

# Metastatic Hepatocellular Carcinoma in a Non-Cirrhotic Liver without Viral Hepatitis: A Case Report and Literature Review

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## Abstract

**Background:** Hepatocellular carcinoma (HCC) usually develops in the setting of cirrhosis or chronic liver disease. Its occurrence in a non-cirrhotic liver and in the absence of viral hepatitis is rare and represents a diagnostic challenge due to the lack of risk factors and routine surveillance. **Case Presentation:** We report the case of a 45-year-old patient with no history of chronic liver disease and no infection with hepatitis B or C viruses, who presented with right upper quadrant pain and deterioration of general condition. Laboratory investigations showed preserved liver function and normal alpha-fetoprotein levels. Liver imaging revealed a hepatic mass in a liver with normal morphology, showing arterial enhancement with portal washout, associated with multiple pulmonary lesions, confirming the metastatic nature of the disease. A liver biopsy confirmed the diagnosis of metastatic hepatocellular carcinoma. The patient was treated with sorafenib, with a favorable clinical and radiological response. **Conclusion:** This case illustrates a rare presentation of HCC arising in a non-cirrhotic liver, metastatic at diagnosis, in the absence of viral hepatitis, and occurring in a relatively young patient. It highlights the importance of considering this diagnosis even in the absence of classical risk factors and underscores the role of systemic therapies in medical oncology.

## Keywords

Hepatocellular Carcinoma, Non-Cirrhotic Liver, Absence of Viral Hepatitis, Metastatic Disease, Systemic Therapy

## 1. Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and represents a major cause of cancer-related mortality worldwide [1]. It most commonly develops in the setting of cirrhosis or chronic liver disease, secondary to hepatitis B or C virus infection, chronic alcohol abuse, or metabolic disorders [1] [2]. However, up to 10% - 20% of HCC cases may arise in a non-cirrhotic liver, often without any identifiable risk factors [2] [3]. These forms are characterized by a frequently delayed diagnosis, large tumor size, and sometimes the presence of metastatic disease at the time of diagnosis [2] [3]. Sorafenib was the first multikinase inhibitor to demonstrate an improvement in survival in this population and remains a first-line option when other treatments are unavailable or contraindicated [4]. Among these alternatives are lenvatinib, immunotherapy combinations with anti-VEGF antibodies (e.g., atezolizumab plus bevacizumab), and the combination of durvalumab plus tremelimumab, all of which have shown significant benefits in survival and tumor response [5] [6]. We report here the case of a young patient with no history of chronic liver disease or viral infection, presenting with metastatic HCC arising in a non-cirrhotic liver, confirmed by biopsy and treated with sorafenib with a favorable response. This case highlights the value of appropriate systemic management and the importance of maintaining diagnostic vigilance even in the absence of classical risk factors.

## 2. Case Presentation

### 2.1. Demographic Data and Medical History

A 45-year-old man with no history of chronic liver disease, no significant alcohol consumption, and no known viral risk factors (negative for hepatitis B and C) presented with right upper quadrant pain.

The patient had a body mass index (BMI) of 24.5 kg/m<sup>2</sup>, with no history of diabetes or dyslipidemia. Laboratory assessments including fasting glucose, HbA1c, and lipid profile were within normal limits, suggesting the absence of metabolic dysfunction-associated steatotic liver disease (MASLD).

### 2.2. Initial Symptoms

The patient reported progressive right upper quadrant pain associated with a moderate deterioration in general condition, including fatigue and anorexia. Performance status was preserved (ECOG 1).

