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Hepatocellular Carcinoma Presenting With Worsening Microcytic Anemia and Intratumoral Hemorrhage

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Asha Thambi [1], Paul Thambi [1], Yehuda Galili [1], Munira Malik [2], Steve Carlan [3]

1. Hematology-Oncology, Cleveland Clinic Florida, Weston, USA 2. Pathology, HCA Florida Westside Hospital, Plantation, USA 3. Obstetrics, Orlando Regional Medical, Orlando, USA

Corresponding author: Steve Carlan, stevecarlan@gmail.com

Abstract

Hepatocellular carcinoma (HCC) typically presents with right upper quadrant pain, jaundice, or ascites. Acute spontaneous tumor rupture is a well-recognized emergency, but insidious, chronic bleeding into the tumors, presenting as iron deficiency anemia (IDA) before an acute hemorrhagic crisis, is exceedingly rare. This diagnostic challenge is further compounded in patients with concurrent hereditary hemoglobinopathies.

A 69-year-old postmenopausal woman with alpha-thalassemia minor and no prior history of chronic liver disease presented with progressive fatigue. Laboratory evaluation revealed profound IDA. While awaiting gastrointestinal endoscopic evaluation to rule out occult luminal bleeding, she developed sudden, severe abdominal pain. Abdominal MRI and CT showed hepatomegaly with multiple bilateral hepatic masses with signs of subcapsular intratumoral hemorrhage, along with an elevated alpha-fetoprotein (AFP) level (110 IU/mL). Upper endoscopy and colonoscopy identified no source of gastrointestinal bleeding. The patient subsequently developed a catastrophic tumor rupture with active bleeding from two distinct lesions, and her hemoglobin fell below 6 g/dL. She underwent emergent transarterial embolization of three hepatic tumors, which achieved stabilization. A core needle biopsy confirmed well-differentiated HCC. Because of her high tumor burden, she was started on systemic immunotherapy but unfortunately passed away one month later.

In rare cases, chronic, occult intratumoral hemorrhage from HCC can masquerade as standard IDA before progressing to serious and potentially life-threatening rupture. Hepatic malignancies should be considered in the differential diagnosis of unexplained microcytic anemia when standard endoscopic evaluations are negative, particularly when underlying hemoglobinopathies cloud the clinical presentation. Maintaining clinical awareness and considering early cross-sectional abdominal imaging in these atypical scenarios may assist in identifying subcapsular lesions before macro-structural failure.

Categories: Hematology, Oncology, Internal Medicine
Keywords: alpha-thalassemia, carcinoma, hepatocellular carcinoma (hcc), iron deficiency anemia (ida), magnetic resonans imaging

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and represents a major global health burden [1]. The clinical presentation of HCC is highly variable, although patients most frequently present with symptoms of advanced liver dysfunction or mass effect, including abdominal pain, jaundice, ascites, weight loss, or palpable hepatomegaly [2]. Spontaneous intratumoral hemorrhage is a well-recognized and potentially catastrophic complication of HCC, occurring in 3% to 15% of cases [3,4]. Typically, this complication manifests as an acute abdominal crisis accompanied by hemodynamic instability due to sudden tumor rupture into the peritoneal cavity.

In contrast, chronic, insidious blood loss from an HCC tumor leading to profound iron deficiency anemia (IDA) before an acute hemorrhagic event is an exceedingly rare clinical phenomenon. When IDA does occur in the setting of hepatic malignancy, it is often misattributed to more common etiologies such as gastrointestinal luminal bleeding, nutritional deficiencies, or anemia of chronic disease. Diagnostic recognition is further confounded in patients with coexisting hereditary hemoglobinopathies, where baseline microcytosis masks the onset of new iron kinetics. We present a unique case of advanced HCC in a postmenopausal woman with alpha-thalassemia minor, where unexplained IDA was the primary and sole initial manifestation of disease. This case underscores the diagnostic challenge of occult intratumoral hemorrhage, which progressed silently before culminating in severe, acute tumor rupture.

