**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 72143

**Manuscript Type:** CASE REPORT

**Hepatic epithelioid hemangioendothelioma after thirteen years’ follow-up: A case report and review of literature**

Mo WF *et al*.Long-term follow-up of hepatic epithelioid hemangioendothelioma

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**Author contributions:** Mo WF collected the data and wrote the manuscript; Tong YL designed the report; all authors have read and approve the final manuscript.

**Supported by** Zhejiang Medical and Health Science and Technology Project, No. 2021429795; and Scientific Research Project of Zhejiang Education Department, No. Y202043306.

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**Received:** November 25, 2021

**Revised:** January 24, 2022

**Accepted:** April 22, 2022

**Published online:**

**Abstract**

BACKGROUND

Hepatic epithelioid hemangioendothelioma (EHE) is a rare vascular endothelial cell tumor of the liver, consisting of epithelioid and histiocyte-like vascular endothelial cells in mucus or a fibrotic matrix. Immunohistochemistry is usually positive for vascular markers, such as factor VIII-related antigen, CD31, and CD34. Hepatic EHE can have a varied clinical course; treatment includes liver transplantation, liver resection, chemotherapy, and radiation therapy.

CASE SUMMARY

A 46-year-old woman with abdominal discomfort and elevated serum carcinoembryonic antigen was found to have multiple low-density lesions in the liver and lung on computed tomography (CT) evaluation. An ultrasound-guided fine needle aspiration biopsy revealed a fibrous stroma with dendritic cells, containing intracellular vacuoles. Immunohistochemical staining found that the tumor cells were positive for CD34, CD31, and factor VIII-related antigen. The patient received four courses of combined chemotherapy and was followed-up for 13 years, at which time the patient was in stable condition without disease progression and a confined neoplasm, as evidenced by CT scans.

CONCLUSION

The histology and immunohistochemical characteristics of hepatic EHE are well described. Chemotherapy may be effective in patients with extrahepatic lesions.

**Key Words:** Epithelioid hemangioendothelioma; Liver neoplasm; Immunohistochemistry; Antineoplastic combined chemotherapy protocols; Treatment; Case report

Mo WF, Tong YL. Hepatic epithelioid hemangioendothelioma after thirteen years’ follow-up: A case report and review of literature. *World J Clin Cases* 2022; In press

**Core Tip:** The gold standard diagnosis for hepatic epithelioid hemangioendothelioma includes epithelioid and histiocyte-like vascular endothelial cells in mucus or a fibrotic matrix, and positive vascular markers. Chemotherapy may be an effective treatment; close follow-up is necessary.

**INTRODUCTION**

Hepatic epithelioid hemangioendothelioma (EHE) is a rare malignant tumor of vascular origin, with an incidence of 0.1-0.2/100000[1,2]. Oral contraceptives, polyvinyl chloride, asbestos, thorotrast contrast medium, hepatic trauma, and viral hepatitis have been identified as risk factors for subsequent development of disease[3]. While laboratory findings always reveal abnormal liver function, tumor markers are always at normal levels. The patient described in this case report had a history of hepatitis A and normal liver function, but with a mildly elevated tumor marker [carcinoembryonic antigen (CEA) at 6.9 ng/mL]. The patient received four courses of chemotherapy and was found to remain in stable condition after 13 years of follow-up.

**CASE PRESENTATION**

***Chief complaints***

A 46-year-old woman with no significant past medical history presented at the hospital with a 1-mo history of epigastric discomfort and asthenia.

***History of present illness***

The patient had no other symptoms.

***History of past illness***

The patient had a history of acute hepatitis that had resolved without complications 20 years previously.

***Personal and family history***

The patient had no personal or family history of other diseases.

***Physical examination***

Physical examination revealed no remarkable findings.

***Laboratory examinations***

Laboratory testing on admission showed no abnormalities in markers of inflammation or abnormal liver function, or in peripheral blood panel or biochemical tests. Hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb) and hepatitis C virus antibody (HCVAb) were negative. Tumor markers were in the normal ranges, except for a mildly elevated CEA (6.9 ng/mL; normal range: 0-5.0 ng/mL).

