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Fourteen-Year Course of Multiple Recurrent and Distantly Metastatic Hepatic Epithelioid Hemangioendothelioma With Serial Ki-67 Evolution: A Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Female, 48-year-old

Final Diagnosis: Hepatic epithelioid hemangioendothelioma (HEHE)

Symptoms: Asymptomatic liver lesion

Clinical Procedure: —

Specialty: Gastroenterology and Hepatology • Pathology

Objective: Rare disease

Background: Hepatic epithelioid hemangioendothelioma (HEHE) is a rare vascular tumor of endothelial origin with variable clinical behavior, posing significant diagnostic and therapeutic challenges. Due to its nonspecific presentation and diverse imaging features, it is frequently misdiagnosed. We present a unique case of HEHE with recurrent liver involvement and distant metastases over a 14-year period, emphasizing diagnostic markers, treatment strategies, and the prognostic value of serial biomarker assessment.

Case Report: A 48-year-old woman underwent right partial hepatectomy in 2011 after a routine health check-up incidentally revealed a liver lesion. Histological examination revealed characteristic epithelioid and dendritic tumor cells, confirmed by immunohistochemistry (CD31+, CD34+, Ki-67 5%). Postoperative surveillance detected tumor recurrence 7 years later in the left lobe, necessitating laparoscopic left partial hepatectomy. In 2020, further progression to the caudate lobe and regional lymph nodes prompted complex resection, with Ki-67 rising to 15%. Serial Ki-67 assessments across sequential specimens demonstrated a progressive increase in proliferative activity: 5% (2011), 15% (2020), and ultimately 40% in a pleural metastasis biopsy (2024), correlating closely with clinical progression. The patient received repeated surgical resections and adjuvant interferon alpha-2b, with palliative nab-paclitaxel attempted during the terminal stage but proving ineffective. The patient died in August 2025, approximately 14 years after initial diagnosis.

Conclusions: This case highlights the importance of the Ki-67 index as a dynamic biomarker for monitoring tumor evolution and guiding treatment decisions in recurrent HEHE. Regular long-term follow-up and a multidisciplinary approach are crucial for managing this unpredictable neoplasm, given its potential for late recurrence and metastasis.

Keywords: Hemangioendothelioma, Epithelioid • Recurrence

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Introduction

Hepatic epithelioid hemangioendothelioma (HEHE) is an exceedingly rare vascular malignancy of endothelial origin that occupies the biological spectrum between a benign hemangioma and a highly aggressive angiosarcoma [1]. Its incidence is estimated to be less than 0.1 per 100 000 individuals. The clinical presentation is often nonspecific or asymptomatic, and radiological findings can be diverse and mimic those of other more common liver tumors, leading to frequent misdiagnoses or delayed diagnosis [2]. Molecularly, most HEHE cases harbor a recurrent WWTR1-CAMTA1 gene fusion resulting from t(1;3)(q36;q25), which leads to constitutive activation of the Hippo-YAP signaling pathway and is considered a key diagnostic hallmark of this tumor entity [3]. Currently, there is no standardized management protocol for HEHE, particularly for cases that present with or progress to multifocal or metastatic disease.

The objective of this case report is 3-fold: first, to document the unusually prolonged clinical course of a patient with HEHE who experienced multiple local recurrences and distant metastases over 14 years; second, to report serial Ki-67 proliferation index changes across sequential pathological specimens; and third, to highlight the limitations of current systemic therapies for advanced disease. This report is intended to generate hypotheses and illustrate the natural history of aggressive HEHE, rather than to definitively test therapeutic efficacy.

Case Report

A 48-year-old woman was admitted in October 2011, 10 days after a routine health check-up revealed a space-occupying lesion in her liver. She was previously healthy, had no chronic medical history, and was entirely asymptomatic, with no abdominal pain, distension, fever, or weight loss. Her medical history was unremarkable for surgery, trauma, long-term medication, smoking, or alcohol use. Family history was negative for malignancies. Physical examination upon admission was unremarkable, and she was in good general condition with stable vital signs, no palpable lymphadenopathy, jaundice, skin abnormalities, or chronic liver disease stigmata.