### 2.3. Laboratory Findings

Initial laboratory investigations showed:

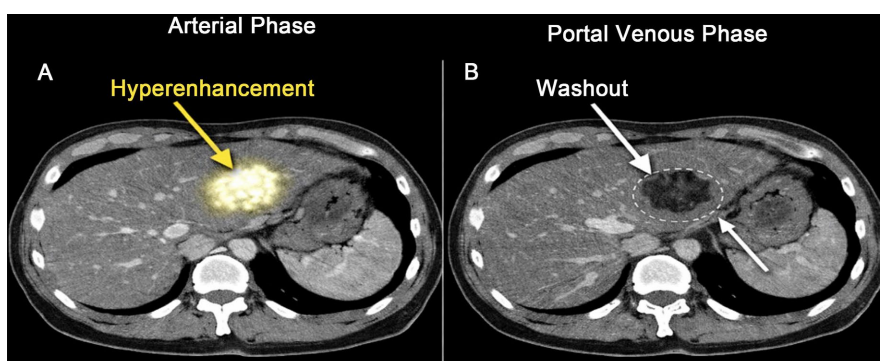
- Preserved liver function (normal AST and ALT levels)
- Normal bilirubin level
- Alpha-fetoprotein (AFP) within normal limits
- Normal complete blood count and renal function

- Serum PIVKA-II levels were measured and found to be within the normal range, consistent with the AFP-negative status of the tumor.

## 2.4. Imaging Studies

Triphasic (three-phase) contrast-enhanced computed tomography (CT) of the liver, including arterial, portal venous, and delayed phases, revealed (**Figure 1**):

- A single 7 cm hepatic mass in segment VII, showing intense arterial phase enhancement with portal venous washout, consistent with hepatocellular carcinoma.
- A liver with normal morphology and no signs of cirrhosis.



**Figure 1.** Triphasic contrast-enhanced CT of a non-cirrhotic liver with hepatocellular carcinoma. (A) Arterial phase: the hepatic lesion (segment VII) shows intense hyperenhancement (yellow arrow). (B) Portal venous phase: the lesion demonstrates washout (white arrow) and capsular enhancement (dashed line), consistent with hepatocellular carcinoma.

Dynamic liver magnetic resonance imaging (MRI) confirmed these findings. Chest CT demonstrated multiple bilateral pulmonary nodules consistent with distant metastases, confirming metastatic disease at diagnosis.

## 2.5. Biopsy and Histopathology

A percutaneous biopsy of the hepatic mass was performed under CT guidance. Histopathological examination revealed:

- A malignant tumor proliferation with trabecular and pseudo-glandular architecture.
- Tumor cells were pleomorphic, with abundant eosinophilic cytoplasm, round to oval hyperchromatic nuclei, and visible nucleoli.
- Frequent mitotic figures and focal areas of necrosis were present.
- Immunohistochemical analysis showed:
  - Positivity for HepPar-1 and Glypican-3, confirming hepatic origin.
  - Focal positivity for CK8/18 and negativity for CK7 and CK20.
- A Ki-67 proliferation index estimated at approximately 30% - 40%, indicating a moderate to high proliferative activity.
- Immunohistochemical staining was negative for TTF-1 and CDX2, ruling out

primary lung or gastrointestinal malignancies as the source of hepatic metastases.

These findings were consistent with hepatocellular carcinoma arising in a non-cirrhotic liver. The biopsy confirmed the diagnosis despite the absence of chronic liver lesions and normal AFP levels.

## 2.6. Therapeutic Management

After discussion at a multidisciplinary tumor board meeting, the patient was treated with sorafenib due to the metastatic nature of the disease, the absence of contraindications, and the unavailability of other therapeutic alternatives (immunotherapy and other multikinase inhibitors).

Treatment was initiated at a standard dose of 400 mg twice daily, with gradual dose escalation over 3 days to monitor tolerance. The patient was closely monitored with weekly laboratory tests at treatment initiation, followed by assessments every 2 - 3 weeks, and imaging evaluations every 8 - 12 weeks.

The treatment was well tolerated, with moderate cutaneous toxicity (palmar-plantar erythema) and no significant impairment of liver or renal function. No other severe adverse events were reported.

## 2.7. Outcome and Follow-Up

The patient was regularly followed with imaging studies and laboratory assessments.