***Imaging examinations***

Abdominal ultrasound revealed multiple irregular hypoechoic lesions in the liver. Color doppler flow imaging showed spots of avascular reflective material. Contrast-enhanced computed tomography (CT) showed multiple low-density lesions in the right lobe of the liver. The largest was located in segment 8 and was 2.9 cm, 2.3 cm. Some lesions had mild-moderate enhancement during the arterial contrast-enhanced phase. The density was lower than the normal liver parenchyma during the portal vein and lag phase (Figure 1). Magnetic resonance (MR) T1-weighted images showed multiple low signal ovoid lesions in the right lobe of the liver that had a high signal on T2-weighted images (Figure 2). Chest X-rays yielded no remarkable findings. Ultrasound revealed enlarged bilateral lymph nodes in the neck, axilla, and groin.

**Laboratory examinations**

Laboratory testing on admission showed no abnormalities in markers of inflammation or abnormal liver function, or in peripheral blood panel or biochemical tests. HBsAg, HBcAb and HCVAb were negative. Tumor markers were in the normal ranges, except for a mildly elevated CEA (6.9 ng/mL; normal range: 0-5.0 ng/mL).

**FINAL DIAGNOSIS**

An ultrasound-guided fine needle aspiration biopsy revealed few hepatocytes and fibrous tissue with mildly heteromorphic spindle cell (dendritic cell) infiltration. The neoplastic cells were medium to large, with eosinophilic cytoplasm and vesicular nuclei having small, inconspicuous nucleoli. Signet ring cell-like structures were seen with intracytoplasmic lumina, occasionally containing red blood cells (Figure 3). Immunohistochemical staining indicated that the tumor cells were positive for CD31 (H12164PD590, EuroBioscience), CD34 (H12166F, EuroBioscience), and factor VIII-related antigen (FVIII-RAG, BH0012044, Goybio) (Figure 4A-C), while cells were negative for Pan Cytokeratin (CK+AFs-AE1/AE3+AF0-)(PD00330, Dako) (Figure 4D). Other results were lysozyme+-, P53+-/+ACY-ndash+ADs-, vimentin+-, EMA+-, CK8+ACY-ndash+ADs-, AFP+ACY-ndash+ADs-, CK18+ACY-ndash+ADs-, hepatocyte+ACY-minus+ADs-, CK20+ACY-minus+ADs-, and CD68+ACY-minus+ADs-,which weren't been shown in this article. Immunohistochemical staining results revealed evidence of+ACY-nbsp+ADs- endothelial differentiation, and consistent with hepatic epithelioid hemangioendothelioma (EHE).

**TREATMENT**

During the patient’s hospital stay, she was given four cycles of combined chemotherapy with ifosfamide, cisplatin, epirubicin and recombinant human (rh) endostatin (Endostar; Simcere, Nanjing, China) injection.

**OUTCOME AND FOLLOW-UP**

After 13 years of follow-up, the patient remains in stable condition. A repeated CT scan found that the size of the lesions had not changed (Figure 5) and her liver function was normal.

**DISCUSSION**

Hepatic EHE is a rare tumor of vascular origin, with an incidence of 0.1-0.2/100000[1,2]. Fewer than 600 cases involving the liver are available in the literature, and it was first reported by Ishak *et al*[4] in 1984. Hepatic EHE is as a low-to-moderate grade tumor with a malignant potential intermediate between hemangioma and hemangiosarcoma[4]. Its metastasis rate is 27%-45% and the most common tissues of origin are the lungs (81%) and celiac lymph nodes (39%)[1]. The median age has been reported as 41.7 years, with a female predominance of 3:2[3], and the clinical manifestations are variable. The most frequent symptoms are right upper quadrant pain (48.6%), hepatomegaly (20.4%), and a constitutional syndrome with progressive liver damage and weight loss (15.6%)[3]. Some patients present with Budd-Chiari syndrome or liver failure, while others present with incidental findings[1, 5]. Laboratory findings may reveal abnormal liver function. Nearly 75% of patients have elevated alkaline phosphatase (AKP), 2.7% have elevated alpha-fetoprotein (AFP), and 18.8% have elevated serum CEA[1,3]. Our patient had good liver function, with normal AKP, AST, ALT, and AFP. Her CEA was elevated but other markers were in their normal ranges. Oral contraceptives, polyvinyl chloride, asbestos, thorotrast contrast agent, and hepatic trauma have been identified as risk factors for subsequent disease development[3], and viral hepatitis is considered as an etiology[1,4,6]. This patient had a history of viral hepatitis A, but it had resolved without complication 20 years before she presented with hepatic EHE, making a viral etiology implausible. Because of its nonspecific manifestation, the diagnosis of hepatic EHE depends mainly on radiology and histopathology.