The initial laboratory investigations revealed normal liver function. Hepatitis B serology showed a protective antibody titer (HBsAb 92.83 IU/L) with a negative core antibody. Tumor markers, including CEA, AFP, CA19-9, and CA125, were within normal limits. Abdominal ultrasound identified a hypoechoic nodule measuring 3.0 × 3.0 × 3.6 cm in the right hepatic lobe and a gallbladder polyp measuring 0.6 cm. Contrast-enhanced computerized tomography (CT) revealed a 26 × 24 mm low-density focus in the anterior superior segment of the right lobe, showing mild peripheral enhancement with a subsequent reduction in size in the delayed phase (**Figure 1A**). Magnetic resonance imaging (MRI) confirmed a 29 × 31 mm lesion with low T1 and high T2 signal intensities, slight hyperintensity on diffusion-weighted imaging (DWI), and peripheral enhancement with delayed contraction (**Figure 1B**). The imaging features of the recurrent lesions in the left lobe (2018) and caudate lobe (2020) are shown in **Figure 1C and 1D,** respectively. The imaging features were atypical and not diagnostic, raising the need for differential diagnosis of atypical hemangiomas, cholangiocarcinomas, or other malignancies.

A multidisciplinary team discussion concluded that a definitive preoperative diagnosis was challenging, and surgical intervention was indicated for diagnosis and potential cure. The patient underwent a right partial hepatectomy (segment VII) in October 2011. Histopathological examination revealed epithelioid and dendritic tumor cells infiltrating hepatic sinusoids and portal areas. The immunohistochemical results were strongly positive for CD34 and CD31, confirming the diagnosis of HEHE. The Ki-67 proliferation index was approximately 5% (**Figure 2A**). The patient recovered well and was regularly followed up.

In April 2018, a recurrence was detected in the left hepatic lobe. The patient underwent a laparoscopic left partial hepatectomy. Histological examination confirmed recurrent HEHE with a similar immunophenotype (**Figure 2B**).

By November 2020, the disease had progressed to involve the caudate lobe and regional lymph nodes. The patient underwent complex hepatectomy of the caudate lobe and metastatic lymph node resection. Pathological examination confirmed HEHE with vascular tumor thrombi and lymph node metastasis (3/13 nodes positive). The Ki-67 index increased to 15%. Ki-67 proliferation index was assessed by immunohistochemistry on formalin-fixed, paraffin-embedded tissue sections using the MIB-1 antibody. The 2018 archived specimen was retrospectively tested in September 2025 alongside the 2024 pleural biopsy to ensure methodological comparability. All assessments were performed in the same pathology laboratory using standardized protocols. The reported values represent descriptive observations from clinical materials rather than a controlled longitudinal biomarker study. Postoperatively, the patient received adjuvant interferon alpha-2b therapy (5 million IU subcutaneously, 3 times per week) for 2 years. The treatment was tolerated, with manageable adverse effects, including leukopenia and rash. The patient remained radiologically stable during the study period.

From 2024 onward, the disease entered a terminal phase, with widespread metastases to the lungs, bones, and pleura (**Figure 3A-3D**). Although taxanes are not a standard treatment for HEHE, and the literature indicates generally poor response rates, palliative chemotherapy with nab-paclitaxel (200 mg/m^2

