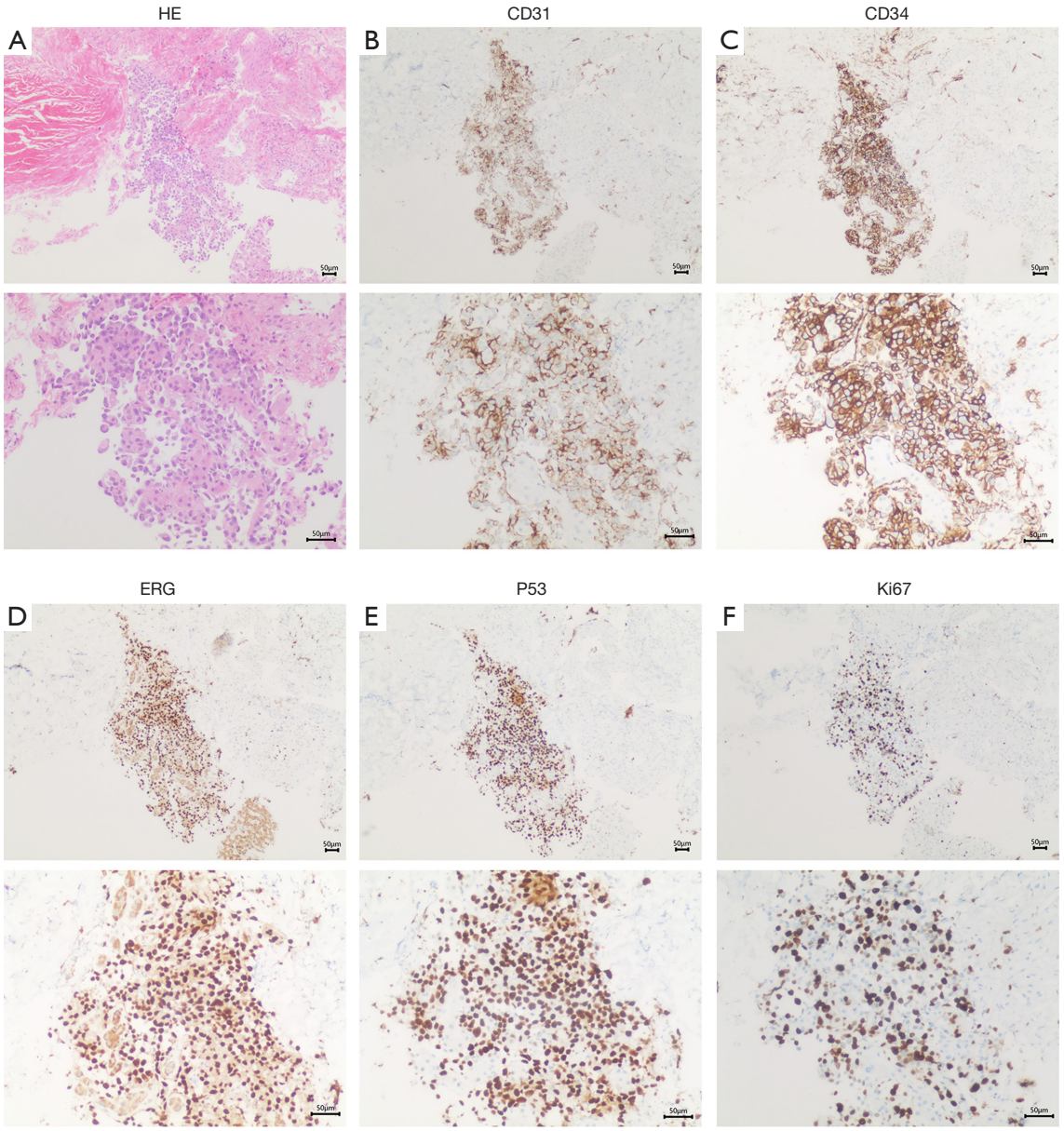

Figure 5 Results of liver biopsy of the patient. (A) HE staining (×40 and ×100) of the liver tissue showed that part of the cells in blood sinuses were enlarged and markedly heterogeneous. Scale bars: 50 μm. (B-F) Immunohistochemical staining (×40 and ×100) of the liver tissue indicated that the cells were positive for CD31, CD34, ERG, P53, Ki67 (positive rate of 70%). Scale bars: 50 μm. HE, hematoxylin and eosin.

Necrosis and hemorrhage, commonly appear in PHA, complicate the imaging findings (3,6,11,12). Both increased or similar uptake of ^{18}F-FDG compared to the normal liver parenchyma on PET-CT images have been reported (13,14). In our case, CT and MRI findings indicated aggressive multifocal tumor with hemorrhage and cystic change. The enhanced CT images demonstrated circular enhancement at the edges of the lesions and progressive enhancement in the portal venous and delayed phases. The PET-CT result suggested the lesions to be hypermetabolic. Under CEUS, the specific characteristics of a central unenhanced area and peripheral irregular enhancement in the arterial and portal phases, as well as complete late-phase wash-out, provide potential clues for PHA diagnosis (11). CEUS is reported

to be of great help in distinguishing lesions from necrotic and hemorrhagic areas because inactive tissues do not show enhancement, so as to reduce false-negative results from biopsy (15).