Most lesions are peripheral, extending to the capsularmargin and are frequently hypoechoic with heterogeneous internal architecture on sonography[7,8]. On CT, lesions are almost hypodense with peripheral contrast enhancement[7,9-11]. Capsular retraction adjacent to the mass is seen in fewer than 25% of patients[9,12]. On MR, T1-weighted images of lesions frequently have a low signal and T2-weighted images have heterogeneous-increased signals. Peripheral enhancement with a thin nonenhancing rim corresponding to a narrow vascular zone can be seen with arterial contrast[7, 11-13]. A lollipop sign, which is indicative of hepatic or portal veins terminating at or just within the periphery of lesions, seems to be specific for hepatic EHE[14]. The mean apparent diffusion coefficients of lesions were found to be high compared with other hepatic malignancies, which may be helpful in suggesting the diagnosis[15]. MR appears to be superior to CT, and MR with contrast may be important.

Pathologic diagnosis depends on the vascular nature of the tumor. Histologically, it is comprised of a fibrous stroma with myxohyaline areas including dendritic and epithelioid cells, often with intracellular vacuoles[1,4]. Immunohistochemical staining is positive for the expression of endothelial antigens, such as FVIII-RAG (98%), CD34 (94%), or CD31 (86%), and negative for epithelial markers[1,6]. This tumor was CD34+, vimentin+, and CD31+, and negative for epithelial markers like CK (AE1/AE3) and CK18. Podoplanin was shown to be specifically expressed in hepatic EHE (78%), and may be useful as a diagnostic marker of EHE in liver tumors[9]. Characteristic ultrastructural features include investing basal lamina, cytoplasmic intermediate filaments, Weibel–Palade bodies, and pinocytotic vesicles[4]. High cellularity, more than mitotic count, predicts an unfavorable prognosis[1,3,4]. A recent study reported that these tumors often have t(1;3) (p36.3; q25) translocations, resulting in WWTR1-CAMTA1 fusion[16]. YAP 1-TFE3 fusions have also been identified in about 10% of patients[17].

Treatment options are limited by the rarity of the tumor and currently include liver transplantation (44.8%), chemotherapy or radiotherapy (21.0%), and liver resection (9.4%), with 24.8% of patients receiving no treatment[3]. Complete liver resection should be performed if possible, but the multicentric origin of the tumor and multinodular growth make that difficult to accomplish[18]. Liver transplantation is an effective treatment for patients who are not candidates for resective surgery and those with extrahepatic manifestations or progressive liver failure[19,20]. Hepatic EHE is not sensitive to radiotherapy or chemotherapy, but some studies have found that 5-fluorouracil, doxorubicin, thalidomide, and interferon were effective[14,21,22]. One-year survivals following liver transplantation, without treatment, radiotherapy or chemotherapy, and liver resection have been reported as 96%, 39.3%, 73.3%, and 100%. The corresponding 5-year rates were 54.5%, 4.5%, 30%, and 75%[3]. Hepatic EHE is of vascular origin, vascular endothelial growth (VEGF) receptors have been detected in EHE tumor cells, and VEGF has a role in tumor growth[23]. Combination treatment anti-VEGF drugs and cell cycle inhibitors, such as bevacizumab and capecitabine[24,25], pegylated liposomal doxorubicin[26], and metronomic cyclophosphaide[27] have been effective. For patients with extrahepatic lesions, it has been reported that adjuvant chemotherapy may prevent recurrence[28].