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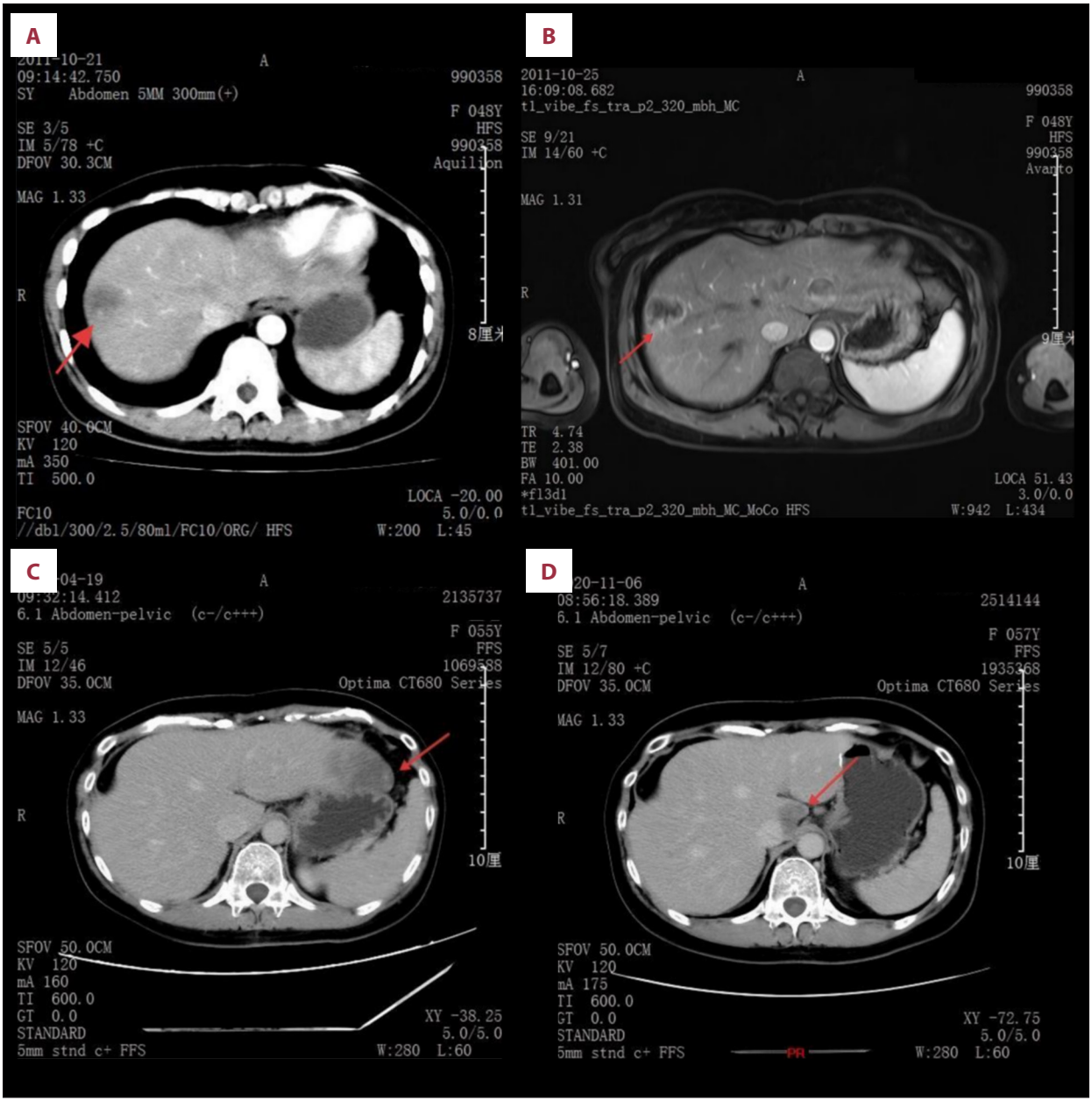