Case Presentation

A 69-year-old postmenopausal woman from the Virgin Islands with a known history of alpha-thalassemia minor (baseline hemoglobin: 9.0-10.0 g/dL) presented to her primary care physician with progressive,

worsening fatigue. Her past medical, family, and obstetric histories were otherwise unremarkable, and she reported no history of chronic liver disease, recent weight loss, or appetite changes. Social history was negative for alcohol, tobacco, or illicit substance use. Physical examination was notable for pallor but revealed no abdominal tenderness, hepatosplenomegaly, jaundice, or stigmata of chronic liver disease.

Initial laboratory evaluation revealed a hemoglobin of 8.5 g/dL, prompting a referral to hematology. Additional iron indices demonstrated restricted iron availability, with a total iron of 33 µg/dL and a transferrin saturation of 11.2%. Her initial ferritin was 178 ng/mL (considered a normal baseline in the setting of concurrent thalassemia). Although this value does not document classic depleted iron stores, it represents a complex kinetic profile frequently seen in patients with concurrent thalassemia minor and underlying neoplastic processes. Systemic inflammatory markers (such as C-reactive protein) and hepcidin assays were not performed. The patient had no prior history of iron treatment and received no iron replacement therapy during this evaluation.

A comprehensive metabolic panel (CMP) demonstrated hepatic abnormalities, including an alkaline phosphatase (ALP) of 273 U/L and an aspartate aminotransferase (AST) of 48 U/L (Table *1*).

Variable	Normal lab values	Baseline (2023)	First encounter	~3 weeks	Post-transfusion
White blood cell (cells/µL)	4,500–11,000	7,000	9,300	14,300	13,700
Hemoglobin (g/dL)	12.3–15.3	9.5	8.5	5.8	9.4
Mean corpuscular volume (fL)	80–100	68.6	65.7	64.8	69.8
Platelet count (k/µL)	150–400	398	491	748	676
Ferritin (ng/mL)	15–205	NA	178.0	664.0	NA
Total iron (µg/dL)	41–186	74.0	33.0	16.0	NA
Transferrin saturation (%)	15–57	23.0	11.2	7.0	NA
Alkaline phosphatase (IU/L)	44–147		273		
Aspartate aminotransferase (U/L)	10–40		48		

TABLE 1: Serial critical lab values

The patient denied hematochezia, melena, or bright red blood per rectum. She was urgently referred to gastroenterology, and endoscopic evaluations were scheduled to investigate suspected occult gastrointestinal luminal blood loss. Ten days before her scheduled endoscopic procedures, the patient experienced a sudden onset of sharp, severe abdominal pain. An emergent hepatic ultrasound revealed marked hepatomegaly (19.8 cm) secondary to multiple bilateral hepatic solid masses (Figure *1*).