Because the disease was multifocal in our patient, orthotopic liver transplantation may have been justified as a curative procedure. Unfortunately, a donor shortage and cost limitations made immediate transplantation unrealistic. Consequently, we choose to treat her with combined chemotherapy that included ifosfamide, cisplatin, epirubicin and rh-endostatin. rh-endostatin is purified in an *Escherichia* *coli* system, with an additional nine amino acid sequence of soluble protein[29]. It targets neovascular endothelial cells and has antiangiogenetic and antitumor activity. Preclinical and clinical studies showed synergistic effects of rh-endostatin and other agents that inhibit the growth of malignant tumors, with minimal toxicity[30-32]. A review by Xu *et al*[33] suggests that the combination of rh-endostatin with chemotherapy, radiotherapy, and biotherapy (*i.e.* fusion protein, or molecular-targeted therapy on cancers, *etc.*) may be the optimal strategy for cancer treatment[33]. Ling *et al*[34] reported that the antiangiogenic activity of rh-endostatin was mediated *in vitro* and *in vivo* by blocking VEGF-induced tyrosine phosphorylation of KDR/Flk-1 in endothelial cells. The vascular nature and endothelial origin of our patient’s tumor led us to choose rh-endostatin for her treatment. To date, the size of her lesions has not increased, and the patient is in stable condition with normal liver function. The patient is followed-up regularly, and liver transplantation is still recommended.

**CONCLUSION**

In conclusion, hepatic EHE is a rare tumor, and its atypical symptoms and varied radiographic appearance make it hard to differentiate from other tumors. Diagnosis depends on histopathology. Liver resection is the treatment of choice in patients with resectable lesions, and liver transplantation is justiﬁed as a curative procedure for multinodular disease. Donor shortage and a long waiting time, among other reasons, limit the use of liver transplantation. Chemotherapy including rh-endostatin may increase the effectiveness of hepatic EHE treatment. The focus is on its therapeutic efficacy while awaiting a suitable donor liver and for patients with extrahepatic manifestations. Further research is needed.

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**Footnotes**

**Informed consent statement:** Consent was obtained from the patient, who signed a written informed consent for publication of this case report.

**Conflict-of-interest statement:** The authors declare that they have no competing interests.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** November 25, 2021