Figure 1. Preoperative abdominal imaging findings from the 3 surgeries of the patient. (**A**) Contrast-enhanced abdominal computed tomography (CT) scan in 2011 shows a mass-like low-density shadow (approximately 26 × 24 mm) in the anterior superior segment of the right hepatic lobe, with blurred margins, mild peripheral enhancement after contrast, and reduced size on the delayed phase. (**B**) Contrast-enhanced abdominal magnetic resonance imaging (MRI) scan (4 days later) reveals a clumpy abnormal signal focus (approximately 29 × 31 mm) in the anterior superior segment of the right hepatic lobe, exhibiting low signal intensity on T1-weighted imaging, high signal intensity on T2-weighted imaging, slightly high signal on diffusion-weighted imaging, early peripheral enhancement after contrast, and significant size reduction on the delayed phase. (**C**) Contrast-enhanced abdominal CT scan in April 2018 demonstrates a low-density nodule (approximately 34 × 52 mm) in the left hepatic lobe, with clear boundaries, nodular mild peripheral enhancement on the delayed phase, and reduction in lesion size. (**D**) Contrast-enhanced abdominal CT scan in November 2020 shows an oval, slightly low-density focus (approximately 21 × 23 mm) in the caudate lobe, with mild enhancement. Red arrows indicate the tumor locations.

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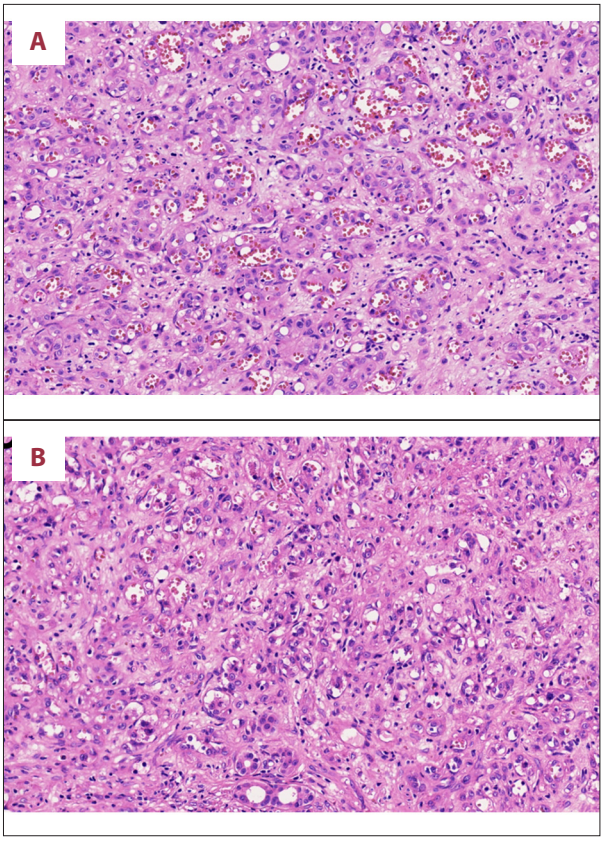

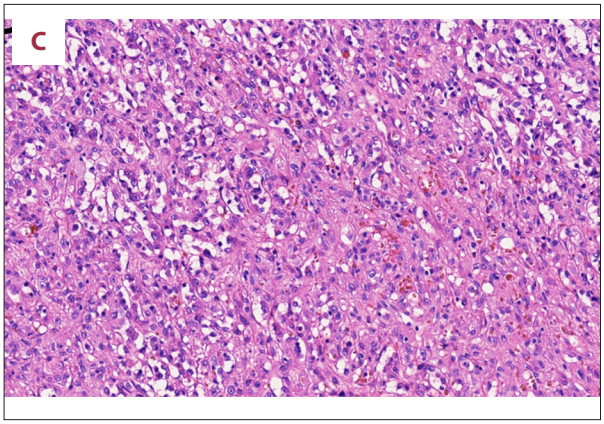

Figure 2. Postoperative pathological examination results from the three surgeries of the patient with hematoxylin and eosin (H&E) staining with immunohistochemistry (CD31, CD34, Ki-67). (**A**) Right hepatic tumor tissue (×200 magnification), showing epithelioid and dendritic tumor cells infiltrating the hepatic sinusoids and portal areas. (**B**) Left hepatic recurrent tumor tissue (×400 magnification), displaying dendritic and epithelioid cells with vascular differentiation, intracytoplasmic lumina, stromal fibrosis, and myxoid change. (**C**) Caudate lobe metastatic focus (×400 magnification), showing tumor cells consistent with the previous morphology in (**B**), accompanied by lymph node metastasis.