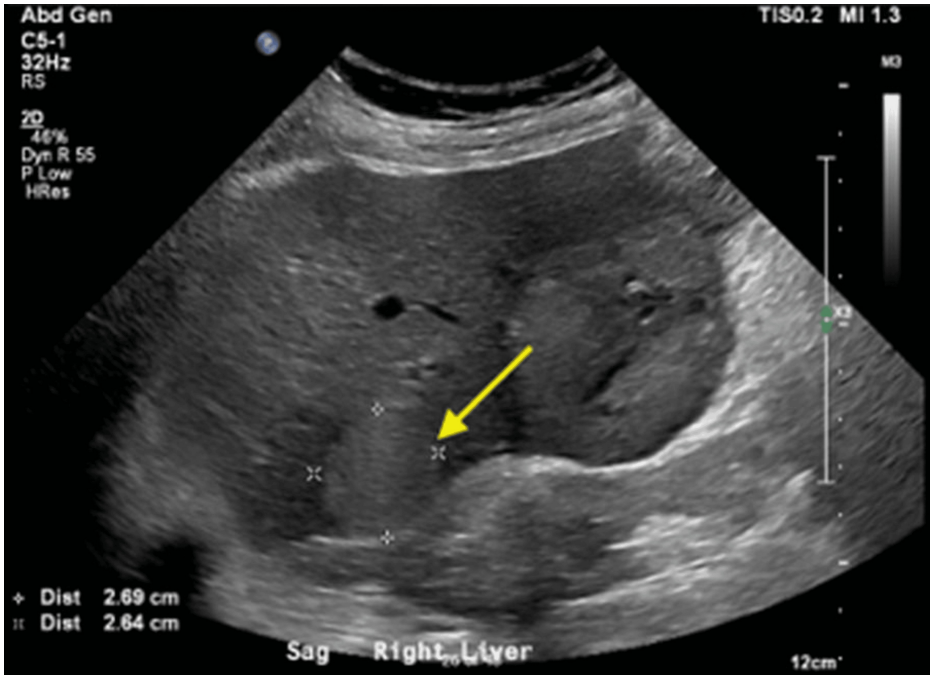


FIGURE 1: Sagittal grayscale ultrasound of the right hepatic lobe

The image demonstrates a well-defined, mildly hypoechoic focal mass (yellow arrow) measuring approximately 2.69 × 2.64 cm. The surrounding liver parenchyma appears homogeneous, with areas of mild heterogeneity

A subsequent abdominal MRI performed three days later confirmed 11-12 distinct liver lesions suspicious for malignancy (Figure *2*), accompanied by a markedly elevated serum alpha-fetoprotein (AFP) level of 110 IU/mL (reference range: 0-5.8 IU/mL).

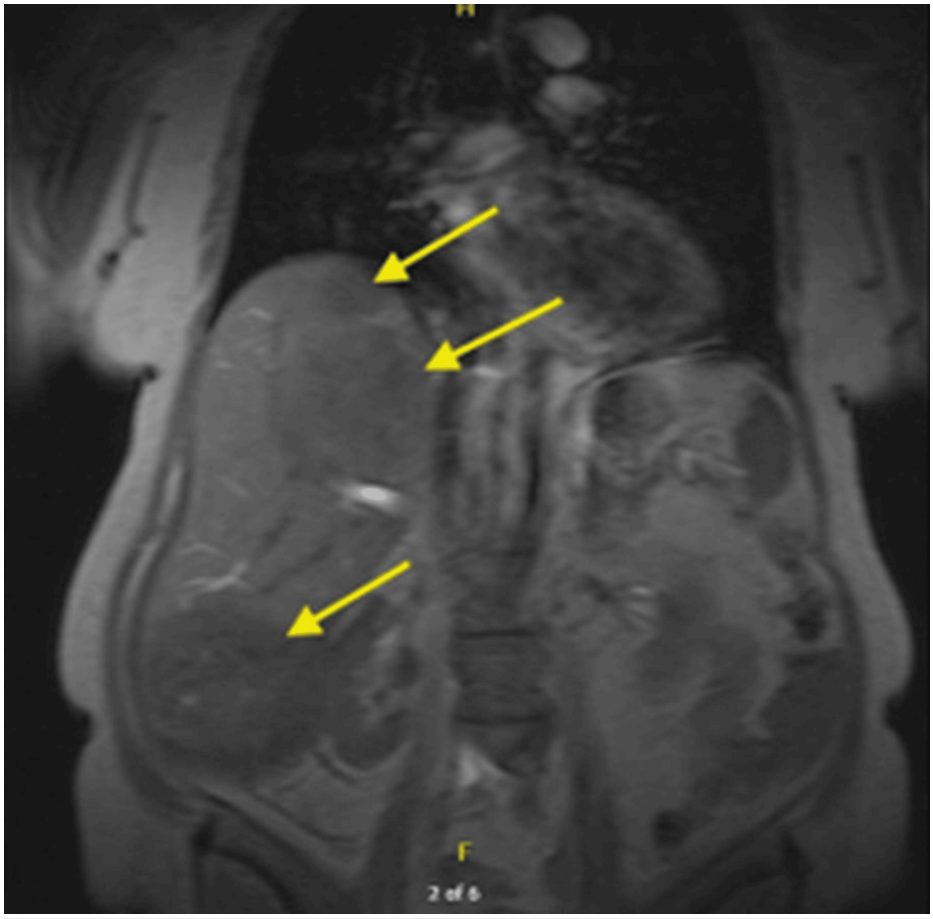


FIGURE 2: Coronal T2-weighted abdominal MRI

The image demonstrates multiple large, well-defined, mildly heterogeneous masses within the right lobe of the liver (yellow arrows)