**First decision:** January 12, 2022

**Article in press:**

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

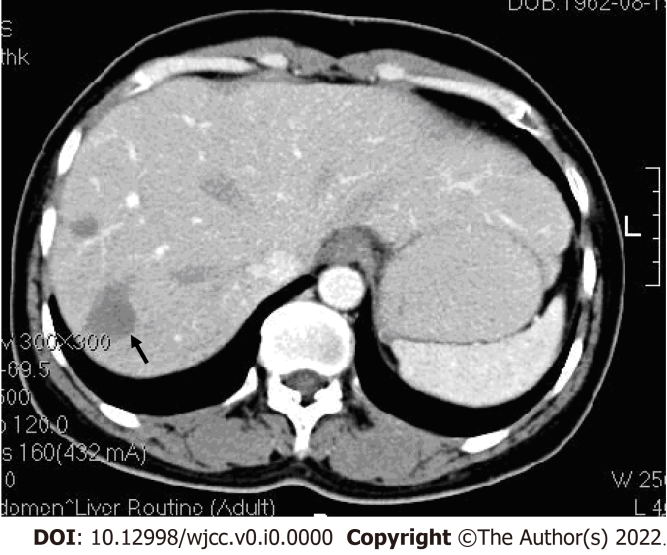
Grade C (Good): C, C

Grade D (Fair): 0

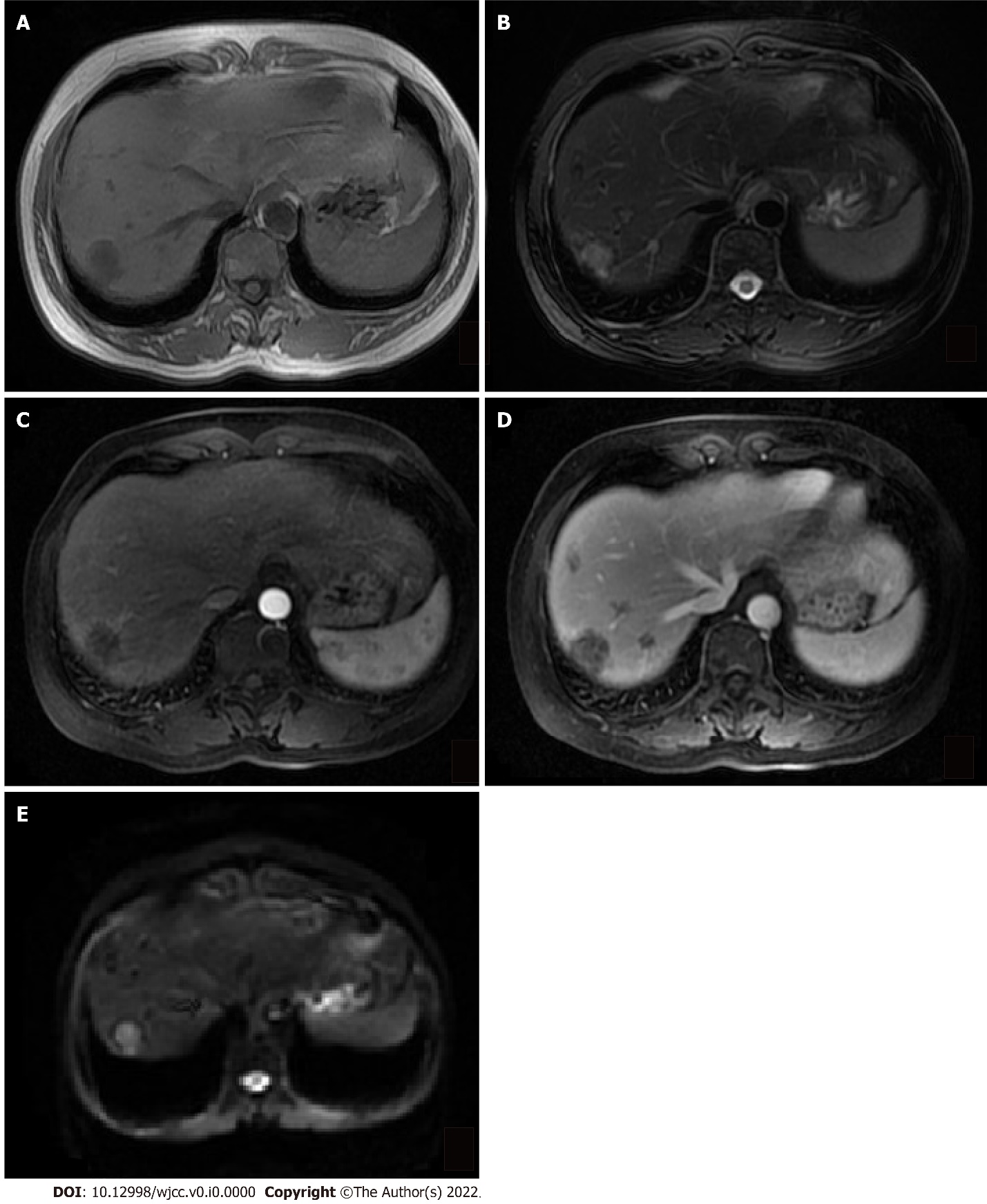
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**P-Reviewer:** Mohey NM, Egypt; Yang M, China **S-Editor:** Xing YX **L-Editor:** A **P-Editor:** Xing YX