on days 1 and 8 of a 21-day cycle) was initiated given the lack of established options for advanced disease [4]. However, after 2 cycles, restaging CT scans showed progressive disease in the lungs and bones, accompanied by Grade III bone marrow suppression. Therefore, chemotherapy was discontinued. The patient developed severe complications, including malignant pleural effusion, esophagogastric variceal bleeding, cachexia, and electrolyte imbalance. Management focused on supportive care, including thoracocentesis, blood transfusions, hemostatic measures, and anti-infective therapies. In August 2025, she was readmitted for gastrointestinal bleeding. After receiving comprehensive supportive care, the family requested discharge. Shortly thereafter, the patient died.

The total survival from the initial diagnosis in October 2011 to death in August 2025 was approximately 14 years. Notably, retrospective testing performed in September 2025 showed Ki-67 indices of 5% in the 2018 archived specimen and 40% in the 2024 pleural metastasis biopsy, demonstrating increased proliferative activity over the course of the disease (**Figure 2C**).

Ki-67 proliferation index was assessed by immunohistochemistry using the MIB-1 antibody on formalin-fixed, paraffin-embedded tissue sections. The 2018 archived specimen was retrospectively tested in September 2025 alongside the 2024 pleural biopsy to ensure methodological comparability (**Table 1**).

Discussion

This case confirms several known features of HEHE: its indolent but progressive nature, the diagnostic challenges posed by nonspecific imaging findings, and the limited efficacy of conventional systemic therapies. The novel contribution of this report is the documentation of serial Ki-67 proliferation index increases (from 5% to 15% to 40%) across 3 sequential pathological specimens obtained over 14 years of disease progression. To our knowledge, this is one of the few reports tracking Ki-67 dynamics longitudinally in recurrent and metastatic HEHE [5].

Additionally, the clinical course can be prolonged but is marked by late recurrences and metastases, as seen in this 14-year history. Surgical resection offers the best chance for long-term survival in patients with localized disease, as evidenced by the 7-year disease-free interval after the first resection [2]. However, the efficacy of systemic therapies for advanced disease remains limited. Although interferon alpha-2b provided a period of disease stabilization to our patient, its effect was transient, consistent with reports of modest and often non-durable responses [6]. The lack of response to nab-paclitaxel during the terminal stage is consistent with the literature, which indicates that taxanes are not a standard treatment for HEHE and that response rates to systemic chemotherapy are