- **After 8 weeks of treatment:** An initial clinical response was observed, with a moderate reduction in the hepatic mass and stabilization of pulmonary nodules. Symptoms such as right upper quadrant pain and fatigue began to improve.
- **After 16 weeks of treatment:** Follow-up CT imaging showed complete stabilization of the hepatic mass, with slight reduction in some pulmonary nodules. No new metastatic lesions were identified.
- **At 6- and 12-month follow-up:** The disease remained stable at both hepatic and pulmonary sites, with satisfactory treatment tolerance. The only reported side effects were moderate cutaneous toxicity (palmoplantar erythrodysesthesia) and transient fatigue, all managed symptomatically.

To date, the patient continues sorafenib therapy with preserved performance status (ECOG 1) and sustained radiological and clinical disease stability, confirming the long-term efficacy and tolerability of systemic therapy in this context of metastatic hepatocellular carcinoma arising in a non-cirrhotic liver.

The main clinical, biological, radiological, and therapeutic characteristics of the patient are summarized in **Table 1**.

## 3. Discussion

Hepatocellular carcinoma (HCC) arising in a non-cirrhotic liver represents a rare and often underestimated clinical entity, with distinct diagnostic and prognostic

features compared with HCC developing in cirrhotic livers [1] [2]. This case illustrates metastatic HCC in a non-cirrhotic liver in a young patient without classical risk factors, highlighting the challenges related to early diagnosis, therapeutic decision-making, and clinical follow-up. Analysis of this observation allows comparison with published data and emphasizes the role of systemic therapies in atypical clinical settings.

**Table 1.** Clinical, biological, radiological, and therapeutic characteristics of the patient.

Category	Findings
Age/Sex	45-year-old male
Body mass index (BMI)	24.5 kg/m <sup>2</sup>
Medical history	No chronic liver disease, no alcohol abuse
Viral hepatitis status	Hepatitis B and C negative
Metabolic risk factors	No diabetes, no dyslipidemia
Liver function	Preserved (normal AST, ALT, bilirubin)
Alpha-fetoprotein (AFP)	Within normal range
PIVKA-II	Within normal range
Imaging findings	Single 7 cm hepatic mass (segment VII) with arterial hyperenhancement and portal venous washout
Liver morphology	Normal, non-cirrhotic
Extrahepatic disease	Multiple bilateral pulmonary metastases
Histopathology	Trabecular and pseudo-glandular hepatocellular carcinoma
Immunohistochemistry	HepPar-1 (+), Glypican-3 (+), CK8/18 (+), CK7 (-), CK20 (-), TTF-1 (-), CDX2 (-)
Ki-67 index	30% - 40%
Treatment	Sorafenib 400 mg twice daily
Treatment tolerance	Moderate palmoplantar erythrodysesthesia
Radiological response	Disease stabilization
Follow-up	12 months
Outcome	Sustained clinical and radiological stability

### 3.1. Demographic Data and Risk Factors

HCC typically occurs in a cirrhotic liver, most often secondary to viral infection, alcohol abuse, or steatohepatitis [1] [2]. The non-cirrhotic form remains uncommon, accounting for approximately 10% - 20% of cases [2] [3]. These patients are frequently diagnosed at a late stage, as symptoms are nonspecific and biological markers such as AFP may be normal [2] [3] [7]. Our patient, a 45-year-old man with no history of liver disease or viral infection, exemplifies this atypical presen-

tation. This situation underscores the need to consider HCC even in the absence of classical risk factors and not to rely solely on biological markers when initiating diagnostic investigations.

### **3.2. Clinical Presentation and Laboratory Findings**

HCC arising in non-cirrhotic livers often presents with subtle or nonspecific symptoms, such as abdominal pain, fatigue, or weight loss [2] [7]. AFP levels are normal in 30% - 40% of cases [7] [8], complicating early diagnosis. In our case, the patient presented with abdominal pain and moderate fatigue, and liver function was preserved, in line with data from the literature describing the clinical presentation of these atypical HCCs.