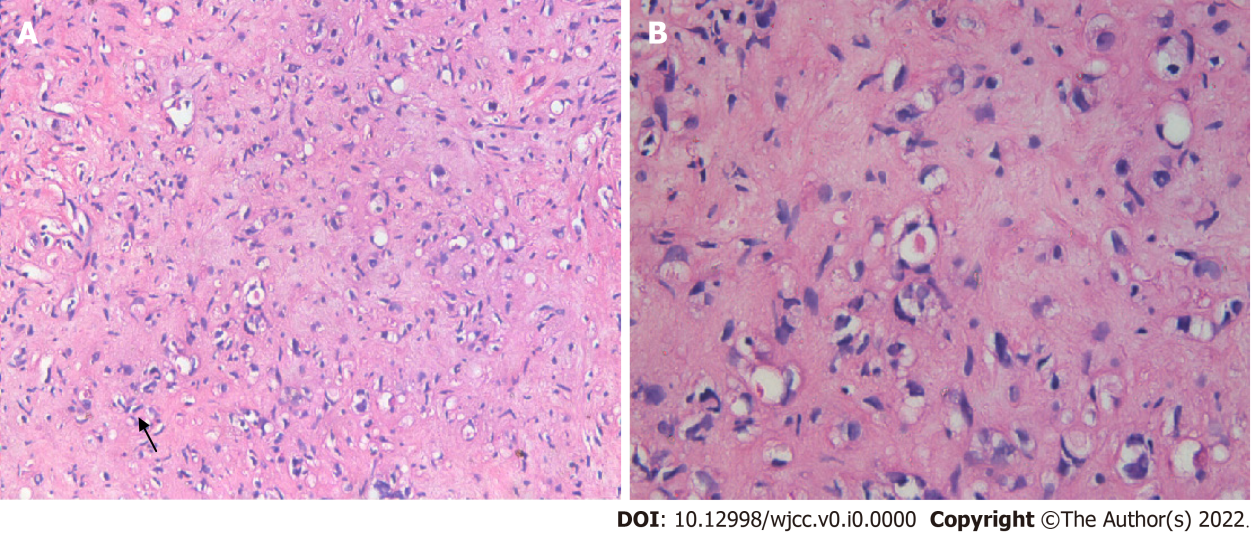
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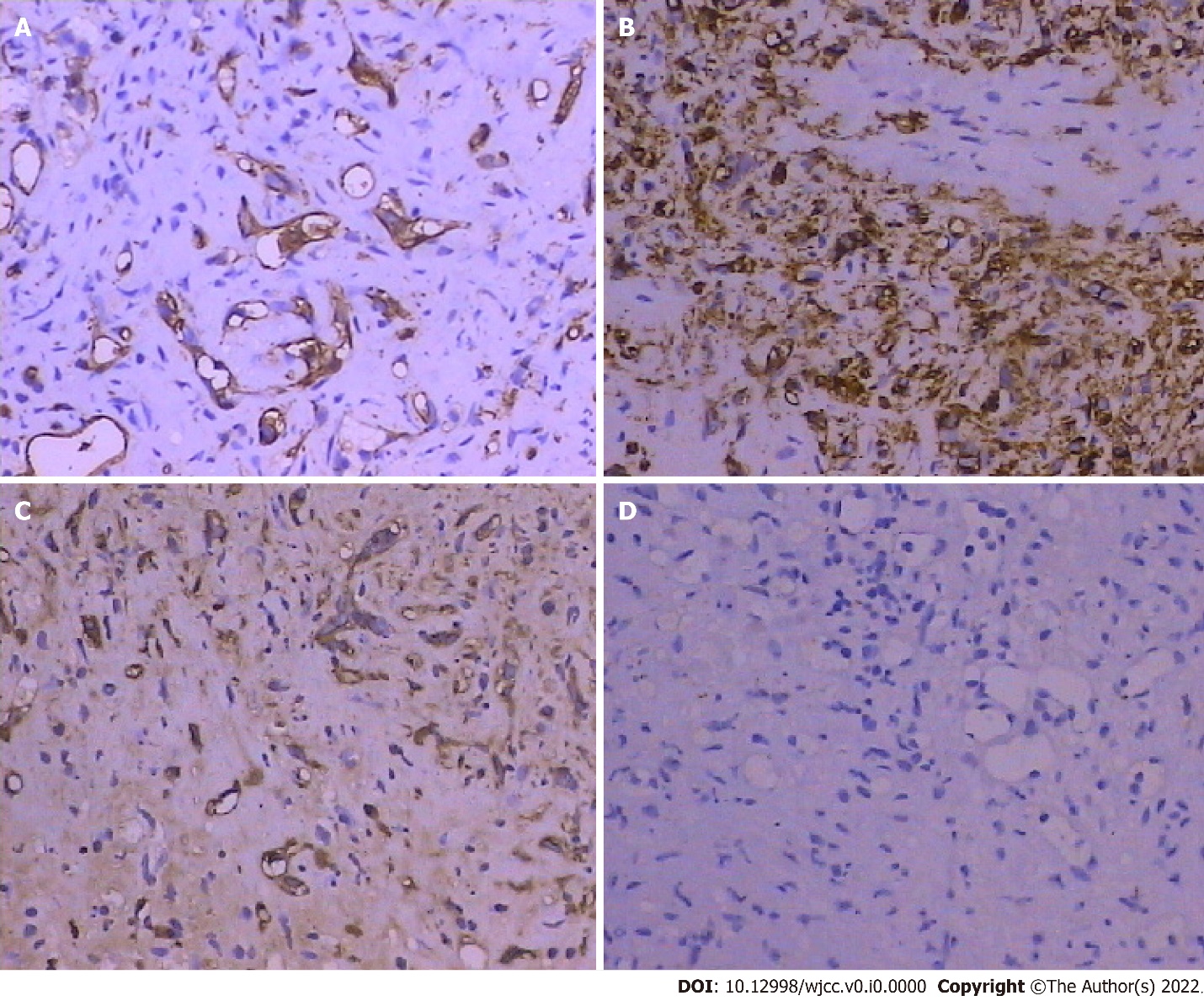
**Figure 1 Contrast-enhanced computed tomography.** Multiple low-density lesions (black arrow) with mild-moderate peripheral enhancement are seen in the right lobe of the liver.