MRI: magnetic resonance imaging

Upon returning to the hematology clinic one week later, the patient demonstrated profound clinical and laboratory deterioration. Her hemoglobin dropped precipitously to 5.8 g/dL, with a transferrin saturation of 7% and total iron of 16 µg/dL. Her ferritin spiked sharply to 664 ng/mL, reflecting a profound acute-phase inflammatory response to localized tissue injury. Subsequent upper endoscopy and colonoscopy revealed no macroscopically visible source of luminal bleeding, though this standard bidirectional evaluation does not completely exclude obscure small-bowel or occult gastrointestinal sources. She was immediately transfused with two units of packed red blood cells (PRBCs), achieving a post-transfusion hemoglobin stabilization at 9.6 g/dL. The full chronological correlation of these laboratory shifts with subsequent imaging and therapeutic interventions is detailed in Table *2*.

Timeline marker	Date	Clinical status, diagnostic investigations, and interventions	Key synchronized lab values
Baseline	2023	Routine outpatient check-up. Baseline evaluation reflecting chronic hereditary hemoglobinopathy status.	Hb: 9.5 g/dL. MCV: 68.6 fL. Platelets: 398,000/μL
First encounter	Initial presentation	Presents with progressive fatigue and pallor; urgent referral to hematology and gastroenterology initiated	Hb: 8.5 g/dL. Total iron: 33.0 μg/dL. Transferrin saturation: 11.2%
Interval presentation	Days 14–17 post-encounter	Develops sudden, severe abdominal pain. Abdominal ultrasound and subsequent MRI confirm 11-12 distinct bilateral hepatic masses. AFP noted at 110 IU/mL	Imaging confirmation of occult bleeding
Acute drop and transfusion	Dec 3, 2024	Profound clinical and hematologic deterioration in clinic. Admitted for immediate transfusion of 2 units of PRBCs	Hb: 5.8 g/dL (nadir). Ferritin: 664.0 ng/mL. Transferrin saturation: 7.0%
Post-transfusion check	Dec 4, 2024	Post-transfusion laboratory validation confirming transient stabilization. Upper and lower endoscopies show no gastrointestinal luminal bleeding source	Hb: 9.6 g/dL. MCV: 69.8 fL. Platelets: 676,000/μL
Acute rupture and intervention	10 days post-transfusion	Re-presents in hemorrhagic shock (Hb < 6.0 g/dL). Emergency CT documents explicit capsular rupture and free hemoperitoneum. Emergent transarterial embolization successfully targets three tumors (two actively bleeding, one prophylactic)	Acute hemorrhagic shock and structural stabilization
Biopsy and oncology course	Subsequent weeks	Core needle biopsy of a dominant lesion confirms well-differentiated HCC. Deemed ineligible for liver transplantation or surgical resection due to extensive bilobar tumor extent and recent capsule rupture	Histopathological confirmation
Final clinical outcome	1 month post-immunotherapy	Relocates out of state to family care. Initiated on palliative systemic immunotherapy (atezolizumab and bevacizumab). Passes away exactly one month later due to advanced disease progression	Terminal status

TABLE 2: Chronological timeline of symptoms, diagnostic investigations, and clinical interventions

A sequential, multi-day map tracking the progression of the patient's case over an 80-day timeline. It correlates the initial presentation of progressive worsening anemia with the onset of acute abdominal pain, cross-sectional hepatic imaging findings (ultrasound and MRI), the precipitous laboratory drop leading to blood transfusion, and the final emergency presentation with capsular rupture and hemoperitoneum managed via multi-site transarterial embolization. The timeline anchors her final palliative oncological course and post-immunotherapy survival tracking within a defined, relative clinical sequence

MRI: magnetic resonance imaging; AFP: alpha-fetoprotein; PRBCs: packed red blood cells; Hb: hemoglobin; CT: computed tomography; HCC: hepatocellular carcinoma; MCV: mean corpuscular volume

Ten days post-transfusion, a CT scan of the chest, abdomen, and pelvis confirmed the stable presence of the hepatic lesions alongside evidence of acute hemorrhage within the subcapsular tumors (Figure *3*).