### **3.3. Non-Cirrhotic Versus Cirrhotic Hepatocellular Carcinoma: Clinical, Prognostic, and Therapeutic Considerations**

Compared with hepatocellular carcinoma arising in cirrhotic livers, HCC developing in a non-cirrhotic liver exhibits several distinctive features. It often occurs in younger patients without identifiable risk factors, with preserved liver function and frequently normal alpha-fetoprotein levels [1] [3]. The absence of routine surveillance in this population contributes to delayed diagnosis, with larger tumors and, in some cases, metastatic disease at presentation [2] [7]. From a prognostic perspective, several studies suggest that preserved hepatic function in non-cirrhotic patients may allow better tolerance to systemic therapies and potentially prolonged survival, despite advanced disease at diagnosis [7] [9] [10]. Our case is consistent with these observations and illustrates the atypical but increasingly recognized profile of non-cirrhotic HCC reported in the literature.

### **3.4. Imaging and Disease Extension**

Triphasic contrast-enhanced CT and dynamic MRI are essential for characterizing HCC, with arterial phase hyperenhancement followed by portal venous wash-out being a highly suggestive imaging hallmark [4] [8]. In our case, the single 7 cm hepatic mass exhibited these features in a morphologically normal liver. The presence of pulmonary metastases at diagnosis, although uncommon, has been reported in aggressive HCCs arising in non-cirrhotic livers [8] [9]. These findings reinforce the need for systematic staging, including thoracic and skeletal evaluation.

### **3.5. Biopsy and Pathological Findings**

Although imaging may be sufficient in typical cases, biopsy remains crucial for HCC arising in non-cirrhotic livers, particularly when AFP levels are normal [7] [10]. In our observation, biopsy revealed trabecular and pseudo-glandular architecture, tumor cells with eosinophilic cytoplasm, hyperchromatic nuclei, frequent mitoses, and focal necrosis. Immunohistochemistry showed positivity for Hep-Par-1 and Glypican-3, with a moderate Ki-67 index (30% - 40%), confirming he-

patic origin. These findings are consistent with published data on HCC in non-cirrhotic livers and highlight the importance of accurate histological diagnosis to guide therapeutic strategy.

### 3.6. Therapeutic Management

Sorafenib, a multikinase inhibitor, was the first systemic therapy to demonstrate a significant survival benefit in advanced HCC [4]. However, data regarding its use in metastatic HCC arising in non-cirrhotic livers are limited, as such patients are often underrepresented or excluded from clinical trials [7] [10].

In our case, the choice of sorafenib was guided by:

- 1) The metastatic nature of the disease, making local treatments (resection or ablation) inappropriate [11];

- 2) The absence of contraindications and the lack of availability of alternative therapies such as lenvatinib or immunotherapy/anti-VEGF combinations [5] [6].

The administered dose (400 mg twice daily, with gradual introduction over 3 days) corresponds to the regimen used in pivotal trials [4]. The tolerance observed in our patient was consistent with literature data, with moderate cutaneous toxicity and no significant impairment of liver or renal function [4] [9]. Thus, this case illustrates that sorafenib can be used safely and effectively in metastatic HCC arising in non-cirrhotic livers when other therapeutic options are unavailable, supporting its relevance in rarer clinical contexts not well represented in randomized trials [7] [8].

Recent advances have substantially changed the first-line management of advanced hepatocellular carcinoma. The combination of atezolizumab plus bevacizumab demonstrated a significant improvement in overall survival and progression-free survival compared with sorafenib, with a median overall survival of 19.2 months versus 13.4 months and an objective response rate of approximately 30% [5]. Similarly, the combination of durvalumab plus tremelimumab showed a durable survival benefit, with a median overall survival of 16.4 months compared with 13.8 months for sorafenib [6]. Although these pivotal trials predominantly included patients with underlying cirrhosis, the mechanisms of action of immune checkpoint inhibitors and anti-VEGF therapies are not directly dependent on the presence of cirrhosis. Therefore, their efficacy may reasonably be extrapolated to patients with non-cirrhotic hepatocellular carcinoma. Moreover, preserved liver function in non-cirrhotic patients may contribute to improved treatment tolerance and sustained exposure to systemic therapy.