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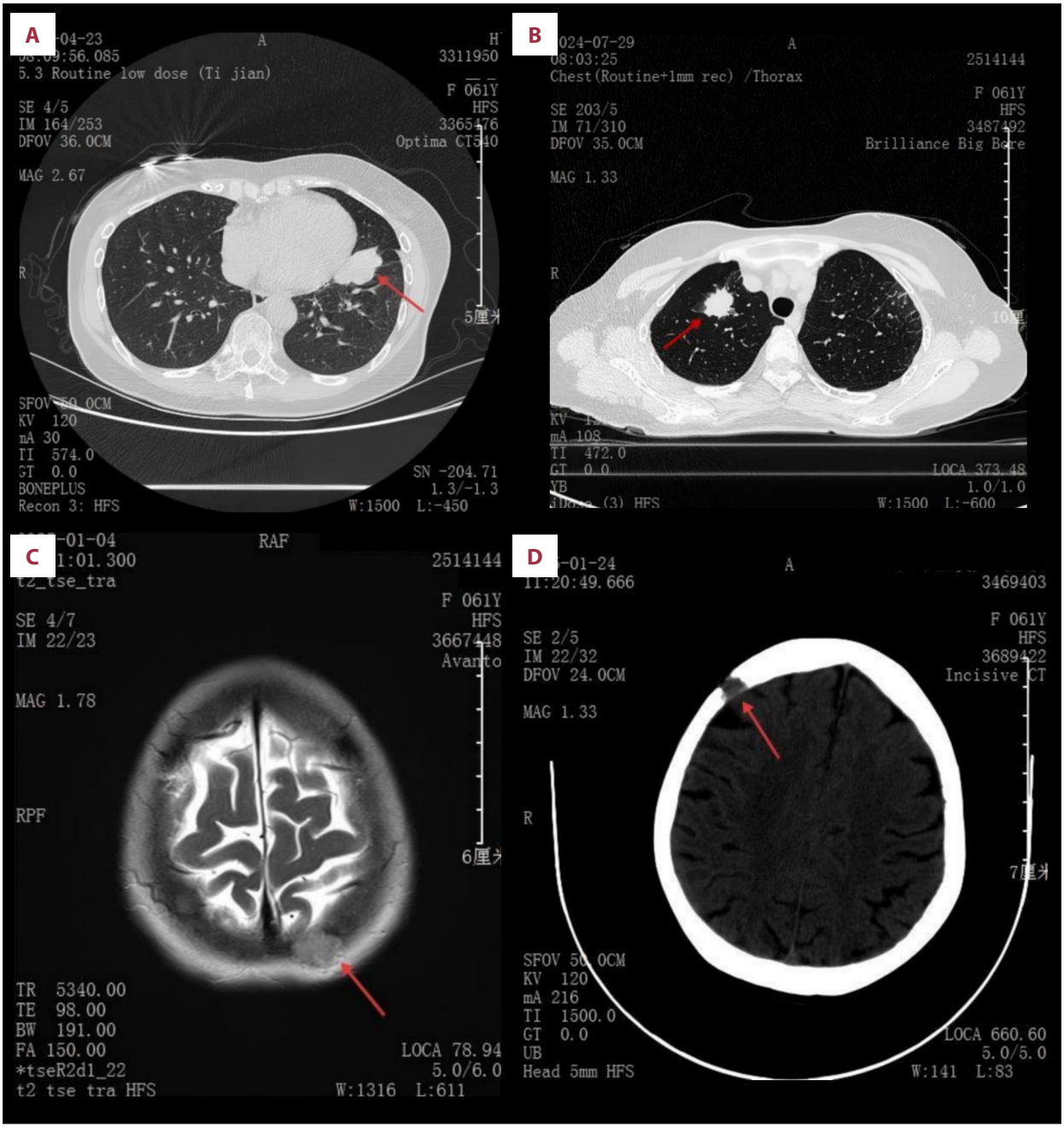

Figure 3. Imaging of multi-system metastases during the terminal stage. (**A**) Chest computed tomography (CT) without contrast (April 2024) shows multiple solid masses in both lungs: the lesion in the left lower lobe measures approximately 35 × 22 mm^2, accompanied by lobulation and pleural indentation. (**B**) Chest CT without contrast (July 2024) reveals an enlarged nodule in the right upper lobe measuring approximately 12 × 18 mm^2. (**C**) Brain magnetic resonance imaging without contrast (January 2025) shows multiple nodular abnormal signals in the skull bones bilaterally, suggestive of metastatic lesions. (**D**) Brain CT without contrast (3 weeks later) confirms the bilateral presence of multiple metastatic tumors in the skull bones. Red arrows indicate the metastatic tumors.

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Table 1. Serial Ki-67 proliferation index across sequential pathological specimens.