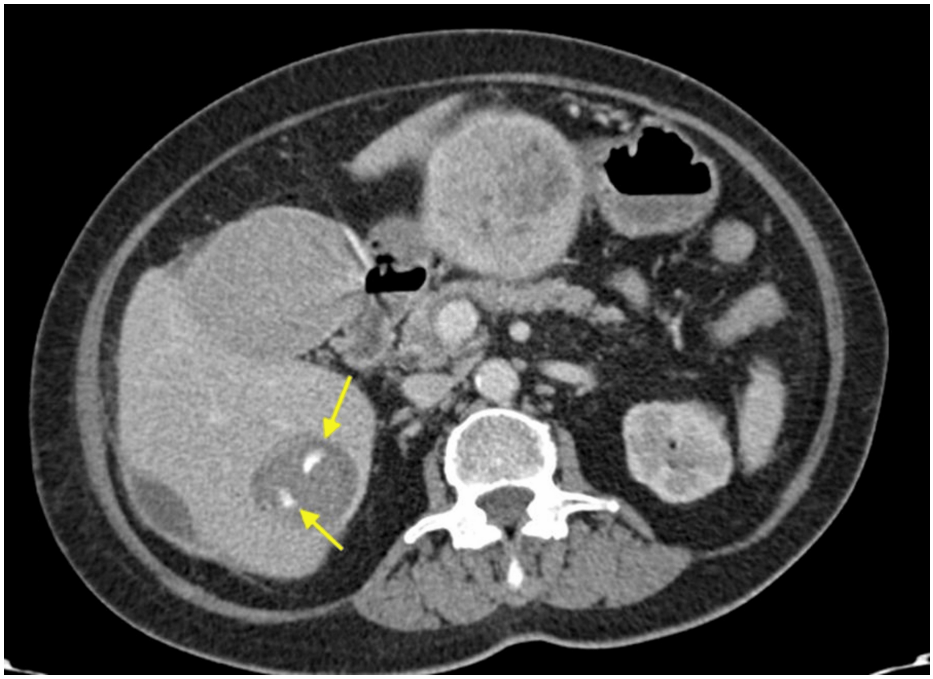


FIGURE 3: Axial abdominal CT

Axial portal venous phase contrast-enhanced abdominal CT scan demonstrating multiple large, low-attenuation space-occupying lesions throughout the liver parenchyma and a large rounded mass in the epigastrium. The yellow arrows indicate focal, hyperdense areas of active intralesional contrast extravasation ("vascular blush") pooling within a low-attenuation subcapsular hematoma in the posterior aspect of the right hepatic lobe, confirming active intratumoral hemorrhage

CT: computed tomography

The following day, the patient presented to an outside emergency department with a recurrence of severe, intractable abdominal pain and systemic signs of hemorrhagic shock, with her hemoglobin falling below 6.0 g/dL. Urgent repeat imaging demonstrated a frank disruption of the hepatic capsule and a high volume of free hemoperitoneum originating from two dominant subcapsular tumors, confirming that the hemorrhage was no longer contained within the lesions.

Interventional radiology was emergently consulted for transcatheter angiography. Angiography confirmed active contrast extravasation from these two primary lesions in segments six and eight; additionally, a third adjacent hypervascular tumor demonstrating a high risk for imminent rupture was identified. The patient underwent successful transarterial embolization targeting all three distinct tumors, achieving immediate hemodynamic and clinical stability. Five weeks after her initial presentation, a core needle biopsy of a dominant hepatic lesion was performed, confirming a diagnosis of well-differentiated HCC (Figures *4*-*5*).