However, in the present case, immunotherapy was not accessible due to local regulatory restrictions, limited availability, and logistical constraints. In addition, enrollment in clinical trials was not feasible at the time of treatment initiation. Consequently, sorafenib remained the most appropriate and evidence-based first-line systemic option available. Despite these limitations, the patient achieved prolonged disease stabilization for 12 months, highlighting that tyrosine kinase inhibitors may still provide meaningful clinical benefit in selected patients with pre-

served liver function, particularly in non-cirrhotic hepatocellular carcinoma.

### 3.7. Treatment Response and Outcome

The patient's response to sorafenib was early and sustained, with stabilization of the hepatic mass and slight regression of pulmonary nodules after 16 weeks, and prolonged disease stability up to 12 months. These results are consistent with published data: in the SHARP and Asia-Pacific trials, sorafenib achieved radiological disease stabilization in approximately 43% - 54% of patients, although most had underlying cirrhosis [4]. Our observation extends these findings to a young, non-cirrhotic patient, demonstrating that responses may be comparable or even prolonged in this population.

When compared specifically with published cohorts of hepatocellular carcinoma arising in non-cirrhotic livers, the survival outcome observed in our patient appears consistent with, or slightly superior to, previously reported data. Several retrospective studies have shown that patients with non-cirrhotic HCC often present with larger or more advanced tumors but may experience improved treatment tolerance and prolonged survival due to preserved liver function [1] [8]. Median overall survival in advanced or metastatic non-cirrhotic HCC has been reported to range between 8 and 14 months, depending on tumor burden and access to systemic therapy [10].

In this context, the 12-month sustained disease stabilization achieved in our patient under sorafenib compares favorably with outcomes reported in non-cirrhotic HCC cohorts and supports the hypothesis that preserved hepatic reserve may positively influence both treatment tolerance and clinical outcomes [1] [11].

The absence of underlying cirrhosis may represent a favorable factor for treatment tolerance and clinical outcomes in advanced hepatocellular carcinoma. Patients with preserved liver function are more likely to receive systemic therapy at full dose and for longer durations, with a lower risk of treatment-related hepatic decompensation [12]. In addition, several studies have reported improved treatment tolerance and survival in non-cirrhotic HCC compared with cirrhotic patients, underscoring the prognostic importance of hepatic reserve [1] [11].

Finally, this case underscores the importance of regular follow-up with imaging and laboratory tests and shows that even in metastatic HCC with pulmonary involvement, sorafenib can provide prolonged clinical and radiological stabilization, validating its role in atypical clinical situations [8] [11].

### 3.8. Perspectives and Key Messages

This case highlights several important points:

- 1) HCC can occur in the absence of cirrhosis and classical risk factors, and AFP levels may be normal.
- 2) Biopsy remains essential to confirm the diagnosis and guide treatment decisions.
- 3) Sorafenib can achieve prolonged disease stabilization, even in the presence

of pulmonary metastases at diagnosis.

4) The availability and accessibility of targeted therapies and immunotherapies remain major challenges in the management of advanced HCC.

#### 4. Conclusion

Hepatocellular carcinoma arising in a non-cirrhotic liver is a rare entity, often diagnosed at a late stage due to the absence of classical risk factors and specific biological markers. This case demonstrates that, even in the presence of pulmonary metastases, systemic treatment with sorafenib can achieve prolonged clinical and radiological disease stabilization while maintaining good tolerability. It also highlights the importance of biopsy for accurate diagnosis, regular follow-up, and therapeutic adaptation based on treatment availability and contraindications. Finally, this observation supports the relevance of sorafenib use in atypical clinical settings and emphasizes that preserved liver function plays a key role in both treatment tolerance and efficacy. These insights may help guide the management of future patients with metastatic HCC arising in non-cirrhotic livers and underscore the need to complement existing data with prospective studies and multicenter case series.

#### Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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