Year	Specimen	Ki-67 (%)	Assessment type
2011	Primary tumor (right lobe resection)	~5	Original assessment
2018	First recurrence (left lobe resection)	5	Retrospective testing (2025)
2020	Second recurrence (caudate lobe resection)	15	Original assessment
2024	Pleural metastasis (biopsy)	40	Original assessment

generally poor, reflecting the broad chemoresistance characteristic of advanced HEHE [7].

While the WWTR1-CAMTA1 fusion gene has been established as a key diagnostic hallmark of HEHE, molecular testing for this fusion was not performed in the present case. The diagnosis was firmly established based on characteristic histomorphology and a positive immunophenotype (CD31, CD34). The absence of molecular confirmation represents a limitation of this case report. Nevertheless, this limitation also serves to highlight the value of incorporating molecular testing, such as WWTR1-CAMTA1 or YAP1-TFE3 fusion detection, in future suspected or confirmed HEHE cases, as it may enhance diagnostic accuracy and potentially guide targeted therapeutic strategies.

A related issue concerns the potential relationship between the 2-year adjuvant interferon alpha-2b therapy administered after the third resection (2020-2022) and the subsequent emergence of widespread metastases in 2024. One might hypothesize whether this immunomodulatory therapy could have paradoxically contributed to the eventual aggressive tumor behavior. Several observations argue against this possibility. First, the interval between cessation of interferon therapy and the development of widespread metastases was approximately 1 to 2 years, with no temporally close relationship evident. Second, existing literature has reported the use of interferon alpha-2b in patients with HEHE, generally demonstrating disease stabilization or modest benefit without clear evidence of inducing aggressive transformation [8]. Third, the serial Ki-67 increase from 5% to 15% to 40% across sequential specimens suggests a progressive biological evolution of the tumor itself over time, rather than an abrupt shift attributable to a single therapeutic intervention. That said, the hypothesis that long-term immunomodulation might theoretically influence clonal selection cannot be completely excluded based on a single case, and further research would be needed to clarify this issue.

The observed progressive increase in Ki-67 from 5% to 40% across sequential specimens represents a hypothesis-generating longitudinal observation in this patient. While this trend correlates temporally with increasing tumor aggressiveness, causal inferences regarding prognosis or treatment guidance cannot be drawn from a single case [9]. These observations support the need for larger, controlled studies to evaluate Ki-67 as a potential prognostic biomarker in HEHE.

The therapeutic dilemma in advanced HEHE underscores the need for novel approaches. Molecular studies have identified WWTR1-CAMTA1 gene fusions in most HEHE cases, leading to the constitutive activation of the Hippo-YAP signaling pathway, which promotes cell proliferation and survival [10]. This pathogenic mechanism might explain the limited efficacy of conventional chemotherapy and interferon. Future approaches should focus on targeted therapies (eg, mTOR inhibitors and antiangiogenic agents) and the exploration of immunotherapy guided by molecular profiling [7,11].

Conclusions

In conclusion, this 14-year case of recurrent and metastatic HEHE offers 3 principal clinical lessons. First, HEHE may follow a prolonged but progressively aggressive course, with late recurrences and distant metastases occurring many years after initial resection. Second, the observed increase in Ki-67 from 5% to 15% to 40% across sequential pathological specimens is a hypothesis-generating observation that suggests repeat biomarker evaluation may help contextualize disease evolution, although prognostic and therapeutic implications require validation in larger cohorts. Third, this case highlights the critical importance of long-term surveillance, even after apparently successful initial surgical resection, given the potential for late recurrence and metastasis.

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Patient Consent

Ethical approval for this case report was granted by the Ethics Committee of Shangyu People's Hospital of Shaoxing, and written informed consent was obtained from the patient's next-of-kin.

Statement

This study was supported by the Medical and Health Science and Technology Program of Zhejiang Province [2025KY1708 to FG] and the Health Science and Technology Project of Shaoxing City (Health Science and Technology Project) [2023SKY112 to LTZ]. The funders did not have any role in the paper design, data collection, interpretation, and writing of the paper.

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