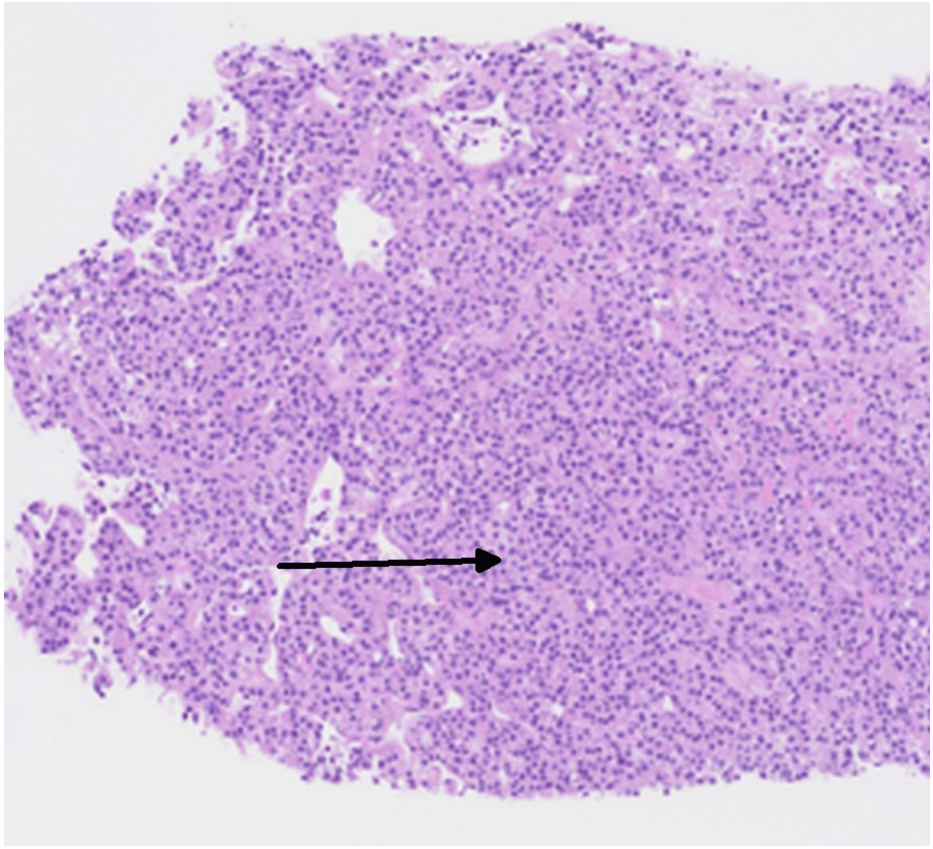


FIGURE 4: Liver biopsy

H&E-stained liver biopsy specimen (original magnification, 20×). The arrow points to an area of prominent trabecular widening, demonstrating a loss of the normal thin-cord architecture seen in non-neoplastic liver tissue