It is not rare for PHA to be misdiagnosed as other liver diseases due to its rarity and nonspecific clinical and radiologic presentation. Previous case reports have reported that PHA can show centripetal or centrifugal enhancement similar to hepatic peliosis or cavernous hemangioma, but the enhancement pattern of PHA tends to be more bizarre and disordered than these benign hemangiomas (16-18). The lack of wash out and vascular invasion in PHA distinguishes it from hepatocellular carcinoma, but it is difficult to differentiate single PHA nodule from atypical hepatocellular carcinoma nodules (18,19). In the few cases showing only hypovascular hepatic masses or nodules, PHA needs to be differentiated from hypervascular metastatic disease (18).

An accurate diagnosis depends on pathology results. Histologically, the diagnosis of PHA can be made if clear areas of vascular formation are seen in tumors (20). PHA typically consists of highly heterogeneous and deeply stained nuclear tumor endothelial cells that grow in the hepatic sinusoids. In immunohistochemistry, the expression of vimentin and vascular lineage markers such as ERG, CD34, CD31, factor VIII-related antigen (FVIIIRAg) have been hypothesized to serve as diagnostic markers of angiosarcoma (11,21,22).

Due to the absence of an obvious trigger, the rare incidence of PHA in young people and the lack of typical symptoms and specific tumor markers, it is difficult to recognize young patients with PHA. Although liver needle biopsy is the primary means of obtaining pathologic results to confirm the diagnosis, necrosis and hemorrhage may increase the difficulty of obtaining the focal tissue and interfere with the pathological results. CEUS has advantages in displaying necrosis of PHA and guiding biopsy, and therefore has enormous clinical significance in diagnosing PHA. Although this patient eventually obtained an accurate diagnosis of PHA with CEUS-guided liver biopsy, the first needle biopsy still delayed diagnosis and treatment, resulting in missed opportunities for early treatment.

There are no formal treatment guidelines for PHA yet. Radical resection of the tumor or hepatic resection is the main treatment for PHA, supplemented by radiotherapy and chemotherapy. In multiple retrospective analyses, patients who underwent treatment had a longer median survival compared to those who did not. Among the treatments available, surgery affords the best survival outcomes, with radical resection being the preferred option. However, a high incidence of serious surgical complications, such as intraperitoneal hemorrhage, or the occurrence of postoperative recurrence, still makes PHA a poor prognosis. The results of the retrospective study conducted by Martínez *et al.* suggest that the median survival of surgically resected patients was 8 months, which was significantly longer than the median survival of 2 months for non-operated patients. In the research cohort of Wilson *et al.*, the median overall survival of surgical resection could reach up to 33.4 months (3,7,23). Liver transplantation is not recommended due to the high recurrence rate (2,15). PHA exhibited resistance to radiotherapy treatments (7). Patients with PHA who received systemic chemotherapy had a longer survival time and a lower risk of death compared to those who did not receive any chemotherapy, especially in the metastatic stage. More cases of PHA are still needed to explore whether there are long-term benefits of chemotherapy treatment (2,7). Nonetheless, these treatments had a very limited effect on prolongation of survival. This suggests that the current treatment, either resection or chemotherapy, is not effective (24).

In this case, the patient presented with abdominal hemorrhage in the preliminary imaging examinations before the first liver needle biopsy and rapidly worsened. This indicated that the tumor had progressed to a critical stage of spontaneous rupture and hemorrhage shortly after the patient's symptoms onset. The patient had to be treated with blood transfusion. In cases of PHA presenting with spontaneous rupture and life-threatening intra-abdominal hemorrhage, transarterial embolization (TAE) is the first choice to control bleeding and save a life, providing an opportunity for subsequent surgical treatment. However, ruptured tumors with TAE still have a high risk of recurrent bleeding, leading to elevated mortality rates (1,25). Transcatheter arterial chemoembolization, as a means of embolizing arteries and implementing local chemotherapy, is effective in emergency control of tumor rupture and bleeding, and also has the potential to control tumor growth and metastasis. Immunotherapy provides new research directions for the treatment of patients with PHA. Recently, monoclonal antibodies targeting the programmed death 1 receptor and its ligand have been considered effective in the treatment of various types of cancer. The use of tyrosine kinase inhibitors, including sorafenib and anlotinib, has been reported for treating angiosarcoma. The

same as bevacizumab, a monoclonal antibody for vascular endothelial growth factor A (VEGFA), as the overexpression of vascular endothelial growth factor (VEGF) is considered the most important angiogenic factor in angiosarcoma. A few cases applying the aforementioned immunotherapy or combined transcatheter arterial chemoembolization have emerged and have shown therapeutic promise (26,27). Due to the difficulty in treating PHA and the presence of multiple severe comorbidities, such as infections, impaired liver function, and peritoneal effusions, a multidisciplinary treatment can ultimately improve the patient's prognosis.

Conclusions

In conclusion, PHA is hard to distinguish. Imaging tests can help with the initial diagnosis of PHA. The final diagnosis of PHA requires pathological results. CEUS guidance helps improve the accuracy of liver needle biopsy. Surgical resection is the cornerstone of treatment, but complications can make surgery difficult. TAE should be considered for controlling life-threatening bleeding in hepatic angiosarcoma when tumor rupture and hemoperitoneum occur, although there is a risk of re-bleeding. To improve the poor prognosis of PHA, new methods for early diagnosis and standardized treatments are urgently needed.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tgh.amegroups.com/article/view/10.21037/tgh-24-19/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tgh.amegroups.com/article/view/10.21037/tgh-24-19/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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