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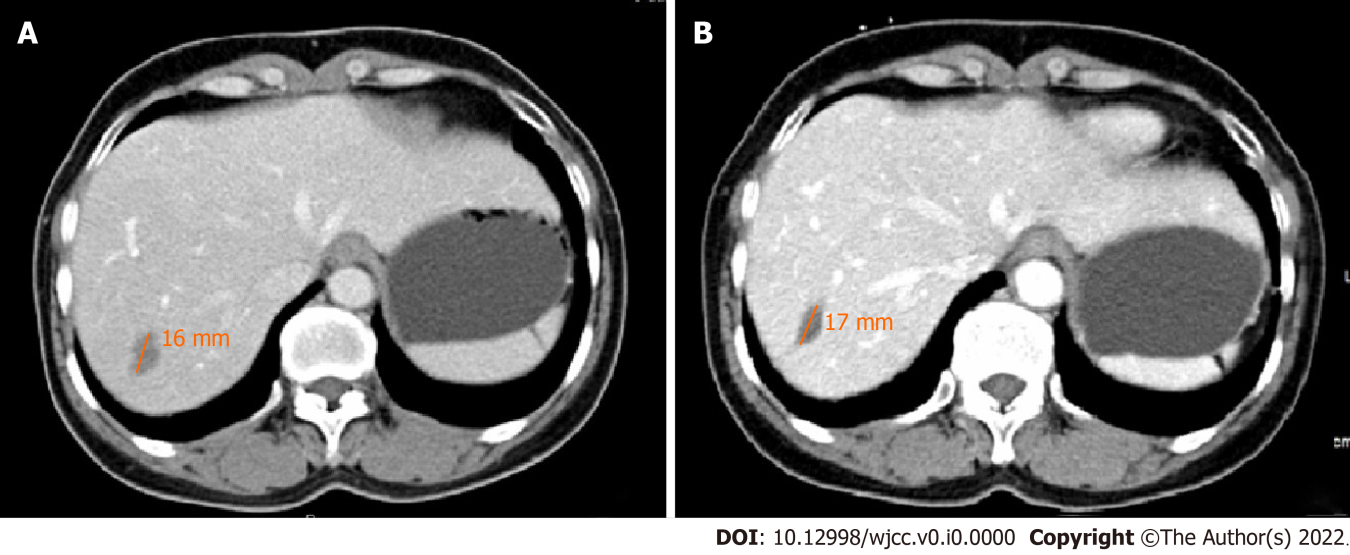
**Figure 2 Magnetic resonance weighted image.** A: T1-weighted image shows low signal ovoid lesions in the right lobe of liver; B: The lesions have a heterogeneous high signal in the T2-weighted image; C: The largest lesion in the right lobe is mildly heterogeneous with peripheral enhancement and an arterial contrast enhancement pattern; D: Peripheral enhancement of lesions is increased in spots visible in a venous contrast enhancement pattern; E: Lesions show diffusion restriction on a diffusion-weighted image.

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**Figure 3 Liver biopsy.** A: Mildly heteromorphic spindle cells (dendritic cells) with interdigitating processes (hematoxylin and eosin, 200 ×); B: Intracellular vascular lumina containing a red blood cell (black arrow) (hematoxylin and eosin, 400 ×).

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**Figure 4 Histopathology, immunostaining of tumor cells.** A: Anti-CD31+ (200 ×); B: Anti-CD34+ (200 ×); C: Anti-factor VIII-related antigen+ (200 ×); D: Anti-CK− (Pan) (200 ×).

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**Figure 5 Contrast-enhanced follow-up computed tomography scans.** A: After 4 years, diameter of the low-density lesion was 16 mm; B: After 12 years, diameter of the low-density lesion was 17 mm.