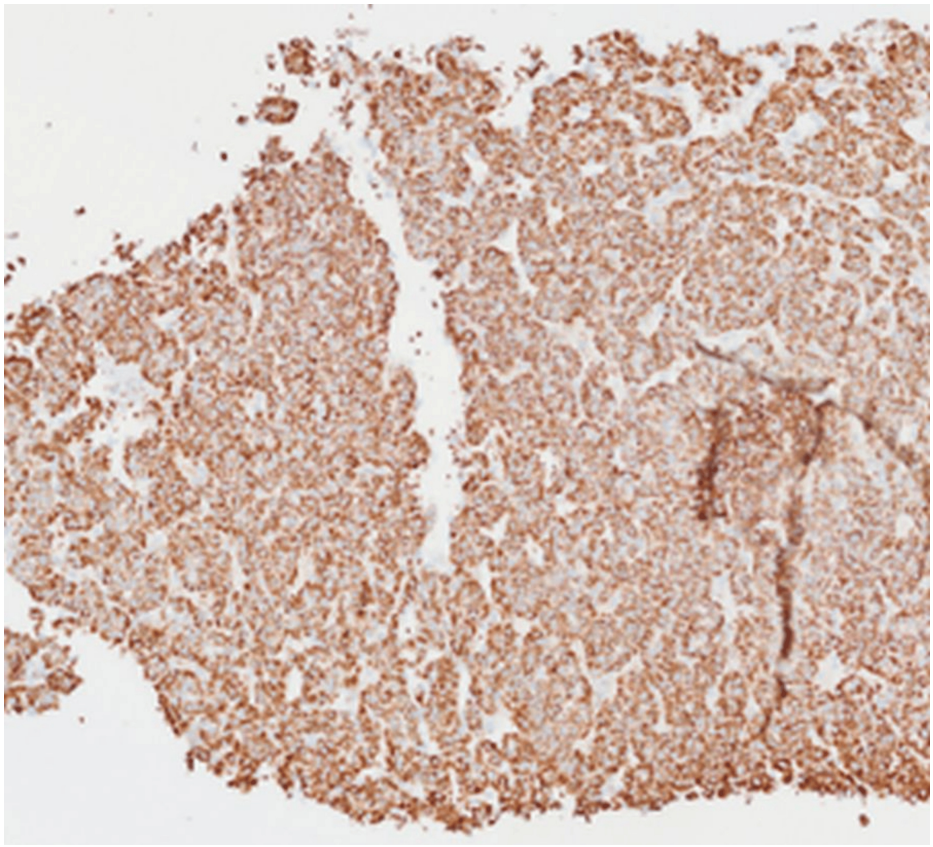


FIGURE 5: Immunohistochemical staining of the liver biopsy

Immunohistochemical staining of the liver biopsy specimen (original magnification, 10×). The tumor cells show strong, diffuse cytoplasmic HepPar-1 positivity, confirming the carcinoma's hepatocellular origin

Given the extensive tumor burden, bilateral lobar involvement, and recent catastrophic capsule rupture, the patient was determined to be an absolute non-candidate for orthotopic liver transplantation or surgical resection. She subsequently relocated out of state to be closer to her family and was initiated on a palliative first-line systemic immunotherapy regimen consisting of the combination of atezolizumab and bevacizumab. Unfortunately, her clinical condition rapidly declined due to the extensive malignancy and worsening hepatic insufficiency. She passed away under hospice care exactly one month following the initiation of her systemic immunotherapy regimen.

Discussion

This case illustrates a highly unusual, insidious presentation of advanced HCC in which severe IDA was the primary clinical manifestation. Spontaneous tumor rupture with catastrophic intraperitoneal hemorrhage is a well-documented, life-threatening emergency in HCC, with an incidence of 3% to 15% [3,4]. However, slow, occult intratumoral bleeding that causes systemic iron depletion before an acute rupture is an exceptionally rare sequence [5].

In this patient, diagnostic recognition was further confounded by a baseline history of alpha-thalassemia minor. Hereditary hemoglobinopathies typically present with chronic microcytic anemia, which can mask new, concurrent microcytic changes driven by iron kinetics. The sudden drop in hemoglobin from her baseline to 5.8 g/dL, together with a severe decrease in transferrin saturation, reflected true iron depletion. Crucially, her ferritin paradoxically rose to 664 ng/mL. This picture shows how ferritin acts as an acute-phase reactant, rising sharply in response to hepatic tissue injury and localized tumor inflammation, which can mislead clinicians into excluding absolute iron deficiency [6]. While primary or metastatic gastrointestinal malignancies frequently cause occult blood loss, primary hepatic tumors are rarely considered in the differential diagnosis of IDA when initial gastrointestinal endoscopies are negative [7].

Only a few reports have linked HCC variants directly to chronic iron deficiency. One earlier publication by Engelman and Riordan [8] described tumor-driven hepcidin dysregulation in a 36-year-old male with localized fibrolamellar HCC who presented with profound microcytic anemia (hemoglobin 6.3 g/dL). In that case, the tumor actively upregulated hepcidin expression, which locked systemic iron inside macrophages and enterocytes and rendered the anemia entirely refractory to parenteral iron replacement. Normal iron

metabolism was restored only after complete surgical resection of the hepatic mass. A second case reported by Abouzied et al. [9], involving metastatic gastrointestinal blood loss, described a 69-year-old male presenting with severe IDA one year post-hepatectomy. In that case, advanced molecular imaging ultimately showed that the blood loss was caused by rare, actively bleeding gastric wall metastases rather than intrahepatic tumors.

Distinguishing between absolute IDA and functional iron restriction remains a well-recognized diagnostic challenge in oncological hematology. According to the European Society for Medical Oncology (ESMO) [10] diagnostic guidelines, malignancy frequently triggers a functional iron deficiency marked by low serum iron and low transferrin saturation despite normal or elevated ferritin levels. This state is typically driven by inflammation-induced cytokine release, which stimulates hepatic production of hepcidin, a key peptide hormone that degrades ferroportin channels, trapping iron within macrophages and hepatocytes and restricting its availability for erythropoiesis.

While Engelman and Riordan [8] postulated a similar hepcidin-mediated iron-trapping mechanism in a case of fibrolamellar hepatocellular carcinoma presenting with iron-refractory anemia, direct molecular confirmation of tumor-driven hepcidin overexpression remains an ongoing area of study. In our patient, a mixed anemia etiology was highly probable. The severe, restricted iron kinetics were likely driven by a combination of inflammation-mediated functional iron trapping and insidious, occult subcapsular intratumoral bleeding. Negative upper and lower endoscopy does not completely exclude obscure small-bowel or occult gastrointestinal sources. Nevertheless, while the chronic component of this blood loss remains a plausible clinical inference, it is strongly supported by the subsequent structural failure of the hepatic capsule and high-volume open hemoperitoneum.

Our patient represents a distinct clinical phenomenon compared to these published cases. Unlike the case described by Abouzied et al. [9], endoscopy in our patient confirmed a completely pristine gastrointestinal lumen, indicating that her systemic blood loss arose strictly from continuous, slow-volume hemorrhage inside the subcapsular hepatic tumors themselves. Furthermore, her disease was characterized by multiple bilateral lesions that rapidly progressed from chronic, occult intratumoral bleeding to catastrophic tumor rupture, making her ineligible for curative surgical resection.

A key limitation in the diagnostic timeline of this case was the initial reliance on standard luminal gastrointestinal protocols, which deferred cross-sectional abdominal imaging while outpatient endoscopies were arranged. This delay, heavily influenced by the diagnostic distraction of her baseline alpha-thalassemia microcytosis, created a critical window during which the occult tumor bleeding evolved into a localized rupture.

This clinical progression highlights a critical takeaway. When evaluating severe microcytic anemia in a patient with a baseline hemoglobinopathy, a negative upper and lower endoscopic workup must not provide total clinical reassurance. If mild elevations in transaminases or alkaline phosphatase co-occur, clinicians should maintain a low threshold for early abdominal cross-sectional imaging. Identifying subcapsular hepatic masses before they manifest as an acute abdominal crisis is vital to preventing sudden tumor rupture and allowing timely, potentially life-saving oncologic interventions [11].

The determination of transplant ineligibility in this case relies on well-established staging and selection criteria [12]. The presence of more than a dozen multinodular, bilobar tumors classified this patient as Advanced Stage, making systemic therapy the only viable intervention [13,14]. Additionally, the clinical sequence of acute, high-volume spontaneous tumor rupture further precluded transplantation. Spontaneous rupture is considered a definitive contraindication to liver transplantation, as the leakage of tumor cells into the peritoneal cavity during the hemorrhagic event greatly increases the risks of peritoneal seeding, extrahepatic dissemination, and catastrophic post-transplantation recurrence under systemic immunosuppression.

Conclusions

Intratumoral hemorrhage in HCC can present insidiously, masquerading as chronic IDA before the onset of an acute abdominal crisis. This unusual diagnostic scenario highlights a rare clinical variant in which an underlying hereditary hemoglobinopathy, such as alpha-thalassemia minor, can mask the primary hematologic shift. While standard bidirectional gastrointestinal endoscopic evaluation remains the mandatory first-line investigation for unexplained microcytic anemia, this case suggests that it is reasonable to consider primary hepatic neoplasms when luminal evaluations are unrevealing and concurrent laboratory indicators of hepatic pathology are present. Maintaining clinical awareness of these atypical, isolated presentations could facilitate earlier abdominal cross-sectional imaging in similar scenarios, potentially allowing identification of subcapsular masses before they manifest as an acute abdominal crisis.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Steve Carlan, Paul Thambi, Yehuda Galili

Drafting of the manuscript: Steve Carlan, Asha Thambi, Paul Thambi

Acquisition, analysis, or interpretation of data: Asha Thambi, Munira Malik

Supervision: Paul Thambi, Yehuda Galili

Critical review of the manuscript for important intellectual content: Yehuda Galili, Munira Malik

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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